Review Article

# Antibiotic Strategies in Neonatal Intensive Care: A Narrative Review

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## ABSTRACT

**Background:** Antibiotics are among the most frequently prescribed therapies in neonatal intensive care units (NICUs), largely because neonates are highly susceptible to infection and neonatal sepsis has nonspecific clinical manifestations. Although early empirical antibiotic therapy is essential and often lifesaving, increasing evidence suggests that inappropriate initiation, prolonged duration, and excessive use of broad-spectrum antibiotics may contribute to antimicrobial resistance, disruption of the neonatal microbiome, and unfavorable short- and long-term outcomes.

**Objectives:** This review aimed to synthesize current evidence on antibiotic utilization in NICUs and identify key challenges in optimizing their use.

**Methods:** A comprehensive narrative review was conducted by searching electronic databases, including PubMed, Scopus, and Web of Science. Articles published in English addressing antibiotic utilization, indications for therapy, duration of treatment, and outcomes in neonates admitted to NICU were reviewed.

**Results:** Findings from the reviewed literature indicate that a large proportion of neonates admitted to NICU receive antibiotic therapy, with the highest antibiotic exposure observed among preterm and low-birth-weight infants. Empirical antibiotics are frequently initiated for suspected early- and late-onset sepsis, often without microbiological confirmation, leading to unnecessary prolonged exposure. Such practices have been linked to increased risks of antimicrobial resistance, NEC, invasive fungal infections, and persistent alterations in gut microbiota.

**Conclusion:** Antibiotic use in NICUs remains widespread and heterogeneous across institutions. Enhancing antibiotic stewardship interventions, emphasizing evidence-based guidelines, and promoting timely de-escalation or discontinuation of therapy are crucial to improving neonatal outcomes and mitigating the growing threat of antimicrobial resistance.

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## Introduction

The neonatal period is a highly vulnerable stage, during which infections, such as sepsis and meningitis, are major causes of early death. Globally, approximately 2,202 neonates per 100,000 live births develop sepsis each year, totaling nearly 3 million cases, with mortality rates of 11–19% [1-3]. Infectious diseases account for roughly one-third of neonatal deaths and nearly half of deaths among children under five years of age [1]. Delayed diagnosis and treatment may result in persistent neurodevelopmental impairment and long-term disability [4, 5].

Early antibiotic exposure may disrupt gut colonization and airway microbiome development, increasing the risk of atopic diseases, such as atopic dermatitis and asthma by altering immune maturation [6-9].

Despite a high infection burden, ethical, logistical, regulatory, and technical barriers have restricted neonatal participation in clinical trials. Consequently, of the 40 antibiotics approved for adults since 2000, only four provide dosing information [10]. Antibiotics are extensively administered in neonatal intensive care units (NICUs), with 30–35% of term infants, over 75% of infants weighing less than 1,500 g, and more than 80% of those under 1,000 g receiving treatment [11]. Nevertheless, 40–80% of medications in NICUs are prescribed off-label or without formal neonatal approval, often extrapolated from adult studies [2, 12]. This practice increases the risk of inappropriate therapy, adverse drug reactions, and medication errors due to limited pharmacokinetic data to the neonatal population (Figure 1) [13].

Neonatal sepsis is a life-threatening organ dysfunction resulting from a dysregulated host response to infection. Early-onset sepsis (EOS), occurring within the first 72 hours of life, is mainly associated with maternal or intrauterine factors. Its incidence varies geographically, from 0.28–2.1 per 1,000 live births in Europe to 0.31 per 1,000 in term infants and 7.4 per 1,000 in preterm infants in the United States (Figure 2) [13-17].

Late-onset sepsis (LOS) develops after the initial 72 hours of life and is commonly acquired through horizontal transmission in hospital settings or the community. Early recognition is challenging due to subtle clinical signs and limited predictive value of laboratory biomarkers, often complicating clinical management [4, 18]. Overuse of empirical antibiotics drives the development of antimicrobial-resistant strains, representing a serious global health concern. Extended antibiotic exposure is associated with a 1.24-fold higher risk of sepsis, necrotizing enterocolitis (NEC), and mortality (Table 1) [19-21].

Although mortality rates are lower in full-term compared to preterm neonates, sepsis remains a major clinical concern, particularly in neonates with immune deficiencies, meconium aspiration, galactosemia, or congenital cardiopulmonary anomalies. In very low birth weight (VLBW) neonates, sepsis accounts for up to 20% of deaths [10, 16]. Preterm and VLBW neonates are particularly vulnerable due to invasive interventions, such as central catheters, mechanical ventilation, and total parenteral nutrition (TPN), as well as prolonged hospitalization, all of which increase the risk of systemic infection [12, 13]. The risk of nosocomial infections is also heightened by poor hand hygiene, overcrowding, insufficient equipment disinfection, and delayed initiation of breastfeeding, which can extend the time required to reach full enteral feeding (Figure 2) [20].

Empirical antibiotic regimens often deviate from World Health Organization (WHO) guidelines, and geographic differences in antimicrobial susceptibility necessitate tailoring therapy to local pathogen prevalence, contributing to variability in dosing recommendations [21-23]. Blood culture–negative or "suspected" sepsis cases complicate clinical decision-making, as negative cultures cannot definitively exclude infection and may result in unnecessary prolonged antibiotic therapy [20].

Effective antimicrobial stewardship in NICUs is crucial to optimize antibiotic use, minimize unnecessary exposure, and curb antimicrobial resistance. Core strategies include multidisciplinary team coordination, infection surveillance, narrow-spectrum antibiotic guidelines, and routine adherence audits [20]. However, compliance with stewardship programs varies widely, with significant gaps reported between recommended guidelines and actual clinical practice [19].

Developmental pharmacokinetic and pharmacodynamic (PK/PD) variability refers to age-related physiological differences in neonates that significantly influence drug absorption, distribution, metabolism, elimination, and therapeutic response. Despite advances in neonatal intensive care, important challenges remain in optimizing antimicrobial therapy in neonates. Limited neonatal-specific clinical evidence, widespread off-label antibiotic use, and increasing antimicrobial resistance complicate treatment decisions in NICUs. Furthermore, the absence of standardized dosing strategies and the frequent reli-

**Table 1.** Antimicrobial spectrum, and neonatal clinical notes

| Class | Examples | Microbial Coverage | Clinical Notes in Neonates | Ref. |
|---|---|---|---|---|
| Penicillins | Ampicillin, Amoxicillin | Gram-positive (Streptococcus, Enterococcus), some Gram-negative (*E. coli*, Listeria) | Often combined with aminoglycosides for early-onset neonatal sepsis | [12] |
| Anti-staphylococcal Penicillins | Nafcillin, Oxacillin | MSSA | Used for Gram-positive infections | [12] |
| 3rd-generation cephalosporins | Cefotaxime, Ceftazidime | Gram-negative (*E. coli*, Klebsiella, Enterobacter), some gram-positive (Streptococcus) | Used for severe infections including CSF; clearance increases with gestational age/GFR; adjust dosing in renal impairment | [12, 42-44] |
| β-lactam/β-lactamase inhibitors | Avibactam, clavulanate (with β-lactam partner) | MDR Gram-negative (including carbapenemase-producing Enterobacteriaceae, Pseudomonas, Acinetobacter) | Approved >3 months; used for resistant infections Overcome β-lactamase-mediated resistance | [12, 42-44, 89] |
| 5$^{th}$-generation cephalosporins | Ceftaroline, Cefobiprole | MRSA, MDR *S. pneumoniae* | SSSIs, CAP, LOS; safe in neonates; mild adverse effects | [42, 92] |
| Carbapenems | Meropenem, Imipenem | Broad Gram-positive and Gram-negative, including many MDR GNB | Reserved for severe or resistant infections | [10, 40, 41] |
| Aminoglycosides | Gentamicin, Amikacin, Netilmicin | Gram-negative (*E. coli*, Klebsiella, Pseudomonas) | First-line for neonatal Gram-negative sepsis; usually combined with β-lactams | [20, 32, 52] |
| Glycopeptides/lipoglycopeptides | Vancomycin, Teicoplanin, Dalbavancin, Oritavancin | MRSA, CoNS | For resistant Gram-positive infections; TDM recommended; teicoplanin has prolonged half-life | [14, 16, 55, 56, 92] |
| Oxazolidinones | Linezolid | MRSA, MRCoNS, VRE | Treats sepsis or pneumonia caused by resistant Gram-positive bacteria | [61-64] |
| Polymyxins | Colistin | MDR Gram-negative (Acinetobacter, Pseudomonas, Klebsiella) | Restricted to confirmed invasive infections due to nephro/neurotoxicity | [71, 73, 82] |
| Fluoroquinolones | Ciprofloxacin | Resistant *Enterobacter* spp. | Not first-line; used in severe, resistant infections | [66-68] |
| Antifungals | Fluconazole, amphotericin B | *Candida* spp., other systemic fungi | For invasive candidiasis or systemic fungal infections; prophylaxis/treatment in VLBW neonates; Amphotericin B used for severe or refractory infections | [18, 68, 80, 81] |

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GP: Gram-positive; GN: Gram-negative; MRSA: Methicillin-resistant Staphylococcus aureus; MRCoNS: Methicillin-resistant coagulase-negative Staphylococcus; VRE: Vancomycin-resistant Enterococcus; MDR-GNB: Multidrug-resistant Gram-negative bacteria; XDR: Extensively drug-resistant; PDR: Pan-drug-resistant; LOS: Late-onset sepsis; VLBW: Very low birth weight; CVC: Central venous catheter; TPN: Total parenteral nutrition; TDM: Therapeutic drug monitoring.

ance on prolonged empirical therapy may contribute to treatment failure, adverse outcomes, drug toxicity, and resistance development, particularly in preterm and VLBW infants (Table 2) [2, 21].

This review highlights the importance of individualized antimicrobial therapy and antimicrobial stewardship approaches to optimize treatment outcomes and minimize unnecessary antibiotic exposure in NICU patients.

## Materials and Methods

This narrative review was based on published literature related to neonatal sepsis and antimicrobial therapy in NICU. Relevant articles were identified through searches in PubMed, Scopus, and Web of Science. This review focused on antimicrobial pharmacokinetics/pharmacodynamics (PK/PD) principles, dosing optimization, therapeutic drug monitoring, antimicrobial stewardship, resistance patterns, and the safety and efficacy of antibacterial and antifungal agents used in neonatal populations.

English-language publications, including original studies, clinical and observational studies, meta-analyses, review articles, and consensus statements, were evaluated. Additional relevant studies were identified through manual screening of reference lists.

**Table 2.** PK/PD targets and clinical dosing considerations of antimicrobial agents in neonates

| Drug | Class/Type | PK/PD Target in Neonates | Factors Affecting Clearance/Distribution | Dosing/Administration Notes | Special Considerations/Monitoring | Ref. |
|---|---|---|---|---|---|---|
| Ampicillin | β-lactam | %fT>MIC ≥40–50%; severe infections: 100% fT>MIC | PMA, serum creatinine | Dose based on PMA and weight to achieve target | - | [12, 32] |
| Piperacillin/Tazobactam | β-lactam | %fT>MIC ≥40–50%; severe: 100% | Weight, PMA | Dose optimized based on weight and PMA | - | [32, 73] |
| Cefotaxime | β-lactam | fT>MIC ≥75% of the dosing interval | Weight, GA, PNA, liver & renal function | Dose adjustment in hepatic/renal impairment | - | [101] |
| Ceftazidime | β-lactam | - | GA, GFR | Changes in Vd and t½ between days 3–10 | - | [12] |
| Meropenem | Carbapenem | GA < 20 weeks: fT>MIC 100% (MIC 2 mg/L) GA 23–40 weeks: fT>MIC 50% (MIC 4 mg/L), fT>MIC 75% (MIC 2 mg/L) | Weight, GA, PNA | Dose based on weight and age | Well tolerated; PK less defined in preterms | [42] |
| Imipenem | Carbapenem | 100% T>MIC | Weight, GA, PNA | Used after first-line failure; dose based on weight & age | - | - |
| Gentamicin | Aminoglycoside | Cmax 15–25 µg/mL, Ctrough <1 µg/mL GA<27Weeks: Cmax 5–12 mg/L, Ctrough <0.5 mg/L GA ≤28–36: Cmax/MIC ≥8–10 GA 30–34Weeks: Ctrough <1 µg/mL | GFR, GA, PNA, birthweight, TBW | 3.5–5 mg/kg q36–48h, EID | TDM required; nephrotoxicity risk | [3, 5, 22, 55] |
| Amikacin | Aminoglycoside | Cmax 24–40 µg/mL, Ctrough <5 µg/mL C | GFR, GA, PNA, birthweight | Loading 5 mg/kg; maintenance 2.5–5 mg/kg q18–36h | TDM; adjust interval in apnea/ibuprofen | [12, 22, 32] |
| Vancomycin | Glycopeptide | $AUC_{0–24}$/MIC >400 (MIC ≤1 mg/L); neonatal target AUC 267 | Weight, PMA, creatinine | Dose based on weight & age; Ctrough monitoring | Free drug (F_U) important | [12, 32, 58] |
| Linezolid | Oxazolidinone | $AUC_{0–24}$/MIC 80–100 (children) | BSA, renal maturation, PNA | Dose based on weight & age; monitor Cmin | High interindividual variability; lower clearance in preterms | [61] |
| Ciprofloxacin | Fluoroquinolone | AUC/MIC based on PMA | PMA, weight | 7.5 mg/kg q12h (PMA <34w); 12.5 mg/kg q12h (PMA ≥34w) | Low overdose risk (<8%) | [67] |
| Colistin (CMS → CBA) | Polymyxin | Achieve therapeutic levels | Variable conversion, weight, GFR | IV; CNS: Intraventricular, lungs: Inhalation | Highly variable PK; monitor MIC | [71, 72] |
| Fluconazole | Azole antifungal | - | GA, PNA, weight, renal function | Dose based on weight & age; suitable for CNS | Limited PK data; good distribution | [1, 68] |
| Amphotericin B deoxycholate (D-AMB) | Polyene antifungal | No clearly defined PK/PD target; efficacy related to sustained serum concentrations and CNS exposure | Higher CNS penetration in neonates (up to ~40% of serum levels vs. 5–10% in adults); high renal tissue concentrations; tissue distribution extrapolated from adult and preclinical data | 0.5–1.0 mg/kg once daily via 2–4 h IV infusion; minimum treatment duration ≥21 days | Nephrotoxicity; electrolyte disturbances (hypokalemia, hypomagnesemia); close monitoring of renal function and electrolytes required | [80, 82, 83] |
| Lipid-based amphotericin B formulations (L-AmB, ABLC, ABCD) | Lipid-based polyene | No established PK/PD target; generally lower CNS and urinary exposure than D-AMB | Lower kidney concentrations than D-AMB; body weight is the primary determinant of clearance; Vd and clearance similar to older children; CSF concentrations typically low or undetectable | Allow higher dosing due to reduced nephrotoxicity; often reserved for critically ill neonates or those with renal impairment | Reduced nephrotoxicity; potentially suboptimal for CNS and renal candidiasis; outcome interpretation may be confounded by indication bias | [80, 83] |

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Abreviations: β-lactam: Beta-lactam antibiotic; PK: Pharmacokinetics; PD: Pharmacodynamics; %fT>MIC: Percentage of time free drug concentration remains above MIC; PMA: Postmenstrual age; GA: Gestational age; PNA: Postnatal age; Vd: Volume of distribution; t½: Elimination half-life; GFR: Glomerular filtration rate; TBW: Total body water; EID: Extended-interval dosing; Cmax: Maximum serum concentration; Ctrough: Trough serum concentration; TDM: Therapeutic drug monitoring; BSA: Body surface area; $AUC_{0-24}$: Area under the concentration–time curve over 24 hours; MIC: Minimum inhibitory concentration ; F_U: Fraction of unbound (free) drug; CMS: Colistimethate sodium; CBA: Colistin base activity; IV: Intravenous; CNS: Central nervous system.

**Table 3.** Neonatal sepsis diagnostic parameters

| Diagnostic Parameter | Key Points/Notes | Timing/Kinetics | Sensitivity/Specificity | Limitations/Considerations | Ref. |
|---|---|---|---|---|---|
| Blood culture | Gold standard | - | High specificity | Slow results; may miss low-level bacteremia | [1, 4, 5, 8, 19, 21, 71] |
| CRP | Acute-phase protein; used for diagnosis & monitoring | Rises 6–12 h after infection; half-life 24–48 h | Improved with serial measurements; persistently normal → high specificity for ruling out infection | Cannot reliably distinguish infection from non-infectious cause. Delayed rise → not ideal <24 h; affected by PROM, maternal fever, meconium, fetal stress; lower baseline in preterm | [1, 4, 14, 19, 20] |
| CBC (WBC, ANC, I:T ratio) | Evaluates leukocyte patterns | - | WBC <5,000–7,500/mm$^3$: sensitivity ~29%, specificity 91%; I:T >20% may indicate infection | WBC highly variable by GA & PNA; low sensitivity (0.3–54.5%); thrombocytopenia nonspecific. Asymptomatic term neonates with abnormal CBC should not recieve emprical antibiotics or NICU admission unless clinically indicated | [1, 4, 14, 93] |
| Lumbar puncture/ CSF analysis | Essential for meningitis diagnosis based on medical history, maternal risk factors, and clinical condition; especially important in VLBW and preterm neonates | EOS: after blood culture, ideally before antibiotics; LOS: part of routine evaluation | - | Should not compromise cardiopulmonary stability; or delaying empirical antibiotic initiation, not routine in stable neonates | [4, 19, 54, 94] |
| PCT | Early infection marker; more sensitive than CRP | Rises 4–6 h post-endotoxin; peaks 6–8 h; half-life 25–30 h; physiological fluctuations: Low at birth → peak ~24h → baseline ~48h | More sensitive than CRP; slightly less specific | Affected by non-infectious conditions: resuscitation, maternal chorioamnionitis, GBS colonization, PROM; cord blood useful for EOS Limited specifity; GA-independent; Cord blood PCT may help identify EOS | [1, 4, 14] |
| HeRO Monitoring | Heart rate variability score for early sepsis detection | Continuous | Useful for early risk identification | Needs specialized equipment; adjunctive tool | [4, 14, 19] |
| PCR/DNA Microarray | Molecular pathogen detection | Rapid detection | High sensitivity | Mostly research or supplementary; not routine | [5, 9, 19, 21, 71] |
| IL-6/IL-8/TNF-α | Early infection biomarkers; IL-6 higher in Gram-negative bacteremia (Guiding diagnostic strategies) | Early rise during bacterial infection | Limited clinical use; not standalone | Host-response indicators, Standardized cutoffs not established; routine use limited, Useful for diagnosing neonatal sepsis and monitoring treatment efficacy | [1, 4, 14, 20, 95-97] |
| β-D-Glucan/GM | Biomarkers for invasive fungal infection; GM produced by Aspergillus | - | Sensitivity/specificity 30–90% | GM detectable in serum, plasma, CSF, BAL; assay variability | [1, 96] |
| LDH | Marker for metabolic/ respiratory disorders, NEC, asphyxia | - | - | Non-specific for infection | [1, 98] |
| Coagulation profile (PT, hypercoagulability) | Reflects sepsis-related coagulopathy. Often coincide with Gram-negative infections, higher nSOFA scores, and worse clinical outcomes. | Prolonged prothrombin time | - | Altered in Gram-negative sepsis; preterm Gram-positive → hypercoagulability associated with increased glycoprotein expression; potential therapeutic target | [4, 14, 99, 100] |
| Multifactorial scoring systems | Kaiser Sepsis Calculator, SNAP-II, SNAPPE-II, and HeRO, combine clinical, laboratory, and maternal history data | Improve identification of high-risk EOS in neonates and guide empirical antibiotic therapy | - | - | [4, 14, 18, 19] |

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Abbreviations: PROM: Premature rupture of membranes; GBS: Group B streptococus; PT : Prothrombin time; SOFA: Sequential organ failure assessment score; EOS: Early-onset sepsis; CRP: C-reactive protein; PCT: Procalcitonin; GM: Galactomannan; LDH: Lactate dehydrogenase.

**Table 4.** PK/PD alterations in preterm and term neonates: Clinical implications

| PK/PD Parameter | Alterations in Preterm Neonates | Mechanistic Basis | Clinical Implications | Ref. |
|---|---|---|---|---|
| Absorption | Reduced oral absorption; delayed Cmax | Low gastric acid, bile secretion, pancreatic enzymes; immature intestinal motility and villi; high gastric pH; prolonged gastric emptying | Oral bioavailability lower; slower onset of effect; lipophilic drugs particularly affected | [4, 10, 11, 26] |
| Distribution | ↑ Vd for hydrophilic drugs, ↓ Vd for lipophilic drugs; ↑ free fraction of protein-bound drugs | High total body water (~80%), low body fat (~3%), low plasma proteins (albumin, α1-acid glycoprotein) | Higher doses of hydrophilic antibiotics may be needed; increased risk of toxicity for highly protein-bound drugs | [11, 28-31] |
| Metabolism | Reduced hepatic metabolism; prolonged half-life; variable prodrug activation | Immature CYP450 enzymes (CYP3A7 predominant at birth), limited glucuronidation and hydroxylation; gradual maturation over weeks to years | Dose adjustments needed; monitoring for accumulation; some prodrugs may be less effective | [10-12, 29, 32] |
| Excretion | Reduced renal clearance; slower tubular secretion and reabsorption | Immature GFR, tubular function; nephrogenesis incomplete (~34 weeks); low renal blood flow | Lower doses or extended dosing intervals for renally cleared drugs; serum creatinine initially unreliable | [11, 12, 31] |
| PD | Altered drug sensitivity and efficacy | Immature receptor systems and intracellular signaling | Response may differ from term neonates; careful monitoring required | [12] |
| Overall clinical implications | Weight-based dosing may need adjustment; risk of subtherapeutic or toxic levels | Combination of PK/PD immaturity, altered Vd, metabolism, and excretion | Careful dose calculation, therapeutic drug monitoring, consideration of extracorporeal support (e.g. ECMO) | [2, 12, 28, 32, 101] |

PD: Pharmacodynamics.

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Priority was given to recent and clinically relevant studies involving preterm neonates, VLBW infants, and critically ill NICU patients. Landmark studies were included to provide an updated and clinically oriented overview of antimicrobial therapy in neonatal sepsis management.

This review acknowledges limitations, including variability in study designs, regional differences in microbial epidemiology, and the paucity of high-quality clinical trials in preterm populations.

## Diagnosis and monitoring of neonatal sepsis

Early diagnosis of neonatal sepsis (EOS and LOS) remains a major challenge in neonatal intensive care [8, 19]. Table 3 presents key diagnostic and monitoring parameters and tools used for neonatal sepsis.

If clinically stable neonates have negative blood cultures and no clear infection, empiric antibiotics for EOS should be stopped after 36 hours, especially if CRP is reassuring. If antibiotics are continued beyond 36 hours, reassess therapy at least every 24 hours [14, 24, 25].

## Pharmacokinetics and pharmacodynamics of drugs in preterm neonates

PK and PD are markedly altered in preterm neonates due to physiological immaturity, organ development, and clinical factors (Table 4) [12].

Absorption: Oral drug absorption is reduced in preterm neonates due to lower gastric acid and bile secretion, decreased pancreatic enzyme activity, and immature intestinal motility. Intestinal villi and mucosa are underdeveloped until approximately 20 weeks of gestation, further reducing absorption. Moreover, reduced bile acids, pancreatic enzymes, and ileal bile reabsorption contribute to the limited absorption of lipophilic medications. High gastric pH, delayed gastric emptying, prolonged intestinal transit, immature transporter expression, and limited first-pass metabolism contribute to decreased oral bioavailability and delayed peak plasma concentrations (Cmax) [4, 11, 26].

**Table 5.** Safety profile and adverse effects of common antimicrobials used in NICUs

| Drug | Common/Notable Adverse Effects in Neonates | Rare/Serious Adverse Effects | Special Notes/Risk Factors | Ref. |
|---|---|---|---|---|
| β-lactams (ampicillin, cephalosporins, carbapenems) | Mild GI upset, hypersensitivity reactions | Rare nephrotoxicity, seizures, cytopenias (meropenem) | Prolonged broad-spectrum cephalosporin use linked to late-onset sepsis, NEC, invasive candidiasis, higher NICU mortality | [12, 14, 42] |
| New Agents Ceftazidime/Avibactam, Ceftolozane/Tazobactam, Meropenem/Vaborbactam | Mild hypersensitivity, GI upset | - | Safety profile similar to adult data in limited neonatal reports | [14, 42] |
| Gentamicin | Mild nephrotoxicity; transient biomarker elevations | Nephrotoxicity, ototoxicity (dose- and exposure-dependent) | Extremely preterm, low birthweight, concurrent NSAIDs/vasopressors increase risk; prolonged/sequential exposure increases nephrotoxicity | [10-12] |
| Amikacin | Usually spares renal function | Transient enzyme elevation; rare neuromuscular blockade | Longer half-life and Vd than gentamicin; reserved for resistant cases | [10-12] |
| Vancomycin | - | AKI (ATN, AIN), oxidative tubular injury | Risk factors: Ctrough >15 mg/L, duration >7 days, obesity, critical illness, CKD; TDM recommended | [12, 58] |
| Linezolid | Mild GI disturbances, anemia, myelosuppression | Linezolid-induced thrombocytopenia (~20%) | Hematologic monitoring recommended for prolonged or high exposure | [61-63, 67] |
| Ciprofloxacin | Reversible musculoskeletal effects (arthropathy) | Potential neurotoxicity (uncertain in neonates) | Co-administration with inotropes may reduce clearance | [67] |
| Colistin (CMS) | Reversible nephrotoxicity (3–10%), electrolyte disturbances, mild neurotoxicity | Acute tubular necrosis, neuromuscular blockade, cranial nerve dysfunction | Concomitant nephrotoxic drugs increase risk; use CMS and avoid IM injections | [71, 76, 77] |
| Fluconazole | Well tolerated; minimal adverse effects | Rare hepatotoxicity or renal impairment | Monitoring of renal and hepatic function recommended during prolonged therapy | [1, 4] |
| Amphotericin B deoxycholate (D-AMB) | Nephrotoxicity; electrolyte disturbances including hypokalemia and hypomagnesemia | Severe renal impairment leading to treatment discontinuation; increased mortality associated with VLBW neonates | Higher renal tissue accumulation increases nephrotoxicity risk; preterm neonates and birth weight <750 g have the highest mortality risk; requires intensive renal and electrolyte monitoring | [80, 82] |
| Lipid-based amphotericin B formulations (L-AmB, ABLC, ABCD) | Reduced nephrotoxicity compared with D-AMB | Potential suboptimal clearance of renal and CNS infections due to low kidney and CSF concentrations | Often reserved for critically ill neonates or those with renal dysfunction, which may confound mortality outcomes (indication bias); weight is a key determinant of clearance | [80, 83] |

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Abreviations: GI: Gastrointestinal; NEC: Necrotizing enterocolitis; NICU: Neonatal intensive care unit; AKI: Acute kidney injury; ATN: Acute tubular necrosis; AIN: Acute interstitial nephritis; Vd: Volume of distribution; NSAIDs: Non-steroidal anti-inflammatory drugs; CKD: Chronic kidney disease; TDM: Therapeutic drug monitoring; CMS: Colistimethate sodium; IM: Intramuscular

Lactase activity is decreased, while sucrase, maltase, and isomaltase are relatively preserved. Gastric volume, motility, and emptying are reduced, and intestinal transit is prolonged up to four times that of adults. These factors, along with immature transporter expression and limited first-pass metabolism, result in lower oral bioavailability and delayed peak plasma concentrations [26, 27].

Distribution: Preterm neonates have distinct body composition compared to term infants and adults, with total body water around 80% vs 70% in term neonates and body fat approximately 3% vs 12% in term neonates. These differences enlarge the volume of distribution (Vd) for hydrophilic drugs and reduce it for lipophilic agents. Lower levels of plasma proteins, including albu-

min and α1-acid glycoprotein, elevate the free fraction of highly protein-bound drugs, increasing toxicity risk, particularly in hypoalbuminemic infants. Extracorporeal support, such as extracorporeal membrane oxygenation (ECMO), may further expand Vd through hemodilution [11, 28, 29].

Although neonates have limited fat and skeletal muscle, the Vd of lipophilic drugs (e.g. fluoroquinolones, macrolides, ketolides, metronidazole, rifampin, trimethoprim/sulfamethoxazole, linezolid) can be high because fat-rich organs (brain and liver) are relatively large compared with body weight. In neonates, Vd is affected by body composition and lower plasma proteins (albumin and α1-acid glycoprotein), increasing the unbound fraction and active drug. For beta-lactams, efficacy depends on the duration the free drug concentration exceeds the minimum inhibitory concentration (MIC) (fT>MIC). Reduced protein binding can increase both activity and toxicity. At birth, albumin and α1-acid glycoprotein levels are low and gradually reach adult values by around one year. Reduced protein binding, altered fetal albumin affinity, elevated bilirubin, and free fatty acids can increase the unbound drug fraction. Rapid changes in body composition and extracellular fluid affect the Vd, while renal and hepatic clearance mature over time but remain lower than in adults. Both gestational age (GA) and postnatal age (PNA) should be considered when determining antibiotic dosing in neonates [11, 30, 31].

Metabolism: Hepatic metabolism is immature. Plasma protein levels gradually increase during early infancy, reaching adult levels by approximately 10–12 months of age [32]. Cytochrome P450 enzymes begin maturing around 25 weeks gestation, with adult levels reached by ~2 years. Fetal hepatic cytochrome (CYP) enzyme expression reaches only approximately 30–60% of adult levels. Reduced metabolism prolongs drug half-life and increases the risk of drug accumulation. Prodrugs that require metabolic activation may exhibit less efficacy. Interindividual variability and NICU polypharmacy increase susceptibility to adverse drug reactions [11, 12, 29].

Some biotransformation pathways, including P450-mediated hydroxylation and glucuronidation, are limited at birth. Phase I CYP450 enzymes exhibit isoform-specific developmental profiles: CYP3A7 is predominant at birth, but its activity declines over the first year, while CYP3A4, the main adult drug-metabolizing isoform, gradually increases. CYP maturation depends on both PNA and postmenstrual age (PMA). Drug metabolism occurs mainly in the liver, with minor contributions from kidneys, gut, blood cells, and lungs [11, 27].

Excretion: Renal clearance is limited in preterm neonates due to immature glomerular filtration and tubular function. Nephrogenesis is completed around 34 weeks of gestation. Glomerular filtration rate (GFR) is ~50% of adult values at three months and reaches adult levels by two years. Factors, such as prematurity, low birth weight, and nephrotoxic drugs, further reduce clearance. Serum creatinine at birth is an unreliable marker of neonatal renal function because it initially reflects maternal levels and becomes accurate only after several weeks. Moreover, severe illness, inflammation, and augmented renal clearance can further modify drug PKs [11, 12, 33].

Active tubular secretion and reabsorption are immature at birth, reaching only ~20–30% of adult capacity. Tubular secretion matures gradually, attaining adult levels by 7–12 months, whereas tubular reabsorption continues to develop slowly into adolescence, with the steepest increase between 1–3 years. Drug elimination via these processes depends on renal blood flow, which rises with increasing GFR. In neonates, reduced protein binding can enhance clearance of renally handled drugs due to higher free drug concentrations [11, 33].

Pharmacodynamics: Drug effects in preterm neonates are influenced by immature receptor systems and intracellular signaling pathways, resulting in altered sensitivity and efficacy [12].

## Empiric antibiotic use in critically Ill neonates

### Early-onset sepsis

### Pathophysiology

EOS arises primarily from vertical transmission of pathogens during labor or immediately postpartum. Maternal genital tract colonization with Group B *Streptococcus* (GBS) or *Escherichia coli* accounts for most cases. Less frequently, Listeria monocytogenes, *Staphylococcus aureus*, and anaerobic bacteria may be involved (Figure 2) [18, 34].

## Risk factors

### Maternal risk factors

Chorioamnionitis or intra-amniotic infection; Prolonged rupture of membranes (PROM >18 hours); Maternal fever during labor (>38 ˚C); Untreated maternal GBS colonization; Prior infant with GBS infection; Bacteriuria or colonization with E. coli or other uropathogens [18, 34].

Neonatal risk factors:

Prematurity, VLBW; male sex; birth asphyxia, traumatic delivery; need for resuscitation or mechanical ventilation; congenital anomalies; Immature immune function and low maternal immunoglobulin G transfer [18, 34].

Low-risk neonates, such as preterm infants delivered by cesarean section for non-infectious indications without labor induction or membrane rupture, may not require empiric antibiotics [35].

### Clinical presentation

EOS often presents with subtle or nonspecific signs:

Respiratory distress, apnea; cardiovascular compromise: Shock, bradycardia, hypotension; neurological abnormalities: Seizures, lethargy; feeding intolerance, hypoglycemia, temperature instability; Laboratory indicators: Elevated CRP, abnormal white blood cell counts [18, 34].

Red flags (apnea, need for resuscitation, shock) warrant immediate empiric therapy, whereas non-red-flag signs may be assessed using clinical judgment or sepsis risk calculators [18].

## Microbial epidemiology

High-income countries: GBS and *E.coli* are predominant, although GBS incidence has declined due to intrapartum prophylaxis [18, 34]. Preterm/VLBWneonates: *E.coli* predominates and frequently exhibits ampicillin resistance [34]. LMICs: Gram-negative bacteria (GNB) are more prevalent, including Klebsiella and Enterobacter species [34].

### Empiric antibiotic therapy

First-line empiric therapy in most preterm or less critically ill neonates: Ampicillin+gentamicin, covering GBS, *E. coli*, Listeria, and other common pathogens [34, 35].

Cefotaxime-based regimens are reserved for:

Critically ill neonates with severe respiratory failure; Gentamicin contraindications (renal impairment); Suspected Gram-negative meningitis [35].

Prolonged use of third-generation cephalosporins increases risk of multidrug-resistant (MDR) bacteremia, invasive candidiasis, and gut dysbiosis [35, 36]. Ceftriaxone is avoided in neonates due to risk of hyperbilirubinemia, kernicterus, and calcium precipitation [18].

### Adjunctive strategies

β-lactam/β-lactamase inhibitor combinations (e.g. ampicillin-sulbactam) may broaden coverage against extended-spectrum beta-lactamase (ESBL)-producing Gram-negatives without resorting to carbapenems [37]. Empiric antifungal therapy is indicated only for high-risk VLBW neonates with risk factors or suspected fungal sepsis [4].

Empiric therapy should be reassessed at 48–72 hours and discontinued if cultures are negative and the infant remains clinically stable [35].

## Late-onset sepsis

## Epidemiology and risk factors

LOS generally occurs after 72 hours of life and is predominantly nosocomial, associated with:

Prolonged NICU stay; central venous catheters and invasive devices; mechanical ventilation and parenteral nutrition; critical illness and prematurity [4, 18, 34].

Other contributing factors include maternal and perinatal complications (pre-eclampsia, chorioamnionitis, intrauterine growth restriction), and prolonged hospital exposure (Figure 2) [34].

## Pathogen profile

### High-income countries: Gram-positive bacteria predominate

Coagulase-negative staphylococci (CoNS, 50–55% of cases in preterm infants); *S. aureus*, *Enterococcus* spp., GBS [4, 34].

### LMICs: Gram-negative bacteria predominate

Enterobacteriaceae (*Klebsiella, E. coli, Enterobacter* spp.); *Pseudomonas aeruginosa* [4].

## Fungal pathogens

*Candida* spp., including *Candida albicans* and emerging *Candida auris*, particularly in VLBW infants or those exposed to broad-spectrum antibiotics [4].

Viral agents are rare but include herpes simplex virus, enteroviruses, enteroviruses, cytomegalovirus, respiratory syncytial virus [4].

## Empiric therapy

### Empiric LOS therapy should cover both gram-positive and gram-negative pathogens

Community-acquired LOS: Ampicillin+gentamicin. Hospital-acquired LOS: Vancomycin (or anti-staphylococcal β-lactam)+aminoglycoside to cover CoNS and methicillin-resistant *S. aureus* (MRSA) [34]. Gram-negative coverage: β-lactam/β-lactamase inhibitor combinations±aminoglycoside; carbapenems reserved for ESBL-producing organisms. Anaerobic coverage: Clindamycin or metronidazole in NEC or suspected intra-abdominal infection. CNS involvement: Third- or fourth-generation cephalosporins or carbapenems; piperacillin-tazobactam avoided due to poor CNS penetration [34]. Fungal infections: Empiric amphotericin B in high-risk infants [4].

Vancomycin-resistant *S. aureus* (VRSA), ESBL-producing Enterobacteriaceae, *Acinetobacter* species, and fungal pathogens, such as Candida and Aspergillus, have markedly increased morbidity and mortality among neonates. Reserve antibiotics (linezolid, daptomycin, fosfomycin, colistin, ciprofloxacin) are used only for culture-proven MDR infections under infectious disease guidance [1, 34].

In critically ill neonates requiring mechanical ventilation for respiratory distress, empiric antibiotics are indicated for suspected congenital pneumonia and/or EOS. American Academy of Pediatrics guidelines recommend starting empiric therapy in high-risk neonates and discontinuing within 3 days if bacterial sepsis is excluded, as prolonged empiric therapy beyond 5–7 days is associated with adverse outcomes, including LOS, NEC, and increased mortality. Broad-spectrum regimens (e.g. ampicillin plus cefotaxime), may disrupt gut microbiota, increase MDR bacteremia, prolong hospitalization, raise in-hospital mortality, and predispose neonates to invasive candidiasis. Despite this, such regimens are commonly used in neonates with risk factors, including PROM, maternal fever, clinical signs of sepsis, or elevated biomarkers. Many neonates receive broad-spectrum antibiotics even with negative blood cultures to avoid undertreatment, which increases EOS mortality risk. Low-risk preterm infants delivered by cesarean section for non-infectious maternal indications, without labor induction, membrane rupture, or intrapartum antibiotic prophylaxis, may be safely managed without routine empiric antibiotics [35-38].

Diagnosing neonatal sepsis is challenging due to unclear definitions, and identifying bacterial, viral, or non-infectious causes depends on microbial cultures requiring up to 48 hours. Rapid tests and combined biomarkers can help prevent unnecessary empiric antibiotic therapy [37].

In settings with high resistance, the empiric use of very broad-spectrum agents, including carbapenems, is increasing. However, this practice risks further resistance. The WHO categorizes antimicrobials as the Access, Watch, and Reserve. Gentamicin and ampicillin belong to Access category, while cefotaxime is classified as Watch, and resistance levels to all have reached alarming levels. Standard susceptibility testing does not account for additive or synergistic effects. Combining β-lactams with β-lactamase inhibitors (e.g. sulbactam, clavulanic acid) may extend coverage against ESBL-producing Gram-negative pathogens without resorting to carbapenems [37].

## Antimicrobial therapy in neonates

### βlactams (cephalosporins and carbapenems)

#### Clinical use in neonatal intensive care units

β-lactams are among the most commonly used antibiotics in neonates. Their bactericidal effect is mediated through inhibition of transpeptidase enzymes, preventing cross-linking of peptidoglycan strands and thus disrupting bacterial cell wall synthesis. The most frequently used β-lactams in the NICU include penicillins (e.g. ampicillin), cephalosporins (e.g. cefotaxime, ceftazidime), and carbapenems (e.g. meropenem, imipenem) [12, 19, 32].

Ampicillin is extensively renally excreted (~90%), with serum concentrations largely dependent on renal function. CNS penetration is limited under normal conditions but increases to ~39% during meningitis. It remains the drug of choice for suspected or confirmed Listeria meningitis, particularly in the first week of life [12, 39].

Meropenem is the preferred carbapenem in neonates for LOS and complicated intra-abdominal infections, while imipenem is reserved for critically ill neonates after first-line therapy failure. Meropenem is effective against resistant Gram-negative infections, including neonatal meningitis, but is associated with higher ventilation failure rates. Extended broad-spectrum therapy (≥10 days) is linked to colonization by resistant GNB [10, 40, 41].

Third-generation cephalosporins such as cefotaxime and ceftazidime are widely used for gram-negative sepsis, with ceftazidime/avibactam (CAZAVI) emerging as a novel option against MDR pathogens in infants >3 months [12, 42-44].

## Neonatal pharmacokinetics/pharmacodynamics Considerations

β-lactams are time-dependent antibiotics; their efficacy correlates with the duration that free drug concentrations remain above the pathogen MIC (%fT>MIC). Optimal pharmacodynamic targets are at least 40–50% fT>MIC, but in severe infections, achieving 100% fT>MIC is recommended. For ampicillin, PMA and serum creatinine are major covariates affecting renal clearance. Piperacillin/tazobactam PK models identified body weight and PMA as key clearance covariates, with weight being the main determinant of volume of distribution. These covariates can be used to optimize neonatal dosing regimens to achieve desired exposure [12, 32, 45, 46].

Plasma and hepatic esterases hydrolyze cefotaxime to form its active metabolite, desacetyl-cefotaxime. Approximately 50–60% of the administered dose is eliminated unchanged in the urine, while 15–20% appears as desacetyl-cefotaxime. The formation of desacetyl-cefotaxime decreases with hepatic injury, and cefotaxime clearance declines markedly when creatinine clearance is <10 mL/min. Therefore, dose adjustment may be required in neonates with hepatic or renal impairment. Pharmacokinetic assessments show that current body weight, GA, and PNA are major determinants of cefotaxime disposition [12, 32, 47].

Ceftazidime clearance increases with GA and GFR, particularly in the first 10 days of life, while distribution volume and elimination half-life decrease significantly between days 3–10 [12, 48, 49].

Meropenem is well-tolerated. PK in preterm neonates is less well defined; Imipenem, a broad-spectrum antibiotic, is reserved for cases unresponsive to first-line therapy. Neonatal dosing of both is tailored to body weight, GA, and PNA [12, 50, 51].

## Therapeutic drug monitoring

Most β-lactams have favorable safety profiles; therapeutic drug monitoring (TDM) is rarely required. It may be considered in high-dose therapy or in neonates with significant renal impairment to ensure therapeutic concentrations while minimizing neurotoxicity risk [12].

## Safety, adverse effects

β-lactams are generally safe in neonates. Adverse events are uncommon. Ampicillins, cephalosporins, and carbapenems rarely cause nephrotoxicity, seizures, or cytopenias (rare with meropenem). Cefotaxime may cause mild hypersensitivity reactions and gastrointestinal disturbances [12, 14].

Prolonged use of broad-spectrum cephalosporins is linked to LOS, NEC, invasive candidiasis, and mortality. Emerging β-lactam/β-lactamase inhibitor combinations, such as CAZAVI, ceftolozane/tazobactam, and meropenem/vaborbactam, appear safe in limited neonatal reports and show safety profiles consistent with adults (Table 5) [14, 42].

## Challenges: Resistance, ESBL, MDR, and carbapenem use

Increasing prevalence of extended-spectrum beta-lactamase (ESBL) and carbapenem-resistant Enterobacteriaceae CRE limits treatment options. Many Gram-negative pathogens may co-produce multiple β-lactamases, reducing efficacy of inhibitor combinations. Carbapenems remain the mainstay for severe neonatal MDR infections, while older agents (colistin, fosfomycin, tigecycline) are reserved for highly resistant cases [14, 42].

Siderophore cephalosporins (cefiderocol) and newer agents (CAZAVI, imipenem/relebactam, meropenem/vaborbactam) represent promising therapeutic options against MDR Gram-negative pathogens in NICU settings. Siderophore cephalosporins have shown success in individual case reports for preterm neonates with LOS due to *Klebsiella pneumoniae* carbapenemase- or Verona integron-encoded metallo-β-lactamase-producing *K. pneumoniae* [42].

## Evidence gaps and research needs

PK/PD data in extremely premature neonates (GA <32 weeks) remain limited, especially for high-dose or combination regimens. The long-term safety of newer β-lactams and β-lactam/β-lactamase inhibitor combinations in neonates is largely unknown [12, 14].

## Aminoglycosides

### Clinical use in the neonatal intensive care units

Aminoglycosides (AGs), primarily gentamicin, amikacin, and netilmicin, are first-line agents for neonatal Gram-negative infections and are routinely used with

β-lactams for empirical EOS [2, 12]. Their bactericidal effect results from irreversible binding to the 30S ribosomal subunit, which inhibits bacterial protein synthesis [11]. Both antibacterial effects and toxicity are linked to overactivation of cellular respiration, causing oxidative stress and disruption of the translation machinery, resulting in misfolded and aberrant proteins [2].

The potent Gram-negative activity, synergy with β-lactams, low intrinsic resistance, and cost-effectiveness support their widespread use in both term and preterm infants. AG-based regimens are generally preferred over cefotaxime for neonatal sepsis due to declining bacterial susceptibility and a lower risk of resistance development [20, 32, 52].

## Neonatal pharmacokinetics/pharmacodynamics considerations

Gentamicin and amikacin are primarily (90%) eliminated via glomerular filtration, making renal maturation, GA, PNA, birthweight, and total body water key determinants of pharmacokinetic variability. Nephrogenesis occurs between 5–35 weeks of gestation, and preterm infants have reduced drug clearance due to immature glomerular filtration, tubular secretion, lower renal blood pressure, and limited osmotic gradients. TDM is critical, with gentamicin trough <1 μg/mL and peak 15–25 μg/mL, and amikacin trough <5 μg/mL and peak 30–40 μg/mL. Dose calculation as Equation 1:

1. $Dose = target\ Cmax \times CL \times \tau$ (2, 10)

AGs exhibit concentration-dependent bactericidal activity, with efficacy closely linked to the C_max/MIC ratio, optimally ≥8–10. The post-antibiotic effect allows bacterial killing to continue after serum concentrations fall below MIC, permitting EID to maximize efficacy while minimizing toxicity. C_trough levels are strongly associated with nephrotoxicity and ototoxicity, and maintaining C_trough <1 mg/L is recommended in neonates [11, 22, 32].

Key physiological determinants include a large Vd in neonates due to higher total body water, necessitating higher mg/kg doses, and reduced GFR in preterm infants, which requires prolonged dosing intervals, sometimes exceeding 48 hours [12, 32]. Incomplete nephrogenesis in infants <34 weeks GA further reduces clearance and increases exposure [12].

Gentamicin is a hydrophilic drug (logP=–3.1) that primarily distributes in the extracellular fluid, making a full physiologically based pharmacokinetic (PBPK) model unnecessary. Due to its low cellular penetration, it is assumed to distribute rapidly throughout the perfused tissue volume; thus, a flow-limited distribution model was applied [2].

Gentamicin is the most commonly used aminoglycoside in NICU. Typical dosing for preterm neonates ranges 3.5–5 mg/kg every 36–48 hours, with extremely preterm infants (<28 weeks GA) often requiring higher doses (5 mg/kg) to achieve therapeutic C_max [2, 12].

Amikacin dosing generally begins with a loading dose of 5 mg/kg, followed by 2.5–5 mg/kg maintenance doses at 18–36-hour intervals depending on GA, with interval adjustments of +10–12 hours recommended during apnea, hypothermia, or concurrent ibuprofen therapy. Tobramycin regimens generally mirror gentamicin strategies [12, 22, 32, 53].

Extended-interval dosing (EID) is preferred in neonates, as it allows higher C_max for enhanced bacterial killing, lower C + trough to reduce toxicity, and improved PK/PD target attainment compared with multiple-daily dosing [11, 32].

## Therapeutic drug monitoring

Routine TDM is strongly recommended for AGs in neonates due to their narrow therapeutic window and potential for nephro- and ototoxicity [22, 52, 54]. Monitoring should include early assessment of C_max and C_trough after 2–3 doses or earlier in clinically unstable infants to ensure therapeutic exposure while avoiding toxic troughs [32].

## Safety and adverse effects

AGs toxicity is dose- and exposure-dependent, with nephrotoxicity and ototoxicity as the most significant concerns [11, 12]. Extremely preterm infants, low birthweight neonates, and those receiving co-medications, such as nonsteroidal anti-inflammatory drugs or vasopressors, are particularly vulnerable. A study demonstrated that the severity of (AKI) correlates inversely with GA and birthweight, highlighting increased susceptibility in very preterm neonates [12].

Gentamicin may increase serum creatinine and urinary biomarkers (kidney injury molecule-1, glutathione S-transferase alpha 1-1, glutathione S-transferase pi 1), indicating nephrotoxicity. Amikacin usually spares overall renal function, but can transiently elevate urinary N-acetyl-β-D-glucosaminidase and may cause neuromuscular blockade, although less than other AGs. Prolonged or sequential exposure to AGs increases the risk of nephrotoxicity. Gentamicin combined with ampicillin reduces neonatal mortality and is associated with shorter duration of ventilation and hospital stay. Amikacin is reserved for resistant cases, has a longer half-life and higher volume of distribution, and is associated with longer ventilation (Table 5) [10].

## Emerging challenges: Resistance, multidrug-resistant, and clinical limitations

Although resistance remains relatively limited, increasing MICs among Gram-negative pathogens may render AG monotherapy insufficient when MIC exceeds 2 mg/L, necessitating combination therapy or alternative regimens [11, 32]. Despite these limitations, AGs remain central to NICU antimicrobial therapy due to their broad Gram-negative coverage, synergy with β-lactams, and cost-effectiveness [2, 20].

## Evidence gaps and research needs

PK/PD data in extremely preterm neonates (<32 weeks GA) remain sparse [20, 32]. Long-term ototoxicity outcomes are insufficiently studied, and variability in current dosing recommendations persists due to heterogeneous data sources [22]. Further studies are required to refine PBPK models, validate EID, define optimal PK/PD targets for various gram-negative pathogens, and prevent the emergence of antimicrobial resistance [2, 12, 32].

## Vancomycin

### Clinical use in the neonatal intensive care units

Preterm and VLBW neonates are particularly susceptible to severe Gram-positive infections during NICU hospitalization, often associated with central venous catheters and TPN. This heightened vulnerability largely stems from an immature immune system that fails to mount an adequate antimicrobial response. *S. aureus* and coagulase-negative staphylococci account for approximately 55% of late-onset hospital-acquired infections in this population [12, 55].

Vancomycin, a glycopeptide antibiotic, is widely used to treat MRSA infections in both preterm and term neonates. The drug is water-soluble, exhibits limited plasma protein binding (e.g. to IgA and albumin), and is primarily eliminated via glomerular filtration and tubular secretion. Compared with adults, neonates have a higher extracellular fluid volume and lower renal clearance. Consequently, vancomycin clearance can vary 2- to 3-fold depending on PMA, comorbidities, and renal function, necessitating individualized dosing and TDM [12, 56].

Several dosing algorithms have been proposed in clinical practice, including fixed weight-based dosing, PMA-based dosing, PMA plus weight, PMA plus PNA, and serum creatinine-based dosing. Population PK modeling with Monte Carlo simulations has been used to compare these strategies, evaluating target trough concentrations (5–15 mg/L) and higher MRSA-specific targets (15–20 mg/L). Trough concentrations do not reliably predict efficacy or area under the receiver operating characteristic curve $(AUC_0)_{-24}$ h/MIC, highlighting the clinical value of AUC-guided dosing adjustments [12, 57].

## Neonatal pharmacokinetics/pharmacodynamics considerations

The primary PK/PD target for vancomycin is an $AUC_{0–24}$/MIC>400 for pathogens with MIC≤1 mg/L, though some authors suggest that lower targets may suffice in neonates. This target was originally defined in adult MRSA pneumonia and has not been formally validated for neonatal staphylococcal sepsis [12, 32, 58].

Recent studies indicate that the fraction of free vancomycin in neonates is substantially higher (mean 0.9) than in adults (mean 0.6), highlighting developmental differences in protein binding. As a result, using total drug concentrations for target attainment approximates adult exposures, whereas targeting free drug may be a more physiologically relevant approach, with a proposed neonatal target $AUC_{0–24}$/MIC of 400. Covariates influencing clearance include body weight, PMA, and serum creatinine [12, 59].

Vancomycin dosing must account for the high inter-individual variability in neonates, including differences in Vd and renal clearance. TDM is strongly recommended to ensure therapeutic efficacy while minimizing toxicity [12, 32]. Simulation studies suggest that trough concentrations of 5-15 mg/L are generally sufficient to achieve $AUC_{0–24}$>400, whereas higher troughs (15–20 mg/L), typically used in adults, are not necessary for neonates [12].

### Safety and adverse effects

Vancomycin-associated AKI is well-documented and usually occurs 4–17 days post-exposure. AKI can present as:

### Acute tubular necrosis: Characterized by oliguria and acute rise in serum creatinine

Acute interstitial nephritis: Typically non-oliguric AKI with sterile pyuria and non-nephrotic proteinuria 7–14 days after exposure; rash, fever, and eosinophilia may occur but are present in <10% of cases. Histopathology classically shows interstitial edema with eosinophilic and lymphocytic infiltration; occasionally, granulomatous interstitial nephritis is observed. Non-crystalline vancomycin casts have also been reported, predominantly in distal tubules, occasionally associated with macrophage infiltration, suggesting inflammatory injury. High intracellular vancomycin concentrations induce oxidative stress, mitochondrial dysfunction, and apoptosis in proximal tubular cells via reactive oxygen species generation, cytochrome C release, caspase activation, DNA damage, poly(ADP-ribose) polymerase 1 activation, nicotinamide adenine dinucleotide/adenosine triphosphate depletion, and mitogen-activated protein kinase-mediated cell death pathways [12, 58, 60].

Risk factors for vancomycin-induced AKI include trough concentrations >15 mg/L, treatment duration >7 days, obesity, critical illness, and underlying chronic kidney disease. Prevention strategies involve TDM to avoid supratherapeutic levels, avoiding concomitant nephrotoxic drugs, and maintaining adequate hydration. Management typically includes drug discontinuation and supportive care; corticosteroids may be considered in acute interstitial nephritis, and high-flux hemodialysis has been reported, but is rarely employed [58].

## Linezolid

### Clinical use in NIC

Linezolid is a synthetic oxazolidinone antibiotic used to treat neonatal sepsis or pneumonia caused by methicillin-resistant coagulase-negative Staphylococcus or MRSA [61]. It is also approved for treating skin and soft tissue infections (SSTIs), community-acquired or hospital-acquired pneumonia, and infections caused by vancomycin-resistant Enterococcus in pediatric populations [62, 63]. Linezolid exhibits high tissue penetration, making it effective against Gram-positive infections in neonates [62, 64].

### Neonatal pharmacokinetics/pharmacodynamics considerations

Linezolid demonstrates significant interindividual variability in PK in neonates, particularly in preterm infants. Key determinants of clearance include body surface area (BSA) and renal maturation, as neonatal renal function is closely related to organ maturity and hemodynamic stability [26, 61].

The target PD parameter in adults is an $AUC_{0–24}$/MIC ratio of 80–120, while for children, a ratio of 80–100 has been suggested as an efficacy threshold [61]. A relatively linear correlation exists between trough concentration (C_min) and $AUC_{0–24}$h, making C_min a practical marker for efficacy and safety monitoring in neonates [26, 61]. Neonatal clearance of linezolid varies with PNA: Neonates older than 7 days exhibit approximately threefold higher clearance than neonates younger than 7 days [26, 63, 65].

Optimal intravenous dosing of linezolid in preterm neonates depends on BSA and the pathogen MIC [61]. Monte Carlo simulations suggest:

BSA 0.11 $m^2$: 6 mg/kg q8h; BSA 0.13 $m^2$: 7 mg/kg q8h; BSA 0.15 $m^2$: 9 mg/kg q8h

For pathogens with MIC=2 mg/L, slightly higher doses are recommended to achieve an adequate probability of target attainment (~90%). Adjust dosing based on steady-state C_min, clinical response, and adverse reactions. The Bayesian approach and population PK models are valuable tools to guide individualized dose adjustment [61].

Linezolid can be administered orally or intravenously, with almost 100% bioavailability, allowing easy conversion between routes in clinically stable neonates without dose adjustment [26, 63].

### Therapeutic drug monitoring

Target trough concentrations for linezolid are typically 2–8 μg/mL, and $AUC_{0–24}$h should range from 80–300 mg. h/L. Monitoring C_min is practical in neonates to ensure therapeutic efficacy while minimizing toxicity [26, 61].

### Safety, adverse effects

The major safety concern with linezolid in neonates is linezolid-induced thrombocytopenia, which occurs in approximately 20% of treated neonates [61]. Other

reported adverse events include mild gastrointestinal disturbances, myelosuppression, and anemia [62, 64]. Pediatric patients generally experience fewer bone marrow toxicities than adults [62]. Close monitoring of hematologic parameters is recommended, especially at higher exposures or prolonged therapy [63]. Linezolid has a low risk of Clostridium difficile infection despite diarrhea being a common side effect (Table 5) [63].

### Emerging challenges

Pharmacokinetic parameters vary widely among preterm and term neonates [26, 61]. Neonatal-specific PK/PD targets have not yet been well established [61, 63]. Under- or overexposure is possible depending on the pathogen MIC and patient characteristics [61, 63]. Furthermore, clinical data are limited for neonates with severe renal or hepatic impairment [63].

### Evidence gaps and research needs

Future studies are needed to validate population PK models in larger and more diverse neonatal populations [61]. Neonatal-specific PK/PD targets for different pathogens and clinical scenarios also need to be established [61, 63]. Long-term safety, particularly hematologic toxicity during prolonged therapy, should be investigated [62, 64]. Optimal dosing strategies in neonates with renal or hepatic dysfunction need to be determined [61, 63]. Finally, the effects of oral versus intravenous administration in neonates should be explored [26, 63].

## Ciprofloxacin

### Clinical use in the neonatal intensive care units

Ciprofloxacin, a synthetic fluoroquinolone antibiotic, is occasionally used in neonates to treat sepsis caused by MDR organisms. Although current neonatal sepsis guidelines do not recommend ciprofloxacin as a first-line therapy, its use has been increasing, particularly in severe infections caused by *Enterobacter* spp. resistant to standard therapy or when there is a high risk of secondary brain abscess formation or meningitis [66-68].

Broad-spectrum antibiotics, such as ciprofloxacin in NICU, may drive antimicrobial resistance and influence long-term childhood outcomes [68]. Musculoskeletal effects, such as arthropathy, are rare and typically reversible in pediatrics. Prospective studies are still needed to determine ciprofloxacin's safety in neonates [68].

### Neonatal pharmacokinetics/pharmacodynamics considerations and dosing

Ciprofloxacin is primarily eliminated via the kidneys, with approximately 65% of the unchanged drug excreted by glomerular filtration and tubular secretion. In neonates, PKs differ from other age groups due to higher extracellular fluid volume, immature renal and hepatic function at birth, and postnatal maturation of these organs. Birth weight and PNA are important covariates influencing ciprofloxacin clearance, but limited data are available, especially in preterm neonates. For practical dosing, neonates are stratified by PMA. Simulation studies suggest that 7.5 mg/kg every 12 hours for neonates with PMA <34 weeks and 12.5 mg/kg every 12 hours for neonates with PMA≥34 weeks achieve target AUC/MIC ratios in 90% and 84% of patients, respectively These calculations assume MIC~0.5 mg/L according to EUCAST standards The risk of overdose, defined as AUC above 291 mg.h/L, is low (<8%). Higher MICs require proportionally higher doses to achieve effective exposure [64].

### Safety considerations

Ciprofloxacin has a complex safety profile. Musculoskeletal adverse effects, including arthropathy, are generally reversible and not associated with long-term consequences. In animal models, potential neuroprotective or neurotoxic effects have been observed, but clinical significance in neonates remains uncertain. Co-administration of inotropic agents can reduce ciprofloxacin clearance, likely due to decreased renal perfusion, whereas mechanical ventilation or intrauterine growth restriction does not appear to significantly affect PKs (Table 5) [64, 69, 70].

## Colistin

### Clinical use in neonatal intensive care units

Colistin, a cationic polypeptide antibiotic in the polymyxin family, is increasingly used in NICUs for infections caused by MDR-GNB, particularly *Acinetobacter* spp., *Pseudomonas* spp., *Klebsiella* spp., and other carbapenem-resistant Enterobacterales. Colistin exhibits bactericidal activity primarily against aerobic Gram-negative bacilli by disrupting the bacterial outer membrane and interfering with divalent cation homeostasis, leading to cell lysis. Despite its historic nephrotoxicity and neurotoxicity concerns, colistin has re-emerged as a critical therapeutic option due to the global rise of MDR-GNB and the scarcity of new antimicrobials. Its clinical application in neonates should be guided by confirmed or

strongly suspected invasive infections, preferably after consultation with a neonatologist or pediatric infectious disease specialist. Use is generally restricted to sterile sites such as blood, cerebrospinal fluid (CSF), pleural or joint fluid, and should not be employed for colonization or non-invasive infections without clear clinical evidence [71-73].

## Neonatal pharmacokinetics/pharmacodynamics considerations

Neonates and young infants present unique PK/PD challenges due to immature renal and metabolic function, as well as altered volume of distribution. Colistin is administered as colistimethate sodium (CMS), a prodrug hydrolyzed in vivo to the active compound colistin base activity (CBA). This conversion is variable, leading to wide interindividual differences in plasma concentrations. Achieving therapeutic drug levels can be particularly challenging in neonates, especially when treating pathogens with MICs near the upper limits of susceptibility. Clinical and Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing breakpoints guide interpretation: For *Enterobacterales* and *Acinetobacter* spp., MICs ≤2 mg/L are considered susceptible or intermediate, while MICs ≥4 mg/L indicate resistance; for *P. aeruginosa*, MICs ≤4 mg/L are susceptible and >4 mg/L are resistant. The limited penetration of intravenously administered colistin into CSF and pulmonary tissue necessitates alternative routes to achieve adequate local concentrations. Intraventricular administration for CNS infection and inhalation for severe pulmonary infections may be required [72, 74, 75].

Optimal neonatal dosing requires consideration of both loading and maintenance doses. A loading dose of 4–5 mg CBA/kg body weight (approximately 118,000–150,150 IU/kg) is recommended for all neonates and infants, administered prior to initiating maintenance therapy to rapidly achieve therapeutic concentrations. Maintenance dosing in children over two years is typically 2.5 mg CBA/kg every 12 hours (≈74,000 IU/kg), while younger children follow the same dosing strategy pending further pharmacokinetic data [72]. Administration can be via slow intravenous bolus over 3–5 minutes or extended infusion over 30 minutes, with volume adjustments according to fluid requirements. In CNS infections or severe pulmonary infections, intraventricular or inhalation routes should be considered to overcome limited IV penetration [71].

## Therapeutic drug monitoring

Although routine TDM in neonates is often unavailable, monitoring plasma concentrations is highly recommended in critically ill patients due to the narrow therapeutic window and significant interindividual variability in CMS conversion. Achieving a target $AUC_{0–24}h$ of approximately 50 mg·h/L correlates with effective bacterial killing against isolates with MICs ≤2 mg/L, although neonatal data are limited and mostly extrapolated from adult studies [72].

## Safety and adverse effects

Intravenous colistin most commonly causes nephrotoxicity, with recent neonatal and pediatric studies reporting reversible kidney injury in 3–10% of patients, often exacerbated by concomitant nephrotoxic medications [71, 76]. The underlying mechanism involves acute tubular necrosis due to increased permeability of tubular epithelial membranes. Electrolyte imbalances—including hypokalemia, hypomagnesemia, hypocalcemia, metabolic alkalosis resembling Bartter syndrome, and hyponatremia—have also been observed and sometimes require electrolyte replacement [76]. Neurotoxicity is less frequent, generally reversible, and can present as paresthesia, ataxia, neuromuscular blockade, or cranial nerve dysfunction, particularly after prolonged therapy [71, 77]. Using CMS instead of colistin sulfate for parenteral administration, avoiding intramuscular injections, and careful monitoring have contributed to lower toxicity rates than historical data (Table 5) [71].

## Emerging challenges (resistance, multidrug-resistant)

Although colistin is considered a last-line agent for MDR-GNB, resistance has been increasingly reported, especially in *P. aeruginosa* and, to a lesser extent, in *Acinetobacter baumannii* and *K. pneumoniae* [71, 76]. Resistance mechanisms are predominantly adaptive or mutational, involving the PmrA–PmrB and PhoP–PhoQ regulatory systems, which modify the bacterial outer membrane and reduce colistin binding [76, 78]. The emergence of extensively drug-resistant (XDR) strains underscores the need for combination therapy, particularly in septic neonates with critical infections, where a second active agent (e.g. meropenem, tigecycline, or AGs) may improve outcomes and limit further resistance development [71, 79].

## Evidence gaps and research needs

Data on colistin use in neonates are limited, with dosing largely extrapolated from adults and minimal evidence for intraventricular or inhaled use. Further research is needed to optimize dosing, combination therapy, and assess long-term renal and neurological safety, including the role of TDM-guided and MIC-targeted strategies [71, 72].

## Amphotericin B

### Clinical use in neonates

Amphotericin B deoxycholate (D-AMB) remains the most commonly used antifungal agent for invasive candidiasis (IC) in neonates, although the use of lipid formulations of amphotericin B and echinocandins, such as caspofungin, is increasing [80, 81]. Invasive candidiasis in neonates is most frequently bloodstream-based (~70% of cases), with other sources including urine (~15%) and (CSF; ~10%). The cumulative incidence of IC is inversely proportional to birth weight, reaching up to 12% in infants weighing 401–750 g, and <1% in those weighing >1500 g. Approximately 80% of cases occur in preterm neonates within the first 42 days of life. Both birth weight and age at infection are strong predictors of subsequent mortality, which can reach 40% in neonates <750 g [82].

## Neonatal pharmacokinetics/pharmacodynamics considerations

PK data on amphotericin B formulations in neonates are limited, and tissue distribution is primarily extrapolated from preclinical and adult studies [80]. Preclinical studies indicate that lipid-based amphotericin B formulations achieve lower kidney concentrations than equivalent doses of D-AMB. In adults, liposomal amphotericin B (L-AmB) also shows lower renal penetration compared to D-AMB, but achieves relatively higher brain concentrations. In neonates, D-AMB appears to penetrate the CNS more effectively than in adults [80, 82]. Recent population PK studies of lipid amphotericin B complexes (e.g. ABLC) in neonates with invasive candidiasis demonstrate lower urinary exposure and undetectable or minimal CSF concentrations, similar to other lipid formulations [80, 83].

D-AMB: Recommended dose is 0.5–1.0 mg/kg once daily via 2–4 hour intravenous infusion. CNS penetration in preterm neonates may reach up to 40% of serum concentrations, compared to 5–10% in adults.

Lipid formulations: Three types of lipid-based amphotericin B are commonly used: Lipid complex, colloidal dispersion, and liposomal formulations. These allow higher dosing while reducing nephrotoxicity. Pharmacokinetic studies of the lipid complex by Würthwein et al. indicated that weight is the only significant factor influencing clearance. Vd and clearance were similar to those in older children, and CSF penetration remained low or undetectable [83].

## Safety and adverse effects

D-AMB is associated with nephrotoxicity and electrolyte disturbances (hypokalemia, hypomagnesemia), requiring close monitoring of renal function and electrolytes [82]. Lipid formulations reduce nephrotoxicity and allow higher doses, but may be suboptimal for clearing renal infections due to lower kidney concentrations (Table 5) [80, 83].

## Emerging challenges

The use of lipid formulations is often reserved for more critically ill neonates or those intolerant to D-AMB due to renal impairment. This may confound outcomes, potentially overestimating mortality associated with lipid formulations [80]. Resistance to amphotericin B is rare but has been reported in some Candida glabrata and Candida krusei isolates [82].

## Evidence gaps and research needs

PKs and PD data on amphotericin B in neonates are limited, and randomized trials comparing deoxycholate and lipid formulations are lacking. While the optimal treatment duration is unclear, at least 21 days of systemic therapy is typically recommended due to frequent CNS involvement. Further studies are needed to refine dosing and confirm the safety of high-dose lipid formulations in this group [83]

## Fluconazole

## Clinical use in neonatal intensive care units

Fluconazole, recommended by the infectious diseases society of America (IDSA), is used to treat invasive candidiasis, a common and often fatal infection in VLBW preterm neonates [68]. Fungal infections are more prevalent in preterm neonates and in those recently on antibiotics, with *C. albicans* being the most frequent species. Candida species are the third leading cause of LOS in VLBW, often linked to central venous catheters. *C. auris* has emerged in high-risk extremely preterm neonates exposed to broad-spectrum antibiotics and invasive procedures [4, 18].

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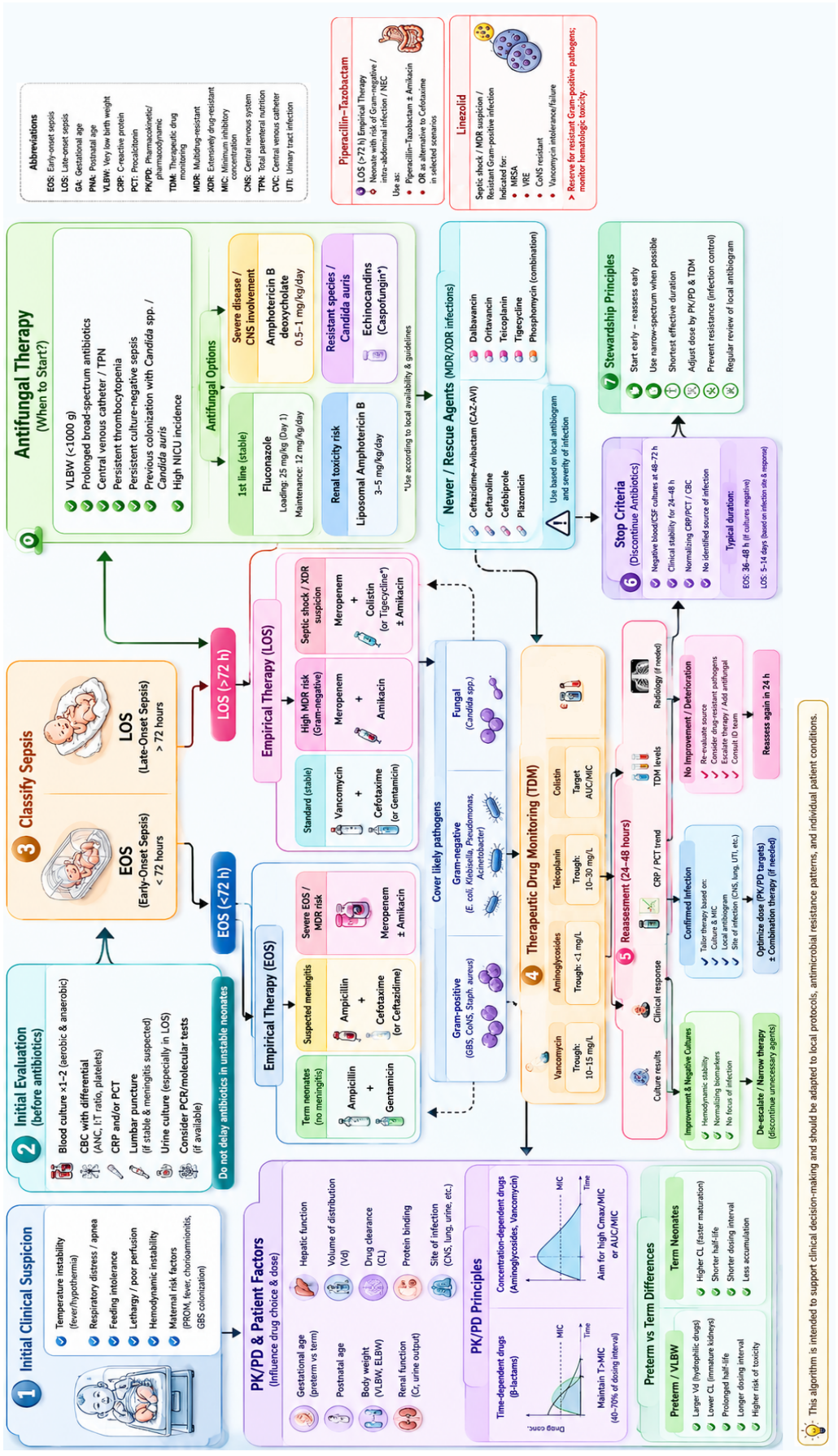



**Figure 1.** Evidence-based antimicrobial decision algorithm for neonatal sepsis management in the NICU

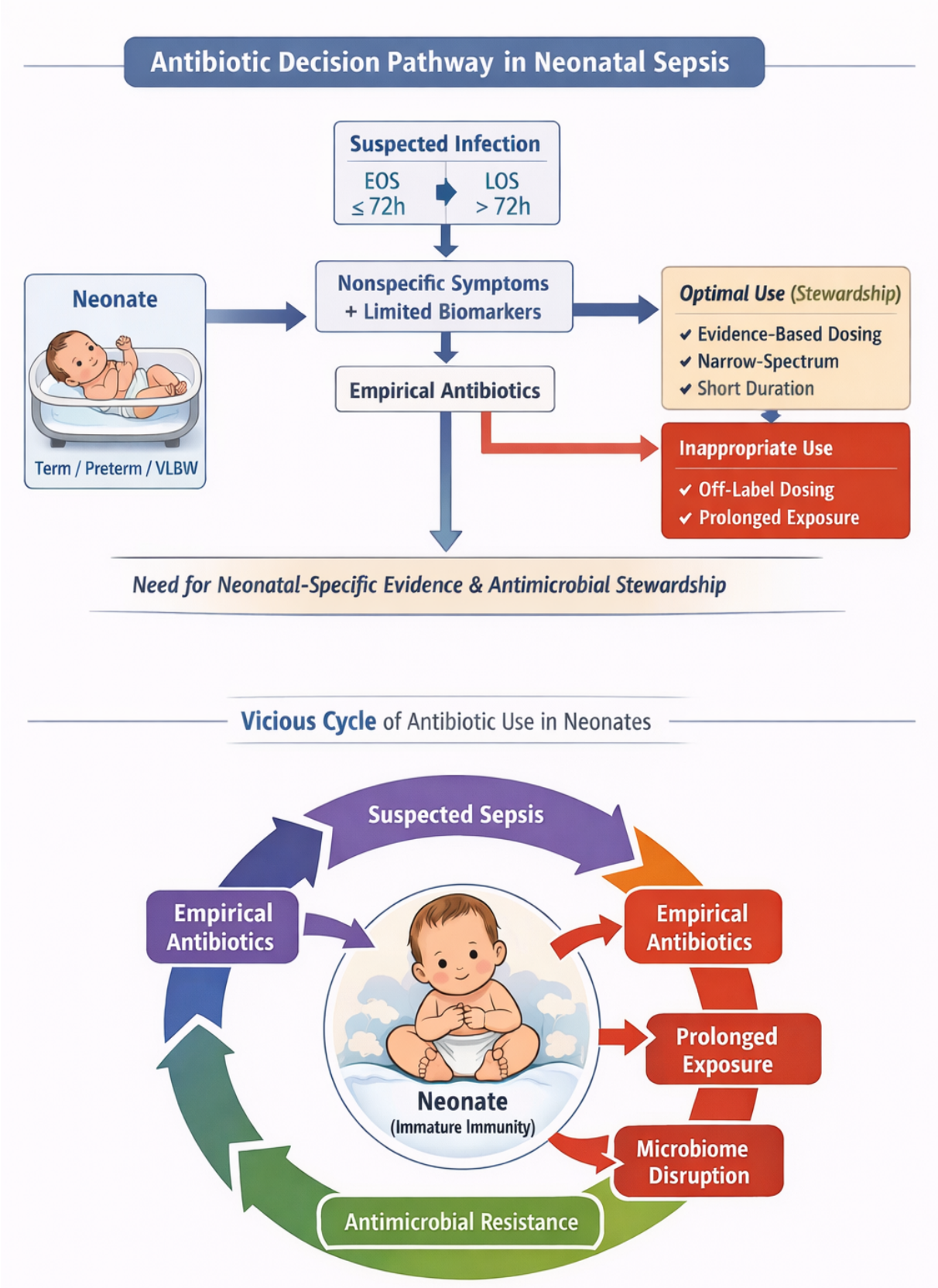



**Figure 2.** Antibiotic decision pathway in neonatal sepsis

In addition to systemic antifungal therapy, further evaluation is warranted for neonates with positive sterile body fluid or urine cultures for Candida species. Lumbar puncture and ophthalmologic examination are recommended to assess CNS and ocular involvement. Persistent positive cultures should prompt imaging of the genitourinary tract, liver, and spleen to identify disseminated infection [84].

Invasive fungal infections, including candidemia and systemic mycoses, are associated with high mortality rates in NICU patients, approximately 60% in critically ill neonates. In developed countries, candidiasis mortality is about 37%, while in LMICs it can reach up to 75%. Survivors of invasive candidiasis often develop neurodevelopmental impairment, with moderate to severe neurological deficits reported in approximately 57% of infants at 18 months corrected age [1].

## Neonatal pharmacokinetics/pharmacodynamics considerations

Fluconazole is generally well tolerated in neonates and can be used for both prophylaxis and treatment of susceptible fungal strains. Data on pharmacokinetics in neonates are limited, but the drug distributes widely into body fluids and tissues, including CSF, making it suitable for systemic infections with CNS involvement. Neonatal PK is affected by GA, PNA, and body weight, and renal function because fluconazole is primarily excreted unchanged via the kidneys [1, 68].

Neonates have a larger Vd (≈1 L/kg) and longer half-life (30–50 h) than adults. Dose intervals may be extended to 48 hours in infants with elevated creatinine (>1.2 mg/dL for >3 doses) to prevent drug accumulation [85].

In NICUs with high invasive candidiasis rates, prophylactic fluconazole can be considered for neonates weighing less than 1000 g [84]. For treatment, daily fluconazole at 12 mg/kg is typically used to achieve an AUC>400 mg·h/L, with a 25 mg/kg loading dose on day 1 to rapidly reach target levels. Fluconazole is well absorbed in infants and achieves roughly 80% of plasma concentrations in the CSF. Loading doses may be considered in the first 1–2 days to rapidly achieve therapeutic levels. For prophylaxis in high-risk neonates, 3–6 mg/kg twice weekly from birth to six weeks is effective, with dosing adjusted based on local Candida MICs [84-86].

Fluconazole can be administered prophylactically or therapeutically in neonates with susceptible fungal infections. Exact dosing regimens vary by GA and weight, and should be guided by local protocols, microbiological data, and, when possible, therapeutic drug monitoring [1, 68].

## Safety and adverse effects

Fluconazole is generally well-tolerated in neonates compared to other antifungals, such as amphotericin B and voriconazole, which are associated with nephrotoxicity, hepatotoxicity, thrombocytopenia, and dosing difficulties in preterm infants. Reported adverse effects of fluconazole in neonates are minimal, but monitoring is recommended, particularly for renal function and hepatic enzymes, during prolonged therapy or prophylaxis (Table 5) [1, 86].

## Emerging challenges

The emergence of MDR fungal strains, such as *C. auris*, poses challenges for prophylaxis and treatment in NICUs [4]. Infection control measures, environmental decontamination, adherence to sterilization protocols, and judicious use of antifungal agents are essential to reduce the incidence of invasive fungal infections in high-risk neonates [1, 4]. The emergence of MDR Candida strains, including *C. auris*, poses challenges for both treatment and prophylaxis [85].

## Evidence gaps and research needs

Prospective data on optimal fluconazole PK/PD targets in neonates remain limited, including loading doses and dose adjustments based on renal function. Further studies are needed to refine dosing strategies, evaluate prophylactic regimens, and determine long-term safety and resistance risks [84, 85].

## Newer agents

Novel options for CRE infections include aztreonam/avibactam, vaborbactam/meropenem (Carbavance), and plazomicin. These agents show promising activity, but neonatal evidence remains limited [14, 87, 88].

Third-Generation Cephalosporins – Ceftazidime is a third-generation cephalosporin approved for children >1 month. Neonatal use is limited to severe infections, particularly those involving CSF. In preterm neonates, CL increases with GA and GFR. During the first 10 days of life, CL accelerates alongside rising GFR, while Vd and elimination half-life decrease notably between days 3–10. Typical dosing is 25–50 mg/kg BW twice daily, but concomitant drugs reducing GFR, such as indomethacin, should be considered. Emerging XDR or

pan-drug-resistant (PDR) GNB pose a major concern in NICUs, with high mortality and limited treatment options. CAZAVI, combining ceftazidime with the novel β-lactamase inhibitor avibactam, is effective against resistant Enterobacteriaceae (including carbapenemase-producing *K. pneumoniae*), *P. aeruginosa*, and *A. baumannii*. CAZAVI is currently approved for use in infants >3 months [12, 43, 89].

Glycopeptides –Teicoplanin exhibits bactericidal activity against Gram-positive bacteria, including MRSA and CoNS, comparable to vancomycin. Unlike vancomycin (protein binding 30–55%, half-life 6–12 h), teicoplanin binds strongly to serum albumin (~90%), resulting in a prolonged half-life of 100–170 h. This allows once-daily IV or IM dosing. Teicoplanin is associated with lower nephrotoxicity and fewer adverse effects, making it a common choice in NICUs. A standard regimen consists of a 16 mg/kg loading dose on day 1, followed by 8 mg/kg daily maintenance, aiming for C_trough of 10–30 mg/L based on infection severity. Neonatal teicoplanin pharmacokinetics are highly variable, influenced primarily by body weight and estimated creatinine clearance, highlighting the need for TDM [12].

Phosphomycin and Tigecycline: Phosphomycin achieves high concentrations in body fluids, but monotherapy can rapidly induce resistance; combination therapy is recommended. Tigecycline is active against MDR Gram-positive and GNB but ineffective against *P. aeruginosa*. Its neonatal use is limited due to potential adverse effects on bone growth [14, 90, 91].

Ceftaroline and Cefobiprole : Ceftaroline, a fifth-generation cephalosporin, and Cefobiprole, a new-generation cephalosporin, are both effective against MDR Staphylococci. Ceftaroline is specifically active against MRSA and MDR *Streptococcus pneumoniae*, and it is approved for the treatment of SSTIs and community-acquired pneumonia in neonates and adults [92].

Early-phase studies in neonates demonstrated that the pharmacokinetics and safety profiles of both drugs are similar to those observed in older pediatric populations [14]. Additionally, a case series of Ceftaroline in LOS reported no treatment failures, with mild adverse events such as diarrhea, rash, and transient transaminase elevation [42].

Dalbavancin, oritavancin, and telavancin are lipoglycopeptides that are active against resistant gram-positive pathogens. PK and PD studies in neonates indicate that these agents achieve adequate target attainment and have a favorable safety profile [14, 92].

## Conclusion

Neonatal sepsis remains a major cause of morbidity and mortality, particularly in preterm and VLBW infants. Early diagnosis is challenging due to nonspecific signs, limited sensitivity of biomarkers, PK/PD variations, and widespread off-label antibiotic use, which increase the risk of suboptimal treatment and adverse drug effects. Optimized antimicrobial stewardship, early and accurate pathogen identification, and locally tailored empiric therapy are essential. Future research should focus on well-designed neonatal studies to refine dosing strategies, validate diagnostic tools, and address the challenges posed by resistant infections in this vulnerable population.

## Ethical Considerations

### Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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### Authors' contributions

Conceptualization, literature search, manuscript drafting, supervision, and critical revision: Faezeh Shadfar; and Leila Shadfar; Manuscript review: Ebrahim Salehifar.

### Conflict of interest

The authors declared no conflicts of interest.

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