Supplemental Online Content

eMethods

Eligibility Criteria of the Study

Pediatric subjects admitted to the pediatric intensive care unit (PICU) who meet the inclusion/exclusion criteria were eligible for enrollment into this study. Parents or legally authorized representatives of children in the intensive care unit who were prescribed vancomycin by their providers were invited to give permission for their child to enroll in the study. Children whose parents or legally authorized representatives provided permission using Institutional Review Board-approved consent documents were then screened for eligibility and enrolled. 302 subjects were recruited in the non-extracorporeal therapy (non-ECT) group and additional 33 subjects were recruited in the ECT group across two sites: the University of Maryland Hospital for Children at the University of Maryland Medical Center (UMMC), and the Texas Children's Hospital at Baylor College of Medicine. The eligibility criteria were designed to exclude subjects who might have medical conditions that could pose a safety risk and subjects whose medical conditions might interfere with the objectives and results of the study.
*The ECT group was excluded from the analysis in this paper.

1. Inclusion Criteria

Subjects were eligible to participate in this study if they met all of the following inclusion criteria:

1) Parents or legally authorized representatives are willing to provide permission and sign the informed consent document; subjects assent, when appropriate.
2) Admitted to one of the pediatric ICUs at the participating site.
3) Age ≥ 90 days of life to <18 years at the time of enrollment.
4) Receiving IV vancomycin, regardless of indication.
5) For subjects in the ECT group, must be receiving extracorporeal membrane oxygenation (ECMO), continuous renal replacement therapy (CRRT), or extracorporeal liver support (ELS, albumin-assisted dialysis).

2. Exclusion Criteria

Subjects eligible to participate in this study did not meet any of the following exclusion criteria:

1) Has end-stage renal disease and is on chronic peritoneal dialysis or hemodialysis.
2) On oral or intraperitoneal vancomycin only.
3) Not applicable to the ECT group: Has undergone cardiopulmonary bypass within 7 days of starting vancomycin.
4) The attending physician believes it is not appropriate for subject to be enrolled.
5) Will only receive a single dose of vancomycin.
6) Known to be pregnant (pregnancy tests will not be performed as part of the study procedures, but if a subject is known to be pregnant, she will not be eligible).
7) Is brain dead or has suspected brain death.
8) Subjects may not be simultaneously enrolled in studies[&] in which the total volume of blood taken collected taken across studies may put the child at greater than minimal risk.[*]

[&]*Simultaneous participation in another study is acceptable if the other study is observational, or if the interventions in the other study are standard of care, or, if the other study is interventional, it does not involve nephrotoxic agents.*

[*]*Minimal risk means "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."*

3. Removal of Subjects from Therapy or Assessment

A subject had the right to withdraw from the study any time for any reason, without penalty or consequence. Subjects who withdrew consent were terminated from the study. A subject could withdraw or be withdrawn from participation in this study if any of the following reasons occurred:

- Subject no longer met eligibility criteria.
- As deemed necessary by the site principal investigator or appropriate sub-investigator for noncompliance or other reasons.
- Subject or parent/guardian withdrawal of consent/assent.

- Medical disease or condition, or any new clinical findings for which continued participation, in the opinion of the site principal investigator or appropriate sub-investigator, would compromise the safety of the subject, or would interfere with the subject's successful completion of this study, or would interfere with the evaluation of responses.

Target Attainment Analysis

A sensitivity analysis was performed to evaluate the dependency of the target attainment on the PK sampling scheme. The final model and "true" PK parameters were used to simulate vancomycin concentrations at peak and trough following 7 days of dosing for the 4 regimens. Then, predicted CL from post-hoc Bayesian prediction was obtained for each virtual patient using 1) the simulated peak and trough samples, and 2) the simulated trough samples only. The AUC_{24} for each scenario was calculated as follows:

$$AUC_{24} = \frac{Dose\ (mg)}{CL} \times \frac{24}{Dose\ Frequency}$$

Where: CL represents the "true" clearance for an individual patient or the predicted clearance for an individual patient using the specified sampling scheme.

The calculated AUC_{24} values for each sampling strategy were then used to obtain the AUC_{24}/MIC ratios for MIC values of 0.5, 1.0, and 2.0 mcg/mL, and compared with the ratios from the simulation based upon having infinite number of samples.

Population Pharmacokinetic Model Development and Evaluation

1. Handling of Missing Data

1.1 Missing Dosing Data

If dosing dates or times were missing, the reasons for the missing data were investigated. If missing dates or times were due to either an undocumented missed dose or suspected, but unconfirmed, patient noncompliance, or if the reason for the missing data was inconclusive, then the dosing records and pharmacokinetic (PK) samples measured after the dose and prior to the next known or assumed dose were excluded from the analysis dataset. If no information was available to support rational imputation of the dose amount, then the dosing records and any associated PK samples prior to the next known or assumed dose were excluded from the analysis dataset. If sufficient data were available to support a rational decision regarding the correct amount that was administered, then the dose amount was imputed.

1.2 Missing Pharmacokinetic Data

If a vancomycin concentration for a PK sample was missing, the concentration value was not imputed for analysis. If the date or time for a PK sample or for the dose immediately prior to a PK sample was missing, the relevant concentration was either excluded from the analysis dataset, or, if feasible, the date or time was imputed according to protocol specifications or based on a logical interpretation of available information from data proximate to the missing data.

1.3 Missing Covariate Data

If a patient's sex, race, or ethnicity was missing, the covariate was imputed to the most common category for the covariate. If the baseline value for any other covariate treated as stationary was missing, the value was imputed from the value recorded at the nearest subsequent visit. If the covariate was missing for all visits, a value was imputed based upon the sex- or study-specific median baseline value for all patients contributing such information. If < 10% of the analysis dataset values for a time-varying covariate were missing, the following procedure was followed:

- Data were imputed, within an individual, using the last observation carried forward method.
- Missing baseline values were imputed backward from the next available value.

When all values for an individual were missing, then the sex- or study-specific median (as appropriate for that data element) of the baseline value was used as the imputed value. If deemed appropriate, the imputed value was derived based upon disease status or other relevant factors. If the percent of missing data was > 10% for a particular covariate, no imputations were made and the variable was evaluated only in exploratory graphical displays. All patients and records with imputed values were flagged in the dataset by an indicator variable to allow further evaluation of the impact of any imputations, if necessary, during the course of the analysis.

2. Exploratory Data Analysis

Exploratory data analyses (EDA) and data visualization techniques were used to understand the informational content of the final datasets with respect to the anticipated models, search for extreme values and potential outliers, assess possible trends in the data, and determine if any errors were made in the manipulation of the data and creation of the analysis datasets. This EDA was also used to confirm the appropriateness of the models tested and verify model assumptions.

3. Statistical Methods for Nonlinear Mixed Effects Models

The first-order conditional estimation with interaction method was used during all stages of the model development process unless convergence problems were encountered, or the interaction option was deemed unnecessary by virtue of the choice of residual variability model. For each analysis, NONMEM computed the value of the objective function (VOF), a statistic that is proportional to minus twice the log likelihood of the data. In the case of hierarchical models, the change in the VOF produced by the inclusion of a parameter is asymptotically χ^2-distributed, with the number of degrees of freedom (df) equal to the number of parameters added to or deleted from the model. For nonlinear mixed effects models developed using NONMEM, goodness of fit was assessed according to the following criteria and/or considerations:

- Convergence of the estimation and covariance routines
- Estimation of ≥ 3 significant digits for each fixed and random effect parameter
- Size of gradients associated with each parameter at the final iteration of estimation
- Reasonable parameter estimates based upon the expected relationship

- Adequate precision of parameter estimates as measured by the relative standard error expressed as a percent (%RSE = standard error/parameter estimate × 100)
- Agreement in scatterplots of measured versus predicted and individual predicted observations assessed visually
- Lack of trend or pattern in scatterplots of conditional weighted residuals (CWRES) versus predicted observations and time assessed visually
- Lack of trend or pattern in scatterplots of individual weighted residuals versus individual predicted observations assessed visually
- Estimates of between-subject variability (BSV) and residual variability (RV) for the specified model versus comparator models
- Estimates of eta and epsilon shrinkage for the specified model versus comparator models

4. Base Structural Model Development

One- and two-compartment models with allometric scaling of the parameters were evaluated. The various population PK models were described by the estimation of mean structural model parameters (such as, central volume [Vc], peripheral volume [Vp], CL, and intercompartmental clearance [Q]), magnitude of BSV in these parameters, and magnitude of RV.

4.1 Statistical Models for Between-subject Variability

Between-subject variability in parameters was modeled in NONMEM using exponential between-subject variability model.

$$X_i = \tilde{X}_i \times exp(\eta_i^x)$$

Where:

X_i is the individual-specific estimate of the X parameter in the *i*th patient;
$\tilde{X}_i$ is the typical value of the X parameter in the *i*th patient; and
η_i^x is a random variable that represents the persistent difference between the "true" individual-specific estimate and the typical value of the X parameter in the *i*th patient; the η_i^x are independent, identically distributed statistical variable with a mean of 0 and a variance equal to ω_x^2.

With this variability model, the estimates are presented as coefficients of variation expressed as a percent (%CVs) as follows:

$$\%CV_x = \sqrt{exp(\omega_x^2) - 1} \times 100$$

4.2 Statistical Models for Residual Variability

Residual variability represents a composite of assay variability, intraindividual variability, model misspecification, errors in timing of dose and sample information, patient noncompliance, and other unexplained errors. The goodness-of-fit plots (in particular, scatterplots of individual weighted residuals versus individual predicted observations) were examined for potential biases in the selected RV model and alternative models were evaluated, as necessary, using 1 of the forms shown below.

4.2.1 Additive Residual Variability Error Model

$$Y_{ij} = \hat{Y}_{ij} + \varepsilon_{ij}$$

Where:

Y_{ij} is the jth measured value in the *i*th patient;
$\hat{Y}_{ij}$ is the jth predicted value in the *i*th patient using the specified model; and
ε_{ij} is a random variable which represents the discrepancy between the *j*th measured value in the *i*th patient and the predicted value from the specified model; the ε_{ij} are independent, identically distributed statistical errors with a mean of 0 and a variance of σ^2.

The additive model for RV assumes that the variance remains constant with regard to the predicted values and the estimate is expressed as a standard deviation (σ).

4.2.2 Constant Coefficient of Variation or Proportional Residual Variability Error Model

$$Y_{ij} = \hat{Y}_{ij} \times (1 + \varepsilon_{ij})$$

Where:

Y_{ij} is the jth measured value in the *i*th patient;
$\hat{Y}_{ij}$ is the jth predicted value in the *i*th patient using the specified model; and

ε_{ij} is a random variable which represents the discrepancy between the *j*th measured value in the *i*th patient and the predicted value from the specified model; the ε_{ij} are independent, identically distributed statistical errors with a mean of 0 and a variance of σ^2.

The proportional model for RV assumes that the variance increases in proportion to the predicted values and the estimate is expressed as a percent coefficient of variation as follows:

$$\%CV_x = \sqrt{exp(\omega_x^2) - 1} \times 100$$

4.2.3. Additive Plus Constant Coefficient of Variation Residual Variability Error Model

$$Y_{ij} = \hat{Y}_{ij} + \varepsilon_{1ij} + \hat{Y}_{ij} \times \varepsilon_{2ij}$$

Where:

Y_{ij} is the jth measured value in the *i*th patient;

$\hat{Y}_{ij}$ is the jth predicted value in the *i*th patient using the specified model;

ε_{1ij} is the random variable representing the additive component of RV; the ε_{1ij} are independent, identically distributed statistical errors with a mean of 0 and a variance of σ_1^2; and

ε_{2ij} is the random variable representing the CCV (proportional) component of RV; the ε_{2ij} are independent, identically distributed statistical errors with a mean of 0 and a variance of σ_2^2.

Using this error model, the variance of the difference between the measured and predicted values can be expressed using the equation below:

$$var\left(Y_{ij} - \hat{Y}_{ij}\right) = \sigma_1^2 + \sigma_2^2 \times \left(\hat{Y}_{ij}\right)^2$$

Where:

σ_1^2 is the variance of ε_{1ij} which represents the additive component of RV; and

σ_2^2 is the variance of ε_{2ij} which represents the CCV (proportional) component of RV.

This model allows for the variance to have a positive (non-zero) lower limit and then increase in proportion to the predicted concentration. The estimate is expressed as a percent coefficient of variation and, when modeled using the equation above, can be calculated based on the following:

$$\%CV_{RV} = \frac{\sqrt{\sigma_1^2 + \sigma_2^2 \times \left(\hat{Y}_{ij}\right)^2}}{\hat{Y}_{ij}} \times 100$$

4.2.4 Log Error Model for Residual Variability

$$log\left(Y_{ij}\right) = log\left(\hat{Y}_{ij}\right) + \varepsilon_{ij}$$

Where:

Y_{ij} is the jth measured value in the *i*th patient;

$\hat{Y}_{ij}$ is the jth predicted value in the *i*th patient using the specified model; and

ε_{ij} is a random variable which represents the discrepancy between the *j*th measured log-transformed value in the ith patient and the log-transformation of the value predicted from the specified model; the ε_{ij} are independent, identically distributed statistical errors with a mean of 0 and a variance of σ^2.

The log error model for RV assumes that the variance is constant with respect to the log of the predicted value. This model is mathematically and numerically equivalent to the exponential error model for the estimation methods used. The estimate is expressed as a standard deviation (σ) in log-transformed concentration units.

5. Covariate Analysis

Following the development of appropriate base structural models, the influence of covariates (listed in eTable 1) on selected parameters was evaluated. Typically, covariate effects are only considered for parameters in which BSV is estimated but may not necessarily have been evaluated on all parameters with BSV. Graphical and statistical approaches were used to develop the covariate models and to assess the mathematical form of their relationships and their statistical significance. The forward selection followed by backward elimination approach for covariate evaluation is shown within the flowchart depicting the overall model-building process (Figure 1).

To avoid potential multicollinearity or confounding of effects in covariate sub-models, the correlation between covariates was examined prior to covariate analysis. If covariates were found to be highly correlated ($|r| > 0.6$) with other covariates (for example, body weight and BMI or body surface area), only 1 of the highly correlated covariates was selected for evaluation based on the likelihood of a mechanistic relationship with a parameter or the

degree of correlation with a parameter based on univariate analyses. Two or more highly correlated covariates were not included in a single covariate-parameter sub-model.

For categorical covariates (for example, race), if a particular subgroup represented less than 10% of the overall population, the categories may have been regrouped, as appropriate (for example, white race versus non-white race) to reduce the likelihood of poorly estimated parameters.

5.1 Functional Forms for Covariate Models

5.1.1 Continuous Variables

Continuous covariates were evaluated in NONMEM using 1 or a combination of functional forms shown below, as appropriate:

Linear

$$\tilde{X}_i = \theta_X^{int} + \theta_X^{cov} \times (cov_i - \overline{cov})$$

Power

$$\tilde{X}_i = \theta_X^{int} \times \left(\frac{cov_i}{\overline{cov}}\right)^{\theta_X^{cov}}$$

Where:

$\tilde{X}_i$ is the estimated typical parameter value in the *i*th patient;
θ_X^{int} is the population typical value parameter estimate for patients with the mean or median value of a particular covariate;
θ_X^{cov} for linear models, is the typical value estimate describing the change in the parameter value per unit change in a particular covariate; for power models, is the typical value estimate describing the change in the log parameter estimate per unit change in the log of a particular covariate;
cov_i is the measured value of a particular covariate in the *i*th patient; and
$\overline{cov}$ is the mean or median value of a particular covariate in the population.

If the functional form of the relationship between the parameter and the continuous covariate was not obvious from the diagnostic plots, multiple forms were tested in NONMEM.

5.1.2 Dichotomous and Categorical Variables

Dichotomous and categorical variables were evaluated using an exponential form in NONMEM as follows:

Exponential Shift

$$\tilde{X}_i = \theta_X \times e^{\theta_X^{cov} \times cov_i}$$

Where:

$\tilde{X}_i$ is the estimated typical parameter value in the *i*th patient;
θ_X is the typical parameter value for patients with cov_i=0;
θ_X^{cov} is the typical value of the exponent associated with an increase or decrease in θ_X for patients with cov_i=1; and
cov_i is the value of the covariate (either 0 or 1) defined for a specific dichotomous covariate in the *i*th patient.

For categorical variables with *n* groups, *n*-1 indicator variables were created to evaluate the effect of each group as compared to the group defined as the base population. Additional exponential terms were used for each separate indicator variable.

If diagnostic plots indicated that the parameter versus covariate relationship was not continuous for a continuous covariate, a spline was used to help redefine the continuous covariate as a categorical variable (for example, age less than or equal to a cut-off value and age greater than the cut-off value), and either an additive/proportional shift or piecewise linear model was used.

5.2 Forward Selection Procedure

Using the base structural model, Bayesian estimates of relevant parameters were generated for each patient. For each of these parameters, the delta-parameter was calculated for each patient as the Bayesian parameter estimate minus the typical value of the parameter. Diagnostic plots of the delta-parameter versus each of the covariates (delta plots) were generated. Assuming η-shrinkage < 30% in a given parameter, these delta plots were evaluated for observable trends and assisted in determining the functional form of the relationship between the parameter and the covariate. If η-shrinkage was ≥ 30% in a given parameter, all parameter-covariate models were tested in NONMEM for that parameter and diagnostic information reliant upon empirical Bayesian estimates was not considered in the assessment of covariate models. Shrinkage in the η-estimate distributions was calculated for each parameter by NONMEM. In specific cases when a subset of patients did not contribute information to the η-distribution for a

particular parameter (for example, patients with no PK data informing first-order absorption rate constant because all PK samples were taken following IV administration), the calculation of η-shrinkage was appropriately restricted to patients contributing relevant information.

Typical functional forms utilized for covariate analyses include linear, power, and additive or proportional shifts; the equations for these functional forms are shown above.

Univariate analyses of covariate-parameter relationships were performed for all covariates and functional forms. Covariates contributing a change in the minimum VOF of at least 6.64 (a = 0.01, 1 df) and resulting in a decrease in BSV in the parameter of interest were considered significant. Covariates which did not result in an BSV decrease of at least 5% were further examined and may have been included in the model if supported by graphical or other diagnostics. After the initial univariate analyses were completed, the covariate contributing the most significant change in the minimum VOF (smallest $P < 0.01$) and a reduction in BSV in the parameter of interest of at least 5% (1,2) was included in the base covariate model. The new base covariate model (structural model plus 1 significant covariate) was then used to generate new Bayesian estimates of the parameters and recompute the delta-parameters. Diagnostic plots of the delta-parameters versus all covariates were then regenerated and evaluated for potential relationships as described previously.

Remaining covariates were individually added to the new base covariate model according to the same procedure and tested for statistical significance using NONMEM. After this series of univariate analyses was completed, the covariate contributing the most significant reduction in the VOF and producing at least a 5% reduction in BSV in the parameter of interest was added to the new base covariate model. This process was repeated until there were no further covariates that produced significant changes in the VOF. The resultant model was considered the full multivariable model.

5.3 Evaluation of the Full Multivariable Model and Statistical Error Models

The models for BSV and RV in the full multivariable model were evaluated following completion of forward selection. This evaluation included the possible addition of new BSV terms to other parameters in the model, re-evaluation of the appropriateness of the functional form for each BSV term and the RV model, and assessment of possible correlations between η variables. To assess the possibility of correlations, the individual estimates of the η variable for each parameter with BSV term were plotted against the individual η estimates for all other parameters included in the model (η biplots). If correlations were observed between the η variables for any of the parameters, efforts were made to estimate the corresponding covariance between the BSV terms in the model. Covariance terms will only be tested between η variables that apply to the same population. All BSV and RV models were evaluated for bias and alternative models were evaluated as necessary.

5.4 Backward Elimination Procedure

Univariate stepwise backward elimination proceeded after all adjustments were made to the BSV and RV models. Each covariate was removed from each parameter equation separately. A covariate was considered significant if it resulted in a change in the VOF of at least 10.83 ($\alpha = 0.001$, 1 df for χ^2-distribution) when removed from the model. The most nonsignificant covariate (the highest $P > 0.001$) was removed from the model first and this reduced model then served as the new base multivariable model. The backward elimination procedure was repeated until all remaining covariates were significant at $\alpha = 0.001$.

6. Model Refinement

The reduced multivariable model, with all significant covariates, was evaluated for any remaining biases in the BSV and RV models. Diagnostic plots of the unexplained BSV in the parameters versus all covariates were evaluated to detect any inadequacies or biases in the covariate models and to assure no trends remained that may indicate a potential relationship had not been sufficiently described by the model. The model was checked for possible simplifications of covariate equations, such as power functions that could be reduced to linear functions (power term approximately 1.0) or significant discrete group covariates that could be redefined using fewer groups or parameters.

7. Model Evaluation

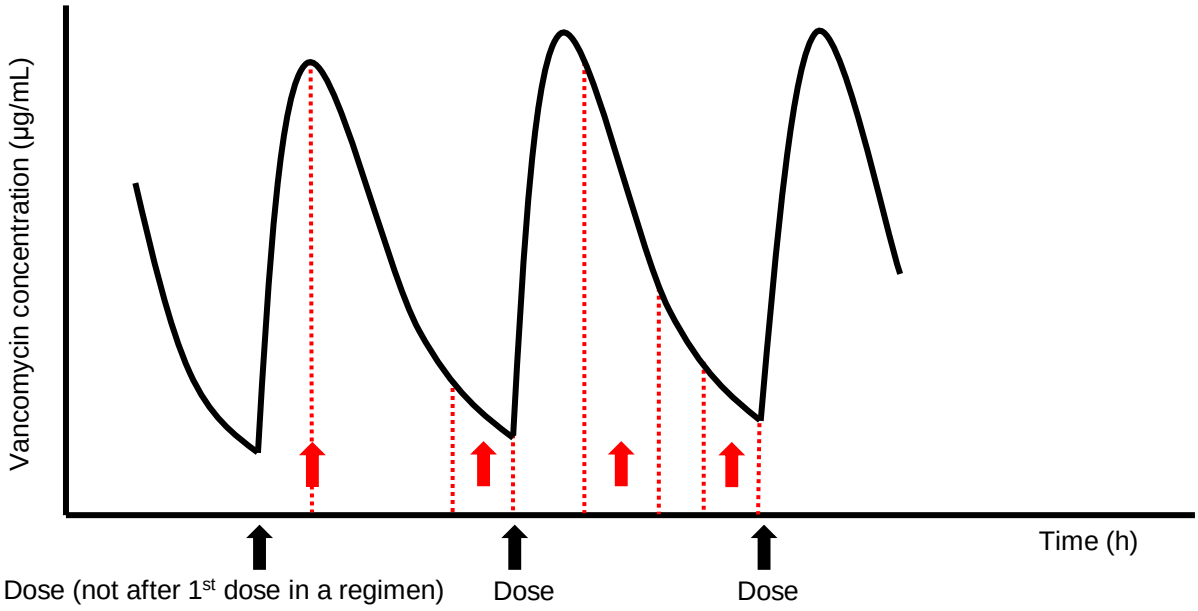
Assuming that uncertainty in the final model parameters was small relative to other sources of variability, the adequacy of the final model was evaluated using a simulation-based, prediction-corrected visual predictive check (VPC) method (3,4). Utilizing NONMEM, the final models were used to simulate a large number of replicates of the analysis dataset sufficient to achieve at least 10,000 patients overall, or 10,000 patients per stratum if the VPC was stratified. Statistics of interest were calculated from the simulated and observed data for comparison; for example, the 5th, 50th (median), and 95th percentiles of the distributions of simulated and observed concentrations were

compared. These percentiles were plotted versus time, with the original observed dataset and/or percentiles based on the observed data overlaid to visually assess concordance between the model-based simulated data and the observed data. In addition, the percentages of observed data falling below or above the simulation-based prediction interval were calculated.

8. Sub-Analysis: Model-Based Comparison of eGFR Using Schwartz Versus CKID Equation as a Predictor of Clearance

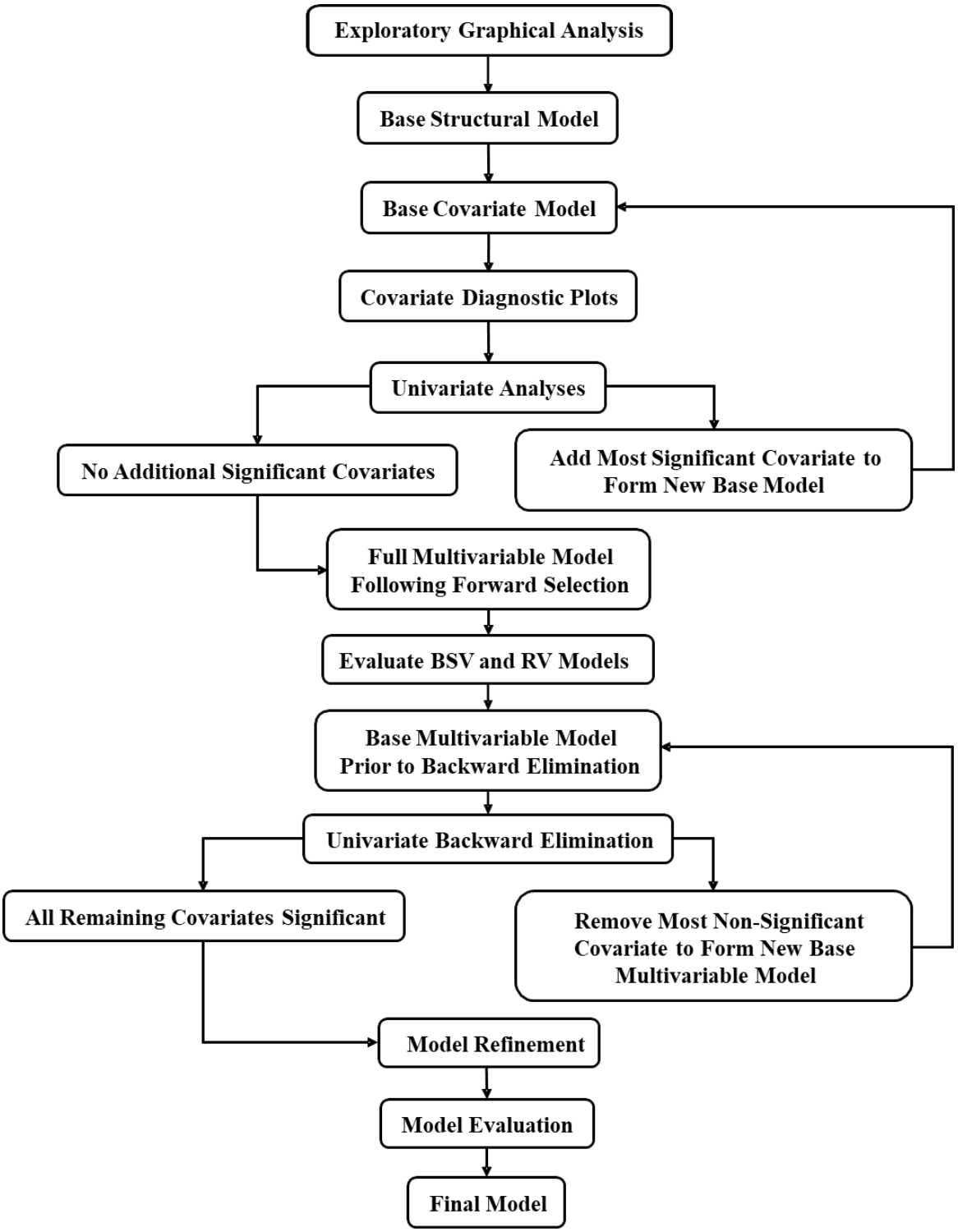
After the final PK model was selected, a sub-analysis was performed using the patients who had both measured serum creatinine and cystatin C. The final model including the effect of eGFR (bedside Schwartz equation) (5,6) was rerun in the subset of patients using the eGFR calculated using the CKID equation (7,8) instead of the bedside Schwartz equation. The model predictions using the CKID equation were compared with observed concentrations and CL predictions using the bedside Schwartz equation.

eFigure 1. Scheme of Vancomycin PK Samples



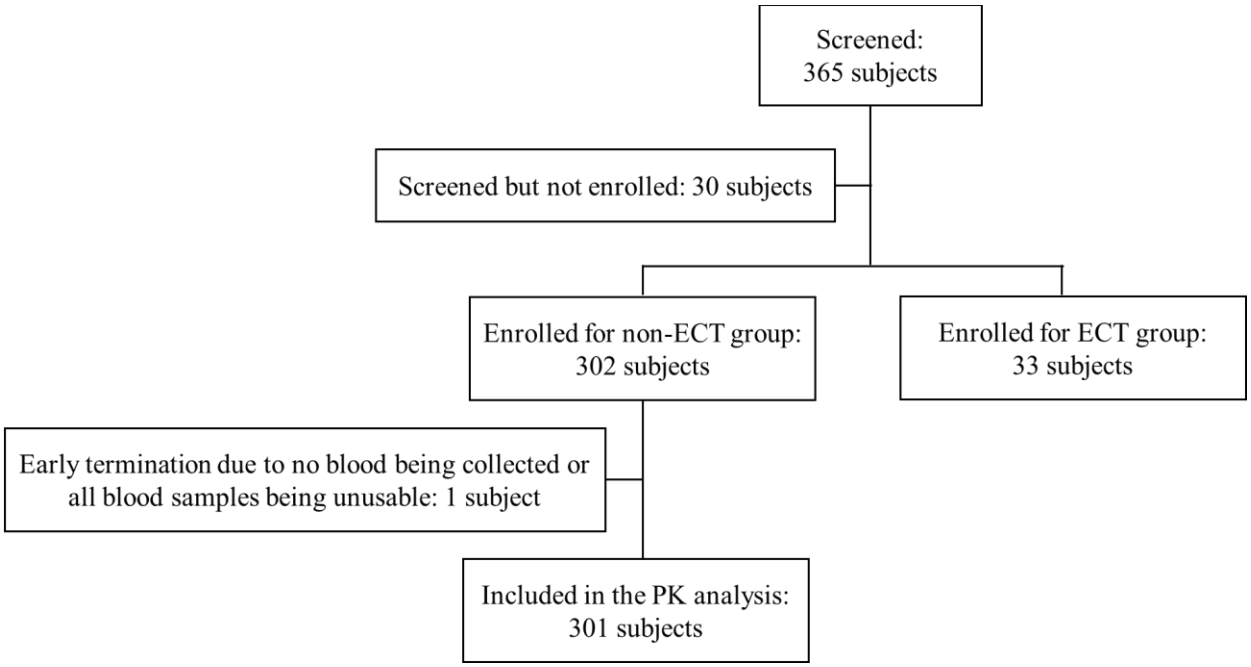
Black arrows represent the time when vancomycin was administered and red arrows for the time when vancomycin PK sample was obtained. First sample was taken at peak level after 1 hour of vancomycin infusion (not after the first dose in a regimen), second one at trough level before the subsequent dose, third one at mid-interval at 2-5 hours after the subsequent dose, and fourth one at trough level before the subsequent dose. For those who had positive microbiologic culture, another pair of peak and trough levels was obtained between 5th and 7th day of the vancomycin therapy. Other times in the sampling interval were also considered acceptable for individual patients as necessary due to other patient care needs.

eFigure 2. Flow Chart of the Population PK Model Development



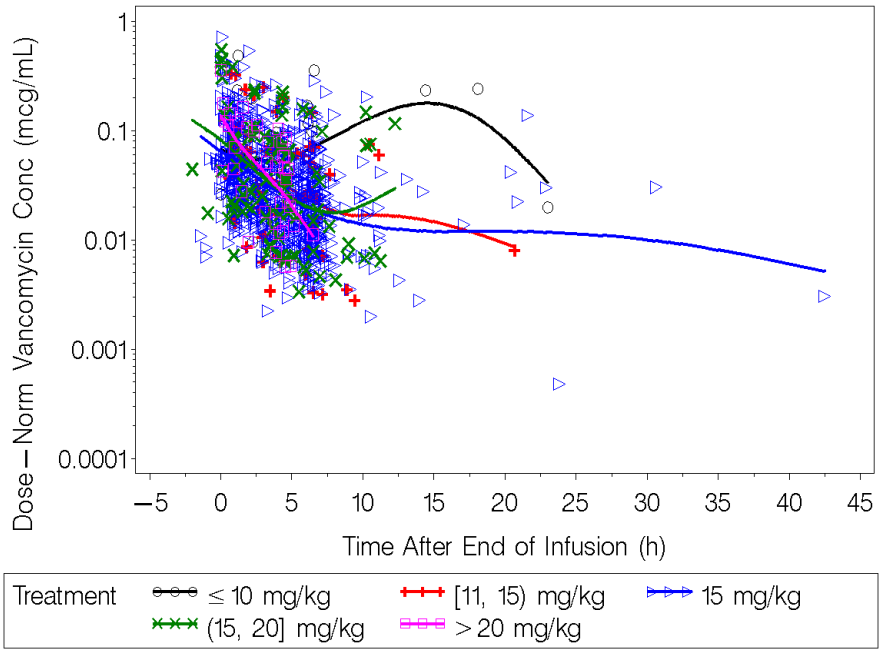
Abbreviations: BSV, between subject variability; RV, residual variability.

eFigure 3. Flow Diagram of Subject Enrollment



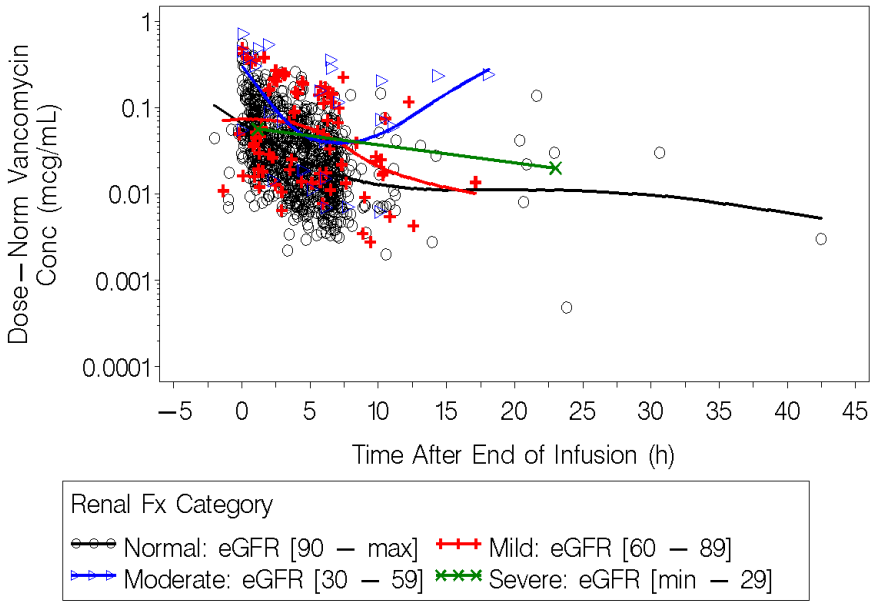
Abbreviations: ECT, extracorporeal therapy; PK, pharmacokinetics.
The ECT group was excluded from the analysis in this paper.

eFigure 4. Scatterplot of Dose-Normalized Concentration vs. Time Since End of Previous Infusion, Stratified by Vancomycin Dose



The lines represent smoothing splines fit to the data.
Two samples collected between 90−100 hours after the end of infusion are not displayed.
Abbreviations: Norm, normalized; Conc, concentration; mcg/mL, µg/mL. [or] indicates respective endpoint is included in the interval and (or) indicates respective endpoint is not included in the interval.

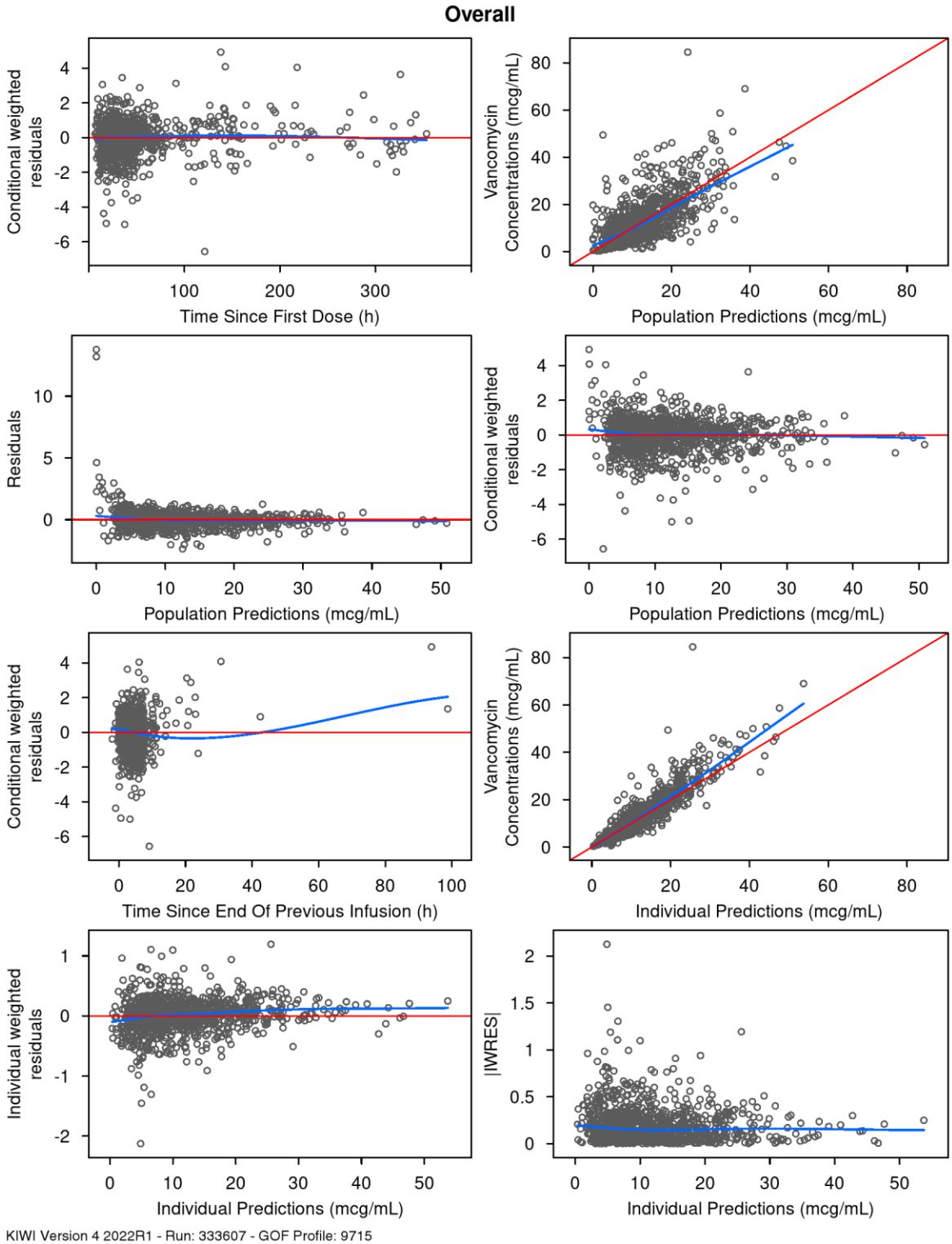
eFigure 5. Scatterplot of Dose-Normalized Concentration vs. Time Since End of Previous Infusion, Stratified by Renal Function



The lines represent smoothing splines fit to the data.
[or] indicates respective endpoint is included in the interval.
(or) indicates respective endpoint is not included in the interval.

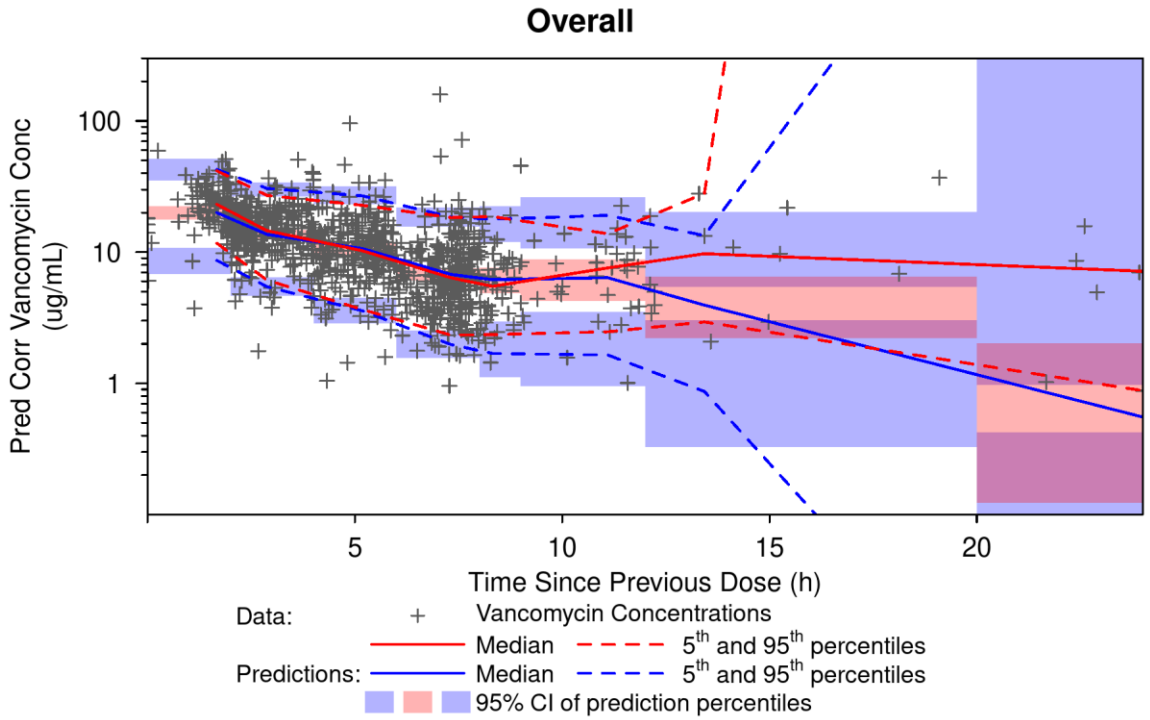
Abbreviations: Norm, normalized; Conc, concentration; Fx, function; eGFR, estimated glomerular filtration rate using the Bedside Schwartz equation (mL/min/1.73 m2); mcg/mL, µg/mL; max, maximum; min, minimum.

eFigure 6. Goodness-of-Fit Plots for the Final Population PK model



Abbreviations: |IWRES|, absolute value of the individual weighted residuals; mcg/mL, µg/mL

eFigure 7. Prediction-Corrected Visual Predictive Check for the Final Population PK Model



Medians and percentiles are plotted at the median time since previous dose of the data observed within each time since previous dose interval.

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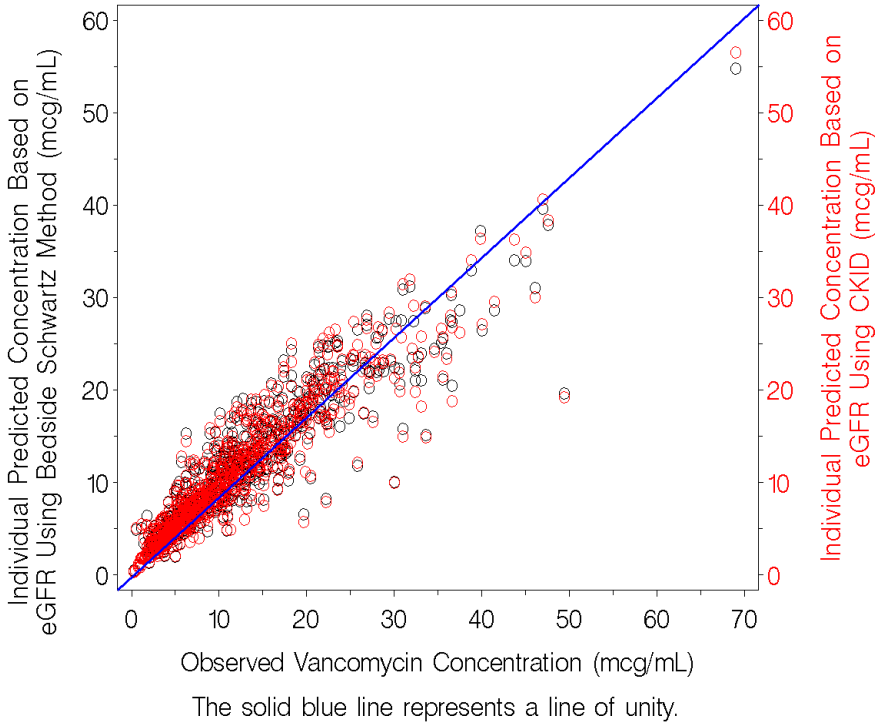
Abbreviations: Pred Corr, prediction corrected; Conc, concentration.

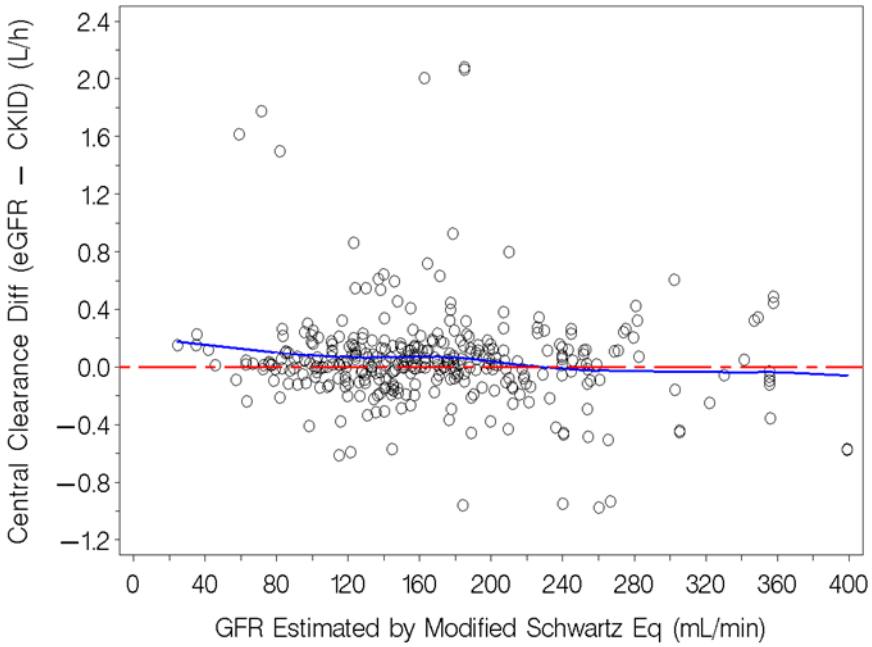
eFigure 8. Individual-Predicted Vancomycin Concentrations Versus Observed Vancomycin Concentrations, Stratified by Glomerular Filtration Estimation Method



Abbreviations: BUN, blood urea nitrogen; CKID, chronic kidney disease; cysC, serum cystatin C; eGFR, estimated glomerular filtration rate; ht, height; SCr, serum creatinine.

Note: Bedside Schwartz method eGFR (mL/min/1.73 m^2) = [0.413 × Height (cm) / SCr (mg/dL)] and CKID eGFR (mL/min/1.73 m^2) = $39.8 \times [ht/SCr]^{0.456} \times [1.8/cysC]^{0.418} \times [30/BUN]^{0.079} \times [1.076^{male}] \times [1.00f^{female}] \times [ht/1.4]^{0.179}$.

eFigure 9. Difference in Individual Population Pharmacokinetic Model Estimated Clearance Versus Estimated Glomerular Filtration Using the Bedside Schwartz Equation

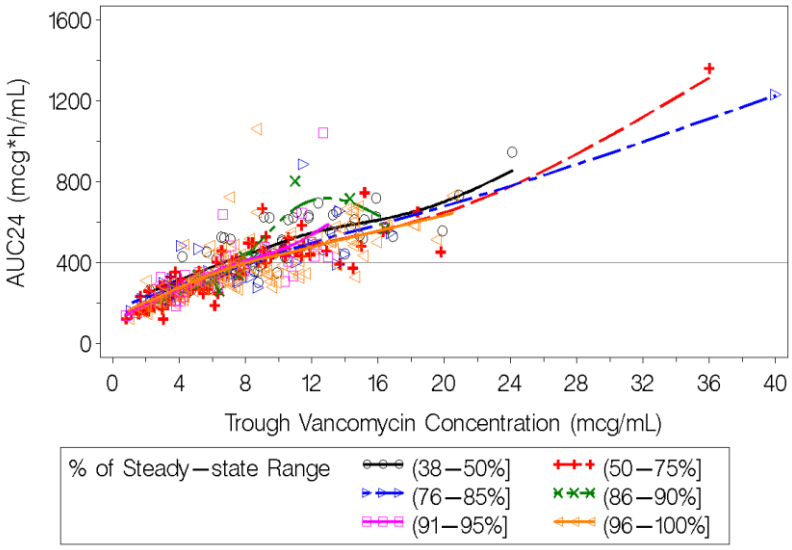


Abbreviations: BUN, blood urea nitrogen; CKID, indicates the model using the CKID (chronic kidney disease) equation for estimated glomerular filtration rate; cysC, serum cystatin C; Diff, difference; eGFR, indicates the model using the bedside Schwartz equation for estimated glomerular filtration rate; Eq, equation; GFR, glomerular filtration rate; ht, height; SCr, serum creatinine.

Note: Bedside Schwartz equation GFR (mL/min/1.73 m^2) = [0.413 × Height (cm) / SCr (mg/dL)] and

CKID GFR (mL/min/1.73 m^2) = $39.8 \times [ht/SCr]^{0.456} \times [1.8/cysC]^{0.418} \times [30/BUN]^{0.079} \times [1.076^{male}] \times [1.00^{female}] \times [ht/1.4]^{0.179}$.

eFigure 10. Regression Analysis of Model-Predicted AUC_{24} to Trough Vancomycin Concentration, Stratified by Percent Steady State



The lines represent smoothing splines fit to the data.
[or] indicates respective endpoint is included in the interval.
(or) indicates respective endpoint is not included in the interval.

Abbreviations: AUC_{24}, 24-hour are under the concentration-time curve; mcg*h/mL, µg/mL·h. The percent of steady state was calculated using the average model-predicted terminal half-life of 6 hours.

eTable 1. Planned Evaluation of Covariates in Population PK Model of Vancomycin in PICU Patients

Covariate	Time Varying	Pharmacokinetic Parameters	
	Yes/No	Clearance	Volume of Distribution
Body weight (kg)	Yes	X	X
BMI (kg/m^2)	Yes	X	X
Age (years)	No	X	X
Sex (0 = male, 1 = female)	No	X	X
Race[a]	No	X	X
Ethnicity (1 = non-Hispanic, 2 = Hispanic)	No	X	X
Nephrotoxic comedication[b]	Yes	X	
PRISM-3 or PIM-2 score	No	X	X
Percent fluid overload	Yes	X	X
GFR (bedside Schwartz method[c])	Yes	X	
Scr (mg/dL)	Yes	X	
BUN (mmol/L)	Yes	X	
Acute kidney injury (AKI and AKI_MID)	Yes	X	
Pediatric logistic organ dysfunction (PELOD) score	Yes	X	

Abbreviations: BMI, body mass index; PRISM-3, day of admission severity of illness score – pediatric risk of mortality; PIM-2, day of admission severity of illness score – pediatric index of mortality 2; GFR, glomerular filtration rate; Scr, serum creatinine; BUN, blood urea nitrogen; AKI, acute kidney injury (serum creatinine upper limit); AKI_MID, acute kidney injury (serum creatinine midpoint). Body weight and BMI at closest time prior to dose of vancomycin when sample was taken.

[a] 1 = white, 2 = black or African American, 3 = Asian, 4 = American Indian or Alaska native, 5 = native Hawaiian or other Pacific Islander, 6 = multi-racial, 7 = unknown

[b] 0 = no, 1 = yes; aminoglycosides, amphotericin B, diuretic (intravenous [IV] or by mouth [PO]), IV contrast dyes, non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin receptor blockers (ARBs), cisplatin, carboplatin, oxaliplatin, cyclosporine, tacrolimus, piperacillin-tazobactam, and cyclophosphamide

[c] GFR (mL/min/1.73 m^2) = [0.413 × height (cm) / Scr (mg/dL)]

eTable 2. Forward Selection of Covariates: Step 1 Summary Table

Parameter Affected	Covariate Added	Functional Form	Ver	Change in VOF[a]	df	*P* value[b]	% Change in BSV in CL[c]	% Change in BSV in V_c[c]	Notes
Reference Model, VOF = -448.433 (2-compartment model with allometric scaling)									
CL	BUN	Linear	01	0					Failed to minimize
CL	GFR[d]	Linear	01	0					Failed to minimize
CL	Pediatric Logistic Organ Dysfunction Score	Additive	01	0					Failed to minimize
CL	Scr	Linear	01	0					Failed to minimize
CL	GFR[d]	Power	01	-74.51	1	0	-18.1	-2.71	
CL	BUN	Power	01	-36.237	1	<0.01	-10.3	0.131	
CL	Age	Linear	01	-21.537	1	<0.01	-6.35	4.93	
CL	Scr	Power	01	-16.057	1	<0.01	-4.09	1.65	
CL	Age	Power	01	-15.539	1	<0.01	-4.86	4.67	
CL	PRISM-3 Score	Exponential	01	-5.214	1	<0.1	-1.04	0.373	
CL	Sex	Additive	01	-3.863	1	<0.1	-1.38	2.75	
V_c	Percent Fluid Overload	Exponential	01	-3.745	1	<0.1	-1.02	0.941	
CL	Ethnicity	Exponential	01	-3.481	1	<0.1	-0.989	1.19	
CL	Pediatric Logistic Organ Dysfunction Score	Exponential	01	-8.072	4	<0.1	-1.85	1.95	
V_c	PIM-2 Score	Exponential	01	-2.598	1	>0.1	-0.328	-0.905	
V_c	Age	Power	01	-2.377	1	>0.1	-1.54	0.330	
V_c	Age	Linear	01	-2.15	1	>0.1	-1.68	1.41	
V_c	Ethnicity	Additive	01	-1.931	1	>0.1	-0.259	1.83	
CL	Ethnicity	Additive	01	-1.711	1	>0.1	-0.457	0.826	
V_c	Sex	Additive	01	-1.646	1	>0.1	-0.48	0.64	
CL	Race	Additive	01	-3.206	2	>0.1	-0.722	-0.232	
CL	PIM-2 Score	Exponential	01	-1.23	1	>0.1	-0.276	-0.289	
CL	Sex	Exponential	01	-1.126	1	>0.1	-0.726	2.56	

eTable 2. Forward Selection of Covariates: Step 1 Summary Table

Parameter Affected	Covariate Added	Functional Form	Ver	Change in VOF[a]	df	*P* value[b]	% Change in BSV in CL[c]	% Change in BSV in V_c[c]	Notes
V_c	BMI	Power	01	-.751	1	>0.1	-0.394	2.42	
CL	Race	Exponential	01	-1.851	2	>0.1	-0.445	-0.318	
CL	Nephrotoxic Comedication	Exponential	01	-.703	1	>0.1	-0.212	0.488	
CL	BMI	Power	01	-.672	1	>0.1	-0.194	0.796	
V_c	PRISM-3 Score	Exponential	01	-.57	1	>0.1	-0.760	1.66	
V_c	BMI	Linear	01	-.058	1	>0.1	-0.0938	0.338	
CL	Nephrotoxic Comedication	Additive	01	-.025	1	>0.1	-0.0239	0.0799	
V_c	Race	Additive	01	-.251	2	>0.1	-0.552	1.92	
V_c	Ethnicity	Exponential	01	-.022	1	>0.1	-2.53	-2.12	
V_c	Race	Exponential	01	-.133	2	>0.1	-0.480	2.06	
CL	Percent Fluid Overload	Exponential	01	-.004	1	>0.1	-0.410	1.75	
CL	BMI	Linear	01	-.001	1	>0.1	-0.00225	0.0168	
V_c	Sex	Exponential	01	0	1	1.0	-0.00562	0.0198	

Abbreviations: Ver, version number of the control stream; VOF, value of the objective function; df, number of degrees of freedom associated with this addition to the model; *P*, probability; BSV, between-subject variability; CL, clearance; V_c, central volume of distribution; BUN, blood urea nitrogen; GFR, glomerular filtration rate; SCr, serum creatinine; PRISM-3, day of admission severity of illness score - pediatric risk of mortality; PIM-2, day of admission severity of illness score - pediatric index of mortality 2; BMI, body mass index.

[a] Change in the value of the objective function relative to the reference model.

[b] Statistical significance ($\alpha = 0.01$). <0.01 represents a value less than 0.01, <0.1 represents a value greater than 0.01 and less than 0.1, and >0.1 represents a value greater than 0.1 and less than 1.0.

[c] Change in the magnitude of BSV on the indicated parameter expressed as a percentage relative to the reference model.

[d] Bedside Schwartz GFR (mL/min/1.73 m^2) = [0.413 × Height (cm) / SCr (mg/dL)].

eTable 2. Forward Selection of Covariates: Step 2 Summary Table

Parameter Affected	Covariate Added	Functional Form	Ver	Change in VOF[a]	df	*P* value[b]	% Change in BSV in CL[c]	% Change in BSV in V_c[c]	Notes
Reference Model, VOF = -522.943 (2-compartment model with allometric scaling + Bedside Schwartz GFR as a covariate)									
CL	Age	Linear	01	0					Failed to minimize
CL	BUN	Linear	01	0					Failed to minimize
CL	Pediatric Logistic Organ Dysfunction Score	Additive	01	0					Failed to minimize
CL	Sex	Additive	01	0					Failed to minimize
CL	Age	Power	01	-15.381	1	<0.01	-4.56	2.14	
CL	BUN	Power	01	-9.956	1	<0.01	-3.75	7.99	
V_c	Age	Power	01	-6.412	1	<0.1	DIV / 0	DIV / 0	
V_c	Percent Fluid Overload	Exponential	01	-6.225	1	<0.1	-0.591	7.53	
V_c	Age	Linear	01	-5.522	1	<0.1	-4.01	6.41	
V_c	BMI	Power	01	-4.616	1	<0.1	-2.30	7.37	
CL	BMI	Linear	01	-4.223	1	<0.1	-1.37	0.701	
V_c	Ethnicity	Additive	01	-4.183	1	<0.1	-1.61	9.85	
CL	Pediatric Logistic Organ Dysfunction Score	Exponential	01	-8.141	4	<0.1	-1.90	3.10	
V_c	PIM-2 Score	Exponential	01	-2.89	1	<0.1	-0.598	1.55	
V_c	PRISM-3 Score	Exponential	01	-2.478	1	>0.1	-1.69	8.39	
CL	Sex	Exponential	01	-2.158	1	>0.1	-0.384	-0.281	
CL	PRISM-3 Score	Exponential	01	-2.044	1	>0.1	-0.444	-0.219	
CL	BMI	Power	01	-1.866	1	>0.1	-0.808	0.700	
V_c	Sex	Exponential	01	-1.462	1	>0.1	-1.62	9.76	
CL	PIM-2 Score	Exponential	01	-1.232	1	>0.1	-0.410	0.0639	
V_c	BMI	Linear	01	-.914	1	>0.1	-0.696	0.0687	
CL	Ethnicity	Exponential	01	-.803	1	>0.1	-0.170	-0.151	
CL	Race	Exponential	01	-1.523	2	>0.1	-0.476	-0.292	
CL	Percent Fluid Overload	Exponential	01	-.484	1	>0.1	-0.235	-0.00107	

eTable 2. Forward Selection of Covariates: Step 2 Summary Table

Parameter Affected	Covariate Added	Functional Form	Ver	Change in VOF[a]	df	*P* value[b]	% Change in BSV in CL[c]	% Change in BSV in V_c[c]	Notes
V_c	Race	Exponential	01	-1.345	2	>0.1	-0.989	7.00	
V_c	Ethnicity	Exponential	01	-.2	1	>0.1	-0.0142	-0.210	
CL	Nephrotoxic Comedication	Additive	01	-.196	1	>0.1	-0.0398	0.0731	
CL	Race	Additive	01	-.527	2	>0.1	-0.142	-0.332	
CL	Nephrotoxic Comedication	Exponential	01	-.033	1	>0.1	0.00591	0.0443	
V_c	Race	Additive	01	-.245	2	>0.1	-0.0363	-0.555	
CL	Ethnicity	Additive	01	-.021	1	>0.1	0.00906	-0.0112	

Abbreviations: Ver, version number of the control stream; VOF, value of the objective function; df, number of degrees of freedom associated with this addition to the model; *P*, probability; BSV, between-subject variability; CL, clearance; V_c, central volume of distribution; BUN, blood urea nitrogen; BMI, body mass index; PIM-2, day of admission severity of illness score - pediatric index of mortality 2; PRISM-3, day of admission severity of illness score - pediatric risk of mortality.

[a] Change in the value of the objective function relative to the reference model.

[b] Statistical significance (α = 0.01). <0.01 represents a value less than 0.01, <0.1 represents a value greater than 0.01 and less than 0.1, and >0.1 represents a value greater than 0.1 and less than 1.0.

[c] Change in the magnitude of BSV on the indicated parameter expressed as a percentage relative to the reference model.

eTable 3. Regression Analysis of Model-predicted AUC_{24} versus Observed Vancomycin Trough Concentration

Parameter	Estimate	%RSE
Coefficient of trough concentration = 7 µg/mL	366	1.98
Additive shift for dose frequency < 8 hours	54.9	24.2
Slope of (DOSE [mg] -500)	0.0894	17.9
Exponent of trough concentration	0.495	3.92
Residual variability (CV%)	20.2	18.8

Abbreviations: %RSE, % relative standard error; CV%, % coefficient of variation

eTable 4. Values of AUC_{24}/MIC for the Simulated Dosing Regimen

Dosing Regimen	Sample Strategy	Number of Patients	AUC_{24}/MIC, Median [IQR]		
			MIC = 0.5	MIC = 1	MIC = 2
15mg/kg q6h	Infinite	2250	904 [663, 1260]	452 [331, 630]	226 [166, 315]
	Peak/Trough	2250	902 [675, 1230]	451 [338, 614]	226 [169, 307]
	Trough	2250	901.5 [690, 1220]	451 [345, 612]	225.5 [172, 306]
15mg/kg q8h	Infinite	2250	678 [497, 945]	339 [248, 473]	169.5 [124, 236]
	Peak/Trough	2250	677 [505, 920]	338 [252, 460]	169 [126, 230]
	Trough	2250	679.5 [517, 923]	340 [259, 461]	170 [129, 231]
20mg/kg q6h	Infinite	2250	1210 [883, 1680]	603 [442, 840]	301 [221, 420]
	Peak/Trough	2250	1200 [900, 1640]	601 [450, 819]	301 [225, 409]
	Trough	2250	1200 [919, 1630]	601.5 [460, 816]	300.5 [230, 408]
30mg/kg q8h	Infinite	2250	1360 [994, 1890]	678 [497, 945]	339 [248, 473]
	Peak/Trough	2250	1350 [1010, 1840]	677 [505, 920]	338 [252, 460]
	Trough	2250	1360 [1030, 1850]	679.5 [517, 923]	340 [259, 461]

Abbreviations: AUC_{24}, 24-hour area under the concentration-time curve; MIC, minimum inhibitory concentration (mcg/mL); IQR, interquartile range; 6hr, administered every 6 hours; q8h, administered every 8 hours.

References

1. Willavize S, Fiedler-Kelly J: Reduction in interindividual variability and clinical significance ratio in covariate assessment. Poster presented at: American Conference on Pharmacometrics (ACoP); May 12-15, 2013; Fort Lauderdale, FL. https://www.simulations-plus.com/resource/reduction-interindividual-variability-clinical-significance-ratio-covariate-assessment.

2. Tunblad K, Lindbom L, McFayden L, et al: The use of clinical irrelevance criteria in covariate model building with application to dofetilide pharmacokinetic data. *J Pharmacokinet Pharmacodyn*. 2008; 35:503-26.

3. Bergstrand M, Hooker AC, Wallin JE, et al: Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. *AAPS J*. 2011; 13:143-151.

4. Holford N: The visual predictive check: superiority to standard diagnostic (Rorschach) plots. Poster presented at: Population Approach Group in Europe (PAGE); 2005 Jun 16-17; Pamplona, Spain.

5. Schwartz GJ, Work DF: Measurement and estimation of GFR in children and adolescents. *Clin J Am Soc Nephrol.* 2009; 4:1832-43.

6. Counahan R, Chantler C, Ghazali S, et al: Estimation of glomerular filtration rate from plasma creatinine concentration in children. *Arch Dis Child*. 1976; 51:875-8.

7. Schwartz GJ, Schneider MF, Maier PS, et al: Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. *Kidney Int.* 2012; 82:445-53.

8. Grubb A, Blirup-Jensen S, Lindstrom V, et al: First certified reference material for cystatin C in human serum ERM-DA471/IFCC. *Clin Chem Lab Med*. 2010; 48:1619-21.