MAJOR ARTICLE

Relationship between Initial Vancomycin Concentration-Time Profile and Nephrotoxicity among Hospitalized Patients

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Background. Data suggest that higher doses of vancomycin can increase the risk of nephrotoxicity. No study has been undertaken to determine the pharmacodynamic index (ie, the area under the curve [AUC] or the trough value) that best describes the relationship between vancomycin exposure and onset of nephrotoxicity.

Methods. A retrospective study was conducted among patients who received vancomycin for a suspected or proven gram-positive infection during the period from 1 January 2005 through 31 December 2006 at Albany Medical Center Hospital. Patients were included in our study if they (1) were ⩾18 years old, (2) had an absolute neutrophil count of ⩾1000 cells/mm^3, (3) received vancomycin for >48 h, (4) had ⩾1 vancomycin trough level collected within 96 h of vancomycin therapy, and (5) had a baseline serum creatinine level of <2.0 mg/dL. Patients were excluded if they (1) had a diagnosis of cystic fibrosis, (2) received intravenous contrast dye within 7 days of starting vancomycin or during therapy, or (3) required vasopressor support during therapy. Demographics, comorbid conditions, and treatment data were collected. The highest observed vancomycin trough value within 96 h of initiation of vancomycin therapy and the estimated vancomycin AUC were analyzed as measures of vancomycin exposure. The vancomycin AUC value from 0 to 24 h at steady state (in units of mg × h/L) for each patient was estimated by use of the maximum a posteriori probability Bayesian procedure in ADAPT II. Nephrotoxicity was defined as an increase in serum creatinine level of 0.5 mg/dL or 50%, whichever was greater, following initiation of vancomycin therapy. Logistic and Cox proportional hazards regression models identified the vancomycin pharmacodynamic index that best describes the relationship between vancomycin exposure and toxicity.

Results. During the study period, 166 patients met the inclusion criteria. Both initial vancomycin trough values and 0–24-h at steady state AUC values were associated with nephrotoxicity in the bivariate analyses. However, the vancomycin trough value, modeled as a continuous variable, was the only vancomycin exposure variable associated with nephrotoxicity in the multivariate analyses.

Conclusions. The results indicate that a vancomycin exposure–toxicity response relationship exists. The vancomycin trough value is the pharmacodynamic index that best describes this association.

Emerging data suggest that maintaining vancomycin trough values of ⩾15 mg/L increases the risk of nephrotoxicity [1–3]. We recently reported that the vancomycin regimens (ie, ⩾4 g of vancomycin per day) that were used to achieve this higher trough value are associated with an elevated risk of nephrotoxicity [4]. Although these data suggest that high concentrations of vancomycin increase the risk of nephrotoxicity, to our knowledge, no study has definitively determined the pharmacodynamic index that best describes the relationship between vancomycin exposure and onset of nephrotoxicity. The aim of our study was to delineate the pharmacodynamic index that best describes that relationship. With advances in mathematical modeling, it is now possible with limited blood concentration data to estimate the vancomycin concentration-time profile of a given patient using Bayesian estimation techniques [5, 6]. Once exposure data for the population are available, the pharmacodynamic index (ie, the area under

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Table 1. Bivariate Analysis of the Relationship between the Vancomycin Exposure Profile and Nephrotoxicity

Antibiotic exposure profile	Patients with nephrotoxicity (n = 21)	Patients without nephrotoxicity (n = 145)	P
Initial vancomycin trough value, mean mg/L ± SD	14.6 ± 8.3	9.6 ± 5.1	.014
Initial vancomycin trough value ⩾9.9 mg/L	16 (76.2)	56 (38.6)	.001
$AUC_{0–24ss}$ value, mean mg × h/L ± SD	1318.4 ± 1147.2	898.5 ± 475.9	.11
$AUC_{0–24ss}$ value >1300 mg × h/L	7 (33.3)	20 (13.8)	.05

NOTE. Data are no. (%) of patients, unless otherwise noted. $AUC_{0–24ss}$, vancomycin area under the curve from 0 to 24 h at steady state; SD, standard deviation.

the curve [AUC] value or the trough value) associated with toxicity can be delineated. Identifying the minimum vancomycin exposure threshold associated with increased toxicity enables clinicians to design empirical dosing strategies that maximize the likelihood of achieving the critical pharmacodynamic target associated with efficacy while minimizing toxicity [7].

METHODS

Study design and population. A retrospective study was conducted among patients who received vancomycin for a suspected or proven gram-positive infection during the period from 1 January 2005 through 31 December 2006 at Albany Medical Center Hospital. During the study period, 1412 unique patients were treated with vancomycin for >48 h. Of these patients, 351 (25%) were randomly selected for review using the random selection function in SPSS, version 11.5 (SPSS).

The randomly selected patients were included in our study if they (1) were ⩾18 years old, (2) had an absolute neutrophil count of ⩾1000 cells/mm^3, (3) received vancomycin for >48 h, (4) had ⩾1 vancomycin trough level collected within 96 h of vancomycin therapy, and (5) had a baseline serum creatinine (S_{CR}) level of <2.0 mg/dL. Patients were excluded if they (1) had a diagnosis of cystic fibrosis, (2) received intravenous contrast dye within 7 days of starting vancomycin or during therapy, or (3) required vasopressor support during therapy.

For several reasons, we limited our study to patients' initial vancomycin trough values. First, it is difficult to establish a causal relationship between vancomycin trough values obtained over the course of therapy, especially those collected in close proximity to the nephrotoxic event. Because vancomycin is mainly eliminated by glomerular filtration, a decrease in renal function, whatever the cause, will increase the vancomycin serum concentration and confound the association between vancomycin serum concentrations and renal dysfunction. By limiting the analysis to the initial trough values, we improve our ability to determine whether a causal exposure-response relationship exists. Second, if a causal relationship between the initial vancomycin exposure profile and onset of nephrotoxicity is found, it will have important implications for clinical practice. On the basis of the initial vancomycin level, clinicians could make inferences about the toxicity potential of the regimen and adjust accordingly early in therapy.

Data. Patient data and microbiology data were extracted from medical records by a trained reviewer using a structured data instrument, as previously described elsewhere [4]. Treatment data included all antibiotics and concurrent nonantibiotic and nephrotoxic medications (eg, aminoglycosides, amphotericin, cyclosporine, and tacrolimus). Treatment data were collected 10 days before the start of vancomycin therapy until 72 h after therapy. All vancomycin levels (date, time, and relationship to next dose) were collected, and the highest initial trough concentration within 96 h of initiation of vancomycin therapy was documented.

There were no standardized vancomycin dosing practices at Albany Medical Center Hospital during the study period. During the study period, the American Thoracic Society and the Infectious Diseases Society of America guidelines for hospital-acquired, ventilator-associated, and healthcare-associated pneumonia were released, and these guidelines resulted in many clinicians adopting vancomycin trough concentrations in the therapeutic range of 15–20 mg/L for vancomycin, irrespective of source of infection [8]. This higher targeted trough range resulted in the use of higher vancomycin dosing regimens, and the dosing practices used to achieve these higher trough ranges were not uniform.

Initial vancomycin trough values were modeled 3 ways: as a continuous variable, a dichotomous variable (by use of a classification and regression tree [CART]–derived breakpoint), and a categorical variable (with initial vancomycin trough values of <10 mg/L, 10–15 mg/L, 15–20 mg/L, and >20 mg/L). The vancomycin trough values were dichotomized by use of CART [9], an analytical tool used to identify breakpoints within an ordinal or continuous variable, where the outcome of interest is distinctly different between the resulting groups. The breakpoint in vancomycin trough values maximizes the difference in nephrotoxicity, allowing the population to be divided into 2 groups: those with a high likelihood of nephrotoxicity and those with a low likelihood of nephrotoxicity.

The categorical variable comprised 4 trough strata drawn

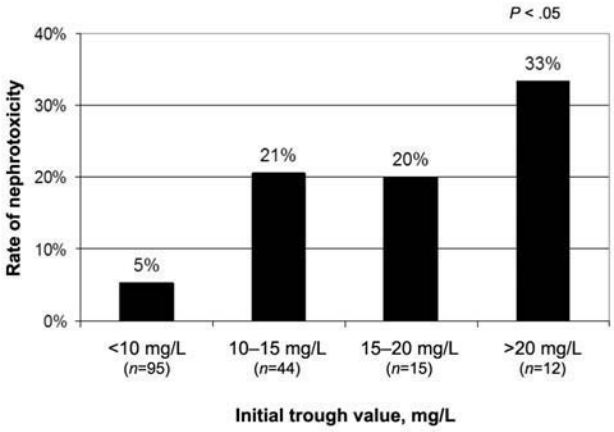

Figure 1. Bar graph showing the relationship between the initial vancomycin trough value and the rate of nephrotoxicity for the 166 patients who met the inclusion criteria.

from clinical practice to reflect subtherapeutic (<10 mg/L), therapeutic (10–20 mg/L), and supratherapeutic trough ranges (>20 mg/L). We further divided the therapeutic trough values into 2 groups (ie, 10–15 and 15–20 mg/L) to refine our analyses.

The vancomycin AUC value from 0 to 24 h at steady state ($AUC_{0–24ss}$) for each patient was estimated by a 2-compartment open vancomycin model [10–12]. In this model, vancomycin clearance was made proportional to creatinine clearance (CL_{CR}) plus an intercept term (CL_{int}); here, vancomycin clearance is defined as $CL_{slope} \times CL_{CR} + CL_{int}$, where CL_{slope} is the slope clearance, CL_{CR} is the creatinine clearance, and CL_{int} is the intercept of clearance. The mean parameter vector and full covariance matrix from this population pharmacokinetic model was embedded in the PRIOR subroutine of the ADAPT II package of programs by D'Argenio and Schumitzky [5]. The pharmacokinetic parameter values for each patient were estimated by use of the maximum a posteriori probability (MAP) procedure in ADAPT II: the volume of distribution in the central compartment (V_c), the intercompartment transfer rate constants (k_{12}, k_{21}), CL_{slope}, and CL_{int}. After the MAP-Bayesian step, the $AUC_{0–24ss}$ value (in units of mg × h/L) was estimated for each patient by dividing the vancomycin daily dose given during the first 24 h of therapy by vancomycin clearance ($CL_{slope} \times CL_{CR} + CL_{int}$). For the purposes of the analyses, the initial vancomycin $AUC_{0–24ss}$ value was modeled as a continuous variable and as a dichotomous variable (CART-derived breakpoint).

Outcomes data. Occurrence of nephrotoxicity was defined as an increase in the S_{CR} level of 0.5 mg/dL or 50%, whichever was greater, on at least 2 consecutive days during the period from initiation of vancomycin therapy to 72 h after completion of therapy [1–4, 13]. The time period associated with the above changes was recorded. The highest S_{CR} level observed within 72 h of completion of therapy was used to estimate the percent change in creatinine clearance (CL_{CR}) from baseline. Creatinine clearance was estimated by the Cockcroft-Gault formula [14].

Data analysis plan. For bivariate analyses, categorical variables were compared using Fisher's exact test, and continuous variables were compared using the Student's *t* or the Mann-Whitney *U* test. The CART technique was used to identify significant breakpoints in continuous clinical features that were associated with an increased proportion of nephrotoxicity [9].

The analyses examined both time to nephrotoxicity as well as toxicity occurrence. For the former, we employed stratified Kaplan-Meier analysis and Cox proportional hazards regression analysis. Occurrence of toxicity was evaluated by logistic regression analysis. All variables associated with nephrotoxicity in the bivariate analysis ($P < .2$) were considered for inclusion in the models. A stepwise approach was used to derive a parsimonious model, and variables remained in the final model if the associated *P* value was <.05. Adjusted odds ratios (aORs) were computed for variables in the final model. Potential confounders were put back into the model to assess their impact on the aORs. Effect modification was also assessed. All calculations were computed using SPSS, version 11.5 (SPSS), SAS, version 9.1.2 (SAS), and CART software (Salford Systems).

RESULTS

Of the 351 randomly selected patients, 166 met the inclusion criteria. The median baseline S_{CR} level was 0.8 mg/dL (interquartile range [IQR], 0.7–1.1 mg/dL). Only 9 (5.4%) of the 166 patients had a baseline S_{CR} level >1.5 mg/dL, and the highest observed baseline S_{CR} level was 1.8 mg/dL. The median baseline CL_{CR} value was 69.5 mL/min (IQR, 48.9–93.5 mL/min). Of these 166 patients, 21 (12.7%) experienced nephrotoxicity; the median peak S_{CR} level was 2.0 mg/dL (IQR, 1.6–3.0 mg/dL). Between the baseline value and the lowest value within 72 h

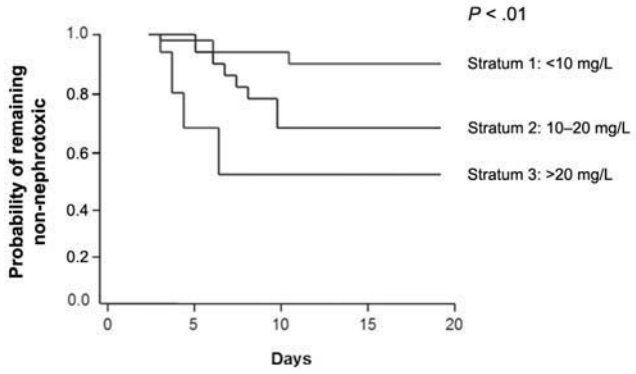

Figure 2. Stratified Kaplan-Meier analysis of time to nephrotoxicity for patients with initial vancomycin trough values of <10 mg/L (stratum 1, <10 mg/L), 10–20 mg/L (stratum 2, 10–20 mg/L), and >20 mg/L (stratum 3, >20 mg/L).

Table 2. Bivariate Comparison of Demographics, Comorbid Conditions, and Clinical Characteristics between Patients Who Experienced Nephrotoxicity and Those Who Did Not

Characteristic	Patients with nephrotoxicity (n = 21)	Patients without nephrotoxicity (n = 145)	P
Age, mean years ± SD	56.1 ± 15.4	55.8 ± 18.6	.94
Male sex	12 (57.1)	77 (53.1)	.73
Height, mean inches ± SD	66.6 ± 4.0	66.1 ± 4.1	.62
Total body weight, mean kg ± SD	92.5 ± 42.8	78.2 ± 22.4	.15
Weight ⩾101 kg	7 (33.3)	20 (13.8)	.05
Ideal body weight, mean kg ± SD	63.4 ± 10.6	62.3 ± 10.9	.66
Diabetes mellitus	9 (42.9)	43 (29.7)	.22
Heart failure	4 (19.0)	18 (12.4)	.40
Chronic obstructive pulmonary disease	5 (23.8)	22 (15.2)	.32
Hepatic dysfunction	0 (0)	3 (2.1)	.99
Decubitus ulcers	1 (4.8)	11 (7.6)	.64
HIV infection	1 (4.8)	9 (6.2)	.99
Previous surgery	5 (23.8)	28 (19.3)	.57
History of healthcare exposure	9 (42.9)	59 (40.7)	.85
Length of stay prior to initiation of antibiotics, median days (IQR)	3 (0–6.25)	2 (0–7)	.76
Residence in intensive care unit at onset	14 (66.7)	56 (38.6)	.02
Baseline creatinine clearance, mean mL/min ± SD	66.5 ± 22.6	73.3 ± 29.7	.31
APACHE II score at initiation of antibiotics, mean ± SD	12.0 ± 6.4	10.9 ± 6.2	.45
Coadministration of aminoglycosides	1 (4.8)	16 (11.0)	.70
Coadministration of nonaminoglycoside nephrotoxic agents	5 (23.8)	39 (26.9)	.77
Indication for therapy			
Bloodstream infection	5 (23.8)	30 (20.7)	.56
Central nervous system	2 (9.5)	7 (4.8)	
Infective endocarditis	0 (0)	4 (2.8)	
Intra-abdominal	1 (4.8)	5 (3.4)	
Osteomyelitis	2 (9.5)	5 (3.4)	
Prophylaxis	0 (0)	4 (2.8)	
Respiratory tract	7 (33.3)	32 (22.1)	
Skin and soft tissue	4 (19.0)	41 (28.3)	
Unknown	0 (0)	11 (7.6)	
Urinary tract	0 (0)	6 (4.1)	
Presence of MRSA in clinical culture	6 (28.6)	43 (29.7)	.92

NOTE. Data are no. (%) of patients, unless otherwise indicated. APACHE, Acute Physiology and Chronic Health Evaluation; HIV, human immunodeficiency virus; IQR, interquartile range; MRSA, methicillin-resistant *Staphylococcus aureus*; SD, standard deviation.

of completion of therapy among patients who had a nephrotoxic event, the CL_{CR} value decreased a median of 48.3% (IQR, 31.6%–67.1%). The median time to nephrotoxicity was 6 days (IQR, 5–10 days), and the median duration that the S_{CR} level remained 50% greater than baseline was 7 days (IQR, 3–20 days). Vancomycin therapy was discontinued in 13 (62.0%) of the 21 patients who experienced nephrotoxicity.

The mean initial vancomycin trough value was significantly higher among patients who experienced nephrotoxicity, compared with those who did not (table 1). Using CART, it was found that patients with initial trough values of ⩾9.9 mg/L had a significantly higher incidence of nephrotoxicity, compared with patients with initial trough values of <9.9 mg/L (22.2% vs. 5.3% of patients; $P = .001$). Although the difference was not statistically significant, a higher mean vancomycin $AUC_{0–24ss}$ value was observed among patients who experienced nephrotoxicity, compared with patients who did not. However, patients with an $AUC_{0–24ss}$ value of ⩾1300 mg × h/L had a significantly higher incidence of nephrotoxicity, compared with patients with an $AUC_{0–24ss}$ value of <1300 mg × h/L (25.9% vs. 10.1% of patients; $P = .05$).

An exposure-response relationship was observed between the initial vancomycin trough value and the occurrence of nephrotoxicity (figures 1 and 2). The occurrence of nephrotoxicity significantly increased as the initial trough value increased (figure 1). These results are consistent with the stratified Kaplan-

Table 3. Logistic Regression Model for the Occurrence of Nephrotoxicity

Parameter	aOR (95% CI)	*P*
Empiric trough value[a]	1.13 (1.05–1.21)	.001
Residence in ICU	3.25 (1.18–8.97)	.023

NOTE. CI, confidence interval; ICU, intensive care unit.

[a] The adjusted odds ratio (aOR) for the initial vancomycin trough value reflects the increased likelihood of nephrotoxicity for each 1-unit change in the initial vancomycin trough value.

Meier time-to-nephrotoxicity analysis (figure 2), which found a significant difference in nephrotoxicity between initial vancomycin trough strata.

The demographic and clinical variables significantly associated with an occurrence of nephrotoxicity in the bivariate analysis were a weight of ⩾101 kg (CART-derived breakpoint) and residence in the intensive care unit (ICU) (table 2). The relationship between the vancomycin trough categories and nephrotoxicity was stratified by residence in ICU, weight of ⩾101 kg, concomitant use of aminoglycosides, and concomitant use of nonaminoglycoside nephrotoxins. There was insufficient evidence from these stratified analyses to suggest the presence of substantive confounding or effect modification (data not shown).

Variables independently associated with the occurrence of nephrotoxicity in the multivariate logistic regression analysis were empiric trough value (aOR, 1.13; 95% confidence interval, 1.05–1.21; $P = .001$) and ICU residence (aOR, 3.25; 95% confidence interval, 1.18–9.98; $P = .02$) (table 3). The initial vancomycin trough value was modeled continuously, such that the aOR was representative of a 1-point increase in vancomycin trough concentration. A graphic representation of the logistic regression–derived nephrotoxicity probability functions is shown in figure 3. For patients in the ICU, the predicted probability of nephrotoxicity was >20% for patients with initial vancomycin trough values of >10 mg/L. In contrast, the predicted probability of nephrotoxicity exceeded 20% for non-ICU patients when initial vancomycin trough values were >20 mg/L. Consistent with the logistic regression, the Cox model demonstrated that the empiric initial vancomycin trough value, residence in the ICU at start of therapy, and a weight of ⩾101 kg were independently associated with time to nephrotoxicity (table 4).

DISCUSSION

Early in its life cycle, vancomycin was associated with significant adverse effects, including infusion-related toxicities, nephrotoxicity, and ototoxicity [15–17], many of which were largely attributed to impurities in the original formulations. Modern fermentation methods were thought to minimize the onset of these toxicities, particularly nephrotoxicity [15–17]. This notion was supported by animal model data that demonstrated the safety of the "purer" formulations at therapeutic doses [18].

A number of studies assessed the relationship between vancomycin and nephrotoxicity [19–23] after the purification of vancomycin. Although the observed rates of nephrotoxicity were highly variable, vancomycin-induced nephrotoxicity was considered to be infrequent (ie, 5%–7% of patients treated with vancomycin) and reversible [15–17]. Although several evaluations noted vancomycin nephrotoxicity rates as high as 35%, particularly among patients with vancomycin trough values of ⩾10 mg/L, the associations between vancomycin exposure and nephrotoxicity were largely attributed to baseline differences in disease severity and concomitant nephrotoxin use across trough groups [19–23]. In light of these data, several opinion papers questioned the need to monitor vancomycin levels, because of the perception that there was no relationship between exposure and nephrotoxicity [24–26].

The recent recommendation to maintain higher vancomycin trough levels has spurred renewed interest in this question [8], and several recent publications have noted a significant association [1–4]. However, these studies were plagued by some of the confounding issues and biases that daunted earlier investigations. For example, 10 of the 11 patients in the nephrotoxicity group in the study by Hidayat et al. [1] received amphotericin B, tobramycin, or tacrolimus. In addition, there were many patients who received concomitant vasopressor support and intravenous contrast dye in the nephrotoxicity group in the study by Jefferies et al. [2]. Cognizant of these issues, we recently designed a study that examined the relationship between empiric vancomycin dosing and nephrotoxicity among patients with a S_{CR} level of <2.0 mg/L at the start of vancomycin therapy and no recent history of receipt of intravenous contrast dye or vasopressor therapy [4]. Overall, the rate of nephrotoxicity was significantly higher among patients receiving ⩾4 g of vancomycin daily than it was among patients receiving <4

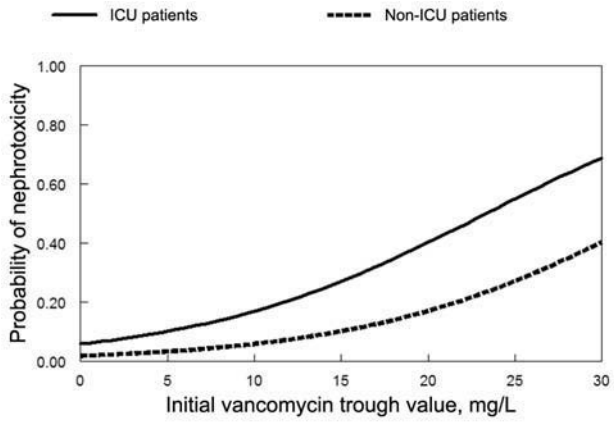

Figure 3. Graphic representation of the logistic regression–derived nephrotoxicity probability functions. ICU, intensive care unit.

Table 4. Cox Proportional Hazards Model for Time to Nephrotoxicity

Parameter	aHR (95% CI)	*P*
Empiric trough value[a]	1.13 (1.06–1.20)	<.001
Residence in ICU	2.67 (1.071–6.56)	.035
Weight ⩾101 kg	3.17 (1.18–8.53)	.022

NOTE. CI, confidence interval; ICU, intensive care unit.

[a] The adjusted hazard ratio (aHR) for the initial vancomycin trough value reflects the increased hazards of nephrotoxicity for each 1-unit change in the initial vancomycin trough value.

g of vancomycin daily, and the probability of nephrotoxicity increased as a function of duration of therapy. In addition, this observed relationship did not appear to be modulated by concurrent nephrotoxin use or disease severity [4].

Although our previous study suggests a causal relationship between vancomycin exposure and toxicity, it is well known that a given dosing regimen will provide a range of concentration-time profiles for a given patient population [4]. The intent of this study was to solidify the linkage between vancomycin exposure and onset of nephrotoxicity by delineating the definitive concentration-time profile associated with an increased probability of nephrotoxicity [1–3].

In our evaluation, both initial trough and AUC_{0-24ss} values were associated with nephrotoxicity in the bivariate analysis. However, the initial vancomycin trough value was the only predictor of nephrotoxicity in the multivariate analyses. Interestingly, rather than a single trough threshold predicting risk, an exposure-response relationship appears to exist (figure 3). In both the stratum-specific vancomycin trough analysis (figure 1) and the stratified Kaplan-Meier analysis (figure 2), the probability of nephrotoxicity increased as a function of the initial trough value. These findings were supported by the multivariate analyses. The initial vancomycin trough value, expressed as a continuous variable, was the only exposure variable independently associated with nephrotoxicity, and the aORs reflect the increased likelihood of nephrotoxicity for each 1-unit change in the initial vancomycin trough value. A graphic representation of the logistic regression–derived nephrotoxicity probability functions (figure 3) highlights this exposure-response relationship. Furthermore, the incidence of nephrotoxicity increased as both a function of intensity and duration of exposure as evident by the results of the stratified Kaplan-Meier and Cox proportional hazards analyses. These findings are largely consistent with recent publications and support the current notion that highly intensive, prolonged vancomycin therapy increases the risk of nephrotoxicity [1–4].

Our results also elucidate why it is that, in recent clinical trials, very little nephrotoxicity was observed among patients undergoing vancomycin therapy for complicated skin and soft-tissue infection [27–29]. Such patients rarely resided in the ICU, generally had trough values of <10 mg/L, and typically received therapy for <10 days. Our results indicate that this population was at a <5% risk for nephrotoxicity. Vancomycin-induced nephrotoxicity primarily occurred among patients undergoing intensive or prolonged therapy. This is consistent with the observed vancomycin-induced nephrotoxicity rate in the daptomycin-versus-vancomycin *Staphylococcus aureus* bacteremia and endocarditis clinical study, in which over 30% of patients had a 25% reduction in CL_{CR} level from baseline. In this study, patients typically had trough values of >10 mg/L and were on vancomycin therapy for >10 days [30, 31].

The observed results are biologically plausible [32–38]. Recent animal data suggest that vancomycin is an oxidative stressor in proximal renal tubular cells [32–37]. In addition, the use of antioxidants and cilastatin has been found to protect against vancomycin-induced kidney damage, further supporting the notion that vancomycin is an oxidative stressor in the proximal renal tubular cells [33, 35–37]. Human data also suggest vancomycin toxicity involves both the proximal tubules and the medullary region [38].

Residence in the ICU and a weight of ⩾101 kg were also associated with the occurrence of nephrotoxicity. As shown in figure 3, patients who resided in the ICU had an elevated baseline risk of nephrotoxicity independent of vancomycin exposure (higher intercept on graph for ICU vs. non-ICU patients), and this risk is amplified substantially by the addition of vancomycin therapy. This increased risk is most likely secondary to the greater physiologic impairment and disease severity observed among patients who resided in the ICU. We speculate that the relationship between a body weight of ⩾101 kg and nephrotoxicity was due to the more intensive vancomycin exposure profile observed among patients at the higher end of the weight continuum. The mean ($\pm$ standard deviation) vancomycin trough values were 12.5 $\pm$ 7.3 mg/L among patients weighing ⩾101 kg and 9.8 $\pm$ 5.4 mg/L among patients weighing <101 kg ($P = .03$). The higher trough values were not primarily due to a higher dose of vancomycin; the mean daily vancomycin dose used for patients who weighed ⩾101 kg was not significantly different from that for patients who weighed <101 kg ($P = .5$). Rather, the higher trough values were secondary to the differences in V_c. The mean V_c value, standardized by actual body weight, estimated in the MAP procedure in ADAPT II was significantly lower for patients weighing <101 kg than it was for patients weighing ⩾101 kg ($P < .001$). This indicates that V_c did not increase proportionally with weight and that V_c accounted for the higher trough values observed among patients weighing ⩾101 kg. Further studies are still needed to delineate the exact cause of this association, but our results suggest that it is due to disproportional changes in V_c resulting in more intensive exposure profiles.

In conclusion, the results of our study suggest that a van-

comycin exposure–toxicity response relationship exists and that the vancomycin trough value was the pharmacodynamic index that best described this association. Our findings have important clinical implications. First, the results highlight the prognostic value of the initial trough value in forecasting the probability of nephrotoxicity. Maintaining higher trough concentrations, especially >20 mg/L, was found to engender an unacceptable risk of nephrotoxicity. Second, because the exposure targets for efficacy are rather high for vancomycin (with a ratio of AUC_{0-24ss} to minimum inhibitory concentration of 350–400), the results suggest that it will be difficult to achieve the exposure endpoint associated with success for serious methicillin-resistant *S. aureus* infections with higher minimum inhibitory concentrations without subjecting the patient to an undue risk of nephrotoxicity. As with all observational, single-center studies, our findings need to be interpreted cautiously and verified with a multicenter, prospective trial.

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