

Association between Vancomycin Trough Concentration and Area under the Concentration-Time Curve in Neonates

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National treatment guidelines for invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections recommend targeting a vancomycin 24-h area under the concentration-time curve (AUC_{0–24})-to-MIC ratio of >400. The range of vancomycin trough concentrations that best predicts an AUC_{0–24} of >400 in neonates is not known. This understanding would help clarify target trough concentrations in neonates when treating MRSA. A retrospective chart review from a level III neonatal intensive care unit was performed to identify neonates treated with vancomycin over a 5-year period. Vancomycin concentrations and clinical covariates were utilized to develop a one-compartment population pharmacokinetic model and examine the relationships between trough and AUC_{0–24} in the study neonates. Monte Carlo simulations were performed to examine the effect of dose, postmenstrual age (PMA), and serum creatinine level on trough and AUC_{0–24} achievement. A total of 1,702 vancomycin concentrations from 249 neonates were available for analysis. The median (interquartile range) PMA was 39 weeks (32 to 42 weeks) and weight was 2.9 kg (1.6 to 3.7 kg). Vancomycin clearance was predicted by weight, PMA, and serum creatinine level. At a trough of 10 mg/liter, 89% of the study neonates had an AUC_{0–24} of >400. Monte Carlo simulations demonstrated that troughs ranging from 7 to 11 mg/liter were highly predictive of an AUC_{0–24} of >400 across a range of PMA, serum creatinine levels, and vancomycin doses. However, a trough of ≥10 mg/liter was not readily achieved in most simulated subgroups using routine starting doses. Higher starting doses frequently resulted in troughs of >20 mg/liter. A vancomycin trough of ~10 mg/liter is likely adequate for most neonates with invasive MRSA infections based on considerations of the AUC_{0–24}. Due to pharmacokinetic and clinical heterogeneity in neonates, consistently achieving this target vancomycin exposure with routine starting doses is difficult. More robust clinical dosing support tools are needed to help clinicians with dose individualization.

Vancomycin is frequently used in neonates, with almost 10% of neonates admitted to a neonatal intensive care unit (NICU) receiving at least one dose (1). It is first-line therapy for serious infections due to coagulase-negative staphylococci (CoNS) and methicillin-resistant *Staphylococcus aureus* (MRSA). CoNS is the most frequent pathogen isolated in the NICU (2, 3), and traditional vancomycin dosing strategies in neonates to treat CoNS infections have targeted trough concentrations of 5 to 10 mg/liter (4).

Invasive MRSA infections are much less common in neonates (5). However, morbidity and mortality are high in those infected, and the optimization of vancomycin dosing is an important component of treatment success (6). Higher drug exposures may be necessary when there is a deep focus of infection in order to ensure adequate tissue penetration. To help standardize vancomycin practices in children and adults when treating invasive MRSA infections, national guidelines have been developed by the Infectious Diseases Society of America (IDSA) (6). A key recommendation is the utilization of therapeutic drug monitoring to confirm adequate vancomycin exposure. The best predictor of successful outcomes when treating invasive MRSA infection is the 24-h area under the concentration-time curve (AUC_{0–24})-to-MIC ratio (AUC_{0–24}/MIC) of >400 (6, 7). Due to the practical limitations of calculating the AUC_{0–24} in individual patients, the trough concentration is more routinely applied in clinical practice for drug monitoring.

To achieve an AUC_{0–24}/MIC of >400 in adults, a vancomycin trough of 15 to 20 mg/liter is recommended (6, 8). However, the relationship in adults between trough and AUC_{0–24} may not ex-

trapolate to infants and children. For example, recent studies in children have shown that vancomycin trough concentrations of 15 to 20 mg/liter are not necessary to achieve an AUC_{0–24} of >400, and lower trough concentrations are adequate to achieve this target (9, 10). Neonates also represent a unique population, due to the impact of maturation and development on pharmacokinetics (11), and the extrapolation of findings in adults or children to neonates is potentially prone to error. The vancomycin trough concentrations predictive of an AUC_{0–24} of >400 have not been examined in neonates, but this understanding would be helpful for framing target trough concentrations in neonates in whom MRSA infection is a concern. The objective of this study was to determine the relationship between vancomycin trough concentration and AUC_{0–24} in neonates.

MATERIALS AND METHODS

A retrospective chart review was conducted for all neonates treated with vancomycin at a level III neonatal intensive care unit (NICU) located in a tertiary care academic medical center from January 2007 to November 2012. The study was approved by the Stanford University institutional review board. Neonates in whom vancomycin was used were identified via

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a query of the electronic medical record. Neonates were excluded if a complete vancomycin dosing history was not available, extracorporeal membrane oxygenation (ECMO) was required during the vancomycin course, or a diagnosis of congenital kidney disease or major congenital heart disease (diagnosis other than ventricular septal defect, atrial septal defect, or patent ductus arteriosus) was made. For those meeting the enrollment criteria, the data collected included demographics (race, sex, gestational age at birth, birth weight, current weight, and 5-min Apgar score), serum creatinine level, and complete vancomycin dose and drug concentration history.

At the time of study, the recommended vancomycin dose embedded in the computerized order entry system for neonates with a serum creatinine level of <1 mg/dl was 20 mg/kg of body weight every 24 h (q24h) if <2 kg and 15 mg/kg q12h if ≥ 2 kg. For any neonate with a serum creatinine of ≥ 1 mg/dl, a dose of 24 mg/kg was recommended, with further dosing guided by therapeutic drug monitoring (TDM). Vancomycin was administered intravenously over 60 min. TDM is performed in all neonates, which includes peak and trough concentrations to be measured after the first, second, or third dose. Dose adjustments are then made in consultation with a pediatric clinical pharmacist. Vancomycin trough concentrations were recommended to be determined just prior to the next dose, and peak concentrations were recommended to be determined 1 to 2 h after the end of infusion.

Quantitative determination of the vancomycin concentrations was performed by the Stanford Clinical Laboratory using a homogenous particle-enhanced turbidimetric inhibition immunoassay (PETINIA) (VANC Flex reagent cartridge using the Dimension clinical chemistry system; Siemens Healthcare Diagnostics, Inc., Newark, DE). The reportable range of the assay was 0.8 mg/liter to 50 mg/liter. The within-run and total coefficients of variation for the assay were $<6\%$. Serum creatinine was measured by a modification of the kinetic Jaffe reaction (CREA Flex reagent cartridge using the Dimension clinical chemistry system, Siemens Healthcare Diagnostics, Inc.).

Population pharmacokinetic analysis. To predict the vancomycin AUC_{0-24} in the study patients, a population pharmacokinetic model was first developed from the vancomycin concentration time data using the nonlinear mixed-effects modeling program NONMEM (version 7.2; Icon Development Solutions, Ellicott City, MD). The first-order conditional estimation method with interaction was used throughout the model building and evaluation process. A one-compartment pharmacokinetic model with first-order elimination was implemented. Interindividual variability was evaluated on clearance (CL) and volume of distribution (V) using an exponential error model. To model the residual variability (i.e., intraindividual or measurement error that captures the difference between the model-predicted concentration for an individual and the observed concentration in that individual), both additive and proportional error models were evaluated. Selection between the models was based on the difference in the NONMEM objective function value (OFV) and a visual comparison of standard diagnostic plots. The difference in OFV between two models has an approximate χ^2 distribution, with the degrees of freedom equal to the difference in the number of parameters between the models. Significance was set at an OFV decrease of >10.83 , corresponding to a P value of <0.001 .

Based on principles of pediatric clinical pharmacology and previous population pharmacokinetic models in neonates and children for a range of compounds, including vancomycin, covariates related to size (weight), maturation (age), and kidney function (serum creatinine) were evaluated for their influence on vancomycin pharmacokinetics (12–14). If a covariate was not measured on the date of a vancomycin dose or concentration, the value was imputed using the last observation carried forward. The effect of weight on CL and V was implemented using an allometric model, with the exponents defining the relationship fixed to 0.75 and 1, respectively (13). The effect of maturational changes on vancomycin CL was explored using gestational age (GA), postnatal age (PNA), and postmenstrual age (PMA = GA + PNA). Linear, exponential, first-order, and

sigmoid maximum effect (E_{max}) maturation functions were tested (15). The effect of serum creatinine on vancomycin CL was modeled, assuming an exponential relationship.

The covariate model was built using a standard forward addition backward deletion procedure. Covariates were added to the model in a stepwise manner in the order of their reduction in the OFV. During forward stepwise addition, a covariate was allowed to enter the model as long as the decrease in OFV due to its addition was >3.84 , corresponding to a P value of <0.05 . After the stepwise addition terminated, the model was pruned using backward elimination. The covariates were eliminated one at a time, until the removal of a covariate resulted in an OFV increase of >10.83 , corresponding to a P value of <0.001 .

To evaluate the accuracy and stability of the final pharmacokinetic model, a nonparametric bootstrap resampling method was performed using the NONMEM support software Perl-speaks-NONMEM (PsN) (version 3.6.2). A total of 2,000 bootstrap data sets were generated from the original data set by repeated sampling with replacement, and the final pharmacokinetic model was used to estimate the model parameters for each data set. In addition, the final pharmacokinetic model was assessed using an internal evaluation procedure by computing the normalized prediction distribution errors (NPDE) of 5,000 simulated data sets compared to those of the observed data set (16, 17).

Trough concentration and AUC_{0-24} relationship. Bayesian estimates of CL for each neonate from the developed population pharmacokinetic model were used to calculate the AUC_{0-24} at the time of vancomycin trough concentration measurement (18). The AUC_{0-24} was calculated as the vancomycin dose received in 24 h divided by the vancomycin CL. AUC_{0-24} is measured in units of mg · h/liter; however, for simplicity, the units have been omitted for presentation when referring to AUC_{0-24} of >400 . To evaluate the achievement of steady state at the time of vancomycin trough concentration measurement, the number of half-lives that passed was calculated as the time of trough/half-life ($t_{1/2}$), where the time of trough is the amount of time elapsed since the start of the vancomycin dosing regimen, and $t_{1/2}$ is the vancomycin half-life for a neonate using the Bayesian estimates of V and CL ($t_{1/2} = 0.693 \times V/CL$). The relationships between trough concentration and AUC_{0-24} were then examined. Specifically, for a given trough concentration, the proportion of children with that trough concentration who achieved an AUC_{0-24} of >400 was calculated. For example, at a trough concentration of 10 mg/liter, this was calculated as the number of neonates with a trough concentration of 10 to 10.9 mg/liter who achieved an AUC_{0-24} of >400 divided by the total number of neonates with a trough concentration of 10 to 10.9 mg/liter. An AUC_{0-24} of >400 would predict an AUC_{0-24}/MIC of >400 for an MIC of ≤ 1 mg/liter.

To examine the impact of PMA, serum creatinine level, and dose on the relationship between trough and AUC_{0-24} achievement, a Monte Carlo simulation sensitivity analysis was performed. Using the final population pharmacokinetic model, the pharmacokinetic profiles of 5,000 hypothetical neonates were repeatedly simulated at steady state. For a given simulation, the PMA, serum creatinine level, and dose were fixed. Between the simulation runs, one predictor variable was changed. PMAs of 28, 34, 40, and 46 weeks were evaluated. The serum creatinine levels were 0.4, 0.8, 1.2, or 1.6 mg/dl, and doses of 20 mg/kg every 24 h, 20 mg/kg every 12 h, 15 mg/kg every 12 h, 15 mg/kg every 8 h, and 15 mg/kg every 6 h were tested. The median weight for a given PMA from the Fenton growth chart was used (19). For each simulation, the proportion of neonates achieving an AUC_{0-24} of >400 at a given trough concentration was calculated as described above. In addition, the percentage of patients with a potentially toxic trough concentration of >20 mg/liter was assessed.

RESULTS

Patients. A total of 249 eligible neonates had vancomycin dose and concentration data available for analysis. The patient characteristics are shown in Table 1. Nineteen neonates had a gestational age listed in the medical record as full-term, and for these neo-

TABLE 1 Patient characteristics^a

Characteristic ^b	Median	IQR ^c	Minimum	Maximum
Gestational age at birth (wk)	34	27–39	22	42
Birth wt (kg)	2.0	0.9–3.1	0.4	4.4
Wt at vancomycin treatment (kg)	2.9	1.6–3.7	0.5	6.3
PNA at vancomycin treatment (days)	19	10–42	0	173
PMA at vancomycin treatment (wk)	39	32–42	24	54
Female (no. [%])	121 (49)			
Race (no. [%])				
White	170 (68)			
Black	11 (4)			
Asian	57 (23)			
Hawaiian	2 (1)			
Other	9 (4)			
Apgar score at 5 min	8	7–9	1	10
Serum creatinine at vancomycin treatment (mg/dl)	0.4	0.3–0.6	0.1	2.7
Gentamicin (no. [%])	22 (9)			
Furosemide (no. [%])	41 (16)			
Dopamine (no. [%])	22 (9)			
Indomethacin (no. [%])	2 (0.8)			

^a *n* = 249.^b PNA, postnatal age; PMA, postmenstrual age.^c IQR, interquartile range.

nates, a gestational age of 40 weeks was used. Birth weight and Apgar score at 5 min were not recorded in 53 and 66 neonates, respectively. Sixty neonates had a birth weight of <1,000 g, and 38 had a weight of <1,000 g at time of vancomycin dosing. Eight neonates did not have creatinine levels available around the time of vancomycin dosing. Seven of these neonates had a PMA of ≥ 42 weeks and PNA of ≥ 2 weeks, except one who had a PMA of 39 weeks and PNA of 6 days. For these 8 neonates, the median serum creatinine level for the study population of 0.4 mg/dl was used. For the 241 neonates with a creatinine level, imputation using the last observation carried forward was performed for 697 of the 2,057 days when vancomycin was administered. The median number of days carried forward was 2 (interquartile range, 1 to 3). The median starting dose was 15 mg/kg every 12 h for 121 neonates and 20 mg/kg every 24 h for 115 neonates. Eleven neonates received 15 mg/kg every 8 h, and two received 12 mg/kg every 6 h. A total of 1,702 vancomycin drug concentrations were available for analysis and included a large number of concentrations within the first 3 h from the end of vancomycin infusion (Table 2). Of the 249 neonates, 234 (94%) had at least one concentration measured within 3 h from the end of vancomycin infusion. Nineteen concentrations were below the level of quantification (BLQ) (<0.8 mg/liter), and these were set to 0.4 mg/liter and included in the analysis.

Population pharmacokinetic analysis. Vancomycin concentrations were adequately described by a one-compartment model with first-order elimination. The addition of weight scaled via allometry to predict CL and *V* significantly improved the model (ΔOFV , $-1,603$; $P < 0.001$). CL maturation was best described by a sigmoid E_{max} maturation function: $F_{\text{mat}} = 1/(1 + [\text{PMA}_{\text{weeks}}/\text{TM}_{50}])^{-\text{Hill}}$, where $\text{PMA}_{\text{weeks}}$ is the PMA of the patient in weeks, TM_{50} is the value of PMA when maturation reaches 50% adult clearance, and Hill is the slope parameter for the sigmoid E_{max}

TABLE 2 Time of vancomycin concentrations

Time since end of vancomycin infusion (h)	No. of available concns
0–1	182
1–2	539
2–3	76
3–4	15
4–6	85
6–8	175
8–12	406
12–24	203
>24	21

model. The inclusion of F_{mat} for the prediction of CL in the population pharmacokinetic model resulted in a ΔOFV of -976 ($P < 0.001$). After weight and F_{mat} were included in the model, serum creatinine level remained a significant predictor of vancomycin CL (ΔOFV , -147 ; $P < 0.001$). All covariates identified were supported by individual Bayesian pharmacokinetics (PK) parameter estimates versus covariate plots. The final vancomycin population pharmacokinetic model, including parameter estimates and their relative standard errors (RSE), are presented in Table 3. Standard goodness-of-fit plots of the final model showed no systematic bias (Fig. 1). The parameter estimates as found by bootstrap were in agreement with those obtained by the final population pharmacokinetic model (Table 3), indicating the robustness and stability of the final model estimates. An internal model evaluation also demonstrated that the final model performed well in describing the observed data. The mean NPDE was 0.01 (theoretical mean is zero), with 93.3% of the observations falling inside the theoretical 90% prediction interval. In addition, there were no trends in NPDE across time, weight, postmenstrual age, or creatinine level (Fig. 2).

Trough concentration and AUC_{0-24} relationship. In the analysis examining the relationship between trough concentration and AUC_{0-24} , 233 of the 249 neonates were included. Sixteen neonates had a concentration drawn >2 h prior to the end of a dosing interval and were excluded. The median number of half-lives that passed at the time of trough concentration measurement was 4.4, with 69% of the trough concentrations measured at >3 half-lives.

Across the 233 neonates, the median AUC_{0-24} was 403 (range, 124 to 869) mg · h/ml. The AUC_{0-24} achieved by various trough concentrations in neonates is shown in Fig. 3A. In general, as trough concentration increased, a higher AUC_{0-24} was achieved ($r^2 = 0.63$). However, individual variation existed, such that the AUC_{0-24} ranged up to 3-fold across neonates for a given trough concentration. Therefore, the AUC_{0-24} could not be predicted with precision for an individual neonate based on trough concentration alone. Instead, the probability of a trough concentration predicting the achievement of a target AUC_{0-24} was examined by calculating the proportion of neonates with a given trough concentration who achieved an AUC_{0-24} of >400. Figure 3B shows the proportion of neonates achieving an AUC_{0-24} of >400 by vancomycin trough concentration. At a trough concentration of 10 to 11 mg/liter, >90% of the neonates achieved an AUC_{0-24} of >400. At this trough concentration, the median AUC_{0-24} was 505 (range, 299 to 853) mg · h/ml.

The impact of PMA, serum creatinine level, and dose on the relationship between trough concentration and AUC_{0-24} achieve-

TABLE 3 Final population PK model parameter estimates and bootstrap results

Population PK parameter ^a	Final model		Bootstrap	
	Estimate	%SE ^b	Median	95% CI ^c
CL _{typical} for wt 2.9 kg, PMA 39 wks, Cr 0.4 mg/dl (liters/h) ^{d,e}	0.276	23.1	0.276	0.192–0.459
TM ₅₀	34.8	10.5	34.9	29.5–44.2
Hill	4.53	16.5	4.46	3.47–6.35
Exponent for Cr effect	0.267	26.0	0.267	0.134–0.392
V _{typical} (liters) ^f	1.75	1.5	1.74	1.70–1.79
Interindividual variability				
CL (%CV)	21.6	17.0	21.6	18.2–25.5
V (%CV)	10.9	42.7	10.6	4.4–14.6
Residual variability				
Proportional (%CV)	20.5	31.6	19.7	12.2–24.7
Additive (SD)	1.3	73.8	1.3	0.8–2.5

^a CL, clearance; PMA, postmenstrual age; Cr, serum creatinine; TM₅₀, value of PMA when clearance maturation reaches 50% of adult; Hill, slope parameter for the sigmoid E_{\max} maturation model; V, volume of distribution; %CV, coefficient of variation $\times 100$; SD, standard deviation.

^b %SE, relative standard error $\times 100$.

^c 95% confidence interval (CI) corresponding to parameter estimate at the 2.5th and 97.5th percentiles.

^d CL (liters/h) = $0.345 (\text{wt}/2.9 \text{ kg})^{0.75} \times F_{\text{mat}} \times (1/\text{Cr}_{\text{mg/dl}})^{0.267}$.

^e $F_{\text{mat}} = 1/(1 + [\text{PMA}_{\text{wk}}/\text{TM}_{50}]^{-\text{Hill}})$.

^f V (liters) = $1.75 (\text{wt}/2.9 \text{ kg})$.

ment was evaluated by Monte Carlo simulation using the final vancomycin population pharmacokinetic model. The results of the Monte Carlo simulation at vancomycin starting doses within the range of current recommendations (4, 20, 21) are shown in Table 4. For each PMA, the serum creatinine level used for simulations closest to the median serum creatinine in our study cohort

is presented. The “target” trough that was predictive of >90% of the simulated neonates achieving an AUC_{0–24} of >400 ranged from 7 to 11 mg/liter across the PMA. Trough concentrations of 15 to 20 mg/liter were not needed to achieve an AUC_{0–24} of >400. Dosing strategies with either higher or lower total daily doses for a given PMA than those presented in Table 4 resulted in vancomy-

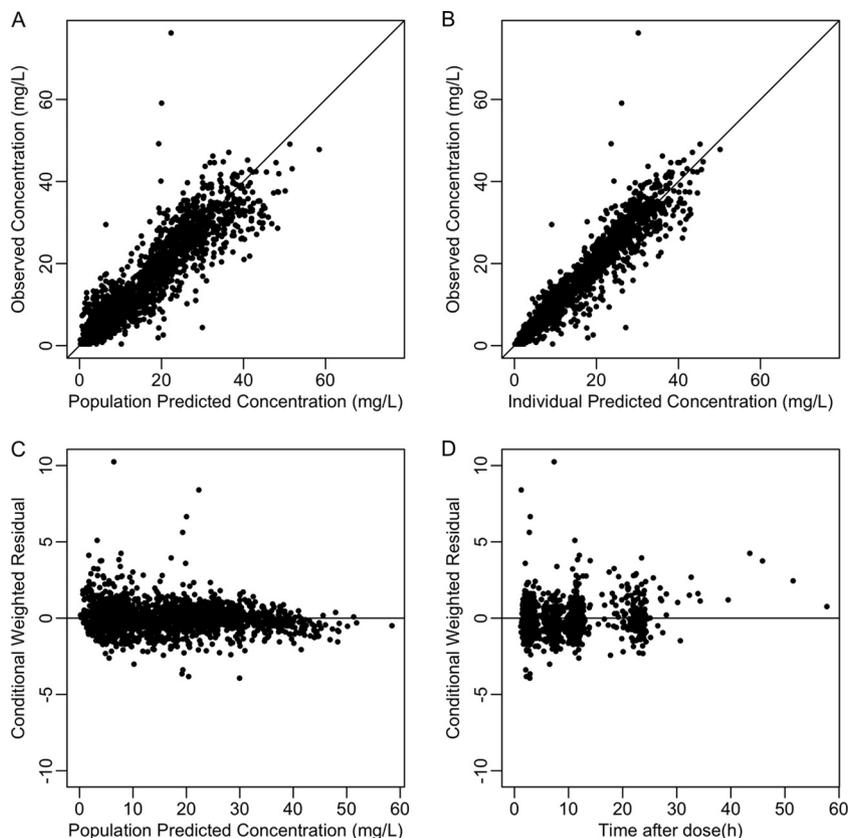


FIG 1 Goodness-of-fit plots of final pharmacokinetic model: observed versus population predictions (A) or individual predictions (B), and conditional weighted residuals versus population predictions (C) or time after dose (D). (A and B) Solid line indicates the line of unity.

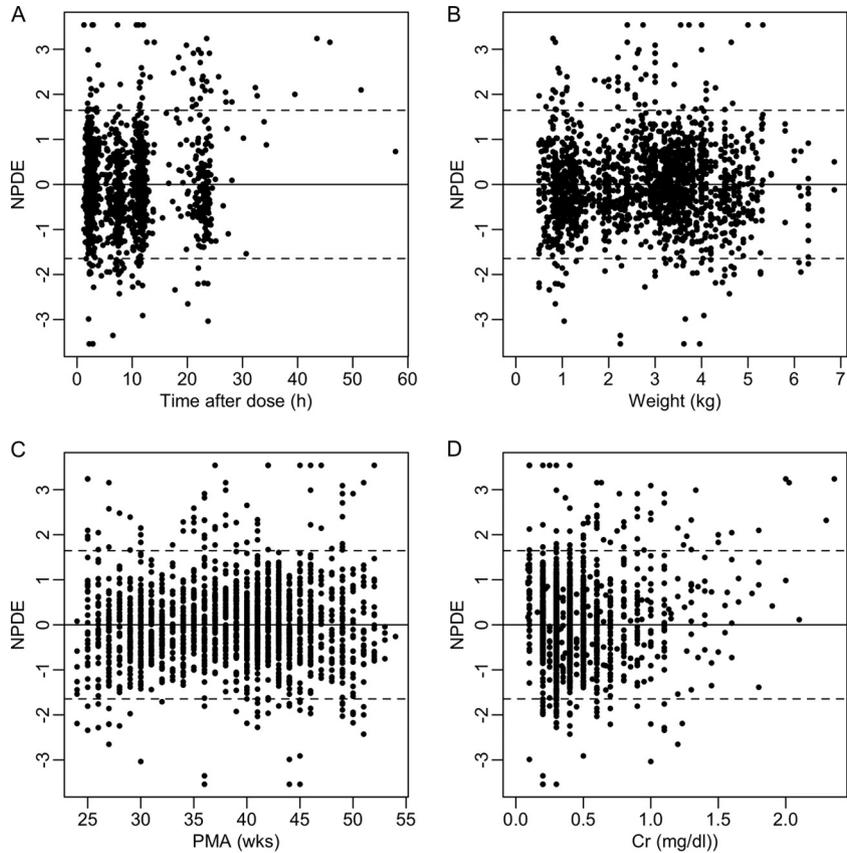


FIG 2 Normalized prediction distribution errors (NPDE) of final pharmacokinetic model by time after dose (A), weight (B), postmenstrual age (PMA) (C), and serum creatinine (Cr) (D). The dashed lines represent 5% and 95% of a standard normal distribution (i.e., 90% of the NPDE should fall between this range).

cin exposures that were unacceptably high (i.e., >20% of the simulated neonates had a trough concentration of >20 mg/liter) or unacceptably low (i.e., >40% of the simulated neonates had a trough concentration of <5 mg/liter), respectively.

The percentage of the simulated neonates achieving the target

trough concentration (i.e., the trough concentration predictive of achieving an AUC_{0-24} of >400 in >90% of the neonates) is also shown in Table 4. Even at empirical doses within the range of what is commonly recommended (4, 20, 21), at best, only 40 to 60% of the simulated neonates achieved the target trough concentration

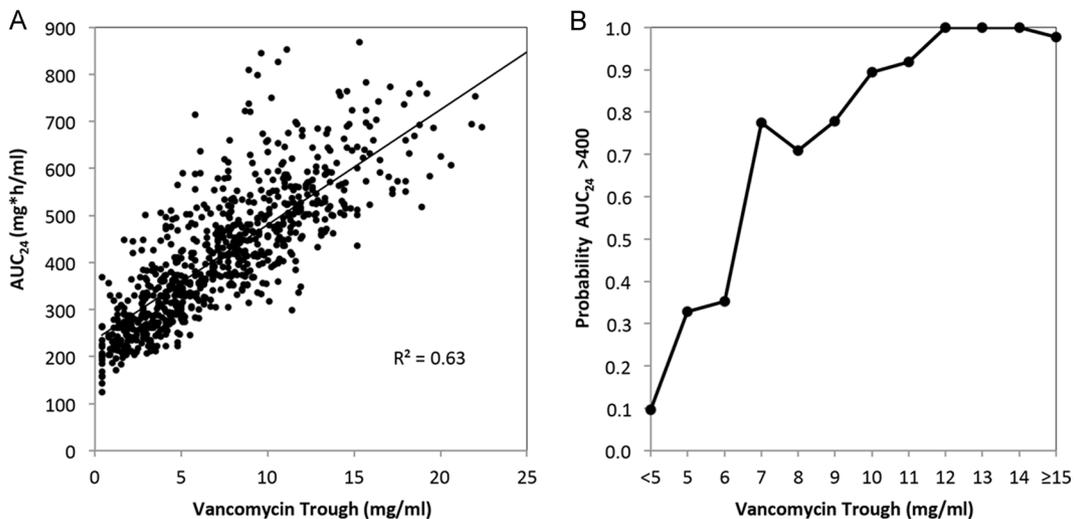


FIG 3 (A) Vancomycin AUC_{0-24} versus trough concentration. (B) Proportion of neonates who achieved a vancomycin AUC_{0-24} of >400 for a given trough concentration.

TABLE 4 Monte Carlo simulation analysis examining AUC₀₋₂₄ and trough achievement^a

AUC/trough achievement	Result by dosage for PMA and serum creatinine level of:							
	28 wk, 0.8 mg/dl		34 wk, 0.4 mg/dl		40 wk, 0.4 mg/dl		46 wk, 0.4 mg/dl	
	20 mg/kg every 24 h	15 mg/kg every 12 h	15 mg/kg every 12 h	20 mg/kg every 12 h	20 mg/kg every 12 h	15 mg/kg every 8 h	15 mg/kg every 8 h	15 mg/kg every 6 h
Target trough concn predictive of AUC ₀₋₂₄ of >400 in >90% of neonates (mg/liter)	8	7	11	9	9	11	11	10
% achieving target trough concn	41	99	18	56	25	46	29	82
% AUC ₀₋₂₄ > 400	73	>99	46	90	61	80	61	95
% trough concn ≥20 mg/liter	1	39	1	4	<1	5	2	19

^a *n* = 5,000 per simulation.

while not concurrently having a trough concentration of >20 mg/liter.

The serum creatinine level impacted the trough concentration and AUC₀₋₂₄ achieved for a given dose, with a higher serum creatinine level resulting in higher vancomycin exposure. However, the relationship between trough and AUC₀₋₂₄ remained similar, with a trough of 7 to 11 mg/liter predicting an AUC₀₋₂₄ of >400 in >90% of the patients across serum creatinine (range, 0.4 to 1.6 mg/dl).

DISCUSSION

The current study examines the relationship between vancomycin trough concentration and AUC₀₋₂₄ in neonates. The major finding was that vancomycin trough concentrations of ~7 to 11 mg/liter were highly predictive of an AUC₀₋₂₄ of >400 (which is recognized as the exposure target for invasive MRSA infections) across neonates of different developmental age and levels of kidney function as measured by serum creatinine level. The relationship between the trough concentration and AUC₀₋₂₄ in neonates is similar to what was recently reported in children (9, 10), and our findings suggest that higher trough concentrations of 15 to 20 mg/liter, which are recommended in adults (6), are likely to be unnecessary in neonates based on AUC₀₋₂₄/MIC considerations when treating invasive MRSA infections with an MIC of ≤1 mg/liter. At the same time, however, we found that only about half of the neonates would actually be expected to achieve initial trough concentrations of 7 to 11 mg/liter using the recommended starting doses.

The optimization of vancomycin dosing and exposure is an important component in the treatment of invasive MRSA infections. Due to the rising burden of invasive MRSA infections along with concerns about treatment failure, recent guidelines by the IDSA have addressed standardized treatment approaches in adults and children (6). To maximize the exposure and achievement of an AUC₀₋₂₄/MIC of >400, the therapeutic target associated with clinical outcomes in adults, higher starting vancomycin doses have been recommended for invasive MRSA infections. For example, in children, the recommended starting vancomycin dose was increased from 15 mg/kg every 8 h (45 mg/kg/day) to 15 mg/kg every 6 h (60 mg/kg/day). This updated dosing in children is predicted to routinely achieve an AUC₀₋₂₄/MIC of >400 for MICs of ≤1 mg/liter (22, 23). Vancomycin dosing strategies in neonates are not specifically addressed by the IDSA guidelines, and instead, the American Academy of Pediatrics (AAP) Red Book is referenced for guiding vancomycin dosing in neonates. However, published vancomycin dosing strategies in neonates, such as those

found in the AAP Red Book and Neofax, were developed based on the goal of achieving a trough concentration of 5 to 10 mg/liter (4, 20, 21). A consideration of AUC₀₋₂₄ achievement for a vancomycin dosing strategy has not been investigated in neonates, and an understanding of the relationship between vancomycin trough concentration and AUC₀₋₂₄ can help guide vancomycin dosing and exposure targets for neonates in whom MRSA infection is a concern.

To calculate the vancomycin AUC₀₋₂₄ in our study neonates, we developed a population pharmacokinetic model using retrospective therapeutic drug monitoring data collected as part of routine clinical care. The final one-compartment model adequately described the concentration data in the study neonates. Vancomycin clearance was predicted by weight, developmental age as measured by PMA, and serum creatinine level. Each of these covariates was highly significant in the model and is supported by a current understanding of how size, maturation, and renal function impact the pharmacokinetics of renally eliminated drugs in neonates (12, 13, 24). Previous published population pharmacokinetic models of vancomycin in neonates have also found weight, developmental age, and serum creatinine level to be significant predictors of clearance (4, 15, 25-27). For the typical neonate in our study (weight, 2.9 kg; PMA, 39 weeks; serum creatinine, 0.4 mg/liter), the final PK model predicted a clearance of 0.095 liters/h/kg. The same neonate would have a similar predicted clearance of 0.087 liters/h/kg using the PK model described by Capparelli (4), which is the basis for the current AAP Red Book vancomycin dose recommendations in neonates (21). The volume of distribution found in our study (0.6 liter/kg) was also similar to that in previous reports (4, 15, 25-27).

Using the final PK model, the AUC₀₋₂₄ (equal to the daily dose divided by clearance) was calculated in each neonate, and the relationships between AUC₀₋₂₄ and the measured trough concentration were analyzed. Trough concentration alone did not precisely predict vancomycin AUC₀₋₂₄ in an individual neonate, and this limitation of the trough concentration was previously shown in children and adults (10, 28). To address the imprecision in predicting vancomycin AUC₀₋₂₄ based on a trough concentration, we instead applied a probabilistic framework in which for a given trough concentration, the proportion of neonates who achieved an AUC₀₋₂₄ of >400 was examined. Specifically, the trough concentration for which >90% of the neonates achieved an AUC₀₋₂₄ of >400 was selected as a reasonable trough concentration target. Within this framework, the achievement of a trough concentration of ~10 mg/liter in the study neonates was highly predictive of an AUC₀₋₂₄ of >400. Monte Carlo analysis also dem-

onstrated that trough concentrations over an equivalent range (i.e., 7 to 11 mg/liter) were highly predictive of an AUC_{0-24} of >400 across simulated neonates for various PMAs, serum creatinine (Cr) levels, and dosing strategies. Therefore, targeting this trough concentration will help predict the achievement of AUC_{0-24}/MIC of >400 for MRSA infections with MICs of ≤ 1 mg/liter. However, it should be noted that if MRSA isolates with MICs of 2 mg/liter are considered, an AUC/MIC of >400 will not be readily achieved in neonates even at trough concentrations of 15 to 20 mg/liter (data not shown). Taken together, the current study findings suggest that trough concentrations of ~ 10 mg/liter are likely adequate for most neonates in whom MRSA infection is a concern. Targeting higher trough concentrations of 15 to 20 mg/liter in neonates will likely provide no further clinical benefit and only increase the risk of vancomycin toxicity (29).

The advantage of applying a trough concentration-only target approach in clinical practice is its simplicity and the fact that no calculations are necessary. The measured trough concentration of a patient can be readily compared to a defined target trough concentration. However, this approach has significant limitations. Most importantly, the AUC_{0-24} , which is the exposure that predicts a clinical response for invasive MRSA infections and is recommended by the IDSA national guidelines (6), is not directly calculated. In addition, the interpretation of the trough concentration assumes that it is drawn at the appropriate time and at steady state, both of which are often not accurate. Lastly, patient characteristics (weight, developmental age, and serum creatinine level), dose history (including dose amount and dosing interval), and prior vancomycin concentrations measured as part of therapeutic drug monitoring are not incorporated. Such information is patient specific and is important to consider when developing a personalized vancomycin therapeutic approach. Bayesian methods that allow the integration of such data in order to develop a more personalized therapeutic approach were previously developed (18, 30–32) and shown in adults receiving vancomycin to help predict therapeutic targets, including AUC_{0-24} , using a trough concentration only (28, 33). Given the variation of drug PK in neonates, the development of similar clinical dosing support tools will be needed to further advance vancomycin therapeutic approaches for neonates. With the ubiquitous access to computers in the clinical setting and real-time access to data in the electronic medical record, previous technological limitations are no longer present, and user-friendly automated clinical dosing support tools realistically can be developed.

The limitations to our study include the use of a convenience sample of neonates that relied on retrospective data collected as part of clinical care and the lack of intensive PK sampling in neonates. However, the population pharmacokinetic approach is well-suited to handle complicated data structures, and concentrations across a range of times after the vancomycin infusion ended were available, since the peak concentrations were routinely collected. The broad inclusion of neonates was essential to help capture the variability in vancomycin pharmacokinetics between patients and lends greater generalizability to actual clinical practice. An additional limitation to our study is that trough concentrations in the study neonates may not have been measured at steady state, which might impact the relationship between trough concentration and AUC_{0-24} . However, the general agreement in the vancomycin trough concentration predictive of an AUC_{0-24} of >400 between the actual study neonates and simulated neo-

nates (for whom steady state was simulated) is reassuring and strengthens our study findings. The current study used data from only a single center, and the specific characteristics of our center may have influenced the population PK model developed. For example, the vancomycin concentration measured can vary depending on the analytical method used (34). Similarly, the measured serum creatinine levels in neonates vary by assay type, and the Jaffe method may result in higher serum creatinine than that obtained using enzymatic methods (35). Therefore, confirmation of the study findings at other centers is warranted. Finally, the relationship between AUC_{0-24} and clinical outcome in neonates has not been directly examined.

In conclusion, our study has several findings relevant to vancomycin dosing in neonates. First, since MRSA infections are relatively rare in this population and may occur in outbreak settings, these results should not lead to a modification of the standard dosing recommendations for most neonates, in whom MRSA is not suspected. Second, for neonates for whom a concern about MRSA infection is high or confirmed, our results provide guidance for TDM and suggest targeting a trough concentration of ~ 10 mg/liter to achieve an AUC_{0-24} of >400 . Finally, dose selection and adjustment in neonates are challenging, and until more robust clinical dosing support tools are developed, clinicians should interact closely with clinical pharmacists to select an appropriate vancomycin dose that best aligns with the individualized therapeutic approach for neonates.

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