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A Monte Carlo Simulation Approach for Beta-Lactam Dosing in Critically Ill Patients Receiving Prolonged Intermittent Renal Replacement Therapy

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Abstract

Cefepime, ceftazidime, and piperacillin/tazobactam are commonly used beta-lactam antibiotics in the critical care setting. For critically ill patients receiving prolonged intermittent renal replacement therapy (PIRRT), limited pharmacokinetic data are available to inform clinicians on the dosing of these agents. Monte Carlo simulations (MCS) can be used to guide drug dosing when pharmacokinetic trials are not feasible. For each antibiotic, MCS using previously published pharmacokinetic data derived from critically ill patients was used to evaluate multiple dosing regimens in 4 different prolonged intermittent renal replacement therapy effluent rates and prolonged intermittent renal replacement therapy duration combinations (4 L/h × 10 hours or 5 L/h × 8 hours in hemodialysis and hemofiltration modes). Antibiotic regimens were also modeled depending on whether drugs were administered during or well before prolonged intermittent renal replacement therapy therapy commenced. The probability of target attainment (PTA) was calculated using each antibiotic's pharmacodynamic target during the first 48 hours of therapy. Optimal doses were defined as the smallest daily dose achieving ≥90% probability of target attainment in all prolonged intermittent renal replacement therapy effluent and duration combinations. Cefepime 1 g every 6 hours following a 2 g loading dose, ceftazidime 2 g every 12 hours, and piperacillin/tazobactam 4.5 g every 6 hours attained the desired pharmacodynamic target in ≥90% of modeled prolonged intermittent renal replacement therapy patients. Alternatively, if an every 6-hours cefepime regimen is not desired, the cefepime 2 g pre-prolonged intermittent renal replacement therapy and 3 g post-prolonged intermittent renal replacement therapy regimen also met targets. For ceftazidime, 1 g every 6 hours or 3 g continuous infusion following a 2 g loading dose also met targets. These recommended doses provide simple regimens that are likely to achieve the pharmacodynamics target while yielding the least overall drug exposure, which should result in lower toxicity rates. These findings should be validated in the clinical setting.

Keywords

cefepime, ceftazidime, Monte Carlo simulation, piperacillin/tazobactam, pharmacokinetics, renal replacement therapy

The primary cause of acute kidney injury (AKI) in critically ill patients is sepsis. AKI is associated with high mortality rates (>50%)[1] and often requires treatment with renal replacement therapy. Currently, different types of renal replacement therapy are used in intensive care units (ICUs) including intermittent hemodialysis, continuous renal replacement therapy (CRRT), and hybrids of conventional renal replacement therapies that are known by many names, including sustained low-efficiency dialysis (SLED), extended daily dialysis, or prolonged intermittent renal replacement therapy.[2] The hybrid renal replacement therapies are gaining usage because of improved patient mobility compared with CRRT, lower renal replacement therapy operation cost compared with CRRT, and better hemodynamic tolerance compared with intermittent hemodialysis.[2–6] Despite the advantages of prolonged intermittent renal replacement therapy, some clinicians are hesitant to use it because of the lack of pharmacokinetic studies (fewer than 1% of drugs have been studied[7] to support appropriate antibiotic dosing regimens).[8,9] This is concerning because the 2016 Surviving Sepsis Campaign guideline recommends not only antibiotic therapy to be administered as soon as possible but also antibiotic dosing strategies to be optimized based on specific drug

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properties in patients with sepsis to improve patient outcomes.[10] In silico analyses via Monte Carlo simulation (MCS) have been used to provide initial dosing guidance to clinicians if conducting pharmacokinetic studies is not feasible or when they have not been conducted.[11–14] The MCS approach can incorporate the influence of different renal replacement therapies and pharmacokinetic profiles derived from specific patient populations. In this case, existing antibiotic pharmacokinetic data derived from critically ill patients can be linked with known renal replacement therapy drug clearance characteristics allowing clinical researchers to predict the efficacy and safety of any drug dosing and renal replacement therapy combination.

Ceftazidime and cefepime are third- and fourth-generation cephalosporins, respectively, with antimicrobial activity against gram-positive and gram-negative bacteria, including *Pseudomonas aeruginosa*.[15,16] Piperacillin/tazobactam is a beta-lactam/beta-lactamase inhibitor antibiotic combination product with broad-spectrum antibacterial activity against *P. aeruginosa* and CTX-M beta-lactamase-producing *Enterobacteriaceae*.[17] The antibacterial effect of piperacillin/tazobactam is primarily attributable to the activity of piperacillin, whereas tazobactam inhibits piperacillin hydrolysis by beta-lactamases. Like other cephalosporins and beta-lactams, ceftazidime, cefepime, and piperacillin/tazobactam exhibit time-dependent bactericidal activity, and their clinical outcome may be predicted by the time of the free serum concentration above the minimum inhibitory concentration (fT>MIC) of the causative pathogen.[18] Maximum bactericidal activity and suppression of bacterial resistance may be achieved when the free drug concentration is between 1 and 4 × MIC.[18] Even though beta-lactam typically has a time-dependent activity, these drugs have been shown to exhibit concentration-dependent bactericidal activity up to an MIC of 4.[18,19] We chose pharmacodynamics targets to be free concentration at least 50% (piperacillin/tazobactam)[19] and 60% (cefepime and ceftazidime)[20] above 4 × MIC of the dosing interval (fT>4 × MIC) to maximize bactericidal activity within the first 48 hours.[18,21–23] Cefepime therapy has recently been associated with neurotoxicity, particularly in patients with renal impairment.[24] Numerous case reports have documented cefepime-related neurological toxicity, including encephalopathy, confusion, myoclonus, and seizures, with coma and death observed in some cases.[24–26] Because of the rising incidence of cefepime-induced toxicity, the US Food and Drug Administration released a safety announcement in 2012 to remind clinicians of the need to reduce cefepime doses in patients with renal impairment.[27] Both ceftazidime and piperacillin are also associated with neurotoxicity.[28] Currently, there is limited information on dosing cefepime, ceftazidime, and piperacillin/tazobactam in critically ill patients receiving prolonged intermittent renal replacement therapy.

In this study, MCS was performed to formulate cefepime, ceftazidime, and piperacillin/tazobactam dosing recommendations for critically ill patients receiving 4 common settings of prolonged intermittent renal replacement therapy. The objectives of this MCS study were: (1) to determine probability of target attainment over 48 hours of therapy for many dosing regimens, and (2) to predict empiric dosing regimens for listed beta-lactams that are most likely to attain the pharmacodynamic target to treat *P. aeruginosa* infections in critically ill patients receiving daily prolonged intermittent renal replacement therapy.

Methods

Mathematical Pharmacokinetic Model

A 1-compartment, first-order, and multiple-dose pharmacokinetic model was developed to evaluate the effect of prolonged intermittent renal replacement therapy on the plasma concentration-time profile of cefepime, ceftazidime, and piperacillin/tazobactam. Table 1 outlines demographic and pharmacokinetic parameters that were used in this MCS study. Pharmacokinetic data (volume of distribution [V_d], unbound fraction, and nonrenal clearance [CL_{NR}]) were collected from published studies via PubMed searches.[8,29–52]

Four different prolonged intermittent renal replacement therapy settings commonly used in practice were simulated: 8 hours a day (ultrafiltration rate/dialysate flow rate of 5 L/h) or 10 hours a day (ultrafiltration rate/dialysate flow rate of 4 L/h) of hemofiltration (HF) or hemodialysis (HD). Ultrafiltrate replacement using the predilution technique (all replacement solutions were infused before hemodiafilter) was modeled for all HF simulations. The timing of cefepime, ceftazidime, and piperacillin/tazobactam dose relative to prolonged intermittent renal replacement therapy was also evaluated at the 2 possible extremes. The first dose administered at the start of prolonged intermittent renal replacement therapy (T0) or 14 to 16 hours before the next session of prolonged intermittent renal replacement therapy (T14 and T16); see Figure 1A and B. Blood flow rate (Q_b) was fixed at 300 mL/min for all settings. Drug clearance during hemodialysis and hemofiltration modalities of prolonged intermittent renal replacement therapy was estimated using the following equations:

Equation 1. Hemofiltration clearance

$$CL_{HF} = S_C \times Q_{uf} \times \frac{Q_{plasma}}{(Q_{plasma} + Q_{uf})}$$

Table 1. Demographic and Pharmacokinetic Parameters Used in Monte Carlo Simulations

	Cefepime	Ceftazidime	Piperacillin	Tazobactam
Weight (kg)	86.6 ± 29.2 kg (≥40 kg)[29]	86.6 ± 29.2 kg (≥40 kg)[29]	86.6 ± 29.2 kg (≥40 kg)[29]	86.6 ± 29.2 kg (≥40 kg)[29]
Vd (L/kg)	0.48 ± 0.24 (0.16-1.11)[30–35]	0.34 ± 0.20 (0.13-1.1)[38–43]	0.40 ± 0.21 (0-1.11)[29,48–50]	0.50 ± 0.37 (0-2.13)[49]
Free fraction	0.79 ± 0.09 (0.72-0.85)[31]	0.86 ± 0.05[39,40,43] (0-1)	0.76 ± 0.2[49,51,52] (0-1)	0.74 ± 0.27[49] (0-1)
CL_{NR} (mL/min)	24.33 ± 11.25 (13–44)[30–35]	15.9 ± 9.9[38–40,42–44] (8-37.7)	48.5 ± 37[8,29,49,50] (0-187)	40.4 ± 70[49] (0-381)
Sieving coefficient	0.86 ± 0.15 (0-1)	0.66 ± 0.13 (0-1)	0.5 ± 0.3 (0-1)	0.76 ± 0.26 (0-1)
Saturation coefficient	0.52 ± 0.10 (Q_{ef} 4 L/h) 0.45 ± 0.08 (Q_{ef} 5 L/h)	0.43 ± 0.09 (Q_{ef} 4 L/h) 0.36 ± 0.07 (Q_{ef} 5 L/h)	0.6 ± 0.28 (0-1)	0.8 ± 0.36 (0-1)
Hemofiltration clearance (mL/min)	34.7 (Q_{ef} 4 L/h) 37.5 (Q_{ef} 5 L/h)[31,32]	33.4 (Q_{ef} 4 L/h) 39.4 (Q_{ef} 5 L/h)[38,39,41,43–45]	25 (Q_{ef} 4 L/h) 30 (Q_{ef} 5 L/h)[51,52]	38 (Q_{ef} 4 L/h) 45 (Q_{ef} 5 L/h)[51,52]
Hemodialysis clearance (mL/min)	46.4 (Q_{ef} 4 L/h) 54.6 (Q_{ef} 5 L/h)[31,32,36,37]	28.7 (Q_{ef} 4 L/h) 30 (Q_{ef} 5 L/h)[39,40,42,43,45–47]	40 (Q_{ef} 4 L/h) 50 (Q_{ef} 5 L/h)[8,48–50]	53 (Q_{ef} 4 L/h) 67 (Q_{ef} 5 L/h)[49]
Correlation between weight and Vd (r^2)	0.4197	0.0237	0.0567	0.0049
Correlation between weight and CL_{NR} (r^2)	0.038	0.1254	0.036	0.0098

CL_{NR}, nonrenal clearance; Vd, volume of distribution; Q_{ef}, effluent rate.
All values are mean ± SD (minimum-maximum limits).

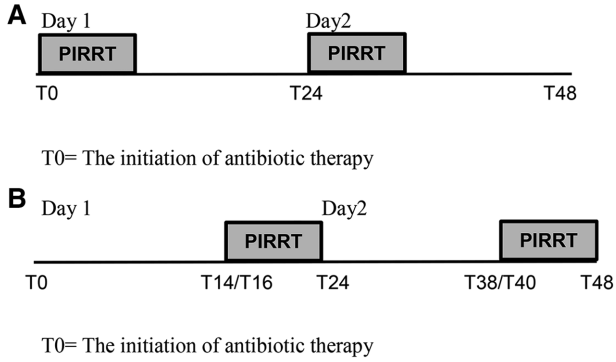

Figure 1. (A) prolonged intermittent renal replacement therapy initiated at the beginning of the antibiotic therapy (T0) for 8- and 10-hour hemofiltration or hemodialysis. (B) prolonged intermittent renal replacement therapy initiated 14 hours after the first antibiotic dose (T14 with 10-hour/T16 with 8-hour) hemofiltration or hemodialysis.

where CL_{HF} represents the transmembrane clearance during predilution hemofiltration, S_C represents the sieving coefficient, Q_{uf} represents the ultrafiltration flow rate, and Q_{plasma} represents the plasma flow rate.

Equation 2. Plasma flow rate

$$Q_{plasma}(L/h) = Q_b(L/h) \times (1 - \text{hematocrit})$$

where Q_b represents the blood flow rate.

Equation 3. Hemodialysis clearance

$$CL_{HD} = S_A \times Q_d$$

where CL_{HD} represents the transmembrane clearance during hemodialysis, S_A represents the saturation coefficient, and Q_d represents the dialysate flow rate.

Based on published data in different types of renal replacement therapies, regression analysis was used to estimate saturation and sieving coefficients for the effluent flow rates used in our model. Hematocrit was assumed to be 30% for the plasma flow rate calculation, as this is a common hematocrit in subjects receiving prolonged intermittent renal replacement therapy,[53] and the replacement fluid flow rate equaled the fluid removal rate during predilution HF (no net fluid loss).

Dosing Simulations

Many different dosing regimens were simulated in the MCS for cefepime, ceftazidime, and piperacillin/tazobactam (Table 2). All modeled doses were administered either every 6 hours, every 8 hours, every 12 hours, every 24 hours, by extended infusion (4 hours), by continuous infusion (24 hours), or at the start (pre) and end (post) of prolonged intermittent renal replacement therapy. For continuous infusion (CI) dosing regimens, the loading dose was infused over 0.5 hours, followed immediately by the CI dose, which was infused at a rate of the CI dose/24 hours. Plasma drug concentration-time profiles were generated by the MCS (Crystal Ball, Oracle) in 5000 virtual subjects for each dosing regimen. Variability within the virtual subjects was embedded within our model by using the mean and standard deviation (SD) of the pharmacokinetic parameters (eg, weight, V_d, free

Table 2. Dosing Regimens Simulated for Cefepime, Ceftazidime, Piperacillin, and Tazobactam

	Administration Strategies			
Frequency	Cefepime	Ceftazidime	Piperacillin	Tazobactam
Every 6 hours	1 g	1 g	2 g	0.375 g
	2 g LD, 1 g	2 g LD, 1 g	2 g EI	0.375 g EI
	3 g LD, 1 g[a]		3 g	0.5 g
			3 g EI	0.5 g EI
			4 g	
			4 g EI	
Every 8 hours	1 g	1 g	2 g	0.5 g
	1 g EI	2 g LD, 1 g	3 g	
	2 g[a]	2 g[b]	4 g	
	2 g EI[a]			
Every 12 hours	1 g	1 g	N/A	N/A
	1 g EI	1 g EI		
	2 g	2 g		
	2 g EI	2 g EI[b]		
	3 g LD, 2 g			
	4 g LD, 2 g[a]			
Beginning (Pre) and end (Post) of PIRRT	2 g Pre, 2 g Post	2 g Pre, 1 g Post	N/A	N/A
	2 g Pre, 3 g Post	2 g Pre, 2 g Post		
	3 g Pre, 2 g Post			
	3 g LD, 2 g Pre, 2 g Post			
Continuous infusion	2 g LD, 4 g CI[a]	2 g LD, 3 g CI	12 g CI	1.5 g CI
			16 g CI	2 g CI

All listed dosing regimens represent probability of target attainment (PTA) ≥ 90% at 1 × minimum inhibitory concentration (MIC) for the first 48 hours. Underlined dosing regimens represent probability of target attainment ≥ 90% at 4 × MIC for the first 48 hours.

CI, continuous infusion (over 24 hours); EI, extended infusion (over 4 hours); LD, loading dose; N/A, not available; PIRRT, prolonged intermittent renal replacement therapy.

[a]Depending on when drug is infused relative to prolonged intermittent renal replacement therapy often results in mean cefepime trough concentration > 70 mg/L, a value that has been linked to toxicity.[62]

[b]Depending on when drug is infused relative to prolonged intermittent renal replacement therapy often results in mean ceftazidime trough concentration >100 mg/L, a value that has been linked to toxicity.[63,64]

fraction, CL_{NR}, S_A/S_C) in a log-Gaussian distribution with preset limits. The weight for all virtual subjects was limited to a minimum of 40 kg with no maximum limit. The minimum and maximum values for CL_{NR} and V_d were from the published clinical studies. For S_A and S_C, variability of 20% was assumed with limits set to 0 and 1. Last, the reported correlations between body weight and V_d or CL_{NR} (Table 1) from each study were incorporated into our MCS.

Pharmacodynamic Targets

The pharmacodynamic targets in this study were >50% fT>4 × MIC (piperacillin),[19,21–23] >50% fT threshold tazobactam concentration,[54] and >60% fT>4 × MIC (cefepime and ceftazidime)[18–21] for the first 48 hours of antibiotic therapy. Maintaining an even higher free-drug concentration (eg, 4 × MIC) may be pivotal in critically ill patients to maximize bacterial killing and suppress bacterial resistance.[18]

Our goal for reaching these targets within the first 48 hours was based on the Surviving Sepsis Guidelines, which stress rapid administration of appropriate antimicrobial therapy. Because we could not assess appropriateness of antibiotic spectrum of activity in these virtual patients, we interpreted "rapid" and "appropriate" as dosing antibiotics to reach therapeutic pharmacodynamic targets.[10] These pharmacodynamic targets were chosen as they are associated with maximization of bacterial killing and suppression of antibiotic resistance[23] and have been used in other Monte Carlo analyses.[54–56] The reference organism used in this trial was *P. aeruginosa* because this common pathogen is associated with increased mortality rates in the ICU and is a common clinical indication for the 3 study antibiotic agents.[57] Based on Clinical and Laboratory Standards Institute (CLSI), the clinical break point of *P. aeruginosa* for cefepime and ceftazidime is 8 mg/L and for piperacillin is 16 mg/L.[58] We used a tazobactam concentration of 4 mg/L, as this is the concentration that was used for susceptibility testing.[58] Thus, we evaluated the attainment of pharmacodynamic targets of >50% fT>4 × MIC of 16 mg/L (equals 64 mg/L) for piperacillin, >50% fT>4 mg/L for tazobactam, and >60% fT>4 × MIC of 8 mg/L (equals 32 mg/L) for cefepime and ceftazidime for the first 48 hours of antibiotic therapy to determine the optimal dosing regimen. Commonly, %fT>MIC refers to %fT>MIC in a single dosing interval with the assumption of

constant drug clearance. However, this assumption of constant drug clearance cannot be applied in our patient population because patients have 2 distinct clearances depending on whether they are receiving prolonged intermittent renal replacement therapy for 8-10 hours each day. To better represent the clinical situation, we conducted simulations with prolonged intermittent renal replacement therapy occurring at the 2 extremes of time of day relative to the first antibiotic dose for each drug-dosing regimen (T0 and T14/T16). Two prolonged intermittent renal replacement therapy sessions always were performed within the first 48 hours of antibiotic therapy regardless of timing relative to antibiotic dose. Ideally, the drug infusion would not occur as prolonged intermittent renal replacement therapy is starting, but in clinical practice prolonged intermittent renal replacement therapy and drug dose timing cannot always be timed optimally; hence, even the least optimal scenario was simulated.

Optimal Dosing Regimen

A probability of target attainment (PTA) of 90% is a standard threshold to determine the optimal drug dosing regimen in simulation studies.[11,59] At that threshold, MCS predicts that at least 90% of the virtual patient population will achieve the predetermined pharmacodynamic target. The risk of toxicity should be evaluated along with the benefit of attaining probability of target attainment ≥ 90%. Focus was placed on cefepime, ceftazidime, and piperacillin, drugs with a higher risk of toxicity in patients with kidney disease.[28,60,61] Trough cefepime serum concentration >70 mg/L and ceftazidime serum concentration >100 mg/L have been associated with seizures.[60,61] Neurotoxicity has been reported in 50% of critically ill patients who had piperacillin trough serum concentrations >361.4 mg/L.[28] Keeping trough concentrations below these critical values was considered preferable to reduce the risk of drug-induced neurotoxicity within this MCS.[28,62–64] The drug regimen considered "optimal" was one that achieved a probability of target attainment of ≥90% with the lowest daily dose regardless of when prolonged intermittent renal replacement therapy was initiated relative to the first antibiotic dose while maintaining trough concentrations below toxic concentrations in as many virtual patients as possible.

Results

For all drugs in this study, dosing simulations for the 8- and 10-hour HD models and 8- and 10-hour HF models yielded similar probability of target attainment results, suggesting that the prolonged intermittent renal replacement therapy modality did not appreciably influence target attainment (data not shown). Table 2 lists all simulated drug regimens and shows all regimens that resulted in a probability of target attainment ≥ 90% for the first 48 hours, with the pharmacodynamic target of fT>1 × MIC. Considerably fewer antibiotic regimens achieved the higher pharmacodynamic target of fT>4 × MIC.

Cefepime doses of ≥6 g/day were required to reach 90% probability of target attainment. The mean ± SD percent of the first 48 hours of therapy that the serum concentration was above fT>4 × MIC for all 5000 subjects was 89.8% ± 31% and 83.7% ± 31%, with a 2 g loading dose followed by 1 g every 6 hours for prolonged intermittent renal replacement therapy at T0 and T16, respectively. Similarly, in the 5000 patients, cefepime 2 g pre-prolonged intermittent renal replacement therapy and 3 g post-prolonged intermittent renal replacement therapy resulted in 81% ± 33% and 82% ± 30% of the dosing interval being above fT>4 × MIC, respectively, when prolonged intermittent renal replacement therapy was initiated at T0 or T16, respectively in the first 48 hours of cefepime therapy. Figure 2 illustrates the probability of target attainment during the first 48 hours of many different cefepime dosing regimens when 8-hour HD was initiated at T0 (Figure 2A) or at T16 (Figure 2B). These figures also show the percentage of patients with cefepime trough concentrations >70 mg/L (a toxicity measure) with each of these regimens.

For ceftazidime, the mean ± SD percent of the first 48 hours of therapy that the serum concentration was above fT>4 × MIC for all 5000 subjects was 84.6% ± 9.7% (prolonged intermittent renal replacement therapy 8-hour HD at T0) and 92.6% ± 11.4% (prolonged intermittent renal replacement therapy 8-hour HD at T16), with a regimen of 2 g every 12 hours. Moreover, ceftazidime 1 g every 6 hours resulted in 83.9 ± 10.8% (prolonged intermittent renal replacement therapy 8-hour HD at T0) and 88% ± 11.7% (prolonged intermittent renal replacement therapy 8-hour HD at T16) of the dosing interval being above fT>4 × MIC in the first 48 hours of therapy. Last, a ceftazidime 2 g loading dose followed by a 3 g continuous infusion resulted in 96% ± 11% and 97% ± 9% of the first 48 hours fT>4 × MIC when prolonged intermittent renal replacement therapy was initiated at T0 or T16, respectively. Figure 3 illustrates the probability of target attainment during the first 48 hours of many different ceftazidime dosing regimens when 8-hour HD is initiated at T0 (Figure 3A) or at T16 (Figure 3B). Figure 3 also shows the percent of patients with ceftazidime trough concentration > 100 mg/L (a toxicity measure) with each of these regimens.

Piperacillin 4 g every 6 hours infused over 30 minutes remained fT>4 × MIC for 78% ± 22% (prolonged intermittent renal replacement therapy

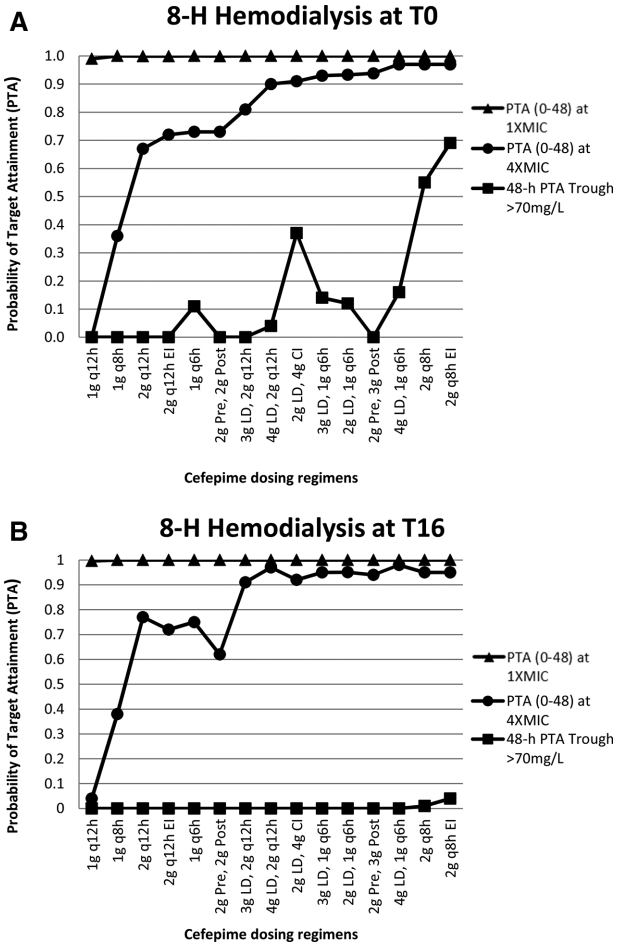

Figure 2. (A) Probability of target attainments when 8-hour hemodialysis was initiated at the same time the first cefepime dose was given (T0) for a series of cefepime dosing regimens. (B) Probability of target attainments when the first cefepime dose was administered 16 hours (T16) before the next session of 8-hour hemodialysis for a series of cefepime dosing regimens. 1 × MIC, 1 times the minimum inhibitory concentration; 4 × MIC, 4 times the minimum inhibitory concentration; CI, continuous infusion over 24 hours; EI, extended infusion over 4 hours. LD, loading dose; MIC, minimum inhibitory concentration. The pharmacodynamic target for cefepime is determined by the time of the free serum concentration above the MIC over 60% of the first 48 hours of cefepime therapy. The probability of target attainments for 1 × MIC (triangles) and 4 × MIC (circles) for the first 48 hours of antibiotic therapy are illustrated. The percentage of virtual patients who attained trough cefepime concentrations of >70 mg/L, which may be associated with neurotoxicity, with each regimen are depicted with squares.

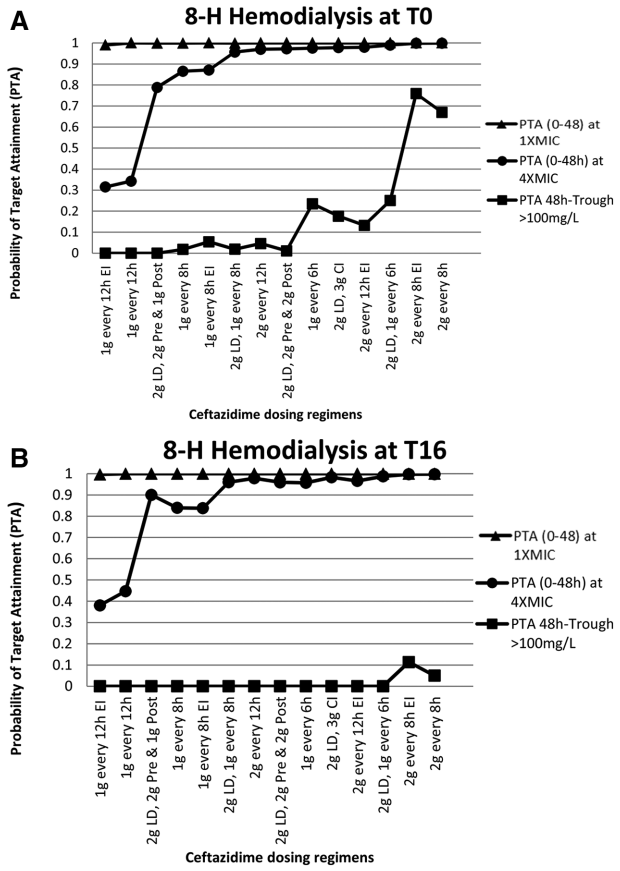

Figure 3. (A) Probability of target attainments when an 8-hour hemodialysis was initiated at the same time the first ceftazidime dose was given (T0) for a series of ceftazidime dosing regimens. (B) Probability of target attainments when the first ceftazidime dose was administered 16 hours (T16) before the next session of 8-hour hemodialysis for a series of ceftazidime dosing regimens. 1 × MIC, 1 times the minimum inhibitory concentration; 4 × MIC, 4 times the minimum inhibitory concentration; CI, continuous infusion over 24 hours; EI, extended infusion over 4 hours; LD, loading dose; MIC, minimum inhibitory concentration. The pharmacodynamic target for ceftazidime is determined by the time of the free serum concentration above the MIC over 60% of the first 48 hours of ceftazidime therapy. The probability of target attainments for 1 × MIC (triangles) and 4 × MIC (circles) for the first 48 hours of antibiotic therapy are illustrated. With each regimen, the percentage of virtual patients who attained trough ceftazidime concentrations of >100 mg/L, which may be associated with neurotoxicity, are shown with squares.

8-hour HD at T0) and 69% ± 28% (prolonged intermittent renal replacement therapy 8-hour HD at T16) for the first 48 hours of therapy in the 5000 virtual patients. Lengthening piperacillin infusion time had a modest effect on the percent of time the serum concentration was fT>4 × MIC in the first 48 hours. An extended infusion (4 g every 6 hours over 4 hours) yielded 79% ± 22% and 81% ± 23% fT>4 × MIC, and continuous infusion (16 g every 24 hours) reached 78% ± 22% and 80% ± 24% for prolonged intermittent renal replacement therapy at T0 and T16, respectively, for the first 48 hours of therapy. Finally, tazobactam probability of target attainment was ≥95% regardless of when the prolonged intermittent renal replacement therapy 8-hour HD was initiated relative to the initial drug dose for all 3 tested drug-dosing regimens (Table 2). Figure 4 illustrates the probability of target attainment during the first 48 hours of many different piperacillin dosing regimens when 8-hour HD was initiated at T0 (Figure 4A) or at T16 (Figure 4B). Figure 4 also shows the percent of patients with piperacillin trough concentration

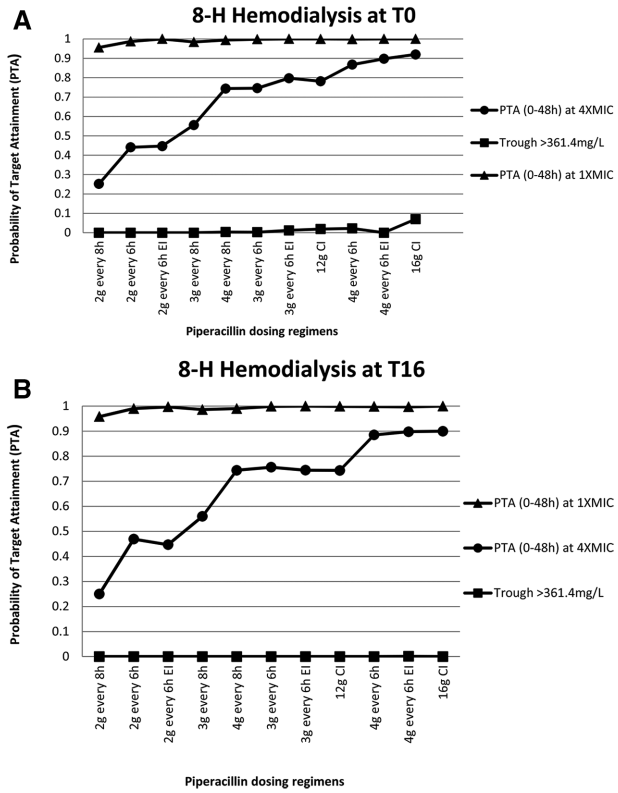

Figure 4. (A) Probability of target attainments when 8-hour hemodialysis was initiated at the same time the first piperacillin dose was given (T0) for a series of piperacillin dosing regimens. (B) Probability of target attainment when the first piperacillin dose was administered 16 hours (T16) before the next session of 8-hour hemodialysis for a series of piperacillin dosing regimens. 1 × MIC, 1 times the minimum inhibitory concentration; 4 × MIC, 4 times the minimum inhibitory concentration; CI, continuous infusion over 24 hours; EI, extended infusion over 4 hours; LD, loading dose; MIC, minimum inhibitory concentration. The pharmacodynamic target for piperacillin is determined by the time of the free serum concentration above the MIC over 50% of the first 48 hours of piperacillin therapy. The probability of target attainments for 1 × MIC (triangles) and 4 × MIC (circles) for the first 48 hours of antibiotic therapy are illustrated. The 50% of virtual patients who attained trough piperacillin concentrations of >361.4 mg/L is associated with neurotoxicity, with each regimen shown with squares.

>361.4 mg/L (a toxicity measure) with each of these regimens.

Discussion

In this MCS, common prolonged intermittent renal replacement therapy settings (4 L/h × 10 hours or 5 L/h × 8 hours of HD or HF) were used to evaluate the effect of different modalities (HD vs HF), treatment durations, effluent rates, and timing of drug administration relative to prolonged intermittent renal replacement therapy. The probability of target attainment showed no differences between 2 modalities and treatment durations. Even though convection usually yields higher drug clearance per effluent volume than diffusion, especially for larger solutes, we used predilution replacement HF in this study, as is usually done clinically, which caused a decrease in clearance because of the dilution factor.

Conversely, the timing of the drug administration relative to prolonged intermittent renal replacement therapy had more of an effect on toxicity measures than on efficacy probability of target attainment. To reflect the clinical setting as much as possible, the two possible extremes were modeled in this study. The probability of target attainments were lower (fewer virtual patients reached the pharmacodynamic target) when beta-lactams were administrated concomitantly with prolonged intermittent renal replacement therapy initiation (T0) compared with when prolonged intermittent renal replacement therapy was started as late as possible after the drug dose (T14/T16). For cefepime and ceftazidime, extended and continuous infusion dosing provided limited improvements in probability of target attainment while consistently increasing the trough concentrations (higher risk of drug-related toxicity). Interestingly, when both cefepime and ceftazidime were administered at T16 (drug and prolonged intermittent renal replacement therapy were maximally apart), the probability of virtual patients reaching the toxic trough concentration at the 48-hour point drastically decreased while maintaining the high probability of target attainment for the pharmacodynamic efficacy goals (compare Figure 2A with Figure 2B and Figure 3A with Figure 3B). It is well known that the timing of administration of a drug relative to prolonged intermittent renal replacement therapy greatly influences attainment of the pharmacodynamic target.[65] However, this study highlights that the importance of the timing of drug administration relative to prolonged intermittent renal replacement therapy initiation may influence drug toxicity risk as well.

We were challenged to develop a single best-dosing regimen, given the toxicity concerns of beta-lactams in renally impaired patients. For cefepime, MCS of the typical doses used in normal and CRRT patients (1-2 g every 12 hours) did not meet our 90% probability of target attainment goal. Increasing the dose to 2 g every 8 hours (the maximum labeled dose for cefepime) produced mean modeled trough concentrations that were nearly twice that observed with every 12-hour dosing, raising the concern for potential toxicity. Simulations with pre- and post-prolonged intermittent renal replacement therapy dosing achieved our target probability of target attainment of ≥90%, but only when the total daily dose was at least 5 g (2 g pre-prolonged intermittent renal replacement therapy, 3 g post-prolonged intermittent renal replacement therapy). Cefepime 1 g every 6 hours after a 2 g loading dose (dose on day 1 = 5 g) was the regimen that we modeled with the lowest daily

dose that reached our goal. Cefepime dosing in critically ill patients has been evaluated in numerous studies. Several of these studies have shown that the typical dosing regimens of 1-2 g every 12 hours are unlikely to provide adequate exposures for organisms with MICs of 8 mg/L.[52,66,67] Our study supports these findings, as none of these doses reached the ≥90% probability of target attainment threshold. A more frequent dosing regimen, such as 1 g every 6 hours that we recommend, has not been studied. It has been established that extended dosing or continuous infusion of cefepime provides greater likelihood of target attainment,[68] but our study suggests that toxicity may be more likely.

The ceftazidime dosing regimens that met the target in our simulations are consistent with those recommended for CRRT[69] and are much higher than the dose recommended for anuric patients (500 mg every 48 hours) or for subjects receiving intermittent hemodialysis (1 g after each intermittent hemodialysis treatment).[70] Because ceftazidime and cefepime pharmacokinetics are similar, similar doses of 1-2 g every 12 hours are often advocated for both drugs.[71] However, our study in prolonged intermittent renal replacement therapy indicates that slightly different doses are necessary to meet our probability of target attainment criteria with ceftazidime. Cefepime has a higher nonrenal clearance rate and renal replacement therapy clearance rate and consequently merits a different dosing strategy. Our finding is consistent with other studies that report better target attainment for ceftazidime than cefepime.[52] A recent study by Konig and colleagues showed a probability of target attainment of 98% for the pharmacodynamic target of 50% fT≥1 × MIC, with 1 g every 8 hours in 16 critically ill patients receiving prolonged intermittent renal replacement therapy.[72] The authors recommended ceftazidime 1 g every 8 hours to reach their pharmacodynamic target (50% fT≥1 × MIC) and 2 g every 12 hours to reach a more aggressive pharmacodynamic target (100% fT≥1 × MIC). Even though our pharmacodynamic targets for ceftazidime were slightly different from Konig's study (60% fT≥1 × MIC for traditional and 60% fT≥4 × MIC for aggressive pharmacodynamic targets), the dosing recommendations of Konig et al would reach our pharmacodynamic targets in >90% of our virtual patients (Table 2).

For piperacillin and tazobactam, recommended dosing regimens from previous studies in different renal replacement therapy modalities were evaluated in our study. Recommended piperacillin/tazobactam doses for patients receiving other types of renal replacement therapy include 4.5 g every 8 hours for patients receiving CRRT[69] and 2.25 g every 8 hours to 3.375 g every 6 hours for patients receiving SLED.[8] Our MCS results indicate that those CRRT/SLED piperacillin/tazobactam dosing regimens did not meet the 90% probability of target attainment threshold of patients receiving prolonged intermittent renal replacement therapy. Our MCS indicates that piperacillin/tazobactam 4.5 g every 6 hours for critically ill patients receiving prolonged intermittent renal replacement therapy is preferable, which is the same dose recommended by the manufacturer to treat patients with normal renal function.[73] Although our recommendation is a relatively high dose, this same piperacillin/tazobactam dose (4.5 g every 6 hours) and the same probability of target attainment have been assessed in patients receiving CRRT with a mean effluent rate of 33-65 mL/min.[74] This study found that only 66% of patients receiving the same piperacillin/tazobactam dosing regimen attained the therapeutic target in the first 48 hours of therapy. Conversely, a prospective observational study concluded 4.5 g every 8 hours was frequently insufficient in critically ill patients receiving renal replacement therapy (n = 10).[75] Only 62% and 57% reached their pharmacodynamic target on day 1 and day 4, respectively.[75] Our MCS could not evaluate the probability of target attainment for both drugs simultaneously in the same virtual patients. Thus, we separately evaluated the probability of target attainment for piperacillin and tazobactam in different sets of 5000 virtual patients. We found that piperacillin 4 g every 6 hours attained the therapeutic target in ~90% of 5000 simulated patients, and tazobactam 0.5 g also achieved the efficacy target in >90% of another 5000 virtual patients. Piperacillin/tazobactam have been frequently evaluated for alternate dosing strategies in critically ill patients, who often require higher MIC targets because of their increased risk of bacterial resistance.[42,63,76–79] These studies investigated whether prolonging infusion time increases fT>MIC and consequently improves patient outcomes. A recent meta-analysis, including data from 632 randomized patients, showed continuous piperacillin/tazobactam infusion was associated with decreased hospital mortality compared with intermittent infusion (≤30-minute infusion) in critically ill patients with severe sepsis.[80] Thus, we included 4-hour extended infusion piperacillin/tazobactam and CI regimens with and without a loading dose, to evaluate if these alternative dosing strategies would result in better target attainment than a conventional intermittent infusion. Our study found that prolonging piperacillin/tazobactam infusions did not yield significantly better target attainment in patients receiving prolonged intermittent renal replacement therapy.

This study has several limitations including that our model assumed that all virtual patients had negligible renal clearance. Patients with acute kidney injury have the potential for renal recovery. Obviously, if patients

had residual renal function or recovered renal function, then higher antibiotic doses would be necessary. Also, our recommendations are only applicable to patients who receive daily prolonged intermittent renal replacement therapy at the modeled flow rates. In scenarios in which prolonged intermittent renal replacement therapy was not administered daily or if different blood and effluent rates were used, dosing adjustments would be necessary. For drugs like aminoglycosides or vancomycin, therapeutic drug monitoring (TDM) can be used to guide drug dosing. Beta-lactam TDM would be a very helpful tool in this setting [81,82] but is unavailable at most hospitals. MCS, like the ones conducted here, is the best-available option to obtain good initial empiric beta-lactam doses for these patients. Although the patient demographics that served as the basis for this MCS came from a single American center,[29] the population was quite large (n = 100) and likely representative of the types of patients who would receive prolonged intermittent renal replacement therapy and these antibiotics.

Last, these drug-dosing recommendations are based on that with the target of ~90% of critically ill patients receiving prolonged intermittent renal replacement therapy, the pharmacodynamic target will be attained. This means that up to 10% of patients might not meet the goal. Selected patient populations might be responsible for this 10%. For example, increased weight has been described as a factor for inadequate therapy for several studies.[83–85] Rich et al found that cefepime doses of 2 g every 8 hours are necessary to maintain an adequate fT>MIC throughout the dosing interval for morbidly obese patients (body mass index >40 kg/m^2), with an estimated glomerular filtration rate of 108.4 ± 34.6 mL/min.[84] Even though their patients did not have renal dysfunction nor were receiving renal replacement therapy, their dose recommendation is still vastly different than the conventional dose of 1-2 g every 12 hours for patients. Our MCS model was not able to calculate body mass index; however, a post hoc analysis of our virtual patients that were >120 kg indicates that our recommended doses for cefepime 2 g loading dose, 1 g every 6 hours, ceftazidime 2 g every 12 hours, and piperacillin/tazobactam 4.5 g every 6 hours all had 100% probability of target attainment at the 1 × MIC threshold, no matter when the dose was administered relative to prolonged intermittent renal replacement therapy.

The dose recommendations from our MCS were based on the susceptibility break point of *P. aeruginosa* established by the CLSI for drugs.[58] In some respects the recommended doses should be more than sufficient for organisms that are more sensitive than the break points used in the study. Similarly, organisms that are more resistant and have higher break points should not be receiving these antibiotics at all.

Conclusion

In a pharmacokinetic model of critically ill patients receiving 8 hours (5 L/h) or 10 hours (4 L/h) of daily prolonged intermittent renal replacement therapy, cefepime 1 g every 6 hours with a 2-g loading dose, ceftazidime 2 g every 12 hours, and piperacillin/tazobactam 4.5 g every 6 hours will reach the pharmacodynamic targets for *P. aeruginosa*. Although administering drugs during a prolonged intermittent renal replacement therapy session is not ideal, delaying antibiotic therapy cannot be condoned, and use of these doses appears to meet the 90% probability of target attainment threshold for the first 48 hours, regardless of when the dose is given relative to prolonged intermittent renal replacement therapy. A validation study in the clinical setting is warranted.

Declaration of Conflicting Interests

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