Original Research

Title: 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 PIRRT effluent rate and PIRRT duration combinations (4L/h×10h or 5L/h×8h in hemodialysis and hemofiltration modes). Antibiotic regimens were also modeled depending on whether drugs were administered during or well before PIRRT therapy commenced. The probability of target attainment (PTA) was calculated using each antibiotics' pharmacodynamic target during the first 48h of therapy. Optimal doses were defined as the smallest daily dose achieving ≥90% PTA in all PIRRT effluent and duration combinations. Cefepime 1g q6h following a 2g loading dose, ceftazidime 2g q12h and piperacillin/tazobactam 4.5g q6h attained the desired pharmacodynamic target in ≥90% of modeled PIRRT patients. Alternatively, if a q6h cefepime regimen is not desired, the cefepime 2g pre-PIRRT and 3g post-PIRRT regimen also met targets. For ceftazidime, 1g q6h or 3g continuous infusion following a 2g loading dose also met targets. These recommended doses provide simple regimens that are likely 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.

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

Introduction

The primary cause of acute kidney injury (AKI) in critically ill patients is due to sepsis. AKI is associated with high mortality rates (>50%)[1] and often requires treatment with renal replacement therapy (RRT). Currently, different types of RRTs are utilized in the intensive care units (ICU) including intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), and hybrids of conventional RRTs that are known by many names, including sustained low efficiency dialysis (SLED), extended daily dialysis (EDD), or prolonged intermittent renal replacement therapy (PIRRT).[2] The hybrid RRTs are gaining

usage due to improved patient mobility compared to CRRT, lower RRT operation cost compared to CRRT and better hemodynamic tolerance compared to IHD.[2-6] Despite the advantages of PIRRT, some clinicians are hesitant to use PIRRT due to 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 properties in patients with sepsis to improve patient outcomes.[10] In silico analyses via Monte Carlo Simulation (MCS) have been utilized 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 RRTs 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 RRT drug clearance characteristics allowing clinical researchers to predict the efficacy/safety of any drug dosing and RRT 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 β-lactam/β-lactamase inhibitor antibiotic combination product with broad-spectrum antibacterial activity against *Pseudomonas aeruginosa* and CTX-M beta-lactamase producing *Enterobacteriaceae*.[17] The antibacterial effect of piperacillin/tazobactam is primarily attributable to the activity of piperacillin while tazobactam inhibits piperacillin hydrolysis by β-lactamases. Like other cephalosporins and β-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 at between 1-4×MIC.[18] Even though β-lactam typically has a time-dependent activity, these drugs have 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] Due to 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 associated with neurotoxicity.[28] Currently, there is limited information on dosing cefepime, ceftazidime and piperacillin/tazobactam in critically ill patients receiving PIRRT.

In this study, MCS were performed to formulate cefepime, ceftazidime, and piperacillin/tazobactam dosing recommendations for critically ill patients receiving four common settings of PIRRT. The objectives of this MCS study were: 1) to determine probability of target attainment (PTA) 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 PIRRT.

Methods

Mathematical Pharmacokinetic Model

A one-compartment, first order, and multiple-dose pharmacokinetic model was developed to evaluate the effect of PIRRT 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 non-renal clearance (CL_{NR})] were collected from published studies via PubMed searches.[8, 29-52]

Four different PIRRT settings commonly used in practice were simulated: 8 hours/day (ultrafiltration rate/dialysate flow rate of 5L/h) or 10 hours/day (ultrafiltration rate/dialysate flow rate of 4L/h) of hemofiltration (HF) or hemodialysis (HD). Ultrafiltrate replacement using the pre-dilution 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 PIRRT was also evaluated at the two possible extremes. The first dose administered at the start of PIRRT (T0) or 14 to 16 (T14 and T16) hours before the next session of PIRRT (Figure 1A-B). Blood flow rate (Q_b) was fixed at 300 mL/min for all settings. Drug clearance during hemodialysis and hemofiltration modalities of PIRRT was estimated using the following equations:

(Eq. 1) Hemofiltration Clearance

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

Where CL_{HF} represents the transmembrane clearance during pre-dilution hemofiltration,

S_C represents the sieving coefficient,

Q_{uf} represents the ultrafiltration flow rate,

Q_{plasma} represents the plasma flow rate,

(Eq. 2) Plasma flow rate

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

Where Q_b represents the blood flow rate

(Eq. 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,

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 PIRRT[53], and the replacement fluid flow rate equaled the fluid removal rate during pre-dilution 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 q6h, q8h, q12h, q24h, extended infusion (4-hour), continuous infusion (24-hour), or at the start (pre) and end (post) of PIRRT. For continuous infusion (CI) dosing regimens, the loading dose was infused over 0.5h followed immediately by the CI dose which was infused at a rate of the CI dose/24h. Plasma drug concentration-time profiles were generated by the MCS (Crystal Ball, Oracle) in 5,000 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 (e.g., weight, V_d, free 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, a variability of 20% was assumed with limits set to 0 and 1. Lastly, 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 (e.g., 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 *Pseudomonas aeruginosa* since this common pathogen is associated with increased mortality rates in the ICU and is a common clinical indication for the three study antibiotic agents.[57] Based on Clinical and Laboratory Standards Institute (CLSI), the clinical breakpoint of *P. aeruginosa* for cefepime and ceftazidime is 8 mg/L and 16mg/L for

piperacillin.[58] We used a tazobactam concentration of 4mg/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 16mg/L (=64mg/L for piperacillin), >50% fT>4mg/L (tazobactam) and >60% fT>4×MIC of 8mg/L (=32mg/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 assumption of a constant drug clearance. However, this assumption of a constant drug clearance cannot be applied in our patient population since patients have two distinct clearances depending on whether they are receiving PIRRT for 8-10 hours each day. To better represent the clinical situation, we conducted simulations with PIRRT occurring at the two extremes of time of the day relative to the first antibiotic dose for each drug dosing regimen (T0 and T14/T16). Two PIRRT 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 PIRRT is starting, but in clinical practice PIRRT 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 PTA ≥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 concentrations >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 to be preferable to reduce the risks of drug-induced neurotoxicity within this MCS.[28, 62-64] The drug regimen considered to be "optimal" was one that achieved a PTA of ≥90% with the lowest daily dose regardless of when PIRRT 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 PTA results, suggesting that PIRRT modality did not appreciably influence target attainment (data not shown). Table 2 lists all simulated drug regimens and shows all regimens that resulted PTA ≥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 grams/day were required to reach 90% PTA. The mean ±SD percent of the first 48 hours of therapy that the serum concentrations were above fT>4×MIC for all 5000 subjects was 89.8±31% and 83.7±31% with a 2g loading dose followed by 1g every 6 hours for PIRRT at T0 and T16, respectively. Similarly, in the 5000 patients, cefepime 2 g pre-PIRRT and 3g post-PIRRT resulted in 81±33% and 82±30% of the dosing interval being above fT>4×MIC when PIRRT was initiated at T0 or T16, respectively in the first 48 hours of cefepime therapy. Figure 2 illustrates the PTA during the first 48 hours of many different cefepime dosing regimens when 8-hour HD is initiated at T0 (Figure 2A) or at T16 (Figure 2B). These figures also show the percent of patients with cefepime trough concentrations >70mg/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 concentrations were above fT>4×MIC for all 5000 subjects were 84.6±9.7% (PIRRT 8h-HD at T0) and 92.6±11.4% (PIRRT 8h-HD at T16) with a 2g every 12 hours regimen. Moreover, ceftazidime1g every 6 hours resulted 83.9±10.8% (PIRRT 8h-HD at T0) and 88±11.7% (PIRRT 8h-HD at T16) of the dosing interval being above fT>4×MIC in the first 48 hours of therapy. Lastly, a ceftazidime 2g loading dose followed by a 3g continuous infusion resulted in 96±11% and 97±9% of the first 48 hours fT>4×MIC when PIRRT was initiated at T0 or T16, respectively. Figure 3 illustrates the PTA 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 concentrations >100mg/L (a toxicity measure) with each of these regimens.

Piperacillin 4g every 6 hour infused over 30 minutes remained fT>4×MIC for 78±22% (PIRRT 8h-HD at T0) and 69±28% (PIRRT 8h-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 (4g every 6 hours over 4 hours) yielded 79±22% and 81±23% fT>4×MIC, and continuous infusion (16g every 24 hours) reached 78±22% and 80±24% for PIRRT at T0 and T16 for the first 48 hours of therapy. Finally, tazobactam PTA was ≥95% regardless of when the PIRRT 8-h HD was initiated relative to the initial drug dose for all three tested drug dosing regimens (Table 2). Figure 4 illustrates the PTA during the first 48 hours of many different piperacillin dosing regimens when 8-hour HD is initiated at T0 (Figure 4A) or at T16 (Figure 4B). Figure 4 also shows the percent of patients with piperacillin trough concentrations >361.4mg/L (a toxicity measure) with each of these regimens.

Discussion

In this MCS, common PIRRT settings (4L/h×10h or 5L/h×8h 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 PIRRT. The PTA showed no differences between two modalities and treatment durations. Even though convection usually yields higher drug clearances per effluent volume than diffusion, especially for larger solutes, we used pre-dilution replacement HF in this study, as is usually done clinically, which caused a decrease in clearance due to the dilution factor.

Conversely, the timing of the drug administration relative to PIRRT had more of an effect on toxicity measures than on efficacy PTA. To reflect the clinical setting as much as possible, the two possible extremes were modeled in this study. The PTAs were lower (less virtual patients reached the pharmacodynamic target) when beta-lactams were administrated concomitantly with PIRRT initiation (T0) compared to when PIRRT 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 PTA while consistently increasing the trough concentrations (higher risk of drug-related toxicity). Interestingly, when both cefepime and ceftazidime were administered at T16 (drug and PIRRT were maximally apart) the probability of virtual patients reaching the toxic trough concentration at the 48-hour time point drastically decreased while maintaining the high PTA 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 a drug administration relative to PIRRT greatly influences the pharmacodynamic target attainment.[65] However, this study highlights the importance of the timing of drug administration relative to PIRRT 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 (1-2g every 12h) did not meet our 90% PTA goal. Increasing the dose to 2g every 8h (the maximum labeled dose for cefepime) produced mean modeled trough concentrations that were nearly twice that observed with every 12h dosing, raising the concern for potential toxicity. Simulations with pre- and post-PIRRT dosing achieved our target PTA of ≥90%, but only when the total daily dose was at least 5g (2g pre-PIRRT, 3g post-PIRRT). Cefepime 1g every 6h after a 2g loading dose (dose on Day 1 = 5g) 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 1-2g every 12h 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% PTA threshold. A more frequent dosing regimen, such as 1g every 6h 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 h) or for subjects receiving IHD (1g after each IHD treatment).[70] Since ceftazidime and cefepime pharmacokinetics are similar, similar doses of 1-2 g every 12h are often advocated for both drugs.[71] However, our study in PIRRT indicates that slightly different doses are necessary to meet our PTA criteria with ceftazidime. Cefepime has a higher non-renal clearance rate and RRT 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 PTA of 98% for the pharmacodynamic target of 50% fT≥1×MIC with 1g every 8h in 16 critically ill patients receiving PIRRT.[72] The authors recommended ceftazidime 1g every 8h to reach their pharmacodynamic target (50% fT≥1×MIC), and 2g every 12h 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 RRT modalities were evaluated in our study. Recommended piperacillin/tazobactam doses for patients receiving other types of RRT include 4.5g every 8h for patients receiving CRRT[69] and 2.25g every 8h to 3.375g every 6h for patients receiving SLED.[8] Our MCS results indicate that those CRRT/SLED piperacillin/tazobactam dosing regimens did not meet the 90% PTA threshold of patients receiving PIRRT. Our MCS indicate that piperacillin/tazobactam 4.5g every 6h for critically ill patients receiving PIRRT 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 (4.5g every 6h) and the same PTA has been assessed in patients receiving CRRT with the mean effluent rates 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 4.5g every 8h was frequently insufficient in critically ill patients receiving RRT (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 PTA for both drugs simultaneously in the same virtual patients. Thus, we separately evaluated the PTA for piperacillin and tazobactam

in different sets of 5,000 virtual patients. We found that piperacillin 4g every 6h attains the therapeutic target in ~90% of simulated 5,000 patients and tazobactam 0.5g also achieves the efficacy target in >90% of another 5,000 virtual patients. Piperacillin/tazobactam have been frequently evaluated for alternate dosing strategies in critically ill patients who often require higher MIC targets due to 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. Recent meta-analysis, including data from 632 randomized patients, showed continuous piperacillin/tazobactam infusion was associated with decreased hospital mortality compared to intermittent infusion (≤ 30min infusion) in critically ill patients with severe sepsis.[80] Thus, we included 4-hour EI piperacillin/tazobactam and CI regimens with or 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 PIRRT.

This study has several limitations including that our model assumed that all virtual patients had a 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 antibiotics doses would be necessary. Also, our recommendations are only applicable to patients who receive daily PIRRT at the modeled flow rates. In scenarios where PIRRT is 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, consequently MCS like the ones conducted here are the best available option to obtain good initial empiric beta lactam doses for these patients. While the patient demographics that

served as the basis for this MCS came from a sole American center, [29] the population was quite large (n=100) and likely is representative of the types of patients that would receive PIRRT and these antibiotics.

Lastly, these drug dosing recommendations are based on the target of ~90% of critically ill patients receiving PIRRT will attain the pharmacodynamic target. 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 2g every 8h are necessary to maintain an adequate fT>MIC throughout the dosing interval for morbidly obese patients (body mass index >40 kg/m^2) with estimated glomerular filtration rate of 108.4±34.6mL/min.[84] Even though their patients did not have renal dysfunction nor receiving renal replacement therapy, their dose recommendation is still vastly different than conventional dose of 1-2g every 12h for patients. Our MCS model was not able to calculate BMI, however a post-hoc analysis of our virtual patients that were >120 kg indicates that our recommended doses for cefepime 2g LD, 1g q6h, ceftazidime 2g q12h, and piperacillin/tazobactam 4.5g q6h all had 100% PTA at the 1X MIC threshold no matter when the dose was administered relative to PIRRT.

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

Conclusion

In a pharmacokinetic model of critically ill patients receiving 8 hours (5L/h) or 10 hours (4L/h) of daily PIRRT, cefepime 1g every 6h with a 2g loading dose, ceftazidime 2g every12h and piperacillin/tazobactam 4g every 6h will reach the pharmacodynamic targets for *P. aeruginosa*. While administering drugs during a PIRRT session is not ideal, delaying antibiotic therapy cannot be condoned and use of these doses appears to meet the 90% PTA threshold for the first 48 hours regardless of when the dose is given relative to PIRRT. A validation study in the clinical setting is warranted.

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

	Cefepime	**Ceftazidime**	**Piperacillin**	**Tazobactam**
Weight (kg)	86.6 ± 29.2kg (≥40kg)[29]	86.6 ± 29.2kg (≥40kg)[29]	86.6 ± 29.2kg (≥40kg)[29]	86.6 ± 29.2kg (≥40kg)[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} 4L/h) 0.45 ± 0.08 (Q_{ef} 5L/h)	0.43 ± 0.09 (Q_{ef} 4L/h) 0.36 ± 0.07 (Q_{ef} 5L/h)	0.6 ± 0.28 (0 - 1)	0.8 ± 0.36 (0 - 1)
Hemofiltration clearance	34.7 (Q_{ef} 4L/h) 37.5 (Q_{ef} 5L/h)[31,	33.4 (Q_{ef} 4L/h) 39.4 (Q_{ef} 5L/h)[38,	25 (Q_{ef} 4L/h) 30 (Q_{ef} 5L/h)[51, 52]	38 (Q_{ef} 4L/h) 45 (Q_{ef} 5L/h)[51, 52]

(mL/min)	[32]	[39, 41, 43-45]		
Hemodialysis clearance (mL/min)	46.4 (Q_{ef} 4L/h) 54.6 (Q_{ef} 5L/h)[31, 32, 36, 37]	28.7 (Q_{ef} 4L/h) 30 (Q_{ef} 5L/h)[39, 40, 42, 43, 45-47]	40 (Q_{ef} 4L/h) 50 (Q_{ef} 5L/h)[8, 48-50]	53 (Q_{ef} 4L/h) 67 (Q_{ef} 5L/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).				

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

Administration Strategies				
Frequency	**Cefepime**	**Ceftazidime**	**Piperacillin**	**Tazobactam**
Q6H	1 g 2 g LD, 1 g 3 g LD, 1 g*	1 g 2 g LD, 1 g	2 g 2 g EI 3 g 3 g EI 4 g 4g EI	0.375 g 0.375 g EI 0.5 g 0.5 g EI
Q8H	1 g 1 g EI 2 g* 2 g EI*	1 g 2 g LD, 1 g 2 g+	2 g 3 g 4 g	0.5 g
Q12H	1 g 1 g EI 2 g 2 g EI 3 g LD, 2 g 4 g LD, 2 g*	1 g 1 g EI 2 g 2 g EI+	N/A	N/A
Beginning (Pre) and End (Post) of PIRRT	2 g Pre, 2 g Post 2 g Pre, 3 g Post 3 g Pre, 2 g Post 3g LD, 2g Pre, 2g Post	2 g Pre, 1 g Post 2 g Pre, 2 g Post	N/A	N/A
Continuous Infusion	2 g LD, 4 g CI*	2 g LD, 3 g CI	12 g CI 16 g CI	1.5 g CI 2 g CI

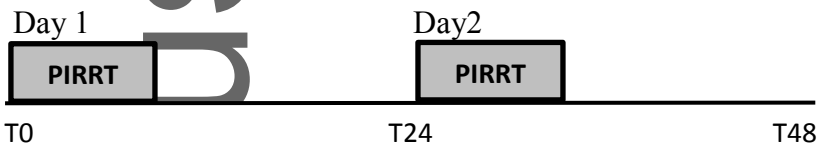
CI – continuous infusion (over 24 hours); EI - extended infusion (over 4 hours); LD - loading dose; N/A – not available; PIRRT – prolonged intermittent renal replacement therapy

* depending on when drug is infused relative to PIRRT often results in mean cefepime trough concentration >70mg/L, a value that has been linked to toxicity[62]

+ depending on when drug is infused relative to PIRRT often results in mean ceftazidime trough concentration >100mg/L, a value that has been linked to toxicity[63, 64]

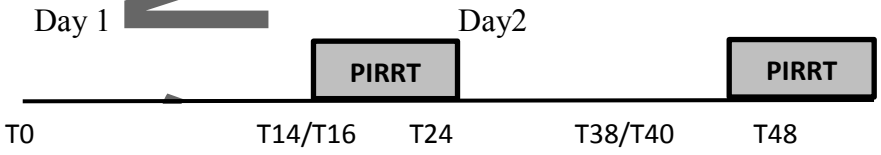
Note: All listed dosing regimens represent probability of target attainment (PTA) ≥90% at 1×minimum inhibitory concentration (MIC) for the first 48 hours. Underlined dosing regimens represent PTA ≥90% at 4×MIC for the first 48 hours.

Figure 1A. PIRRT initiated at the beginning of the antibiotic therapy (T0) for 8-hour and 10-hour hemofiltration or hemodialysis

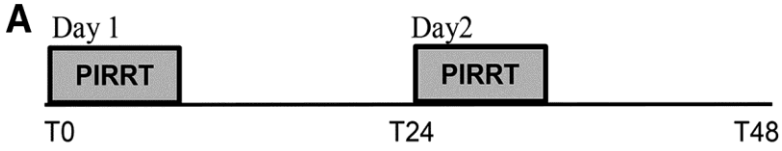


T0= The initiation of antibiotic therapy

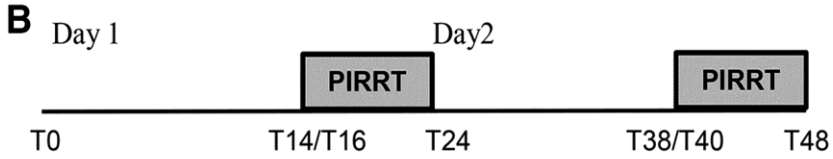
Figure 1B. PIRRT initiated 14 hours after the first antibiotic dose (T14 with 10-hour/ T16 with 8-hour) hemofiltration or hemodialysis



T0= The initiation of antibiotic therapy



T0= The initiation of antibiotic therapy



T0= The initiation of antibiotic therapy

Figure 2A: Probability of target attainments when an 8-hour hemodialysis was initiated at the same time the first cefepime dose as given (T0) for a series of cefepime dosing regimens.

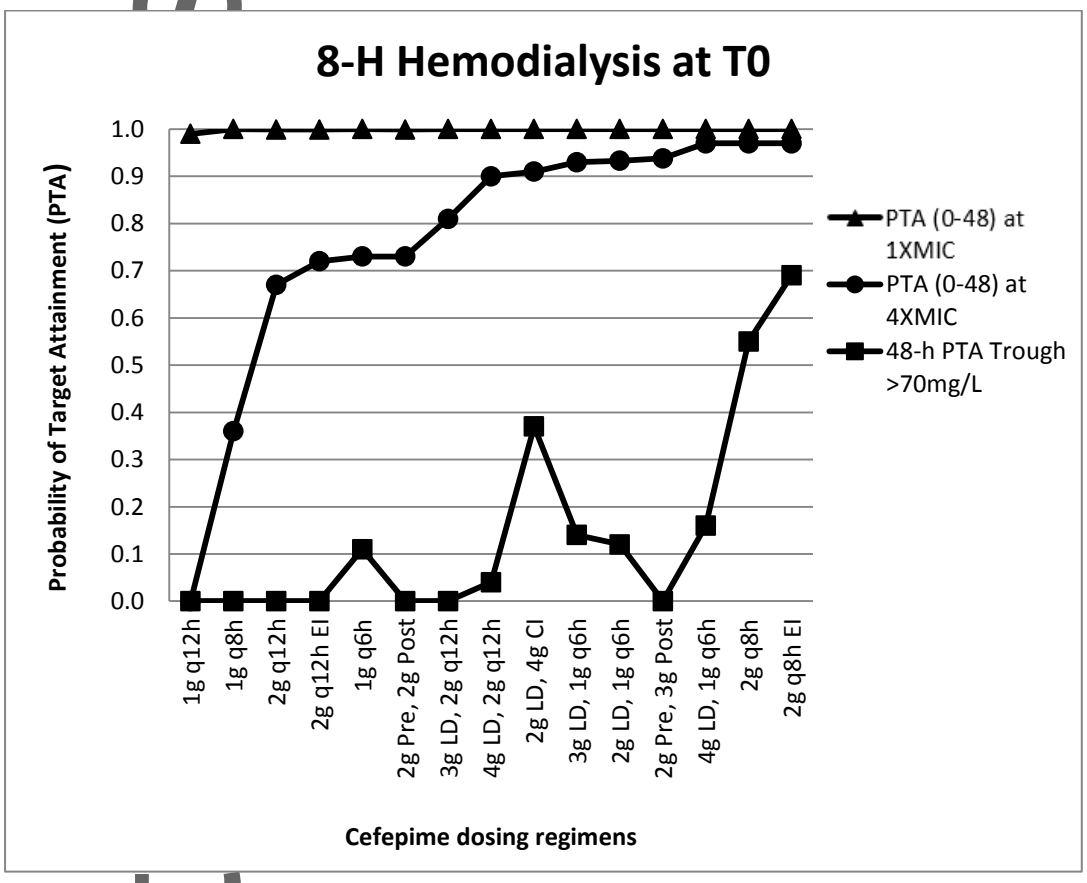
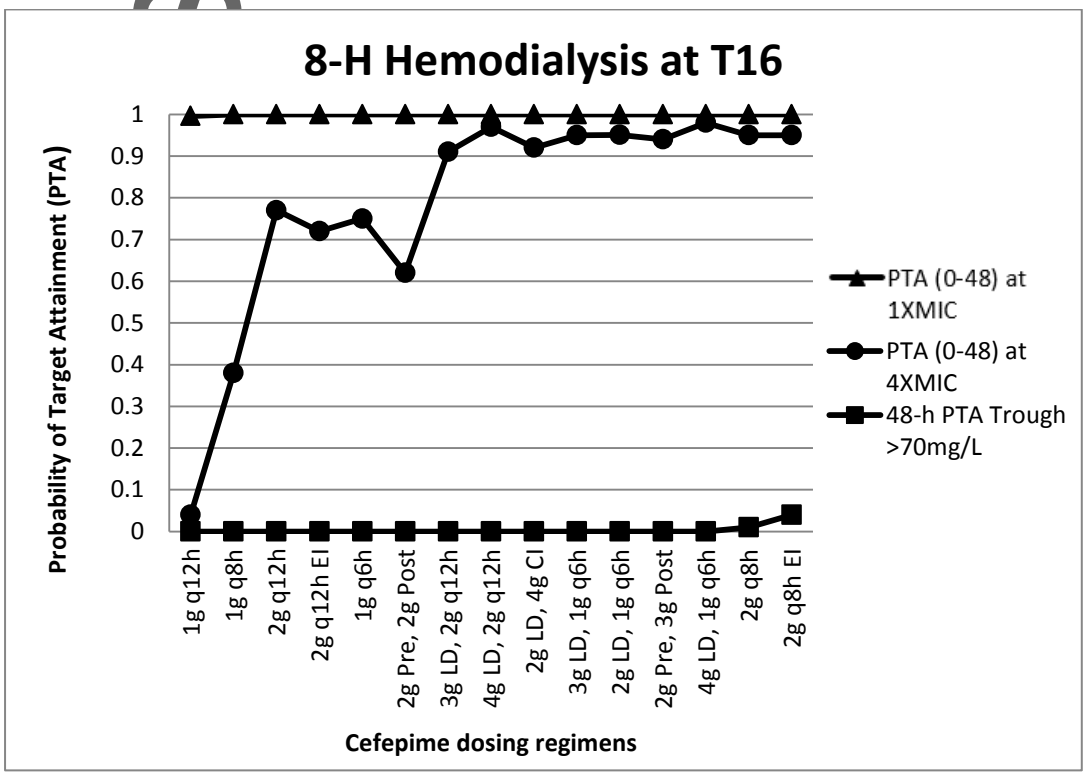


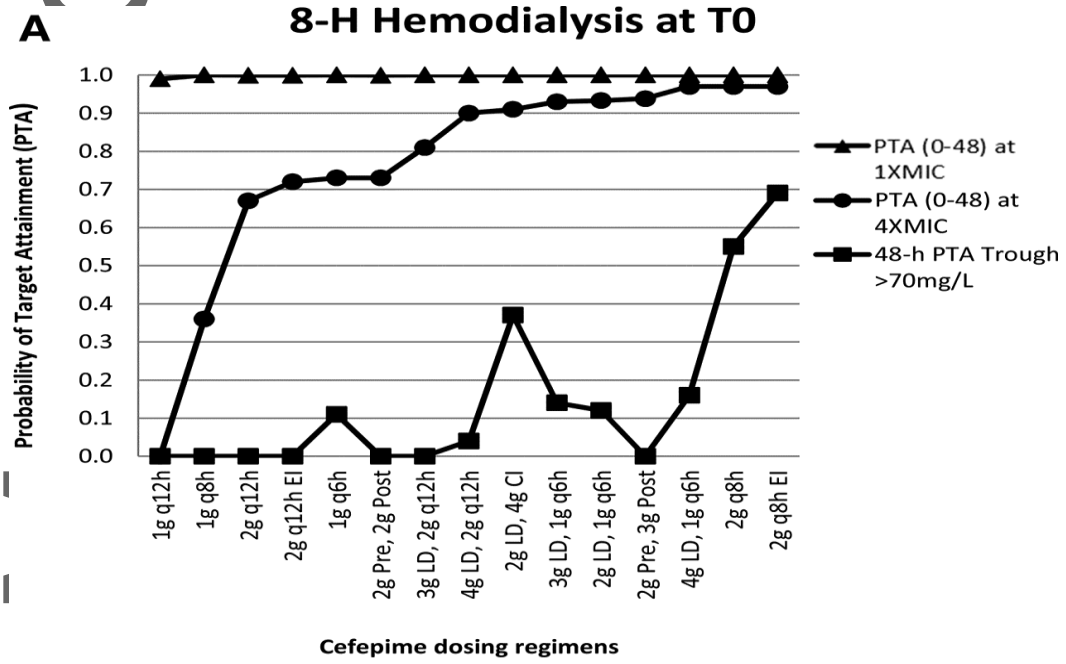
Figure 2B Probability of target attainments when the first cefepime dose was administered 16 hours (T16) before the next session of 8-hour hemodialysis for a series of cefepime dosing regimens.



Legend for Figures 2A and 2B:

Abbreviations: 1×MIC = one times minimum inhibitory concentration; 4×MIC = four times minimum inhibitory concentration; CI = continuous infusion over 24 hours; EI = extended infusion over 4 hours; LD = loading dose; MIC = minimum inhibitory concentration; q = every

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 PTA for 1X MIC (triangles) and 4X MIC (circles) for the first 48 hours of antibiotic therapy are illustrated. The percent 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.



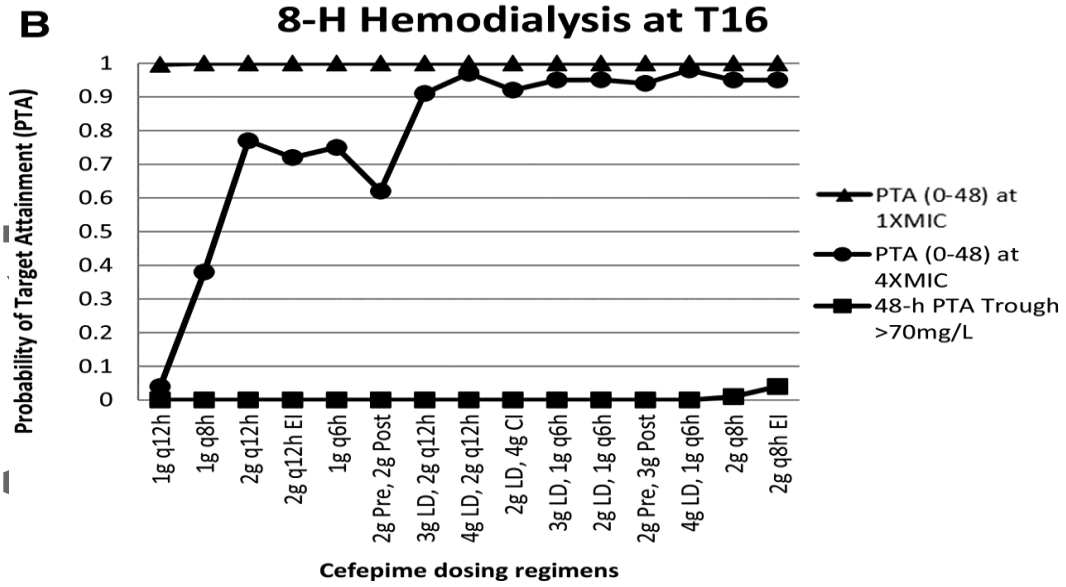


Figure 3A: Probability of target attainments when an 8-hour hemodialysis was initiated at the same time the first ceftazidime dose as given (T0) for a series of ceftazidime dosing regimens.

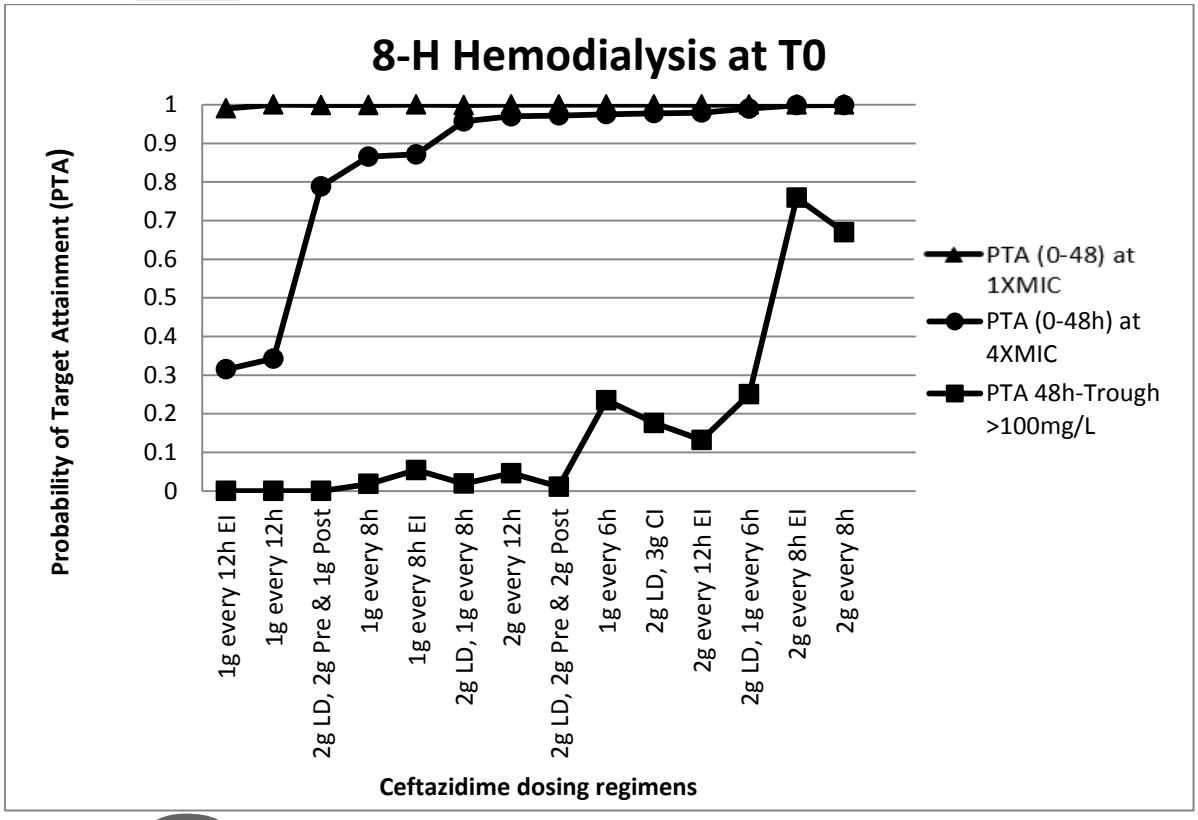
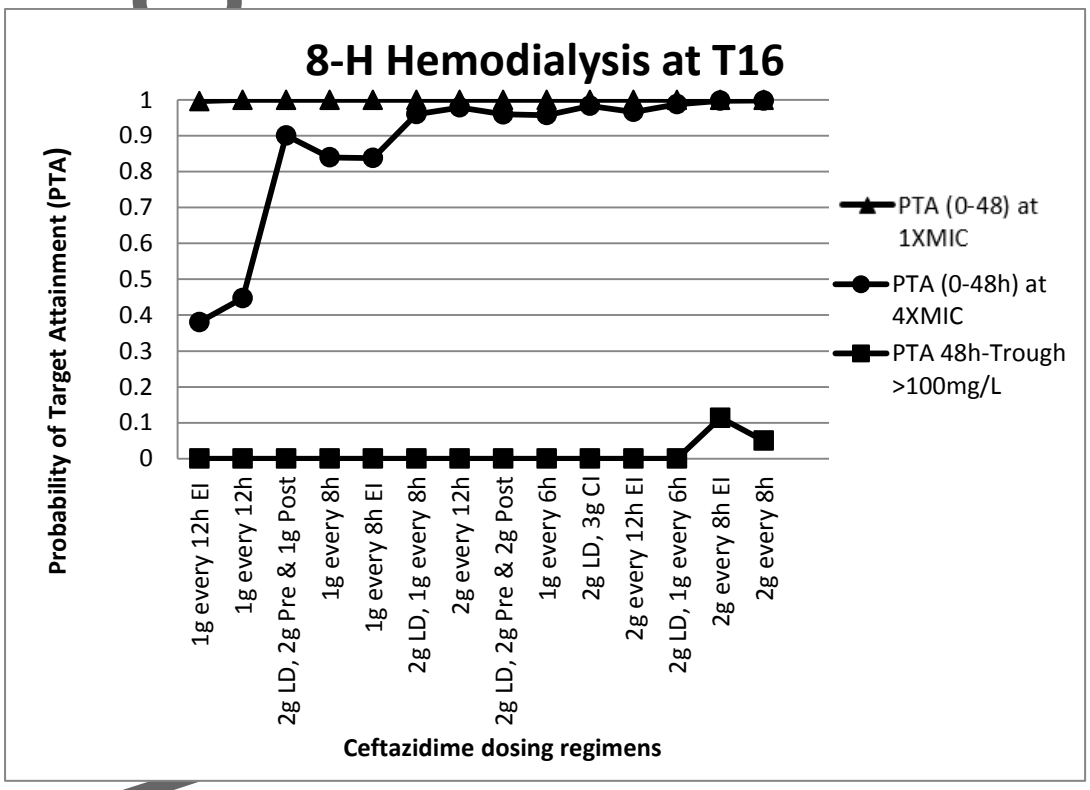


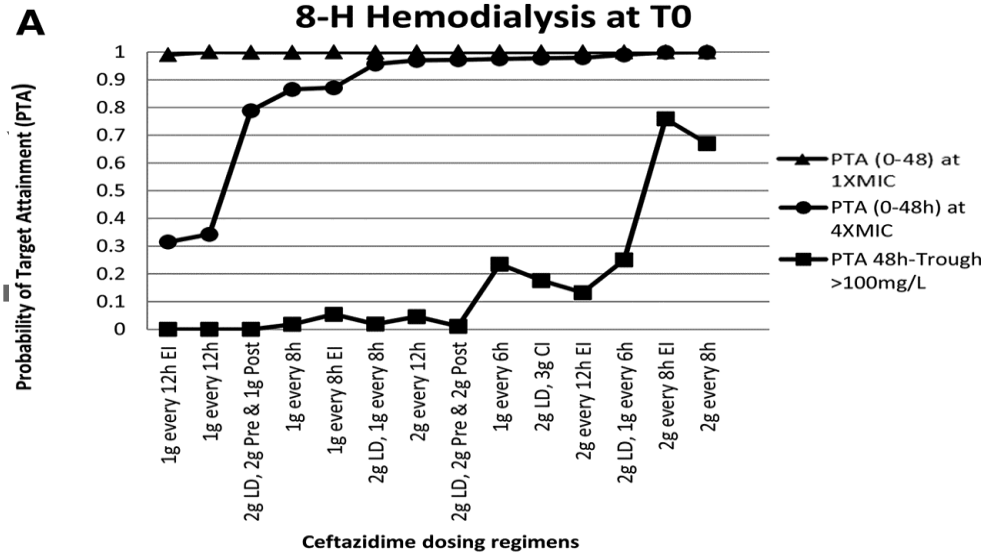
Figure 3B: Probability of target attainments when the first ceftazidime dose was administered 16 hours (T16) before the next session of 8-hour hemodialysis for a series of ceftazidime dosing regimens.



Legend for Figures 3A and 3B:

Abbreviations: 1×MIC = one times minimum inhibitory concentration; 4×MIC = four times minimum inhibitory concentration; CI = continuous infusion over 24 hours; EI = extended infusion over 4 hours; LD = loading dose; MIC = minimum inhibitory concentration; q = every

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 PTA for 1X MIC (triangles) and 4X MIC (circles) for the first 48 hours of antibiotic therapy are illustrated. The percent of virtual patients who attained trough ceftazidime concentrations of >100 mg/L, which may be associated with neurotoxicity, with each regimen are shown with squares.



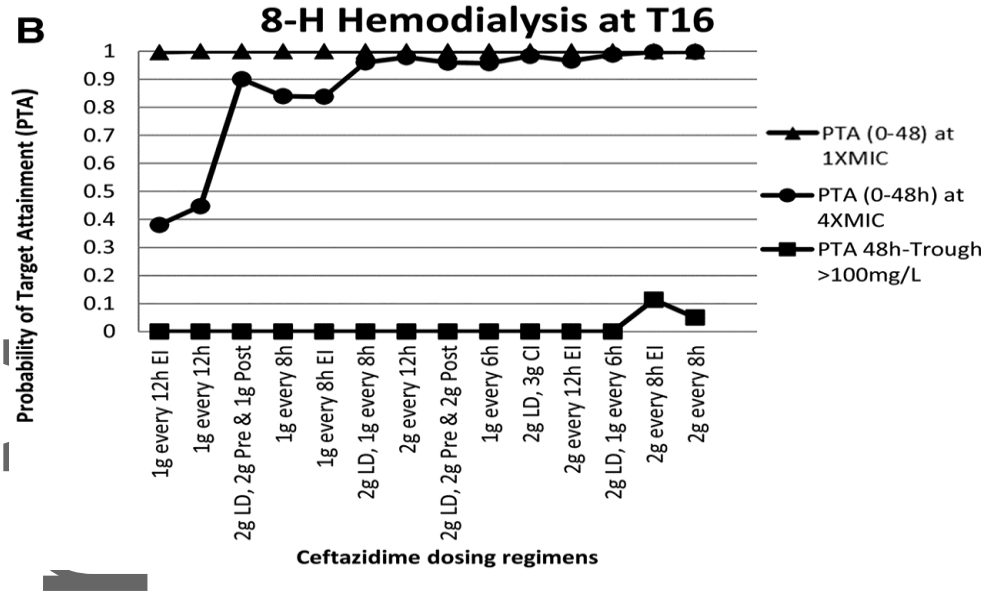


Figure 4A: Probability of target attainments when an 8-hour hemodialysis was initiated at the same time the first piperacillin dose as given (T0) for a series of piperacillin dosing regimens.

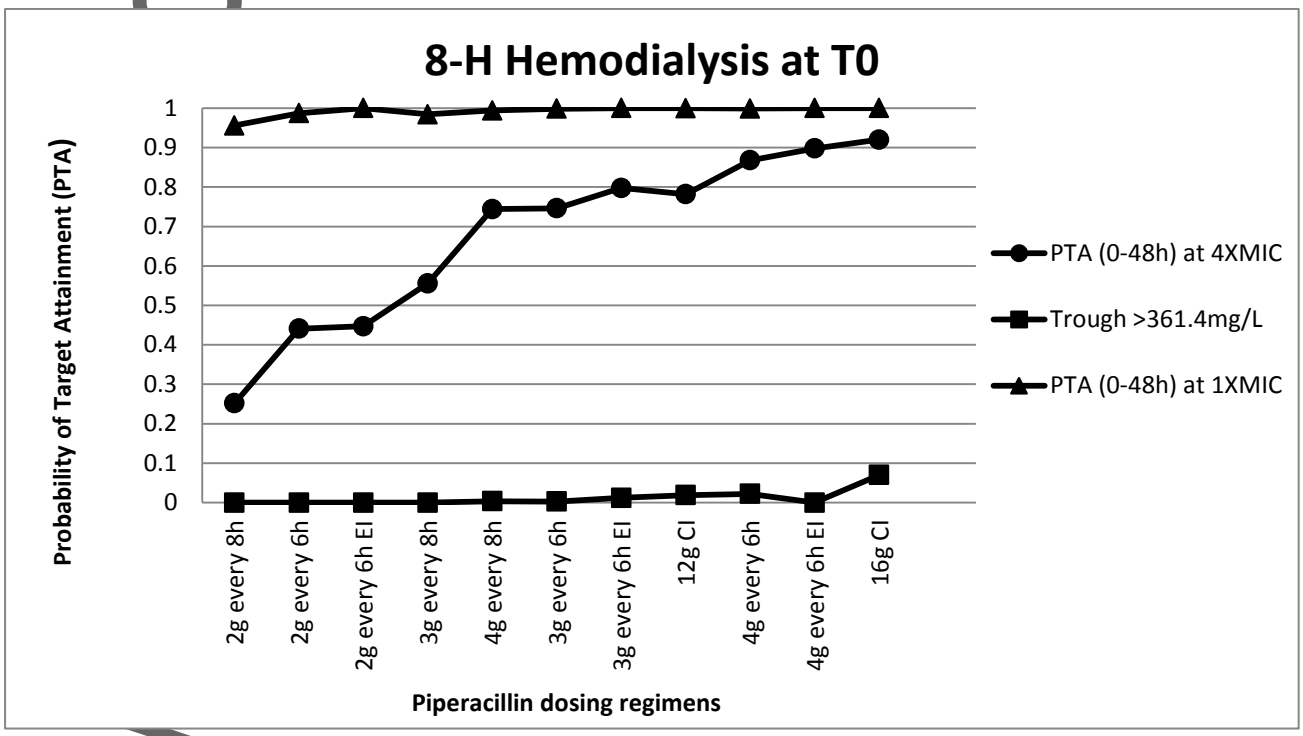
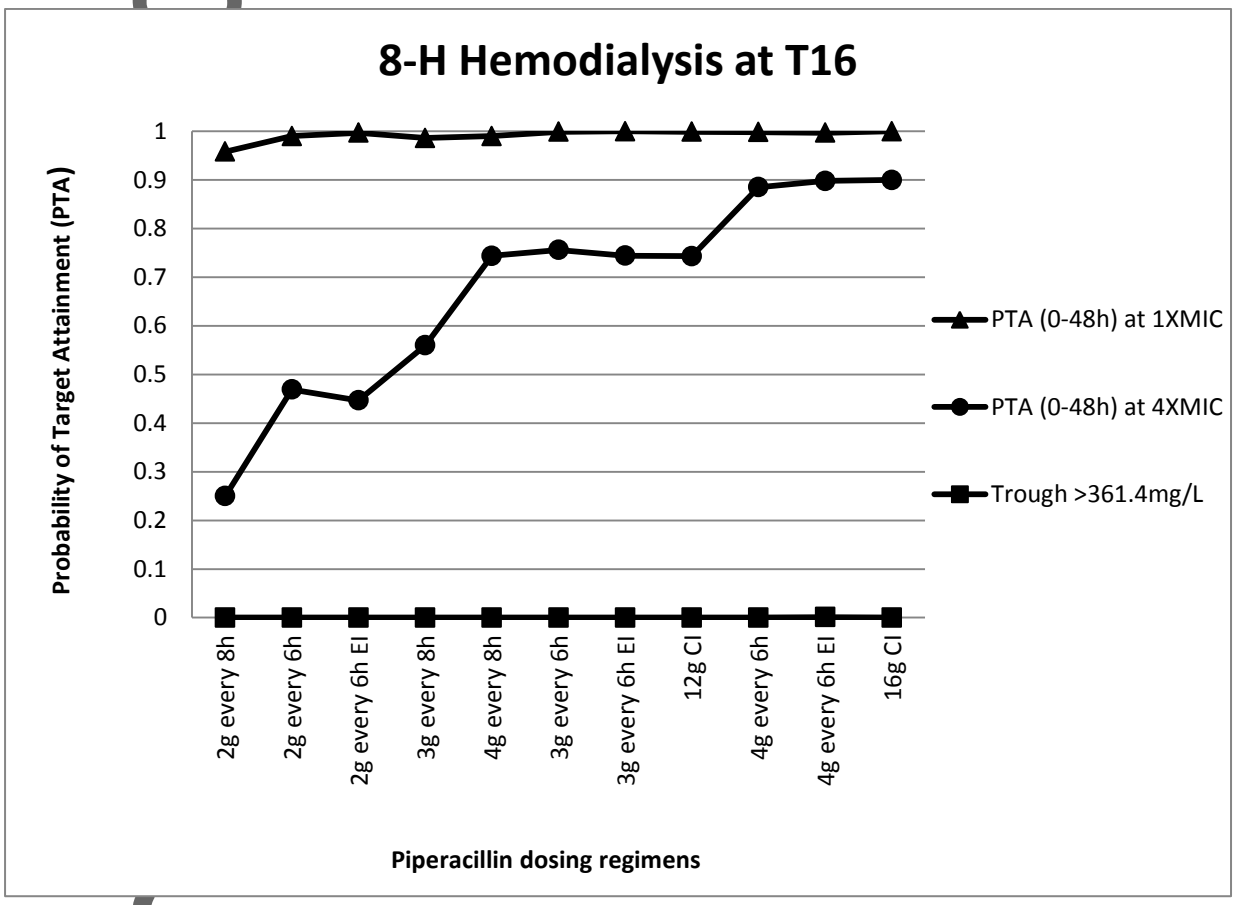


Figure 4B: Probability of target attainments when the first piperacillin dose was administered 16 hours (T16) before the next session of 8-hour hemodialysis for a series of piperacillin dosing regimens.



Legend for Figures 4A and 4B:

Abbreviations: 1×MIC = one times minimum inhibitory concentration; 4×MIC = four times minimum inhibitory concentration; CI = continuous infusion over 24 hours; EI = extended infusion over 4 hours; LD = loading dose; MIC = minimum inhibitory concentration; q = every

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 PTA for 1X MIC (triangles) and 4X 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 are shown with squares.