

Vancomycin Dosing in Critically Ill Patients: Robust Methods for Improved Continuous-Infusion Regimens[∇]

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Despite the development of novel antibiotics active against Gram-positive bacteria, vancomycin generally remains the first treatment, although rapidly achieving concentrations associated with maximal efficacy provides an unresolved challenge. The objective of this study was to conduct a population pharmacokinetic analysis of vancomycin in a large population of critically ill patients. This was a retrospective data collection of 206 adult septic critically ill patients who were administered vancomycin as a loading dose followed by continuous infusion. The concentration-versus-time data for vancomycin in serum was analyzed by a nonlinear mixed-effects modeling approach using NONMEM. Monte Carlo simulations were performed using the final covariate model. We found that the best population pharmacokinetic model consisted of a one-compartment linear model with combined proportional and additive residual unknown variability. The volume of distribution of vancomycin (1.5 liters/kg) was described by total body weight and clearance (4.6 liters/h) by 24-hour urinary creatinine clearance (CrCl), normalized to body surface area. Simulation data showed that a 35-mg/kg loading dose was necessary to rapidly achieve vancomycin concentrations of 20 mg/liter. Daily vancomycin requirements were dependent on CrCl, such that a patient with a CrCl of 100 ml/min/1.73 m² would require at least 35 mg/kg per day by continuous infusion to maintain target concentrations. In conclusion, we have found that higher-than-recommended loading and daily doses of vancomycin seem to be necessary to rapidly achieve therapeutic serum concentrations in these patients.

Infections in critically ill patients occur frequently and may lead to the development of sepsis or septic shock. The morbidity and mortality rates for sepsis and septic shock remain unacceptably high, with septic shock still associated with a 35 to 65% in-hospital mortality rate (5, 9). A significant body of work now describes the importance of early and appropriate antibiotic therapy as the intervention likely to minimize therapeutic failure (10, 17, 18).

Of significant concern for clinicians is the increasing prevalence of multidrug-resistant bacteria, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), which has been found to be the causative pathogen in more than 10% of infections resulting in septic shock (9). Furthermore, data from the United States have reported that 25.8% of bacteremias are due to MRSA (4), with mortality rates for MRSA bacteremia in critically ill patients being reported as between 45 and 55% (3, 13). Certainly, mortality rates for MRSA pneumonia in critically ill patients may be even higher (12). While newer agents are now available, vancomycin remains the standard of care for treatment of MRSA infections in the intensive care unit (ICU) (30).

Despite vancomycin being in ubiquitous use for over 50 years, dosing in specific populations, particularly the critically

ill, remains confused. Conventional dosing regimens of 500 mg every 6 h or 1 g every 12 h have little evidence supporting their efficacy (7), while data from the work of Moise-Broder et al. (22) for MRSA pneumonia suggest that standard dosing approaches are unlikely to achieve the required pharmacodynamic index of vancomycin exposure needed for optimal activity. Pursuant to this, a consensus review in 2009 by the American Society of Health System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Disease Pharmacists (ASHP/IDSA/SDIP) recommended more-aggressive vancomycin dosing to achieve the pharmacodynamic index associated with efficacy (30).

Continuous infusion (CI) of vancomycin allows more rapid achievement of therapeutic drug concentrations than does intermittent infusion and may optimize its bactericidal activity. Recent publications recommend a loading dose of 15 mg/kg of body weight followed by a daily dose of 30 mg/kg (33); however, data on the efficacy of this strategy in a septic population are scarce.

In this respect, the aim of this study was to conduct a population pharmacokinetic (PK) analysis of vancomycin continuous administration in a large cohort of critically ill patients, in order to better inform dosing in this population and to reduce the risks for subtherapeutic drug exposure.

MATERIALS AND METHODS

Patients and data collection. We reviewed all the medical charts of patients with a diagnosis of sepsis (18) admitted to the Intensive Care Unit (ICU) at Erasme Hospital (Brussels, Belgium) between January 2008 and December 2009, to whom continuous infusion (CI) of vancomycin, either in monotherapy or

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combined with other antimicrobials, was administered. Patients meeting any of the following criteria were excluded: (i) age less than 18 yrs; (ii) previous administration of vancomycin by intermittent infusion (<48 h from the onset of CI); (iii) renal replacement therapy; (iv) duration of CI of vancomycin of <48 h; and (v) pregnancy, burns, or cystic fibrosis (because of altered pharmacokinetics, independent of sepsis). The study period was limited to the ICU stay. Ethical approval to conduct the study was granted by the local ethics committee.

For all study patients, data were collected in an institutional database. The severity of illness of each patient was characterized using the Acute Physiology and Chronic Health Evaluation (APACHE) II (16) and sepsis organ failure assessment (SOFA) (32) scores determined on the first day of antibiotic treatment. Urinary creatinine clearance (CrCl) was collected as a routine procedure in all of the patients, calculated daily, and normalized to body surface area (BSA). Treatment of patients with catecholamines or mechanical ventilation was also recorded, as was length of ICU and hospital stay, overall mortality, and cause of death.

Vancomycin treatment. Administration of vancomycin (Vancocin; Eli Lilly, Indianapolis, IN) was by continuous infusion in accordance with local guidelines and often empirical in the setting of presumed or documented Gram-positive hospital- or ICU-acquired infections, especially when MRSA or other resistant Gram-positive bacteria (i.e., *Staphylococcus epidermidis* or ampicillin-resistant *Enterococcus*) were suspected. Continuous infusion is the preferred method of administration in the unit where the data collection occurred because we believe dose adjustment to achieve therapeutic concentrations to be easier with continuous infusion than with intermittent infusion. Previous clinical outcome studies have shown equivalent outcomes for vancomycin administered by either approach (33). In this study, the choice of antibiotic regimen was at the discretion of the clinician; published recommendations (15-mg/kg loading dose followed by 30-mg/kg daily dose calculated on the total body weight [TBW]) (33), with doses rounded off to 125 mg, were used in some patients. In others, local simplified recommendations were used, consisting of a 750-mg (if TBW was <70 kg) or a 1,000-mg (if TBW was >70 kg) loading dose diluted in 100 ml of 5% dextrose in water and administered over 30 min, followed by a 2,000-mg (if TBW was <70 kg) or a 3,000-mg (if TBW was >70 kg) daily dose of vancomycin, diluted in 250 ml of 5% dextrose in water and infused over 24 h in the case of normal renal function. In the case of renal failure, the loading dose was unchanged but the daily dose was adapted to the renal clearance. The aim of this regimen was to provide serum drug concentrations between 20 and 30 mg/liter (28). Where concentrations were less than 20 mg/liter, a loading dose of 500 mg was used and an increase of 500 to 1,000 mg per day of total dose was made. In patients where concentrations were greater than 30 mg/liter, CI was discontinued for 4 h and the total dose was reduced by 500 to 1,000 mg per day.

Vancomycin assay. Concentrations of vancomycin in serum were determined by fluorescence polarization immunoassay (TDx; Diagnostic Division, Abbott Laboratories, Irving, TX). The assay limits and intraday and between-day coefficients of variation for vancomycin were 0.6 mg/ml and 0.6%, respectively. The linearity (r^2) of the assay was 0.999.

Blood samples (5 ml) for drug assays were taken every day at 8 a.m. and sent immediately to the central laboratory. As the aim was to examine the “pseudo-steady-state” phase of the drug regimen, at least 16 h from the onset of CI was allowed before sampling. We use the term “pseudo-steady-state” because whether steady state is ever achieved in ICU patients with sepsis is debatable. The exact sampling time was recorded by the nursing or medical staff in a computerized ICU system.

Pharmacokinetic and statistical analysis. The concentration-versus-time data for vancomycin in serum were analyzed by a nonlinear mixed-effects modeling approach (2) using NONMEM (version 6.1; GloboMax LLC, Hanover, MD) with double precision with the Compaq VISUAL FORTRAN compiler. The NONMEM runs were executed using Wings for NONMEM (WFN 6.1.3). Data were analyzed using the first-order conditional estimation method with the Interaction program.

For the population pharmacokinetic (PK) analysis, the serum vancomycin concentrations were fitted to one-, two-, or three-compartment linear models using subroutines from the NONMEM library (2). The concentration-time profile can be described by equation 1:

$$Y_{ij} = f_{ij}(\theta_i, x_{ij}) \cdot e^{\epsilon_{ij}} + \epsilon_{2ij} \tag{1}$$

where y_{ij} is the j th observed concentration at time points x_{ij} for the i th subject. Also, θ_i represents the fixed-effects parameter of the structural model to be estimated. f_{ij} is the function for the prediction of the j th response for the i th subject. Finally, ϵ_{ij} designates the j th measurement error for the i th subject. In other words, ϵ_{ij} is the difference of the observed concentration from the predicted

concentration. It is assumed to be independent and identically distributed with a normal distribution around the mean zero and variance σ^2 .

Between-subject variability. Between-subject variability was modeled using an exponential variability model (equation 2):

$$\theta_i = \theta \cdot e^{\eta_i} \tag{2}$$

where θ_i is the value of the parameter for the i th subject, θ is the typical value of the parameter in the population, and finally η_i is a random vector with normal distribution, zero mean, and variance-covariance matrix of between-subject variability Ω to be estimated.

Model diagnostics. To assess model validity, statistical comparison of nested models was undertaken in NONMEM based on a χ^2 test of the difference in the objective function. A decrease in the objective function of 3.84 units ($P < 0.05$) was considered significant. Goodness of fit was evaluated by visual inspection of diagnostic scatter plots, including observed and predicted concentrations versus time, weighted residual versus time, and residual versus predicted concentrations.

Bootstrap. A nonparametric bootstrap method (23) ($n = 1,000$) was used to study the uncertainty of all pharmacokinetic parameter estimates in the final base model. From the bootstrap empirical posterior distribution, we have been able to obtain the 95% confidence interval (2.5 to 97.5% percentile) for the parameters, as described previously (21).

Covariate screening. The covariates analyzed were age, TBW, creatinine clearance estimated from urinary 24-hour collection, gender, SOFA score, and body mass index. Possible covariates were added in a stepwise fashion into the model. Covariates were considered for inclusion in the model if they were biologically plausible and there was improvement of the base model, i.e., decrease in objective function (at least 3.84 units), decrease in the unexplained between-subject variability of the parameter, or decrease in residual unexplained variability.

Dosing simulations. Three sets of Monte Carlo dose simulations were undertaken.

First, the effect of an initial TBW-based loading dose was simulated using doses of 5 mg/kg (administered over 60 min), 15 mg/kg (administered over 60 min), 20 mg/kg (administered over 90 min), 25 mg/kg (administered over 120 min), 30 mg/kg (administered over 180 min), 35 mg/kg (administered over 180 min), and 40 mg/kg (administered over 180 min). The different durations of infusion were chosen based on local clinical practice. The same daily continuous-infusion dose was simulated for each of the loading doses (35 mg/kg for a patient with a CrCl of 100 ml/min/1.73 m²).

Second, the effects of different creatinine clearances on vancomycin concentrations were simulated. The CrCl_s simulated were 50 ml/min/1.73 m², 100 ml/min/1.73 m², 150 ml/min/1.73 m², 200 ml/min/1.73 m², and 250 ml/min/1.73 m². Each patient received a simulated loading dose of 35 mg/kg (over 180 min; the duration was prolonged to minimize the likelihood of infusion-related toxicity), and the simulated continuous infusion dose was kept constant at 35 mg/kg per day. The ability of each dosing regimen to achieve predefined pharmacodynamic targets, a steady-state concentration (C_{ss}) of >20 mg/liter, was then assessed. We also simulated the following CrCl_s to determine dose requirements for continuous infusion after a 35-mg/kg loading dose: 20 ml/min/1.73 m², 30 ml/min/1.73 m², and 40 ml/min/1.73 m².

Third, the effects of different weight-based dosing CI regimens on vancomycin concentrations were simulated. The simulated patients each had a CrCl of 100 ml/min/1.73 m² and received a 35-mg/kg loading dose over 180 min. The weight-based regimens simulated were 20 mg/kg/day, 25 mg/kg/day, 30 mg/kg/day, 35 mg/kg/day, and 40 mg/kg/day. The ability of each dosing regimen to achieve predefined pharmacodynamic targets, a steady-state concentration (C_{ss}) of >20 mg/liter, was then assessed.

RESULTS

The study included 206 patients, whose demographic details are described in Table 1. Population pharmacokinetic modeling was performed using the concentration data from serum samples. The best base model, using the model building criteria, consisted of a one-compartment linear model with zero-order input and combined proportional and additive residual unknown variability. Other models could not be supported because they did not result in an improvement in objective function value or between-subject variability. Between-subject variability was included for both clearance and volume of dis-

TABLE 1. Demographic and clinical characteristics of patients

Variable	Value ^a
Age (yr)	58.1 ± 14.8
Weight (kg)	74.8 ± 15.8
Height (cm)	171 ± 8
Body mass index (kg/m ²)	25.9 ± 5.4
Gender (% male)	61.6
Creatinine clearance (ml/min/1.73 m ²)	90.7 ± 60.4
APACHE II score	21 (16–27)
SOFA score	7.6 ± 4.2

^a Data are described as mean ± standard deviation or median (interquartile range).

tribution. The final objective function for the base model was 2,817.420.

The covariate that best described vancomycin volume of distribution was TBW. The addition of this covariate reduced the objective function by 6.129 (statistically significant change is 3.84 units). The covariate that best described vancomycin clearance was urinary CrCl normalized to 100 ml/min/1.73 m². The addition of this parameter improved the between-subject variability for clearance by 10% and improved the goodness-of-fit plots. The final population model for vancomycin was represented by equations 3 and 4:

$$TVV = (\theta_1 \cdot TBW) \quad (3)$$

$$TVCL = (\theta_2 \cdot CrCl/100) \quad (4)$$

where TVV is the typical value of volume of distribution, TBW is total body weight, and TVCL is the typical value of vancomycin clearance. None of the other covariates statistically significantly improved the model, and therefore, they could not be included.

The values of the parameters for the final model are given in Table 2 and include the 95% confidence intervals for the parameters computed from all bootstrap runs. The population value for clearance of vancomycin was 4.6 liters/h (95% confidence interval, 4.1 to 5.2), and that for volume of distribution was 1.5 liters/kg (95% confidence interval, 1.3 to 1.7) (Table 2).

Figure 1 displays the goodness-of-fit plots for the final model. Each of the patients contributed 2 to 3 samples, and of the 579 samples included in the analysis, 10 samples had a concentration greater than 2 standard deviations outside that predicted by the model, which we considered acceptable given the level of sickness severity and likely pharmacokinetic heterogeneity of the patient cohort. All subsequent dosing simulations were then based on this model. All other visual predictive checks were acceptable and confirmed the goodness of fit of the model. The plots in Fig. 1 show that the final pharmacokinetic model describes the measured vancomycin concentrations adequately.

Dosing simulations. A loading dose of at least 35 mg/kg TBW would have been necessary to rapidly achieve vancomycin concentrations of >20 mg/liter within a few hours from the onset of infusion (Fig. 2). A standard loading dose of 15 mg/kg would have resulted in inadequate drug concentrations for the first 24 h of therapy, despite an appropriate maintenance regimen. The respective values for area under the concentration-time curve from 0 to 24 h (AUC_{0–24}) for these simulations from 0 to 24 h were as follows: 5 mg/kg, 245 mg · h/liter; 15

TABLE 2. Bootstrap parameter final estimates of the final covariate model

Parameter	Mean	95% confidence interval	
		2.5 percentile	97.5 percentile
Fixed effects			
Clearance (liters/h)	4.58	4.09	5.19
Volume of distribution (liters/kg)	1.53	1.31	1.71
Random effects: between-subject variability, Ω_{BSV} (% coefficient of variation)			
Clearance	38.9	28.3	55.6
Volume of distribution	37.4	16.6	54.9
Random error			
Residual unexplained variability (% coefficient of variation)	19.9	14.5	24.6
SD (mg/liter)	2.4	1.3	3.0

mg/kg, 330 mg · h/liter; 20 mg/kg, 370 mg · h/liter; 25 mg/kg, 409 mg · h/liter; 30 mg/kg, 442 mg · h/liter; 35 mg/kg, 485 mg · h/liter; and 40 mg/kg, 532 mg · h/liter.

Figure 3 describes the impact of different values of creatinine clearance on vancomycin concentrations. In spite of an effective loading dose of 35 mg/kg, a daily dose of 35 mg/kg could not keep vancomycin concentrations within target levels if the CrCl was 100 ml/min/1.73 m². If patients had even higher CrCls, a larger daily dose would have been necessary to maintain desired drug levels over the first 24 h of therapy. In the case of an altered CrCl (50 ml/min/1.73 m²), a 35-mg/kg daily dose could raise vancomycin levels to concentrations of >30 mg/liter within the first 24 to 48 h of infusion (Fig. 3). To demonstrate the importance of adequate maintenance doses for maintaining therapeutic exposures, the respective AUCs for these simulations of CrCl from 24 to 48 h were as follows: 50 ml/min, 811 mg · h/liter; 100 ml/min, 542 mg · h/liter; 150 ml/min, 387 mg · h/liter; 200 ml/min, 293 mg · h/liter; and 250 ml/min, 232 mg · h/liter. When lower CrCl values were simulated to determine doses to be infused over 24 h to maintain vancomycin concentrations within the range of 20 to 25 mg/liter, the simulations suggested the following requirements: 7 mg/kg over 24 h when the CrCl was 40 ml/min/1.73 m², 10 mg/kg over 24 h when the CrCl was 30 ml/min/1.73 m², and 14 mg/kg over 24 h when the CrCl was 40 ml/min/1.73 m².

Figure 4 describes the vancomycin concentrations resulting from various weight-based dosing infusions after an adequate 35-mg/kg loading dose to rapidly achieve a target concentration of 20 mg/liter. The simulations show that a dose of at least 35 mg/kg is required to maintain a therapeutic concentration for a patient with a CrCl of 100 ml/min/1.73 m². The respective AUCs for these simulations of CrCl from 24 to 48 h were as follows: 20 mg/kg, 362 mg · h/liter; 25 mg/kg, 419 mg · h/liter; 30 mg/kg, 475 mg · h/liter; 35 mg/kg, 532 mg · h/liter; and 40 mg/kg, 589 mg · h/liter.

DISCUSSION

This paper has provided a rational approach for optimized vancomycin dosing by continuous infusion in critically ill pa-

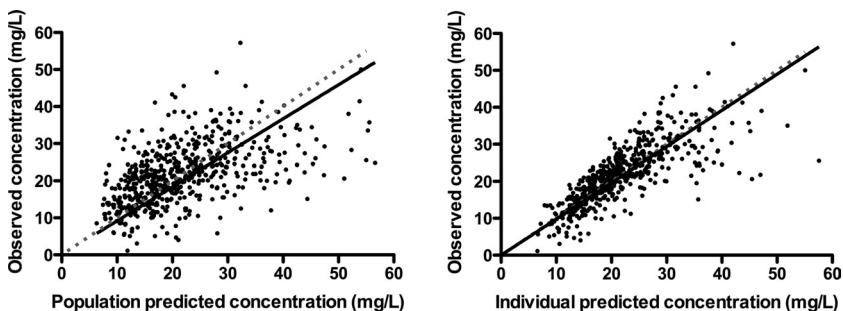


FIG. 1. Diagnostic plots for the final population pharmacokinetic covariate model. (Left) Observed concentrations versus the population predicted concentrations ($r^2 = 0.07$). (Right) Observed concentrations versus the individual predicted concentrations ($r^2 = 0.60$). The nonlinear regression line of fit is shown by the solid black line, and the line of $x = y$ is the gray dotted line.

tients and is the largest pharmacokinetic study on vancomycin in this setting. Our results show that a loading dose based on TBW is mandatory to rapidly achieve therapeutic concentrations and suggest that a minimum loading dose of 35 mg/kg is necessary to achieve target steady-state concentrations of 20 mg/liter or greater. To maintain this concentration, the dose to be administered by continuous infusion can be accurately calculated using data from CrCl. A daily dose of at least 35 mg/kg would be necessary to maintain steady-state drug levels in the therapeutic range. Such an approach to dosing will increase the likelihood of achieving vancomycin concentrations associated with improved antimicrobial activity and, potentially, positive clinical outcomes (15, 22).

Achieving pharmacokinetic/pharmacodynamic targets is likely to be very important for optimizing the clinical efficacy of vancomycin. Consensus supports the view that the pharmacokinetic-pharmacodynamic parameter best correlated with the efficacy of vancomycin is the AUC_{0-24} -to-MIC (AUC_{0-24}/MIC) ratio (8, 11, 29). In a retrospective study, Moise-Broder et al. (22) evaluated the relationship between AUC_{0-24}/MIC ratio and clinical outcomes in patients with MRSA pneumonia. The authors found that an AUC_{0-24}/MIC ratio of ≥ 350 was associated with clinical success and suggested an AUC_{0-24}/MIC ratio of ≥ 400 as a target predictive of optimal outcomes. On the basis of the results of this study and the frequency with which lung infections occur in critically ill patients, it has been

advocated that achieving this pharmacokinetic-pharmacodynamic target of AUC_{0-24}/MIC ratio of ≥ 400 should optimize clinical benefit (6). Although AUC_{0-24} is not routinely monitored in clinical practice, Jeffres et al. (14) have shown that trough concentrations from intermittent dosing are correlated with AUC and thus are regarded as an appropriate surrogate measure for the AUC_{0-24} and as the most practical method to monitor vancomycin dosing (26, 28). Some studies have successfully described use of a nomogram to guide continuous-infusion dosing (24).

We have shown that dosing to meet these targets needs to be individualized according to the patient's TBW and renal function. Data supporting the strong relationship between vancomycin volume of distribution and TBW have been described in various vancomycin pharmacokinetic studies, particularly in obese patients (1). Data supporting the importance of renal function on vancomycin clearance are also prominent (25). Augmented renal clearance is common in hyperdynamic critically ill patients and may increase the risk for subtherapeutic vancomycin exposure (27, 31). This population analysis extends upon these previous data and demonstrates how both TBW and CrCl explain a significant amount of the pharmacokinetic variability in critically ill patients.

Curiously, we did not observe an effect of the level of sickness severity on volume of distribution, as has previously been described for aminoglycosides (20). We believe that this may be due to the dominant contribution of TBW as well as the inherently larger volume of distribution of vancomycin (0.8 to

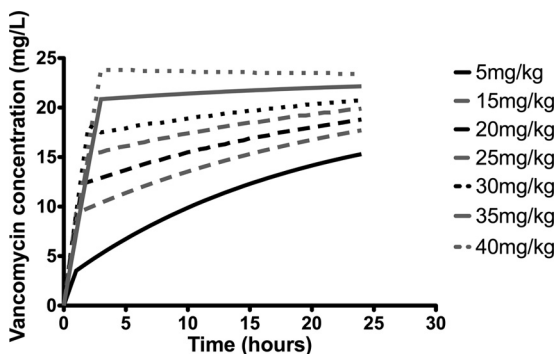


FIG. 2. The effect of loading dose on rapid attainment of target vancomycin concentrations. Different weight-based doses are simulated for a critically ill patient with a creatinine clearance of 100 ml/min/1.73 m², followed by administration as a 35-mg/kg/day continuous infusion.

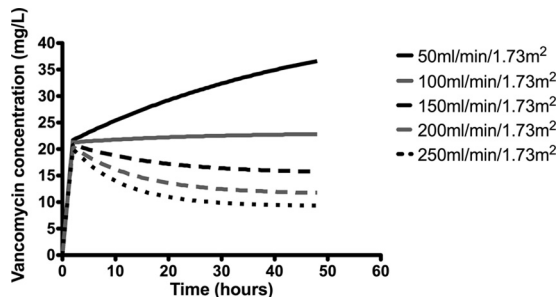


FIG. 3. The effect of creatinine clearance on vancomycin concentrations administered by continuous infusion (35 mg/kg per day after 35-mg/kg loading dose).

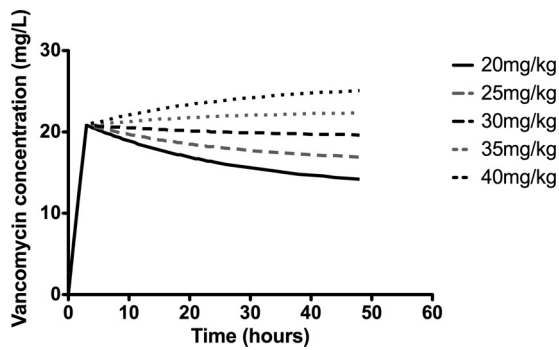


FIG. 4. The effect of different doses (mg/kg) on vancomycin concentrations administered by continuous infusion after a 35-mg/kg loading dose in a patient with a creatinine clearance of 100 ml/min/1.73 m².

1.4 liters/kg [19]) compared with that of aminoglycosides (~0.3 liter/kg [20]).

There are some limitations of our study. First, this modeling approach utilized sparse samples, such that we were not able to describe a two-compartment model, which mechanistically would be more in keeping with the pharmacokinetics of vancomycin. However, use of the program NONMEM for this modeling process is widely recognized to be robust for such analyses and the predictive performance of the model was deemed sufficient. Second, this was an analysis of retrospective data, which may have resulted in unforeseen errors in data collection. We believe that this effect would be very minor because of the use of continuous infusion of vancomycin and sampling after a pharmacokinetic steady state had been reached, in addition to the accuracy of the data collected on CrCl. Third, the suggested approach to dosing should be used only in patients who match the demographic and clinical characteristics of the enrolled cohort. Therefore, it cannot be used for patients requiring different types of renal replacement therapies and should be used with caution in obese patients and those with low creatinine clearances. Finally, the simulations suggest more aggressive doses than those that are typically prescribed, and therefore, any prospective validation study would need to closely monitor for potential vancomycin toxicities to confirm that these are not increased in frequency by this approach to dosing.

In conclusion, dose optimization of vancomycin by CI can be best accomplished using a rational approach that considers individual patient and disease characteristics. Specifically, TBW should be considered for initial dosing, as it is an accurate descriptor of volume of distribution of vancomycin. Maintenance dosing can then be guided by CrCl. Such an approach to administration of vancomycin by CI can increase the likelihood of achieving therapeutic concentrations and reduce the possibility of subtherapeutic drug exposure. Recommended loading and daily doses would result in insufficient drug concentrations during the early phase of sepsis, and higher doses should be used in this setting. We would advocate that a clinical study be undertaken to validate the findings of these simulations.

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