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COMMENT

The imperfect science of neonatal sepsis

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Neonatal clinicians have long debated how to define neonatal sepsis, a condition—however it is defined—that is a significant cause of neonatal morbidity and mortality worldwide.[1,2] There are compelling reasons for defining sepsis in any population. First, accurate longitudinal and comparative sepsis surveillance requires a reproducible definition that can be applied across different centers, databases, regions, and care models. Definitions based on microbiologic culture have allowed for meaningful analysis of large national neonatal databases in the United States.[3,4] Second, functional definitions of sepsis can guide early recognition and institution of life-saving clinical interventions. This is especially impactful among populations that are relatively healthy at baseline, for whom a specified degree of laboratory test abnormality, symptomatology, and/or measures of organ dysfunction should prompt specific and time-sensitive interventions such as intravascular volume and antibiotic administration. The International Surviving Sepsis Campaign, for example, provides best practice guidance for clinicians caring for adult patients with sepsis or septic shock.[5] Finally, reproducible definitions are optimally required for the conduct of intervention trials of therapeutics to prevent or treat sepsis. To conduct and recruit for antimicrobial trials, for example, clear inclusion criteria, objective parameters to monitor response, and explicit measurable outcomes are critically important.[6]

Both concern for the consequences of excessive and indiscriminate empiric antibiotic use among newborns (particularly those born preterm), and fear of the often serious and potentially fatal consequences of neonatal infection inform clinical trials addressing prevention, identification, and optimal management of neonatal sepsis.[4,7] These trials have variably defined sepsis, leading to an inability to pool trial results and to accurately measure impact. In light of these considerations, Hayes and colleagues aimed to catalog definitions of neonatal sepsis in published randomized controlled trials.[8] The authors identified 80 trials from 1986 to 2019, comprising almost 41,000 neonates from multiple international sites. It is worth noting that the trials included are themselves quite heterogeneous, addressing early- and late-onset neonatal sepsis, sepsis treatment and sepsis prevention, and neonatal sepsis both as the primary aim of the study as well as a secondary outcome in trials of obstetric interventions. The sepsis definitions were revealed to be equally varied. Because they did not fall into discrete bins, the authors broke down contingent or algorithmic definitions into their component primary criteria and relevant secondary criteria, and included a sub-analysis of definition qualifiers. The majority relied on microbiological culture and/or clinical signs of infection. Biochemical, hematological, and radiological signs of and clinical risk factors for infection were less frequently utilized. The authors contrasted their findings with adult and pediatric sepsis definitions, which more commonly rely on evidence of organ dysfunction. They conclude by calling for an international consensus-based definition of neonatal sepsis to allow for meta-analysis that might better interpret and translate results to improve outcomes.

While we acknowledge the potential benefits of a consensus neonatal sepsis definition for the purpose of interventional trials, this review highlights multiple characteristics of neonatal sepsis that serve to defy a unified definition. Nearly a quarter of the studies included in this review are trials of obstetric practice, illustrating the critical link between maternal and fetal physiology in the pathophysiology of early-onset neonatal sepsis. Several trials focus on supplementation of nutritional elements or immune factors, while other focus on the technicalities of intensive care or the administration of different antimicrobial agents targeting bacteria, fungi, or viruses. Although some elements of neonatal immune defense and inflammatory response may be common to early and late-onset bacterial, fungal, and viral sepsis, the at-risk populations, associated risk factors, and microbial etiologies are so diverse as to suggest that the development of a "consensus definition" could itself hijack the results of an intervention. For example, how can we reasonably expect to interpret the impact of two different antibiotic regimens when applied to infants with sepsis defined by acute respiratory failure, leukopenia, thrombocytopenia, and elevated C-reactive protein—when both a term infant with streptococcal infection and a preterm infant with postnatal cytomegalovirus infection may share this presentation?

There may, in fact, be some role for each of the defining elements identified by Hayes and colleagues. The prevention of specific types of infection (bacterial, fungal, viral, and, in some instances, parasitic); the prevention or amelioration of inflammation; and the means of reversing and compensating for organ dysfunction are distinct elements of sepsis research. Infection surveillance, clinical sepsis risk assessment, and the conduct of clinical trials in neonatal sepsis are likewise distinct enterprises. Obtaining consensus on how to best utilize different definitions for specific purposes may be a more functional goal. Microbiological definitions of neonatal sepsis provide concrete and reproducible outcomes that can be extracted with fidelity from databases and electronic medical records. Such definitions of neonatal sepsis provide epidemiologic information to inform empiric therapeutic choices as well as warning of emerging

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pathogens—and may be the most indisputable outcome for trials of specific preventative therapies. This does not mean, however, that microbiologic definitions relying on technology to isolate or identify specific pathogens are always the most appropriate measures for the purpose of clinical practice. In particular, when such technologies are not available in low- and middle-income countries, physiologic definitions of neonatal sepsis may be more important to guide timely administration of empiric therapies and appropriate transfer to advanced healthcare facilities. Inflammatory biomarkers and acute-phase reactants have multiple limitations in the immediate newborn period and perform poorly in identifying newborns at the highest risk of sepsis, impacted by universal patterns of change induced by birth itself as well as by a range of birth-related insults that can impact acute-phase reactants.[9,10] Such measures are not optimal for identifying infants for trial enrollment nor in defining an outcome of neonatal sepsis, even if useful when trended over time in individual infants. Finally, clinical signs of organ dysfunction are uniquely problematic in the immediate newborn period, when findings such as respiratory distress or temperature instability may characterize a normal newborn period of physiologic transition. Markers of severe organ dysfunction, including hypoxia, hypotension, azotemia, hyperbilirubinemia, ileus, encephalopathy, seizures, coagulopathy, and cytopenias are prevalent among newborns with perinatal asphyxia as well as among those born extremely preterm or with congenital anomalies. The use of organ dysfunction to define neonatal sepsis in the immediate newborn period will provide imprecision that could obscure the true impact of an intervention when appropriately applied. In contrast, once physiologic stability—or at the very least, a consistent pattern of dysfunction—is established in a term or preterm infant, a change from baseline might be utilized effectively to enroll at-risk patients in specific intervention trials. Analogous to the definitions of severe retinopathy of prematurity used for entry into trials of retinal ablative therapy, a metric such as the nSOFA (neonatal sequential organ failure assessment) score (which encompasses graded assessments of hemodynamic, respiratory, and bone marrow dysfunction and correlates with infection-related mortality)[11] may be useful in identifying patients at such high risk of death as to justify enrollment into clinical trials of novel therapies.

Much of contemporary medicine now focuses on unique aspects of either disease or patient to develop "precision" therapies, targeting therapeutics that harness our evolving ability to deeply phenotype a tumor, genetic condition, or pathogen. It could be argued that the development of an all-encompassing definition of neonatal sepsis is a step in the opposite direction. The unique newborn transitional physiology, as well as the biologic and technical complexities of caring for extremely preterm infants and those born with severe congenital anomalies—may simply preclude a blanket definition of neonatal sepsis. Hayes and colleagues have highlighted a critically important aspect of neonatal sepsis trials that the neonatal research community should ponder carefully. Is there truly a need for an international consensus-based definition of neonatal sepsis to inform all future trials—or is there actually a need for the neonatal research community to step back and consider the precision approach? In truth, many of the 80 trials cited by Hayes and colleagues did not result in improved neonatal outcomes, including large trials of broadly applied interventions such as intravenous immunoglobulin and lactoferrin.[12,13] Might we do better to focus on defining when discrete definitions are best applied, and focus future clinical trials on a specific element of neonatal sepsis, specific neonatal phenotypes, and specific time periods of risk? There may not be a perfect approach to the study of neonatal sepsis—so perhaps it is time for the neonatal research community to embrace the imperfect science of defining neonatal sepsis.

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ADDITIONAL INFORMATION

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