REVIEW

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Dosing antibiotics in neonates: review of the pharmacokinetic data

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Antibiotics are often used in neonates despite the absence of relevant dosing information in drug labels. For neonatal dosing, clinicians must extrapolate data from studies for adults and older children, who have strikingly different physiologies. As a result, dosing extrapolation can lead to increased toxicity or efficacy failures in neonates. Driven by these differences and recent legislation mandating the study of drugs in children and neonates, an increasing number of pharmacokinetic studies of antibiotics are being performed in neonates. These studies have led to new dosing recommendations with particular consideration for neonate body size and maturation. Herein, we highlight the available pharmacokinetic data for commonly used systemic antibiotics in neonates.

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Drug dosing in neonates has long been a challenge due to the scarcity of available data, which are limited due to: ethical concerns with enrolling children; few available patients with the target disease; a lack of feasible trial design; a lack of expertise in neonatal pharmacokinetic (PK)/pharmacodynamic (PD) simulation; and the large blood volumes required for PK samples [1]. Historically, neonatal dosing has been extrapolated from adult studies and adjusted based on weight [2]. This often results in either underdosing (leading to efficacy failures) or overdosing (leading to increased risk of toxicity) [3]. Efficacy of some drugs, such as antibiotics, can be extrapolated from adult data to neonates using measures of drug activity against pathogens. However, safety is typically more challenging to extrapolate to this population undergoing rapid developmental changes and for whom long-term adverse effects are difficult to predict. In the pediatric population, there are many concerns about safety, and this in part is from the lack of data available.

Neonates admitted to a neonatal intensive care unit (NICU) are exposed to many drugs early in life. The average extremely low birth weight neonate is exposed to 17 drug courses, and 25% of the exposures are antibiotics [4]. The unique physiology of neonates affects drug disposition, and comorbidities and concomitant medications can further disrupt drug absorption, distribution, metabolism and elimination. Some of these physiologic changes include a relatively lower stomach acidity (pH of 1–3) and slower gastric emptying time (6–8 h) that can contribute to higher drug absorption [5–7]. Gastric emptying is slower and more linear in both full-term and preterm neonates compared with adults, which leads to longer mucosal contact and the potential for higher systemic drug concentrations. Drug distribution is affected by the relatively large extracellular and total body water space characteristic of neonates (70–75% total water), which can contribute to a relatively higher volume of distribution and need for higher initial doses. Both drug metabolism and elimination are influenced by body size and maturation, requiring dose adjustments as neonates grow and mature [6,8–9]. Drug metabolism can occur in the kidneys, gastrointestinal tract, blood cells and

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lungs, but the bulk of it occurs in the liver, while drug elimination for most antibiotics occurs primarily through the renal system. Renal function is low at birth, especially in preterm neonates, and nephrogenesis is not complete until about 34 weeks [10].

In addition to these maturational covariates, there are also nonmaturational covariates that can affect the PK of certain drugs in neonates. Disease characteristics, comorbidities and even concomitant medications (e.g., indomethacin use for patent ductus arteriosus can affect renal clearance) must be considered as well when evaluating medication dosing in neonates [11]. Therefore, for optimal dosing in neonates, these factors need to be considered to reduce the risk of adverse effects and efficacy failures [10,12].

Therapeutic drug monitoring (TDM) also plays an important role in neonates, particularly for certain drugs with a narrow therapeutic index. TDM is most commonly used when: there is a weak correlation between dose and concentration and the concentration is more related to toxicity or effect than the dosage; the drug has a narrow therapeutic index (i.e., risk for toxicity is high); when the inter-individual variability is high; and for some drugs with nonlinear PK [13].

In recent years, the USA and EU have passed legislation to encourage inclusion of children and neonates in drug trials [14,15]. This has led to 406 labeling changes in the USA, but only 24 of those occurred in the neonatal population, with 50% in the infectious disease category [3,6,12]. The European Medicines Agency legislation has led to 30 drug approvals and several new investigational pediatric studies [14,15]. While these efforts have successfully incentivized and funded pediatric studies, studying drugs in neonates still presents logistical and ethical challenges. To address this, new trial design strategies have been developed, including using minimal-risk methods to evaluate drug PK. Also, sparse PK sampling (which allows for fewer samples) has been combined with opportunistic sampling (in which biological fluid is collected as part of standard care draws) to increase study feasibility. In addition, dried matrix spot testing, which requires a biological fluid volume for PK sampling that is ten-times lower, is increasingly being evaluated as a potential alternative to liquid sampling in neonates [16,17]. Finally, population PK analysis techniques continue to be employed in this

population, providing information regarding PK parameters for the study population and each individual as well as estimates of inter-individual and intraindividual variability. The use of these methodologies in neonates has led to increased data with minimal risk to participants, which mitigates the ethical challenges associated with neonatal studies.

In this article, we will review and focus on the PK data available for 13 of the most common systemic antibiotics used in neonates and provide recommended dosing regimens for these drugs [4]. The PD of the drugs are not addressed, though it should be acknowledged that the studies presented here frequently use different PK targets to support their dosing regimens. We will also briefly discuss some of the newer antibiotics in development and their potential applications in the neonatal population.

Neonatal PK data for specific antibiotics

To identify studies of the 13 most commonly prescribed systemic antibiotics in neonates, we used data from a recent study that ranked drugs by frequency of administration in US NICUs (Table 1) [4]. Systemic antibiotics were defined as drugs administered intravenously, intramuscularly or orally. Topical antibiotics (e.g., ophthalmic drops, creams, ointments) were not considered to be systemic antibiotics. PK studies concerning these antibiotics were identified via a PubMed search using the drug of interest plus the following keywords: neonate, infant, premature and pharmacokinetics. Studies were included if they met the following criteria: were written in English; were available through PubMed; included ≥ 15 neonates; included PK modeling techniques using compartmental and noncompartmental models and/or Monte Carlo simulations; and included administration of systemic antibiotics.

• Ampicillin

Ampicillin is a β -lactam antibiotic and is the most widely used systemic drug in the NICU [4,18]. It is commonly used as empiric therapy for early onset sepsis and provides coverage against pathogens including Group B *Streptococcus*, *Listeria monocytogenes* and *Escherichia coli*. Ampicillin works by irreversible inhibition of transpeptidase, an essential component of bacterial cell-wall synthesis and binary fission. Like all β -lactams, it exhibits time-dependent killing over minimum

Table 1. Most common antibiotics used in the neonatal intensive care unit along with food and drug administration-labeled indications and dosing.

Antibiotic	NICU rank	Rank among antibiotics	Labeled indication for neonates	Dosing information for neonates in drug label	PK/PD relationship
Ampicillin	1	1	None	No specific dosing for neonates	Time-dependent
Gentamicin	2	2	Gram-negative sepsis caused by <i>Pseudomonas aeruginosa</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> and <i>Enterobacter</i> spp.	– Infants and neonates >1 week PNA: 7.5 mg/kg/day – Premature and full-term infants <1 week PNA: 5 mg/kg/day	Concentration-dependent and post-antibiotic effect
Vancomycin	4	3	Methicillin-resistant <i>Staphylococcus aureus</i> , ampicillin-resistant <i>Enterococcus</i> spp., coagulase-negative <i>Staphylococcus</i> spp.	– Neonates <1 week PNA: initial dose 15 mg/kg/dose followed by 10 mg/kg q 12 h – Neonates 1–4 weeks PNA: 10 mg/kg q 8 h	AUC/time-dependent
Cefotaxime	15	4	Bacteremia, central nervous system infections, skin infections, lower respiratory tract infections	– Neonates including preterm neonates <1 week PNA: 50 mg/kg q 12 h – >1 week to <4 weeks PNA: 50 mg/kg q 8 h	Time-dependent
Tobramycin	23	5	Septicemia caused by <i>Pseudomonas</i> , <i>Escherichia coli</i> and <i>Klebsiella pneumoniae</i>	– Neonates >1 week PNA: 6–7.5 mg/kg/day – Premature or full-term neonates <1 week PNA: 4 mg/kg/day	Concentration-dependent and post-antibiotic effect
Clindamycin	28	6	– Anaerobic infections including lung abscess, empyema and complicated intra-abdominal infections – Infections due to <i>Staphylococcus</i> and <i>Streptococci</i> spp.	– Neonates <4 weeks PNA: 15–20 mg/kg/day q 6–8 h – No dosing for preterm neonates	AUC/time-dependent
Ceftazidime	38	7	Same indications as cefotaxime plus infections due to <i>Pseudomonas aeruginosa</i>	Neonates <4 weeks PNA: 30 mg/kg q 12 h	Time-dependent
Piperacillin/tazobactam	41	8	None	None for <2 months PNA	Time-dependent
Metronidazole	44	9	None	None	Concentration-dependent
Amikacin	48	10	Serious infections with susceptible Gram-negative organisms	Neonates: loading dose 10 mg/kg, then 7.5 mg/kg q 12 h	Concentration-dependent and post-antibiotic effect
Meropenem	52	11	Complicated intra-abdominal infections	– Neonates <32 weeks and PNA <2 weeks: 20 mg/kg q 12 h – Neonates <32 weeks with PNA >2 weeks AND neonates >32 weeks and PNA <2 weeks: 20 mg/kg q 8 h – Neonates >32 weeks and PNA >2 weeks: 30 mg/kg q 8 h	Time-dependent

AUC: Area under the curve; NICU: Neonatal intensive care unit; PD: Pharmacodynamic; PK: Pharmacokinetic; PNA: Postnatal age; q: Every.

Table 1. Most common antibiotics used in the neonatal intensive care unit along with food and drug administration-labeled indications and dosing (cont.).					
Antibiotic	NICU rank	Rank among antibiotics	Labeled indication for neonates	Dosing information for neonates in drug label	PK/PD relationship
Cefepime	60	12	None	None for <2 months PNA	Time-dependent
Daptomycin	N/A	N/A	None	None	Concentration-dependent and post-antibiotic effect
AUC: Area under the curve; NICU: Neonatal intensive care unit; PD: Pharmacodynamic; PK: Pharmacokinetic; PNA: Postnatal age; q: Every.					

inhibitory concentration ($T > MIC$). The majority of ampicillin elimination is through renal excretion via tubular secretion and glomerular filtration, with only 10% hepatic metabolism. Ampicillin has been studied previously in small cohorts of infants, but until recently, dosing recommendations were mostly a result of extrapolation from studies of adults and older children [18–23].

An opportunistic PK study performed as part of the Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care Study (POPS) characterized the population PK of ampicillin in 73 preterm neonates (mean gestational age [GA] 36 weeks) [18]. The median dose administered was 200 mg/kg/day (range 100–350 mg/kg/day) every 6–12 h. In this study, postmenstrual age (PMA), body weight and serum creatinine were significant factors affecting drug clearance. These findings are consistent with the route of drug elimination as renal function matures with increasing PMA. Concurrently, median terminal elimination half-life decreased after the first week of life from 3 to 5 h (postnatal age [PNA] ≤ 7 days) to 2–4 h (PNA 8–28 days), which had a substantial effect on the recommended dose. With the PK data collected in this trial, simulations of a neonatal-specific dosing regimen showed achievement of the therapeutic target in >97% of neonates, compared with the previous dosing recommendations that achieved this target in >90% of neonates. Given these findings, a simplified dosing regimen was proposed based on GA and PNA [18] (Table 2).

• Aminoglycosides

Aminoglycosides are among the most common antibiotics used in the neonatal period. These drugs display concentration-dependent killing, and clinical response is associated with the ratio of the peak concentration over the MIC. Aminoglycosides also exhibit a post-antibiotic effect, which along with their killing mechanism results in the ability to administer the drugs less frequently [24]. The mechanism of action involves binding irreversibly to the 30S subunit of the bacterial ribosome, which results in inhibition of protein synthesis and induction of translational errors. Aminoglycosides are excreted unchanged through the kidneys, which explains the high serum concentrations observed in younger infants with decreasing GA at birth. Ototoxicity and nephrotoxicity have been reported, particularly in individuals with concentrations that exceed the recommended trough for each drug and who receive concomitant ototoxic and nephrotoxic drugs [24,25].

Of the aminoglycosides, gentamicin is the most widely used in neonates. It is prescribed with ampicillin for early onset sepsis and is commonly used in the setting of hypoxic ischemic encephalopathy (HIE) during therapeutic hypothermia [26,27]. Population PK studies of gentamicin have determined the extent of this drug’s inter-individual and intra-individual variability as well as the effect of PNA, GA and birth weight on clearance [28,29]. This was further evaluated in one of the largest studies to date, which included 994 preterm and 455 term neonates, that noted the PK was largely dependent

Table 2. Proposed recommendations for ampicillin dosing.			
Gestational age (weeks)	Postnatal age (days)	Maintenance dose (mg/kg/dose)	Dosing interval (h)
≤ 34	≤ 7	50	12
≤ 34	≥ 8 and ≤ 28	75	12
> 34	≤ 28	50	8

on growth status (body weight) and maturation (GA and PNA) [30]. The dosing used for this study was 3–4 mg/kg/dose per day. In another study, investigators used a previous model [31] to perform Monte Carlo simulations of 1854 neonates based on GA, PNA and weight [28]. They extracted covariate data from previous studies to generate a dataset of infants with an average birth weight of 2100 g, a current weight of 2100 g and a PNA of 1.7 days. The authors were able to compare dosing guidelines recommended in traditional references (NeoFax, Redbook, British National Formulary for Children, and Dutch Knowledge Centre for Pharmacotherapy in Children) with proposed dosing recommendations. They evaluated the obtainment of adequate peak and trough levels (5–12 mg/l and <1 mg/l, respectively). The resulting proposed dosing regimen was based on birth body weight and PNA. A more recent study that included 65 neonates, 75% of which were premature with an average PNA of 1 day, also evaluated the trough and peak concentrations of three dosing regimens [29]. This analysis showed that an adequate peak (>8 mg/l, range 8–15 mg/l) and acceptable trough level (<1 mg/l) were obtained with a single dose of 5 mg/kg at intervals of 24, 36 and 48 h. They further analyzed these results with a Monte Carlo simulation using a two-compartmental model using PMA as a covariate on drug clearance and concluded that a uniform dosing regimen of 5 mg/kg with varying frequency depending on PMA would achieve the desired therapeutic concentration targets against desired Gram-negative organisms (Table 3) [29].

As previously mentioned, gentamicin is often used in neonates with HIE undergoing hypothermia [32]. Hypothermic neonates had up to a 50% decrease in clearance compared with normothermic neonates. In this initial study, which was comprised mostly of neonates >36 weeks GA, gentamicin PK (peak and trough values) were evaluated. Doses ranged from 4 to 5 mg/kg every 24 h. The authors were able to observe that birth weight and hypothermia were significant predictors of gentamicin

clearance and that the standard dosing interval (i.e., every 24 h) resulted in elevated trough levels (>2 mg/l). These results led to another study examining the effect of hypothermia on gentamicin clearance [33] and evaluating the effect of increasing dosing frequency from the standard 5 mg/kg every 24 h to every 36 h. The proportion of toxic trough concentrations was substantially decreased with this change (38 to 4%). Therefore, the authors recommended a dosing frequency of 36 h for infants with HIE. This regimen of 5 mg/kg every 36 h was further confirmed in another study using an external validation dataset in neonates 36–40 weeks GA from another academic institution [27]. These studies highlight the importance of evaluating the PK of drugs in neonatal subpopulations that may have altered drug disposition in addition to the underlying physiologic factors inherent to neonates.

The second most common aminoglycoside used in neonates is tobramycin. Few studies have examined the PK of tobramycin in neonates. In one of the first studies evaluating tobramycin PK using a retrospective approach and TDM data, 470 neonates were evaluated (GA 23–42 weeks) [34]. The dosing ranged from 2.5 to 3.5 mg/kg every 12–24 h depending on GA. This dosing scheme was not able to achieve the desired peak concentration in approximately 20% of patients and also resulted in undesired trough levels (>2 mg/l) in 33% of patients. A total of 49% of premature neonates (GA <28 weeks) were observed to have elevated trough levels while peak levels were within therapeutic range. The authors then performed a prospective study in 23 preterm and term neonates (GA 24–42 weeks) and concluded that the half-life of tobramycin was longer in premature neonates than in full-term neonates and that the dosing needed to obtain therapeutic levels should be based on PMA (4 mg/kg every 48, 36 and 24 h for ≤32, >32 but <37, and ≥37 weeks, respectively) [34]. In a subsequent study [35], the authors were able to validate the prior dosing recommendation

Table 3. Recommended gentamicin dosing intervals for doses of 5 mg/kg/dose.

Postmenstrual age (weeks)	Dosing interval (h)
<37	48
37 to <40	36
≥40	24
Therapeutic drug monitoring is required.	

Table 4. Proposed tobramycin dosing intervals for doses of 5.5 mg/kg.

Postnatal age (days)	Dosing interval (h)		
	Birth weight <1 kg	Birth weight 1–2 kg	Birth weight >2 kg
≤5	72	60	48
6–10	60	48	36
11–20	48	36	24
≥21	36	24	24

Therapeutic drug monitoring is required.

using TDM in 247 neonates (GA 24–42 weeks and PNA 0–27 days) and using PK/PD modeling and simulation techniques. The new tobramycin regimen was found to provide therapeutic peak concentrations (>5 µg/ml) in 91% of neonates while maintaining the safety margin of trough concentrations in 74% of neonates (Table 4).

Amikacin is the third most common aminoglycoside used in neonates. In 1998, a single PK study involving 177 infants established a dosing regimen based on GA that has been the basis for comparison for more recent studies [36–38]. A study using data from 874 preterm neonates to generate a two-compartmental population PK model compared standard-of-care dosing with a new proposed dosing schedule [36]. The authors were able to propose a new regimen based on PNA and body weight that differed from standard of care and prior recommendations based on GA [37]. A subsequent population PK/PD model and simulation study of 579 preterm and term neonates (median GA 34 weeks [range 24–41], median PNA 2 days [range 1–30]) [39] validated the findings from the prior study and resulted in a new amikacin dosing regimen [36] (Table 5).

In summary, aminoglycoside clearance is affected by both PNA and birth weight, in keeping with its primary method of elimination. Including these factors in the dosing recommendations has the benefit of minimizing the toxicity of the drug without affecting efficacy.

• Glycopeptides

Vancomycin is a glycopeptide antibiotic that is commonly used for resistant Gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), ampicillin-resistant *Enterococcus* and coagulase-negative *Staphylococcus*. This drug inhibits bacterial cell wall biosynthesis by binding to the *D-alanyl-D-alanine* precursor, thereby blocking peptidoglycan polymerization. Finding a commonly applicable dosing regimen for this drug has been difficult, given the variability of its PK as a result of the developmental and physiological changes that occur in neonates. In addition, there is debate about the appropriate PD target of vancomycin in children and neonates. In adults, the area under the curve over the MIC ratio (AUC/MIC) is the best predictor of clinical outcomes for vancomycin treatment. According to the most recent guidelines of the Infectious Diseases Society of America, an AUC/MIC of 400 is ideal for treatment of MRSA [40]. Due to practical limitations in calculating the AUC/MIC, trough levels are used as surrogates for AUC; in adults, trough levels of 15–20 µg/ml correlate with an AUC/MIC of 400 [40]. In children, however, studies have found that this AUC/MIC ratio can be achieved at lower trough concentrations (7–10 µg/ml) [40–43]. These desired trough levels are calculated from the AUC target value and assume that the MIC of the pathogen is ≤1 mg/l; hence, this correlation is not absolute in all patients [13,44]. In neonates,

Table 5. Simplified amikacin dosing regimen.

Body weight (g)	Postnatal age <14 days	Postnatal age ≥14 days
0–800	16 mg/kg q 48 h	20 mg/kg q 42 h
801–1200	16 mg/kg q 42 h	20 mg/kg q 36 h
1201–2000	15 mg/kg q 36 h	18 mg/kg q 30 h
2001–2800	15 mg/kg q 36 h	18 mg/kg q 24 h
>2800	15 mg/kg q 30 h	18 mg/kg q 20 h

q: Every.
 Therapeutic drug monitoring is required.

the optimal trough concentration efficacy target has not been defined [41–43].

Multiple studies have evaluated the PK of vancomycin in neonates. One PK study involved 50 participants, most of whom received uniform dosing of 10 mg/kg every 8 h independent of GA, PNA and corrected GA [42]. Monte Carlo simulations led to a recommended regimen based on body weight instead of PNA or GA. This study found that a shorter dosing interval of 15–20 µg/ml was required to obtain trough levels (after the third dose). However, trough concentrations of 10 µg/ml were readily obtained with a dosing frequency of every 12 h. Another retrospective population PK study of 153 preterm and term neonates evaluated the serum elimination half-life of vancomycin using previous empiric dosing (15 mg/kg with a varying dosing interval according to weight and PNA) [45]. Only 34% of the neonates had a trough level of 10–20 mg/l on the initial dose. This led to a secondary evaluation of 94 neonates using a modified dosing regimen based on PMA and PNA [45]. Both PNA and PMA were found to influence the dosing interval recommended to achieve maximum efficacy. In full-term neonates, half-life decreased more rapidly with increasing PNA compared with preterm neonates. With this new dosing regimen, the overall mean serum trough concentration was 15 µg/ml and approximately 86% of neonates had an AUC_{24}/MIC ratio of 400.

Another consideration with vancomycin dosing has been the use of a loading dose with the intent of achieving therapeutic exposures soon after first-dose administration. This strategy has been used in critically ill adults to maintain serum concentrations above the MIC, optimize efficiency and improve the ease of TDM [46]. The use of a loading dose with the addition of a continuous infusion was also studied in neonates [44]. This regimen showed that therapeutic concentrations were readily obtained, though troughs were variable, highlighting the need for TDM. The utility of a vancomycin regimen including a loading dose was recently externally validated in neonates and older children [47]. Predictions from a previous model [31] were validated using a new dataset comprised of 191 neonates, and Monte Carlo simulations were performed in representative individuals to evaluate target exposure. The Monte Carlo simulations were performed in six representative

individuals: three neonates (GAs 24, 34 and 40, respectively, with PNAs of 14 days) and three children. These simulations evaluated six different regimens (four traditional and two new regimens proposed in the study) with the goal of obtaining $AUC_{24} > 400$ mg/l. Of the two author-proposed regimens, one used intermittent dosing and one used continuous infusion. Both dosing schemes implemented a loading dose, which allowed the desired steady state AUC to be reached sooner, especially considering the longer elimination half-life in neonates compared with older children and adults. The proposed dosing recommendations were based on PNA and birth weight, factors that were most significantly correlated with clearance in the neonatal model (Table 6). While the proposed regimen was validated externally, renal function should be followed closely and TDM is still necessary for neonates receiving vancomycin to ensure appropriate levels. While continuous infusion regimens of vancomycin are becoming an area of interest, they still lack the necessary safety evaluation in neonates required to become standard of care.

Daptomycin is a cyclic lipopeptide approved for adults in 2003 to treat MRSA and other Gram-positive organisms. It is a bactericidal antibiotic causing disruption of the membrane potential and inhibition of DNA, RNA and protein synthesis. The primary method of elimination is via the kidneys and dependent on glomerular filtration rate. Limited PK data are available in the neonatal population. A recent PK study included 20 neonates and infants ranging from 23 to 40 weeks GA who received a single dose of daptomycin 6 mg/kg infused over 60 min [48]. Compared with adults, clearance of daptomycin in neonates was higher, as evidenced by lower mean exposure when compared with adults (262 mg*h/l in neonates vs 417 mg*h/l in adults who were given a 4 mg/kg/dose). This suggests that higher doses or shortening of the dosing interval would be needed to provide exposures comparable to therapeutic exposures observed in adults. Even though this study was limited by its design of evaluating only a single dose of daptomycin, the investigators were able to confirm results seen in prior studies and concluded that clearance decreased with age. The need for higher doses or shortened dosing intervals is also somewhat suggested in a small case report of two preterm neonates (23 weeks GA/PNA 60 days, and 32 weeks GA/PNA

Table 6. Proposed vancomycin dosing with loading dose.

Postnatal age (days)	Birth weight (g)	Loading dose (mg/kg) [†]	Maintenance dose (mg/kg/day)	Dosing interval (h)
0–7	≤700	16	15	8
	700–1000		21	8
	1001–1500		27	8
	1501–2500		30	6
	>2500		36	6
8–14	≤700	20	21	8
	701–1000		27	8
	1001–1500		36	8
	1501–2500		40	6
	>2500		48	6
15–28	≤700	23	24	8
	701–1000		42	8
	1001–1500		45	8
	1501–2500		52	6
	>2500		60	6

[†]Maximum loading dose 1200 mg. Infused slowly. Therapeutic drug monitoring is required.

21 days), both of whom received the same dose of 6 mg/kg/dose every 12 h, which was required to achieve a mean AUC₂₄ comparable with adult dosing of 4 mg/kg every 24 h (peak 58 mcg/ml and trough 7 mcg/ml) [49]. Further studies are still needed to evaluate daptomycin that will provide adequate dosing recommendations in neonates [48–51].

Appropriate dosing for glycopeptides depends on PNA and GA. Further PK studies of daptomycin are still needed to evaluate optimal dosing and safety in neonates.

• Cephalosporins

Cephalosporins have an extended spectrum of activity ranging from Gram-positive organisms to resistant Gram-negative organisms, including *Pseudomonas aeruginosa* [52]. Cephalosporins, which are members of the β -lactam class of antibiotics, have a similar mechanism of action to ampicillin. Though they are similar in terms of mechanism of action, cephalosporins are categorized in five different classes according to spectrum of activity. The newer the generation (i.e., going from first generation to second), the broader the coverage in which they gain Gram-negative organism activity. Clinicians most commonly use these agents for sepsis and meningitis in the neonatal period. Renal excretion is the primary route of elimination, and they are mostly excreted unchanged. Cephalosporins continue to be frequently used in neonates despite concerns

for increased susceptibility to extended-spectrum β -lactamase Gram-negative organisms [53–55]. A recent study evaluated this association using Enterobacteriaceae isolates from 2000 to 2011 in the NICU [54]. The authors were able to evaluate the prevalence of resistant organisms and correlate this with antibiotic exposure in the neonates. They observed an increasing trend of resistance over time, as high as 40% in 2011. In addition, cephalosporin use has also been associated with other negative outcomes in infants, including the development of *Candida* infections. A cohort study of 3702 extremely low-birth weight infants found that third-generation cephalosporin exposure was associated with increased risk of candidiasis [56]. Despite these concerns, cephalosporins continue to be necessary for the treatment of certain bacterial infections in neonates.

Cefotaxime is a semisynthetic third-generation cephalosporin with an excellent safety profile [57]. Compared with ceftriaxone, cefotaxime is less associated with biliary excretion and has less propensity to alter bilirubin–albumin binding. Studies done in the early 1980s and 1990s on the PK of cefotaxime in neonates demonstrated that PNA is an important factor for dosing. The longer half-life seen in the first week of life led to a dosing recommendation of 50 mg/kg/dose every 12 h for the first week of life [57–60]. In a more recent PK study in 37 neonates on extracorporeal membrane oxygenation (ECMO) [52], the authors

Table 7. Dosing recommendations of cefotaxime for neonates with and without extracorporeal membrane oxygenation.

Postnatal age (days)	Dose (mg/kg/dose)	Interval (h)
0–7	50	12
7–28	50	8
>28	37.5	6

found that there was no difference in the clearance of cefotaxime in neonates on ECMO versus those not on ECMO. Though the volume of distribution increased while on ECMO, the renal clearance improved. The increase in renal clearance was attributed to improved organ perfusion and decreased circulatory shock with resulting increase in renal clearance. With this finding, this study was able to characterize the dosing recommendation for neonates on and off ECMO (Table 7). This study did not, however, address whether cefotaxime dosing should be adjusted for different indications, such as meningitis.

Ceftazidime is another third-generation cephalosporin that achieves broad coverage against many Gram-positive and Gram-negative pathogens, with the added benefit of covering *Pseudomonas aeruginosa*. Metabolism and excretion of ceftazidime is also renal, and this drug has demonstrated increased clearance as renal function improves. Multiple previous studies have characterized the PK of ceftazidime and the correlation with glomerular filtration rate maturation and renal function [61–64]. Preterm neonates <34 weeks GA were noted to have higher serum troughs and longer elimination half-lives [62]. Therefore, the authors recommended that dosing be based on GA. In one study comparing once-daily to twice-daily dosing [63], the authors found that preterm neonates <32 weeks had therapeutic troughs (>10 µg/ml) with once-daily dosing, but there were insufficient data to ensure that once-daily dosing was adequate for CNS coverage. Therefore, twice-daily dosing was still recommended when there

are concerns of CNS infection. For preterm neonates <32 weeks without CNS infection, once-daily dosing can be used (Table 8).

Cefepime is a fourth-generation cephalosporin with a broader spectrum of activity that includes extended spectrum and chromosomal β-lactamase producers. Gram-negative sepsis and meningitis are the most common indications for cefepime, given its excellent CNS penetration and broad spectrum of activity [53,65]. There is a growing need for further dosing recommendations due to the increased demand of cefepime with the emergence of multidrug-resistant pathogens. In a population PK study of cefepime in 31 preterm and term neonates and infants <2 months PNA (mean GA 32 weeks and mean PNA 22 days), the authors identified a dosing regimen that would keep the serum trough in the desired therapeutic range for at least 60% of the dosing interval in the entire study population [66]. Another study also used population PK data to evaluate this dosing regimen in older children, infants and neonates (mean GA 29 weeks for infants and neonates <2 months PNA) [67]. This study of 91 patients, which included 32 preterm and 12 term neonates, was able to validate the dosing regimen previously recommended. Investigators observed the obtainment of adequate serum concentration for >60% of the time in neonates at the desired MIC (ranging from >8–30 mcg/ml) at different dosing ranges (30 mg/kg every 12 h vs 50 mg/kg every 12 h). PMA and serum creatinine were noted as the most significant covariates in cefepime clearance, with clearance increasing with older PMA (Table 9).

Table 8. Ceftazidime dosing recommendations in preterm and term neonates.

Gestational age (weeks)	Indication	Dose (mg/kg/dose)	Interval (h)
≤28	– Meningitis: severe sepsis	7.5	12
	– Bacteremia: empiric therapy	25	24
>28 to ≤32	– Meningitis: severe sepsis	10	12
	– Bacteremia: empiric therapy	25	24
>32	All	25	12

Table 9. Cefepime dosing recommendations in preterm and term neonates based on postnatal age.

Gestational age (weeks)	Postnatal age (days)	Dose (mg/kg/dose)	Interval (h)
<36	<30	30–50	12
≥36	<30	50	12

In summary, as expected given the primary renal elimination of cephalosporins, PNA is a significant factor affecting dosing recommendations.

• **Clindamycin**

Clindamycin is a lincosamide antibiotic that works by binding to the 50S subunit of susceptible bacterial ribosomes close to the peptidyl transferase center, thereby inhibiting protein synthesis. In recent years, it has become one of the most commonly prescribed antibiotics in the USA [68], due mostly to its excellent oral availability and activity against community-acquired MRSA [40]. In neonates, clindamycin is used for suspected or confirmed anaerobic infections, including necrotizing enterocolitis (NEC), though there have been concerns that clindamycin may be associated with increased risk of NEC [69].

Limited PK studies on clindamycin are available in preterm and term neonates. In 1986, one of the first studies to evaluate the PK in neonates from 26 to 39 weeks GA recommended a uniform weight-based dosing regimen [70]. This was the only dosing recommendation available until a more recent study that characterized the population PK of clindamycin in preterm and term neonates and infants using an opportunistic study [71]. The authors found that PMA had an effect on clearance, with infants reaching 50% adult clearance by approximately 40 weeks PMA. Therefore, a new dosing regimen based on PMA was developed to match adult exposure proven effective against community-acquired MRSA (Table 10). The proposed dosing was evaluated via simulations, and it achieved the necessary maximal steady-state concentration and AUC from 0 to 8 h across all PMA, PNA and weight categories. A clinical trial (NCT01994993) is

currently underway to evaluate the safety profile for the new dosing schedule in neonates and infants with complicated intra-abdominal infections [72].

• **Piperacillin/tazobactam**

Piperacillin is a semisynthetic β -lactam derived from ampicillin that is used in combination with tazobactam, which is a β -lactamase inhibitor. Piperacillin/tazobactam has a broad-spectrum antimicrobial effect (Gram-positive, Gram-negative and anaerobes) and is used commonly for the treatment of complicated intra-abdominal infections. Piperacillin/tazobactam has been shown to be well tolerated in very low birth weight infants with limited adverse effects [73,74]. Because the drug is primarily eliminated by glomerular filtration and tubular secretion, clearance is expected to be affected by the maturation of renal function in neonates [75]. The dosing in neonates as per standard of care was traditionally based on body weight (<2000 g and >2000 g) and PNA until the first month of life, regardless of GA [76].

The PK of piperacillin/tazobactam has recently been studied using techniques of dried blood spot testing and scavenged samples [77,78]. In a study using scavenged samples, 56 neonates with a median GA of 25 weeks were evaluated at five different sites. Investigators were able to show that addition of maturational covariates such as PMA and PNA on clearance improved the model fit; however, the covariate most predictive of clearance in this cohort was serum creatinine [77]. Given the environmental instability of the drug in scavenged samples and the colinearity between maturational covariates and serum creatinine, the investigators could not discern the effect of each maturational covariate on piperacillin clearance. In a subsequent study of 32 neonates and infants using dried blood spot samples [78], PMA was

Table 10. Clindamycin dosing based on postmenstrual age.

Postmenstrual age (weeks)	Dosing (mg/kg/dose)	Interval (h)
≤32	5	8
>32 and ≤40	7	8
>40 and ≤60	9	8

Table 11. Piperacillin/tazobactam dosing recommendations.

Postmenstrual age (weeks)	Dosing (mg/kg/dose)	Interval (h)
≤30	100	8
>30 and ≤35	80	6
>35 and ≤49	80	4

shown to be an important factor to guide dosing in order to achieve appropriate drug exposures in >90% of infants [77,78]. Investigators also noted no change in therapeutic target attainment rates when comparing standard to prolonged infusion, noting that this can be due to the slow drug elimination. This finding is contrary to studies in adults, in which prolonged infusion is recommended for resistant organisms to achieve therapeutic concentrations [79–81]. This underscores the need to avoid universal extrapolation of dosing recommendations from older children and adults to neonates. The current proposed recommendations (Table 11) are also being evaluated for safety and efficacy in a large randomized trial [72]. The available literature thus emphasizes the importance of PMA and body weight in the dosing of this drug as well as short infusion time.

• Metronidazole

Metronidazole is a nitromidazole antibiotic used for the treatment of anaerobic and protozoal infections. Metronidazole works by entering the cell through passive diffusion. Its nitro side chain undergoes chemical reduction by the pyruvate–ferredoxin reductase complex into a toxic nitro radical, causing DNA destabilization and rupture with cell death. Though the spectrum of activity is limited to these pathogens, there is limited resistance to this drug. Like clindamycin, metronidazole has excellent oral bioavailability, with more than 90% absorbed. Metronidazole is commonly used in preterm infants for anaerobic infections, including NEC, meningitis and bacteremia [82–86]. The metabolism of metronidazole is primarily hepatic [87].

The innovations of dried blood spot sampling, sparse sampling and ultra-low-volume assays have led to recent PK studies of metronidazole in

preterm infants from 24 to 34 weeks [88–90]. In two studies [88,89], population PK analyses were performed using dried blood spots and scavenged samples. In the first study [88], 32 infants from five centers (median GA and PNA 27 weeks and 41 days, respectively) were studied using scavenged samples. In contrast to traditional dosing regimens that relied on PNA, birth weight and GA, the resulting dosing regimen from this study was simplified using PMA. Using this regimen, 90% of the neonates achieved the target (trough concentration >8 mg/l MIC) compared with <70% who achieved target when using prior dosing schemes. In another study [89], dried blood spots from 23 infants from two cohorts (median GA and PNA 25 weeks and 8 days in cohort 1, and 26 weeks and 35 days in cohort 2, respectively) receiving metronidazole were analyzed using population PK – the results confirmed the effect of PMA on metronidazole clearance. In addition to understanding the metabolism of the drug, the investigators were able to compare the trough concentration that was obtained with the standard of care dosing versus the proposed scheduling based on PMA. The investigators found that with traditional dosing, <70% of infants were able to achieve target exposures, compared with 80% of infants with the new recommended schedule (Table 12).

• Meropenem

Meropenem is a broad-spectrum carbapenem with bactericidal activity that works by inhibiting bacterial peptidoglycan synthesis in the cell wall. Meropenem's spectrum of activity includes Gram-positive and Gram-negative pathogens (both aerobes and anaerobes), as well as extended-spectrum and chromosomal β -lactamase producers (Enterobacteriaceae and *Pseudomonas*) [91,92]. For neonates, meropenem is prescribed for

Table 12. Postmenstrual age-based metronidazole dosing recommendation.

Postmenstrual age (weeks)	Loading dose (mg/kg)	Dosing (mg/kg)	Interval (h)
<34	15	7.5	12
34–40			8
>40			6

complicated intra-abdominal infections in which polymicrobial infections are considered, NEC, and sepsis due to resistant Gram-negative pathogens. Meropenem is also used for meningitis, since the drug can achieve CNS concentrations as high as 25% of serum concentrations [91,93–96]. Meropenem, unlike imipenem, has not been associated with increased seizure activity, and compared with cephalosporins was very well tolerated with a high therapeutic success rate [93]. The prime method of excretion is renal elimination, including glomerular filtration and tubular secretion.

Recently, the PK of different dosing and infusion regimens of meropenem have been evaluated in neonates [97]. The largest study included 188 neonates and infants (including premature infants) and found a dosing regimen including a combination of GA and PNA to achieve optimal drug exposure (Table 13) [92]. In this study, serum creatinine was observed to be a significant covariate affecting meropenem clearance. Because of the association between PMA and serum creatinine, the dosing recommended by the authors relied more on PMA than serum creatinine. Dosing for CNS infection has not been appropriately studied in neonates and the current recommendations are extrapolated from older children [98]. There remains some debate regarding the most appropriate meropenem infusion duration. While one PK study demonstrated that 30-min infusions of meropenem are acceptable [97] in most cases, another suggested that prolonged infusions may be more appropriate for resistant organisms [99]. A randomized trial in neonates recently found that prolonged infusion of meropenem may result in improved microbiological effectiveness [100]. Clinicians should therefore balance factors such as age, severity of infection, organism resistance and ease of administration when selecting infusion duration.

Conclusion

In the last decade, more neonatal PK studies of antibiotics have been performed, which is due in large part to legislation requiring the study of drugs in neonates as well as new study design

and analytical methodologies. These include the use of more feasible study designs, ultra-sensitive drug assays and population PK/PD modeling techniques. The results of these PK studies have confirmed the known effects of neonatal physiological changes on antibiotic clearance in neonates, and in turn have resulted in modified dosing regimens in this population. Most of these physiologic changes have been captured using body size (weight), maturation (GA, PNA and PMA) and organ function (serum creatinine) covariates on drug clearance in population PK/PD models.

The use of maturation covariates has not been consistent within and between drugs with similar elimination pathways. This is due, in part, to differences in study sample sizes, GA and PNA distributions of the study population, number of PK samples collected, and timing of PK sample collection. This leaves questions unanswered with regards to the quantification of the contributions of antenatal and postnatal maturation processes into the clearance of antibiotics in neonates. Further evaluation of these questions will further optimize dosing recommendations for neonates. In addition to these covariates, assessment for organ function (renal, liver), concomitant medications and certain underlying conditions (e.g., hypothermia) should also be taken into consideration when evaluating drug disposition in neonates.

In spite of advances in study design and feasibility, validation of PK data from neonatal studies is limited. This suggests that some PK studies in neonates might lack the necessary sample size to generalize findings to other settings or may be sensitive to the characteristics of a very specific patient population. Small PK studies in neonates using sparse samples and limited GA and PNA distributions might need confirmatory PK data in larger safety studies or at other centers to solidify and generalize dosing recommendations for this population.

Future perspective

With the ever-growing pattern of resistance in bacteria and the diminishing options of available

Table 13. Meropenem dosing based on postnatal age and gestational age.			
Gestational age (weeks)	Postnatal age (days)	Dose (mg/kg)	Interval (h)
<32	<14	20	12
	≥14	20	8
≥32	<14	30	8
	≥14		

antibiotics, the field of antibiotic development is expected to expand over the next 5–10 years. Medical advancements in neonatology have led to increased survival at younger gestational ages and increased exposure to antibiotics, adding to the risk for further multidrug-resistant bacteria. In 2015, the US FDA approved the addition of the novel antibiotic ceftazidime/avibactam, which provides broad antimicrobial coverage.

Meropenem/vaborbactam is a combination drug of a carbapenem (meropenem) and a new β -lactamase inhibitor (vaborbactam). Target indications for this antibiotic are carbapenem-resistant Enterobacteriaceae (CRE), serious Gram-negative infections and complicated urinary tract infections. A Phase III trial in adults evaluating its safety profile and efficacy was completed in June 2016 (NCT02166476). There is also a proposed PK and safety trial in pediatric subjects (NCT02687906). This trial will result in new information that may aid in the future treatment of serious and complicated infections caused by new strains of CRE [101]. The Centers for Disease Control and Prevention has postulated that the prevalence of CRE will continue to increase and become an epidemic, noting that in India there is a CRE prevalence of >80% [101]. Preterm neonates with long-term hospitalization in the NICU and repeated exposure to antibiotics form part of the high-risk population in which this new antibiotic will be beneficial.

Zidebactam/cefepime is another combination drug of a cephalosporin (cefepime) and zidebactam, which is a novel β -lactamase inhibitor that has potent intrinsic antimicrobial activity against many bacterial species. This combination is being studied for the coverage of multidrug-resistant Gram-negative pathogens, including *Pseudomonas aeruginosa* and *Acinetobacter* spp. Currently there has been only one clinical trial (Phase I, adults), which enrolled healthy volunteers and was completed in May 2016 (NCT02707107). As with

meropenem/vaborbactam, this antibiotic will increase the number of options available for the treatment of serious and resistant pathogens. This antibiotic has shown excellent activity against *Pseudomonas* spp., which are particularly difficult organisms to treat in the neonatal population.

The increasing knowledge and experience regarding neonatal PK data will aid in future studies and drug development. Existing models will serve as the basis for the development of more sophisticated population PK/PD models for drugs in the same class of antibiotics already studied. All of these factors will contribute to streamlining the process of the development of new antibiotics for neonates.

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EXECUTIVE SUMMARY

- Neonatal physiology differs from that of children and adults due to differences in drug absorption, distribution, metabolism and elimination.
- Obtaining appropriate dosing data in neonates has been difficult given the challenges of conducting studies in neonates.
- Due to increasing novel methodologies for conducting drug trials in neonates and advanced pharmacokinetic/pharmacodynamic methodologies, pharmacokinetic/pharmacodynamic in this group is being studied more broadly, which has led to development of new dosing recommendations based on gestational age, postnatal age and postmenstrual age.
- Most available dosing recommendations still require further evaluation for safety in this population.

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