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Evaluation and Development of Vancomycin Dosing Schemes to Meet New AUC/MIC Targets in Intermittent Hemodialysis Using Monte Carlo Simulation Techniques

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Abstract

Published vancomycin dosing recommendations for patients receiving maintenance hemodialysis were not designed to meet newly recommended 24-hour area under the curve/minimum inhibitory concentration (AUC_{24h}/MIC) pharmacokinetic/pharmacodynamic targets. The aims of this study were to predict pharmacokinetic/pharmacodynamic target attainment rates with a commonly used vancomycin regimen and to design a new dosing scheme incorporating therapeutic drug monitoring (TDM) to maximize target attainment in patients receiving vancomycin and hemodialysis with high- or low-flux hemodialyzers. Vancomycin pharmacokinetic- and dialysis-specific parameters were incorporated into Monte Carlo simulations (MCS). A commonly used vancomycin regimen was modeled to determine its likelihood of attaining AUC_{24h}/MIC targets for 1 week of thrice-weekly hemodialysis treatments. MCS was then used to develop optimal initial vancomycin dosing for patients receiving intradialytic or postdialytic vancomycin administration with either high- or low-flux hemodialyzers. Finally, a new MCS model incorporating TDM was built to further optimize the probability of pharmacokinetic/pharmacodynamic target attainment. Traditional vancomycin dosing methods are unlikely to meet AUC_{24h}/MIC targets. Vancomycin doses necessary to attain AUC_{24h}/MIC targets are significantly influenced by hemodialyzer permeability and whether vancomycin is administered intradialytically or after hemodialysis. Depending on dialyzer type and whether vancomycin is administered during or after hemodialysis, loading doses of 25 to 35 mg/kg followed by maintenance doses of 7.5 to 15 mg/kg are necessary to reach minimum AUC_{24h}/MIC targets in 90% of virtual patients. For a 3-day interdialytic period, a 30% higher maintenance dose is required to maintain target attainment. Dosing based on a single vancomycin serum concentration obtained prior to the second dialysis session greatly enhances the probability of target attainment.

Keywords

Monte Carlo simulation, pharmacodynamics, pharmacokinetics, renal dialysis, vancomycin

Clinical success of vancomycin therapy in nondialysis patients is associated with the attainment of the 24-hour area under the curve/minimum inhibitory concentration (AUC_{24h}/MIC) ratio of $\geq$400.[1] A low initial steady-state AUC_{24h}/MIC (<430 by E-test; <398.5 by broth microdilution) is a significant risk factor for treatment failure and increases the risk of treatment failure by 2-fold.[2] A recent study in nondialysis patients suggests that improved patient outcomes are associated with attainment of an AUC_{24h}/MIC of at least 550 and 650 on the first and second days, respectively, of vancomycin therapy.[3] Conversely, an AUC_{24h} >700 mg·h/L has been reported as the nephrotoxicity threshold in nondialysis patients.[3–7] Previous vancomycin guidelines recommended targeting trough concentrations of 10 to 20 mg/L as a surrogate to attain the optimal pharmacokinetic/pharmacodynamic efficacy index of AUC_{24h}/MIC $\geq$400.[8] However, recent evidence has demonstrated that trough concentration is a poor predictor of true AUC_{24h} and that targeting high troughs significantly increases the risk of nephrotoxicity in nondialysis patients.[6,9–14] Consequently, the new guidelines recommend AUC-guided vancomycin dosing to target AUC_{24h}/MIC of 400 to 600 for maximal efficacy and minimal nephrotoxicity.[1] In dialysis patients, no prospective studies have been conducted to evaluate patient outcomes associated with an AUC-based vancomycin dosing strategy.

Vancomycin is the most commonly prescribed antibiotic among end-stage kidney disease (ESKD) patients receiving intermittent hemodialysis (IHD)[15,16] because of the high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Nonetheless, the optimal vancomycin dosing strategy in IHD

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Table 1. Pharmacokinetic Model Input Parameters[20,25,26,30,31]

Pharmacokinetic Parameter	High-Flux Dialyzer	Low-Flux Dialyzer
Weight, kg	75 ± 23 (40-150)	
Volume of distribution, L/kg	0.9 ± 0.27 (0.38-1.55)	
k_{el_off}, 1/h	0.0035 ± 0.001 (0.0010-0.0061)	
$t_{1/2\_off}$, h	198.0 (113.6-693.0)	
k_{el_on}, 1/h	0.110 ± 0.02 (0.066-0.154)	0.055 ± 0.011 (0.033-0.077)
$t_{1/2\_on}$, h	6.3 (4.5-10.5)	12.6 (9.0-21.0)
Vancomycin bioavailability (F)	0.74 ± 0.15 (0.56-0.84)	0.84 ± 0.17 (0.75-1)

k_{el_off}, the elimination rate constant off hemodialysis; k_{el_on}, the elimination rate constant during hemodialysis; $t_{1/2\_off}$, half-life off hemodialysis; $t_{1/2\_on}$, half-life during dialysis; vancomycin bioavailability (F), the proportion of vancomycin that is not removed by hemodialysis during intradialytic vancomycin infusion. Values are expressed as mean ± SD (range).

patients is unclear because of widely varied pharmacokinetic alterations from ESKD and the influence of dialysis itself. Vancomycin is removed substantially by high-flux hemodialyzers.[17–19] In addition, vancomycin frequently is administered during the dialysis procedure itself, resulting in immediate removal of a fraction of the vancomycin infusion before it can distribute to the tissues.[20] Many studies have generated a wide range of vancomycin dosing recommendations and nomograms for IHD patients based on selected pre- or postdialysis concentration targets but not AUC_{24h}/MIC targets.[20-33] Of note, a single study found that predialysis concentrations of ≥18.6 mg/L was associated with improved patient outcomes in IHD patients with MRSA bacteremia.[34] Suboptimal vancomycin treatment likely has contributed to IHD patients being the source of development of vancomycin-intermediate *S. aureus* or vancomycin-resistant *S. aureus.*[35,36] Infection remains as the second-leading cause of mortality in these patients,[37] suggesting that a better vancomycin dosing approach is needed.

To date, scant data exist to provide an AUC-based dosing approach in patients receiving IHD, and previously published IHD vancomycin dosing recommendations have not been assessed about whether they would attain appropriate AUC_{24h}/MIC targets. The objective of the present study was (1) to evaluate the drug exposure (AUC) achieved with a commonly used contemporary IHD vancomycin dosing protocol proposed by Zelenitsky et al,[30,38] (2) to determine an initial vancomycin dosing scheme to attain an AUC_{24h}/MIC target of ≥400, and (3) to devise a dosing nomogram to individualize the subsequent dosing to attain an AUC_{24h}/MIC ≥400 in virtual IHD patients, using Monte Carlo simulation (MCS).

Methods

Part I. Evaluation of Contemporary Dosing Protocol and Determination of Optimal Initial Vancomycin Dosing

Pharmacokinetic Model Development. A 1-compartment pharmacokinetic model[26,39] with zero-order input and first-order elimination was developed to predict vancomycin disposition in adult patients receiving IHD. A literature search obtained relevant vancomycin pharmacokinetic data. Studies published prior to 1997 were excluded for review because they were likely to employ old vancomycin bioanalysis known to be inaccurate in patients with renal insufficiency[40-42] and/or utilized hemodialyzers with poor vancomycin permeability unlike contemporary hemodialyzers.[21,22,24,43] Pharmacokinetic input data used in this in silico study were derived from studies conducted in contemporary hemodialysis settings[20,25,26,30,31] as outlined in Table 1. The blood and dialysate flow rates employed in these studies approximately ranged from 350 to 450 and from 500 to 800 mL/min, respectively.[20,25,26,30,31] The pharmacokinetic input parameters were assumed to have log-Gaussian distribution. Body weights <40 or >150 kg were truncated based on the obtained data from those relevant pharmacokinetic studies.[20,25,26,30,31] Ranges of pharmacokinetic parameters were obtained from these studies and used as limits for all input variables to avoid spurious simulations. Residual renal function of patients in these studies was minimal.[20,25,26,30,31] The elimination rate constant (k_{el}) during hemodialysis was separately determined for IHD with high-flux and low-flux hemodialyzers. Vancomycin bioavailability (F), the proportion of vancomycin that is not immediately removed by hemodialysis during intradialytic drug infusion, was calculated using the reported vancomycin removal rate (%) during intradialytic infusion[20] and was separately estimated for IHD with high-flux and low-flux hemodialyzers. The equations used in the model are provided in the supplementary material.

Zelenitsky's vancomycin dosing protocol was evaluated in a scenario using intradialytic drug administration and high-flux IHD in concordance with their recommendations.[30] A 4-hour high-flux IHD was modeled to occur 3 times a week (Monday, Wednesday, and Friday), and vancomycin therapy was initiated on Monday. As recommended in the protocol, 3 intradialytic regimens were applied based on body weight—(1)

1000 mg loading dose (LD), followed by a 500 mg maintenance dose (MD) for patients <70 kg; (2) 1250 mg LD, followed by 750 mg MD for patients 70 to 100 kg; and (3) 1500 mg LD, then 1000 mg MD for patients >100 kg[30]—and were simulated for a full week (ie, Monday through Sunday). These recommended doses were infused during the last 30 minutes of an IHD session for a vancomycin dose of 500 mg, during the last 1 hour for vancomycin doses of 750 to 1000 mg, and during the last 1.5 hours for a vancomycin dose of 1500 mg, as described in the protocol.[30]

For the determination of the optimal initial vancomycin dosing attaining the AUC_{24h}/MIC target in IHD, other clinical practice scenarios were modeled in addition to that using Zelenitsky's dosing protocol. The different types of hemodialyzers and drug dose administration timings in relation to dialysis have been found to be the significant factors that influence pharmacokinetics during dialysis.[20,44] Hence, 4 different dialysis and vancomycin administration combination scenarios were schemed into the model. They were: (1) intradialytic vancomycin dosing (ie, infuse over the last 1 to 2 hours of dialysis) in high-flux IHD, (2) intradialytic vancomycin dosing in low-flux IHD, (3) postdialytic vancomycin dosing (ie, infuse immediately after dialysis over 1 to 2 hours) in high-flux IHD, and (4) postdialytic vancomycin dosing in low-flux IHD. A vancomycin regimen in each of the 4 scenarios was simulated to commence on either Monday, Wednesday, or Friday with a 2- to 3-day interdialytic period to construct a broad range of realistic clinical scenarios. A variety of weight-based vancomycin regimens were tested for 4 to 5 days depending on the initiating day of the vancomycin regimen. Each IHD was 4 hours long, and vancomycin infusion time was 1 hour if a vancomycin dose was ≤15 mg/kg and 2 hours if a vancomycin dose was >15 mg/kg. The maximum vancomycin dose was capped as 4 g per dose.[8,45]

MCS and Probability of Pharmacodynamic Target Attainment. The efficacy target was AUC_{24h} of ≥400 mg·h/L for each day of vancomycin therapy, assuming that the pathogens are MRSA species with a MIC of 1 mg/L.[1] MCS (Crystal Ball Classroom Edition, Oracle) was conducted to predict total serum vancomycin concentration-time profiles in a virtual cohort of 5000 for each tested vancomycin regimen. AUC_{24h} on each day of vancomycin therapy was computed with the linear trapezoidal rule. Probability of target attainment (%) was determined by summing up the number of virtual patients attaining AUC_{24h} of ≥400 mg·h/L and then dividing by the total number in the virtual cohort (n = 5000). Vancomycin-induced nephrotoxicity is of less concern for patients with ESKD requiring IHD. However, we took into consideration the accepted drug exposure threshold associated with vancomycin nephrotoxicity (AUC_{24h} ≥700 mg·h/L)[3-7] in determining the optimal dosing regimen. A dosing regimen was considered "optimal" if it attained a AUC_{24h} ≥400 mg·h/L in ≥90% of the virtual cohort with the mean AUC_{24h}/MIC of 400 to 700 mg·h/L. The new guidelines recommend narrower drug exposure targets of AUC_{24h}/MIC of 400 to 600 mg·h/L,[1] but considering the wider variability of vancomycin pharmacokinetic parameters and nephrotoxicity being less an issue in IHD patients, more lenient drug exposure targets (eg, mean AUC_{24h}/MIC of 400 to 700 mg·h/L) were used in this analysis.

Part II. Development of Therapeutic Drug Monitoring-Guided Dosing Algorithm

Vancomycin dosing is routinely adjusted based on therapeutic drug monitoring (TDM) results to ensure pharmacokinetic/pharmacodynamic target attainment. Thus, we incorporated TDM into our model to find out how TDM could be effectively utilized to ensure pharmacokinetic/pharmacodynamic target attainment in patients with IHD with only a single predialysis serum concentration. This TDM-guided dosing nomogram individualizes the optimal subsequent vancomycin dosing to attain and/or maintain AUC_{24h} of 400 to 700 mg·h/L.

The nomogram was developed based on the vancomycin concentrations predicted from the initial vancomycin dosing recommendations derived from Part I simulations. Two assumptions were made regarding the measurement of vancomycin concentrations; (1) the "virtual vancomycin assay" was accurate, and (2) it reflected the model-derived vancomycin concentrations at that point. A predialysis concentration immediately prior to the second IHD session was used as the basis for TDM-directed dosing adjustment. Utilizing the predialysis concentrations and the virtual patients' pharmacokinetic profiles used in the Part I simulation, vancomycin concentrations occurring after a TDM-based dosage adjustment were further constructed to calculate AUC_{24h} for a total of 14 days of vancomycin therapy, which is the minimum recommended duration to treat MRSA bacteremia[46] in each of the same virtual patients. The equation was developed to individualize each subsequent MD attaining an AUC_{24h} of 400 to 700 mg·h/L for most virtual patients.

Statistical analysis. After MCS was performed to determine the optimal initial vancomycin regimen in IHD, a post hoc analysis was conducted to examine the association between pharmacokinetic/pharmacodynamic target attainment and different input variables. Simulated pharmacokinetic and demographic variables in virtual patients with AUC_{24h} <400, 400-700, and

Table 2. PTA and AUC_{24h} Predicted From a Week of a Commonly Used Intradialytic Vancomycin Dosing Protocol[30] for Thrice-Weekly High-Flux IHD

		Probability of Target Attainment, % (Percent of Modeled Patients Attaining AUC_{24h} <400/400-700/>700 mg·h/L) AUC_{24h} (mg·h/L), mean ± SD						
Body Weight	Vancomycin Dosing[a]	Day 1 (Monday)	Day 2 (Tuesday)	Day 3 (Wednesday)	Day 4 (Thursday)	Day 5 (Friday)	Day 6 (Saturday)	Day 7 (Sunday)
45-70 kg	1000 mg LD, 500 mg MD	26 (74/25/1), 341 ± 111	18 (82/18/0), 313 ± 103	42 (58/39/3), 394 ± 140	23 (77/22/1), 332 ± 112	42 (58/39/3), 396 ± 133	33 (67/31/2), 365 ± 125	20 (80/19/1), 318 ± 111
70-100 kg	1250 mg LD, 750 mg MD	10 (89/10/1), 283 ± 91	8 (92/8/0), 265 ± 86	31 (69/30/1), 360 ± 117	16 (84/15/1), 305 ± 100	30 (70/29/1), 356 ± 117	22 (78/21/1), 331 ± 110	13 (87/12/1), 289 ± 99
100-150 kg	1500 mg LD, 1000 mg MD	3 (97/3/0), 231 ± 76	2 (98/2/0), 216 ± 71	17 (83/16/1), 310 ± 103	7 (93/7/00, 263 ± 88	19 (81/18/1), 315 ± 106	14 (86/13/1), 293 ± 100	7 (93/7/0), 256 ± 89

PTA, probability of target attainment; IHD, intermittent hemodialysis; LD, loading dose; MD, maintenance dose.

[a] Each dosing was modeled to be infused intradialytically during the last 0.5-1.5 hours of hemodialysis scheduled on Monday-Wednesday-Friday (shaded boxes) in 5000 virtual patients. First dose was given on Monday.

>700 mg·h/L were compared using analysis of variance. The proportions of patients attaining pharmacokinetic/pharmacodynamic target after the initial optimal doses and the TDM-adjusted doses were compared with a chi-square analysis. A $P < .05$ was considered statistically significant.

Results

Part I. Evaluation of Zelenitsky's Dosing Protocol and Determination of Optimal Initial Vancomycin Dosing

The simulated results of probability of target attainment (PTA) and mean AUC_{24h} for a week of Zelenitsky's intradialytic vancomycin dosing regimen are presented in Table 2. All vancomycin regimens, regardless of body weight stratification, yielded very low PTA (2% to 42%), and the mean AUC_{24h} was <400 mg·h/L on all days of the week. Particularly, the PTA on the first 2 days after the LD was lower than the rest of the days with only 18% to 26%, 8% to 10%, and 2% to 3% PTA in patients with 45 to 70, 70 to 100, and 100 to 150 kg, respectively. In addition, the dosing for patients weighing 100 to 150 kg resulted in the lowest PTA (<20%) and mean AUC_{24h} throughout the week among all patient size groups. However, up to 3% of the simulated patient cohort had AUC_{24h} of >700 mg·h/L with the Zelenitsky regimen.

Table 3 displays the simulation results of selected "intradialytic" vancomycin dosing regimens that are initiated on either Monday, Wednesday, or Friday, whereas Table 4 shows those for those receiving "postdialytic" vancomycin dosing regimens. In these 4 different dialyzer and vancomycin infusion combination scenarios, none of the simulated vancomycin dosing regimens consisting of an LD and an MD successfully attained the efficacy target of PTA ≥90% while meeting the safety goal of a mean AUC_{24h} <700 mg·h/L during the initial 4 to 5 days of vancomycin therapy (Tables 3 and 4). Our model predicts that an intradialytic regimen using an LD of 35 mg/kg and an MD of 15 mg/kg in high-flux IHD or an LD of 30 mg/kg and an MD of 7.5 mg/kg in low-flux IHD and a postdialytic regimen with an LD of 25 mg/kg and an MD 10 mg/kg in high-flux IHD or an LD of 25 mg/kg and an MD of 7.5 mg/kg in low-flux IHD would initially meet "best-possible" or "acceptable" PTA with a mean AUC_{24h} of closest to 400 to 700 mg·h/L (bolded in Tables 3 and 4) and thus are recommended as initial doses. Notably, these model-recommended LDs attained acceptable PTA over a 2- or 3-day interdialytic period, but the model-recommended MD yielded below-acceptable PTA by the time a 3-day intradialytic period occurred. Hence, anytime a MD is followed by a 3-day interdialytic period, a 30% higher dose is necessary to attain appropriate PTA on day 3. This is illustrated in Tables 3 and 4, where model-recommended (bolded) MDs given on Fridays are 30% higher. Subsequent MDs following the initial model-recommended regimens should be determined by TDM as reported in the Part II section below.

The type of hemodialyzer and vancomycin administration time in relation to IHD significantly altered PTA and mean AUC_{24h} for any single vancomycin dosing regimen. Intradialytic administration required 20% to 40% higher LD and up to 50% higher MD to attain PTA ≥90% during 2 or 3 days of an interdialytic period compared with postdialytic administration because of significant drug removal by hemodialysis during intradialytic drug infusion. Dialyzer type had a profound effect on intradialytic doses, with

Table 3. Intradialytic Vancomycin Dosing Regimens Simulated in a Thrice-Weekly (Monday-Wednesday-Friday) Intermittent Hemodialysis Schedule With Probability of Target Attainment and Mean AUC_{24h}

		Probability of Target Attainment, % (Percent of modeled patients attaining AUC_{24h} <400 / 400-700 / >700 mg·h/L) AUC_{24h} mg·h/L, Mean±SD													
		Vancomycin Initiated on Monday				Vancomycin Initiated on Wednesday					Vancomycin Initiated on Friday				
Hemodialyzer Type	Dosing	Day 1 (Monday)	Day 2 (Tuesday)	Day 3 (Wednesday)	Day 4 (Thursday)	Day 1 (Wednesday)	Day 2 (Thursday)	Day 3 (Friday) —30% Higher MD	Day 4 (Saturday)	Day 5 (Sunday)	Day 1 (Friday)	Day 2 (Saturday)	Day 3 (Sunday)	Day 4 (Monday)	Day 5 (Tuesday)
High flux	25 mg/kg LD, 15 mg/kg MD	65 (35/58/7), 473 ± 146	58 (42/52/6), 448 ± 139	84 (16/62/22), 575 ± 179	74 (26/61/13), 516 ± 163	65 (35/58/7), 473 ± 143	58 (42/53/5), 48 ± 131	85 (15/63/22), 575 ± 176	75 (25/62/13), 520 ± 161	64 (36/56/8), 472 ± 150	65 (35/57/8), 476 ± 148	60 (40/54/6), 455 ± 143	51 (49/47/4), 425 ± 136	77 (23/62/15), 532 ± 169	70 (30/58/12), 498 ± 161
	30 mg/kg LD, 7.5 mg/kg MD	84 (16/65/19), 566 ± 171	79 (21/64/15), 537 ± 163	68 (32/59/9), 486 ± 151	53 (47/48/5), 430 ± 136	84 (16/64/20), 570 ± 176	79 (21/63/16), 540 ± 168	68 (32/58/10), 489 ± 155	54 (46/49/5), 436 ± 140	42 (58/39/3), 395 ± 130	84 (16/65/19), 562 ± 170	79 (21/64/15), 537 ± 164	72 (28/62/10), 502 ± 156	54 (46/49/5), 436 ± 138	44 (56/41/3), 402 ± 130
	30 mg/kg LD, 10 mg/kg MD	84 (16/65/19), 564 ± 171	79 (21/64/15), 534 ± 163	78 (22/63/15), 532 ± 165	65 (35/57/8), 472 ± 149	84 (16/64/20), 567 ± 172	79 (21/63/16), 538 ± 164	78 (22/63/15), 536 ± 165	66 (34/57/9), 480 ± 150	54 (46/50/4), 436 ± 139	84 (16/65/19), 565 ± 168	79 (21/63/16), 539 ± 162	72 (28/61/11), 504 ± 154	67 (33/58/9), 484 ± 149	58 (42/53/5), 450 ± 141
	35 mg/kg LD, 10 mg/kg MD	94 (6/58/36), 657 ± 202	91 (9/62/29), 623 ± 193	86 (14/63/23), 590 ± 185	75 (25/61/14), 523 ± 167	94 (6/58/36), 659 ± 201	91 (9/61/30), 624 ± 191	87 (13/63/24), 590 ± 184	77 (23/62/15), 527 ± 167	66 (34/56/10), 478 ± 154	94 (6/60/34), 655 ± 202	91 (9/62/29), 625 ± 194	86 (14/62/23), 584 ± 184	78 (22/63/15), 531 ± 168	68 (32/58/10), 490 ± 158
	35 mg/kg LD, 15 mg/kg MD	**94 (6/57/37), 659 ± 201**	**91 (9/61/30), 624 ± 192**	**95 (5/54/41), 687 ± 213**	**89 (11/62/27), 613 ± 193**	**94 (6/59/35), 655 ± 199**	**91 (9/62/29), 621 ± 189**	95 (5/55/40), 684 ± 210	89 (11/62/27), 615 ± 191	82 (18/63/19), 558 ± 177	**94 (6/58/36), 657 ± 201**	**91 (9/60/31), 627 ± 193**	**86 (14/62/24), 586 ± 184**	**91 (9/60/31), 626 ± 196**	**84 (16/61/23), 582 ± 186**
	35 mg/kg LD, 20 mg/kg MD	94 (6/58/36), 659 ± 198	91 (9/61/30), 624 ± 189	99 (1/34/65), 825 ± 150	96 (4/52/44), 700 ± 216	94 (6/59/35), 657 ± 201	90 (10/61/29] (623 ± 192	**99 (1/35/64), 823 ± 254**	**96 (4/52/44), 704 ± 222**	**91 (9/59/32), 639 ± 206**	94 (6/59/35), 653 ± 195	91 (9/61/30), 624 ± 187	87 (13/63/24), 587 ± 179	98 (2/50/48), 722 ± 219	94 (6/56/38), 667 ± 206
Low flux	25 mg/kg LD, 15 mg/kg MD	87 (13/64/23), 585 ± 172	83 (17/65/18), 557 ± 164	99 (1/39/60), 794 ± 235	97 (3/51/46), 714 ± 215	88 (12/66/22), 583 ± 168	83 (17/65/18), 555 ± 161	99 (1/39/60), 791 ± 230	97 (3/50/47), 715 ± 212	93 (7/58/35), 651 ± 197	88 (12/66/22), 582 ± 170	84 (16/67/17), 556 ± 164	78 (22/65/13), 524 ± 157	98 (2/51/47), 723 ± 215	95 (5/56/39), 679 ± 206
	30 mg/kg LD, 7.5 mg/kg MD	**97 (3/55/42), 696 ± 204**	**95 (5/59/36), 662 ± 196**	**97 (3/54/43), 696 ± 208**	**91 (9/63/28), 618 ± 188**	**97 (3/53/44), 703 ± 206**	**95 (5/58/37), 669 ± 198**	97 (3/52/45), 704 ± 210	91 (9/61/30), 628 ± 192	84 (16/62/22), 572 ± 180	**97 (3/54/43), 699 ± 204**	**96 (5/59/37), 668 ± 196**	**92 (8/62/30), 630 ± 188**	**92 (9/61/31), 630 ± 189**	**86 (14/63/23), 583 ± 179**
	30 mg/kg LD, 10 mg/kg MD	97 (3/54/43), 700 ± 209	95 (5/57/38), 666 ± 200	99 (1/45/54), 760 ± 230	95 (5/56/39), 677 ± 208	97 (3/54/43), 698 ± 204	95 (5/59/36), 664 ± 195	**99 (1/45/54), 757 ± 224**	**96 (4/57/39), 678 ± 204**	**90 (10/62/28), 618 ± 190**	97 (3/52/45), 703 ± 205	95 (5/56/39), 671 ± 197	92 (8/60/32), 633 ± 190	96 (4/53/43), 690 ± 207	92 (8/58/34), 642 ± 197
	35 mg/kg LD, 10 mg/kg MD	99 (1/37/62), 804 ± 234	99 (1/43/56), 764 ± 225	99 (1/33/66), 834 ± 247	98 (2/46/52), 742 ± 224	99 (1/35/64), 814 ± 241	99 (1/41/58), 774 ± 230	99 (2/31/68), 844 ± 251	98 (2/44/54), 753 ± 257	95 (5/54/41), 686 ± 212	99 (1/36/63), 815 ± 243	99 (1/42/57), 779 ± 234	98 (2/48/49), 734 ± 225	99 (1/45/54), 763 ± 234	97 (3/52/45), 708 ± 221
	35 mg/kg LD, 15 mg/kg MD	99 (1/35/64), 814 ± 243	99 (1/42/57), 774 ± 232	99 (1/19/81), 964 ± 290	99 (1/30/69), 863 ± 264	99 (1/36/63), 812 ± 238	99 (1/42/57), 772 ± 229	100 (0/18/82), 961 ± 286	99 (1/29/70), 863 ± 262	99 (1/40/59), 786 ± 244	99 (1/36/63), 816 ± 245	99 (1/42/57), 780 ± 236	98 (2/48/49), 735 ± 227	99 (1/28/71), 880 ± 270	99 (1/36/63), 821 ± 257
	35 mg/kg LD, 20 mg/kg MD	99 (1/36/63), 814 ± 246	99 (1/42/57), 774 ± 236	100 (0/9/91), 1,094 ± 334	99 (1/17/82), 975 ± 302	99 (1/36/63), 812 ± 240	99 (1/41/58), 772 ± 231	100 (0/9/91), 1,091 ± 326	100 (1/17/83), 975 ± 296	99 (1/15/84), 889 ± 277	99 (1/35/64), 815 ± 238	99 (1/41/58), 778 ± 230	98 (2/47/51), 739 ± 223	100 (0/15/85), 1003 ± 299	99 (1/21/78), 931 ± 284

Data illustrate "intradialytic" vancomycin therapy initiated on either Monday, Wednesday, or Friday in end-stage kidney disease patients receiving thrice-weekly intermittent hemodialysis scheduled on Monday-Wednesday-Friday.

Shaded boxes indicate the days of a 4-hour hemodialysis session and intradialytic vancomycin infusion.

Bold dosing regimens are those attaining ≥90% of probability of target attainment (PTA) while a mean AUC_{24h} closest to <700 mg·h/L over a 2- or 3-day interdialytic period.

Note that when a maintenance dose is given when there will be a 3-day interdialytic period afterward (eg, Friday), a 30% higher dose is used in the model. The 30% higher dose is necessary to attain PTA ≥90% on the third day of a 3-day interdialytic period.

Table 4. Postdialytic Vancomycin Dosing Regimens Simulated in a Thrice-Weekly (Monday-Wednesday-Friday) Intermittent Hemodialysis Schedule With Probability of Target Attainment and Mean AUC_{24h}

		PTA, % (Percent of Modeled Patients Attaining AUC_{24h} <400/400-700/>700 mg·h/L) AUC_{24h} (mg·h/L), Mean ± SD													
		Vancomycin Initiated on Monday				Vancomycin Initiated on Wednesday					Vancomycin Initiated on Friday				
Type of Hemodialyzer	Dosing	Day 1 (Monday)	Day 2 (Tuesday)	Day 3 (Wednesday)	Day 4 (Thursday)	Day 1 (Wednesday)	Day 2 (Thursday)	Day 3 (Friday) —30% Higher MD	Day 4 (Saturday)	Day 5 (Sunday)	Day 1 (Friday)	Day 2 (Saturday)	Day 3 (Sunday)	Day 4 (Monday)	Day 5 (Tuesday)
High flux	20 mg/kg LD, 10 mg/kg MD	81 (19/67/14), 536 ± 152	72 (28/63/9), 497 ± 142	93 (7/62/31), 631 ± 181	77 (23/64/13), 521 ± 153	81 (19/66/15), 538 ± 152	72 (28/62/10), 499 ± 143	94 (6/62/32), 634 ± 182	80 (20/64/16), 540 ± 158	67 (33/59/8), 480 ± 144	81 (19/67/14), 538 ± 152	76 (24/65/11), 513 ± 146	72 (28/64/8), 495 ± 142	84 (16/67/17), 557 ± 161	72 (28/63/9), 499 ± 148
	25 mg/kg LD, 7.5 mg/kg MD	97 (3/59/38), 669 ± 190	93 (7/64/29), 620 ± 177	94 (6/61/32), 641 ± 186	78 (22/64/14), 528 ± 157	97 (3/58/39), 680 ± 191	94 (6/64/30), 630 ± 179	95 (5/62/33), 651 ± 186	83 (17/66/17), 552 ± 162	70 (30/61/9), 491 ± 148	97 (3/58/39), 676 ± 190	95 (5/61/34), 646 ± 183	92 (8/63/29), 620 ± 177	85 (15/66/19), 562 ± 163	73 (27/63/10), 503 ± 149
	25 mg/kg LD, 10 mg/kg MD	**96 (4/59/37), 668 ± 189**	**93 (7/65/28), 619 ± 177**	**99 (1/53/46), 714 ± 205**	**88 (12/65/23), 588 ± 174**	**96 (4/58/38), 670 ± 189**	**93 (7/65/28), 621 ± 177**	99 (1/51/47), 715 ± 204	91 (9/65/26), 607 ± 177	80 (20/65/15), 539 ± 162	**96 (4/59/37), 671 ± 190**	**94 (6/62/32), 641 ± 184**	**89 (11/66/23), 590 ± 172**	**93 (7/63/30), 627 ± 183**	**84 (16/65/19), 563 ± 168**
	25 mg/kg LD, 13 mg/kg MD	97 (3/59/38), 669 ± 187	93 (7/65/28), 620 ± 175	99 (1/43/56), 769 ± 220	95 (5/59/36), 663 ± 193	97 (3/58/39), 673 ± 188	93 (7/64/29), 625 ± 176	**99 (1/36/63), 809 ± 229**	**97 (3/56/41), 688 ± 199**	**90 (10/62/28), 611 ± 182**	97 (3/59/38), 674 ± 188	95 (5/62/33), 644 ± 181	93 (7/64/29), 621 ± 177	98 (2/52/46), 712 ± 203	93 (7/61/32), 639 ± 187
	25 mg/kg LD, 15 mg/kg MD	96 (4/58/38), 669 ± 189	93 (7/65/28), 620 ± 177	99 (1/33/66), 826 ± 232	98 (2/52/46), 713 ± 208	96 (4/58/38), 672 ± 194	92 (8/62/30), 623±182)	100 (0/29/71), 868 ± 254	99 (1/48/51), 739 ± 221	93 (7/58/35), 656 ± 202	97 (3/58/39), 678 ± 192	95 (5/62/33), 648 ± 185	94 (6/65/29), 626 ± 181	99 (1/42/57), 772 ± 229	97 (3/55/42), 694 ± 205
	30 mg/kg LD, 10 mg/kg MD	100 (0/35/65), 810 ± 228	99 (1/46/53), 751 ± 214	99 (1/42/57), 771 ± 222	95 (5/58/37), **664 ± 195**	100 (0/37/63), 803 ± 226	99 (1/47/52), 744 ± 212	99 (1/38/61), 798 ± 230	96 (4/57/39), 677 ± 200	89 (11/64/25), 602 ± 182	100 (0/36/64), 810 ± 230	99 (1/42/57), 774 ± 222	99 (1/48/51), 743 ± 215	98 (2/54/44), 702 ± 207	92 (8/62/30), 629 ± 190
Low flux	20 mg/kg LD, 10 mg/kg MD	82 (18/66/17), 541 ± 153	75 (25/64/11), 508 ± 146	97 (2/55/32), 688 ± 198	89 (11/63/26), 601 ± 177	82 (18/68/14), 539 ± 152	76 (24/65/11), 507 ± 144	99 (1/53/46), 717 ± 202	91 (9/65/26), 609 ± 176	83 (17/67/16), 549 ± 163	82 (18/68/14), 536 ± 151	76 (24/66/10), 512 ± 145	74 (26/65/9), 504 ± 144	93 (7/64/29), 624 ± 179	85 (15/66/19), 568 ± 166
	25 mg/kg LD, 7.5 mg/kg MD	**97 (3/59/38), 673 ± 189**	**94 (6/63/31), 633 ± 180**	**99 (1/47/52), 746 ± 212**	**92 (8/64/28), 623 ± 182**	**96 (4/59/38), 71 ± 190**	**93 (7/63/30), 31 ± 180**	99 (1/48/51), 742 ± 211	92 (8/62/30), 629 ± 184	85 (15/65/20), 567 ± 170	**96 (4/58/38), 671 ± 190**	**94 (6/62/32), 641 ± 183**	**93 (7/63/30), 627 ± 181**	94 (6/61/33), 643 ± 188	**88 (12/66/12), 583 ± 174**
	25 mg/kg LD, 10 mg/kg MD	97 (3/59/38), 674 ± 193	94 (6/63/31), 634 ± 183	99 (1/40/59), 786 ± 228	97 (3/56/41), 686 ± 202	97 (3/58/39), 672 ± 189	94 (6/63/31), 631 ± 180	**99 (1/35/64), 817 ± 233**	**97 (3/54/43), 693 ± 204**	**91 (9/62/29), 624 ± 204**	97 (3/59/38), 671 ± 187	95 (5/63/32), 641 ± 181	94 (6/64/30), 629 ± 179	98 (2/52/46), 712 ± 204	94 (6/60/34), 647 ± 190
	25 mg/kg LD, 13 mg/kg MD	97 (3/58/39), 674 ± 188	94 (6/63/31), 634 ± 179	99 (1/26/73), 872 ± 247	99 (1/44/55), 762 ± 220	96 (4/58/38), 671 ± 192	93 (7/62/31), 630 ± 182	100 (0/23/77), 906 ± 262	99 (1/43/56), 769 ± 227	97 (3/54/43), 692 ± 209	97 (3/60/37), 671 ± 189	95 (5/64/31), 640 ± 182	94 (6/64/30), 630 ± 180	99 (1/39/60), 793 ± 227	98 (2/51/47), 721 ± 211
	25 mg/kg LD, 15 mg/kg MD	97 (3/59/38), 669 ± 191	94 (6/63/31), 629 ± 182	100 (0/22/78), 922 ± 267	99 (1/38/61), 806 ± 238	96 (4/58/38), 673 ± 189	94 (6/64/30), 633 ± 179	100 (0/15/85), 970 ± 274	99 (1/34/65), 824 ± 238	98 (2/46/52), 742 ± 220	97 (3/59/38), 668 ± 189	94 (6/63/31), 638 ± 182	93 (7/63/30), 628 ± 181	99 (1/31/68), 844 ± 243	99 (1/29/70), 768 ± 226
	30 mg/kg LD, 10 mg/kg MD	100 (0/36/64), 807±227)	99 (1/44/56), 759 ± 215	99 (1/25/75), 883 ± 253	99 (1/42/57), 770 ± 225	100 (0/37/63), 801 ± 227	99 (1/45/54), 753 ± 215	100 (0/22/78), 916 ± 263	99 (1/42/57), 776 ± 228	97 (3/53/44), 699 ± 211	100 (0/37/63), 804 ± 227	99 (1/42/57), 767 ± 218	99 (9/45/54), 751 ± 214	99 (1/38/61), 797 ± 229	98 (2/49/49), 723 ± 212

Data illustrate "postdialytic" vancomycin therapy initiated on either Monday, Wednesday, or Friday in end-stage kidney disease patients receiving thrice-weekly intermittent hemodialysis scheduled on Monday-Wednesday-Friday.

Shaded boxes indicate the days of a 4-hour hemodialysis session and vancomycin infusion delivered "after" dialysis session ended.

Bold dosing regimens are those attaining ≥90% of probability of target attainment (PTA) while a mean AUC_{24h} close to <700 mg·h/L over a 2- or 3-day interdialytic period.

Note that when a maintenance dose is given when there will be a 3-day interdialytic period afterward (eg, Friday),

a 30% higher dose is used in the model. The 30% higher dose is necessary to attain a PTA ≥90% on the third day of a 3-day interdialytic period.

recommended MD needing to be twice as high with high-flux dialyzers (15 mg/kg) compared with low-flux dialyzers (7.5 mg/kg) to achieve targets (Table 3). Recommended MD given after dialysis with high-flux dialyzers were only slightly higher than when low-flux dialyzers were used (10 vs 7.5 mg/kg; Table 4).

Part II. Development of Therapeutic Drug Monitoring-Guided Dosing Algorithm

Figure 1A-C portrays the distribution of vancomycin AUC_{24h} prior to and after TDM is used to individualize dosing, when the model-recommended vancomycin regimen was initiated on Monday with a thrice-weekly (Monday-Wednesday-Friday) IHD schedule. Model-recommended doses were able to maintain the majority of simulated patients within AUC_{24h} 400 to 700 mg·h/L after the LD and the first MD. These figures also illustrate the relatively low AUC_{24h} attainment by Zelenitsky's dosing regimens. Although model-recommended LDs did ensure that ≥90% of simulated patients met efficacy targets, there was great variability in these AUC_{24h}, and many patients had values of >700 mg·h/L to ensure that ≥90% met efficacy targets (Figure 2A). The first modeled MDs reduced variability (Figure 2C), but again many patients still had an AUC_{24h} well above 700 mg·h/L. However, once TDM was used to determine MD, a more acceptable AUC was attained (Figure 2E). In contrast, Figure 2B,D,F describes those in simulated patients receiving Zelenitsky's different weight-based dosing regimen, and in these instances AUC_{24h} ≥400 mg·h/L was attained in less than 50% in all cases.

The post hoc analysis showed that differences of volume of distribution, nonrenal clearance, and vancomycin bioavailability during intradialytic administration were significant (P <.05) between the simulated patient groups with AUC_{24h} <400, 400-700, and >700 mg·h/L. Compared with those that attained an AUC_{24h} of 400 to 700 mg·h/L, the group with a result of AUC_{24h} <400 mg·h/L was characterized with a larger volume of distribution, faster nonrenal clearance (k_{e_off}), and lower vancomycin bioavailability during intradialytic administration. Conversely, the virtual group with AUC_{24h} >700 mg·h/L had a smaller volume of distribution, slower nonrenal clearance, and higher vancomycin bioavailability.

Simulation results suggest that predicted predialysis vancomycin serum concentrations correlate well with AUC_{24h} in IHD patients, except the initial 2 days with model-recommended LD (Figure 2A,C,E). A predialysis concentration of 20 mg/L ensures an AUC_{24h} of >480 mg·h/L; thus, the new MD is to be adjusted proportionally from the previous MD to achieve a predialysis concentration of 20 mg/L.

$$\text{New subsequent maintenance dose} = \frac{\text{Previous maintenance dose} \bullet 20}{\text{Predialysis vancomycin concentration}}$$

(If new MD is administered over a 3-day interdialytic period, a 30% higher dose is necessary.)

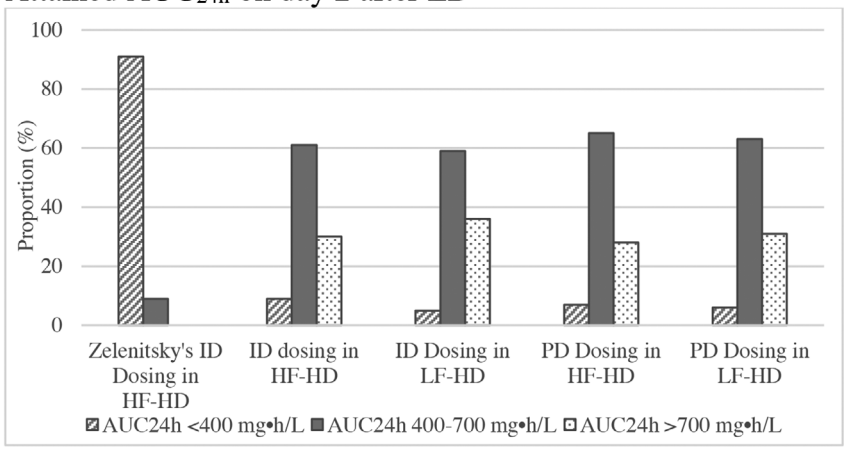
Figure 1C displays the AUC_{24h} distribution on the seventh day (Sunday) of vancomycin therapy following the application of the new subsequent MD, which was determined by TDM and given on day 5 (Friday). Of note, this new MD was 30% higher than the dose calculated using the equation above, as are all recommended MDs given before a 3-day interdialytic period. As soon as the individualized dose was administered, most simulated patients attained AUC_{24h} ≥400 mg·h/L, and the proportion of patients achieving an AUC_{24h} of 400-700 mg·h/L was increasingly higher over a 3-day interdialytic period. Figure 2E portrays the distribution of predicted AUC_{24h} and predialysis vancomycin serum concentrations produced after TDM-guided dosing individualization that were narrower than those with the initial LD (Figure 2A) and MD (Figure 2C).

Discussion

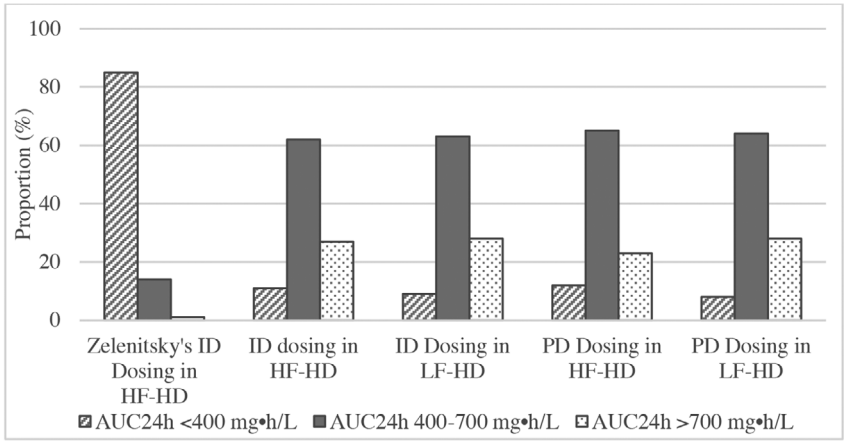
To our knowledge, this is the first in silico study to determine initial vancomycin dosing to attain an efficacy target of AUC_{24h}/MIC ≥400 in patients receiving thrice-weekly IHD in all its forms. Many studies have attempted to determine optimal vancomycin dosing in patients with IHD, but recommended doses have been rarely evaluated regarding their ability to reach this pharmacokinetic/pharmacodynamic index of AUC_{24h}/MIC ≥400. Our simulation results support using predialysis concentrations as a surrogate marker to attain target AUC_{24h} and to guide optimal dosing in IHD patients. Although the Bayesian approach is recommended to estimate AUC_{24h} in the new guidelines,[1] this method has not been prospectively validated in IHD patients[3,6]; thus, its utility in this population remains limited.[47] Conversely, our MCS technique enabled us to assess the impact of different pharmacokinetic and IHD variables as well as those of vancomycin administration time in relation to HD on drug exposure (AUC_{24h}) to predict optimal dosing in thousands of virtual patients constructed from published vancomycin pharmacokinetic variables. Finally, this is the first study to incorporate "virtual TDM" to guide individualized dosing within an MCS.

All dosing scenarios were tested with vancomycin therapy initiated on Monday, Wednesday, or Friday. We attempted to determine the optimal initial doses that work in all clinical scenarios. However, because of the substantial variability in vancomycin pharmacokinetics,[48,49] simulated vancomycin doses

A. Attained AUC_{24h} on day 2 after LD



B. Attained AUC_{24h} on day 4 after first MD



C. Attained AUC_{24h} on day 7 after Zelenitsky's second intradialytic MD vs. the first individualized dose with TDM following the initial model-recommended doses

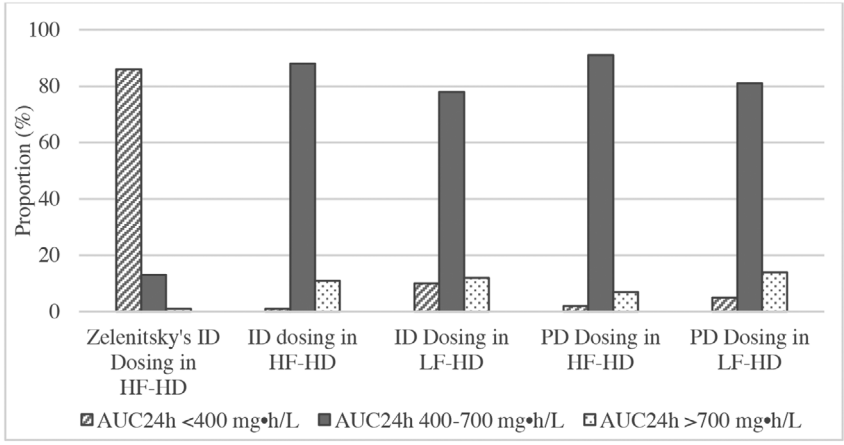


Figure 1. Comparison of AUC_{24h} attainment rates by dialyzer type and dosing technique. ID, intradialytic; PD, postdialytic; HF, high flux; LF, low flux; HD, hemodialysis; TDM, therapeutic drug monitoring; ID dosing in HF-HD, LD 35 mg/kg, then MD 15 mg/kg; ID dosing in LF-HD, LD 30 mg/kg, then MD 7.5 mg/kg; PD dosing in HF-HD, LD 25 mg/kg, then MD 10 mg/kg; PD dosing in LF-HD, 25 mg/kg, then MD 7.5 mg/kg. §All illustrated dosing regimens were initiated on Monday in end-stage kidney disease patients receiving thrice-weekly intermittent hemodialysis scheduled on Monday-Wednesday-Friday. Zelenitsky's doses were based on reference 30.

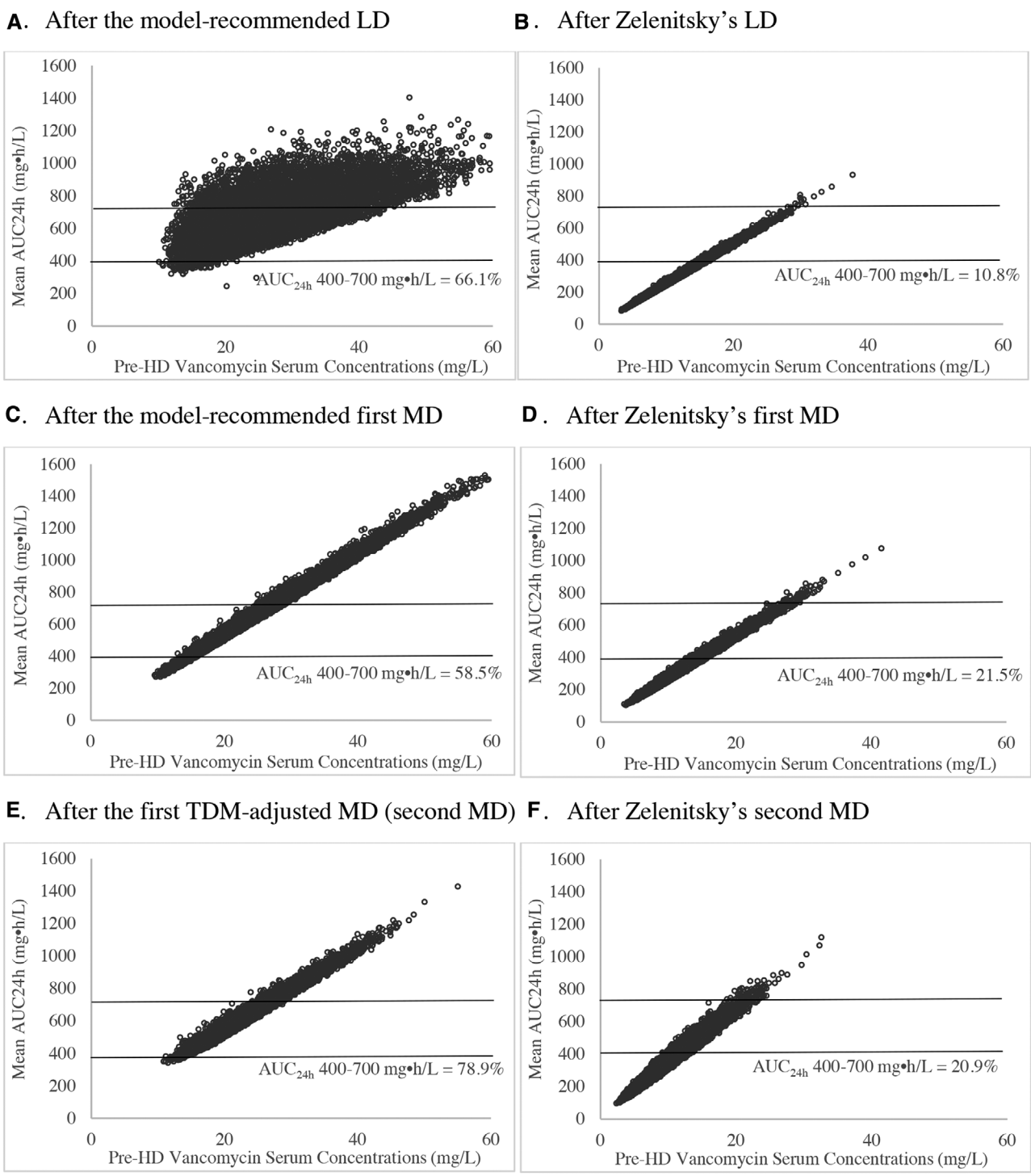


Figure 2. Predicted relationship of mean AUC_{24h} and predialysis vancomycin serum concentrations in patients receiving commonly used intradialytic regimens (n = 15,000) versus patients receiving the model-recommended dosing regimens (n = 20,000). (A, C, E) Relationship of mean AUC_{24h} and predialysis concentrations in all simulated patients (n = 20,000) with 4 combination scenarios receiving model-recommended initial doses and the first TDM dose on Monday, Wednesday, and Friday. (B, D, F) Relationship of mean AUC_{24h} and predialysis concentrations in all simulated patients (n = 15,000) with all different weight ranges (40-70, 70-100, and 100-150 kg) receiving a week of Zelenitsky's intradialytic doses on Monday, Wednesday, and Friday. §Mean AUC_{24h} (A, B) from days 1 and 2 of vancomycin therapy after LDs, (C, D) Days 3 and 4 after first MDs. (E, F) Days 5 to 7 after first TDM-adjusted MD and Zelenitsky's second MD, respectively. ¶Two straight horizontal lines in each figure indicate mean AUC_{24h} of 400 and 700 mg·h/L, and the values (%) denote the proportion of patients who attained a mean AUC_{24h} of 400 to 700 mg·h/L with the given doses. Zelenitsky's doses were based on reference 30.

yielded broad ranges of AUC_{24h} values, and none of them perfectly met PTA ≥90% with the mean AUC_{24h} within the 400-700 mg·h/L target. In general, the model-recommended LD from the simulation results (30 to 35 mg/kg for intradialytic administration and 25 mg/kg for postdialytic administration) was similar to or higher than previously published recommended doses.[6,24,25,28,29,31] To attain AUC_{24h} ≥400 mg·h/L in ≥90% of patients over both a 2- or 3-day interdialytic period, a high LD was necessary. These model-recommended LDs are similar to 25- to 30-mg/kg doses recommended in patients with normal renal function. However, this is not surprising, as vancomycin LD is independent of renal function, and ESKD patients are often volume-overloaded,[29,50] which may cause a larger vancomycin volume of distribution. The MCS results further highlight that patients receiving IHD should not be given reduced LD. Another MCS study by Rungprai et al determining optimal vancomycin dosing among patients with "high-efficiency IHD" also highlighted the necessity of a higher LD in the treatment of similar patients.[33] This study evaluated achievability of AUC_{24h} ≥400 mg·h/L only during the first day of vancomycin therapy in a different simulation scenario in which vancomycin was administered 8 to 16 hours prior to a 4-hour IHD treatment.[33] These authors proposed an LD of 30 mg/kg, with a 25 mg/kg of postdialytic supplemental dose or an LD of 35 mg/kg with 10 mg/kg of a postdialytic supplemental dose,[33] which can require a total of 45 to 55 mg/kg on the first day of vancomycin therapy. These regimens are even higher than our recommended doses.

Published vancomycin MD recommendations in IHD patients range widely in terms of dose and frequency.[26,28,30,31,51] Our simulation results show that MDs of 7.5 to 15 mg/kg are required to maintain the pharmacokinetic/pharmacodynamic efficacy target following the recommended LD. Notably, these MDs resulted in a PTA of 80% to 85% on the third day if given prior to a 3-day interdialytic period shown in Tables 3 and 4. To maintain a PTA of ≥90% on the third day of a 3-day interdialytic period, a 30% higher MD (eg, 10 to 20 mg/kg) was needed, but unavoidably, the mean AUC_{24h} on the first day of a 3-day interdialytic period exceeded the safety AUC_{24h} threshold depicted in Tables 3 and 4.

Not only have published vancomycin dosing recommendations for IHD been inconsistent, but also it remains elusive how best to perform TDM to optimize the the subsequent MD. The optimal TDM sampling time and efficacy target of vancomycin therapy for IHD patients have not been studied extensively. With the previous guideline,[8] a predialysis serum concentration of 5 to 20 mg/L has been extrapolated from the trough target for patients with normal renal function and has been commonly used in clinical practice assuming its correlation with AUC_{24h} ≥400 mg·h/L.[29] In general, the attainment of an AUC_{24h} of 400-700 mg·h/L with the model-recommended initial vancomycin doses was correlated with predialysis concentrations of 15 to 25 mg/L. Because targeting higher predialysis concentrations (eg, ≥18.6 mg/L) was associated with better clinical outcomes,[34] virtual TDM was designed to target a predialysis concentration of 20 mg/L in the model. TDM-guided individualized dosing following the model-recommended initial doses resulted in a higher proportion of AUC_{24h} of 400 to 700 mg·h/L attainment with a significantly reduced number of patients with AUC_{24h} <400 or >700 mg·h/L. The mean proportion of patients with AUC_{24h} 400 to 700 mg·h/L after receiving the first TDM adjusted dose over a 3-day interdialytic period was 78.9% compared with 66.1% and 58.5% after LD and MD, respectively (P <.00001; Figure 2A,C,E). Importantly, the mean AUC_{24h} with the TDM-adjusted doses was maintained as 500 to 600 mg·h/L over 14 days of modeled vancomycin therapy. The mean intradialytic vancomycin MDs adjusted by TDM following the initial regimens were 13 to 14 mg/kg and 7 mg/kg for high-flux and low-flux IHD, respectively. The mean adjusted postdialytic MDs were 9 mg/kg and 6-7 mg/kg for high-flux and low-flux IHD, respectively. If the dose was administered on Friday for a 3-day interdialytic period, 30% higher doses were still required. Any changes to patient clinical status and/or IHD treatment warrant another TDM to ensure the therapeutic target attainment in these patients.

Some limitations should be noted prior to the application of the findings from this in silico study. First, pharmacokinetic modeling and simulation were conducted with the assumption that patients are adults receiving a typical 4-hour IHD thrice weekly and have stable pharmacokinetic parameters. The subjects had demographic and pharmacokinetic characteristics with variances consistent with those derived from the literature with ESKD patients on maintenance IHD. Vancomycin doses were also given on the day of IHD treatment. Thus, application of our recommended doses would be appropriate only for those with similar demographic characteristics and clinical scenarios. We did not model what would happen if vancomycin therapy is initiated on a non-IHD day. If clinicians were faced with this scenario, we would recommend using the same LD with MD determined by TDM. Second, the maximum vancomycin dose in our simulation was capped at 4 g per dose, and all doses were infused over 1 or 2 hours. Thus, a dose >2 g given over 2 hours may be faster than some institutional vancomycin infusion rate policies. We modeled infusion rates in this fashion because standardization was necessary to simultaneously simulate 5000 virtual patients with different

vancomycin doses. Last, the model-recommended initial vancomycin doses were selected primarily based on the attainment of the "efficacy" target (AUC_{24h} ≥400 mg·h/L) in ≥90% of simulated cohorts assuming a MRSA MIC of 1 mg/L. Inevitably, these selected doses yielded high drug exposure in some virtual patients, exceeding the reported toxicity threshold of AUC_{24h} >700 mg·h/L. Although nephrotoxicity is less of a concern in these patients, a higher AUC_{24h} may increase the risk of other vancomycin toxicities such as ototoxicity. Interestingly, up to 10% of patients still did not achieve n AUC_{24h} ≥400 mg·h/L with the model-recommended initial doses (Figure 2A). Hence, clinicians should consider their patient's body weight, IHD setting, and clinical condition to weigh the benefit versus risk prior to the application of our model-recommended initial doses (bolded values in Tables 3 and 4). After initiation of the model-recommended doses, TDM must be performed to individualize the subsequent doses to target or maintain the optimal drug exposure.

Conclusion

The optimization of vancomycin dosing in ESKD patients receiving IHD has been a challenge because of multifaceted patient and dialysis variables influencing pharmacokinetics and a paucity of data regarding optimal vancomycin dosing to attain the efficacy target of AUC_{24h} ≥400 mg·h/L. Our in silico study used MCS to predict the initial doses that are most likely to attain an AUC_{24h} ≥400 mg·h/L in these patients with MRSA infections with a MIC of 1 mg/L in 4 different clinical scenarios as follows: (1) intradialytic administration of an LD of 35 mg/kg and an MD of 15 mg/kg in high-flux IHD, (2) intradialytic administration of an LD of 30 mg/kg and an MD of 7.5 mg/kg in low-flux IHD, (3) postdialytic administration of an LD of 25 mg/kg and an MD of 10 mg/kg in high-flux IHD, and (4) postdialytic administration of an LD of 25 mg/kg and an MD of 7.5 mg/kg in low-flux IHD. After the model-recommended initial dosing, TDM targeting predialysis concentration of 20 mg/L can assist clinicians in individualizing the subsequent optimal doses. In the absence of an appropriate pharmacokinetic study, the findings from this in silico study can guide clinicians' selection of more appropriate vancomycin doses attaining AUC_{24h} ≥400 mg·h/L, whereas clinical validation is necessary to confirm our dosing recommendations.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

The authors have no funding sources to report.

Data Sharing

Data for this study can be accessed by contacting the corresponding author.

Author Contributions

Susan J. Lewis and Bruce A. Mueller have contributed to the conception or design of the work, the execution, analysis and interpretation for the work, and writing the article; approved the final version; and agreed to be accountable for all aspects of the work.

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