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Optimization of cefepime dosage regimens for *Pseudomonas aeruginosa* infections in Japanese patients based on a pharmacokinetic/pharmacodynamic analysis considering efficacy and safety: Is a 6 g daily dose and continuous infusion necessary?

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Abstract: In Japan, the approved maximum daily dose of cefepime (4 g) is lower than international standards (6 g), potentially compromising efficacy against *Pseudomonas aeruginosa* (*P. aeruginosa*) infections. Using Monte Carlo simulations with a population pharmacokinetic model for Japanese patients, we determined optimal dosing regimens across renal function levels. The target was 60% *f*T > MIC (percentage of time free drug concentration exceeds minimum inhibitory concentration), with ≥ 90% probability of target attainment for minimum inhibitory concentration (MIC) up to 8 mg/L. Lower doses sufficed for impaired renal function, while higher doses with prolonged infusion (2 g q8 (3 h)) were needed for creatinine clearance (CCr) 101–130 mL/min. For augmented renal clearance (CCr > 130 mL/min), continuous infusion (2 g loading dose followed by 4 g continuous infusion) achieved optimal attainment below neurotoxicity thresholds. Current approved dosing in Japan may be insufficient; adjustments including prolonged or continuous infusions are crucial for optimizing therapy.

***Keywords*:** cefepime, pharmacokinetics/pharmacodynamics, Monte Carlo simulations, sepsis

1. Introduction

The global increase in antimicrobial resistance necessitates judicious use of antibiotics, particularly in treating *Pseudomonas aeruginosa* (*P. aeruginosa*) infections. This bacterial pathogen ranks as the fifth most frequent cause of hospital-acquired infections in the USA and is a significant cause of ventilator-associated pneumonia and bloodstream infections worldwide (*1,2*). In Japan, a nationwide surveillance study from 2015 to 2017 reported that *P. aeruginosa* accounted for 8.0% of pathogens isolated from patients with healthcare-associated infections, with rates of antimicrobial resistance being a high concern (*3*). Cefepime, a fourth-generation cephalosporin with broad-spectrum activity and stability against many β-lactamases, is crucial for treating *P. aeruginosa* infections (*4*). However, a notable discrepancy exists regarding approved maximum daily cefepime dosing: Japan has approved 4 g/day, whereas many other countries have adopted 6 g/day. The efficacy of cefepime relates to its pharmacokinetic/pharmacodynamics (PK/PD) parameters, specifically the percentage of time that free drug concentration exceeds the minimum inhibitory concentration (%*f*T > MIC), with an optimal target of 60–70% *f*T > MIC (*5,6*). Achieving optimal PK/PD targets in septic patients is particularly challenging due to significant pathophysiological changes during critical illness. Sepsis induces complex alterations in drug disposition through mechanisms including increased cardiac output, enhanced renal blood flow, capillary leak syndrome, and changes in protein binding. For hydrophilic antibiotics, the volume of distribution can increase by up to 100% in septic patients compared to non-critically ill patients (*7*). Additionally, augmented renal clearance (ARC), defined as creatinine clearance ≥ 130 mL/min, can lead to suboptimal antimicrobial exposure (*8*). The 2024 Japanese Sepsis Guidelines recommend extended or continuous infusion of β-lactam antibiotics based on evidence suggesting improved target attainment and potentially better clinical outcomes in critically ill patients (*9*).

Furthermore, cefepime-induced neurotoxicity can

occur in patients with elevated trough concentrations (*10*). Despite the importance of optimizing cefepime dosages, PK/PD-based dosing strategies for *P. aeruginosa*-infected Japanese patients remain limited, particularly regarding renal function (*11,12*). This study aimed to determine optimal cefepime dosing regimens using Monte Carlo simulations (MCS) while evaluating whether proposed regimens maintain trough concentrations below neurotoxicity risk thresholds, addressing whether 6 g daily doses and continuous infusion are necessary for Japanese patients.

2. Pharmacokinetic parameters and Monte Carlo simulation

MCS were performed to generate concentration-time profiles for 1,000 virtual patients (body weight: 60 kg) stratified by renal function. A population pharmacokinetic (PPK) model developed by Yoshitsugu *et al.* was used in this study (*12*). The model is based on a two-compartment model with first-order elimination. The PPK analysis incorporated body weight and creatinine clearance (CCr) as covariates and was used to predict serum concentration-time profiles. Details of the model are presented in Supplementary Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=115*). The model was validated for patients weighing 35–82 kg, with the upper limit for reliable predictions estimated to be approximately 90 kg (*12*). The unbound fraction of cefepime was set at 0.85, based on multiple literature sources reporting values between 0.79 and 0.90 (*13-15*).

Based on previous studies defining ARC as creatinine clearance ≥ 130 mL/min (*8*), simulations included scenarios up to 150 mL/min CCr to evaluate dosing requirements in patients with ARC. The choice of 60 kg body weight was based on a report by Yoshitsugu *et al.* (*12*), who demonstrated that for patients with 40–90 kg body weight and 10–50 mL/min CCr, the variations in serum concentration profiles and $T > MIC_{90}$ due to body weight differences were not significant. Therefore, for our simulations, we fixed the body weight at 60 kg to focus on effects of variations in renal function. Simulations were performed for the following dosing regimens: 1 g q24 (1 h), 1 g q12 (1 h), 2 g q12 (1 h), 2 g q8 (1 h), and 2 g q8 (3 h). Additionally, a continuous infusion regimen consisting of a 2 g loading dose (1 h) followed by 4 g continuous infusion was also simulated. Analysis was conducted using Phoenix™ version 8.3 software. The set PK/PD target of 60% *f*T > MIC was based on a study by Crandon *et al.*, who demonstrated the clinical relevance of cefepime against *P. aeruginosa* infections (*16*). For the MCS, a range of minimum inhibitory concentrations (MICs) (0.5–32 mg/L) was chosen to encompass typical cefepime MIC distribution for *P. aeruginosa*, including both susceptible and resistant strains. The probability of target attainment (PTA) was calculated for each dosing regimen across MICs, with a 90% or higher PTA considered as threshold for optimal dosing. For neurotoxicity assessment, we considered a trough concentration of 20 mg/L as the threshold for increased neurotoxicity risk for intermittent infusion regimens, whereas a steady-state concentration of 35 mg/L was used as the risk threshold for continuous infusion regimens (*10,17*). These thresholds were based on findings from Huwyler *et al.* (*10*), who observed that patients with trough levels exceeding 20 mg/L had a 5-fold higher risk of neurological events for intermittent dosing, whereas no toxicity was seen at any sample concentration below 35 mg/L for continuous infusions.

3. Optimal dosing regimens based on renal function

MCS results evaluating the PTA by different cefepime dosing regimens for different MICs against *P. aeruginosa* across various CCr ranges are shown in Figure 1. Table 1 provides a concise overview of optimal dosing strategies with an MIC of 8 mg/L for *P. aeruginosa* across different levels of renal function, as determined by our MCS results. For patients with severe renal impairment (CCr: 0–20 mL/min), a dosing regimen of 1 g q24 (1 h) achieved a 90% or higher PTA for MICs up to 8 mg/L. As renal function improved to 21–40 mL/min CCr, a dose of 1 g q12 (1 h) was sufficient to maintain a 90% or higher PTA for MICs up to 8 mg/L. For patients with 41–60 mL/min CCr, the optimal regimen was 2 g q12 (1 h), which provided adequate coverage (≥ 90% PTA) for MICs up to 8 mg/L. For patients with 61–100 mL/min CCr, an increase in dosing regimen to 2 g q8 (1 h) was needed to achieve a 90% or higher PTA for MICs up to 8 mg/L. However, this regimen failed to achieve the target PTA for MICs of 16 mg/L in patients with 80 mL/min or higher CCr. For patients with 101–130 mL/min CCr, extended infusion times were beneficial, with a regimen of 2 g q8 (3 h) maintaining a 90% or higher PTA for MICs up to 8 mg/L, outperforming the 1 h infusion at the same dose and frequency. Finally, for patients with ARC (CCr > 130 mL/min), continuous infusion was the optimal strategy, with a regimen of 2 g loading dose (1 h) followed by 4 g continuous infusion achieving a 90% or higher PTA for MICs up to 8 mg/L.

4. Safety profile: Neurotoxicity risk assessment

Our simulations of steady-state cefepime concentrations for the recommended dosing regimens (Supplementary Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=115*) provided valuable insights into risk of neurotoxicity and potential benefits of continuous infusion. The majority of recommended regimens maintained trough concentrations below their respective thresholds, suggesting a lower risk of cefepime-induced neurotoxicity while still achieving

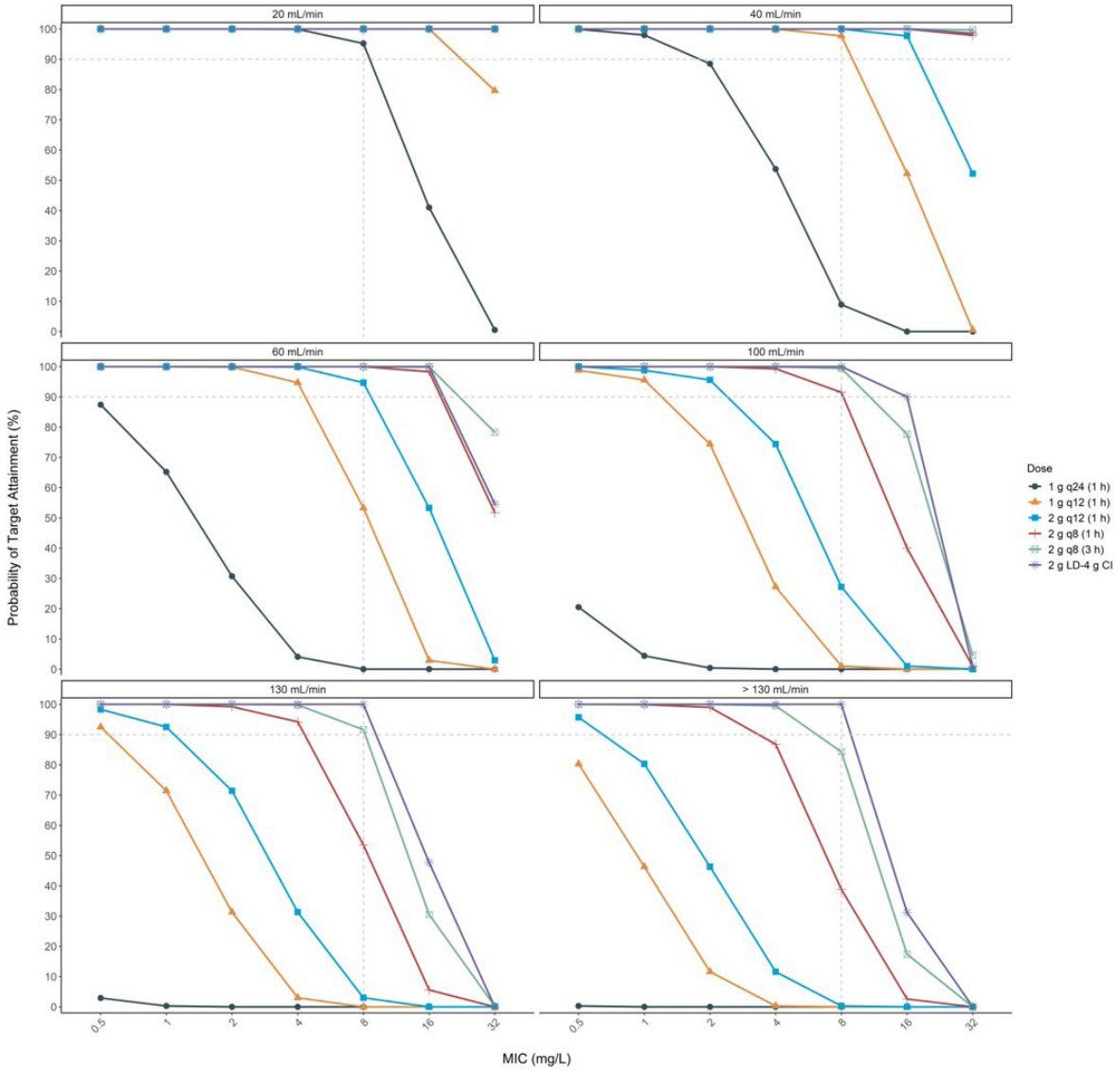

Figure 1. Probabilities of target attainment for 60% *f*T > MIC (percentage of time free drug concentration exceeds minimum inhibitory concentration) at various creatinine clearance (CCr) levels and minimum inhibitory concentrations (MICs). Simulation results were obtained for various dosing regimens, including intermittent infusions of different durations and continuous infusion. The results are stratified by CCr levels and MICs. *Abbreviations*: LD, loading dose; CI, continuous infusion.

Table 1. Recommended cefepime dosing regimens with a minimum inhibitory concentration of 8 mg/L for *Pseudomonas aeruginosa*

CCr (mL/min)	Dosing Regimen
0–20	1 g q24 (1 h)
21–40	1 g q12 (1 h)
41–60	2 g q12 (1 h)
61–100	2 g q8 (1 h)
101–130	2 g q8 (3 h)
> 130	2 g LD (1 h)–4 g CI

Abbreviations: CCr, creatinine clearance; LD, loading dose; CI, continuous infusion.

the desired PK/PD targets. However, for patients with CCr of 10 mL/min, 1 g q24 (1 h) resulted in trough concentrations above the safety threshold (geometric mean: 20.47 mg/L, 95% CI: 20.00–20.95). Therefore, for patients with CCr ≤ 10 mL/min, doses less than 1 g should be considered based on individual MIC values. Importantly, our simulation results for continuous infusion regimens demonstrated stable steady-state concentrations well below the neurotoxicity threshold of 35 mg/L, even in patients with ARC (CCr > 130 mL/min). For instance, the continuous infusion regimen maintained steady-state concentrations, with a geometric mean of 14.43 mg/L (95% CI: 14.26–14.60) for 140 mL/min CCr and 13.64 mg/L (95% CI: 13.48–13.81) for 150 mL/min CCr. This finding highlights the potential of continuous infusion in allowing for higher daily doses of cefepime without increasing risk of neurotoxicity, which is particularly relevant in patients with difficult-to-treat infections or ARC.

5. Clinical implications and comparison with international standards

The present study is one of the few to evaluate efficacy and safety of high-dose cefepime in Japanese patients. Our results suggest that cefepime doses higher than the current standard in Japan may be required for specific MICs against *P. aeruginosa* under different renal function levels. A Japanese study by Yamashita *et al.* found that in patients with CCr exceeding 100 mL/min, the current standard dosing regimen of 1 g q8 (3 g/day) was insufficient to achieve optimal therapeutic targets. They demonstrated that patients with normal renal function required 2 g q8 dosing to achieve adequate therapeutic concentrations, which aligns with international dosing recommendations. Their findings support our conclusion that higher doses (6 g/day) are necessary for Japanese patients with normal renal function, particularly when treating *P. aeruginosa* infections (*11*). The approved cefepime dosage in Japan (maximum 4 g/day) differs significantly from international standards, with several studies supporting efficacy and safety of the higher doses used globally. The Infectious Diseases Society of America guidelines recommend 2 g q8 (6 g/day) for severe infections (*18*), which has been supported by multiple clinical studies demonstrating improved clinical outcomes without increasing adverse events (*19,20*). The importance of continuous or extended infusion for β-lactam antibiotics, particularly in critically ill patients, has been increasingly recognized. The 2024 Japanese Sepsis Guidelines recommend extended or continuous infusion of β-lactam antibiotics based on evidence suggesting improved target attainment in critically ill patients (*9*). Recent practical guidelines from the Italian and French Societies of Infectious Diseases also support this approach.

Interestingly, PK differences do not appear to explain dosage discrepancies between Japan and other countries. A cefepime review report by the Japanese Pharmaceuticals and Medical Devices Agency showed similar maximum concentration (Cmax), steady-state area under the curve (AUC), and minimum concentration (Cmin) values between Japanese and non-Japanese patients across all levels of renal function. These findings suggest that racial differences in blood concentration profiles are unlikely to be the primary cause of the dosage discrepancies. Instead, other factors such as differences in prevalence of resistant bacteria or historical differences in clinical practice may have contributed to the lower approved dosage in Japan. Our study had several important limitations. First, our simulations were based on theoretical models and previously reported thresholds, which may not fully represent the complexity of individual patient responses. Clinical validation through prospective trials combining PK monitoring with neurological assessments is needed. Second, our data were based on serum concentrations and did not consider tissue concentrations at infection sites. Third, we targeted *P. aeruginosa* only and did not evaluate efficacy against other important pathogens. Finally, we did not consider PK/PD profiles in special patient populations, such as immunocompromised individuals or those with severe sepsis.

6. Recommendations for clinical practice

This study highlights the importance of reassessing cefepime dosing strategies in Japan. Our simulations indicated that the current standard dosing may not achieve optimal therapeutic targets in certain clinical scenarios, especially for less susceptible pathogens or patients with altered pharmacokinetics. Given complex pathophysiological changes in sepsis and the growing challenge of antimicrobial resistance in ICUs, continuous or extended infusions of β-lactams are increasingly important for optimizing therapeutic outcomes. Based on our simulations, we propose CCr-based cefepime dosing recommendations for an MIC of 8 mg/L against *P. aeruginosa* (Table 1). Although higher doses aligned with international practices may be beneficial, risk of neurotoxicity necessitates a cautious and individualized approach. Further clinical trials are needed to validate these findings and assess efficacy and safety of higher cefepime doses in Japanese patients, particularly focusing on continuous infusion strategies in septic patients with altered pharmacokinetics.

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