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REVIEW ARTICLE

A comprehensive review of advances in biomarkers for the early diagnosis and management of neonatal sepsis

Una revisión integral de los avances en biomarcadores para el diagnóstico temprano y la gestión de la sepsis neonatal

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Abstract Neonatal sepsis markers are key tools for early diagnosis and monitoring this condition in newborns. Neonatal sepsis is a severe infection that can be difficult to identify due to its nonspecific clinical presentation. C-reactive protein (CRP), procalcitonin (PCT), and blood cultures are the most common markers. CRP is an acute-phase protein that increases in response to inflammation and can help detect sepsis, although its sensitivity improves with repeated measurements within the first 24-48 hours of symptoms. PCT, another acute-phase reactant, rises rapidly in bacterial sepsis, making it useful for early diagnosis and monitoring the response to antibiotic treatment. Blood cultures remain the standard for confirming the diagnosis, although their sensitivity can vary. New markers such as presepsin and endocan are under investigation, but their use remains limited. Combining these biomarkers and clinical assessment enhances the ability to differentiate sepsis from other conditions and guides appropriate treatment. Early identification and timely treatment are crucial to reducing mortality and complications associated with neonatal sepsis.

Keywords neonatal sepsis, acute-phase markers, C-reactive protein, procalcitonin, early diagnosis.

Resumen Los marcadores de sepsis neonatal son herramientas clave para el diagnóstico temprano y el monitoreo de esta condición en recién nacidos. La sepsis neonatal es una infección grave que puede ser difícil de identificar debido a su presentación clínica inespecífica. Entre los marcadores más comunes se incluyen la proteína C reactiva (PCR), la procalcitonina (PCT) y los hemocultivos. El objetivo de esta revisión bibliográfica fue analizar los avances y aplicaciones de los marcadores biomédicos en el diagnóstico temprano y el monitoreo de la sepsis neonatal. Se describen las características, utilidad clínica y limitaciones de los marcadores tradicionales como la proteína C reactiva (PCR), la procalcitonina (PCT) y los hemocultivos, así como explorar el potencial de nuevos biomarcadores como la presepsina y el endocano. Además, se analiza la eficacia de la combinación de estas herramientas diagnósticas con la evaluación clínica para mejorar la diferenciación de la sepsis neonatal frente a otras patologías, destacando su impacto en la reducción de la mortalidad y las complicaciones asociadas.

Palabras clave sepsis neonatal, marcadores de fase aguda, proteína C reactiva, procalcitonina, diagnóstico precoz.

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Introduction

Neonatal sepsis is one of the leading causes of morbidity and mortality in newborns, particularly in those with low birth weight or prematurity. This condition is characterized by a systemic inflammatory response to infection, and early diagnosis is crucial to avoid severe complications. However, timely identification remains challenging due to the nonspecificity of clinical symptoms and the need to differentiate between bacterial infections and other neonatal conditions. In this context, sepsis markers have emerged as key tools to optimize diagnosis and treatment in neonatal intensive care units (NICU) (Briggs-Steinberg & Roth, 2023).

Common markers are C-reactive protein (CRP) and procalcitonin (PCT), which have proven helpful in identifying bacterial infections. Recent studies highlight the sensitivity of PCT in the early detection of neonatal sepsis, especially in early-onset infections. Other emerging biomarkers include inflammatory cytokines such as IL-6 and IL-8, which reflect the activation of the immune system in response to pathogens. However, heterogeneity in reference values and measurement techniques still presents limitations for their widespread clinical implementation (Rees et al., 2023).

While individual biomarkers are commonly used, combined approaches have gained relevance, such as using multiplex panels to evaluate multiple markers simultaneously. These strategies promise to improve diagnostic accuracy and reduce the empirical use of antibiotics, minimizing the risk of antimicrobial resistance. As research progresses, these markers are expected to play an increasingly critical role in personalizing neonatal sepsis management, tailored to the specific needs of each patient and clinical setting (Briggs-Steinberg & Roth, 2023; Rees et al., 2023). Considering the above, this literature review aims to analyze the advancements and applications of biomedical markers in the early diagnosis and monitoring of neonatal sepsis.

Neonatal sepsis

Neonatal sepsis is a clinical syndrome characterized by systemic signs of infection associated with bacteremia, affecting neonates from birth to 28 days of life. Diagnosis requires clinical evaluation, maternal history of infection, and microbiological confirmation through blood cultures and cerebrospinal fluid (CSF) cultures. Despite advances in intensive care and antimicrobial therapies, this condition remains a significant challenge in neonatology, particularly in developing countries, where high morbidity and mortality rates persist (Pérez et al., 2021).

Although neonatal infections have decreased in recent years due to improvements in Neonatal Intensive Care Units (NICUs), neonatal sepsis continues to be one of the leading causes of morbidity and mortality, especially in preterm neonates. In developed countries, the incidence ranges from 0.6 to 1.2% of live births, while in developing countries, it can reach up to 40% of cases, with mortality rates as high as 50%. In this context, between 2 and 10 cases of early neonatal sepsis occur for every 1000 live births (Wynn, 2016).

Neonatal sepsis is classified according to the timing of onset as early (within the first 72 hours to 7 days of life) and late (after this period). Maternal factors such as chorioamnionitis, premature rupture of membranes (PROM), and elevated C-reactive protein (CRP) levels are identified as high-risk elements. CRP, one of the most studied acute-phase reactants, continues to be widely used in NICUs due to its sensitivity and specificity in detecting neonatal sepsis, providing essential support in differentiating between neonates with or without sepsis (Cortés et al., 2019).

Early neonatal sepsis

Early neonatal sepsis is acquired during the peripartum period, before or during delivery, and the causative microorganisms generally come from the maternal genitourinary tract. According to data from the American Neonatology Network, gram-positive microorganisms are responsible for 62% of early neonatal sepsis cases, with Streptococcus agalactiae being identified in 43%. In contrast, gram-negative microorganisms account for 37% of the etiological agents of this form of sepsis, with Escherichia coli responsible for 29% of the cases (Guamán, 2020).

Risk factors for early neonatal sepsis include several conditions related to maternal health and delivery. One of the main risk factors is colonization by S. agalactiae, as a pregnant woman colonized with this microorganism and without intrapartum prophylaxis is 25 times more likely to have a newborn with early neonatal sepsis than a non-colonized mother. Group B streptococcal colonization rates can reach up to 35% in vaginal or rectal cultures from term women (Pichler et al., 2018). Another significant risk factor is the rupture of the amniotic membrane for more than 18 hours, as newborns from mothers with prolonged rupture are four times more likely to develop an infection compared to those born to mothers without rupture (Camacho-Gonzalez et al., 2013). Finally, chorioamnionitis also increases the likelihood of early neonatal infection (Romaine et al., 2016).

Late neonatal sepsis

Late neonatal sepsis is an infection that occurs after a newborn's first 72 hours of life. This condition is more common in very low birth weight infants who require prolonged hospitalization in the Neonatal Intensive Care Unit (NICU), as well as in late preterm infants or term infants who also need several days of hospitalization. In preterm infants with a birth weight of 1500 g or less, the incidence of at least one first positive blood culture after 72 hours of life ranges from 20 to 35%, depending on the medical service evaluated (Greenberg et al., 2017; de Souza et al., 2014).

The microorganisms most commonly associated with late neonatal sepsis are Gram-positive bacteria, with coagulase-negative Staphylococcus being the most frequent, accounting for approximately 79% of cases. Infections caused by Gram-negative microorganisms have also been observed, and an increase in the incidence of fungal sepsis has been documented in various medical centers. Additionally, it is important to note that many newborns hospitalized in the NICU have reported viral infections, presenting a clinical picture similar to bacterial neonatal sepsis. The most common viruses include respiratory syncytial and rhinovirus (Pichler et al., 2018).

The most significant risk factors for the development of late neonatal sepsis include various clinical and medical aspects. Prematurity is one of the most prominent factors, as premature infants are at greater risk due to an underdeveloped immune response, reduced transfer of antibodies from the mother to the fetus, and lower production of inflammatory molecules, which compromise cell-mediated immunity (Camacho-Gonzalez et al., 2013). Due to the softness and fragility characteristic of neonates, skin and mucosal lesions can serve as entry points for bacterial invasion, thus increasing the risk of infection. Furthermore, long-term central catheters, necessary for administering medications or fluids, can facilitate the entry of bacteria into the infant's body, increasing the risk of late neonatal sepsis.

Invasive procedures, such as endotracheal intubation, also raise the risk of late neonatal sepsis, as accidental extubations requiring frequent reintubation can increase the likelihood of infection. Using H2 blockers, which are employed to reduce gastric acidity, may also compromise the body's natural defense barrier, facilitating bacterial proliferation and invasion (Romaine et al., 2016). Additionally, prolonged use of empirical antibiotics, especially for more than five days to treat early neonatal sepsis, has been associated with an increased risk of late sepsis, particularly in units with low use of breast milk and excessive prescription of third-generation cephalosporins (Greenberg et al., 2019).

Causes of neonatal sepsis

Neonatal sepsis is an invasive infection, generally bacterial, although it can also be of viral or fungal origin. The microorganisms most commonly associated with early-onset neonatal sepsis include *Streptococcus agalactiae* (GBS) and *E. coli* (Shane et al., 2017; Chauhan et al., 2017). Evaluating the microbiological profile is crucial for determining initial empirical therapy, as this profile may vary by region, country, or hospital (Alvarado-Gamarra et al., 2016). A study conducted in the United States between 2006 and 2009 involving 400,000 newborns reported that of 389 cases of early-onset sepsis, 43% were caused by GBS and 29% by *E. coli* (Shane et al., 2017). In Lima, the most frequently isolated microorganisms were *Staphylococcus epidermidis* (38.3%) and *Staphylococcus aureus* (12%), with a predominance of gram-positive microorganisms in other national studies. GBS cases are less frequent in Latin America than in other regions, while gram-negative microorganisms predominate (Pérez et al., 2015).

Late-onset sepsis is acquired from the environment, and staphylococci are responsible for 30 to 60% of cases, mainly due to intravascular devices, such as central venous catheters. *E. coli* is increasingly becoming a cause of late-onset sepsis, particularly in extremely low birth weight newborns. Additionally, when outbreaks of pneumonia or hospital-acquired sepsis caused by *Pseudomonas aeruginosa* occur, contamination of respiratory equipment should be suspected (Shane et al., 2017; Pérez et al., 2015).

Neonatal sepsis markers

Among the most commonly used markers for diagnosing neonatal sepsis are various hematological indices, acute phase reactants, cytokines, and newer markers such as presepsin or endotoxin. Although microorganism isolation from blood or sterile body fluids remains the most specific method for diagnosis, there are other complementary laboratory tests, such as leukocyte counts and quantitative measurement of C-reactive protein and interleukins, which help differentiate neonatal sepsis from other clinical conditions (Robledo-Restrepo et al., 2015).

Acute phase reactants are endogenous peptides produced mainly in the liver in response to an infection, and they can also cause damage to various tissues. The use of these markers in the diagnosis of neonatal sepsis requires experience in the management of newborns since the combination of clinical signs, often nonspecific in the early stages of sepsis, together with blood tests and acute phase reactant results, allows decisions to be made about antibiotic therapy before blood cultures confirm a definitive diagnosis.

C-reactive protein (CRP), for example, is one of the most studied and widely used markers in clinical practice. Although it may be expected in the early stage of infection, serial measurements within the first 24-48 hours after symptom onset increase its sensitivity. CRP is also useful for monitoring therapeutic response, with a typical value below 1 mg/dl (Briceño, 2019).

CRP as a biomarker in neonatal sepsis

C-reactive protein (CRP) is a pentameric protein that belongs to the family of acute-phase reactive proteins. Its synthesis mainly occurs in hepatocytes, and various cytokines stimulate its production. The half-life of CRP is 24 to 48 hours (Sharma et al., 2018). It is important to note that the elevation of CRP levels may take between 10 and 12 hours to manifest, which limits its sensitivity and, therefore, its usefulness for the early diagnosis of neonatal sepsis (Sharma et al., 2018; Chauhan et al., 2017).

CRP can increase in various inflammatory conditions, including neonatal sepsis, as well as in a wide range of non-infectious inflammatory disorders, such as perinatal asphyxia or intraventricular hemorrhage. This situation implies certain limitations in its clinical utility, as an increase in CRP levels does not necessarily indicate a bacterial infection but may result from a nonspecific inflammatory response. Therefore, it is essential to consider these factors when interpreting CRP results in diagnosing neonatal sepsis (Celik et al., 2022; Sharma et al., 2018).

Procalcitonin

The calcitonin precursor peptide (PCT) is released by parenchymal cells in response to bacterial toxins, increasing serum levels in patients with bacterial infections (Celik et al., 2022). This marker belongs to the acute-phase reactants and plays a significant role in the vascular response and immunomodulation associated with Systemic Inflammatory Response Syndrome (SIRS) (Chauhan et al., 2017). The half-life of PCT is between 24 and 30 hours, and its rapid increase in cases of bacterial sepsis makes it a valuable indicator for early neonatal sepsis diagnosis, especially when compared to C-reactive protein (CRP) (Hahn et al., 2015).

Initially, it was believed that an advantage of PCT was that its increase in neonatal sepsis was not influenced by gestational age. However, a study has shown that reference levels of PCT in infants with gestational age less than 32 weeks can be altered, requiring more cautious interpretation (Hahn et al., 2015). In this context, the need to develop specific nomograms based on gestational age has been suggested, both for term neonates and preterm infants, as evidenced by a study conducted in 2000, which correlated PCT levels during the first four days of life with gestational age (Turner et al., 2006).

Although procalcitonin is more sensitive than C-reactive protein, its specificity is lower (Pérez et al., 2015). Therefore, a combination of biomarkers, including procalcitonin and C-reactive protein, maybe more helpful in determining the duration of antibiotic treatment (Shane et al., 2017; Pérez et al., 2015).

Blood culture

For blood cultures, it is recommended to obtain at least 0.5-1 ml of blood, preferably from two different sites (Shane et al., 2017; Sharma et al., 2018). Positive results from blood cultures obtained from umbilical or central venous catheters can be challenging to interpret, as they may indicate contamination or catheter colonization rather than an actual systemic infection. Therefore, obtaining an additional peripheral blood culture is necessary to interpret the results correctly (WHO, 2010). Blood culture is the gold standard for confirming sepsis in patients with compatible signs and symptoms. However, its sensitivity may range from 30 to 80%, depending on biological factors and the collection procedure used. In the case of neonatal sepsis, blood culture should always be performed if there are risk factors or maternal or neonatal history, as well as at the onset of symptoms (Sharma et al., 2018).

Clinical signs and symptoms of neonatal sepsis

Newborns with bacterial sepsis may present a variety of nonspecific signs and symptoms in addition to focal signs of infection. These symptoms include thermal instability, hypotension, poor perfusion with pallor and mottled skin, metabolic acidosis, tachycardia or bradycardia, apnea, respiratory failure, grunting, cyanosis, irritability, lethargy, seizures, feeding intolerance, abdominal distension, jaundice, petechiae, purpura, and bleeding (Shane et al., 2017; Celik et al., 2022). Tachycardia is common in neonatal sepsis, although it is not specific to this condition, and bradycardia may also occur. Poor perfusion and hypotension are more sensitive indicators of sepsis, although they generally appear in more advanced stages.

In a national prospective surveillance study, 40% of neonates with sepsis required volume expansion, while 29% needed vasopressor support (Stoll et al., 2011). These fin-

dings underscore the severity of neonatal sepsis and the need for timely diagnosis and treatment. The need for volume expansion and vasopressor support indicates hemodynamic dysfunction and a severe systemic response to bacterial infection.

Despite the emergence of new sepsis markers, such as presepsin or endocan, the information available about them in our environment is still limited. Therefore, the most commonly used markers for early diagnosis, monitoring, and treatment of neonatal sepsis continue to be C-reactive protein (CRP), procalcitonin, and blood cultures (Shane et al., 2017; Celik et al., 2022).

Conclusions

Neonatal sepsis markers play a crucial role in the early detection and proper management of this potentially life-threatening condition. Among them, inflammatory biomarkers such as procalcitonin, C-reactive protein, and interleukins (IL-6, IL-8) have proven valuable tools for differentiating bacterial infections from other inflammatory conditions. However, their specificity and sensitivity may vary depending on the timing of measurement and the population studied. Additionally, emerging technologies that combine genomic and proteomic analyses have opened new possibilities for identifying more precise biomarkers. Despite these advances, there remains a need to develop integrated diagnostic protocols that combine multiple markers with clinical judgment to improve accuracy and treatment outcomes.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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