**Review article**

# Neonatal Sepsis in The Modern Era: Trends, Challenges and Recent Advances.

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**Abstract:**
Neonatal sepsis remains one of the leading causes of morbidity and mortality in newborns worldwide, particularly in low- and middle-income countries. Despite advancements in medical care, early diagnosis and effective management of sepsis continue to pose significant challenges due to the nonspecific nature of clinical symptoms and the diverse microbial agents involved. In the modern era, the landscape of neonatal sepsis is shaped by several evolving factors, including changes in microbial resistance patterns, improved neonatal care practices, and novel diagnostic and therapeutic strategies. This review explores the current trends in neonatal sepsis, the challenges that healthcare systems face in managing it, and the recent advances that hold promise for improving outcomes. The article covers the pathophysiology of sepsis in neonates, risk factors such as prematurity, low birth weight, and invasive procedures, and the role of microbial pathogens, with an emphasis on emerging resistant organisms. Additionally, we discuss modern diagnostic techniques, including molecular methods, which have improved early detection, as well as advancements in antimicrobial therapies. The review also examines the impact of sepsis on neurodevelopmental outcomes, highlighting the long-term consequences for infants who survive severe infections. Finally, the article considers strategies for prevention, antimicrobial stewardship, and the importance of a multidisciplinary approach to managing neonatal sepsis. Understanding these evolving trends and challenges is essential to reducing the global burden of neonatal sepsis and improving neonatal survival rates and long-term health.

**Keywords:** Neonatal sepsis, early diagnosis, antimicrobial resistance, preterm infants, infection prevention

## Introduction:

Neonatal sepsis, an infection occurring in the first 28 days of life, remains a critical cause of neonatal morbidity and mortality worldwide. The condition is often difficult to diagnose due to the subtle and nonspecific nature of its symptoms, making it one of the most challenging infections to manage in the neonatal period.[1,2] Sepsis in neonates can be caused by a wide range of pathogens, including bacteria, viruses, and fungi, and can present in different clinical forms, such as early-onset sepsis (EOS) or late-onset sepsis (LOS). EOS typically occurs within the first 72 hours of life and is primarily associated with maternal or vertical transmission of pathogens during labor and delivery. LOS, on the other hand, presents after the first 72 hours and is commonly linked to nosocomial infections, especially in vulnerable infants, such as those in neonatal intensive care units (NICUs). [3,4]

The global burden of neonatal sepsis is substantial, with an estimated 2.5 million neonatal deaths annually, a significant proportion of which are attributable to infections. Low- and

middle-income countries (LMICs) bear the highest burden, where limited access to quality healthcare services, inadequate sanitation, and lack of timely medical interventions exacerbate the severity of infections. However, even in high-resource settings, neonatal sepsis remains a major cause of neonatal mortality, albeit with better survival rates due to advances in neonatal intensive care, antibiotics, and early diagnosis. [5-8]

The landscape of neonatal sepsis has evolved considerably in recent decades. In high-income countries, the introduction of improved prenatal care, the use of prophylactic antibiotics, and better infection control measures in NICUs have led to a reduction in the incidence of neonatal infections. Nevertheless, the rise of antibiotic-resistant organisms has emerged as a significant challenge. Pathogens such as Klebsiella pneumoniae, Escherichia coli, and Staphylococcus aureus have developed resistance to commonly used antibiotics, complicating treatment strategies.

In parallel, the rapid advances in molecular diagnostics and the development of more sensitive, faster tests have improved early detection of neonatal sepsis, facilitating timely treatment and better outcomes. Techniques like polymerase chain reaction (PCR), multiplex PCR, and other genomic approaches allow for the identification of pathogens within hours, which is a significant improvement over traditional culture-based methods. Additionally, the use of biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) has helped clinicians assess the severity of the infection and make informed decisions about treatment.

Despite these advances, neonatal sepsis remains a multifaceted challenge, requiring a coordinated approach to prevention, early diagnosis, and treatment. Neonates, especially preterm infants, are particularly vulnerable to sepsis due to their immature immune systems, underdeveloped barriers to infection, and exposure to invasive procedures such as mechanical ventilation and central venous catheterization. These risk factors not only increase the likelihood of infection but also contribute to the complexity of its management. In addition, the long-term consequences of neonatal sepsis, including neurodevelopmental delays and increased risk of chronic health conditions, underscore the importance of early intervention and effective management. [9]

As the global burden of neonatal sepsis persists, this review examines the trends, challenges, and recent advances in the diagnosis and management of neonatal sepsis. By highlighting the evolving nature of the condition, we aim to provide a comprehensive overview of current practices and emerging solutions that are shaping neonatal care in the modern era.

**Discussion:**

**Pathophysiology of neonatal sepsis:**

Neonatal sepsis remains one of the most critical conditions in neonatal medicine, characterized by a systemic inflammatory response to infection in newborns, which can lead to severe multi-organ dysfunction and, if not managed promptly, death. The pathophysiology of neonatal sepsis involves the interaction between the invading pathogens, the neonate's immune system, and the inflammatory response. Newborns, particularly preterm infants, have an immature immune system that renders them highly vulnerable to infections. [3,5] The innate immune system, responsible for the first line of defense, is underdeveloped, with neutrophils and macrophages demonstrating limited function. Additionally, the mucosal and skin barriers, which serve as physical defenses against pathogens, are less robust in neonates, particularly preterm infants. This combination of immune immaturity and compromised physical barriers increases the risk of bacterial, viral, and fungal pathogens invading the bloodstream.

Once a pathogen enters the bloodstream, it triggers a cascade of inflammatory responses. The body attempts to control the infection through the release of pro-inflammatory cytokines and chemokines. However, the neonate's immature immune system may respond either inadequately or excessively. In some cases, this leads to uncontrolled inflammation and multi-organ dysfunction, a phenomenon often referred to as "systemic inflammatory response syndrome" (SIRS). The exaggerated inflammatory response may contribute to tissue damage and organ failure, making the clinical management of neonatal sepsis especially challenging. The early detection of sepsis remains a key challenge because the symptoms are often nonspecific, and the clinical signs may mimic other conditions like birth asphyxia or respiratory distress. [10]

Neonatal sepsis is typically classified into two categories based on the timing of infection. Early-onset sepsis (EOS) occurs within the first 72 hours of life, typically due to pathogens acquired from the mother during labor and delivery, while late-onset sepsis (LOS) usually manifests after 72 hours and is often associated with nosocomial infections acquired in the hospital, especially in NICUs. EOS is commonly caused by Group B Streptococcus (GBS) and Escherichia coli, while LOS is frequently caused by hospital-acquired pathogens such as Klebsiella pneumoniae, Staphylococcus aureus, and fungi like Candida species. The nature of the infection and the pathogens involved influences the treatment approach and overall prognosis. [11]

**Risk factors for neonatal sepsis:**

Prematurity is one of the most significant risk factors for neonatal sepsis, with preterm infants (those born before 37 weeks of gestation) being particularly vulnerable. This is due to their immature immune systems, which struggle to fight off infections, and their underdeveloped skin and mucosal barriers that provide less protection against pathogens. The increased need for invasive procedures, such as intubation, catheterization, and the use of central venous lines, further heightens the risk of nosocomial infections, particularly in NICU settings. These procedures can introduce bacteria into sterile areas of the body, providing a direct route for infections to spread. [12]

Maternal factors are also critical in determining the risk of neonatal sepsis. Conditions such as chorioamnionitis (infection of the fetal membranes), prolonged rupture of membranes, and maternal bacteremia significantly increase the likelihood of neonatal infections. Group B Streptococcus (GBS) colonization is one of the most common causes of early-onset neonatal sepsis, and maternal screening for GBS colonization is an essential strategy for reducing the incidence of EOS. Other factors, such as intrauterine exposure to pathogens like Listeria monocytogenes and Escherichia coli, also contribute to the neonatal risk. [13]

Infants who undergo invasive medical procedures in the neonatal period, such as umbilical catheterization, mechanical ventilation, or surgery, are at greater risk for developing late-onset sepsis. These procedures often require the insertion of foreign materials into the body, which can serve as a conduit for bacterial and fungal infections. Hospital-acquired infections, especially in NICU settings, are a leading cause of late-onset sepsis. The increasing use of invasive technologies and longer hospital stays in NICUs has led to a higher incidence of infections caused by multidrug-resistant organisms, which complicate the treatment of these infections. Congenital anomalies, especially those involving the gastrointestinal or urinary systems, can also increase the risk of sepsis. Infants with structural malformations are more

likely to require surgical interventions or prolonged hospital stays, both of which increase exposure to pathogens. [14-16]

**Microbial etiology of neonatal sepsis:**

The microbial agents responsible for neonatal sepsis are influenced by the timing of infection and the setting in which the infection occurs. Early-onset neonatal sepsis (EOS) is typically caused by pathogens acquired from the mother during delivery, most commonly Group B Streptococcus (GBS) and Escherichia coli. These pathogens can infect the neonate during the birth process, particularly in the case of prolonged rupture of membranes, chorioamnionitis, or maternal bacteremia. EOS is associated with high mortality and morbidity rates, with affected neonates frequently developing pneumonia, meningitis, and septic shock. In high-income countries, the incidence of EOS has decreased significantly due to widespread screening for GBS and the use of intrapartum antibiotic prophylaxis, but it remains a major cause of neonatal sepsis in low- and middle-income countries, where access to preventive care may be limited. [17]

Late-onset neonatal sepsis (LOS) occurs after the first 72 hours of life and is typically associated with hospital-acquired infections. Pathogens that cause LOS are often introduced into the infant's body through invasive medical procedures and devices, such as central venous catheters, endotracheal tubes, and urinary catheters. The most common pathogens responsible for LOS include Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus (including methicillin-resistant strains, MRSA), and Candida species. Nosocomial infections are a growing concern, especially in NICUs, where the prolonged use of antibiotics can alter the neonatal microbiome and promote the emergence of antibiotic-resistant organisms. Escherichia coli and Enterococcus species are also significant contributors to late-onset infections.

The growing problem of antibiotic resistance in neonatal sepsis is an area of major concern. The emergence of multidrug-resistant (MDR) organisms, including Klebsiella pneumoniae, Pseudomonas aeruginosa, and Staphylococcus aureus, has made empirical treatment more difficult. These resistant organisms often require the use of second- and third-line antibiotics, such as carbapenems, colistin, and tigecycline, which are less ideal due to their toxicity profiles. The rise of these resistant pathogens underscores the importance of antimicrobial stewardship and the need for ongoing research into new therapeutic options. [18,19]

**Advances in diagnostic approaches:**

One of the most significant challenges in managing neonatal sepsis is the early and accurate diagnosis of the condition. Neonates often present with nonspecific signs such as lethargy, poor feeding, temperature instability, and respiratory distress, which overlap with other conditions like birth asphyxia or feeding intolerance. Traditionally, blood cultures have been the gold standard for diagnosing neonatal sepsis; however, culture results take 48-72 hours, delaying treatment and potentially leading to worse outcomes.

Recent advancements in molecular diagnostics have significantly improved the speed and accuracy of neonatal sepsis diagnosis. Techniques like polymerase chain reaction (PCR) and multiplex PCR have enabled the rapid identification of pathogens, allowing clinicians to initiate targeted antimicrobial therapy within hours, rather than days. PCR-based assays have been shown to detect a wide range of bacterial, viral, and fungal pathogens, providing a more comprehensive understanding of the infection. Next-generation sequencing (NGS) is another

emerging diagnostic tool that offers a more precise and detailed identification of pathogens and their resistance profiles, facilitating personalized treatment strategies. [20]

In addition to molecular diagnostics, biomarkers have become invaluable tools in the diagnosis and management of neonatal sepsis. Biomarkers such as C-reactive protein (CRP), procalcitonin (PCT), and interleukins (IL-6, IL-8) are used to assess the likelihood of infection and monitor the progression of the disease. CRP, a protein produced by the liver in response to inflammation, rises within 6-12 hours of infection and is one of the most commonly used biomarkers. While it is not specific to sepsis, elevated CRP levels in neonates can signal an ongoing infectious process, especially when accompanied by other clinical signs.

Procalcitonin (PCT) is another key biomarker used in neonatal sepsis management. Unlike CRP, PCT is more specific to bacterial infections, and its levels increase significantly during bacterial sepsis. PCT levels correlate with the severity of the infection, and studies have suggested that it can be used to guide antibiotic therapy. Elevated PCT levels are associated with a higher risk of bacterial sepsis, and a decrease in PCT levels over time can indicate a favorable response to therapy.

In recent years, novel biomarkers like neutrophil CD64 expression have shown promise for improving the diagnostic accuracy of neonatal sepsis. Neutrophil CD64 is a receptor that is upregulated during infection, and its expression has been shown to be a reliable indicator of neonatal sepsis, with some studies suggesting that it is more sensitive and specific than traditional biomarkers like CRP and PCT. [21]

Advances in point-of-care testing are also improving the speed of diagnosis, bringing these biomarkers to the bedside and allowing for more rapid decision-making. Devices that can quickly detect CRP, PCT, and other markers at the point of care are making a significant difference in the ability to diagnose neonatal sepsis early, reducing delays in treatment and improving outcomes.

**Antibiotic therapy and resistance:**

Antibiotic therapy remains the cornerstone of neonatal sepsis treatment. In cases where sepsis is suspected, empirical therapy with broad-spectrum antibiotics is typically initiated immediately. The most common regimen for early-onset neonatal sepsis includes ampicillin and gentamicin, which target Group B Streptococcus (GBS), Escherichia coli, and other Gram-positive and Gram-negative organisms. For late-onset infections, treatment may include broader-spectrum antibiotics like vancomycin, meropenem, or piperacillin-tazobactam, particularly when hospital-acquired pathogens are suspected.

However, the rise of multidrug-resistant (MDR) organisms has complicated treatment regimens. Extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli and carbapenem-resistant Klebsiella pneumoniae are increasingly prevalent in NICU settings, requiring the use of more potent, less well-tolerated antibiotics like colistin or tigecycline. These drugs are often associated with significant side effects, including nephrotoxicity and neurotoxicity, raising concerns about their long-term use. [22]

In response to the growing threat of antibiotic resistance, antimicrobial stewardship programs are being implemented in NICUs to optimize the use of antibiotics. These programs aim to ensure the appropriate use of antibiotics based on the severity of the infection, the local resistance patterns, and the susceptibility profiles of the pathogens involved. One of the most important aspects of antimicrobial stewardship is the de-escalation of antibiotic therapy based on the results of culture and sensitivity tests. Reducing unnecessary or broad-spectrum

antibiotic use can help limit the development of resistance while ensuring effective treatment of infections.

Despite these efforts, the need for new antibiotics to address the rising tide of resistance remains urgent. Research into new antimicrobial agents, including novel antibiotics and bacteriophage therapy, is ongoing. Bacteriophage therapy, in particular, has shown promise as a potential alternative treatment for drug-resistant infections, although its use in neonates remains investigational. [23-25]

**Preventive measures:**

Preventing neonatal sepsis is critical for improving outcomes, particularly for high-risk infants. Several prevention strategies have been developed and implemented to reduce the incidence of neonatal sepsis, especially in preterm and low-birth-weight infants. One of the most effective measures in preventing early-onset sepsis is maternal screening for Group B Streptococcus (GBS) during pregnancy. GBS colonization can be detected through vaginal and rectal swabs taken at 35-37 weeks of gestation. When mothers are identified as carriers of GBS, intrapartum antibiotic prophylaxis with penicillin or ampicillin significantly reduces the risk of neonatal infection.

Another key prevention strategy is proper infection control practices in neonatal intensive care units (NICUs). Hand hygiene remains the most effective method for reducing the transmission of pathogens in the hospital setting. Neonates, especially those in NICUs, are highly susceptible to hospital-acquired infections, and strict adherence to hand hygiene protocols among healthcare workers is crucial in reducing the risk of nosocomial sepsis. [26]

In addition to infection control measures, the promotion of breastfeeding has been shown to provide important immunological benefits that reduce the risk of sepsis, particularly in preterm and low-birth-weight infants. Breast milk contains antibodies, antimicrobial peptides, and immune cells that protect against infections, and breastfeeding has been associated with a lower incidence of both early- and late-onset neonatal sepsis.

Lastly, neonatal sepsis can be reduced through improved maternal care, such as timely management of infections during pregnancy and appropriate antibiotic use during labor. Proactive screening for infections, proper management of prolonged ruptured membranes, and early interventions to manage infections in both mothers and neonates are essential components of any effective prevention strategy. [2,8,11]

**The role of artificial intelligence in neonatal sepsis:**

Artificial intelligence (AI) is increasingly being recognized as a transformative tool in the management of neonatal sepsis, a condition that requires early detection and rapid intervention to prevent severe morbidity and mortality. AI technologies, particularly machine learning (ML) and deep learning (DL), are being integrated into clinical practice to enhance diagnostic accuracy, predict disease progression, and optimize treatment strategies.

One of the primary challenges in managing neonatal sepsis is the timely and accurate diagnosis. Traditional methods, such as blood cultures, can take several days to yield results, delaying appropriate treatment. AI-driven systems may be developed to analyze a wide array of clinical data—such as vital signs, laboratory results, and even imaging—much more rapidly than human clinicians. By analyzing this data, AI algorithms can identify patterns that may indicate sepsis before clinical symptoms are obvious, enabling earlier intervention. For example, predictive models trained on large datasets of neonatal vital signs, lab results, and clinical

outcomes can generate real-time risk scores, alerting clinicians to the likelihood of sepsis and prompting timely antibiotic administration.

Machine learning models can also be integrated with biomarkers such as C-reactive protein (CRP), procalcitonin (PCT), and other inflammatory markers into diagnostic workflows. These biomarkers, while helpful, are often nonspecific and need to be considered alongside clinical signs. AI systems can combine biomarkers with clinical data to create more precise predictive models, reducing the need for excessive or broad-spectrum antibiotic use while ensuring the rapid initiation of targeted therapy.[27]

AI is also being explored to improve antibiotic stewardship in neonatal care. By predicting the likely pathogen or resistance pattern, AI tools can guide clinicians in selecting the most appropriate antibiotics from the outset, reducing the development of multidrug-resistant organisms. Additionally, AI systems are being designed to support antimicrobial de-escalation, helping to reduce unnecessary prolonged use of antibiotics, which is a key strategy in combating antibiotic resistance.[28] The application of AI in neonatal sepsis holds immense promise, not only in improving diagnostic accuracy but also in guiding treatment decisions, reducing morbidity, and optimizing healthcare resources in the neonatal intensive care unit (NICU). However, continued validation and integration of these systems into clinical practice are essential for realizing their full potential.

**Conclusion:**

Neonatal sepsis remains a leading cause of neonatal morbidity and mortality globally. While significant advancements have been made in early diagnosis, treatment, and prevention, the rising challenge of antimicrobial resistance and the vulnerability of preterm infants necessitate ongoing research and improvements in care. Early detection through molecular diagnostics, combined with the judicious use of antibiotics, is crucial in managing neonatal sepsis effectively. As the global burden of infection persists, continued investment in healthcare infrastructure, prevention strategies, and antimicrobial stewardship is critical to reducing neonatal sepsis-related deaths and improving long-term outcomes for survivors.

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**Submitted:** 05/09/2024
**Revised:** 11/09/2024
**Accepted:** 10/11/2024
**Published:** 30/12/2024

**Cite this article:**
Dr. Pankaj Soni, Dr.Jenny Cheriathu. Neonatal Sepsis in The Modern Era: Trends, Challenges and Recent Advances. Jour Med Dent Fron 2024;1(2):7-15