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Drugs for the Prevention and Treatment of Sepsis in the Newborn

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INTRODUCTION

Antimicrobial medication use is exceedingly common among neeonates. Perinatal antibiotic exposure includes *in-utero* exposure to maternal intrapartum antibiotic prophylaxis (IAP), whether for Group B *Streptococcus* (GBS) colonization or concern for maternal intraamniotic infection (IAI), as well as exposure to empiric antibiotics given directly to the neonate for risk of early-onset sepsis (EOS). These combined indications mean that ~30-35% of term neonates in United States are exposed to antibiotics in the immediate perinatal period. Among extremely preterm neonates cared for in the neonatal intensive care unit (NICU), antimicrobial exposure is even higher averaging ~80% for very low birth weight (VLBW) neonates[1]. Antibiotics comprise 3 of the 4 most commonly-prescribed medications in the NICU[2]. The frequency of antimicrobial administration and the critical, life-saving role these medications play in neonatal care, demand that the neonatal provider have detailed and current knowledge of their mode of action, spectrum of action, and potential toxicities. Over the last two decades, reports of highly resistant 'superbugs' have called attention to inappropriate prescribing practices and prompted closer monitoring of resistance patterns. Pharmacokinetic (PK) studies in the neonatal population have described

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dosing regimens that are specific to the unique physiology of neonates and can allow safer and more efficacious dosing. In this review, we will discuss parenteral antibiotics most commonly used in the management of perinatal bacterial infections[2,3].

ANTIMICROBIAL PHARMACOLOGY

PK considerations of using antimicrobials in neonates:

The effect of an antimicrobial medication on the neonate (pharmacodynamic effect, PD) and the effect of the neonate's physiology on drug exposures (PK) depend on multiple factors that are distinct in neonates compared to older children and adults. Dynamic organ development, changing body composition, evolving gene/enzyme expression, and co-morbid conditions (e.g. prematurity) can all impact drug exposure, efficacy and toxicity. A paucity of neonatal-specific studies contributes to the significant variation in dose recommendations characteristic of different formulary sources[4]. Standard regimens are often derived from older studies that are limited by lower representation of the extremely preterm neonate, use of intramuscular administration, small sample sizes, and extrapolation from older populations[5]. A study of NICU dosing regimens across 89 NICUs in 21 countries found significant variability across sites, with a tendency to use higher than recommended doses of penicillins and wide variability in vancomycin use[6]. The authors attributed this variability to the scarcity of neonatal studies, discrepancies between standard recommendations and changes derived from newer PK studies, and difficulties in the dissemination of available information.

Dosing determinations for antimicrobials are based on achieving drug concentrations that are above the Minimum Inhibitory Concentration (MIC) of a pathogen, the level at which an antimicrobial inhibits growth of the organism *in vitro.* While a critical determinant of antimicrobial efficacy is attaining and maintaining *in vivo* drug concentrations above the infecting pathogen's MIC, antimicrobials differ in the exposure metrics associated with pathogen killing. Bacterial killing can depend on: 1) the peak concentration (Cmax) relative to the MIC (concentration-dependent killing); 2) how long the serum level stays above the MIC (time-dependent killing); or 3) a combination of factors estimated by the total drug exposure which is represented by the area under the concentration curve for a given dose (AUC-dependent killing). Examples of drugs with each characteristic and its implication for dosing are found in Table 1[7]. Initial concentrations depend on the volume of distribution of the drug. Preterm infants may need a higher dose to achieve the same concentration given their higher water content and larger volume of distribution. However, drug elimination is also affected by prematurity[8]. Most antimicrobials used for early infection depend on the kidneys for clearance (with the exception of nafcillin, cleared by the liver). Renal clearance is lower after birth and increases in the first 1-2 weeks of life. Neonates less than 32-34 weeks gestation often have significantly lower renal clearance than neonates born at older gestation. While renal clearance increases with postnatal age, it often remains lower than term counterparts during their NICU stay. Thus, PK studies in neonates often result in altered dosing schedules based on gestational age, postnatal age, and/or postmenstrual age to maintain similar drug exposure across different age groups.

Mechanisms of antibiotic action and resistance:

Parenteral antibiotics commonly used in neonates have three primary mechanisms of action: 1) disruption of the bacterial cell wall (beta lactams and vancomycin inhibit peptidoglycan linking in bacterial cell wall); 2) inhibition of protein synthesis (aminoglycosides and macrolides bind to the 30s ribosomal subunit and clindamycin to the 50s ribosomal subunit, inhibiting translation); and 3) inhibition of nucleic acid function (metronidazole disrupts DNA structure and rifampin inhibits RNA formation required for DNA synthesis)[9]. Although fluoroquinolones inhibit DNA replication and sulfonamides disrupt bacterial metabolic pathways, these antibiotics are rarely used in neonates.

Bacterial susceptibility to an antibiotic usually results from interference with a pathway essential for the organism's growth and survival. Intrinsic resistance occurs when the organism's inherent genotype and/or phenotype renders an antibiotic ineffective. Enterococci are intrinsically resistant to cephalosporins as penicillin-binding protein does not bind to cephalosporins. Gram-negative organisms are resistant to vancomycin because the large size of the molecule prevents penetration through the outer lipid membrane. Similarly, the thick gram-positive cell wall confers intrinsic resistance to aminoglycosides by slowing entry into the intracytoplasmic site of action. Acquired resistance can occur from non-genetic mechanisms (e.g. non-dividing bacteria), chromosomal mutation, or horizontal acquisition via mobile genetic elements (e.g. transposons, plasmids). Beyond the natural tendency of organisms to acquire resistance, antimicrobial use exerts selection pressures for proliferation of resistant strains[10]. Various medical organizations have all recognized that judicious use of antibiotics is needed to prevent the spread of antimicrobial-resistant organisms[11,12]. Single-center and time-trend studies reveal increasing antimicrobial resistance in neonatal late-onset infections and increasing resistance among GBS and *E.coli* isolates in early-onset infections[13-17]. The known resistance patterns of common pathogens combined with local antibiograms can inform antibiotic choices of empiric and definitive therapy (Table 2).

Synergy:

Combining beta-lactams with aminoglycosides to increase bactericidal potential occurs frequently in neonates. Synergy is defined as a combination of antimicrobials demonstrating greater activity (greater than 2 log bactericidal activity) against an organism compared to either used alone[18]. Synergy can compensate for some forms of antimicrobial resistance. For example, synergy between cell-wall active beta-lactams and aminoglycosides can overcome intrinsic resistance by allowing the aminoglycoside to penetrate the cell wall[19,20]. Synergism is used for highly invasive and difficult to sterilize GBS or enterococcal infections such as endocarditis, meningitis or infections associated with medical devices. Although both GBS and enterococci can acquire modes of resistance to aminoglycosides which will render synergy ineffective[22], some experts recommend treating GBS meningitis with a beta-lactam antibiotic and gentamicin until CSF sterility is achieved[23] and others recommend using both drugs for the first 5 days of therapy before completing treatment with a beta-lactam alone[24]. However, clinical demonstration of *in vitro* synergy has been inconsistent and no advantage was found for using a beta-lactam with aminoglycoside versus using beta-lactams alone in a

meta-analysis of 69 trials of adult sepsis, with a higher incidence of renal injury with combination therapy[21].

INTRAPARTUM ANTIMICROBIAL PROPHYLAXIS

Prevention of perinatal infection with Group B Streptococcus:

Transplacental fetal exposure to intrapartum maternally-administered antibiotics is the most common form of perinatal antibiotic treatment. IAP to prevent early-onset GBS disease (GBS EOD) is the primary indication for perinatal antibiotic administration. GBS emerged as an important cause of EOS in the United States in the 1970s and subsequent studies identified maternal gastrointestinal and genitourinary colonization with GBS as the primary risk factor for GBS-specific EOS. The high rate of vertical transmission (~50%) and subsequent infection (~1% of infants born to colonized mothers become infected) and the severity of GBS-associated morbidity and mortality prompted the search for public health approaches to disease prevention. Current recommendations focus on universal antenatal screening of pregnant women for GBS colonization using vaginal-rectal cultures obtained at 35-37 weeks gestation or in the event of preterm labor or preterm rupture of membranes[43]. Antibiotics used for IAP include penicillin G, ampicillin, cefazolin, clindamycin, and vancomycin (Table 2). IAP is hypothesized to prevent neonatal GBS disease in three ways: 1) by temporarily decreasing maternal colonization burden; 2) by preventing surface and mucus membrane colonization of the fetus/neonate; and 3) by reaching the MIC of the antibiotic for killing GBS[25,26].

Penicillin G and Ampicillin:

Penicillin G and ampicillin are beta-lactam antibiotics that differ in structure by a single amino group. These antibiotics inhibit bacterial cell synthesis and are bactericidal. Although penicillin G is metabolized in the liver, it is largely excreted unchanged in urine. GBS remains susceptible to beta-lactam antibiotics with ampicillin and penicillin G best studied for their role as GBS IAP. Maternally-administered penicillin G readily crosses the placenta, reaches cord blood peak levels by one hour, and rapidly declines by 4 hours reflecting elimination of the antibiotic by the fetal kidney into amniotic fluid[27]. Both peak and nadir cord blood levels are above the GBS MIC when administered to the mother every 4 hours. Ampicillin has been detected in cord blood within 30 minutes and in amniotic fluid within 45 minutes of maternal administration[25]. One study measured ampicillin levels in 115 newborns after maternal IAP and detected levels above the GBS MIC at 4 hours of age when maternal dosing occurred at least 15 minutes prior to delivery[28]. Ampicillin IAP has been shown to decrease maternal vaginal colonization within 2 hours of administration and to prevent neonatal surface colonization in 97-100% of cases if IAP was given at least 4 hours prior to delivery[26,29].

Cefazolin:

cefazolin is a first-generation cephalosporin. Like ampicillin and penicillin, cefazolin inhibits cell-wall synthesis and is bactericidal. The drug is recommended for GBS IAP for women with non-anaphylaxis penicillin allergy. Cefazolin rapidly crosses the placenta and is detected in cord blood a levels above the GBS MIC with 20 minutes after maternal

administration[30,31]. One study included 25 women administered cefazolin 20 minutes to 7 hours prior to planned Cesarean section delivery. Cord blood and amniotic fluid levels of cefazolin above the GBS MIC were detected in virtually all cases regardless of the timing relative to delivery[32].

Clindamycin:

Clindamycin is a synthetic lincosamide antibiotic derivative recommended for IAP among women with serious (anaphylaxis) penicillin allergy if the colonizing GBS isolate is sensitive. Clindamycin inhibits bacterial protein synthesis and is considered bacteriostatic. Few data inform the potential effectiveness of clindamycin as GBS IAP. One study of GBS-positive women found that vaginal cultures had no viable GBS if clindamycin was administered 4 hours prior to delivery[33]. In another study, peak cord blood levels of clindamycin occurred ~20 minutes after the maternal dose was given, but levels were only ~50% of simultaneous maternal levels[34]. Clindamycin was not detected in amniotic fluid in 9 specimens obtained 30-90 minutes after maternal dose. Clindamycin is metabolized by the liver; one study of oral maternally-administered clindamycin found the drug concentrates in fetal liver but accumulates in amniotic fluid only after multiple maternal doses[35].

GBS are increasingly resistant to clindamycin as well as to macrolide antibiotics such as erythromycin. The same genetic elements responsible for clindamycin resistance also cause erythromycin resistance[36]. Antibiotic sensitivity testing for GBS should include erythromycin and clindamycin; strains identified as erythromycin-resistant but clindamycin-sensitive should also be assessed by D-test to identify inducible clindamycin resistance. Clindamycin resistance was identified in 12.7% of ~3500 tested GBS isolates collected in 4 states from 1998-2003, with an increasing trend over time[37]. Erythromycin resistance was also identified in 1/3 of all GBS isolates and is no longer recommended for GBS IAP. One report from Canada in 2010-2011 found 26.6% of 158 GBS isolates resistant[38] while another study in upstate New York found resistance in 38.4% of 688 GBS isolates[39]. The bacteriostatic mechanism of antimicrobial action, incomplete placental transfer and unclear fetal/neonatal PK suggest that clindamycin may not provide the same level of protection from GBS infection as provided by beta-lactam antibiotic IAP, even with susceptible isolates.

Vancomycin.

GBS are universally sensitive to vancomycin, a bactericidal glycopeptide antibiotic that inhibits cell wall synthesis of gram-positive bacteria. Vancomycin is recommended for GBS IAP in women with serious (anaphylaxis) penicillin allergy if colonized with clindamycin-resistant GBS. Ex vivo studies with placental lobules suggest that vancomycin crosses the placental poorly, with fetal-side blood levels only ~10% of maternal levels[40]. In contrast, a study of 13 women undergoing elective Cesarean section delivery found that cord blood levels of vancomycin above the GBS MIC could be achieved within 30 minutes of maternal drug administration[41]. No data was reported in this study concerning amniotic fluid or newborn blood levels of vancomycin after birth. As with clindamycin, there is insufficient evidence to inform the efficacy of vancomycin for prevention of neonatal GBS disease.

Prevention of all-bacterial cause EOS:

The American College of Obstetricians and Gynecologists (ACOG) recommends the use of IAP for the prevention of neonatal EOS when there is concern for suspected or confirmed maternal IAI. ACOG guidance defines a *confirmed* diagnosis of IAI as that made by amniotic fluid Gram stain and/or culture or by placental histopathology. *Suspected* IAI is defined by maternal intrapartum fever (either a single maternal intrapartum temperature ≥39.0°C or persistent temperature of 38.0°C–38.9°C) in combination with maternal leukocytosis, purulent cervical drainage and/or fetal tachycardia. In addition, current ACOG guidance is for the administration of IAP when otherwise unexplained maternal fever occurs in isolation. Recommended intrapartum antibiotic regimens for treatment of confirmed or suspected IAI or isolated fever include ampicillin, cefazolin, clindamycin or vancomycin, each in combination with gentamicin[42].

ANTIMICROBIAL THERAPY FOR NEONATAL EARLY-ONSET SEPSIS

Early-onset sepsis:

Neonatal early-onset sepsis (EOS) is defined as blood or cerebrospinal fluid (CSF) culture-confirmed infection that occurs 0-6 days after birth[43]. This is the primary indication for antibiotic use in the immediate neonatal period. Antibacterial choice for empiric therapy is based on the population epidemiology of EOS, while definitive therapy is tailored to the specific organism cultured and to the reported antimicrobial susceptibilities. The two most frequent EOS pathogens in United States are GBS (0.22 cases per 1000 live births) and *E. coli* (0.18 cases per 1000 live births)[44]. The proportionate contribution of *E. coli* to EOS has increased with decreasing incidence of early-onset GBS disease such that it is the most common pathogen in some areas[17,44] and in the VLBW population[45]. Fungal species (most commonly *Candida albicans* and *Candida parapsilosis*) account for <1% of EOS cases and occur primarily among VLBW infants[46]; therapy for fungal EOS will not be addressed in this review. EOS remains a significant cause of neonatal morbidity; mortality is unusual (<2%) among infected term infants but is as high as 30-50% among neonates born <29 weeks gestation[47,48].

Choice of empiric therapy for EOS:

The most frequent choice for empiric EOS therapy is a beta-lactam such as ampicillin plus gentamicin[1,3]. This combination provides adequate coverage for most common gram-positive pathogens including GBS, viridans streptococci, *Enterococcus* sp. and *Listeria monocytogenes* and as well as *E. coli* and other gram-negative bacteria. However, the evolving resistance patterns in *E. coli* have led to concerns about the adequacy of current empiric choices[17]. In a multi-state surveillance report of EOS cases, 78% of the *E. coli* isolates were resistant to ampicillin and 10% resistant to gentamicin[44]. Additionally, 24/25 cases of gentamicin-resistant strains were also resistant to ampicillin. A single center report from Spain similarly found that among 65 *E. coli* isolates over 21 years, 75% were resistant to ampicillin and 12% to gentamicin[17].

Few randomized trials have compared neonatal empiric regimens and a 2004 Cochrane review found insufficient studies to determine an optimal regimen[49]. An open-label, cluster-

randomized trial among 283 neonates with suspected EOS compared regimens of gentamicin combined with either ampicillin or penicillin and found no difference in treatment failure. A trend to increased all-cause mortality was observed among infants born <26 weeks gestation treated with penicillin, unexplained by early mortality or later colonization[50,51]. Most other studies have been observational in design. The NeonIN prospective surveillance study across multiple units in the United Kingdom over a 10-year period found that the combination of penicillin or aminopenicillin and an aminoglycoside provided 93–96% coverage with better performance of ampicillin (vs. penicillin) in the preterm population[3]. In a cohort of 258 neonates with *E. coli* bacteremia, 123 (48%) cases had ampicillin-resistant isolates. Neonates with ampicillin-resistant *E. coli* were more likely to be born to mothers treated with antenatal antibiotics but were otherwise similar. There were no overall difference in mortality and no impact of the composition of the empiric antibiotic regimen on 30-day mortality or duration of bacteremia[52].

While third generation cephalosporin susceptibility remains high in *E. coli*, multiple factors argue against use of cephalosporins as initial empiric therapy. A study investigating the odds of neonatal mortality in 24,111 episodes of empiric ampicillin/cefotaxime use with 104,803 episodes of empiric ampicillin/gentamicin use in the first 21 days of life, found a significant increased odds of mortality with cefotaxime when controlling for multiple patient level characteristics[53]. Other studies have associated cephalosporin use with increased risk of subsequent fungal infection[54] and selection of highly resistant organisms[10]. Cefotaxime lacks intrinsic activity against other common early pathogens such as Listeria and Enterococcus. Additionally, although ~80% of VLBW infants are started on empiric therapy[1], only ~5% will have an *E. coli* infection[55]. The majority of these isolates will be sensitive to gentamicin. Thus, ampicillin and gentamicin remains the optimal empiric choice, with broader spectrum use limited to high-risk infants with poor response or when preliminary microbiologic results identify gram-negative organisms.

Antibiotics used in management of EOS:

In the following sections we describe the common antimicrobials used for EOS in the NICU and factors that determine use. Specific dose recommendations can be found in available formularies and the AAP Red Book®.

Ampicillin: As noted above, ampicillin is a semi-synthetic formulation derived from penicillin where the extra amino groups increases its penetration in gram-negative cell membrane, broadening its antimicrobial activity. It is indicated for treatment of EOS with *L. monocytogenes,* susceptible *H. influenzae, Streptococci spp., Enterococcus spp.,* and gram-negative organisms when susceptibility has been documented.

Ampicillin mediates time-dependent bacterial killing and frequent dosing allows the drug concentration to remain above the MIC for prolonged periods which is thought to improve efficacy. Because ampicillin undergoes renal clearance, neonates (both premature and term) with relatively immature renal function will maintain required levels with less frequent dosing. Although this is also the case for infants with acute renal dysfunction, ampicillin doses are rarely adjusted for renal insufficiency due to lack of neonatal PK data and

relatively low drug toxicity. An open label PK study of 28 infants born <34 weeks gestation and 45 infants born >34 weeks gestation demonstrated a significant increase in clearance with increasing gestation and postnatal age[56]. This supports gestation-specific dosing regimens to achieve the required drug exposure above MIC for GBS and *E.coli.* Ampicillin-associated adverse effects in older children such as diarrhea, rash and increased bleeding tendency are rarely reported in neonates. Increased colonization with *Klebsiella pneumonia* has been noted with empiric early use compared to penicillin use[50]. Increased risk of seizures have been shown with high doses in simulated models[57] that emphasize the need for PK and toxicity studies in neonates.

Gentamicin:

Aminoglycosides irreversibly bind to the 30s subunit of the bacterial ribosome, inhibiting protein synthesis and ultimately killing the organism. Gentamicin, tobramycin and amikacin are the most frequently used aminoglycosides in neonates[2]. Tobramycin provides superior coverage for most strains of *Pseudomonas* and amikacin may be chosen for treatment of gentamicin-resistant organisms[17]. But in the absence of drug shortage, gentamicin remains the most appropriate choice for empiric therapy for EOS. While many gram-negative organisms are susceptible to aminoglycosides, concern for cumulative toxicity with prolonged therapy and poor outcomes in adult patients with gram-negative sepsis managed with aminoglycoside monotherapy[58] has led to gentamicin being used largely in combination therapy.

Extended interval, high-dose regimens in neonatal EOS are designed to achieve peak concentrations over MIC of 8-10 while still achieving trough concentration of <2 mg/L[59] Aminoglycosides peak concentrations above MIC are related to bacterial killing. Higher doses are needed in preterm neonates to achieve a similar peak concentration due their greater volume of distribution. Since gentamicin is eliminated through the kidneys, neonates with renal immaturity or injury clear the drug less efficiently. As a result, longer dosing intervals are recommended in premature neonates, neonates with kidney injury, and neonates in the first few days of life when renal clearance is lower. Retrospective analysis of clinically-obtained gentamicin levels in 994 preterm and 455 term infants found a significant effect of both gestational age and postnatal age on drug clearance[60]. This study validated the need for higher doses (5 mg/kg/dose) in extremely preterm neonates along with extended frequency of dosing (every 48 hours) to reach required therapeutic targets. Longer interval dosing of every 36 hours has also been recommended for neonates with hypoxic injury undergoing therapeutic hypothermia to obtain required trough levels[61]. The prevalence of renal and ototoxicity is difficult to establish in neonates due to multiple competing factors. Prolonged therapy and therapy in neonates with significant renal compromise should be managed by following serum drug levels to ensure appropriate trough levels.

Cefotaxime:

Cefotaxime is the most common systemic cephalosporin used in neonates[2]. A broad-spectrum, low-toxicity antibiotic with excellent CSF penetration[62], cefotaxime targets specific penicillin-binding proteins which results in an extended spectrum compared to ampicillin. Cefotaxime is most frequently added to empiric regimens to broaden coverage

against gram-negative bacilli (particularly when ampicillin-resistant *E. coli* is a concern) or provide coverage in suspected meningitis. Cefepime and ceftazidime may be used when cefotaxime is unavailable but the very broad-spectrum coverage provided by these antibiotics (e.g., for *Pseudomonas* and other ESBL organisms) is not currently indicated for empiric treatment of neonatal EOS. Ceftriaxone is rarely used in newborns due to its high avidity for serum albumin and increased risk of hyperbilirubinemia as well as its incompatibility with calcium-containing fluids.

Similar to ampicillin and other renally-cleared drugs with time-dependent killing, low-dose, frequent-interval regimens maximize the time cefotaxime levels remains above MIC. A study using scavenged blood specimens from 100 neonates born at 23-42 weeks gestation found that failure to shorten the dosing interval after the first week among neonates born >32 weeks gestation was associated with sub-therapeutic cefotaxime levels. This study recommended interval adjustments by gestational age at birth as well as by postnatal age[63]. Adverse drug reactions with cephalosporins (including allergy, diarrhea, bleeding, seizures, bone marrow suppression) have been primarily reported in adults. As noted above, neonatal cephalosporin use is associated with increased fungal colonization, infection, and increased mortality[10,53].

Penicillin:

Penicillin G is a water-soluble intravenous formulation with a narrow spectrum and a long therapeutic history of use in neonates. Other formulations used include benzathine and procaine penicillin that allow for slow release from deep IM injections and are indicated for management of congenital syphilis. Penicillin and an aminoglycoside are used in combination as empiric therapy in some neonates[3], but not commonly in the U.S. Penicillin remains the recommended definitive therapy for GBS, groups C and G streptococci, *Treponema pallidum,* and susceptible strains of viridans streptococci and enterococci[64].

Pathogen killing by penicillin is determined by the time for which unbound drug in the serum remains above the MIC. It is recommended that levels be above the MIC for ~ 50% of the dosing interval. Like other beta-lactam antibiotics, penicillin is cleared by the kidney and interval adjustments should be made for preterm neonates and term neonates in the first days after birth[65]. A study of 18 infants born <28 weeks gestation found that a common penicillin dose recommendation (50,000 units/kg/dose every 12 hours) resulted in peak and trough concentrations in these infants that exceeded the MIC_{90} value for GBS (MIC value that inhibits 90% of isolates) by 1000- and 100-fold, respectively. Current recommendations involve much higher doses for treatment of GBS meningitis[64] (250,000-450, 000 units/kg/day in three divided doses). The authors of that study noted that even with reduced penicillin penetration of the blood brain barrier (CSF: serum concentration ratio of ~5-10%)[66] current regimens would consistently exceed MIC for GBS in the CSF, an observation that has been made by others[7]. Such studies highlight the difficulties of optimizing dosing recommendations among high-risk very preterm neonates with serious infections.

Piperacillin-tazobactum:

A semi-synthetic beta-lactam, piperacillin is a broad-spectrum antibiotic with activity against *S. aureus,* most *Streptococci sp., H. influenzae, Neisseria. meningitidis, L. monocytogenes,* multiple gram-negative rods and many anaerobes. The tazobactum component acts to protect the piperacillin component from beta lactamase degradation. This antibiotic is infrequently indicated in the immediate neonatal period and more commonly used for late-onset sepsis and necrotizing enterocolitis. Piperacillin-tazobactam use showed the highest absolute increase from 2005-2010 among antimicrobials used in 305 NICUs in the United States[2]. Its wide spectrum includes anaerobes and its safety profile makes it a useful choice in polymicrobial infection and in cases of intrabdominal pathology. While some extended-spectrum beta lactamase (ESBL) producing enterobacteriaceae demonstrate *in vitro* sensitivity to piperacillin-tazobactam, carbepenems remain the recommended drug of choice[64] with superior results demonstrated in adults[67].

As with most penicillins, piperacillin-tazobactam mediates time-dependent killing with renal clearance that increases with gestational and postnatal age. A PK study in 71 neonates born 26-41 weeks gestation found that birth weight and postmenstrual age significantly affected the dosing regimen[68]. Another study of 32 neonates born at 23-40 weeks gestation found that postmenstrual age alone was adequate to determine dosing regimen and prolonged infusions were not necessary to achieve therapeutic targets.[69]. Adverse effects are rarely noted in neonates[70].

Meropenem:

Meropenem is a carbapenem beta-lactam antibiotic with a broad spectrum against pseudomonas and ESBL-producing bacteria. Unlike imipenem, it is labelled for use in premature neonates by the FDA. Methicillin-resistant staphylococci and most enterococci are resistant to meropenem. Meropenem is the drug of choice when an ESBL bacteria is isolated, or when there is known maternal ESBL colonization.

Meropenem also mediates time-dependent killing with renal clearance and requires interval adjustments with increases in gestational and postnatal age. A significant impact of postmenstrual age and serum creatinine levels was reported in a prospective PK study of 188 neonates born at 23-40 weeks gestation with suspected intraabdominal infection[71]. Although CSF levels measured in 9 neonates were variable, they were consistently above the therapeutic target. Meropenem is considered safer than imipenem for decreasing the seizure threshold by binding with GABA receptors in the brain[7]. In a review of adverse events associated with meropenem administration in 200 neonates, only 2 cases were considered drug-related, including one case of fungal infection[72]. In a randomized control trial of 102 infants with late-onset, gram-negative sepsis, continuous infusion of meropenem compared to intermittent bolus dosing was associated with less renal dysfunction[73].

Vancomycin:

This glycopeptide acts by inhibiting peptidoglycan cell wall formation and is infrequently indicated shortly after birth. Vancomycin is primarily used for beta-lactam resistant organisms such as Enterococci, Staphylococci and *Streptococcus pneumonia*[64].

Vancomycin is excreted unchanged by the kidneys and demonstrates time-dependent killing that is best reflected in 24-hour area under the curve for serum concentration divided by MIC (AUC_{24}). Neonatal vancomycin dosing regimens remain subject to debate[6,74]. In adults, efficacy is associated with doses that achieve an exposure target of AUC/MIC >400 or serum steady state trough levels of 15-20 mg/L. This has been determined to be a useful surrogate measure of AUC/MIC 400 when the MIC is ≤1mg/L[75]. However, in neonates, a trough level of 7-11 mg/L resulted in ~90% of cases attaining AUC_{24}>400[76]. This AUC/MIC efficacy exposure target is difficult to achieve for organisms with an MIC>1 mg/L[74]. Nephrotoxicity and ototoxicity along with rash, red-man syndrome, and altered colonization have been reported in adults with vancomycin use, but the incidence among neonates is unclear[74]. Overall, the unexplained variability of drug exposure in PK studies support the use of trough drug levels to tailor prolonged management[77].

Oxacillin/Nafcillin:

These semi-synthetic derivatives of penicillins are not affected by penicillinases produced by staphylococci. In adults with methicillin-sensitive *S. aureus* (MSSA) infection, the use of beta-lactam antibiotics is associated with improved survival compared to vancomycin[78]. Oxacillin/nafcillin are the drug of choice for MSSA, which is isolated in neonatal EOS in <5% of cases[44]. Nafcillin is cleared by the liver and oxacillin by the kidney. Few recent studies have informed neonatal PK dosing[5,79]. Both drugs have a similar safety profile to other penicillins and demonstrate time-dependent killing.

CONCLUSION:

Monitoring the incidence and microbiology of perinatal infections is critical to informing the choice for antibacterial infection and prophylaxis therapy. Changes in antimicrobial susceptibilities of common pathogens and increasing survival of extremely preterm neonates highlight the inadequacies of available drug information for the neonate. The goals of antibiotic therapy should be to attain the desired effect with minimal toxicity for the individual while reducing selection pressures for the unit and the community. Placental antibiotic kinetics and neonatal-specific PK studies are needed to better define optimal prophylactic and therapeutic dosing regimens for perinatal infection prevention and treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS

- Early onset sepsis remains a common clinical concern in neonates with persistently high morbidity and mortality, particularly among preterm infants.
- Antibiotics administered to the mother during the intrapartum period can reduce the risk of some perinatal infections by reducing ascending bacterial colonization and via transplacental antibiotic transfer to the fetus/newborn.
- Ampicillin and gentamicin remain the first-line choice for empiric treatment of early-onset sepsis.
- Understanding antibiotic pharmacology can allow neonatal providers to optimize antibiotic choice and minimize resistance-promoting selection pressures.

SYNOPSIS

Antimicrobial medications are the most commonly used medications in the neonatal intensive care unit (NICU). Antibiotics are used for infection prophylaxis, empiric treatment, and definitive treatment of confirmed infection. The choice of medication should be informed by the epidemiology and microbiology of infection in specific clinical scenarios and by the clinical condition of the infant. Understanding evolving pathogen susceptibility to antimicrobials and key pharmacotherapy determinants in neonates can inform optimal antibiotic use.

Table 1:

Pharmacodynamic considerations when dosing antimicrobials

Killing pattern	Antimicrobial Drug	Goal of Dosing	PK/PD parameter
Concentration-dependent killing	Aminoglycosides	Maximize Peak (C_{max}) High dose, long dosing interval	C_{max}/MIC
Time-dependent killing	Penicillins Carbapenams Cephalosporins	Maximize duration of exposure above MIC Short dosing interval and long infusion times	% time >MIC
AUC-dependent killing	Vancomycin Fluconazole	Maximize C_{max} and duration of exposure above MIC. High dose and short interval	AUC_{24}/MIC

Adapted from Table 37-3, Remington and Klein's Infectious Disease of the Fetus and Newborn. 8th edition. Elsevier: Philadelphia. Saunders; 2016; with permission.

Table 2.

Antibiotics used for intrapartum prophylaxis

Antibiotic	Intrapartum Indication	Placental Kinetics
Penicillin G[27]	Recommended for GBS prophylaxis	Cord blood levels > MIC for GBS <1 hour after administration
Ampicillin[25,26,28,29]	Recommended for GBS prophylaxis	• Cord blood levels >MIC for GBS with 30 minutes of maternal administration • Rapid (<1 hour after maternal dose) transfer into amniotic fluid • Neonatal serum levels >MIC for GBS at 4 hours of age, if dose administered to mother >15 minutes prior to delivery
Cefazolin[30-32]	Recommended for GBS prophylaxis in case of mild maternal penicillin allergy (non-anaphylaxis)	• Cord blood levels >MIC GBS within 20 minutes of maternal administration
Clindamycin[33-35]	Recommended for GBS prophylaxis in case of serious maternal penicillin allergy *and* GBS isolate sensitive to clindamycin	• Cord blood levels ~50% of maternal levels and above MIC for GBS • Poor transfer into amniotic fluid
Vancomycin[40,41]	Recommended for GBS prophylaxis in case of maternal serious penicillin allergy *and* GBS isolate resistant to erythromycin or clindamycin	• *Ex vivo* placental studies predict cord blood levels < 10% of maternal levels. • Study of 13 women demonstrated cord blood levels >MIC for GBS by 30 minutes after 60-90 minute maternal infusion completed
Ampicillin and gentamicin [34,42]	Recommended when there is concern for intrapartum maternal intraamniotic infection	• Gentamicin reaches lower levels in pregnant compared to non-pregnant women • Cord blood levels ~40% of maternal levels • Poor transfer into amniotic fluid
Cefazolin and gentamicin	Recommended when there is concern for intrapartum maternal intraamniotic infection, in case of mild maternal penicillin allergy	
Vancomycin and gentamicin	Recommended when there is concern for intrapartum maternal intraamniotic infection, in case of serious maternal penicillin allergy	

Ampicillin-sulbactam, piperacillin-tazobactam, cefoxitin, cefotetan and ertapenem are alternative regimens for empiric treatment of maternal intraamniotic infection.

Table 3:

Microbiology and antibiotic susceptibilities of EOS pathogens

Bacteria in EOS (% of cases)*	Ampicillin susceptibility	Gentamicin susceptibility	Cephalosporin susceptibility	General comments
GBS [22,44,64] (35.8%)	100% susceptible	Intrinsic resistance but when paired with a beta-lactam, aminoglycosides can act synergistically	100% susceptible	• Drug of choice: penicillin G; ampicillin is alternate • GBS meningitis: higher dose and longer therapy. Some guidelines include gentamicin for synergy (5 days). Complicated or unresponsive cases may require repeat CSF testing to determine therapy duration. • Reports of high-level gentamicin-resistant GBS strains in adults with concern for loss of synergy
E. coli [13,44,80,81] (24.8%)	~22% susceptible	~90% susceptible Combination therapy with a beta lactam in meningitis	Case reports of ESBL *E. coli* sepsis in NICUs after maternal travel in high-prevalence areas and in late-onset sepsis	• Drug of choice: based on susceptibility. Commonly cefotaxime • Reports of gentamicin-resistance with retained susceptibility to amikacin • ESBL *E. coli* treated with carbapenems • Peripartum transmission of ESBL *E. coli* strains from mother to infant highlight possible role of maternal isolate data to inform antimicrobial choices in infants with poor response to standard empiric therapy
Viridans streptococci[64,82] (18.9%)	Variable susceptibility; population surveillance susceptibility 67%	Added for synergy in endocarditis where isolate has intermediate-level resistance to penicillin	Majority susceptible (87% found susceptible to cefepime)	• Drug of choice: penicillin G when penicillin susceptible • Cephalosporin second line for penicillin-resistant strains • Alternate agent: vancomycin
H. influenzae[64,83] (4.5%)	Worldwide susceptibility reported ~82%	Susceptible at baseline but not recommended for definitive therapy. Acquired resistance with use has been reported.	Worldwide susceptibility high (100% to ceftriaxone)	• Drug of choice: ampicillin in susceptible variants. • Alternate: cephalosporins • Beta-lactamase negative, ampicillin-resistant variants are difficult to test for susceptibility because the MIC are only slightly elevated from susceptible variants. Such cases may require use of cephalosporins.
Staphylococcus aureus[44,78,84] (3.5%)	Most strains resistant due to production of beta lactamases	Susceptible at baseline but not recommended due to better alternates. Variable increase in resistance has been reported worldwide	Variable susceptibility	• Drug of choice for MSSA: oxacillin or nafcillin has better outcomes than vancomycin. • Drug of choice for MRSA: vancomycin

Bacteria in EOS (% of cases)*	Ampicillin susceptibility	Gentamicin susceptibility	Cephalosporin susceptibility	General comments
				• MRSA in EOS is still rare. In a population study of EOS pathogens *S. aureus* accounted for 0.03 cases/ 1000 live births in USA and 1/23 cases were MRSA • Maternal history of MRSA colonization/disease can inform antimicrobial choices. • In cases of endocarditis and device-related MRSA infection, addition of gentamicin and rifampin is recommended
Enterococcus spp. (3.1%)	*E. fecalis* mostly sensitive and more frequent cause of EOS. *E. faecium* largely resistant	Intrinsic resistance but has been used synergistically in endocarditis.	Intrinsically resistant	• Drug of choice: Penicillin or ampicillin • Alternate: Vancomycin • Rare case reports of neonatal late-onset vancomycin resistant enterococci treated with linezolid • Gentamicin not recommended if acquired high level resistance is documented
Group D streptococcus (1.4%) e.g. *S bovis*	Universally susceptible	May be used for synergy	Susceptible	• Drug of choice: penicillin G
L. monocytogenes (1.3%)[85]	Susceptible but bacteriostatic	Intracellular form of listeria is protected from gentamicin. May be added for synergy	Intrinsically resistant	• Drug of choice: ampicillin with a aminoglycoside • Alternate agent: vancomycin • Reports of ampicillin resistance present in adults and in the food industry
Klebsiella pneumoniae [11,86] (<1%) and other Enterobacteriaceae	Increasingly resistant	Susceptible at baseline. Acquired resistance has been described. Amikacin susceptibility may be retained despite gentamicin resistance	Susceptible. ESBL isolates most cephalosporins including cefepime.	• Drug of choice: based on susceptibility with ampicillin or cefotaxime • ESBL pathogen - drug of choice is a carbapenam • *K. pneumoniae* is the most common ESBL Enterobacteriaceae reported in NICU, in late onset sepsis. Risk factors includes prior antibiotic exposure. • Synergistic therapy with gentamicin in meningitis has been recommended
Streptococcus pneumoniae[11] (<1%) and other GPC	Increasing penicillin resistance	Intrinsic resistance	Variable susceptibility	• Drug of choice: based on susceptibility, penicillin or cephalosporin if susceptible and vancomycin with rifampin if penicillin- and cephalosporin-resistant

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* Top 10 pathogens associated with invasive EOS occurring 2005-2014 in United States using absolute frequencies[44]. Resistant patterns are noted in perinatal infection only for GBS and E .Coli. Remaining susceptible patterns are based on case reports or information on older infants and adults[87,88]