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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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jcph.1727.

Declaration of Conflicting Interests

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no funding sources to report.

Data Sharing

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

Authors Contributions:

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

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 (Zelenitski, 2012) was modeled to determine its likelihood of attaining AUC_{24h}/MIC targets for one-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 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 25-35mg/kg followed by maintenance doses of 7.5-15mg/kg are necessary to reach minimum AUC_{24h}/MIC targets in 90% of virtual patients. For a 3-day interdialytic period, 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 probability of target attainment.

Key words : vancomycin, renal dialysis, Monte Carlo simulation, pharmacokinetics, pharmacodynamics

Introduction

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 ≥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 two-fold.[2.] A recent study in nondialysis patients suggests that improved patient outcomes are associated with attainment of AUC_{24h}/MIC of at least 550 and 650 on the first and second days of vancomycin therapy.[3] Conversely, an AUC_{24h} >700 mg•h/L has been reported as the nephrotoxicity threshold in non-dialysis 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 ≥400.[8] However, recent evidence demonstrates 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 400-600 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] due to the high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Nonetheless,

the optimal vancomycin dosing strategy in IHD 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] Additionally, 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 been generated a wide range of vancomycin dosing recommendations and nomograms for IHD patients based on selected pre- or post-dialysis concentration targets but not AUC_{24h}/MIC targets.[20-33] Of note, a single study found that pre-dialysis 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* (VISA) or vancomycin-resistant *S. aureus* (VRSA).[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 AUC-based dosing approach in patients receiving IHD and previously published IHD vancomycin dosing recommendations have not been assessed as to 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 AUC_{24h}/MIC target of ≥400, and 3) to devise a dosing nomogram to individualize the subsequent dosing to attain 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 one 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 the year of 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 ml/min 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 <40kg or >150kg 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 three times a week (Monday-Wednesday-Friday) and vancomycin therapy was initiated on Monday. As recommended in their protocol, three intradialytic regimens were applied based on body weight: (1) 1000 mg loading dose (LD) followed by 500 mg maintenance dose (MD) for patients <70kg, (2) 1,250 mg LD, followed by 750 mg MD for patients 70-100 kg, and (3) 1,500 mg LD then 1,000 mg MD for patients >100 kg[30] and were simulated for a full week (i.e. 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 750-1,000 mg, and during the last 1.5 hours for a vancomycin dose of 1,500 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 the one using Zelenitsky's dosing protocol. The different types of hemodialyzers and drug dose administration timing in relation to dialysis have been found to be the significant factors that influence pharmacokinetics during dialysis.[20, 44] Hence, four different dialysis and vancomycin administration combination scenarios were schemed into the model. They were 1) intradialytic vancomycin dosing (i.e. infuse over the last one to two hours of dialysis) in high-flux IHD, 2) intradialytic vancomycin dosing in low-flux IHD, 3) postdialytic vancomycin dosing (i.e. infuse immediately after dialysis over one to two hours) in high-flux IHD, and 4) postdialytic vancomycin dosing in low-flux IHD. A vancomycin regimen in each of four scenarios was simulated to commence on either Monday, Wednesday, or Friday with 2 to 3 days of 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-hour long and vancomycin infusion times were 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 gram 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 MIC of 1 mg/L.[1] MCS (Crystal Ball Classroom Edition, Oracle) was conducted to predict total serum vancomycin concentration-time profiles in 5,000 virtual cohort for each tested vancomycin regimen. AUC_{24h} on each day of vancomycin therapy was computed with the linear trapezoidal rule. Probability of Target Attainment (PTA) (%) 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=5,000). Concern for 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 AUC_{24h} ≥400 mg•h/L in ≥90% of the virtual cohort with the mean AUC_{24h}/MIC of 400-700 mg•h/L. The new guidelines recommend narrower drug exposure targets of AUC_{24h}/MIC of 400-600 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 (e.g. mean AUC_{24h}/MIC of 400-700 mg•h/L) were used in this analysis.

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

Vancomycin dosing is routinely adjusted based on TDM results to ensure pharmacokinetic/pharmacodynamic target attainment. Thus, we incorporated TDM into our model to find how TDM could be effectively utilized to ensure the pharmacokinetic/pharmacodynamic target attainment in patients with IHD with only a single pre-dialysis serum concentration. This TDM-guided dosing nomogram individualizes the optimal subsequent vancomycin dosing to attain and/or maintain AUC_{24h} 400-700 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 time point. A pre-dialysis concentration immediately prior to the 2nd IHD session was used as the basis for TDM-directed dosing adjustment. Utilizing the pre-dialysis concentrations and the virtual patients' pharmacokinetic profiles used in 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 AUC_{24h} 400-700 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 mg•h/L,

400-700 mg•h/L, and >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 value of $p < 0.05$ was considered statistically significant.

Results

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

The simulated results of PTA and mean AUC_{24h} for a week of Zelenitsky's intradialytic vancomycin dosing regimen is presented in Table 2. All vancomycin regimens, regardless of body weight stratification, yielded very low PTA (2-42%) and the mean AUC_{24h} was <400 mg•h/L in all days of the week. Particularly, PTA on the first two days after the LD was lower than the rest of the days with only 18-26%, 8-10%, and 2-3% PTA in patients with 45-70kg, 70-100kg, and 100-150kg respectively. Additionally, the dosing for patients weighing 100-150 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 a higher AUC_{24h} of greater than 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 on Monday, Wednesday, or Friday, while Table 4 for those receiving "postdialytic" vancomycin dosing regimens. In these four different dialyzer and vancomycin infusion combination scenarios, none of the simulated vancomycin dosing regimens consisting of a LD and a MD successfully attained the efficacy target of PTA ≥90% while meeting the safety goal of mean AUC_{24h} <700 mg•h/L during the initial 4-5 days of vancomycin therapy (Table 3 & 4). Our model predicts that an intradialytic regimen using a

LD of 35 mg/kg and a MD of 15 mg/kg in high-flux IHD or a LD of 30 mg/kg and a MD of 7.5 mg/kg in low-flux IHD, and a postdialytic regimen with a LD of 25 mg/kg and a MD 10 mg/kg in high-flux IHD, or a LD of 25 mg/kg and a MD of 7.5 mg/kg in low-flux IHD would initially meet "best-possible", or "acceptable" PTA with mean AUC_{24h} of closest to 400-700 mg•h/L (bolded in Table 3 & 4), 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 on Table 3 & 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 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 20-40% higher LD and up to 50% higher MD to attain PTA ≥90% during 2- or 3-days of an interdialytic period compared to postdialytic administration due to significant drug removal by hemodialysis during intradialytic drug infusion. Dialyzer type had a profound effect on intradialytic doses, with recommended MD needing to be twice as high with high flux dialyzers (15 mg/kg) compared 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 mg/kg vs. 7.5 mg/kg) (Table 4).

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

Figures 1 A/B/C portray 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 thrice weekly (Monday-Wednesday-Friday) IHD schedule. Model-recommended doses were able to maintain the majority of simulated patients within AUC_{24h} 400-700 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. While 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 in order to ensure that ≥90% met efficacy targets (Figure 2A). The first modeled MDs reduced variability (Figure 2C), but again many patients still had AUC_{24h} well above 700 mg•h/L. However, once TDM is used to determine MD, a more acceptable AUC is attained (Figure 2E). In contrast, figures 2 B/D/F describe those in simulated patients receiving Zelenitsky's different weight-based dosing regimen, and in these instances AUC_{24h} ≥400 mg•h/L is attained in less than 50% in all cases.

The post-hoc analysis showed that differences of volume of distribution, non-renal clearance, and vancomycin bioavailability during intradialytic administration are significant ($p<0.05$) between the simulated patient groups with AUC_{24h} <400 mg•h/L, 400-700 mg•h/L, and >700 mg•h/L. Compared to those attained AUC_{24h} 400-700 mg•h/L, the group with resulted AUC_{24h} <400 mg•h/L were characterized with larger volume of distribution, faster non-renal clearance (ke_{off}), and lower vancomycin bioavailability during intradialytic administration. Conversely, the virtual group with AUC_{24h} >700 mg•h/L had smaller volume of distribution, slower non-renal clearance and higher vancomycin bioavailability.

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

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

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

Figure 1C displays the AUC_{24h} distribution on the 7th day (Sunday) of vancomycin therapy respectively 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 MD 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 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 pre-dialysis vancomycin serum concentrations produced after TDM-guided dosing individualization that were narrower than that 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 in order 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 pre-dialysis 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 been not 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, due to the substantial variability in vancomycin pharmacokinetics,[48,49] simulated vancomycin doses yielded broad ranges of AUC_{24h} 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 (30-35 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] In order 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 25-30 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 $AUC_{24h} \geq 400$ mg•h/L only during the first day of vancomycin therapy in a different simulation scenario where vancomycin was administered 8-16 hours prior to a 4 hour IHD treatment.[33] These authors proposed a LD of 30 mg/kg with 25 mg/kg of postdialytic supplemental dose or an LD 35 mg/kg with 10 mg/kg of postdialytic supplemental dose,[33] which can require a total of 45-55 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 doses and frequency.[26,28,30,31,51] Our simulation results show that MDs of 7.5-15 mg/kg are required to maintain pharmacokinetic/pharmacodynamic efficacy target following the recommended LD. Notably, these MDs resulted in PTA of 80-85% on the third day if given prior to a 3-day interdialytic period shown in Table 3 & 4. In order to maintain PTA of ≥90% on the third day of a 3-day interdialytic period, a 30% higher MD (e.g. 10-20 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 & 4.

Not only have published vancomycin dosing recommendations for IHD been inconsistent, but also how best to perform TDM to optimize the subsequent MD remain elusive. The optimal TDM sampling time and efficacy target of vancomycin therapy for IHD patients has not been studied extensively. With the previous guideline,[8] a pre-dialysis serum concentration of 5-20 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 $AUC_{24h} \geq 400$ mg•h/L.[29] In general, the attainment of AUC_{24h} 400-700

mg•h/L with the model-recommended initial vancomycin doses was correlated with pre-dialysis concentrations of 15-25 mg/L. Because targeting higher pre-dialysis concentrations (e.g. ≥18.6 mg/L) was associated with better clinical outcomes,[34] virtual TDM was designed to target a pre-dialysis 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} 400-700 mg•h/L attainment with significantly reduced number of patients with AUC_{24h} <400 or >700 mg•h/L. The mean proportion of patients with AUC_{24h} 400-700 mg•h/L after receiving the first TDM adjusted dose over a 3-day interdialytic period was 78.9% compared to 66.1% and 58.5% after LD and MD respectively ($p<0.00001$) (Figure 2 A/C/E). Importantly, the mean AUC_{24h} with the TDM-adjusted doses was maintained as 500-600 mg•h/L over 14 days of modeled vancomycin therapy. The mean intradialytic vancomycin MDs adjusted by TDM following the initial regimens were 13-14 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 with patient's 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. Secondly, the maximum vancomycin dose in our simulation was capped at 4 gram per dose and all doses were infused over 1 or 2 hours. Thus, a dose greater than 2 gram 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 5,000 virtual patients with different vancomycin doses. Lastly, the model-recommended initial vancomycin doses were selected primarily based on the attainment of "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 a high drug exposure in some virtual patients, exceeding the reported toxicity threshold of AUC_{24h} >700 mg•h/L. Although nephrotoxicity is less of concern in these patients, higher AUC_{24h} may increase the risk of other vancomycin toxicities such as ototoxicity. Interestingly, up to 10% of patients still did not achieve 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 vs. risk prior to the application of our model-recommended initial doses (bolded values in Tables 3 & 4). After the 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, due to multifaceted patient and dialysis variables influencing pharmacokinetics

and 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 AUC_{24h} ≥400 mg•h/L in these patients with MRSA infections with MIC of 1 mg/L in four different clinical scenarios as follows: 1) intradialytic administration of a LD of 35 mg/kg and a MD of 15 mg/kg in high-flux IHD, 2) intradialytic administration of a LD of 30 mg/kg and a MD of 7.5 mg/kg in low-flux IHD, 3) postdialytic administration of a LD of 25 mg/kg and a MD 10 mg/kg in high-flux IHD, and postdialytic administration of a LD of 25 mg/kg and a MD of 7.5 mg/kg in low-flux IHD. After the model-recommended initial dosing, TDM targeting pre-dialysis concentration of 20 mg/L can assist clinicians to individualize the subsequent optimal doses. In the absence of 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, while clinical validation is necessary to confirm our dosing recommendations.

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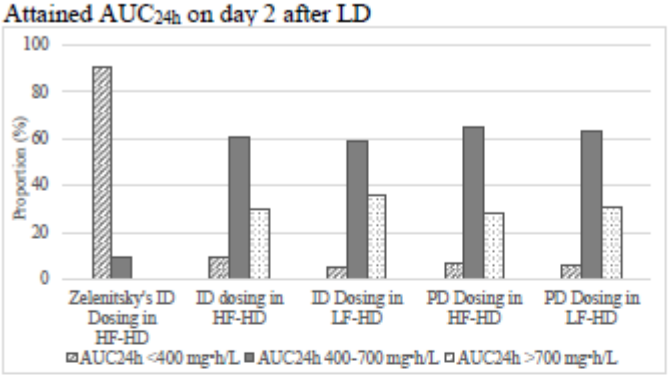
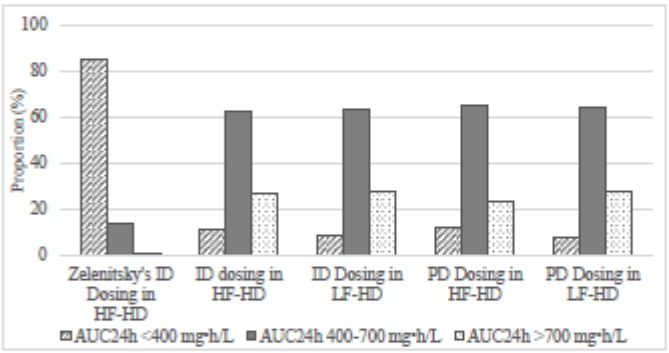
Figure 1. Distribution of AUC_{24h} with Commonly Used Contemporary Intradialytic Dosing [30] and the Model-Recommended Vancomycin Dosing in Four Different Settings on Day 2, 4, and 7 of Vancomycin Therapy

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

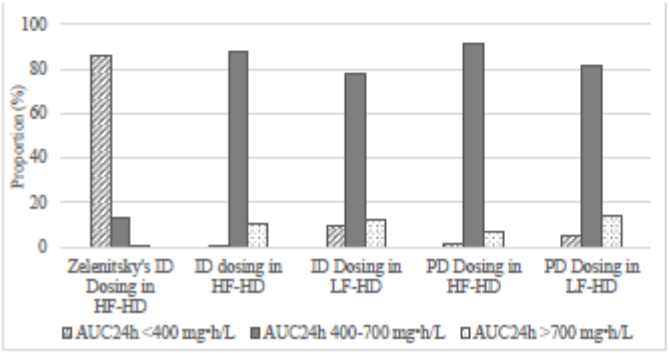
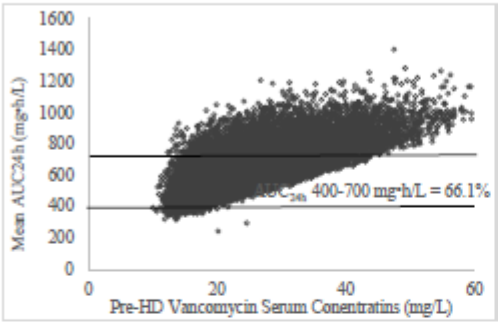
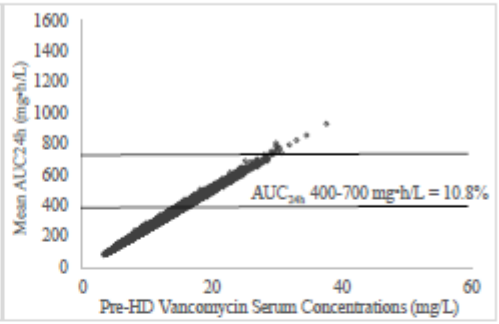


Figure 2. Predicted Relationship of Mean AUC_{24h} and Pre-dialysis Vancomycin Serum Concentrations in Patients Receiving Commonly Used Intradialytic Regimens (n=15,000) vs. Patients Receiving the Model-Recommended Dosing Regimens (n=20,000)

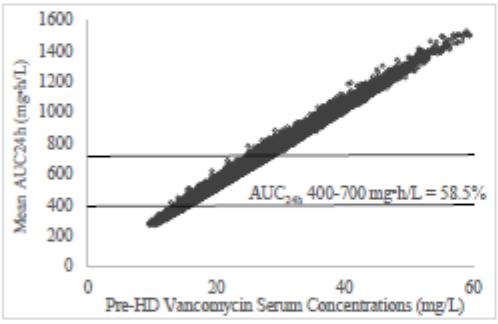
A. After the model-recommended LD



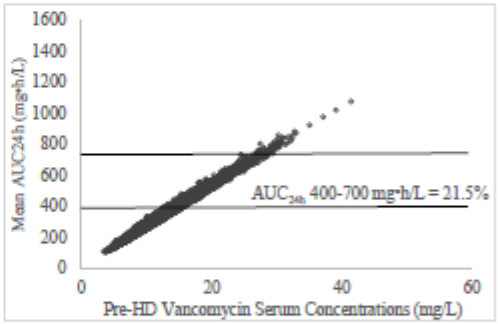
B. After Zelenitsky's LD



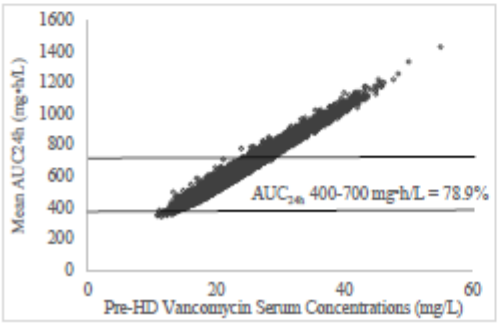
C. After the model-recommended first MD



D. After Zelenitsky's first MD



E. After the first TDM-adjusted MD (second MD)



F. After Zelenitsky's second MD

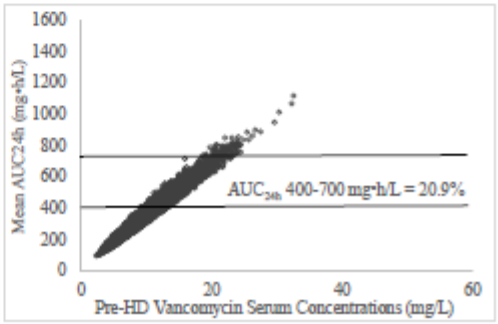


Table 1. Pharmacokinetic Model Input Parameters [20,25,26,30,31]

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} (hr^{-1})	0.0035 ± 0.001 [0.0010-0.0061]	
$t_{1/2\_off}$ (hr)	198.0 [113.6-693.0]	
k_{el_on} (hr^{-1})	0.110 ± 0.02 [0.066-0.154]	0.055 ± 0.011 [0.033-0.077]
$t_{1/2\_on}$ (hr)	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]

Table 1 Legend

*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]

Table 2. PTA and AUC_{24h} Predicted from a Week of a Commonly Used Intradialytic Vancomycin Dosing Protocol[34] for Thrice Weekly High-Flux IHD

Body Weight	Vancomycin Dosing †	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)						
		Day 1 (Mon)	Day 2 (Tue)	Day 3 (Wed)	Day 4 (Thu)	Day 5 (Fri)	Day 6 (Sat)	Day 7 (Sun)
45-70 kg	1,000 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	1,250 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	1,500 mg LD, 1,000 mg MD	3 [97/3/0] (231±76)	2 [98/2/0] (216±71)	17 [83/16/1] (310±103)	7 [93/7/0] (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

†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 5,000 virtual patients. First dose was given on Monday.

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 (Mon)	Day 2 (Tue)	Day 3 (Wed)	Day 4 (Thu)	Day 1 (Wed)	Day 2 (Thu)	Day 3 (Fri) **(30% higher MD)**	Day 4 (Sat)	Day 5 (Sun)	Day 1 (Fri)	Day 2 (Sat)	Day 3 (Sun)	Day 4 (Mon)	Day 5 (Tue)
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] (448±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	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)

	MD														
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	99 [1/36/	99 [1/42/	100 [0/9/91	99 [1/17/	99 [1/36/	99 [1/41/	100 [0/9/91	100 [1/17/	99 [1/15/	99 [1/35/	99 [1/41/	98 [2/47/	100 [0/15/8	99 [1/21/

*Data illustrates "intradialytic" vancomycin therapy initiated on either Monday, Wednesday or Friday in end stage renal 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.

§**Bolded** dosing regimen are the ones attaining ≥90% of probability of target attainment (PTA) while 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 afterwards (e.g. 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 Hemo-dialyzer	Dosing	Day 1 (Mon)	Day 2 (Tue)	Day 3 (Wed)	Day 4 (Thu)	Day 1 (Wed)	Day 2 (Thu)	Day 3 (Fri) (30% higher MD)	Day 4 (Sat)	Day 5 (Sun)	Day 1 (Fri)	Day 2 (Sat)	Day 3 (Sun)	Day 4 (Mon)	Day 5 (Tue)
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] (671±190)**	**93 [7/63/30] (631±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	100 [0/36/64] (807±	99 [1/44/56] (759±	99 [1/25/75] (883±	99 [1/42/57] (770±	100 [0/37/63] (801±	99 [1/45/54] (753±	100 [0/22/78] (916±	99 [1/42/57] (776±	97 [3/53/44] (699±	100 [0/37/63] (804±	99 [1/42/57] (767±	99 [9/45/54] (751±	99 [1/38/61] (797±	98 [2/49/49] (723±

	MD	227)	215)	253)	225)	227)	215)	263)	228)	211)	227)	218)	214)	229)	212)

*Data illustrates "postdialytic" vancomycin therapy initiated on either Monday, Wednesday or Friday in end stage renal 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.

§**Bolded** dosing regimen are the ones attaining ≥ 90% of Probability of Target Attainment (PTA) while 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 afterwards (e.g. 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.