Neonatal sepsis: Need for consensus definition, collaboration and core outcomes

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Overview of Neonatal sepsis and definitions

Sepsis represents a major contributor to global mortality and has been declared as a priority by the WHO (1). The highest sepsis incidence across all age groups is found in neonates affecting an estimated 3 million babies worldwide (22 per 1000 live births) with a mortality of 11-19% and unquantified long-term neurological defects (2,3).

However international data is difficult to standardise in the absence of unified criteria for neonatal sepsis. Recently in adults the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) have defined sepsis as a life-threatening organ dysfunction caused by a dysregulated response to infection (4). The new consensus definition moved away from the concept of systemic inflammatory response syndrome which formed part of the definition of sepsis in the past 20 years. Sepsis-3 criteria were developed and validated on large cohorts of electronic health record data derived episodes from adults with sepsis. Despite the clear merits of the approach chosen by the Sepsis-3 taskforce, there are several pitfalls towards the translation of Sepsis-3 to neonates. The criteria to define infection and sepsis are essential in the neonatal population to limit overdiagnosis, but they are not part of the adult Sepsis-3 definitions. Sepsis-3 is based only on short term outcomes but in neonates integration of predictors of long term disability are critical. The criteria for organ dysfunction according to gestational and postnatal age need to be defined through systematic reviews and retrospective studies and validated in prospective studies.

The Sequential Organ Failure Assessment Score (SOFA) reflects changes in organ function altering from baseline. The pSOFA has been proposed and was found to be a reliable predictor of in-hospital mortality in children (5). The recently described neonatal SOFA (nSOFA) predicted mortality on VLBW infants with late onset sepsis (6). In this issue of the journal an international group has provided an overview of the diverse definitions of neonatal sepsis with the aim of working towards international consensus.

Why neonates are different

Neonates differ substantially to adults and older children due to altered immune function and potential intrauterine exposure to infection(7,8). The fetus is immune privileged *in utero* often resulting in endotoxin tolerance. This is altered by labour from a predominantly Th2 response to a more “adult” immune phenotype with an enhanced pro-

inflammatory response (8,9). These differences are particularly prominent in preterm infants. However neonatal immunology is not clearly delineated, and much has been extrapolated from research in umbilical cord blood which although easily accessible for study is more immunotolerant and does not entirely reflect postnatal immune responses (10). There are difficulties in determining the true risk of neonatal sepsis as the *in utero* environment cannot be easily assessed. For example, the duration of rupture of membranes and the presence of intrauterine infection are hard to diagnose with certainty. Placental pathology is likewise not entirely predictive and also not usually available at the time of sepsis evaluation. The lack of specificity of the majority of clinical signs and symptoms further complicate the identification of sepsis on the neonate.

Although Sepsis-3 concentrates on organ dysfunction in the diagnosis of sepsis, microbiological results are often still included in neonatal sepsis. Blood culture is only positive in approximately 0.5% (11,12) due to the small blood volume for blood cultures and antenatal maternal antibiotic use. There is no reliable single marker of sepsis and mortality and morbidity are high so empiric antibiotics are commenced in infants at risk. However, there is a need to balance the risk of morbidity and mortality from untreated infection versus the short- and long-term adverse effect of exposure to antibiotics. The risks of overuse of antibiotics are well-described in the era of antibiotic resistance and the negative effects of altering the microbiome include an increased rate of serious complications including mortality and necrotizing enterocolitis association with antibiotic exposure.

In addition, neonatal sepsis is a heterogeneous condition, related to differences in gestational age, timing and source of infection. Coagulase negative *Staphylococci* are often considered a contaminant or commensal in adults and older children but are associated with significant morbidity in preterm neonates, including adverse neurodevelopment (13). The difference in the NICU is that it may be more difficult to differentiate contamination from true infection and the long-term impact of these infections is greater on the developing brain. There are major differences between a baby arriving to the emergency room with a fever in the first month of life compared to a preterm infant born following severe chorioamnionitis and prolonged rupture of membranes. These varied populations of infants at risk of “neonatal sepsis” differ in many aspects of the disease, including clinical signs and symptoms, most likely pathogens and risk of mortality and long-term morbidity.

Current markers of neonatal sepsis

Surrogate biomarkers of sepsis are commonly used due to the limitations of blood cultures alone to diagnose sepsis. Maternal infectious status is also important and placental pathology can provide a diagnosis of chorioamnionitis, although the relationship between histologic chorioamnionitis and neonatal sepsis is complex and ill-defined. Markers of systemic inflammation and immune responses include serial white cell counts and immature-to-mature granulocyte (IT) ratio (14-17). Serial full blood count values and IT ratios can predict the absence of early onset sepsis (EOS) with an AUC~0.8 and negative predictive value for proven and suspected sepsis of 99% and 78%, respectively (12). In addition, CRP and Procalcitonin demonstrate that biomarkers can be useful to shorten antibiotic treatment in patients who improve rapidly after treatment and have negative blood cultures (17-19). In addition, a recent meta-analysis and systematic review demonstrated that use of the neonatal EOS calculator is associated with a substantial reduction in the use of empirical antibiotics for suspected EOS (16).

In view of the insensitivity of blood cultures alone to define neonatal infection other techniques hold promise such as 16s rRNA and PCR which detects <3 copies bacterium. Positives identified by PCR were higher than by blood culture (10 versus 5%) and when blood culture was used as control, the sensitivity and specificity of PCR was 100% and 97.85%, respectively and the index of accurate diagnosis was 0.979 (19). Multiplex PCR (n=803 infants and children) showed a positive test in 16% compared to 10% using blood culture (20). This is further improved in CSF samples increasing detection from 9 to 45%. However, challenges still exist in the identification of clinically significant Gram-positive infections, understanding the significance of of DNA of bacteria in the blood (DNAemia) and sustained inflammation on long-term outcomes.

Conclusions

The recent introduction of Sepsis-3 for adults has triggered plans to translate this to children and newborn infants and involvement in the Surviving Sepsis campaign (www.survivingsepsis.org). However, there are significant reasons that extrapolation is not appropriate in this setting. Sepsis is challenging for many reasons as it is not a single static disease but a dynamic continuum of inflammatory responses. This situtation makes single

biomarkers insufficient as different pathogens, immune status and duration of sepsis vary the systemic immune response.

Clinical trials have not routinely accounted for these variations and despite promise in defined subgroups have failed to prove benefit in larger populations. There are multiple definitions of neonatal sepsis used internationally which encompass clinical, microbiological and biochemical data as well as treatment initiation and duration. The difficulties in comparing early and late onset sepsis as well as differences between term and preterm infants make a single definition or management plan challenging. In EOS the presence of antenatal inflammation or chorioamnionitis may not be definitely recognised until the placental histology is completed and whether this information is included as a factor in early management is controversial. Histological confirmation of chorioamnionitis may or may not be helpful for the diagnosis of neonatal sepsis (21)

More recently the neurodevelopmental sequelae of infection have been highlighted apart from the immediate morbidity and mortality. The inflammatory response following sepsis and necrotising enterocolitis are associated with adverse neurological outcomes. Even coagulase negative *Staphloccoccal* infections which were previously considered as contaminants and harmless skin commensals are associated with abnormal neurodevelopmental outcome in preterm infants (22). Tertiary mechanisms of brain injury involve persistent dysregulated inflammation. Once inflammation is triggered, there can be a sustained response (23).

In addition to the lack of an internationally accepted consensus definition of neonatal sepsis, there are no definitions associated with long-term outcomes. This lack hinders ongoing collaborative research and benchmarking. Core outcomes are required to standardise clinical trials of sepsis and allow comparison between trials. In addition, prioritising research goals with families is essential (24,25) Therefore a consensus definition is required that can be universally generalisable and validated in international datasets and correlated with neurodevelopmental outcomes.

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