

Population Pharmacokinetics of High-Dose, Prolonged-Infusion Cefepime in Adult Critically Ill Patients with Ventilator-Associated Pneumonia[∇]

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A population pharmacokinetic model of cefepime was constructed from data from adult critical care patients with ventilator-associated pneumonia (VAP). A total of 32 patients treated with high-dose cefepime, 2 g every 8 h (3-h infusion) or a renal function-adjusted equivalent dose, were randomized into two groups—26 for the initial model and 6 for model validation. Serum samples of cefepime were collected at steady state. Nonparametric adaptive grid population modeling was employed using a two-compartment K_{slope} pharmacokinetic model relating the elimination rate constant (K_{10}) to renal function, as defined by creatinine clearance (CL_{CR}), and central distribution volume (V_1) to total body weight (TBW). The final model was described by the following equations: $K_{10} = 0.0027 \times CL_{CR} + 0.071 \text{ h}^{-1}$ and $V_1 = TBW \times 0.21 \text{ liter/kg}$. The median inter-compartmental transfer constants K_{12} and K_{21} were 0.780 h^{-1} and 0.472 h^{-1} , respectively. Using these median parameter estimates, the bias, precision, and coefficient of determination for the initial model were 11.3 $\mu\text{g/ml}$, 24.0 $\mu\text{g/ml}$, and 26%, respectively. The independent validation group displayed a bias, precision, and coefficient of determination of $-1.64 \mu\text{g/ml}$, 17.1 $\mu\text{g/ml}$, and 62%, respectively. Time-concentration profiles were assessed for various dosing regimens, using 5,000-patient Monte Carlo simulations. Among the regimens, the likelihoods of 2 g every 8 h (3-h infusion) achieving free drug concentrations above the MIC for 50% of the dosing interval were 91.8%, 78.1%, and 50.3% for MICs of 8, 16, and 32 $\mu\text{g/ml}$, respectively. This study provides a pharmacokinetic model capable of predicting cefepime concentrations in critically ill patients with VAP.

Cefepime is a fourth-generation parenteral cephalosporin with activity against gram-positive and gram-negative organisms, including *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (1, 6). Because of its broad coverage and favorable adverse event profile, cefepime is extensively used as an empirical antimicrobial therapy for serious infections in intensive care units (ICU). In patients with normal renal function, cefepime is typically dosed according to the manufacturer's recommendations: 1 g every 12 h in mild to moderate infections, 2 g every 12 h in severe infections, and 2 g every 8 h in neutropenic patients, all utilizing a 30-min infusion time.

With the rise of multidrug-resistant, gram-negative bacilli (10, 20), there is the potential for poor infection-related outcomes, particularly in high-risk patients, such as the critically ill whom are receiving mechanical ventilation. Moreover, various studies have illustrated that the manufacturer's recommended doses may fall short against less-susceptible gram-negative pathogens (2, 17, 23). This has led some investigators to explore or suggest alternative cefepime dosing strategies, including prolonged and continuous infusions (3, 4, 8, 22, 24). Like other β -lactams, cefepime displays time-dependent bactericidal activity whereby efficacy is optimized when free drug concentrations exceed the MIC for at least 50% of the dosing

interval (50% $fT > \text{MIC}$) (19). As a result of these pharmacodynamic characteristics, prolonging the infusion duration from the standard 30 min to 3 to 4 h or administering β -lactam antibiotics as continuous infusions over 24 h will increase the probability of pharmacodynamic target attainment at higher MICs (9, 11, 13, 18, 21, 24).

Recently at our 840-bed tertiary care hospital, the high prevalence of resistant organisms, including *P. aeruginosa*, as a cause of ventilator-associated pneumonia (VAP) led to the development of a clinical pathway incorporating high-dose, prolonged-infusion antibiotic regimens (14). In this pathway, cefepime is empirically administered as a 2-g dose every 8 h, with each dose infused over 3 h, or a renal function-adjusted equivalent dose. The current population pharmacokinetic analysis was conducted to demonstrate that this new cefepime dosing regimen was effectively achieving the intended concentration-time profiles in patients treated for VAP at our institution, with the goal of empirically achieving 50% $fT > \text{MIC}$ in the majority of patients infected with organisms harboring cefepime MICs of up to 32 $\mu\text{g/ml}$. The utility of this model not only allowed confirmation of dosing regimens in our patient population but also provided a means of estimating pharmacokinetic parameters for those patients receiving cefepime for the treatment of VAP who do not have concentration data available.

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MATERIALS AND METHODS

Patient population and setting. Blood sample collection was performed on patients who were admitted to the medical, surgical, or neurotrauma ICU at

Hartford Hospital between April 2007 and December 2007 and received cefepime as part of the VAP clinical pathway (approved by the Pharmacy and Therapeutics and Medical Executive Committees) (14). Hartford Hospital, located in Hartford, CT, is a 840-bed tertiary care hospital, consisting of two 12-bed medical ICUs, a 12-bed surgical ICU, a 12-bed cardiothoracic ICU, and an 18-bed neurotrauma ICU. When placed on the clinical pathway, patients empirically received vancomycin, tobramycin (or a fluoroquinolone if tobramycin was contraindicated), and high-dose cefepime (2 g every 8 h, infused over 3 h). Doses were adjusted for renal function by using the Cockcroft-Gault equation, without the application of weight for estimating creatinine clearance (CL_{CR}) (7). Cefepime doses were originally developed based on a 5,000-patient Monte Carlo simulation, applying previously published pharmacokinetic data from patients with various degrees of renal function (23). A waiver of consent for the collection of blood samples was granted by Hartford Hospital's Institutional Review Committee, since these data were part of an ongoing quality assurance assessment of the VAP pathway. All information was kept confidential and secured by the Center for Anti-Infective Research and Development, Hartford, CT, in compliance with the Health Insurance Portability and Accountability Act of 1996, and patient identifiers were destroyed after data analyses were complete. Inclusion criteria consisted of adult patients (≥ 18 years old) in the ICU, who were placed on the VAP clinical pathway and prescribed cefepime. Patients with severely impaired renal function requiring dialysis and those deemed poor candidates for blood collection were excluded.

Blood sampling. Blood samples (2 to 3 per patient) were collected from an *in situ* venous line in a nonanticoagulant tube after at least three consecutive doses of cefepime in order to ensure steady-state concentrations. The blood samples were collected immediately after infusion, at 3 to 7 h after the start of infusion, and prior to the next dose, when possible. Once collected, blood samples were immediately centrifuged, and the serum was stored at $-80^{\circ}C$ until drug analysis.

Analytic methods. Cefepime concentrations in human serum were determined using a validated high-performance liquid chromatography assay (4). Intraday and interday coefficients of variation for the low (2 mg/liter) and high (40 mg/liter) quality control samples were all $<6\%$.

Pharmacokinetic analysis. Population modeling of cefepime concentrations were performed using the nonparametric adaptive grid program in the MM-USC*PACK collection (5, 15). A two-compartment pharmacokinetic model with zero-order infusion and first-order elimination, applying creatinine clearance (CL_{CR}) as a function, was chosen based on log-likelihood values and Akaike's information criterion (25). The following parameters were estimated for each patient: volume of distribution in the central compartment (V_1 [liter/kg]), elimination rate constant (K_{10} [h^{-1}]), and intercompartmental transfer constants (K_{12}, K_{21} [h^{-1}]). Total body clearance (CL_T [liter/kg/h and liter/h]) was then derived from the above-described estimates. Demographic variables were used to

determine correlation with pharmacokinetic parameters. These variables included age, gender, ethnicity, body weight, APACHE II (*acute physiology and chronic health evaluation*) score on the day of cefepime sampling (12), and CL_{CR} . A K_{slope} population pharmacokinetic analysis was performed with CL_{CR} for the elimination rate parameter (K_{10}) according to the following equation: $K_{10} = K_i + K_s \times CL_{CR}$, where K_i is the intercept, K_s is the slope parameter, and CL_{CR} was calculated using an adjusted Cockcroft-Gault equation that excluded weight from the numerator and denominator [$CL_{CR} = (140 - \text{age})/\text{serum creatinine}$; the result of this equation is multiplied by 0.85 for females]. Body weight was considered a function of V_1 . The overall assay error variance model with a gamma function (γ) was determined by fitting a first-order polynomial to the plot of the assay standard deviations (SD) versus the measured cefepime concentrations on an interday basis, generating the following formula: $SD = \gamma(0.0224 + 0.056 \times C)$, where C was concentration and γ was identified to be 1.07. The modeling procedure weighted the individual concentrations in the serum by the reciprocal of the assay error variance pattern, giving more influence to the precisely measured cefepime concentrations and less weight to the less-precise values. Measures of predictive performance and coefficients of determination were applied to observed-predictive plots. An independent group of randomly selected patients ($n = 6$) was withheld from the initial model-building process in order to test model bias and precision.

Pharmacodynamic analysis. A 5,000-patient Monte Carlo simulation (Crystal Ball version 2000; Decisioneering Inc., Denver, CO) using an open two-compartment model was conducted using the pharmacokinetic parameter median estimates, dispersion, and a lower triangular covariance matrix acquired from the final model to generate steady-state concentration-time profiles for various cefepime dosing regimens. Protein binding of 15% was applied by multiplying the cefepime dose by the fraction unbound before performing each simulation. The probability of target attainment (PTA) was calculated for each dosing regimen as a function of increasing MIC dilutions, using $50\% fT > MIC$ as the pharmacodynamic target (19). Cefepime dosage regimens, including package insert-recommended dosing as well as higher-dose prolonged 3-h infusion regimens, were simulated for three categories of renal function (based on CL_{CR} ranges), as follows: 50 to 120 ml/min, 30 to 49 ml/min, and 10 to 29 ml/min, using the K_{10} equation described above.

Statistical analysis. Dichotomous variables (e.g., gender, combination therapy, type of infection) were compared using a chi-square test. Continuous variables were compared using Student's *t* test or the Mann-Whitney U test, where appropriate. An a priori *P* value of <0.05 was statistically significant. All statistical tests were conducted on SigmaStat statistical software version 2 (SPSS Inc., Chicago, IL).

TABLE 1. Comparative demographics of patients receiving cefepime for VAP between the experimental and validation groups

Characteristic ^a	Experimental group (<i>n</i> = 26)			Validation group (<i>n</i> = 6)		
	Mean \pm SD	Median (range)	No. (%) of patients	Mean \pm SD	Median (range)	No. (%) of patients
Continuous variables						
Age	57.0 \pm 21.3	60.5 (19–91)		62.0 \pm 8.3	63.5 (49–72)	
Wt (kg)	84.0 \pm 23.2	78.6 (50.4–158.4)		86.9 \pm 15.7	85.4 (70.5–106.8)	
APACHE II score ^b	19.5 \pm 4.6	19 (11–29)		18.3 \pm 5.0	16.5 (15–28)	
SCr (mg/dl)	0.9 \pm 0.4	0.8 (0.4–2.3)		1.0 \pm 0.5	0.9 (0.4–1.8)	
CL_{CR} (ml/min) ^c	100.5 \pm 40.7	97.5 (26.1–186.7)		93.7 \pm 56.2	80.7 (40.6–193.4)	
Dichotomous variables						
Male gender			17 (65)			4 (67)
ICU type						
SICU			13 (50)			3 (50)
NTICU			13 (50)			3 (50)
Concomitant treatment with:						
Tobramycin			19 (73)			5 (83)
Vancomycin			22 (85)			5 (83)
Fluoroquinolone			4 (15)			0 (0)
Tobramycin + vancomycin			18 (69)			5 (83)

^a SICU, surgical intensive care unit; NTICU, neurotrauma intensive care unit; SCr, serum creatinine; CL_{CR} , creatinine clearance.

^b APACHE II score was measured at the time of the first blood sample from the patient.

^c CL_{CR} was calculated using the Cockcroft-Gault equation, independent of weight.

TABLE 2. Pharmacokinetic parameters of the cefepime population model^a

Parameter	Mean	Median	SD
K_i (h^{-1})	0.094	0.071	0.06
K_S (h^{-1})	0.006	0.003	0.011
K_{12} (h^{-1})	1.337	0.78	1.023
K_{21} (h^{-1})	1.046	0.472	1.082
V_1 (liter/kg)	0.263	0.206	0.187

^a $K_{10} = K_i + (K_S \times CL_{CR})$. CL_T , total body clearance; K_i , y-intercept constant; K_S , slope constant; K_{12} , intercompartmental transfer rate constant from the central to the peripheral compartment; K_{21} , intercompartmental transfer rate constant from the peripheral to the central compartment; V_1 , volume of distribution of the central compartment.

RESULTS

Population demographics. Of the 32 total patients (88 collected serum samples), 26 patients (72 serum samples) were used to develop the cefepime population pharmacokinetic model (experimental group). The six remaining patients (16 collected serum samples) were used to validate the model (validation group). Not all patients had three blood samples collected, due to nursing shift changes or deterioration in the patient's clinical status. No significant differences were observed among the patient characteristics (Table 1). APACHE II scores were similarly high, suggesting that both groups of patients were severely ill at time of blood sample collection. One patient placed on the VAP pathway actually had an intra-abdominal infection, but the pharmacokinetics of this patient was similar to that of the others and, therefore, was kept in the analysis. High-dose cefepime of 2 g every 8 h (3-h infusion) or a dose consistent with renal adjustment was administered to 29 of the 32 critically ill patients (24 in the experimental group and 5 in the validation group); the remaining patients received package insert-recommended doses. In the experimental group, renal function was normal (CL_{CR} , 50 to 120 ml/min) in 22 patients and poor in four patients (three patients with CL_{CR} values of 30 to 49 ml/min and one patient with a CL_{CR} of 10 to 29 ml/min). Within the validation group, five patients had normal renal function, while one patient had a CL_{CR} between 30 and 49 ml/min. In addition to cefepime, tobramycin or a fluoroquinolone was used concurrently in 28 of the 32 patients. Most patients ($n = 24$) received tobramycin concomitantly with cefepime. No patient experienced adverse events attributed to the high-dose prolonged-infusion cefepime dosages.

TABLE 3. Covariance matrix in lower triangular form

Parameter	Covariance				
	K_i	K_S	K_{12}	K_{21}	V_1
K_i	0.0037				
K_S	-0.0001	0.0001			
K_{12}	-0.0370	0.0008	1.0466		
K_{21}	-0.0136	-0.0015	0.7208	1.1717	
V_1	0.0026	-0.0011	-0.0455	0.0346	0.0348

K_i , the y intercept of the elimination rate constant; K_S , the slope of the elimination rate constant; K_{12} , intercompartmental transfer rate constant from the central to the peripheral compartment; K_{21} , intercompartmental transfer rate constant from the peripheral to the central compartment; V_1 , volume of distribution of the central compartment.

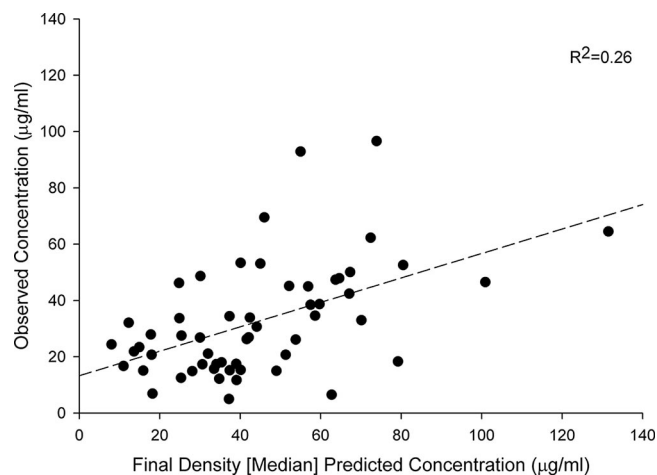


FIG. 1. Scatter plot of observed versus predicted cefepime concentrations, using the population pharmacokinetic model with covariates.

Pharmacokinetic parameters. Population pharmacokinetic parameters for cefepime for the 26 subjects are provided in Tables 2 and 3. Model building using log-likelihood values and Akaike's information criterion identified the optimal model, with K_{10} as a function of CL_{CR} , whereby $K_{10} = 0.071 + 0.0027 \times CL_{CR}$, and with V_1 as a function of total body weight (TBW), whereby $V_1 = TBW \times 0.21$ liter/kg. Other tested covariates had no identifiable influence on the pharmacokinetic parameters. Using these median parameter estimates, the bias, precision, and coefficient of determination for the initial model were 11.3 $\mu\text{g/ml}$, 24.0 $\mu\text{g/ml}$, and 26%, respectively (Fig. 1). Examining the data using the maximum a posteriori Bayesian estimation step as a reference, the bias, precision, and coefficient of determination for the model were 0.28 $\mu\text{g/ml}$, 7.39 $\mu\text{g/ml}$, and 98%, respectively. The independent validation group displayed a bias, precision, and coefficient of determination of -1.64 $\mu\text{g/ml}$, 17.1 $\mu\text{g/ml}$, and 62%, respectively (Fig. 2). This model was considered acceptable for predicting cefepime concentrations in our population. For comparisons with other research in the field, we also examined CL_T as a function of CL_{CR} and identified CL_T by using the formula $0.048 \times CL_{CR} + 1.2$. Our mean (SD) V_1 was 22.1 liters (6.1 liters), and our mean CL_T was 7.6 liters/h (3.3 liters/h). The clearance parameter was calculated as the product of the elimination rate parameter and V_1 .

Pharmacodynamic analysis. The probabilities of achieving a target of 50% $fT > MIC$ for cefepime with various dosing regimens in three groups of critically ill patients with various renal functions (CL_{CR} of 50 to 120, 30 to 49, and 10 to 29 ml/min) are shown in Fig. 3A to C. In patients with CL_{CR} of 50 to 120 ml/min, the high-dose, prolonged-infusion regimen (2 g every 8 h, as a 3-h infusion) achieved 91.8%, 78.1%, and 50.3% PTAs at MICs of 8 $\mu\text{g/ml}$ (susceptibility breakpoint), 16 $\mu\text{g/ml}$ (intermediate), and 32 $\mu\text{g/ml}$ (resistance breakpoint), respectively (Fig. 3A). Traditional 0.5-h infusion dosing regimens achieved significantly lower PTAs at these respective MICs. Among simulated patients with a CL_{CR} of 30 to 49 ml/min, a 2-g dose every 12 h infused over 3 h achieved PTAs of 93.8%, 79.8%, and 50.7% at MICs of 8 $\mu\text{g/ml}$, 16 $\mu\text{g/ml}$, and 32 $\mu\text{g/ml}$, respectively (Fig. 3B). The same dose administered as a 0.5-h

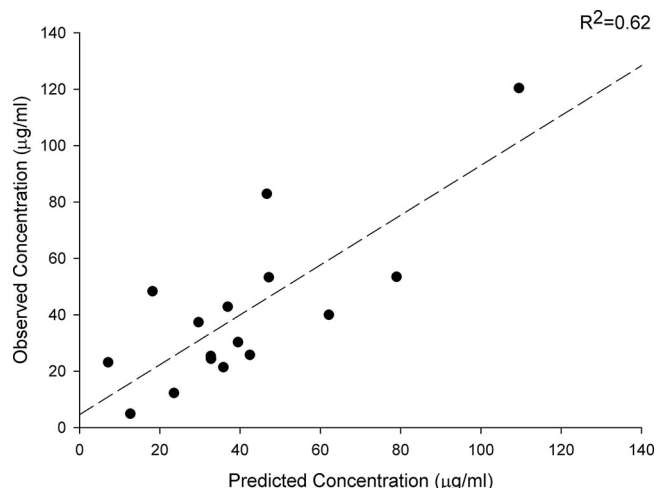


FIG. 2. Scatter plot of observed and predicted cefepime concentrations of the validation group, in accordance with the median parameter values of the pharmacokinetic population model.

infusion had slightly lower probabilities in this MIC range. In patients with CL_{CR} of 10 to 29 ml/min, all regimens achieved similar PTAs across the tested MIC range (Fig. 3C); however, no regimen achieved a PTA against MICs of 16 µg/ml and 32 µg/ml as high as those of the other CL_{CR} groups.

DISCUSSION

Herein, we created a population pharmacokinetic model to describe the concentration data obtained in patients receiving a high-dose, prolonged-infusion cefepime dosing regimen (2 g every 8 h, infused over 3 h) according to our hospital’s VAP pathway. The model was generated from critically ill patients predominately diagnosed with VAP. CL_{CR} and body weight were shown to be the covariates most influential of K₁₀ and V₁, thus enabling for the prediction of individual cefepime serum concentrations. A unique characteristic of our model-building process was the use of a randomly selected independent population of VAP patients for validation. Compared with the population pharmacokinetic model that influenced the development of our hospital’s VAP clinical pathway (23), our model had similar intercompartmental transfer and elimination rate constants. Although the intercept values and slopes are slightly different, the final regression equation published by Tam and colleagues (CL_T = 0.055 × CL_{CR} + 0.329; median values) (23) produced values of drug clearance at 50 ml/min and 100 ml/min that were virtually identical to ours: 3.1 versus 3.6 liters/h and 5.8 versus 6.0 liters/h, respectively.

Although there have been several cefepime population pharmacokinetic models developed in the literature (16, 23), there are few that specifically observe an adult critically ill patient population (8, 22), and only one has explored the utilization of a prolonged infusion of cefepime (24). The importance of observing this patient population is centered upon the patient heterogeneity and the large interindividual pharmacokinetic parameters within the ICU populations. Additionally, our population model is believed to be the first generated using a prolonged-infusion cefepime dose. Recently, another

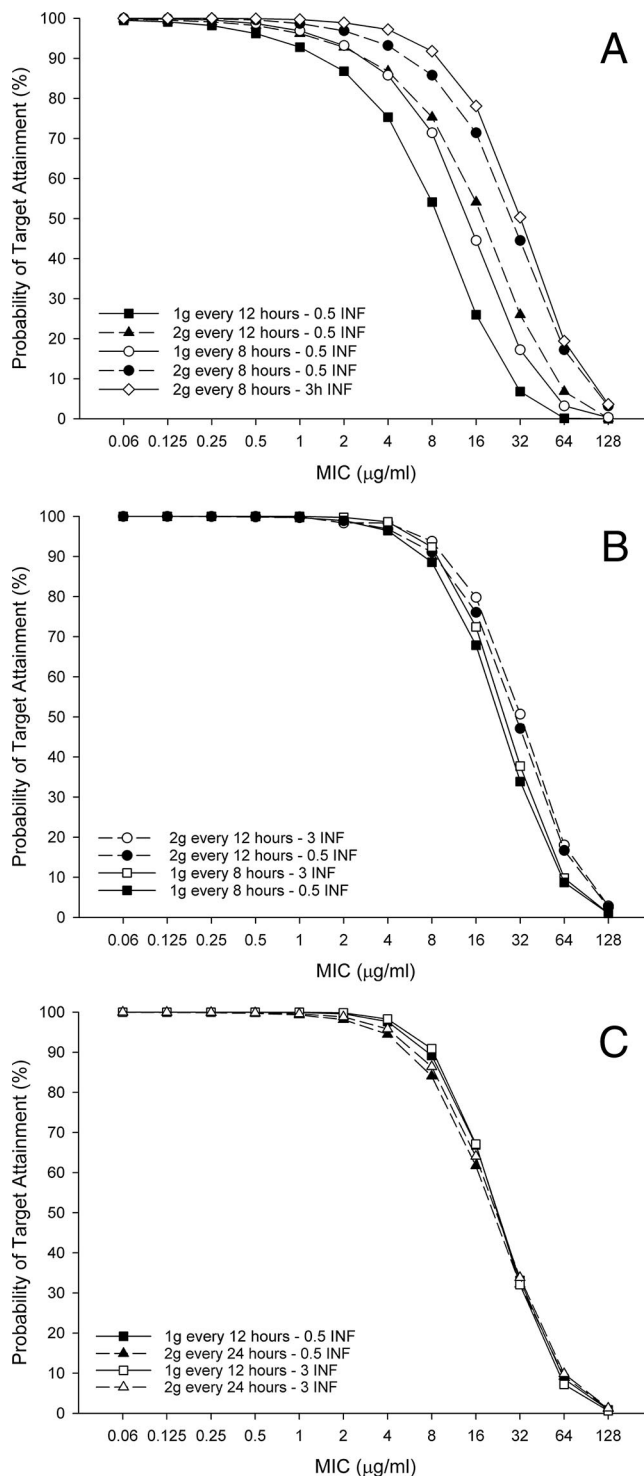


FIG. 3. PTA for cefepime regimens achieving 50% fT>MIC at various CL_{CR} levels: 50 to 120 ml/min (A), 30 to 49 ml/min (B), 10 to 29 ml/min (C). 0.5 INF, 0.5-h (30-min) infusion; 3h INF and 3 INF, 3-h infusion.

cefepime model with a similar population utilized doses of 4 g administered continuously over 24 h (8). Despite receiving a different dosing strategy and using a different parameter-covariant relationship (CL_T to serum creatinine), V₁ and CL_T

rates were comparable to those in our assessment. Other cefepime pharmacokinetic studies have observed mean V_1 and CL_T rates in critical care patients in the ranges of 23 to 27 liters and 6 to 7 liters/h, respectively, results which are similar to our mean values of 22.1 liters and 7.6 liters/h, respectively (17, 22, 23).

Because of the high prevalence of multidrug-resistant, gram-negative organisms as a cause of VAP in critically ill patients, the need for appropriate antibiotic therapy and optimal drug dosing is paramount. Although *P. aeruginosa* is considered susceptible to cefepime when the MIC is ≤ 8 $\mu\text{g/ml}$, a recent report noted increased mortality at this MIC in patients with bacteremia who were treated with standard cefepime dosages (2). Based on these data and the frequency of isolates nonsusceptible to this antibiotic at our institution, we employed a high-dose, prolonged-infusion (2 g every 8 h, with each dose infused over 3 h) aimed at achieving 50% $fT > \text{MIC}$ for pathogens with cefepime MICs of up to 32 $\mu\text{g/ml}$ (i.e., resistant). The actual pharmacokinetics observed in our patient population demonstrated that this dosage regimen did indeed achieve this pharmacodynamic exposure, with a high likelihood at MICs of 8 $\mu\text{g/ml}$, 16 $\mu\text{g/ml}$, and to a lower probability, 32 $\mu\text{g/ml}$. As shown in this study (Fig. 3A), as well as with other β -lactams, the prolonged-infusion regimen increased the $fT > \text{MIC}$ against organisms with higher MICs compared to that of traditional 30-min infusion (9, 11, 13, 18). The prolonged-infusion strategy also permits ample time for other drugs to be administered through the same intravenous line during the breaks in infusion time.

We also evaluated different dosing regimens based on CL_{CR} ranges to confirm that optimal exposure was maintained when doses were adjusted for renal dysfunction. Among simulated patients with a CL_{CR} of 30 to 49 ml/min, 2-g doses administered every 12 h as either 0.5- or 3-h infusions achieved nearly identical PTAs at higher MICs as those achieved by the max dose (2 g every 8 h, as 3-h infusion) in patients with normal CL_{CR} . This suggests that the benefit of the prolonged infusion lessens as a patient's renal function declines; we currently advocate the administration of a 2-g dose every 12 h (0.5-h infusion) empirically for VAP patients with a CL_{CR} of 30 to 49 ml/min at our hospital to target nonsusceptible organisms, reserving the prolonged infusion for those with normal renal function only. For patients with a CL_{CR} range of 10 to 29 ml/min, all of the simulated dosage regimens achieved similar PTAs, but none were able to maintain high probabilities of achieving 50% $fT > \text{MIC}$ at 16 $\mu\text{g/ml}$ (~66%) or 32 $\mu\text{g/ml}$ (~33%). We currently utilize a regimen of 1 g every 12 h (0.5-h infusion) for these patients, but further study is required to determine a dose that achieves higher PTAs at 50% $fT > \text{MIC}$ at 16 or 32 $\mu\text{g/ml}$ while retaining a low likelihood for toxicity.

In summary, this is the first cefepime population pharmacokinetic model developed and validated for critically ill patients with VAP treated with a high-dose, prolonged-infused regimen. These data demonstrate that cefepime dosed 2 g every 8 h as a 3-h prolonged infusion will improve the likelihood of pharmacodynamic target attainment over that of standard 30-min infusions. This report also provides suggestions for doses that are able to maintain these PTAs in patients with decreased renal function. Lastly, this covariate model will be useful in

predicting cefepime exposures in VAP patients who do not have concentration data available.

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