Development of population and Bayesian models for applied use in patients receiving cefepime.

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Abstract

Understanding exposures of cefepime, a β-lactam antibiotic, is crucial for developing regimens to achieve optimal exposure and improved clinical outcomes. This study sought to develop and evaluate a unified population pharmacokinetic model in both pediatric and adult patients receiving cefepime treatment.

Multiple physiologically relevant models were fit to pediatric and adult subject data. To evaluate the final model performance, a withheld group of twelve pediatric and two separate adult populations were assessed. Seventy subjects with a total of 604 cefepime concentrations were included in this study. All adults (n=34) on average weighed 82.7 kg and displayed a mean creatinine clearance (CrCL) of 106.7 mL/min. All pediatric subjects (n=36) had mean weight and CrCL of 16.0 kg and 195.64 mL/min, respectively. A covariate-adjusted two compartment model described the observed concentrations well (population model $R^2$, 87.0%; Bayesian model $R^2$, 96.5%). In the evaluation subsets, the model performed similarly well (population $R^2$, 84.0%; Bayesian $R^2$, 90.2%). The identified model serves well for population dosing and as a Bayesian prior for precision dosing.
Key points:

- A unified cefepime population pharmacokinetic model has been developed from adult and pediatric patients and evaluates well in independent populations.
- When paired with real time beta-lactam assays, precision dosing approach will optimize drug exposure and improve clinical outcomes.
1. Introduction

Cefepime is a commonly utilized antibiotic for nosocomial infections. Rising resistance, manifesting as increased cefepime minimum inhibition concentrations (MICs), has led to more frequent clinical failures [1, 2]. In order to advise clinical outcomes according to MIC, the Clinical and Laboratory Standards Institute (CLSI) updated the susceptibility breakpoints and then created a category of susceptible-dose dependent for MICs of 4 and 8 mg/L for Enterobacteriaceae spp. [3]. Achieving goal pharmacokinetic exposures to effectively treat these higher MICs can require a precision dosing approach.

Cefepime, like other β-lactams, has pharmacodynamic activity governed by ‘time-dependent’ activity. The fraction of time that the unbound drug concentration exceeds the MIC (fT>MIC) for the dosing interval is the pharmacokinetic/pharmacodynamic (PK/PD) efficacy target for cefepime [4], and a target of 68%-74% has been established [5]. For the currently approved cefepime product and combination agents in the pipeline [6, 7], understanding cefepime disposition and variability is crucial to optimally treat the patients. Since inter- and intra-patient pharmacokinetic variability can impact the achievement of pharmacodynamic goals, understanding the precision of population dosing is important. Further, to fully realize precision dosing, individualized models (e.g. Bayesian models) are needed. Once developed, these models will form the basis for adaptive feedback and control strategies when paired with real time drug assays.

The purpose of this study was to: 1) develop and evaluate a unified cefepime population PK model for adult and pediatric patients, and 2) construct an individualized model that can be utilized to deliver precision cefepime dosing.
2. Material and methods

2.1 Study Populations

Data from four clinical cefepime PK studies representing unique groups of patients were compiled. Subject demographics and study methodologies have been previously described [8-11]. In brief, populations represented were febrile neutropenic adults with hematologic malignancies [10, 11], those with critical illness [9] and children with presumed or documented bacterial infections [8]. For the two studies that evaluated adults with neutropenic fever, Sime et al. prospectively enrolled 12 patients receiving chemotherapy and/or stem cell transplant who subsequently developed febrile neutropenia and were administered maximum doses of cefepime [10]. A total of 53 cefepime plasma concentrations in presumably steady-state dosing intervals (third, sixth, and ninth) were analyzed for PK target attainment. Whited et al. prospectively studied similar patients (n=9) who were admitted to hematology-oncology services and were receiving cefepime at maximum dosage for febrile neutropenia [11]. Cefepime PK samples were obtained during steady state and analyzed for population parameters. Critically ill adults were studied by Roberts et al. as a prospective multinational PK study and included 14 patients who received cefepime [9]. Lastly, Reed et al. characterized cefepime PK in hospitalized pediatric patients (above 2 months of age) who received cefepime as monotherapy for bacterial infections [8]. For our study, only those who received intravenous cefepime were included for model development.

2.2 Model Building Populations

Adult (n=34) and partial pediatric (n=36) subjects were utilized for PK model building (Fig. 1) while model evaluation was performed with other datasets consisting of independent adult (n=25) and pediatric (n=12) patients. Pediatric patients from Reed et al. [8] were randomized into the model building or the evaluation dataset. All clinical patient level data included age, weight, and serum creatinine (SCr). An estimated creatinine clearance (CrCL) was calculated for each patient [12]. The Cockcroft Gault formula served as a standardized descriptor for elimination rate constant (Supplemental Fig. 1). This study was exempted by the Institutional Review Board at Midwestern University Chicago College of Pharmacy.

2.3 Pharmacokinetic Models
To construct the base PK models, the Nonparametric Adaptive Grid (NPAG) algorithm \[13, 14\] within the Pmetrics (Version 1.5.2) package \[14\] for R \[15\] was utilized. Multiple physiologically relevant one- and two compartmental PK models were built and assessed. The one-compartment structural model included an intravenous cefepime dose into and parameterized total cefepime elimination \((K_e)\) from the central compartment \((V_c)\). The two-compartment model included additional parameterizations of intercompartmental transfer constants between central and peripheral compartments \((K_{CP} \text{ and } K_{PC})\). In candidate models, total cefepime elimination was explored according to full renal and partial renal clearance \((CL)\) models \[i.e. non-renal elimination \((K_e\text{Intcpt})\) and renal elimination descriptor \((K_e0\) vectorized as a function of glomerular filtration estimates)\] \[6, 16\].

Assay error was included into the model using a polynomial equation in the form of standard deviation \((SD)\) as a function of each observed concentration, \(Y\) \[i.e. SD = C_0 + C_1 \cdot Y\]. Observation weighting was performed using gamma \[i.e. error = SD \cdot \text{gamma}\], a multiplicative variance model to account for extra process noise. Gamma was initially set at 4 with \(C_0\) and \(C_1\) equal to 0.5 and 0.15, respectively.

Covariate relationships were assessed using the ‘PMStep’ function in Pmetrics by applying stepwise linear regressions (forward selection and backwards elimination) of all covariates on PK parameters. Additionally, \textit{a priori} analyses examined the effect of covariates (e.g. weight, CrCL) on cefepime elimination rate constant \((K_e)\) because of their known importance in describing cefepime disposition \[6, 17, 18\]. Weight and CrCL were standardized to 70 kilogram \((kg)\) and 120 mL/min, respectively. Further, an allometric scaler was applied to standardized weight \[i.e. (quotient of weight in kg divided by 70 kg raised to the 0.75\textsuperscript{th} power)\] as a covariate adjustment to \(K_e\) (Supplemental Fig. 1). Ultimate model retention was governed according to criteria described below.

The best structural and error model was identified by the change in objective function value \((OFV)\) calculated as differences in \(-2\log\text{-likelihood} \((-2LL)\), with a reduction of 3.84 in OFV corresponding to \(p <0.05\) based on chi-square distribution and one degree of freedom. Further, the best-fit model was selected based on rule of parsimony and the lowest Akaike’s information criterion \((AIC)\) scores. Goodness-of-fit of
the competing models were evaluated by regression on observed vs. predicted plots, coefficients of
determination, and visual predictive checks. Predictive performance was assessed using bias and
imprecision in both population and individual prediction models. Bias was defined as mean weighted
prediction error; imprecision was defined as bias-adjusted mean weighted squared prediction error.
Posterior-predicted cefepime concentrations for each study subject was calculated using individual median
Bayesian posterior parameter estimates. Using Bayesian posterior-predicted concentrations (at every 0.2 h)
from the final model, noncompartmental analyses (NCA) were performed to estimate additional PK
parameters [i.e. half-life, clearance (CL)].

2.4 Model Evaluation
To evaluate the final adjusted model, the NPAG algorithm [13, 14] was employed to assess the
performance with separate data sets (Fig. 1). The population joint density from the final adjusted model
were employed as Bayesian prior for the randomly withheld pediatric and adult data. In the evaluation
process, structural model, model parameters, assay error, and observation weighting were unchanged.
Goodness-of-fit of the competing models were determined as described above.

2.5 Simulations and probability of target attainment (PTA)
Simulation was performed to examine the exposures predicted by the final adjusted PK model [14, 19].
Covariate values were fixed per subject based on arithmetic means of observed weight and CrCL for adult
and pediatric in the model development populations. Monte Carlo sampling was performed from the
multimodal, multivariate distribution of parameters with limits fixed by the bounded parameter space.
Maximum dosing regimens were simulated for adult and pediatric populations: 2 grams every 8 hours (h)
infused over 0.5 h and 50 mg/kg every 8 h infused over 0.5 h. Protein binding of 20% (i.e. 80% free
fraction of total cefepime dose) was accounted for in predicting 48-h cefepime concentrations [6]. For each
scenario, 2,000 parameter sets or patients were generated. PK/PD target of $T_{\text{MIC}} \geq 68\%$ was utilized
across doubling MICs of 0.25-32 mg/L over the first 48 h of cefepime therapy [5]. Estimates are provided
from the first 24 h of simulations as timely administration of effective antimicrobial agents is associated
with increased survival [20].
3. Results

3.1 Demographics

A total of 70 clinically diverse subjects, contributing 683 cefepime concentrations, were included in this study (n=45 subjects for model development; n=25 subjects for evaluation). Adult subjects (n=34) had a mean weight [SD] of 82.7 kg [21.5] and mean CrCL [SD] of 106.7 mL/min [58.4]. For the pediatric cohort (n=36), means [SD] of weight and CrCL were 16.0 kg [16.1] and 195.64 mL/min [40.5], respectively. Adult subjects ranged in age from 22-82 years (mean, 55.4 years) while pediatric subjects ranged from approximately 2 months to 16 years of age (mean, 3.9 years).

3.2 PK model selection, parameters, and evaluation

A total of 604 cefepime observations were available for analysis. Cefepime concentrations ranged from 0.5-249.7 μg/mL. The base one- and two-compartment models (no covariate adjustment) produced reasonable fits for observed and Bayesian posterior-predicted cefepime concentrations (R²=84.7% and 85.2%, respectively), but population estimates were unsatisfactory (R²=22.7% and 27.8%, respectively) (Table 1). After standardizing weight (to 70 kg) without an allometric scaler in the base two-compartment model, fits for both population and Bayesian posterior estimates against the observed data improved (R²=60.7% and 96.5%, respectively; OFV change, 4). Bias and imprecision for Bayesian posterior fits were -0.18 and 1.12, respectively. When covariates (i.e. weight to volume of distribution and Ke; CrCL to Ke) and the allometric scaler were applied in the two-compartment model, Bayesian posteriors fit well (R²=96.5%; Fig. 2 right) with low bias and imprecision (-0.15 and 1.07, respectively), and population PK model produced good fits of the observed cefepime concentrations (R²=87.0%, bias=0.53, imprecision=7.75; Fig. 2 left). The OFV change from the weight-adjusted, two-compartment model to final model was significant at -34 (p<0.05) (Table 1). Thus, a two-compartment model with weight and CrCL as covariate adjustment and allometric scaling was selected as the final PK model. The population parameter values from the final PK model are summarized in Table 2. Structural model and differential equations that define the population PK are listed in Supplemental Materials. The population parameter
value covariance matrix can be found in Table 3. For the evaluation subset, Bayesian priors resulted in reasonably accurate and precise predictions (population $R^2=84.0\%$, Bayesian $R^2=90.2\%$; Fig. 3).

### 3.3 Simulation and PTA

Results of PTA analysis are shown in Table 4 and Figure 4 for the first 24 h of therapy. Two cefepime regimens were utilized to simulate PTA for adult and pediatric subjects. Cefepime dosage of 2 grams every 8 h infused over 30 minutes produced PTAs of $>90\%$ for MICs of 0.25-2 mg/L while a more than 2-fold drop of PTA was observed from MIC of 4 mg/L to 8 mg/L. The second cefepime regimen of 800 mg every 8 h infused over 30 minutes achieved PTA of $>90\%$ only at an MIC of 0.25 mg/L, PTA at 81.1\% at MIC of 0.5 mg/L and performs poorly across subsequent higher doubling MICs.
4. Discussion

This study created a population and individual PK model for adult and pediatric patients and can serve as a Bayesian prior for precision dosing. When paired with a real time assay for cefepime, this model will allow for precise and accurate predictions of cefepime disposition via adaptive feedback control. In the absence of real time assays, these cefepime PK parameters facilitate more accurate population-based dosing strategies. Previous work by Rhodes et al. has shown an absolute difference of approximately 20% in survival probability across the continuum of achieving 0-100% $f_{T>MIC}$ in adult patients with Gram-negative bloodstream infections, thus understanding the dose and re-dosing interval necessary to achieve optimal PK exposures should greatly improve clinical outcomes for patients treated with cefepime [5].

Individualized dosing and therapeutic drug monitoring (TDM) of $\beta$-lactam antibiotics (e.g. cefepime) are critically important to achieving optimal drug exposure (i.e. optimal $f_{T>MIC}$ as the PK/PD target) and improving clinical outcomes [4, 21, 22]. Precision medicine has been named as a major focus for the National Heath Institute with $215$ million invested [23], yet precision medicine has mostly focused on genomic differences [24, 25]. Precision dosing is an important facet of precision medicine, and renewed efforts in precision dosing in the real-world setting are being pursued [26]. Cefepime is a highly relevant example. While rigorous reviews and analyses are conducted during the development phase of an antibiotic, dose optimization is far less ideal for the types of patients who ultimately receive the drug. This is highlighted by the fact that although cefepime-associated neurotoxicity is rare. This serious and potentially life-threatening adverse event has been increasingly reported, yet few strategies exist for optimizing and delivering precision exposures [27, 28]. Lamoth et al. conducted a study to investigate the PK/PD threshold for cefepime-associated neurotoxicity [29]. Their final model predicted that a cefepime trough concentration of $\geq22$ mg/L ($p=0.05$) has a 50% probability of predicating neurotoxicity. In contrast, Rhodes et al. performed simulations from literature data and found that such threshold by Lamoth et al. is suboptimal as a predictive trough cutpoint [30]. Moreover, high intercorrelation amongst all PK parameters (i.e. $\text{AUC}_{0-\infty}$, $C_{\text{MAX}}$, and $C_{\text{MIN}}$) was observed by Rhodes et al., suggesting more work is needed to establish PK/TD profile for cefepime. Similarly, Huwyler et al. found a different trough ($\geq35$ mg/L) as the predictive cefepime neurotoxic threshold, contrasting that of Lamoth et al. [31]. In addition to
complications by these less-than-ideal PK/TD data, clinicians are left to treat patients with extreme age
differences, organ dysfunction, and comorbid conditions affect antibiotic PK/PD [22]. These ‘real-world’
patients are often under-represented, and thus not well understood, from a PK/PD and PK/TD standpoint
during the drug approval process. Bridging to the more typical patients that are clinically treated is
important and central to the mission of Precision Medicine. Findings of this study can be used to guide
cefepime dosing in these ‘real-world’ patients.

Several other studies have reviewed population cefepime PK. Sime et al. observed that patients with
neutropenic fever had a mean clearance (CL) of 8.6 L/h, mean elimination half-life of 2.7 h [10]. Nicasio
et al. studied 32 critically ill patients receiving intravenous cefepime for ventilator-associated pneumonia
and observed that means of total CL and elimination half-life (as calculated from mean total CL and mean
volume of distribution) were 7.6 L/h and 2.0 h, respectively [32]. The NCA conducted (in model
development adult population) in our study produced similar results (CL, 7.59 L/h; elimination half-life,
2.98 h). Shoji et al. studied 91 pediatric patients and observed a mean of CL of approximately 1.86 L/h and
a mean elimination half-life of 3.5 h (23). In our pediatric population, means of CL and elimination half-
life were 3.1 L/h and 3.0 h, respectively. Our simulation findings are similar to those of Shoji et al. that a
maximum pediatric cefepime dosing of 50 mg/kg every 8 h or 12 h did not adequately achieve optimal
exposure to target higher MICs. Other studies also performed simulation for PTA with different cefepime
regimens and renal functions, Tam et al. found that with a PD target of 67%, 2 grams every 8 h (30-minute
infusion) achieved approximately 90% PTA for MIC of 8 mg/L in patients with CrCL of 120 mL/min while
2 grams every 12 h achieved barely above 80% PTA for MIC of 4 mg/L in the same population [33].
Nicasio et al. also conducted a simulation using a PD target of 50% in the critically ill with varying renal
function. Maximum recommended dosage (2 grams every 8 h) in patients with CrCL between 50-120
mL/min achieved a PTA of 78.1% at MIC=16 mg/L; however, when the same regimen was infused over
0.5 h, the PTA achieved was significantly lower [32]. Collectively, these findings suggest that cefepime
exposure is highly variable and may be clinically suboptimal in a large number of patients commonly
treated with cefepime. These findings support the need of precision dosing and TDM for β-lactam
antibiotics to reach optimal PK/PD target given the high variability in drug exposures.
Our study is not without limitations. Although a relatively large and diverse cohort was included in model development and evaluation, we did not specifically assess certain subgroups such as patients with morbidly obesity, severe renal dysfunction, etc. These conditions may require patient-specific models.

Secondly, many studies to date included “real-world” patients with various disease states (e.g. neutropenic fever, renal failure, sepsis, etc.); however, all studies were conducted under research protocol where doses, administration times, etc. were all carefully confirmed. Additional efforts will be needed to evaluate performance in clinical contexts.
5. Conclusions

A unified population model for cefepime in adults and pediatric populations was developed and demonstrated excellent performance on evaluation. Current cefepime dosages are often suboptimal, and population variability is high. Precision dosing approaches and real time assays are needed for cefepime to optimize drug exposure and improve clinical outcomes.
References

1. Bhat SV, Peleg AY, Lodise TP, Jr., Shutt KA, Capitano B, Potoski BA, et al. Failure of current cefepime breakpoints to predict clinical outcomes of bacteremia caused by gram-negative organisms. Antimicrob Agents Chemother. 2007 Dec;51(12):4390-5.

2. Rhodes NJ, Liu J, McLaughlin MM, Qi C, Scheetz MH. Evaluation of clinical outcomes in patients with Gram-negative bloodstream infections according to cefepime MIC. Diagn Microbiol Infect Dis. 2015 Jun;82(2):165-71.

3. CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 26th ed. CLSI supplement M100.Waye, PA: Clinical and Laboratory Standards Institute; 2016.

4. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis. 1998 Jan;26(1):1-10; quiz 1-2.

5. Rhodes NJ, Kuti JL, Nicolau DP, Van Wart S, Nicasio AM, Liu J, et al. Defining Clinical Exposures of Cefepime for Gram-Negative Bloodstream Infections That Are Associated with Improved Survival. Antimicrob Agents Chemother. 2015 Dec 14;60(3):1401-10.

6. Hospira, Inc. Maxipine (cefepime hydrochloride) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050679s036lbl.pdf. Revised June 2012. Accessed August 16, 2019.

7. Daigle D, Hamrick J, Chatwin C, Kurepina N, Kreiswirth BN, Shields RK, et al. Cefepime/VNRX-5133 Broad-Spectrum Activity Is Maintained Against Emerging KPC- and PDC-Variants in Multidrug-Resistant K. pneumoniae and P. aeruginosa. Open Forum Infect Dis. 2018 Nov;5(Suppl 1):S419-20.

8. Reed MD, Yamashita TS, Knupp CK, Veazey JM, Jr., Blumer JL. Pharmacokinetics of intravenously and intramuscularly administered cefepime in infants and children. Antimicrob Agents Chemother. 1997 Aug;41(8):1783-7.

9. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, et al. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis. 2014 Apr;58(8):1072-83.

10. Sime FB, Roberts MS, Tiong IS, Gardner JH, Lehman S, Peake SL, et al. Adequacy of high-dose cefepime regimen in febrile neutropenic patients with hematological malignancies. Antimicrob Agents Chemother. 2015 Sep;59(9):5463-9.

11. Whited L, Grove M, Rose D, Rhodes NJ, Scheetz MH, O'Donnell JN, et al. Pharmacokinetics of Cefepime in Patients with Cancer and Febrile Neutropenia in the Setting of Hematologic Malignancies or Hematopoietic Cell Transplantation. Pharmacotherapy. 2016 Sep;36(9):1003-10.

12. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

13. Leary RJ, Roger & Schumitzky, Alan & Van Guilder, M. . . An adaptive grid non-parametric approach to pharmacokinetic and dynamic (PK/PD) population models. Proceedings of the IEEE Symposium on Computer-Based Medical Systems. February, 2001:389-94.

14. Neely MN, van Guilder MG, Yamada WM, Schumitzky A, Jelliffe RW. Accurate detection of outliers and subpopulations with Pmetrics, a nonparametric and parametric pharmacometric modeling and simulation package for R. Ther Drug Monit. 2012 Aug;34(4):467-76.

15. R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

16. Okamoto MP, Nakahiro RK, Chin A, Bedikian A. Cefepime clinical pharmacokinetics. Clin Pharmacokinet. 1993 Aug;25(2):88-102.
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17. Kovarik JM, ter Maaten JC, Rademaker CM, Deenstra M, Hoepelman IM, Hart HC, et al. Pharmacokinetics of cefepime in patients with respiratory tract infections. Antimicrob Agents Chemother. 1990 Oct;34(10):1885-8.

18. Georges B, Conil JM, Seguin T, Dieye E, Cougot P, Decun JF, et al. Cefepime in intensive care unit patients: validation of a population pharmacokinetic approach and influence of covariables. Int J Clin Pharmacol Ther. 2008 Apr;46(4):157-64.

19. Goutelle S, Bourguignon I, Maire PH, Van Guilder M, Conte JE, Jr., Jelliffe RW. Population modeling and Monte Carlo simulation study of the pharmacokinetics and antituberculosis pharmacodynamics of rifampin in lungs. Antimicrob Agents Chemother. 2009 Jul;53(7):2974-81.

20. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006 Jun;34(6):1589-96.

21. Ambrose PG, Bhavnani SM, Rubin CM, Louie A, Gumbo T, Forrest A, et al. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. Clin Infect Dis. 2007 Jan 1;44(1):79-86.

22. Huttner A, Harbarth S, Hope WW, Lipman J, Roberts JA. Therapeutic drug monitoring of the beta-lactam antibiotics: what is the evidence and which patients should we be using it for? J Antimicrob Chemother. 2015 Dec;70(12):3178-83.

23. United States, Office of the Press Secretary. "FACT SHEET: President Obama's Precision Medicine Initiative". January 30, 2015, obama whitehouse.archives.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative. The White House. 2015.

24. Ginsburg GS, Phillips KA. Precision Medicine: From Science To Value. Health Aff (Millwood). 2018 May;37(5):694-701.

25. Gameiro GR, Sinkunas V, Liguori GR, Auler-Junior JOC. Precision Medicine: Changing the way we think about healthcare. Clinics (Sao Paulo). 2018 Dec 3;73:e723.

26. Precision Dosing: Defining the Need and Approaches to Deliver Individualized Drug Dosing in the Real-World Setting. Food and Drug Administration White Oak Campus. U.S. Food and Drug Administration. 2019; 2019.

27. FDA Drug Safety Communication: Cefepime and risk of seizure in patients not receiving dosage adjustments for kidney impairment. Food and Drug Administration. 2016.

28. Appa AA, Jain R, Rakita RM, Hakimian S, Pottinger PS. Characterizing Cefepime Neurotoxicity: A Systematic Review. Open Forum Infect Dis. 2017 Fall;4(4):ofx170.

29. Lamoth F, Buclin T, Pascual A, Vora S, Bolay S, Decosterd LA, et al. High cefepime plasma concentrations and neurological toxicity in febrile neutropenic patients with mild impairment of renal function. Antimicrob Agents Chemother. 2010 Oct;54(10):4360-7.

30. Rhodes NI, Kuti JL, Nicolau DP, Neely MN, Nicasio AM, Scheetz MH. An exploratory analysis of the ability of a cefepime trough concentration greater than 22 mg/L to predict neurotoxicity. J Infect Chemother. 2016 Feb;22(2):78-83.

31. Huwyler T, Lenggenhager L, Abbas M, Ing Lorenzini K, Hughes S, Huttner B, et al. Cefepime plasma concentrations and clinical toxicity: a retrospective cohort study. Clin Microbiol Infect. 2017 Jul;23(7):454-9.

32. Nicasio AM, Ariano RE, Zelenitsky SA, Kim A, Crandon JL, Kuti JL, et al. Population pharmacokinetics of high-dose, prolonged-infusion cefepime in adult critically ill patients with ventilator-associated pneumonia. Antimicrob Agents Chemother. 2009 Apr;53(4):1476-81.
Tam VH, McKinnon PS, Akins RL, Drusano GL, Rybak MJ. Pharmacokinetics and pharmacodynamics of cefepime in patients with various degrees of renal function. Antimicrob Agents Chemother. 2003 Jun;47(6):1853-61.
Table 1. Population Pharmacokinetic Model Builds and Comparisons

| Models   | -2LL | AIC | Change in OFV | Population Bias | Imprecision | R²  | Bayesian Bias | Imprecision | R²  |
|----------|------|-----|---------------|-----------------|--------------|-----|---------------|--------------|-----|
| Base one | 3223 | 3229| -             | 0.82            | 21.3         | 0.23| -0.05         | 1.66         | 0.847|
| Base two | 2994 | 3004| 239           | 1.91            | 41.9         | 0.28| 0.70          | 3.87         | 0.852|
| Two *    | 2990 | 3000| 4             | 2.17            | 68.4         | 0.61| -0.18         | 1.12         | 0.965|
| Two **   | 2966 | 2978| 34            | 0.53            | 7.75         | 0.87| -0.15         | 1.07         | 0.965|

*weight adjusted
**weight adjusted and allometric scaler applied
Table 2. Population PK Parameter Estimates from the Final Model

| Parameter          | Median | SD   | CV%  | Shrinkage% |
|--------------------|--------|------|------|------------|
| V0 (L)             | 11.17  | 2.52 | 22.66| 14.7       |
| KeIntcpt (h⁻¹)     | 0.506  | 0.29 | 59.24| 15.1       |
| Ke0 (h⁻¹)          | 0.236  | 0.71 | 133.95| 6.8        |
| KCP (h⁻¹)          | 1.716  | 1.53 | 68.82| 7.7        |
| KPC (h⁻¹)          | 1.502  | 1.19 | 60.63| 8.8        |
Table 3. Population Parameter Value Covariance Matrix for the Final Model

|        | $V_0$ | $K_e$ Intcpt | $K_e$ O | $K_{CP}$ | $K_{PC}$ |
|--------|-------|--------------|---------|----------|----------|
| $V_0$  | 6.366 |              |         |          |          |
| $K_e$ Intcpt | -0.106 | 0.085       | -       | -        |          |
| $K_e$ O   | -0.238 | -0.152     | 0.499   | -        | -        |
| $K_{CP}$ | -1.576 | 0.005       | 0.145   | 2.354    | -        |
| $K_{PC}$ | -0.680 | 0.027       | -0.188  | 1.441    | 1.414    |
Table 4. Probability of Target Attainment at Different Cefepime MICs (Maximum Recommended Dosages for Adults and Pediatrics) for the First 24 Hours of Therapy

| Cefepime regimen | Cefepime MICs (mg/L) |
|------------------|----------------------|
| Dose (mg)        | Dosing interval (hr) | Infusion time (hr) | 0.25 | 0.5 | 1   | 2   | 4   | 8   | 16  | 32  |
| 2000             | 8                    | 0.5                | 100% | 99.5% | 97.6% | 94.3% | 78.5% | 36.6% | 5.5% | 0.3% |
| 800              | 8                    | 0.5                | 93.6 | 81.1% | 75.2% | 58.8% | 33.1% | 11.4% | 1.7% | 0.3% |
Model Development:
Data 1, n = 9 [1]
Data 2 partial, n = 24 [2]

Model Evaluation:
Data 3, n = 12 [3]
Data 4, n = 13 [4]
Data 2 partial, n = 12 [2]
1. Whited L, Grove M, Rose D, Rhodes NJ, Scheetz MH, O'Donnell JN, et al. Pharmacokinetics of Cefepime in Patients with Cancer and Febrile Neutropenia in the Setting of Hematologic Malignancies or Hematopoietic Cell Transplantation. Pharmacotherapy. 2016 Sep;36(9):1003-10.
2. Reed MD, Yamashita TS, Knupp CK, Veazey JM, Jr., Blumer JL. Pharmacokinetics of intravenously and intramuscularly administered cefepime in infants and children. Antimicrob Agents Chemother. 1997 Aug;41(8):1783-7.
3. Sime FB, Roberts MS, Tiong IS, Gardner JH, Lehman S, Peake SL, et al. Adequacy of high-dose cefepime regimen in febrile neutropenic patients with hematological malignancies. Antimicrob Agents Chemother. 2015 Sep;59(9):5463-9.
4. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, et al. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis. 2014 Apr;58(8):1072-83.
Figure 2. Goodness-of-fit Plots for Best-Fit Population Cefepime Model

Solid line denotes linear regression; dashed line denotes reference line
For population predicted (blue), $R^2=0.87$, slope=0.946 (95% CI, 0.912 to 0.981), bias=0.529, imprecision=7.75; for individual predicted (red), $R^2=0.965$, slope=1.01 (95% CI, 0.996 to 1.03), bias=-0.148, imprecision=1.07
Figure 3. Goodness-of-fit Plots for Evaluation of Population Cefepime Model

Solid line denotes linear regression; dashed line denotes reference line
For population predicted (blue), $R^2=0.84$, slope=1.02 (95% CI, 0.967 to 1.08); for individual predicted (red), $R^2=0.902$, slope=0.947 (95% CI, 0.908 to 0.985)
Figure 4. Probability of Target Attainment at Different Cefepime MICs
Supplementary Materials

Differential equations for two-compartment population PK model with covariate adjustments are:

\[
\frac{dX_1(t)}{dt} = \text{RateIV}(t) - (K_{CP} + K_e) \cdot X_1 + K_{PC} \cdot X_2
\]

\[
\frac{dX_2(t)}{dt} = K_{CP} \cdot X_1 - K_{PC} \cdot X_2
\]

\[
V_c = V_0 \cdot \left(\frac{\text{weight}}{70}\right)
\]

\[
K_e = (K_e \text{Intcpt} + \left(\frac{\text{CrCL}}{120}\right) \cdot K_e 0) \cdot \left(\frac{\text{weight}}{70}\right)^{-0.25}
\]

where $V_c$ is the central cefepime volume of distribution, $K_e$ is the elimination rate constant from the central compartment (h\(^{-1}\)), $K_{CP}$ is the rate constant from central to peripheral compartment (h\(^{-1}\)), and $K_{PC}$ is the rate constant from peripheral to central compartment (h\(^{-1}\)).