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Clinical Pharmacokinetics and Pharmacodynamics of Cefepime

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Abstract

Cefepime is a broad-spectrum fourth-generation cephalosporin with activity against Gram-positive and Gram-negative pathogens. It is generally administered as an infusion over 30–60 min or as a prolonged infusion with infusion times from 3 h to continuous administration. Cefepime is widely distributed in biological fluids and tissues with an average volume of distribution of ~

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0.2 L/kg in healthy adults with normal renal function. Protein binding is relatively low (20%), and elimination is mainly renal. About 85% of the dose is excreted unchanged in the urine, with an elimination half-life of 2–2.3 h. The pharmacokinetics of cefepime is altered under certain pathophysiological conditions, resulting in high inter-individual variability in cefepime volume of distribution and clearance, which poses challenges for population dosing approaches. Consequently, therapeutic drug monitoring of cefepime may be beneficial in certain patients including those who are critically ill, have life-threatening infections, or are infected with more resistant pathogens. Cefepime is generally safe and efficacious, with a goal exposure target of 70% time of the free drug concentration over the minimum inhibitory concentration for clinical efficacy. In recent years, reports of neurotoxicity have increased, specifically in patients with impaired renal function. This review summarizes the pharmacokinetics, pharmacodynamics, and toxicodynamics of cefepime contemporarily in the setting of increasing cefepime exposures. We explore the potential benefits of extended or continuous infusions and therapeutic drug monitoring in special populations.

1 Introduction

Cefepime is a broad spectrum fourth-generation cephalosporin with activity against many Gram-positive and Gram-negative pathogens that cause nosocomial infections. First approved in 1993 in Europe and 1996 in the USA with indications for pneumonia, complicated urinary tract infections, skin and soft-tissue infections, complicated intra-abdominal infections, and neutropenic fever [1], experience with cefepime is robust among the contemporarily used cephalosporins. In the hospital, cefepime is the ninth most commonly used antibiotic for all indications and is the sixth most commonly used antibiotic for the treatment of active infections [2]. The pharmacokinetics (PK) and pharmacodynamics (PD) of cefepime have been well characterized and susceptibility guidelines have defined population dosing strategies that are effective with standard and higher dose cefepime dosing schemes. However, less clarity exists regarding the exposure–response relationship for neurotoxic adverse effects and other toxicities. This contemporary review focuses on the known exposure–response relationships for cefepime.

2 Cefepime PK

2.1 PK in Healthy Adults

Cefepime is primarily given as an intravenous (IV) infusion over 30–60 min [3] or as a prolonged infusion of 3–24 h [4-6]. Several smaller studies have also reported IV push administration over 3, 5, 10, or 15 min [7]. Maximum plasma concentrations occur rapidly and are two to three times higher after IV administration compared to intramuscular (IM) administration [8]. Maximum concentration is ± 30.7 mcg/mL 30 min after a 2-g IV dose [9] compared with a maximum concentration of 57.5 ± 9.5 mcg/mL h after a 2-g IM dose [10]. In addition, there are recent reports on the off-label use of cefepime by subcutaneous administration [11, 12].

Cefepime is reasonably distributed in biological fluids and tissues [13-18], and is hydrophilic with a partition coefficient (log P) and distribution coefficient (log D) <− 2.5

[19]. The apparent volume of distribution (V_d) in adults with normal renal function is ~ 0.2 L/kg [20] (Table 1, Fig. 1). Cefepime clearance (CL) typically follows first-order kinetics, where concentrations decrease in a log-linear manner. Thus, cefepime doses are adjusted according to the half-life change. [9, 10]. Cefepime CL is largely renal and explained by the glomerular filtration rate; at least 85% of cefepime is excreted unchanged in urine. The terminal half-life ($t_{1/2}$) of cefepime in healthy subjects with normal renal function after IV administration is approximately 2 h [9, 10]. The t_{1l2} increases and CL decreases proportionately with declining kidney function [21, 22]. Patients with glomerular hyperfiltration or augmented renal CL, such as those with cystic fibrosis, have a greater cefepime CL and a shorter t_{1l2} [23] (Table 1, Fig. 2). At a physiologic pH, the non-renally cleared component undergoes hydrolysis to *N*-methylpyrrolidine (NMP) and the 7-epimer of cefepime. NMP is then oxidized to NMP N-oxide. Less than 1% of the dose administered is recovered from urine as NMP, 6.8% as NMP N-oxide, and 2.5% as the 7-epimer [24].

2.2 PK and Pharmacokinetic Variability in Specific Disease States

2.2.1 Pneumonia—Cefepime PK has been extensively studied in patients with pneumonia (Table 1, Figs. 1 and 2). In a prospective study of 21 patients with nosocomial pneumonia treated empirically with cefepime (2 g every 12 h for patients with CrCL 50 mL/minute or 2 g every 24 h for patients with $CL_{CR} < 50$ mL/minute (30-min infusions)), peak serum concentrations demonstrated a two- to three-fold variation, with up to 40-fold variation in trough concentrations [25]. Direct correlations were observed between CrCL and cefepime elimination (K_e), and between hemodilution and V_d. Similarly, in 26 critically ill patients with ventilator-associated pneumonia treated with high-dose cefepime (2 g every 8 h (3-h infusion) or a renal function-adjusted equivalent dose), CrCL and body weight were the covariates significantly impacting K_e and ~$_d$. Notably, the authors observed a total CL of 7.6 L/h in their critically ill patient population on a prolonged cefepime infusion [26], which is similar to total CL rates of 6–7 L/h observed in the critical care patient population in other studies [27-30]. In summary, patients with pneumonia display inter-patient variability in cefepime concentrations. Empiric dosing relies mostly on estimating cefepime CL in relation to CrCL.

2.2.2 Febrile Neutropenia—Cefepime PK has been evaluated in patients with febrile neutropenia secondary to hematological malignancies (Table 1, Figs. 1 and 2) [31-34]. Patients with febrile neutropenia exhibit intra-individual and inter-individual variability of pharmacokinetic parameters, mainly due to an increased V_d (26.43 L vs 18.4 L) and increased renal CL (12.88 L/h vs 8.58 L/h) compared with healthy volunteers [9]. Such PK changes are often driven by patient and disease state factors in this group. Sime and colleagues have suggested that the observed significant expansion in V_d may be attributable to a combination of various factors including capillary fluid extravasation, high-volume fluid therapy, and markedly increased body mass index/obesity [33]. In addition, these authors have pointed out that higher cefepime CL could be a consequence of augmented renal CL that is very often observed in febrile neutropenic patients with apparently normal renal function. Variability in PK parameters may partially account for the increased mortality observed with cefepime in the treatment of patients with febrile neutropenia and documented bacterial infection [32, 35, 36].

2.2.3 Sepsis and Shock—Cefepime is frequently administered to those with sepsis and shock (Table 1, Figs. 1 and 2). As with many other drugs, pharmacokinetic variability is high in those with septic shock [37]; coefficient of variation for CL or K_e can exceed 100% [38, 39]. In these patients, poor blood circulation [40] in infected tissues may decrease drug concentrations at the site of infection [41]. Additionally, augmented renal CL, defined as a $CL_{CR} > 130$ mL/min for renally excreted drugs [42], is often discussed in this population [39, 43]. Many of these patients undergo renal replacement therapy and CL is affected by filtration flow rates and filter downtime [44]. Changes in cardiac output can increase CL while higher V_d secondary to protein dysregulation may lead to subtherapeutic serum concentrations [42]. As a result, these patients frequently do not achieve time over minimum inhibitory concentration (T>MIC) goals, especially at MICs of 4–8 mg/L.

2.3 Infection-Site Considerations, Clinical Therapeutic Drug Monitoring

2.3.1 Pulmonary—Using cefepime 20 mg/kg every 8 h in intensive care unit patients with pneumonia, Klekner et al. failed to detect measurable cefepime concentrations in the sputum samples of the patients [45]; however, cefepime does not achieve high concentrations in the sputum. Conversely, more precise studies investigating epithelial lining fluid (ELF) found that cefepime penetrated well into the ELF with a mean ELF:serum concentration of 100% [46]. In a study by Boselli et al., cefepime concentrations in plasma and bronchoalveolar lavage fluid were obtained at various timepoints (8, 12, and 16 h). The concentration of cefepime in ELF was then calculated using urea to standardize for diffusion. This study demonstrated that normal and injured lungs achieve ~ 100% of serum concentrations in the lung and do so within 5 h [47]. This penetration to ELF has been confirmed by others. The parenchyma of lung is reached via distribution as demonstrated by 16 patients who received cefepime 2 g every 12 h before going to lung surgery. Cefepime plasma and lung homogenate concentration was quantified and the mean of the lung-to-plasma concentration ratio was 1.01 (range 0.7–1.3) [48]. A mean (standard deviation [SD]) percentage penetration of cefepime to bronchial mucosa of 59.8% (12.5%) was reported in one study that included 20 patients who received a single 2-g dose of cefepime [17]. Thus, cefepime appears to reliably achieve therapeutic concentrations in necessary respiratory matrices.

2.3.2 Intra-Abdominal—Cefepime appears well distributed into the abdominal space as well. Eight patients undergoing a laparotomy received cefepime 1 g every 6 h over 30 min and had cefepime plasma and peritoneal fluid concentrations measured at different timepoints. The mean cefepime maximum concentration was around 30% lower in the peritoneal fluid compared with the plasma, but the concentration was similar in both matrices 2 h after starting the infusion [49]. In 35 patients with appendicitis who received cefepime 2 g every 12 h, cefepime concentration was measured in the plasma, appendix tissue, and peritoneal fluid. The ratios of cefepime concentration in the appendix to plasma (mean 0.66, SD 0.52) and in the peritoneal fluid to plasma (mean 0.66, SD 0.51) were similar [15].

2.3.3 Central Nervous System—As with most beta-lactams, cefepime often does not fully transit the blood–brain barrier, and penetration has high inter-patient variability.

A study assessed 13 patients who received cefepime 2 g over 30 min and had plasma and cerebrospinal fluid (CSF) samples collected, eight with ventricular drainage and five obtained via lumbar puncture. The cefepime concentration in the CSF of the ventricular drainage group was higher than the lumbar puncture group. Additionally, the CSF:plasma ratio range was 0.30–2.14 in the ventricular drainage group and 0.03–1.14 in the lumbar puncture group. The maximum concentration was reached after 1–2 h in the ventricular drainage group compared with 4 h in the lumbar puncture group (mean ± SD 22.5 ± 14.1 vs ± 3.7 mg/L) [50]. Similar results were noted from seven patients with a ventricular drain who received cefepime 2 g every 12 h. A population PK model was developed using plasma and CSF samples and the mean (SD) area under the curve for CSF to area under the curve for plasma (AUC_{CSF}:AUC_{plasma}) derived from the simulations was 0.23 (0.57). Because of the degree of heterogeneity, the probability of target attainment (50% and 100% fT>MIC) was below 80% for MICs > 0.5 mg/L, even when simulating a cefepime 6 g/24 h continuous infusion [51]. A richly sampled rat model demonstrated highly similar penetration ratios (i.e., median penetration 20%, interquartile range 18–45%) and showed that penetration was very rapid with all animals demonstrating a time to maximum concentration of less than 2 h [52].

Cefepime has good penetration in the central nervous system (CNS) of children for the treatment of bacterial meningitis. In a study of 43 infants and children, mean CSF concentrations ranged from 5.7 μg/mL at 0.5 h after a 50-mg/kg dose to 3.3 μg/mL at 8 h after administration [53]. These concentrations are well above typical MIC_{90} for common causes of pediatric bacterial meningitis, such as *Streptococcus pneumoniae* and *Neisseria meningitis*.

2.3.4 Joint and Bone—Cefepime penetration to the bone is generally rapid and approaches concentrations obtained in the blood. A prospective study was performed with 18 patients with periprosthetic join infections who received cefepime 2 g and daptomycin 10 mg/kg intraoperatively. Each patient had two bone biopsies and one synovial membrane biopsy taken at a median time of 10 min after the end of the cefepime infusion. The median cefepime serum concentration was 28.6 mg/L (interquartile range 21.5–37.9). Among the 54 tissue samples taken, cefepime was detected in 35 (64%). The median (interquartile range) cefepime tissue concentration was 17.9 mg/L (1.1–24.3) in the synovial membrane, 17.1 mg/L (9.35–32.5) in the femur, 11.7 mg/L (5.4–29.0) in the cup, and 8.75 mg/L (7.55–24.9) in the tibia [54]. In another study, ten patients undergoing a total hip replacement received cefepime 2 g and had plasma and bone tissue samples collected 1.5 h later. The mean (SD) bone:plasma cefepime concentration ratio was 1.06 (0.23) in cancellous bone tissue and 0.87 (0.37) in cortical bone tissue [55]. Using a model to predict cefepime concentration in the intervertebral disc, Zhu et al. found that cefepime 2 g infused over 30 min every 12 h can achieve disc concentrations between 1.1 and 4.2 times an MIC of 8 mg/L in 2 days. A dose of 1 g every 12 h failed to consistently achieve disc concentrations above this MIC [56].

2.4 Special Populations

2.4.1 Extracorporeal Membrane Oxygenation—There are limited clinical data on the impact of extracorporeal membrane oxygenation (ECMO) on cefepime exposure.

Physiochemical properties of cefepime (i.e., a hydrophilic drug with low protein binding) predict low ECMO sequestration and most pharmacokinetic changes result as a function of fluid shifts [57]. Ex vivo work suggests there is a circuit/volume-related decrease in cefepime concentration with an average cefepime recovery from the ECMO circuit of 67% at 48 h [58]. Clinically, critically ill pediatric patients receiving cefepime while on ECMO demonstrated a central V_d increase of over two-fold in the setting of a blood transfusion, while a decrease in Vd was observed as ECMO circuit oxygenators increase in age [59]. Cefepime CL in this population was lower than previously reported in a similar population, not on ECMO [59, 60]. It is likely that underlying renal function is a more significant driver of CL than ECMO; however, hemodilution lowers effective concentrations. More studies are needed to clarify the effects, if any, of ECMO on cefepime clearance.

2.4.2   Renal Replacement Therapy—Cefepime is removed significantly by hemodialysis and its CL is directly proportional to the flow rate and filter efficiency [21, 61]. In one study, about 70% of cefepime was eliminated after 3.5 h of high-flux hemodialysis and the reported intra-dialytic and inter-dialytic half-lives were 1.6 and 22 h, respectively [62]. With only 30% of cefepime remaining, a regimen of 1–2 g of cefepime after each hemodialysis session may be reasonable [62, 63]. In peritoneal dialysis, the half-life of cefepime was 18 h with peritoneal dialysis CL of 4 mL/min. With a half-life approximately eight-fold higher than normal, cefepime 1–2 g every 48 h (i.e., the same dose with a dosing interval stretched eight-fold greater than normal) would be appropriate to maintain the concentration above the MIC of the susceptible bacteria [64, 65].

In continuous renal replacement therapy (CRRT), CL often approaches rates of patients with normal kidney function, necessitating more frequent dosing. Cefepime accumulation is affected by the CRRT flow rates and filter downtime [44, 66, 67]. Dosing adjustments for patients receiving CRRT may be based on flow rates (Table 2), which are similar to adjustments based on estimated glomerular filtration rate/CrCL rates in mL/min [68]. Patients on CRRT can exhibit a large inter-individual variability as a function of different filters utilized and therapeutic drug monitoring may result in the most appropriate exposures. Literature-suggested population-based maximal dosing as a function of flow rate is shown in Table 2. Similar to patients with 'normal renal function' (CrCL > 100 mL/min), more aggressive doses such as 1 g every 6 h or 2 g every 8 h may be needed to achieve pharmacokinetic/pharmacodynamic targets against select pathogens. Additionally, when MICs are elevated as discussed below, extended or continuous infusions may offer superior target attainment when compared to intermittent infusion [44, 67, 69].

2.4.3   Burn Patients, Patients with Cystic Fibrosis, Elderly Patients, Obese Patients—Several studies have looked at a variety of other notable patient populations. For these patient populations, CrCL and V_d remain the most important variables and can aid in predicting cefepime disposition. In cystic fibrosis, CL of cefepime is increased [70] as these patients often display augmented renal CL. In acute cholecystitis, CL of cefepime is increased [71]. Elderly patients display longer half-lives of cefepime as a function of decreasing CrCL [72, 73] and obese patients have larger V_d and CL compared with non-obese individuals [74, 75]. As such, elderly patients can require lower doses and less

frequent administration of cefepime whereas obese individuals can require higher doses and more frequent dosing. Finally, burn patients can display either larger V_d and higher CL or more normal values, resulting in large potential dosing differences among individual patients [76-78]. All of these groups may have a large inter-patient variability, which may be better understood with individualized therapeutic drug monitoring.

2.5 Children—The PK of cefepime has been evaluated in children of all ages (Table 1) [79-82]. Studies involving infants have generally found that CL is lower in the first few months of life compared with in older children [79, 80, 82], which is consistent with many renally eliminated drugs. A secondary population pharmacokinetic analysis of data from two of these studies [79, 82] reported that CL was more than 50% lower in the first 30 days of life (1.08 ± 0.38 mL/min/kg) compared with children older than 30 days (2.59 mL/min/kg) [83]. The age-dependent increase in CL plateaued around 2–3 years of age in this analysis [83]. In contrast, the median CL among 85 infants in a study by Zhao et al. was similar to values described in older children (median 3.0 mL/min/kg) [81]; however, this study may have been limited by the inclusion of only 100 cefepime concentrations from these 85 subjects. An additional, large population pharmacokinetic study involving 230 adults and 36 children did not report pediatric-specific pharmacokinetic parameters aside from K_e, which was substantially higher in children (1.03 h^{-1}) compared with adults (0.32 h^{-1}) [84].

Age-specific effects can also be seen in cefepime V_d. Consistent with the known affinity of cefepime for total body water, studies regularly demonstrate that V_d is larger in neonates and infants than in older children [79-82]. As a result, steady-state peak concentrations are higher in older children when equivalent weight-based (i.e., mg/kg) doses are given [80, 82]. As with adults, the majority of cefepime is excreted unchanged in the urine. In the study by Reed et al. [82], approximately 57–68% of doses were recovered in the urine over an 8-h period.

Although cefepime is typically administered intravenously in children, it can also be administered intramuscularly. While near-complete bioavailability has been reported for adults [3], the average bioavailability via an IM injection in children was roughly 82% in the study by Reed and colleagues, though individual bioavailability estimates ranged from 61 to 124% [82]. Owing to larger volumes of distribution and longer mean residence times when administered intramuscularly compared with intravenously [82], peak concentrations and area under the concentration–time curve are lower via the IM route [85]. As with adults, limited data exist on the free fraction of cefepime in clinical practice, and the actual free fraction may be highly variable in children. Thus, caution must be used when interpreting total drug concentrations in clinical practice.

3 Cefepime PD for Efficacy (e.g., fT>MIC)

3.1 Preclinical Animal Data—Cefepime is unique from other commercially available cephalosporins because it is a zwitterionic compound; the cephem nucleus has both a positive charge on the C-3' group nitrogen as well as a negative charge on the C-4 carboxylic group [11]. This zwitterionic property allows cefepime to rapidly penetrate the outer membranes of Gram-negative bacteria [12, 13]. As members of the beta-lactam

class of antibiotics, cephalosporins are classified as time-dependent agents because their antibacterial activity is predicated on maintenance of the free drug concentration above the minimum inhibitory concentration (fT>MIC) [86-88]. As noted, determining the free fraction for cefepime can be difficult. Thus, some studies utilize the total drug concentration above the minimum inhibitory concentration (C_T>MIC), or extrapolate free fractions from measured total concentrations based on population estimates for the fraction unbound (~80%) [3]. Multiple animal pharmacodynamic models of infection have been used to define the optimal conditions for the antibacterial activity and clinical efficacy. Early in vivo animal studies of ticarcillin antibacterial activity against *Pseudomonas aeruginosa* and cefazolin against *Escherichia coli* utilized a neutropenic murine thigh infection model and have been widely cited for class beta-lactam effects [89]. Results showed that a T>MIC threshold of 40–60% was likely required for the suppression of bacterial growth. Notably, increased bacterial killing was observed as T>MIC increased up to 100%; beta-lactam concentrations up to four times the organism MIC were also associated with maximal bactericidal activity [89]. Infections due to Gram-positive organisms such as *Staphylococcus* and *Streptococcus* species required lower exposure thresholds than Gram-negative organisms; likely owing to a post antibiotic effect of the studied agents (cefazolin against *S. aureus* and erythromycin against *S. pneumoniae*) [90]. Similarly, early neutropenic murine thigh and lung infection models with *Enterobacteriaceae* and *Klebsiella pneumoniae* treated with cefotaxime demonstrated that antibacterial effects of cephalosporins were optimized when free drug concentrations in serum (*f*) were maintained above the MIC for 35–40% of the dosing interval, with an effect plateau observed when fT> MIC was 60–70% of the dosing interval [91, 92]. Overall, these early in vivo studies reported that fT>MIC of 40–70% or greater was the pharmacodynamic parameter for maximal bactericidal activity with beta-lactams. Important differences in the fT>MIC required for maximal bactericidal activity was observed for Gram-negative (requiring higher percent fT>MIC) and Gram-positive (requiring lower percent fT>MIC) organisms [93]. Subsequent cefepime-specific studies have been reported owing to the development of beta-lactamase inhibitors that are being paired with cefepime [94]. Monotherapy studies have demonstrated stasis in the neutropenic thigh model with a %fT>MIC range from 0 to 37.7% for *E. coli* and *K. pneumoniae* strains [95]. Considerable discussion has occurred on the importance of the endpoint (stasis vs 1-log vs 2-log kills) in murine studies. The general consensus is that stasis is a more appropriate target for non-serious serious infections and   1-log kills are appropriate targets for more serious infections [96, 97]. However, the lower range of %fT>MIC that has been observed in vivo for the efficacy of cefepime demonstrates the often-unmeasured variability of these systems (including MIC variability, variability in measuring free fractions, starting inoculum variability, genus/species/isolate variability in response). Thus, all targets can be regarded as estimates of the pharmacokinetic/pharmacodynamic exposures needed with an expected variability. Ultimately, it is reasonable to conclude that optimal pharmacodynamic activity for cefepime from the murine model ranges from 40 to 70% fT>MIC, with some variability around those estimates.

3.2 Clinical Studies

Efforts to elucidate the optimal PD of cefepime in humans have resulted in heterogenous findings which differ from in vivo animal data in some cases. Clinical evidence suggests

that the optimal pharmacodynamic index for microbiological and clinical success may be higher than the pre-clinical fT>MIC target of 40–70% that was previously identified. Several small studies of cefepime PD in humans have suggested that serum cefepime concentrations four to eight times the MIC for　90% of the dosing interval were associated with an increased likelihood of microbiological success [98, 99]. The most frequently cited study by Tam et al. evaluated 36 patients and identified microbiologic success correlated with 100% T>MIC of 4.3 × MIC [99]. Others have found a fT>MIC threshold of 75–100% as a favorable predictor of treatment outcomes among critically ill adults, patients with sepsis, and the elderly [100-103]. The Defining Antibiotic Levels in Intensive Care Unit Patients (DALI) study was a prospective pharmacokinetic point-prevalence study of eight common beta-lactam antibiotics, including cefepime. The investigators observed that maintenance of beta-lactam concentrations above 50% fT>MIC and 100% fT>MIC was associated with a 1.02-fold and 1.56-fold higher likelihood of clinical cure. Sixteen percent of patients in the study cohort did not achieve 50% fT>MIC and these patients were 32% less likely to achieve clinical cure. Notably, there was significant heterogeneity in the achievement of beta-lactam pharmacodynamic targets (fT>MIC) when standard empiric doses were utilized. The results of the DALI study helped to support the findings of previous small studies that suggested that higher drug exposures are associated with improved outcomes among the critically ill [100, 101, 104]. Additionally, analysis of trough cefepime concentrations amongst study participants demonstrated an approximately 100-fold range of concentrations, further emphasizing the degree of inter-patient variability present. More recent work by Rhodes et al. has also shown that each 1% increase in cefepime fT>MIC from 0 to 100% independently predicted a higher odds of survival (adjusted odds ratio, 1.02; 95% CI 1.00–1.01; $p = 0.015$) among patients with Gram-negative bacteremia. Two sensitivity analyses identified that fT>MIC >68% and > 74% thresholds predicted increased survival with multivariate-adjusted odds ratios of ~ 7 for each [102]. Similarly, a study by Crandon et al. found fT>MIC targets of > 60% and > 64% for pneumonia and skin/skin structure infections [105]. An analysis of the same data from Rhodes et al. [102] probed the interrelationship between patient co-morbidity (quantified as the mAPACHEII score) and fT>MIC [106] and demonstrated a window of mAPACHE II scores in which optimized PK/PD provided the most benefit. Specifically, the benefit of optimized cefepime PK/PD was observed between mAPACHE II 9 and 22 (Fig. 3).

Similar to animal findings, variability existed in the identified pharmacokinetic/pharmacodynamic target for clinical efficacy. Differences compared to preclinical studies are likely due to increased variability in study design, individual patient factors, disease states, variable use of free versus total cefepime concentrations, and organism MICs. In addition, clinical studies were small retrospective evaluations at single centers and would be expected to result in point estimates with greater variability. In summary, both pre-clinical and clinical pharmacokinetic/pharmacodynamic studies for cefepime have identified that optimal outcomes are explainable as a continuum from low to high fT>MIC. It is reasonable to acknowledge variability (i.e., no exposure guarantees an outcome) [107] and set target minimum goals of fT>MIC >100% [106] for cefepime, thus ensuring that fT>MIC does not fall below 70% when known individual patient variability is accounted for [106, 108].

In patients with febrile neutropenia with underlying hematological malignancies, utilizing cefepime as prolonged or continuous infusions is most important for pathogens with an elevated MIC (such as *K. pneumoniae* or *P. aeruginosa*) [31, 32]; however, pathogen identification and susceptibility testing are often delayed. Thus, pharmacokinetic optimization may maximize positive outcomes for those that are pharmacodynamically challenged [31]. Additional studies are needed to define dosing schemes and PK parameters in high-risk and low-risk patients with febrile neutropenia secondary to hematological malignancies [32] and to define subsets of this patient population who may most benefit from therapeutic drug monitoring [109].

Pharmacokinetic variability is highest in critically ill patients with septic shock (Table 1, Figs. 1 and 2). As a result, these patients frequently miss their T>MIC goals, especially at MICs of 4–8 mg/L. In the Conil et al. study, a cefepime dose of 2 g every 8 h (20-min infusions) was insufficient to reach a target of 100% $T > 4 \times MIC$ in 80% of burn patients [76], while in the Taccone et al. study, only 16% of patients achieved the intended target of $> 70\% \ T > 4 \times MIC$ [110]. To assess the expected probability of target attainment of various cefepime dosing regimens against the common pathogens in the intensive care unit, a cefepime pharmacodynamic model was developed [28]. The expected probability of target attainment calculated from the probability of target attainment vs MIC profiles demonstrate that cefepime 4 g/day given as intermittent bolus or CI for *E. coli* and *K. pneumoniae* should achieve the T>MIC target, while higher doses of cefepime (>4 g/day) are required for *P. aeruginosa* (where MICs distributions were obtained from Australian laboratories provided by the Queensland Health Pathology Service). From these same surveillance data, cefepime 6 g/day administered as a continuous infusion still fails to reliably achieve the bactericidal target for *A. baumannii*. This study and others [4, 27, 111] emphasize the importance of individually dosing patients to achieve targets against the highest susceptible MICs (i.e., 8 mg/L) and then decreasing doses according to specific pathogen MICs in this critically ill patient population.

The heterogeneity in the efficacy targets and their achievement is also due, in part to MIC determination and the utilized method. Many of these pharmacodynamic clinical studies utilized an imputed MIC (which is the highest achievable susceptible MIC) because they did not have organism-specific MIC. Pharmacodynamic outcomes studies have used actual [27, 76, 98-102, 105, 106, 111] and imputed [28, 31, 32, 101, 103, 110] MICs.

4   Cefepime Toxicodynamics

The exposure-related major treatment-limiting toxicities from cefepime are neurotoxicity and cytopenias. Below we discuss the exposure–response relationships for each of these toxicities. Allergic rashes and hypersensitivities are not discussed as they are not related to gradient exposures. The interested reader is referred to excellent reviews of beta-lactam allergies [112, 113].

4.1   Neurotoxicity

Cefepime neurotoxicity rates have been estimated between 3.0 and 23.2% [114-118]; though estimates are difficult and may be either overestimated because of publication

bias or underdiagnosed in the intensive care unit as many patients are under sedation. Diagnosis is also challenging and requires a careful clinical assessment of the encephalopathic patient given that patients receiving cefepime often have multiple reasons for obtundation. Clinically, cefepime neurotoxicity is manifested as encephalopathy (disturbance of consciousness including confusion, hallucinations, stupor, and coma), which may be accompanied by other symptoms including aphasia, myoclonus, seizures, and status epilepticus [1, 115, 119, 120]. Electroencephalograms may aid in the diagnosis. Electroencephalogram results of patients with cefepime neurotoxicity exhibited changes that range from moderate to severe nonspecific diffuse slowing of the background, to seizures and nonconvulsive status epilepticus [115]. A recent study [121] showed that generalized rhythmic delta activity was the electroencephalogram pattern most frequent encountered, followed by generalized periodic discharges with and without triphasic morphology, generalized spike and wave discharges, and lateralized periodic discharges. Except for generalized rhythmic delta activity, all the other patterns are associated with an increased risk of seizures [122] and, in the same study, seizures were documented in 36% of the patients. It is important to notice that none of those electroencephalogram abnormalities is pathognomonic of cefepime neurotoxicity, but in the right clinical context may aid with diagnosis.

Clinical and demographic data appear to predict the risk of cefepime neurotoxicity. Kidney dysfunction is a major complicating factor of those that experience cefepime neurotoxicity; 87% of patients with cefepime neurotoxicity had renal dysfunction and 29% had end-stage renal disease [123]. Both dose administered and decreased CL lead to higher-than-normal systemic cefepime concentrations and are likely synergistic for toxicity. One systematic review that included 37 studies with a total of 135 cases of cefepime-related neurotoxicity found that neurotoxicity occurred in 48% of patients who were overdosed, and in 26% of patients who were appropriately dosed based on their renal function [124]. As approximately 85% of the administered dose of cefepime is excreted unchanged in the urine, renal dysfunction can increase the $t_{1/2}$ of cefepime from 2 to 19 h [1, 21, 64, 125], thus significantly increasing cefepime exposure in these patients. Older age has also been associated with cefepime neurotoxicity; the average/median age of those experiencing neurotoxicity is 67/70 [123]. It is unknown if older adults have a lower threshold for toxicity or if decreased kidney function drives toxicity. Renal dysfunction can also lead to uremia, accumulation of toxic organic acids, or alteration of pH, which may contribute to the impaired active transport of cefepime from CSF to blood [126-130].

Inflammatory conditions during sepsis, CNS infection, critical illness, severe infection, diabetes mellitus [131], and previous brain injury may disrupt the blood–brain barrier integrity, resulting in increased CNS penetration of cefepime [132]. Cerbrospinal fluid/plasma cefepime concentration ratios from 9.1 to 45% have been reported in patients with cefepime neurotoxicity [133-135], which as previously noted is not substantially different from ratios in those without neurotoxicity. It is possible that an altered blood–brain barrier permeability on an individual level may influence cefepime neurotoxicity. Additionally, and as expected, pre-existing CNS conditions increase the likelihood that neurotoxicity will be observed during cefepime therapy. A total of 8% of patients in a meta-analysis [124] had underlying CNS conditions including lymphoma that had infiltrated the brain, non-herpetic

acute limbic encephalitis, encephaloma [136], stroke [137], seizures [138], and infection of the surgical site following lumbar spinal stenosis surgery [133]. It is possible that pre-existing CNS conditions result in altered blood–brain barrier permeability and decrease the seizure threshold [124, 126, 133, 136-139].

The pharmacokinetic/toxicodynamic index prediction of cefepime neurotoxicity remains uncertain [140]. Most studies have reported trough thresholds because they only measured or only analyzed trough concentrations [114, 120, 141]. The first study identified probabilities of neurotoxicity of 50, 75, and 95% at trough concentrations of 22 mg/L, 25 mg/L, and 30 mg/L, respectively [120]. However, these thresholds (even when accounting for under-reporting) have not harmonized with observed neurotoxicity rates in the treated population [140]. More recently, trough concentrations of > 35 mg/L [116, 124], > 36 mg/L [114], > 38.1 mg/L [142], and > 49 mg/mL [142] have been suggested as thresholds for neurotoxicity. Boschung-Pasquier et al. suggested a 50% probability of neurotoxicity at trough concentrations 16 mg/L; [114] however, these troughs are regularly obtained and a 50% probability is discordant with most other clinical reports [140]. Taking into consideration interindividual pharmacokinetic and analytical variabilities, the probability of the neurotoxic threshold lying between the 35–49 mg/mL range seems plausible, yet none of these concentration thresholds has been particularly discriminatory.

Limitations in these studies, including their retrospective nature [114, 116, 120, 141, 142], the heterogeneity in the definition of neurotoxicity [114, 116, 120, 141, 142], measurement or analysis of only trough concentrations [114, 120, 141], and potential technical variability in the analytical methods [116], make it difficult to compare across studies. In addition, the timing of when the concentrations were obtained (following the discontinuation of cefepime) or concomitant use of opioids or previous chemotherapy may have contributed to lowering the neurotoxicity threshold [120]. Future studies should also consider other measures such as cumulative area under the concentration–time curve from time zero to infinity to account for accumulation.

In summary, pharmacokinetic/toxicodynamic predictive thresholds for neurotoxicity are much more variable than the relationships observed for efficacy; however, reports have consistently demonstrated that both kidney dysfunction and elevated cefepime concentrations increase the risk of cefepime neurotoxicity. Additional work is needed to improve the specificity of the prediction; nonetheless, it is reasonable to exercise additional caution in patients with renal dysfunction and avoid concentrations well in excess of what is necessary for efficacy.

4.2 Cytopenias

Cytopenias due to cefepime administration are less well characterized; though class-effect drug-induced cytopenias for beta-lactams can be due to an immunogenic adverse reaction or can be exposure/time related, resulting in depressed myeloid cell proliferation [143, 144]. Thrombocytopenia defined as a platelet count reduced by 50% was found in 0.1–1.0% of patients receiving cefepime in early clinical trials [1]. A 2011 case study described a typical response in that cefepime-induced thrombocytopenia in a critically ill patient resolved on discontinuation of the drug [145]. Cefepime-induced neutropenia (defined as

500 cells/uL) has been reported in 0.2% of cefepime courses during early clinical trials [1, 146]. In one case review of 134 patients receiving IV antibiotics for osteomyelitis, 8 of 13 patients receiving extended cefepime courses resulted in neutropenia, compared with none in the 121 patients who received other antibiotics. The patients who developed neutropenia received extended courses of cefepime treatment (> 14 days), suggesting a time-mediated depression of neutrophil proliferation as the underlying mechanism [147]. Further supporting the correlation between treatment duration and occurrence of cytopenias, prolonged use of cefepime in cystic fibrosis patients for 22–24 days [148] and for the treatment of post-surgical infection for 24 days [149] resulted in neutropenia. A single study reported cefepime administration by a rapid IV push was associated with a higher risk of cefepime-induced neutropenia [150]. A prospective pharmacovigilance evaluation determined that the most frequent cause of non-chemotherapy-induced agranulocytosis (neutrophil count < 500 cell/mm^3) was the use of antimicrobial drugs and cefepime had the highest incidence rate of 83.85 per 10,000 defined daily doses (Poisson 95% confidence interval 67–102.89) [151]. Finally, decreased hematocrit levels have been observed in cefepime clinical trials with an incidence of 0.1–1% [1]. In addition, a single case of immune-mediated hemolytic anemia has been reported [152].

5 Other Considerations, Clinical Therapeutic Drug Monitoring

5.1 Protein Binding

Cefepime is oft quoted in pharmacokinetic studies to have a protein binding of 20%, an estimate derived from in vivo experiments [153, 154]. However, at least one study in adult patients found a median protein binding of 39%, with a range from 1 to 48% [155], and other studies have found the estimated free fraction of cefepime to be unreliable [59]. Several factors may affect the in vitro protein-binding estimates including pH, temperature, centrifugal force, length of sample storage, and associated freeze-thaw cycles. It is recommended to control all these factors when conducting such experiments [156-158]. However, until more data are available and the free fraction determination is standardized, it is not clear that individually measured free fractions are representative of the physiologic environment or are reproducible [59]. Thus, measurement of total cefepime concentrations with a population-adjustment for protein binding (e.g., 80% free fraction) is a reasonable approach.

5.2 Drug Stability

Availability of accurate assays to measure drug concentrations is essential for implementing a therapeutic drug monitoring program for cefepime. A well-validated assay is pertinent for both research purposes and clinical application, but component priorities within these domains may differ slightly. In research, samples are often collected and batched for future analysis. Stability must be demonstrated at various concentrations, over time, and under specific storage conditions. Specifications for these analyses are governed by FDA guidance for bioanalytical method validation [159]. In clinical practice, stability in the presence of commonly used coexistent medications and conditions, ability to detect levels across the expected clinically relevant range, and rapidity of the test turnaround affect clinical utility (in addition to the accuracy and precision requirements). Early reports cast doubt on whether

cefepime would be stable long enough for a clinical assay, a finding that unless cefepime was treated immediately with a buffer or water, significant degradation occurred within 1 hour at typical ambient temperatures. The recent emphasis placed on developing new beta-lactam pharmacokinetic models, particularly using scavenged blood specimens [28, 84, 160-162], and applied therapeutic drug monitoring [163-165] has led to the proliferation of cefepime assay validation reports using contemporary blood collection media/additives [157, 166-170].

One study described the development and validation of a rapid high-performance liquid chromatography tandem mass spectrometry method for characterizing cefepime concentrations [166]. Sample stability was compared between ambient (20–25 °C), refrigerated (2–8 °C), or frozen (– 20 °C or – 70 °C) temperatures over 35 days and with several freeze/thaw cycles. When frozen at – 70 °C, cefepime was stable for up to 35 days with up to three freeze/thaw cycles. Others have demonstrated extended stability to 3 months at – 80 °C, though degradation of cefepime at room temperature was 30.1% at 24 h [167]. Under ambient and refrigerated conditions, stability lasted up to 4 h and 24 h, respectively. These findings build upon previous data that describe rapid degradation of cefepime at room temperature [171]. Another study demonstrated the concentration dependence of cefepime degradation at 37 °C. At 10 mg/L, cefepime concentration decreased by 50% within 2 h, whereas at a concentration of 500 mg/L, well in excess of a normal physiologic exposure, a 50% decrease in cefepime concentration took 6 h [157]. Under refrigerated or frozen conditions, varying the concentration within the typical analytical range did not affect cefepime stability. Use of different tubes and anticoagulants or separator gels resulted in an average difference in concentration from the serum of < 10% [166]. Consistent cefepime assay performance was observed at low, medium, and high drug concentrations [166, 168]. No assay interference was detected from the top 25 prescribed drugs, commonly used concomitant medications, or drugs of abuse. These included relevant medications in the critically ill such as other antimicrobials, antiarrhythmics, analgesics, sedatives, vasopressors, and antithrombotics. Hyperbilirubinemia, hemolysis, and lipemia did not affect assay performance [166]. Reports demonstrate high-throughput assays with short cycle times (less than 10 min) make bedside application feasible [166, 167, 172, 173].

5.3   Cefepime Therapeutic Drug Monitoring

While the impact of real-time therapeutic drug monitoring for cefepime has not been prospectively studied to our knowledge, a small report found a mortality benefit for patients receiving a continuous infusion of cefepime when compared with a traditional intermittent infusion [174]. Separately, higher pathogen MICs [175] and lower rates of target attainment [102] were associated with worse mortality for Gram-negative bloodstream infections. It follows that improving exposures could improve patient outcomes; however, this remains to be prospectively studied.

6   Conclusions

Cefepime is often safe and efficacious even in high doses when administered as an extended or continuous infusion. Therapeutic drug monitoring is warranted in special populations

including patients with critical illness, renal insufficiency, and underlying neurological disorders. In these cases, monitoring is suggested to avoid underdosing in the case of patients with increased CL and/or Vd, and to prevent adverse neurological effects due to an accumulation of cefepime in patients with neurological conditions or renal insufficiency.

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Key Points

Cefepime is generally safe and efficacious, however, reports of neurotoxicity have increased in recent years, specifically in patients with impaired renal function.

Cefepime is 85% eliminated as an unchanged drug in the urine. Serum concentrations are affected by changes in renal clearance and volume of distribution; substantial inter-patient variability exists in infected individuals, which poses challenges for population dosing approaches.

Therapeutic drug monitoring is facilitated by liquid chromatography tandem mass spectrometry assays and can be considered in inflammatory conditions and critical illness where high variability is observed in the cefepime volume of distribution and clearance.

Administration by prolonged and continuous infusion can help maximize pharmacodynamic benefit by increasing cefepime free drug concentrations above the minimum inhibitory concentration of bacteria for prolonged periods of time.
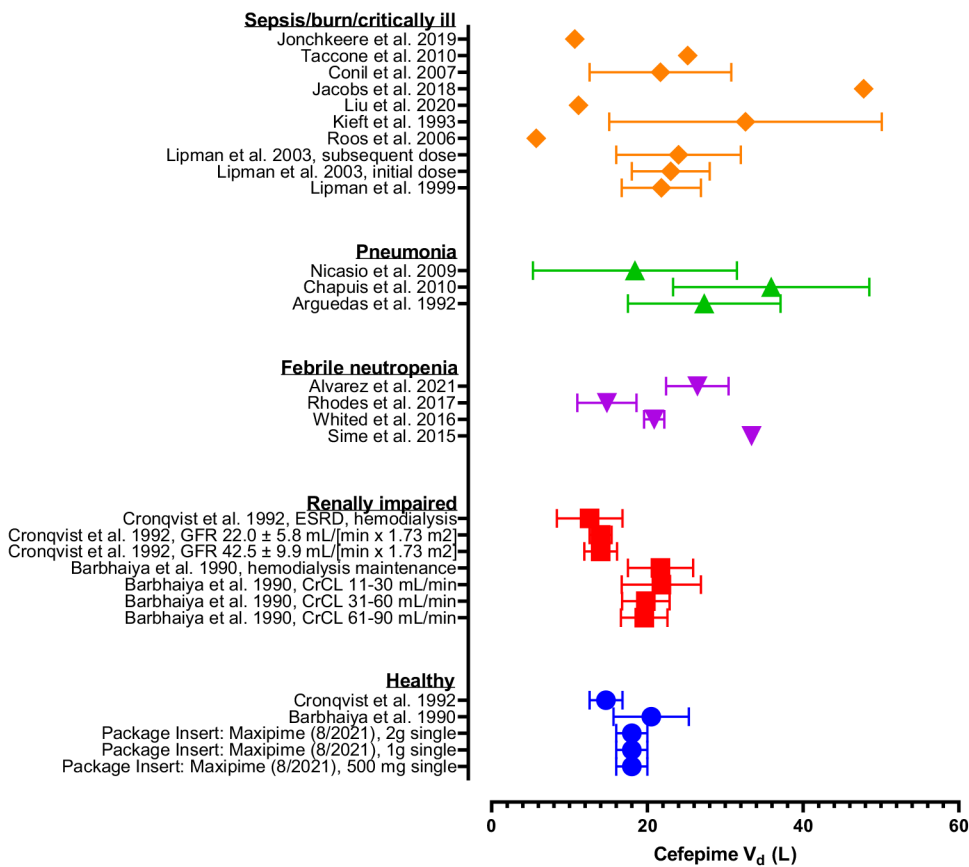
Fig. 1.
Variability in cefepime volume of distribution (V_d) in different pathological conditions.
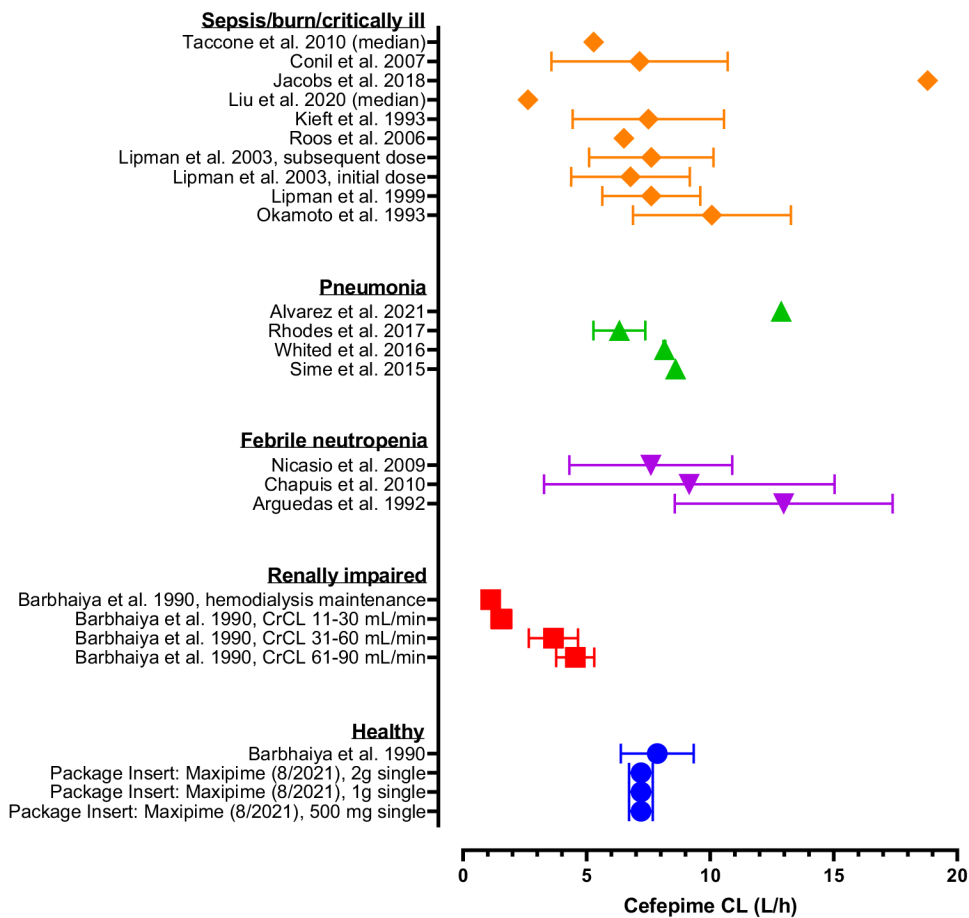*CrCL* creatinine clearance, *ESRD* end-stage renal disease, *GFR* glomerular filtration rate

Fig. 2.

Variability in cefepime clearance (CL) in different pathological conditions. *CrCL* creatinine clearance
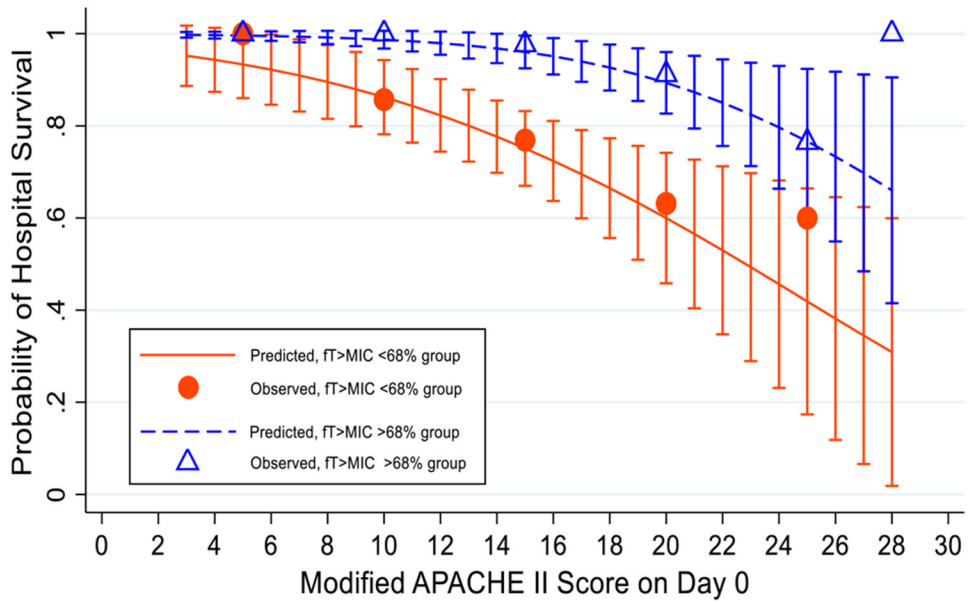
Fig. 3.
Hospital survival for those that reach their cefepime pharmacodynamic goal (blue triangles) and those who do not (red circles) as a function of the APACHE II score [106]

Table 1

Representative parameter estimates in various populations

Dosage regimen	Patient population	PK model	No. of pts	Cmax (mg/L)	MRT (h)	AUC (mg.h/L)	V_SS (L)	V (L/kg)	V_1 (L)	t_{1/2} (h)	CL (mL/min)	CL (L/h)	CL (mL/min/kg)	References
500 mg Single	Healthy adults	NA	9	39.1 ± 3.5	NA	70.8 ± 6.7	18 ± 2	NA	NA	2 ± 0.3	**120 ± 8**	7.2 ± 0.48	NA	Maxipime prescribing information 2021
1 g Single	Healthy adults	NA	9	81.7 ± 5.1	NA	148.5 ± 15.1	18 ± 2	NA	NA	2 ± 0.3	**120 ± 8**	7.2 ± 0.48	NA	Maxipime prescribing information 2021
2 g Single	Healthy adults	NA	9	163.9 ± 25.3	NA	284.8 ± 30.6	18 ± 2	NA	NA	2 ± 0.3	**120 ± 8**	7.2 ± 0.48	NA	Maxipime prescribing information 2021
1 g Single, infused over 30 min	CrCL >90 mL/min	Non-compartmental	5	63.5 ± 7.79	2.86 ± 0.24	131 ± 22.8	20.5 ± 4.84	NA	NA	2.29 ± 0.55	**131.0 ± 24.6**	7.86 ± 1.476	NA	Barbhaiya et al. (1990) [21]
1 g Single, infused over 30 min	CrCL 61–90 mL/min	Non-compartmental	5	70.5 ± 20.8	4.60 ± 0.58	225 ± 37.7	19.6 ± 2.99	NA	NA	3.33 ± 0.74	**75.7 ± 12.9**	4.542 ± 0.774	NA	
1 g Single, infused over 30 min	CrCL 31–60 mL/min	Non-compartmental	5	73.9 ± 19.5	5.88 ± 1.16	292 ± 89.3	19.8 ± 3.05	NA	NA	4.89 ± 0.82	**61.0 ± 16.6**	3.66 ± 0.996	NA	
1 g Single, infused over 30 min	CrCL 11–30 mL/min	Non-compartmental	5	68.9 ± 16.0	14.7 ± 3.39	683 ± 192	21.8 ± 5.10	NA	NA	10.5 ± 2.96	**25.9 ± 6.73**	1.554 ± 0.4038	NA	
1 g Single, infused over 30 min	CrCL < 10 mL/min, hemodialysis maintenance	Non-compartmental	5	65.5 ± 9.18	20.0 ± 3.84	928 ± 202	21.7 ± 4.20	NA	NA	13.5 ± 2.65	**18.7 ± 5.18**	1.122 ± 0.3108	NA	
1 g Single, infused over 5 min	GFR 107 ± 4.1 mL/[min × 1.73 m²], healthy adults	Non-compartmental	5	109.2 ± 22.6^c	2.39 ± 0.09	153 ± 30^c	0.21 ± 0.03	NA	NA	1.8	NA	NA	97.2 ± 7.8 (ml/[min × 1.73 m2])	Cronqvist et al. (1992) [22]
1 g Single, infused over 5 min	GFR 42.5 ± 9.9 mL/[min × 1.73 m²]	Non-compartmental	6	114.9 ± 15.3	6.75 ± 1.56	482 ± 142	NA	0.20 ± 0.03	NA	4.7	NA	NA	34.6 ± 9.6 (ml/[min × 1.73 m2])	
1 g single, infused over 5 min	GFR 22.0 ± 5.8 mL/[min × 1.73 m2]	Non-compartmental	7	117.7 ± 21.6	11.43 ± 3.68	897 ± 257	NA	0.20 ± 0.02	NA	7.55	NA	NA	19.8 ± 6.3 (ml/[min × 1.73 m2])	

Dosage regimen	Patient population	PK model	No. of pts	Cmax (mg/L)	MRT (h)	AUC (mg.h/L)	Vss (L)	V (L/kg)	V1 (L)	t1/2 (h)	CL (mL/min)	CL (L/h)	CL (mL/min/kg)	References
1 g Single, infused over 5 min	End-stage renal disease, hemodialysis	Non-compartmental	3	130.4 ± 23.4	31.56 ± 6.11	2,659 ± 361	NA	0.18 ± 0.06	NA	21.13	NA	NA	6.3 ± 2.3 (ml/[min × 1.73 m2])	Kovarik et al. (1990) [73]
1g q12h	Respiratory tract infection	Multi-compartmental	10	71.2 ± 17.2	3.57 ± 0.73	251 ± 97.5	NA	NA	NA	3.92 ± 1.28	NA	NA	73 ± 19.7 (ml/[min × 1.73 m2])	
50 mg/kg q8h	Cystic fibrosis	Non-compartmental	12	141.3 ± 34.9	2.28 ± 1.00	277 ± 103	NA	0.39 ± 0.14 L/kg	NA	1.73 ± 0.69	NA	NA	3.09 ± 1.05	Arguedas et al. (1992) [23]
2g q12h	Acute cholecystitis	NA	15	122.1 ± 28.5	2.4 ± 0.4	216.1 ± 62.7	NA	0.26 ± 0.07 L/kg	NA	1.79 ± 0.38	167.9 ± 0.38	10.074 ± 0.0228	NA	Okamotol et al. (1993) [71]
2g q12h, Infused over 30 min	Nosocomial pneumonia	Non-compartmental	11	97 ± 8	5.3 ± 5.9	226 ± 107	0.413 ± 0.118 L/Kg	0.513 ± 0.180 L/Kg	NA	4.33 ± 4.32	NA	NA	2.18 ± 1.4	Chapuis et al. (2010) [25]
2 g q8 h, Infused over 3 h	Ventilator-associated pneumonia	Two compartment	26	NA	NA	NA	NA	0.263 ± 0.187 L/kg	22.1 ± 6.1	7.37 ± 11.55[a]	NA	7.6 ± 3.3	126.7 ± 55	Nicasio et al. (2009) [26]
2g q8h	Febrile neutropenia	Non-compartmental	12	NA	NA	269	33.4	NA	NA	2.7	NA	8.6	NA	Sime et al. (2015) [33]
2g q8h	Febrile neutropenia	One compartment	9	NA	NA	NA	20.9 ± 1.3	NA	NA	1.78 ± 1.7[a]	NA	8.15 ± 0.04[a]	NA	Whited et al. (2016) [34]
2g q8h	Febrile neutropenia	Two compartment	9	NA	NA	NA	NA	NA	14.8 ± 3.8	1.62 ± 0.19[a]	NA	6.33 ± 1.05	NA	Rhodes et al. (2017) [31]
2g q8h	Febrile neutropenia	Two compartment	15	NA	NA	NA	NA	NA	26.43 ± 4.01	0.80[a]	NA	12.88	NA	Alvarez et al. (2021) [32]
2g Single, infused over 3 min (1 day)	Critically ill septic	Two compartment	10	NA	3.1 ± 1.1	283 ± 85	21.8 ± 5.1	NA	NA	3.0 ± 1.2	127 ± 33	7.62 ± 1.98	NA	Lipman et al. (1999) [27]
2g Single, infused over 3 min	Critically ill septic	Non-compartmental (initial dose)	13	NA	NA	339 ± 149	23 ± 5	NA	NA	3.3 ± 1.5	113 ± 40	6.78 ± 2.4	NA	Lipman et al. (2003) [30]
2g q12h, Infused over 3 min	Critically ill septic	Non-compartmental (subsequent dose)	12	NA	NA	346 ± 225	24 ± 8	NA	NA	3.2 ± 2.1	127 ± 42	7.62 ± 2.52	NA	
2g q12h, Infused over 3 min	Critically ill septic	Three compartment	13	NA	NA	NA	NA	NA	5.74	NA	NA	6.51	NA	Roos et al. (2006) [28]

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Dosage regimen	Patient population	PK model	No. of pts	Cmax (mg/L)	MRT (h)	AUC (mg.h/L)	Vss (L)	V (L/kg)	V1 (L)	t1/2 (h)	CL (mL/min)	CL (L/h)	CL (mL/min/kg)	References
2g q12h, Infused over 30 min	Sepsis syndrome	Non-compartmental	7	94.2 ± 23.9	4.4 ± 1.2	305 ± 115	32.6 ± 17.5	NA	NA	3.42 ± 1.12	125 ± 51	7.5 ± 3.06	NA	Kieft et al. (1993) [37]
NA	Adult and pediatric	Two compartment	33	NA	NA	NA	11.172 (median)	NA	1.716 (median)	2.936 (median)	NA	2.63 (median)	NA	Liu et al. (2020) [38]
NA	Septic patients with ARC	One compartment	11	40.7 (35.4–48.3) median (IQR)	NA	NA	47.8	NA	NA	2.5 (2.0-3.0) median (IQR)	NA	18.8	NA	Jacobs et al. (2018) [39]
2g q8h, Infused over 20 min	Burn patients	NA	13	140.4 ± 58.7	NA	840	NA	0.31 ± 0.13	NA	2.9 ± 3.2	119.1 ± 59.6	7.146 ± 3.57	NA	Conil et al. (2007) [76]
2g single, Infused over 30 min	Sepsis patients	One compartment	19	68 (51–86) median (range)	NA	310 (234-422) median (range)	NA	0.36 (0.33–0.44) median (range)	NA	3.37 (2.26-5.34) median (range)	NA	5.292 (4.494-8.19) median (range)	1.26 (1.07-1.95) median (range)	Taccone et al. (2010) [110]
1.3-1.8g target controlled infustion, 4days	Critically ill	Two compartment	21	NA	NA	NA	NA	NA	10.7	NA	NA	NA	NA	Jonchkeere et al. (2019) [111]
4 g/d, Continuous infusion	Critically ill	NA	26	NA	NA	612 ± 369	NA	NA	NA	NA	NA	NA	NA	Georges et al. (2005) [4]
2g q12h, Infused over 30 min	Critically ill	NA	24	115	NA	623 ± 319	NA	NA	NA	NA	NA	NA	NA	
NA	Pediatric, ECMO	Two compartment	17	NA	NA	NA	NA	NA	1.17/5.8 kg	NA	7.1/5.8kg	0.426/5.8 kg	1.22	Zuppa et al. (2019) [59]
4g/d, 76.6 mg/min Intermittent infusion	Adult, ECMO	Two compartment	5	NA	NA	NA	15.09 ± 3.33	NA	NA	4.3 ± 1.49	NA	2.43 ± 1.55	NA	Cheng et al. (2021) [60]
2g q8h, By continuous venovenous hemodiafiltration	Adult, ECMO	Two compartment	1	NA	NA	NA	16.63	NA	NA	NA	NA	1.04	NA	
1g Single, infused over 30 min	Hemodialysis	NA	5	NA	NA	NA	NA	NA	NA	NA	60.1 ± 2.6 for 100 mL/min dialysis blood flow rate	3.606 ± 0.156 for 100 mL/min dialysis blood flow rate	NA	Maynor et al. (2008) [61]
2g 3x/wk Post-dialysis	Hemodialysis	Non-compartmental	6– intradialytic	78.6 ± 10.2	NA	178.2 ± 32.2	NA	NA	16.7 ± 5.6	1.6 ± 0.29	126.8 ± 24.0	7.608 ± 1.44	NA	Schmaldienst et al. (2000) [62]

Dosage regimen	Patient population	PK model	No. of pts	Cmax (mg/L)	MRT (h)	AUC (mg.h/L)	Vss (L)	V (L/kg)	V1 (L)	t1/2 (h)	CL (mL/min)	CL (L/h)	CL (mL/min/kg)	References
~ 1g 3x/wk Post-dialysis as a 5-10 min infusion	Hemodialysis	Non-compartmental	interdialytic	93.6 ± 40.1	NA	2327.3 ± 288.9	NA	NA	NA	22 ± 2.14	14.5 ± 1.7	0.87 ± 0.102	NA	Descombes et al. (2016) [63]
		NA	9	10.7 ± 3.9 (pre-dialysis)	NA	NA	NA	NA	NA	NA	NA	NA	NA	
				1.96 ± 1.2 (post-dialysis)	NA	NA	NA	NA	NA	NA	NA	NA	NA	
2g q8h, Infused over 30 min	CRRT	One compartment	3	74.5 (52.0–75.0)	NA	NA	19.4 (15.8–23.1) median (range)	0.26 (0.24–0.28) median (range)	NA	4.3 (1.5–9.7) median (range)	NA	**0.0524 (0.0273–0.1209)**	NA	Beumier et al. (2014) [66]
			6	93.4 (50.5–165.0)	NA	NA	19.2 (11.4–32.9) median (range)	0.21 (0.16–0.51) median (range)	NA	8.0 (6.0–35.3) median (range)	NA	**0.023 (0.005–0.058) median (range)**	NA	
2g q8h, Infused over 4h, extended or continuous infusion	CRRT	Five compartment	10	NA	NA	NA	26.76 ± 15.09	NA	NA	9.9 ± 13.89	NA	1.87 ± 0.753	NA	Al-Shaer et al. (2021) [44]
2g q8h or 2g q12h, Infused over 30 min	CRRT	One compartment	13	NA	NA	NA	40.9	NA	NA	NA	NA	**4.4**	NA	Carlier et al. (2015) [67]
2g Loading dose followed by 1g q6h	Extended or continuous infusion	One compartment	5000	NA	NA	NA	NA	0.48 ± 0.24	NA	NA	**24.33 ± 11.25 (non-renal)**	1.46 ± 0.675	NA	Jang et al. (2018) [69]
1 g Single, infused over 30 min	Peritoneal dialysis	Non-compartmental	5	62.9 ± 15.8	24.0 ± 3.1	1166 ± 356	21.7 ± 4.8	NA	NA	17.6 ± 2.9	**15.4 ± 4.9**	0.924 ± 0.294	NA	Barbhaiya et al. (1992) [64]
2 g Single, infused over 30 min	Adult, non-infected, continuous ambulatory peritoneal dialysis	Non-compartmental	5	124 ± 14	26.8 ± 1.5	2405 ± 213	22.5 ± 2.8	NA	NA	18.8 ± 1.6	**14.0 ± 1.3**	0.84 ± 0.078	NA	
15 mg/kg ip	Adult, non-infected, automated peritoneal dialysis	Mono-exponential model	6	38.5 ± 5.1	NA	NA	NA	0.34 ± 0.07	NA	13.8 ± 3.2	**16.5 ± 4.4**	0.99 ± 0.264	NA	Elwell et al. (2005) [65]

Dosage regimen	Patient population	PK model	No. of pts	Cmax (mg/L)	MRT (h)	AUC (mg.h/L)	V_{SS} (L)	V (L/kg)	V_1 (L)	$t_{1/2}$ (h)	CL (mL/min)	CL (L/h)	CL (mL/min/kg)	References
50 mg/kg q8 h	Children	Non-compartmental	31	184.2 ± 38	NA	NA	NA	0.33 ± 0.1	NA	1.8 ± 0.6	NA	NA	**2.8 ± 1.4**	Reed et al. (1997) [82]
50 mg/kg q12 h	Neonates	One compartment	55	89 ± 27[b]	NA	NA	NA	0.43 ± 0.13	NA	4.9 ± 2.1	NA	NA	**1.15 ± 0.45**	Cappareli et al. (2005) [79]
50 mg/kg q12 h	Neonates	One compartment	31	120.9 ± 38.5	NA	NA	NA	0.41 ± 0.12	NA	4.32 ± 1.8	NA	NA	**1.20 ± 0.49**	Lima-Rogel et al. (2008) [80]
30 mg/kg q12 h	Neonates	One compartment	85	NA	NA	112 to 379	NA	0.62 ± 0.24	NA	2.387 ± 3.02	NA	NA	3.0 ± 0.83	Zhao et al. (2020) [81]

Values are expressed as mean ± SD.

NA not available

[a] calculated

[b] Estimated for a 30 mg/kg every 12 h dose .

[c] Two subjects were excluded after being given half the intended dose by mistake.

ECMO, extracorporeal membrane oxygenation; ARC, augmented renal clearance; CRRT, continuous renal replacement therapy Clearance in bold is taken from the reference. Clearance in plain type is converted into the corresponding units.

Table 2

Recommendations for maximum population-based cefepime dosing regimens in critically ill patients receiving continuous renal replacement therapy

Study, year	Effluent rates (L/h)[a]	CVVH	CVVHD or CVVHDF
Trotman et al. (2005) [176]	Not available	1–2 g q12h	2 g q12h
Heintz et al. (2009) [177]	Not available	1–2 g q12h	1 g q8h or 2 g q12h
Scheetz et al. (2006) [68]	1	2g q24h	2 g q24h
	2	2g q12h	2 g q12h
	3	2g q8h	2 g q8h
Carlier et al. (2015) [67]	1	1 g q8h	1 g q8h
	2	2 g q8h	2 g q8h or 1 g q6h
	3	2 g q8h	2 g q8h or 1 g q6h
Chaijamorn et al. 2018)[b] [178]	1	1.75 g LD then 1.5 g q8h	1.75 g LD then 1.5 g q8h
	2	2 g LD then 1.5 g q8h	1.75 g q8h
	3	2 g LD then 1.5-1.75 g q8h	2 g q8h
Philpott et al. (2019) [179]	1	Not available	Not available
	2	2 g q8h as a 4-h infusion	2 g q8h as a 4-h infusion
	3	2 g q8h as a 4-h infusion	2 g q8h as a 4-h infusion

CVVH continuous venovenous hemofiltration, *CVVHD* continuous venovenous hemodialysis, *CVVHDF*, *h* hour, *LD* loading dose, *q6h* every 6 h, *q8h* every 8 h, *q12h* every 12 h, *q24h* every 24 h

[a]Effluent rates in mL/kg/h were converted to L/h

[b]Dosing for minimum inhibitory concentrations up to 8 μg/mL