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Evaluation of Vancomycin Dose Needed to Achieve 24-Hour Area Under the Concentration-Time Curve to Minimum Inhibitory Concentration Ratio Greater Than or Equal to 400 Using Pharmacometric Approaches in Pediatric Intensive Care Patients

Dawoon Jung, BPharm[1]
Omayma A. Kishk, PharmD[2,3]
Adnan T. Bhutta, MBBS[4,5]
Ginny E. Cummings, CRNP[6]
Hana M. El Sahly, MD[7]
Manpreet K. Virk, MD[8]
Brady S. Moffett, PharmD, MPH, MBA[9,10,11]
Jennifer L. Morris Daniel, PharmD[9,10,12]
Amy Watanabe, MS[13]
Nicholas Fishbane, MSc[13]
Karen L. Kotloff, MD[6]
Kenan Gu, PhD[14]
Varduhi Ghazaryan, MD, PhD[14]
Jogarao V. S. Gobburu, PhD, MBA[1]
Ayse Akcan-Arikan, MD[15]
James D. Campbell, MD, MS[6]

OBJECTIVES: To investigate which independent factor(s) have an impact on the pharmacokinetics of vancomycin in critically ill children, develop an equation to predict the 24-hour area under the concentration-time curve from a trough concentration, and evaluate dosing regimens likely to achieve a 24-hour area under the concentration-time curve to minimum inhibitory concentration ratio (AUC_{24}/MIC) greater than or equal to 400.

DESIGN: Prospective population pharmacokinetic study of vancomycin.

SETTING: Critically ill patients in quaternary care PICUs.

PATIENTS: Children 90 days old or older to younger than 18 years who received IV vancomycin treatment, irrespective of the indication for use, in the ICUs at the University of Maryland Children's Hospital and Texas Children's Hospital were enrolled.

INTERVENTIONS: Vancomycin was prescribed at doses and intervals chosen by the treating clinicians.

MEASUREMENTS AND MAIN RESULTS: A median of four serum levels of vancomycin per patient were collected along with other variables for up to 7 days following the first administration. These data were used to characterize vancomycin pharmacokinetics and evaluate the factors affecting the variability in achieving AUC_{24}/MIC ratio greater than or equal to 400 in PICU patients who are not on extracorporeal therapy. A total of 302 children with a median age of 6.0 years were enrolled. A two-compartment model described the pharmacokinetics of vancomycin with the clearance of 2.76 L/hr for a typical patient weighing 20 kg. The glomerular filtration rate estimated using either the bedside Schwartz equation or the chronic kidney disease in children equation was the only statistically significant predictor of clearance among the variables evaluated, exhibiting equal predictive performance. The trough levels achieving AUC_{24}/MIC = 400 were 5.6–10.0 μg/mL when MIC = 1 μg/mL. The target of AUC_{24}/MIC greater than or equal to 400 was achieved in 60.4% and 36.5% with the typical dosing regimens of 15 mg/kg every 6 and 8 hours (q6h and q8h), respectively.

CONCLUSIONS: The pharmacokinetics of vancomycin in critically ill children were dependent on the estimated glomerular filtration rate only. Trough concentrations accurately predict AUC_{24}. Typical pediatric vancomycin dosing regimens of 15 mg/kg q6h and q8h will often lead to AUC_{24}/MIC under 400.

KEYWORDS: area under the concentration-time curve to minimum inhibitory concentration ratio; critically ill pediatric patients; pediatric intensive care unit; pharmacokinetics; vancomycin

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KEY POINTS

Question: Which independent variable(s) have an impact on the pharmacokinetic of vancomycin in critically ill children?

Findings: In this population pharmacokinetic study conducted in critically ill children, estimated glomerular filtration rate (eGFR) calculated using either the bedside Schwartz equation or the chronic kidney disease in children equation was found to be the sole statistically significant predictor of vancomycin clearance among the variables analyzed. As the eGFR increased, the clearance of vancomycin showed a less than proportional increase. Adjustment of initial dose based upon eGFR is expected to improve the target attainment of 24-hour area under the concentration-time curve to minimum inhibitory concentration ratio greater than or equal to 400.

Meaning: eGFR has a substantial effect on the pharmacokinetics of vancomycin in critically ill children.

Pediatric patients in the ICU are frequently treated with vancomycin for suspected or proven infections caused by Gram-positive bacteria (1–3). Guidelines published in 2020 recommend the pharmacokinetic/pharmacodynamic target for vancomycin for suspected serious infections with methicillin-resistant *Staphylococcus aureus* as 24-hour area under the concentration-time curve to minimum inhibitory concentration ratio (AUC_{24}/MIC) of 400–600 assuming MIC of less than or equal to 1 μg/mL (4). Based on the AUC_{24}/MIC values derived from adult data, the recommended initial vancomycin dosing is 60–80 mg/kg/d divided every 6 hours (q6h) for children 3 months to younger than 12 years old or 60–70 mg/kg/d divided q6h to every 8 hours (q8h) for those 12 years old or older with normal renal function (4). The narrow therapeutic window in populations with serious infections requires complex dosing strategies to achieve optimal outcomes. Unfortunately, there is a paucity of prospectively collected data available to guide therapy in children.

Currently available evidence regarding monitoring of vancomycin levels in adults cannot necessarily be applied to pediatric patients due to the differences in renal function and variable volumes of distribution, especially in critically ill children (4–6). The volume of distribution in these children is frequently altered due to increased fluid intake for resuscitation and medication delivery, as well as inflammation-derived endothelial activation, capillary leak, and alteration in serum proteins (7–14). Furthermore, acute kidney injury is frequent in critically ill children and has profound effects on vancomycin clearance due to the primary route of vancomycin elimination being glomerular filtration (15–18). Given the heightened complexity and homeostatic aberrations of critically ill children with respect to their pharmacology and multiple factors and interventions that can impact the pharmacokinetics, novel dose-optimization procedures are needed. While many institutions use trough concentrations as a surrogate for achieving the target of AUC_{24}/MIC ratio, it remains uncertain whether trough concentrations are a suitable marker for appropriate vancomycin dosing in critically ill children. Additionally, the typical dosing regimens for children have not yet been evaluated to determine if they achieve an AUC_{24}/MIC greater than or equal to 400 in critically ill children. Bayesian estimated AUC_{24}-guided monitoring can be beneficial in pediatric patients, as it allows incorporation of different ages, weights, and renal function. However, comprehensive information on the variables impacting foundational pharmacokinetic parameters, particularly in critically ill pediatric patients, is still lacking, and no models have been directly used to provide personalized dosing recommendations (4).

To describe the pharmacokinetic characteristics of vancomycin in critically ill pediatric patients, we performed a prospective population pharmacokinetic study to evaluate multiple variables and their effect on reaching the AUC_{24} target. Furthermore, we developed an equation to predict the AUC_{24} value from a trough concentration. Finally, we simulated four different dosing regimens, including typical ones, to evaluate their target attainment of AUC_{24}/MIC greater than or equal to 400.

METHODS

Study Design

We conducted a multicenter, prospective population pharmacokinetic study in critically ill pediatric

patients receiving IV vancomycin therapy. Children 90 days old or older of life to younger than 18 years old were eligible for this study if they were prescribed IV vancomycin between April 15, 2018, and February 6, 2020, were not supported on any form of extracorporeal therapy and had not undergone cardiopulmonary bypass surgery within 7 days of initiating vancomycin therapy (**eMethods**, http://links.lww.com/CCX/B406). Blood samples were collected from all enrolled patients to measure vancomycin levels for up to 7 days following the first administration. During the 7-day study period, relevant demographic, clinical, and laboratory data were collected from the medical chart to evaluate their effects on the pharmacokinetic of vancomycin (**eTable 1**, http://links.lww.com/CCX/B406). Medical teams caring for the patient decided on vancomycin dosing regimens.

Four to six serum vancomycin levels for each subject were targeted to be obtained (**eFig. 1**, http://links.lww.com/CCX/B406). A total of four samples were collected for subjects whose blood cultures did not grow bacteria (negative microbiologic culture), whereas subjects with positive microbiologic culture who continued vancomycin IV had two additional later levels (peak and trough) drawn between the 5th and 7th day of their vancomycin therapy.

Approximately 0.5 mL of blood was drawn for vancomycin level measurement by venipuncture or from an indwelling catheter that had not been used for vancomycin infusion. The time was recorded when samples were processed, aliquoted into serum storage tubes, frozen, and shipped to the central laboratory for the assay in accordance with the manual of procedures. Serum vancomycin levels were assayed by a validated liquid chromatography tandem mass spectrometry method.

The study protocol was approved by the University of Maryland Baltimore (UMB) and Baylor College of Medicine (BCM) Institutional Review Boards: HP-00076841 (UMB) and H-41119 (BCM), "A population pharmacokinetic study to evaluate the dose needed to achieve AUC_{24}/MIC ≥ 400 in pediatric intensive care patients on vancomycin," approved on October 2, 2017 in both institutes. The study was conducted in accordance with the ethical principles of the responsible committee on research involving human subjects and with the Declaration of Helsinki, as revised in 2013. Written informed consent and assent, when required, were obtained from the study subjects and/or their legally authorized representatives.

Population Pharmacokinetic Model Development and Evaluation

An initial exploratory analysis was conducted to identify the structure of the population pharmacokinetic model and potential covariates as a preliminary step. Subsequently, a base pharmacokinetic model was developed, and covariate effects were examined to determine which independent variables (eTable 1, http://links.lww.com/CCX/B406) influence each pharmacokinetic parameter of vancomycin. A *p* value of 0.01, more stringent than the typically used 0.05, was prespecified to determine a covariate effect, as we sought a more pronounced effect. Last, model refinement and evaluation were performed to determine a final pharmacokinetic model. **eFigure 2** (http://links.lww.com/CCX/B406) describes the workflow of the pharmacokinetic model development, and the procedure of each step is described in eMethods (http://links.lww.com/CCX/B406). After the final model was selected, a subanalysis was conducted to compare the model predictive performance of estimated glomerular filtration rate (eGFR) calculated using different equations (eMethods, http://links.lww.com/CCX/B406).

Evaluation of the Relationship Between AUC_{24} and Vancomycin Trough Levels

To investigate whether the concentration from a single blood sample could be used to adequately predict the AUC_{24}/MIC ratio, a nonlinear regression analysis of the model-predicted AUC_{24} to the observed trough vancomycin concentrations was performed with subjects who had a trough concentration collected. A trough vancomycin concentration was defined as any concentration collected within either a ± 25% window or a ± 2 hours window of the planned dosing interval, following at least two prior doses, whichever was shorter, and collected prior to the next vancomycin dose. For each subject, a model-predicted steady state AUC_{24} was calculated as dose divided by the individual model-predicted clearance × (24/tau) where tau is the dosing interval calculated as the actual time between two doses in hours. The steady-state AUC_{24}

values were plotted against the observed trough concentrations, stratified by percentage of steady state to assess the potential relationships. The percentage of steady state was calculated based upon model-predicted individual half-life and an average half-life of 6 hours.

Target Attainment Analysis

To estimate the probability of attaining the pharmacokinetic/pharmacodynamic target measure of AUC_{24}/MIC greater than or equal to 400, the following procedures were performed: 1) generation of a virtual population; 2) simulation of steady-state AUC_{24} for four dosing regimens; 3) calculation of AUC_{24}/MIC ratios for MIC values of 0.5, 1, and 2 μg/mL; and 4) summarization of the proportion of subjects with AUC_{24}/MIC greater than or equal to 400 for each MIC value. The virtual population of 2250 subjects was generated by randomly sampling with replacement the baseline covariate vector of subjects from the study. A sensitivity analysis was performed to evaluate the dependency of the target attainment on the pharmacokinetic sampling scheme as described in eMethods (http://links.lww.com/CCX/B406).

Evaluation of AUC_{24}/MIC Ratio With Microbiologic Cultures

As a prespecified exploratory outcome, we analyzed the subset of children with positive microbiologic cultures to determine the relationship between AUC_{24}/MIC and microbiologic and clinical cure. Microbiologically cured was defined in the protocol as children who initially had a culture positive for an organism treated with vancomycin, and subsequently, during the study enrollment, had negative cultures. Clinically cured was defined as recovery from the infection while on vancomycin, based on the opinion of the treating team regarding whether the subject was clinically cured of the infection. Subjects were considered evaluable if the positive microbiologic culture was collected within 48 hours before or 24 hours after the start of a vancomycin dosing regimen; the regimen was at least 48 hours duration with at least three vancomycin doses with intervals of less than 24 hours. Model-predicted clearance was taken from the time-varying covariates at the end of the dosing regimen, as was dosing amount to compute AUC_{24} based upon the equation in eMethods (http://links.lww.com/CCX/B406).

All analysis and presentations of data were performed using SAS, Version 9.4 (SAS Institute, Cary, NC) and KIWI, Version 4 202111 (Cognigen division of Simulations Plus, Buffalo, NY). Population modeling was performed using NONMEM, Version 7.3.0 (ICON plc, Dublin, Ireland).

RESULTS

Patient Characteristics

We enrolled 302 subjects in the study; one subject was excluded from the analysis due to unavailable pharmacokinetic data (**eFig. 3**, http://links.lww.com/CCX/B406). The median age and weight of the population were 6.0 years (interquartile range [IQR], 1.6–13.0 yr) and 20.1 kg (IQR, 10.7–41.6 kg), respectively. **Table 1** presents a summary of the characteristics of the study population. A median of 4 (IQR, 3–6) vancomycin pharmacokinetic samples per subject were collected. The actual dosing amounts and frequencies, reflecting any clinical adjustments, ranged from 5 to 31 mg/kg q6h, with the most frequent regimens being 1-hour infusions of 15 mg/kg every 6–9 hours.

Population Pharmacokinetic Model

Vancomycin serum concentrations generally declined in a biphasic manner with the second phase beginning at approximately 8 hours after the end of infusion (**eFig. 4**, http://links.lww.com/CCX/B406). Clearance for subjects with normal renal function was higher compared with those with impaired renal function (**eFig. 5**, http://links.lww.com/CCX/B406). A two-compartment model allometrically scaled with body weight with linear elimination adequately described the pharmacokinetic of vancomycin following multiple doses. Among multiple variables analyzed, eGFR was found to be the only statistically significant predictor of clearance (**eTable 2**, http://links.lww.com/CCX/B406). As eGFR increased, clearance demonstrated a less than proportional increase. The estimated typical values for a subject weighing 20 kg were 2.76 L/h (for eGFR of 141 mL/min/1.73 m^2) for clearance, 8.63 L for central volume (Vc), 3.81 L/hr for intercompartmental clearance, and 9.57 L for peripheral volume (Vp) (**Table 2**). The goodness-of-fit

TABLE 1.
Patient Characteristics

Baseline Characteristics (*n* = 302)	
Age (yr), median (IQR)	6.0 (1.6–13.0)
Sex, *n* (%)	
Male	176 (58.3)
Race, *n* (%)	
White	220 (72.8)
Black or African American	51 (16.9)
Others	31 (10.3)
Ethnicity, *n* (%)	
Hispanic or Latino	123 (40.7)
Body weight (kg), median (IQR)	20.1 (10.7–41.6)
Body mass index (kg/m^2), median (IQR)	17.9 (16.0–21.3)
Scr (mg/dL), median (IQR)	0.3 (0.2–0.5)
Blood urea nitrogen (mg/dL), median (IQR)	12.0 (8.0–17.0)
Estimated glomerular filtration rate (mL/min/1.73 m^2)[a], median (IQR)	138.3 (101.5–179.8)
Renal impairment[b], *n* (%)	
Normal	247 (81.8)
Mild	36 (11.9)
Moderate	15 (5.0)
Severe	3 (1.0)
Unknown	1 (0.3)
Day of admission severity of illness score–Pediatric Risk of Mortality-3 score, median (IQR)	5.0 (2.0–10.0)
Day of admission severity of illness score–Pediatric Index of Mortality-2 score, median (IQR)	–3.5 (–4.9 to –3.0)
Pediatric Logistic Organ Dysfunction score, median (IQR)	11.0 (2.0–21.0)
At least one nephrotoxic comedication[c], *n* (%)	Present, 291 (96.4)
Number of samples per patient, median (IQR)	4.0 (3.0–6.0)
Time-Varying Characteristics (*n* = 1027)	
Sample time after end of previous infusion (hr), median (IQR)	4.1 (–2.0 to 98.8)
Sample time after first dose (hr), median (IQR)	32.3 (6.7–353.3)
Percent fluid overload[d], median (IQR)	0.9 (–0.9 to 3.2)
AKI stage (Scr upper limit)[e], *n* (%)	
No AKI	989 (96.3)
Stage 1	30 (2.9)
Stage 2	6 (0.6)
Stage 3	2 (0.2)

(*Continued*)

TABLE 1. (*Continued*)
Patient Characteristics

Time-Varying Characteristics (*n* = 1027)	
AKI stage (Scr midpoint)[e], *n* (%)	
No AKI	985 (95.9)
Stage 1	23 (2.2)
Stage 2	15 (1.5)
Stage 3	4 (0.4)

AKI = acute kidney injury, IQR = interquartile range, *n* = number of patients for baseline characteristics and number of sample records for time-varying characteristics, Scr = serum creatinine.
[a]Bedside Schwartz equation was used to calculate glomerular filtration rate (GFR) in the study: GFR (mL/min/1.73 m^2) = (0.413 × height [cm]/Scr [mg/dL]).
[b]The degree of renal impairment is categorized into four groups based on estimated GFR (eGFR) values: normal (≥ 90 mL/min), mild (60–89 mL/min), moderate (30–59 mL/min), and severe (15–29 mL/min) (Food and Drug Administration Renal Impairment Guidance for Industry, September 2020) (19).
[c]Aminoglycosides, amphotericin B, diuretic (IV or by mouth), IV contrast dyes, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzymes inhibitors, angiotensin II receptor blockers, proton pump inhibitors, cisplatin, carboplatin, oxaliplatin, cyclosporine, tacrolimus, piperacillin-tazobactam, and cyclophosphamide. A patient with unknown information was counted as having no comedication.
[d]Percent fluid overload was calculated as: (Σ daily [fluid intake (L)–total output (L)]/baseline body weight [kg]) × 100.
[e]AKI was defined as an increase in Scr by ≥ 0.3 mg/dL within 48 hr; or an increase in Scr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 d; or urine volume < 0.5 mL/kg/hr for 6 hr or more. Subjects with AKI was staged as per Kidney Disease-Improving Global Outcomes (20) calculations.
Note that body weight and body mass index are presented in a baseline value and first chemistry laboratory results for Scr, blood urea nitrogen, and eGFR.

TABLE 2.
Final Population Pharmacokinetic Model of Vancomycin in PICU Patients

Parameter	Estimate	RSE	Between Subject Variability As Coefficient of Variation (RSE)
Clearance (L/hr)	$2.763 \times (WT/20)^{0.75} \times (\text{estimated glomerular filtration rate}/141)^{0.5259}$	2.746% for 2.763; 14.92% for 0.5259	38.12% (15.94%)
Central volume (L)	8.63 × (WT/20)	14.39%	102.6% (28.64%)
Intercompartmental clearance (L/hr)	$3.808 \times (WT/20)^{0.75}$	20.45%	NE
Peripheral volume (L)	9.566 × (WT/20)	14.46%	NE
Residual variability (log scale)	0.1096	12.69%	0.3310 SD

NE = not estimated, RSE = relative SE, WT = body weight (kg).
Shrinkage estimates: 13.2% for between subject variability as coefficient of variation (BSV) in clearance (L/hr) and 48.2% for BSV in central volume (L).

plots (**eFig. 6**, http://links.lww.com/CCX/B406) and prediction-corrected visual predictive check (**eFig. 7**, http://links.lww.com/CCX/B406) showed that the final population pharmacokinetic model was adequately developed.

For the subgroup of subjects (*n* = 248) who had both serum creatinine and cystatin C measures, individual predicted concentrations were compared between models using eGFR based upon the bedside Schwartz and the chronic kidney disease in children (CKiD) (21, 22) equations. The analysis indicated that both models were similar in their ability to predict observed vancomycin concentrations and clearance (**eFigs. 8** and **9**, http://links.lww.com/CCX/B406).

Relationship Between AUC_{24} and Vancomycin Trough Levels

This analysis included a total of 365 trough concentrations from 238 subjects. The equation drawn from the analysis is as follows (**eTable 3**, http://links.lww.com/CCX/B406):

$$AUC_{24}\left(\frac{\mu g \times hr}{mL}\right) = (366 + 54.9 \times [DFRQ8] + 0.0894 \times [Dose\,(mg) - 500]) \times \left(\frac{C_{tr}}{7}\right)^{0.495}$$

Where: DFRQ8 is 1 if the dosing frequency is less than 8 hours and 0 otherwise; **Dose** (**mg**) is the total amount of a single dose in mg; and $\mathbf{C_{tr}}$ is the observed trough vancomycin concentration in μg/mL as defined in the *Methods* section.

This equation provided an unbiased prediction of AUC_{24} across the observed range of trough vancomycin concentrations with a residual error of 20.2%. In addition, the regression analysis showed that the error associated with the regression-predicted AUC_{24} was not associated with the level of steady state, which had been achieved based on a median vancomycin half-life of 6 hours (**eFig. 10**, http://links.lww.com/CCX/B406). Considering that trough levels are routinely monitored in clinical practice, the minimum trough concentrations achieving AUC_{24}/MIC greater than or equal to 400 were estimated using the equation as shown in **Table 3**. For MIC of 1 μg/mL, the range of trough levels achieving AUC_{24}/MIC of 400 is 5.6–10.0 μg/mL.

Target Attainment of AUC_{24}/MIC Greater Than or Equal to 400

Table 4 shows the target attainment of AUC_{24}/MIC greater than or equal to 400 based upon sample strategy and three MIC values after administering four different dosing regimens. When standard dosing regimens of 15 mg/kg q6h and q8h are administered, 60.4% and 36.5% of virtual subjects achieved the target of AUC_{24}/MIC greater than or equal to 400, respectively, for MIC of 1 μg/mL. The highest percentage of the target attainment, 86.8%, was obtained following a dose of 30 mg/kg q8h. The values of AUC_{24}/MIC and the ratio of subjects achieving target attainment based upon the sparse sampling schemes (peak/trough or trough only) were similar to those based upon the infinite sampling scheme, indicating that target attainment was generally insensitive to the sampling scheme used. The values of AUC_{24}/MIC ratio for each scenario are presented in **eTable 4** (http://links.lww.com/CCX/B406).

TABLE 3.

Trough Vancomycin Concentration Achieving 24-Hour Area Under the Concentration-Time Curve to Minimum Inhibitory Concentration Ratio Equal to 400 From Regression Analysis

Dosing Regimen	Body Weight (kg)	Trough Vancomycin Concentration (μg/mL)		
		MIC = 0.5	MIC = 1	MIC = 2
15 mg/kg q6h	10	1.8	7.4	29.9
	20	1.7	6.9	28.0
	40	1.5	6.1	24.6
15 mg/kg q8h	10	2.5	10.0	40.7
	20	2.3	9.3	37.6
	40	2.0	8.0	32.4
20 mg/kg q6h	10	1.8	7.2	29.3
	20	1.6	6.6	26.8
	40	1.4	5.6	22.6
30 mg/kg q8h	10	2.3	9.3	37.6
	20	2.0	8.0	32.4
	40	1.5	6.1	24.7

MIC = minimum inhibitory concentration (μg/mL), q6h = administered every 6 hr, q8h = administered every 8 hr.

Evaluation of AUC_{24}/MIC Ratio With Microbiologic Cultures

Twelve of 45 subjects who had at least one positive microbiologic culture were considered evaluable for the analysis. All 12 subjects were microbiologically cured. The cultured organisms were *S. aureus*, coagulase-negative *Staphylococci*, and others. Four had no MIC available, and MIC was imputed as 1 μg/mL. Three (25%) of 12 subjects achieved AUC_{24}/MIC greater than or equal to 400, whereas the other 9 (75%) had AUC_{24}/MIC less than 400.

DISCUSSION

In this large prospective study evaluating vancomycin pharmacokinetics in critically ill children, we found that a two-compartment model appropriately

TABLE 4.

Target Attainment of 24-Hour Area Under the Concentration-Time Curve to Minimum Inhibitory Concentration Ratio Greater Than or Equal to 400 for the Simulated Dosing Regimens

Dosing Regimen	Sample Strategy	No. of Patients	% Patients With 24-hr Area Under the Concentration-Time Curve/MIC ≥ 400		
			MIC = 0.5	MIC = 1	MIC = 2
15 mg/kg q6h	Infinite	2250	96.2	60.4	13.2
	Peak/trough	2250	97.2	60.3	11.1
	Trough	2250	98.2	62.1	10.4
15 mg/kg q8h	Infinite	2250	86.8	36.5	5.1
	Peak/trough	2250	88.1	35.3	3.4
	Trough	2250	89.9	35.3	3.3
20 mg/kg q6h	Infinite	2250	99.4	80.8	27.8
	Peak/trough	2250	99.6	82.1	26.4
	Trough	2250	99.6	84.4	26.4
30 mg/kg q8h	Infinite	2250	99.8	86.8	36.5
	Peak/trough	2250	99.8	88.1	35.3
	Trough	2250	100	89.9	35.3

MIC = minimum inhibitory concentration (μg/mL), q6h = administered every 6 hr, q8h = administered every 8 hr.
In the simulation, vancomycin infusion was 1 hr.

described the pharmacokinetics of vancomycin, and only eGFR showed a significant correlation with vancomycin clearance among evaluated variables.

Four other reported vancomycin population pharmacokinetic models may be used as comparators (23–26). The value of clearance for a patient with a weight of 20 kg and an eGFR of 141 mL/min/1.73 m^2 from the literature models ranged from 2.17 to 3.18 L/hr. Clearance estimated from the model in this study was comparable to the range as 2.76 L/hr, particularly similar to the clearance (2.64 L/hr) reported by Downes et al (26) where critically ill children were involved, whereas the other reported models did not include critically ill patients. However, for volume of distribution, we observed significantly larger Vc (8.63 L) and Vp (9.566 L) in our study compared with those reported by Downes et al (26) where Vc and Vp were 2.59 L and 5.74 L, respectively. We suspect that the larger volume may be attributed to fluid overload, even though our observation during covariate model development indicated that fluid overload did not significantly affect Vc. Although fluid overload did not prove to be significant in this study, the notably large between-subject variability (102.6%) suggests that it could be a significant factor in future studies, particularly those including patients with more pronounced fluid overload. The other published models were all one-compartment models, and we could not determine if the volume of distribution in critically ill pediatric patients is comparable to that of patients that are not critically ill.

We investigated the impact of multiple covariates on the pharmacokinetic of vancomycin in critically ill pediatric patients including age, race, use of nephrotoxic comedication, pediatric risk of mortality, acute kidney injury, and others. However, eGFR was the sole significant predictor of clearance. Kim et al (27) also found eGFR as a significant predictor of clearance in adults, whereas Le et al (28) found that age and serum creatinine were predictors of clearance in children. Still, Le et al (28) did not evaluate eGFR as a covariate, making it challenging to determine if our findings differ from theirs. Zhang et al (29) noted that eGFR calculated using the Schwartz equation overestimated vancomycin clearance in children. But, given that our study focused on critically ill children, it could yield distinct observations. In addition, we investigated if eGFR calculated using the CKiD equation provides a better prediction of clearance for patients with both

serum creatinine and cystatin C measures; however, it showed the same prediction as the model with eGFR using the bedside Schwartz equation.

Vancomycin exposure (AUC_{24}) decreased as the eGFR increased. Although conventional practice is to adjust dose or interval when the eGFR is low, our data suggest that adjusting the initial dose upwards for supranormal eGFRs would lead to more uniform drug exposure for all patients. Although eGFR is regularly monitored as a part of routine care, especially for critically ill pediatric patients, more frequent monitoring may be prudent, in this situation, to balance achieving the therapeutic target and reducing the risk of nephrotoxicity.

Clinicians may not have the ability to calculate AUC_{24} and often rely on troughs to determine whether vancomycin levels are adequate and safe. In our study, the error related to regression-predicted AUC_{24} was independent of the level of steady state. When MIC is 1 μg/mL, the range of trough levels achieving AUC_{24}/MIC = 400 was 5.6–10.0 μg/mL, which is lower than some previous reports (30, 31). Recent studies also found a comparable range of trough concentrations to ours, 7–10 μg/mL, in children with AUC_{24}/MIC of 400 (28, 32). Although the regression-predicted AUC_{24} will require the appropriate sample time of trough concentration, employing a single trough concentration appeared to be a viable approach for estimating drug exposure and correlating it with the AUC_{24}/MIC value in critically ill children receiving empiric vancomycin.

In the dosing regimen simulations where MIC is 1 μg/mL, only 60.4% and 36.5% of virtual patients achieved the target of AUC_{24}/MIC greater than or equal to 400 when receiving the typical dosing regimens of 15 mg/kg q6h and q8h, respectively. For MIC of 2 μg/mL, an even smaller percentage of patients achieved the target: 13.2% and 5.1% for the same dosing regimens, respectively, although MIC of 2 μg/mL or greater is rarely observed at these sites. Other researchers have also found that achieving the target with the typical dosing regimens may be difficult in clinical practice (33–35). On the other hand, more than 80% of virtual patients in the simulations achieved the target when treated with the regimens of 20 mg/kg q6h and 30 mg/kg q8h (MIC = 1 μg/mL) where the total daily doses are 33–100% higher than the commonly recommended. However, due to the increased risk of nephrotoxicity, these higher dosing regimens may not be preferred. Despite these findings, failures of vancomycin therapy have been infrequently reported (4, 36), thus, leading some to question the applicability of the target of AUC_{24}/MIC greater than or equal to 400 in children (36). Hahn et al (33) could not establish a relationship between AUC_{24}/MIC and treatment failure in children, while the association was confirmed in adults (37–40). In our study, 75% (n = 9) of the patients who were microbiologically cured had AUC_{24}/MIC of less than 400. The limited number of evaluable patients available for the analysis make the findings only hypothesis-generating. Additional studies are required to evaluate whether AUC_{24}/MIC greater than or equal to 400 is a suitable objective for vancomycin dosing targets in children and, if not, to identify the optimal target. Following such studies, the dosing regimen may need to be optimized to achieve the target.

While we characterized the pharmacokinetic of vancomycin in critically ill children on a relatively large scale, the collected data have limitations in generalizability for patients with medical conditions not included in the current dataset. Future research is necessary to validate our results using data from patients with different characteristics, such as varying renal function, severity of disease, primary sites of infection, and pathologies.

In this study, we report that the typical vancomycin dosing regimens of 15 mg/kg q6h and q8h often result in an AUC_{24}/MIC ratio below 400 for MIC = 1 μg/mL. These findings indicate that higher doses are needed to consistently attain that target. However, higher doses may also lead to toxicity and that target may not be the most appropriate for all children receiving vancomycin. Therefore, one of the most important next steps is to determine the appropriate therapeutic target. This will require studying a much larger number of children infected with organisms susceptible to vancomycin and with multiple types of infections. These studies will likely require larger, multisite consortia to be fully answered.

CONCLUSIONS

A two-compartment, allometrically scaled model with linear elimination adequately characterized the pharmacokinetic of vancomycin in critically ill pediatric patients. Among multiple variables analyzed, eGFR using any method was the only statistically significant predictor of clearance. A nonlinear regression analysis of model-predicted AUC_{24} to observed vancomycin trough

concentration provided an unbiased equation explaining their relationship. For MIC value of 1 μg/mL, the maximum percentage of virtual patients achieving target attainment (AUC_{24}/MIC ≥ 400) was 86.8% following a dose regimen of 30 mg/kg q8h. The typical dosing regimens of 15 mg/kg q6h and q8h achieved the target attainment (AUC_{24}/MIC ≥ 400) in 60.4% and 36.5% of children, respectively. The predicted target attainment was generally insensitive to sampling schemes as compared with an infinite number of samples.

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1 *Center for Translational Medicine, University of Maryland School of Pharmacy, Baltimore, MD.*

2 *Department of Pharmacy, University of Maryland Medical Center, Baltimore, MD.*

3 *U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Silver Spring, MD.*

4 *Division of Pediatric Critical Care Medicine, Department of Pediatrics, University of Maryland School of Medicine, Baltimore, MD.*

5 *Pediatric Critical Care Medicine, Indiana University School of Medicine/Riley Children's Health, Indianapolis, IN.*

6 *Department of Pediatrics, Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, MD.*

7 *Departments of Molecular Virology and Microbiology and Medicine, Baylor College of Medicine, Houston, TX.*

8 *Department of Pediatrics, Section of Critical Care Medicine, Texas Children's Hospital Baylor College of Medicine, Houston, TX.*

9 *Department of Pharmacy, Texas Children's Hospital, Houston, TX.*

10 *Department of Pediatrics, Baylor College of Medicine, Houston, TX.*

11 *Medical Science Liaison, Novartis, Houston, TX.*

12 *Imagine Pediatrics, Houston, TX.*

13 *The Emmes Company, LLC, Rockville, MD.*

14 *Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, MD.*

15 *Divisions of Critical Care Medicine and Nephrology, Department of Pediatrics, Texas Children's Hospital Baylor College of Medicine, Houston, TX.*

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For information regarding this article, E-mail: Jcampbel@som.umaryland.edu

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