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Infection control and other stewardship strategies in late onset sepsis, necrotizing enterocolitis, and localized infection in the neonatal intensive care unit

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ABSTRACT

Suspected or proven late onset sepsis, necrotizing enterocolitis, urinary tract infections, and ventilator associated pneumonia occurring after the first postnatal days contribute significantly to the total antibiotic exposures in neonatal intensive care units. The variability in definitions and diagnostic criteria in these conditions lead to unnecessary antibiotic use. The length of treatment and choice of antimicrobial agents for presumed and proven episodes also vary among centers due to a lack of supportive evidence and guidelines. Implementation of robust antibiotic stewardship programs can encourage compliance with appropriate dosages and narrow-spectrum regimens.

Antibiotic use in the Neonatal Intensive Care Unit (NICU)

Antibiotics are the most commonly prescribed medications in the NICU.[1] Antibiotic overuse has been linked to serious adverse outcomes in low birth weight (LBW) infants, including bronchopulmonary dysplasia, necrotizing enterocolitis (NEC), invasive candidiasis, and even death.[2-5] While the beneficial effects of antibiotics for the treatment of bacterial infections is unquestioned, the duration of treatment in the NICU is often arbitrary and is often based on the physician's perceived risk of infection, rather than a positive culture.[6] Prolonged therapy (≥ 5 days) in the NICU has been reported in up to 26% of total antibiotic use, despite negative cultures.[7] In that single center report, prolonged therapy in the NICU was mostly provided for suspected pneumonia (16%, 54.3 therapy days per 1000 patient days) and culture-negative sepsis (8%, 28.4 therapy days per 1000 patient days), and the length of treatment varied from 5 to 14 days.[7]

The majority of antibiotic use in the NICU is empiric.[8-10] Nearly 1/4th of antibiotic courses are inappropriately given in the NICU, and represent 35% of infants who receive intravenous antibiotics after 72 h of age.[11] Due to months-long hospitalizations of the highest risk extremely preterm babies, suspected or proven late-onset sepsis (LOS), NEC, urinary tract infections (UTI), and ventilator associated pneumonia (VAP) occurring after the first postnatal days contribute significantly to the total antibiotic exposures in NICUs.[6] In this article, our objective is to discuss the rationale behind using antibiotics for these conditions, review the evidence for antibiotic choices, dosages, and duration of therapy, and identify strategies to reduce unnecessary antibiotic use.

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LOS and meningitis

Epidemiology of LOS: LOS, defined as culture-confirmed infection occurring after the first postnatal week, affects 38% of extremely premature infants in the NICU.[12] LOS is acquired by horizontal transmission of pathogens from their environment after birth.[13] Gram-positive bacteria are the most common pathogens causing LOS, accounting for over 70% of all cases of LOS in the NICU.[12] Other causes of LOS include Gram-negative bacteria, isolated in 17% of LOS cases, and fungal infections, which account for 10% of LOS in very low birth weight (VLBW) infants.[12,14] Coagulase negative staphylococci (CoNS) accounts for >50% of all Gram-positive isolates, though mortality associated with CoNS bacteremia is relatively low.[12,15] Other Gram-positive pathogens that cause LOS include *Staphylococcus aureus, Streptococcus pneumonia*, and *Streptococcus pyogenes*.[16] The average mortality in extremely premature infants with LOS is 26%.[12] Mortality is higher in infants with gram-negative infections than infants with gram-positive infections.[14,17]

Epidemiology and etiology of late-onset meningitis (LOM): Meningitis occurs most frequently in infants under 2 months of age, and is associated with a high risk of mortality and morbidity.[18] As many as 50% of infants who survive meningitis develop seizures, cognitive deficiencies, motor abnormalities, and hearing and visual impairments.[19-22] The incidence of meningitis in developed countries is about 0.3 per 1000 live births, and it occurs in up to 66% of VLBW infants with LOS.[23,24] The etiologic organisms associated with LOM are similar to that of LOS with gram-positive organisms being the leading cause, followed by gram-negatives and fungal pathogens.[23]

Need for antibiotic stewardship: Prescribing practices of antibiotics across NICUs vary. The California Perinatal Quality Care Collaborative reported that across units, antibiotic treatment ranges from 2.4% to 97.1% of patient-days.[9] In one study, it was found that 35% of infants receiving antibiotics for over 72 h received them inappropriately.[11] The study defined inappropriate antibiotic therapy to include inappropriate initiation, continuation, type, and nonadherence to the Centers for Disease Control and Prevention (CDC) 12-Step program to prevent antimicrobial resistance.[11] Forms of misuse of antibiotics in this study included the use of gentamicin for a gentamicin-resistant pathogen, continued use of 2 agents when a single agent is adequate, and the use of a carbapenem for empiric treatment of LOS (without evidence of NEC or multi-drug resistance).[11] Cosgrove et al found that 28% of antimicrobial treatments did not follow the CDC's recommended 12 steps for prevention of antimicrobial resistance leading to the overuse of antibiotics in the NICU.[25]

The variability in neonatal antimicrobial drug dosing clearly highlights the need for antibiotic stewardship strategies. In a survey of antibiotic guidelines across 44 French NICUs, up to 32 different dosage regimens per drug were identified for 41 antibiotics.[26] Another study spanning 89 NICUs from 21 countries in Europe found wide variations in antibiotic dosing, with both under- and over-dosing when compared with the recommendations in the British National Formulary for Children.[27] These variations stem from the lack of high quality evidence for dosing in neonates; most neonatal dosing is extrapolated from adult studies and is adjusted based on weight.[28,29] This is suboptimal, as infants display distinctly different pharmacokinetics (PK) that vary based on gestational and postnatal age.[30] Under-dosing of antibiotics leads to ineffective treatment of infection and promotes the development of microbial resistance, whereas over-dosing results in toxicity and compromised safety.[31] Multiple PK studies of antibiotics have been performed in infants to define dosing that optimizes therapeutic exposures for infants (Table 1).

Strategies for antibiotic stewardship: Adoption of preventive strategies to reduce the incidence of LOS and LOM are the first step to reducing prolonged antibiotic use: strategies reported to have the most marked impact involve of a bundle of care focusing on a combination of hand washing, central line management, and infection control practices.[32-34]

A second key step in appropriate antibiotic use for LOS/LOM is the choice of antibiotic. In a survey of neonatologists' practice for infants with suspected LOS, 60% of clinicians prescribed vancomycin for empiric therapy.[35] The choice of vancomycin is directed by concerns for methicillin-resistant *Staphylococcus aureus* (MRSA) infection, and the predominance of CoNS in the setting of LOS.[36] However, there are multiple studies showing that restricting empirical vancomycin use does not result in increased mortality or morbidity.[37-40] Chiu et al reported the effectiveness of implementing a restrictive vancomycin use guideline at 2 tertiary care centers.[38] The investigators waited until CoNS susceptibility results were available prior to initiating vancomycin, and were able to safely and successfully decrease vancomycin use without an increase in attributable morbidity or mortality.[38] One center retrospectively found no change in mortality or morbidity after changing the standard empiric treatment for LOS from vancomycin and cefotaxime to oxacillin and gentamicin.[40] Thus, it is prudent to use an antistaphylococcal penicillin, such as oxacillin or nafcillin, along with an aminoglycoside for the initial empiric treatment of LOS.[7,36,38-43] Vancomycin should be considered judiciously in areas where MRSA is prevalent, or if the culture is positive for CoNS.[41-43] In the setting of a negative blood culture, with optimal collection technique, discontinuation of antibiotics should be considered.[44] The use of biomarkers, such as acute phase reactants, cytokines and chemokines, for the diagnosis of LOS and to guide length of therapy is promising.[45] However, most of these biomarkers are non-specific, and would be better used for their negative predictive value.[45] If meningitis is suspected, ideally a lumbar puncture should be performed and treatment should be initiated immediately after cerebrospinal fluid is obtained.[46] The most commonly prescribed antibiotics for late-onset meningitis are vancomycin, gentamicin, cefotaxime, and ampicillin.[47,48] The recommended regimen to treat LOM in infants includes a combination of an antistaphylococcal antibiotic (nafcillin or vancomycin) plus a third-generation cephalosporin with or without aminoglycosides.[43,49] Traditionally, infants with meningitis are treated with empirical antibiotics for 14–21 days.[43] It is recommended that infants with meningitis caused by Gram-negative bacteria be treated with antibiotics for at least 21 days.[49,50]

Lastly, antibiotic stewardship programs can improve appropriate antibiotic use by implementing interventions that decrease infection related mortality and morbidity without

Table 1 – Most commonly used antibiotics in neonatal intensive care units with recommended dosages from the Harriet Lane textbook compared with recommended dosage from pharmacokinetic studies.

Name of antibiotic[1]	FDA approved for use in premature infants	Recommended dosage for infants in Harriet Lane[142]	Recommended dosage for infants from pharm acokinetic studies
Ampicillin	Yes	<7 days: <2 kg: 100 mg/kg/day q12 h ≥ 2 kg: 150 mg/kg/day q8 h ≥7 days: <1.2 kg: 100 mg/kg/day q12 h 1.2–2 kg: 150 mg/kg/day q8 h >2 kg: 200 mg/kg/day q6 h	≤34 weeks GA:[143,144] ≤7 days PNA: 50 mg/kg/dose q12 h ≥8 and ≤28 days PNA: 75 mg/kg/dose q12 h ≥34 weeks GA:[143,144] ≤28 days PNA: 50 mg/kg/dose q8 h
Gentamicin	Yes	≤29 weeks GA: 0-7 days PNA: 5 mg/kg/dose q48 h 8-28 days PNA: 4 mg/kg/dose q36 h >28 days PNA: 4 mg/kg/dose q24 h 30-34 weeks GA: 0-7 days PNA: 4.5 mg/kg/dose q36 h >7 days PNA: 4 mg/kg/dose q24 h ≥35 weeks GA: 4 mg/kg/dose q24 h; q36 h dosing used for infants undergoing whole-body cooling	<37 weeks PMA: 5 mg/kg/dose q48 h[145] 37 to <40 weeks PMA: 5 mg/kg/dose q36 h[145] ≥40 weeks PMA: 5 mg/kg/dose q24 h[145] 5 mg/kg/dose q36 h for infants undergoing whole-body cooling[146]
Vancomycin	Yes	Bacteremia: 10 mg/kg/dose Meningitis, pneumonia: 15 mg/kg/dose Intervals: ≤29 weeks GA: 0-14 days PNA: q18 h >14 days PNA: q12 h 30-36weeks GA: 0-14 days PNA: q12 h >14 days PNA: q8 h 37-44weeks GA: 0-7 days PNA: q12 h >7 days PNA: q8 h ≥45 weeks GA: All: q6 h	Birthweight≤700g:[147] PNA 0-7 days: 16 mg/kg x1, followed by 15 mg/kg/day q8 h PNA 8-14 days: 20 mg/kg x1, followed by 21 mg/kg/day q8 h PNA 15-28 days: 23 mg/kg x1, followed by 24 mg/kg/day q8 h Birthweight 701-1000g:[147] PNA 0-7 days: 16 mg/kg x1, followed by 21 mg/kg/day q8 h PNA 8-14 days: 20 mg/kg x1, followed by 27 mg/kg/day q8 h PNA 15-28 days: 23 mg/kg x1, followed by 42 mg/kg q8 h Birthweight 1001-1500g:[147] PNA 0-7 days: 16 mg/kg x1, followed by 27 mg/kg/day q8 h PNA 8-14 days: 20 mg/kg x1, followed by 36 mg/kg/day q8 h PNA 15-28 days: 23 mg/kg x1, followed by 45 mg/kg/day q8 h Birthweight 1501-2500g:[147] PNA 0-7 days: 16 mg/kg x1, followed by 30 mg/kg/day q6 h PNA 8-14 days: 20 mg/kg x1, followed by 40 mg/kg/day q6 h PNA 15-28 days: 23 mg/kg x1, followed by 52 mg/kg/day q Birthweight >2500g:[147] PNA 0-7 days: 16 mg/kg x1, followed by 36 mg/kg/day q6 h PNA 8-14 days: 20 mg/kg x1, followed by 48 mg/kg/day q6 h PNA 15-28 days: 23 mg/kg x1, followed by 60 mg/kg/day q6 h
Cefotaxime	Yes	PNA ≤7 days: <2 kg: 100 mg/kg/day q12 h ≥2 kg: 100–150 mg/kg/day q8–12 h PNA >7 days: <1.2 kg: 100 mg/kg/day q12 h 1.2–2 kg: 150 mg/kg/day q8 h >2 kg: 150–200 mg/kg/day q6-8 h	PNA 0-7 days:[148] 50 mg/kg q12 h PNA > 7 days:[148] GA < 32 weeks: 50 mg/kg q8 h GA >32 weeks: 50 mg/kg q6 h

Table 1 (*continued*)

Name of antibiotic[1]	FDA approved for use in premature infants	Recommended dosage for infants in Harriet Lane[142]	Recommended dosage for infants from pharm acokinetic studies
Tobramycin	Yes	≤29 weeks GA: 0-7 days PNA: 5 mg/kg/dose q48 h 8-28 days PNA: 4 mg/kg/dose q36 h >28 days PNA: 4 mg/kg/dose q24 h 30-34 weeks GA: 0-7 days PNA: 4.5 mg/kg/dose q36 h >7 days PNA: 4 mg/kg/dose q24 h ≥35 weeks GA: 4 mg/kg/dose q24 h; q36 h dosing used for infants undergoing whole-body cooling	Birthweight <1 kg:[149] PNA ≤5 days: 5.5 mg/kg/dose q72 h PNA 6-10 days: 5.5 mg/kg/dose q60 h PNA 11-20 days: 5.5 mg/kg/dose q48 h PNA ≥21 days: 5.5 mg/kg/dose q36 h Birthweight 1-2 kg:[149] PNA ≤5 days: 5.5 mg/kg/dose q60 h PNA 6-10 days: 5.5 mg/kg/dose q48 h PNA 11-20 days: 5.5 mg/kg/dose q36 h PNA ≥21 days: 5.5 mg/kg/dose q24 h Birthweight >2 kg:[149] PNA ≤5 days: 5.5 mg/kg/dose q48 h PNA 6-10 days: 5.5 mg/kg/dose q36 h PNA 11-20 days: 5.5 mg/kg/dose q24 h PNA ≥21 days: 5.5 mg/kg/dose q24 h
Clindamycin	Yes	PNA ≤7 days: ≤2 kg: 5 mg/kg/dose q12 h >2 kg: 5 mg/kg/dose q8 h PNA >7 days: <1 kg: 5 mg/kg/dose q12 h for PNA 8–14 days, and q8 h for PNA ≥15 days 1–2 kg: 5 mg/kg/dose q8 h >2 kg: 5 mg/kg/dose q6 h	≤32 weeks PMA:[150] 5 mg/kg/dose q8 h >32 and ≤40 weeks PMA:[150] 7 mg/kg/dose q8 h >40 and ≤60 weeks PMA:[150] 9 mg/kg/dose q8 h
Ceftazidime	Yes	PNA ≤7 days: <2 kg: 100 mg/kg/day q12 h ≥2 kg: 100–150 mg/kg/day q8–12 h PNA >7 days: <1.2 kg: 100 mg/kg/day q12 h ≥1.2 kg: 150 mg/kg/day q8 h	≤28 weeks GA:[151, 152] Meningitis: 7.5 mg/kg/dose q12 h Bacteremia: 25 mg/kg/dose q24 h >28 to ≤32 weeks GA:[151, 152] Meningitis: 10 mg/kg/dose q12 h Bacteremia: 25 mg/kg/dose q24 h >32 weeks GA:[151,152] 25 mg/kg/dose q12 h
Piperacillin/ tazobactam	No	Weight <1 kg: PNA ≤14 days: 100 mg/kg/dose q12 h PNA 15–28 days: 100 mg/kg/dose q8 h Weight ≥1 kg: PNA ≤7 days: 100 mg/kg/dose q12 h PNA 8–28 days: 100 mg/kg/dose q8 h	≤30 weeks PMA: 100 mg/kg/dose q8 h[153,154] >30 and ≤35 weeks PMA: 80 mg/kg/dose q6 h[153, 154] >35 and ≤49 weeks PMA: 80 mg/kg/dose q4 h[153, 154]
Metronidazole	No	Weight <1 kg: PNA ≤14 days: 15 mg/kg × 1 loading dose followed by 7.5 mg/kg/dose q48 h PNA 15–28 days: 15 mg/kg/dose q24 h Weight 1–2 kg: PNA ≤7 days: 15 mg/kg × 1 loading dose followed by 7.5 mg/kg/dose q24–48 h PNA 8–28 days: 15 mg/kg/dose q24 h Weight > 2 kg: PNA ≤7 days: 15 mg/kg/dose q24 h PNA 8–28 days: 15 mg/kg/dose q12 h	<34 weeks PMA:[155] Loading dose 15 mg/kg x1, followed by 7.5 mg/kg q12 h 34-40 weeks PMA:[155] Loading dose 15 mg/kg x1, followed by 7.5 mg/kg q8 h >40 weeks PMA:[155] Loading dose 15 mg/kg x1, followed by 7.5 mg/kg q6 h
Amikacin	No	≤29 weeks GA: 0-7 days PNA: 18 mg/kg/dose q48 h 8-28 days PNA: 15 mg/kg/dose q36 h >28 days PNA: 15 mg/kg/dose q24 h 30-34 weeks GA: 0-7 days PNA: 18 mg/kg/dose q36 h >7 days PNA: 15 mg/kg/dose q24 h ≥35 weeks GA: 15 mg/kg/dose q24 h; q36 h dosing used for infants undergoing whole-body cooling	Weight ≤800 g:[156, 157] <14 days PNA: 16 mg/kg q48 h ≥14 days PNA: 20 mg/kg q42 h Weight 801-1200g:[156, 157] <14 days PNA: 16 mg/kg q42 h ≥14 days PNA: 20 mg/kg q36 h Weight 1201-2000g:[156, 157] <14 days PNA: 15 mg/kg q36 h ≥14 days PNA: 18 mg/kg q30 h Weight 2001-2800g:[156, 157] <14 days PNA: 15 mg/kg q36 h ≥14 days PNA: 18 mg/kg q24 h Weight >2800g:[156, 157] <14 days PNA: 15 mg/kg q30 h ≥14 days PNA: 18 mg/kg q20 h

FDA: Food and Drug Administration; GA: gestational age; PNA: postnatal age; PMA: postmenstrual age.

increasing antibiotic resistance. One recommended intervention is daily prospective audit and feedback. Daily prospective audit and feedback includes accessing the needs for antimicrobial therapy of a patient to optimize treatment. This intervention involves a relationship between the physician and the prescribing provider such as an infectious disease specialist or a pharmacist specializing in pediatric antibiotic stewardship. In a study conducted by Thampi et al., antibiotic usage measured as days of treatment per 1000 patient-days decreased by 14% with daily prospective audit and feedback.[51] The proportion of admitted babies who received antibiotics also decreased (63% versus 59%).[51] Interventions such as education about the risks of broad-spectrum antibiotic use and adjusting empiric antibiotic regimens have also been found to reduce the use of broad-spectrum antibiotic usage.[38,52] Nzegwu et al demonstrated a significant reduction in ampicillin days of antibiotic therapy (DOT) when educational methods were combined with prospective audit and feedback.[53] Chiu et al. showed that by creating guidelines for the use of vancomycin, the use of the antibiotic could be decreased by 40–49%.[38] Other methods of intervention include setting hard stops to antibiotic usage and utilizing risk calculators. Tzialla et al found that DOT was decreased by 27% with the implementation of an automatic stop to antibiotic treatment when cultures are sterile for 48 h, as well as a five-day automatic stop to antibiotic treatment for culture-negative sepsis or suspected pneumonia.[54] Predictive model for risk stratification such as the use of a risk calculator has decreased antibiotic usage for EOS among near-term and full term neonates by 42%.[55] More research into the feasibility of determining the risk of LOS and LOM using a risk calculator is necessary.

NEC

Epidemiology of NEC: NEC is an acquired gastrointestinal inflammatory disease, and is a leading cause of death in extremely low birth weight (ELBW) infants.[56] The incidence of NEC has remained relatively stable and, in some reports, appears to be slightly decreased over the past decade.[57-59] In extremely preterm infants born between 22 and 28 weeks gestational age, the incidence of NEC increased from 7% in 1993, to 13% in 2008, before decreasing to 9% in 2012.[58] In a recent report of Vermont Oxford Network data, the rate dropped from 6.6% to 4.0% among VLBW inborn infants, and from 10.4% to 6.6% among ELBW inborn infants from 2008 to 2017.[59] Mortality secondary to NEC has also increased over the years, and went from 23% in 2000–2003, to 30% in 2008–2011.[56] Infants who do survive, particularly ELBW infants who undergo surgical intervention, have long-term impairments including growth delay and poor neurodevelopmental outcomes.[60]

Etiology of NEC and rationale for antibiotic therapy: The exact etiology of NEC is unknown and it is considered to be multifactorial in origin. In addition to immaturity of the intestinal function secondary to prematurity, intestinal ischemia, type of enteral feeds, and importantly, aberrant bacterial colonization play a role.[61,62] In up to 35% of cases of NEC, concurrent bacteremia is documented.[63] Although no specific microorganism has been consistently identified to be causative, a wide range of pathogens are associated with NEC.[63] These include *Escherichia coli* (*E. coli*), *Klebsiella* spp, *Enterobacter* spp, *Pseudomonas* spp, *Salmonella* spp, *Clostridium perfringes*, *Clostridium difficile*, *Clostridium butyricum*, coagulase-negative staphylococci, *Enterococcus* spp, coronavirus, rotavirus and enterovirus.[63] Early stool colonization with *Clostridium perfringens*[64] and abnormal duodenal colonization with *Enterobacteriaceae* among VLBW infants has been associated with later development of NEC.[65]

Poor early antibiotic stewardship may contribute to development of NEC: Premature infants almost universally receive broad-spectrum antibiotics after birth, and many receive prolonged courses to treat culture-positive or presumed culture-negative sepsis.[66,67] Prolonged exposure to antibiotics early in life increases the risk of abnormal intestinal bacterial colonization.[68,69] A retrospective cohort analysis of ELBW infants born between 1998 and 2001 admitted in NICHD Neonatal Research Network (NRN) centers found an association between a prolonged initial antibiotic course of ≥5 days and an increased risk of developing NEC.[2] Other smaller studies also supported this association.[4,70,71] A more recent study of over 5000 infants from the same network born between 2008 and 2014 did not find a significant association between early prolonged antibiotics of NEC.[72] This is likely related to a decrease in the proportion of early prolonged antibiotics being used, as well as more widespread use of human donor milk, maternal breast milk, and probiotics (Table 2).[72]

Medical therapy for NEC and antibiotic stewardship: Treatment strategy for NEC depends on severity of illness and may be medical or surgical in nature.[73,74] Medical therapy for NEC includes broad-spectrum antibiotics with coverage for anaerobic intra-abdominal bacteria.[63,75] However, there is a paucity of data guiding the specific medical therapy for NEC, leading to wide practice variation in the antibiotic choice and duration of administration.[76] In a small randomized, controlled trial of 42 premature infants with radiographic evidence of NEC, there was no difference seen in the incidence of intestinal perforations or mortality in those who received a combination of ampicillin, gentamicin, and clindamycin compared with those who only received ampicillin and gentamicin.[77] However, a higher rate of intestinal strictures was found in the group receiving clindamycin.[77] In a retrospective study of 6737 VLBW infants born at Pediatrix Medical Group NICUs Infants who received anaerobic antibiotics, had a higher rate of intestinal strictures [odds ratio (OR) 1.73; 95% CI, 1.11 – 2.72]. When restricting to infants with surgical NEC, however, anaerobic antimicrobial therapy had less mortality (OR 0.71; 95% CI, 0.52 – 0.95). There was no improvement in outcomes of infants with medical NEC conditional to anaerobic antimicrobial therapy.[78] In a recent retrospective cohort study of 4089 infants using the same database and overlapping infants, investigators used a PK simulation model to determine the effect of the highest estimated clindamycin exposure quartile and found a reduced odds of death with higher clindamycin exposure (OR 0.67; 95% CI 0.46 – 0.98).[79]

Alternative treatment regimens have been explored. One randomized controlled trial of 20 infants evaluated the role of oral gentamicin added to parenteral ampicillin and gentamicin. In this study, no significant difference was found in mortality, intestinal perforations or strictures between the comparison groups.[80] One study from the 1980s compared alternative treatment

Table 2 – Summary of interventions to prevent necrotizing enterocolitis.

Author and study design	Population	Intervention groups	Results
Human milk feeding			
Corpeleijn et al.[158]; randomized controlled trial	373 very low birth weight infants (birth weight <1500g)	Pasteurized donor milk (n=183) vs preterm formula (n=190)	No difference in the incidence of NEC ≥ stage 2, mortality, or late-onset sepsis
Cristofalo et al.[159]; randomized controlled trial	53 extremely premature infants with birth weights between 500 - 1250g	Exclusive fortified human milk (n=29) vs bovine milk–based preterm formula (n=24)	Significantly greater duration of parenteral nutrition (p=0.04) and higher rate of surgical NEC (p=0.04) in infants receiving formula
Sullivan et al.[160]; randomized controlled trial	207 extremely premature infants with birth weights between 500 – 1250g	Human milk fortified with pasteurized donor human milk–based fortifier (n=138) vs human milk fortified with bovine milk–based fortifier (n=69)	Significantly lower rates of NEC (p=0.02) and surgical NEC (p=0.007) in infants receiving exclusively human milk diet
Schanler et al.[161]; randomized controlled trial	108 premature infants 26 – 30 weeks gestational age	Human milk fortified with human milk based fortifier (n=62) vs exclusive preterm formula (n=46)	Significantly lower incidence of NEC (p≤0.01) and late-onset sepsis (p=0.03) in infants receiving human milk diet
Probiotics			
Güney-Varal et al.[162]; randomized controlled trial	110 preterm infants, ≤32 weeks gestational age with birthweight ≤1500g	Multi-combined probiotic (*Lactobacillus rhamnosus + Lactobacillus casei + Lactobacillus plantorum + Bifidobacterium animalis*) group (n=70) vs no probiotics group (n=40)	Significantly decreased incidence of NEC (p=0.016) and mortality rate (p=0.001) in probiotic group
Jacobs et al.[163]; randomized controlled trial	1099 preterm infants, <32 weeks gestational age with birthweight <1500g	Probiotic combination (*Bifidobacterium infantis + Streptococcus thermophiles + Bifidobacterium lactis*) group (n=548) vs no probiotic group (n=551)	Significantly decreased incidence of NEC of Bell stage 2 or more in the probiotic group (2.0% vs 4.4%, p=0.03)
Braga et al.[164]; randomized controlled trial	231 infants with birth weights between 750 to 1499g	Probiotic (*Lactobacillus casei + Bifidobacterium breve*) group (n=119) vs no probiotic group (n=112)	Significantly decreased occurrence of NEC (Bell's stage ≥2) in probiotic group (p=0.05)
Lin et al.[165]; randomized controlled trial	434 very low birth weight infants (birth weight <1500g)	Probiotic (*Bifidobacterium bifidum + Lactobacillus acidophilus*) group (n=217) vs no probiotics group (n=217)	Significantly lower incidence of death or NEC (Bell's stage ≥2) (p=0.002) and of NEC (Bell's stage ≥2) (p<0.02)
Restricting initial empiric antibiotics			
Cotten et al.[2]; retrospective cohort analysis	4039 infants with birth weights 401 – 1000g who received empirical antibiotic treatment in the first 3 postnatal days	N/A	Prolonged (≥ 5 days) initial antibiotic therapy was associated with increased odds of NEC or death (p<0.01) and of death (p<0.001)
Alexander et al.[71]; retrospective case-control analysis	124 infants with NEC, matched with 248 control infants	N/A	Increased risk of NEC with duration antibiotic exposure. Approximately threefold increase in NEC risk with >10 days of antibiotic exposure

regimens in 90 infants with clinical and radiographic evidence of NEC.[81] 46 infants received ampicillin (100 mg/kg/day) and gentamicin (5 – 7.5 mg/kg/day), while the other 44 infants were treated with cefotaxime (150 mg/kg/day) and vancomycin (30–45 mg/kg/day). All antibiotics were administered for 7–10 days. Infants with a birthweight <2200 g who received the cefotaxime/vancomycin regimen were less likely to die, and had a lower risk of culture-positive peritonitis.[81] Similar outcomes with either antibiotic combination were seen in infants with birthweights ≥ 2200 g.[81] The recently concluded antibiotic safety (SCAMP) trial compared the safety of various antibiotic regimens for complicated intra-abdominal infections, and provides valuable information regarding the safety and efficacy of the most commonly used antimicrobials for NEC.[82] This partially randomized trial compared the following antibiotic combinations: ampicillin/gentamicin/metronidazole, ampicillin/gentamicin/clindamycin and

piperacillin-tazobactam/gentamicin. The preliminary results showed that all 3 drug regimens were well tolerated, and no clinically significant difference in adverse events, including death, intestinal strictures or perforations, was observed. Thus, even though antibiotics are the mainstay of therapy for NEC, at present, there is no conclusive evidence to suggest superiority of one anaerobic antimicrobial over the other, despite their widespread use. In the interest of antibiotic stewardship, we recommend using the narrowest appropriate coverage, especially in the setting of positive blood or urine cultures. In many cases, the narrowest appropriate coverage will be ampicillin/gentamicin/metronidazole, which provides coverage against aerobic and anaerobic organisms with some penetration to the central nervous system. The recommended length of broad-spectrum parenteral antibiotic therapy is 7–10 days.[74] However, some centers reportedly administer antibiotics for 10–14 days, which may be excessive in cases of mild disease.[63] Therefore, we recommend limiting antibiotic duration to 7–10 days, and extending it only in cases of clinical deterioration.

Urinary tract infection (UTI)

Epidemiology of UTIs: UTIs are common among infants admitted to the NICU, with an incidence of 3–25% among VLBW infants.[83-86] UTIs typically occur later during the course of an infant's NICU hospitalization; they are rarely detected in the first 72 h of age (0–1%), and no cases have been reported to occur in the first 24 h of age, even in premature infants.[85,87] Structural renal abnormalities increase the risk of neonatal UTIs, an estimated 20% of cases are associated with vesicoureteral reflux (VUR).[88,89] Term and preterm infants with UTIs commonly present with poor feeding, emesis, lethargy, and fever ($\geq$ 38 °C), and over 50% of preterm infants with UTIs also present with respiratory symptoms, such as tachypnea, hypoxia and apnea.[86,90,91] Infants with UTIs are at risk for concomitant bacteremia and meningitis; in one study of infants <121 days of age, 127/976 (13%) episodes of UTI had concordant bacteremia, and 2/77 (3%) UTI episodes also had meningitis.[92] This concordance is more likely to occur in infants born at <26 weeks gestation.[92] In ELBW infants, *Candida* UTIs are associated with death and neurodevelopmental impairments.[93]

Etiologic organisms for UTI in the NICU: Nearly 80% of cases of UTIs are caused by *E. coli*, making it the most common causative organism in all age groups, including the neonatal period.[88,94-96] Male infants with VUR are more likely to present with less common pathogens, such as *Enterobacter aerogenes, Pseudomonas aeruginosa, and Klebsiella oxytoca*.[88,90] Studies from NICUs have reported a high incidence of CoNS UTIs.[92,97] In a large retrospective study of over 500,000 preterm and term infants admitted to the NICU, CoNS was isolated in 14% of catheterized urine cultures in infants with UTIs, and was concordant with a blood culture in 18% of cases.[92] In ELBW infants, *Candida* UTIs occur commonly.[93] In a prospective cohort study of 1515 ELBW infants (birthweight $\leq$ 1000 g), 137 infants were identified as having invasive candidiasis, of which 52/137 (38%) infants were diagnosed with candiduria from urine specimens collected by catheterization or suprapubic aspiration.[98] In a study of hospital-acquired UTIs occurring in infants admitted in the NICU, *Candida* spp. were responsible for 42% of infections. The mean gestational age of these infants was 26 weeks, which was significantly lower than the gestational age of infants diagnosed with a bacterial UTI (28 weeks).[99]

Diagnosis of UTI: UTIs are variably defined in NICUs.[100] Variable definitions and diagnoses lead to unnecessary antibiotic use, which represents an opportunity to improve antibiotic stewardship in the setting of suspected UTIs. A commonly used definition is the growth of a single known organism from a catheterized urine sample at: $\geq$ 50, 000 colony-forming units (CFU) per milliliter, or $\geq$ 10, 000 CFU/mL in association with a positive dipstick test or urinalysis.[88,94,101] The 3 common methods of collecting urine in infants are: sterile bag collection, urinary catheterization, and suprapubic aspiration. Although sterile bag collection is non-invasive and easy to perform, it does have high contamination rates. A prospective study of children $\leq$ 24 months found that of the 7584 urine cultures obtained, 63% of bagged specimens were contaminated, compared to 9% of samples obtained via catheterization.[102] Given the high false-positive culture prevalence of UTIs with bagged specimens, urethral catheterization and suprapubic aspiration are the preferred methods of collection. However, these methods are more invasive, and given the perceived pain associated with the procedure, along with limited feasibility and relatively lower success rates of performing these in small and critically ill infants, sterile bag collection is used more frequently in clinical practice.[103,104] This is problematic, as clinicians may find it difficult to ignore a 'positive' culture, leading to unnecessary antibiotic treatments.[105] Moreover, the absence of nitrites and leukocyte esterase on dipstick are unreliable in the infant population because of small bladders and frequent micturition.[106] Based on the available data, we recommend obtaining urine via catheterization whenever possible, and avoidance of bag collection for cultures. If the infant is being treated for sepsis regardless of urine culture results, bagged specimens may be considered to help tailor therapy in the presence of bacterial growth.

Treatment of UTI: Before committing to treatment for a UTI, clinicians should take method of urine collection into consideration. Most urine parameters in infants are misleading, leading to misdiagnoses and antibiotic overuse, thus optimizing specimen collection to avoid contaminants provides an opportunity for antibiotic stewardship. Initial management for UTIs in the NICU consists of parenteral broad spectrum therapy, typically ampicillin and gentamicin, or ampicillin and a 3rd generation cephalosporin, followed by narrowing of the regimen based on culture sensitivity results.[107] In the US, the reported incidence of ampicillin resistant neonatal *E. coli* strains is as high as 75%, and resistance to gentamicin is as high as 12–17%.[108,109] A retrospective study of 73 cases of neonatal UTIs in Iran reported over 90% resistance of *E. coli* strains against ampicillin.[110] Despite this, a clinical response was seen in 50% of infants, suggesting discordance between *in vivo* and *in vitro* activity, or higher urinary concentration of the drug.[110,111] The American Academy of Pediatrics (AAP) recommends 7–14 days of antimicrobial therapy for UTIs in children between the ages of 2–24 months.[112] Similar guidelines do not exist for infants less than 2 months of age, especially for those born prematurely and admitted to the NICU. Given the lack of data regarding the safety, bioavailability, and efficacy of oral antibiotics in extremely premature infants, parenteral therapy is preferred for 7–14 days, depending on clinical status and other complications.

Ventilator associated pneumonia (VAP)

Definition of VAP: The CDC defines VAP as an episode of pneumonia in invasively ventilated patients that occurs at least 48 hours after initiation of mechanical ventilation.[113] Although this definition does not outline specific criteria for diagnosis in the newborn period, most studies in the NICU also use this definition.[114] The exact incidence of VAP in the NICU is difficult to estimate because of the lack of well-established diagnostic criteria in this population. The incidence of VAP in developed countries is reported between 2.7 and 10.9 cases per 1000 ventilator days, whereas in developing countries it may reach up to 37.2 episodes per 1000 ventilator days.[115-118] In a study of 12 NICUs, the incidence of VAP in infants weighing less than 1000 was 0 – 21.2 per 1000 ventilator days.[119]

Epidemiology of VAP: Factors that place infants in the NICU at a higher risk for developing VAP include prolonged mechanical ventilation, and a functionally immature respiratory and immune system. A prospective cohort study of 742 neonates found that low birth weight and mechanical ventilation were the main risk factors for the development of VAP.[120] In another prospective cohort study of extremely preterm infants born <28 weeks gestation, with a birthweight ≤ 2000 g, bloodstream infection was found to be an independent risk factor for VAP, after adjustment for the duration of endotracheal intubation.[118] Moreover, VAP was also an independent risk factor for mortality. No one particular organism has been linked to VAP. In the above mentioned prospective study of extremely preterm infants, 94% of cases of neonatal VAP were secondary to gram negative organisms.[118] Similar findings were reported in a single-center retrospective study of 259 infants in China, in which 82% of the VAP cases were due to gram-negative organisms.[121] Other authors have found that VAP is mostly polymicrobial in nature.[122] Of note, these studies are limited by the fact that samples were retrieved by endotracheal aspiration as opposed to invasive sampling of the lower respiratory tract, and therefore may represent oropharyngeal colonization instead of true infection.

Diagnosis of VAP: Distinguishing true infection from oropharyngeal colonization is critical in order to avoid unnecessary antibiotic therapy. The lack of diagnostic criteria for VAP in infants makes accurate diagnosis difficult. The CDC criteria have not been validated in infants, making the diagnosis in clinical practice open to subjective interpretation.[114] Moreover, differentiating pneumonia from underlying chronic lung disease from radiographs of LBW infants is difficult.[123] Bronchoalveolar lavage (BAL) samples, or those taken from a protected specimen brush, are invasive tests used to diagnose VAP in adults.[124] Given the small size of the airways, these tests are impractical in infants. Instead, tracheal aspirate cultures and Gram stains are used to evaluate suspected pneumonia in infants. These tests have low specificity, sensitivity, and positive predictive value for distinguishing between VAP and tracheal colonization.[125] In a cohort study of VLBW infants, VAP, defined by the presence of pathogens in the trachea or blood, as well as clinical and radiographic findings, was diagnosed in only 10% of infants with purulent tracheal aspirates.[126] The presence of white blood cells on tracheal aspirates has also been shown to have low specificity (54%) and sensitivity (67%) for VAP, even when there is bacterial growth on culture.[127]

Nonbronchoscopic BAL (NB-BAL) or blind BAL has emerged as a more reliable and feasible sampling method to diagnose VAP in infants.[128] In this method, a suction catheter is advanced into the lower airway until resistance is met. Saline lavage is then performed to collect a sample.[128] The utility of this method has been described in an observational, prospective study of 198 preterm and term infants who were intubated for > 48 h. 16 infants who were clinically suspected to have VAP had a blind BAL performed, and no complications associated with the procedure were reported.[115] Moreover, the authors report a lower incidence of polymicrobial etiology, likely related to reduced contamination from a more invasive and sterile technique.[115] In another observational study using the NB-BAL technique in ventilated preterm infants, airway neutrophil counts of those diagnosed with VAP or congenital pneumonia were compared to those without infection.[129] The median number of neutrophils in infants diagnosed with pneumonia was significantly higher than those without (24 cells/field vs 4 cells/field). This difference was only observed after the first 2 days on mechanical ventilation.[129] The authors also performed receiver operator characteristics analysis for neutrophil count to diagnose pneumonia. Within the first 2 days of mechanical ventilation, an airway neutrophil count had moderate accuracy of diagnosing pneumonia, with 4 cells/field having a 90% sensitivity, and 59% specificity for diagnosis. Unfortunately, after 2 days of mechanical ventilation, neutrophil count was found to be no longer reliable.[129] The NB-BAL method has not been adopted over tracheal aspirates in neonatal practice, but is a promising and well tolerated method to reduce high false positive rates of VAP, and over-treatment. We recommend avoidance of tracheal aspirates, and instead use of the blind BAL/NB-BAL approach along with the CDC's diagnostic criteria.[113]

Treatment for VAP: Given the controversy in diagnosis of neonatal VAP, there is also no clear consensus regarding optimal treatment regimens or duration of antimicrobials. Treatment for VAP involves initial empiric therapy with broad spectrum antibiotics, followed by de-escalation once culture results are available, or discontinuation when VAP is no longer suspected. When selecting initial therapy, clinicians should be aware of the antibiotics that have previously been administered, as well as prior culture results and colonization data. The use of aerosolized antibiotics has been studied comprehensively in pediatric patients with cystic fibrosis. The FDA approval for the use of inhaled tobramycin in children is limited to patients with cystic fibrosis who are known to be colonized with *Pseudomonas aeruginosa*.[130] The advantageous effects of inhaled tobramycin in this population was demonstrated in 2 randomized, multi-centered, placebo-controlled clinical trials. Children who received inhaled tobramycin had significant improvement in lung function, compared to those who did not. Additionally, there was a significant reduction in the number of *Pseudomonas aeruginosa* colonies in the sputum of children in the treatment group.[131] Although inhaled antibiotics are being used in infants, there is little data from this population to support this and its' use is extrapolated from studies in the pediatric and adult population. Small single center studies have reported successful use of aerosolized colistin in the treatment of *Acinetobacter* VAP.[132,133] Clinical trials are needed to determine the efficacy of inhaled antibiotic therapy in this population. At this time, no guidelines exist regarding empiric coverage or length of treatment for VAP in infants. One

study found that in term and late preterm infants, 4 days of antibiotic therapy along with a 24-h observation period was comparable to 7 days of therapy.[134] The same institution reported a decrease in the days of antibiotic therapy for pneumonia by recommending 5 days of treatment for suspected pneumonia during an antibiotic stewardship intervention study.[7] During the intervention period, there was no increase in short-term clinical safety outcomes.[7] Based on this, in those diagnosed with neonatal VAP, parenteral antimicrobial therapy can be given for 5–7 days, which can be modified based on clinical status and resistance patterns.[7,135] Therapy should be based on clinical status and culture results, ideally obtained from the lower airways.

Prevention of VAP: The CDC has published guidelines for the prevention of VAP, which are also applicable to the neonatal population.[113] Since most VAPs are caused by oropharyngeal flora, the CDC recommends suctioning of the oropharynx prior to adjustment or removal of the endotracheal tube.[113] Traditional open endotracheal suctioning involves disconnection from the ventilator and is associated with arrhythmias, increased intracranial pressure and mean blood pressures in infants.[136] Closed suction systems were introduced in the 1980s, and have the potential to reduce environmental contamination of the endotracheal tube. On the other hand, closed suctioning may increase risk of bacterial contamination from pooled secretions re-introduced into the system with repeated suctioning.[124] In a randomized study of 133 LBW infants comparing closed and open suctioning systems, no differences were found in the rates of VAP or bloodstream infection between the two groups.[137] 91% of nurses in the study deemed the closed suctioning system to be easier, less time-consuming, and better tolerated by the infants.[137] At this time, the CDC does not recommend one system over the other. Since prolonged intubation is a risk factor for VAP, reducing days on invasive mechanical ventilation by assessing for extubation readiness, and the use of noninvasive measures such as high flow cannulas and nasal continuous positive airway pressure have been shown to reduce rates of VAP.[138,139] In a prospective study aimed to reduce NICU nosocomial infection rates, aggressive weaning off the ventilator, in addition to other measures, led to the decrease in VAP rates from 3.3 to 1.0 per 1000 ventilator days.[140] Lastly, enforcement of strict hand hygiene policies is one of the most important measures to reduce nosocomial infections such as VAP. In a prospective study lasting 2 years, increased hand hygiene compliance from 43% to 80% resulted in the reduction of VAP rates from 3.35 to 1.06 infections per 1000 patient days.[141] Reducing the number of ventilated days and implementing hygiene techniques is the cornerstone in the prevention of VAP.

Summary and recommendations

- LOS, LOM, NEC, UTIs and VAP are notable late onset infections in the NICU, and approximately 1/4th of antibiotic courses administered during this period are given inappropriately.[11,58]
- Gram-positive bacteria are the most common pathogens causing LOS and LOM.[23,43] Initial antibiotic treatment for LOS includes an antistaphylococcal penicillin with an aminoglycoside; in areas where MRSA is prevalent, vancomycin should be considered.[41-43]
- Meningitis is diagnosed via a lumbar puncture, and treatment of LOM includes a combination of an antistaphylococcal antibiotic plus a third-generation cephalosporin with or without aminoglycosides.[43] Traditional length of treatment is for 14–21 days, and in cases of Gram-negative meningitis is 21 days.[43,49,50]
- The incidence of NEC has slightly decreased over time, and its etiology is considered to be multifactorial, with aberrant bacterial colonization shown to play a role.[59,61,62]
- Standard medical therapy for NEC includes broad-spectrum antimicrobials; however, there is a lack of data guiding specific antibiotic choice and duration, and various studies have not shown superiority of one anaerobic microbial over the other.[63,75,76,79-82]
- We recommend using the narrowest appropriate coverage for the medical treatment of NEC, especially in the setting of positive blood or urine cultures for 7–10 days, and extending it in cases of clinical deterioration.[74]
- The varying diagnostic techniques for UTIs are an opportunity for antibiotic stewardship, and the gold standard for urine collection is via urethral catheterization.[100]
- Initial management for UTIs in the NICU consists of parenteral broad spectrum therapy, typically ampicillin and gentamicin, or ampicillin and a 3rd generation cephalosporin, followed by narrowing of the regimen based on culture sensitivity results.[107] Therapy is preferred for 7–14 days, based on clinical status and other complications.[112]
- The lack of diagnostic criteria for VAP makes accurate diagnosis and treatment difficult. In cases of clinically suspected VAP, we recommend avoidance of routine tracheal aspirates for the diagnosis of VAP. The more recently published blind BAL/NB-BAL approach may offer more specific diagnosis, and the CDC's diagnostic criteria should also be considered.[113]
- In those diagnosed with VAP, we recommend parenteral antimicrobial therapy for 5–7 days, which can be extended based on clinical status and resistance patterns.[7,135]
- Comprehensive antibiotic stewardship programs, bundles of preventive care strategies, and improved diagnostic methods are the key to reducing prolonged antibiotic use for these indications.

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