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New Antibiotic Dosing

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Abstract

Infection is common in premature infants and can cause significant morbidity and mortality. To prevent these devastating consequences, most infants admitted to the neonatal intensive care unit (NICU) are exposed to antibiotics. However, dosing regimens are often extrapolated from data in adults and older children, increasing the risk for drug toxicity and lack of clinical efficacy because they fail to account for developmental changes in infant physiology.

Despite legislation promoting and, in some cases, requiring pediatric drug studies, infants remain therapeutic orphans who often receive drugs "off-label" without data from clinical trials. Pharmacokinetic (PK) studies in premature infants have been scarce due to low study consent rates; limited blood volume available to conduct PK studies; difficulty in obtaining blood from infants; limited use of sensitive, low-volume drug concentration assays; and a lack of expertise in pediatric modeling and simulation. However, newer technologies are emerging with minimal-risk study designs, including ultra-low-volume assays, PK modeling and simulation, and opportunistic drug protocols. With minimal-risk study designs, PK data and dosing regimens for infants are now available for antibiotics commonly used in the NICU, including ampicillin, clindamycin, meropenem, metronidazole, and piperacillin/tazobactam. The discrepancy between previous dosing recommendations extrapolated from adult data and newer dosing regimens based on infant PK studies highlights the need to conduct PK studies in premature infants.

Keywords

neonates; infants; antibiotics; dosing; pharmacokinetics; prematurity

INTRODUCTION

Blood culture proven infection affects approximately 20% of very low birth weight (VLBW, <1500 g birth weight) infants and causes death in up to 18% of infected infants; those with sepsis are three times more likely to die than those without sepsis (35% vs. 11%).[1, 2] Survivors often suffer from significant morbidities, including periventricular leukomalacia

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and neurodevelopmental impairment.[3] VLBWs with sepsis are also exposed to longer periods of mechanical ventilation and are significantly more likely to develop bronchopulmonary dysplasia; they are also more likely to have longer hospital stays, resulting in higher costs of care.[1]

Because infection is such a common and significant complication in this population, most infants admitted to the neonatal intensive care unit (NICU) are exposed to antibiotics, with ampicillin and gentamicin being the most commonly prescribed medications in the NICU.[4] Despite the widespread use of antibiotics in premature (<37 weeks gestation) infants, dosing regimens are often extrapolated from data in adults or older children, increasing the risk of drug toxicity and lack of clinical efficacy. Furthermore, these dosing regimens may be incorrect because they do not account for infants' developmental changes in renal function, metabolic capacity, body composition and surface area, gastrointestinal absorption, and immunocompetence.[5]

Mechanisms for the study of drugs in children

In 2002 and 2003, the Food and Drug Administration (FDA) implemented the Best Pharmaceuticals for Children Act (BPCA), which provides incentives for pediatric drug studies, and the Pediatric Research Equity Act (PREA), which requires pediatric studies of safety and effectiveness for drugs that may be of meaningful therapeutic benefit to children. The FDA reauthorized the BPCA and PREA under the FDA Amendments Act in 2007 and made them permanent in 2012 under the FDA Administration Safety and Innovation Act.

Despite these legislative initiatives, infants, especially those born prematurely, continue to be therapeutic orphans due to the inherent difficulties of conducting clinical trials in this unique and vulnerable population. Pharmacokinetic (PK) studies in premature infants have been scarce due to low study consent rates; limited blood volume available to conduct PK studies; difficulty in obtaining blood from infants; limited use of sensitive, low-volume drug concentration assays; and a lack of expertise in pediatric modeling and simulation. However, newer techniques are emerging with minimal-risk study designs, including ultra-low-volume assays, PK modeling and simulation, and opportunistic drug protocols.[6] These new techniques provide more efficient ways to conduct PK studies in infants with smaller blood volumes and less frequent blood sampling.

However, implementation of these techniques has been slow and most drugs used in infants lack FDA labeling. Thus, clinicians often prescribe these drugs "off-label" to infants without evidence-based dosing regimens from clinical trials. In response to this, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) sponsored the Pediatric Trials Network (PTN) to conduct pediatric clinical trials in order to generate or revise pediatric drug labeling in infants and children. With new data emerging from trials conducted by the PTN and other groups, safer, more accurate, antibiotic dosing regimens are becoming available for premature infants.

Ampicillin

Ampicillin is a beta-lactam antibiotic and is the most commonly prescribed drug in hospitalized infants.[4] In the NICHD Neonatal Research Network, 96% of extremely low birth weight (ELBW, <1000 g birth weight) infants received empiric treatment with a combination of 2 antibiotics, with ampicillin and gentamicin being the most common combination.[7] In spite of the frequency of use, the FDA label has no specific dosing of ampicillin for infants.

The PK of ampicillin in infants was recently evaluated by the PTN in the National Institutes of Health (NIH)-sponsored PK of Understudied Drugs Administered to Children per Standard of Care Study (POPS Trial, clinicaltrials.gov # NCT01431326).[8] The POPS trial enrolls children who are on a drug of interest (e.g., ampicillin, clindamycin) as part of standard of care and collects low volume PK and dried blood spot samples. The ampicillin study included 9 centers and 73 infants with postnatal age (PNA) <29 days and median gestational age (GA) 36 weeks. Investigators found that postmenstrual age (PMA) and serum creatinine were strongly correlated with clearance (CL). Elimination half-life was inversely proportional to PNA; moreover, ampicillin CL increased by 27% after the first week of life, and increased by 56% from the younger cohort (GA ≤34 weeks) to the older (GA >34 weeks) cohort. These results are consistent with the developmental maturation of renal function in infants and the predominantly renal elimination of ampicillin.

Using the final PK model developed from the POPS Trial, Monte Carlo simulations were used to evaluate the efficacy of multiple dosing regimens, including standard regimens from *Neofax*[9] and *The Harriet Lane Handbook* (Table 1),[10] as well as the simplified regimen stratified by GA and PNA suggested by the POPS trial (Table 2). The pharmacodynamic (PD) target for beta-lactams most associated with efficacy is time above minimum inhibitory concentration (T>MIC). The investigators chose MICs of 2 and 8 μg/mL, representing MICs for two pathogens that can cause severe and fatal infections in infants, *Listeria monocytogenes* and *Escherichia coli*. The higher doses used in the POPS trial achieved the surrogate target of ≥8 μg/mL in >97% of virtual subjects versus 90% of virtual subjects using traditional dosing regimens. The investigators proposed using the simplified dosing regimen suggested from the POPS trial stratified by GA and PNA, because this regimen provides fewer dosing groups, accounts for maturation of renal function, and incorporates less frequent dosing while still achieving the therapeutic target in over 90% of subjects (Table 2).[8] It is important to note that this study did not account for cerebrospinal fluid (CSF) penetration of ampicillin, which was reported to be from 11 to 65% in one study of infants with meningitis.[11] Infants with meningitis will likely need higher ampicillin doses for optimal CSF penetration. The safety and efficacy of the proposed dosing regimen based on GA and PNA is currently being evaluated in a large, multi-center randomized trial comparing antibiotic regimens in infants with complicated intra-abdominal infection (SCAMP Trial, clinicaltrials.gov # NCT01994993).

Clindamycin

Clindamycin is a lincosamide antibiotic often used to treat anaerobic infections, pneumonia, osteomyelitis, and skin and skin structure infections. Despite its widespread use, the FDA label does not adequately address dosing in premature infants and infants less than one month of age. However, PK data for clindamycin are also emerging using opportunistic study designs.

In the POPS trial, PK samples were collected from 125 children at 24 centers, including 20 infants born at ≤32 weeks GA receiving intravenous (IV) clindamycin as standard of care. Investigators used ultra-low volume samples to create a PK model. Investigators found that clindamycin CL increases with increasing body weight and PMA and reaches 50% of adult CL at approximately 44 weeks PMA.[12]

Using the final PK model and Monte Carlo simulations, investigators evaluated multiple pediatric dosing regimens with the goal to match median adult clindamycin exposure following IV administration of 600 mg every 8 hours, the dose recommended in adults for community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections. A virtual adult patient (70 kg weight) administered clindamycin 600 mg IV every 8 hours had a median (2.5th, 97.5th percentiles) area under the concentration versus time curve from 0–8 hours at steady state ($AUC_{0–8ss}$) of 42.9 (14.2, 132) mcg*h/mL. PMA-based dosing in simulated infants <5 months PNA resulted in median $AUC_{0–8ss}$ comparable to the virtual adult estimate (administered every 8 hours): 42.9 mcg*h/mL (5 mg/kg, PMA ≤32 weeks); 42.1 mcg*h/mL (7 mg/kg, PMA >32–40 weeks); 42.7 mcg*h/mL (9 mg/kg, PMA >40–60 weeks). Thus, for infants <5 months PNA, investigators recommended a PMA-based dosing regimen (Table 3).[12]

The safety and efficacy of the proposed PMA-based dosing regimen is currently being evaluated in the SCAMP Trial (clinicaltrials.gov # NCT01994993). Safety data in infants are scarce, though one retrospective case-control study described an increased risk of necrotizing enterocolitis (NEC) with increased duration of cumulative antibiotic exposure in infants without culture-proven sepsis; there was a significantly higher proportion of clindamycin use in the cases diagnosed with NEC compared to matched controls without NEC [unadjusted OR=4.16 (1.29–13.44)].[13]

Meropenem

Meropenem is a broad-spectrum carbapenem antibiotic often used in infants with complicated intra-abdominal infections that cause significant morbidity and mortality. NEC is the most common life-threatening emergency of the neonatal gastrointestinal tract and occurs in up to 11% of VLBW infants.[14,15] Reported NEC mortality is as high as 42%; those who survive are at risk for severe growth delay and poor neurodevelopmental outcomes.[16, 17] Thus, infants with suspected or confirmed NEC or intra-abdominal infections are often empirically treated with broad-spectrum or combination antibiotic therapy.[18]

Meropenem PK in infants with suspected or confirmed intra-abdominal infection or NEC was evaluated as part of the NIH-sponsored 24-center, prospective, PK study using ultra-low volume assays under the BPCA mechanism. Based on data from 188 infants with a median GA at birth of 28 weeks, investigators created a PK model showing that meropenem CL was strongly associated with serum creatinine and PMA and was 30–40% lower than the average reported CL in adults.[18] This is consistent with meropenem's method of elimination (renal) and the maturation of neonatal renal function because glomerular filtration rate (GFR) which does not reach 90% of the adult GFR until 1 year PNA.[19]

The dosing strategy used in the study was stratified by GA and PNA (Table 4) and was based on previous meropenem PK studies in older infants that evaluated regimens to maintain plasma meropenem concentrations above the MIC for different pathogens, including *Pseudomonas aeruginosa*.[18, 20] Investigators defined the therapeutic target as T>MIC of 4 μg/mL for 50% of the dose interval and >2 μg/mL for 75% of the dose interval because the MIC breakpoint of meropenem for *Pseudomonas aeruginosa* is ≤4 μg/mL and over 80% of isolates are susceptible at a MIC of 2 μg/mL. Using the dosing strategy in Table 4, over 90% of infants in the study achieved this therapeutic target. Because trough meropenem concentrations exceeded this therapeutic target (2 μg/mL) in >80% of infants enrolled in this trial, meropenem doses as outlined in this trial should be sufficient for a clinical and microbiological cure across GA and PNA for infants <91 days of age. Using this dosing strategy in critically ill infants with suspected or proven intra-abdominal infection, meropenem was well tolerated with no adverse events probably or definitely related to meropenem.[21]

Metronidazole

Metronidazole is a nitroimidazole antibiotic that is FDA-labeled for anaerobic infections, but not specifically labeled for infants. Despite this, it is often used in premature infants for the treatment of NEC, anaerobic bacteremia, and central nervous system infections. Limited PK data of metronidazole in this population have led to various dosing recommendations.[22–24]

Several recent studies evaluated the PK of metronidazole in infants using a variety of innovative techniques including sparse sampling, ultra-low volume assays, and scavenge and dried blood spot sampling.[25–27] In an NIH-sponsored open-label, multicenter (N=5), opportunistic study of 32 infants ≤32 weeks GA and <120 days of age receiving IV metronidazole as part of their routine medical care, investigators measured metronidazole concentrations using a combination of ultra-low volume (0.3 mL) timed plasma samples and scavenged samples. Investigators showed that metronidazole CL increased proportionally with weight and disproportionally with PMA, which accounts for its predominantly hepatic metabolism.[26] The investigators further evaluated the change in metabolism in a second, 3-center study. By calculating a parent-metabolite ratio they found that weight-normalized CL increased with increasing metabolic ratio, and older infants had the highest metabolic ratios.[27]

Given these findings, the recommended dosing regimen for metronidazole is based on PMA (Table 5). The surrogate efficacy target was defined as a steady state trough concentration ≥8 mg/L. This trough was based on the MIC of 8 mg/L as the susceptibility breakpoint for anaerobic organisms. Simulations using the final PK model evaluated dosing available in *Neofax* and *The Harriet Lane Handbook* versus the proposed PMA-based dosing regimen. Less than 70% of subjects achieved the target when using traditional dosing recommendations whereas 90% of subjects achieved the target when the PMA-based dosing regimen was used in simulated data sets.[26]

Data are lacking on the safety and efficacy of metronidazole in premature infants. The safety and efficacy of the proposed PMA-based dosing regimen for metronidazole is currently being evaluated by the PTN in the SCAMP Trial (clinicaltrials.gov # NCT01994993).

Piperacillin/Tazobactam

Piperacillin is a semisynthetic derivative of ampicillin with enhanced activity against resistant Gram-negative bacteria; piperacillin/tazobactam combines a β-lactam antibiotic with a β-lactamase inhibitor and is primarily renally excreted.[28] Piperacillin/tazobactam is FDA-labeled in patients ≥2 months for appendicitis and peritonitis, but it is often used in younger infants to treat systemic and intra-abdominal infections.[29]

Piperacillin/tazobactam PK studies in infants have recently been reported using a combination of timed plasma samples, scavenged blood samples, and dried blood spot sampling.[30, 31] In an NIH-sponsored open-label PK and safety study using ultra-low volume samples and involving 4 centers and 32 infants <61 days of age with a mean GA of 30 weeks treated for suspected systemic infection, piperacillin/tazobactam CL was strongly associated with body weight, PMA, PNA, and serum creatinine. Piperacillin/tazobactam CL increased by 100% after the first 2 weeks of life.[31]

The surrogate target endpoint for piperacillin/tazobactam efficacy was defined as concentration above the MIC for 75% of the dosing interval in >90% of simulated infants. MICs of 16 and 32 mg/L were chosen because they represented the MICs of common pathogens in premature infants such as *Enterobacteriaceae* (16 mg/L) and *Pseudomonas aeruginosa* (32 mg/L). Using data generated from the study above, a population PK model was developed that evaluated the impact of multiple clinically relevant covariates (e.g., PMA, GA, PNA, creatinine). A PMA-based PK model was used as the final model for piperacillin CL and was used to perform Monte Carlo simulations to identify the optimal dose for the infant population (Table 6). Simulations showed that the PMA-based dosing regimen achieved the surrogate PD target (piperacillin concentrations 32 mg/L for 75% of dosing interval) in >90% of simulated infants. In addition, this dosing regimen achieved comparable exposures to those seen in adult patients receiving piperacillin/tazobactam for intra-abdominal infections.

The performance of dosing regimens currently recommended in pediatric dosing guidelines (*Neofax* and *The Harriet Lane Handbook*) vs. PMA-based dosing were also evaluated. The simulation results indicate that the *Neofax* and *The Harriet Lane Handbook* regimens achieved high target attainment rates (>90% patients with concentrations at 75% at steady

state ($C75_{ss}$) greater than the MIC) for MICs ≤8 mg/L. As the MIC increased beyond 8 mg/L, overall target attainment rates of *Neofax* and *The Harriet Lane Handbook* regimens dropped to 75% and 37%, and 78% and 28% for MICs of 16 and 32 mg/L, respectively.

Because prolonged infusions of piperacillin/tazobactam have higher efficacy in adults,[32–34] a PMA-based dosing regimen employing prolonged infusion (2–4 hours) was also evaluated. The PMA-based dosing regimen with prolonged infusion was able to achieve >90% target attainment rates for MIC ≤32 mg/L overall and for each study group; however, no clear advantage was observed over the short (30-minute) infusion. The SCAMP Trial is currently also evaluating the safety and efficacy of the proposed PMA-based dosing regimen (clinicaltrials.gov # NCT01994993).

SUMMARY

Antibiotics are the most commonly used medications in the NICU.[4] In order to maximize therapeutic benefit and minimize drug toxicity, it is important to determine appropriate dosing regimens for this population. PK studies in premature infants have been scarce, but studies are now more feasible with the emergence of ultra-low-volume assays, PK modeling and simulation, and opportunistic study designs. More appropriate dosing regimens based on PK data are now available for antibiotics commonly used in the NICU, including ampicillin, clindamycin, meropenem, metronidazole, and piperacillin/tazobactam. The discrepancies between previous dosing recommendations and newer dosing regimens based on infant PK studies highlight the need to conduct PK studies specifically for premature infants.

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KEY POINTS

- Infection is common and devastating in premature infants, and antibiotics are the most commonly used medications in the neonatal intensive care unit.
- Antibiotic dosing regimens in premature infants are often extrapolated from data in adults and older children and may be incorrect because they do not account for developmental changes in infant physiology
- Pharmacokinetic (PK) studies in infants are scarce due to low study consent rates; limited blood volume available to conduct PK studies; difficulty in obtaining blood from infants; limited use of sensitive, low-volume drug concentration assays; and a lack of expertise in pediatric modeling and simulation.
- New studies using innovative techniques and requiring smaller sample volumes are providing PK data in premature infants.
- PK data in infants provide appropriate dosing regimens for commonly used antibiotics including ampicillin, clindamycin, meropenem, metronidazole, and piperacillin/tazobactam.

Table 1

Comparison of antibiotic dosing recommendations extrapolated from adults and older children vs. dosing recommendations based on infant PK data.

Antibiotic	Previous Recommendation	New Recommendation
Ampicillin	25–100 mg/kg q4–12h	50–75 mg/kg q8–12h
Clindamycin	5–7.5 mg/kg q6–12h	5–9 mg/kg q8h
Meropenem	20 mg/kg q8–12h	20–30 mg/kg q8–12h
Metronidazole	Loading 0–15 mg/kg Maintenance 7.5–15 mg/kg q 6–48h	Loading 15 mg/kg Maintenance 7.5 mg/kg q6–12h
Piperacillin/Tazobactam	75–100 mg/kg q6–12	80–100 mg/kg q4–8h

Data from:

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Table 2

Recommended Dosing Regimen for Ampicillin

GA (weeks)	PNA (days)	Maintenance Dose (mg/kg)	Dosing Interval (hours)
≤ 34	≤ 7	50	12
	≥ 8 and ≤ 28	75	12
> 34	≤ 28	50	8

GA: gestational age at birth; PNA: postnatal age

Data from Tremoulet A, Le J, Poindexter B, et al. Characterization of the Population Pharmacokinetics of Ampicillin in Neonates Using an Opportunistic Study Design. Antimicrob Agents Chemother 2014;58:3013–20.

Table 3

Recommended Dosing Regimen for Clindamycin

PMA (weeks)	Maintenance Dose (mg/kg)	Dosing Interval (hours)
≤ 32	5	8
> 32 and ≤ 40	7	8
> 40 and ≤ 60	9	8

PMA: postmenstrual age

Data from Gonzalez D, Melloni C, Yogev R, et al. Use of Opportunistic Clinical Data and a Population Pharmacokinetic Model to Support Dosing of Clindamycin for Premature Infants to Adolescents. Clin Pharmacol Ther 2014.

Table 4

Recommended Dosing Regimen for Meropenem

GA (weeks)	PNA (days)	Maintenance Dose (mg/kg)	Dosing Interval (hours)
< 32	< 14	20	12
	≥ 14	20	8
≥ 32	< 14		
	≥ 14	30	8

GA: gestational age at birth; PNA: postnatal age

Data from Smith PB, Cohen-Wolkowiez M, Castro LM, et al. Population pharmacokinetics of meropenem in plasma and cerebrospinal fluid of infants with suspected or complicated intra-abdominal infections. Pediatr Infect Dis J 2011;30:844–9

Table 5

Recommended Dosing Regimen for Metronidazole

PMA (weeks)	Loading Dose (mg/kg)	Maintenance Dose (mg/kg)	Dosing Interval (hours)
< 34	15	7.5	12
34 – 40			8
> 40			6

PMA: postmenstrual age

Data from Cohen-Wolkowiez M, Ouellet D, Smith PB, et al. Population pharmacokinetics of metronidazole evaluated using scavenged samples from preterm infants. Antimicrob Agents Chemother 2012;56:1828–37.

Table 6

Recommended Dosing Regimen for Piperacillin/Tazobactam

PMA (weeks)	Maintenance Dose (mg/kg)	Dosing Interval (hours)
≤ 30	100	8
30 – 35	80	6
35 – 49	80	4

PMA: postmenstrual age

Data from Cohen-Wolkowiez M, Watt KM, Zhou C, et al. Developmental pharmacokinetics of piperacillin and tazobactam using plasma and dried blood spots from infants. Antimicrob Agents Chemother 2014;58:2856–65.