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# Bayesian Estimation of Vancomycin Pharmacokinetics in Obese Children: Matched Case-Control Study

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## Abstract

**Purpose**—The study objective was to compare different body size descriptors that best estimate vancomycin $V_d$ and clearance (CL).

**Methods**—Patients between 3 months and 21 years old who received vancomycin for 48 hours from 2003 to 2011 were evaluated in this matched case-control study. Cases had body mass index in the 85th percentile; controls were nonobese individuals who were matched by age and baseline serum creatinine (SCr). Using a 1-compartment model with first-order kinetics, Bayesian post hoc individual $V_d$ and CL were estimated.

**Findings**—Analysis included 87 matched pairs with 389 vancomycin serum concentrations. Median ages were 10.0 (interquartile range [IQR], 4.8–15.2) years for cases (overweight and obese children) and 10.2 (IQR, 4.5–14.8) years for controls (normal-weight children). Median weights were 44.0 (IQR, 23.4–78.1) kg for cases and 31.3 (IQR, 16.8–47.1) kg for controls. Mean (SD) for the baseline SCr values were also similar between the groups: 0.51 (0.22) (IQR, 0.34–0.67) mg/dL and 0.48 (0.20) (IQR, 0.30–0.60) mg/dL for the cases and controls, respectively. Actual weight and allometric weight (ie, weight$^{0.75}$) were used in the final model to estimate $V_d$ and CL, respectively. The mean $V_d$ and CL, based on weight, for cases were lower than controls by 0.012 L/kg and 0.014 L/kg/h, respectively.

**Implications**—In obese children, actual weight and allometric weight are reasonable, convenient estimations of body fat to use for estimating vancomycin $V_d$ and CL, respectively. However, these pharmacokinetic differences between obese children and those with normal weights are small and may not likely to be clinically relevant in dose variation.

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**Keywords**

## INTRODUCTION

Vancomycin is a first-line antibiotic for treating invasive methicillin-resistant *Staphylococcus aureus* infections.[1] The pharmacokinetic (PK) profile and dosing information of vancomycin for obese children remain suboptimal. Coupled to the age-related PK variation between adults and children, excessive adipose tissue (ie, obesity) may significantly affect the distribution and clearance of drugs. With the extensive use of vancomycin in pediatrics and an epidemic of obesity, we believe that it is essential to first analyze the PK parameters of vancomycin that are necessary to optimize dosing in obese children, especially in light of limited population-based PK studies.[1]

Previous PK studies on vancomycin dosing in obese pediatric and adult patients evaluated different body size descriptors (primarily total weight and secondarily lean body mass [LBM] and ideal weight [IW]) for estimating $V_d$ and clearance (CL).[2–7] In obese adults, weight-adjusted $V_d$ was decreased, whereas weight-adjusted CL was either similar or decreased.[4–7] Pediatric studies did not yield significant conclusions regarding differences in weight-adjusted $V_d$ and CL.[2,3,8,9] Notably, none of these pediatric PK studies used Bayesian analysis, which is better in predicting $V_d$ and CL in an obese population based on an understanding of the population PK properties and interindividual and intra-individual variability.

With the limited population-based PK studies that incorporate Bayesian estimation, we aimed to compare 7 different measures of body size descriptors, including actual weight, adjusted weight (AW), IW, allometric weight (ALWT), body mass index (BMI), body surface area (BSA), and LBM, and their influences on vancomycin $V_d$ and CL and in overweight and obese children. Enhancing the accuracy in estimating $V_d$ and CL would result in better empiric dosing recommendation in this population to rapidly achieve a therapeutic exposure without unnecessary vancomycin renal toxicity.

## PATIENTS AND METHODS

This matched case-control study was conducted at 2 children's hospitals. Miller Children's Hospital of Long Beach 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 is 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 these institutions with the use of a waiver of informed consent for retrospective, deidentified data collection and analysis.

As part of routine patient care at Miller Children's Hospital of Long Beach and Rady Children's Hospital of San Diego, clinical pharmacists conduct therapeutic drug monitoring

for all patients receiving vancomycin. Patients were monitored daily while they were taking vancomycin; blood samples to evaluate vancomycin concentrations were generally obtained after the third 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 serum creatinine (SCr).

### Data Collection

Patients aged 3 months to 21 years were included if they received vancomycin for 48 hours from September 1, 2003, through July 30, 2011, and had 1 serum vancomycin concentration collected within 96 hours of drug therapy initiation. Patients were excluded if they were undergoing hemodialysis or receiving amphotericin B formulations or immunosuppressive medications, including cyclosporine, tacrolimus, and sirolimus, which may have interfered with vancomycin CL within 7 days before or during vancomycin therapy. Demographic characteristics (eg, sex, age, weight, and height) and clinical and laboratory data (eg, SCr and vancomycin concentrations) were extracted for each patient on standardized case report forms. The growth charts from the Centers for Disease Control and Prevention were used to categorize overweight and obesity based on age and sex.[10] Overweight was defined as weight or BMI in the 85th to 94.9th percentile and obesity at the 95th percentile.[11] Actual body weight was used to categorize overweight or obesity in patients <2 years old and BMI for those 2 years old. Overweight and obese patients served as cases and were matched to controls consisting of individuals with normal weights. Matching criteria were age (within 1 year), SCr (within 0.4 mg/dL), the use of concurrent nephrotoxic medications, and stay in the intensive care unit. Different measures of body composition were calculated using various equations (Table I).

### Population-Based PK Model

Assays to measure serum vancomycin concentrations and SCr at each study site have been published previously.[21] Population-based PK analyses were performed using the nonlinear mixed-effect modeling software NONMEM, version 7.2 (Icon, Dublin, Ireland), and Perl-Speaks-NONMEM, version 3.7.6 (Free Software Foundation using General Public License). Because most vancomycin samples were collected after the distribution phase, a 1-compartment model was used to describe the vancomycin PK parameters $V_d$ and CL. On the basis of a large population-based PK study in children, age and SCr were identified as important covariates for CL.[21] Consequently, these measures were included as covariates in the base model, and different measures of body size descriptors were evaluated in subsequent intermediate models.

Models were fitted using the first-order conditional estimation subroutine and the interaction option. The maximum a posteriori Bayesian analysis of each patient's data using the final population model and the POSTHOC option were used to generate the parameter estimates for $V_d$ and CL for each patient. Residual error was modeled with the proportional and combination methods. Weight measures that improved the model fit using a likelihood ratio test with a reduction in the minimum objective function (MOF) of 4 ($P$ 0.05 for 1 $df$) were selected for further analysis. The uncertainty in the final model was evaluated using a bootstrap analysis of 1000 replicates selected from our cohort to calculate the 95% CIs for

the population estimates. The model was considered reliable if the parameter estimates were within the 95% CIs.

Accuracy, which represents the tendency to over-predict or underpredict a parameter, was calculated by $(X_{estimated} - X_{final\ model}) \div X_{final\ model}$. The boundaries for accuracy used in published reports ranged from <5% to 20%.[22–26] In this study, we aimed for <5% accuracy. Data were analyzed between case and control groups using appropriate tests (ie, paired *t* test for continuous variables and McNemar test for categorical variables with continuity correction). Pearson correlation was used to derive the $R^2$ for the graphs. $P = 0.05$ for a 2-sided test was assumed when calculating results. All descriptive and statistical analyses were performed using R software, version 3.0.1.[27]

## RESULTS

A total of 87 matched pairs (n = 87 overweight or obese cases and n = 87 normal-weight controls) with 389 vancomycin concentrations were included in the PK analysis. Ninety-eight (n = 42 overweight or obese cases and n = 56 normal-weight controls) participants had 2 vancomycin concentrations. The numbers of drug samples measured were as follows: from the end of infusion to 1 hour, 4 (1%); 1.1 to 2 hours, 10 (3%); 2.1 to 5 hours, 145 (37%); and >5 hours, 230 (59%). The median age for all participants was 10.1 (interquartile range [IQR], 4.7–14.9) years, and the mean baseline SCr concentration was 0.49 (IQR, 0.32–0.61) mg/dL, which were similar between cases and controls. The median weight and BMI in the different age groups were significantly different between cases and normal-weight controls for age >2 years (Table II).

For each weight measure, models were created to characterize $V_d$ and CL (Table III). Age and SCr were preselected independent covariates on CL for all models using a previous study.[20] The differences in the MOFs for weight, BMI, and ALWT in estimating $V_d$ were not significant; thus, weight was selected in the final model for estimation of $V_d$. Although BSA and adjusted weight produced the lowest MOFs for CL estimation, ALWT was selected for the final model because (1) the reduction in MOF was <4 (the threshold that is considered statistically significant at a $P$ 0.05 for 1 *df*), and (2) its integration into clinical practice is feasible because ALWT does not require height information or IW estimations using different equations that are based on age and sex.

The final PK model incorporated weight for $V_d$ and ALWT for CL (Table IV). Minimization and the covariance step were successful for the final model. The mean (SD) post hoc Bayesian estimates of $V_d$ and CL, based on weight, were 0.56 (0.06) L/kg and 0.11 (0.04) L/kg/h, respectively, with significant differences in CL between only the case and control groups (Table V). Age and SCr did not affect vancomycin $V_d$ in both cases and controls (Figure 1). However, CL was inversely proportional to age and SCr for both case and control groups, although the trend was not as robust for SCr in controls and for SCr >1.0 mg/dL in cases (Figure 2). Scatterplots revealed good fit between observed and predicted (both individual and population) concentrations (Figure 3). Model prediction of concentrations measured at >15 hours (which was <2% of total observed concentrations) was less accurate than early concentrations because these late concentrations were obtained

from 4 cases who had increasing SCr values while undergoing vancomycin therapy (Figure 4). In these 4 cases with increasing SCr values during vancomycin therapy, SCr values increased more rapidly (by 34.8%) than respective decreases in drug CL (by −6.9%).

The accuracy was consistently improved in $V_d$ estimation for controls compared with cases, and <6% accuracy was observed between weight and other weights for both groups (Table VI). For CL estimation in both groups, the accuracy was within 2% for weight, BSA, and adjusted weight (Table VI). The post hoc Bayesian population estimates for $V_d$ and CL were similar to the median bootstrap analysis values and were all within the 95% CIs obtained from the bootstrap analysis (Table VII).

## DISCUSSION

In this study, we evaluated the influence of different body size descriptors measures on vancomycin $V_d$ and CL in obese children using population-based PK modeling with Bayesian estimation, which has been previously found to improve predictions of vancomycin PK parameters.[28–30] Using a matched case-control design with a good sample size, we also compared the different body size measures between normal-weight and overweight or obese children.

Previous studies have reported decreased vancomycin weight-adjusted $V_d$ and CL in obese adult and pediatric patients compared with those who were nonobese by 13% to 53% and 20% to 37%, respectively (Table VIII).[3–7] Consistent with previous studies, our study found that the weight-adjusted $V_d$ and CL decreased by 2.2% and 10.8%, respectively, in obese and overweight children compared with those with normal weight. One potential explanation for the small decrease in weight-adjusted $V_d$ is the hydrophilicity of and large size of vancomycin, which hinders drug distribution into adipose tissue.[2,31] Notably, the observed decrease in weight-adjusted $V_d$ corresponds to an increase in the non–weight-adjusted $V_d$ that are sometimes evaluated in adult studies.[32]

The correlation between vancomycin $V_d$ or CL and weight in obese adults were variable based on previous studies. The correlation between $V_d$ and weight ranged from $r = 0.36$ to $r = 0.943$ for $V_d$.[4–7] Two studies[4,7] reported strong correlation between CL and weight, whereas another study[5] considered WT alone to be weak predictor of CL compared with SCr and age. One pediatric study found no statistical difference between different weight groups for weight-adjusted $V_d$ and CL.[3] In our study, we incorporated SCr, age, and ALWT for CL estimation.

Compared with weight, we found that BSA, AW, ALWT, and LBM were all strong determinants of vancomycin CL in this study. The use of BSA yielded the lowest MOF, perhaps because the total number of glomeruli and kidney weight in large humans are directly proportional to BSA.[33] Although BSA provided the best determinant for CL, it was not used in the final model because the reduction in MOF was <4, indicating an insignificant PK modeling change as described in the Patients and Methods section. In addition, BSA is generally used for highly toxic chemotherapeutic agents (rather than antibiotics like vancomycin) and requires height information that can be challenging to measure in young

children. The use of weight only requires measuring actual weight, without the need for a second variable of height measurement. In contrast, AW and LBM require age, height, and sex information and thus are not always pragmatic. More importantly, although LBM appears to an appropriate body size descriptor for predicting drug CL based on one meta-analysis, LBM has not been well studied in the obese population and unconfirmed in children.[23,24]

ALWT was selected for the final model in estimating vancomycin CL because it uses a simple exponential function of weight. The exponent used in the allometric scaling of weight can vary; however, we selected a fixed exponent of 0.75 that has been found to accurately predict drug CL in children aged >5 years and those who are obese.[26,34] On the basis of one meta-analysis of 458 articles, allometric scaling of weight was the most appropriate approach used to describe drug CL in both pediatrics and adults because CL was nonlinear to weight to account for different metabolic rates.[24] Furthermore, allometry has been suggested for use during pediatric drug development in children aged >6 years to predict their drug CL. Our final model with ALWT is a good approximation to models using BSA or AW, with accuracy for weight-adjusted CL within 1% for the cases.

There were several study limitations. First, the vancomycin samples were analyzed at 2 separate clinical laboratories that used immunoassays and thus may have produced some variability in CL estimations. Second, only one drug concentration was measured in 35% of participants, which may result in suboptimal estimation of $V_d$, produce over-parameterization of the PK parameters, and dictate the use of a 1-compartment model. However, on the basis of a recent review article and subsequent large population-based PK study, a 1-compartment model appears to be the adequate model to characterize vancomycin PK in children.[21,35] Furthermore, our final model and the bootstrap analysis of 1000 replicates achieved minimization. Third, our final PK model was based on serum vancomycin concentrations only, with the lack of drug concentrations in adipose tissues, which may shed light on the extent of drug penetration in this specific compartment through physiologically based PK modeling. Fourth, we did not distinguish between obese and overweight children, which were respectively 62% and 38% of the case group; thus, any PK variability between these groups remains undefined.

## CONCLUSION

We found that weight and ALWT can be used to estimate vancomycin $V_d$ and CL, respectively, in obese children between the ages of 4 and 16 years. Using these measures of weight for $V_d$ and CL estimation, clinicians can then optimally dose vancomycin. Further studies using Bayesian estimation and Monte Carlo simulation are needed to validate our findings and evaluate optimal vancomycin dosing.

## Acknowledgments

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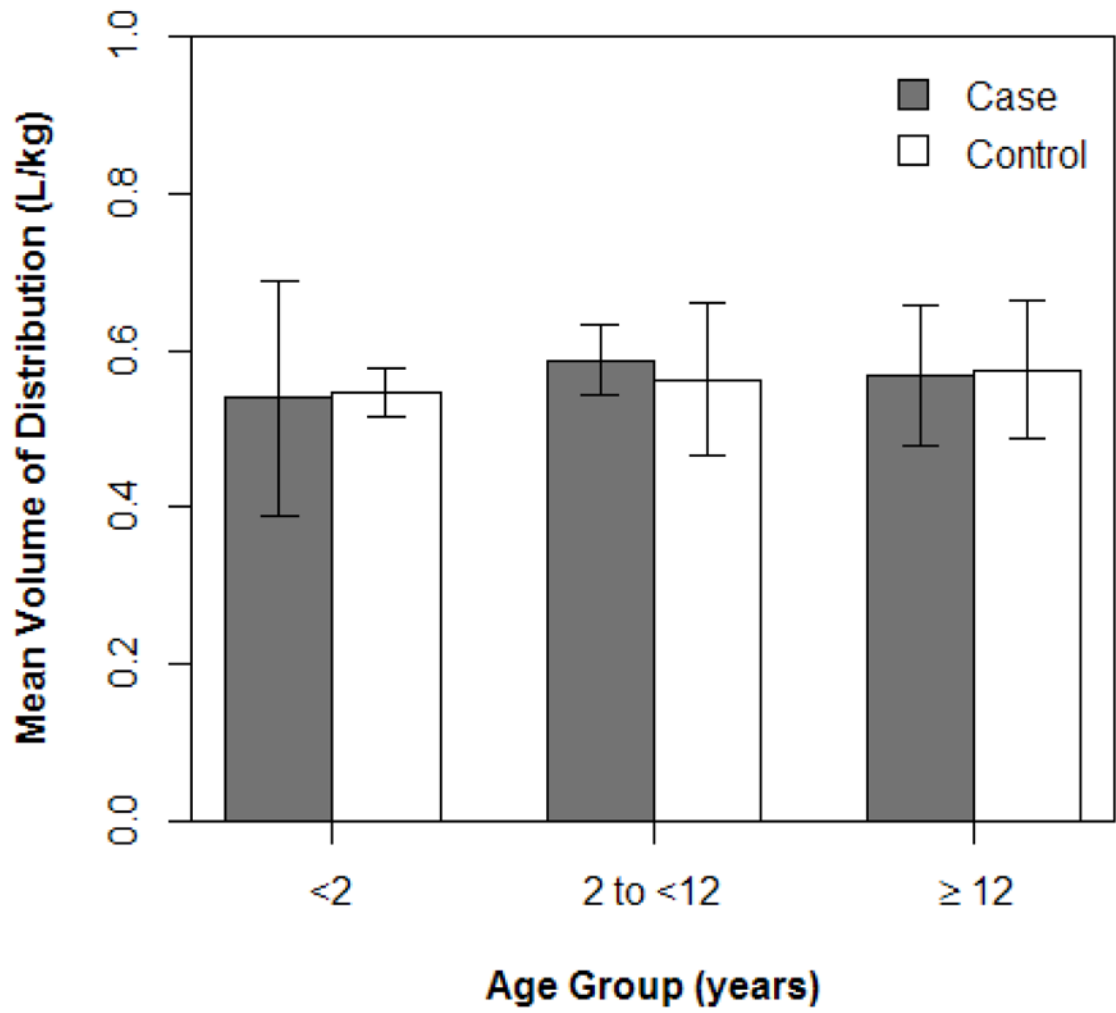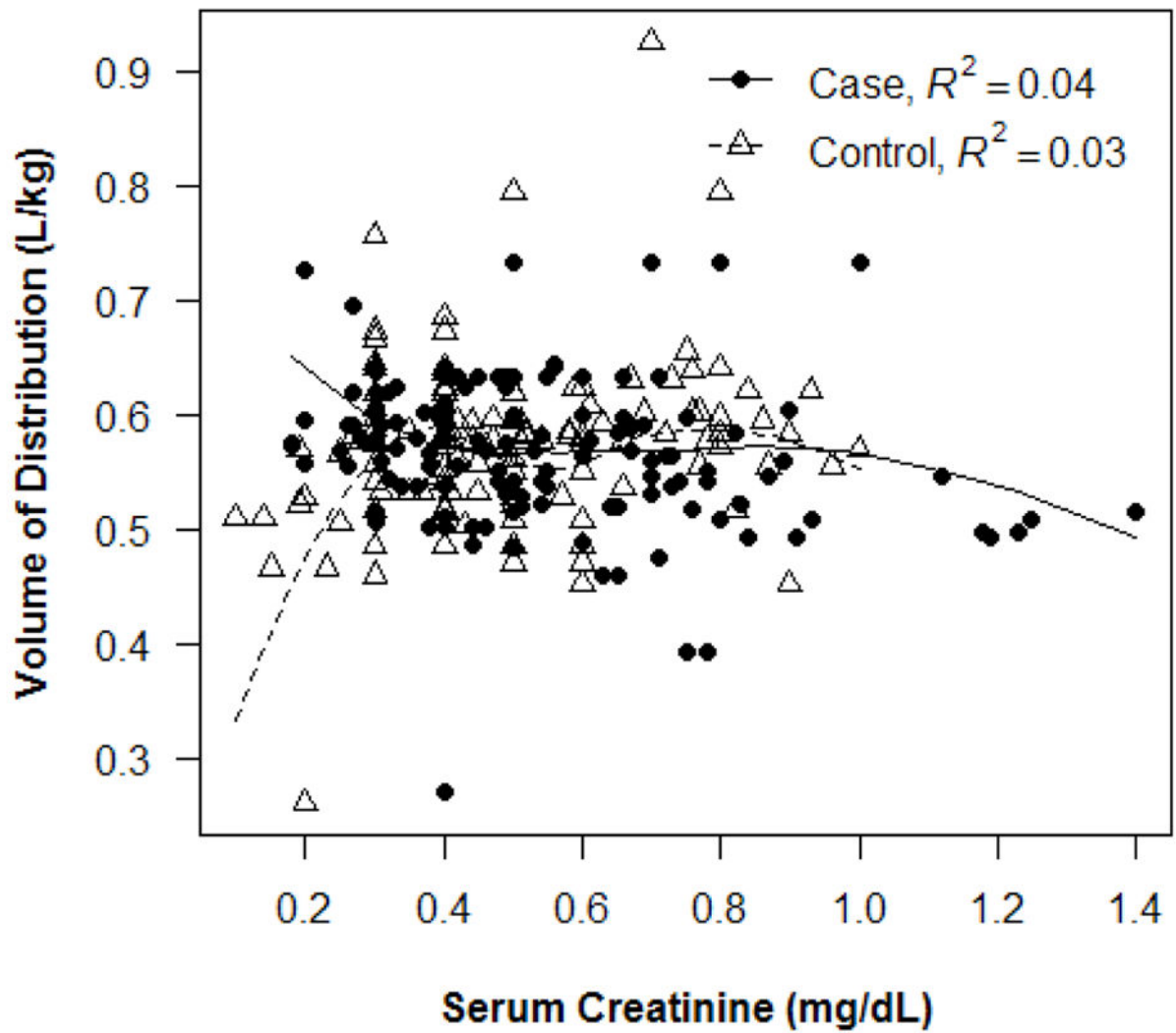
(A)
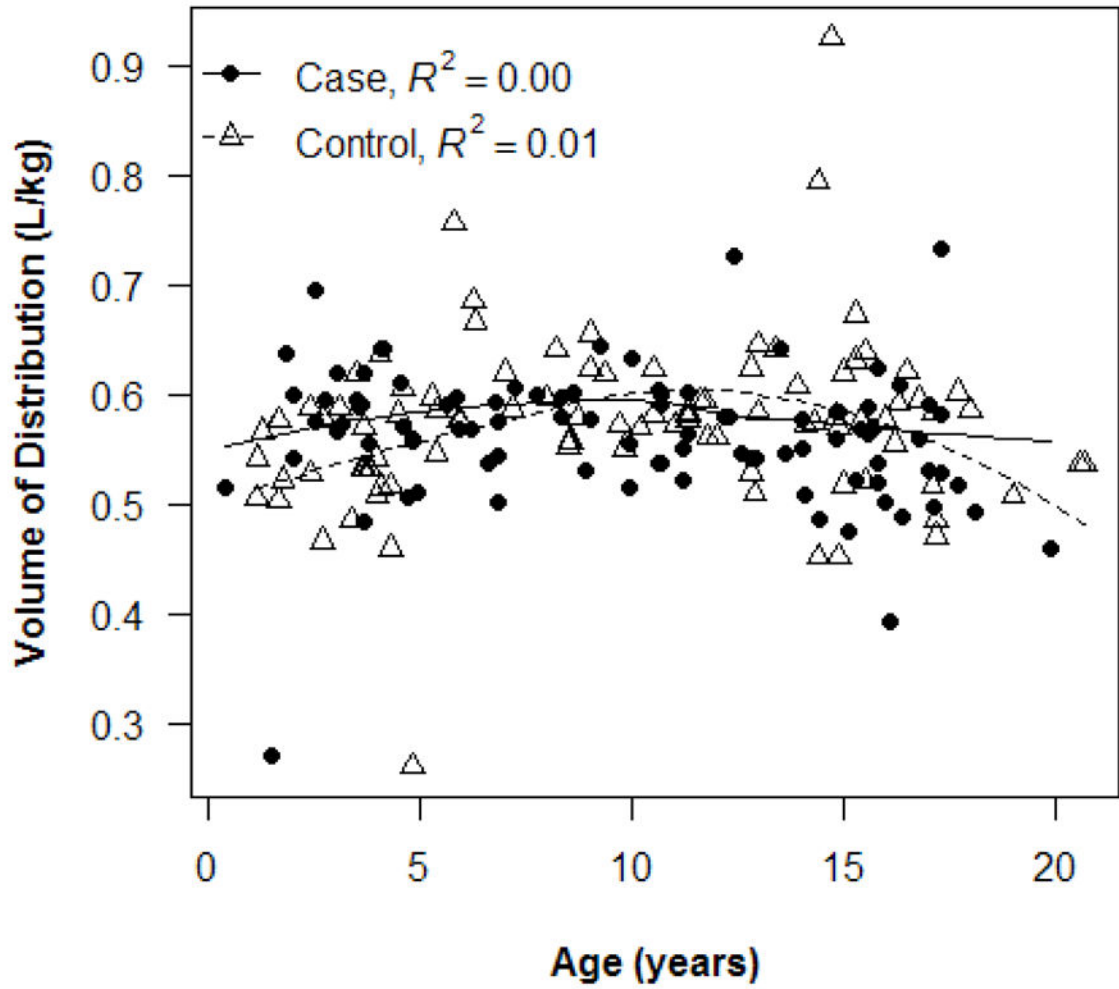


$R^2$ represents Pearson correlation, and curves are 90% Loess fit.

(B)



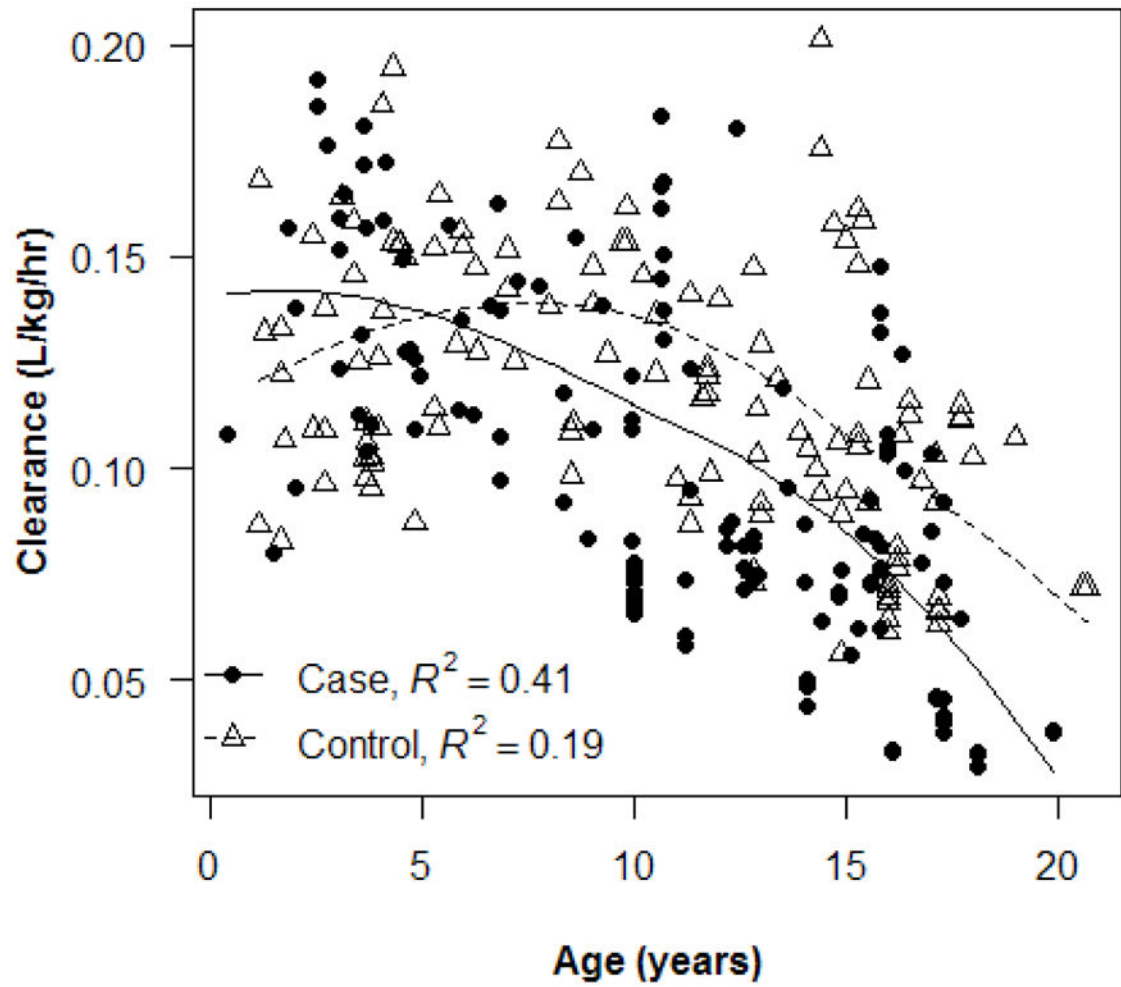Error bar represents one standard deviation

(C)



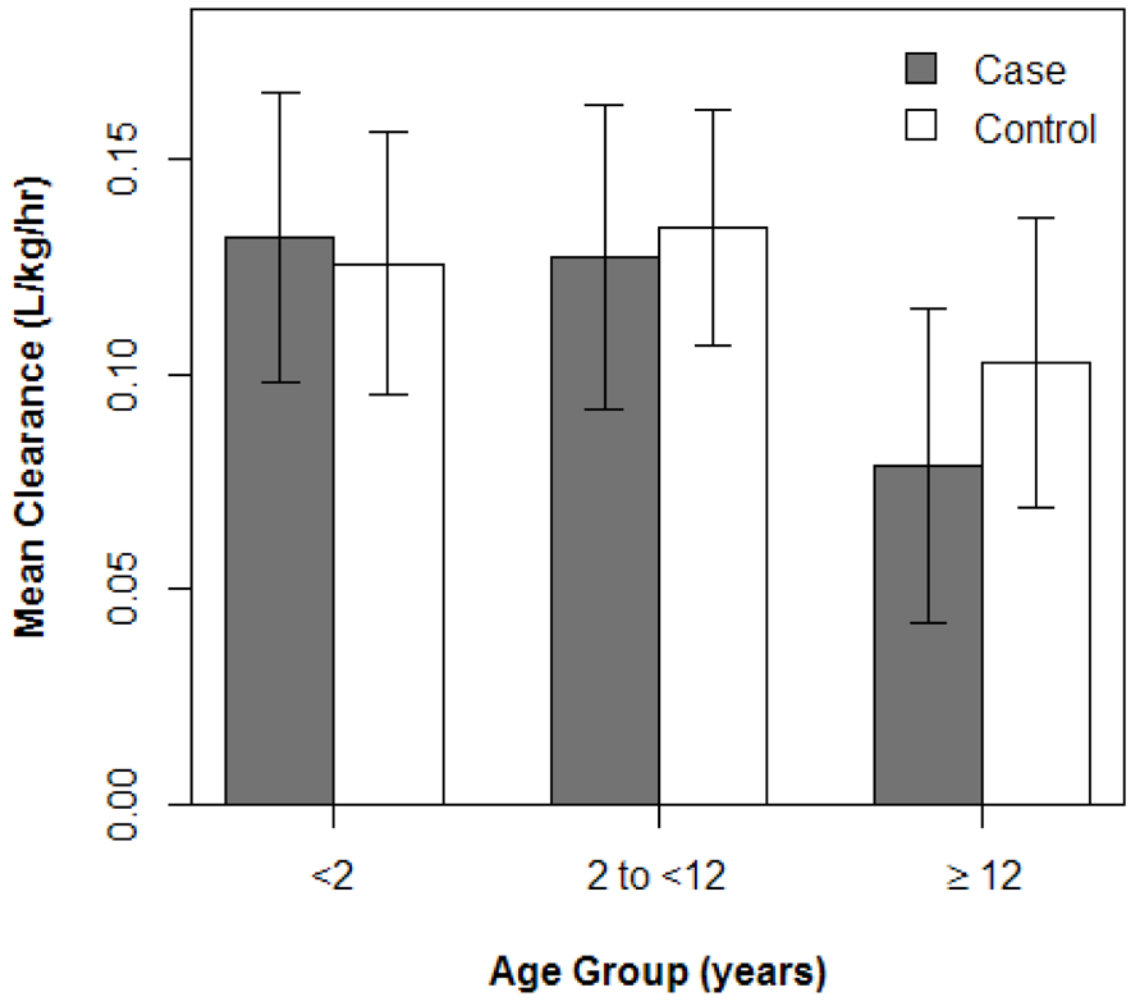$R^2$ represents Pearson correlation, and curves are 90% Loess fit.

**Figure 1.**
Effect of age (A and B) and serum creatinine (C) on vancomycin $V_d$. $R^2$ represents Pearson correlation, and curves are 90% Loess fit. Error bars indicate 1 SD.
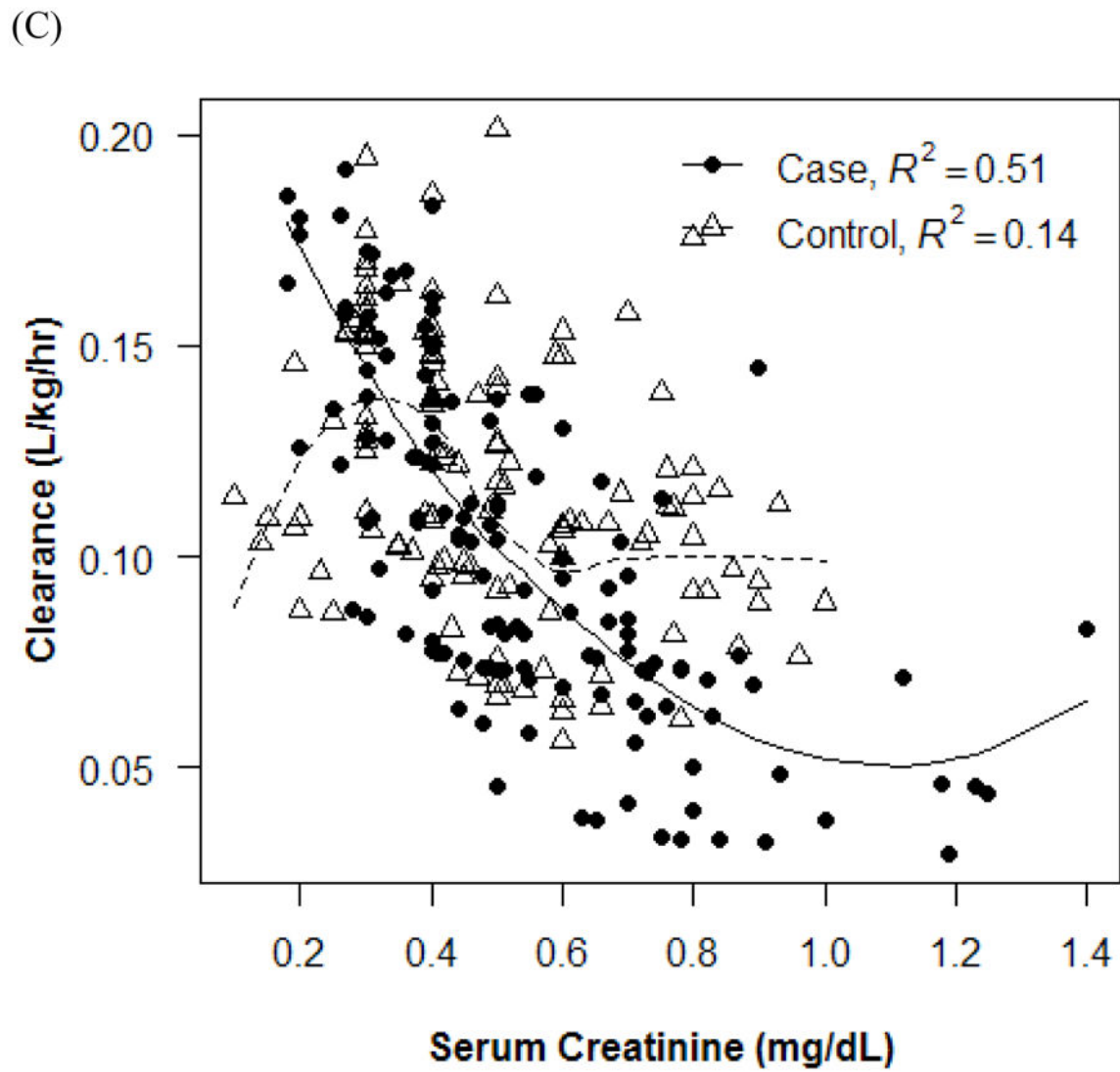
(A)



$R^2$ represents Pearson correlation, and curves are 90% Loess fit.

(B)



Error bar represents one standard deviation

(C)



R² represents Pearson correlation, and curves are 90% Loess fit.

**Figure 2.**
Effect of age (A and B) and serum creatinine (C) on vancomycin clearance. $R^2$ represents Pearson correlation, and curves are 90% Loess fit. Error bars indicate 1 SD.

(A)



Figure legend: Case, $R^2 = 0.82$; Control, $R^2 = 0.87$; Line of Unity

Axes: Individual Predicted (mg/dL) vs Observed (mg/dL)
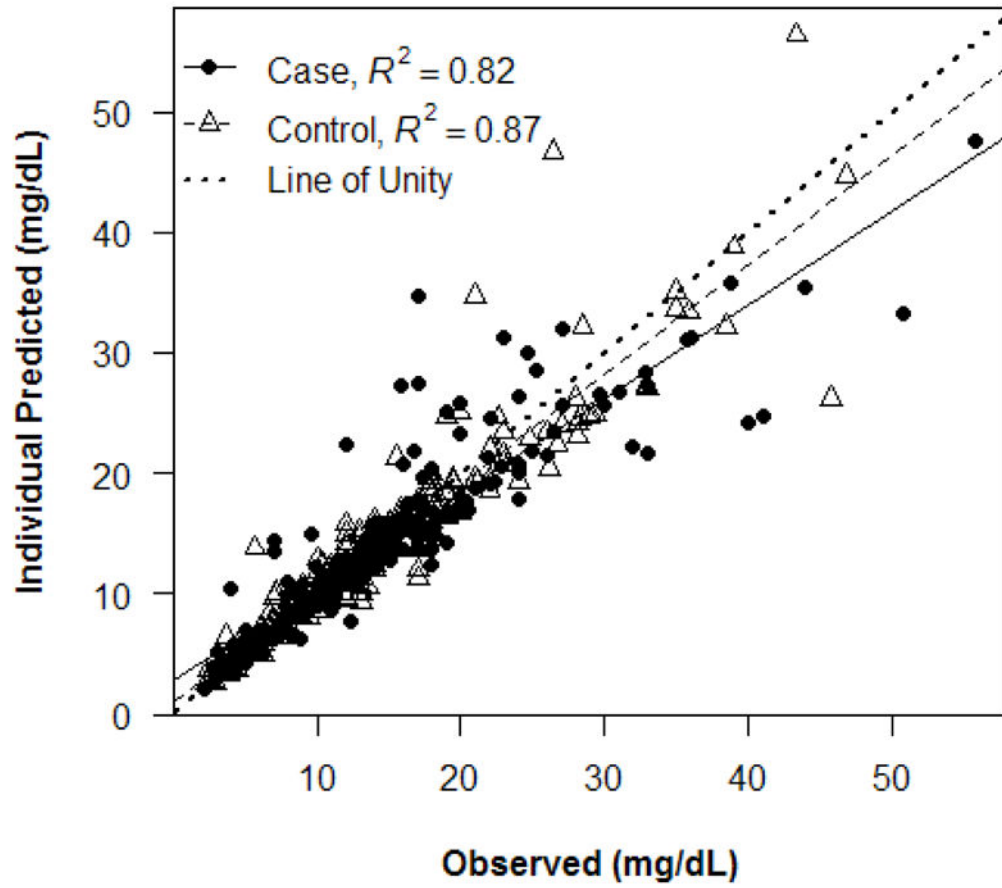
(B)
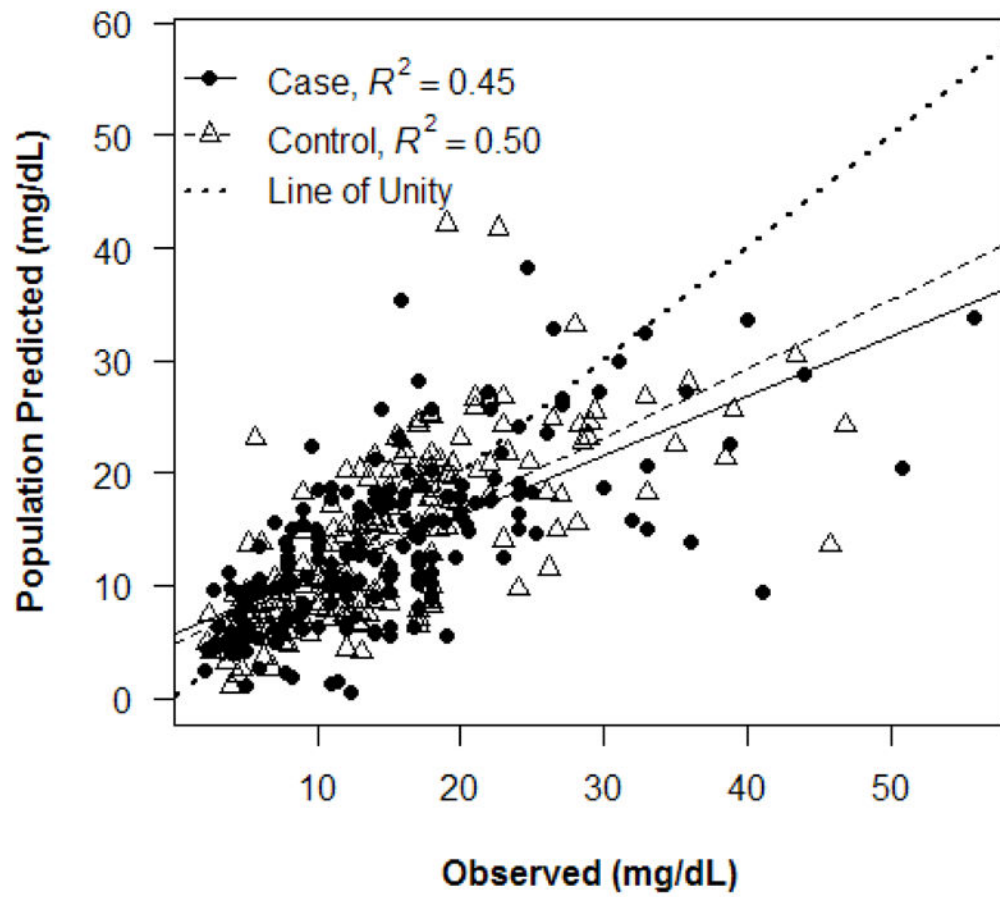


**Figure 3.**
Observed versus individual (A) and population (B) predicted concentrations.

(A) Conditional weighted residual plot with 90% Loess fit

**Figure 4.**
Plots of residuals in concentrations. Conditional weighted residual plot with 90% Loess fit (A) and natural log plot (B).

**Table I**

Equations for measures of weight.

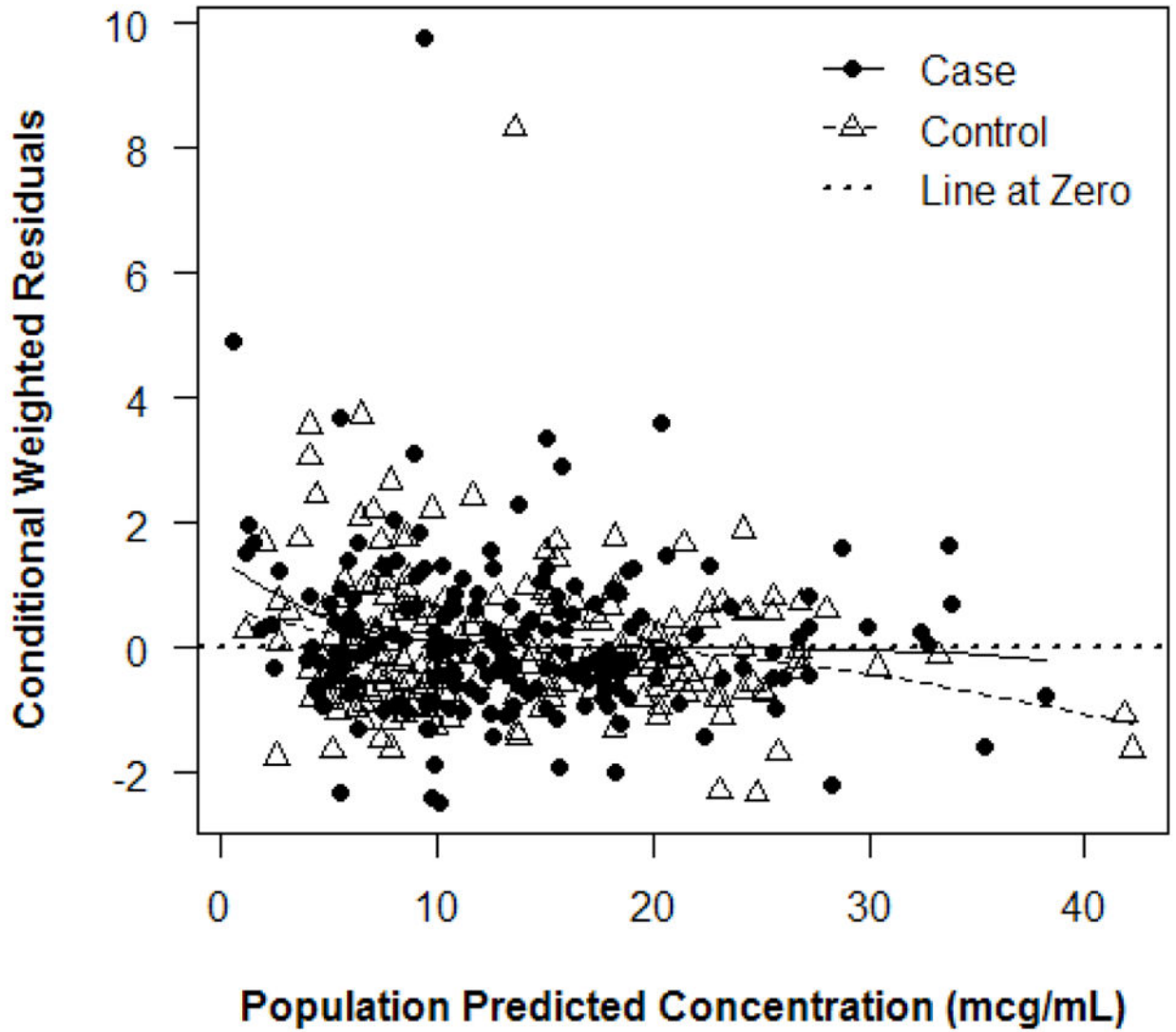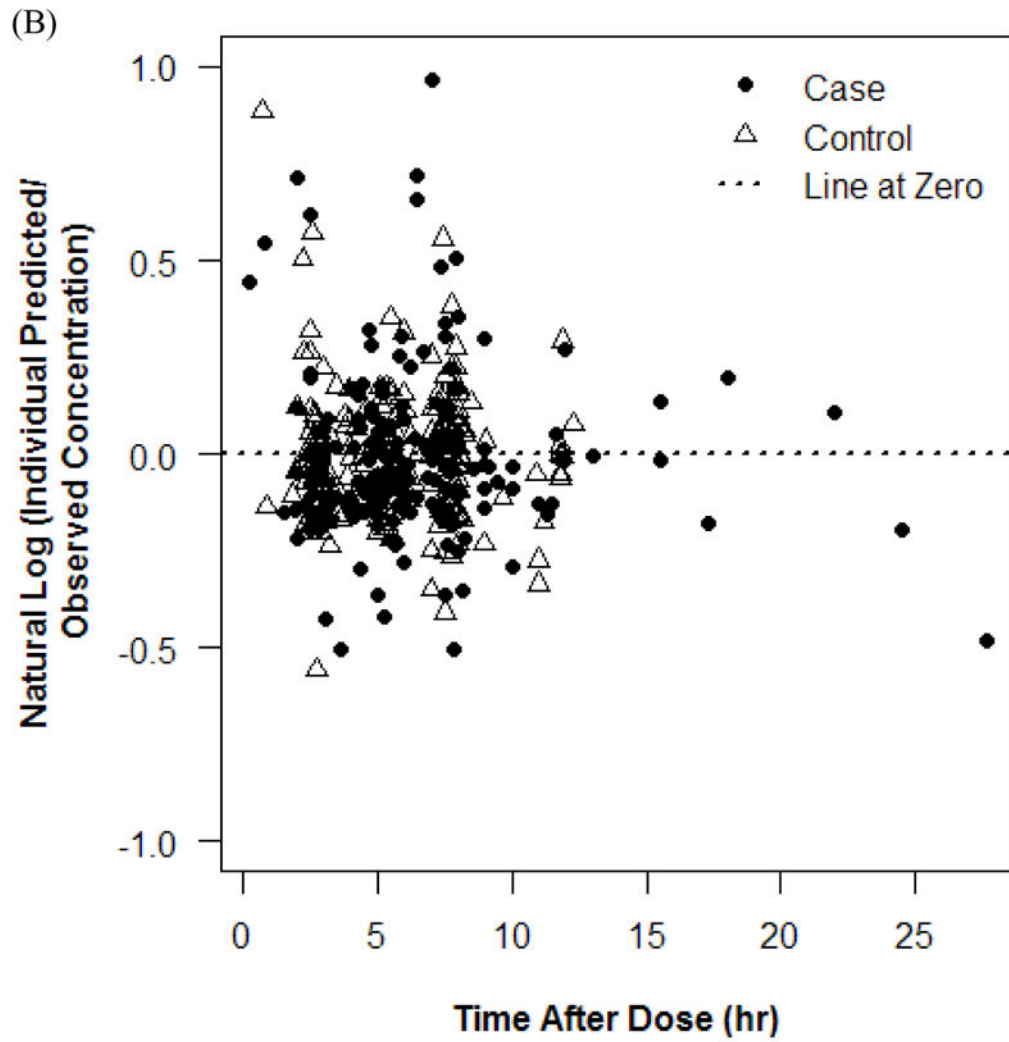| Weight Type | Equation |
|---|---|
| Actual weight | |
| Allometric weight (ALWT)[12,13] | ALWT (kg) = Weight (kg)$^{0.75}$ |
| Body surface area (BSA)[14] | BSA (m$^2$) = (Height [cm] × Weight [kg]/3600)$^{0.5}$ |
| Lean body mass (LBM)[15,16] | |
| 5 years | LBM (kg) = 0.0817 ×eight (kg)$^{0.6469}$ × Height (cm)$^{0.7236}$ |
| >5 years, male | ln(LBM [kg]) = −2.8990 + 0.8064 ln (Height [cm]) + 0.5674 ln(Weight [kg]) + 0.0000185 Weight (kg)$^2$ − 0.0153 BMIz$^2$ + 0.0132 Age (y) |
| >5 years, female | ln(LBM [kg]) = −3.8345 + 0.954 ln (Height [cm]) + 0.6515 ln(Weight [kg]) − 0.0102 BMIz$^2$ |
| Ideal weight (IW)[14,17–19] | |
| 1–18 years, <5 ft | IW (kg) = Height (cm)$^2$ × 1.65/1000 |
| 1–18 years, 5 ft, male | IW (kg) = 2.27 kg/in × Height (in) above 5 ft + 39 kg |
| 1–18 years, 5 ft, female | IW (kg) = 2.27 kg/in × Height (in) above 5 ft + 42.2 kg |
| >18 years, male | IW (kg) = 2.3 kg/in × Height (in) above 5 ft + 50 kg |
| >18 years, female | IW (kg) = 2.3 kg/in × Height (in) above 5 ft + 45.5 kg |
| Adjusted weight(AW) (kg)[20] | |
| Weight > IW | AW (kg) = IW (kg) + 0.4 × (Weight [kg] − IW) |
| Weight IW | AW (kg) = Weight (kg) |
| Body Mass Index (BMI) (kg/m$^2$) | BMI (kg/m$^2$) = Weight (kg)/Height (m)$^2$ |

**Table II**

Baseline characteristics of the 174 study participants.[*]

| Characteristic | Controls (n = 87) | Cases (n = 87) | P |
|---|---|---|---|
| Age, median (IQR), y | 10.2 (4.5–14.8) | 10.0 (4.8–15.2) | –[†] |
| Age group, y | | | |
| <2 | 6 (6.9) | 3 (3.5) | – |
| 2 to <12 | 45 (51.7) | 49 (56.3) | – |
| 12 to <18 | 33 (37.9) | 33 (37.9) | – |
| 18 | 3 (3.4) | 2 (2.3) | – |
| Weight, median (IQR), kg | 31.3 (16.8–47.1) | 44.0 (23.4–78.1) | <0.001 |
| Weight by age group, y | | | |
| <2 | 11.4 (10.0–12.0) | 13.0 (10.7–13.2) | 0.77 |
| 2 to <12 | 17.7 (16.0–28.6) | 26.6 (18.4–43.3) | 0.008 |
| 12 to <18 | 53.2 (41.8–58.4) | 80.0 (73.5–95.3) | <0.001 |
| 18 | 68.7 (59.6–70.4) | 123.4 (120.8–126.1) | 0.006 |
| Body mass index, median (IQR), kg/m$^2$ | 16.73 | 23.43 | <0.001 |
| Overweight | – | 33 (37.9) | – |
| Obese | – | 54 (62.1) | – |
| Overweight or obese by age group, y | | | |
| <2 | 17.3 (16.9–17.5) | 21.9 (20.1–23.1) | 0.09 |
| 2 to <12 | 15.0 (14.3–16.7) | 20.2 (18.7–22.9) | <0.001 |
| 12 to <18 | 19.6 (17.4–20.5) | 30.0 (27.9–34.3) | <0.001 |
| 18 | 18.5 (17.6–20.4) | 40.9 (40.2–41.6) | 0.002 |
| Male | 42 (48.3) | 44 (50.6) | 0.9 |
| Intensive care unit stay | 33 (37.9) | 33 (37.9) | –[†] |
| Concurrent use of nephrotoxic medications | 28 (32.2) | 28 (32.2) | –[†] |
| Empiric vancomycin dose, mean (SD) [IQR], mg/kg/d | 47.4 (13.0) [39.9–53.3] | 41.9 (12.0) [33.4–50.1] | 0.004 |
| Dosing interval | | | 0.3 |
| Every 6 hours | 31 (35.6) | 37 (42.5) | – |
| Every 8 hours | 49 (56.3) | 39 (44.8) | – |
| Every 12 hours | 6 (6.9) | 11 (12.6) | – |
| Serum creatinine, mean (SD) [IQR], mg/dL | 0.48 (0.20) [0.30–0.60] | 0.51 (0.22) [0.34–0.67] | –[†] |

IQR = interquartile range.

[*] Data are presented as number (percentage) of patients unless otherwise indicated.

[†] Cases were matched to controls by age (within 1 year), serum creatinine (within 0.4 mg/dL), the use of concurrent nephrotoxic medications, and stay in the intensive care unit.

**Table III**

Covariate screening during pharmacokinetic model development.

| Covariate | Minimum Objective Function | Change in Minimum Objective Function | P |
|---|---|---|---|
| $V_d$, L [*] | | | |
| Actual weight, kg (base model) | 1751.044 | – | 0.028 |
| Body mass index, $kg/m^2$ | 1750.359 | −0.685 | 0.019 |
| Allometric weight, kg | 1751.486 | 0.442 | 0.037 |
| Adjusted weight, kg | 1751.667 | 0.623 | 0.041 |
| Body surface area, $m^2$ | 1752.198 | 1.154 | 0.056 |
| Lean body mass, kg | 1752.203 | 1.159 | 0.056 |
| Ideal weight, kg | 1752.832 | 1.788 | 0.082 |
| Clearance, L/h [†] | | | |
| Allometric weight, kg (final model) | 1680.621 | – | 0.011 |
| Body surface area, $m^2$ | 1676.776 | −3.846 | 0.001 |
| Adjusted weight, kg | 1680.388 | −0.233 | 0.009 |
| Lean body mass, kg | 1681.874 | 1.252 | 0.021 |
| Ideal weight, kg | 1682.739 | 2.118 | 0.035 |
| Actual weight, kg | 1682.968 | 2.348 | 0.041 |
| Body mass index, $kg/m^2$ | 1685.685 | 5.064 | 0.224 |

[*] The change in minimum objective function for the volume of distribution was calculated from the base model using actual weight.

[†] Actual weight was the covariate for $V_d$ used in all models to estimate clearance. The change in minimum objective function for clearance was calculated from the final model that incorporated the log function of age (in days) and serum creatinine (in milligrams per deciliter) as covariates along with different weights.

## Table IV

Vancomycin final pharmacokinetic model.

| Parameter Estimate | Intersubject Variability, % | Residual Error, % |
|---|---|---|
| CL (L/h) = 0.286 × ALWT (kg) × (0.4/SCr [mg/dL])$^{0.290}$ × (ln[Age*]/8.3)$^{0.755}$ | 30 | 24 |
| $V_d$ (L) = 0.574 × Weight (kg) | 29 | |

ALWT = allometric weight (equivalent to weight$^{0.75}$); CL = clearance; SCr = serum creatinine.

*
Age expressed in days.

**Table V**

Baseline parameter estimations using final pharmacokinetic model.[*]

| Variable | Controls (n = 87) | Cases (n = 87) | *P* |
|---|---|---|---|
| Serum creatinine, mg/dL | 0.48 (0.20) [0.30–0.60] | 0.51 (0.22) [0.34–0.67] | 0.2 |
| Clearance, L/kg/h | 0.12 (0.03) [0.10–0.15] | 0.11 (0.04) [0.08–0.14] | 0.003 |
| $V_d$, L/kg | 0.58 (0.08) [0.53–0.61] | 0.56 (0.06) [0.53–0.60] | 0.3 |
| Half-life, h | 3.4 (0.8) [2.8–3.9] | 4.1 (1.7) [2.9–4.8] | <0.001 |
| Elimination rate constant, $h^{-1}$ | 0.21 (0.05) [0.18–0.25] | 0.19 (0.06) [0.14–0.24] | 0.002 |

[*]
Data are presented as mean (SD) [interquartile range].

**Table VI**

Accuracy of different measures of weight on vancomycin pharmacokinetic properties.

| Weight Type | Accuracy, %[*] | | | |
| | $V_d$ | | Clearance | |
| | Controls (n = 87) | Cases (n = 87) | Controls (n = 87) | Cases (n = 87) |
|---|---|---|---|---|
| Actual weight, kg | – | – | −0.30 | −0.19 |
| Allometric weight, kg | 0.13 | −0.89 | – | – |
| Body surface area, m² | 0.48 | −3.00 | 0.90 | −0.34 |
| Adjusted weight, kg | 1.03 | −2.77 | 1.15 | −0.59 |
| Lean body mass, kg | 0.36 | −3.55 | 0.94 | −0.80 |
| Ideal weight, kg | 0.97 | −5.72 | 3.13 | −0.76 |
| Body mass index, kg/m² | −3.00 | 4.27 | 2.73 | 2.47 |

[*] Accuracy was determined relative to actual weight for volume of distribution and allometric weight for clearance.

**Table VII**

Estimates of final population pharmacokinetic parameters and random effects.[*]

| Parameter | Estimate | SE of Estimate | Median Bootstrap Estimate (95% CI) |
|---|---|---|---|
| $\theta_1$ | 0.574 | 0.031 | 0.572 (0.514–0.632) |
| $\theta_2$ | 0.286 | 0.009 | 0.285 (0.268–0.304) |
| $\theta_3$ | 0.290 | 0.057 | 0.291 (0.165–0.395) |
| $\theta_4$ | 0.755 | 0.264 | 0.742 (0.194–1.263) |
| $\eta_1$ | 0.084 | 0.048 | 0.080 (0.002–0.182) |
| $\eta_2$ | 0.092 | 0.016 | 0.090 (0.061–0.124) |
| E | 0.056 | 0.007 | 0.056 (0.042–0.069) |

$\eta_1$ = intersubject random effect associated with $V_d$; $\eta_2$ = intersubject random effect associated with CL; $\varepsilon$ = residual random effect.

[*] Final pharmacokinetic model was $V_d$ (L) = $\theta_1 \times$ Weight and CL (L/h) = $\theta_2 \times$ ALWT $\times (0.4/\text{SCr})^{\theta_3} \times (\ln[\text{Age}]/8.3)^{\theta_4}$, where ALWT indicates allometric weight and SCr indicates serum creatinine.

**Table VIII**

Summary of vancomycin pharmacokinetic properties in obese children and adults.

| Year of Publication | Age, mean (SD) or range, y | Sample Size | $V_d$, Mean (SD) or Median (Range), L/kg | Weight Used for Volume Estimation | Clearance, Mean (SD) or Median (Range), L/kg/h | Weight Used for Clearance Estimation | Obesity Definition |
|---|---|---|---|---|---|---|---|
| **Pediatric** | | | | | | | |
| 2011[8] | 2–17 | 70 Overweight or obese | – | – | – | – | BMI ≥85th percentile for age and sex (CDC) |
| | | 162 Normal weight | – | – | – | – | BMI <85th percentile |
| 2011[2] | 6.8 (4.31) | 24 Obese | 0.35 (0.15) (n = 4) | Weight | – | – | BMI >95th percentile for age and sex (CDC) |
| | 7.2 (4.80) | 24 Normal weight | – | – | – | – | 25%–75th percentile for age and sex |
| 2012[3] | 5; 0.5–18 | 18 Overweight* | 0.81 (0.37) | Weight | 0.16 (0.05) | Weight | BMI ≥98th percentile for 0–2 y and BMI ≥85th percentile for 2–18 y |
| | | 31 Normal weight* | 1 (0.35) | Weight | 0.2 (0.08) | Weight | BMI = 2 in the 98th percentile for 0–2 y and 5 in the 85th percentile for 2–18 y |
| | | 13 Underweight* | 0.97 (0.54) | Weight | 0.18 (0.09) | Weight | BMI ≤2nd percentile for 0–2 y and BMI ≤5th percentile for 2–18 y |
| 2013[9] | 8.9 (5.1) | 21 Obese | – | – | – | – | BMI ≥95th percentile |
| | 9.7 (4.7) | 21 Overweight | – | – | – | – | BMI = 85th–94th percentile |
| | 9.5 (4.9) | 84 Normal weight | – | – | – | – | BMI ≤84th percentile for age and sex (CDC) |
| **Adults** | | | | | | | |
| 1982[4] | 27–37 | 6 Morbidly obese | 0.26 (0.03) | Weight | 0.066 (0.01) | Weight | Weight >190% IW |
| | 25–30 | 4 Normal weight | 0.68 (0.07) | IW | 0.174 (0.04) | IW | Weight <115% IW |
| 1993[5] | 54.3–60.0[†] | 107 Obese | 0.39 (0.06) | Weight | 0.065 (0.004) | Weight | Weight >120% LBM |
| | 36.4–58.1[†] | 113 Normal weight | (0.81) | Weight | 0.0366–0.051[†] | Weight | Weight <120% LBM |
| 1994[6] | 50.0; 46.8–53.2[‡] | 108 Obese | 0.89 (0.82–0.97[‡]) | IW | 0.0624–0.066[†] | Weight | Weight >130% IW |
| | | | 0.56 (0.52–0.59[‡]) | Weight | | | |
| | 43.3; 42.0–44.6[‡] | 559 Normal weight | 0.65 (0.63–0.67[‡]) | IW | | | Weight = 80%–130% IW |
| | | | 0.64 (0.62–0.66[‡]) | Weight | | | |
| | 45.4; 39.2–51.7[‡] | 37 Underweight | 0.62 (0.55–0.68[‡]) | IW | | | Weight <80% IW |

| Year of Publication | Age, mean (SD) or range, y | Sample Size | $V_d$, Mean (SD) or Median (Range), L/kg | Weight Used for Volume Estimation | Clearance, Mean (SD) or Median (Range), L/kg/h | Weight Used for Clearance Estimation | Obesity Definition |
|---|---|---|---|---|---|---|---|
| 1998[7] | 41 (7) | 24 Morbidly obese | 0.83 (0.74–0.92[‡]) | Weight | | | |
| | | | 0.32 (0.05) | Weight | 0.072 (0.012) | Weight | Weight >190% IW |
| | | | 0.83 (0.08) | IW | 0.186 (0.042) | IW | |
| | 40 (7) | 24 Normal weight | 0.68 (0.24) | Weight | 0.066 (0.018) | Weight | Weight = 85%–115% IW |
| | | | 0.64 (0.26) | IW | 0.06 (0.024) | IW | |
| 2015[22] | 43.0; 38.5–53.0 | 31 | 0.51 | Weight | 6.54 | – | BMI 40 kg/m² |

BMI = body mass index; CDC = Centers for Disease Control and Prevention; IW = ideal weight; LBM = lean body mass.

[*] Trough concentrations for 51 patients total.

[†] Range of means.

[‡] 95% CI.