

Review Article

Antimicrobial Agent Dosing in Infants



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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) © 2016 Elsevier HS Journals, Inc. All rights reserved.

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

Accepted for publication June 30, 2016.

<http://dx.doi.org/10.1016/j.clinthera.2016.06.017>

0149-2918/\$ - see front matter

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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 disproportionately 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 $\mu\text{g/mL}$ 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
Ampicillin ²³	<i>wk</i>	<i>d</i>	<i>wk</i>	<i>mg/kg</i>	<i>h</i>		
	≤ 34	≤ 7		50	12		
Gentamicin ²⁵	> 35	8–28		75	12	1000–2000	4–6
	< 32	< 28		50	8		
		≤ 14		5	48		
		> 14		5	36		
Cefotaxime ²⁴	32–36	≤ 7		4	36	4–7(mg/kg)	24
		> 7		4	24		
	≥ 37	≤ 28		4	24		
		≤ 28	≤ 29		12		
		> 28			8		
		≤ 14	30–36		12	1000–2000	8–12
Meropenem ⁵⁹		> 14		50	8		
		≤ 7	37–44		12		
		> 7			8		
	< 32	< 14		20	12		
		≥ 14		20	8		
Piperacillin-tazobactam ⁷⁹	≥ 32	< 14		20	8	500–2000	8
		≥ 14		30	8		
	< 30			100	8		
Metronidazole ⁸⁷	30–35			80	6	3375	6
	> 35			80	4	4500	6–8
Clindamycin ⁹³				15			
				(loading)			
			< 34	7.5	12	1000	
			34–40	7.5	8	(loading) 500	6
			> 40	7.5	6		
Vancomycin ^{64,68}			≤ 32	5	8		
			> 32–40	7	8	150–600	6–8
			> 40	9	8		
			10		500	6	
			(loading)				
			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 $\mu\text{g/mL}$, 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 al⁷¹ 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 $\mu\text{g/mL}$ and 32 $\mu\text{g/mL}$, 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 $\mu\text{g/mL}$ 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 μ g/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 al⁹⁸ 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
	<i>mg/kg</i>	<i>h</i>	<i>mg</i>	<i>h</i>
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 $\mu\text{g/mL}$.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
	<i>wk</i>	<i>mg/kg</i>	<i>h</i>	<i>mg</i>	<i>h</i>
Acyclovir ^{31,116}	<30	20	12		
	>30	20	8	5-10	8
Ganciclovir ¹¹⁸⁻¹²¹		6	12	5(mg/kg)	divided 12-24
Valganciclovir (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.

ACKNOWLEDGMENTS

Both authors contributed equally to the completion of this article. Dr. Laughon is supported by the US government for his work in pediatric and neonatal clinical pharmacology (HHSN267200700051C [Principal Investigator: Benjamin]), the National Institute of Child Health and Human Development (K23 HD068497), and the National Heart, Lung, and Blood Institute (R34 HL124038).

CONFLICTS OF INTEREST

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

REFERENCES

1. Hsieh EM, et al. Medication use in the neonatal intensive care unit. *Am J Perinatol.* 2014;31:811–821.
2. De Souza, et al. Off-label use and harmful potential of drugs in a NICU in Brazil: a descriptive study. *BMC Pediatr.* 2016;16:13.

3. Kearns GL, et al. Developmental pharmacology-drug disposition, action, and therapy in infants and children. *N Engl J Med.* 2003;349:1157–1167.
4. Dunne J, et al. Extrapolation of adult data and other data in pediatric drug-development programs. *Pediatrics.* 2011;128:1242–1249.
5. Paisley JW, Smith AL, Smith DH. Gentamicin in newborn infants. Comparison of intramuscular and intravenous administration. *Am J Dis Child.* 1973;126:473–477.
6. Driessen OH, et al. Pharmacokinetic aspects of therapy with ampicillin and kanamycin in newborn infants. *Eur J Clin Pharmacol.* 1978;13:449–457.
7. Koren G. Therapeutic drug monitoring principles in the neonate. *Clin Chem.* 1997;43:222–227.
8. Butler DR, Kuhn RJ, Chandler MH. Pharmacokinetics of anti-infective agents in paediatric patients. *Clin Pharmacokinet.* 1994;26:374–395.
9. McCracken GH, et al. Pharmacologic evaluation of orally administered antibiotics in infants and children: effect of feeding on bioavailability. *Pediatrics.* 1978;62:738–743.
10. Cohen-Wolkowicz M, et al. Pediatric antifungal agents. *Curr Opin Infect Dis.* 2009;22:553–558.
11. Strolin BM, Baltes EL. Drug metabolism and disposition in children. *Fundam Clin Pharmacol.* 2003;17:281–299.
12. McLeod HL, et al. Disposition of antineoplastic agents in the very young child. *Br J Cancer Suppl.* 1992;18:S23–S29.
13. Anderson GD, Lynn AM. Optimizing pediatric dosing: a developmental pharmacologic approach. *Pharmacotherapy.* 2009;29:680–690.
14. Black MJ, et al. When birth comes early: effects on nephrogenesis. *Nephrology (Carlton).* 2013;18:180–182.
15. Rhodin MM, et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. *Pediatr Nephrol.* 2009;24:67–76.
16. Alcorn J, McNamara PJ. Ontogeny of hepatic and renal systemic clearance pathways in infants: part II. *Clin Pharmacokinet.* 2002;41:1077–1094.
17. Leake RD, Trygstad CW. Glomerular filtration rate during the period of adaptation to extrauterine life. *Pediatr Res.* 1977;11:959–962.
18. Arant BS Jr. Developmental patterns of renal functional maturation compared in the human neonate. *J Pediatr.* 1978;92:705–712.
19. Zarowitz BJ, Robert S, Peterson EL. Prediction of glomerular filtration rate using aminoglycoside clearance in critically ill medical patients. *Ann Pharmacother.* 1992;26:1205–1210.
20. Strolin BM, Whomsley R, Baltes EL. Differences in absorption, distribution, metabolism and excretion of xenobiotics between the paediatric and adult populations. *Expert Opin Drug Metab Toxicol.* 2005;1:447–471.
21. Jacobs RF, et al. Renal clearance of imipenem in children. *Eur J Clin Microbiol.* 1984;3:471–474.
22. Kimberlin D.W., et al. Red Book, 30th Edition (2015): 2015 Report of the Committee on Infectious Diseases, 30th Edition. American Academy of Pediatrics, Elk Grove Village, IL.
23. Tremoulet A, et al. Characterization of the population pharmacokinetics of ampicillin in neonates using an opportunistic study design. *Antimicrob Agents Chemother.* 2014;58:3013–3020.
24. Neofax. Truven Health Analytics, v7.2.0.2016-Q2. Accessed June 28, 2016.
25. Nelson's Pocket Book of Pediatric Antimicrobial Therapy. In: Bradley JS, Nelson JD, Kimberlin DK, editors. 21st ed. American Academy of Pediatrics, Elk Grove Village, IL; 2015.
26. Nahata MC, Vashi VI, Swanson RN, Messig MA, Chung M. Pharmacokinetics of ampicillin and sulbactam in pediatric patients. *Antimicrob Agents Chemother.* 1999;43:1225–1229.
27. Boe RW, et al. Serum levels of methicillin and ampicillin in newborn and premature infants in relation to postnatal age. *Pediatrics.* 1967;39:194–201.
28. Giapros VI, et al. Renal function and effect of aminoglycoside therapy during the first ten days of life. *Pediatr Nephrol.* 2003;18:46–52.
29. Medillin-Garibay SE, et al. Population pharmacokinetics of gentamicin and dosing optimization for infants. *Antimicrob Agents Chemother.* 2015;59:482–489.
30. Fuchs A, et al. Population pharmacokinetic study of gentamicin in a large cohort of premature and term neonates. *Br J Clin Pharmacol.* 2014;78:1090–1101.
31. Gentamicin [package insert]. Lake Zurich, IL: Fresenius Kabi USA; 2013.
32. Best EJ, et al. Once-daily gentamicin in infants and children: a prospective cohort study evaluating safety and the role of therapeutic drug monitoring in minimizing toxicity. *Pediatr Infect Dis J.* 2011;30:827–832.
33. Ali MZ, Goetz MB. A meta-analysis of the relative efficacy and toxicity of single daily dosing versus multiple daily dosing of aminoglycosides. *Clin Infect Dis.* 1997;24:796–809.
34. Bailey TC, et al. A meta-analysis of extended-interval dosing versus multiple daily dosing of aminoglycosides. *Clin Infect Dis.* 1997;24:786–795.
35. Barza M, et al. Single or multiple daily doses of aminoglycosides: a meta-analysis. *BMJ.* 1996;312:338–345.
36. Ferriols-Lisart R, Alos-Alminana M. Effectiveness and safety of once-daily aminoglycosides: a meta-analysis. *Am J Health Syst Pharm.* 1996;53:1141–1150.
37. Galloe AM, et al. Aminoglycosides: single or multiple daily dosing? A

- meta-analysis on efficacy and safety. *Eur J Clin Pharmacol.* 1995;48:39–43.
38. Hatala R, Dinh T, Cook DJ. Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis. *Ann Intern Med.* 1996;124:717–725.
 39. Munckhof WJ, Grayson ML, Turnidge JD. A meta-analysis of studies on the safety and efficacy of aminoglycosides given either once daily or as divided doses. *J Antimicrob Chemother.* 1996;37:645–663.
 40. Contopoulos-Ioannidis DG, et al. Extended-interval aminoglycoside administration for children: a meta-analysis. *Pediatrics.* 2004;114:e111–e118.
 41. De Broe ME, Verbist L, Verpooten GA. Influence of dosage schedule on renal cortical accumulation of amikacin and tobramycin in man. *J Antimicrob Chemother.* 1991;27 (suppl C):41–47.
 42. Tran Ba Huy P, Bernard P, Schacht J. Kinetics of gentamicin uptake and release in the rat: comparison of inner ear tissues and fluids with other organs. *J Clin Invest.* 1986;77:1492–1500.
 43. Alshaik B, et al. Extended interval dosing of gentamicin in premature neonates \leq 28-week gestation. *Acta Paediatr.* 2012;101:1134–1139.
 44. Lingvall M, et al. The effect of sepsis upon gentamicin pharmacokinetics in neonates. *Br J Clin Pharmacol.* 2005;59:54–61.
 45. Sullins AK, Abdel-Rahman SM. Pharmacokinetics of antibacterial agents in the CSF of children and adolescents. *Pediatr. Drugs.* 2013;15:93–117.
 46. Clark RH, et al. Empiric use of ampicillin and cefotaxime, compared with ampicillin and gentamicin, for neonates at risk for sepsis is associated with an increased risk of neonatal death. *Pediatrics.* 2006;117:67–74.
 47. Cotten CM, et al. The association of third-generation cephalosporin use and invasive candidiasis in extremely low birth-weight infants. *Pediatrics.* 2006;118:717–722.
 48. Lassman HB, Coombes JD. Metabolism of cefotaxime: a review. *Diagn Microbiol Infect Dis.* 1984;2:35–12S.
 49. Kearns GL, Young RA. Pharmacokinetics of cefotaxime and desacetylcefotaxime in the young. *Diagn Microbiol Infect Dis.* 1995;22:97–104.
 50. Bertels RA, et al. Serum concentrations of cefotaxime and its metabolite desacetylcefotaxime in infants and children during continuous infusion. *Infection.* 2008;36:415–420.
 51. Aujard Y, Brion F, Jacqz-Aigrain E, et al. Pharmacokinetics of cefotaxime and desacetylcefotaxime in the newborn. *Diagn Microbiol Infect Dis.* 1989;12:87–91.
 52. Stockmann C, et al. Considerations in the pharmacologic treatment and prevention of neonatal sepsis. *Paediatr Drugs.* 2014;16:67–81.
 53. Pfaller MA, Jones RN. A review of the in vitro activity of meropenem and comparative antimicrobial agents tested against 30,254 aerobic and anaerobic pathogens isolated worldwide. *Diagn Microbiol Infect Dis.* 1997;28:157–163.
 54. Solomkin JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis.* 2010;50:133–164.
 55. Neu J, Walker WA. Necrotizing enterocolitis. *N Engl J Med.* 2011;364:255–264.
 56. Ljungberg B, Nisllsson-Ehle I. Pharmacokinetics of meropenem and its metabolite in young and elderly healthy men. *Antimicrob Agents Chemother.* 1992;36:1437–1440.
 57. van den Anker JN, et al. Meropenem pharmacokinetics in the newborn. *Antimicrob Agents Chemother.* 2009;53:3871–3879.
 58. Clark RH, et al. Reported medication use in the neonatal intensive care unit: data from a large national data set. *Pediatrics.* 2006;117:1979–1987.
 59. Smith PB, 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;30:844–849.
 60. Cohen-Wolkowicz M, et al. Safety and effectiveness of meropenem in infants with suspected or complicated intra-abdominal infections. *Clin Infect Dis.* 2012;55:1495–1502.
 61. Stoll BJ, et al. Late-onset sepsis in very low birth weight neonates: the experiences of the NICHD Neonatal Research Network. *Pediatrics.* 2002;110:285–291.
 62. Clark R, et al. Nosocomial infection in the NICU: a medical complication or unavoidable problem. *J Perinatol.* 2004;24:382–388.
 63. Rubin LG, et al. Evaluation and treatment of neonates with suspected late-onset sepsis: a survey of neonatologists' practices. *Pediatrics.* 2002;110:e42.
 64. Rybak M, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm.* 2009;66:82–98.
 65. Liu C, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis.* 2011;52:285–292.
 66. Patel AD, et al. Intermittent versus continuous infusion of vancomycin

- in neonates. *Arch Dis Child*. 2012; 97:e20.
67. Pawlowsky F, et al. Constant rate of infusion of vancomycin in premature neonates: a new dosage schedule. *Br J Clin Pharmacol*. 1998;46:163–167.
 68. Plan O, et al. Continuous-infusion vancomycin therapy for preterm neonates with suspected or documented gram-positive infections: a new dosage schedule. *Arch Dis Child Fetal Neonatal Ed*. 2008;93:F418–F421.
 69. Zhao W, et al. Vancomycin continuous infusion in neonates: dosing optimisation and therapeutic drug monitoring. *Arch Dis Child*. 2013;98:449–453.
 70. Ackerman BH, Vannier AM, Eudy EB. Analysis of vancomycin time-kill studies with *Staphylococcus* species by using a curve stripping program to describe the relationship between concentration and pharmacodynamic response. *Antimicrob Agents Chemother*. 1992;36:1766–1769.
 71. Kim J, et al. Determination of vancomycin pharmacokinetics in neonates to develop practical initial dosing recommendations. *Antimicrob Agents Chemother*. 2014;58:2830–2840.
 72. Berger A, et al. Safety evaluation of piperacillin/tazobactam in very low birth weight infants. *J Chemother*. 2004;16:166–171.
 73. Sorgel F, Kinzig M. The chemistry, pharmacokinetics and tissue distribution of piperacillin/tazobactam. *J Antimicrob Chemother*. 1993;31:39–60.
 74. Felton TW, et al. Population pharmacokinetics of extended-infusion piperacillin-tazobactam in hospitalized patients with nosocomial infections. *Antimicrob Agents Chemother*. 2012;56:4087–4094.
 75. Roberts JA, et al. First-dose and steady-state population pharmacokinetics and pharmacodynamics of piperacillin by continuous or intermittent dosing in critically ill patients with sepsis. *Int J Antimicrob Agents*. 2010;35:156–163.
 76. Shea KM, et al. Comparative pharmacodynamics of intermittent and prolonged infusions of piperacillin/tazobactam using Monte Carlo simulations and steady-state pharmacokinetic data from hospitalized patients. *Ann Pharmacother*. 2009;43:1747–1754.
 77. Cies JJ, et al. Population pharmacokinetics of piperacillin/tazobactam in critically ill young children. *Pediatr Infect Dis J*. 2014;33:168–173.
 78. Cohen-Wolkowicz M, et al. Population pharmacokinetics of piperacillin using scavenged samples from preterm infants. *Ther Drug Monit*. 2012;34:312–319.
 79. Cohen-Wolkowicz M, et al. Developmental pharmacokinetics of piperacillin and tazobactam using plasma and dried blood spots from infants. *Antimicrob Agents Chemother*. 2014;58:2856–2865.
 80. Brook I. Bacteremia due to anaerobic bacteria in newborns. *J Perinatol*. 1990;10:351–356.
 81. Thompson AM, Bizzarro MJ. Necrotizing enterocolitis in newborns: pathogenesis, prevention and management. *Drugs*. 2008;68:1227–1238.
 82. Loft S, et al. Influence of dose and route of administration on disposition of metronidazole and its major metabolites. *Eur J Clin Pharmacol*. 1986;30:467–473.
 83. Jager-Roman E, et al. Pharmacokinetics and tissue distribution of metronidazole in the newborn infant. *J Pediatr*. 1982;100:651–654.
 84. Upadhyaya P, Bhatnagar V, Basu N. Pharmacokinetics of intravenous metronidazole in neonates. *J Pediatr Surg*. 1988;23:263–265.
 85. Suyagh M, et al. Metronidazole population pharmacokinetics in preterm neonates using dried blood-spot sampling. *Pediatrics*. 2011; 127:e367–e374.
 86. Cohen-Wolkowicz M, et al. Population pharmacokinetics of metronidazole evaluated using scavenged samples from preterm infants. *Antimicrob Agents Chemother*. 2012;56:1828–1837.
 87. Cohen-Wolkowicz M, et al. Determining population and developmental pharmacokinetics of metronidazole using plasma and dried blood spot samples from premature infants. *Pediatr Infect Dis J*. 2013;32:956–961.
 88. Herigon JC, Hersh AL, Gerber JS, Zaoutis TE, Newland JG. Antibiotic management of *Staphylococcus aureus* infections in US children's hospitals, 1999–2008. *Pediatrics*. 2010;125. e1294–E1300.
 89. Wynalda M, Hutzler J, Koets M. In vitro metabolism of clindamycin in human liver and intestinal microsomes. *Drug Metab Dispos*. 2003;31:878–887.
 90. Son DS, Osabe M, Shimoda M, Kokue E. Contribution of alpha 1-acid glycoprotein to species difference in lincosamides-plasma protein binding kinetics. *J Vet Pharmacol Ther*. 1998;21:34–40.
 91. Koren G, et al. Pharmacokinetics of intravenous clindamycin in newborn infants. *Pediatr Pharmacol (New York)*. 1986;5:287–292.
 92. Bell MJ, et al. Pharmacokinetics of clindamycin phosphate in the first year of life. *J Pediatr*. 1984;105:482–486.
 93. Gonzalez D, 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;96:429–437.
 94. Gonzalez D, et al. Clindamycin pharmacokinetics and safety in preterm and term infants. *Antimicrob Agents Chemother*. 2016;60:2888–2894.
 95. Atkinson AJ, Bennet JE. Amphotericin B pharmacokinetics in humans. *Antimicrob Agents Chemother*. 1978;13:271–276.

96. Starke JR, et al. Pharmacokinetics of amphotericin B in infants and children. *J Infect Dis.* 1987;155:766-774.
97. Koren G, et al. Pharmacokinetics and adverse effects of amphotericin B in infants and children. *J Pediatr.* 1988;113:559-563.
98. Linder N, et al. Treatment of candidaemia in premature infants: comparison of three amphotericin B preparations. *J Antimicrob Chemother.* 2003;52:663-667.
99. Nahata MC, Tallian KB, Force RW. Pharmacokinetics of fluconazole in young infants. *Eur. Drug Metab Pharmacokinet.* 1999;24:155-157.
100. Saxén H, Hoppu K, Pohjavuori M. Pharmacokinetics of fluconazole in very low birth weight infants during the first two weeks of life. *Clin Pharmacol Ther.* 1993;54:269-277.
101. Wade KC, et al. Population pharmacokinetics of fluconazole in young infants. *Antimicrob Agents Chemother.* 2008;52:4043-4049.
102. Wenzl TG, et al. Pharmacokinetics of oral fluconazole in premature infants. *Eur J Pediatr.* 1998;157:661-662.
103. Piper L, et al. Fluconazole loading dose pharmacokinetics and safety in infants. *Pediatr Infect Dis J.* 2011;30:375-378.
104. Benjamin DK, et al. Effect of fluconazole prophylaxis on candidiasis and mortality in premature infants: a randomized controlled trial. *JAMA.* 2014;311:1742-1749.
105. Manzoni P, et al. A multicenter, randomized trial of prophylactic fluconazole in preterm neonates. *N Engl J Med.* 2007;356:2483-2495.
106. Cleminson J, Austin N, McGuire W. Prophylactic systemic antifungal agents to prevent mortality and morbidity in very low birth weight infants. *Cochrane Database Syst Rev.* 2015;10. CD003850.
107. Wade KC, et al. Fluconazole dosing for the prevention or treatment of invasive candidiasis in young infants. *Pediatr Infect Dis J.* 2009;28:717-723.
108. Chen SC, Slavin MA, Sorrell TC. Echinocandin antifungal drugs in fungal infections: a comparison. *Drugs.* 2011;71:11-41.
109. Benjamin DK, et al. Safety and pharmacokinetics of repeat-dose micafungin in young infants. *Clin Pharmacol Ther.* 2010;87:93-99.
110. Heresi GP, et al. The pharmacokinetics and safety of micafungin, a novel echinocandin, in premature infants. *Pediatr Infect Dis J.* 2006;25:1110-1115.
111. Hope WW, et al. Population pharmacokinetics of micafungin in neonates and young infants. *Antimicrob Agents Chemother.* 2010;54:2633-2637.
112. Kawada M, et al. Pharmacokinetics of prophylactic micafungin in very-low-birth-weight infants. *Pediatr Infect Dis J.* 2009;28:840-842.
113. Smith PB, et al. Pharmacokinetics of an elevated dosage of micafungin in premature neonates. *Pediatr Infect Dis J.* 2009;28:412-415.
114. Corey L, Wald A. Maternal and neonatal herpes simplex virus infections. *N Engl J Med.* 2009;361:1376-1385.
115. Wagstaff AJ, Faulds D, Goa KL. Acyclovir: a reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. *Drugs.* 1994;47:153-205.
116. Sampson MR, et al. Population pharmacokinetics of intravenous acyclovir in preterm and term infants. *Pediatr Infect Dis J.* 2014;33:42-49.
117. Kimberlin DW, et al. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. *Pediatrics.* 2001;108:230-238.
118. Acosta EP, et al. Ganciclovir population pharmacokinetics in neonates following intravenous administration of ganciclovir and oral administration of a liquid valganciclovir formulation. *Clin Pharmacol Ther.* 2007;81:867-872.
119. Trang JM, et al. Linear single-dose pharmacokinetics of ganciclovir in newborns with congenital cytomegalovirus infections. NIAID Collaborative Antiviral Study Group. *Clin Pharmacol Ther.* 1993;53:15-21.
120. Zhou XJ, et al. Population pharmacokinetics of ganciclovir in newborns with congenital cytomegalovirus infections. NIAID Collaborative Antiviral Study Group. *Antimicrob Agents Chemother.* 1996;40:2202-2205.
121. Whitley RJ, et al. Ganciclovir treatment of symptomatic congenital cytomegalovirus infection: results of a phase II study. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *J Infect Dis.* 1997;175:1080-1086.
122. Kimberlin DW, et al. Pharmacokinetic and pharmacodynamic assessment of oral valganciclovir in the treatment of symptomatic congenital cytomegalovirus disease. *J Infect Dis.* 2008;197:836-845.
123. Kimberlin DW, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. *N Engl J Med.* 2015;372:933-943.
124. Turner K, et al. Fluconazole pharmacokinetics and safety in premature infants. *Curr Med Chem.* 2012;19:4617-4620.
125. Lexicomp Online[®], Pediatric & Neonatal Lexi-Drugs[®], Hudson, Ohio: Lexi-Comp, Inc; April 5, 2016.

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