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The Host Response to Sepsis and Developmental Impact

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Abstract

Invasion of the human by a pathogen necessitates an immune response to control and eradicate it. When this response is inadequately regulated, systemic manifestations can result commonly manifested in physiologic changes described as “sepsis”. Recognition, diagnosis, and management of sepsis remain among the greatest challenges shared by the fields of neonatology and pediatric critical care medicine. Sepsis remains among the leading causes of death in both developed and under-developed countries with an incidence that is predicted to increase each year. Despite these sobering statistics, promising therapies derived from pre-clinical models have universally failed to obviate the substantial mortality and morbidity associated with sepsis. Thus, there remains a need for well-designed epidemiologic and mechanistic studies of neonatal and pediatric sepsis to improve our understanding of the causes—both early and late—of deaths attributed to the syndrome. In reviewing the definitions and epidemiology, developmental influences and regulation of the host response to sepsis, it is anticipated that an improved understanding of this host response will assist clinician-investigators in identifying improved therapeutic strategies.

Keywords

sepsis; septic shock; developmental influence; hemodynamics; coagulation cascade; immune function

Definitions characterizing the host responses in sepsis

“Sepsis” referring to the “decomposition of animal or vegetable organic matter in the presence of bacteria”¹ first appeared over 2700 years ago in the poems of Homer. Hippocrates also used the term “sepsis” and believed the decomposition could release “dangerous principles” that could cause “auto-intoxication”². Lewis Thomas furthered this concept when he proposed that the clinical responses seen in sepsis were the result of the host's response to the infectious agent³. In 1991, an American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference was convened to create a framework in which to define the systemic response to sepsis which resulted in defining criteria for the *systemic inflammatory response syndrome (SIRS)*, *sepsis*, *severe sepsis* and *septic shock*^{4, 5}. These criteria were refined a decade later (2001) by the participants of the International Sepsis Definitions Conference⁶ and were based exclusively on adult criteria. The International Consensus Conference on Pediatric Sepsis and Organ Dysfunction was convened in 2002 to develop pediatric-specific definitions

for SIRS, sepsis, severe sepsis, septic shock and multiple organ dysfunction syndrome (MODS) ⁷.

Through clinical observations, pediatricians and neonatologists had recognized that the systemic inflammatory response of tachycardia, tachypnea, hyperthermia and leukocytosis (Table 1) most commonly triggered by infection, could also be present following trauma, burn injury, pancreatitis and various other insults. As a result, this physiologic response was defined as the systemic inflammatory response syndrome (SIRS) with no reference to the presence of infection. *Sepsis* was defined as a SIRS response associated with infection based on either microbiologic cultures or strong clinical evidence of the presence of an infection. *Severe sepsis* was defined as sepsis plus evidence of organ dysfunction defined around pediatric parameters (Table 2) while *septic shock* was defined as sepsis criteria plus the presence of “cardiovascular dysfunction” present after the administration of at least 40 ml/kg in 1 hour of fluid. Cardiovascular dysfunction included: age-specific hypotension (Table 3 shows age-related normal values); requirement of a vasoactive agent to maintain normal blood pressure; or evidence of poor end-organ perfusion (Table 2).

Though this report listed criteria for both “newborns” (aged 0 to 7 days) and “neonates” (aged 1 wk to month), preterm newborns were specifically excluded from the definitions ⁷. This omission related to a number of factors including: the charge of the Consensus Conference, insufficient representation by practitioners in neonatology, and a general agreement that premature infants fell outside the scope of clinical practice of the majority of Conference attendees. Furthermore, the diagnosis of sepsis can be challenging in the very preterm infant undergoing the physiologic transitional period immediately after birth. Other features complicating the delineation of this diagnosis include the subtlety of non-specific presenting signs and the contribution of transitional physiology making it imperative that clinicians maintain a high index of suspicion. This reliance on clinical “gestalt” has been substantiated by evidence showing that a physician’s clinical suspicion of culture positive sepsis has significant positive predictive value (>70%) in excess of most laboratory studies ^{8, 9}. In some neonatal cases, the clinical presentation may be overtly obvious with significant apnea or respiratory distress, cyanosis, hypotension, bradycardia, poor perfusion, acidosis, and lethargy. Alternatively, the presence of one or more subtle and non-specific signs such as feeding intolerance, self-resolving apnea or bradycardia, mild tachypnea or tachycardia, abnormal serum glucose, or decreased activity may be the only warning before fulminant clinical deterioration ^{10, 11}. Though some useful ancillary laboratory tests for the diagnosis of neonatal sepsis exist, the diagnosis remains a significant clinical challenge ¹².

Epidemiology of pediatric sepsis

Worldwide, sepsis is one of the most common causes of death in children. One of the first pediatric-specific studies analyzing data from 5 centers reported over 21 to 25% of the 726 patients met criteria for “sepsis syndrome” with a mortality of 11% ¹³. Proulx *et al.* ¹⁴ analyzed over 1000 admissions over a one-year period and observed that SIRS was present in 82% of PICU patients while sepsis was present in 23% with severe sepsis and septic shock was detected in 4% and 2% of patients. Though sepsis-specific mortality rates were not reported, the overall mortality rate of the entire cohort (n=1058) was 6% and did differ among those patients with multiple organ dysfunction, many of whom were triggered by sepsis ¹⁴. Watson *et al.* examined discharge data to show that severe sepsis accounted for 9675 of the 1.6 million discharges of patients ≤19 years old resulting in a national estimate of 42,371 cases of pediatric sepsis per year (0.6 cases/1,000 population) ¹⁵. Not all centers reported data for premature low birth weight or very low birth weight neonates which were by convention included as “infants” in the analysis ¹⁵. The grouping of “infants” (any child < 1 year) comprised nearly half the children with severe sepsis and nearly half the sepsis cohort had at least one co-morbid condition. The

highest incidence of severe sepsis was found in neonates (5.2 cases/1,000 population) compared to 5 to 14 year olds (0.2 cases/1,000 population) and the mortality rate reported across the entire cohort (including some neonates within the infant category) with severe sepsis was 10.3% estimating 4,364 deaths per year nationally. These data positioned sepsis as the third leading cause of death in children nationwide. In a follow up study from 1995 and 1999, Watson et al found the rate of severe sepsis had increased 11% mostly due to an increase in the number of very low birth weight neonates succumbing to sepsis¹⁶. Despite this increase in cases of severe sepsis, the mortality due to severe sepsis in previously healthy children was found to be 9%¹⁶.

Odetola et al. conducted a similar retrospective study of hospitalized children (age 0 to 19 years) with severe sepsis (sepsis with at least one organ dysfunction as estimated from ICD-9 coding) within the 2003 Kids' Inpatient Database (KID) which included almost 3 million pediatric discharges from 3438 hospitals in 36 states¹⁷. The authors identified nearly 13,000 hospitalizations for severe sepsis in the database providing a national estimate of 21,448 severe sepsis admissions with an overall mortality rate of 4.2%. There was similar increase in the prevalence of and mortality from severe sepsis in the younger aged cohort (less than 4 years), with a notable increase in adolescents as compared to 4–10 year olds. Perhaps most importantly, these investigators noted the significant association of both co-morbid conditions and existing organ dysfunction to worsening outcomes and higher resource utilization¹⁷.

In the most recent epidemiology study of pediatric sepsis, Czaja and colleagues investigated readmission rates and late mortality for children (1 month to 18 years old) following severe sepsis¹⁸. 7183 children were diagnosed with severe sepsis from 1990 through 2004, 6.8% of whom died during with the authors termed the “sentinel admission” or within 28 days of discharge. Importantly, death certificates confirmed that an additional 434 (6.5%) of those who had survived an initial 28 days after admission, subsequently died during the follow-up period with the highest late death rate occurring within 2 years of the initial hospitalization¹⁸. Although most of the early, as well as the late deaths, occurred in children with co-morbidities (8% early death, 10.4% late death), 8% of children with no co-morbidities died during their initial hospitalization.

Neonatal sepsis is also a significant global killer responsible for over 1 million deaths annually and is among the top ten causes of neonatal death in the United States¹⁹. Stoll et al. reported that the incidence of neonatal sepsis is dependent upon gestational age and time of onset (early-onset sepsis-**EOS** [<72 hours after birth] versus late-onset sepsis-**LOS** [>72 hours after birth])^{20–23}. Deficiencies in the immune system function of neonates further delineated below increase the risk of morbidity for survivors (only 28% alive and considered normal at 18 months) and mortality that exceeds 70% for the most immature neonates²⁴. Risk factors for developing sepsis in the premature neonate have been described and are reviewed^{10, 20, 21, 25–30}. Notable findings from the 1996 Neonatal Network report included the observation that culture-proven EOS was uncommon, occurring in only 1.9% of nearly 8000 VLBW neonates. Group B streptococcus (31%), *Escherichia coli* (16%) and *Haemophilus influenzae* (12%) were the most common pathogens associated with EOS in this era. The fact that antibiotic therapy for suspected sepsis was often started at birth in VLBW neonates and continued for 5 or more days, despite a negative blood culture result in 98% of cases²⁷ underscores the challenge of excluding sepsis in the symptomatic VLBW neonate. In this report, 26% of VLBW neonates with EOS died but it was not clear that all deaths were attributable to infection as only 4% of the 950 deaths that occurred in the first 72 hours of life were attributed to infection²⁷. Key maternal factors such as Group B *Streptococcus* (**GBS**) positive vaginal culture, prolonged rupture of membranes, intrapartum fever, and chorioamnionitis are strongly associated with EOS²⁸. Gender (male), birth weight (<1000 g), and gestational age (<30 weeks) as well as common clinical interventions associated with prematurity (e.g. intubation, mechanical

ventilation, and central venous access) are also associated with an increased risk of sepsis^{20, 21, 24}. These data illustrate that sepsis is a major health problem in pediatrics.

Key developmental differences impacting neonatal and pediatric sepsis

Severe sepsis manifests with concurrent derangements in almost every single organ system. The degree to which any of these derangements are manifest is variable and influenced by multiple host and pathogen factors, including the patient's age^{15, 31}, gender^{32, 33}, race^{34, 35}, and genetic background^{36–39}, as well as the presence of co-morbid conditions^{15, 40–42}, the patient's underlying immune status^{15, 40}, and the specific pathogen involved^{43, 44} (see accompanying article). There are several key developmental differences in the host response to infection and therapy that clearly delineate pediatric sepsis as a separate, albeit related, entity from adult sepsis. A complete picture of pediatric sepsis therefore requires a thorough understanding of those developmental differences and how they contribute to organ dysfunction in the pediatric patient with septic shock.

Developmental differences in hemodynamics

Septic shock is due to a combination of decreased intravascular volume (either absolute or relative hypovolemia), myocardial dysfunction, and abnormalities in peripheral vasoregulation. Absolute hypovolemia (i.e. decreased intravascular volume secondary to poor oral intake, vomiting, diarrhea, or increased insensible losses, etc.) or relative hypovolemia (i.e. decreased intravascular volume secondary to capillary leak, increased venous capacitance, etc.) is the most common cause of shock in children^{45, 46}. However, abnormalities in peripheral vasoregulation and/or myocardial dysfunction likely play a greater role in the hemodynamic derangements associated with pediatric septic shock, especially in neonates and young infants^{47–51}. Ceneviva and colleagues⁵² categorized 50 children with fluid-refractory shock based upon hemodynamic data obtained with a pulmonary artery catheter into three categories: (i) a hyperdynamic state characterized by a high cardiac output (> 5.5 L/min/m² BSA) and low systemic vascular resistance (< 800 dynes sec/cm⁵) (classically referred to as *warm shock*); (ii) a hypodynamic state characterized by low cardiac output (< 3.3 L/min/m² BSA) and normal to low systemic vascular resistance (SVR); or (iii) a hypodynamic state characterized by low cardiac output and high SVR (> 1200 dynes sec-cm⁵) (classically referred to as *cold shock*). Thus, in contrast to adults in which septic shock is characterized by a high cardiac output and low SVR, most children had low cardiac output and high systemic vascular resistance (*cold shock*) and required vasodilators to decrease SVR, increase CI, and improve peripheral perfusion⁵². These findings were confirmed in multiple studies^{53–58}. For example, Feltes et al⁵⁸ reported decreased left ventricular systolic function and increased afterload in 5 out of 10 children with septic shock. Thus, myocardial depression is a common pathophysiological feature in pediatric septic shock raising the question as to differences unique to myocardial function.

Significant developmental differences in both myocardial structure and function compromise the compensatory response of children and neonates to sepsis^{49, 59, 60}. For example, changes in excitation-contraction coupling occur due to the immaturity of the calcium regulation system (T tubules, sarcoplasmic reticulum, L-type Ca²⁺ channels). These developmental differences lead to alterations in the normal mechanisms regulating the Ca²⁺-induced Ca²⁺ release (CICR) that triggers excitation-contraction coupling, such that the neonatal myocardium is more dependent upon extracellular calcium versus intracellular calcium for contractility as compared to the mature heart^{61–64} explaining why neonates are more sensitive to calcium channel antagonists⁶². Further differences in the neonatal myocardium include decreased expression of ATP-sensitive K⁺ channels (K_{ATP})⁶⁵ and alterations in β -adrenergic receptor signal transduction⁶⁶. K_{ATP} channels are inhibited by intracellular ATP and activated by intracellular

nucleoside diphosphates (e.g. ADP). These channels are activated in response to ischemia or hypoxia and are therefore important for the adaptations that must occur in sepsis ^{67–69}.

The infant's myocardium also has a relatively decreased left ventricular mass in comparison to the adult myocardium ^{70, 71}, as well as an increased ratio of type I collagen (decreased elasticity) to type III collagen (increased elasticity) ⁷². In addition, the infantile myocardium functions at a relatively high contractile state, even at baseline ^{49, 73}. Collectively, these developmental changes result in a relatively limited capacity to increase stroke volume during stress ^{49, 71, 74}, and hence neonates and young infants are critically dependent upon an increase in heart rate to generate increased cardiac output. However, while adults can easily double their heart rate to compensate for decreased stroke volume, infants are unable to compensate in this manner due to the relatively higher baseline heart rate ⁷⁵. In addition, myocardial perfusion occurs to the greatest degree during diastole and depends directly upon the difference between diastolic blood pressure and left atrial pressure, and inversely with heart rate. Thus, as the heart rate increases, diastolic filling will eventually reach a point at which further increases in cardiac output are limited. Cardiac output, however, is maintained for a time via peripheral vasoconstriction (increased systemic vascular resistance = increased afterload) in an attempt to maintain adequate preload ^{54–56, 76}. Finally, systolic performance in neonates and young infants is critically dependent upon afterload ^{73, 77}. An increase in systemic afterload in the setting of septic shock therefore results in markedly reduced left ventricular systolic performance and myocardial dysfunction. Collectively, these hemodynamic changes which are clinically manifested as *cold shock* (decreased CI, increased SVR) are more commonly observed in critically ill children with septic shock.

Developmental differences in the coagulation cascade

Sepsis is one of the most common causes of disseminated intravascular coagulation (DIC) which results from uncontrolled thrombin generation and subsequently leads to both microvascular thrombosis that contributes to end organ dysfunction and paradoxically, bleeding diathesis due to the consumption of coagulation factors ^{78–80}. One of the seminal findings that has contributed to an improved molecular understanding of sepsis-induced organ dysfunction is this observed “switch” from a homeostatic balance of anti- versus pro-coagulant factors to a skewing towards pro-coagulation with impaired anti-coagulation favoring microvascular thromboses. A number of factors contribute to dysregulation of the coagulation cascade in sepsis: activation of procoagulant pathways, consumption of clotting factors, alterations in fibrinolysis, and reduced anti-coagulant activity resulting in what is commonly described as disseminated intravascular coagulation (DIC) (reviewed in ^{79, 81–83}). Simultaneous to enhanced fibrin production, attenuated fibrinolysis caused by increased plasminogen activator inhibitor type 1 (PAI-1), as well as dysfunction and/or depletion of natural anti-coagulants [antithrombin III, protein C, protein S and tissue factor pathway inhibitor (TFPI)] occurs. A correlation between low AT III and mortality in sepsis provided the impetus for studying AT III replacement; however, no consistent benefit has been observed in either adults ^{84–87}, children ^{88, 89}, or neonates ⁹⁰.

Patients with sepsis also have substantial depletion of protein C (Reviewed: ^{91–93}). Given encouraging pre-clinical studies with the use of APC in sepsis, clinical trials in adults were commenced (e.g. Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial ⁹⁴). In this study, APC was associated with a statistically significant reduction in 28-day mortality in sepsis in adults. In further analysis, APC appeared to confer benefit only on those with the highest severity of illness (APACHE score >25); subsequent studies have been executed in an attempt to identify the adult patient population most benefiting from this therapy ^{94–96}. The pediatric Phase III study employing APC in severe sepsis was stopped after an interim analysis showed that APC was unlikely to improve the resolution of organ dysfunction and that its use

was associated with an increased risk of serious adverse events in children less than 60 days^{97,98}. To date, only case reports have examined the use of APC in neonatal sepsis^{99–101}. Taken together, the current state of the use of APC in sepsis remains controversial in adults and appears to be of no benefit in either children or neonates.

There are important developmental differences in the coagulation and fibrinolytic system that impact the pathophysiology and management of DIC in children versus adults¹⁰². For example, neonates and infants are at an increased risk for bleeding complications, primarily due to lower circulating levels of vitamin K-dependent procoagulant factors (factor II, VII, IX, and X), a decreased capacity to generate thrombin, and decreased circulating levels of coagulation inhibitors. The neonatal coagulation system contains all of the essential factors necessary for an intact coagulation system, though the amounts of factors are decreased relative to adult levels¹⁰². Similarly, while there are no distinct differences in platelet quantity between children and adults, platelets are relatively hyporesponsive to physiologic agonists¹⁰³. These unique differences may explain the increased risk of mortality in younger children with DIC, compared to older children¹⁰⁴ and adults and why the therapeutic response to modulators of coagulation differ.

Developmental differences in the inflammatory response to sepsis

In order to contextualize the developmental differences in the host response to sepsis, specific contributions of some mediators and mechanisms must be briefly summarized. Key mediators of the inflammatory response to host invasion include numerous gene products (e.g. cytokines and chemokines, coagulation-related factors, and immune active proteins) all of which are critical to ensuring recruitment and activation of immune cells necessary for pathogen eradication. Literally hundreds of gene products play some role in the complex host response to sepsis and a comprehensive review of these beyond the scope of any single report on this subject. The reader is directed to recent reviews of the mediators of this pathophysiologic response in sepsis^{105–108} and gene expression profiling (accompanying article). Here, we briefly highlight some key developmental differences in the host innate and adaptive immune responses (reviewed¹⁰⁹ and summarized in Table 4).

While a number of mediators responsible for the initiation and propagation of sepsis were identified early on, few studies attempted to identify those responsible for the eventual resolution of inflammation. This concept appeared to be important as failure to reduce proinflammatory mediators over the course of sepsis was associated with higher mortality rates^{110–112}. Also, patients who died from ARDS produced lower levels of IL-10 as compared to survivors¹¹³. More recently, the hypothesis that an over-exuberant counter-regulatory process can lead to gene deactivation in sepsis and thus, increase mortality in both children¹¹⁴ and adults¹¹⁵ has identified a need to better understand this mechanism.

We now understand that immune activation triggered by pathogens also drives expression of endogenous counter-regulators of inflammation resulting in a state termed the “compensatory anti-inflammatory response syndrome (CARS)”. Such mediators include both cytokine antagonists (e.g. soluble TNF receptor, IL-1Ra) and “anti-inflammatory” cytokines (e.g. IL-10 and TGF- β) (reviewed^{116–118}). Clearly other regulatory cytokines (e.g. TGF- β , IL-13) possess anti-inflammatory properties and contribute to the endogenous regulation of the acute inflammatory response to sepsis. Based on additional observations, there is a growing recognition that this compensatory anti-inflammatory response may play a greater role in the pathobiology of septic shock and multiple organ failure in children as compared to adults¹¹⁹.

For example, Wynn and colleagues compared the host inflammatory response and subsequent mortality in a fecal slurry model of generalized peritonitis between neonatal mice (age 5–7

days) and young adult mice (age 7–10 weeks). Compared with young adult mice, sepsis in the neonatal mice was associated with a markedly attenuated systemic inflammatory response, decreased bacterial clearance, and increased mortality¹²⁰. Similar studies in a hemorrhagic shock model demonstrated decreased lung inflammation and injury in immature mice versus adult mice¹²¹.

Consistent with these results, Barsness and colleagues collected peritoneal macrophages during laparoscopic surgery in children (mean age 3.6 years) and adults (mean age 46.9 years) and treated them *ex vivo* with IL-1 β and LPS¹²². Both IL-1 β - and LPS-induced pro-inflammatory cytokine (TNF- α and IL-6) production were markedly increased in the peritoneal macrophage cultures obtained from children versus adults. Importantly, the anti-inflammatory response, as determined by IL-10 production, was much greater in the cultures obtained from children such that the ratio of IL-10 to TNF- α was significantly higher macrophage cultures from children as compared to adults, suggesting a predominant anti-inflammatory phenotype¹²². These data have provided the impetus to further understand the immune function differences that exist across the entire spectrum of ages all of which are subject to sepsis.

Developmental differences in the immune system

There are other significant differences in the host immune response between the different ages. Clearly, compared to immunologically mature populations, neonates have an increased risk for the development and progression of a systemic infection. Broad deficits across both innate and adaptive immune function have been identified and have been reviewed in detail (summarized in Table 4)^{123–125}. In particular, the preterm neonate exhibits significant vulnerability due to exacerbated immunologic immaturity as well the need for life-sustaining clinical interventions that increase the likelihood for infection. Adaptive immune function is hindered by deficiencies in: 1) T cell function: T_H2 skewed cytokine responses, increased requirement for CD4 T cell stimulation, decreased CD8 T cell cytolytic activity, abundant and potent T regulatory population; 2) B cell function: weak immunoglobulin (Ig) production [predominantly IgM], poor Ig class switching, decreased maternal-derived serum IgG due to premature delivery, poor antibody response to polysaccharide antigens, poor T cell-dependent B cell stimulation, and limited antecedent antigen exposure prior to birth; and 3) underdeveloped secondary lymphoid tissues.

While the contribution of the distinct adaptive immune system function in neonates in the setting of sepsis has not been fully defined in humans, experimental work in mice suggests substantial differences exist. In contrast to findings in adult mice, transgenic neonatal mice lacking an adaptive immune system showed no difference in sepsis survival when compared to wild-type neonatal mice¹²⁵. Altered adaptive immune system function leaves the neonate largely dependent upon the innate immune system for defense against pathogenic challenge. The neonatal innate immune system is also limited in function as compared to adults and children. Deficits exist in: barrier integrity, circulating complement components, expression of antimicrobial proteins and peptides (intercellular and circulating), production of type I interferons and T_H1 polarizing cytokines. Furthermore, there are quantitative and qualitative impairments in neutrophil, monocyte, macrophage, and dendritic cell function and decreased response to most Toll-like receptor agonists. The net effect of these deficits is a functional immunocompromised state that leaves the premature neonate extremely susceptible to microbial invasion. Future studies aimed at characterizing the unique neonatal pathophysiologic response, including defining critically important elements and the capacity for positive immunomodulation, are necessary¹²⁶.

Conclusion

Sepsis, a syndrome characterized by variable, systemic physiologic changes triggered by infection, continues to provide an extraordinary challenge to clinicians managing critically ill neonates, children and adolescents. The incidence of sepsis continues to increase with a mortality rate—both early and late—that position it among the leading causes of death in children. Developmental differences that impact the hemodynamic, inflammatory, coagulation and immune responses make it difficult to extrapolate data from adult studies to these vulnerable pediatric populations. In light of emerging data that suggest developmental influences on epigenetic regulation of gene expression in sepsis, it is imperative that neonatal and pediatric clinician-investigators drive and execute sepsis studies in their respective populations. Only by mechanistic studies complemented with well-crafted, network-based interventional trials, will we impact on this most challenging pathologic syndrome.

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Abbreviations

EOS	early-onset-sepsis
LOS	late-onset-sepsis
SIR	systemic inflammatory response syndrome
MODS	multiple organ dysfunction syndrome
DIC	disseminated intravascular coagulation
APC	activated protein C

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Table 1

Definitions of systemic inflammatory response syndrome (SIRS), infection, sepsis, severe sepsis, and septic shock

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Systemic Inflammatory Response Syndrome: The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:

- Core temperature of $>38.5^{\circ}\text{C}$ or $<36^{\circ}\text{C}$.
- 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
- For children <1 yr old: bradycardia, defined as a mean heart rate <10 th 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.
- 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.

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)

Sepsis

- SIRS in the presence of or as a result of suspected or proven infection.

Severe sepsis

- Sepsis plus one of the following:
  - cardiovascular organ dysfunction as defined in Table 2.
  - acute respiratory distress syndrome
  - two or more other organ dysfunctions as defined in Table 2.

Septic shock

- Sepsis and cardiovascular organ dysfunction as defined in Table 2.
-

Modified from ⁷.

Table 2**Organ dysfunction criteria**

Cardiovascular dysfunction: Despite administration of isotonic intravenous fluid bolus ≥ 40 mL/kg in 1 hr   - Decrease in BP (hypotension) < 5th percentile for age or systolic BP < 2 SD below normal for age (See Table 3)   OR   - Need for vasoactive drug to maintain BP in normal range (dopamine > 5 g/kg/min or dobutamine, epinephrine, or norepinephrine at any dose)   OR   - Two of the following   - Unexplained metabolic acidosis: base deficit > 5.0 mEq/L   - Increased arterial lactate > 2 times upper limit of normal   - Oliguria: urine output < 0.5 mL/kg/hr   - Prolonged capillary refill: > 5 secs   - Core to peripheral temperature gap $> 3^{\circ}\text{C}$
Respiratory   - PaO₂/FIO₂ < 300 in absence of cyanotic heart disease or preexisting lung disease   OR   - PaCO₂ > 65 torr or 20 mm Hg over baseline PaCO₂   OR   - Proven need or $> 50\%$ FIO₂ to maintain saturation $\geq 92\%$ OR   - Need for non-elective invasive or noninvasive mechanical ventilation
Neurologic   - Glasgow Coma Score ≤ 11 OR   - Acute change in mental status with a decrease in Glasgow Coma Score ≥ 3 points from abnormal baseline
Hematologic   - Platelet count $< 80,000/\text{mm}^3$ or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients)   OR   - International normalized ratio > 2
Renal   Serum creatinine ≥ 2 times upper limit of normal for age or 2-fold increase in baseline creatinine
Hepatic   - Total bilirubin ≥ 4 mg/dL (not applicable for newborn)   OR   - ALT 2 times upper limit of normal for age

Modified from ⁷.

Table 3

Age-specific vital signs and laboratory variables

Age Group	Heart Rate (Beats/Min)		Respiratory Rate (Breaths/Min)	Leukocyte Count (Leukocytes × 10 ³ /mm)	Systolic Blood Pressure (mm Hg)
	Tachycardia	Bradycardia			
0 days to 1 wk	>180	<100	>50	>34	<65
1 wk to 1 mo	>180	<100	>40	>19.5 or <5	<75
1 mo to 1 yr	>180	<90	>34	>17.5 or <6	<100
2–5 yrs	>140	NA	>22	>15.5 or <6	<94
6–12 yrs	>130	NA	>18	>13.5 or <4.5	<105
13 to <18 yrs	>110	NA	>14	>11 or <4.5	<117

Modified from ⁷.

Table 4

Timing of acquisition of mature, immune function where gray shading indicates the estimated age range when near-adult level function is attained.

	Premature	Term	<1 year	1-2yrs	2-5yrs	5-10yrs	10-20yrs
Innate function							
Barriers							
Pathogen recognition							
Complement							
Phagocytic							
Cytokine-chemokine production							
NK cell							
Antimicrobial proteins and peptides							
Adaptive function							
Antigen presentation							
T cell							
B cell							
IgG level							
IgA level							
IgM level							
Secondary lymphoid tissue							

Insufficient data