Original Research

Title: 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 (MCS) can be used to integrate prior information on model parameters to a new renal replacement therapy (RRT) to develop optimal drug dosing when pharmacokinetic trials are not feasible. This study utilized MCS 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 (non-renal clearance, free fraction, volume of distribution, extraction coefficients) with variability were used to develop pharmacokinetic model. MCS of 5,000 patients evaluated multiple regimens in 4 different PIRRT effluent/duration combinations (4 L/hour x 10 hours or 5 L/hour x 8 hours in hemodialysis or hemofiltration) occurring at the beginning or 14-16 hours after drug infusion. Probability of target attainment (PTA) was calculated using ≥ 40% free serum concentrations above 4 times the 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 2mg/L for *Pseudomonas aeruginosa*, optimal doses were doripenem 750 mg q8h, imipenem 1 g q8h or 750 mg q6h, and meropenem 1 g q12h or 1 g pre- and post-PIRRT. Ertapenem 500 mg followed by 500 mg post-PIRRT was optimal at the MIC of 1mg/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 due to the unique drug clearance characteristics of PIRRT. These results warrant clinical validation.

Keywords: doripenem, ertapenem, imipenem, meropenem, pharmacokinetics, prolonged intermittent renal replacement therapy

Introduction

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 non-septic acute kidney injury (70% vs. 52%),[1] representing a profound healthcare 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 in determining optimal empiric dosing regimens. Many different types of RRTs have been employed to treat acute kidney injury in the ICU, but pharmacokinetic studies for many RRTs are unavailable, leading to use of widely varying antibiotic dosing regimens.[3] Particularly, prolonged intermittent renal replacement therapy (PIRRT) is gaining interest as studies show similar patient outcomes to conventional RRT with better hemodynamic tolerance, improved patient mobility, and lower RRT operation cost.[4-8] However, pharmacokinetic studies in PIRRT are currently available for less 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 (MCS) can be highly valuable to simulate the real world patient population and to predict efficacy/safety of drug dosing regimens. This approach maximizes the utility of existing antibiotic data and our current 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 percent of time during a dosing interval that free serum concentrations exceed the minimum inhibitory concentration (*f*T>MIC) for the infecting pathogen.[15] Near-maximal bactericidal activity for carbapenems is achieved when *f*T>MIC is ≥ 40% of the dosing interval. However, it may be prudent to achieve free concentrations in excess of the MIC (e.g., 4xMIC) 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 four daily PIRRT settings, 2) performance of MCS for multiple dosing regimens in a virtual cohort, and 3) determination of 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 pre-defined pharmacodynamic target to treat serious infections in critically ill patients receiving daily PIRRT using MCS.

Subjects & 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 two important parameters – effluent flow rate (dialysate flow rate or/and ultrafiltration flow rate) and a measure of how well the drug crosses the hemodiafilter membrane (generically known as extraction coefficient; specifically sieving coefficient for hemofiltration and saturation coefficient for hemodialysis). The model incorporated four commonly employed PIRRT settings with two different effluent flow rate/duration combinations in two different RRT modalities.[7,17] They were; 1) hemofiltration with ultrafiltrate flow rate of 4 L/hour for 10 hours/day, 2) hemofiltration with ultrafiltrate flow rate of 5 L/hour for 8 hours/day, 3) hemodialysis with dialysate flow rate of 4 L/hour for 10 hours/day, and 4) hemodialysis with dialysate flow rate of 5 L/hour for 8 hours/day. Blood flow rate was 300 mL/min in all PIRRT settings. For hemofiltration, all replacement solutions were modeled to be infused in the pre-dilution mode as in clinical practice. Extraction coefficients estimate the concentration of drug in ultrafiltrate or dialysate in relation to plasma and approximate 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 extraction coefficient expressed as 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 following:

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 (for hemodialysis)

k_{on} = (CL_{NR} + CL_{HF}) / V (for hemofiltration)

k_{off} = CL_{NR} / V

where CL_{HF} is transmembrane clearance in hemofiltration, SC is sieving coefficient, Q_{uf} is ultrafiltrate flow rate, Q_{plasma} is plasma flow rate [Q_{plasma} = Q_{blood}*(1- hematocrit); hematocrit is 30%[46]], $Q_{replacement}$ is replacement fluid flow rate [$Q_{replacement}$ = Q_{uf}], CL_{HD} is transmembrane clearance in hemodialysis, SA is saturation coefficient, Q_d is 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 non-renal clearance, and k_{off} is the elimination rate constant off PIRRT.

Monte Carlo Simulations (MCS)

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 (e.g. pre- and post-PIRRT regimens). Infusion times were 0.5 hour (ertapenem, imipenem ≤500 mg, and meropenem) or 1 hour (doripenem, and imipenem >500mg).[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 derived

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

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

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

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

MCS (Crystal Ball Classroom Edition, Oracle) were performed to generate free serum concentration-time profiles of 5,000 virtual subjects in 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 was that study patients were adults. For volume of distribution and non-renal 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 (i.e. coefficient of determination, r^2) between body weight vs. volume of distribution or non-renal 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 two extreme scenarios in each of four 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 hours or 16 hours prior to PIRRT (late PIRRT). Dosing regimens were simulated for 48 hours to include two daily PIRRT sessions.

Prediction of Probability of Target Attainment (PTA)

PTA was calculated for each dosing regimen using the pharmacodynamic target of ≥ 40% *f*T>4xMIC for the first 48 hours at doubling MIC dilutions ranging from 0.125-32 mg/L. Briefly, *f*T>4xMIC, as a percentage of the dosing interval, was calculated for each of the 5,000 virtual patients at a given MIC. PTA was calculated by summation of the number of patients achieving ≥ 40% *f*T>4xMIC 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 the 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 for ertapenem against *S. pneumoniae* is 1 mg/L.[54] Thus, we evaluated attainment of ≥ 40% *f*T>8 mg/L for doripenem, imipenem, and meropenem against *P. aeruginosa* and attainment of ≥ 40% *f*T>4 mg/L for ertapenem against *S. pneumoniae*. Optimal dosing regimens were selected if they provided ≥ 90% PTA regardless of when PIRRT was given relative to the first antibiotic dose. However, benefits of achieving the pharmacodynamic target should be weighed against the risk of drug toxicity. No data exist to define carbapenem exposure and toxicity concentration threshold yet. 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 ≥ 90% PTA with the smallest daily

dose to minimize the risk of toxicity. Additionally, sensitivity analyses were performed to investigate the influence of different PIRRT regimens on carbapenem dosing in PIRRT. Since effluent flow rate is considered the most important covariate to determine extracorporeal drug clearance in RRT, PTA of the recommended carbapenem dosing regimens from this present study was re-evaluated in a wide array of effluent flow rates ranging from 2 to 8L/hr. 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 *f*T>4xMIC 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 PTA in early or late PIRRT settings with the four different combinations of modalities and effluent rates were all within 1-2% of each other. For example, imipenem 1 g q8h yielded PTA of 97-98% in both early and late PIRRT settings in the four 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 q12h or 1 g pre- and post-PIRRT, imipenem 1 g q8h or 750 mg q6h, doripenem 750 mg q8h, and ertapenem 500 mg initially followed by 500 mg post-PIRRT. Most carbapenem doses recommended for other forms of RRT did not attain ≥ 90% PTA. Those regimens accounting for the increased drug clearance during PIRRT (e.g. pre- and post-PIRRT regimens) did not result in better PTA than standard schedule dosing regimens. Figure 1 illustrates the PTA at 40% *f*T>4xMIC 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 PTA of various carbapenem dosing regimens in the other three 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 to published clinical data from continuous RRT (CRRT) 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 were resulted in similar ranges as extended daily dialysis.

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

Discussion

This is the first *in silico* study using MCS 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 dosing practice when extensive clinical trials cannot be conducted. In this present study, MCS allowed us to create a large number (n=5,000/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 pre-defined pharmacodynamic target (40% *f*T>4xMIC in ≥ 90% of virtual patients) while minimizing toxicity risk in these virtual patients with PIRRT.

The key component of this study is 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 non-renal 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 assumption of free fraction and non-renal clearance can confound PTA estimation.[61,62] Our pharmacokinetic models integrated four different, commonly-used, PIRRT operating parameters, including different RRT modalities (convection and dialysis), and RRT treatment durations (5 L/hour for 8 hours and 4 L/hour for 10 hours). We modeled ultrafiltrate fluid replacement in the pre-dilution mode in hemofiltration and corrected hemofiltration PIRRT drug clearance accordingly,[45,46] because administration of pre-filter hemofiltration replacement solutions decreases drug clearance by reducing hemofiltration efficiency. In general, drug clearance is higher in hemofiltration compared to hemodialysis. However, with correction for pre-dilution mode, carbapenem clearance in hemofiltration PIRRT approached that in hemodialysis PIRRT in all cases. Additionally, 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 this premise is especially true for drugs with longer half-lives given infrequently (e.g., q12h-24h) but not for drugs given more frequently (q6h-8h) if the pharmacodynamic target is *f*T>MIC. For example, meropenem 500 mg q12h and ertapenem 500 mg q24h yielded significantly different PTA 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 to "when" give a drug in relation to RRT is also more important than what the effluent rate is during PIRRT. Table 4 demonstrates that varying PIRRT intensity from 2L/hr up to 8L/hr while the duration of PIRRT is kept the same makes strikingly little difference in PTA. Recommended doses that achieved acceptable PTA at the PIRRT regimens tested also met acceptable PTA even when effluent rates ran as high as 8L/hr. Only meropenem PTA dropped below 90% when faster effluent rates were modelled. Obviously at slower effluent rates (<4L/hr), 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 utilizing increased drug clearance during PIRRT (e.g. 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 1g pre- and post-PIRRT to compare PTA with those using a standard schedule (q12h). However, pre- and post-PIRRT regimens did not result in 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. Further, recommended CRRT carbapenem doses in critically ill patients receiving CRRT often yield subtherapeutic concentrations and do not achieve optimal PTA.[61] Therefore, clinicians should not directly compare published CRRT dosing regimens to our PIRRT findings to determine their appropriateness. In the present study, carbapenem removal by PIRRT was greater than those 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 utilizes higher flow rates (4-5 L/hour) than conventional CRRT (1-3 L/hour),[66,67] yielding faster dialytic drug clearance (Table 3). In scenarios where 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% fT>4xMIC).

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 2g/day (1 g q12h or 1g pre- and post-PIRRT) agrees with those suggested in published studies in other types of PIRRT including 8-hour extended daily dialysis (0.5-1 g q8h) or sustained low efficiency dialysis(1 g q12h)] (Table 5).[40,68] These studies utilized higher effluent flow rates (160 ml/min) than the PIRRT modelled in this present study, resulting in shorter meropenem half-

lives (3.6-3.7 hours vs. 4.9 hours in our study). However, 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 pharmacodynamic exposures, but 1 g q12h 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 due to its uniquely elevated non-renal clearance reported in critically ill patients with acute kidney injury.[26,28,36] Doripenem displays the highest extracorporeal drug clearance due to its highest free fraction (≥ 90%). Based on our simulations, optimal empiric doses achieving ≥ 90% PTA were 2400 mg/day and 1800 mg/day for imipenem and doripenem, respectively. However, 1 g q8h and 750 mg q8h 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 q24h) as those recommended for CRRT (0.5-1 g q24h) [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 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 non-renal 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 higher doses to achieve optimal exposures compared to doses utilized 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 CNS 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 PTA in 90% of virtual patients. Previous studies have shown that carbapenems are cleared by RRT and our MCS confirms 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 q12h, imipenem 1 g q8h, doripenem 750 mg q8h, 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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Table 1. Demographic and Pharmacokinetic Parameters Utilized in Monte Carlo Simulations

Carbapenem	Meropenem	Imipenem	Doripenem	Ertapenem
Weight	86.6 ± 29.2	86.6 ± 29.2	86.6 ± 29.2	86.6 ± 29.2
(kg)	[≥ 40]	[≥ 40]	[≥ 40]	[≥ 40]
Volume of Distribution	0.41 ± 0.18	0.34 ± 0.1	0.47 ± 0.15	0.188 ± 0.07
(L/kg)	[0.08-1.07]	[0.21-0.63]	[0.2-1.2]	[0.13-0.34]
Non-renal Clearance	54.9 ± 49	100.5 ± 28	51 ± 45	11 ± 3
(ml/min)	[0-251]	[53-160]	[0-231]	[10-19]
Free Fraction	0.79 ± 0.09	0.8 ± 0.16	0.92 ± 0.18	0.25-0.45
	[0-1]	[0-1]	[0-1]	[0-1]
Sieving Coefficient	0.84 ± 0.17	1 ± 0.2	0.65 ± 0.13	0.2 ± 0.06
	[0-1]	[0-1]	[0-1]	[0-1]
Saturation Coefficient	0.6 ± 0.12	0.5 ± 0.1	0.65 ± 0.13	0.2 ± 0.06
	[0-1]	[0-1]	[0-1]	[0-1]
Correlation between Weight vs. Volume of Distribution (r^2)	0.1435	0.17	N/A	0.3318
Correlation between Weight vs. Non-renal	0.0072	0.013	N/A	0.1156

Clearance (r^2)

All values are mean ± SD [assigned model limits].

Data obtained from references 17-44.

N/A: not applied due to insufficient data

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

Carbapenem	Dosing	Early PIRRT		Late PIRRT	
		PTA (%) (>40% *f*T>4xMIC[a])	%*f*T>4xMIC[a] (mean ± SD)	PTA (%) (>40% *f*T>4xMIC[a])	%*f*T>4xMIC[a] (mean ± SD)
Meropenem	500mg q12h	56	46 ± 25	63	52 ± 29
	1g q12h	**89**	**75 ± 22**	**92**	**81 ± 23**
	11.6mg/kg q12h	87	74 ± 24	90	80 ± 24
	500mg q8h	84	69 ± 24	84	72 ± 27
	1g q8h	97	88 ± 17	97	91 ± 17
	1g pre & post PIRRT	**90**	**79 ± 24**	**89**	**78 ± 25**
Imipenem	500mg q12h	1	17 ± 10	4	21 ± 12
	500mg q8h	35	35 ± 17	35	35 ± 17
	750mg q8h	85	59 ± 18	87	61 ± 19
	1g q8h	**98**	**73 ± 17**	**98**	**75 ± 18**
	500mg q6h	72	53 ± 20	77	56 ± 21
	750mg q6h	**98**	**79 ± 16**	**99**	**81 ± 16**
Doripenem	250mg q12h	7	9 ± 16	12	14 ± 19
	500mg q12h	58	47 ± 26	68	56 ± 29
	250mg q8h	36	29 ± 28	36	30 ± 29
	500mg q8h	86	71 ± 23	87	75 ± 25
	750mg q8h	**97**	**86 ± 15**	**97**	**89 ± 17**
Ertapenem	500mg q24h	65	50 ± 20	97	75 ± 14
	750mg q24h	94	77 ± 21	99	90 ± 09
	1g q24h	98	90 ± 16	100	95 ± 7
	500mg initially, then 500mg post PIRRT	**99**	**91 ± 8**	**98**	**80 ± 15**

[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>4xMIC denotes the percent of time in the first 48 hours of therapy that the free fraction was four times greater that the target MIC for that drug.

Bolded dosing regimens are the ones that attained ≥ 90% of PTA, using the smallest daily dose.

Table 3. Carbapenem Clearances and Half-Lives in PIRRT in Comparison to Published Data in CRRT and EDD

Present Study in PIRRT	Meropenem	Imipenem	Doripenem	Ertapenem
$CL_{on\text{-}PIRRT}$ (L/hr)	5.9 ± 2.5	8.5 ± 1.5	6.1 ± 2.3	1.7 ± 0.3
$CL_{off\text{-}PIRRT}$ (L/hr)	3.1 ± 2.4	5.9 ± 1.4	2.9 ± 2.2	0.7 ± 0.1
CL_{PIRRT} (L/hr)	2.8 ± 0.5	2.6 ± 0.5	3.2 ± 0.6	1.0 ± 0.3
$t_{½\ on\text{-}PIRRT}$ (hr)	4.9 ± 3.4	2.7 ± 1.4	5.2 ± 3.1	7.5 ± 3.9
$t_{½\ off\text{-}PIRRT}$ (hr)	14.2 ± 16.7	3.9 ± 2.2	16.5 ± 17.7	18.2 ± 9.6
Published Data in CRRT & EDD				
CL_{CRRT} (L/hr)	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]
$t_{½\ CRRT}$ (hr)	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/hr)	2.3 (0.7-3.7) [40]	N/A	N/A	2.97 ± 0.65 [69]
$t_{½\ EDD}$ (hr)	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, $t_{½}$:half-life, CRRT : continuous renal replacement therapy; EDD : extended daily dialysis; N/A : not available

Numbers in brackets represent references. Numbers in parentheses represent data ranges. Clearance and half-life data in PIRRT were from on- and off- 8 hour hemodialysis PIRRT.

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

40% *f*T>4xMIC[a]				
8 hour Hemodialysis PIRRT				
Dialysate Flow Rate (L/hr)	Meropenem 1g q12h	Imipenem 1g q8h	Doripenem 750mg q8h	Ertapenem 500mg initially, then 500mg post PIRRT
2	90	99	97	99
3	90	98	97	99
4	89	98	97	99
5*	**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/hr)	Meropenem 1g q12h	Imipenem 1g q8h	Doripenem 750mg q8h	Ertapenem 500mg initially, then 500mg post PIRRT
2	91	99	97	99
3	90	99	97	99
4	89	98	97	99
5*	**88**	**98**	**97**	**99**
6	88	98	97	99
7	87	97	97	99
8	87	97	97	99

[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*).

*Reference flow rate used in this study

PTA data were from 8-Hour PIRRT using a 5 L/hour effluent flow rate (dialysate or ultrafiltrate flow rate) with blood flow rate of 300 ml/min.

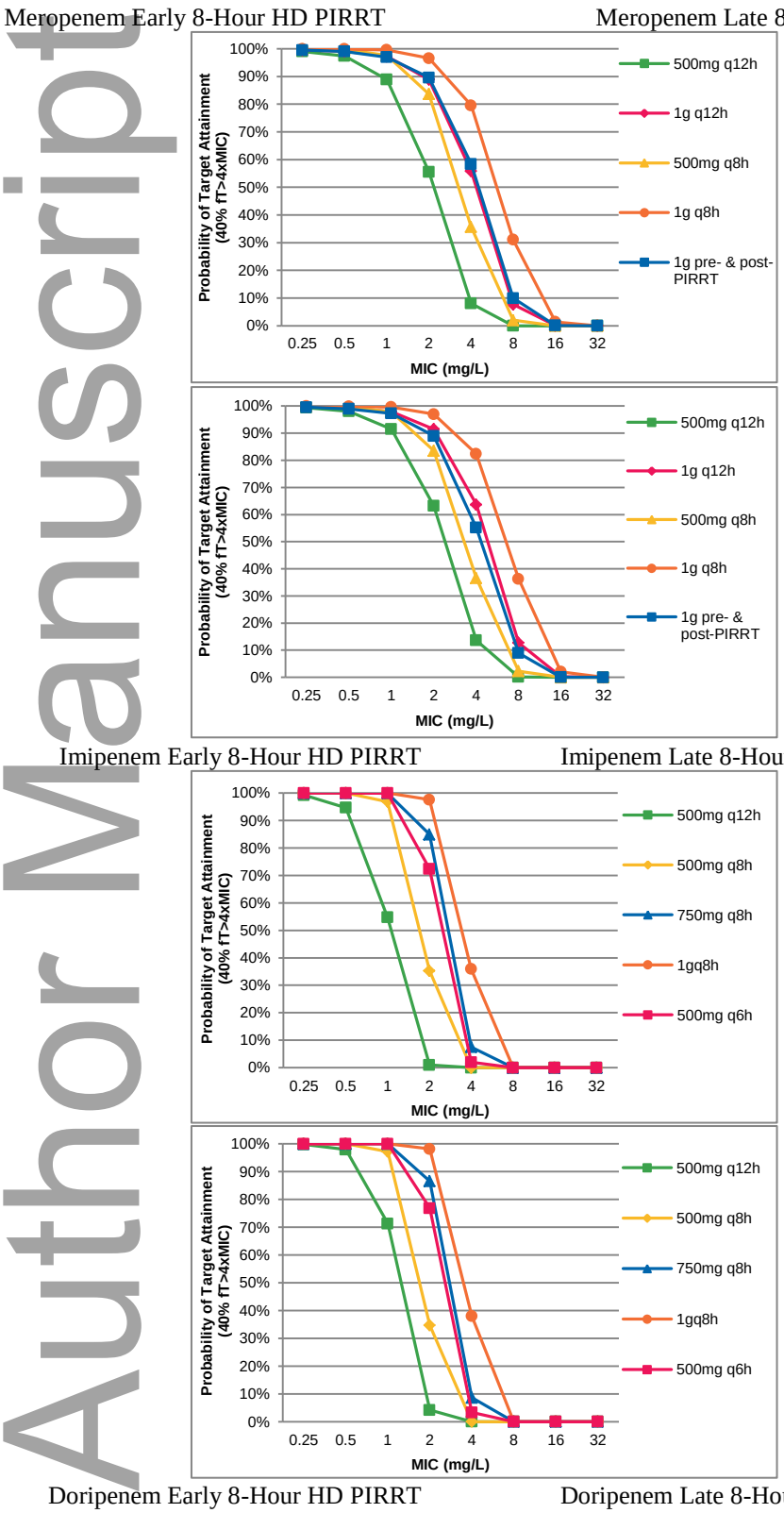
Table 5. Comparison of Published Carbapenem Dosing Regimens

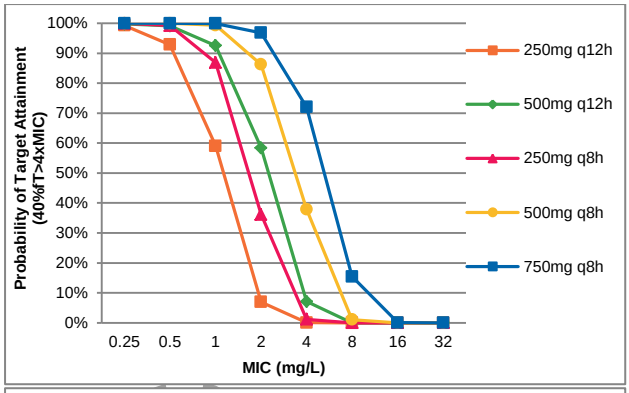
	Meropenem	Imipenem	Doripenem	Ertapenem
Normal kidney function	1g q8h [47]	1g q6-8h [48]	500mg q8h [49]	1g q24h [50]
Impaired kidney function (CrCl 10-50ml/min)	500mg-1g q12h [47]	500 q12h-750mg 8h [48]	250mg q12h-500mg q8h [49]	500mg q24h [50]
IHD	250mg-1g q24h with supplemental dose post- IHD [41,42]	500mg q12h post-IHD [48]	500mg q12h on Day 1, then 500mg q24h [70]	500mg q24h with 150mg supplemental dose 6 hours prior to IHD [50]
CRRT	500mg q12h-1g q8h [18-23,37-38]	500mg q6h-q12h [26-28,36,37]	250mg q12h or 500mg q8h [29,30]	500mg-1g q24h [32]
EDD/SLED	1g q12h or 500mg-1g q8h [40,68]	N/A	N/A	1g q24h [69]
PIRRT (Present study)	1g q12h	1g q8h	750mg q8h	500mg initially, then 500mg post-PIRRT

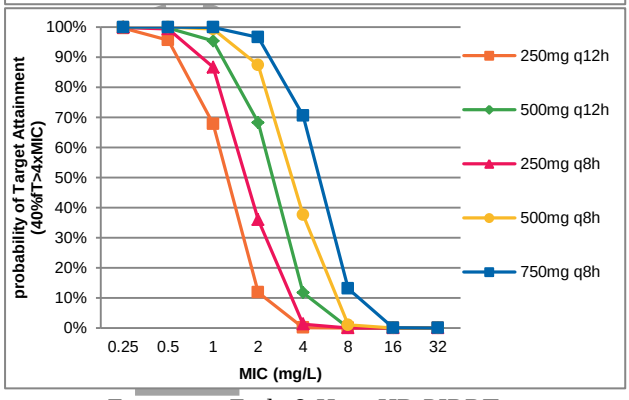
IHD: Intermittent Hemodialysis, CRRT: Continuous Renal Replacement Therapy, EDD/SLED: Extended Daily Dialysis / Sustained Low-Efficiency Dialysis, N/A: Not Available

Numbers in parentheses represent references.

Figure 1. Probability of Target Attainment in the First 48 Hours of Carbapenem Dosing Regimens at Different MICs

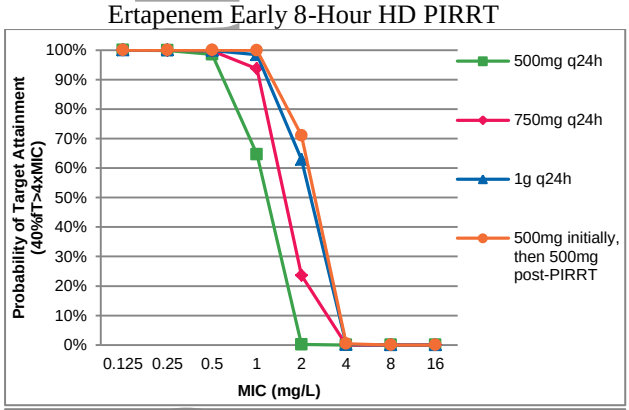






Ertapenem Early 8-Hour HD PIRRT

Ertapenem Late 8-Hour HD PIRRT



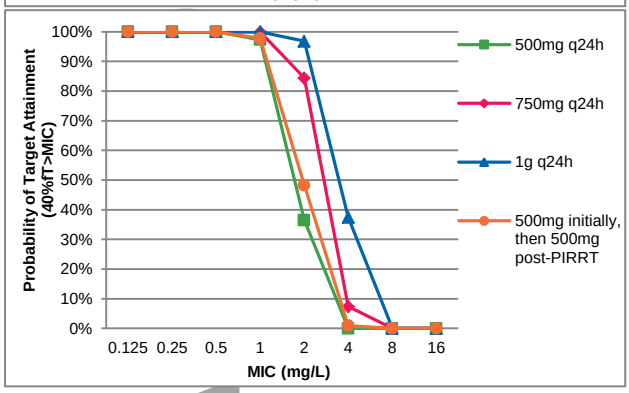


Figure 1. Legend.

HD: hemodialysis

Early PIRRT is when the first carbapenem dose is administered at the start of an 8-hour hemodialysis PIRRT session with a 5L/hr dialysate flow rate. Late PIRRT is when the first carbapenem dose is administered 16 hours before a daily 8-hour hemodialysis PIRRT session.