

## Larger Vancomycin Doses (at Least Four Grams per Day) Are Associated with an Increased Incidence of Nephrotoxicity<sup>∇</sup>

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Recent guidelines recommend vancomycin trough concentrations between 15 and 20 mg/liter. In response, some clinicians increased vancomycin dosing to  $\geq 4$  g/day. Scant data are available regarding toxicities associated with higher vancomycin doses. The purpose of this study was to examine vancomycin-associated nephrotoxicity at  $\geq 4$  g/day. To accomplish the study objective, a cohort study among a random selection of patients receiving vancomycin or linezolid between 2005 and 2006 was performed. Patients were included if they (i) were  $\geq 18$  years of age, (ii) were nonneutropenic, (iii) were on therapy for  $> 48$  h, (iv) had baseline serum creatinine levels of  $< 2.0$  mg/dl, (v) did not suffer from cystic fibrosis, and (vi) had no intravenous contrast dye within the previous 7 days. For drug exposure, three treatment strata were created: standard vancomycin dose ( $< 4$  g/day), high vancomycin dose ( $\geq 4$  g/day), and linezolid. Nephrotoxicity was defined as a serum creatinine increase of 0.5 mg/dl or 50%, whichever was greater, after therapy initiation. Stratified Kaplan-Meier analysis and Cox modeling were used to compare times to nephrotoxicity across groups. During the study, 246 patients on vancomycin (26 patients taking  $\geq 4$  g/day and 220 patients taking  $< 4$  g/day) and 45 patients on linezolid met the criteria. A significant difference in nephrotoxicity between patients receiving  $\geq 4$  g vancomycin/day, those receiving  $< 4$  g vancomycin/day, and those receiving linezolid was noted (34.6%, 10.9%, and 6.7%, respectively;  $P = 0.001$ ), and Kaplan-Meier analysis identified significant differences in time to nephrotoxicity for the high-vancomycin-dose cohort compared to those for patients taking the standard dose and linezolid. In the Cox model, patients taking  $\geq 4$  g vancomycin/day, a total body weight of  $\geq 101.4$  kg, estimated creatinine clearance of  $\leq 86.6$  ml/min, and intensive care unit residence were independently associated with time to nephrotoxicity. The data suggest that higher-dose vancomycin regimens are associated with a higher likelihood of vancomycin-related nephrotoxicity.

Methicillin-resistant *Staphylococcus aureus* (MRSA) now accounts for over 50% of *S. aureus* infections in the health care setting (23). In addition, the recent emergence of community-associated MRSA has caused the treatment paradigm to shift for serious community-associated staphylococcal infections (31). While new drugs such as daptomycin and linezolid (8) are welcome therapeutic alternatives, vancomycin remains the first-line therapy for MRSA infection (19).

There is growing concern that vancomycin may provide sub-optimal therapy for severe MRSA infection, and research conducted during the past several years has begun to shed light on this issue (8, 19). Some data suggest this may be related to strains with the *agr* group II genotype (12, 21, 22, 26–28, 30), while other data point to increases in MICs or, in the clinical parlance, “MIC creep.” In addition, several new strains have emerged: glycopeptide-intermediate *S. aureus* (GISA), hetero-resistant strains, and fully vancomycin-resistant isolates (25). Furthermore, the exposures needed to optimize vancomycin microbiological kill are considerably larger than previously thought, a problem exacerbated by MIC creep (20, 22, 30).

These issues are now well understood by expert guideline development committees. Guidelines for hospital-acquired

pneumonia (HAP), ventilator-associated pneumonia (VAP), and health care-associated pneumonia (HCAP) have recommended initial vancomycin doses of 15 mg/kg every 12 h, with plasma concentration monitoring (1). Trough vancomycin concentrations between 15 and 20 mg/liter were deemed appropriate. Since the publication of HAP/VAP/HCAP guidelines, these concentration targets have been adopted by many clinicians as the therapeutic range for all patients treated with vancomycin irrespective of infection source.

Because the recommended vancomycin dose and schedule of 1 g every 12 h are unlikely to reach target trough concentrations, many clinicians increased vancomycin dosing to  $\geq 4$  g per day. This practical application of the guidelines is rational given the higher MICs and the target exposures required to optimize microbiological activity (20).

Against this backdrop of expert recommendation and clinical application, two components of optimal antimicrobial chemotherapy are important: first, therapy should be *efficacious*; second, therapy should be *nontoxic*. A potentially serious adverse effect associated with vancomycin therapy is nephrotoxicity (2, 4, 7, 9, 11, 13, 17, 24, 29; S. L. Pestotnik, J. F. Lloyd, and J. P. Burke, presented at the 35th Annual Meeting of the Infectious Diseases Society of America, 1997). Many vancomycin-treated patients are quite ill. A large number will take up residence in intensive care unit (ICUs). It was noted that hospitalized patients who developed even modest alterations in renal function (e.g., 0.5-mg/dl increase in serum creatinine [SCr] levels) experienced significantly increased risk of mor-

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tality, hospital length of stay, and hospital costs even after adjustment for age, gender, chronic kidney disease, and morbidity upon admission (3). Specifically, an increase in SCr of  $\geq 0.5$  mg/dl was associated with a 6.5-fold (95% confidence interval, 5.0- to 8.5-fold) increase in the odds of death, a 3.5-day increase in the length of hospital stay, and nearly 7,500 dollars in excess hospital costs. Consequently, therapies that result in nephrotoxicity may have dire consequences for patients, especially in the ICU environment.

In the 1950s, vancomycin was administered as a relatively impure fermentation product that was so brown that the drug garnered the nickname "Mississippi mud" (18). This preparation was associated with a relatively high rate of nephrotoxicity. Modern fermentation methods provided a very pure vancomycin preparation, and the nephrotoxicity rate was reduced dramatically (18). However, there are almost no safety data for the very pure product when administered at high doses, particularly in the  $\geq 4$ -g/day range. To date, limited data suggest that higher vancomycin trough values ( $\geq 15$  mg/liter) are associated with higher rates of nephrotoxicity. In these investigations, it is difficult to establish a casual relationship between vancomycin trough values of  $\geq 15$  mg/liter and nephrotoxicity. Since vancomycin is eliminated in the main by glomerular filtration, a decrease in renal function from any cause will increase vancomycin serum concentrations and make an association between higher vancomycin serum concentrations and renal dysfunction difficult to discern (14, 15). It was the intent of this investigation to examine the toxic impact of increasing vancomycin dosing into the range of  $\geq 4$  g/day. We also included patients treated with linezolid, a drug not known to cause nephrotoxicity, in the analysis to serve as a control group and as a measure of the underlying level of nephrotoxicity in the study population unrelated to vancomycin.

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#### MATERIALS AND METHODS

**Study design and population.** A retrospective cohort study was conducted among patients who received vancomycin for a suspected or proven gram-positive infection between 1 January 1 2005 and 31 December 31 2006 at Albany Medical Center Hospital. With the advent of the HAP/VAP/HCAP guidelines, some clinicians empirically increased vancomycin dosing to improve the probability of attaining vancomycin trough concentrations in the 15- to 20-mg/liter range (1). During the study period, 1,412 unique patients had vancomycin ordered for  $>48$  h, and 115 unique patients had linezolid ordered for  $>48$  h. Of these patients, the random selection function of SPSS was used to select a random sample for chart review. Of the 1,412 patients on vancomycin, 351 (25%) were randomly selected; of the 115 linezolid patients, 86 (75%) were randomly selected.

The randomly selected patients were included in the analysis if they (i) were  $\geq 18$  years old, (ii) had an absolute neutrophil count of  $\geq 1,000$  cells/mm<sup>3</sup>, (iii) had received either vancomycin or linezolid for  $>48$  h, and (iv) had a baseline SCr value of  $<2.0$  mg/dl. Patients were excluded if they (i) had a diagnosis of cystic fibrosis, (ii) received intravenous contrast dye within 7 days of the start of either vancomycin or linezolid treatment or during therapy, or (iii) were receiving vasopressors at start of vancomycin or linezolid treatment.

Patients that met the eligibility criteria were divided into three groups for the analysis: *standard* vancomycin dose ( $<4$  g per day), *high* dose ( $\geq 4$  g per day), or linezolid.

**Data.** Data were extracted from patients' medical records by a trained reviewer using a structured data instrument. Data elements included age, sex, height, weight, laboratory values, medical history and comorbidities, concomitant medications received, health care institution exposure for greater than 72 h within

180 days of hospital admission, length of hospitalization prior to vancomycin or linezolid administration (total and ICU), hospital unit residence at start of vancomycin or linezolid therapy, illness severity at start of vancomycin or linezolid therapy (as calculated by the Acute Physiological and Chronic Health Evaluation [APACHE-II] score) (16), microbiologic data, indication for vancomycin or linezolid use, treatment data (date, time, dosing regimen, and duration) for vancomycin and linezolid, and vancomycin levels (date, time, and temporal relationship to vancomycin dose).

The presence of the following comorbid conditions was documented: diabetes mellitus heart failure (New York Heart Association classes I to IV), chronic obstructive pulmonary disease, hepatic dysfunction, human immunodeficiency virus infection, decubitus ulcers (stages II to IV), malignancy, and surgery requiring  $>48$  h of hospitalization in the 30 days prior to admission. The APACHE-II score was defined as the worst physiological score that was calculated during the first 24 h of vancomycin or linezolid therapy.

SCr values were collected beginning 5 days prior to the start of targeted antibiotic therapy until 72 h after therapy completion. Creatinine clearance (CrCl) was estimated by the Cockcroft-Gault formula (6).

Treatment data included all antibiotics and concurrent nonantibiotic medications (date, time, dose, route, and duration) administered to the patient while receiving targeted antibiotic therapy. Specifically, we collected data on known nephrotoxic agents (e.g., aminoglycosides, amphotericin, cyclosporine, and tacrolimus). Treatment data were collected for the following time period: 10 days prior to the start of targeted antibiotic until 72 h after therapy completion. All vancomycin levels (date, time, and relationship to next dose) were collected, and the peak initial trough (within 96 h of initiation of vancomycin therapy) and peak primary trough (after 96 h of vancomycin therapy) were documented.

Microbiologic data were collected from 5 days prior to the start of the vancomycin or linezolid to 7 days after initiation of the target antibiotic. Positive cultures at different periods of time were not recorded. Susceptibility testing was done by the Kirby-Bauer method and was interpreted according to Clinical and Laboratory Standards Institute (CLSI) guidelines (5).

The indication for vancomycin or linezolid therapy was determined from assessments of microbiology reports and/or clinical description by the physician in the medical record. For the purpose of analysis, indication for vancomycin or linezolid therapy was divided into the following categories: bloodstream infection not complicated by infective endocarditis, central nervous system infection, infective endocarditis, intra-abdominal infection, osteomyelitis, prophylaxis, respiratory tract infection, skin and soft tissue infections, and unknown.

**Outcome data.** In the primary analysis, occurrence of nephrotoxicity was defined as an increase in SCr levels of 0.5 mg/dl or an increase of 50%, whichever was greater, on at least two consecutive days during the period from initiation of vancomycin or linezolid therapy to 72 h after the completion of therapy. The time period associated with the above-described changes was recorded. The highest SCr level observed within 72 h of completion of therapy was used to estimate the percent change in CrCl from the baseline. In the secondary analysis, nephrotoxic events that occurred within 48 h of initiation of therapy were excluded. Patients that experienced an elevation in SCr levels within the first 48 h of therapy were excluded because we believe that this increase was most likely related to sepsis rather than drug exposure.

**Data analysis plan.** For bivariate analyses, categorical variables were compared by the Pearson chi-square or Fisher's exact test, and continuous variables were compared by Student's *t* or Mann-Whitney *U* test. For comparisons involving more than two groups, the Pearson chi-square test was used for categorical variables, and analysis of variance or the Kruskal-Wallis test was used for continuous variables. Classification and regression tree (CART) analysis was used to identify significant breakpoints in continuous clinical features that were associated with an increased proportion of nephrotoxicity (32). Both CART-derived dichotomous variables and continuous variables were evaluated in the multivariate analyses.

The analyses examined both time to nephrotoxicity and toxicity occurrence. For the former, we employed stratified Kaplan-Meier analysis and Cox proportional hazards regression to evaluate the role of other patient covariates. Two Cox proportional hazards regression models were evaluated. In the first model, treatment (high vancomycin dose versus standard vancomycin dose versus linezolid) was entered as strata (stratified Cox proportional hazards regression). In the second model, treatment was entered as a covariate. Toxicity occurrence was evaluated by logistic regression analysis.

All covariates that differed between treatment groups ( $P \leq 0.2$ ) or that were associated with nephrotoxicity ( $P \leq 0.2$ ) in the bivariate analysis were considered for model entry into the above-mentioned multivariate analyses. The variable with the greatest log likelihood was entered into the model first, and the likelihood ratio test was used to determine the appropriateness of

TABLE 1. Comparison of demographics, comorbid conditions, and clinical characteristics across treatment strata<sup>a</sup>

Demographic or clinical characteristic	Value for group			<i>P</i> value <sup>e</sup>	Value for patients with:		<i>P</i> value <sup>h</sup>
	High vancomycin dose <sup>b</sup>	Standard vancomycin dose <sup>c</sup>	Linezolid <sup>d</sup>		Nephrotoxicity <sup>f</sup>	No nephrotoxicity <sup>g</sup>	
Mean (SD) age (yr)	51.9 (16.1)	57.8 (17.9)	57.4 (18.6)	0.3	60.2 (17.0)	56.7 (18.0)	0.3
No. (%) of male patients	20 (76.9)	113 (51.4)	28 (62.2)	0.03	21 (58.3)	140 (54.9)	0.7
Mean (SD) height (in.)	67.5 (3.6)	66.0 (4.4)	66.7 (4.3)	0.2	66.2 (4.3)	66.2 (4.3)	1.0
Mean (SD) total body wt (kg)	86.9 (40.8)	78.4 (22.6)	80.0(21.7)	0.3	87.5 (36.1)	78.3 (22.4)	0.3
No. (%) of patients with total body wt of $\geq 101.4$ kg	5 (19.2)	33 (15.0)	7 (15.6)	0.9	12 (33.3)	33 (12.9)	0.002
Mean (SD) ideal body wt (kg)	64.3 (10.7)	60.1 (10.9)	62.0 (11.8)	0.2	61.9 (10.9)	60.6 (11.1)	0.5
No. (%) of patients with diabetes mellitus	7 (26.9)	72 (32.7)	12 (26.7)	0.6	15 (41.7)	76 (29.8)	0.2
No. (%) of patients with heart failure	1 (3.8)	34 (15.5)	7 (15.6)	0.3	9 (25.0)	33 (12.9)	0.05
No. (%) of patients with COPD	3 (11.5)	37 (16.8)	8 (17.8)	0.8	7 (19.4)	41 (16.1)	0.6
No. (%) of patients with hepatic dysfunction	3 (1.4)	0 (0)	1 (2.2)	0.8	0 (0)	4 (1.6)	0.5
No. (%) of patients with decubitus ulcers	0 (0)	19 (8.6)	3 (6.7)	0.3	3 (8.3)	19 (7.5)	0.9
No. (%) of patients with human immunodeficiency virus	1 (3.8)	10 (4.5)	0 (0)	0.3	1 (2.8)	10 (3.9)	0.7
No. (%) of patients with malignancy	3 (11.5)	49 (22.3)	8 (17.8)	0.4	6 (16.7)	54 (21.2)	0.5
No. (%) of patients with prior surgery	3 (11.5)	58 (26.4)	11 (24.4)	0.3	9 (25.0)	63 (24.7)	1.0
No. (%) of patients with history of health care exposure	18 (40.0)	12 (46.2)	91 (41.4)	0.9	15 (41.7)	106 (41.6)	1.0
Median (range) length of stay prior to initiation of antibiotics (days)	1 (0.38–4)	2 (0–6.75)	4 (0.5–9.5)	0.3	2 (0–6)	2 (0–7)	0.7
No. (%) of patients in ICU at onset	18 (69.2)	83 (37.7)	20 (44.4)	0.008	22 (61.1)	99 (38.8)	0.01
Mean (SD) baseline CrCl level (ml/min)	78.8 (26.7)	70.1 (29.0)	70.9 (27.2)	0.3	60.3 (22.4)	72.5 (29.0)	0.02
No. (%) of patients with baseline CrCl level of $\leq 86.6$ ml/min	18 (69.2)	162 (73.6)	33 (73.3)	0.9	32 (88.9)	181 (71.0)	0.02
Mean (SD) APACHE-II score at initiation of antibiotics	11.8 (5.4)	10.8 (6.3)	11.9 (5.2)	0.4	11.9 (5.8)	11.0 (6.1)	0.4
No. (%) of patients with coadministration of aminoglycosides	7 (26.9)	21 (9.5)	8 (17.8)	0.02	4 (11.1)	32 (12.5)	0.8
No. (%) of patients with coadministration of nonaminoglycoside nephrotoxic agents	7 (26.9)	47 (21.4)	6 (13.3)	0.3	9 (25.0)	51 (20.0)	0.5
No. (%) of patients with indication for therapy:				<0.001			0.8
Bloodstream infection	4 (15.4)	44 (20.0)	11 (24.4)		10 (27.8)	49 (19.2)	
Central nervous system infection	6 (23.1)	7 (3.2)	0 (0)		2 (5.6)	11 (4.3)	
Infective endocarditis	0 (0)	6 (2.7)	0 (0)		0 (0)	6 (2.4)	
Intra-abdominal infection	0 (0)	0 (0)	8 (3.6)		3 (8.3)	13 (5.1)	
Osteomyelitis	1 (3.8)	8 (3.6)	2 (4.4)		2 (5.6)	9 (3.5)	
Prophylaxis	1 (3.8)	10 (4.5)	0 (0)		2 (5.6)	9 (3.5)	
Respiratory tract infection	12 (46.2)	43 (19.5)	14 (31.1)		9 (25.0)	60 (23.5)	
Skin and soft tissue infection	0 (0)	67 (30.5)	3 (6.7)		6 (16.7)	64 (25.1)	
Unknown	2 (7.7)	14 (6.4)	3 (6.7)		1 (2.8)	18 (7.1)	
Urinary tract infection	0 (0)	13 (5.9)	4 (8.9)		1 (2.8)	16 (6.3)	
No. (%) of patients with presence of MRSA in clinical culture	5 (19.2)	57 (25.9)	12 (26.7)	0.7	8 (22.2)	66 (25.9)	0.6
Mean (SD) initial vancomycin trough level (mg/dl)	18.4 (7.9)	9.1 (4.5)	NA	<0.0001	14.6 (8.3)	9.6 (5.1)	<0.001
Mean (SD) primary vancomycin trough level (mg/dl)	18.9 (9.4)	12.4 (5.0)	NA	0.04	18.5 (7.4)	12.0 (4.9)	<0.001

<sup>a</sup> COPD, chronic obstructive pulmonary disease; NA, not applicable.

<sup>b</sup> Dose of  $\geq 4$  g per day ( $n = 26$ ).

<sup>c</sup> Dose of  $< 4$  g per day ( $n = 220$ ).

<sup>d</sup>  $n = 45$ .

<sup>e</sup> *P* values for comparisons between treatment groups.

<sup>f</sup>  $n = 36$ .

<sup>g</sup>  $n = 255$ .

<sup>h</sup> *P* values for comparisons of patients with nephrotoxicity to those without.

model expansion. This ratio was defined as twice the log-likelihood difference between the base and the expanded models evaluated against a chi-square distribution with the appropriate number of degrees of freedom. The *P* value criterion for expansion was  $< 0.05$ . For all analyses, *P* values of  $< 0.05$  were considered to be significant for two-tailed tests. All calculations were performed with SYSTAT for windows (version 11.0) and CART software (Salford Systems, San Diego, CA).

## RESULTS

Of 351 randomly selected vancomycin patients, 246 met inclusion criteria: 26 received  $\geq 4$  g/day, and 220 received  $< 4$  g/day. Of 86 randomly selected linezolid patients, 45 met inclusion criteria. The demographics, comorbid conditions, and

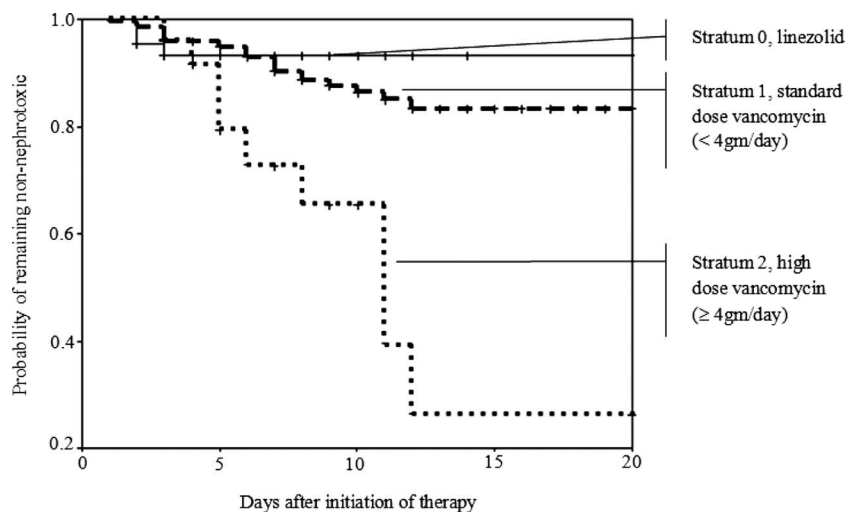


FIG. 1. Stratified Kaplan-Meier analysis of time to nephrotoxicity for patients treated with linezolid (stratum 0), those treated with a standard dose of vancomycin (<4 g/day) (stratum 1), and those treated with a high dose of vancomycin ( $\geq 4$  g/day) (stratum 2). The overall differences are significant ( $P < 0.0001$  by Mantel test). Pairwise analysis demonstrated that strata 0 and 1 are not different. Strata 0 and 2 and strata 1 and 2 are significantly different. For the pairwise analyses,  $\alpha$  decay was performed by Bonferroni adjustment.

population clinical characteristics are presented in Table 1. Overall, the groups were well matched, but sex, ICU residence at treatment initiation, concomitant aminoglycoside use, and indication for treatment differed significantly across strata. There were no significant differences in disease severity, as measured by APACHE II score, across strata. Of the 246 vancomycin patients, 168 patients (20 in the group receiving  $\geq 4$  g/day vancomycin and 148 in the group receiving <4 g/day vancomycin) had an initial vancomycin trough level (collected within 96 h of initiation of vancomycin therapy), and 74 patients (7 in the group receiving  $\geq 4$  g/day vancomycin and 67 in the group receiving <4 g/day vancomycin) had a primary vancomycin trough level (collected after 96 h of vancomycin therapy). The initial and primary mean vancomycin trough values were both significantly higher in the group receiving a high vancomycin dose than in the group receiving a standard vancomycin dose (Table 1).

There were 36 episodes of nephrotoxicity. The median time to onset of nephrotoxicity was 7 days (interquartile range, 4 to 11 days). The median peak SCr level observed within 72 h of completion of therapy was 2.1 mg/dl (interquartile range, 1.7 to 2.9 mg/dl), and the median change in peak SCr level from baseline SCr level was 0.95 mg/dl (interquartile range, 0.60 to 1.70 mg/dl). Of the 36 episodes of nephrotoxicity, three patients had a peak SCr that exceeded 6.0 mg/dl. The median decrease between baseline CrCl levels and the lowest CrCl level observed within 72 h of completion of therapy was 45.6% (interquartile range, 33.8% to 63.4%). A significant difference in nephrotoxicity was noted between patients receiving  $\geq 4$  g vancomycin/day, those receiving <4 g vancomycin/day, and those receiving linezolid (34.6%, 10.9%, and 6.7%, respectively;  $P = 0.001$ ). When patients that experienced nephrotoxicity within the first 48 h of treatment were excluded (six patients [three patients each in the groups receiving the standard vancomycin dose and linezolid]), a similar but more pronounced difference in nephrotoxicity was observed between patients receiving  $\geq 4$  g vancomycin/day, those receiving <4 g

vancomycin/day, and those receiving linezolid (34.6%, 9.7%, and 2.4%, respectively;  $P < 0.001$ ). In a subset analysis that included only patients that resided in the ICU, a significant difference in nephrotoxicity was noted between patients receiving  $\geq 4$  g vancomycin/day, those receiving <4 g vancomycin/day, and those receiving linezolid (38.9%, 15.7%, and 10.0%, respectively;  $P = 0.04$ ).

Results of the stratified Kaplan-Meier time-to-nephrotoxicity analysis are shown in Fig. 1. The differences between treatment strata (high-dose vancomycin versus standard-dose vancomycin versus linezolid) are statistically significant ( $P < 0.0001$ ). Pairwise comparisons demonstrated significant differences between standard- and high-dose vancomycin treatments as well as between linezolid and high-dose vancomycin treatments. These differences remained significant after  $\alpha$  decay by a Bonferroni adjustment. The differences between linezolid and standard-dose vancomycin treatments were not significant. Results of the secondary stratified Kaplan-Meier time-to-nephrotoxicity analysis (analysis that excluded patients that experienced a nephrotoxic event within 48 h of initiation of treatment) were consistent with the primary analysis.

The relationships between clinical features and occurrence of nephrotoxicity are presented in Table 1. Using CART, significant breakpoints were identified for weight and baseline CrCl levels. Clinical features associated with nephrotoxicity by bivariate analysis included a weight of  $\geq 101.4$  kg, heart failure, ICU stay at initiation of treatment, baseline CrCl level, and baseline CrCl level of  $\leq 86.6$  ml/min. The only variable that differed ( $P \leq 0.2$ ) between both treatment strata and associated with nephrotoxicity was ICU stay at initiation of treatment. The concomitant use of aminoglycosides was not associated with nephrotoxicity. Among the high-dose vancomycin group, no cases of nephrotoxicity were observed among patients who received an aminoglycoside.

Multivariate analyses of time to nephrotoxicity and toxicity occurrence were conducted by Cox proportional hazards modeling (stratified and nonstratified) and logistic regression. The

TABLE 2. Final stratified Cox proportional hazards model for time to occurrence of nephrotoxicity<sup>a</sup>

Parameter	Hazard ratio	95% Confidence interval	P value
Wt of $\geq 101.4$ kg	3.65	2.52–5.28	<0.0001
CrCl of $\leq 86.6$ ml/min	3.66	2.12–6.32	0.020
ICU at initiation of treatment	1.95	1.38–2.76	0.050

<sup>a</sup> The final log likelihood was  $-140.97$ , and the treatment stratum *P* value was  $<0.0001$  (Mantel test). All covariates were dichotomous. The overall *P* value was  $<0.0001$ .

stratified Cox model demonstrated that total patient weight of  $\geq 101.4$  kg, estimated CrCl level of  $\leq 86.6$  ml/min, and ICU residence at the start of therapy each independently influenced the time to nephrotoxicity (Table 2). With model building, we entered the weight breakpoint covariate first. The log likelihood was  $-146.47$ . When the CrCl breakpoint was added, the log likelihood was  $-142.87$ . Finally, with ICU stay at the initiation of therapy, the final log likelihood was  $-140.96$ . Consistent with the stratified Kaplan-Meier analysis, the stratified Cox proportional hazards analysis demonstrated a highly significant relationship between treatment strata and time to nephrotoxicity (treatment stratum *P* value of  $<0.0001$  [Mantel test]). No other variables were significant in the final model.

In a second Cox proportional hazards regression model, treatment was dichotomized to  $\geq 4$  g vancomycin per day and  $\geq 4$  g nonvancomycin per day based on the results of the stratified Kaplan-Meier analysis and entered as a covariate. Consistent with the stratified Cox model,  $\geq 4$  g vancomycin per day, total patient weight of  $\geq 101.4$  kg, and estimated CrCl level of  $\leq 86.6$  ml/min each independently influenced the time to nephrotoxicity (Table 3). With model building, treatment with  $\geq 4$  g vancomycin per day was entered into the model first. The log likelihood was  $-181.95$ . When the weight breakpoint covariate was added, the log likelihood was  $-176.66$ . The final covariate added to the model was the CrCl breakpoint, and the final log likelihood was  $-173.30$ . No other variable was entered into the final model. ICU residence at the start of therapy was not found to significantly modulate time to nephrotoxicity; ICU residence at the start of therapy was of borderline significance (final log likelihood of  $-171.88$  and associated *P* value of 0.09).

In the logistic regression analysis, the differences among strata were identical to that of the stratified Kaplan-Meier analysis described above: differences between vancomycin strata and between linezolid and high-dose vancomycin treatment were noted, yet no differences between linezolid and standard-dose vancomycin treatments were noted. Based on these observations, treatment was dichotomized to  $\geq 4$  g van-

TABLE 3. Final Cox proportional hazards model for time to occurrence of nephrotoxicity<sup>a</sup>

Parameter	Hazard ratio	95% Confidence interval	P value
Vancomycin at $\geq 4$ g per day	4.37	2.96–6.45	<0.001
Wt of $\geq 101.4$ kg	3.44	2.40–4.93	0.001
CrCl level of $\leq 86.6$ ml/min	3.27	1.92–5.56	0.03

<sup>a</sup> The final log likelihood was  $-173.33$ . All covariates were dichotomous. The overall *P* value was  $<0.0001$ .

TABLE 4. Final logistic regression model for the occurrence of nephrotoxicity<sup>a</sup>

Parameter	Adjusted odds ratio	95% Confidence interval	P value
Vancomycin at $\geq 4$ g per day	4.4	1.7–11.8	0.003
Wt of $\leq 101.4$ kg	3.4	1.5–7.9	0.004
CrCl level of $\leq 86.6$ ml/min	3.7	1.2–11.5	0.020
ICU residence	2.2	1.1–4.6	0.045

<sup>a</sup> The overall *P* value (likelihood ratio test) was  $<0.0001$ .

comycin per day and  $\geq 4$  g vancomycin per day for the logistic regression. The final logistic regression model is presented in Table 4. The Hosmer-Lemeshow statistic had a *P* value of 0.6, indicating a good fit.

## DISCUSSION

Clinicians are increasingly concerned about MRSA as an infectious threat in the hospital and now in the community (23, 31). For many decades, vancomycin has been the drug of choice for the treatment of MRSA (18, 19). Recent research suggests that clinical response rates have become suboptimal, particularly for patients with HAP/VAP/HCAP. This has been attributed to a number of factors including poor epithelial lining fluid penetration, MIC creep, and the emergence of GISA, hetero-GISA, and fully vancomycin-resistant staphylococci (8, 12, 19–22, 25–28, 30).

Investigation of the relationship between drug exposure and the ultimate clinical and microbiological outcomes resulted in a recommendation that the ratio of the area under the concentration-time curve (AUC) for 24 h to MIC for vancomycin needs to be between 350 (clinical outcome) and 400 (microbiological outcome) (20). These exposures are hard to achieve with standard vancomycin dosing (15 mg/kg every 12 h), particularly at MICs exceeding 1.0 mg/liter. Consequently, the HAP/VAP/HCAP guidelines recommend this starting regimen but then recommend achieving trough concentrations of between 15 and 20 mg/liter (1).

The likelihood of achieving targeted trough values is low (circa 15%) with this dose and schedule, even with an estimated CrCl level as low as 40 ml/min (10). Consequently, some clinicians have taken to frontloading the vancomycin regimen. Doses of  $\geq 4$  g/day have sometimes been employed in our institution. Since little was known about the toxicity profile of vancomycin at these higher exposures (14, 15), this investigation described the relationships between vancomycin dose and nephrotoxicity occurrence and vancomycin dose and the time to nephrotoxicity.

A significant relationship between high-dose vancomycin and both occurrence and time to nephrotoxicity was observed in this analysis. Importantly, we employed linezolid as a control for non-vancomycin-related causes of nephrotoxicity, as this drug does not have nephrotoxicity as a known part of its toxicity profile. For the group receiving high doses of vancomycin, 9 of 26 (34.6%) patients experienced an event, and all events occurred by day 12. For the group receiving a standard dose of vancomycin, 24 of 220 patients (10.9%) experienced an event, and similarly, all events occurred by day 12. Only 2 of 45 linezolid group patients (6.7%) demonstrated evidence of

nephrotoxicity as defined here, and these events occurred before day 4. This implies that nephrotoxicity due to other confounders, such as septic shock or other nephrotoxins, tended to occur earlier in the course of therapy (linezolid group), while vancomycin-related toxicity occurred later (by day 12).

The results of the stratified Kaplan-Meier analysis and multivariate analyses demonstrated a highly significant relationship between vancomycin dose and the time to nephrotoxicity. We also found that estimated CrCl levels of less than 86.6 ml/min, weights greater than 101.4 kg, and ICU residence also modulated the time to nephrotoxicity, with heavier patients, patients with poor renal function, and patients in ICU all contributing to greater nephrotoxicity.

These covariates make clinical sense. The resulting drug exposure (AUC) for any fixed dose of vancomycin will increase as the renal function deteriorates. Also, we saw that heavier weight had an impact on the time to nephrotoxicity, and we did not see this effect when ideal body weight was used. This implies that dosing from total (including fat) mass will increase the dose if dosing is weight based and, therefore, increase the vancomycin AUC, thus shortening the time to event. Residence in the ICU implies greater physiologic impairment and also makes clinical sense as a modulator of the time to nephrotoxicity. When these variables were entered into the logistic regression model, they all remained significant predictors of the probability of nephrotoxicity.

In summary, the data suggest that higher-dose vancomycin regimens are related to a higher likelihood of vancomycin-related nephrotoxicity exacerbated by weight, estimated CrCl, and ICU residence. It is important that this study found an association between vancomycin doses of  $\geq 4$  g/day and nephrotoxicity, and these data may not be generalizable to the every-day clinician, given the current rarity of giving such high doses of vancomycin in "the real world." This investigation was retrospective and, as such, is primarily suggestive and cautionary. The findings should be verified with a prospective randomized, double-blind trial. Furthermore, such a trial would need to identify the actual concentration-time profile of vancomycin in individual patients in order to solidify the linkage between exposure and toxicity. It should also be noted that this has importance for the issue of clinical and microbiological response. As the targets for exposure relative to the MIC (ratio of AUC for 24 h to MIC) are rather high for this drug (350 to 400), standard vancomycin doses will be unlikely to achieve the exposure goal and provide optimal outcomes for the patient, particularly when vancomycin MICs exceed 1 mg/liter (20). Obviously, higher doses will increase the likelihood of good clinical and microbiological results but perhaps not without the added burden of higher rates of nephrotoxicity.

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