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Neonatal Sepsis: Diagnostic Challenges, Empirical Antibiotic Choices, And Stewardship

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Abstract: Neonatal sepsis remains a formidable challenge in pediatric medicine, contributing significantly to neonatal morbidity and mortality worldwide. This narrative review synthesizes current knowledge regarding the diagnostic complexities, empirical antibiotic strategies, and the critical role of antimicrobial stewardship in managing neonatal sepsis. Early-onset sepsis (EOS) and late-onset sepsis (LOS) present distinct epidemiological profiles, pathogen distributions, and clinical manifestations, necessitating tailored diagnostic and therapeutic approaches. The non-specific nature of clinical signs in neonates, coupled with limitations of conventional diagnostic tools, often leads to diagnostic delays or overuse of broad-spectrum antibiotics. This review explores advanced diagnostic modalities, including novel biomarkers and risk assessment tools like the Neonatal Early-Onset Sepsis Calculator, which aim to refine diagnostic accuracy and reduce unnecessary antibiotic exposure. Furthermore, it critically examines current empirical antibiotic regimens, emphasizing the need for local epidemiological data and resistance patterns to guide appropriate choices. The imperative for robust antimicrobial stewardship programs (ASPs) in neonatal intensive care units (NICUs) is highlighted, focusing on strategies to optimize antibiotic use, mitigate antimicrobial resistance, and improve long-term neurodevelopmental outcomes. We discuss emerging pathogens, challenges in low- and middle-income countries (LMICs), and areas requiring further research to enhance the care of this vulnerable population.

Keywords: Neonatal sepsis, Early-onset sepsis (EOS), Late-onset sepsis (LOS), Antimicrobial stewardship, Antimicrobial resistance, Empirical antibiotic therapy, Neonatal intensive care unit (NICU), Biomarkers, Neonatal Early-Onset Sepsis Calculator, Diagnostic accuracy, Broad-spectrum antibiotics, Pathogen distribution, Low- and middle-income countries (LMICs), Neurodevelopmental outcomes, Neonatal morbidity and mortality.

Introduction

Neonatal sepsis, defined as a systemic inflammatory response syndrome (SIRS) in the presence of suspected or proven infection in an infant within the first 28 days of life, continues to be a leading cause of morbidity and mortality globally [1, 2]. The epidemiological burden is particularly pronounced in low- and middle-income countries (LMICs), where incidence rates can be substantially higher than in high-income settings [1, 7]. Annually, over 550,000 newborn deaths are attributed to neonatal infections, underscoring the profound clinical relevance of this condition [1]. Preterm infants, especially those with extremely low birth weight (ELBW), face a disproportionately higher risk of sepsis and associated mortality, with rates exceeding 20% in ELBW neonates compared to 5–10% in term infants [1, 3, 4].

The clinical presentation of neonatal sepsis is often subtle and non-specific, mimicking various non-infectious conditions, which poses significant diagnostic challenges [2]. This diagnostic ambiguity frequently leads to the empirical initiation of broad-spectrum antibiotics, a practice that, while life-saving in confirmed cases, contributes to the escalating crisis of antimicrobial resistance (AMR) and adverse long-term outcomes in infants without infection [1, 3, 16, 17]. The delicate balance between

timely, effective treatment and judicious antibiotic use is central to improving neonatal outcomes and preserving the efficacy of existing antimicrobials. This narrative review aims to provide a comprehensive overview of neonatal sepsis, focusing on the intricate diagnostic challenges, the rationale behind empirical antibiotic choices, and the pivotal role of antimicrobial stewardship in optimizing patient care. We will explore the pathophysiology, epidemiology, clinical presentation, current diagnostic and management strategies, complications, special populations, and existing controversies and evidence gaps, drawing upon landmark studies, recent meta-analyses, and authoritative guidelines from organizations such as the American Academy of Pediatrics (AAP), World Health Organization (WHO), and European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).

Pathophysiology

Neonatal sepsis arises from an immature immune system that is uniquely vulnerable to infection. The neonatal immune response is characterized by functional deficiencies in both innate and adaptive immunity, including impaired neutrophil chemotaxis, reduced phagocytic activity, decreased complement levels, and a naive T-cell repertoire [8]. These factors render neonates less capable of localizing infection and mounting an effective systemic response, often leading to a rapid progression from localized infection to systemic sepsis. Pathogens can be acquired vertically from the mother (transplacental, ascending infection, or during passage through the birth canal) or horizontally from the environment (nosocomial infections) [2]. The inflammatory cascade triggered by invading pathogens involves the release of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) and anti-inflammatory mediators, leading to widespread endothelial dysfunction, microvascular compromise, and ultimately, multi-organ failure [8]. Genetic predispositions and epigenetic factors are also increasingly recognized as contributors to individual susceptibility and severity of neonatal sepsis [28].

Epidemiology

Neonatal sepsis is broadly categorized into early-onset sepsis (EOS) and late-onset sepsis (LOS), based on the timing of infection [2]. EOS typically occurs within the first 72 hours of life, though some definitions extend this to 7 days, particularly for infants hospitalized since birth [2]. It is primarily acquired vertically, with Group B Streptococcus (GBS) and *Escherichia coli* being the predominant pathogens in high-income countries [1]. Universal GBS screening and intrapartum antibiotic prophylaxis have significantly reduced the incidence of GBS EOS in many regions [1, 20, 21]. However, this success has been accompanied by a relative increase in *E. coli* infections and the emergence of resistant strains [1, 9]. In LMICs, the pathogen profile for EOS is often dominated by multidrug-resistant Gram-negative organisms [1].

LOS occurs after 72 hours (or 7 days) of life and is typically associated with nosocomial acquisition from the hospital environment or community [2]. Risk factors include prematurity, prolonged hospitalization, invasive procedures (e.g., central venous catheters, mechanical ventilation), and prolonged antibiotic exposure [1]. Coagulase-negative *Staphylococci* (CoNS) are the most common cause of LOS in NICUs in high-income countries, followed by Gram-negative bacteria like *Klebsiella* and *Enterobacter* species [1]. Fungal infections, particularly *Candida* species, are also significant contributors to LOS, especially in ELBW infants [1]. The global epidemiology of neonatal sepsis is dynamic, influenced by local infection control practices, antibiotic prescribing patterns, and the prevalence of resistant organisms [1, 27].

Clinical Presentation

The clinical signs of neonatal sepsis are notoriously non-specific and can be subtle, making early recognition challenging [2]. Neonates, particularly preterm infants, often lack the classic signs of infection seen in older children and adults. Instead, they may present with a constellation of vague symptoms, including [8]:

- **Respiratory distress:** Tachypnea, grunting, nasal flaring, retractions, apnea.
- **Thermoregulation instability:** Hypothermia (more common than fever), temperature lability.
- **Cardiovascular signs:** Tachycardia, bradycardia, poor perfusion, hypotension.
- **Neurological signs:** Lethargy, irritability, poor suck, hypotonia, seizures.

- **Gastrointestinal signs:** Poor feeding, vomiting, abdominal distension, diarrhea.
- **Skin changes:** Pallor, mottling, jaundice, petechiae.

These non-specific signs necessitate a high index of suspicion in any neonate exhibiting clinical deterioration, especially in the presence of risk factors. The absence of definitive clinical markers underscores the reliance on a combination of clinical judgment, laboratory investigations, and risk assessment tools for timely diagnosis.

Diagnosis

The accurate and timely diagnosis of neonatal sepsis is critical but fraught with challenges. The gold standard for diagnosis remains a positive bacterial culture from a sterile site (e.g., blood, cerebrospinal fluid, urine) [2]. However, cultures can take 24-72 hours to yield results, and many clinically suspected cases are culture-negative, leading to diagnostic uncertainty and prolonged empirical antibiotic use [2, 3].

Conventional Diagnostic Tools

- **Complete Blood Count (CBC) with Differential:** While commonly used, parameters such as total white blood cell count, absolute neutrophil count, immature-to-total neutrophil ratio (I:T ratio), and platelet count have limited sensitivity and specificity for neonatal sepsis [8].
- **C-Reactive Protein (CRP):** An acute phase reactant, CRP levels rise in response to inflammation. Serial CRP measurements can be useful, but a single elevated CRP lacks sufficient diagnostic accuracy, and levels may not rise until 6-12 hours after infection onset [8].
- **Procalcitonin (PCT):** PCT is a prohormone that increases significantly during bacterial infections. It has shown promise as a more sensitive and specific biomarker than CRP, particularly for guiding antibiotic duration [13]. However, its utility in the immediate postnatal period can be confounded by physiological elevations [8].
- **Cerebrospinal Fluid (CSF) Analysis:** Lumbar puncture is essential for diagnosing meningitis, a severe complication of sepsis. CSF cell count, glucose, and protein levels, along with culture, are crucial [8].

Advanced Diagnostic Modalities and Risk Assessment Tools

To overcome the limitations of conventional methods, significant research has focused on developing more rapid and accurate diagnostic tools:

- **Molecular Diagnostics:** Polymerase chain reaction (PCR) assays and other nucleic acid amplification tests offer rapid detection of bacterial DNA, potentially reducing the time to diagnosis. However, their clinical utility is still evolving, particularly in distinguishing colonization from true infection [19].
- **Novel Biomarkers:** Research into new biomarkers, such as IL-6, IL-8, presepsin, and soluble CD14 subtype (sCD14-ST), aims to identify early indicators of sepsis with higher predictive value [2, 19]. However, none have yet replaced conventional methods as standalone diagnostic tests.
- **Neonatal Early-Onset Sepsis Calculator:** Developed by Kaiser Permanente, this risk assessment tool integrates maternal risk factors (e.g., GBS status, intrapartum fever, duration of rupture of membranes) and clinical signs in the neonate to estimate the probability of EOS [4, 10]. It has been shown to safely reduce unnecessary antibiotic exposure in well-appearing infants by guiding risk-stratified management [14, 15]. The AAP 2018 guidelines recommend its use as one of the strategies for managing neonates at risk for EOS [4, 5].

Management

The management of neonatal sepsis involves a multi-pronged approach encompassing timely empirical antibiotic therapy, supportive care, and robust antimicrobial stewardship.

Empirical Antibiotic Choices

The initial choice of empirical antibiotics is critical and must be guided by the likely pathogens, local epidemiology, and resistance patterns. Delay in appropriate antibiotic administration is associated with increased mortality [1].

- **Early-Onset Sepsis (EOS):** For suspected EOS, the recommended empirical regimen in many high-income settings typically includes ampicillin (or penicillin G) combined with an aminoglycoside (e.g., gentamicin) [1, 4]. This combination provides broad coverage against GBS, *E. coli*, and other common EOS pathogens. In regions with high rates of ampicillin-resistant *E. coli*, a third-generation cephalosporin (e.g., cefotaxime) may be considered, though this should be balanced against concerns for resistance development [1].
- **Late-Onset Sepsis (LOS):** Empirical therapy for LOS often requires broader coverage due to the diverse range of potential nosocomial pathogens, including CoNS, Gram-negative bacteria, and fungi. A common regimen includes vancomycin (for Gram-positive coverage, including methicillin-resistant *Staphylococcus aureus* [MRSA] and CoNS) combined with an aminoglycoside or a third-generation cephalosporin [1]. In cases of suspected fungal sepsis, amphotericin B or fluconazole may be added [1].

Duration of therapy is typically 7-10 days for uncomplicated bacterial sepsis and longer for specific infections like meningitis (14-21 days) or fungal sepsis. De-escalation to narrower-spectrum antibiotics should occur once culture results and sensitivities are available [1].

Non-Pharmacological Management and Supportive Care

Supportive care is paramount in managing neonatal sepsis and includes:

- **Fluid and Electrolyte Management:** Maintaining adequate hydration and electrolyte balance is crucial, especially in septic shock.
- **Respiratory Support:** Mechanical ventilation may be required for respiratory failure.
- **Cardiovascular Support:** Vasoactive medications (e.g., dopamine, dobutamine) may be necessary to maintain blood pressure and perfusion in septic shock [11].
- **Nutritional Support:** Early enteral feeding, preferably with breast milk, is encouraged to support gut integrity and immune function [22].
- **Temperature Control:** Maintaining normothermia is essential.
- **Infection Control:** Strict adherence to hand hygiene, aseptic techniques for invasive procedures, and environmental cleaning are vital to prevent nosocomial infections [1].

Antimicrobial Stewardship

Antimicrobial stewardship programs (ASPs) are indispensable in NICUs to optimize antibiotic use, reduce AMR, and improve patient outcomes [1, 3, 24]. Key strategies include [1, 3, 25, 26]:

- **Development and Implementation of Local Guidelines:** Tailoring empirical antibiotic regimens and duration of therapy based on local epidemiology and resistance patterns.
- **Prospective Audit and Feedback:** Regular review of antibiotic prescriptions by an ASP team with feedback to prescribers.
- **Pre-authorization/Restriction:** Requiring approval for certain broad-spectrum antibiotics.
- **Rapid Diagnostics:** Utilizing rapid diagnostic tests to facilitate early de-escalation or discontinuation of antibiotics.
- **Education:** Ongoing education for healthcare providers on appropriate antibiotic use.

- **Use of Sepsis Calculators and Biomarkers:** Integrating tools like the Neonatal Early-Onset Sepsis Calculator and serial PCT measurements to guide clinical decisions [1, 13, 14].
- **Quality Improvement Initiatives:** Implementing structured quality improvement (QI) projects to address specific challenges in antibiotic use, such as reducing antibiotic exposure for culture-negative sepsis [3].

Successful ASPs have demonstrated significant reductions in antibiotic use, decreased rates of AMR, and improved clinical outcomes in NICUs [3, 25].

Complications

Neonatal sepsis can lead to a range of severe complications, both acute and long-term, significantly impacting neonatal morbidity and mortality [1].

- **Acute Complications:** These include septic shock, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), acute kidney injury (AKI), necrotizing enterocolitis (NEC), and meningitis [8]. Meningitis, in particular, carries a high risk of neurodevelopmental impairment.
- **Long-Term Complications:** Survivors of neonatal sepsis, especially preterm infants, are at increased risk for adverse neurodevelopmental outcomes, including cerebral palsy, cognitive impairment, hearing loss, and visual impairment [1, 13]. Prolonged or unnecessary antibiotic exposure itself has been linked to an increased risk of NEC, late-onset sepsis, retinopathy of prematurity, and bronchopulmonary dysplasia [3, 16, 17]. Disturbances in the developing microbiome due to antibiotics may also have long-term health implications [3].

Special Populations

Certain neonatal populations are at higher risk for sepsis and require particular consideration:

- **Preterm Infants:** Due to their extreme immaturity, underdeveloped immune systems, and frequent need for invasive procedures, preterm infants (especially ELBW) are highly susceptible to both EOS and LOS [1, 8]. Their clinical presentation can be even more subtle, and their response to infection more severe. Management often involves a lower threshold for initiating antibiotics and a more cautious approach to de-escalation.
- **Infants with Congenital Anomalies or Immunodeficiencies:** These infants have underlying vulnerabilities that increase their risk of infection and may require individualized management strategies, including specific prophylactic measures or tailored antibiotic regimens.
- **Infants in LMICs:** Neonates in LMICs face unique challenges, including higher incidence of sepsis, different pathogen profiles (often with higher rates of multidrug resistance), limited access to advanced diagnostics, and resource constraints for optimal management and supportive care [1, 7]. WHO guidelines often provide simplified, evidence-based recommendations for these settings [6].

Controversies and Evidence Gaps

Despite significant advancements, several controversies and evidence gaps persist in the field of neonatal sepsis:

- **Definition of Sepsis:** A universally accepted, clear consensus definition for neonatal sepsis remains elusive, leading to variability in research and clinical practice [2]. The exclusion of neonates from the 2024 consensus statement on pediatric sepsis and septic shock highlights this ongoing challenge [1].
- **Optimal Biomarker Use:** While several biomarkers show promise, their optimal integration into clinical algorithms for diagnosis and management, particularly for guiding antibiotic duration, requires further research and validation [2, 19].

- **Duration of Empirical Antibiotics:** The optimal duration of empirical antibiotic therapy for culture-negative suspected sepsis remains a subject of debate. Balancing the risk of undertreatment with the harms of prolonged exposure is a continuous challenge [3].
- **Impact of Microbiome Disruption:** The long-term consequences of early-life antibiotic exposure on the developing neonatal microbiome and its impact on health outcomes (e.g., allergies, obesity, neurodevelopment) are areas of active research [3].
- **Novel Therapeutic Strategies:** Beyond antibiotics, research into immunomodulatory therapies, probiotics, and other adjunctive treatments for neonatal sepsis is ongoing, but robust evidence for widespread clinical application is still lacking.
- **Addressing AMR in LMICs:** Developing effective, sustainable strategies to combat AMR in neonatal sepsis in resource-limited settings, where the burden is highest, is a critical global health priority [1, 7].

Conclusion

Neonatal sepsis continues to be a major global health concern, demanding vigilance, rapid diagnosis, and judicious management. The non-specific clinical presentation and limitations of current diagnostic tools necessitate a high index of suspicion and the empirical initiation of antibiotics, particularly in high-risk neonates. However, the escalating threat of antimicrobial resistance and the adverse long-term effects of unnecessary antibiotic exposure underscore the critical importance of antimicrobial stewardship. Key clinical takeaways include the need for individualized risk assessment, guided by tools like the Neonatal Early-Onset Sepsis Calculator, and the implementation of evidence-based local guidelines for empirical antibiotic choices. Robust ASPs, incorporating prospective audit and feedback, rapid diagnostics, and continuous education, are essential to optimize antibiotic use in NICUs.

Practice gaps remain in achieving a universally accepted definition of neonatal sepsis, refining the utility of novel biomarkers, and determining the optimal duration of antibiotic therapy for culture-negative cases. Future research priorities should focus on developing more rapid and accurate diagnostic tests, understanding the long-term impact of antibiotic exposure on the neonatal microbiome, and exploring novel therapeutic and preventive strategies. Collaborative efforts, particularly in LMICs, are crucial to address the global burden of neonatal sepsis and mitigate the rise of multidrug-resistant pathogens, ultimately improving outcomes for the most vulnerable patients.

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