

# Pharmacodynamic Characteristics of Nephrotoxicity Associated With Vancomycin Use in Children

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**Background.** Limited studies incorporating population-based pharmacokinetic modeling have been conducted to determine pharmacodynamic indices associated with nephrotoxicity during vancomycin exposure in children.

**Methods.** A retrospective cohort analysis was conducted from September 2003 to December 2011 at 2 hospitals. Nephrotoxicity was defined as an increase in serum creatinine concentration (SCr) by  $\geq 0.5$  mg/dL, or  $\geq 50\%$  increase in baseline SCr, either persisting for  $\geq 2$  consecutive days. A 1-compartment model with first-order kinetics was used in NONMEM 7.2 to estimate trough concentrations ( $C_{\min}$ ) and area under the curve over 24 hours (AUC). Univariate, classification and regression tree (CART), and multivariate analyses were conducted to identify factors contributing to nephrotoxicity.

**Results.** The analyses included 680 pediatric subjects with 1576 vancomycin serum concentrations. Based on univariate analysis, median  $C_{\min}$  (14.2 [interquartile range, IQR, 7.1–25.4] vs 8.4 [IQR, 5.5–12.4] mcg/mL;  $P = .001$ ) and AUC (544 [IQR, 359–801] vs 378 [IQR, 304–494];  $P < .001$ ) were significantly higher in the nephrotoxic group compared with the non-nephrotoxic group. Using CART, we discovered that subjects with doses  $\geq 60$  mg/kg per day and AUC  $> 1063$  mg-h/L had a significantly higher occurrence of nephrotoxicity ( $P = .005$ ). Adjusting for intensive care unit stay and concomitant nephrotoxic drugs, steady-state vancomycin  $C_{\min} \geq 15$  mcg/mL (adjusted odds ratio [aOR], 2.5; 95% confidence interval [CI], 1.1–5.8;  $P = .028$ ) and AUC  $\geq 800$  mg-h/L (aOR, 3.7; 95% CI, 1.2–11.0;  $P = .018$ ) were associated with increased risk of nephrotoxicity.

**Conclusions.** Our study describes the pediatric exposure-nephrotoxicity relationships for vancomycin. Vancomycin  $C_{\min} \geq 15$  mcg/mL and AUC  $\geq 800$  mg-h/L in children are independently associated with a  $> 2.5$ -fold increased risk of nephrotoxicity and may provide justification for use of alternative antibiotics in selected situations.

**Key words.** nephrotoxicity; pediatrics; pharmacodynamic; pharmacokinetics; vancomycin.

Vancomycin, a bactericidal glycopeptide antibiotic, is the treatment of choice for certain methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Observations of increasing vancomycin minimum inhibitory concentrations (MICs) in MRSA that are still interpreted as “susceptible,” associated with apparent poor clinical responses, has led to the use of higher doses of vancomycin in adults [1–5]. The area under the curve over 24 hours (AUC) to MIC ratio (AUC/MIC) is the pharmacodynamic (PD) index that

best predicts the efficacy of vancomycin [6]. A study involving adult patients with *S aureus* lower respiratory infections reported that an AUC/MIC  $\geq 400$  was associated with a statistically significant improved clinical response and microbiological eradication compared with an exposure below this level [7]. In addition, AUC/MIC  $\geq 400$  best correlates to serum trough concentrations ( $C_{\min}$ ) of 15–20 mcg/mL, and doses up to 3–4 g/day may be necessary to achieve this AUC/MIC target in adults with normal

renal function [1, 8]. In a recent large, 2-center study in children, doses of 60–70 mg/kg per day, calculated using a population-based pharmacokinetic (PK) model with Monte Carlo simulation, could be used to treat children infected by pathogens whose MIC's were  $\leq 2$  mg/L, to achieve an AUC/MIC  $\geq 400$  in 75% of subjects. At this dosage, the predicted  $C_{\min}$  was noted to be only 8–9 mcg/mL [9, 10].

Not unexpectedly, higher vancomycin dosages maybe associated with an increase in nephrotoxicity [11–16]. Studies in adults suggest increasing rates of nephrotoxicity with escalating doses of vancomycin to achieve the  $C_{\min}$  of 15–20 mcg/mL [12–14, 16]. The vancomycin exposure-nephrotoxicity response in adults is best predicted by initial vancomycin  $C_{\min} \geq 9.9$  mcg/mL and doses  $>4$  grams/day [11, 12].

Studies of vancomycin serum trough concentrations in children with respect to nephrotoxicity are limited, but an association between serum trough concentrations  $\geq 15$  mcg/mL and nephrotoxicity has been reported [15, 17]. Previous pediatric studies have not incorporated population-based modeling using post hoc Bayesian analysis to evaluate the exposure-response relationship between vancomycin exposure and nephrotoxicity. In particular, the vancomycin AUC has not been examined in the context of achieving a specific AUC/MIC target in exposure-toxicity studies in children, although an AUC/MIC of 400 (compared with a  $C_{\min}$  of 15–20 mcg/mL) has been demonstrated to be a more achievable target in children [9, 10, 18]. The primary objective of this study was to determine the PK indexes (including  $C_{\min}$  and AUC) that best predict nephrotoxicity in children receiving vancomycin.

## METHODS

### Study Design

This retrospective cohort analysis was conducted in children who received vancomycin from September 2003 to December 2011 at 2 pediatric hospitals. Miller Children's Hospital (MCH) is a community-based, tertiary care, teaching hospital with 249 beds (34 pediatric intensive care, 69 neonatal intensive care, 94 general pediatrics, and 52 hematology/oncology beds). Rady Children's Hospital of San Diego (RCHSD) is a tertiary care, teaching hospital with 308 beds (44 pediatric intensive care, 49 neonatal intensive care, 177 general medical/surgical, and 38 hematology/oncology beds). This study was approved by the institutional review boards at each institution with the use of a waiver of informed consent for retrospective, deidentified data collection and analysis. Subjects were included if they: (1) were 3 months to 21 years of age; (2) received vancomycin for  $\geq 48$  hours; and (3) had normal baseline serum creatinine

(SCr) as defined by age at the start of vancomycin therapy (see Supplementary Table 1) [19, 20]. Subjects were excluded if they received dialysis or certain concomitant medications that are associated with nephrotoxicity, including amphotericin B, methotrexate, ifosfamide, cyclosporine, and tacrolimus.

Subject demographic and microbiologic data (eg, cultures, MIC) were collected from the electronic medical records (Epic Systems Corporation at MCH and Chartmaxx at RCHSD) and pharmacy records. Concurrent medications (including all anti-infectives, vasopressors, diuretics, and contrast dye) received 2 days before initiation of vancomycin were recorded. All vancomycin regimens (ie, date, time, dosing regimen, and duration) were documented using flowsheets that pharmacists used to conduct therapeutic drug monitoring. In addition, SCr concentration values were recorded daily from the first day of (or the day before initiation of vancomycin therapy) to 72 hours after therapy completion or until discharge (whichever was sooner). The serum concentrations of vancomycin in all subjects were determined by hospital laboratory assays available at each site [10].

### Data Analysis

The methodologies for the population-based PK analyses have been described previously [10]. Using the first-order conditional estimation subroutine and the interaction option in NONMEM 7.2, a 1-compartment model with first-order kinetics was used to estimate Bayesian post hoc values for volume of distribution (Vd), clearance (CL), AUC, and  $C_{\min}$ . The AUC (mg-h/L) was calculated by 24-hour dose (mg/day)  $\div$  CL (L/h); and steady-state  $C_{\min}$  was determined by the intermittent short infusion model with a 1-h infusion time (Dose =  $[(C_{\min})(CL)(\text{tin})(1 - e^{-k\tau})]/[(1 - e^{-kt_{\min}})(e^{-kt_{\min}})]$ , where  $\text{tin}$  = infusion time,  $\tau$  = dosing interval,  $k$  = elimination rate constant, and  $t_{\min}$  = time to  $C_{\min}$  as calculated from the end of infusion).

The primary endpoint was the onset of nephrotoxicity and was defined as an SCr increase of  $\geq 0.5$  mg/dL, or a  $\geq 50\%$  increase in baseline SCr, on at least 2 consecutive days, as has been previously defined in other vancomycin studies [12, 15, 25]. Analyses of patient demographics were summarized by descriptive statistics using SPSS version 21 (IBM, Chicago, IL). For univariate analyses, categorical variables were compared using Pearson  $\chi^2$  test, and continuous variables were compared using the Student's  $t$  test. Initial steady-state (assumed to occur by a timepoint defined as  $>3.3$  half-lives of vancomycin) factors (including  $C_{\min}$ , AUC, and mg/kg per day doses) achieved within the first 72 hours were dichotomized using classification and regression tree (CART). Using some variables significantly

associated with nephrotoxicity in the univariate analyses ( $P < .05$ ) and CART, specific factors were then categorized (ie,  $C_{\min} \leq 9.9$ , 10–14.9 mcg/mL, 15–19.9 and  $\geq 20$  mcg/mL; AUC  $< 800$  and  $\geq 800$  mg-h/L; and dose  $< 60$  and  $\geq 60$  mg/kg per day) and analyzed using multivariate logistic regression modeling. 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), which were adjusted for pediatric intensive care unit (PICU) stay and concurrent use of nephrotoxic drugs, were computed for variables in the final multivariate model [15]. Stratified Kaplan-Meier analysis was used to examine time to nephrotoxicity. The nonparametric, 2-tailed Spearman's rank correlation coefficient was calculated to determine the statistical dependence between AUC and  $C_{\min}$ .

## RESULTS

In total, 1698 subjects were screened and 1018 were excluded (see Supplementary Figure 1). The remaining 680 subjects had a total of 1576 vancomycin serum concentrations used in the population-based PK modeling. Nineteen subjects had multiple vancomycin treatment courses that were accounted for separately.

Demographic variables, including median age 6.7 years, weight 23 kg, and baseline SCr 0.38 mg/dL, were not statistically significant between subjects with ( $n = 45$ ) and

without ( $n = 635$ ) nephrotoxicity (Table 1). However, there was a statistically significant increase in the proportion of subjects who experienced nephrotoxicity and either (1) received concurrent nephrotoxic agents (ie, loop diuretics, vasopressors, aminoglycosides, contrast dye, and intravenous acyclovir) ( $P = .001$ ) or (2) stayed in the PICU ( $P < .001$ ) (Table 1). In addition, the median number of days of vancomycin therapy was significantly higher in those with toxicity compared with those who did not demonstrate toxicity (8 vs 4 days, respectively;  $P < .001$ ).

Nine models were created to characterize Vd and CL (see Supplementary Table 2). Only age, SCr, and weight were independent covariates with respect to CL and weight was an independent covariate with respect to Vd in both univariate and multivariate analyses. These covariates were used in the final model to produce post hoc Bayesian estimates for CL, Vd,  $C_{\min}$ , and AUC (see Supplementary Table 3). In the final model, minimization and the covariance step were successful. The median post hoc Bayesian estimates of Vd and CL on the first day of vancomycin therapy were 0.63 L/kg and 0.12 L/kg per hour respectively, for our study population, and both were not statistically significant between subjects with and without nephrotoxicity. The post hoc Bayesian estimates for Vd and CL were similar to the median bootstrap analysis values and were within the 95% confidence intervals (CIs) obtained from the bootstrap analysis (see Supplementary Table 4).

**Table 1.** Univariate Analysis of Demographics Overall and Between Subjects With or Without Nephrotoxicity

	Overall N = 680	With Nephrotoxicity n = 45	Without Nephrotoxicity n = 635	P Value
Median age (IQR), years	6.7 (2.2–13.7)	5.1 (1.5–14.3)	6.8 (2.4–13.6)	.605
<1, no. (%)	88 (12.9)	10 (22.2)	78 (12.3)	–
1 to <2, no. (%)	65 (9.6)	1 (2.2)	64 (10.1)	–
2 to <12, no. (%)	305 (44.9)	19 (42.2)	286 (45.0)	–
$\geq 12$ , no. (%)	222 (32.6)	15 (33.3)	207 (32.6)	–
Median weight (IQR), kg	23.1 (12.8–46.7)	23.4 (12.9–42.4)	23 (12.8–47.3)	.573
Median ideal body weight (IQR), kg	23.4 (12.8–38.6)	21.2 (12.0–37.1)	23.8 (12.8–38.6)	.508
Median body surface area (IQR), m <sup>2</sup>	0.9 (0.6–1.4)	0.9 (0.6–1.3)	0.9 (0.6–1.4)	.525
Median body mass index (IQR), kg/m <sup>2</sup>	17.6 (15.6–21.0)	17.4 (15.6–22.0)	17.6 (15.6–20.9)	.932
Race/Ethnicity				.579
Hispanic, no. (%)	247 (36.3)	16 (35.6)	231 (36.3)	–
White, no. (%)	90 (13.2)	6 (13.3)	84 (13.2)	–
African-American, no. (%)	42 (6.2)	2 (4.4)	40 (6.3)	–
Asian, no. (%)	14 (2.1)	2 (4.4)	12 (1.9)	–
Other/Unknown, no. (%)	287 (42.2)	19 (42.2)	268 (42.2)	–
Male gender, no. (%)	361 (53.1)	20 (44.4)	341 (53.7)	.229
Intensive care unit stay, no. (%)	271 (39.9)	32 (71.1)	239 (37.6)	<.001
Concurrent use of nephrotoxic agents, no. (%)	264 (38.8)	28 (62.2)	236 (37.2)	.001
Median baseline serum creatinine (IQR), mg/dL	0.4 (0.3–0.5)	0.3 (0.2–0.6)	0.4 (0.3–0.5)	.380
Mean empiric vancomycin dose $\pm$ SD (IQR), mg/kg per day	46.7 $\pm$ 11.6 (39.8–57.2)	50.2 $\pm$ 11.8 (43.5–60.2)	46.4 $\pm$ 11.6 (39.7–59.6)	.033
Every 6 h, no. (%)	281 (41.3)	18 (40.0)	263 (41.4)	–
Every 8 h, no. (%)	343 (50.4)	26 (57.8)	317 (49.9)	–
Every 12 h, no. (%)	50 (7.4)	0 (0)	50 (7.9)	–
Every 16–24 h, no. (%)	6 (0.9)	1 (2.2)	5 (0.8)	–
Median duration of vancomycin therapy (IQR), days	4 (3–7)	8 (6–11)	4 (3–7)	<.001

Abbreviations: IQR, interquartile range; SD, standard deviation.

Using univariate analyses, we noted that the median  $C_{min}$  and AUC were significantly higher in the nephrotoxic vs nonnephrotoxic groups (14.2 vs 8.4 mcg/mL [ $P = .001$ ] and 544 vs 378 mg-h/L [ $P < .001$ ], respectively) (Figure 1, A and B). There was a significant positive correlation between nephrotoxicity and high initial steady-state vancomycin  $C_{min}$  ( $P < .001$ ; Figure 2). We also noted a significant positive correlation between doses  $\geq 60$  mg/kg per day compared with doses  $< 60$  mg/kg per day (14.4% vs 5.3%, respectively;  $P = .001$ ). The incidence of nephrotoxicity in those with steady-state vancomycin  $C_{min} \geq 15$  mcg/mL and doses  $\geq 60$  mg/kg per day were 17% (n = 117) and

14.4% (n = 97), respectively. Using univariate logistic regression, we noted that the mean steady-state vancomycin trough concentration, AUC, and dose were significantly higher among patients who experienced nephrotoxicity compared with those who did not (Table 2). It is also noteworthy that 10%, 33%, and 57% of subjects who achieved AUC  $\geq 400$ , 800, and 1000 mg-h/L, respectively, experienced nephrotoxicity. The AUC was significantly correlated to  $C_{min}$  (Spearman's coefficient = 0.963;  $P < .001$ ).

Classification and regression tree analysis was used to identify 2 subgroups in the initial population of 680 patients (see Supplementary Figure 2). The first dichotomization was steady-state AUC  $> 1063$  mg-h/L, which had a significantly higher incidence of nephrotoxicity ( $P = .013$ ). For subjects with AUC  $> 1063$  mg-h/L, the second dichotomization was steady-state dosing of  $\geq 60$  mg/kg per day, in which subjects experienced nephrotoxicity significantly more than those who received steady-state dosing of  $< 60$  mg/kg per day ( $P = .005$ ). According to our CART analysis, AUC seems to be a factor predictive of nephrotoxicity, as do, to a lesser degree, initial daily doses. Furthermore, significantly more subjects with nephrotoxicity, compared with those without, received concurrent use of nephrotoxic agents (62.2% vs 37.2%;  $P = .001$ ) and stayed in the intensive care unit (71.1% vs 37.6%;  $P < .001$ ). After adjusting for PICU stay and concurrent use of nephrotoxic drugs, we discovered that steady-state vancomycin  $C_{min} \geq 15$  mcg/mL (aOR, 2.5; 95% CI, 1.1–5.8;  $P = .028$ ) and AUC  $\geq 800$

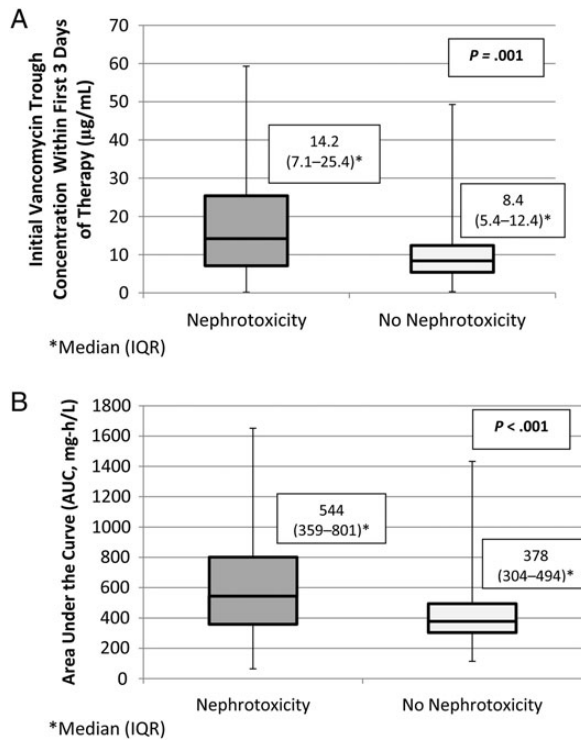


Figure 1. (A) Univariate analysis for steady-state vancomycin trough concentration within the first 3 days of therapy (µg/mL). (B) Univariate analysis for steady-state, area under the curve over 24 hours.

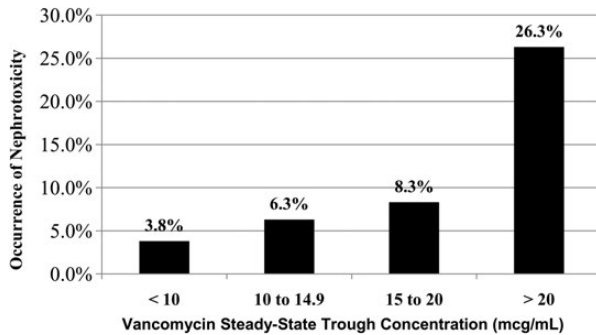


Figure 2. Relationship between steady-state vancomycin trough concentration and the occurrence of nephrotoxicity.

Table 2. Univariate Analysis of Vancomycin Exposure Profile and Nephrotoxicity<sup>a</sup>

Antibiotic Exposure Profile	Patients With Nephrotoxicity (n = 45)	Patients Without Nephrotoxicity (n = 635)	P
Steady-state trough concentration, median (IQR) in mg/L	14 (7–25)	8 (5–12)	.001
$\geq 15$ mcg/mL <sup>b</sup>	20 (17)	97 (83)	$< .001$
$< 15$ mcg/mL <sup>b</sup>	25 (4)	538 (96)	
Steady-state AUC over 24 h, median (IQR) in mg-h/L	544 (359–801)	378 (304–494)	$< .001$
$\geq 400$ mg-h/L <sup>b</sup>	31 (10)	276 (90)	.001
$< 400$ mg-h/L <sup>b</sup>	14 (4)	359 (96)	
$\geq 800$ mg-h/L <sup>b</sup>	11 (33)	22 (67)	$< .001$
$< 800$ mg-h/L <sup>b</sup>	34 (5)	613 (95)	
$\geq 1000$ mg-h/L <sup>b</sup>	8 (57)	6 (43)	$< .001$
$< 1000$ mg-h/L <sup>b</sup>	37 (6)	629 (94)	
Initial dose, median (IQR) in mg/kg per day	47.8 (44.4–60.0)	45.0 (39.7–56.2)	.04
$\geq 60$ mg/kg per day <sup>b</sup>	13 (14)	78 (86)	.002
$< 60$ mg/kg per day <sup>b</sup>	32 (5)	557 (95)	

Abbreviations: AUC, area under the curve; IQR, interquartile range.

<sup>a</sup>Data are no. (%) of subjects, unless otherwise noted.

<sup>b</sup>Percentages are based on total subjects within the specified AUC targets.

mg-h/L (aOR, 3.7; 95% CI, 1.2–11.0;  $P = .018$ ) were associated with increased risk of developing nephrotoxicity (Table 3). Because most hospital microbiology laboratories report MIC results as 1, 2, or 4 mg/L, we chose an AUC of 800 (to correlate with an MIC of 2) when calculating the aOR, rather than using an AUC of 1000 identified from CART. In addition, no significant interaction between PICU stay and vancomycin exposure using both  $C_{\min} \geq 15$  mcg/mL ( $P = .477$ ) and  $AUC \geq 800$  mg-h/L ( $P = .106$ ) was observed in multivariate regression analysis.

The mean time to nephrotoxicity was  $3.6 \pm 2.9$  days (median 3, range 1–15 days), but there was no significant difference in the time to nephrotoxicity using Kaplan-Meier analysis stratified by the vancomycin  $C_{\min}$ , AUC, or dose ( $<9.9$ ,  $10$ – $14.9$ ,  $15$ – $19.9$ , and  $\geq 20$  mcg/mL,  $P = .225$ ;  $<10$  and  $\geq 10$  mcg/mL,  $P = .652$ ;  $<800$  and  $\geq 800$  mg-h/L,  $P = .573$ ;  $<60$  and  $\geq 60$  mg/kg per day,  $P = .756$ , respectively). However, subjects who were hospitalized in the PICU had a higher probability of developing nephrotoxicity compared with those who were hospitalized on the wards. The predicted probability of nephrotoxicity was approximately 15% for subjects in the PICU with steady-state vancomycin  $C_{\min} \geq 15$  mcg/mL, compared with a probability of approximately 5% for those hospitalized on the wards ( $P = .001$ ) (see Supplementary Figure 3). For those hospitalized on the wards, nephrotoxicity was observed in approximately 15% of those with a higher steady-state  $C_{\min}$  of  $\geq 25$  mcg/mL (see Supplementary Figure 3).

## DISCUSSION

There are adequate studies evaluating the PK of vancomycin-associated nephrotoxicity in adults using PD dosing targets, but very few studies exist in children. In a meta-analysis of 14 adult studies and 1 pediatric study, vancomycin  $C_{\min} \geq 15$  mcg/mL was associated with a 2.67-fold increase

in nephrotoxicity, which occurred between 4.3 and 17 days after initiation of vancomycin therapy [16]. The time to nephrotoxicity in our study ranged from 1 to 15 days, implicating the challenge in predicting the time to toxicity for an individual patient. Studies show an incremental risk of nephrotoxicity associated with vancomycin doses  $>4$  g/day and exposure determined by  $C_{\min} \geq 15$  mcg/mL. The risk also increases with longer duration of vancomycin use, concomitant use of other nephrotoxic agents, and in patients who are critically ill or have compromised renal function [12–16].

This is the first study in children uniquely utilizing population-based PK/PD modeling with Bayesian estimation to evaluate significant PD indices of vancomycin-associated nephrotoxicity. With Bayesian estimation, descriptions of PK data in specific populations and plausible explanations for PK/PD variability for drug exposure and toxicity in these populations can be quantified. These defined parameters can then be used to better predict outcomes from analytical models constructed for the population, with implications for the individual patient. Furthermore, Bayesian analysis allows for more accurate quantification of parameters of interest (ie,  $V_d$  and  $CL$  that can then be used to estimate  $C_{\min}$  and AUC) than standard statistical analysis of PK data, and predictive statements can be more easily derived [21]. Our study also distinctively incorporated an age-based definition for normal baseline SCr values, which is important because renal function changes with age.

Three published pediatric studies have associated vancomycin use with the development of nephrotoxicity, albeit in the presence of other risk factors, such as ICU stay and concurrent nephrotoxic agents [15, 17, 22, 23]. Consistent with multiple adult studies, 1 study reported a 28% incidence of nephrotoxicity in children with vancomycin  $C_{\min} \geq 15$  mcg/mL, which is a 3-fold increase compared with those with  $C_{\min} < 15$  mcg/mL [12–15, 24, 25]. Another study reported a 19% incidence of nephrotoxicity in children with an initial vancomycin  $C_{\min} \geq 15$  mcg/mL and ICU admission as independent predictors of nephrotoxicity that doubled the risk of acute kidney injury [17]. However, in 1 of the studies of children, vancomycin was not associated with nephrotoxicity, probably attributable to the low vancomycin exposure with  $C_{\min} < 5$ – $10$  mcg/mL [22]. Our study demonstrated that vancomycin  $C_{\min} \geq 15$  mcg/mL and  $AUC \geq 800$  mg-h/L increased the risk of nephrotoxicity by more than 2.5-fold and 3.7-fold, respectively.

In our CART analysis, we found that elevated  $AUC > 1063$  mg-h/L was an important predictor of nephrotoxicity. The median AUC for children who developed

**Table 3.** Multivariate Logistic Regression Model for the Occurrence of Vancomycin-Associated Nephrotoxicity<sup>a,b</sup>

Parameter	Adjusted Odds Ratio (95% CI)	P Value
AUC over 24 h <sup>c</sup> , $\geq 800$ mg-h/L	3.7 (1.2–11.0)	.018
Trough concentration, $\geq 15$ mcg/mL	2.5 (1.1–5.8)	.028

Abbreviations: AUC, area under the curve; CI, confidence interval; PICU, pediatric intensive care unit.

<sup>a</sup>Adjusted for stay in the intensive care unit and use of concurrent nephrotoxic medications.

<sup>b</sup>The interaction between PICU stay and vancomycin exposure using both  $C_{\min} \geq 15$  mcg/mL ( $P = .477$ ) and  $AUC \geq 800$  mg-h/L ( $P = .106$ ) was not significant.

<sup>c</sup>The adjusted odds ratio (95% CI) for  $AUC \geq 1000$  mg-h/L was 8.7 (2.3–32.8),  $P = .001$ .

nephrotoxicity was 544 (interquartile range [IQR], 359–801) mg-h/L. In addition, 10%, 33%, and 57% of subjects who achieved  $AUC \geq 400$ , 800, and 1000 mg-h/L, respectively, experienced nephrotoxicity, suggesting a strong exposure-toxicity relationship with high exposure resulting in increased toxicity. Although our CART analysis demonstrated  $AUC > 1063$  mg-h/L as the natural “breakpoint” above which nephrotoxicity was more likely to occur with the highest statistical probability, we examined the odds of nephrotoxicity using  $AUC \geq 800$  mg-h/L in our multivariate analysis because it permits the relatively safe treatment of organisms with MICs of 2 mg/L, associated with a target AUC of 800 mg-h/L. Clinical and microbiologic efficacy associated with this target AUC is likely to be achieved for organisms with MICs of 2 mg/L, suggesting that, out of concerns for toxicity, an alternative anti-MRSA agent is preferred for pathogens with MICs exceeding 2 mg/L. It is interesting to note that  $AUC \geq 700$  mg-h/L has been associated with increased risks of nephrotoxicity in adults [12, 26, 27].

In this study, both  $C_{\min} \geq 15$  mcg/mL and  $AUC \geq 800$  mg-h/L were associated with increased risk of nephrotoxicity after controlling PICU stay and concomitant nephrotoxic drugs. Although there may exist some correlation between  $C_{\min}$  and AUC (ie, higher doses leads to higher  $C_{\min}$  and AUC), AUC is unaffected by changes in dosing interval provided that total daily doses remain the same (ie, 3000 mg/day every 6 or 8 hours produce the same AUC, but  $C_{\min}$  will vary).

Large vancomycin doses have been correlated with nephrotoxicity. In 1 retrospective study of 246 adults, a significant difference in nephrotoxicity was distinguished between subjects who received vancomycin  $\geq 4$  g/day,  $< 4$  g/day, and linezolid (34.6%, 10.9%, and 6.7%, respectively;  $P = .001$ ) [11]. In fact, vancomycin  $\geq 4$  g/day was associated with an increased risk of nephrotoxicity (aOR, 4.4; 95% CI, 1.7–11.8;  $P = .003$ ) [11]. When normalized to the average adult weight of 70 kg, vancomycin 4 g/day is equivalent to approximately 60 mg/kg per day in an average child. This finding is consistent with our CART analysis showing that vancomycin doses  $\geq 60$  mg/kg per day, albeit to a lesser degree than AUC, was an important predictor of nephrotoxicity.

Stay in the PICU was associated with nephrotoxicity in the Kaplan-Meier analysis (see Supplementary Figure 3). This finding is similar to published adult and pediatric studies [12, 15, 28]. In 1 adult study, the probability of nephrotoxicity was 10%–15% higher in ICU patients compared to those not in the ICU [28]. Patients in the PICU are at an increased risk for developing nephrotoxicity potentially due to underlying comorbid conditions that

significantly decrease renal blood flow (eg, shock) and use of concurrent medications that may compromise renal function. The addition of vancomycin, which is essential for many children in the PICU, only aggravates this risk of renal injury. After adjusting for stay in the PICU and concurrent nephrotoxic agents in our multivariate logistic regression, vancomycin  $AUC \geq 800$  mg-h/L and  $C_{\min} \geq 15$  mcg/mL remained as independent predictors of nephrotoxicity.

In one study in which pediatric patients in the ICU were evaluated, nephrotoxicity was not linked to high  $C_{\min}$  of 15–20 mcg/mL when compared with  $C_{\min}$  of 5–15 mcg/mL [23]. Our results differ from that study, perhaps owing to the younger age of subjects in that study (ie, median age 2 years vs 6.7 years). In addition, nephrotoxicity was defined by Cies and Shankar [23] as an absolute increase in SCr of 0.3 mg/dL, or a 50% increase from baseline value in that study, which differed from our study. It is noteworthy that subjects who achieved the high vancomycin  $C_{\min}$  were compared with historical control subjects with low  $C_{\min}$  rather than comparing both groups during the same time interval.

Multiple studies in adults have reported that an  $AUC/MIC \geq 400$  is associated with improved clinical outcome [7, 13, 29]. Although the Infectious Diseases Society of America guidelines recommend vancomycin  $C_{\min}$  of 15–20 mcg/mL in adults to target this target  $AUC/MIC$  for complicated MRSA infections (eg, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia), our previous study in children correlated lower  $C_{\min}$  of 8–9 mcg/mL to an  $AUC \sim 400$  mg-h/L [1, 7, 10]. Although we acknowledge the need for rapid achievement of therapeutic concentrations, this correlation infers that high  $C_{\min}$  of 15–20 mcg/mL may not be necessary in children, especially in light of the increased risk of nephrotoxicity with  $C_{\min} \geq 15$  mcg/mL, and assuming that one targets an  $AUC$  of  $\sim 400$  mg-h/L for pathogens with an MIC of  $\leq 1$  mcg/mL [10, 15]. One adult study by Neely et al [27], in which non-parametric population PK modeling was used, reported that 60% of 5000 simulated subjects had  $C_{\min} < 15$  mcg/mL despite achieving therapeutic  $AUC/MIC \geq 400$  mg-h/L.

There were several study limitations to our analysis. Vancomycin concentrations were analyzed at 2 separate clinical laboratories using different assays [10]. We were unable to determine how dose adjustment, which is often necessary in children, contributes to decreased nephrotoxicity. Although our multivariate analysis validated our overall conclusions when adjusting for confounders, our concern is the degree, if any, in which frequently coadministered medications (with a risk of nephrotoxicity also)

contribute to nephrotoxicity. We did not use the pediatric risk, injury, failure, loss and end-stage renal disease criteria to define nephrotoxicity, because most children receiving vancomycin only receive them for a defined course, with early indications of renal injury being less concerning given the benefits of vancomycin, and end-stage renal failure with vancomycin being exceedingly rare [30].

For children infected by strains of MRSA with MICs of  $\geq 2$  mg/L, future prospective, controlled studies should focus on subjects receiving vancomycin at doses  $\geq 60$  mg/kg per day, compared with subjects receiving an antibiotic not known to cause nephrotoxicity (such as linezolid or clindamycin), to better ascertain the high-dose vancomycin-attributable nephrotoxicity in this population.

## CONCLUSIONS

Vancomycin exposure using  $AUC \geq 800$  mg-h/L and  $C_{\min} \geq 15$  mcg/mL are strong predictors for nephrotoxicity in children. When aggressive vancomycin regimens are initiated empirically in children, clinicians should be vigilant in assessing signs of nephrotoxicity, especially in the presence of concurrent use of nephrotoxic medications or for children in the PICU. For children infected by strains of MRSA demonstrating an MIC  $> 2$  mg/L, an alternative anti-MRSA antibiotic should be considered because the risk of nephrotoxicity associated with vancomycin significantly increases when  $AUC \geq 800$  mg-h/L and  $C_{\min} \geq 15$  mcg/mL.

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## Supplementary Data

Supplementary materials are available at the *Journal of the Pediatric Infectious Diseases Society* online (<http://jpid.oxfordjournals.org>).

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