Review Article

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Revolutionizing Early Diagnosis: Evaluating the Impact of the Early Onset Sepsis Calculator

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ABSTRACT

Early onset neonatal sepsis (EONS) represents a significant source of morbidity and mortality among newborns, necessitating timely diagnosis and treatment. This review article explores the development and application of a calculator designed to aid in the early identification of EONS in neonates. The calculator integrates clinical risk factors, laboratory findings, and maternal history to provide risk stratification for infants at birth, thereby assisting healthcare professionals in making informed decisions regarding the need for empirical antibiotic therapy and further diagnostic evaluations. By reviewing relevant literature on EONS risk factors, current diagnostic protocols, and the utility of predictive modeling in neonatology, this article aims to highlight the importance of individualized assessment in managing at-risk newborns. Furthermore, we discuss the implications for clinical practice and potential areas for future research in improving outcomes for this vulnerable population.

Keywords: Early onset neonatal sepsis; Neonatal risk assessment; Risk calculator; Maternal history; Risk stratification; Empirical therapy; Newborn sepsis.

INTRODUCTION

Neonatal sepsis is defined as a systemic inflammatory response caused by pathogens invading the neonatal blood circulation, where they grow, multiply and produce toxins. Early-onset sepsis (EOS) is one of the leading causes of neonatal death and morbidity worldwide.[1] Depending on the age at which the sepsis begins and the timing of it, neonatal sepsis has been categorised as either early-onset or late-onset. Early onset infections typically show clinical symptoms within the first 72 hours of life. Early-onset infections, particularly those caused by group B streptococcus (GBS), are defined by some doctors as infections that manifest before the age of seven days. Early-onset infections are typically vertical mother-to-infant transmission, meaning they are acquired prior to or during delivery. Late-onset infections are caused by microorganisms that are obtained by contact with the hospital environment or the community. They manifest after delivery, or after 3 to 7 days of age. It is also conceivable to think about chorioamnionitis and maternal hematogenous transfer as factors that could cause EOS. Aspiration and digestion of amniotic fluid contaminated with in utero. Maternal antibiotic medication may reduce infant infections since the vaginal bacterial flora of mothers is the most prevalent source of pathogens. Protozoa, fungi, viruses and bacteria are the entities that can determine EOS; bacteria are the most common.

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Escherichia coli and Streptococcus agalactiae are the agents most frequently involved, followed by Pseudomonas aeruginosa, Listeria monocytogenes, Streptococcus pyogenes, Viridans streptococci, Streptococcus pneumoniae, Haemophilus influenza and Staphylococcus aureus.[2]

Neonate with early-onset sepsis (EOS) cannot be reliably identified from non-specific clinical characteristics. Culture results can take up to 72 hours to report, are positive in 25-45% of instances and can result in low-yield or false-positive results if the mother was exposed to antibiotics during pregnancy. Moreover, the majority of district hospitals in India lack the capability to conduct culture tests. In this case, risk factor-based scoring systems and culture-independent diagnostics are essential for the diagnosis and prediction of neonatal sepsis.

This article reviews the development, validation and clinical application of EONS risk calculators, highlighting their potential to optimize neonatal care while minimizing unnecessary interventions.

Risk Factors for Early Onset Sepsis

Perinatal asphyxia, amniotic fluid meconium contamination, maternal group B streptococcus colonization, mothers with chorioamnionitis, premature rupture of membranes, lowgestational age, maternal urinary or reproductive tract infection, perinatal fever, very low birth weight and vaginal examination ≥3 times were perinatal risk factors for EONS.[3] Premature rupture of membranes ≥18 h has been reported to be an independent risk factor for acute chorioamnionitis and neonates born to mothers with premature rupture of membranes and chorioamnionitis are approximately twice as likely to have EONS compared to neonates born to mothers with premature rupture of membranes alone.[4] lower gestational age and very low birth weight are perinatal risk factors for EONS. Newborns have an immature immune system and cannot produce an adequate immune response, which increases their risk of developing the disease.[5]

Evolving Early Onset Sepsis Over the past 20 years, there have been notable advancements in understanding, diagnosing and managing this condition. Research has identified various maternal and neonatal factors that increase the risk of EONS, such as premature rupture of membranes, maternal colonization with Group B Streptococcus (GBS), chorioamnionitis and maternal intrapartum fever. Screening protocols for GBS colonization in pregnant women have become standard practice, leading to the implementation of intrapartum antibiotic prophylaxis for colonized mothers, significantly reducing the incidence of GBS-related EONS. There have been advancements in diagnostic tools and techniques for EONS, including rapid molecular tests and biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT), which aid in early detection and decision-making regarding antibiotic therapy. With growing concerns about antimicrobial resistance, there has been a shift towards more judicious use of antibiotics in neonatal care, including EONS. This includes efforts to limit unnecessary antibiotic exposure and duration of therapy whenever possible. Improvements in neonatal intensive care unit (NICU) technology and practices have enhanced supportive care for neonates with EONS, including better respiratory support, temperature regulation and nutritional management, which are crucial for their overall outcomes. There is ongoing research into novel treatment modalities for EONS, such as adjunctive therapies like immunoglobulins and probiotics, which may help bolster the neonate's immune response and prevent or treat infection. Recognizing the interconnectedness of maternal and neonatal health, there has been increased emphasis on optimizing maternal health during pregnancy to reduce the risk of EONS, including efforts to address maternal infections and improve prenatal care.

While studies conducted in developing nations have identified Klebsiella spp., Staphylococcus aureus and Escherichia coli as the primary causes of EOS, group B Streptococcus is the predominant cause in industrialised nations. Negative coagulase In wealthy countries, Staphylococcus aureus is the primary cause of length of stay (LOS), while in undeveloped countries, it continues to be the primary cause of LOS(5)

The rate of EOS secondary to GBS has dropped from 1.7 cases per 1,000 newborns in 1993 to 0.28 instances per 1,000 births, according to the Centres for Disease Control and Prevention (CDC).[6]

Investigation

Procalciton (PCT) and C-reactive protein (CRP), non specific biomarkers like white blood cell count, immature to mature neutrophils are appropriate measures for the detection and monitorantibiotics therapy. Blood culture has been considered as a gold standard method but the identification of EOS is complicated by a high false-negative results.[7]

In a study conducted by Lubei Rao on diagnostic value of progranulin (PGRN) for detecting early-onset neonatal sepsis and to compare its

effectiveness with other routinely used biomarkers like procalcitonin (PCT) and C-reactive protein (CRP). The study observed diagnostic sensitivity and negative predictive value of PGRN were 94.34% and 91.7%, respectively. The combination of PGRN and PCT could significantly improve diagnostic performance for EOS, with a specificity of 89.06% and a positive predictive value of 81.10%.[8] In another study conducted by Yu He *et al*., among 121 neonates with suspected EOS, plasma levels of IL-27, IL-6, IL-8, heat shock protein (HSP) 70, macrophage inflammatory protein (MIP)-1α, MIP-1β, tumor necrosis factor (TNF)-α and matrix metalloproteinase (MMP)-8 were measured using multiplex cytokine profiling and correlated along with C-reactive protein (CRP) and procalcitonin (PCT). Results showed that elevated IL-27 strongly corresponds with EOS and also it can provide further diagnostic value along with PCT.[9]

EOS Calculator

After conducting a retrospective analysis of 608,014 live births in 14 hospitals located in California and Massachusetts between 1993 and 2007, the Kaiser team created the EOS Risk Assessment Calculatorat a gestational age of ≥34 weeks, based on maternal risk factors for perinatal infection and early postnatal clinical presentation which was first presented in 2011.[10]

Among the variables included in the calculator, the mother-related risk factors: the maximum maternal temperature at delivery, time of premature rupture of membranes, maternal antibiotic use at delivery (type of antibiotic and time of use) and maternal GBS colonization status, were weighted as 58%, 13%, 10% and 2%, respectively, in the calculator. Before entering the risk factor data, the base incidence of EOS should be entered to quantify the initial risk of EOS at birth (also known as the a priori probability) according to the local incidence of EOS.

By estimating individualized risk, these calculators help identify neonates who may benefit from empiric antibiotic treatment while sparing low-risk infants from unnecessary interventions. Implementation of risk calculators in clinical practice promotes evidence-based care and resource utilization, contributing to improved outcomes for newborns.

Article Reviewed

In a retrospective study conducted by Maria Paula Cuoco in Australia among 577 infants showed that rates of antibiotic treatment could potentially decrease from 4.3% to 2.4% when the calculator applied.[11]

A study conducted by Yi He *et al.* in China between January 2017 to December 2018 with a total of 501 neonates, including 353 infected and 148 uninfected infants, by combining EOS risk calculator with PCT, CBC and CRP. The study showed the EOS risk calculator and PCT showed good predictive value compared to CBC and CRP. Risk scores from the EOS risk calculator strongly correlated with EOS and the EOS risk calculator offered increased predictive value when used in combination with blood biomarkers.[12]

In a study conducted in Saudi Arabia in the year 2021, Roya Huseynova *et al.* evaluated 44 cases of neonates who were ≥34 weeks of gestation started on empiric antibiotics within 72 hours after birth due to suspected EOS at the neonatal intensive care unit (NICU). The results showed unnecessary antibiotic usage for 12 (27.3%) neonates, decrease in the number of NICU admission (RRR 20.4%; 95% CI 14.3% - 28%), laboratory tests (RRR 20.4%; 95% CI 14.3% - 28%) and length of stay (RRR 25%; 95% CI 38% - 95%).[13]

A retrospective analysis with 1,187 newborns who met inclusion criteria was carried out in a low-risk community between January 1, 2012 and August 29, 2019 by Kelley M. Sonney *et al.* Within 72 hours of delivery, 234 (19.7%) neonates had blood cultures using categorical risk assessment and 170 (14.3%) of them received antibiotics in line with normal clinical practice. Respiratory distress was the most common reason for assessment in 173 (14.6%) of the patients. After applying the Neonatal Early-Onset Sepsis Calculator to this cohort, 166 individuals (14%), 164 individuals (13.8%) and 1,021 individuals (86%), received recommendations to obtain a blood culture, begin or seriously consider initiating empirical antibiotics and neither initiate nor strongly consider initiating antibioticsThe frequency of blood cultures would have decreased (19.7 vs. 14%, $p < 0.0001$) if the calculator's recommendations had been followed, however the usage of empiric antibiotics would not have decreased (14.3 vs. 13.8%, $p = 0.53$). There were no EOS cases discovered that have cultural proof.

In June 2018 and December 2019, Pontello *et al.* conducted a study involving 4363 newborn newborns who were more than 35 weeks gestation. 1021 neonates out of 4363 were found to have neonatal sepsis risk factors. This study revealed that using the EOS calculator greatly decreased the use of empirical antibiotics, which had been at 3%. It also significantly decreased laboratory

assessment and vital parameter monitoring, as well as the length of hospital stay. Furthermore, there was no readmission to hospital during that time.

In a retrospective study conducted by Michelle Fernandes *et al.*, among 60 neonates who received parenteral antibiotics to compare the NICE guideline and EOS risk calculator in a level 2 NICU at a district general hospital. After applying EOS calculator, antibiotic usage could be reduced by 68%.[16]

In a prospective study conducted in Qatar by vellamgot *et al.* among chorioamniotic exposed term neonates. Out of 3837 infants admitted in NICU, 464 (12%) were chorioamnionitis exposed babies. EOS calculator reduced antibiotic usage in 270 neonate and blood culture in 106 neonates. Implementation of EOS calculator would safely reduce the usage of antibiotics and unnecessary blood investigation among chorioamniotic exposed infants.[10]

CONCLUSION

Early onset sepsis risk calculators represent a valuable tool for precision neonatal care, offering clinicians an evidence-based approach to identify and manage neonates at risk of sepsis and reduces the unnecessary use of antibiotics and decreases the number of investigations significantly. Continued research and collaboration are essential to further refine and validate these calculators, ultimately improving outcomes for newborns while minimizing unnecessary interventions and healthcare costs.

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