Population-Based Pharmacokinetic Modeling of Vancomycin in Children with Renal Insufficiency

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Abstract

Background—Vancomycin dosing to achieve the area-under-the-curve to minimum inhibitory concentration (AUC/MIC) target of 400 in children with renal insufficiency is unknown. Our objectives were to compare vancomycin clearance (CL) and initial dosing in children with normal and impaired renal function.

Methods—Using a matched case-control study in subjects 3 months old who received vancomycin 48 hr, we performed population-based modeling with empiric Bayesian post-hoc individual parameter estimations and Monte Carlo simulations. Cases, defined by baseline serum creatinine (SCr) 0.9 mg/dL, were matched 1:1 to controls by age and weight.

Results—Analysis included 63 matched pairs with 319 serum concentrations. Mean age ($\pm$ SD) was 13 ± 6 yr and weight, 51 ± 25 kg. Mean baseline SCr was 0.6 ± 0.2 mg/dL for controls, and 1.3 ± 0.5 for cases. Age, SCr, and weight were independent covariates for CL. Final model parameters and inter-subject variability (ISV) were: CL(L/hr) = $0.235*Weight^{0.75}*(0.64/SCr)^{0.497}*(\ln(DOL)/8.6)^{1.19}$ ISV=39%, where DOL is day of life. Target AUC/MIC 400 was achieved in 80% of cases at vancomycin 45 mg/kg/day, but required 60 mg/kg/day for controls. Drug CL improved in 87% of cases due to recovery of renal function.

Conclusion—Due to reduced CL, a less frequent dosing at 15 mg/kg every 8 hr (i.e., 45 mg/kg/day) may be appropriate for some children with renal impairment. Close monitoring of renal function and drug concentrations is prudent to ensure adequate drug exposure, especially in those with renal impairment since recovery of renal function may occur during therapy.

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Keywords

Vancomycin; Children; Pediatrics; Renal disease; Renal insufficiency; Antibiotic; Methicillin-resistant *Staphylococcus aureus* (MRSA); *Staphylococcus aureus*; Antibiotic resistance; Pharmacokinetic-pharmacodynamic; Population-based pharmacokinetic modeling; Monte Carlo simulation; Area-under-the curve

INTRODUCTION

The emergence of multidrug resistant bacteria has been a major concern in the United States and worldwide over the past decades. In particular, methicillin resistant *Staphylococcus aureus* (MRSA) accounts for up to 50% of *S. aureus* infections in hospitalized children in the United States and Canada [1,2]. Vancomycin is effective in treating infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and continues to be frequently prescribed for hospitalized children [3]. For serious infections caused by MRSA, studies in adults support a vancomycin target of area-under-the-curve to minimum inhibitory concentration ratio (AUC/MIC) 400, equivalent to a trough concentration (Cmin) 15 mg/L. Based on limited pharmacokinetic studies, vancomycin 60 to 70 mg/kg/day appear to be reasonable regimens for empiric therapy to achieve target AUC/MIC 400 in children with normal renal function [3–7]. While patients with renal impairment are expected to have reduced clearance (CL) of vancomycin, a drug primarily cleared by the kidneys, the extent to how it affects dosing is unknown. Appropriately dosing vancomycin in children with renal impairment is crucial in light of evidence supporting increased nephrotoxicity associated with high drug exposure, especially in critically-ill children or those receiving concurrent nephrotoxic medications [8,9].

Serum creatinine (SCr) is an endogenous biomarker used to estimate glomerular filtration rate, which serves as practical index for kidney function. Since vancomycin primarily undergoes renal elimination, creatinine clearance (CLcr) has been widely used to determine vancomycin CL. Three methods to compute CLcr, including the Schwartz, Traub and modified Schwartz equations, have been studied in children [10–12]. It remains unclear as to which method best predicts vancomycin CL.

Using a matched case-control study design, the primary objectives of our study were to compare vancomycin CL and determine empiric dosing regimens in children with impaired (case) and normal (control) renal function.

METHODS

Medical records of subjects 3 months to 21 years of age who received vancomycin for 48 hr from September 2003 to December 2011 and had 1 vancomycin concentration (usually trough concentrations) measured at steady-state were identified from two pediatric hospitals, including Miller Children's Hospital of Long Beach (308-bed, not-for-profit, community-based, teaching hospital) and Rady Children's Hospital of San Diego (an integrated pediatric healthcare system with 248 hospital beds). Subjects were excluded if

they were receiving amphotericin B, cyclosporine, and tacrolimus at the time of vancomycin administration. Institutional Review Boards at both sites approved this research.

Cases, defined by SCr 0.9 mg/dL, were matched 1:1 to controls (i.e., SCr < 0.9 mg/dL) by age (within 1 yr) and weight category (normal, overweight, and obese). Blood samples for therapeutic drug monitoring were collected as part of routine patient care. Serum concentrations of vancomycin in all subjects were measured by clinical assays available at each study site. Data were collected on standardized forms; extracted from electronic medical information systems; and consisted of demographics, vancomycin dosing information, concurrent nephrotoxic medications, urine output, and laboratory values.

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

To examine the pharmacokinetic-pharmacodynamic profile of vancomycin, we conducted a population-based modeling using a nonlinear mixed effects modeling software, NONMEM 7.2 (Icon, Dublin, Ireland) [13]. Most vancomycin samples avoided the distribution phase, and as such, introduced bias in peak estimation but have minimal impact on later concentrations. As such, we used a one-compartment model with first-order conditional estimation subroutine (Advan1, Trans2) to generate Bayesian individual parameter estimates for CL, volume of distribution (V) and AUC. Analysis occurred in a stepwise fashion with the: (1) formulation of basic pharmacokinetic model; (2) selection of covariates (age, weight, gender, SCr, and concurrent use of nephrotoxic medication) using multiple linear regression with forward selection at p 0.05 and backward selection at p 0.005 in Perl-speaks-NONMEM 3.5.3; (3) careful inspection of graphical data to evaluate the observed versus predicted parameters (e.g., goodness-of-fit); (4) final population-based model selection; and (5) assessment of parameter reliability (i.e., confidence intervals) using the bootstrap technique of 1000 to calculate the 95% confidence intervals for the population estimates [8]. The model was considered reliable if the parameter estimates were within the 95% confidence intervals. An allometric approach was utilized to account for variability in size for estimating drug CL [14].

Monte Carlo simulation

To compare empiric vancomycin dosing regimens that achieved the pharmacodynamic target of AUC/MIC   400 between children with normal and impaired renal function, we incorporated population-based Bayesian estimates for CL and V from the final model into the Monte Carlo simulations to predict AUC and trough concentrations. The steady-state AUC (mg-hr/L) was calculated by 24-hr dose (mg/kg/day) ÷ CL (L/hr); and steady-state Cmin determined by the intermittent short infusion model with a 1-hr infusion time (Dose = $[(Cmin)(CL)(tin)(1-e^{-k\tau})]/[(1-e^{-ktin})(e^{-ktmin})]$ where tin = infusion time, τ = dosing interval, k = elimination rate constant, tmin = time to Cmin). The MIC values were determined for 116 blood and respiratory isolates using the Epsilometer-test (E-test, bioMérieux Clinical Diagnostics, Durham, NC). The MIC results has been previously described and averaged 15% at 0.25 mcg/mL, 22% at 0.5, 10% at 0.75, 33% at 1, 9% at 1.5, and 11% at 2 for the two study sites [7].

We simulated 10,000 subjects derived from our study population using the following regimens: 45 mg/kg/day (15 mg/kg every 8 hr), 60 mg/kg/day (15 mg/kg every 6 hr), and 70 mg/kg/day (17.5 mg/kg every 6 hr). For each regimen, we calculated the probability of target attainment, which represented the percent of subjects achieving target AUC/MIC   400 or Cmin   15 mcg/mL.

Statistical analyses

To achieve 80% power with a two-sided type 1 error rate and an alpha   0.05 (standard deviation = 20), a sample of 64 pairs was needed to detect a difference in vancomycin dose of 10 mg/kg/day using STATA, version 10.1 (College Station, TX). We conducted statistical analyses using the post-hoc dataset that was derived from the final pharmacokinetic model and contained Bayesian estimates for CL, V, AUC and Cmin for each patient's entire duration of therapy. Study subjects were divided into two groups (controls and cases), and compared by demographic, laboratory and dosing data. Categorical variables were analyzed using McNemar's test for cross-tabulations; continuous variables by the paired t-test. The Wilcoxon rank-sum test was used to evaluate for differences in probabilities of target attainment between controls and cases.

Vancomycin CL was adjusted for body surface area before analyzing for covariates (or predictors). We calculated Pearson's coefficients (r) and performed univariable mixed effects linear regression analysis to ascertain the correlation between vancomycin CL and CLcr, as determined by the Schwartz, Traub and modified Schwartz equations. In addition, we selected matched pairs between 1 and 16 years of age (i.e., age limit for use of CLcr equations) and had SCr measured by the recent assay to analyze fixed and random effects on vancomycin CL longitudinally using multivariable linear mixed effects model and generalized estimating equations (GEE).

Both linear and profile models were used to assess CL changes over the first 10 days of vancomycin therapy. Predictors consisted of age groups (e.g., 1–2 yr, 2–12 yr and   12 yr), weight, study group, and CLcr by modified Schwartz (CLms). Study group and CLms were analyzed separately due to collinearity (i.e., cases have reduced CLms at baseline resulting

from high SCr values). Since age and weight were unchanged during the 10-day treatment period, we evaluated time effects by additive and interaction models for CLms or study group only. The final model for our longitudinal data was selected based on the lowest values using the Akaike's information criterion and corrected quasi likelihood under independence model criterion. All statistical tests was performed with two-tailed analyses using SPSS GradPack version 20 (IBM, Chicago, Illinois), and a $p < 0.05$ was considered significant for all evaluations.

RESULTS

We analyzed 63 matched pairs with 319 vancomycin serum concentrations. Only 2% of concentrations were measured within 2 hr after completion of dose administration. Demographic data was not significantly different between cases and controls, expect for baseline SCr and vancomycin CL (Table 1). Aminoglycosides, meropenem, and vasopressors were the most common nephrotoxic medications used during vancomycin therapy. The initial vancomycin daily doses in cases and controls were similar. These initial doses reflected differences in institutional guidelines rather than lack of appropriate adjustment for renal function.

Eights models were created to characterize Vd and CL (Table 2). Multivariable linear regression analysis identified age, SCr, and allometric weight as covariates for CL, and weight for V. As such, the final pharmacokinetic model incorporated these covariates, and predicted 120% greater CL in an 18 year old vs a 3 month old with same SCr (Table 3). The inter-subject variability in Vd was not characterized based on limited samples reflecting the distribution phase. Scatter plots demonstrated good fit between observed and predicted concentrations (Figures 1a and 1b). Vancomycin CL declined with age in the control group, but slightly increased with age amongst the cases since younger children had higher SCr in this group (Figure 2a). Vancomycin CL declined with increasing SCr (Figure 2b). Despite a high initial SCr value, a one-year old boy had good drug CL since he had a significant decline in SCr during vancomycin therapy.

The posthoc Bayesian population estimates for Vd and CL were similar to the median bootstrap analysis values, and were within the 95% confidence intervals obtained from the bootstrap analysis (Table 4).

Correlation to creatinine clearance

We selected 37 matched pairs with ages between 1 and 16 years and had SCr measured by the recent SCr assay to analyze the time effect of CLcr on drug CL. Based on goodness-of-fit scatter plots, CLcr was correlated to drug CL (Figure 3). The modified Schwartz and Traub estimations for CLcr were identical (r = 1). Among covariates including weight, age group, study group, SCr and CLcr, Pearson's coefficient and univariable mixed effects linear regression analyses demonstrated that CLcr estimation by modified Schwartz and Traub were best correlated to vancomycin CL (Table 5). In addition, univariable analysis showed a significant time effect, both additive and interaction, of CLcr (estimated by modified Schwartz and Traub) on drug CL (p-values 0.017). Serum creatinine was an important covariate, but this variable was already incorporated into the estimations of CLcr.

Longitudinal analysis

Adjusted CL, but not age, exhibited a normal distribution. As such, age was categorized into three groups (Table 5). Three predictors, including weight, age group, and study group (or CLcr by modified Schwartz [CLms]), were selected for longitudinal analysis. The duration of vancomycin therapy ranged between 48 hr to 20 days, but only the first 10 days of therapy were analyzed longitudinally. Data were available for 70% of subjects 3 days, 50% for 5 days, and 25% for 10 days. The plots for adjusted vancomycin CL indicated a linear relationship over the 10-day course, particularly for the case group (Figure 4a). Mean vancomycin CL and CLms for case subjects increased, which was likely contributed by recovery of renal function as evident from reduction in SCr (Figures 4b and 4c).

Study group (or CLms), age group and weight were analyzed initially using multivariable mixed effects linear. Time effects, both additive and interaction, were estimated with creatinine clearance only, not weight and age groups as these covariates are expected to remain unchanged during the first 10 days of vancomycin therapy. Age and weight were insignificant predictors in these preliminary models and thus were eliminated from the final model.

The profile mixed effects model (i.e., profile random intercept model) was selected to describe the interplay between study group and drug CL. Weight and age group were excluded from this model since they were insignificant predictors of CL (p=0.2 and p=0.5, respectively). Study group, with additive and interaction time effects, were a significant predictor of vancomycin CL (p 0.038). The mean difference in CL between study groups was 25.7 mL/min/1.73m^2 at baseline day 0, but decreased to 8.6 mL/min/1.73m^2 on day 10 (Table 6, Figure 4a). This reflected similarity in vancomycin CL between controls and cases by day 10. For cases, the largest incremental increase in drug CL (range 2.7 to 7.5 mL/min/1.73m^2 per day) occurred within the first 5 days (Figure 4a). For controls, drug CL decreased by 6.9 mL/min/1.73m^2 for each 0.1 mg/dL increase in SCr from day 2 to 10. However, this decline in vancomycin CL was not clinically significant since it bottomed out ~78 mL/min/1.73m^2 on day 10 and remained there after day 10. The decline in drug CL in the control group was explained largely by SCr changes. Age and weight did not contribute to the decrease in vancomycin CL in control subjects. Over 93% variability in CL was explained by inter-subject differences.

The linear random intercept model was selected to describe the interplay between CLms and drug CL. Similar to study group, weight and age group were insignificant predictors (p=0.1 and p=0.2, respectively) and thus were eliminated from further analysis. CLms alone, without additive nor interaction time effect, was a significant predictor for vancomycin CL (p<0.001). At baseline, mean drug CL was 58 mL/min/1.73m^2. An increase in CLms by 1 mL/min/1.73m^2 resulted in a 0.34 mL/min/1.73m^2 increase in drug CL (Table 6). Over 96% of variability in drug CL arose from differences between patients.

Eighteen patients (7 controls and 11 cases) received vancomycin for 10 days. In close evaluation of these patients, their mean vancomycin CL remained relatively constant from day 10 to end of therapy (77.4 ± 8.7 for controls and 72.3 ± 34.5 mL/min/1.73m^2 for cases).

Probability of target attainment

Using Monte Carlo simulations, both AUC and trough concentrations were significantly reduced in cases as compared to controls for all vancomycin dosing regimens (Table 7, p<0.001). Over 80% of cases reached target attainment of AUC/MIC   400 at vancomycin 45 mg/kg/day, but controls required doses of 60 mg/kg/day for controls to reach the same target (Figure 5). Cmin   15 mcg/mL was a less achievable target in both control and case groups. However, Cmin   10 mcg/mL was achieveable in 80% of subjects in cases receiving vancomycin 45 mg/kg/day, but in only 73% of controls at 60 mg/kg/day. Examining the correlation between AUC and Cmin, we observed that AUC ~ 400 mg-hr/L correlated to mean Cmin ~ 8 mcg/mL for regimens 45 to 60 mg/kg/day.

In addition to SCr as demonstrated by case-control groups, age also contributed to variation in achieving AUC/MIC   400. Interestingly, children   2 years of age consistently had lower AUC/MIC target attainment, ranging from 77 to 92%, as compared to those younger than < 2 years who had 100% target attainment for all dosing regimens evaluated. However, the variation on target attainment by age was minimal compared to the effect of SCr, evident by analyses using the mixed effects models.

DISCUSSION

To our knowledge, this is the first report of vancomycin dosing to optimize attainment of AUC/MIC   400 in children with renal insufficiency. We selected a matched case-control design to provide us a modality to compare children with and without renal insufficiency. Using population-based pharmacokinetic modeling, we determined that SCr, age, and weight were independent covariates for vancomycin CL and inter-subject variability accounted for 40% of the differences in CL. Our model was precise as evidenced by population CL and V point estimates similar to the median bootstrap values and narrow 95% confidence intervals.

The predicted drug CL for children with normal renal function from our final pharmacokinetic model was similar to previous studies [8]. For children with renal insufficiency, the baseline vancomycin CL was 0.07 L/kg/hr, which was 30% lower than those with normal renal function. By our study design, the mean difference in vancomycin CL was substantial between cases and controls at baseline. However, this difference diminished by day 10 of vancomycin therapy, with convergence of drug CL between cases and controls to a clinically insignificant quantity. This convergence was largely contributed by the recovery of renal function in children with baseline renal insufficiency and therefore vancomycin CL, especially within the first 5 days of therapy. This demonstrated that these children had acute (i.e., not chronic) renal insufficiency, perhaps from hypoperfusion. As such, close monitoring of renal function, particularly in children with renal impairment, is prudent to ensure that adequate drug exposure is maintained throughout the duration of therapy. Close monitoring of renal function, in addition to therapeutic drug monitoring, aligns with recent evidence to suggest that optimal estimations of pharmacokinetic parameters require time-dependent models that reflect dynamic changes in renal function [15].

Using the average MIC distribution from the study sites, 60 mg/kg/day (or 15 mg/kg every 6 hr) achieved the AUC/MIC 400 target in ~ 80% of subjects without renal insufficiency. A less frequent dosing regimen of 45 mg/kg/day divided every 8 hr achieved this target in 90% of children with renal impairment. In a recent study, vancomycin was administered once or twice daily to adult Japanese patients with renal insufficiency that was defined as CLcr < 80 mL/min [16]. A dosing interval of less than every 8 hr in children with renal insufficiency may not be prudent since less frequent dosing will lead to reduction in Cmin which was not readily attainable at a target of 15 mcg/mL.

Confirming recent studies, Cmin 15 mcg/mL was not easily achieved, as compared to AUC/MIC exposure target, for all regimens [7,17]. In fact, more than half of children with renal impairment who met AUC/MIC target did *not* reach Cmin 15 mcg/mL with vancomycin 45 mg/kg/day. Using Cmin 10 mcg/mL, target attainments for all regimens were somewhat similar to AUC/MIC attainments, especially for children with renal insufficiency. However, the disparity in target attainments by Cmin 10 mcg/mL and AUC/MIC persisted in children with normal renal function. The clinical significance of this is unknown.

We identified that the modified Schwartz and Traub estimations for CLcr were the best correlate for vancomycin CL in children between 1 and 16 years of age. In fact, the modified Schwartz and Traub estimations for CLcr were identical. As such, either equation can be applied in clinical practice to estimate renal function in order to optimize dosing of vancomycin.

The major limitation of our study was the use of a strict definition for renal impairment (i.e., SCr 0.9 mg/dL). This may have excluded patients with renal impairment despite SCr below 0.9 mg/dL, such as infants and young children whose normal baseline SCr can be as low as 0.1 mg/dL. In addition, the mean baseline SCr for our case subjects was 1.3 mg/dL and only 13% of cases had SCr 2.0 mg/dL; therefore, we cannot extrapolate our findings to patients with severe renal impairment or end-stage renal disease. Most importantly, the SCr threshold of 0.9 mg/dL may be restrictive for adolescents; especially older boys since this SCr threshold may reflect actual muscle mass. However, in further examining our case subjects who were 12 years old, their mean baseline SCr was 1.2 ± 0.4 mg/dL.

Another limitation of our study was the high drop-out rate by day 5 and 10 of vancomycin therapy. Since this was an opportunistic study designed to optimize the use of clinical data completed as part of routine care, vancomycin was discontinued based on culture and susceptibility results. The subjects who remained in the study, as opposed to those who had therapy discontinued, may reflect a sicker population with infection. Perhaps, this may have contributed to the decreased vancomycin CL evident in the control group on day 10. A third study limitation was insufficient representation of infants and young children < 2 years. Only 8 (6%) subjects were younger than 2 years. As such, our vancomycin CL estimation and dosing recommendation should extrapolate primarily to older children and adolescents. In addition, while MIC values from our study sites were used in the simulations to predict target attainment, vancomycin dosing recommendations will vary for institutions with different MIC distribution. Lastly, our final pharmacokinetic model only supported

estimation of the inter-subject variability for CL (not V). The small sample size and limited sampling strategy that consisted most of trough concentrations likely contributed to this outcome.

With the dearth of studies evaluating vancomycin dosing in children with renal impairment, this study represents the first step towards understanding renal-based dosing in children, particularly in achieving the AUC/MIC 400 target and integrating current SCr assays [7]. Furthermore, if vancomycin dosing alteration is required in our case subjects who primarily had mild to moderte renal insufficiency, then dose reduction is definitively necessary in patients with severe renal dysfunction. Recognizing this need for dosing adjustment is crucial in light of evidence to suggest association between in high exposure to vancomycin and nephrotoxicity [8]. Further studies in children with renal impairment, including those who are younger or have severe kidney disease, are needed. In addition, the integration of age-specific SCr thresholds in future studies should be explored to determine age- and renal-based vancomycin dosing regimens.

CONCLUSION

Vancomycin 15 mg/kg every 6 hr appears to be a reasonable regimen for empiric therapy to achieve target AUC/MIC in children with normal renal function. Due to reduced drug CL, some children with renal impairment may achieve similar target with less frequent dosing at 15 mg/kg every 8 hr. While this initial low vancomycin dose may be adequate in some children with renal insufficiency, subsequent increases in the dose may be necessary to ensure adequate drug exposure since recovery of renal function usually occurs. Therapeutic drug monitoring and close monitoring of renal function is prudent to ensure optimal drug exposure throughout the duration of vancomycin therapy.

Acknowledgments

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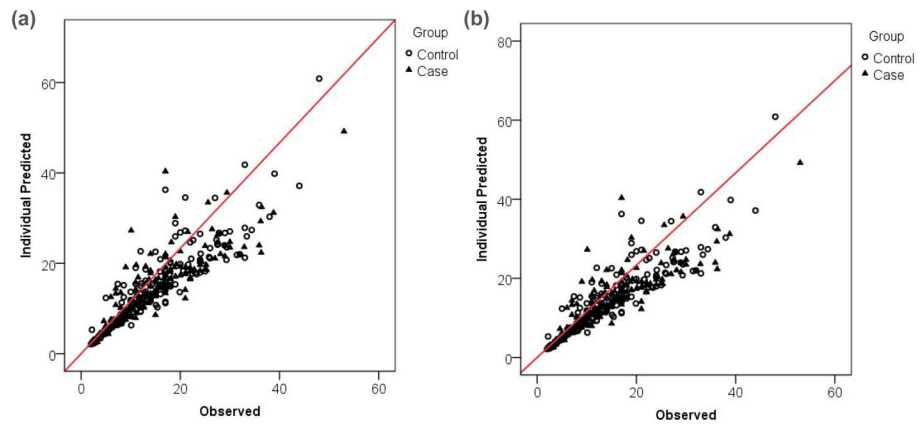
Figure 1.
Observed versus Predicted Concentrations from Final Pharmacokinetic Model.
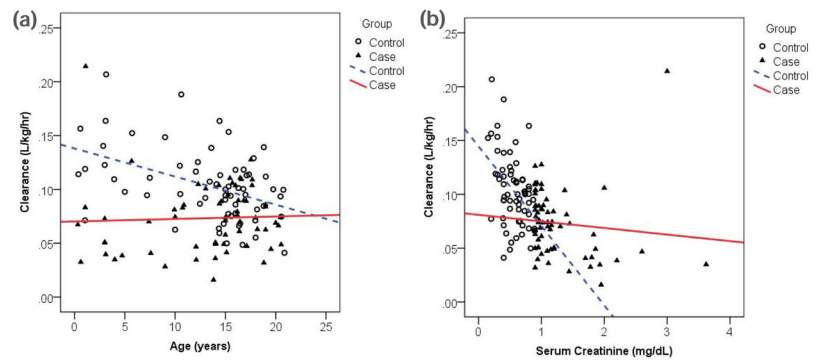
Figure 2.
Effect of Age and Serum Creatinine on Baseline Vancomycin Clearance using the Final Pharmacokinetic Model.
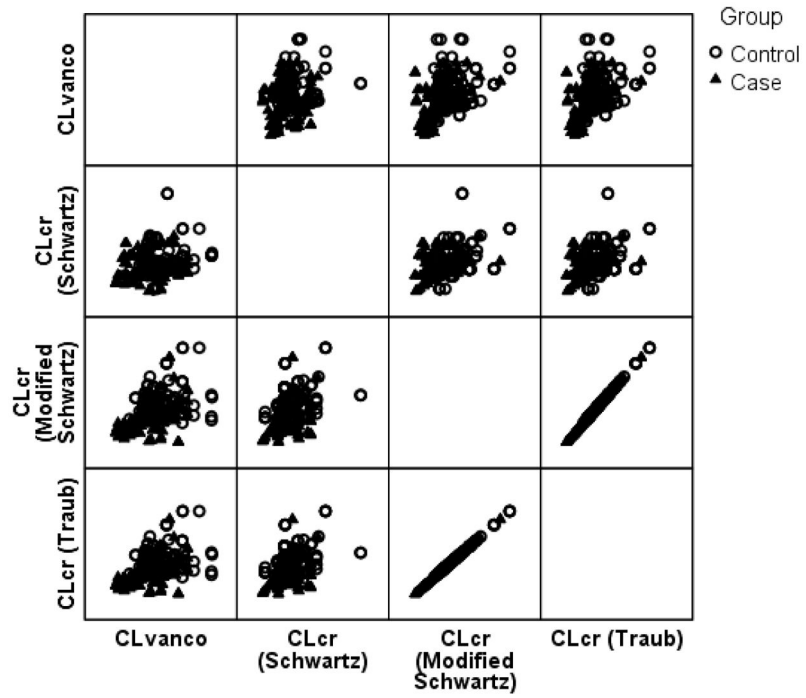
Figure 3.
Matrix Plots of Vancomycin Clearance (CLvanco) and Predictors Creatinine Clearance
(CLcr by various methods).
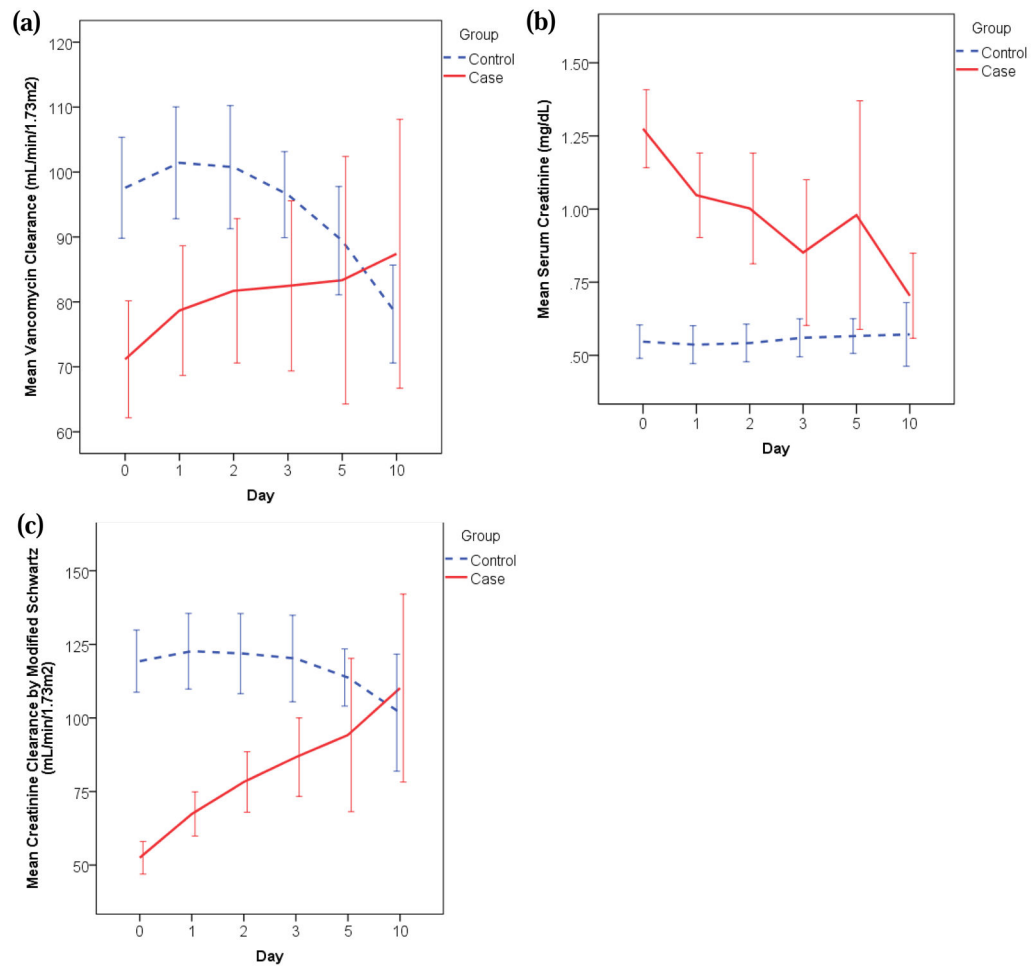
Figure 4.

Mean Vancomycin Clearance, Serum Creatinine and Creatinine Clearance in Children with Impaired (Case) and Normal (Control) Renal Function[a].

[a]Error bars represent 90% confidence interval.

Figure 5.
Vancomycin Target Attainment by Area-under-Curve over 24 hours to Minimum Inhibitory Concentration (AUC/MIC) versus Trough Concentration (Cmin) using Monte Carlo Simulations in Children with Impaired (Case) and Normal (Control) Renal Function.

Table 1

Clinical Characteristics.
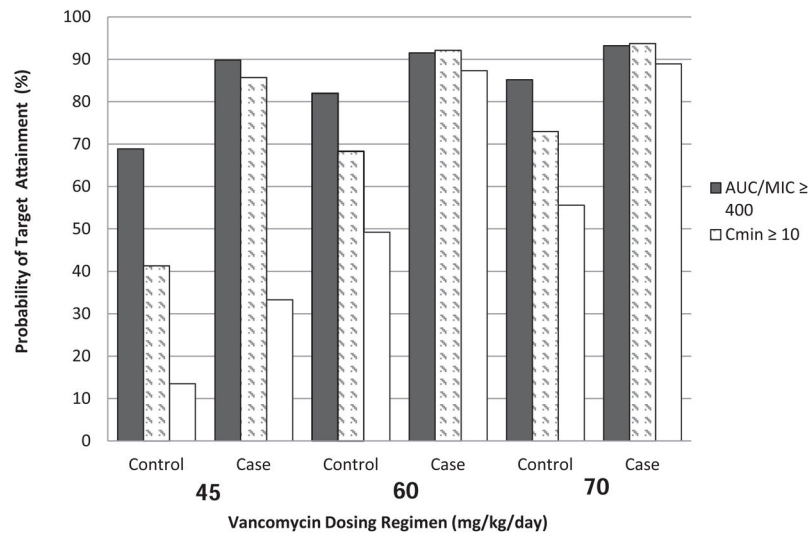
Characteristics	Control (n=63)	Case (n=63)	P-value
Age, yr	13 ± 6	13 ± 6	
< 1, n (%)	2 (3)	2 (3)	
1 to < 2, n (%)	2 (3)	2 (3)	0.7
2 to < 12, n (%)	14 (22)	14 (22)	
12, n (%)	45 (72)	45 (72)	
Male Gender, n (%)	31 (49%)	40 (63%)	0.4
Weight, kg	50 ± 25	52 ± 26	0.1
Body Surface Area, m^2	1.4 ± 0.5	1.4 ± 0.5	0.3
Body Mass Index, kg/m^2	21 ± 5	22 ± 5	0.08
Race/Ethnicity			
Hispanic	22 (35)	32 (51)	
Caucasian	24 (38)	8 (13)	
African-American	6 (10)	11 (18)	-
Asian	0	2 (3)	
Other/Unknown	11 (18)	10 (16)	
Intensive care unit stay, n (%)	22 (35)	33 (52)	0.3
Concurrent use of nephrotoxic medications, n (%)	25 (40)	26 (41)	0.2
Baseline Serum Creatinine, mg/dL	0.6 ± 0.2	1.3 ± 0.5	<0.001
Serum creatinine 2.0, n (%)	--	8 (13)	
Baseline Clearance of Vancomycin, L/kg/hr	0.10 ± 0.03	0.07 ± 0.03	<0.001
Baseline Volume of Distribution, L/kg	0.56 ± 0.01	0.56 ± 0.01	0.9
Urine Output, mL/kg/hr	1.9 ± 1.4	2.9 ± 7	0.2
Empiric Vancomycin Dose, mg/kg/day	42 ± 13	38 ± 14	0.09
Every 6 hr, n (%)	18 (28)	11 (17)	-
Every 8 hr, n (%)	35 (56)	29 (46)	-
Every 12 hr, n (%)	10 (16)	20 (32)	-
Every 24 hr, n (%)	-	3 (5)	-

Numbers represent mean ± standard deviation unless otherwise stated.

Table 2

Vancomycin Pharmacokinetic Model Development.

Covariate for Clearance[1]	Change in Minimum Objective Function from Base Model
Weight (*base model*)	--
Weight and gender	0
Weight and concurrent use of nephrotoxic agents	0
Weight and age	− 4
Weight and SCr	− 26
Weight, SCr and gender	− 26
Weight, SCr and concurrent use of nephrotoxic agents	− 26
Weight, SCr and age	− 60

[1]Actual weight was covariate for volume of distribution in all models; allometric weight was covariate for clearance in all models except the base (first) model in which actual weight was used.

Units (abbreviation): Weight in kg, SCr (serum creatinine) in mg/dL, age in days, and clearance in L/hr.

Table 3

Final Population-Based Pharmacokinetic Model.

Parameter	Inter-subject Variability	Residual Error
CL (L/hr) = 0.235 * Wt$^{0.75}$ * (0.64/SCr)$^{0.407}$ * [ln(age)/8.6]$^{1.09}$	39%	28%
Vd (L) = 0.564 * Wt	-- [a]	

Abbreviations: CL = Clearance, Wt = Weight in kg, Age expressed in days, SCr = Serum creatinine in mg/dL, Vd = Volume of distribution

[a]Intersubject variability in Vd was not characterized due to limited samples.

Table 4

Estimates of of Final Population Pharmacokinetic Parameters and Random Effects[1].

Parameter	Estimate	Standard Error of Estimate	Median Bootstrap Estimate	95% Confidence Interval Bootstrap
θ_1	0.564	0.025	0.563	0.521 – 0.623
θ_2	0.235	0.009	0.235	0.219 – 0.254
θ_3	0.407	0.095	0.418	0.248 – 0.648
θ_4	1.090	0.427	1.144	0.240 – 2.072
η_1	0.154	0.029	0.145	0.093 – 0.214
ε	0.076	0.001	0.075	0.073 – 0.098

[1]Final pharmacokinetic model was Vd (L) = θ_1* Wt and CL (L/hr) = θ_2 * Wt$^{0.75}$ * $(0.64/SCr)^{\theta_3}$ * [ln(Age)/8.6]$^{\theta_4}$

Abbreviations and units: η_1 = 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

Correlation and Univariable Mixed Effects Regression Analysis for Vancomycin Clearance[a].

Covariate	Pearson's Coefficient[b]	Estimate	95% Confidence Interval	P-value
Study Group[c]	-	18.0	3.5 to 32.6	0.016
Age Group, yr	0.178[d]	-	-	0.6 (overall)
1 to < 2	-	14.2	−33.4 to 61.8	0.5
2 to <12	-	−6.6	−22.6 to 9.5	0.4
12	-	-[c]	-	-
Weight, kg	0.186	0.16	−0.12 to 0.45	0.3
Creatinine Clearance Estimations, mL/min/1.73m^2				
Modified Schwartz[e]	0.460	0.36	0.33 to 0.40	<0.001
Schwartz[f]	0.222	0.19	0.14 to 0.23	<0.001
Traub[e]	0.460	0.31	0.28 to 0.34	<0.001
Serum Creatinine, mg/dL[f]	−0.340[d]	−29.8	−33.6 to −26.1	<0.001

[a]All covariates were tested using the linear random intercept model. A covariate was considered significant at p-value 0.05. Time effects, both additive and interaction, were estimated with creatinine clearance only, not weight and age groups as these covariates are expected to remain unchanged during the first 10 days of vancomycin therapy.

[b]P-values were 0.001 for all variables.

[c]Reference groups were case and age group 12 yr.

[d]Natural log function of covariate

[e]Time effects, both additive and interaction, were observed at p-value 0.017.

[f]Time effects, both additive and interaction, were not observed.

Table 6

Mixed Effects Linear Regression Analysis of Predictors for Vancomycin Clearance[a,b].

Covariate	Covariate Effect	95% Confidence Interval	P-value
Study Group[c]	−25.7	−40.6 to −10.7	0.001[d]
Creatinine Clearance by Modified Schwartz, mL/min/1.73m^2	0.34	0.31 to 0.38	<0.001[e]

[a]Age group and weight were insignificant predictors in multivariable mixed effects linear regression analyses and thus eliminated from the final model selection.

[b]Study group was tested using the profile random intercept model; creatinine clearance by the linear random intercept model.

[c]The reference group was controls on first day of therapy.

[d]Significant time effects, both additive and interaction, were observed for case-control groups (p 0.001).

[e]Additive and interaction time effects were *not* observed for creatinine clearance by modified Schwartz estimation (p=0.2 and 0.8, respectively).

Table 7

Monte Carlo Simulations of Vancomycin Regimens in Children with Normal (Control) and Impaired (Case) Renal Function[a,b].

Dosing Regimen	Parameter	Control	Case
45 mg/kg/day *(15 mg/kg every 8 hr)*	Cmin, mcg/mL	9 (5–18)	19 (13–34)
	AUC, mcg-hr/mL	429 (316–677)	691(544–1075)
60 mg/kg/day *(15 mg/kg every 6 hr)*	Cmin, mcg/mL	14 (9–27)	28 (20–49)
	AUC, mcg-hr/mL	572 (421–903)	922 (725–1434)
70 mg/kg/day *(17.5 mg/kg every 6 hr)*	Cmin, mcg/mL	17 (10–32)	33 (24–57)
	AUC, mcg-hr/mL	668 (491–1053)	1075 (846–1673)

Abbreviations: Cmin = minimum or trough concentration; AUC = Area-Under-Curve over 24 hr

[a]Numbers represent median (interquartile range).

[b]Using the paired t-test, the p-values for all Cmin and AUC between control and case groups were <0.001.