

## ADVANCES AND CHALLENGES IN THE TREATMENT OF NEONATAL INFECTIONS: A NARRATIVE REVIEW

Thalyta Alves Teixeira<sup>1</sup>  
Afrânio Côgo Destefani<sup>2</sup>  
Vinícius Côgo Destefani<sup>3</sup>

**ABSTRACT:** Neonatal infections continue to be a significant cause of morbidity and mortality worldwide, particularly in preterm and low birth-weight infants. Despite advances in neonatal care, the incidence of neonatal sepsis remains high. This narrative review summarizes the latest developments and challenges in treating neonatal infections. Key topics include antimicrobial therapy, immunotherapy, and prevention strategies. Optimizing antimicrobial use through appropriate selection, dosing, and monitoring is essential, but preventing infections should be the priority. Infection control bundles, maternal immunization, and antimicrobial stewardship initiatives have shown promise in reducing neonatal infections and antibiotic resistance. However, the paucity of high-quality studies in neonates is a significant barrier to advancing treatment, highlighting the urgent need for more research in this field.

**Keywords:** Neonatal Infections. Antimicrobial Therapy. Immunotherapy. Infection. Prevention. Antibiotic Resistance.

### INTRODUCTION

Neonatal infections continue to be a significant cause of morbidity and mortality worldwide, especially in preterm and low birth-weight infants (1). Despite advances in neonatal care, the incidence of neonatal sepsis remains around 7 per 1,000 live births (2). The urgency of this issue cannot be overstated, as the epidemiology of neonatal infections has shifted over the past decade, with a reduction in early-onset sepsis and a relative increase in nosocomial infections, particularly those caused by coagulase-negative staphylococci (3).

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<sup>1</sup>UNIFEV .

<sup>2</sup> Santa Casa de Misericórdia de Vitoria Higher School of Sciences - EMESCAM. Santa Luíza - Vitória - ES - Brazil Molecular Dynamics and Modeling Laboratory (DynMolLab)

<sup>3</sup> Molecular Dynamics and Modeling Laboratory (DynMolLab) - Av. N. S. da Penha, 2190, Santa Luíza - Vitória - ES - Brazil

The immature immune system of neonates, especially those born preterm, makes them highly susceptible to infections (4). Traditional approaches to enhance neonatal host defense have included granulocyte infusions, fresh frozen plasma, exchange blood transfusions, and immunoglobulin therapy. However, the latest research has focused on novel strategies to boost the neonate's endogenous immune mechanisms and optimize antimicrobial therapy (5). This narrative review summarizes the latest advances and emphasizes their crucial role in the ongoing battle against neonatal infections.

## METHODOLOGY

A literature search was conducted in PubMed, Scopus, Web of Science, and Cochrane Library databases using combinations of the keywords "neonate," "newborn," "infection," "sepsis," "treatment," "antibiotics," "immunotherapy," and "prevention." Articles published in English between 1996 and 2023 were considered. Reference lists of included studies and relevant reviews were also screened. The most pertinent and high-quality studies were selected for inclusion, focusing on randomized controlled trials, systematic reviews, and expert guidelines. Critical information was extracted, synthesized, and organized into thematic sections.

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## RESULTS

### Antimicrobial Therapy

Empiric antibiotic regimens for neonatal sepsis typically include ampicillin plus an aminoglycoside or a third-generation cephalosporin (6). However, the increasing prevalence of antibiotic-resistant pathogens, particularly among gram-negative bacteria, presents a significant challenge (7). Judicious use of antibiotics is critical to prevent further development of resistance.

Newer antibiotics, such as cefiderocol and eravacycline, have shown promise against multidrug-resistant gram-negative infections in adults, but data in neonates are limited (8). Some older antibiotics, like colistin, are being reexamined to treat resistant infections, although toxicity concerns remain (9).

Optimizing antibiotic dosing is vital in neonates, given their unique pharmacokinetics. Extended-interval dosing of aminoglycosides is now preferred to minimize toxicity (6,10). Therapeutic drug monitoring can help personalize dosing, especially for drugs with narrow therapeutic indices (11).

## **Immunotherapy**

Various immunomodulatory therapies have been investigated to enhance neonatal host defense against infection. Intravenous immunoglobulin (IVIG) has been extensively studied, but evidence for its efficacy in neonatal sepsis is conflicting (12). A 2020 Cochrane review concluded that IVIG may reduce mortality in infants with suspected or proven infection, but study quality was low (13).

Granulocyte and granulocyte-macrophage colony-stimulating factors (G-CSF and GM-CSF) stimulate neutrophil production and function. Small trials have suggested potential benefits in neonatal sepsis, but more extensive studies are needed (14). A 2003 Cochrane review found no significant reduction in mortality with G-CSF or GM-CSF treatment (15).

Pentoxifylline, a phosphodiesterase inhibitor with anti-inflammatory effects, showed promise in small studies of neonatal sepsis (16). However, a 2015 Cochrane review found insufficient evidence to support its use (17).

Probiotics and lactoferrin have been proposed to prevent neonatal infections by promoting healthy gut colonization and enhancing mucosal immunity. Meta-analyses suggest probiotics may reduce the risk of necrotizing enterocolitis and sepsis in preterm infants, although optimal strain selection and dosing remain unclear (18,19). Lactoferrin supplementation may decrease late-onset sepsis, but more research is warranted (20).

## **Prevention Strategies**

Infection prevention is paramount in neonatal care settings. Strict hand hygiene, aseptic techniques, and minimizing invasive procedures are crucial to reducing nosocomial infections (2). Bundles combining multiple evidence-based practices have decreased central

line-associated bloodstream infections and ventilator-associated pneumonia rates in NICUs (21,22).

Maternal immunization is an attractive strategy to protect infants via passive placental antibody transfer. Influenza and pertussis vaccination during pregnancy reduces disease in young infants (23). Potential maternal vaccines against group B streptococcus and respiratory syncytial virus are developing (24).

Antimicrobial stewardship programs are critical to promote appropriate antibiotic use and limit resistance. Prospective audits, feedback, and automatic stop orders are effective stewardship interventions in NICUs (25). Rapid diagnostic tests enabling earlier targeted therapy are an active area of research (26).

## DISCUSSION

Despite the progress in developing new antibiotics and immunotherapies, managing neonatal infections remains a significant challenge. The vulnerability of the neonatal population, the changing epidemiology of pathogens, and the looming threat of antibiotic resistance all contribute to the urgency of this issue. While some progress has been made, evidence for many adjunctive treatments is still limited and inconsistent, underscoring the need for further research and innovation.

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Optimizing antimicrobial therapy through appropriate antibiotic selection, dosing, and monitoring is essential. However, preventing infections should be the priority. Infection control bundles, maternal immunization, and antimicrobial stewardship initiatives have reduced neonatal infections and antibiotic resistance.

The paucity of high-quality studies in neonates is a significant barrier to advancing treatment. This underscores the urgent need for more research in this field. Challenges include ethical concerns, low recruitment, high practice variability, and difficulty assessing subtle outcomes. Your contribution to overcoming these challenges through novel trial designs and multicenter collaborations is crucial to evaluate new therapies efficiently. Long-term outcomes beyond survival, such as neurodevelopment and immune function, should also be considered.

As the pathogenesis of neonatal sepsis is further elucidated, more targeted immunomodulatory strategies may emerge, offering hope in the fight against neonatal infections. For example, therapies that enhance innate immune training or correct immune cell dysfunction could hold promise (27). Systems biology approaches integrating multiple "-omics" data may enable better patient stratification for precision therapies (28). This potential for future breakthroughs should inspire optimism in the medical community.

## CONCLUSION

In conclusion, while some strides have been made in treating neonatal infections, significant challenges remain. Judicious use of antibiotics, strict infection control practices, and ongoing research into novel therapies are all critical pieces of the puzzle. However, to effectively tackle this complex problem and improve outcomes for these most vulnerable patients, strong collaboration between clinicians, researchers, policymakers, and parents is essential. Only through such collaborative efforts can we hope to make significant progress in neonatal care.

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