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ABSTRACT

Introduction: The pharmacokinetics of vancomycin are highly variable among neonates, which makes dosing challenging in this population. However, adequate drug exposure is critical, especially when treating methicillin-resistant *Staphylococcus aureus*

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(MRSA) infections. Utilization of population pharmacokinetic models and Bayesian methods offers the potential for developing individualized therapeutic approaches. To meet this need, a neonatal vancomycin population pharmacokinetic model was recently published. The current study sought to externally evaluate the predictive performance and generalizability of this model.

Methods: A retrospective chart review of neonates who received vancomycin and had ≥ 1 peak and ≥ 1 trough concentrations at five Intermountain Healthcare neonatal intensive care units from 2006 to 2013 was performed and served as the external validation cohort. The published population pharmacokinetic model was implemented in NONMEM 7.2 with the structural and variance parameter values set equal to the estimates reported previously. The model was then used to predict the first peak and trough concentration for each neonate in the validation cohort and the model prediction error and absolute prediction error were calculated. Normalized prediction distribution errors (NPDE) were also evaluated.

Results: A total of 243 neonates were studied with a median postmenstrual age of 33 (range:

23–54) weeks and a median weight of 1.6 (range: 0.4–6.8) kg. The model predicted the observed vancomycin concentrations with reasonable precision. For all vancomycin concentrations, the median prediction error was -0.8 (95% CI: -1.4 to -0.4) mg/L and the median absolute prediction error was 3.0 (95% CI: 2.7–3.5) mg/L. No trends in NPDE across weight, postmenstrual age, serum creatinine, or time after dose were observed.

Conclusion: An evaluation of a recently published neonatal vancomycin population pharmacokinetic model in a large external dataset supported the predictive performance and generalizability of the model. This model may be useful in evaluating neonatal vancomycin dosing regimens and estimating the extent of drug exposure.

Keywords: Infectious diseases; MRSA; Neonates; Pharmacokinetics; *Staphylococcus aureus*; Vancomycin

INTRODUCTION

Optimizing vancomycin dosing to rapidly achieve adequate drug exposure is imperative in treating neonatal sepsis, particularly when treating invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections [1]. However, this has been challenging in neonates as the pharmacokinetics of vancomycin are highly variable among neonates due to developmental and pathophysiological changes [2, 3]. Recent studies have shown that standard neonatal vancomycin dosing strategies, such as those outlined in NeoFax[®] (Truven Health Analytics), do not reliably achieve trough concentrations >10 mg/L [4, 5]. In addition, the ratio of the 24-h area under the

concentration–time curve (AUC_{24}) to the minimum inhibitory concentration (MIC)—the best predictor of successful outcomes when treating invasive MRSA infections—is not routinely utilized to assess the appropriateness of vancomycin dosing in neonates, presumably due to practical limitations associated with calculating the AUC_{24} .

Innovative vancomycin dosing strategies are therefore needed in neonates that: (1) incorporate known patient-specific determinants of vancomycin pharmacokinetics such as size, maturation, and renal function in the dose selection, and (2) allow for assessment of AUC_{24} based on the dosing history and vancomycin concentration(s) measured as part of routine therapeutic drug monitoring [3, 6, 7]. To develop such an individualized therapeutic approach in neonates, utilization of population pharmacokinetic models and Bayesian methods will be essential [8–11]. We recently developed a neonatal vancomycin population pharmacokinetic model that capitalized on patient data readily available in the electronic medical record: weight (an indicator of size), postmenstrual age (an indicator of maturation), and serum creatinine (an indicator of renal function) [7]. The model has the potential to improve our ability to define vancomycin dosing regimens that reliably achieve recommended exposure targets; however, it is critical to first evaluate whether this model and its findings are generalizable to neonates outside of the original population used to develop the model. The objective of the current study was to conduct an external evaluation of this published pharmacokinetic model and to enhance our understanding of the relationship between vancomycin trough concentration and AUC_{24} in neonates.

METHODS

Validation Cohort

Approval to conduct this study was granted by the University of Utah and Primary Children's Hospital (PCH) Institutional Review Boards. PCH is a freestanding children's hospital with a level IV neonatal intensive care unit that is staffed by University of Utah neonatologists. PCH is owned and operated by Intermountain Healthcare, which is a large, not-for-profit, vertically integrated healthcare delivery system that serves Utah, Idaho, Wyoming, Nevada, and Montana. In addition to PCH, four other level II-III neonatal intensive care units operated by Intermountain Healthcare were included in this study.

A retrospective chart review was conducted for all neonates who had vancomycin therapeutic drug monitoring performed from 2006 to 2013 at five Intermountain Healthcare neonatal intensive care units. Neonates were included if they were <54 weeks postmenstrual age and had ≥ 2 doses of vancomycin, ≥ 1 peak concentration, ≥ 1 trough concentration, and ≥ 1 serum creatinine level. Vancomycin concentrations were quantified using a particle-enhanced turbidimetric inhibition immunoassay on an Abbott Architect System platform (Abbott Laboratories, Abbott Park, IL, USA). Vancomycin concentrations were defined based on their temporal relationship to dosing records. Trough concentrations were defined as concentrations obtained within 3 h of the next vancomycin dose and peak concentrations were defined as concentrations obtained within 3 h of the preceding dose. Serum creatinine levels collected within ± 48 h of vancomycin dosing and concentration records were carried forward and backward and were used in the analyses. To

account for the known difference in measured serum creatinine concentrations between the Jaffe method (used in the original model derivation cohort) and the enzymatic method (used in the current external validation cohort), a previously described linear conversion factor was applied to all of the enzymatic serum creatinine concentrations included in this external validation (enzymatic concentration = $1.050 \times$ Jaffe method concentration – 0.122) [12]. Exclusion criteria included a diagnosis of congenital kidney disease, major congenital heart disease (other than ventricular septal defect, atrial septal defect, or patent ductus arteriosus), or extracorporeal membrane oxygenation during the vancomycin course.

Model Evaluation

The published neonatal vancomycin population pharmacokinetic model was implemented in the non-linear mixed effects modeling software NONMEM 7.2 (ICON Development Solutions, Ellicott City, MD, USA) as previously described [7]. Briefly, a one compartment model with first-order elimination was used to describe vancomycin pharmacokinetics. Clearance (CL) was predicted by weight (an indicator of size), postmenstrual age (PMA; an indicator of maturation) and serum creatinine (Cr; an indicator of renal function) according to the following equation:

$$CL \text{ (L/h)} = 0.345 \times \left(\frac{\text{Weight}}{2.9\text{kg}} \right)^{0.75} \times \frac{1}{1 + \left(\frac{\text{PMA}_{\text{weeks}}}{34.8} \right)^{-4.53}} \times \left(\frac{1}{\text{Cr}_{\text{mg/dL}}} \right)^{0.267} \quad (1)$$

Volume of distribution (V) was predicted by weight:

$$V (L) = 1.75 \times \left(\frac{\text{Weight}}{2.9 \text{ kg}} \right) \quad (2)$$

After accounting for known predictors, the remaining variation between neonates was described by an exponential error model for both CL (% coefficient of variation [% CV] 21.6%) and V (% CV 10.9%). Residual variability (a measure of the difference between the model predicted concentration for a neonate and the observed concentration in that neonate) was captured using a combined proportional (% CV 20.5%) and additive error model (standard deviation [SD] ± 1.3 mg/L).

For each neonate in the external validation cohort, vancomycin concentrations were then predicted using the parameters of the population pharmacokinetic model and simulating the actual dosing regimen given to the neonate (using the NONMEM MAXEVAL = 0 POSTHOC command). Only concentrations at times for which a neonate had therapeutic drug monitoring performed were simulated. Model predicted vancomycin concentrations (PRED from the NONMEM output) were then compared with the corresponding observed vancomycin concentrations. As described by Sheiner and Beal [13], the bias and precision of the model were assessed by calculating the median prediction error and median absolute prediction error for the first trough and peak concentration according to the following formulas:

$$\text{Prediction error (bias): } \left(\frac{\text{Conc}_{\text{pred}} - \text{Conc}_{\text{obs}}}{\text{Conc}_{\text{obs}}} \right), \quad (3)$$

Absolute prediction error (precision):

$$\left(\frac{|\text{Conc}_{\text{pred}} - \text{Conc}_{\text{obs}}|}{\text{Conc}_{\text{obs}}} \right), \quad (4)$$

where $\text{Conc}_{\text{pred}}$ refers to the model predicted vancomycin concentration and Conc_{obs} refers to the observed vancomycin concentration. Model predicted vancomycin concentrations calculated using each patient's individual Bayesian estimate of CL and V (i.e., the IPRED from the NONMEM output, which incorporates the patient's drug concentrations in addition to the fixed covariate effects in the model predictions) were also evaluated using the same approach.

The predictive performance of the model was further evaluated using simulation-based diagnostic methods. Normalized prediction distribution errors (NPDE) were calculated by simulating 1,000 data sets and comparing the predicted concentrations to the observed concentrations using the NPDE command in NONMEM [14, 15]. The NPDE should follow a normal distribution with a theoretical mean of 0 and variance equal to 1 [14].

Trough Concentration and AUC_{24} Relationship

Following model evaluation, the relationship between trough concentration and AUC_{24} was examined. Bayesian estimates of CL for each neonate from the population pharmacokinetic model were used to calculate AUC_{24} at the time that vancomycin trough concentrations were collected [8]. AUC_{24} was calculated as the daily dose \div CL. For a given trough concentration, the proportion of neonates with that trough concentration who achieved an $\text{AUC}_{24} \geq 400$ was calculated. An $\text{AUC}_{24} \geq 400 \text{ mg} \times \text{hr/L}$ would predict an $\text{AUC}_{24}/\text{MIC} \geq 400$ for an MIC of ≤ 1 mg/L. AUC_{24} calculations, descriptive statistics, and graphical analyses were

performed in R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

External Validation Cohort

Overall, 243 neonates had vancomycin dose and concentration data available and served as the external validation cohort (see Fig. S1 in the electronic supplementary material [ESM]). The median dose was 15.5 (interquartile range [IQR]: 13.9–19.3) mg/kg and the median dosing interval was 11.5 (IQR: 8.0–12.5) h. Demographic and clinical characteristics of the neonates in the external validation cohort are shown in Table 1. For comparison, demographic and clinical characteristics of the neonates in the cohort used to develop the original published pharmacokinetic model are

also shown. Overall, the validation cohort was of lower weight and age and had higher serum creatinine concentrations.

In the external validation cohort, a total of 734 vancomycin concentrations were available for analysis. Each neonate contributed a mean of 3.0 (± 1.8) vancomycin concentrations. The time of vancomycin concentration collection relative to the previous dose is shown in Table 2. All neonates had at least one concentration measured within three hours of the end of the vancomycin infusion. No concentrations were below the lower limit of quantitation.

Model Evaluation

The vancomycin pharmacokinetic model adequately described the observed vancomycin concentrations in the external cohort of

Table 1 Demographic and clinical characteristics of neonates who received vancomycin and had therapeutic drug monitoring performed

Characteristic	Model development cohort ($n = 249$) ^a		External validation cohort ($n = 243$) ^b	
	Median/No.	Range	Median/No.	Range
Female, n (%)	121 (49%)	–	103 (42%)	–
Gestational age, weeks	34	23–42	30	22–41
Birth weight, kg	2.0	0.4–4.4	1.3	0.5–5.1
Weight, kg	2.9	0.5–6.3	1.6	0.4–6.8
Postnatal age, days	19	0–173	12	0–196
Postmenstrual age, weeks	39	24–53	33	23–54
APGAR at 5 min	8	1–10	8	1–10
Serum creatinine, mg/dL ^d	0.4	0.1–2.7	0.6	0.3–1.5

APGAR Newborn scale based on Appearance, Pulse, Grimace, Activity, and Respiration

^a Patient characteristics of the 249 neonates used to develop the neonatal vancomycin population pharmacokinetic model described by Frymoyer et al. [7]

^b Patient characteristics of the 243 neonates used in the current external validation

^c The serum creatinine concentration in the model derivation cohort was measured using the Jaffe method. The serum creatinine concentration in the external validation cohort was measured using the enzymatic method and was converted to a Jaffe-standardized equivalent using a linear equation described by Srivastava et al. [12]. Converted values are presented in the table above

neonates (Fig. 1a). Model predicted vancomycin concentrations (PRED) were slightly lower than the observed concentrations (median prediction error -0.8 [95% CI: -1.4 to -0.4] mg/L). The precision of the model was

Table 2 Timing of 734 neonatal vancomycin concentrations relative to the end of the most recent 1-h infusion

Time since the end of the most recent infusion (h)	N (%)
0–1	122 (17%)
1–2	192 (26%)
2–4	27 (4%)
4–6	63 (9%)
6–8	66 (9%)
8–12	152 (21%)
12–24	107 (15%)
>24	5 (1%)

reasonable with a median absolute prediction error of 3.1 (95% CI: 2.7 – 3.2) mg/L. The predictive performance of the model for peak and trough concentrations is featured in Table 3. When incorporating patient concentrations to obtain Bayesian estimates of pharmacokinetic parameters for each neonate, the precision of the model predicted vancomycin concentrations (IPRED) improved (Table 4). For example, the median IPRED absolute prediction error was 1.7 (95% CI: 1.5 – 1.8) mg/L.

Simulation-based diagnostics of the vancomycin pharmacokinetic model demonstrated a mean NPDE of 0.05 and a variance of 0.96 , indicating no bias and an ability of the model to reasonably capture the underlying variability in the external validation cohort. Additionally, there were no trends in NPDE across weight, postmenstrual age, serum creatinine, or time after dose (Fig. 2).

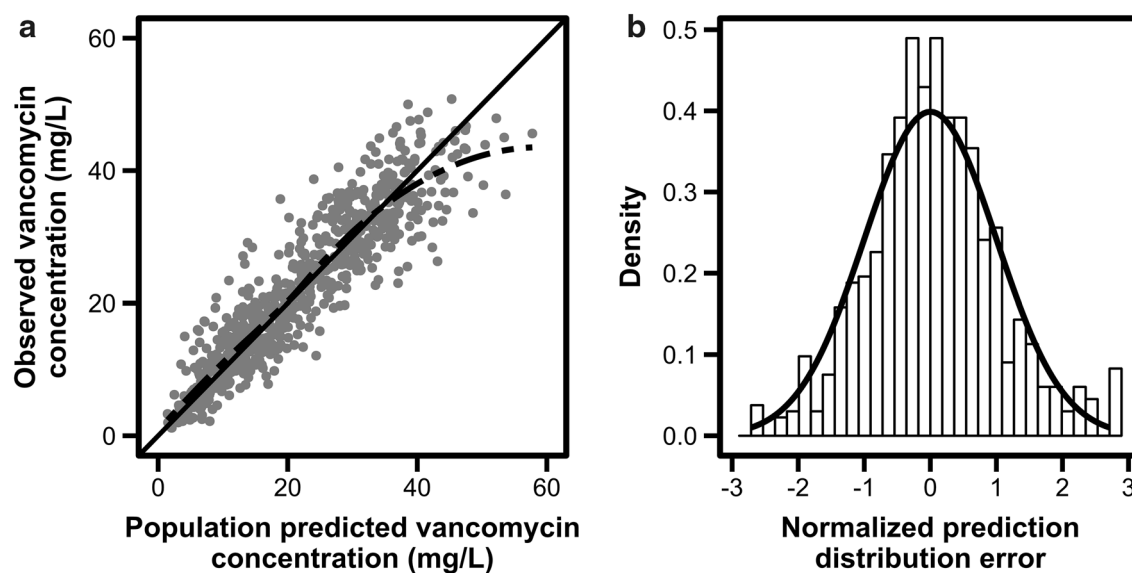


Fig. 1 An external evaluation of the predictive performance of a previously published neonatal vancomycin population pharmacokinetic model [7]. **a** Diagnostic plot depicting the model fit for observed versus population predicted vancomycin concentrations. The *dashed black line*

represents the locally weighted scatterplot smoothed fit of the data. **b** Kernel density plot of the normalized prediction distribution errors with a histogram depicting a normal, Gaussian distribution overlaid for comparative purposes

Table 3 Predictive performance of the neonatal population pharmacokinetic model in the external validation cohort

Predictive measure	All concentrations	First peak	First trough
Prediction error			
Median	−0.8	−2.0	−0.1
95% confidence interval	−1.4 to −0.4	−2.9 to −1.4	−0.5 to 0.2
Percent prediction error			
Median	−4.5%	−7.5%	−1.5%
95% confidence interval	−7.2% to −2.2%	−9.4% to −4.9%	−4.5% to 2.7%
Absolute prediction error			
Median	3.0	3.9	2.1
95% confidence interval	2.7 to 3.5	3.4 to 4.1	1.7 to 2.7
Absolute percent prediction error			
Median	15.2%	12.6%	20.1%
95% confidence interval	14.1% to 17.3%	10.9% to 14.4%	16.8% to 24.0%

Table 4 Predictive performance of the neonatal population pharmacokinetic model in the external validation cohort after incorporating patient drug concentrations in predictions (e.g., IPRED method)

Predictive measure	All concentrations	First peak	First trough
Prediction error			
Median	−0.7	−1.7	−0.2
95% confidence interval	−0.9 to −0.5	−2.2 to −1.4	−0.4 to 0.1
Percent prediction error			
Median	−3.8%	−5.8%	−1.7%
95% confidence interval	−4.9% to −3.2%	−7.5 to −4.6%	−3.4% to 0.6%
Absolute prediction error			
Median	1.7	2.7	0.9
95% confidence interval	1.5 to 1.8	2.1–3.1	0.7–1.1
Absolute percent prediction error			
Median	8.8%	8.4%	9.1%
95% confidence interval	8.1–9.7%	7.3–9.6%	7.3% to 10.8%

Trough Concentration and AUC₂₄ Relationship

A linear relationship between increased AUC₂₄ and higher trough concentrations was observed

in the external validation cohort ($r^2 = 0.60$; Fig. 3a). AUC₂₄ was highly variable at a given trough concentration (i.e., a two- to threefold range of AUC₂₄ was achieved at a given trough concentration), and therefore, AUC₂₄ could not

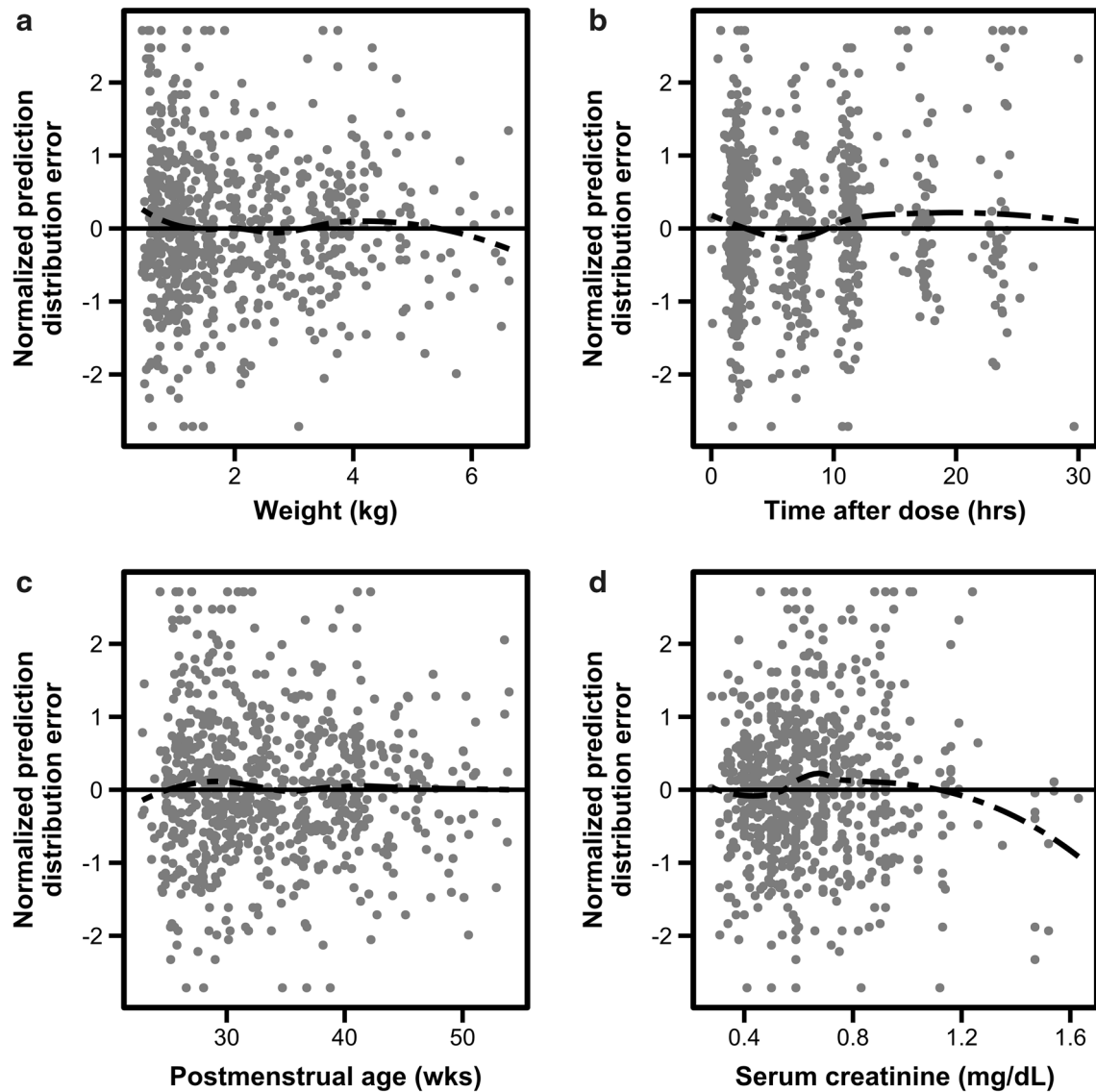


Fig. 2 Assessment of the predictive performance of the neonatal vancomycin population pharmacokinetic model. **a** Normalized prediction distribution errors versus weight, measured in kilograms. **b** Normalized prediction distribution errors versus the time elapsed since the last vancomycin dose, measured in hours. **c** Normalized prediction

distribution errors versus postmenstrual age, measured in weeks. **d** Normalized prediction distribution errors versus serum creatinine concentrations, measured in milligrams per deciliter. The *dashed black lines* represent locally weighted scatterplot smoothed fits of the data

be precisely predicted for an individual neonate based on a trough concentration alone. However, a trough concentration of 11 mg/L predicted the achievement of an $AUC_{24} \geq 400$ in 93% of neonates (Fig. 3b). The median (range) AUC_{24} at this trough concentration was 542 (308 to 649) mg \times hr/L.

DISCUSSION

External validation of a population pharmacokinetic model is described by the United States Food and Drug Administration as “the most stringent method for testing a developed model” [16]. Yet, external validation

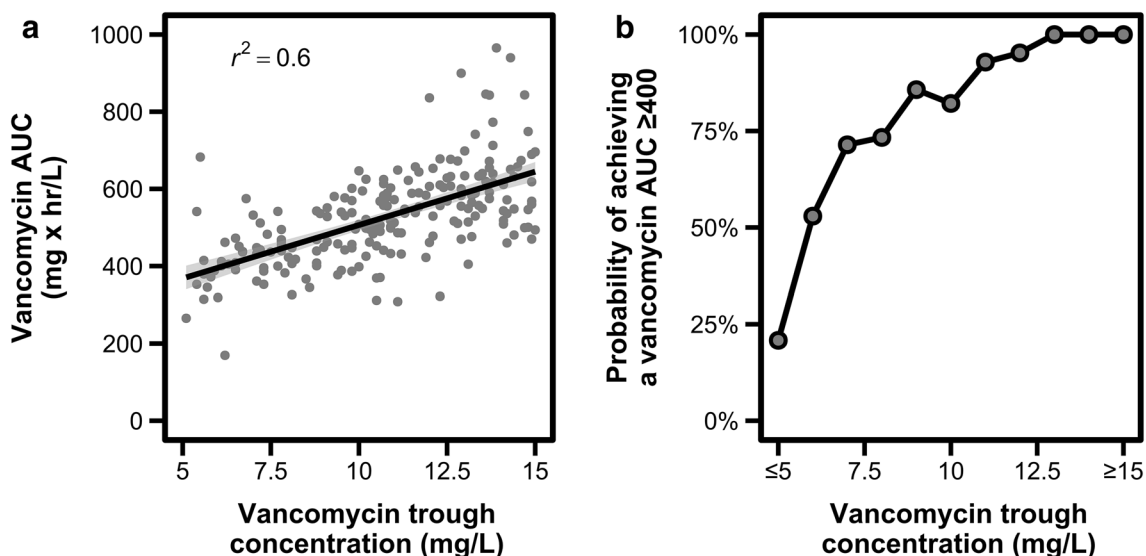


Fig. 3 The association between vancomycin trough concentrations and the extent of drug exposure, as measured by the 24-h area under the curve (AUC_{24}). **a** Higher vancomycin trough concentrations were associated with higher AUC_{24} values, although substantial variability was noted. **b** The probability of achieving a pharmacokinetic/pharmacodynamic target associated with clinical and

microbiological success for invasive methicillin-resistant *Staphylococcus aureus* infections (an $AUC_{24} \geq 400$) increased with higher vancomycin trough concentrations. All neonates with a trough ≥ 12 mg/L had an $AUC_{24} \geq 400$, although many neonates achieved the AUC_{24} target with lower trough concentrations

is performed in <10% of published pharmacokinetic models and concerns about the clinical utility of the model often remain [17]. The external validation performed in the current study strengthens a previously published neonatal vancomycin population pharmacokinetic model. Namely, we found the pharmacokinetic model to be unbiased across the largest cohort of neonates used in a validation study to date. The precision of the model when utilizing only a neonate's postmenstrual age, weight, and serum creatinine was 12.6% for peak concentrations and 20.1% for trough concentrations. When a neonate's drug concentrations are incorporated into the model (such as would occur after therapeutic drug monitoring in the NICU), the precision further improved to 8.4 and 9.1% for peak and trough concentrations, respectively. This level of precision suggests that the model

may be useful in evaluating vancomycin dosing regimens and estimating the extent of drug exposure in the clinical setting.

A recent clinical study by Ringenberg et al. [4] highlights the current challenges with vancomycin dosing in neonates. In a multicenter retrospective evaluation, vancomycin dosing guidelines from Neofax resulted in only 25% of the neonates studied achieving a target trough concentration of 10–20 mg/L with empiric dosing [4]. Moreover, the authors reported that 20% of the neonates included in their study had a trough concentration <5 mg/L (Theresa Ringenberg, personal communication, April 15, 2015). Even after therapeutic drug monitoring and dose adjustment, only 45% of neonates achieved the goal trough concentration of 10–20 mg/L at any point during their course of therapy. This study clearly reveals the

significant clinical challenge associated with reliably achieving therapeutic and safe vancomycin concentrations in this highly variable patient population [4]. More innovative vancomycin dosing strategies and approaches are needed in neonates that can help providers personalize empiric dose selection, interpret therapeutic drug monitoring data, and adjust dosing so that exposure targets are achieved.

Population pharmacokinetic models are a powerful tool that can aid clinicians and help inform dosing decisions [18, 19]. By incorporating patient-specific characteristics, dosing information, drug concentrations, and consideration of the variability between patients, population pharmacokinetic models offer the opportunity to provide a more personalized approach to therapeutic decision making. This is especially valuable in a highly variable population, such as neonates, receiving a narrow therapeutic window drug such as vancomycin.

In adults, Bayesian approaches utilizing population pharmacokinetic models have already been shown to have the potential to help support vancomycin dosing decisions [19, 20]. Advancement of similar approaches in neonates is needed. The development and external validation of a neonatal vancomycin population pharmacokinetic model lays the foundation for this future work. For example, our group is currently developing a model-based approach to individualize the empiric dose in neonates that incorporates the predictors of weight, postmenstrual age, and serum creatinine. Using a simulation framework, the vancomycin dose for a given neonate that is most likely to achieve an $AUC_{24} \geq 400$ while still maintaining a trough concentration < 20 mg/L is calculated. A user-friendly, web-based application is currently

being developed to facilitate the adoption of this model in our neonatal intensive care units, including integration into the electronic health record. In addition, the ability to estimate AUC_{24} and assist providers with dose adjustment within the clinical workflow would be of high value.

Until more robust clinical dosing support tools are developed, clinicians will continue to rely on trough concentration monitoring to help guide vancomycin dosing in neonates. Our findings reinforce the large variability observed in vancomycin trough concentrations among neonates and the inability of a trough concentration alone to reliably predict an individual neonate's AUC_{24} . Targeting an $AUC_{24}/MIC \geq 400$ is recommended by the Infectious Disease Society of America when treating invasive MRSA infections and a trough concentration of 15–20 mg/L is suggested in adults to achieve this target [1, 21]. The current study provides further support that in neonates a vancomycin trough concentration of 15–20 mg/L is unnecessary to achieve an $AUC_{24}/MIC \geq 400$ with an $MIC \leq 1$ mg/L and that lower trough concentrations are likely adequate based on AUC_{24} considerations [7]. Accordingly, a trough concentration of approximately 10 mg/L is likely a reasonable first-line target that will provide adequate exposure for invasive MRSA while also appropriately covering for coagulase negative staphylococcal infections. Further dose adjustment and individualization of the therapeutic approach should be guided by the specific pathogen identified, susceptibility testing, clinical status, etc. For example, for MRSA infections with $MICs \geq 2$ mg/L, an alternative to vancomycin may be necessary since an $AUC_{24}/MIC \geq 400$ will not be achieved in neonates even at trough concentrations of 15–20 mg/L [7]. Lastly, the extent to which the

target $AUC_{24}/MIC \geq 400$ is generalizable to neonates is unclear and requires further study.

CONCLUSIONS

In summary, an evaluation of a recently published neonatal vancomycin population pharmacokinetic model in a large external dataset supported the predictive performance and generalizability of the model. The model may be useful in evaluating vancomycin dosing regimens and for estimating the extent of drug exposure in neonates.

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K08HS023320). JB, EKK, MGS, and CMTS declare that they have no conflicts of interest.

Compliance with ethics guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. A waiver of informed consent was granted by the Institutional Review Boards of the University of Utah and Primary Children's Hospital for the retrospective data presented in this study.

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