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Development of a vancomycin dosing approach for critically ill patients receiving hybrid hemodialysis using Monte Carlo simulation

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Abstract

Objectives: Prolonged intermittent renal replacement therapy is an increasingly popular treatment for acute kidney injury in critically ill patients that runs at different flow rates and durations than conventional hemodialysis or continuous renal replacement therapies. Pharmacokinetic studies conducted in patients receiving prolonged intermittent renal replacement therapy are scarce; consequently, clinicians are challenged to dose antibiotics effectively. The purpose of this study was to develop vancomycin dosing recommendations for patients receiving prolonged intermittent renal replacement therapy.

Methods: Monte Carlo simulations were performed in thousands of virtual patients derived from previously published demographic, pharmacokinetic, and dialytic information derived from critically ill patients receiving vancomycin and other forms of renal replacement therapy. We conducted "in silico" vancomycin pharmacokinetic/pharmacodynamics analyses in these patients receiving prolonged intermittent renal replacement therapy to determine what vancomycin dose would achieve vancomycin 24-h area under the curve (AUC_{24h}) of 400–700 mg·h/L, a target associated with positive clinical outcomes. Nine different vancomycin dosing regimens were tested using four different, commonly used prolonged intermittent renal replacement therapy modalities. A dosing nomogram based on serum concentration data achieved after the third dose was developed to individualize vancomycin therapy.

Results: An initial vancomycin dose of 15 or 20 mg/kg immediately followed by 15 mg/kg after subsequent prolonged intermittent renal replacement therapy treatments achieved AUC_{24h} of ≥400 mg·h/L for ≥90% of patients regardless of prolonged intermittent renal replacement therapy duration, modality, or time of vancomycin dose relative to prolonged intermittent renal replacement therapy. Many patients experienced AUC_{24h} of ≥700 mg·h/L, but once the dosing nomogram was applied to serum concentrations obtained after the third vancomycin dose, 67%–88% of patients achieved AUC_{24h} of 400–700 mg·h/L.

Conclusion: An initial loading dose of 15–20 mg/kg followed by a maintenance regimen of 15 mg/kg after every prolonged intermittent renal replacement therapy session coupled with serum concentration monitoring should be used to individualize vancomycin dosing. These predictions need clinical verification.

Keywords

Renal failure, kidney failure, pharmacokinetics, pharmacodynamics, dialysis, vancomycin

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Introduction

Infectious complications are associated frequently with acute kidney injury (AKI) in critically ill patients. The number of patients with AKI requiring renal replacement therapy (RRT) has increased by 10% annually and the deaths among these patients more than doubled in the United States during the past decade.[1] One of the profound challenges to improve these poor outcomes is limited pharmacokinetic data to ensure sufficient initial antibiotic doses to attain pharmacodynamic targets.[2,3] Particularly, antibiotic dosing data in hybrid types of RRT like prolonged intermittent renal replacement therapy (PIRRT) are available for less than 15 drugs.[4,5]

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Table 1. Input Parameters Used in In Silico Vancomycin Dosing Trials.

	Input parameters	Hemofiltration		Hemodialysis	
PIRRT parameters	Blood flow rate (mL/min)	300			
	Ultrafiltrate or dialysate flow rate (mL/min)	83.3	66.7	83.3	66.7
	Duration (h)	8	10	8	10
	Frequency	Daily			
Demographic and pharmacokinetic parameters (mean ± *SD* (range))	Weight (kg)	86.6 ± 29.2 (40–170)[17]			
	Volume of distribution (L/kg)	0.6 ± 0.27 (0.27–1.4)[19–24]			
	Non-renal clearance (mL/min)	17.9 ± 13(0–61)[19–24]			
	Saturation/sieving coefficient	0.75 ± 0.15 (0–1)[19–24]			
	Correlation between weight and volume of distribution (r^2)	0.15			
	Correlation between weight and non-renal clearance (r^2)	0.36			

All values are represented as mean ± *SD* (assigned model limits).

PIRRT runs typically for 6–12 h at different flow rates than conventional intermittent hemodialysis (IHD) or continuous RRT (CRRT). They are growing in popularity due to better hemodynamic tolerance and improved patient mobility compared to conventional RRT.[6–8] However, the paucity of PIRRT data can potentially lead to underdosing or overdosing of these lifesaving drugs.[9]

Methicillin-resistant *Staphylococcus aureus* (MRSA) is the most frequent multi-drug resistant pathogen associated with nosocomial infection and high morbidity and mortality in the intensive care unit.[10–12] Vancomycin remains the first-line antibiotic therapy for MRSA infection. Available evidence suggests that the 24-h area under the curve (AUC_{24h}): minimum inhibitory concentration (MIC) ratio of ≥400 is the optimal pharmacodynamic target to predict vancomycin clinical efficacy against MRSA infections.[13] Current vancomycin therapeutic guidelines indicate that targeting a steady-state trough concentrations of 15–20 mg/L would attain an AUC_{24h}: MIC ratio of ≥400 in most adult patients with normal kidney function if the organism's MIC is ≤1 mg/L.[14] For pathogens with the vancomycin MIC of ≥2 mg/L, this pharmacodynamic target of AUC_{24h}: MIC ratio of ≥400 is not achievable with conventional vancomycin dosing methods.[14] Thus, the guidelines suggest considering alternative antibiotic agents if the vancomycin MIC is ≥2 mg/L.[14] However, emerging data show attaining a higher AUC_{24h}: MIC (550–650) using the broth microdilution method, the most commonly used MIC test method, during the initial 48 h of therapy is associated with a 50% lower treatment failure and mortality rate.[15] Conversely, AUC_{24h} of ≥700 mg·h/L have been associated with the increased risk of vancomycin toxicity.[16] Although vancomycin therapeutic drug monitoring (TDM) is routinely practiced, determination of an initial dose that will attain the pharmacodynamic target in patients with AKI receiving daily PIRRT is challenging because vancomycin clearance will be significantly higher during the 8–10 h of PIRRT each day and lower when PIRRT is not running.[9] Consequently, "when" the dose is administered in relation to PIRRT may also be as important as "how much" vancomycin is given to attain the pharmacodynamic target.[9]

The purpose of this study was to (1) determine initial optimal vancomycin dosing recommendations for patients receiving daily PIRRT and (2) develop a serum concentration-guided dosing system to guide individualized dosing to attain or maintain the pharmacodynamic target.

Materials and methods

Part 1

Pharmacokinetic model development. The model incorporated relevant demographic and pharmacokinetic parameters with their associated variability, and four different daily PIRRT regimens with different effluent flow rates (dialysate or ultrafiltrate flow rate) and different treatment durations.[17,18] These input parameters used in the present in silico analyses have been outlined in Table 1. Body weight estimates were obtained from one of these PIRRT studies.[17] The pharmacokinetic parameters were derived from published vancomycin pharmacokinetic studies in critically ill patients receiving RRT.[19–24] These demographic and pharmacokinetic parameters were assumed to have log-Gaussian distribution. Range limits and correlation (e.g. coefficient of determination, r^2 between body weight vs volume of distribution or non-renal clearance) on input parameters estimated from those data were also included in the models to construct a realistic virtual population. The relationships between these parameters were tested and found to be weak. ($r^2 < 0.15$ between body weight and volume of distribution, and $r^2 < 0.36$ between body weight and non-renal clearance). For body weight, values were truncated at <40 kg and >170 kg, assuming that patients were adults without severe obesity. For volume of distribution and non-renal clearance, the minimal and maximal values reported from the relevant vancomycin

pharmacokinetic studies[19–24] were used as the lower and upper limits in the model. For sieving and saturation coefficients which measure what percentage of drug crosses the hemodiafilter membrane in hemofiltration and hemodialysis, respectively, the values were built to be ≤ 1. Patients were assumed to be anuric in our model as critically ill patients receiving RRTs were anuric in most vancomycin pharmacokinetic studies.[19–21,23,24]

Four different daily PIRRT regimens used in the model were (1) 8-h hemofiltration per day with an ultrafiltrate flow rate of 88.3 mL/min, (2) 8-h hemodialysis per day with a dialysate flow rate of 88.3 mL/min, (3) 10-h hemofiltration per day with an ultrafiltrate flow rate of 66.7 mL/min, and (4) 10-h hemodialysis per day with a dialysate flow rate of 66.7 mL/min. In all PIRRT settings, blood flow rate was fixed as 300 mL/min, which is commonly used for PIRRT.[17] All replacement solutions in hemofiltration were modeled to be infused in the pre-dilution mode as is done in most clinical practices. The equations used in the model were as follows:

Equations.

$$CL_{HF}\left(mL/min\right)^{25,26} = SC \times Q_{uf} \times \left[\frac{Q_{plasma}}{Q_{plasma} + Q_{replacement}}\right]$$

$$CL_{HD}\left(mL/min\right) = SA \times Q_d$$

$$V_d\left(L\right) = WT\ \left(kg\right) \bullet V_d\left(L/kg\right)$$

$$K_{el_on} = \frac{CL_{NR} + CL_{HF}}{V_d}\ \left(\text{for hemofiltration}\right)$$

$$K_{el_on} = \frac{CL_{NR} + CL_{HD}}{V_d}\ \left(\text{for hemodialysis}\right)$$

$$K_{el_off} = \frac{CL_{NR}}{V_d}$$

where CL_{HF} is transmembrane clearance in hemofiltration, SC is sieving coefficient, Q_{uf} is ultrafiltrate flow rate, Q_{plasma} is plasma flow rate ($Q_{plasma} = Q_{blood} \times (1 - \text{hematocrit})$; hematocrit is 30%[26]), $Q_{replacement}$ 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_d is volume of distribution, WT is body weight, K_{el_on} is the elimination rate constant during PIRRT, CL_{NR} is non-renal clearance, and K_{el_off} is the elimination rate constant off PIRRT.

Monte Carlo simulations. Pharmacokinetic exposures were modeled for nine vancomycin regimens as shown in Table 2. Infusion times were 1 h for a vancomycin dose of ≤1 g and 2 h for a vancomycin dose >1 g. Total serum concentration-time profiles were simulated for each vancomycin regimen for the initial 48 h, utilizing mean ± standard deviation estimates and range limits of aforementioned demographic and pharmacokinetic parameters and a one compartment model with constant intravenous input and first order elimination

$$C\left(t\right) = \left[\frac{Dose/T}{k_{el} \bullet V_d}\right] \bullet \left(1 - e^{-k_{el} \cdot t}\right)\ \left(\text{during the infusion}\right)$$

$$C\left(t\right) = \left[\frac{Dose/T}{k_{el} \bullet V_d}\right] \bullet \left(1 - e^{-k_{el} \cdot t}\right) \bullet e^{-kel \bullet (t-T)}\ \left(\text{after the infusion}\right)$$

where C(t) is the vancomycin concentration at a specific time, T is infusion time, k_{el} is the elimination rate constant (k_{el_on} was used during PIRRT and k_{el_off} off PIRRT in the model), V_d is volume of distribution, and t is the time from the infusion initiation.

Monte Carlo simulation (MCS) (Crystal Ball Classroom Edition, Oracle) was performed to generate individual vancomycin total serum concentration profiles in 5000 virtual subjects for each vancomycin dosing regimen. Considering a wide variety of clinical situations where vancomycin can be administered at different times in relation to PIRRT, the four different PIRRT settings were modeled to occur at the two possible extremes as illustrated in Figure 1: (1) at the beginning of vancomycin infusion ("early PIRRT") and (2) 14 or 16 h after vancomycin infusion ("late PIRRT"). Thus, nine different vancomycin dosing regimens were simulated for each of the eight different PIRRT setting scenarios (8- and 10-h hemofiltration and 8- and 10-h hemodialysis in either early or late PIRRT).

Prediction of probability of target attainment. Probability of target attainment (PTA) for each dosing regimen was evaluated based on the pharmacodynamic target of AUC_{24h}: MIC ≥400 for the initial 48 h. AUC_{24h} on day 1 and day 2 was calculated using the linear-trapezoidal formula. PTA was calculated by summation of the number of patients achieving AUC_{24h}: MIC ≥400 and then dividing by the total number of patients (n = 5000). The reference organism for this in silico study was *S. aureus* with MIC of 1 mg/L.[27] This MIC was chosen because for infections with *S. aureus* species with a vancomycin MIC ≥2 mg/L, the required AUC_{24h} for efficacy (≥800 mg·h/L) exceeds the threshold concentrations linked with vancomycin toxicity (≥700 mg·h/L).[16] In these cases, it may not be advisable to use vancomycin.[14] A priori, dosing regimens were considered "therapeutic" if PTA was achieved in ≥90% of virtual patients both on day 1 and day 2 regardless of when PIRRT occurred in relation to the first vancomycin

Table 2. Influence of 8-h Dialysis-based PIRRT Timing on PTA and AUC_{24h} on First and Second Days of Therapy in Virtual Patients with the Tested Vancomycin Regimens.

Vancomycin dosing regimens	Early PIRRT				Late PIRRT			
	Day 1		Day 2		Day 1		Day 2	
	PTA (%) (AUC_{24h}: MIC <400/400–700/>700) (%)	AUC_{0-24h} (mg·h/L) mean ± SD	PTA (%) (AUC_{24h}: MIC <400/400–700/>700) (%)	AUC_{0-24h} (mg·h/L) mean ± SD	PTA (%) (AUC_{24h}: MIC <400/400–700/>700) (%)	AUC_{0-24h} (mg·h/L) mean ± SD	PTA (%) (AUC_{24h}: MIC <400/400–700/>700) (%)	AUC_{0-24h} (mg·h/L) mean ± SD
1 g q24h	2 (98/2/0)	248 ± 64	19 (81/19/0)	331 ± 81	43 (57/37/6)	401 ± 172	71 (29/56/15)	519 ± 184
15 mg/kg q24h	11 (89/11/0)	305 ± 76	52 (48/50/2)	417 ± 121	63 (37/58/5)	461 ± 136	93 (7/65/28)	614 ± 163
20 mg/kg q24h	48 (52/47/1)	407 ± 102	83 (17/65/18)	559 ± 163	90 (10/60/30)	614 ± 181	99 (1/31/68)	820 ± 219
25 mg/kg q24h	81 (18/73/8)	514 ± 127	95 (5/47/48)	709 ± 203	97 (3/43/54)	753 ± 223	100 (0/11/89)	1010 ± 270
1 g q12h	65 (35/54/11)	488 ± 172	98 (2/40/58)	762 ± 220	76 (24/47/29)	591 ± 246	98 (2/30/68)	859 ± 246
10 mg/kg q12h	42 (58/42/0)	391 ± 99	94 (6/66/28)	622 ± 159	65 (35/60/5)	465 ± 131	98 (2/55/43)	689 ± 173
15 mg/kg q12h	90 (10/70/20)	577 ± 148	100 (0/16/84)	929 ± 239	94 (6/51/43)	682 ± 199	100 (0/10/90)	1024 ± 265
15 mg/kg initially, then 15 mg/kg post-PIRRT	**94** (6/56/38)	**661 ± 193**	**93** (7/49/44)	**694 ± 227**	63 (37/55/8)	472 ± 152	92 (8/51/41)	681 ± 224
20 mg/kg initially, then 15 mg/kg post-PIRRT	100 (0/34/66)	818 ± 222	94 (6/43/51)	734 ± 222	**89** (11/59/30)	**616 ± 183**	**96** (4/58/38)	**665 ± 179**

PIRRT: prolonged intermittent renal replacement therapy; PTA (%) indicates the proportion of virtual patients attaining AUC_{24h}: MIC ≥ 400; AUC_{24h}: MIC <400/400–700/>700 (%) indicates the proportion of virtual patients attaining AUC_{24h}: MIC of <400, 400–700, and >700, respectively; AUC_{24h}: 24-h area under the curve; MIC: minimum inhibitory concentration.
Data illustrate 8-h HD in early and late PIRRT, but are illustrative of all modeled PIRRT settings. Because PIRRT could happen "early" or "late" with respect to the vancomycin dose, large differences can be observed in the proportion of virtual patients below/meeting/above the set pharmacodynamic targets on the first 2 days of vancomycin therapy. **Bolded dosing regimens** are the ones that attained ≥90% of PTA in both day 1 and day 2, with mean AUC_{24h} of <700 mg·h/L.

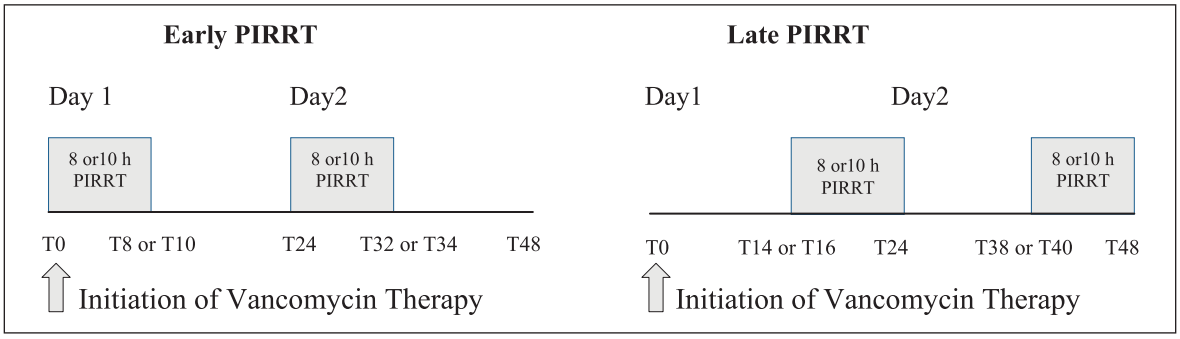


Figure 1. PIRRT schedule in relation to the initiation of vancomycin therapy.
T refers to time (hours) of the simulated 48 h of vancomycin therapy with daily PIRRT institution. Early PIRRT refers to when vancomycin is initiated at the beginning of 8- or 10-h PIRRT session while late PIRRT refers to when a PIRRT session occurs 14 or 16 h after vancomycin initiation.

administration. In addition, in order to balance the benefits of attaining the efficacy target, the safety profile, we chose the "optimal" dosing regimen as the one that achieves AUC_{24h}: MIC ≥400 in ≥90% of virtual study patients with the mean AUC_{24h} of less than 700 mg·h/L to minimize the risk of drug toxicity.

Statistical analysis. Once the optimal regimen was identified for each PIRRT schedule, an analysis to determine what factors predicted pharmacodynamic target attainment was conducted. Pharmacokinetic and demographic factors between virtual patients who did not attain pharmacodynamics target of AUC_{24h} < 400 mg·h/L were compared to those who attained the target using a two-tailed, unpaired sample Student's *t* test in Excel. A value of $p < 0.05$ was considered statistically significant.

Part 2

Development of serum concentration-guided dosing algorithm and nomogram. TDM can help individualize subsequent vancomycin dosing after the initial 48 h of dosing to optimize drug exposure in the clinical setting and we sought to determine whether TDM could inform dosing in this in silico trial. Thus, we modeled how TDM should be utilized to ensure the attainment of the pharmacodynamic target in patients receiving daily PIRRT. Current guidelines suggest that targeting vancomycin trough concentrations of 15–20 mg/mL would attain AUC_{24h}: MIC ≥400 for MRSA infection in patients with normal renal function.[14] To address the intermittent daily vancomycin clearance by PIRRT, we developed a TDM-based dosing algorithm to calculate AUC_{24h} to determine the optimal subsequent dosing targeting AUC_{24h} of 400–700 mg·h/L after the initial 48 h of therapy.

The algorithm assumed that the initial vancomycin dosing was based on the optimal initial 48-h dosing derived from the initial MCS modeling. AUC-based, TDM-guided dosing was calculated from two serum concentrations obtained after the third dose: (1) 2-h post vancomycin infusion and (2) immediately prior to PIRRT initiation. The assumption was that the "virtual assay" was accurate and that it reflected the model-derived concentration at that time point. Derivation of the TDM-based equations to compute AUC_{24h} using two concentration measurement is elucidated in the supplementary material. AUCs were modeled using the linear-trapezoidal formula to calculate each Part 1 virtual patient's AUC_{24h} beyond the initial 48 h. Using the calculated AUC_{24h} and virtual patients' pharmacokinetic profiles constructed in Part 1, a nomogram was developed to guide the subsequent vancomycin dosing. This nomogram was designed to determine the new dose that attains or maintains targeted drug exposure (AUC_{24h} of 400–700 mg·h/L) for each individual virtual patient. The relationship between the new dose and calculated AUC_{24h} was drawn based on proportional adjustment of current dose to attain AUC_{24h} of 500 mg·h/L as shown in the following equation:

$$\text{New vancomycin dose} = \frac{500\,\text{mg}\cdot\text{h/L} \bullet \text{current dose}}{\text{calculated } AUC_{24h}}$$

The target of AUC_{24h} of 500 mg·h/L was chosen because it yielded highest proportion of the virtual patients who attained the adequate drug exposure in the models.

Results

Part 1. Initial vancomycin dosing recommendations in PIRRT

Table 2 depicts the simulation results of PTA and mean AUC_{24h} for nine vancomycin regimens during the initial 48 h of therapy from the 8-h hemodialysis in silico trials as a representative example. Simulation results indicate that PIRRT will remove a significant fraction of vancomycin, lowering the vancomycin concentration by an average of 50% from the beginning of a PIRRT session to the end of the session.

The initial dose differed depending on when vancomycin therapy was initiated in relation to PIRRT schedule (i.e. early

Table 3. Vancomycin Clearance and Half-lives in PIRRT.

PIRRT setting	8-h HF	10-h HF	8-h HD	10-h HD
CL_{PIRRT}	43.3 ± 6.6 mL/min	36.7 ± 6.6 mL/min	60 ± 10 mL/min	48.3 ± 8.3 mL/min
$CL_{Total\ on\text{-}PIRRT}$	61.7 ± 13.3 mL/min	53.3 ± 11.7 mL/min	78.3 ± 15 mL/min	65 ± 13.3 mL/min
$t_{½\ on\text{-}PIRRT}$	10.3 ± 5.6 h	11.5 ± 6.2 h	8.1 ± 4.5 h	9.5 ± 5.1 h
$t_{½\ off\text{-}PIRRT}$	51 ± 48 h	48 ± 38 h	53 ± 52 h	48 ± 37 h

HF: hemofiltration; HD: hemodialysis; CL: clearance by PIRRT (either by hemofiltration or hemodialysis); $CL_{Total\ on\text{-}PIRRT}$: total clearance during PIRRT; $t_{½\ on\text{-}PIRRT}$: half-life on-PIRRT; $t_{½\ off\text{-}PIRRT}$: half-life off PIRRT; PIRRT: prolonged intermittent renal replacement therapy.

PIRRT vs late PIRRT). For example, if PIRRT was started soon after the vancomycin dose (early PIRRT), then a higher vancomycin dose was needed to account for PIRRT drug removal and ensure sufficient vancomycin exposure. Meanwhile, PIRRT modalities (hemofiltration vs hemodialysis) and PIRRT effluent rates and duration (an effluent rate of 88.3 mL/min for 8 h or 66.7 mL/min for 10 h) used in this study yielded insignificant differences in PTA of each vancomycin dosing regimen. Vancomycin clearance by 8-h PIRRT (either HF or HD) was higher than that by 10-h PIRRT due to a higher effluent rate (88.3 mL/min vs 66.7 mL/min) as depicted in Table 3. The 10-hr PIRRT had slower clearance per hour but the longer treatment compensated for this lower vancomycin clearance, resulting in similar PTA. Vancomycin half-life off PIRRT was 48–53 h but during the 8- or 10-h PIRRT, ranged from 8–12 h.

The regimen of 15 mg/kg initially, followed by 15 mg/kg post-PIRRT in early PIRRT and that of 20 mg/kg initially, followed by 15 mg/kg post-PIRRT in late PIRRT attained ≥90% of PTA with mean AUC_{24h} of <700 mg·h/L on both day 1 and day 2. The regimen of 15 mg/kg q12h also attained ≥90% of PTA in virtual subjects in all modeled scenarios. However, this regimen utilizing higher dose per day consequently yielded higher means of AUC_{24h} (≥700 mg·h/L) and was not considered an "optimal" regimen.

Part 2. Dosing algorithm and nomogram development

Figure 2 illustrates equations and the process required to calculate AUC_{24h} after the third dose using the two serum concentrations, and the derived vancomycin dosing nomogram to determine subsequent individualized dosing, based on the calculated AUC_{24h}. Vancomycin pharmacokinetics displayed considerable variability in these virtual patients receiving PIRRT. The initial recommended "optimal" dosing that achieved PTA for ≥90% of virtual patients but yielded a wide range in AUC_{24h} as displayed in Figure 3 (top). To ensure that 90% of patients attained minimally acceptable vancomycin exposure (AUC_{24h} ≥ 400 mg·h/L), many subjects received dosing regimens producing AUC_{24h} ≥700 mg·h/L. Indeed, the mean AUC_{24h} with the initial regimens ranged from 616–694 mg·h/L depending if PIRRT were early or late (Table 2). Even with these high mean AUC_{24h} values for this initial dosing, ~7% of virtual patients did not achieve the minimum AUC_{24h} target of 400 mg·h/L. Compared to those who attained AUC_{24h} ≥400 mg·h/L, these ~7% of underdosed virtual patients were characterized to have significantly smaller body weights, higher non-renal clearance, and larger volume of distribution. Differences of these pharmacokinetic parameters between two groups were all statistically significant. ($p < 0.05$) Consequently, vancomycin mean half-lives in these patients who did not attain AUC_{24h} ≥400 mg·h/L were found to be significantly faster than those of who attained (21.8 vs 52.4 h off PIRRT, and 6.3 vs 8.0 h during PIRRT).

Figure 3 (bottom) illustrates the application of the dosing nomogram. Nomogram use yielded far better AUC_{24h} values as soon as the first individualized dose was used. After receiving the adjusted dose determined from the nomogram, almost 100% of virtual patients attained AUC_{24h} ≥ 400 mg·h/L with the majority (67%–88%) of those patients attaining AUC_{24h} of 400–700 mg·h/L.

Discussion

To our knowledge, this is the first in silico pharmacokinetic trial using MCS to determine optimal initial vancomycin dosing recommendation in critically ill patients receiving PIRRT. By using the MCS technique, we successfully conducted in silico trials in tens of thousands of virtual patients who had realistic demographic and pharmacokinetic characteristics receiving each of four different PIRRT settings. This novel approach permitted us to predict the PTA of a wide variety of vancomycin regimens that are frequently prescribed in clinical practice. This is also the first simulation analyses to allow therapeutic dosing after the initial 48 h of therapy guided by the use of virtual TDM.

As indicated in Table 2, patients receiving early PIRRT required at least 30 mg/kg on the first day in order to attain ≥90% PTA. The regimens of ≥ 15 mg/kg initially, followed by a 15 mg/kg dose post PIRRT, and 15 mg/kg q12h provide at least 30 mg/kg on the first day and thus attained ≥90% PTA on day 1 and day 2. However, greater than 15 mg/kg on the following day yielded a higher mean AUC_{24h} (≥700 mg·h/L). For example, 15 mg/kg q12h resulted in mean AUC_{24h} of 682 mg·h/L on day 1, but 1024 mg·h/L by day 2. Thus, patients

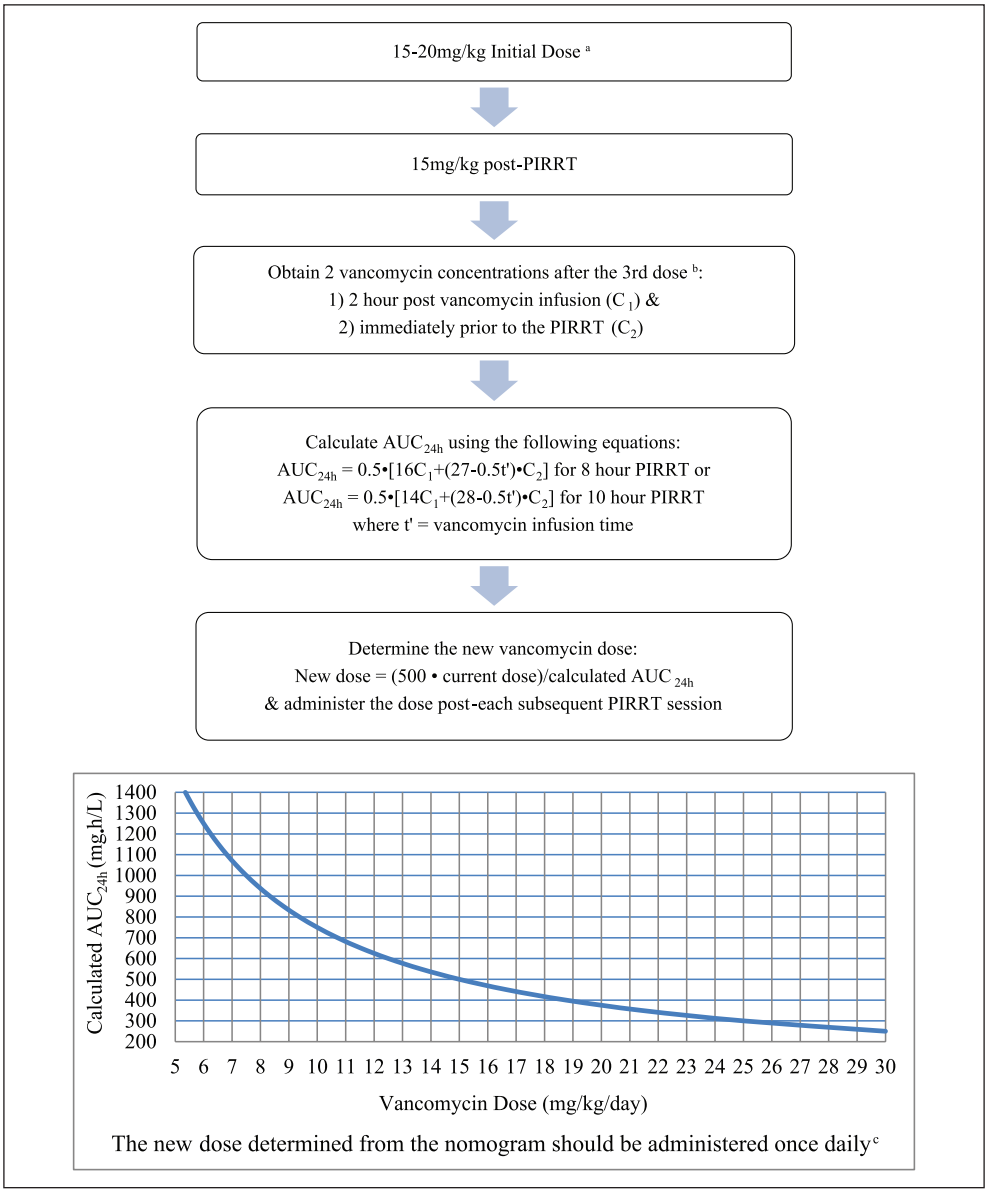


Figure 2. Serum concentration-guided vancomycin dosing algorithm and nomogram to individualize optimal dosing in patients receiving daily PIRRT.

[a]Initial dose of 15 or 20 mg/kg should be used if vancomycin therapy starts during or off PIRRT, respectively.

[b]We recommend repeating the measurement of two serum concentrations to calculate AUC_{24h} and the dose determination from the nomogram every 3–4 days to account for any significant changes in patients' status.

[c]The dosing nomogram in the box above should be used for subsequent post-PIRRT doses, based on the calculated AUC from the two vancomycin serum concentrations obtained after the third vancomycin dose. The nomogram above is based on the calculations described in Figure 2.

who receive vancomycin during a PIRRT session should receive a 15 mg/kg initial dose followed by a 15 mg/kg dose when PIRRT ends. Patients who are not scheduled to receive PIRRT for many (12+) hours after the vancomycin dose required an initial dose of 20 mg/kg to attain ≥90% PTA on day 1 and 15 mg/kg on day 2 while maintaining mean AUC_{24h} < 700 mg·h/L. More aggressive doses such as ≥20 mg/kg q24h and 15 mg/kg q12h in late PIRRT setting can ensure that ≥90% of patients achieve PTA goals, but these regimens yielded mean AUC_{24h} above the reported toxicity of ≥700 mg·h/L threshold, limiting their utility in these vulnerable patients that already may have experienced AKI. Patients receiving early PIRRT required a higher initial dose than those in late PIRRT setting because PIRRT removes a significant proportion of vancomycin during distribution stage, decreasing drug exposure. The recommended initial vancomycin 15 or 20 mg/kg dose, followed by 15 mg/kg post PIRRT were the lowest possible doses that could achieve the pharmacodynamic target of AUC_{24h}: MIC ≥ 400 while minimizing the number of patients achieving AUC_{24h} associated with toxicity.

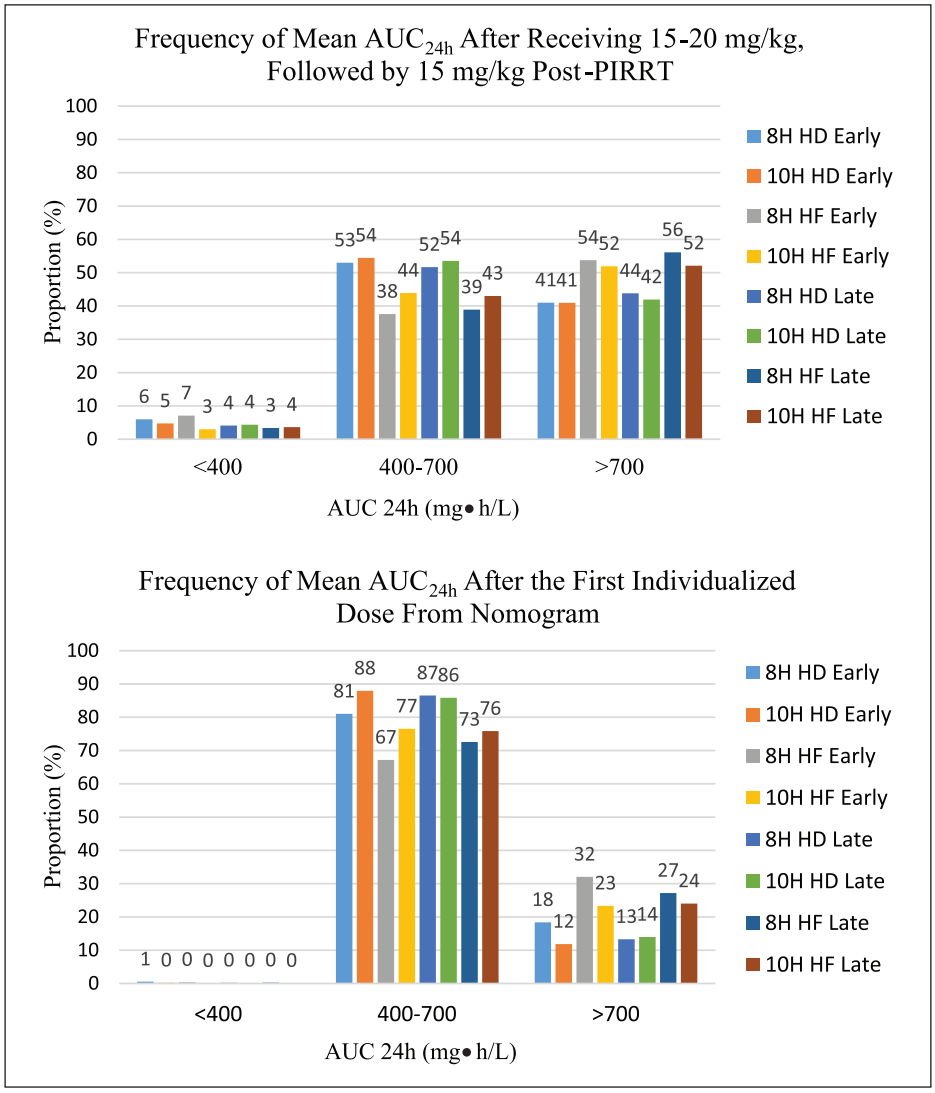


Figure 3. Frequency distribution of AUC_{24h} with the recommended initial dosing versus the subsequently individualized dosing.
The top figure illustrates the proportion of mean AUC_{24h} <400 mg·h/L, 400–700 mg·h/L, and >700 mg·h/L yielded by initial empiric recommended dosing in 5000 virtual patients. Virtual patients received 15 mg/kg of an initial dose in early PIRRT, and 20 mg/kg in late PIRRT. Recommended doses achieve AUC_{24h} above 400 mg·h/L in >90% of virtual patients, but many of them have AUC_{24h} above the 700 mg·h/L upper limit. However, use of the nomogram in any of the PIRRT settings results in many more subjects falling into the AUC_{24h} target of 400–700 mg·h/L by the first nomogram-derived dose.

The wide range of resultant AUC_{24h} from initial dosing seen in the present study is consistent with observations in clinical practice. Fortunately, the ability to perform vancomycin TDM allows for rapid dose individualization in the clinical setting. We took the practice of TDM into consideration to determine optimal individualized dosing in PIRRT. Because PIRRT can occur at different times in relation to the vancomycin doses, we anticipated that it would be difficult for clinicians to determine the appropriate time to measure serum concentration to monitor the therapy with the q24h or q12h regimens due to the robust influence of PIRRT on drug serum concentrations. In order to attain appropriate drug exposure and to monitor therapy with TDM in patients receiving 8 or 10 h daily PIRRT, the timing of vancomycin infusion relative to PIRRT is critical. Our models indicated that post-PIRRT vancomycin dosing would allow a better utilization of TDM while maximizing drug exposure in patients receiving PIRRT in all scenarios.

Although trough serum concentration measurement is the current standard method to monitor vancomycin therapy, it was not the best surrogate parameter to estimate drug exposure in patients receiving daily PIRRT. The present study indicates that the marked decline (on average 50%) of vancomycin serum concentrations during an 8- or 10-h PIRRT session diminishes the predictive value of a trough concentration. For example, the recommended vancomycin regimen of 15 or 20 mg/kg initial dose, followed by 15 mg/kg post-PIRRT dosing regimen resulted in ≥90% of AUC_{24h}: MIC ratio of ≥ 400 in 5000 virtual patients in all PIRRT settings, but only 30%–60% of those patients demonstrated the

trough concentrations prior to the third dose to be ≥15mg/L. If the vancomycin dose were adjusted based on one single trough concentration, many of these patients may be subject to receive unnecessarily high doses, increasing the risk of drug toxicity.

As an alternative, this present study utilized two vancomycin serum concentration measurements to optimize the subsequent dosing after the initial 48 h of therapy. This two serum concentration approach allows AUC_{24h} calculation for any individual patient receiving PIRRT and tailoring the dosing to attain the AUC_{24h} 400–700 mg·h/L target. Figure 3 illustrates that the recommended initial dose resulted in the wide range of mean AUC_{24h}, highlighting the wide variability in vancomycin pharmacokinetics (made even wider by addition of PIRRT). Even this "best-case" dosing scenario that had ≥90% of patients ≥400 mg·h/L resulted in only 38%–54% virtual patients who attained AUC_{24h} of 400–700 mg·h/L in the first 48 h. However, a much higher proportion (67%–88%) of the same virtual patients attained this target range with substantially reduced number of patients with AUC_{24h} ≥700 mg·h/L after receiving the first individualized nomogram-based dose based on calculated AUC_{24h}. The proportion of those who did not attain AUC_{24h} ≥400 mg·h/L decreased from ~7% to <1% after receiving the first nomogram-adjusted dose. Rarely, we found some calculated AUC_{24h} to be <250 mg·h/L. Using the nomogram, these virtual patients required more than the maximum recommended dose (30 mg/kg/day). Consequently, in this situation, we recommend dividing the maximum dose into two doses and administering them as q12h dosing to reduce the risk of infusion-related adverse effects. This scenario occurred in <0.2% of virtual patients.

This approach to vancomycin dosing in PIRRT reflects newer findings regarding vancomycin exposure targets and enables practitioners to confirm the target attainment of vancomycin therapy through the use of TDM. The vancomycin nomogram should be utilized every 3–4 days to ensure the therapeutic target attainment and to minimize vancomycin toxicity throughout the entire vancomycin course of therapy. Critically ill patients receiving RRT can experience dynamic changes in fluid status and vancomycin renal and non-renal clearance necessitating frequent TDM.

Our study has several limitations to consider. Pharmacokinetic modeling was performed under the assumption that these patients receiving PIRRT were adult-sized and had negligible renal drug clearance. The constructed virtual adult patients had demographic and pharmacokinetic parameters with variances based on literature values taken from critically ill patients with AKI. The assumption was that these parameters do not change over the course of modeling, but actual critically ill patients are dynamic. These dosing recommendations should be applied only to patients from this demographic who receive daily PIRRT using the blood and dialysate flows and treatment durations used in these models. In scenarios where PIRRT is not administered daily, dosing alterations would be necessary. The post hoc analysis of the optimal initial vancomycin dose achieving ≥90% PTA still meant that up to 10% of patients may not achieve the desired pharmacodynamic target with the recommended initial dose. The analysis suggests that smaller patients may have a higher risk of failure to attain the pharmacodynamic target. Finally, our recommended initial dose yielded ≥90% PTA, but apparently many patients had AUC_{24h} ≥700 mg·h/L, the known toxicity threshold. We weighed the risk of antibiotic underdosing more heavily than the risk of toxicity in critically ill patients with serious infections. Attainment of the efficacy target (AUC_{24h} ≥400 mg·h/L) was regarded as the most important goal to determine the optimal dose during the initial 48 h of vancomycin therapy. Clinicians should be aware that our recommended initial dose may yield a higher drug exposure in some patients and must perform TDM to individualize the subsequent doses to optimize drug exposure and to minimize the risk of toxicity.

In conclusion, MCS can be used to generate dosing estimates in patients receiving a variety of RRT, including PIRRT. Our MCS models indicate that an initial vancomycin 15–20 mg/kg, followed by 15 mg/kg post PIRRT would be effective to achieve the pharmacodynamic target in patients with *S. aureus* infections with the vancomycin MIC of ≤1 mg/L for the first 48 h of therapy. Following this recommended regimen, the vancomycin dose can be individualized to achieve the pharmacodynamic target by using TDM and the developed dosing nomogram. A clinical validation study of our finding is warranted to confirm the recommended vancomycin dosing and the nomogram.

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Ethical approval

Not applicable because this is an in silico study.

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