Diagnostic Challenges in Early-Onset Neonatal Sepsis

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Introduction

Early-onset neonatal sepsis (EOS) is defined as sepsis that occurs within the first 72 hours of life and represents a distinct clinical subset of neonatal sepsis. (Lemma & Berhane, 2024) This early presentation results from the transmission of pathogens from mother to infant during pregnancy and/or delivery. On the other side, the broader category of neonatal sepsis includes late-onset infections that arise from environmental sources or healthcare exposures. Early-onset neonatal sepsis (EOS) is defined as sepsis that occurs within the first 72 hours of life and represents a distinct clinical subset of neonatal sepsis (Lemma & Berhane, 2024). Also, recent evidence suggests that EOS is associated with maternal risk factors such as early rupture of membranes, fever, and Group B Streptococcus colonization (Lemma & Berhane, 2024). Moreover, EOS remains a leading cause of high mortality rates worldwide, accounting for 15% of deaths and ranking among the top three causes of death in early life for neonates (Fleischmann et al. 2021). Regardless of the few advances in maternal and neonatal care, mortality rates remain as high as 2-3% for term infants and up to 10% in preterm populations as a global burden of the disease (Fleischmann et al. 2021). Of all neonates, only 5-15% undergo evaluation for suspected EOS despite a much lower incidence of confirmed infection, highlighting a discrepancy between clinical judgment and true disease diagnosis (Puopolo et al. 2018). These findings highlight the need for improved diagnostic accuracy in neonatal sepsis, given the ongoing challenges of overdiagnosis and delayed diagnosis in clinical settings. In this article, the pathophysiology and the diagnostic processes will be discussed. In addition, we will address the diagnostic challenges and some advancements to be considered in the future.

Pathophysiology Process

The pathophysiology of EOS begins with the transmission of pathogens from the mother to the newborn during pregnancy and/or delivery (Raturi & Chandran, 2024). Pathogens such as bacteria known as Group B streptococcus can ascend to the maternal urinary system and be transmitted to the newborn passing through the birth canal, thus leading to early colonization and invasion into the newborn right after birth (Raturi & Chandran, 2024). Generally, bacteria can enter the neonatal bloodstream, initiate inflammatory reactions, and trigger their immature immune system. Raturi & Chandran (2024) described this inflammatory response as mediated by pro-inflammatory cytokines, including interleukin-6 and tumor necrosis factor-alpha, which contribute to widespread endothelial activation and increased vascular permeability (Raturi & Chandran, 2024). Consequently, this inflammatory response results in impaired perfusion, septic shock, and multi-organ dysfunction (Raturi & Chandran, 2024). It is of note that the clinical signs of EOS are nonspecific, as any pathophysiological processes may advance without proper identification, causing delayed diagnosis and disease progression (Raturi & Chandran, 2024).

Diagnostic Process

EOS diagnosis has increasingly shifted to a risk-based approach to improve accuracy and reduce antibiotic exposure (Stoll et al., 2020). Stoll et al. assessed the effectiveness of evidence-based sepsis risk calculators compared to standard categorical risk assessment methods (Stoll et al., 2020). The study demonstrated that standard diagnostic approaches resulted in a high proportion of neonates going through an evaluation and subsequently, higher antibiotic treatment despite a low incidence of confirmed infection (Stoll et al., 2020). Prior to the implementation of the risk calculator, 15% of neonates received antibiotics for suspected EOS, while the confirmed EOS remained low at 0.5-1 per 1,000 live births (Stoll et al., 2020). After implementing the sepsis risk calculator, antibiotic use decreased by 48% without a change in missed EOS cases (Stoll et al., 2020). This diagnostic process emphasized that serial clinical examinations were critical since newborns were at low risk and could be monitored safely without antibiotic medications. Overall, the study highlighted that the primary diagnostic error in EOS was overdiagnosis, which means that a vast number of newborns are treated without a true infection (Stoll et al., 2020).

Diagnostic Challenges

For more than three decades of clinical advancement, EOS continues to have diagnostic challenges with patterns of both overdiagnosis and delayed or missed diagnosis (Teacoe et al., 2024). There is no consensus on a standardized definition, clinical presentation, or limitation on diagnostic tools (Teacoe et al., 2024). Diagnostic error in EOS is not a new issue, but an obstacle within neonatal care systems (Teacoe et al., 2024). For instance, Teacoe et al. clarified that after decades of research, EOS diagnosis remains challenging. The authors highlighted that the variations in definitions, inconsistent interpretation of risk factors, and challenges in identifying newborns contributed to limiting the accuracy of a diagnosis (Teacoe et al., 2024).

From a diagnostic error perspective, McGovern et al. illustrated how definitions are inconsistent and clinical signs are poorly defined, which means that many neonates are evaluated under suspicion rather than diagnostic certainty (McGovern et al., 2020). The study pointed out that any published definition fails to illustrate what clinical signs should count as sepsis and that early signs may vary from subtle feeding to full multiorgan dysfunction (McGovern et al., 2020). Another study stated that the search for an ideal early biomarker with adequate diagnostic accuracy will be critical in mitigating the diagnostic challenges of EOS (Celik et al., 2022).

Additionally, Dr. Beigi discussed that the diagnostic process is challenging, with diagnostic errors caused by incomplete patient histories, premature diagnostic claims, and delayed presentation (Blissy, 2024). These factors can cause misdiagnosis and delayed treatment initiation (Blissy, 2024). Most importantly, the concept of "mismedicine" highlights the systematic diagnostic errors driven by uncertainty and imperfect tools in clinical practice (Misdiagnosis Association and Research Institution, 2024).

Advancements and Future Directions for Neonatal Sepsis Management

Recent studies suggested that neonatal sepsis management is moving from broad treatment approaches to more risk-stratified, standardized, focused care (Glaser et al., 2021). For instance, Glaser et al. described the use of the EOS risk calculator to personalize antibiotic use based on patients' needs as one of the clearest advancements in managing EOS (Glaser et al., 2021).

Additionally, Laccetta et al. compared the EOS risk calculator's effectiveness with evidence-based guidelines (Laccetta et al. 2021). The authors found that 32 of 265 infants (12.1%) were treated with antibiotics within the first 12 hours of life, whereas the EOS calculator would have indicated antibiotic treatment in 55 of 265 infants (20.7%) and 44 of 265 infants (16.6%) based on a local EOS incidence of 2 per 1,000 live births and 1 per 1,000 live births, respectively (Laccetta et al. 2021). Also, the authors emphasized that their evidence-based protocol reduced antibiotic overexposure compared with the EOS calculator and that no culture-positive EOS cases were observed during the study period. This demonstrated the dual benefit of using the EOS risk calculator and the use of evidence-based clinical guidelines for the EOS management.

Furthermore, Henry et al. reported that the most important future direction in neonatal sepsis management is the development of the core outcome set (Henry et al. 2022). These would improve trial comparability and accelerate translation of research into practice. These studies show that the future for neonatal sepsis management is combining better diagnostics, antibiotic stewardship, and standardized research outcomes (Henry et al. 2022).

Conclusion

Early-onset neonatal sepsis remains a complex condition because of its pathophysiology. The diagnostic process is equally challenging because neonatal sepsis often presents with subtle and nonspecific signs. Lastly, diagnostic errors contribute to disease progression, delayed treatment, and mortality of neonates. Future directions should focus on developing accurate diagnostic technologies, improving the definition of clinical criteria, and creating standardized diagnostic approaches.

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