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Defining Neonatal Sepsis

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Abstract

Purpose of the review—Although infection rates have modestly decreased in the neonatal intensive care unit (NICU) as a result of ongoing quality improvement measures, neonatal sepsis remains a frequent and devastating problem among hospitalized preterm neonates. Despite multiple attempts to address this unmet need, there have been minimal advances in clinical management, outcomes, and accuracy of diagnostic testing options over the last three decades. One strong contributor to a lack of medical progress is a variable case definition of disease. The inability to agree on a precise definition greatly reduces the likelihood of aligning findings from epidemiologists, clinicians, and researchers, which, in turn, severely hinders progress towards improving outcomes.

Recent findings—Pediatric consensus definitions for sepsis are not accurate in term infants and are not appropriate for preterm infants. In contrast to the defined multi-stage criteria for other devastating diseases encountered in the NICU (e.g., bronchopulmonary dysplasia), there is significant variability in the criteria used by investigators to substantiate the diagnosis of neonatal sepsis.

Summary—The lack of an accepted consensus definition for neonatal sepsis impedes our efforts towards improved diagnostic and prognostic options as well as accurate outcomes information for this vulnerable population.

Keywords

neonate; preterm; sepsis; consensus; definition

Introduction

In 2010 worldwide, 7.6 million children less than 5 years old died, predominantly due to infectious causes including sepsis; neonatal deaths (in the first 28 days of life), accounted for 40% of the total lives lost (1). In 1990, both the United Nations (UN) and World Health Organization (WHO), prioritized a 2/3rd reduction in the unacceptable child mortality rate

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by 2015. However, in 2013, 44% of deaths in children under the age of five occurred during the neonatal period, up from 37% in 1990. Despite major advances in neonatal care and increasing research, in developed countries, four of every ten infants with sepsis die or experience major disability including significant permanent neurodevelopmental impairment (2).

Prematurely born neonates experience the highest incidence and mortality of sepsis among all age groups (3–8). In the United States, a staggering 36% of neonates born before 28 weeks completed gestation suffer at least one episode of blood stream infection (BSI) during their birth hospitalization with up to a 50% associated mortality (3). Compared to term infants, sepsis in preterm infants is up to 1000-fold more common and is associated with higher rates of mortality and life-long neurodevelopmental handicaps (4, 9–13). Of note, it is estimated that 11% of the 135 million births globally occur before 37 weeks competed gestation (preterm), and preterm births have been increasing steadily, especially in developed countries (1, 14).

Common laboratory tests (including the white blood cell indices, acute phase reactants, and heart-rate characteristics) have limited diagnostic accuracy [low positive predictive value (PPV)] for neonatal sepsis (15–18). This limitation in ancillary test accuracy, in combination with the subtle, ambiguous early clinical signs that overlap with the premature infant's struggle to survive after leaving the womb too early, strongly compel neonatologists to "rule-out sepsis". This clinical entity is the most common diagnosis and its treatment (antibiotics) are the most commonly used medications in the Neonatal Intensive Care Unit (NICU) (19). If antimicrobial therapy is withheld until the infant is overtly symptomatic, outcomes are dismal (20); however, liberal antimicrobial use is also associated with adverse clinical outcomes beyond the selection of resistant microorganisms (21–24).

Attempts over the last thirty years by research teams, including thousands of infants and their families alongside basic science and clinical investigators, have not generated significant improvements in diagnostic and prognostic accuracy, clinical management, or outcomes for neonatal sepsis. Although the dynamic nature of sepsis in the context of developmental immaturity has undoubtedly played a role in limiting our diagnostic testing accuracy, a variable case definition for *any* pathologic condition should be expected to retard progress (25).

A case definition is paramount for understanding the epidemiology (incidence, prevalence) and impact (short- and long-term outcomes, mortality) of any disease. In addition, a disease definition is critical for the selection of patients for clinical trials that will examine diagnostic and prognostic testing methods as well as the effect of interventions on the impact of the disease. Lastly, a disease definition is important for education (of epidemiologists, scientists, and providers) as well as for benchmarking hospital outcomes and the quality of patient care. Clear and accepted disease definitions have been established for multiple other major complications in neonatology including retinopathy of prematurity (26), necrotizing enterocolitis (27), respiratory distress syndrome (28), chronic lung disease (29), intraventricular hemorrhage (30), PDA (31), and hypoxic-ischemic encephalopathy (32). Assessment of the impact of treatment strategies on outcomes for these conditions

required concerted efforts that could only be accomplished through the development and acceptance of definitive criteria. Even when investigators use consensus definitions of disease, the impact of issues affecting external validity following well-designed and executed randomized controlled trials is well documented (33). The absence of definitive accepted criteria for sepsis in neonates, and especially in preterm infants, makes implementation of future studies and interpretation of their results difficult or even impossible for organizations, centers, and investigators that use different criteria. If the case definition for a disease is a moving target, is it reasonable to expect valid and reproducible laboratory-based diagnostic and prognostic testing to emerge?

Neonatal sepsis is variably defined

There is remarkable heterogeneity among studies regarding the case definition of neonatal sepsis (34). The presence of a positive blood culture historically constitutes the “gold standard” for the presence of neonatal sepsis (34). This conclusion requires at least 2 assumptions: 1) the infant would not have been evaluated for sepsis (have a blood culture drawn and sent) in the absence of concerning clinical signs that are representative of a systemic inflammatory response syndrome (SIRS), 2) the isolated bacteria did not represent contamination (type I error). Often, the presentation of persistently abnormal clinical signs or inflammatory biomarkers to substantiate the presence of SIRS/sepsis are not recorded or included (34). In a study of 2416 very low birth weight, premature infants (VLBW, <1500 grams at birth, mean gestational age <29 weeks at birth) with clinical and laboratory features compatible with late onset sepsis, the overwhelming majority of the infants that did not have proven LOS (35). Specifically, of the thirteen clinical and laboratory signs reported in that study, the median PPV was 16.8% (25th percentile, 14.8; 75th percentile, 20.2), and the maximum PPV of any clinical or laboratory sign presented was 31.3% (neonatal hypotension). These data suggest that, in most cases, individual clinical signs are not associated with a positive blood culture result. A similar PPV was shown in a smaller study, which used model development and validation cohorts for individual signs (36). In that study, the acute onset of 3 or more signs (clinical and/or laboratory) was associated with a modest sensitivity of 61.5% and a specificity of 76.2% for a positive blood culture.

The majority of sepsis evaluations that are prompted by concerning clinical signs are associated with negative blood culture results. *Hornik et al* reported that of 164,744 blood cultures obtained from 99,796 VLBW infants with suspected LOS, just 8.9% were positive (37). These data strongly suggest the occurrence of the “gold standard” is very rare when clinical concerns prompt an evaluation. Beyond the evaluations performed on preterm infants with ambiguous clinical signs, a sepsis evaluation (blood culture) performed on asymptomatic at-risk term neonates is a daily occurrence that is not well supported by recent data (38).

Because many as 62% of extremely low birth weight infants (<1000g) who survive >12 hours after birth have a positive blood culture during their hospitalization (4). Coagulase-negative *Staphylococci* (CoNS) represents greater than 50% of isolated bacteria from blood cultures of preterm infants in the United States and many centers worldwide (6, 13, 37). The recent report describing the “rise and fall” of CoNS, suggests many culture positive cases of

presumed CoNS bacteremia may either represent episodes of contamination or central line colonization and that this possibility should be a consideration in the development of useful definition for neonates (39).

When blood and other sterile site cultures are negative, but the infant manifests signs consistent with infection they may be considered to have “clinical” sepsis. Importantly, a positive blood culture is not required to meet the consensus definition for sepsis in adults and children (40, 41). In fact, a pathogen may be identified in as little as 36–51% of cases of sepsis in adults (42, 43) even though sepsis is defined as SIRS in response to an inciting infection. A similar rate of culture-negative sepsis is seen in pediatric patients even in the setting of shock (44). In a study of newborns with unequivocal infection documented at autopsy, premortem blood cultures were negative in 14% of cases (45). In another study of 92 neonates ≥34 weeks with documented bacterial meningitis, 35 (38%) had negative blood cultures (46). However, there is a lack of clear and accepted criteria that must be met to support a diagnosis of neonatal clinical sepsis in practice and in research. In neonates, this clinical scenario is far more common than blood-culture positive sepsis (47), and represented nearly 60% of the subjects enrolled in the recent International Neonatal Immunotherapy Study (INIS) that examined treatment of neonatal sepsis with intravenous immune globulin (2). Outside of a false negative result (type II error) (48), the possibility of a non-bacterial cause of sepsis must also be considered as a microbial etiology for clinical sepsis. Fungal and viral infections may also generate SIRS and cause sepsis. There is increasing evidence for novel viral pathogens associated with sepsis-like syndrome in preterm infants (e.g., echovirus, enterovirus, parechovirus, coxsackie, adenovirus, parainfluenza, rhinovirus, coronavirus) (49–52). A prospective cohort study that included 100 infants evaluated and treated for late-onset sepsis demonstrated that 8% had a respiratory virus detected at the time of the sepsis evaluation (53). None of the patients had a respiratory virus with concurrent bacteremia and the incidence of bacteremia was 15% (15/100). These studies indicate that viral infections are contributing to some episodes of clinical deterioration that are associated with a negative blood culture. Evaluation for the presence of non-bacterial pathogens is an important consideration for a definition of neonatal sepsis and in particular, clinical sepsis.

Consensus sepsis definitions are widely used by pediatric and adult intensivists

Adult and pediatric intensivists currently use consensus definitions for sepsis for goal-based therapeutic interventions (40, 41, 54, 55). Many consensus definitions for disease are in place or sought after across multiple disciplines of medicine and are often the result of international collaboration (56–65). The pediatric consensus definition for sepsis, established in 2005 to support the trial of activated protein C for the treatment of pediatric sepsis, was intended for all children (<18 years old) and including term (≥37 weeks completed gestation) neonates (41). Preterm neonates (<37 weeks completed gestation) were specifically excluded from the pediatric consensus definitions and neonatal-perinatal subspecialists were not represented among the international pediatric consensus experts. The adult and pediatric consensus definitions sepsis stipulate that evidence of SIRS be present as a prerequisite to meeting criteria for sepsis. SIRS requires either 1) abnormal WBC count [total WBC increased or decreased for age -*or*- >10% immature neutrophils] *or* 2) abnormal

core temperature (>38.5° or <36°C) (41). *Hofer et al* retrospectively examined 476 term neonates to investigate if the pediatric consensus definitions for SIRS and sepsis applied to term infants and found that the consensus definitions applied to only 53% of cases of culture-positive early-onset sepsis (EOS) (66). Although the accuracy of the pediatric consensus definitions has not been assessed in preterm infants, using these criteria are untenable because of several limitations related to the developmental maturity of preterm infants (34). Establishment of an initial consensus definition for sepsis in neonates will most certainly build on the experiences from our pediatric and adult colleagues through the use of modern molecular techniques for pathogen detection, characterization of the host response, and integration of a severity of illness scoring system (34).

The target audience for the case definition is an important consideration

When choosing a case definition, an important consideration is how well the definition fits the needs and resources of investigators and/or clinicians. For example, clinicians would benefit most by a threshold (static) definition that includes clinical and laboratory signs, but does not require specialized laboratory testing. Uniquely, this group is the largest of the target audiences and has to make a decision in real-time whether to initiate treatment or continue close observations. In contrast, it may appear that an epidemiologist has the benefit of retrospection to identify disease incidence and prevalence. However, one that examines national and global statistics would have neither reliable access to patient-specific granular data such as the specific presence or duration of clinical/laboratory signs, nor the time required to verify that appropriate clinical and laboratory requirements were met in each case because the majority of their data is extracted from coding records (ICD-10) and death certificates (67, 68). Basic science and clinical researchers would likely require the greatest degree of detail to accurately characterize the index population seen in observational studies so interventions can be tested in clinical trials on similar patients. A number of sub-definitions should be expected to evolve as data was collected to accommodate pathogen-, gender-, and developmental age group-specific criteria.

Consensus definitions are not meant to be the last word

Consensus definitions have the potential to unify investigators so their respective findings can be verified and built upon. However, consensus definitions are not without limitations (69, 70). Present consensus definitions for sepsis in children and adults are threshold-based and thus static. Although the change in clinical status over time (disease velocity) can be very informative, time is often not available to inform the static decision to enroll a patient in a prospective interventional trial. This limitation may be particularly relevant to the newborn that is transitioning to extrauterine life with resolving respiratory distress. Thus, a static definition of sepsis will be associated with continued limitations in diagnostic accuracy because sepsis is a dynamic, complex and heterogeneous condition (71). To study the impact of disease velocity, the change in status over time (e.g. time of clinical presentation/biomarker measurement, duration of clinical and laboratory signs) should be collected in diagnostic and observational studies. Using prospective data collection with retrospective classification to a consensus definition of disease, our attention is focused first on definitive disease and improving our understanding of the pathophysiology. A more

complete knowledge base will lead to improved diagnostic and prognostic testing that will, in turn, inform the design and implementation of quality randomized controlled trials.

It is not unreasonable when there is limited data to begin with clinical consensus and move to evidence based definitions (72). Importantly, a consensus definition should only defer to expert opinion when data is not available. An important aspect of any useful case definition is the need for revision and refinement as new data are acquired (59, 73–79). Thus, a consensus definition is not meant to be the last word on how to define sepsis. Rather, the establishment of an accepted definition to be used by clinical researchers is but the first of many steps towards improving outcomes for neonates with sepsis. While considering other potential limitations of consensus definitions (34), it is worth asking how many limits on progress are we presently accepting with a static and variable definition of neonatal sepsis?

Conclusion

Neonatal sepsis remains a significant global problem with little progress made despite major efforts. A variable case definition of disease can only serve to reduce the impact of investigation, and obstruct advances that are so sorely needed. To unify investigators globally and accelerate the pace towards improved outcomes, we must first develop and validate an accepted consensus definition for neonatal sepsis.

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Key points

1. Neonatal sepsis is a common, devastating, and expensive disease with life-long impact plagued by a lack of accurate diagnostic and prognostic testing. Management options and outcomes have not changed for the last 30 years.
2. There is remarkable heterogeneity among studies regarding the case definition of neonatal sepsis.
3. A variable definition of disease severely limits the pace of progress for these important endeavors.
4. Pediatric consensus definitions for sepsis are not accurate for term neonates and were not designed for preterm neonates.
5. The development and acceptance of a consensus definition for neonatal sepsis is an important and necessary step towards the goal of improving outcomes.