

Original Article



Population Pharmacokinetics and Monte Carlo Simulation of Cefepime in Critically Ill Patients with Hospital-Acquired/Ventilator-Associated Pneumonia

Hyeonji Seo ^{1,*}, Yong Kyun Kim ^{1,*}, Sunghoon Park ², Hwan-il Kim ², and Dong-Hwan Lee ³

¹Division of Infectious Diseases, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea

²Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea

³Department of Clinical Pharmacology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Korea

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ABSTRACT

Background: This study aimed to investigate the population pharmacokinetics (PK) profile and determine the optimal dosage regimen of cefepime in critically ill adult patients with hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP).

Materials and Methods: Population-PK models for cefepime were developed using a nonlinear mixed-effect modeling approach. The percentage of time within 24 h in which the free concentration exceeded the minimum inhibitory concentration (MIC) at a steady state ($50\%fT_{>MIC}$, $100\%fT_{>MIC}$, and $100\%fT_{>4\times MIC}$) for various combinations of dosage regimens and renal function was explored using Monte Carlo simulation.

Results: Twenty-one patients were prospectively enrolled in this study. Cefepime PK was best described using a two-compartment model in which creatinine clearance (CL_{CR}) through Cockcroft-Gault (CG) was a significant covariate for the total clearance of cefepime. The simulation results to determine the optimal cefepime dosing regimen for $50\%fT_{>MIC}$ as treatment target with $C_{min} < 20$ mg/L as safety target showed that a dosage regimen of 2 g through intravenous (IV) infusion every 12 h administered over 4 h was optimal at an MIC of 4 mg/L, rather than the currently recommended dosage regimen of 2 g administered through IV infusion every 8 h, in patients with normal renal function ($CL_{CR} = 90 - 130$ mL/min). For a treatment target of $100\%fT_{>MIC}$ with $C_{min} < 35$ mg/L as a safety target, a dosage regimen of 0.75 g administered through continuous infusion over 24 h would be sufficient at an MIC equal to or less than 8 mg/L in patients with renal dysfunction ($CL_{CR} = 10 - 30$ mL/min).

Conclusion: Our results suggest that clinicians should consider renal function and potential neurotoxicity when deciding the dosing regimen of cefepime in critically ill patients with HAP or VAP. Therapeutic drug monitoring (TDM) to adjust cefepime trough levels may be useful to improve clinical outcomes and reduce cefepime neurotoxicity.

Keywords: Cefepime; Population pharmacokinetics; Hospital-acquired pneumonia; Ventilator-associated pneumonia; Monte Carlo simulation

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Corresponding Author:

Dong-Hwan Lee, MD, PhD

Department of Clinical Pharmacology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang 14068, Korea.

Tel: +82-31-380-4778, Fax: +82-31-380-4797

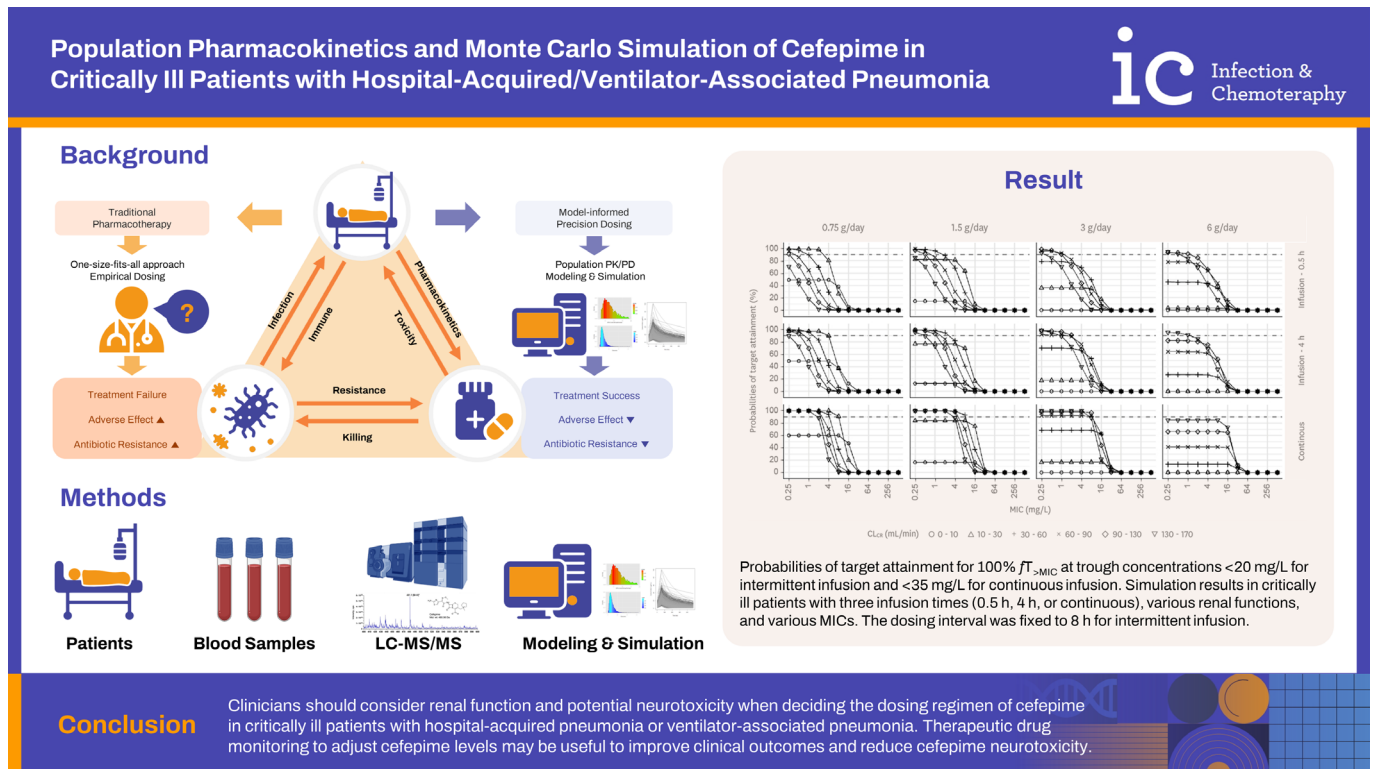
Email: dhlee97@gmail.com

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*These authors equally contributed to the work.

GRAPHICAL ABSTRACT



INTRODUCTION

Cefepime, a fourth-generation cephalosporin, also known as extended-spectrum cephalosporin, is active against most Gram-negative bacilli, including *Pseudomonas aeruginosa*, and maintains its activity against Gram-positive cocci [1]. Cefepime is less susceptible to inactivation by AmpC β -lactamases. Therefore, cefepime is thought to be an alternative to carbapenem for the treatment of infections caused by AmpC β -lactamase-producing *Enterobacteriaceae* [2]. Furthermore, cefepime is considered to exhibit high epithelial lining fluid penetration [3]. Therefore, empirical treatment of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) is recommended [4].

However, there have been concerns regarding the neurological toxicity of cefepime, especially in patients with reduced renal clearance [5], and this is thought to be related to the high plasma concentration of cefepime [6]. Although critically ill patients with organ dysfunction may develop decreased renal clearance, predicting cefepime neurotoxicity is challenging because cefepime therapeutic drug monitoring (TDM) is not routinely performed in all hospitals.

Although previous studies have suggested optimal antibiotic usage based on pharmacokinetics (PK) and

pharmacodynamics (PD) for the treatment of HAP and VAP, especially in critically ill patients [3], this is not always feasible in the clinical setting. The PK variability of β -lactams in critically ill patients has been described in previous studies [7-9]. When patients are in sepsis, they become hyperdynamic, which leads to increased renal blood flow and glomerular infiltration, resulting in increased clearance of β -lactams [9]. Suboptimal dosing is thought to be associated with reduced efficacy [9] and emergence of antibiotic resistance [10].

Therefore, an optimal dosage regimen based on PK/PD data is needed to reduce the potential toxicity and maximize the clinical benefit of cefepime. This study aimed to investigate the population PK profile and determine the optimal dosage regimen of cefepime in critically ill adult patients with HAP or VAP, especially for the prevention of neurotoxicity.

MATERIALS AND METHODS

1. Study design

Eligible patients participated in the initiation of cefepime administration. The enrolled patients were administered 2 g cefepime (Boryung, Seoul, Korea) for 30 min every 8, 12, or 24 h through intravenous (IV) infusion. Seven blood

samples were collected during the first dose period. The planned sampling times for model development were as follows: (1) immediately before dosing and 35, 45, 60, 120, 240, and 480 min after beginning the infusion for the 8-h interval administration; (2) immediately before dosing and 35, 45, 60, 240, 480, and 720 min after beginning the infusion for the 12-h interval administration; and (3) immediately before dosing and 35, 45, 60, 360, 720, and 1,440 min after beginning the infusion for the 24-h interval administration.

2. Ethics statement

This clinical PK study was approved by the Institutional Review Board of Hallym University Sacred Heart Hospital (IRB No. 2019-05-033). A written informed consent form was signed by the subject or the subject's legally authorized representative prior to enrollment. This study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice. For an unconscious patient, a legal representative of each patient signed a written informed consent form prior to participation.

3. Patients

This prospective study was performed at an 840-bed university-affiliated tertiary referral hospital between September 2019 and November 2019 (Hallym University Sacred Heart Hospital, Anyang, Korea). Clinical indications for cefepime include nosocomial pneumonia and the empirical management of septic shock from an unknown source. Patients with a history of β -lactam allergy were excluded.

4. Cefepime assay

Cefepime plasma concentrations were analyzed using a high-performance liquid chromatography (HPLC)-tandem mass spectrometry (MS) assay. The HPLC system consisted of an LC-20A system (Shimadzu, Kyoto, Japan) and Gemini C18 column (Phenomenex, Torrance, CA, USA). MS detection was performed using a quadrupole mass spectrometer (API4000 QTRAP system; SCIEX, Framingham, MA, USA). To prepare the calibration curves, a 100 mm³ aliquot of plasma sample was pipetted into a centrifuge tube. Next, 100 mm³ of acetonitrile containing an internal standard (20 mg/L [Sigma-Aldrich, St. Louis MO, USA]) was added to the tube and vortexed for 1 min. After centrifugation at 12,000 rpm at 4°C for 2 min, the supernatant was transferred to the vial of an autoinjector and diluted 20 times with 20 mM ammonium acetate. An aliquot of 10 mm³ was injected into the LC-MS/MS system. Similar to the calibration curve preparation process, ceftazidime, an internal standard, was added to 100 mm³ of plasma sample, pre-treated with acetonitrile, and then analyzed using LC-MS/MS. From the obtained chromatogram, the ratio of the peak area of cefepime to that of the internal standard was calculated, and the

concentration of cefepime in plasma was calculated using the calibration curve equation (weighted by $1/x^2$) prepared for each batch.

5. Population PK analysis

Population PK analysis was conducted using nonlinear mixed-effects modeling software (version 7.5, NONMEM®, ICON Clinical Research LLC, North Wales, PA, USA). The first-order conditional estimation with the interaction (FOCEI) method was used to estimate the measured and unexplained random effect parameters. The FOCEI allows interaction between the unexplained inter-individual variability (IIV) of PK parameters and the unexplained residual unexplained variability (RUV) of the measured concentrations. RUV was caused by measurement error, assay error, intra-individual variability, and model misspecification. One-, two-, and three-compartment PK model building was performed using ADVAN1 TRANS2, ADVAN3 TRANS4, and ADVAN11 TRANS 4, respectively, from the NONMEM model library. All PK processes, except zero-order infusion, were assumed to follow first-order kinetics. The PK parameter was defined as $\theta_i = \theta \times \exp(\eta_i)$, where θ is the typical value of the PK parameter, θ_i is an individual PK parameter, and η_i is a random variable associated with IIV, which was assumed to have a normal distribution with a mean of 0 and a variance of ω^2 . Additive, proportional, or combined additive and proportional error models were tested for RUV, which was assumed to have a normal distribution with a mean of 0 and a variance of σ^2 .

The models were evaluated and selected based on NONMEM objective function values (OFVs), precision of parameter estimates (relative standard errors), shrinkage of IIV, and diagnostic goodness-of-fit plots. In a log-likelihood ratio test, a decrease in the OFV (Δ OFV) between two nested models, with one degree of freedom greater than 3.84 or two degrees of freedom greater than 5.99, were considered statistically significant at $P < 0.05$ for model improvement. Diagnostic plots included the following: conditional weighted residuals (CWRES) vs. time, CWRES vs. population predictions (PRED), observation vs. PRED, and observation vs. individual predictions [11]. Perl-speaks-NONMEM software (version 5.3.0, PSN, [https://uupharmacometrics.github.io/PSN], Uppsala University, Uppsala, Svealand, Sweden) was used to search for covariates, evaluate a model with a visual predictive check, and conduct nonparametric bootstrap. Stepwise forward selection and backward elimination processes were performed to search for significant covariates for PK parameters. Statistical significance was set at $P < 0.01$ (Δ OFV < -6.635 for one degree of freedom) for selection and $P < 0.001$ (Δ OFV > 10.83 for one degree of freedom) for elimination. A significant covariate should have statistical and clinical relevance. The tested

covariates for PK parameters were sex, age, weight, height, body surface area (BSA), serum protein level, serum albumin level, serum creatinine level, and renal function. The renal function was calculated by applying Cockcroft-Gault (CG) formulations, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), modified CKD-EPI, Modification of Diet in Renal Disease (MDRD), or modified MDRD. The modified CKD-EPI and the modified MDRD estimates were adjusted using individual BSA values, where BSA was calculated by applying the Du Bois formula [12]. Visual predictive check with prediction and variability-correction (VPC_{PVC}) [13] was performed using PSN software by comparing the final PK model with the observed concentrations with 80% prediction intervals from 1,000 virtual datasets. The median and 95% confidence intervals for the PK parameter estimates of bootstrap samples (n = 2,000) were generated to examine the potential predictive variation in estimates of the final PK model. R software (version 4.1.2, [www.rproject.org], Vienna, Austria) was used to post-process the modeling results and for visualization.

6. PD target attainment

Three Monte Carlo simulations were performed. The first simulation was conducted to explore the appropriateness of the recommended dosage regimen for empirical treatment (creatinine clearance [CL_{CR}] >60 mL/min, 2 g every 8 h through extended 4 h IV infusion; for a CL_{CR} of 30 - 60 mL/min, 2 g every 12 h through IV infusion over 4 h; for a CL_{CR} of 11 - 29 mL/min, 2 g every 24 h through IV infusion over 4 h; and for a CL_{CR} <11 mL/min, 1 g every 24 h through IV infusion over 4 h) of nosocomial pneumonia. A total of 2,000 individual PK parameters were generated for virtual patients, assuming a log-normal distribution for each parameter, with the typical parameter values and the IIV of the final PK model. The selected covariate, creatinine clearance calculated using the CG formulations, was generated using a uniform distribution within the range of 0 - 130 mL/min. Virtual patients were assigned to 13 renal function groups (0 - 130 mL/min in increments of 10 mL/min). Then, 2,000 minimum inhibitory concentrations (MICs) from 0.25 - 128 mg/L were generated and randomly assigned to virtual patients. The MIC distribution of cefepime against *Escherichia coli*, *Klebsiella pneumoniae*, and *P. aeruginosa*, collected globally by the European Committee on Antimicrobial Susceptibility Testing (available at: <https://mic.eucast.org/Eucast2/> accessed on 2022-AUG-22), was used to generate MICs. Two thousand concentration-time (in minutes) profiles at steady state were generated using the 2,000 PK parameters and tested for three treatment targets of the PK/PD index. The antimicrobial activity of cefepime is related to the cumulative percentage of a 24 h period during which the unbound drug concentration exceeds the MIC for a pathogen under steady-state conditions

($fT_{>MIC}$; f , fraction unbound). The f was fixed at 81% [14]. The tested treatment targets were 50% $fT_{>MIC}$, 100% $fT_{>MIC}$, and 100% $fT_{>4 \times MIC}$. A dosage strategy was considered adequate if the probability of target attainment (PTA) is greater than or equal to 90%. For each treatment target, three steady-state minimum concentration (C_{min}) levels of less than 7.5 mg/L [15], 20 mg/L, and 35 mg/L [6] were also evaluated as safety targets.

The second and the third simulations were conducted to determine the optimal dosage regimens for 50% $fT_{>MIC}$, 100% $fT_{>MIC}$, and 100% $fT_{>4 \times MIC}$ as treatment targets, with C_{min} <20 mg/L as a safety target. A total of 1,000 individual PK parameters were generated for virtual patients, assuming a log-normal distribution for each parameter, whereas the covariate was generated by applying a uniform distribution within the range of 0 - 170 mL/min. Patients were divided into six renal function groups (0 <CL_{CR} ≤10, 11 ≤CL_{CR} ≤29, 30 <CL_{CR} ≤60, 60 <CL_{CR} ≤90, 90 <CL_{CR} ≤130, and 130 <CL_{CR} ≤170 mL/min). For the second simulation to evaluate the treatment target of 50% $fT_{>MIC}$, the steady-state concentration-time profiles of the 1,000 virtual patients were tested for various combinations of the four doses (0.25, 0.5, 1, and 2 g), three dosing intervals (8, 12, and 24 h), three infusion times (0.5, 2, and 4 h), and various MICs (0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, and 128 mg). For the third simulation, to evaluate the treatment target of 100% $fT_{>MIC}$ and 100% $fT_{>4 \times MIC}$, the PK profiles were tested for various combinations of the four doses (0.25, 0.5, 1, and 2 g), a dosing interval of 8 h, three infusion times (30 min, extended 4 h, and continuous infusion), and various MICs (0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, and 128 mg/L).

RESULTS

1. Patient characteristics

During the study period, 21 patients (12 men, 9 women) were enrolled. The demographic and clinical characteristics of the patients are shown in **Table 1**. The median serum creatinine levels (interquartile range [IQR]) were 0.80 mg/dL (0.53 - 1.12 mg/dL) and the median CL_{CR} values (IQR) by the CG equation were 77.2 mL/min (45.3 - 125 mL/min). Creatinine levels in only two patients were >2 mg/dL (3.44 mg/dL and 2.71 mg/dL).

2. Cefepime assay

The lower limit of quantitation was 0.5 mg/L. In the daily analysis results, concentration precision and accuracy of the calibration standard were 1.37 - 0.65% and 96.95 - 104.45%, respectively, at concentrations of 0.05, 0.2, 0.5, 2, 5, 20, 50, and 200 mg/L. The coefficient of determination indicating the linearity of the calibration curve over a range of 0.05 - 200 mg/L was greater than 0.99 for all three batches per day. In intraday analysis

Table 1. Patients characteristics

Parameters	Mean (SD) or No.	Median (IQR)
Sex	Male 12 / Female 9	
Age (yr)	67.10 (10.47)	67 (62 - 76)
Height (cm)	164.05 (8.64)	165 (155 - 172)
Weight (kg)	59.68 (10.53)	60 (54.4 - 65)
Body surface area (m ²)	1.64 (0.17)	1.60 (1.56 - 1.75)
SOFA	5.05 (3.04)	4 (4 - 5)
APACHE II	17.33 (4.63)	17 (14 - 22)
Protein (g/dL)	5.42 (0.67)	5.5 (4.8 - 5.7)
Albumin (g/dL)	2.87 (0.43)	2.8 (2.5 - 3.3)
BUN (mg/dL)	22.48 (9.60)	22.1 (15.2 - 29.5)
Scr (mg/dL)	1.07 (0.80)	0.80 (0.53 - 1.12)
CL _{CR} , Cockcroft-Gault (mL/min)	79.02 (47.67)	77.2 (45.3 - 125)
GFR, MDRD (mL/min/1.73m ²)	97.12 (59.22)	91.3 (48.9 - 155)
GFR, CKD-EPI (mL/min/1.73m ²)	89.18 (24.68)	94.9 (69.4 - 109)
GFR, modified MDRD (mL/min) ^a	93.00 (57.53)	92 (49.5 - 127)
GFR, modified CKD-EPI (mL/min) ^a	85.31 (26.42)	84.3 (70.2 - 102)

^aThe modified MDRD and CKD-EPI equations adjusted to individual BSA are $GFR (mL/min) = GFR (MDRD \text{ or } CKD-EPI) \times (BSA/1.73m^2)$.

SD, standard deviation; IQR, interquartile range; SOFA, sequential organ failure assessment; BUN, serum blood urea nitrogen level; Scr, serum creatinine level; CL_{CR}, creatinine clearance; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; BSA, body surface area.

of quality control samples, the precision was 6.91% at 0.5 mg/L, 1.99% at 5 mg/L, and 6.33% at 50 mg/L. The accuracy was 97.33% at 0.5 mg/L, 102.47 at 5 mg/L, and 111.60% at 50 mg/L. In inter-day analysis, the precision was 1.61% at 0.5 mg/L, 5.92% at 5 mg/L, and 3.47% at 50 mg/L. The accuracy was 98.18% at 0.5 mg/L, 100.45 at 5 mg/L, and 103.44% at 50 mg/L.

3. Population PK analysis

In total, 144 plasma samples were used for the population PK model of cefepime. The concentration-time profile of cefepime was best described using a two-compartment model. The NONMEM OFVs for the one-, two-, and three-compartment structural models without covariates were 307.124, 162.452, and 147.837, respectively. Although the OFV of the three-compartment model was the lowest, it failed to converge. The structural PK parameters for the two-compartment model were the total clearance (CL), central volume of distribution (V1), peripheral volume of distribution (V2), and intercompartmental clearance (Q) between V1 and V2. Inter-individual variability (IIV) was estimated for CL, V1, Q, and V2 (Table 2). In the final PK model (OFV 140.143), CL_{CR} was estimated using the CG equation as a statistically significant covariate of CL. The IIV for CL was reduced from 59.0% to 33.7% after the covariate was included. The diagnostic goodness-of-fit plots for the final PK model are depicted in Figure 1. The CWRES are randomly distributed around the zero line, indicating no systemic deviation in the structural (a) or RUV models (b). The observations are also evenly

distributed about the line of identity, indicating that there is no evidence of misspecification in the structural, IIV, or RUV models (c, d). **Supplementary Figure 1** shows the VPC_{PVC} plots for cefepime. The observed 10th, 50th, and 90th percentiles fell within the 95% confidence intervals of the simulated 10th, 50th, and 90th percentiles, respectively, indicating that the final PK model appropriately explains the observed cefepime concentrations and has a good predictive performance.

4. PD target attainment

Figure 2 (Supplementary Table 1) and Supplementary Figure 2 (Supplementary Table 2) show the PTA of empirical therapy using the current dosage regimen with extended 4 h infusion and standard 30 min infusion, respectively. For extended infusion, the recommended dosage regimen achieved 90% PTA at 50%*f*_{T>MIC} when patients were infected with *E. coli*, whereas this could not attain 90% PTA at 100%*f*_{T>4xMIC}. When patients were infected with *P. aeruginosa*, which was distributed where the MIC was higher than that of *E. coli*, the current regimen did not achieve 90% PTA at 50%*f*_{T>MIC} (Fig. 2). The probability of achieving the target dropped significantly when a safety target was added to ensure that C_{min} did not exceed 7.5, 20, or 35 mg/L.

When the safety target of C_{min} <20 mg/L was added, the PTAs for the target of 50%*f*_{T>MIC} with various combinations of renal function, four doses, three dosing intervals, three infusion times, and various MICs are

Table 2. Population PK parameter estimates for cefepime

Parameter	Estimates	RSE (%) [Shrinkage (%)]	Bootstrap median (95% confidence intervals)
Structural model			
CL = $\theta_1 \times (CG/77.21)^{0.2}$			
θ_1 (L/h)	6.60	7.91	6.63 (5.55 - 7.64)
θ_2	0.656	10.7	0.650 (0.438 - 0.796)
V1 (L)	13.3	9.79	13.4 (10.8 - 16.5)
Q (L/h)	16.5	18.7	16.2 (9.59 - 23.7)
V2 (L)	13.0	10.6	12.8 (9.87 - 16.3)
Interindividual variability			
CL (%)	33.7	25.2 [0.000]	32.0 (17.0 - 46.8)
V1 (%)	34.1	24.9 [11.2]	32.9 (7.52 - 49.5)
Q (%)	50.8	18.4 [19.6]	46.5 (0.000 - 65.8)
V2 (%)	40.1	21.2 [8.84]	38.6 (16.7 - 54.3)
Residual variability			
Proportional error (%)	7.62	9.43	7.61 (6.10 - 9.23)

PK, pharmacokinetics; RSE, relative standard error; CL, total clearance; V1, central volume of distribution; Q, intercompartmental clearance between V1 and V2; V2, peripheral volume of distribution.

illustrated in Figure 3 (Supplementary Table 3). For patients with a CL_{CR} of 10 - 30 mL/min, a dosage regimen of 0.25 g every 8 h through IV infusion over 0.5 h was optimal when the MIC was 4 mg/L. For patients with a CL_{CR} of 90 - 130 mL/min, a dosage regimen of 2 g every 12 h through IV infusion over 4 h was optimal when the MIC was 4 mg/L, whereas a dosage regimen of 2 g every 8 h through IV infusion over 4 h was not optimal.

Figure 4 (Supplementary Table 4) shows the PTAs for the target of $100\%fT_{>MIC}$ and $100\%fT_{>4xMIC}$ when the safety targets of $C_{min} < 20$ mg/L for intermittent infusion and $C_{min} < 35$ mg/L for continuous infusion were added. For patients with an CL_{CR} of 130 - 170 mL/min, a dosage regimen of 3 g/day through continuous IV infusion was optimal when the target was $100\%fT_{>4xMIC}$ and the MIC was 1 mg/L. For patients with a CL_{CR} of 90 - 130 mL/min, a continuous infusion of 3 g/day was optimal rather than a dosage regimen of 1 g every 8 h through IV infusion over 4 h when the target was $100\%fT_{>MIC}$ and the MIC was 8 mg/L.

DISCUSSION

This study presents the PK properties of cefepime in critically ill adult patients. The PK of cefepime was best described using a two-compartment model in the dense sampling scheme, in which CL_{CR} by CG was a significant covariate of total clearance for cefepime, which was consistent with a previous study reported by Álvarez et al [16]. Our results suggest that current dosing regimens may be inappropriate when the treatment target is $100\%fT_{>MIC}$ and $100\%fT_{>4xMIC}$ rather than $50\%fT_{>MIC}$. Notably, if not only efficacy but also safety were considered as the treatment goals, these goals could not be achieved with the current one-size-fits-all dosing, and TDM should be considered to achieve efficacy and safety targets simultaneously.

Three PK/PD indices of $50\%fT_{>MIC}$, $100\%fT_{>MIC}$, and $100\%fT_{>4xMIC}$ were investigated for efficacy targets. The target of 40 - 50% $fT_{>MIC}$ is appropriate to achieve

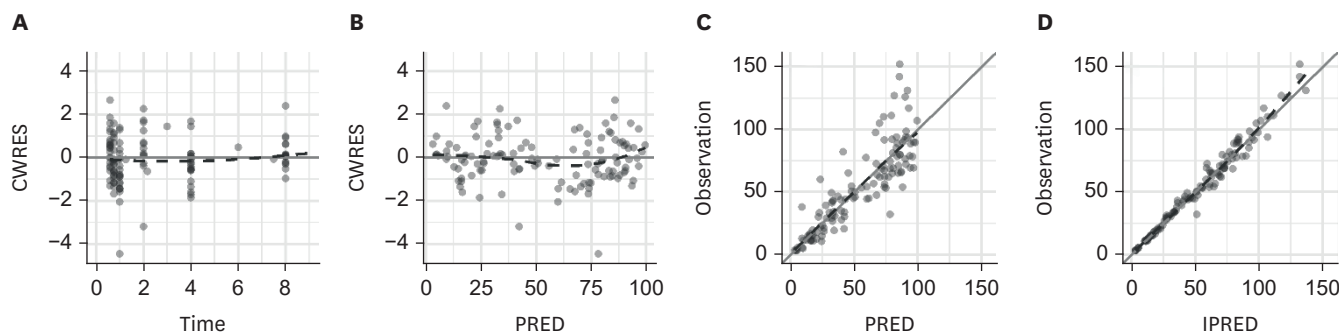


Figure 1. Goodness of fit plots for cefepime: (A) conditional weighted residuals (CWRES) versus time, (B) CWRES versus population predicted concentration (PRED), (C) observed concentration versus PRED, and (D) observed concentration versus individual predicted concentration (IPRED). The dashed lines represent smooth curves.

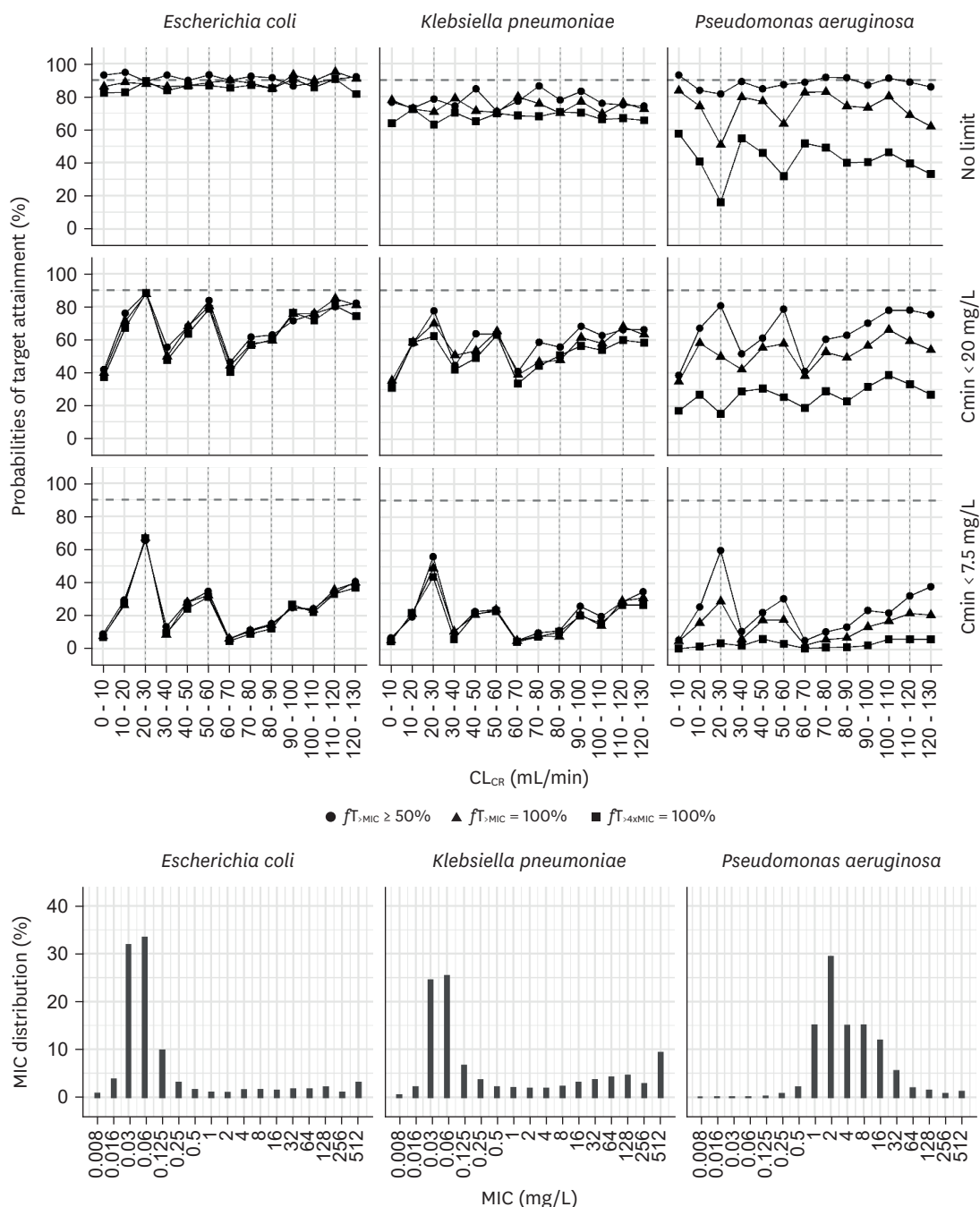


Figure 2. Probabilities of target attainment of empirical therapy using the current dosing regimen with a 4-hour extended infusion for patients with CL_{CR} of 0 - 130 mL/min when there is no target trough concentration (C_{min}) and when the target C_{min} is <20 mg/L or <7.5 mg/L. Bars indicate the MIC distribution for *Escherichia coli* (left), *Klebsiella pneumoniae* (middle), and *Pseudomonas aeruginosa* (right).

MIC, minimum inhibitory concentration.

significant bactericidal activity for amoxicillin and amoxicillin-clavulanate against penicillin susceptible, intermediate resistant, and resistant *Streptococcus pneumoniae* in two *in vivo* animal models, and to lead to

good efficacy with various β -lactams in patients infected with penicillin intermediate resistant and resistant *S. pneumoniae* [17-20]. A more aggressive target of 100% f_{T>MIC} or 100% f_{T>4xMIC} for β -lactams have been

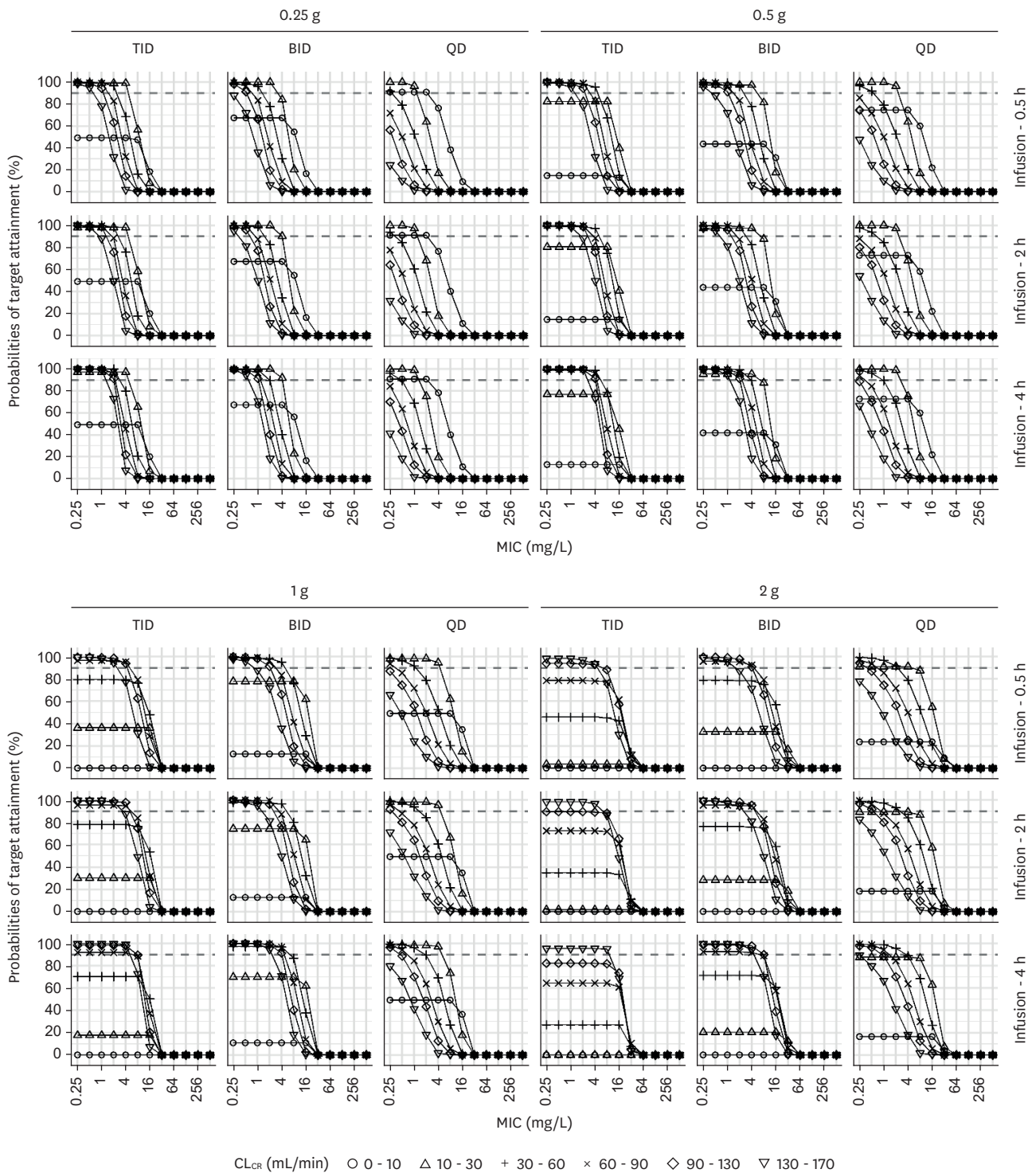


Figure 3. Probabilities of target attainment for 50% $fT_{>MIC}$ at trough concentrations <20 mg/L. Simulation results in critically ill patients with three doses (0.25, 0.5, 1, or 2 g) and three dosing intervals (8, 12, or 24 h), three infusion times (0.5, 2, or 4 h), various renal functions, and various MICs. MIC, minimum inhibitory concentration; TID, three times a day; BID, twice a day; QD, once a day.

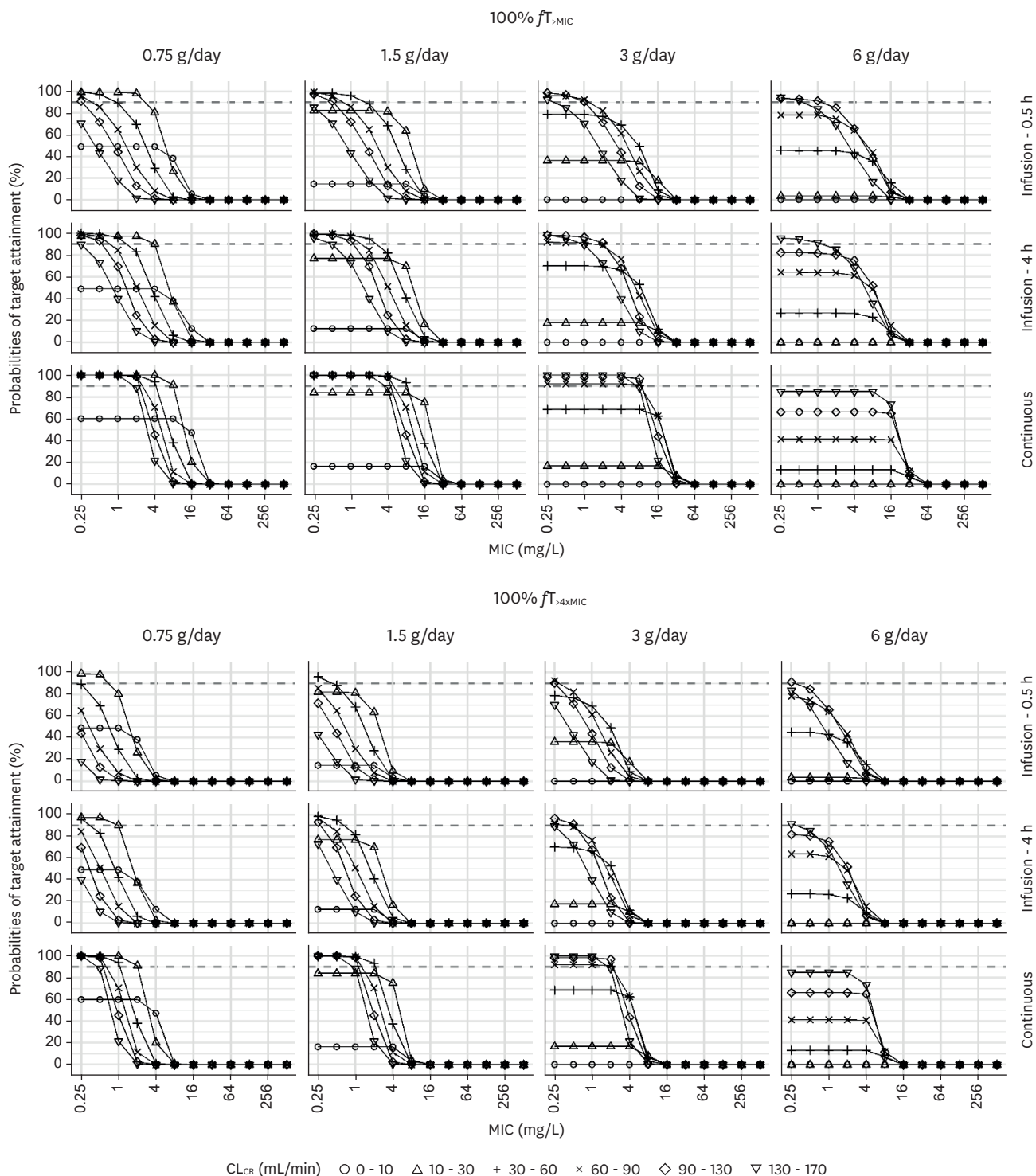


Figure 4. Probabilities of target attainment for 100% $fT_{>MIC}$ or 100% $fT_{>4xMIC}$ at trough concentrations <20 mg/L for intermittent infusion and <35 mg/L for continuous infusion. Simulation results in critically ill patients with three infusion times (0.5 h, 4 h, or continuous), various renal functions, and various MICs. The dosing interval was fixed to 8 h for intermittent infusion. MIC, minimum inhibitory concentration.

proposed in recent studies to achieve improved microbiological and clinical outcomes in critically ill patients [21-26]. We also explored three PK/PD indices of $C_{\min} < 7.5$ mg/L, $C_{\min} < 20$ mg/L, and < 35 mg/L for safety targets, with the three PK/PD indices for efficacy. Boschung-Pasquier et al. suggested targeting a trough concentration of < 7.5 mg/L to avoid the risk of cefepime-induced neurotoxicity [15]. Huwyler et al. reported that patients with trough concentrations > 20 mg/L and > 40 mg/L had a five-fold and a nine-fold higher risk of neurologic events, respectively, and proposed to avoid steady-state $C_{\min} < 20$ mg/L and $C_{\min} < 35$ mg/L in patients receiving intermittent and continuous infusion, respectively [6].

Traditionally, prolonged or continuous infusion of β -lactam agents has been advocated in previous studies [27-29]. Bauer et al. reported that extended infusion of cefepime 2 g every 8 h over 4 h reduced mortality in patients with *P. aeruginosa* infection compared to the 30 min infusion [29]. Huang et al. compared continuous versus intermittent infusion of cefepime in neurosurgical patients and reported that continuous infusion significantly enhanced the antibacterial effect and reduced treatment duration [27]. In our study, in patients with a CL_{CR} of 90 - 130 mL/min, a continuous infusion of 3 g/day was more beneficial than a dosage regimen of 1 g every 8 h through IV infusion over 4 h when the target was $100\%fT_{>MIC}$ and the MIC was ≤ 8 mg/L in case of safety target of $C_{\min} < 35$ mg/L for continuous infusion and that of $C_{\min} < 20$ mg for intermittent infusion were considered. Previous studies have shown that cefepime neurotoxicity is associated with high plasma concentrations, especially in patients with renal dysfunction [5, 6, 15]. In our study, we identified that a dosage regimen of 2 g every 12 h IV infusion over 4 h was optimal at a MIC of 4 mg/L, rather than the currently recommended dosage regimen of 2 g every 8 h through IV infusion, in patients with normal renal function ($CL_{CR} = 90 - 130$ mL/min) through the simulation of the optimal cefepime dosing regimen for $50\%fT_{>MIC}$ as treatment target with $C_{\min} < 20$ mg/L as safety target (Fig. 3, and Supplementary Table 3). Furthermore, in patients with renal dysfunction ($CL_{CR} = 10 - 30$ mL/min), a dosage regimen of 0.75 g over 24 h continuous infusion was sufficient at a MIC ≤ 8 mg/L for a treatment target of $100\%fT_{>MIC}$ with $C_{\min} < 35$ mg/L as safety target (Fig. 4, Supplementary Table 4). Our findings are consistent with a recent study by Cheng et al [30]. Although patient characteristics differed as they evaluated patients receiving extracorporeal membrane oxygenation (ECMO), reduced cefepime clearance in patients receiving ECMO was reported, and the current dosing of cefepime may lead to cefepime toxicity when a safety target of $C_{\min} < 20$ mg/L is considered. Therefore, TDM of cefepime may be beneficial to avoid neurotoxicity and optimize its effect,






which can be reinforced by the current guidelines on antimicrobial stewardship programs in Korea [31].

Previous studies have reported PD target attainment for cefepime in critically ill patients [32-34]. Although it was reported that the current dosing regimen succeeded in achieving PD target attainment for bactericidal effects based on 50% or $65\%fT_{>MIC}$, we evaluated PD target attainment with more diverse parameters, including $50\%fT_{>MIC}$, $100\%fT_{>MIC}$, and $100\%fT_{>4 \times MIC}$, and added a safety target of $C_{\min} < 20$ mg/L or < 35 mg/L to prevent neurotoxicity. A recent study by Álvarez et al. evaluated PK/PD parameters based on $60\%fT_{>MIC}$ and $100\%fT_{>MIC}$. [16], and it was reported that intermittent dosing was suboptimal, and continuous infusion could maximize exposure of cefepime. However, they included patients with hematologic malignancies and febrile neutropenia after chemotherapy and did not include safety targets. Therefore, these findings may be attributed to the differences in the results compared with our study.

Our study had some limitations. First, patients from a single center were included, and we did not perform external validation of our suggested dosage regimen. Further study including patients in multicenter studies are required to confirm our findings. Second, we did not evaluate the results of the PK/PD analysis based on clinical outcomes. Despite these limitations, our findings suggest that a more delicate dosage regimen based on renal function is needed to reduce neurotoxicity.

In conclusion, our results suggest that clinicians should consider renal function and potential neurotoxicity when deciding the dosing regimen of cefepime in critically ill patients with HAP or VAP. TDM to adjust cefepime levels may be useful to improve clinical outcomes and reduce cefepime neurotoxicity.

ORCID iDs

Hyeonji Seo 
<https://orcid.org/0000-0001-6659-6853>
 Yong Kyun Kim 
<https://orcid.org/0000-0002-7935-6952>
 Sunghoon Park 
<https://orcid.org/0000-0001-7004-6985>
 Hwan-il Kim 
<https://orcid.org/0000-0002-0165-5506>
 Dong-Hwan Lee 
<https://orcid.org/0000-0002-8681-099X>

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Conflict of Interest

No conflict of interest.

Author Contributions

Conceptualization: HS, YKK, DHL. Data curation: HS, YKK, DHL. Formal analysis: HS, YKK, DHL. Funding acquisition: YKK. Methodology: HS, YKK, SP, HK, DHL. Software: HS, YKK, DHL. Supervision: YKK, SP, DHL. Writing – original draft: HS, YKK, DHL. Writing – review & editing: HS, YKK, SP, HK, DHL.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Probabilities of target attainment of empirical therapy using the current dosing regimen with a 4-hour extended infusion for patients with CL_{CR} of 0 - 130 mL/min when there is no target trough concentration (C_{min}) and when the target C_{min} is <20 mg/L or <7.5 mg/L. This table corresponds to **Figure 2**

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Supplementary Table 2

Probabilities of target attainment of empirical therapy using the current dosing regimen with a 30-minute infusion for patients with CL_{CR} of 0 - 130 mL/min when there is no target trough concentration (C_{min}) and when the target C_{min} is <20 mg/L or <7.5 mg/L.

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Supplementary Table 3

Probabilities of target attainment for 50% fT>MIC at trough concentrations <20 mg/L. Simulation results in critically ill patients with four doses (0.25, 0.5, 1, or 2 g) and three dosing intervals (8, 12, or 24 h), three infusion times (0.5, 2, or 4 h), various renal functions, and various MICs. This table corresponds to **Figure 3**.

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Supplementary Table 4

Probabilities of target attainment for 100% fT>MIC or 100% fT>4xMIC at trough concentrations <20 mg/L for intermittent infusion and <35 mg/L for continuous infusion. Simulation results in critically ill patients with three infusion times (0.5 h, 4 h, or continuous), various renal functions, and various MICs. The dosing interval was fixed to 8 h for intermittent infusion.

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Supplementary Figure 1

Visual predictive check from simulated concentrations of 1,000 virtual datasets for cefepime (upper, 0 - 24 h; lower, 0 - 5 h). Closed circles, observed concentrations; solid lines, 10th, 50th and 90th percentiles of observations; dashed lines, 10th, 50th and 90th percentiles of simulated

concentrations; and shaded areas, 95% confidence intervals for the 10th, 50th, and 90th percentiles of simulated concentrations.

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Supplementary Figure 2

Probabilities of target attainment of empirical therapy using the current dosing regimen with a 30-minute infusion for patients with CL_{CR} of 0 - 130 mL/min when there is no target trough concentration (C_{min}) and when the target C_{min} is <20 mg/L or <7.5 mg/L. Bars indicate the MIC distribution for *Escherichia coli* (left), *Klebsiella pneumoniae* (middle), and *Pseudomonas aeruginosa* (right).

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