Population Pharmacokinetics of Cefepime in the Neonate

Edmund Capparelli,1* Christine Hochwald,2 Maynard Rasmussen,3,4 Amy Parham,2 John Bradley,3,4 and Fernando Moya2,5

Pediatric Pharmacology Research Unit1 and Department of Pediatrics,4 University of California, San Diego, and Sharp Mary Birch Hospital for Women and Children,3 San Diego, California, and Memorial Hermann Children’s Hospital,2 and Department of Pediatrics, University of Texas Health Science Center,5 Houston, Texas

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Newborn infants cared for in neonatal intensive care units may develop nosocomial infections. Cefepime, a “fourth-generation” cephalosporin (i.e., with activity against virtually all of the chromosomal-beta-lactamase-producing and many extended-spectrum-beta-lactamase-producing organisms), provides excellent activity against many gram-negative pathogens resistant to expanded-spectrum cephalosporins currently used to treat neonatal infections. The purpose of this study was to determine the pharmacokinetics of cefepime in this population to optimize dosing and minimize potential adverse events. Premature and term infants <4 months of age hospitalized in two neonatal intensive care units were studied. Limited pharmacokinetic (PK) sampling occurred following a dose of cefepime at 50 mg/kg of body weight infused over 30 min. Population pharmacokinetic parameters were determined using the program NONMEM. Fifty-five infants were enrolled. Their average (- standard deviation) gestational age at birth was 30.5 ± 5.3 weeks, and their average postnatal age at PK evaluation was 14.5 ± 14.7 days. In the final PK model, cefepime clearance (CL) was strongly associated with serum creatinine (SCR) (CL [ml/min/kg] = 0.26 + 0.59/SCR). The volume of distribution for infants with a postconceptional age of <30 weeks was larger than that for infants with a postconceptional age of >30 weeks (0.51 versus 0.39 liter/kg, respectively). The Bayesian analysis-predicted cefepime trough concentration at a dose of 50 mg/kg every 12 h for infants ≤14 days of age was 29.9 ± 16.6 μg/ml. Cefepime, dosed at 30 mg/kg/dose every 12 h for infants less than 14 days of age, regardless of gestational age, should provide antibiotic exposure equivalent to or greater than 50 mg/kg every 8 h in older infants and children.

Immaturity of humoral, cellular, and myeloid cell line immunity places the neonate at higher risk for infection than older infants and children (21). With advances in medical technology, neonates with extreme prematurity, serious congenital anomalies, and metabolic disorders are surviving with prolonged hospitalizations that are often complicated by fulminant sepsis (14, 23, 24). Nosocomial infections in the neonate, including catheter-related bloodstream infections, pneumonia, urinary tract infections, and surgical-wound infections, may lead to increased mortality and morbidity (1, 11, 25). Gram-negative nosocomial pathogens, particularly those which are resistant to the expanded-spectrum cephalosporins cefotaxime and ceftazidime, are among the most difficult to treat. These pathogens include the Enterobacteriaceae, as well as many nonfermenting environmental pathogens (12, 13). Problematic within the enteric bacilli are organisms that constitutively produce chromosomal beta-lactamases (class I, ampC beta-lactamases), including Enterobacter spp., Serratia spp., and some strains of Citrobacter spp. (17). Just as difficult to treat are enteric bacilli which contain newly evolving beta-lactamases, termed extended-spectrum beta-lactamases (ESBL), most often present in strains of Klebsiella spp. and, increasingly, of Escherichia coli (16, 19). Over 100 ESBL which have substantial activities against the expanded-spectrum cephalosporins have now been described (9). Fortunately, virtually all of the chromosomal beta-lactamases, and many ESBL-producing organisms, are still susceptible to “fourth-generation” cephalosporins, such as cefepime and the carbapenems. Of the non- enteric gram-negative bacilli, Pseudomonas aeruginosa has been well documented as a cause of nosocomial infections in the neonatal intensive care unit (NICU) (12). While community-acquired strains are still often susceptible to ceftazidime, many nosocomial strains are resistant to ceftazidime. Broad-spectrum antibiotics are commonly used as empirical therapy for suspected infections. Cefepime, a fourth-generation cephalosporin, provides expanded coverage for the empirical treatment of most antibiotic-resistant, gram-negative nosocomial neonatal pathogens, including E. coli and Klebsiella, Enterobacter, and Pseudomonas species (6, 7).

Cefepime displays a safety profile similar to that of expanded-spectrum cephalosporins, including less nephrotoxicity than aminoglycosides; however, adverse effects still occur in children being treated (7). Many of these events may be related to the degree of drug exposure. Without specific neonatal dosing guidelines, these adverse events may occur more frequently in neonates with immature renal function and decreased clearance (CL) when dosed according to recommendations for older children, thus increasing morbidity in this population.

Currently, there are little available data for the use of cefepime in newborn infants (20). Due to the unique considerations surrounding the treatment of neonates, particularly premature infants, the existing data cannot be extrapolated for use with such a fragile population. It was therefore our intent to determine the pharmacokinetic parameters of cefepime in neonates to establish dosing that will achieve a level of cef
epime exposure equivalent to that seen in older infants and children in order to maximize safety and efficacy in this population.

MATERIALS AND METHODS
Two similar and concurrent pharmacokinetic studies conducted at separate institutions (Sharp Mary Birch Hospital for Women and Children, San Diego, Calif., and Memorial Hermann Children’s Hospital, Houston, Tex.) provided the data for this analysis. A total of 55 neonates were enrolled in these studies. Informed consent was obtained from parents or guardians prior to enrollment of the children in the study. Cefepime (Elan Pharmaceuticals), at a dose of 50 mg/ kg of body weight, was administered intravenously as a 30-min infusion. Enrollment criteria were similar at the two institutions; however, the pharmacokinetic sampling strategies varied. Details of the individual studies are noted below.

San Diego. Infants at Sharp Mary Birch Hospital for Women and Children were evaluated for entry into the study based on age (less than 2 months of age) and the need for antibiotic therapy or whether they were already receiving cefepime for suspected or documented infection. Exclusion criteria were as follows: a birth weight of less than 800 g; significant renal dysfunction defined as a serum creatinine (Scr) of >1.3 mg/dl or urine output of <1 ml/kg/h; hepatic dysfunction as evidenced by a direct bilirubin level of >3 mg/dl; an aspartate transaminase or alanine aminotransferase (ALT) level over twice the normal amount for chronological age; extracorporeal membrane oxygenation; hematopoietic abnormalities, including an absolute neutrophil count of <500 cells/mm³, a hematocrit of <25%, or a platelet count of <30,000/mm³; a history of seizures; and a life-threatening illness, with survival not expected. Infants receiving other medications known to be nephrotoxic that could possibly alter cefepime CL, such as amphotericin B and indomethacin, were excluded (aminoglycosides were permitted). Infants were also excluded for hypotension or poor perfusion requiring fluid or pharmacologic support with vasopressors. Baseline evaluation included a physical exam and medical history. Safety laboratory tests included a complete blood count, serum blood urea nitrogen and Scr, and ALT/aspartate transaminase. The Scr concentration was determined by an enzymatic method (Ortho-Clinical Diagnostics) free from interference with bilirubin. These test results were obtained within 24 h prior to administering the study dose of cefepime. These tests were also repeated with the last sample of blood drawn for pharmacokinetic assay from infants receiving a single dose of cefepime.

Infants who were not already receiving cefepime for therapy of infections at enrollment were stratified into one of four categories for analysis based on gestational age (GA) (<36 weeks and ≥36 weeks) and postnatal age (≥14 days and >14 days) to receive a single dose of cefepime. Within each stratum, infants were randomized into two groups for blood sample collection: group 1 had blood sampling at 1 to 2, 4 to 6, and 10 to 12 h postdose, and group 2 had blood sampling at 2 to 4, 6 to 8, and 16 to 24 h postdose. Infants receiving cefepime as part of their clinical care were also recruited for limited blood sampling after having received at least four doses of cefepime at 50 mg/kg/dose administered every 12 h. Two blood samples were collected from each of these infants: one sample predose and a second sample 1 to 2 h postdose.

Houston. Premature infants less than 4 months of age in the NICU at Memorial Hermann Children’s Hospital were considered eligible for the study when the clinical staff decided to institute intravenous cefepime therapy for suspected or documented infection. Patients were excluded if they had significant renal dysfunction (Scr of >1.5 mg/dl) or if they had congenital or chromosomal anomalies. Scr concentration was determined by a modified Jaffe method free from interference with bilirubin. Each subject received cefepime at a dose of 50 mg/kg intravenously every 12 h. Following the initiation of the third cefepime dose, three serum cephalosporin levels were obtained at approximately 0.5, 6, and 11 h postdose.

Determination of serum cefepime concentrations. Blood samples were allowed to clot and then centrifuged at 3,000 rpm for 10 min. Within 1 h, the serum was harvested, placed into a labeled vial, and frozen initially at −70°C or colder freezers within 1 week of collection until they were shipped. Samples from both study locations were placed in dry ice and shipped to Hartford Hospital (D. Nicolau) for analysis. The parameters were assumed to have an exponential normal distribution using the full variance-covariance matrix to estimate for intersubject variability. A proportional residual error was used in the analysis. The potential impact of clinical covariates on pharmacokinetic parameters was screened, and covariates were retained in the final pharmacokinetic model if they statistically improved the goodness of fit (decrease in minimum objective function by ≥6.8; P < 0.01). Empirical Bayesian estimates of individual infant pharmacokinetic parameters were generated from the final model using the POSTHOC subroutine. Group comparisons from the individual Bayesian parameters were performed using the Pearson correlation coefficient and Wilcoxon rank sum tests. A P value of less than 0.05 was considered significant.

The appropriateness of the final model was evaluated using cross-validation. Eighteen data sets were constructed by randomly removing three different subjects from each data set. Pharmacokinetic parameter estimates generated from each data set were used to predict the concentrations from the subjects removed from that particular data set. The log ratios of measured/predicted concentrations were used to assess model bias and precision. Monte Carlo simulations of the final model were used to assess the various dosing regimens and the dose interval fraction at which unbound cefepime concentrations would exceed a MIC of 8 µg/ml. These simulations were performed with NONMEM and included demographic characteristics identical to those of the study population.

RESULTS
The patient characteristics are listed in Table 1 with a further breakdown of infant maturity at the pharmacokinetic evaluation listed in Table 2. In one patient, the cefepime concentration was less than half that of all other infants at all time points. This patient had an open abdominal wound with large transmural fluid loss and underwent multiple transfusions during cefepime therapy. Empirical Bayesian analysis estimated that the volume of distribution (V) in this subject was three times higher (exceeding total body water) and the CL was more than double those of all other subjects. The physiological implausibility of these observed concentrations in conjunction with the clinical picture led to the exclusion of this subject’s data from the final population pharmacokinetic model. Therefore, the development of the cefepime population pharmacokinetic model involved the remaining 54 subjects.

Overall, cefepime was well tolerated in infants who received a single dose or multiple doses to treat infections. One infant

<table>
<thead>
<tr>
<th>TABLE 1. Patient characteristics</th>
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<tr>
<td>Characteristic or statistic</td>
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<tr>
<td>Scr level (mg/dl)</td>
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<tr>
<td>Wt (kg)</td>
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<tr>
<td>No. of infants term/preterm</td>
</tr>
<tr>
<td>Postnatal age (days)</td>
</tr>
<tr>
<td>Gender (males/females)</td>
</tr>
<tr>
<td>Gestational age at birth (wk)</td>
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<tr>
<td>No. of patients studied at San Diego/Houston</td>
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* NA, not applicable.

<table>
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<th>TABLE 2. Infant maturity at pharmacokinetic evaluation</th>
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<td>Gestational age (wk)</td>
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<td>&lt;14</td>
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<tr>
<td>&lt;36</td>
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<tr>
<td>≥36</td>
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<td>Total</td>
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with a history of cholestasis secondary to parenteral nutrition had an ALT level elevated to 165 IU/ml (4.1 times the upper limit of normal) after receiving 3 days of cefepime therapy. The ALT level returned to normal the following week after cefepime was discontinued. No other clinical or laboratory adverse events that may have been linked to exposure to cefepime were observed in other study subjects. Six blood cultures, three tracheal cultures, and one peritoneal culture were positive for gram-negative pathogens in 10 patients from the Houston study. *Pseudomonas aeruginosa* was the most common organism, representing 40% of isolates. All of the organisms were susceptible to cefepime at a MIC of ≤2 μg/ml.

In the initial stage of population pharmacokinetic model building, the univariate screen for potentially significant covariate-cefepime pharmacokinetic parameter associations identified relationships between SCr and cefepime CL, postconceptual age and cefepime $V$, postconceptual age and cefepime CL, and gender and cefepime CL. However, in the multivariate evaluation, only SCr (on CL) and postconceptual age (on $V$)

### TABLE 3. Final population pharmacokinetic model

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<thead>
<tr>
<th>Parameter</th>
<th>Estimated level</th>
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<tbody>
<tr>
<td>CL (ml/min/kg)</td>
<td>$0.26 + 0.59/SCr$</td>
<td>$0.096/0.072$</td>
</tr>
<tr>
<td>$V$ (liter/kg)</td>
<td>$0.385 + 0.122 \times PCA30$</td>
<td>$0.0148/0.052$</td>
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Intersubject variability (CV [%])

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CV [%]</th>
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<tbody>
<tr>
<td>CL</td>
<td>25</td>
</tr>
<tr>
<td>$V$</td>
<td>29</td>
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Residual variability (%) | 13  |

$^a$ CV, coefficient of variation.  
$^b$ PCA, postconceptual age.

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**FIG. 1.** Final population model’s goodness-of-fit plots. (a) Population model-predicted cefepime concentrations (Conc) compared with the observed cefepime concentrations. (b) Individual subjects’ cefepime concentrations predicted from Bayesian POSTHOC data fitting with the observed cefepime concentrations.
remained independently significant statistically. The final population pharmacokinetic model is described in Table 3. Overall, the model described the data well (Fig. 1a and b). A few “peak” concentrations were higher than predicted, suggesting that a distributive phase that was not included in the final model may exist. However, the use of a two-compartment model did not improve the overall fit of the data. The SCr level was a strong predictor of cefepime CL, reducing the random interpatient variability for CL from 38 to 25% (Fig. 2). The relationships between SCr and cefepime CL were similar across the range of GAs. The relationship between cefepime CL and GA at birth was not significant ($r = 0.14; P > 0.10$). Even for infants less than 14 days of age, cefepime CL was only slightly lower than that of infants that were born at a later GA (Fig. 3). The $V$ was larger in infants less than 30 weeks postconceptional age (Fig. 4). The infants born at less than 28 weeks and studied at greater than 30 weeks postconception had $V$ values similar to those of infants born at a later GA.

The average empirical Bayesian analysis-estimated CL and $V$ were similar to the population-typical estimates. Using these individual subjects’ parameters, the steady-state trough concentrations were simulated based on a dose of 50 mg/kg every 12 h. These predicted cefepime troughs were higher for infants 14 days of age or less (29.9 ± 16.6 μg/ml) than for infants over 14 days of age (19.9 ± 19.4 μg/ml) ($P = 0.0048$). The predicted troughs were highly correlated with SCr levels ($r = 0.80; P < 0.001$).
The cross-validation median and average (± standard deviation) prediction errors of the log-transformed concentrations were −0.004 and 0.019 ± 0.15. The 95% confidence interval of the prediction error included 0, indicating no overall systematic model bias. The precision, characterized by median and average (± standard deviation) absolute prediction errors of the log concentrations, was 0.048 and 0.081 ± 0.12. These represent median and average absolute predictive errors of 12 and 21%, after transformation back to raw concentration units, which are similar to the population model estimate for a residual error of 13%.

**DISCUSSION**

With the increasing prevalence of antibiotic-resistant, gram-negative bacterial pathogens, cefepime therapy may offer significant benefits over expanded-spectrum cephalosporins such as cefotaxime and ceftazidime. This is true in the NICU, where resistant organisms can lead to high morbidity and mortality. The fourth-generation cephalosporins and carbapenems are relatively safe antibiotics that retain activity against many of these organisms and provide therapeutic options in this setting. However, the safe use of cefepime in neonates requires an understanding of its pharmacokinetic behavior to determine appropriate dosing.

Cefepime exhibits favorable pharmacokinetic behavior following intravenous administration in adults. Its \( V \) is slightly lower than that of total body water, and it exhibits low protein binding of 21% (15). It is almost exclusively eliminated in the urine, with a total CL approximating that of glomerulofiltration (26). Studies of children and older infants have indicated more-rapid elimination than with adults, requiring larger mg/kg doses or more frequent administration or both for pediatric patients.

The development of renal function is an important consideration for antibiotic dosing, including cefepime, in the neonatal population. In premature infants, renal function is impaired due to both anatomical and functional immaturity, including a delayed development of the proximal tubule. Compared to that of the glomerulus. Early studies show that the functional development of the kidney is closely related to postconceptional age (3, 4). Therefore, lower daily doses of renally excreted medications may be required for the immature infant (22).

Cefepime was well tolerated by infants participating in this study. Utilizing sparse sampling and a population analysis approach, we were able to characterize cefepime’s pharmacokinetic behavior in over 50 preterm and term infants. Since cefepime is primarily excreted unchanged in the urine, it is not surprising that preterm and term neonates, with their immature renal function, clear cefepime more slowly than other populations. It was unexpected that SCr level would be such a powerful predictor of cefepime CL. During the first few days of life, infant SCr reflects both infant renal function and mother-to-infant antepartum transfer of creatinine. It is for this reason that many pharmacokinetic studies of newborn infants do not attempt to critically evaluate infant renal function. However, even with this challenge, infant creatinine correlated with cefepime CL during the first 2 weeks of life. A similar relationship was found in infants between SCr and the clearance of vancomycin, which is also eliminated almost exclusively through renal mechanisms (10). The differences in SCr between term and preterm infants during the first 2 weeks of life (0.65 versus 0.95 mg/dl, respectively) could be used to fully predict the maturation of cefepime CL, as other factors, including GA at birth, postnatal age, and postconceptional age, were not independent predictors of cefepime elimination.

Cefepime’s \( V \) was 30% larger and more varied in infants with a postconceptional age of less than 30 weeks. This is consistent with the higher total body water content and higher fraction of extracellular fluid in the extremely premature infants.

Our pharmacokinetic data can be compared to the data for children published by Reed et al., who administered cefepime at a dose of 50 mg/kg/dose every 8 h to children between 2 months and 16 years of age (20). The comparisons are shown in Table 4. These differences in cefepime pharmacokinetics are somewhat expected. The most pronounced difference is in CL, since cefepime elimination is reduced in newborns due to their...
immature renal function. Cefepime CL in newborns is approximately 40% of that in older pediatric populations, which results in a prolonged serum half-life as well as higher trough concentrations. In premature infants, a larger V per kg of body weight also affects the cefepime half-life. It narrows the peak trough fluctuation compared to that of more-mature infants and children. There is also larger variability in pharmacokinetic parameters, as individual newborns differ in their rates of renal function acquisition and development of body composition.

Since cefepime exhibits time-dependent killing of gram-negative and gram-positive pathogens, the minimum goal of therapy is to keep the free serum cefepime concentrations above the MIC of cefepime for greater than 50% of the dosage interval (2). The NCCLS-recommended MIC breakpoint of cefepime for most aerobic gram-negative organisms is ≤ 8 µg/ml (18). Since the 12-h-postdose serum concentrations far exceed the MICs of most pathogens, the cefepime dose of 50 mg/kg given every 12 h should not be required for a clinical and microbiological cure and may be providing an excessive and potentially toxic exposure to the neonate.

Reducing cefepime exposure to values seen in other populations can be accomplished by either reducing the individual dose size or extending the dose interval. If the infants in this study were given cefepime at 30 mg/kg every 12 h, they would have achieved peak concentrations of 89 ± 27 µg/ml and trough concentrations of 18 ± 10 µg/ml (range, 6.3 to 47 µg/ml), with the predicted free concentrations exceeding 8 µg/ml for more than 80% of the dose interval in all subjects less than 14 days of age. This is a level of antibiotic exposure sufficient for maximum killing of susceptible pathogens. All of the predicted troughs with 30 mg/kg every 12 h are equal to or higher than the average troughs seen in older infants and children with 50 mg/kg every 8 h. One could also extend the dosing interval and cefepime dose to 50 mg/kg every 24 h. While this approach would achieve adequate concentrations in most infants, there is an eightfold range of predicted trough concentrations with every 12 h, and extending the dose interval would result in a huge range of trough concentrations and may lead to inadequate cefepime exposure in some infants with more-mature renal function.

The Monte Carlo simulation also supports the proposed dosage of 30 mg/kg every 12 h for infants under 2 weeks of age. The proportions of infants and amounts of time above a cefepime MIC of 8 µg/ml for various doses administered every 12 h are shown in Fig. 5. This evaluation indicates that a dose of 30 mg/kg would maintain free concentrations above 8 µg/ml for more than 50% of the dose interval in more than 99% of infants. While more than 95% of simulated infants receiving doses of 15 or 20 mg/kg also attained this target, only the 30-mg/kg dose maintained free cefepime concentrations at levels that ensure maximal killing in greater than 95% of infants. Given the immature immune system and fragility of newborn infants, the enhanced activity from prolonged concentrations above the MIC with 30 mg/kg is desirable and consistent with current dosing guidelines of beta-lactams in newborns.
A dosing approach based on SCR is intuitively appealing and would be most likely to produce the most-consistent exposures. A SCR-based strategy to change the dose interval could be utilized but would be difficult to implement, and it would be important to recognize the fact that small changes in creatinine have a large potential impact on cefepime concentrations. A 25% decrease in SCR is expected to be associated with more than a 50% reduction in trough cefepime concentration with a 24-h dose interval. The highly dynamic nature of renal function in this population could lead to inadequate dosing for subjects with rapid improvement in renal function, particularly with extending dose intervals. In addition, the benefit of achieving effective antibiotic exposure in this population should be weighed against the relatively low toxicity of cefepime in infants with moderately high cefepime exposures.

This study is limited in its ability to determine cefepime dosing in older infants. While cefepime CL can be extrapolated based on renal function maturation, only one term infant studied was greater than 14 days of age, and there was significant variability in the renal functions of preterm infants greater than 14 days of age. Another potential limitation is that the majority of the data were collected following single-dose administration or following only a few days of cefepime therapy. However, there is very little accumulation of cefepime with repeated dosing, and cefepime pharmacokinetics were not different among subjects who had pharmacokinetic evaluations following single- or multiple-dose administration. It is also important to recognize that these studies were not randomized by nature and that there may be some unintentional patient selection bias through study recruitment. Therefore, the pharmacokinetic associations found through model building are not necessarily causal. However, they are consistent with physiologic development, mechanistically plausible, and useful for developing dosing recommendations.

This study demonstrates the ability to predict cefepime CL based on SCR levels in infants. It also suggests that the Food and Drug Administration-approved dose of 50 mg/kg every 8 to 12 h for infants greater than 2 months of age is excessive for preterm (and term) infants, at least during the first 2 weeks of life. A dose of 30 mg/kg every 12 h for infants less than 14 days of age will achieve concentrations as high or higher than those achieved by doses of 50 mg/kg every 8 h for older populations. This proposed dosing regimen requires validation by prospective clinical studies during the neonatal period.

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REFERENCES