Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 9s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Neonatal Sepsis And Antibiotic Resistance: Emerging Challenges And Future Perspectives

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Cite this paper as: Sachin kumarsharma, Mohit Buddhadev, J John Kirubakaran, Hirni J Patel, Anshul J Harnawa. S P Srinivas Nayak, (2025) Neonatal Sepsis And Antibiotic Resistance: Emerging Challenges And Future Perspectives. *Journal of Neonatal Surgery*, 14 (9s), 536-542.

ABSTRACT

Neonatal sepsis remains a major cause of neonatal morbidity and mortality worldwide, particularly in low- and middle-income countries. The emergence of antibiotic-resistant bacterial strains has further complicated treatment options, leading to increased mortality and prolonged hospital stays. This review explores the epidemiology, risk factors, and common bacterial pathogens associated with neonatal sepsis. It also highlights the mechanisms of antibiotic resistance and current treatment strategies, including the limitations of broad-spectrum antibiotics. Additionally, we discuss the critical challenges in managing neonatal sepsis, such as the lack of neonatal-specific antibiotics and antibiotic stewardship gaps. Finally, future directions, including alternative therapies such as phage therapy, probiotics, and vaccines, are explored as potential solutions to combat neonatal sepsis and antibiotic resistance. Addressing these challenges requires a multidisciplinary approach to enhance infection control, improve antimicrobial stewardship, and develop novel therapeutic interventions to reduce the burden of neonatal sepsis.

Keywords: *Neonatal sepsis, antibiotic resistance, multidrug-resistant bacteria, neonatal infections, antimicrobial stewardship, phage therapy, probiotics, alternative therapies, neonatal microbiome, bacterial pathogens*

1. INTRODUCTION

Neonatal sepsis remains a significant global health concern, contributing to high morbidity and mortality rates among newborns, especially in low- and middle-income countries. It is a life-threatening condition caused by systemic infections, primarily due to bacterial pathogens. The increasing prevalence of antibiotic resistance among neonatal sepsis pathogens has further complicated treatment outcomes, leading to a rising burden on healthcare systems worldwide [1].

Despite advancements in neonatal intensive care and antimicrobial therapies, multidrug-resistant (MDR) organisms are increasingly implicated in neonatal sepsis, making early diagnosis and effective treatment challenging [2]. The overuse and misuse of antibiotics in neonatal care settings have accelerated resistance mechanisms, demanding urgent global efforts to enhance antimicrobial stewardship and develop novel therapeutic strategies [3]. This review explores the epidemiology, risk factors, and the growing threat of antibiotic resistance in neonatal sepsis while highlighting potential solutions for improved neonatal care.

2. EPIDEMIOLOGY & RISK FACTORS

2.1 Incidence of Neonatal Sepsis

Neonatal sepsis is classified into early-onset sepsis (EOS) (occurring within the first 72 hours of life) and late-onset sepsis (LOS) (occurring after 72 hours) [4]. The global incidence of neonatal sepsis varies, with higher rates in resource-limited settings. Studies estimate that 3 to 10 per 1,000 live births are affected by neonatal sepsis in developed countries, whereas incidence rates can exceed 30 per 1,000 live births in developing nations [5]. Neonatal sepsis accounts for nearly 20% of all neonatal deaths worldwide, emphasizing the urgent need for improved preventive and therapeutic strategies [6].

Table.1 neonatal sepsis incidence

Region	Incidence Rate (per 1,000 live births)	Neonatal Deaths Due to Sepsis (%)
Developed Countries	3 – 10	~5%
Developing Countries	>30	~20%

This (table.1) summarizes the variation in neonatal sepsis incidence and its contribution to neonatal mortality in different regions. Let me know if you need further refinements[4]

Neonatal sepsis remains a significant health concern in India (table.2), with incidence and mortality rates varying across different regions and studies.[5][6]

Table.2 incidence and mortality in India

Study/Region	Incidence Rate (per 1,000 live births)	Case Fatality Rate (%)
Rural Gadchiroli (1998-2001)	111	Data not specified
Rural Gadchiroli (2016-2019)	19	Data not specified
Hospital-based studies	30	~20%
Community-based studies	27 – 170	Data not specified
National Estimate	170	25% - 65%

2.2 Causes and Common Pathogens

The causative agents of neonatal sepsis vary based on geographical location, hospital practices, and antibiotic policies.

Early-onset sepsis (EOS): Commonly caused by pathogens acquired from the maternal genital tract, including Group B Streptococcus (GBS), Escherichia coli, Listeria monocytogenes, and Klebsiellapneumoniae [7].

Late-onset sepsis (LOS): Frequently linked to hospital-acquired infections and involves pathogens such as Staphylococcus aureus, Coagulase-negative Staphylococci (CoNS), Pseudomonas aeruginosa, and multidrug-resistant Klebsiellapneumoniae [8].

In recent years, multidrug-resistant Gram-negative bacteria (e.g., extended-spectrum beta-lactamase (ESBL)-producing E. coli and Klebsiella) have emerged as leading causes of neonatal sepsis, complicating treatment regimens and leading to

higher mortality rates [9].

2.3 Hospital-Acquired Infections (HAIs) and Risk Factors

Hospital-acquired neonatal sepsis is primarily linked to prolonged hospitalization, invasive procedures (e.g., mechanical ventilation, central venous catheters), and overcrowded neonatal intensive care units (NICUs) [10].

2.4 Key risk factors for neonatal sepsis include:

Prematurity and Low Birth Weight (<2500g): Premature neonates have underdeveloped immune systems, making them more vulnerable to infections [11].

Prolonged Rupture of Membranes (>18 hours): Increases the risk of ascending bacterial infections from the maternal genital tract [12].

Mechanical Ventilation and Central Line Insertion: Creates direct entry points for nosocomial pathogens, increasing infection risk [13].

Use of Broad-Spectrum Antibiotics: Leads to microbiome disruption and selection of resistant organisms [13].The high burden of HAIs in NICUs underscores the importance of stringent infection control measures, including hand hygiene, antibiotic stewardship, and surveillance programs, to combat neonatal sepsis and antibiotic resistance effectively [14]. Pathogens & Resistance Mechanisms

2.5 Common Bacterial Pathogens in Neonatal Sepsis

Several bacterial pathogens are responsible for neonatal sepsis, many of which have developed resistance to commonly used antibiotics. The most frequently implicated organisms include: Gram-negative bacteria: Klebsiellapneumoniae, Escherichia coli, Pseudomonas aeruginosa, Acinetobacterbaumannii [15]. Gram-positive bacteria: Staphylococcus aureus, Coagulase-negative Staphylococci (CoNS), Group B Streptococcus (GBS) [15]. Other emerging pathogens: Enterobacter spp, Listeria monocytogenes [16].

2.5 Unique pathophysiology of neonatal sepsis

Undertaking drug trials in neonates is challenging. Neonates are a heterogeneous population, with significant variation in postnatal and gestational age and weight. Within the short neonatal period of 4 weeks, important changes occur in the functional maturation of different organ systems. These factors can result in rapidly changing drug absorption, distribution, metabolism and excretion. Furthermore, variability in antibiotic exposure is often complicated by organ dysfunction and limited drug clearance because of comorbid conditions.[16]

Consequently, high-quality pharmacokinetic and pharmacodynamic knowledge is lacking for many drugs used in neonates, which has resulted in considerable variation in dosing guidelines across different formularies.16 In addition, combination antibiotic therapy is often prescribed in neonates, which may complicate estimates of optimal pharmacokinetic and pharmacodynamic parameters. Another challenge lies in the definition and diagnosis of neonatal sepsis, which is the most common indication for antibiotic prescription in this age group. The variable clinical manifestation of neonatal sepsis includes a broad spectrum of illness, and its diagnosis is reliant on combinations of nonspecific clinical symptoms and signs that may be indistinguishable from other minor or life-threatening conditions, including hypoxic complications from a difficult delivery. Thus, definitions of neonatal sepsis vary, resulting in the inclusion of non-standardized populations within clinical trials. [17]

Further challenges include the high rates of culture-negative sepsis evident in neonates – influenced by exposure to intrapartum and postnatal antibiotics – the difficulty of obtaining adequate neonatal blood culture volumes and limited microbiological capacity in many health-care settings. [18].

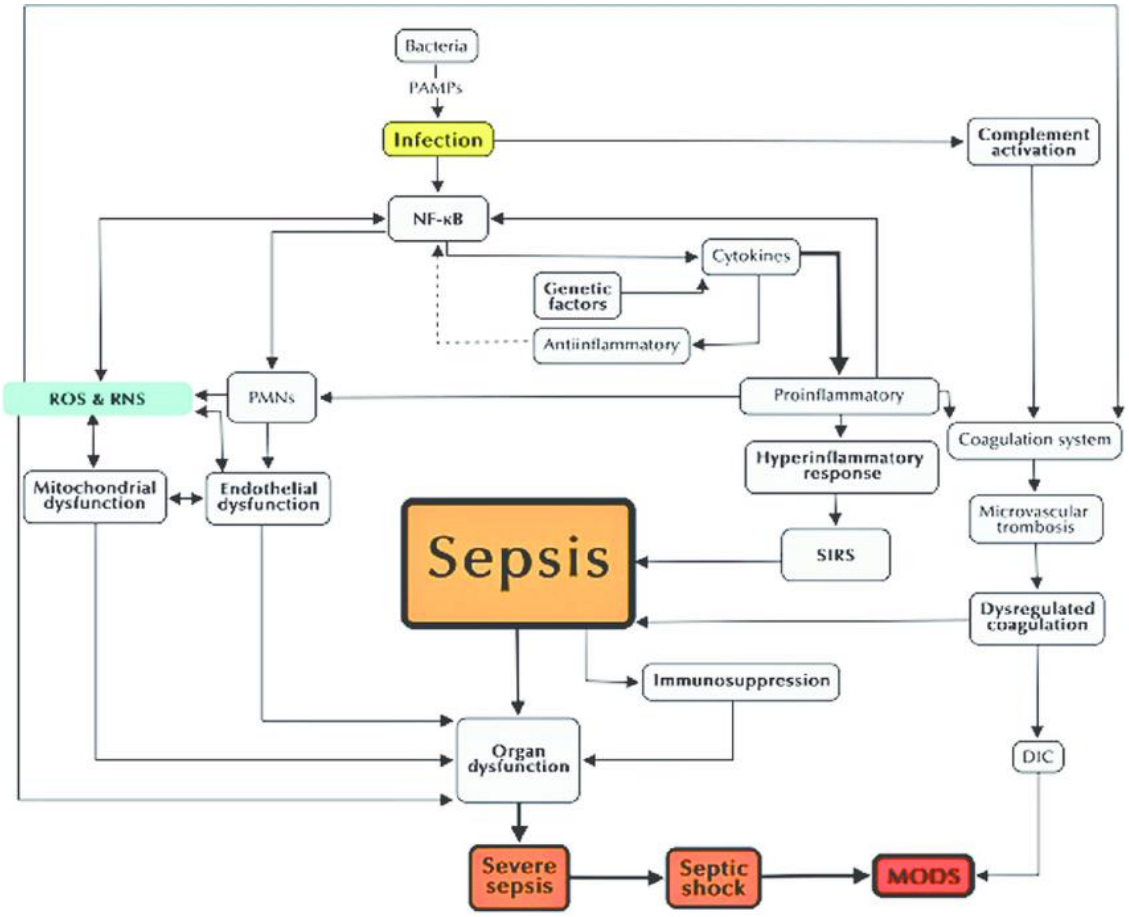

Figure1:- Pathophysiology of neonatal sepsis

3. MECHANISMS OF ANTIBIOTIC RESISTANCE

The increasing prevalence of antibiotic resistance in neonatal sepsis is due to various bacterial resistance mechanisms, including: Beta-Lactamase Production: Many Gram-negative bacteria, including Klebsiellapneumoniae and E. coli, produce extended-spectrum beta-lactamases (ESBLs) and carbapenemases, rendering beta-lactam antibiotics (penicillins, cephalosporins, carbapenems) ineffective [19].

Efflux Pumps: Bacteria like Pseudomonas aeruginosa utilize efflux pumps to actively expel antibiotics, reducing drug efficacy [20]. Biofilm Formation: Staphylococcus aureus and CoNS form biofilms on medical devices (e.g., catheters, ventilators), leading to persistent infections resistant to multiple antibiotics [21]. Modification of Drug Targets: MRSA (Methicillin-Resistant Staphylococcus aureus) alters penicillin-binding proteins, making beta-lactam antibiotics ineffective [22].Horizontal Gene Transfer: Resistance genes, including those for aminoglycoside and fluoroquinolone resistance, can be transferred between bacterial species, accelerating the spread of resistance [23]. The rise of multidrug-resistant neonatal sepsis pathogens necessitates the development of alternative treatments, including phage therapy, probiotics, and immunomodulatory approaches, along with strict antimicrobial stewardship programs to minimize antibiotic misuse [24].

4. CURRENT TREATMENT STRATEGIES

The treatment of neonatal sepsis involves empirical antibiotic therapy followed by targeted treatment based on culture and sensitivity results.

4.1 First-Line Empirical Therapy:

Ampicillin in combination with gentamicin is widely used for the treatment of early-onset sepsis, providing broad-spectrum coverage against common neonatal pathogens, including *Group B Streptococcus (GBS)*, *Escherichia coli (E. coli)*, and *Listeria monocytogenes*. This regimen is particularly effective due to the synergistic action of ampicillin, a beta-lactam antibiotic targeting cell wall synthesis, and gentamicin, an aminoglycoside that disrupts bacterial protein synthesis. However, in healthcare settings with higher resistance to ampicillin, cefotaxime combined with amikacin is often the preferred alternative. Cefotaxime, a third-generation cephalosporin, exhibits enhanced activity against Gram-negative bacteria, while amikacin, a potent aminoglycoside, offers additional coverage against resistant strains.

For the management of multidrug-resistant (MDR) infections, meropenem along with vancomycin is commonly utilized, particularly in cases involving extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* and methicillin-resistant *Staphylococcus aureus* (MRSA). Meropenem, a broad-spectrum carbapenem, effectively targets ESBL-producing organisms, while vancomycin, a glycopeptide antibiotic, is crucial for treating MRSA infections. In more severe cases, where carbapenem-resistant pathogens are implicated, colistin or polymyxin B is employed to combat difficult-to-treat Gram-negative bacteria such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. These polymyxins function by disrupting bacterial membranes, making them essential last-resort options in antibiotic therapy.

Furthermore, novel antimicrobial agents like ceftazidime/avibactam and cefiderocol have been developed to target MDR Gram-negative bacteria. Ceftazidime/avibactam is a combination of a third-generation cephalosporin with a beta-lactamase inhibitor, providing activity against resistant *Enterobacteriaceae*, including those producing carbapenemases. Cefiderocol, a siderophore cephalosporin, uniquely exploits bacterial iron uptake mechanisms to penetrate the outer membrane of resistant Gram-negative bacteria, offering a promising approach in combating MDR infections. These novel therapeutic options are particularly valuable in an era of rising antimicrobial resistance, where conventional antibiotics often fail to achieve effective bacterial eradication. [24-28]

4.2 Adjunct Therapies

- **Lactoferrin& Probiotics**: Helps modulate neonatal immune response and reduce sepsis risk [29].
- **Monoclonal Antibodies (e.g., AR-301 against *S. aureus*)**: Emerging as targeted therapies [30].

1. Challenges, Gaps, and Future Directions

One of the major challenges in managing neonatal sepsis is the **lack of new neonatal-specific antibiotics**, as pharmaceutical companies have shown limited interest in developing novel antimicrobial agents for this vulnerable population [24]. Additionally, the **overuse of broad-spectrum antibiotics** in NICUs has led to a disruption of the neonatal microbiome and a surge in resistant bacterial strains, further complicating treatment [25]. There is an urgent need for **stronger antibiotic stewardship programs** that promote the rational use of antimicrobials, reduce unnecessary prescriptions, and prevent the emergence of drug-resistant infections [26].Future strategies include **alternative therapies**, such as immune-boosting agents that enhance neonatal defenses against infections [27]. **Phage therapy**, an innovative approach using bacteriophages to selectively target and eliminate resistant bacteria, holds promise for treating multidrug-resistant neonatal sepsis [28]. The use of **probiotics** has also been explored as a preventive strategy to support a healthy neonatal gut microbiome and reduce the risk of infections [29]. Moreover, the **development of vaccines** against common neonatal sepsis pathogens, such as *GBS* and *Klebsiellapneumoniae*, could provide long-term protection and reduce the incidence of neonatal infections [30].

5. DISCUSSION

Neonatal sepsis is still a major worldwide health concern, and low- and middle-income nations bear a disproportionately heavy cost of it. The therapy of newborn sepsis is made more difficult by the growing incidence of multidrug-resistant (MDR) pathogens, which also raises morbidity, mortality, and medical expenses. Despite improvements in newborn care, the dynamic nature of bacterial resistance and the absence of regionally consistent treatment regimens make early detection and successful therapy difficult [31]. The growing resistance of newborn sepsis bacteria to first-line antibiotics such as ampicillin and gentamicin emphasizes the critical need for better antimicrobial stewardship programs. Overuse and abuse of broad-spectrum antibiotics promote resistance, requiring the use of tailored treatment based on local epidemiology and antimicrobial susceptibility patterns [31]. Reducing resistance rates and improved clinical results in neonatal intensive care units (NICUs) can be done in a major way via the use of strong preventive measures and customized antibiotic administration.

The scarcity of new medicines made especially to treat infections in newborns is another significant worry. Because of financial limitations & legal hurdles, drug companies have shown little interest in creating novel antibacterial medicines for newborns. Consequently, physicians often turn to off-label antibiotic usage, which results in inconsistent treatment outcomes and heightened development of resistance [32]. Future research should concentrate on creating neonatal-specific antibiotics with better pharmacokinetic and pharmacodynamic characteristics to increase treatment effectiveness.

Promising approaches to addressing newborn sepsis and antibiotic resistance include phage treatment, immunomodulatory drugs, and probiotics. Phage therapy, which targets certain bacterial pathogens using bacteriophages, has shown promise in the treatment of multidrug-resistant illnesses and may be investigated further for use in neonatal settings [31]. Similarly, probiotics and lactoferrin have been studied for their ability to modulate newborn gut microbiota and reduce the risk of sepsis, especially in preterm babies [33]. In addition, the creation of vaccinations to prevent prevalent newborn sepsis bacteria including Klebsiella pneumoniae and Group B Streptococcus offers a long-term way to lower the occurrence of the illness. Maternal-focused immunization programs may improve babies' passive immunity and reduce the overall incidence of neonatal illnesses [34,35]. In order to provide universal protection against newborn sepsis pathogens, more funding must be allocated to vaccine development and international deployment techniques.

6. CONCLUSION

This study highlights the critical burden of neonatal sepsis and the growing threat of antibiotic resistance, emphasizing the urgent need for effective interventions. Strengthening antimicrobial stewardship, early diagnosis, and infection control measures are paramount in combating this challenge. Future research should focus on novel therapeutic strategies and surveillance programs to mitigate resistance patterns. A collaborative global effort is essential to ensure better neonatal outcomes and reduce mortality rates.

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