Review Article

Antimicrobial Agent Dosing in Infants

Jacob K. Johnson, MD; and Matthew M. Laughon, MD, MPH

Department of Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

ABSTRACT

Purpose: The goal of this article was to review infant physiology and its effects on the pharmacokinetic properties of antimicrobial agents.

Methods: A review of the drug development process was performed. A literature search was conducted on the pharmacokinetics of various antimicrobial agents in infants.

Findings: The pharmacokinetic properties of antimicrobial agents in infants are most often affected by the renal maturation of premature infants. Hepatic metabolism and volume of distribution play a common role as well.

Implications: The dosing and dosing intervals of various medications were reviewed and compared with details of adult dosing. It is vital to continue to gather pharmacokinetic data in infants to ensure adequate safety and dosing of medications. (*Clin Ther*. 2016;38:1948–1960)

Key words: Antibiotics, pharmacokinetics, infants, antivirals, antifungals.

INTRODUCTION

Antimicrobial agents are the most common medications given to infants, both in the neonatal intensive care unit and during the first month of life.[1] Although progress is being made, the majority of antimicrobial agents prescribed to infants are still used "off label," meaning that they lack the dosing, safety, or efficacy data as outlined in the label of the US Food and Drug Administration (FDA). Off-label use of antimicrobial agents in infants can lead to an unpredictable response or morbidity due to their unique and evolving physiology.[2] Changes in liver metabolism, gastric absorption, renal elimination, and distribution of such agents need to be taken into account for infants.[3] Over the past 10 years, substantial effort has been made to improve the dosing, safety, and efficacy data of antimicrobial agents for infants.

The present article reviews the process of drug development with a special emphasis on infants, the differences in pharmacokinetic (PK) properties between infants and adults, and dosing of commonly used antimicrobial agents.

MATERIALS AND METHODS

Infant Drug Development Process

The process of developing new medications in infants is similar to the process in adults. For existing medications, there is a procedure whereby a sponsor may receive a label change for children, including infants, as long as certain conditions are met. This process is called "extrapolation."[4] Two basic conditions must be met to extrapolate a medication from adults to children. First, children must have a similar disease progression and second, children must have a similar response to the medication, as established in adults. If these assumptions are met, the medication then has the potential to undergo either partial or full extrapolation depending on other criteria. In full extrapolation, the exposure-response to medications must be reasonably similar, and the medication concentration must be measurable and predictive of clinical response. If both criteria are met for full extrapolation, a trial is conducted to select a dose

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that would achieve similar exposure as in adults, and safety trials are then performed at that dose. Partial extrapolation can occur if it is either not reasonable to assume a similar exposure-response in children or if the medication concentration is not measurable or predictive of clinical response. In partial extrapolation, dose-ranging studies are performed to select the dose that would achieve the target effect, and safety trials are then performed at that dose. If assumptions for extrapolation are not met, the medication must undergo a full development process as noted earlier. Antimicrobial agents are examples of a class of medications that can often be extrapolated from adults to children because the disease progression and response to the medication are similar in adults and children.

To increase the safety and efficacy of medications in children, the federal government has passed legislation to address the gaps. In 1997, as part of the Food and Drug Administration Modernization Act, a financial incentive of an additional 6 months of exclusivity was granted to pharmaceutical companies for patent-eligible medications to encourage more pediatric-specific trials. This action was then reauthorized with the Best Pharmaceuticals for Children Act (BPCA), which also provided mechanisms to study medications in children, both on- and off-patent. Due to the financial incentives of BPCA, the Pediatric Research Equity Act was established in 2003 to require pediatric assessments of any new medication undergoing the labeling process. A pediatric assessment includes ingredients (including excipients), indications, dosing, and route of administration. The next significant legal step was the Food and Drug Administration Amendments Act of 2007, which reauthorized BPCA and the Pediatric Research Equity Act and established a "Priority List" of pediatric therapeutics that is to be reviewed every 3 years by the National Institutes of Health and annually by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. The Food and Drug Administration Safety and Innovation Act of 2012 then made BPCA permanent. It also required advisory by a neonatologist to focus on the neonatal population given its high-risk nature and changing physiology, both with gestational age (GA) and postnatal age (PNA).

As a result of such legislation (specifically the BPCA), the Pediatric Trials Network (www.pediatrictrials.org) was established and sponsored by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. It is an alliance of clinical research sites around the United States; their goal is to promote labeling for medications used in pediatrics by studying dosing, efficacy, and safety.

General Principles of Clinical Pharmacology in Infants

The clinical pharmacology of infants, including PK properties, is often substantially different from older children and adults. Absorption, distribution, metabolism, and excretion are affected by age and physiologic development. In infants, physiologic development is dependent on GA and PNA. In this section, we review some of the major differences between infant and adult PK properties.

Absorption

The absorption of antimicrobial agents in infants usually has less of an effect on PK outcomes because many of these agents are administered intravenously. The most common routes for absorption in infants are via the intramuscular route and through gastric absorption. Intramuscular administration of both ampicillin and gentamicin is as effective as intravenous administration.[5,6] Therefore, these agents can be given intramuscularly, although the intravenous route remains the preferred method because repeated doses are usually given.

Gastric absorption of antimicrobial agents in infants has notable physiologic differences from the same process in children and adults. Gastric emptying in adults and children has an initial fast phase followed by a slower phase.[7] In contrast, infants have a slow, linear gastric absorption that does not reach a similar adult biphasic response until 6 to 8 months of age.[8] Although slower gastric emptying would theoretically make for better gastric absorption, it tends to have minimal use in sick infants.[9] Because of incomplete gastric absorption, the lack of data on bioavailability in infants, and the requirement for certainty of antimicrobial agent delivery, the usual route is intravenous.

Distribution

The PK properties of antimicrobial agents are also affected by the volume of distribution. This parameter is dependent on several characteristics of the agent, including molecular size, ionization, and whether it is water or lipid soluble. In infants, both the blood–brain barrier and the relatively high body water content affect distribution. The blood–brain barrier is not

mature when infants are born, meaning that certain antimicrobial agents can more easily penetrate it. As an example, amphotericin B is an agent that achieves higher central nervous system concentrations in infants than in older children or adults.[10] Infants' heads are disproportionally larger than adults compared with the rest of the body, and infants thus have a relatively larger central nervous system volume. The relatively high body water content of both premature and term infants generally increases the volume of distribution of water-soluble drugs; water-soluble drugs such as gentamicin therefore generally require increased doses.[11,12]

Liver Metabolism

Metabolism commonly occurs in the liver and is dependent on developmental changes in the newborn infant. Metabolism in the liver depends on both blood flow and enzyme activity, both of which are reduced in children although they generally reach adult levels by 1 year of age.[13] The reactions that occur in the liver during metabolism are also immature at birth. These reactions include the cytochrome-P450 enzyme system; some of these enzymes are present at birth, and others change over time. Other processes include methylation, acetylation, and glucuronidation.

Renal Excretion

The dosing of antimicrobial agents in infants often depends on the renal system and its physiologic changes through the infant's first year of life. The glomerular filtration rate (GFR) is extremely low at birth and increases rapidly postnatally. The GFR is even lower in premature infants because of decreased nephron number, and nephron proliferation increases rapidly between 32 and 36 weeks' GA.[14] Premature infants have a slower rise in GFR over the first week of life compared with term infants.[15] GFR then increases over the first 2 years of life to reach adult values.[16] Although GFR rises with increasing GA and PNA in infants, it generally correlates more with postmenstrual age (PMA; ie, GA plus PNA) rather than PNA.[17,18] Because aminoglycosides are commonly prescribed for newborns, an increase in GFR improves clearance of these antimicrobial agents.[19]

Excretion of antimicrobial agents through the renal system is also dependent on the function of the renal tubules. The effects of tubular secretion are decreased at birth and then increase over the first several months of life before reaching adult levels by ~7 months of age.[20] The ability of the renal tubules to reabsorb compounds can also be affected by a lower urinary pH value that occurs in infants, specifically weak acids and bases. Of note, it has been shown that patients with low GFR can still have high clearance of antimicrobial agents, such as imipenem, if tubular secretion is relatively higher.[21] In such patients, more frequent dosing is needed.

EXAMPLES OF ANTIMICROBIAL AGENTS USED IN INFANTS

Ampicillin

Ampicillin is a β-lactam antimicrobial agent and the most commonly used medication in infants in the neonatal intensive care unit.[1] Ampicillin is active against group B streptococci, *Listeria monocytogenes*, and some *Escherichia coli* isolates, all of which are commonly seen infections in infants. Ampicillin is renally eliminated and is therefore dependent on GFR.

Ampicillin is labeled by the FDA for use in pediatric patients for respiratory, soft tissue, gastrointestinal, and genitourinary infections, as well as bacterial meningitis and septicemia. However, there is no specific dosage for infants given on the label. Current dosing recommendations for infants is stratified on the basis of weight and PNA and based on limited data.[22]

To provide more data on dosing for ampicillin in infants, investigators enrolled 73 infants stratified according to both GA (before and after 34 weeks) and PNA (before and after 7 days of life).[23] The surrogate pharmacodynamic target was time above the MIC of 2 and 8 μg/mL for *Listeria* species and *E coli*, respectively. Using Monte Carlo simulations to compare dosing between *Neofax*,[24] the *Harriet Lane Handbook*,[25] and the proposed regimen, most premature infants needed less frequent dosing; both PMA and creatinine were best correlated with the clearance of ampicillin. The proposed regimen accounts for infant renal maturation and allows for less frequent dosing while still achieving the desired therapeutic target in >90% of patients. This finding compares to more frequent dosing noted in adults and older children.[22,26,27] The stratified dosing regimen is summarized in Table I.

Gentamicin

Gentamicin is an aminoglycoside antimicrobial agent that is commonly used with ampicillin in

Table I. Comparison of infant and adult dosing for commonly used antibacterial agents.

Antibacterial Agent	Infant Dosing				Adult Dosing[125]		
	Gestational Age	Postnatal Age	Postmenstrual Age	Dose	Dosing Interval	Maintenance Dose	Dosing Interval
	wk	*d*	*wk*	*mg/kg*	*h*	*mg*	*h*
Ampicillin[23]	≤34	≤7		50	12		
		8–28		75	12	1000–2000	4–6
	>35	<28		50	8		
Gentamicin[25]	<32	≤14		5	48		
		>14		5	36		
	32–36	≤7		4	36	4–7(mg/kg)	24
		>7		4	24		
	≥37	≤28		4	24		
Cefotaxime[24]		≤28	≤29		12		
		>28			8		
		≤14	30–36		12	1000–2000	8–12
		>14		50	8		
		≤7	37–44		12		
		>7			8		
Meropenem[59]	<32	<14		20	12		
		≥14		20	8		
	≥32	<14		20	8	500–2000	8
		≥14		30	8		
Piperacillin-tazobactam[79]	<30			100	8		
	30–35			80	6	3375	6
	>35			80	4	4500	6–8
Metronidazole[87]				15 (loading)			
			<34	7.5	12	1000 (loading)	
			34–40	7.5	8	500	6
			>40	7.5	6		
Clindamycin[93]			≤32	5	8		
			>32–40	7	8	150–600	6–8
			>40	9	8		
Vancomycin[64,68]				10 (loading)		500	6
				10–15*	12	1000	12

*Continuous vancomycin option: 10 mg/kg loading dose followed by 25 to 30 mg/kg/d divided over 24 hours.

infants, and it is the second most commonly prescribed agent in neonatal intensive care units.[1] It has in vitro synergism against gram-negative bacteria, specifically *E coli*, as well as activity against staphylococcal species. The PK properties of gentamicin in infants, children, and adults differ due to changing

renal physiology after birth.[28,29] In addition to changing renal maturation, gentamicin dosing can also be affected by weight, GA, and PNA, which all positively influence clearance.[30]

Gentamicin is labeled by the FDA for use in neonatal sepsis as well as serious bacterial infections of the central nervous system, urinary tract, respiratory tract, and skin and soft tissue, as well as serious intra-abdominal infections. The current FDA label supports recommendations for BID dosing in premature infants and infants aged <1 week and TID dosing for infants aged >1 week.[31] This guidance is in contrast to the recommendations put forth by *Neofax* and *Nelson's Pocket Book of Pediatric Antimicrobial Therapy*, which are stratified according to PMA or GA with PNA, respectively.[24,25]

Because of toxic effects on both the kidneys and the ear, dosing of gentamicin has evolved over time from a multiple daily dosing regimen to a once-daily dosing regimen in pediatric populations and in adults.[32–39] Meta-analysis has also revealed that with once-daily dosing, efficacy is improved, and rates of ototoxicity and nephrotoxicity are comparable.[40] This outcome is likely due to decreased accumulation of aminoglycosides in the inner ear and renal tubules with once-daily dosing.[41,42]

To achieve ideal concentrations, premature infants need higher doses (up to 5 mg/kg) at more extended intervals compared with term infants because of the effects of GA and PNA on weight and renal maturation.[25,30] Extremely premature infants (ie, those <28 weeks' GA) also benefit from extended interval dosing (up to every 48 hours) in which a dose is given and a drug level is then checked before administration of the second dose.[43] Infants with sepsis may have a larger volume of distribution and may also benefit from higher doses to achieve adequate concentrations.[44] In a setting in which extended interval dosing is performed, this approach would likely have minimal effect, as the dosing would be readjusted with each level if needed.

Cefotaxime

Cefotaxime is a third-generation cephalosporin used in infants for suspected or documented serious bacterial infections from a gram-negative organism. Cefotaxime is effective against ampicillin-resistant strains of *E coli*. Cefotaxime also has sufficient cerebrospinal fluid (CSF) penetration.[45] However, this agent is associated with an increase in mortality when used as a "rule out" sepsis at birth and an increase in invasive candidiasis.[46,47] Cefotaxime is metabolized in the liver to its microbiologically active metabolite desacetyl-cefotaxime and then excreted in the urine as metabolized and unmetabolized forms.[48,49] Clearance of cefotaxime increases with increasing PNA and GA.[50,51]

Cefotaxime is labeled by the FDA for use in both the infant and pediatric populations. It is indicated in the treatment of serious susceptible infections, including those of the lower respiratory tract, genitourinary, and central nervous system, as well as intra-abdominal infections and bacteremia. For term infants with susceptible infections (not including those of the central nervous system), the cefotaxime dose is 100 mg/kg/d divided every 12 hours for the first week and then 150 mg/kg/d divided every 8 hours thereafter.[22,25] For premature infants, dosing is based on PMA as well as PNA (Table I). When treating meningitis, the dose is 225 to 300 mg/kg/d to achieve adequate CSF concentrations.[45,52]

Meropenem

Meropenem is a broad-spectrum carbapenem commonly used to treat intra-abdominal infections in infants.[53] Given the high morbidity and mortality of intra-abdominal infections (including necrotizing enterocolitis), and the wide range of organisms associated with these infections (including gram-positive, gram-negative, and anaerobic organisms), clinicians often use broad-spectrum antimicrobial agents.[54,55] Meropenem is primarily cleared through the kidneys in adults.[56] Due to delayed maturation of the kidneys in premature infants, meropenem clearance is higher in term infants compared with premature infants.[57]

Meropenem is labeled for use in complicated skin and soft tissue infections, complicated intra-abdominal infections, and bacterial meningitis. When treating skin and soft tissue infections, as well as bacterial meningitis, the labeling provides guidance for infants aged >3 months.[58] To address the gap in knowledge for those aged <3 months, investigators performed a large multicenter trial to determine the PK properties and safety profile of meropenem in infants.[59] They analyzed plasma meropenem concentrations in 188 premature and term infants. The trial stratified infants into groups based on GA (<32 weeks and ≥32 weeks) and PNA (<14 days

old and ≥14 days old). Plasma meropenem concentrations were monitored, and meropenem clearance was associated with both serum creatinine (reflecting renal function) and PMA. Investigators also found that penetration of meropenem into the CSF was 70%. A follow-up safety study also concluded that there were no adverse events probably or definitely related to meropenem.[60]

Vancomycin

Vancomycin is a glycopeptide antibiotic used as broad treatment for suspected or documented gram-positive bacterial infections. Premature infants are at high risk of infections from both late-onset sepsis and secondary to central venous catheter exposure, and clinicians often use vancomycin because of the risk of coagulase-negative staphylococcal infections, which are usually resistant to ampicillin or methicillin.[61–63] Vancomycin is renally eliminated.

Vancomycin is FDA labeled for use in pediatric and neonatal patients for the treatment of methicillin-resistant *Staphylococcus aureus* infections of the lower respiratory tract, bone, and skin and soft tissue. It is also labeled for the treatment of endocarditis. Current FDA-labeled dosing recommendations in infants are for an initial dose of 15 mg/kg followed by 10 mg/kg every 12 hours in the first week of life and then every 8 hours thereafter. This dosing regimen compares favorably to *Neofax* for term infants although *Neofax* recommends more extended intervals (8–18 hours) with more premature infants.[24] However, because the clearance of vancomycin increases with increasing PMA, monitoring of trough levels is generally performed if the course is more than a few days.

Vancomycin is usually administered intermittently (although continuous dosing has been used [discussed later]) and the target trough concentrations are 15 to 20 μg/mL, although these targets are derived from adult data.[64] Guidelines from the Infectious Diseases Society of America recommend similar trough targets in pediatric patients.[65] The current initial recommendations are displayed in Table I, and close monitoring of trough levels and adjusting them accordingly are often necessary. Continuous infusion (with a constant infusion rate over 24 hours) of vancomycin has been reported in the neonatal population.[66–69] Continuous infusion may have better bactericidal efficacy because vancomycin's bactericidal properties are time dependent.[70] Kim et al[71] found that continuous vancomycin was as successful as intermittent dosing in reaching target trough levels. However, safety and efficacy data do not currently exist for the use of continuous vancomycin.

Piperacillin-Tazobactam

Piperacillin-tazobactam is an antimicrobial agent that combines a β-lactam antibiotic with a β-lactamase inhibitor. Piperacillin-tazobactam is used in complicated intra-abdominal infections, such as necrotizing enterocolitis, and gram-negative bacteremia.[72] Piperacillin-tazobactam is primarily excreted by the kidneys.[73]

Piperacillin-tazobactam is currently labeled by the FDA for use in patients aged ≥2 months with susceptible infections, including appendicitis and peritonitis. Current FDA-labeled dosing recommendations are 80-mg piperacillin/10-mg tazobactam per kilogram every 8 hours for patients between 2 and 9 months of age. As such, there is no current approved dosing recommendation for those aged <2 months, including premature infants. As with vancomycin, it is possible that the efficacy of piperacillin-tazobactam is highest with extended and continuous infusions.[74–77]

Studies of piperacillin-tazobactam have been performed by using scavenged blood, dried blood spot samples, and plasma samples in premature infants.[78,79] In a study sponsored by the National Institutes of Health, infants were stratified according to GA and PNA by using dried blood spot samples and plasma samples.[79] Efficacy end points were chosen and consistent with acceptable MIC levels for *Enterobacteriaceae* and *Pseudomonas aeruginosa* (16 μg/mL and 32 μg/mL, respectively). A PK model was then developed based on these data and compared with dosing from both *Neofax* and the *Harriet Lane Handbook*. When comparing dosing regimens, target attainment rates dropped to <40% with increasing MIC >8 μg/mL using *Neofax* and *Harriet Lane Handbook* dosing compared with the dosing regimen based on the model (Table I).

Metronidazole

Metronidazole is a nitroimidazole antimicrobial agent used in the treatment of anaerobic bacteremia and complicated intra-abdominal infections such as necrotizing enterocolitis.[80,81] It is hepatically metabolized by hydroxylation into its active metabolite, hydroxy-metronidazole.[82] Initial PK studies on metronidazole found that hydroxylation occurred in newborn infants who had received prenatal

betamethasone.[83] Elimination is via renal excretion as well as hepatic oxidation and glucuronidation.[82]

Metronidazole is FDA labeled for use in adult patients in the treatment of intra-abdominal, skin and soft tissue, gynecologic, central nervous system, and lower respiratory tract infections, as well as endocarditis and bacteremia. It is not FDA approved for use in pediatric patients or infants and has extensive off-label use.

Initial PK studies also revealed various dosing intervals ranging from BID options to every other day.[83,84] More recent PK studies have used dried spot sampling, scavenged blood samples, and timed blood samples to analyze data.[85–87] Dried spot sampling found that the half-life decreases rapidly with increasing PMA due to a 5-fold increase in clearance compared with a 2.5-fold increase in volume of distribution.[85] A larger multicenter trial of infants aged <32 weeks and <120 days' PNA showed a similar increase in clearance with increasing weight of patients.[86]

A 2013 study used plasma and dried spot samples to determine the parent/metabolite ratio for metronidazole.[87] Metronidazole weight-normalized clearance increased and half-life decreased with increasing PNA. A target trough concentration to obtain an MIC >8 mg/L against anaerobic bacteria was chosen. A dosing regimen based on PMA is expected to achieve this target in ~80% of infants. Safety and efficacy for this regimen are currently being evaluated as part of the SCAMP (Antibiotic Safety in Infants With Complicated Intra-Abdominal Infections) trial (clinicaltrials.gov identifier NCT01994993).

Clindamycin

Clindamycin is a lincosamide antibiotic used in the treatment of susceptible infections against staphylococcal and streptococcal infections as well as anaerobic infections. Due to its activity against methicillin-resistant *S aureus*, its use in pediatric patients has increased.[88] Clindamycin is metabolized in the liver, primarily by cytochrome P-450 3A4, which undergoes ontogenic changes throughout the first year of life.[89] It is also highly protein bound, specifically to α_1-acid glycoprotein.[90]

Clindamycin is currently FDA labeled for the treatment of lower respiratory tract, intra-abdominal, gynecologic, bone, and skin and soft tissue infections, as well as bacteremia caused by *Staphylococcus*, *Streptococcus*, and anaerobic species. The labeled dose for infants aged <1 month is 15 to 20 mg/kg/d divided into 3 to 4 equal doses although the labeling notes that a lower dose may be adequate for smaller premature infants. This dosing regimen is based on 2 studies that did not include premature infants.[91,92]

To better estimate the PK properties of clindamycin in infants, including premature infants, investigators enrolled 35 infants in a PK study of clindamycin (median GA, 28.8 weeks; median PNA, 9.5 days).[93] The clearance of clindamycin was lower in infants aged <32 weeks. The dosing from this study was based on PMA (Table I). In a more recent study, plasma samples were collected from premature infants and combined with data from 2 previous trials.[94] A total of 62 infants <30 weeks' GA (median GA, 28 weeks; median PNA, 17 days) were included. Clearance was associated with PMA. The volume of distribution was associated with plasma protein concentrations. Dosing simulation was performed based on the PMA-stratified regimen and resulted in >97% of simulated infants obtaining an MIC >0.12 μg/mL for *S aureus*. Investigators also tracked safety and adverse events, none of which related to clindamycin use.

ANTIFUNGAL THERAPEUTICS

Invasive fungal infections, mainly caused by *Candida* species, have high morbidity and mortality in infants. Infants at risk for fungal infections include extremely premature infants, term infants with indwelling central venous catheters, or those receiving extracorporeal membrane oxygenation. Common antifungal agents include amphotericin B, fluconazole, and micafungin (Table II).

Amphotericin B is a fungicidal therapeutic agent that is primarily protein bound and is transferred into solid organs with minimal concentrations excreted in the urine.[95] It is currently FDA labeled for use in pediatric patients aged >1 month with systemic fungal infections. The current PK data reveal high levels of interpatient variability, with lower serum levels achieved at similar adult dosing.[96,97] This finding is believed to be due to a higher clearance in infants. Linder et al[98] studied 56 infants receiving amphotericin B, liposomal amphotericin B, or amphotericin B colloidal dispersion; none of the

Table II. Comparison of infant adult dosing for commonly used antifungal agents.

Antifungal Agent	Infant Dosing		Adult Dosing[125]	
	Dose	Dosing Interval	Maintenance Dose	Dosing Interval
	mg/kg	*h*	*mg*	*h*
Fluconazole[124]	25(loading)			
	12	24	200–800	24
Micafungin[109–113]	10	24	100–150	24

infants had renal dysfunction, suggesting that this condition is less likely to occur in infants compared with adults. The current dosing recommendation for amphotericin B is 1 to 1.5 mg/kg/d every 24 hours for amphotericin B and 2.5 to 7 mg/kg/d every 24 hours for the liposomal formulation, although more PK and pharmacodynamics studies are needed.[24]

Fluconazole is a fungistatic therapeutic that inhibits the cytochrome P-450 system; it synthesizes ergosterol, a cell membrane component of fungi. It is eliminated through the kidney. Fluconazole has a large volume of distribution and increasing clearance with both increasing PNA and PMA.[99–102] However, because steady state of the medication is often not achieved until day 5 of therapy (due to its prolonged half-life of ~24 hours), a loading dose has been found to be helpful at achieving therapeutic concentrations earlier.[101,103]

Because invasive fungal infections cause high mortality and morbidity, prophylactic administration of fluconazole is used by some neonatal intensive care units. Prophylactic fluconazole decreases the risk of colonization and invasive fungal infection but has little effect on mortality.[104–106] Dosing for prophylaxis has been studied at both 3 mg/kg and 6 mg/kg twice weekly, which is equivalent to an AUC of 50 and 100 mg h/L, respectively, and fluconazole concentrations of ≥2 and 4 μg/mL.[107] Selection of dosing for prophylaxis should therefore be dependent on local *Candida* incidence and local MIC values.

Micafungin is an echinocandin that interrupts cell wall biosynthesis and is highly protein bound.[108] It is often used in invasive *Candida* infections that are not responsive to either amphotericin B or fluconazole. It is dependent on hepatic metabolism and fecal elimination for clearance. There are currently 5 PK studies on micafungin in infants that have reported efficacy at doses of 10 mg/kg/d.[109–113]

ANTIVIRAL THERAPEUTIC AGENTS

Viral infections in infants, specifically those caused by herpes simplex virus (HSV) and cytomegalovirus (CMV), have long-term morbidity and increased mortality in infants.[114] Currently, HSV infections are treated with acyclovir, and CMV infections are treated

Table III. Comparison of infant and adult dosing for commonly used antiviral agents. Dosing is intravenous unless otherwise indicated.

Antiviral Agent	Infant Dosing			Adult Dosing[125]	
	Postmenstrual Age	Dose	Dosing Interval	Maintenance Dose	Dosing Interval
	wk	*mg/kg*	*h*	*mg*	*h*
Acyclovir[31,116]	<30	20	12		
	>30	20	8	5–10	8
Ganciciovir[118–121]		6	12	5(mg/kg)	divided 12–24
Valganciciovir (oral)[122]		16	12	900	divided 12–24

with ganciclovir. Both of these medications are phosphorylated preferentially by kinases in the respective viruses and inhibit viral DNA synthesis by competitive inhibition of viral DNA polymerase.

Acyclovir is active against HSV-1 and HSV-2, as well as varicella zoster virus. Its levels are dependent on renal excretion, and CSF levels are approximately one half of plasma levels.[115] Clearance of acyclovir increases with PMA due to renal maturation in infants.[116] Infants with disseminated HSV infections treated with high doses of acyclovir (60 mg/kg/d) have decreased mortality compared with those treated with standard dosing (45 mg/kg/d).[117] A PK study in premature infants studied dosing intervals at a uniform amount of 20 mg/kg per dose.[116] According to modeling from the study, those infants aged <30 weeks will achieve efficacy with every 12-hour dosing, those aged 30 to <36 weeks with every 8-hour dosing, and those aged 36 to 41 weeks with every 6-hour dosing (Table III). The proposed dosing interval for infants of every 6 hours for infants aged >36 weeks has not yet had proper safety and efficacious studies conducted and will need to be validated before being formally recommended.

Valacyclovir, an oral pro-drug converted to acyclovir by the liver, has limited PK data available for infants aged <1 month. Side effects include renal toxicity and neutropenia and are monitored periodically with routine laboratory testing.

Ganciclovir and valganciclovir (the latter an oral pro-drug converted to ganciclovir) are used to treat CMV infection. Both forms are renally excreted, and PK data have revealed that PNA, body surface area, and sex do not have an effect once weight is taken into account.[118–121] For 6–mg/kg dosing, the AUC was 27 mg h/L, similar to adult data.[118] Oral valganciclovir 16 mg/kg every 12 hours has also been shown to have good bioavailability in infants, with the ability to achieve optimal plasma levels.[118,122] Treatment with valganciclovir for 6 months, as opposed to 6 weeks, has been shown to improve audiology and neurodevelopmental outcomes at 2 years.[123]

CURRENT TRIALS OF ANTIMICROBIAL AGENTS

Clinical trials of other medications in this population are currently ongoing. Data have also been collected and results are pending for rifampin and ticarcillin-clavulanate (clinicaltrials.gov identifier NCT01728363). The SCAMP trial is currently collecting data with regard to different combinations of antibiotics used in the treatment of complicated intra-abdominal infections and their safety. The 4 groups in the SCAMP trial are ampicillin/gentamicin/metronidazole, ampicillin/gentamicin/clindamycin, gentamicin/piperacillin-tazobactam, and standard of care antibiotics plus metronidazole. All dosing is based on GA and PNA.

SUMMARY AND FUTURE DIRECTIONS

Antimicrobial agents are commonly administered to infants because bacterial, viral, and fungal infections cause substantial morbidity and mortality. Although progress is being made, the safest and most effective dose for the majority of these agents is unknown in infants. Because the physiology of infants, especially premature infants, matures with age, the doses of antimicrobial agents often change (usually increases) with increasing PNA (or PMA). In addition, because the maturation of drug-handling systems is different from adults and older children, dosing cannot be modeled or estimated from adults and older children when applying it to premature and low birth weight infants. Studies must be performed specifically on these target populations to determine the appropriate dose.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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Address correspondence to: Jacob K. Johnson, MD, University of North Carolina at Chapel Hill, Department of Pediatrics, 101 Manning Drive, CB# 7596, Chapel Hill, NC 27599-7596. E-mail: jacob.johnson@unchealth.unc.edu