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Improved Vancomycin Dosing in Children Using Area-Under-the-Curve Exposure

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Abstract

Background—Our objectives were to: (1) determine the pharmacokinetic [PK] indices of vancomycin in pediatric patients; and (2) compare attainment of two target exposures: AUC/MIC 400 and trough concentration 15 mcg/mL.

Methods—The population-based PK modeling was performed using NONMEM 7.2 for children 3 months old who received vancomycin for 48 hr from 2003 to 2011. A one-compartment model with first-order kinetics was used to estimate clearance (CL), volume of distribution (Vd) and area-under-curve (AUC). Empiric Bayesian post-hoc individual parameters and Monte Carlo simulations (N=11,000) were performed.

Results—Analysis included 702 patients with 1660 vancomycin serum concentrations. Median age was 6.6 (interquartile range [IQR] 2.2–13.4) yr, weight 22.7 (12.6–46) kg, and baseline serum creatinine (SCr) 0.40 (0.30–0.60) mg/dL. Final model PK indices were: $CL(L/h) = 0.248 \cdot Wt^{0.75} \cdot (0.48/SCr)^{0.361} \cdot (\ln(\text{age})/7.8)^{0.995}$; and $Vd(L) = 0.636 \cdot Wt$. Using these parameters and the observed MIC distribution, Monte Carlo simulation indicated that the initial median dose of 44 (39–52) mg/kg/day was inadequate in most subjects. Regimens of 60 mg/kg/day for subjects 12 years old and 70 mg/kg/day for those < 12 years old achieved target AUC/MIC in ~ 75% and trough concentrations 15 in ~ 45% of virtual subjects. An AUC/MIC ~ 400 corresponded to trough concentration ~ 8 to 9 mcg/mL.

Conclusions—Targeted exposure using vancomycin AUC/MIC, compared with trough concentrations, is a more realistic target in children. Depending on age, serum creatinine, and MIC distribution, vancomycin in a dosage of 60 to 70 mg/kg/day was necessary to achieve AUC/MIC 400 in 75% of patients.

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Keywords

Vancomycin; children; pediatrics; antibiotic; *Staphylococcus aureus*; pharmacokinetic; pharmacodynamic

Introduction

Vancomycin plays an important therapeutic role in treating serious infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) in the pediatric population. With a significant increase in MRSA infections reported in children's hospitals across the USA, most pediatric patients hospitalized for suspected serious staphylococcal infections will likely receive vancomycin. Currently, vancomycin is generally considered a first-line agent for empiric therapy, and also serves as the drug-of-choice in serious infections caused by MRSA.^{1, 2} Despite its extensive use, vancomycin dosing information to ensure optimal drug exposure in the pediatric population remains limited.² This is concerning in light of a retrospective review of bacteremia documenting vancomycin treatment failures for MRSA bacteremia, most common in premature infants and immunocompromised children despite achieving vancomycin trough serum concentrations ≥ 15 mcg/mL.³

The importance of proper dosing of vancomycin is illustrated in a consensus national guideline endorsed by prominent professional societies.⁴ Recommendations derived from this guideline were supported by data from adults. Their application to pediatrics requires further exploration. To optimize good clinical outcomes for invasive MRSA infections using pharmacokinetics-pharmacodynamics of vancomycin, studies in adults support targeting area-under-the-curve of the serum concentrations vs. time over 24 hours (AUC) to minimum inhibitory concentration (MIC) ratio of ≥ 400 , which frequently correlates to a minimum concentration (C_{min} or trough serum concentration) of 15–20 mcg/mL when the MIC is 1 mcg/mL.^{4, 5} Pharmacokinetically-derived vancomycin dosing to achieve these targets at varying ages in the pediatric population is limited. Since vancomycin is primarily cleared by glomerular filtration, its clearance correlates well with creatinine clearance. Pharmacodynamic data suggests the commonly recommended dosage of 45 mg/kg/day may be inadequate and doses ranging from 60 to 85 mg/kg/day may be needed in children with normal renal function, particularly those infected by MRSA strains having MICs > 1 mcg/mL.^{2, 6–8} Our primary objectives were to: (1) determine the pharmacokinetics [PK] of vancomycin in children using population-based modeling; and (2) compare target attainment of two pharmacodynamic exposure measures, AUC/MIC ≥ 400 and C_{min} ≥ 15 mcg/mL.

Materials and Methods

This prospectively identified and retrospectively analyzed cohort study was conducted at two pediatric hospitals. Miller Children's Hospital of Long Beach (MCH) is a community-based, tertiary care, teaching hospital with 249 beds (34 pediatric intensive care, 69 neonatal intensive care, 94 general pediatrics, and 52 hematology/oncology beds). Rady Children's Hospital of San Diego (RCHSD) is also a tertiary care, teaching hospital with 308 beds (44 pediatric intensive care, 49 neonatal intensive care, 177 general medical/surgical, and 38 hematology/oncology beds). This study was approved by the institutional review boards at each institution with the use of a waiver of informed consent for retrospective, de-identified data collection and analysis.

Data collection

As part of routine patient care, clinical pharmacists monitored drug concentrations in all patients receiving vancomycin. Pharmacokinetic analyses were performed for patient care to

guide dosing and provide a risk assessment for adverse events. Subjects were monitored daily while on vancomycin; blood samples to evaluate vancomycin C_{min} were obtained after the third vancomycin dose. The entire dosing history and measured serum concentrations, in the context of the timing of the blood sample after vancomycin infusion, were used in the PK modeling. Renal function was monitored closely using baseline and subsequent serum creatinine (SCr) values during therapy as they were obtained by treating clinicians.

Subjects aged 3 months to 21 years (yr) were included if they received vancomycin for 48 hours (hr) between September 1, 2003 and July 30, 2011, and had 1 serum vancomycin concentration to determine C_{min}, collected within 96 hr of drug initiation. Subjects were excluded if they were on hemodialysis, or received medications that may have interfered with vancomycin clearance within 7 days prior to, or during vancomycin therapy (e.g., any amphotericin B formulations and immunosuppressive medications including cyclosporine, tacrolimus, and sirolimus). Neonates, including preemies, in the intensive care unit were also excluded. Some patients were exposed to vancomycin on more than one occasion. Multiple vancomycin use > 12 months apart were considered as separate encounters to improve assessment of intrasubject variability.

Vancomycin and serum creatinine assays

Serum concentrations of vancomycin in all subjects were determined by hospital laboratory assays available at each site. Drug concentrations at MCH were determined by competitive immunoassay using direct chemiluminescence technology (Advia Centaur System, Siemens Medical Solution, Deerfield, IL) with lower and upper limits of detection at 0.67 and 90 mcg/mL, respectively. At RCHSD, vancomycin serum concentrations were determined by fluorescent polarization immunoassay using AxSYM (Abbott Laboratories, Abbott Park, IL). The assay produced predictable, linear results spanning serum concentrations from 2 to 100 mcg/mL. Concentrations > 100 mcg/mL were diluted before final reading.

The SCr assay used was the Jaffe Reaction (Advia 1800 Chemistry System, Siemens Medical Solution, Deerfield, IL) at MCH and Vitros Crea Slide Method (Vitros 5,1 FS Chemistry System, Ortho-Clinical Diagnostics, Rochester, NY) at RCHSD. These assays were initiated in 2006 at MCH and 2008 at RCHSD. The coefficient of variation (precision) for all vancomycin and SCr assays were < 5.5%.

Population-based pharmacokinetic model

Population-based PK analyses were performed using non-linear mixed effect modeling software, NONMEM 7.2 (Icon, Dublin, Ireland). Since most vancomycin samples were collected after the distribution phase, a one-compartment model was used to describe vancomycin PK. Models were fitted using the first-order conditional estimation (FOCE) subroutine and the interaction option. The maximum *a posteriori* Bayesian analysis of each subject's data using the final population model and the POSTHOC option were used to generate individual subject's parameter estimates for volume of distribution (V_d) and clearance (CL). Residual error was modeled with the proportional and combination methods. Prior to exploring potential covariates, parameters were scaled by weight. An allometric approach was utilized to account for variability in weight when estimating drug CL.⁹

The following covariates for V_d and CL were assessed: SCr (mg/dL), age (days), stay in the intensive care unit (ICU), concurrent use of nephrotoxic medications (e.g., aminoglycosides) or chemotherapeutic agents, neutropenia (absolute neutrophil count < 1000 cells/ μ L), study site, and use of new SCr assay. During univariate analysis, covariates that improved the model fit using a likelihood ratio test on the differences in the objective function of 4 (p

0.05 for 1 degree of freedom) were selected for multivariate analysis. A forward selection (objective function reduction of 4, p-value = 0.05) and backward elimination (objective function reduction of 8, p-value = 0.005) were used in the multivariate analysis. The uncertainty in the final model was evaluated using a bootstrap analysis of 1000 patients selected from our cohort to calculate the 95% confidence intervals for the population estimates. The model was considered reliable if the parameter estimates were within the 95% confidence intervals. All statistical analysis was conducted using SPSS GradPack version 20 (IBM, Chicago, Illinois).

Pharmacodynamic relationship

Using empiric Bayesian posthoc values from our final PK model, we conducted Monte Carlo simulations to determine drug exposure for doses ranging from 40 to 100 mg/kg/day divided every 6 hr, except for 45 mg/kg/day. Based on general pediatric growth and development data from the National Health and Nutrition Examination Survey, simulations (N = 11,000 subjects) were performed on patients 3 months to 18 years old with normal SCr (ranging from 0.25 to 0.76 mg/dL) and weights (ranging from 5.5 to 67.2 kg) to estimate the “target attainment” for AUC/MIC = 400 and C_{min} = 15 mcg/mL (e.g., the percent of children who would achieve the specified “target” modeled for each proposed dose). The AUC (mg·hr/L) was calculated by 24-hr dose (mg/kg/day) ÷ CL (L/hr); and steady-state C_{min} determined by the intermittent short infusion model with a 1-hr infusion time (Dose = [(C_{min})(CL)(t_{in})(1 - e^{-kt_{in}})] / [(1 - e^{-kt_{in}})(e^{-kt_{min}})] where t_{in} = infusion time, τ = dosing interval, k = elimination rate constant, t_{min} = time to C_{min}). All MIC values were determined by Epsilometer-test (E-test, bioMérieux Clinical Diagnostics, Durham, NC).

Results

A total of 1631 subjects were screened and 929 excluded (Figure 1). The remaining 702 patients included in the study had a total of 1660 vancomycin concentrations measured, and 454 subjects had ≥ 2 vancomycin concentrations. Eighteen subjects had multiple vancomycin encounters that were accounted for separately. The number of drug samples measured from the end of infusion to 1 hr was 49 (3%); 1.1–2 hr, 332 (20%); 2.1–5, 526 (32%); and >5 hr, 753 (45%).

The median age and weight were 6.6 (IQR 2.2–13.4) yr and weight 22.7 (IQR 12.6–46) kg, respectively (Table 1). A total of 545 (78%) subjects were ≥ 2 years, 276 (39%) received concurrent nephrotoxic drugs (most commonly gentamicin and then furosemide), and 265 (38%) required ICU stay. The median baseline SCr was 0.40 (IQR 0.30–0.60) mg/dL, and median initial dose was 44 (IQR 39–52) mg/kg/day.

Population-based pharmacokinetic model

Eleven models were created to characterize V_d and CL (Table 2). Only age, SCr and weight were independent covariates on CL, and weight on V_d in both univariate and multivariate analyses (Table 3). Minimization and the covariance step were successful for the final model. The covariance between CL and V_d was 13%. Overall, the mean posthoc Bayesian estimates of V_d and CL were 0.63 ± 0.36 L/kg and 0.12 ± 0.04 L/kg/hr, respectively, for our study subjects. The posthoc Bayesian population estimates for V_d and CL were similar to the median bootstrap analysis values, and were within the 95% confidence intervals obtained from the bootstrap analysis (Table 4). Drug CL decreased with increasing SCr and age, particularly after 1 yr (Figure 2). In addition, mean CL was statistically lower in subjects at Hospital B compared with those at Hospital A (0.11 ± 0.04 vs 0.13 ± 0.05 L/kg/hr, p < 0.001), most likely due to the increased SCr evident in patients at Hospital B (0.50 ± 0.34 vs 0.45 ± 0.31 mg/dL, p = 0.05). Scatter plots demonstrated good fit between observed and

predicted concentrations (Figures 3 and 4). Model prediction of concentrations observed > 15 hr (which was < 2% of total observed concentrations) was less accurate than early concentrations since these late concentrations were primarily obtained from subjects who developed nephrotoxicity while on vancomycin therapy (Figure 4b). Vancomycin CL changed more rapidly in these subjects with nephrotoxicity, compared with the changes in their SCr values.

Pharmacodynamic relationship

Susceptibility data were available for 39 MRSA isolates from frozen blood and respiratory samples at hospital A, and 77 from fresh blood samples at hospital B. The initial median dose of ~ 45 mg/kg/day produced mean AUC of 449 ± 216 (IQR 298–551) mg-hr/L and Cmin of 12 ± 8 (IQR 5–16) mg/L (Table 5). At 70 mg/kg/day, mean AUC was 699 ± 333 (IQR 464–857) mg-hr/L and Cmin, 19 ± 13 (IQR 10–25) mg/L.

The MIC distributions were different between the two study sites (Figure 5). Using these MIC distributions in our Monte Carlo simulations (rather than a single MIC value), 70 mg/kg/day achieved a target AUC/MIC ≥ 400 in > 85% of virtual subjects in hospital A with more susceptible isolates, compared with 75% in hospital B with less susceptible isolates. At 70 mg/kg/day, only 50% of children achieved a Cmin ≥ 15 mcg/mL (Figure 6). Using 45 mg/kg/day, attainment of the AUC/MIC exposure target was reduced to 63% in hospital A and 58% in hospital B; only ~21% of children reached a Cmin of ≥ 15 mcg/mL. Regardless of the vancomycin dose, a substantial number of subjects achieved the AUC/MIC target even though their projected Cmin did not reach ≥ 15 mcg/mL.

Age and SCr also contributed to variations in achieving the target AUC/MIC (Tables 6 and 7; Figure 7). Vancomycin 60 mg/kg/day achieved this exposure target in 79 to 88% of subjects who were ≥ 12 years old; 70 mg/kg/day in 75 to 83% of subjects who were 2 to < 12 years old (Table 6). With 60 mg/kg/day, the probability of attaining the AUC/MIC target was below 75% when the SCr < 0.65 mg/dL for Hospital B, which had more MICs at the higher end of the susceptible range than Hospital A (Figure 7). For Hospital A, the SCr cut-off for AUC/MIC exposure below 75% was < 0.46 mg/dL (Table 7). Higher SCr threshold values increased the probability of target attainment as renal elimination of vancomycin reduced with decreased renal function (reflected by higher SCr), resulting in greater exposures (higher AUC) in those children. Incorporating age, SCr and MIC data, our recommendation for empiric vancomycin dosing in non-obese children with normal renal function is provided in Table 8.

Examining the correlation between AUC and Cmin from our Monte Carlo simulations, we observed that AUC ~ 400 mg-hr/L correlated to a mean Cmin ~ 8 to 9 (95% CI, 6–11) mcg/mL for regimens of 60 to 70 mg/kg/day administered every 6 hr (Figure 8).

Discussion

We report the largest study to-date evaluating vancomycin PK in hospitalized children. Consistent with previous studies, our final population-based PK model verified weight as an important covariate for Vd, and age, allometric-scaled weight, and SCr for CL.¹⁰ Our estimates for Vd and CL confirmed findings from previous studies.^{11–17} We selected a one-compartment (rather than two-compartment) model to characterize our PK parameters for two reasons: (1) we had limited samplings (~3%) of concentrations measured within 1 hr after dose administration to describe the distribution phase necessary for a two-compartment model; and (2) we desired to optimize clinical application since a one-compartment model is most often used for therapeutic drug monitoring in practice. Furthermore, a one-

compartment model appears to be the adequate model to characterize vancomycin PK in children.¹⁰

Our study characterized PK parameters for a diverse pediatric population at two different institutions, thereby increased the generalizability of our findings. Some studies focused exclusively on pediatric patients with cancer, cardiac disease, critically-ill status or obesity.^{11–13, 16, 18–20} In contrast, we included children of varying ages (except for neonates and infants < 3 months) and weights (i.e., obese), different concomitant disease states (e.g., cancer), concurrent use of nephrotoxic drugs, and stay in the intensive care unit. This diversity may have contributed to the intersubject variability in our estimate of CL.

Another unique study feature was incorporating the SCr assays into our PK modeling, thereby increasing the relevance of our study findings to current clinical practice. Previous population-based PK studies did not integrate the Jaffe or enzymatic assays. Approximately 95% of our SCr data incorporated these assays. The lower SCr values evident in patients at Hospital A, compared to Hospital B, are consistent with lower determinations from the enzymatic assay.

Despite studies in adults proposing an AUC/MIC 400 as the measure of exposure to optimize treatment success, studies in children have been limited to models utilizing previously published pediatric PK parameters.^{2, 4, 8} These models, in addition to other reports that did not employ population-based PK modeling, suggested that empiric dosing of 40 to 45 mg/kg/day was inadequate to achieve the AUC/MIC target 400.^{6–8, 16, 21} In fact, doses ranging from 60 to 85 mg/kg/day were necessary in children with normal renal function.^{6, 8}

Depending on study sites, 15 to 30% of MRSA isolates had an MIC > 1 mcg/mL. We selected the E-test to evaluate susceptibility of our isolates as this methodology was often used in adult studies to associate an MIC-defined exposure with treatment success. Using these MIC distributions, 60 to 70 mg/kg/day achieved the AUC/MIC target in ~ 75% of subjects. Doses of 90 to 100 mg/kg/day achieved the AUC/MIC target in 90% of subjects but resulted in excessively high concentrations for low MICs. Higher doses may be necessary to achieve the AUC/MIC target if the MICs were at the high end of the susceptible range. However, even increasing the dose to 90 or 100 mg/kg/day did not achieve 90% target when > 30% of isolates had MIC > 1. The mean AUCs for these high-dose regimens ranged from 840 to 940 mg-hr/L, which were more than twice the AUC/MIC target. In addition to observing significant AUC over-exposure, the mean C_{min} produced by 90 to 100 mg/kg/day were > 20 mcg/mL. This was concerning in light of recent evidence to suggest the increased risks of nephrotoxicity and Red Man Syndrome when C_{min} 15 and doses 10 mg/kg in children.^{22, 23} Overall, incorporating the local MIC data is crucial to optimizing vancomycin use.

Attainment of an AUC/MIC 400 also varied by age and SCr values. Based on this exposure target, vancomycin 60 mg/kg/day was optimal for subjects 12 years old, and 70 mg/kg/day for those < 12 years old. In addition, 70 (rather than 60) mg/kg/day was necessary to achieve 75% AUC/MIC target when SCr fell below 0.46 to 0.65, based on specific institution MICs.

We demonstrated that selecting a weight-adjusted empiric vancomycin regimen should be based on: (1) age, with differences evident at 12 years old; (2) SCr, with a potential threshold at 0.46 to 0.65 mg/dL; and (3) the local MIC distribution of MRSA, with the possibility of definitive dosing based on the MIC of the patient's pathogen. This is essential to optimize treatment success while minimizing over-exposure and potentially adverse effects. Vancomycin 60 to 70 mg/kg/day, administered every 6 hr, achieved AUC/MIC

400 in 75% of patients. At these dosing regimens, altering the dosing interval (e.g., every 8 hr) achieves similar AUC/MIC target attainment. However, extending the dosing interval will reduce trough concentrations. Doses higher than 70 mg/kg/day may be necessary to achieve 75% AUC/MIC target in some subjects between 1 and 2 years old, and those with SCr falling below 0.20 to 0.40 mg/dL, depending on institution MICs. However, doses exceeding 80 mg/kg/day may lead to excessively high concentrations and thus should be used with caution.

Despite AUC/MIC being the pharmacodynamic measure of vancomycin exposure evaluated in studies to optimize treatment success, C_{min} is the more common target used in clinical practice. In adults, C_{min} ranging from 15 to 20 mcg/mL are generally required to attain AUC/MIC ~ 400. This C_{min} range is recommended for vancomycin dosing to treat invasive MRSA infections in current guidelines by the Infectious Diseases Society of America.² A very interesting and clinically-significant finding from our study suggested that AUC/MIC ~ 400 corresponded to C_{min} ~ 8 to 9 mcg/mL for regimens 60 to 70 mg/kg/day.

With little evidence to support targeting C_{min} for treatment success specifically in children, it is prudent to monitor vancomycin exposure by AUC (with MIC if available) since it is a more achievable target, and to prevent drug over-exposure and potentially adverse effects. From our study, vancomycin dosing based on C_{min} may lead to an unnecessary increase in drug exposure in 25 to 35% of subjects who may have already achieved the target AUC/MIC. Furthermore, while initial doses should be aggressive to account for potentially serious MRSA infection, targeting C_{min} ~ 15 may not be warranted when, following initial evaluation, MRSA is no longer suspected to be a likely pathogen. In situations requiring doses above 80 mg/kg/day, alternative antibiotics active against MRSA, including linezolid, daptomycin (for non-pulmonary infections), or ceftaroline should be considered.

The concept of “target attainment” allows the clinician to determine the likelihood of achieving the drug exposure parameter that is believed to correlate well to treatment success. For life-threatening MRSA infections, a target attainment of > 95% is needed. If that target cannot be achieved with vancomycin monotherapy alone, then treatment with other MRSA-active agents, or combination therapy with two or more agents (including vancomycin) may produce a better clinical outcome. For non-life-threatening, serious MRSA infections, a lower predicted target attainment may be reasonable, while the child is clinically evaluated during a treatment course, to determine if a change in therapy is needed for clinical or microbiologic failure.

There were several limitations to our study. First, the vancomycin samples were analyzed at two separate clinical laboratories which used immunoassays rather than mass spectrometry, although these assays reflect currently available hospital tests.¹⁰ Second, the probabilities of achieving AUC/MIC target varied between these sites, which is best explained by the differences in vancomycin MIC distributions at the two study sites. Differing susceptibilities at the two institutions may have been related to differences in local vancomycin usage, or in the number of previous exposures to vancomycin in each child, neither of which was evaluated in our study. However, these data highlight the importance of understanding the local vancomycin MIC distributions. In addition, only one drug concentration was measured in 35% of subjects. This may have produced over-parameterization of the PK parameters. Another limitation was the absence of associating drug exposure to clinical outcomes to confirm the targets (i.e., AUC/MIC or C_{min}) derived from adult studies. This is much-needed information that should be investigated in a prospective and controlled setting. If AUC/MIC becomes the optimal target exposure parameter in pediatric clinical practice, clinicians will need to monitor AUC to achieve this target. The optimal method to monitor AUC (i.e., one versus two drug concentrations) requires further exploration. Additional data

on the safety of vancomycin dosages in children when given based on AUC and MIC parameters is essential.

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Figure 1.
Exclusion Algorithm.

Solid line represents with regression line, and dotted line 95% confidence interval

Solid line represents with 90% fit Loess.

Figure 2.
Effect of Age and Serum Creatinine on Vancomycin Clearance.

Figure 3. Observed versus Predicted Concentrations based on Individual (a) and Population Parameters (b).

(a) Conditional weighted residual plot with 90% fit Loess (solid line).

(b) Predicted to observed concentration over time after dose

Figure 4.
Plots of Residuals in Concentrations.

Figure 5. Methicillin-Resistant *Staphylococcus aureus* Susceptibility to Vancomycin at Each Minimum Inhibitory Concentration (MIC) by Hospital.

Figure 6.

Target Attainment by Area-under-Curve over 24 hours to Minimum Inhibitory Concentration (AUC/MIC) versus Trough (Cmin) using Monte Carlo Simulation (N = 11,000 subjects).

*For Hospital A, MIC distribution for methicillin-resistant *S. aureus* isolates was 85% for 1 and 15% for > 1 mcg/mL.

**For Hospital B, MIC distribution for methicillin-resistant *S. aureus* isolates was 68% for 1 and 32% for > 1 mcg/mL.

Figure 7. Probability of Achieving AUC/MIC ≥ 400 based on Serum Creatinine using Monte Carlo Simulation for Vancomycin 60 mg/kg/day. Distribution of minimum inhibitory concentration from Hospital B with 68% of methicillin-resistant *S. aureus* isolates ≤ 1 and 32% isolates > 1 mcg/mL.

Figure 8. Correlation between Area-under-the-Curve and Minimum Concentration by Monte Carlo Simulation for Vancomycin 60 mg/kg/day.

Table 1

Baseline Characteristics, N = 702.

Median age (IQR), years	6.6 (2.2 – 13.4)
< 1, no. (%)	91 (13)
1 to < 2, no. (%)	66 (9.4)
2 to <12, no. (%)	322 (45.9)
12, no. (%)	223 (31.8)
Median weight (IQR), kg	22.8 (12.6 – 46.0)
Race/Ethnicity	
Hispanic	346 (49)
Caucasian	150 (21)
African-American	58 (8)
Asian	27 (4)
Other/Unknown	127 (18)
Male gender , no. (%)	371 (53)
Intensive care unit stay , no. (%)	265 (38)
Concurrent use of nephrotoxic agents , no. (%)	276 (39)
Mean baseline serum creatinine (SCr) $\pm$ SD (IQR), mg/dL	0.48 $\pm$ 0.33 (0.3–0.6)
Mean empiric vancomycin dose $\pm$ SD (IQR), mg/kg/day	45 $\pm$ 12 (39 – 52)
Every 6 hr, no. (%)	256 (37)
Every 8 hr, no. (%)	369 (53)

Abbreviation: IQR = interquartile range

Table 2

Evaluation of Models to Predict Vancomycin Pharmacokinetics Based on Covariates.

Covariate for Clearance ^{1,2}	Change in Minimum Objective Function from Base Model ³
Weight (<i>base model</i>)	--
Weight and neutropenia	319
Weight and study site	204
Weight and SCr assay	200
Weight and concurrent use of nephrotoxic agents	-85
Weight and stay in intensive care unit	-86
Weight and concurrent use of chemotherapeutic agents	-90
Weight and age groups ⁴	-123
Weight and SCr	-177
Weight, SCr and age groups	-188
Weight, SCr and Log(Age)	-284

¹ Actual weight was covariate for volume of distribution in all models.

² The minimum objective function declined with the use of allometric weight in the base model and hence allometric weight was covariate for clearance in all subsequent models.

³ A reduction in minimum objective function by 4 (i.e., corresponding to a p-value = 0.05) significantly improves model fit.

⁴ Age groups consisted of 3mo to 1yr, 1 to < 2yr, 2 to <12yr, and ≥ 12 yr.

Abbreviations and units: Weight in kg, age in days, clearance in L/hr, volume of distribution in L, and SCr (serum creatinine) in mg/dL.

Table 3

Vancomycin Final Pharmacokinetic Model.

Parameter Estimates	Intersubject Variability	Residual Error
$CL\ (L/hr) = 0.248 * Wt^{0.75} * (0.48/SCr)^{0.361} * [\ln(Age)/7.8]^{0.995}$	35%	29%
$Vd\ (L) = 0.636 * Wt$	18%	

Abbreviations and units: Wt = Weight in kg, Age in days, and SCr = Serum creatinine in mg/dL

Table 4Estimates of of Final Population Pharmacokinetic Parameters and Random Effects[/]

Parameter	Estimate	Standard Error of Estimate	Median Bootstrap Estimate	95% Confidence Interval Bootstrap
θ_1	0.636	0.019	0.634	0.598 – 0.672
θ_2	0.248	0.005	0.248	0.240 – 0.257
θ_3	0.362	0.051	0.357	0.257 – 0.459
θ_4	0.995	0.122	0.990	0.758 – 1.239
η_1	0.031	0.033	0.027	0.001 – 0.101
η_2	0.125	0.010	0.125	0.105 – 0.146
ϵ	0.0857	0.007	0.0848	0.073 – 0.098

[/] Final pharmacokinetic model was $V_d (L) = \theta_1 * Wt$ and $CL (L/hr) = \theta_2 * Wt^{0.75} * (0.48/SCr)^{\theta_3} * [\ln(Age)/7.8]^{\theta_4}$

Abbreviations and units: η_1 = intersubject random effect associated with V_d , η_2 = intersubject random effect associated with CL , ϵ = residual random effect, Wt = Weight in kg, Age in days, and SCr = Serum creatinine in mg/dL

Table 5

Monte Carlo Simulations for Vancomycin, N = 11,000.

Dosing Regimen	Median (Interquartile Range)	
40 mg/kg/day (10 mg/kg every 6 hr)	C_{max} , mcg/mL	22 (18–27)
	C_{min} , mcg/mL	8 (5–13)
	AUC , mg-hr/L	337 (248–458)
45 mg/kg/day (15 mg/kg every 8 hr)	C_{max} , mcg/mL	29 (25–35)
	C_{min} , mcg/mL	8 (5–14)
	AUC , mg-hr/L	405 (298–551)
60 mg/kg/day (15 mg/kg every 6 hr)	C_{max} , mcg/mL	33 (28–41)
	C_{min} , mcg/mL	14 (8–21)
	AUC , mg-hr/L	541 (397–735)
70 mg/kg/day (17.5 mg/kg every 6 hr)	C_{max} , mcg/mL	39 (32–49)
	C_{min} , mcg/mL	16 (10–25)
	AUC , mg-hr/L	631 (464–857)
80 mg/kg/day (20 mg/kg every 6 hr)	C_{max} , mcg/mL	43 (35–53)
	C_{min} , mcg/mL	17 (10–26)
	AUC , mg-hr/L	675 (496–917)
90 mg/kg/day (22.5 mg/kg every 6 hr)	C_{max} , mcg/mL	48 (40–60)
	C_{min} , mcg/mL	19 (11–29)
	AUC , mg-hr/L	759 (558–1030)
100 mg/kg/day (25 mg/kg every 6 hr)	C_{max} , mcg/mL	54 (44–67)
	C_{min} , mcg/mL	21 (13–33)
	AUC , mg-hr/L	843 (620–1150)

Abbreviations: C_{max} = maximum or peak concentration at the end of drug infusion;C_{min} = minimum or trough concentration; IQR = Interquartile range

Table 6

Vancomycin Dosing by Age

Dosing Regimen	Age Group (years)	400 Target Attainment (% of Children Treated Achieving the Exposure Required for Cure)	
		Hospital A	Hospital B
60 mg/kg/day ^I	< 1	74	63
	1 to < 2	72	61
	2 to < 12	76	68
	12	88	79
70 mg/kg/day ^I	< 1	82	71
	1 to < 2	80	68
	2 to < 12	84	75
	12	93	84

^IThe dosing interval used in the Monte Carlo simulations was every 6 hr. At the same dosing regimen, extending the dosing interval (e.g., every 8 hr) produces similar AUC/MIC exposure but reduces trough concentrations.

Table 7

Target Attainment of Vancomycin Regimen by Serum Creatinine Threshold Values.

Dosing Regimen	Probability of AUC/MIC 400 Target Attainment (% of Children Treated Achieving the Exposure Required for Cure)	Serum Creatinine (mg/dL) ¹	
		Hospital A ³	Hospital B ⁴
60 mg/kg/day ²	75	0.46	0.65
	85	0.52	1.20
	95	1.20	2.00
70 mg/kg/day ²	75	0.20	0.40
	85	0.45	0.75
	95	0.80	1.50

¹ Below these threshold values, a higher vancomycin dose may be necessary to achieve the AUC/MIC target.

² The dosing interval used in the Monte Carlo simulations was every 6 hr. At the same dosing regimen, extending the dosing interval (e.g., every 8 hr) produces similar AUC/MIC exposure but reduces trough concentrations.

³ For Hospital A, MIC distribution for methicillin-resistant *S. aureus* isolates was 85% for ≤ 1 and 15% for > 1 mcg/mL.

⁴ For Hospital B, MIC distribution for methicillin-resistant *S. aureus* isolates was 68% for ≤ 1 and 32% for > 1 mcg/mL.

Table 8

Empiric Vancomycin Dosing Recommendation for Treating Serious Methicillin-Resistant *S. aureus* Infections in Non-Obese Children with Normal Renal Function by Age Group¹

Dosing Regimen	Age Criteria
60 mg/kg/day ²	2 years old ³
70 mg/kg/day ²	3 months to < 2 years old ⁴

¹Doses were based on attainment of AUC/MIC exposure target in 80% to 85% of patients at an institution where 85% of methicillin-resistant *S. aureus* isolates have minimum inhibitory concentrations 1.5 mcg/mL. Doses should be adjusted once individual patient susceptibility data becomes available.

²The dosing interval used in the Monte Carlo simulations was every 6 hr. At the same dosing regimen, extending the dosing interval (e.g., every 8 hr) produces similar AUC/MIC exposure but reduces trough concentrations.

³For children 2 to < 12 years old, consider 70 mg/kg/day if serum creatinine is < 0.45 mg/dL, or if > 30% methicillin-resistant *S. aureus* isolates have minimum inhibitory concentrations 1.5 mcg/mL.

⁴If > 30% methicillin-resistant *S. aureus* isolates have minimum inhibitory concentrations 1.5 mcg/mL, higher vancomycin doses or other drug regimens may be necessary.