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REVIEW

Antibiotic treatment for neonatal sepsis: changing trends and future directions

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Abstract

Background: Neonatal sepsis is a serious and life-threatening condition with high morbidity and mortality, especially in preterm neonates in a Neonatal Intensive Care Unit (NICU). This article provides an updated review on the aetiology and diagnosis of neonatal sepsis, antibiotic management and antibiotic stewardship.

Methods: A literature search was conducted in PubMed, Embase, Cochrane Library and Scopus in January 2025, using the following MeSH terms: "sepsis", "neonate" and "antibiotic". Meta-analyses, randomized controlled trials, clinical trials and reviews published in the English language from 2005 to 2025 with patients in the neonatal age group were included. A total of 715 articles were identified and screened, and 85 studies were included in the final review.

Results: Neonatal sepsis remains a leading cause of mortality, with distinct pathogens identified in early-onset and late-onset sepsis, ventilator-associated pneumonia, urinary tract infection and fungal infections. Early recognition, accurate diagnosis and timely commencement of empirical antibiotics are paramount for improved outcomes. Fungal prophylaxis is considered for at-risk neonates in some NICUs with a high incidence of fungal infection. Universal group B *Streptococcus* screening decreased the incidence of early onset sepsis, but the emergence of resistant strains of certain organisms present new challenges. Evidence-based antibiotic prescription guidelines, antibiotic stewardship programmes and quality improvement projects are essential for the prevention of antimicrobial resistance in the NICU.

Conclusion: Effective management of neonatal sepsis relies on early pathogen identification, judicious use of antibiotics and good antimicrobial stewardship. Future research directions include development of evidence-based protocols and improvement of rapid diagnostic techniques, combined with close monitoring and individualized care.

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Keywords: antibiotics, antibiotic stewardship, fungal infection, neonate, neonatal intensive care unit, sepsis.

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Introduction

Neonatal sepsis is one of the leading causes of neonatal mortality.[1–3] According to data from the Global Burden of Disease study from the Institute for Health Metrics and Evaluation, over 550,000 newborn deaths per year are caused by neonatal infection.[2] The incidence of neonatal sepsis is highest in low-income and middle-income countries, with age-standardized incidence rates ranging from 152 per 100,000 in low-income to 8.6 per 10,000 in high-income countries, and age-standardized mortality rates ranging from 18–45 per 10,000 in low-income countries to 1–3 per 10,000 in high-income countries.[2] The incidence of neonatal sepsis also varies according to gestational age. Mortality is significantly higher in preterm infants, with over 20% mortality in neonates with extremely low birth weight (ELBW) compared to 5–10% in term

neonates.[3,4] Surveillance studies found striking regional differences in pathogen distribution. Group B *Streptococcus* (GBS) and *Escherichia coli* are the dominating pathogens for early-onset sepsis (EOS) in high-income countries, whilst multidrug-resistant Gram-negative organisms occur frequently in South Asia and sub-Saharan Africa.[2]

Empirical broad-spectrum therapy is frequently initiated early for neonates with suspected infection,[1,3] which may lead to prolonged antibiotic exposure in infants who were sepsis-negative, leading to accelerated antimicrobial resistance. In the past decade, the incidence of antibiotic resistance to aminoglycosides, cephalosporins and carbapenems has increased.[4] It is important for clinicians to ensure timely, effective antimicrobial treatment whilst minimizing unnecessary antibiotic exposure.[1,3,4] Development of universal antibiotic guidelines is challenging due to differences in local epidemiology and diagnostic capacity, and there is an urgent need for individualized approaches guided by local resistance data. Multicentre collaborations and stewardship programmes also provide opportunities to unify practices and provide evidence for quality improvement.

This review aims to examine current epidemiology, emerging pathogens and management of neonatal sepsis. We will also explore antibiotic stewardship strategies and future directions for optimizing antibiotic use in this vulnerable population.

Methods

A comprehensive literature search was conducted in PubMed, Embase, Cochrane Library and Scopus in January 2025. The search strategy employed the MeSH terms "sepsis," "neonate" and "antibiotic". Filters were applied to include clinical trials, randomized controlled trials, meta-analyses, systematic reviews and narrative reviews published in English over the past 20 years, restricted to studies involving human neonates from birth to 1 month of age.

The initial search identified 715 records. After removal of duplicates and exclusion of articles not directly relevant to neonatal sepsis or antibiotic stewardship, 85 studies met the eligibility criteria and were included in the final analysis. Screening and selection followed standard review methodology. This narrative review is based on, but not limited to, the publications retrieved through the search strategy.

Review

EOS in neonates

EOS is defined as neonatal infection with positive cultures occurring within 72 hours after birth.[1,3] EOS is usually caused by intrauterine infection acquired from transplacental transmission, ascending infection after membrane rupture, or exposure to infectious organisms in the birth canal during vaginal delivery.[3–5] The overall incidence of EOS is reported as 0.8 cases per 1000 livebirths in the USA[6] and 0.7 cases per 1000 livebirths in the UK.[5] A higher incidence of 3.9 cases per 1000 live births is reported in low-income and middle-income countries.[7] Preterm infants have three to ten times higher incidence of infection than full-term infants[3]. The incidence of EOS is 6 per 1000, 20 per 1000 and 32 per 1000 at gestations <34 weeks, <29 weeks and 22–24 weeks, respectively.[8–10] Mortality rates from EOS range from 1.6% at >37 weeks to 30% at 25–28 weeks and 50% at 22–24 weeks of gestation.[6,11,12] Survivors are at increased risk of cerebral palsy, impaired cognitive outcome and long-term adverse neurodevelopmental sequelae.[13–15]

GBS is a leading cause of EOS in neonates. In the 1990s, the incidence of GBS was one to two cases per 1000 live births in the USA, with a mortality of 5–10%.[16] In 2002, guidelines on universal GBS screening for all pregnant women at 35–37 weeks of gestation were published by the Centers for Disease Control and Prevention (CDC) and the American College of Obstetricians and Gynecologists.[16–18] Since then, universal GBS screening has been adopted by many countries, including the USA, Canada and various countries in Europe and Asia.[19–21] Other countries, including the UK, use a risk-based approach for GBS screening.[19] In the universal screening programme, GBS screening is performed for all pregnant women between 35 and 37 weeks of gestation, whilst in the risk-based approach, screening is performed for women with risk factors.[19] Intrapartum antibiotics will be given to women with positive GBS screening results and to all high-risk cases as indicated.[22,23] Recommendations for intrapartum antibiotics is penicillin or ampicillin given at least 4 hours before delivery. Cefazolin, clindamycin or vancomycin could be considered for women with penicillin sensitivity.[24–26] After implementation of a GBS screening programme in the USA, early-onset GBS decreased from 1.5 to 0.31 per 1000 live births between 1993 and 2003 (refs. [9,27]) and further decreased to 0.22 per 1000 live births in 2014 (refs. [9,28]), remaining relatively static since then.

Despite the decrease in early-onset GBS infection after implementation of screening, a surveillance study in the USA involving 217,480 neonates still identified GBS as the most common cause of EOS in full-term neonates (52% of cases), followed by *E. coli* (15%).[4] In preterm neonates of 22–36 weeks of gestation, *E. coli* is the most common causative organism (51% of cases), followed by GBS (13%).[4] Other organisms associated with EOS include *Enterobacter*, *Enterococcus*, *Klebsiella*, *Listeria*, other enteric gram-negative bacilli, *Staphylococcus aureus* and *viridans* group or *bovis*

group streptococci.[4,29–31] Surveillance studies in other countries also showed similar results.[32]

Whilst timely antibiotic treatment for neonatal sepsis is essential, it is also important to ensure accurate identification of neonates at risk to avoid overuse of antibiotics in the neonatal period. Numerous tools have been proposed for the assessment of EOS in neonates. The American Academy of Pediatrics guidelines[1,8] and the UK National Institute for Health and Care Excellence (NICE) guidelines[33] provide evidence-based guidance on management of suspected or proven EOS in neonates. The American Academy of Pediatrics guideline recommends the use of either categorical risk assessment, multivariate assessment (using the online Neonatal EOS risk calculator or Sepsis Calculator)[34] and serial observations.[35] The Sepsis Calculator developed by Kaiser Permanente Northern California is a risk-based prediction model for neonates at risk of EOS and is used in many neonatal centres.[36–41] The UK NICE guidelines use 'red flag' and 'non-red flag' indicators to identify infants who require sepsis evaluation and treatment.[33,40] A recent meta-analysis has shown that implementation of these risk assessment tools has resulted in significant reduction of antibiotic usage, laboratory tests and admissions to the neonatal unit, with no difference in mortality, culture-positive EOS and readmissions.[42]

Most contemporary guidelines recommend treatment with a penicillin and an aminoglycoside antibiotic, for example, ampicillin and gentamicin[43,44] or benzylpenicillin and gentamicin.[45] In cases of suspected meningitis, gentamicin is changed to cefotaxime due to poor cerebrospinal fluid penetration of gentamicin, and a meningitic dose of antibiotics should be given.[44–46] Table 1 shows the common organisms and recommended antibiotics and duration for EOS. Of note, whilst GBS strains show almost 100% sensitivity to penicillin,[47] recent studies have shown a significant increase in resistant strains of *E. coli*, especially in very-low-birth-weight (VLBW) neonates. One study showed that only 22.2% *E. coli* isolates were susceptible to ampicillin and 7.8% were resistant to both ampicillin and gentamicin.[4] These changing trends with the increase in resistant *E. coli* strains suggest that ongoing microbiological surveillance, good antibiotic stewardship and research into new prevention strategies are indicated.

Late-onset sepsis

Late-onset sepsis (LOS) is defined as neonatal sepsis with positive blood cultures occurring after 72 hours of life.[3,48] For preterm neonates with prolonged hospital stay, LOS refers to any episode of sepsis occurring between 72 hours till hospital discharge. LOS is primarily caused by nosocomial infection or exposure to pathogens in the community environment.[49] The overall incidence of neonatal LOS is reported as 0.61% to 14.2% in hospitalized neonates.[50] However, the risk of LOS increases with decreasing gestation and birth weight, from 1.6% in full-term[51] up to 50–65.5% in extremely preterm and extremely low birth weight neonates.[52–56] Besides prematurity, risk factors for LOS include small for gestational age, critical illness, presence of central catheters, mechanical ventilation, prolonged total parenteral nutrition, previous culture-positive EOS and history of prolonged antibiotic use.[57,58] These risk factors are attributed to immaturity of the immune system and absence of transplacental transfer of maternal IgG in preterm neonates, as well as the presence of medical devices such as central venous catheter and endotracheal tube, which provide a portal of entry for pathogenic organisms.[57]

Organisms causing LOS vary between different geographical and socioeconomic regions. Surveillance reports from the NICHD (USA),[59] NeonIN network (England)[51] and German Neonatal Network[60] revealed that, in developed, high-income countries, over 50% of LOS is caused by coagulase-negative *Staphylococci* (CoNS). Other common Gram-positive pathogens causing LOS are *S. aureus* (4–18%), *Enterococcus* spp. (3–16%) and GBS (1.8–8%).[51,54,55,60] In neonates with central venous catheters, CoNS and *S. aureus* are the most prevalent organisms, and recent studies showed an increasing incidence of methicillin-resistant *S. aureus* (MRSA), ranging from 11% to 23% within the *S. aureus* group.[51] Some organisms in the CoNS group, especially *S. epidemidis*, have biofilm-forming capabilities, which make them difficult to eradicate and may lead to antimicrobial resistance. Gram-negative organisms account for 16–50% of all LOS.[50] Nationwide surveillance studies showed that the most prevalent Gram-negative organisms in LOS are *E. coli* (3–13%), *Klebsiella* spp. (4–5%), *Pseudomonas* spp. (2–5%) and *Enterobacter* spp. (2.5–21%).[54] A systematic review on Gram-negative LOS in 13 countries (including both high-income and low-income countries) showed that *Klebsiella* spp., *Enterobacter* spp. and *Escherichia* spp. account for 50–70% of Gram-negative LOS. The distribution of organisms found in NICU settings varies. A high prevalence of *E. coli* was found in NICUs in Canada, whilst *Klebsiella* spp. is more prevalent in NICUs in Israel.[50] Many guidelines suggest two antibiotics to cover for Gram-positive and Gram-negative bacterial infection as empirical treatment for LOS.[47] Beta-lactam antibiotics, like ampicillin and oxacillin, can be used for Gram-positive coverage, but vancomycin is preferred if CoNS or MRSA infection is suspected, especially if an indwelling central venous catheter is present. Antibiotics for Gram-negative coverage include aminoglycosides (e.g. gentamicin and amikacin) and third/fourth-generation cephalosporins or carbapenems. The duration of treatment

Table 1. Neonatal sepsis and related infections — definitions, causative organisms and empirical treatment in NICU.[1,8,9,12,43,46,57,59,70–72] Drug doses listed in these tables are provided to the best of our knowledge; clinicians should always verify with approved prescribing references or drug manuals before use.

Condition	Definition	Causative organism(s)	Suggested empirical antibiotics and treatment duration
Early-onset sepsis	Neonatal sepsis with positive blood or cerebrospinal fluid culture within 72 hours after birth	**Term neonates (≥37 weeks):** GBS (predominant) **Preterm neonates (<37 weeks):** *E. coli* (predominant) Others: *Enterobacter*, *Enterococcus*, *Klebsiella*, *Listeria*, other enteric gram-negative *Bacilli*, *S. aureus*, *S. viridans*, *S. bovis*	**NICE guidelines:** - Benzylpenicillin or ampicillin + gentamicin - Benzylpenicillin or ampicillin + cefotaxime if meningitis is suspected **American Academy of Pediatrics Guidelines:** - Ampicillin + gentamicin or cefotaxime - Ampicillin + cefotaxime if meningitis suspected **Listeria risk:** Ampicillin must be included **Gentamicin is generally avoided in meningitis due to poor cerebrospinal fluid penetration** **Duration:** - Uncomplicated sepsis: 7–10 days (culture-directed) - Meningitis: **GBS:** Minimum 14 days **Gram-negative (e.g. *E. coli*, *Klebsiella*):** ≥21 days
Late-onset sepsis	Neonatal sepsis with positive cultures after 72 hours of life until initial hospital discharge	**Gram-positive:** *CoNS*, *S. aureus* (+MRSA), *Enterococcus*, GBS **Gram-negative:** *E. coli*, *Klebsiella* spp., *Pseudomonas* spp., *Enterobacter* spp.	**Combination therapy covering Gram-positive and Gram-negative organisms:** **Gram-positive:** Beta-lactam antibiotics (e.g. ampicillin, oxacillin) or vancomycin (for MRSA) **Gram-negative:** Aminoglycoside (e.g. gentamicin), 3rd/4th-generation cephalosporin
Catheter-related bloodstream infection	Primary bloodstream infection in neonates with a central line within 48 hours prior to sepsis onset	*CoNS*, *S. aureus* (+MRSA), *K. pneumoniae*, *E. coli*, *P. aeruginosa*, *E. cloacae* **Fungal infections:** *Candida* spp.	**Empirical treatment:** - Vancomycin (for Gram-positive coverage: MRSA, CoNS) - Aminoglycoside (e.g. gentamicin, amikacin), 3rd/4th-generation cephalosporin - High resistance risk: piperacillin-tazobactam or carbapenems **Duration:** - **Uncomplicated infections:** 7–14 days (14 days for *S. aureus*, *Enterococcus* and Gram-negative organisms) - **Complicated infections:** Individualized based on complications
Ventilator-associated pneumonia	Pneumonia in mechanically ventilated neonates after ≥48 hours of ventilation	*K. pneumoniae*, CoNS, *P. aeruginosa*, *A. baumannii*	**No consensus guidelines** Empirical treatment should be guided by nosocomial flora and unit-specific resistance patterns
Urinary tract infection	Positive bacterial culture from catheterized urine (CSU) or suprapubic tap urine (SPU) **(CSU/SPU:** ≥10^4 CFU/mL, **Clean catch:** ≥10^5 CFU/mL)	**Term neonates:** *E. coli* (most common), *Klebsiella*, *Proteus*, *Enterobacter*, CoNS, *Enterococcus*, *S. aureus* **Preterm neonates:** *E. coli*, CoNS, *Klebsiella*, *Candida*	**Empirical treatment:** Ampicillin or vancomycin (if hospital-acquired) + aminoglycoside (e.g. gentamicin) **Duration:** 10–14 days

CoNS, coagulase-negative *Staphylococcus*; GBS, group B *Streptococcus*; MRSA, methicillin-resistant *Staphylococcus aureus*.

is usually 7–10 days for uncomplicated ventilator-associated pneumonia (VAP). Due to widespread use of broad-spectrum antibiotics like vancomycin and carbapenem as empirical treatment for suspected LOS, there are growing concerns about the emergence of multidrug-resistant bacteria in NICU.[61–64] Antibiotic stewardship programmes should aim at optimizing treatment whilst reducing resistance.

LOS can occur due to infection in various sites in the body, for example, urinary tract infections, meningitis or necrotizing enterocolitis.

Ventilator-associated pneumonia

Neonates on mechanical ventilation are at risk of VAP. The definition of VAP is pneumonia occurring in mechanically ventilated neonates after more than 48 hours of mechanical ventilation.[65,66] The incidence of VAP ranges from 1.4–7 episodes per 1000 ventilator days up to 16.1–89 episodes per 1000 ventilator days in developing countries.[29] The choice of empirical antibiotics varies according to nosocomial flora, local resistance rates and practice in different NICUs. Clinical features include thick, purulent sputum, desaturation, CO_2 retention or deterioration of ventilation characteristics, with new emergence or progression of radiographical features such as pulmonary infiltration, consolidation or pleural effusion.[66] The definitions in CDC guidelines are widely used for the diagnosis of VAP, but there are no specific criteria for neonates. Some European guidelines like the 'Neo-KISS' module of the German National Nosocomial Infection Surveillance System,[67] provides VAP definitions for VLBW neonates below 1500 g and the Dutch surveillance study for nosocomial NICU infections has used VAP definitions specially for neonates.[68] The most predominant organisms found in VAP are *Klebsiella* spp., *Pseudomonas*, *Acinetobacter* and CoNS. Many guidelines suggest two antibiotics to cover for Gram-positive and Gram-negative bacterial infection as empirical treatment for LOS.[47,61] The antibiotic regimen should be adjusted once the infective organism and antimicrobial sensitivity profile are available. The duration of treatment is usually 7–10 days for uncomplicated VAP. Care bundles for VAP prevention with measures like hand hygiene, ventilator circuit surveillance, oral care and timely extubation are used in many NICUs with significant improvement in VAP rates after implementation.[66]

Catheter-related bloodstream infections

Central venous catheters, including umbilical venous catheters and peripherally inserted central catheters, are essential in NICU care but pose a risk for catheter-related bloodstream infections (CRBSI). Prompt diagnosis and appropriate antibiotic therapy are crucial to improving outcomes.

CRBSI are diagnosed by positive blood cultures obtained from the indwelling catheter and/or peripheral vein. Adequate blood volume of at least 1 mL is needed to ensure accuracy in culture sensitivity testing.[69] Common pathogens include CoNS (~50% of cases), *S. aureus* (including MRSA), Gram-negative bacteria (e.g. *E. coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*) and *Candida* spp., especially in extremely preterm infants.[70] Empirical antibiotics should be initiated promptly after obtaining cultures. The choice of antibiotics depends on local antimicrobial resistance patterns and the infant's risk factors. First-line antibiotic regimens include vancomycin (for Gram-positive coverage, particularly if MRSA or CoNS are suspected) and an aminoglycoside (gentamicin or amikacin) or third-generation cephalosporin for Gram-negative coverage. In cases of severe sepsis or high resistance risk, piperacillin-tazobactam or carbapenems may be used. Antibiotic therapy should be adjusted according to culture results. The duration of treatment is usually 10–14 days, but can be up to 21 days. Catheter removal is strongly advised in *S. aureus*, *P. aeruginosa*, Gram-negative bacilli and *Candida* infections.[71] Many NICUs have strategies to prevent CRBSI,[72,73] including strict aseptic techniques during catheter insertion and maintenance, antimicrobial locks in high-risk cases, early catheter removal when no longer needed, and antimicrobial stewardship programmes.

Urinary tract infections

Urinary tract infections (UTI) occur in 1–3% of term neonates and 3–8.5% of VLBW infants.[74,75] A recent study reported a 7% incidence of UTI in preterm, VLBW neonates delivered at ≤32 weeks of gestation in the NICU.[76] Risk factors include prematurity, male sex, vaginal delivery, urinary catheterization, renal anomalies, prolonged antibiotics and hospitalization. UTIs can arise via ascending infection or haematogenous spread. A large cohort study on 1162 cases of neonatal UTI showed a high concordance rate of 13% with a positive blood culture collected within 3 days with the same pathogenic organism, indicating that haematogenous spread plays an important role in pathogenesis.[77] Ultrasound abnormalities are present in 35–40% of preterm neonates, with 5% showing major anomalies.[78,79] Common pathogens are *E. coli* (70–90%), *Klebsiella* (10–20%) and *Enterobacter* (5–10%).[80–82] The clinical manifestations of UTI in neonates overlap with LOS.[83,84] Therefore, in neonates, empirical broad-spectrum antibiotics covering for LOS are usually prescribed before urine culture results are available. Recent studies have shown a high antimicrobial resistance rate in *E. coli* to ampicillin (87%). Suggested (empirical) antibiotics for the treatment of UTI are shown in Table 1. Once the pathogen and antimicrobial sensitivity are available, the antibiotic regimen should be adjusted accordingly.

Fungal infections

Invasive fungal infections are the third most common cause of LOS in VLBW neonates.[59,83,84] The incidence of invasive fungal infection in the NICU is 0.5–20%[85–87] and is inversely correlated to birth weight, with the highest incidence of 5–20% in ELBW infants.[87] The mortality rate of invasive fungal infection in neonates is 20–40%. Preterm infants are especially vulnerable due to their immature immune system with immature skin and mucosal barriers, along with prolonged use of broad-spectrum antibiotics, which decreases commensal bacteria and allows candida colonization, and disruption of epithelial barriers due to insertion of central venous catheters, endotracheal tubes or urinary catheters. Other risk factors for invasive fungal infections include the use of glucocorticoids, histamine-2 receptor antagonists and intravenous lipid emulsions in total parenteral nutrition.[87] Common organisms causing invasive disease are *Candida albicans*, accounting for 60–75% of invasive candidial infections, and *Candida parapsilosis* (20–30%),[86,87] followed by *Candida tropicalis*, *Candida lusitaniae*, *Candida glabrata* and *Candida krusei*, which together account for 5–10% of invasive candidial infections.

Clinical features of invasive candidiasis can be non-specific. Infants may present with features suggestive of LOS, including apnoea, respiratory distress, haemodynamic instability and lethargy. The likelihood of invasive fungal infection is increased if these features are associated with hyperglycaemia and thrombocytopenia,[88–90] and screening for fungal infection should be performed. Candidaemia can spread to involve multiple organ systems haematogenously or via septic emboli, most commonly in the kidneys (5–30%), heart (5–15%), central nervous system (5–64%), eyes (3–50%), bones, joints, skin and lungs[91–93]. If invasive candidiasis is diagnosed, further investigations are needed to determine the extent of the disease. These include urine and cerebrospinal fluid cultures, echocardiogram to screen for vegetations and atrial thrombi, cranial ultrasound for ventriculitis or cerebral abscess, ultrasound kidneys and abdomen for fungal mass or abscess, and ophthalmological examination for chorioretinitis and endophthalmitis.

Identification of the invasive organism is important for guiding antifungal treatment, as the susceptibility profiles of different *Candida* species may vary. *C. albicans* is usually sensitive to amphotericin B and fluconazole, *C. glabrata* and *C. krusei* are less susceptible to the azole antifungal agents (e.g. fluconazole), *C. lusitaniae* is generally resistant to amphotericin B, and there is emerging evidence showing that *C. auris* is often multidrug resistant.[94, 95]

The occurrence of invasive non-*Candida* fungal infections in neonates is very rare but can cause significant morbidity and mortality. These include aspergillosis, zygomycosis, *Malassezia* infection, trichosporonosis, Pichia sepsis, cryptococcosis, coccidioidomycosis, blastomycosis and dermatophytosis.[89,93,94]

Medications used for treatment of invasive fungal infection in the NICU are shown in Table 2. The most widely used first-line treatment is amphotericin B from the polyene class of antifungal agents.[92,93,95] It exerts its effect by disruption of the integrity of the fungal cell membrane, causing cell death. Despite its efficacy, amphotericin B is associated with side-effects, including nephrotoxicity and infusion-related complications. Lipid-based preparations of amphotericin B, such as liposomal amphotericin B and amphotericin B lipid complex, are associated with a lower risk of toxicity. Another first-line antifungal agent is fluconazole from the azole drug class, which has a broad spectrum of activity and excellent oral bioavailability.[93,95] Fluconazole is also used for fungal prophylaxis in high-risk neonates (see section later). Second-line antifungals include echinocandins (e.g. caspofungin and micafungin), which are used for invasive fungal infections resistant to amphotericin B and fluconazole. Flucytosine, a nucleoside analogue, is occasionally used in disseminated candidiasis.[93,95]

Fungal prophylaxis in the NICU

Numerous studies have demonstrated that the use of fluconazole prophylaxis is effective for the prevention of invasive candidiasis in NICUs with a high incidence of invasive candida disease.[88,96] A Cochrane review on 15 eligible trials (n=1690 patients) found a statistically significant reduction in the incidence of invasive fungal infection in neonates receiving fungal prophylaxis compared to placebo or no drug (risk difference (RD) -0.09, 95% CI -0.12 to -0.06) but no difference in the risk of death prior to hospital discharge.[97] However, the incidence of invasive fungal infection was very high in the control groups of many of the included trials, and there were no results on long-term outcomes. Another meta-analysis in 2023 on eight eligible randomized controlled trials and 1635 participants showed that fluconazole prophylaxis decreased the risk of invasive candidiasis, with a relative risk (RR) of 0.37 (95% CI 0.21–0.65), as well as the risk of fungal colonization (RR 0.32, 95% CI 0.24–0.41) and in-hospital mortality (RR 0.75, 95% CI 0.61–0.91).[98] Enteral or orally administered nystatin has been shown to be effective in reducing invasive candidiasis in preterm infants[97–101] but there was a paucity of data in infants <750 g. The majority of studies have demonstrated the safety of fluconazole prophylaxis and the lack of emergence of resistance.

The Infectious Diseases Society of America guideline published in 2016 recommends the use of intravenous

Table 2. Antifungal agents for neonatal invasive candidiasis.[91,95,99]. Drug doses listed in these tables are provided to the best of our knowledge; clinicians should always verify with approved prescribing references or drug manuals before use.

Drug	Dosage	Indications	Side-effects	Monitoring
Amphotericin B	1 mg/kg/day IV	First-line for disseminated candidiasis, catheter-associated candidaemia, central nervous system infections, invasive *Aspergillus* and *Malassezia* infections, zygomycosis	Nephrotoxicity, liver dysfunction, anaemia, thrombocytopenia, hypokalaemia, infusion reactions Limited central nervous system penetration	CBP, LFT, RFT, electrolytes
Liposomal amphotericin B	3–5 mg/kg/day IV	Alternative to amphotericin B for treatment of invasive fungal infections including candidaemia, fungal meningitis, renal or hepatosplenic candidiasis, and disseminated fungal disease Preferred over amphotericin B in patients with renal impairment and extremely preterm neonates because of its lower risk of nephrotoxicity and improved central nervous system penetration	More expensive than amphotericin B Less effective for lower urinary tract fungal infections due to low urinary excretion	LFT, CBP, RFT, electrolytes
Fluconazole	12 mg/kg/day IV/PO	Alternative first-line treatment for *C. albicans* and *C. parapsilosis* Fungal prophylaxis in high-risk neonates	Renal and hepatic dysfunction	LFT, RFT
Micafungin	4–10 mg/kg/day IV	Resistant *C. albicans* infections; first-line for *C. glabrata*, biofilm infections; adjunct therapy for refractory infections	Renal and hepatic dysfunction, thrombophlebitis (for peripheral infusion) Limited penetration in eye and central nervous system	CBP, LFT
Caspofungin	25 mg/m²/day IV	Infections due to *Candida spp.* resistant to amphotericin B and fluconazole	Hypokalaemia, hepatic dysfunction, transient anaemia, thrombocytopenia	CBP, LFT, electrolytes
Flucytosine	25 mg/kg per dose PO q6h	Occasional use for disseminated candidiasis with central nervous system and urinary tract involvement	Bone marrow toxicity	Peak/trough serum levels, CBP

CBP, complete blood picture; IV, intravenous; LFT, liver function test; PO, oral; RFT, renal function test.

or oral fluconazole prophylaxis at a dose of 3–6 mg/kg twice weekly for 6 weeks in infants with birth weight <1000 g who are admitted to NICUs with high rates (>10%) of invasive candidiasis.[102] Oral nystatin, 100,000 units three times daily for 6 weeks, is an alternative to fluconazole in neonates with birth weights <1500 g in situations in which availability or resistance preclude the use of fluconazole.[101] A recent review has recommended that, even in NICUs with low rates of invasive candidiasis, fluconazole prophylaxis can also be considered in high-risk ELBW infants with central venous catheters and receiving broad-spectrum antibiotics.[103]

Antibiotic stewardship in the NICU

Antibiotics are essential in managing neonatal sepsis and are amongst the most frequently prescribed medications in NICUs.[104–106] As neonatal sepsis can be life-threatening, empirical broad-spectrum antibiotics are often initiated early. However, practices on de-escalation and treatment duration vary widely, with many NICUs lacking standardized guidelines. Schulman et al. reported a 40-fold variation in prescribing across 50,000 patients in 127 California NICUs.[105–108] A multicentre study of four tertiary NICUs found 28% of courses and 24% of antibiotic days non-adherent to CDC criteria, with 32% of vancomycin and 43% of carbapenem days deemed inappropriate.[107–109] A study in Canada between 2020 and 2023 revealed that inappropriate prescriptions occurred in 11.4–26.3% of cases. Inappropriate antibiotic use is associated with adverse outcomes in neonates. Prolonged therapy in preterm neonates is associated with increased risk of abnormal neuroimaging, high-grade retinopathy of

prematurity, bronchopulmonary dysplasia, mortality and neurodevelopmental delay.[110–113] Excessive broad-spectrum use also drives resistance, including cephalosporin-resistant *Enterobacter cloacae*, carbapenem-resistant *Enterobacteriaceae* and vancomycin-resistant *Enterococcus*.[114–115]

Over the past decade, the growing recognition of the adverse consequences of antibiotic overuse in the NICU has led to global efforts to strengthen antimicrobial stewardship. Antibiotic stewardship programmes have emphasized multidisciplinary collaboration between neonatologists, infectious disease specialists, microbiologists, pharmacists and nursing staff to design and implement protocols best suited for local epidemiology and resistance patterns.[116,117]

Core methods of antibiotic stewardship include the implementation of evidence-based guidelines, standardized empirical antibiotic regimens and prospective audits with feedback. Diagnostic methods like the sepsis risk calculators, rapid molecular assays and biomarkers will enable reliable assessment of infection risk and earlier pathogen identification.[41,42,118–120] Therapeutic drug monitoring for antibiotics like aminoglycosides and vancomycin will ensure drug efficacy whilst minimizing toxicity.[121] Moreover, implementation of central venous catheter care bundles, which incorporate strict hand hygiene, environmental decontamination, and standardized line maintenance protocols, has been associated with significant reductions in baseline sepsis rates.[122] Quality improvement methods for antibiotic stewardship include Plan–Do–Study–Act cycles to iteratively refine protocols, mandatory documentation of antibiotic end dates to prevent prolonged courses, prospective audit and feedback to guide prescribers, continuous education sessions to reinforce best practices, and transparent reporting of prescribing trends to sustain culture change.[120,123–126]

Outcomes from quality improvement initiatives have demonstrated significant reductions in antibiotic utilization rates without compromising patient safety. For example, in a large Chinese NICU, total antibiotic consumption fell from 791.1 to 466.3 days of therapy per 1000 patient-days, with discontinuation within 72 hours achieved in 47.5% of rule-out sepsis cases compared to 11.6% at baseline; importantly, the prevalence of multidrug-resistant bacteria declined from 67.2% to 48.9% following stewardship interventions.[123] Similar improvements have been reported in other studies. Paul et al. reported a Plan–Do–Study–Act cycle approach for antibiotic stewardship in a Level 4 NICU, which resulted in a reduction in overall antibiotic utilization from 343 to 270 days of therapy per 1000 patient-days and decreased vancomycin use from 42% to 12% of infants treated empirically, without adverse effects.[120] Juliano et al. implemented targeted antibiotic stewardship for culture-negative sepsis, which led to a decrease in median treatment duration from 7 to 5 days and a reduction of unnecessary antibiotic exposure by 27%.[124] These studies illustrate that antibiotic stewardship not only decreases unnecessary exposure to broad-spectrum agents but also contributes to preventing the emergence of multidrug-resistant organisms in NICUs.

Antibiotic stewardship in NICUs is evolving towards greater precision and integration with new technologies. Future strategies include the use of rapid point-of-care diagnostics and machine learning algorithms to refine risk prediction and guide individualized therapy. Unification of stewardship practices and benchmarking across hospitals can be achieved by multicentre collaborations. There is increasing use of electronic prescribing systems with built-in stop dates, together with real-time surveillance dashboards to track resistance trends.[125] Long-term follow-up studies are needed to evaluate the impact of stewardship on microbiome development and neurodevelopmental outcomes and to guide the directions for future research.

Conclusion

Effective management of neonatal sepsis in the NICU depends on timely diagnosis, appropriate antimicrobial selection and vigilant antibiotic stewardship. Empirical therapy for EOS and LOS should be started immediately after obtaining cultures and then adjusted according to culture results and antimicrobial resistance profiles. Clinicians should maintain a high level of suspicion for fungal infections in high-risk neonates and proactive prophylaxis may be considered. In addition to antimicrobial therapy, NICU care bundles and quality improvement programmes are very important for prevention of device-associated infections such as VAP and CRBSI.

Antibiotic stewardship programmes can decrease antibiotic resistance and minimize the side-effects of prolonged broad-spectrum antibiotic use in neonates. By integrating evidence-based protocols with individualized care, we can improve neonatal outcomes whilst safeguarding the efficacy of existing antimicrobials. A multidisciplinary approach of balancing aggressive treatment with judicious antibiotic use is essential for combating neonatal sepsis.

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