Use of Monte Carlo Simulations to Determine Optimal Carbapenem Dosing in Critically Ill Patients Receiving Prolonged Intermittent Renal Replacement Therapy

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Abstract

Pharmacokinetic/pharmacodynamic analyses with Monte Carlo simulations (MCSs) can be used to integrate prior information on model parameters into a new renal replacement therapy (RRT) to develop optimal drug dosing when pharmacokinetic trials are not feasible. This study used MCSs to determine initial doripenem, imipenem, meropenem, and ertapenem dosing regimens for critically ill patients receiving prolonged intermittent RRT (PIRRT). Published body weights and pharmacokinetic parameter estimates (nonrenal clearance, free fraction, volume of distribution, extraction coefficients) with variability were used to develop a pharmacokinetic model. MCS of 5000 patients evaluated multiple regimens in 4 different PIRRT effluent/duration combinations (4 L/h × 10 hours or 5 L/h × 8 hours in hemodialysis or hemofiltration) occurring at the beginning or 14–16 hours after drug infusion. The probability of target attainment (PTA) was calculated using ≥40% free serum concentrations above 4 times the minimum inhibitory concentration (MIC) for the first 48 hours. Optimal doses were defined as the smallest daily dose achieving ≥90% PTA in all PIRRT combinations. At the MIC of 2 mg/L for *Pseudomonas aeruginosa*, optimal doses were doripenem 750 mg every 8 hours, imipenem 1 g every 8 hours or 750 mg every 6 hours, and meropenem 1 g every 12 hours or 1 g pre- and post-PIRRT. Ertapenem 500 mg followed by 500 mg post-PIRRT was optimal at the MIC of 1 mg/L for *Streptococcus pneumoniae*. Incorporating data from critically ill patients receiving RRT into MCS resulted in markedly different carbapenem dosing regimens in PIRRT from those recommended for conventional RRTs because of the unique drug clearance characteristics of PIRRT. These results warrant clinical validation.

Sepsis is a primary cause of acute kidney injury requiring renal replacement therapy (RRT) in critically ill patients. Septic acute kidney injury is associated with higher mortality than nonseptic acute kidney injury (70% vs 52%),[1] representing a profound health care burden. Along with supportive care, early antibiotic therapy that promptly achieves therapeutic concentrations at the infection site is paramount to cure the infection and to maximize patient survival.[2] However, our knowledge deficit of antibiotic pharmacokinetics in critically ill patients receiving RRT poses a profound obstacle to determining optimal empiric dosing regimens. Many different types of RRTs have been employed to treat acute kidney injury in the intensive care unit (ICU), but pharmacokinetic studies for many RRTs are unavailable, leading to the use of widely varying antibiotic dosing regimens.[3] In particular, prolonged intermittent renal replacement therapy (PIRRT) is gaining interest as studies have shown patient outcomes similar to those with conventional RRT with better hemodynamic tolerance, improved patient mobility, and lower RRT operation cost.[4–8] However, pharma-

cokinetic studies in PIRRT are currently available for fewer than 1% of drugs.[9] Although ideal,[10] it is not feasible to conduct pharmacokinetic studies in critically ill patients receiving every type of RRT. Alternatively, in silico analyses using Monte Carlo simulations (MCSs) can be highly valuable for simulating the real-world patient population and for predicting the efficacy/safety of drug dosing regimens. This approach maximizes the utility of existing antibiotic data and our current

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

Carbapenem	Meropenem	Imipenem	Doripenem	Ertapenem
Weight (kg)	86.6 ± 29.2 (≥40)	86.6 ± 29.2 (≥40)	86.6 ± 29.2 (≥40)	86.6 ± 29.2 (≥40)
Volume of distribution (L/kg)	0.41 ± 0.18 (0.08−1.07)	0.34 ± 0.1 (0.21−0.63)	0.47 ± 0.15 (0.2−1.2)	0.188 ± 0.07 (0.13−0.34)
Nonrenal clearance (mL/min)	54.9 ± 49 (0−251)	100.5 ± 28 (53−160)	51 ± 45 (0−231)	11 ± 3 (10−19)
Free fraction	0.79 ± 0.09 (0−1)	0.8 ± 0.16 (0−1)	0.92 ± 0.18 (0−1)	0.25 − 0.45 (0−1)
Sieving coefficient	0.84 ± 0.17 (0−1)	1 ± 0.2 (0−1)	0.65 ± 0.13 (0−1)	0.2 ± 0.06 (0−1)
Saturation coefficient	0.6 ± 0.12 (0−1)	0.5 ± 0.1 (0−1)	0.65 ± 0.13 (0−1)	0.2 ± 0.06 (0−1)
Correlation between weight and volume of distribution (r^2)	0.1435	0.17	N/A	0.3318
Correlation between weight and nonrenal clearance (r^2)	0.0072	0.013	N/A	0.1156

N/A, not applied because of insufficient data.

All values are mean ± SD (assigned model limits). Data obtained from references 17–44.

understanding of RRT by incorporating them into MCS to predict optimal regimens in these patients with sparse pharmacokinetic data.[11,12]

Carbapenems are β-lactam antibiotics with broad antibacterial activity against most gram-positive and gram-negative aerobes and anaerobes. With the emergence of multidrug resistance, carbapenems are currently recommended for empiric treatment of critically ill patients with sepsis.[13,14] Carbapenems exhibit time-dependent bactericidal activity, and the pharmacodynamic parameter predicting outcomes is the percentage of time during a dosing interval that free serum concentrations exceed the minimum inhibitory concentration (fT>MIC) for the infecting pathogen.[15] Near-maximal bactericidal activity for carbapenems is achieved when fT>MIC is ≥40% of the dosing interval. However, it may be prudent to achieve free concentrations in excess of the MIC (eg, 4×MIC) in critically ill patients to maximize bacterial killing and suppress bacterial resistance.[16] Clinicians must consider the altered pharmacokinetics from acute illness and extracorporeal clearance when determining optimal carbapenem dosing regimens in critically ill patients receiving PIRRT.

In the present study, we performed in silico pharmacokinetic and pharmacodynamic analyses for doripenem, imipenem, meropenem, and ertapenem consisting of (1) development of mathematical pharmacokinetic models with relevant demographic and pharmacokinetic data from published studies and 4 daily PIRRT settings, (2) performance of MCS for multiple dosing regimens in a virtual cohort, and (3) determination of the probability of target attainment (PTA) for each regimen over a range of MICs. The objective of the study was to predict empiric carbapenem dosing regimens that are most likely to attain the predefined pharmacodynamic target to treat serious infections in critically ill patients receiving daily PIRRT using MCS.

Methods

Development of Mathematical Pharmacokinetic Models

The input parameters used in the analyses are outlined in Table 1. Body weights and pharmacokinetic parameters were obtained from a published PIRRT study[17] and carbapenem pharmacokinetic studies in critically ill patients receiving RRT[18–33] to best represent the patient population most likely to receive PIRRT. Calculating transmembrane drug clearance in RRT requires 2 important parameters—effluent flow rate (dialysate flow rate and/or ultrafiltration flow rate) and a measure of how well the drug crosses the hemodiafilter membrane (generically known as the extraction coefficient, specifically the sieving coefficient for hemofiltration and the saturation coefficient for hemodialysis). The model incorporated 4 commonly employed PIRRT settings with 2 different effluent flow rate/duration combinations in 2 different RRT modalities.[7,17] They were: (1) hemofiltration with an ultrafiltrate flow rate of 4 L/h for 10 hours per day, (2) hemofiltration with an ultrafiltrate flow rate of 5 L/h for 8 hours per day, (3) hemodialysis with a dialysate flow rate of 4 L/h for 10 hours per day, and (4) hemodialysis with a dialysate flow rate of 5 L/h for 8 hours per day. Blood flow rate was 300 mL/min in all PIRRT settings. For hemofiltration, all replacement solutions were modeled to be infused in the predilution mode as in clinical practice. Extraction coefficients estimate the concentration of drug in ultrafiltrate or dialysate in relation to plasma and approximate the unbound fraction of drug in plasma. Extraction coefficients for meropenem and imipenem in PIRRT were calculated from published reports using transmembrane clearance and effluent rates. Regression analyses were performed using previously reported transmembrane clearance at various ultrafiltrate or dialysate flow rates in RRT studies as variables.[19–28,34–44] The best-fitting relationships were modeled to extrapolate transmembrane clearance at the desired PIRRT ultrafiltrate or dialysate flow rate and to

determine sieving or saturation coefficient, respectively. The variability of the extraction coefficient expressed as the standard deviation was assumed to be 20% of the mean value. This was extracted from the previous RRT studies, which generally expressed ~20% variability in the unbound fraction data of carbapenems in critically ill patients with RRT.[18,20,22,23,28,34–36,38,39] Because ertapenem and doripenem had far less available critical care pharmacokinetic and RRT clearance data available, estimates and variability around those estimates were excerpted directly from the few clinical trials that were available.[29,30,32] The equations used in the model were:

$$CL_{HD} \, (L/hr) = SA^{*}Q_d$$

$$CL_{HF} \, (L/hr) = SC^{*}Q_{uf}^{*}[Q_{plasma}/(Q_{plasma} + Q_{replacement})]^{45,46}$$

$$V \, (L) = WT^{*}V \, (L/kg)$$

$$k_{on} = (CL_{NR} + CL_{HD})/V \quad \text{(for hemodialysis)}$$

$$k_{on} = (CL_{NR} + CL_{HF})/V \quad \text{(for hemofiltration)}$$

$$k_{off} = CL_{NR}/V$$

where CL_{HF} is transmembrane clearance in hemofiltration, SC is the sieving coefficient, Q_{uf} is the ultrafiltrate flow rate, Q_{plasma} is the plasma flow rate ($Q_{plasma} = Q_{blood}^{*}[1 - \text{hematocrit}]$; hematocrit is 30%), $Q_{replacement}$ is the replacement fluid flow rate ($Q_{replacement} = Q_{uf}$), CL_{HD} is transmembrane clearance in hemodialysis, SA is the saturation coefficient, Q_d is the dialysate flow rate, V is volume of distribution, WT (kg) is body weight, k_{on} is the elimination rate constant during PIRRT, CL_{NR} is nonrenal clearance, and k_{off} is the elimination rate constant off PIRRT.

Monte Carlo Simulations

Pharmacodynamic exposures were modeled for 6–11 unique dosing regimens for each carbapenem. They included those recommended for patients receiving other forms of RRT and those accounting for potentially different drug clearances during or off daily PIRRT (eg, pre- and post-PIRRT regimens). Infusion times were 0.5 hour (ertapenem, imipenem ≤ 500 mg, and meropenem) or 1 hour (doripenem and imipenem > 500 mg).[47–50] The initial 48 hours of free serum concentration–time profiles were simulated for each carbapenem dosing regimen using mean ± standard deviation estimates of pharmacokinetic variables de-

rived above. A 1-compartmental model with constant intravenous input and first-order elimination was used:

$$fC(t) = [(f \times \text{Dose}/T)/(k \times V_d)] \times \left(1 - e^{-k \times t}\right)$$
$$\text{(during the infusion)}$$

$$fC(t) = [(f \times \text{Dose}/T)/(k \times V_d)] \times \left(1 - e^{-k \times t}\right)$$
$$\times e^{-k(t-T)} \quad \text{(after the infusion)}$$

where f is the fraction of unbound drug, $C(t)$ is the carbapenem concentration at a specific time, T is the infusion time, k is the elimination rate constant, V_d is volume of distribution, and t is the time from infusion initiation.

MCSs (Crystal Ball Classroom Edition, Oracle) were performed to generate free serum concentration–time profiles of 5000 virtual subjects in 0.1-hour intervals for each carbapenem regimen. Demographic and pharmacokinetic values were randomly selected from log-Gaussian distributions within assigned limits. The only exception was the ertapenem free fraction, which was randomly selected from a uniform distribution as reported in a previous study with critically ill patients.[33] To prevent spurious simulations, reasonable limits were set for all parameters based on known ranges, as previously described.[51] Body weights < 40 kg were truncated because of the assumption that study patients were adults. For volume of distribution and nonrenal clearance, minimum and maximum values reported from all previously published studies were used as the lower and upper limits, respectively. For free fraction and sieving/saturation coefficient, values were assumed to be between 0 and 1. The correlation (ie, coefficient of determination, r^2) between body weight versus volume of distribution or nonrenal clearance was also integrated into the models to construct a virtual cohort with realistic pharmacokinetic parameters if available from the previous studies with RRT. The relationship found between these parameters appeared to be insignificant (Table 1).

Our objective was to develop optimal empiric dosing recommendations in a wide variety of clinical situations. Carbapenems can be administered at the beginning of, or during the middle of PIRRT or several hours prior to a PIRRT session. To ensure optimal empiric dosing in all situations, we simulated each carbapenem dosing infused in the 2 extreme scenarios in each of 4 PIRRT settings. One scenario is when the first carbapenem dose is given at the beginning of PIRRT (early PIRRT), and the other is when infused 14 or 16 hours prior to PIRRT (late PIRRT). Dosing regimens were simulated to include a daily PIRRT session for 2 days.

Prediction of Probability of Target Attainment

The PTA was calculated for each dosing regimen using the pharmacodynamic target of $\geq 40\% fT > 4 \times MIC$ for the first 48 hours at doubling MIC dilutions ranging from 0.125 to 32 mg/L. Briefly, $fT > 4 \times MIC$ as a percentage of the dosing interval was calculated for each of the 5000 virtual patients at a given MIC. The PTA was calculated by summation of the number of patients achieving $\geq 40\% fT > 4 \times MIC$ and dividing by the total number of patients. Reference organisms used in the in silico analyses were *Pseudomonas aeruginosa* for doripenem, imipenem, and meropenem and *Streptococcus pneumoniae* for ertapenem. These organisms were chosen because they are associated with substantial morbidity and mortality in ICUs and are common indications for carbapenem use.[52,53] The susceptibility breakpoint for doripenem, imipenem, and meropenem against *P. aeruginosa* is 2 mg/L, and the susceptibility breakpoint for ertapenem against *S. pneumoniae* is 1 mg/L.[54] Thus, we evaluated attainment of $\geq 40\% fT > 8$ mg/L for doripenem, imipenem, and meropenem against *P. aeruginosa* and attainment of $\geq 40\% fT > 4$ mg/L for ertapenem against *S. pneumoniae*. Optimal dosing regimens were selected if they provided $\geq 90\%$ PTA regardless of when PIRRT was given relative to the first antibiotic dose. However, the benefits of achieving the pharmacodynamic target should be weighed against the risk of drug toxicity. No data yet exist to define carbapenem exposure and the toxicity concentration threshold. However, carbapenem toxicity has been well documented with higher carbapenem doses (4 g/day) or in patients with severe renal insufficiency.[55,56] Thus, optimal dosing regimens were defined as those achieving $\geq 90\%$ PTA with the smallest daily dose to minimize the risk of toxicity. In addition, sensitivity analyses were performed to investigate the influence of different PIRRT regimens on carbapenem dosing in PIRRT. Because the effluent flow rate is considered the most important covariate for determining extracorporeal drug clearance in RRT, the PTA of the recommended carbapenem dosing regimens from this present study was reevaluated in a wide array of effluent flow rates ranging from 2 to 8 L/h. Sensitivity analyses were performed for all recommended doses in 8-hour treatments in the hemodialysis and hemofiltration modes with early PIRRT.

Results

Table 2 summarizes the PTA of selected dosing regimens and the mean $fT > 4 \times MIC$ for the initial 48 hours at an MIC of 2 mg/L for doripenem, imipenem, and meropenem and 1 mg/L for ertapenem. Differences in the PTA in early or late PIRRT settings with the 4 different combinations of modalities and effluent rates were all within 1%–2% of each other. For example, imipenem 1 g every 8 hours yielded a PTA of 97%–98% in both early and late PIRRT settings in the 4 different PIRRT modalities. Thus, we present the results of the 8-hour hemodialysis PIRRT as a representative example of all regimens. Optimal initial dosing regimens using the smallest daily doses were meropenem 1 g every 12 hours or 1 g pre- and post-PIRRT, imipenem 1 g every 8 hours or 750 mg every 6 hours, doripenem 750 mg every 8 hours, and ertapenem 500 mg initially followed by 500 mg post-PIRRT. Most carbapenem doses recommended for other forms of RRT did not attain $\geq 90\%$ PTA. Those regimens accounting for the increased drug clearance during PIRRT (eg, pre- and post-PIRRT regimens) did not result in better PTA than standard schedule dosing regimens. Figure 1 illustrates the PTA at $40\% fT > 4 \times MIC$ for select dosing regimens at specific MICs in 8-hour PIRRT, which occurred either at the beginning (early PIRRT) or 16 hours after (late PIRRT) carbapenem therapy was initiated. Obviously, smaller doses or less frequent dosing achieved optimal pharmacodynamic exposures at lower MIC values. The additional information on the PTA of various carbapenem dosing regimens in the other 3 PIRRT settings is provided in the Supplementary Material.

Table 3 displays mean model-derived drug clearances and half-lives for each carbapenem during and off an 8-hour PIRRT compared with published clinical data from continuous RRTs (CRRTs) and extended daily dialysis, another type of PIRRT. Overall carbapenem clearance by PIRRT was higher than that seen with CRRT, but similar to those by extended daily dialysis regimens. Consequently, carbapenem half-lives during PIRRT were shorter than those during CRRT, but resulted in ranges similar to those with extended daily dialysis.

Results of the sensitivity analyses are depicted in Table 4. The PTA of the recommended carbapenem dosing regimens from the present study did not differ in simulated 8-hour hemodialysis and hemofiltration PIRRT with various effluent flow rates.

Discussion

This is the first in silico study using MCSs to determine optimal carbapenem dosing regimens in critically ill patients receiving daily PIRRT. This in silico approach has been used in previous studies to predict optimal drug dosing in special patient populations with limited pharmacokinetic data.[51,57,58] Some of these studies were followed by pharmacokinetic validation trials.[58,59] The dosing recommendations from these validation trials were in agreement with those predicted in the previous in silico studies,[58,59] demonstrating that the in silico approach can be useful to guide drug

Table 2. Probability of Target Attainment (%) of Selected Carbapenem Dosing Regimens in 8-Hour Hemodialysis-Based PIRRT Using a 5 L/h Dialysate Flow Rate

Carbapenem	Dosing	Early PIRRT		Late PIRRT	
		PTA (%) (>40% fT>4×MIC[a])	%fT>4×MIC[a] (mean ± SD)	PTA (%) (>40% fT>4×MIC[a])	%fT>4×MIC[a] (mean ± SD)
Meropenem	500 mg every 12 h	56	46 ± 25	63	52 ± 29
	1 g every 12 h	**89**	**75 ± 22**	**92**	**81 ± 23**
	11.6 mg/kg every 12 h	87	74 ± 24	90	80 ± 24
	500 mg every 8 h	84	69 ± 24	84	72 ± 27
	1 g every 8 h	97	88 ± 17	97	91 ± 17
	1 g pre- and post-PIRRT	**90**	**79 ± 24**	**89**	**78 ± 25**
Imipenem	500 mg every 12 h	1	17 ± 10	4	21 ± 12
	500 mg every 8 h	35	35 ± 17	35	35 ± 17
	750 mg every 8 h	85	59 ± 18	87	61 ± 19
	1 g every 8 h	**98**	**73 ± 17**	**98**	**75 ± 18**
	500 mg every 6 h	72	53 ± 20	77	56 ± 21
	750 mg every 6 h	**98**	**79 ± 16**	**99**	**81 ± 16**
Doripenem	250 mg every 12 h	7	9 ± 16	12	14 ± 19
	500 mg every 12 h	58	47 ± 26	68	56 ± 29
	250 mg every 8 h	36	29 ± 28	36	30 ± 29
	500 mg every 8 h	86	71 ± 23	87	75 ± 25
	750 mg every 8 h	**97**	**86 ± 15**	**97**	**89 ± 17**
Ertapenem	500 mg every 24 h	65	50 ± 20	97	75 ± 14
	750 mg every 24 h	94	77 ± 21	99	90 ± 09
	1g every 24 h	98	90 ± 16	100	95 ± 7
	500 mg initially, then 500 mg post-PIRRT	**99**	**91 ± 8**	**98**	**80 ± 15**

Boldface dosing regimens are those that attained ≥90% of PTA using the smallest daily dose.

[a]MIC = 2 mg/L for meropenem, imipenem, and doripenem (susceptibility breakpoint for *Pseudomonas aeruginosa*) and 1 mg/L for ertapenem (susceptibility breakpoint for *Streptococcus pneumoniae*).

%fT>4×MIC denotes the percentage of time in the first 48 hours of therapy that the free fraction was 4 times greater that the target MIC for that drug.

dosing practice when extensive clinical trials cannot be conducted. In this present study, MCS allowed us to create a large number (n = 5000/tested dose) of virtual critically ill patients with acute kidney injury based on the existing data from small studies and to incorporate the influence of PIRRT on carbapenem disposition. Pharmacokinetic/pharmacodynamic analyses determined the carbapenem dosing regimens with the highest likelihood to attain the predefined pharmacodynamic target (40% fT>4×MIC in ≥90% of virtual patients) while minimizing toxicity risk in these virtual patients with PIRRT.

The key component of this study was the relevance of input parameter estimates with associated variability. The demographic data were extracted from a published PIRRT study[17] and pharmacokinetic data from studies in critically ill patients with acute kidney injury receiving RRT,[18–33] which are much different from pharmacokinetics in patients with chronic kidney disease receiving RRT.[60] We also incorporated free fraction and nonrenal clearance parameters from critically ill patients into the model. Lack of consideration for these important parameters has been identified as a limitation of previous clinical trials because as-

sumptions of free fraction and nonrenal clearance can confound PTA estimation.[61,62] Our pharmacokinetic models integrated 4 different commonly used PIRRT operating parameters, including different RRT modalities (convection and dialysis) and RRT treatment durations (5 L/h for 8 hours and 4 L/h for 10 hours). We modeled ultrafiltrate fluid replacement in the predilution mode in hemofiltration and corrected hemofiltration PIRRT drug clearance accordingly[45,46] because administration of prefilter hemofiltration replacement solutions decreases drug clearance by reducing hemofiltration efficiency. In general, drug clearance is higher in hemofiltration than with hemodialysis. However, with correction for predilution mode, carbapenem clearance in hemofiltration PIRRT approached that in hemodialysis PIRRT in all cases. In addition, dosing regimens achieving optimal pharmacodynamic exposures for the 8-hour PIRRT session also achieved optimal exposures for the 10-hour PIRRT session. The increased time of RRT treatment offset differences in effluent rates.

For drug dosing in hybrid-type RRTs like PIRRT, *when* to give a drug in relation to RRT may be more important than *how much* drug to give.[63] Our results demonstrate that this premise is especially true for
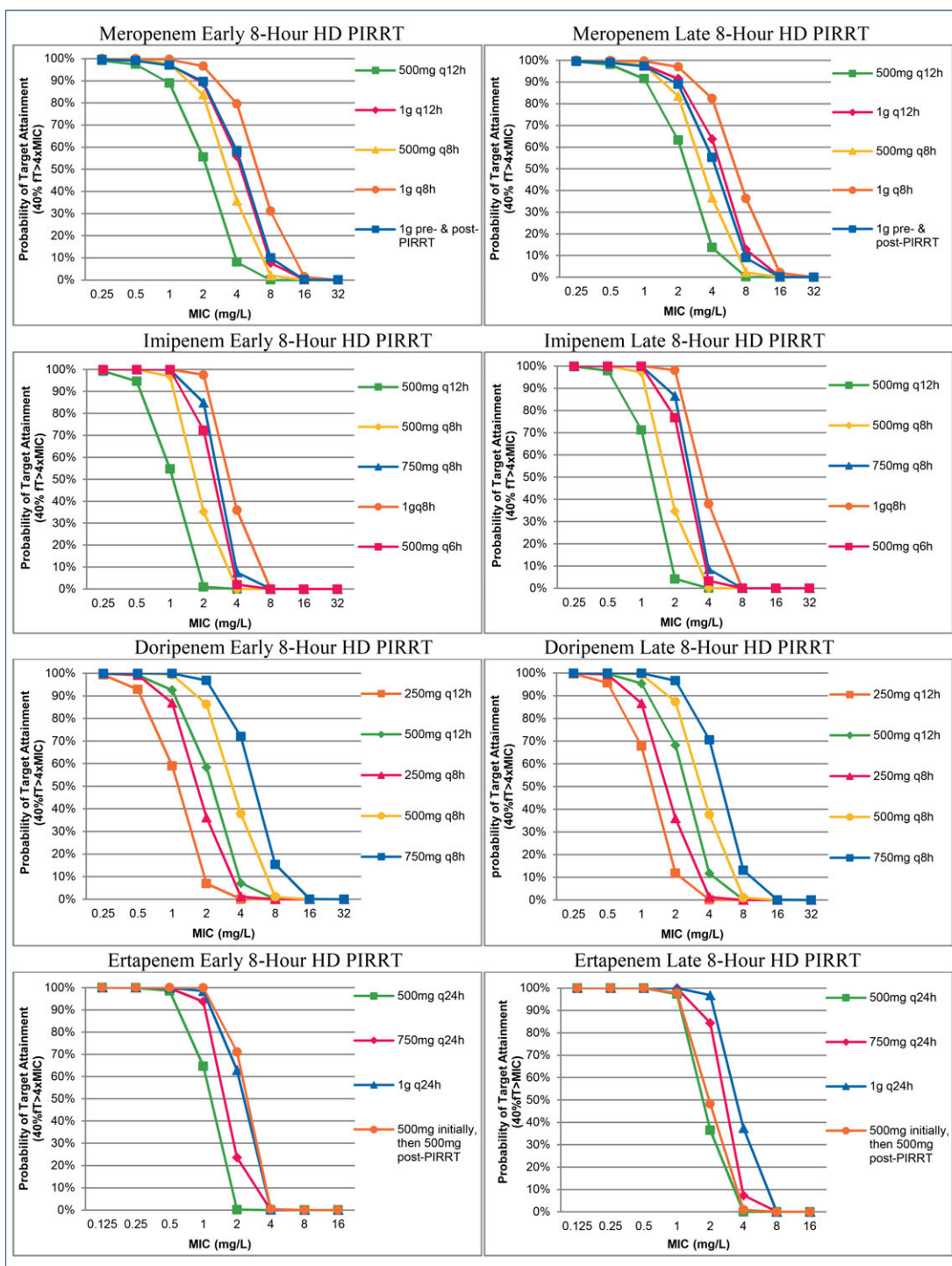
Figure 1. Probability of target attainment in the first 48 hours of carbapenem dosing regimens at different MICs. HD, hemodialysis. Early PIRRT is when the first carbapenem dose is administered at the start of an 8-hour hemodialysis PIRRT session with a 5 L/h dialysate flow rate. Late PIRRT is when the first carbapenem dose is administered 16 hours before a daily 8-hour hemodialysis PIRRT session.

drugs with longer half-lives given infrequently (eg, every 12–24 hours) but not for drugs given more frequently (every 6–8 hours) if the pharmacodynamic target is $fT>MIC$. For example, meropenem 500 mg every 12 hours and ertapenem 500 mg every 24

hours yielded significantly different PTAs depending on when antibiotic therapy was initiated relative to the time of PIRRT (0.56 and 0.65 in early PIRRT vs 0.63 and 0.97 in late PIRRT, respectively; Table 2). Sensitivity analysis suggests that *when* to give a drug

Table 3. Carbapenem Clearances and Half-Lives in PIRRT Compared With Published Data in CRRT and EDD

Present Study in PIRRT	Meropenem	Imipenem	Doripenem	Ertapenem
$CL_{on\text{-}PIRRT}$ (L/h)	5.9 ± 2.5	8.5 ± 1.5	6.1 ± 2.3	1.7 ± 0.3
$CL_{off\text{-}PIRRT}$ (L/h)	3.1 ± 2.4	5.9 ± 1.4	2.9 ± 2.2	0.7 ± 0.1
CL_{PIRRT} (L/h)	2.8 ± 0.5	2.6 ± 0.5	3.2 ± 0.6	1.0 ± 0.3
$t_{1/2\ on\text{-}PIRRT}$ (h)	4.9 ± 3.4	2.7 ± 1.4	5.2 ± 3.1	7.5 ± 3.9
$t_{1/2\ off\text{-}PIRRT}$ (h)	14.2 ± 16.7	3.9 ± 2.2	16.5 ± 17.7	18.2 ± 9.6
Published data in CRRT and EDD				
CL_{CRRT} (L/h)	$1.0-3.5$[18–24,34,37–39]	$0.8-2.7$[26–28,36,37]	$0.8-1.32$[29,30]	0.6 ± 0.24[32]
$t_{1/2\ CRRT}$ (h)	$2.4-8.7$[18–24,34,37–39]	$2.7-2.9$[26–28,36,37]	7.9 ± 0.9[29,30]	15.8[32]
CL_{EDD} (L/h)	$2.3\ (0.7-3.7)$[40]	N/A	N/A	2.97 ± 0.65[69]
$t_{1/2\ EDD}$ (h)	$3.7\ (2.1-4.7)$[40]	N/A	N/A	6.7 ± 0.4[69]

$CL_{on\text{-}PIRRT}$, total drug clearance during PIRRT; $CL_{off\text{-}PIRRT}$, total drug clearance off PIRRT, CL_{PIRRT}, drug clearance by PIRRT; CL_{CRRT}, drug clearance by CRRT; CL_{EDD}, drug clearance during EDD; $t_{1/2}$, half-life, CRRT, continuous renal replacement therapy; EDD, extended daily dialysis; N/A, not available.
Superscript numbers are references. Numbers in parentheses represent data ranges.
Clearance and half-life data in PIRRT were from on- and off-8-hour hemodialysis PIRRT.

in relation to RRT is also more important than what the effluent rate is during PIRRT. Table 4 demonstrates that varying PIRRT intensity from 2 L/h up to 8 L/h while the duration of PIRRT is kept the same makes strikingly little difference in the PTA. Recommended doses that achieved acceptable PTAs with the PIRRT regimens tested also met acceptable PTAs even when effluent rates ran as high as 8 L/h. Only the meropenem PTA dropped below 90% when faster effluent rates were modeled. Obviously at slower effluent rates (<4 L/h), PTA > 90% would continue to be reached at the recommended doses, but lower doses should probably be used to avoid carbapenem toxicity.

We evaluated whether the dosing strategy using increased drug clearance during PIRRT (eg, pre- and/or post-PIRRT regimens) can facilitate pharmacodynamic target attainment, as suggested in another simulation study with gentamicin in patients receiving extended daily dialysis or intermittent hemodialysis.[64] We simulated meropenem 1 g pre- and post-PIRRT to compare PTA with those using a standard schedule (every 12 hours). However, pre- and post-PIRRT regimens did not result in a better PTA than those with the standard schedule (Table 2), likely because of the different pharmacodynamic profiles of carbapenems versus gentamicin.

Because of the paucity of pharmacokinetic data, clinicians may base carbapenem dosing in patients receiving PIRRT on available recommendations designed for patients receiving CRRT (Table 5).[65] Our analysis suggests this is an undesirable approach. CRRT flow rates and treatment durations differ substantially from PIRRT. Furthermore, recommended CRRT carbapenem doses in critically ill patients receiving CRRT often yield subtherapeutic concentrations and do not achieve an optimal PTA.[61] Therefore, clinicians should not directly compare published CRRT dosing regimens with our PIRRT findings to determine

their appropriateness. In the present study, carbapenem removal by PIRRT was greater than that by CRRT, resulting in shorter half-lives than those reported during CRRT, illustrated in Table 3. Consequently, with the exception of ertapenem CRRT dosing recommendations, many carbapenem dosing regimens currently prescribed for CRRT did not achieve optimal pharmacodynamic exposures (Table 2). This is because PIRRT uses higher flow rates (4–5 L/h) than conventional CRRT (1–3 L/h),[66,67] yielding faster dialytic drug clearance (Table 3). In scenarios in which the drug is infused with the initiation of 8-hour hemodialysis PIRRT, 60%–90% of an infused dose (78%, 89%, 71%, and 62% on average for meropenem, imipenem, doripenem, and ertapenem, respectively) was removed during PIRRT, leading to subtherapeutic concentrations. This effect is less pronounced in CRRT, which runs at slower effluent rates. As we attempted to identify optimal dosing regimens for all scenarios in relation to PIRRT, higher carbapenem doses were necessary to meet the pharmacodynamic target ($\geq 40\%\ f\mathrm{T} > 4 \times \mathrm{MIC}$).

Among carbapenems, meropenem is most studied in terms of pharmacokinetic data and provides confidence in the pharmacokinetic parameters and robustness of the pharmacokinetic models. Our meropenem dosing recommendation of 2 g/day (1 g every 12 hours or 1 g pre- and post-PIRRT) agrees with those suggested in published studies in other types of PIRRTs including 8-hour extended daily dialysis (0.5–1 g every 8 hours) or sustained low-efficiency dialysis (1 g every 12 hours); see Table 5.[40,68] These studies used higher effluent flow rates (160 mL/min) than the PIRRT modeled in the present study, resulting in shorter meropenem half-lives (3.6–3.7 vs 4.9 hours in our study). However, the authors of these trials used less rigorous efficacy criteria; consequently, their dosing recommendations were very similar to ours. In the present study, meropenem 1 g administered pre- and post-PIRRT achieved optimal

Table 4. PTA Sensitivity Analyses of Recommended Carbapenem Dosing Recommendation With Various Effluent Flow Rates in PIRRT

40% fT>4×MIC[a]

8-Hour Hemodialysis PIRRT

Dialysate Flow Rate (L/h)	Meropenem 1 g Every 12 h	Imipenem 1 g Every 8 h	Doripenem 750 mg Every 8 h	Ertapenem 500 mg Initially, Then 500 mg Post-PIRRT
2	90	99	97	99
3	90	98	97	99
4	89	98	97	99
5[b]	**89**	**98**	**97**	**99**
6	88	98	97	99
7	88	98	97	99
8	87	98	96	99

8-Hour Hemofiltration PIRRT

Ultrafiltration Flow Rate (L/h)	Meropenem 1 g Every 12 h	Imipenem 1 g Every 8 h	Doripenem 750 mg Every 8 h	Ertapenem 500 mg Initially, Then 500 mg Post-PIRRT
2	91	99	97	99
3	90	99	97	99
4	89	98	97	99
5[b]	**88**	**98**	**97**	**99**
6	88	98	97	99
7	87	97	97	99
8	87	97	97	99

PTA data were from 8-hour PIRRTs using a 5 L/h effluent flow rate (dialysate or ultrafiltrate flow rate) with a blood flow rate of 300 mL/min.
[a]MIC = 2 mg/L for meropenem, imipenem, and doripenem (susceptibility breakpoint for *Pseudomonas aeruginosa*) and 1 mg/L for ertapenem (susceptibility breakpoint for *Streptococcus pneumoniae*).
[b]Reference flow rate used in this study.

pharmacodynamic exposures, but 1 g every 12 hours was chosen for convenience.

Imipenem and doripenem have not been studied in any hybrid-type RRT setting. Our model-derived dosing recommendations for PIRRT are higher than those recommended for CRRT (Table 5).[26,30,36,37] Imipenem differs from the other carbapenems because of its uniquely elevated nonrenal clearance reported in critically ill patients with acute kidney injury.[26,28,36] Doripenem displays the highest extracorporeal drug clearance because it has the highest free fraction (≥90%). Based on our simulations, optimal empiric doses achieving ≥ 90% PTA were 2400 and 1800 mg/day for imipenem and doripenem, respectively. However, 1 g every 8 hours and 750 mg every 8 hours were selected for practical reasons. Currently recommended CRRT dosing regimens did not achieve optimal exposures when modeled in PIRRT.

In contrast to other carbapenems, the optimal ertapenem dosing regimen in PIRRT required a similar dose (1g every 24 hours) to those recommended for CRRT (0.5–1 g every 24 hours)[32] or for patients receiving 8-hour extended daily dialysis with higher flow rates (effluent rate, 160 mL/min vs 66–83 mL/min in the present study; Table 5).[69] This extended daily dialysis study did not evaluate different dosing strategies with

respect to ertapenem administration timing relative to RRT to find the optimal dosing regimen. With high protein binding and slower nonrenal clearance, ertapenem has a longer half-life than other carbapenems, allowing for a smaller dose to achieve optimal exposures if administered after the PIRRT session ends. However, the first dose should be immediately administered regardless of PIRRT schedule to achieve the rapid therapeutic ertapenem concentrations and to yield a successful clinical response.

This study has some important limitations. Pharmacokinetic modeling and simulations were performed assuming the patients were adult-sized with acute kidney injury and negligible renal drug clearance who received daily PIRRT. We constructed virtual patients using demographic and pharmacokinetic data from the literature. Thus, our recommended dosing regimens would be applicable only to patients who match these demographic and clinical characteristics. Because optimal empiric dosing regimens were chosen based on achieving ≥90% PTA, up to 10% of patients may not achieve the pharmacodynamic target using our recommended doses. We chose an aggressive pharmacodynamic target associated with maximal bacterial killing and suppression of bacterial resistance,[15,16] and this aggressive target often resulted in the need for

Table 5. Comparison of Published Carbapenem Dosing Regimens

	Meropenem	Imipenem	Doripenem	Ertapenem
Normal kidney function	1 g every 8 h[47]	1 g every 6–8 h[48]	500 mg every 8 h[49]	1 g every 24 h[50]
Impaired kidney function (CrCl 10–50 mL/min)	500 mg–1 g every 12 h[47]	500 mg every 12 h–750 mg every 8 h[48]	250 mg every 12 h–500 mg every 8 h[49]	500 mg every 24 h[50]
IHD	250 mg–1 g every 24 h with supplemental dose post-IHD[41,42]	500 mg every 12 h post-IHD[48]	500 mg every 12 h on day 1, then 500 mg every 24 h[70]	500 mg every 24 h with 150-mg supplemental dose 6 hours prior to IHD[50]
CRRT	500 mg every 12 h–1 g every 8 h[18–23,37,38]	500 mg every 6 h–every 12 h[26–28,36,37]	250 mg every 12 h or 500 mg every 8 h[29,30]	500 mg–1 g every 24 h[32]
EDD/SLED	1 g every 12 h or 500 mg–1 g every 8 h[40,68]	N/A	N/A	1 g every 24 h[69]
PIRRT (present study)	1 g every 12 h	1 g every 8 h	750 mg every 8 h	500 mg initially, then 500 mg post-PIRRT

IHD, intermittent hemodialysis; CRRT, continuous renal replacement therapy; EDD/SLED, extended daily dialysis/sustained low-efficiency dialysis; N/A, not available. Superscript numbers are references.

higher doses to achieve optimal exposures compared with doses used in contemporary practice. However, these doses are based on empiric coverage of *P. aeruginosa* for meropenem, imipenem, and doripenem (MIC 2 mg/L) and *S. pneumoniae* for ertapenem (1 mg/L). After culture and susceptibility results are known, dosing regimens may be adjusted depending on the sensitivity of the isolated pathogen. In addition, the recommended dosing regimens provide optimal exposures for susceptible *Enterobacteriaceae* because the susceptibility breakpoints for these organisms are lower than those evaluated in this study. The benefit of higher antibiotic doses should be balanced with the potential risk of drug toxicity in these vulnerable patients.[60] Carbapenems are associated with central nervous system toxicity in the presence of renal disease,[55,56] and patients should be monitored closely when employing these dosing regimens.

Conclusions

The use of an in silico approach to develop optimal carbapenem dosing in patients receiving PIRRT resulted in aggressive dosing recommendations that met the PTA in 90% of virtual patients. Previous studies have shown that carbapenems are cleared by RRT, and our MCS confirmed that daily PIRRT substantially influences carbapenem clearance. Many currently prescribed carbapenem dosing regimens[3] for patients receiving hybrid-type RRTs would result in subtherapeutic concentrations. Meropenem 1 g every 12 hours, imipenem 1 g every 8 hours, doripenem 750 mg every 8 hours, and ertapenem 500 mg initially followed

by 500 mg post-PIRRT are recommended empirically to achieve optimal pharmacodynamic exposures in critically ill patients receiving daily 8- to 10-hour PIRRT.

It is unlikely that pharmacokinetic trials for all these antibiotics at varying doses will ever be conducted using all the various ways that PIRRT can be run. Further, in most countries, including our own, clinical assays are unavailable to determine whether therapeutic targets are attained with any dosing regimen. Consequently, this in silico approach provides rational clinical decision support for clinicians treating infected patients receiving PIRRT and should be used until clinical pharmacokinetic trials are conducted in this population.

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