AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

CLINICAL THERAPEUTICS

Pilot Study of a Bayesian Approach To Estimate Vancomycin Exposure in Obese Patients with Limited Pharmacokinetic Sampling

Joseph J. Carreno,[a] Ben Lomaestro,[b] John Tietjan,[b] Thomas P. Lodise[a]

Albany College of Pharmacy and Health Sciences, Albany, New York, USA[a]; Albany Medical Center Hospital, Albany, New York, USA[b]

ABSTRACT This study evaluated the predictive performance of a Bayesian PK estimation method (ADAPT V) to estimate the 24-h vancomycin area under the curve (AUC) with limited pharmacokinetic (PK) sampling in adult obese patients receiving vancomycin for suspected or confirmed Gram-positive infections. This was an Albany Medical Center Institutional Review Board-approved prospective evaluation of 12 patients. Patients had a median (95% confidence interval) age of 61 years (39 to 71 years), a median creatinine clearance of 86 ml/min (75 to 120 ml/min), and a median body mass index of 45 kg/m^2 (40 to 52 kg/m^2). For each patient, five PK concentrations were measured, and four different vancomycin population PK models were used as Bayesian priors to estimate the vancomycin AUC (AUC_{FULL}). Using each PK model as a prior, data-depleted PK subsets were used to estimate the 24-h AUC (i.e., peak and trough data [AUC_{PT}], midpoint and trough data [AUC_{MT}], and trough-only data [AUC_T]). The 24-h AUC derived from the full data set (AUC_{FULL}) was compared to the AUC derived from data-depleted subsets (AUC_{PT}, AUC_{MT}, and AUC_T) for each model. For the four sets of analyses, AUC_{FULL} estimates ranged from 437 to 489 mg·h/liter. The AUC_{PT} provided the best approximation of the AUC_{FULL}; AUC_{MT} and AUC_T tended to overestimate AUC_{FULL}. Further prospective studies are needed to evaluate the impact of AUC monitoring in clinical practice, but the findings from this study suggest that the vancomycin AUC can be estimated with good precision and accuracy with limited PK sampling using Bayesian PK estimation software.

KEYWORDS obesity, pharmacokinetic, vancomycin

Received 21 November 2016 **Returned for modification** 30 December 2016 **Accepted** 4 March 2017

Accepted manuscript posted online 13 March 2017

Citation Carreno JJ, Lomaestro B, Tietjan J, Lodise TP. 2017. Pilot study of a Bayesian approach to estimate vancomycin exposure in obese patients with limited pharmacokinetic sampling. Antimicrob Agents Chemother 61:e02478-16. https://doi.org/10.1128/AAC.02478-16.

Address correspondence to Joseph J. Carreno, joseph.carreno@acphs.edu.

Vancomycin is the drug of choice for treating patients with serious infections due to methicillin-resistant *Staphylococcus aureus* (1, 2). To standardize dosing and monitoring, a consensus statement was recently published and identified an area under the curve (AUC)/MIC ratio of ≥400 as the critical vancomycin pharmacokinetic/pharmacodynamic (PK/PD) index (2). Although the AUC/MIC ratio was deemed the critical target, the statement recommends trough, not AUC monitoring. Since the publication of these guidelines, trough monitoring has been widely adopted across health care institutions across the world (3, 4).

Although troughs were deemed a surrogate for AUCs, numerous studies have established the therapeutic discordance between trough and daily AUC values. Although a trough ensures a minimal daily AUC value, a wide range of AUCs can result from dosing regimens yielding identical trough values (5–8). This finding is not surprising because the AUC reflects the cumulative exposure over a defined period of time. In contrast, the trough represents a single exposure point at the end of the dosing interval and is highly dependent on the dose, dosing frequency, and vancomycin clearance. This has clear implications for clinical practice as a trough of 15 to 20 mg/liter

TABLE 1 Baseline demographics

Baseline demographic	Patient data (n = 12)[a]
Age (yr)	61 (39–71)
No. male	7 (58)
Creatinine clearance (ml/min)	86 (75–120)
No. Caucasian	12 (100)
No. initially admitted to the ICU	1 (8)
BMI	45 (40–52)
Vancomycin dose (mg)	
1,000	6 (50)
1,500	6 (50)
Vancomycin interval (h)	
8	3 (25)
12	9 (75)

[a]Data, unless specified otherwise in column 1, are expressed as the median (IQR) or the number (%) of patients.

may lead to suboptimal AUC/MIC ratios in certain patients. Conversely, troughs of 15 to 20 mg/liter may elevate the risk of acute kidney injury in others (9).

Despite the potential advantages of AUC monitoring, clinicians have been hesitant to move away from trough-only monitoring due to the perceived difficulty in determining the AUC in real-time practice (7). Historically, determination of the AUC in clinical practice involved the collection of multiple PK samples over the same dosing interval. Neely et al. (6), however, recently demonstrated that AUCs can be accurately estimated with low bias and high precision with one trough using commercially available Bayesian software. This represents a major advancement in practice because AUC monitoring may now be clinically practical for clinicians at the "bedside."

Several important questions remain before Bayesian software tools can be implemented widely into clinical practice. In the previous evaluation of this technique (6) there was limited representation of obese patients (6, 10–12). Given potential differences in PK profiles between obese and nonobese (13) and the increasing prevalence of obesity in the United States, (14), the limited PK Bayesian AUC monitoring approach needs to be examined in patients with obesity before widespread adoption. Cognizant of this critical gap in the literature, this pilot study was conducted to determine whether the vancomycin AUC can be accurately predicted using Bayesian estimation techniques with limited PK samples in obese patients.

RESULTS

Baseline characteristics. A total of 12 patients were enrolled in the intensive PK sampling portion of this study. The results from the sampling were used (i) to create a population PK model for obese subjects (model 4) and (ii) to estimate 24-h AUC using four different Bayesian priors and three PK data subsets. Most patients were Caucasian males who were admitted to general practice units. These patients had a wide age range (23 to 74 years) and the median (IQR) body mass index (BMI) was 45 kg/m^2 (40 to 52 kg/m^2). All patients enrolled in the study had a normal estimated renal function (range, 54 to 135 ml/min). Equal amounts of patients received 1,000- and 1,500-mg doses. The most frequent dosing regimen was twice daily. There were a total of 71 vancomycin concentrations (60 study samples, 11 clinical samples [troughs]), which were available across the 12 patients for analysis. Additional details are presented in Table 1.

Population PK model for obese subjects (model 4). The median pharmacokinetic estimates and associated measures of variability for model 4 are displayed in Table 2. Overall, the model fit the data well. Figure 1 displays the posterior-Bayesian observed versus predicted vancomycin concentrations plots. The best-fit linear regression line was observed = predicted × 1.000 to 0.0003. The R^2 of the model was 0.998. The mean bias was 0.002 mg/liter.

TABLE 2 Pharmacokinetic parameter estimates

Parameter[a]	Mean (SD)[b]			
	Model 1 (16)	Model 2 (6)	Model 3 (18)	Model 4 (this study)
V_c	18.25 (8.88)	14.80 (7.90)	0.21 (0.042)	25.76 (11.68)
k_{12}	2.36 (4.23)	1.13 (0.78)	1.12 (0.224)	2.29 (2.42)
k_{21}	2.72 (7.08)	0.66 (0.94)	0.48 (0.096)	1.44 (1.73)
k_e	NA	0.30 (0.19)	NA	NA
CL_{INT}	0.48 (0.30)	NA	0.05 (0.010)	0.18 (0.043)
CL_{SLOPE}	0.83 (0.67)	NA	0.75 (0.2475)	0.60 (0.33)

[a]*V*, volume of the central compartment (liters for models 1, 2, and 4; liters/kg for model 3); CL_{INT} clearance due to nonrenal means (liters/h); CL_{SLOPE}, clearance due to creatinine clearance (liters/h); k_{12}, transfer rate constant from the central compartment to the peripheral compartment (per hour); k_{21}, transfer rate constant from the peripheral compartment to the central compartment (per hour); k_e, elimination constant from the central compartment (per hour). NA, not applicable.

[b]Source references are indicated parenthetically in the subheadings for each of the four models.

Vancomycin AUC estimates. The AUC estimates for each model are displayed in Table 3. Using model 1 as the Bayesian prior, the mean (95% confidence interval [CI]) calculated AUC (AUC_{FULL}) was 437 mg·h/liter (296 to 617 mg·h/liter). When the data set was depleted to only include peak and trough data, the AUC (AUC_{PT}) estimate tended to underestimate the AUC_{FULL}, as noted by a AUC_{PT}/AUC_{FULL} ratio that was <1. The AUC_{PT}/AUC_{FULL} ratio was statistically significantly <1. In contrast, the AUC_{MT}/AUC_{FULL}, ratio was statistically significantly >1, indicating that, on average, the AUC_{MT} was 19% greater than the AUC_{FULL}. The ratio of AUC_T to AUC_{FULL} indicated that AUC_T tended to overestimate AUC_{FULL} by approximately 30%. The AUC_T/AUC_{FULL} ratio was statistically significantly >1. For model 1, the mean (95% CI) prediction errors were −9.01% (−12.84% to −5.20%), 18.95% (+13.07% to +24.84%), and 29.81% (+19.28% to +40.35%) for AUC_{PT}, AUC_{MT}, and AUC_T, respectively.

The use of model 2 as a Bayesian prior resulted in results similar to those seen with the use of model 1 as a Bayesian prior. The mean (95% CI) AUC_{FULL} was 478 mg·h/liter (305 to 683 mg·h/liter). The AUC_{PT}/AUC_{FULL} ratio statistically significantly underestimated the AUC_{FULL} by approximately 4%. Similar to model 1, the AUC_{MT}/AUC_{FULL} ratio

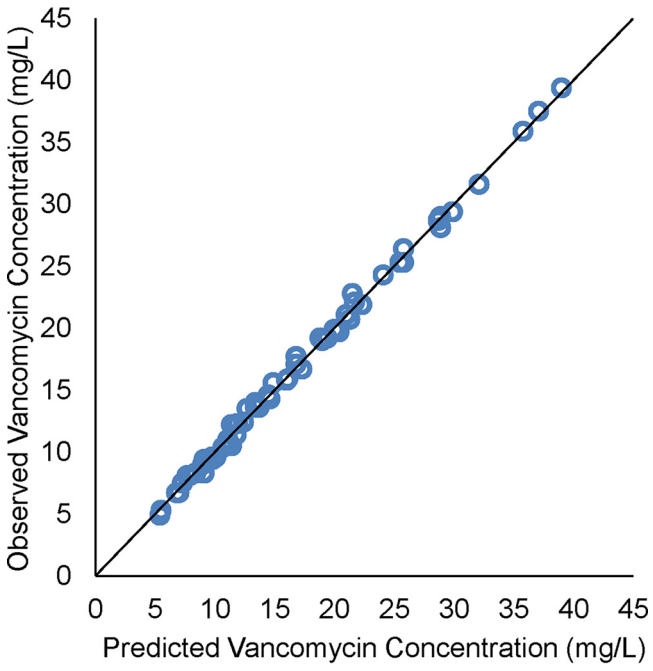

FIG 1 Predicted versus observed vancomycin concentrations using the obesity-specific pharmacokinetic model (model 4) as the Bayesian prior and the complete data set.

TABLE 3 AUC estimates[a]

Model	AUC_{FULL} (95% CI)	AUC_{PT} data			AUC_{MT} data			AUC_T data		
		AUC_{PT} (95% CI)	AUC_{PT}/AUC_{FULL} ratio (95% CI)	R^2	AUC_{MT} (95% CI)	AUC_{MT}/AUC_{FULL} ratio (95% CI)	R^2	AUC_T (95% CI)	AUC_T/AUC_{FULL} ratio (95% CI)	R^2
1	437 (296–617)	393 (275–576)	0.91 (0.87–0.95)	0.997	530 (379–725)	1.19 (1.13–1.25)	0.996	574 (379–725)	1.30 (1.19–1.40)	0.986
2	478 (305–683)	456 (300–659)	0.96 (0.93–0.99)	0.998	541 (403–732)	1.15 (1.07–1.24)	0.992	511 (336–682)	1.04 (0.97–1.13)	0.982
3	469 (314–628)	489 (274–620)	0.99 (0.94–1.04)	0.997	427 (289–606)	0.98 (0.92–1.05)	0.990	401 (275–482)	0.87 (0.77–0.97)	0.974
4	489 (309–604)	412 (308–613)	0.93 (0.84–1.01)	0.990	500 (318–640)	1.01 (0.91–1.10)	0.983	520 (278–735)	1.13 (0.81–1.44)	0.851

[a]Data are means (95% CI). *P* values are compared to AUC_{FULL} and were determined using the Wilcoxon signed-rank test.

indicated that AUC_{MT} was an overestimate of AUC_{FULL} by approximately 15%. In the ratio analysis, the AUC_{MT} was statistically significantly greater than the AUC_{FULL}. Use of the trough only data with model 2 as a Bayesian prior produced results remarkably similar to those obtained using model 1. AUC_T overestimated AUC_{FULL} by approximately 4% in the ratio analysis. The AUC_T was not statistically significantly different than the AUC_{FULL}. For model 2, the mean (95% CI) prediction errors were −3.90% (−7.24% to −0.58%), 15.37% (+7.10% to +23.63%), and 4.80% (−3.08% to +12.67%) for AUC_{PT}, AUC_{MT}, and AUC_T, respectively.

Using model 3 as a Bayesian prior, the mean (95% CI) AUC_{FULL} was 469 mg·h/liter (314 to 628 mg·h/liter). The mean ratios of AUC_{PT} to AUC_{FULL} and AUC_{MT} to AUC_{FULL} were not statistically significantly different than 1. However, the mean ratio of AUC_T to AUC_{FULL} statistically significantly underestimated AUC_{FULL} by approximately 13%. The mean (95% CI) prediction errors were −0.62% (−5.84% to +4.34%), −1.61% (−8.05% to +4.83%), and −12.76% (−22.96% to −2.56%) for AUC_{PT}, AUC_{MT}, and AUC_T, respectively.

The final set of analyses were conducted with the pharmacokinetic model developed in this study (i.e., model 4). Using model 4, the mean AUC_{PT}/AUC_{FULL}, AUC_{MT}/AUC_{FULL}, AUC_T/AUC_{FULL}, and AUC_T/AUC_{FULL} ratios were not statistically significantly different than 1. The mean (95% CI) prediction errors were −7.51% (−15.65% to +0.63%), +0.54% (−8.88% to +9.96%), and 12.45% (−18.86 to +43.76%) for AUC_{PT}, AUC_{MT}, and AUC_T, respectively.

DISCUSSION

This evaluation was undertaken to examine the predictive performance of Bayesian PK AUC estimation software in predicting the vancomycin AUC with limited PK samples in patients with obesity. To evaluate the utility of this approach, we used four different population PK model as Bayesian priors. Three models were derived in nonobese patients, and one was derived in obese patients with various degrees of renal function. We also considered three different sets of depleted PK data sets when estimating the AUC with each Bayesian prior. Combined, the goal was to determine the optimal Bayesian prior that required the smallest number of timed PK samples to accurately estimate the AUC with low bias and high precision.

In contrast to the study by Neely et al. (6), the trough-only depleted PK data set did not result in an accurate estimation of the AUC_{FULL}. Across three of four Bayesian priors, the use of the trough only resulted in biased AUC_{FULL} estimates. The prediction error ranged from 4.80 to 29.81%, indicating that the AUC estimated derived using this technique would be overestimates of the 24-h AUC. As such, the clinical implementation of the trough-only AUC estimation technique could lead to erroneous dose reductions. These erroneous dose reductions could translate to an increased risk of clinical failure and the development of resistance. The use of model 3 also provided biased results; however, model 3 resulted in underestimation of the AUC_{FULL} by 12.76%. In clinical practice, using model 3 with trough-only data could translate to unneeded dose increases that could increase the risk of toxicity. In addition to the biases observed with the trough-only AUC estimates, the 95% confidence intervals for the AUC and prediction errors were highly imprecise. Taken together, these findings suggest that the

biased and imprecise nature of the trough-only approach to estimate the AUC in patients with obesity may not be optimal, but further investigation is warranted.

In order to address the bias and lack of precision seen with the trough-only AUC estimates, we evaluated the AUC estimation technique using a peak in addition to the trough. We chose a peak (1 h after end of infusion) and trough as sampling points because this sampling scheme may be familiar to clinicians. For models 1 to 4, the addition of the peak data resulted in less bias and increased precision compared to the trough-only AUC estimates derived using the same model. In order to test the robustness of the observations with the second level, we calculated AUC estimates with midpoints instead of peaks, while holding the trough consistent. Use of the midpoint-trough PK data set was slightly better than using trough-only data, but this still conferred a biased estimate of the AUC_{FULL}. However, model 3 had the most accurate and precise AUC_{PT}/AUC_{FULL} ratio and 95% CI, and model 3 was the only structural PK model with a volume in the central compartment that was parameterized to the total body weight. Although these numeric differences were observed, it should be noted that this was a pilot study and was not powered to detect differences in AUC estimates between the different Bayesian priors. In addition, although no definitive conclusions can be made in this pilot study, further studies should investigate whether the use of Bayesian priors that scale volume to different body size descriptors improves the predictive performance of AUC estimation with limited PK data relative to other Bayesian priors.

These findings have important implications for clinical practice. The data from this study suggest that obtaining a peak and trough level improves the ability to accurately dose vancomycin in obese patients using Bayesian PK estimation methods. This finding is consistent with emerging literature supporting the use of multiple levels for vancomycin AUC estimation in obese patients (15). Adaptation of this practice should not be problematic at the bedside since the collection of multiple levels for vancomycin dosing was the standard of care prior to 2009. While trough-only monitoring may be appropriate for nonobese patients (6–8), the present study demonstrates one potential shortcoming of trough-only monitoring in obese patients. In addition, we highlight here the need to assess trough-only monitoring in specialized patient populations, especially patient groups thought to have large interpatient variability.

As with any study, this evaluation has potential limitations. Our study was not designed to be a population pharmacokinetic study; as such, we did not perform d-optimal design for our sampling scheme. Our source population also limits the ability to extrapolate this AUC estimation technique to patients outside the source population. Specifically, we did not have patients weighing more than 250 kg, so we still need data on the upper extreme of obesity. In addition, since this was a single center pilot study, it would be prudent to verify these results in a larger multicenter study. As stated above, this pilot study was not powered to detect differences in AUC estimates between the different Bayesian priors. Future studies should be powered to discriminate the predictive performance of different Bayesian priors, especially those that employ structural PK models that scale body size descriptors to PK parameters versus those that do not.

In summary, we evaluated a Bayesian technique for estimating the 24-h AUC in obese patients. We used four different Bayesian priors under three different conditions to select a clinically feasible method of estimating the vancomycin 24-h AUC. Our results suggest that the use of two samples (i.e., peak and trough) enhances the ability to assess PK/PD target attainment compared to a one-sample approach (i.e., trough only). The peak and trough approach outperformed the trough-only approach in each set of analyses. Although current consensus recommendations suggest the deployment of trough-only monitoring for all patient populations, we recommend that for patients with obesity, a peak and trough vancomycin level should be monitored as well. Additional prospective studies are needed to determine the optimal monitoring scheme for vancomycin in obese patients.

TABLE 4 Pharmacokinetic models used[a]

Model(s)	Differential equation
1 and 4	$dX(1)/dt = R(t) - [(CL_{INT} + CL_{SLOPE} \times CL_{CR})/V_c + k_{12}] \times X(1) + k_{21} \times X(2)$ and $dX(2)/dt = k_{12} \times X(1) - k_{21} \times X(2)$
2	$dX(1)/dt = R(t) - [k_e + k_{12}] \times X(1) + k_{21} \times X(2)$; $dX(2)/dt = k_{12} \times X(1) - k_{21} \times X(2)$
3[b]	$dX(1)/dt = R(t) - [CL/(V_c0 \cdot wt)] \times X(1) + k_{21} \times X(2)$; $dX(2)/dt = k_{12} \times X(1) - k_{21} \times X(2)$

[a] $X(1)$ is the amount of drug in the central compartment, and $X(2)$ is the amount of drug in the peripheral compartment. R(t) is a time-delimited zero-order drug input rate (piecewise input function) into the central compartment (milligrams per hour). CL is the clearance from the central compartment (liters per hour), V_c represents the apparent volume of distribution from the central compartment. and k_{12} and k_{21} are first-order intercompartmental transfer rate constants (per hour). k_e is the first-order elimination constant (per hour) from the central compartment. See also Table 2, footnote *a*, for additional definitions.

[b] Model 3 included weight as a linear covariate, such that $V_c = V_c0 \cdot$ weight, where V_c0 was the parameter to be estimated, normalized to weight.

MATERIALS AND METHODS

Study population. We conducted a prospective, open-labeled, pharmacokinetic evaluation of vancomycin in hospitalized, adult obese subjects at Albany Medical Center Hospital. The study enrolled patients who were (i) ≥18 years old, (ii) admitted to Albany Medical Center Hospital, (iii) receiving intravenous vancomycin for treatment of suspected or confirmed Gram-positive infections, and (iv) weighed ≥110 kg. Patients were excluded if they were neutropenic (absolute neutrophil count of <1,000 cells/mm^3), ≥18 years old but admitted to a pediatric unit, pregnant, had baseline renal impairment (serum creatinine of ≥2.0 mg/dl or creatinine clearance of <50 ml/min), unable to give consent (comatose, patients unable to understand the consent process, etc.), or prisoners, or if they had a vancomycin dosing interval of every 6 h (for sampling feasibility). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The study was approved by the Albany Medical Center Institutional Review Board, and informed consent was obtained from each patient (protocol 3847).

Pharmacokinetic sampling. Five ~5-ml blood samples were collected from each patient. The first four levels were drawn at 1, 2, 4, and 6 h after the end of the infusion, with the remaining level drawn at the end of the dosing interval. The acceptable window around each sampling time was within 30 min of the scheduled sampling time. Actual sampling times were recorded and used for all analyses. If a subject had additional vancomycin levels determined as part of the clinical practice within the dosing interval, these additional levels were also used to develop model 4 and to calculate the AUC_{FULL}. All vancomycin levels were analyzed in the inpatient clinical laboratory at Albany Medical Center Hospital. All data were recorded on a standardized case report form.

Vancomycin assay description. Albany Medical Center utilizes the Beckman-Coulter Unicel DxC serum vancomycin assay. This assay has a reportable range of 3.5 to 40 mg/liter. The detection limit of the assay is 3.5 mg/liter. The demonstrated within-run precision coefficient of variance (CV) is 4.0%, and the total run precision CV is 6.0%. Equivalency determined using Deming regression analysis of the patient samples in accordance with accepted clinical methods yielded a slope of 1.096, an intercept of −2.63, and a correlation coefficient of 0.983.

Population PK models used as Bayesian priors. Four different vancomycin population PK models were used as Bayesian priors (Table 4) in the Bayesian AUC estimation analyses. Model 1 was a previously published open two-compartment vancomycin population PK model derived from 21 adult patients with suspected or confirmed infections requiring treatment with vancomycin. Model 1 parameterized vancomycin clearance as a function of creatinine clearance with an intercept term (9, 16).

Model 2 was a two-compartment population pharmacokinetics model derived from 47 adults with various renal function from three different studies. The three studies comprised a diverse set of patients and included patients from outpatient and inpatient settings receiving vancomycin for prophylaxis and/or suspected or confirmed Gram-positive infection. Pharmacokinetic data were available from 47 patients across these studies, and a two-compartment population pharmacokinetic model for vancomycin was fit to the data (model 2). No covariate modeling building was performed in model 2.

Model 3 was a previously published open two-compartment vancomycin population PK model derived from 37 patients with various degrees of renal function who received vancomycin for suspected or documented Gram-positive infection. Model 3 parameterized volume in the central compartment (V_c) as a function of weight (i.e., $V_c = V_0 \times$ actual body weight). In model 3, vancomycin clearance was parameterized as a function of creatinine clearance using the following linear regression formula: vancomycin clearance = $CL_{CR} \times 0.75 + 0.05$. In this equation, the standard deviations for the slope and intercept were 0.2475 (33%) and 0.01 (20%), respectively. The use of model 3 was previously used with Bayesian feedback to refine PK parameter estimates in 95 nonobese and 135 obese adult patients (17, 18).

Data from the pharmacokinetic evaluation in the present study were used to create a population pharmacokinetic model (model 4) using Big Nonparametric Adaptive Grid with Adaptive γ (BigNPAG) of Leary et al. (19) The pharmacokinetic model was parameterized as a standard two compartment model with zero-order infusion and first order elimination and transfer constants. In order to assess the impact of renal function on overall clearance, total vancomycin clearance was made proportional to the estimated creatinine clearance (CL_{CR}) using the following linear regression formula: CL = ($CL_{SLOPE} \times CL_{CR}$) + CL_{INT}, where CL_{SLOPE} is the clearance slope, and CL_{INT} is the clearance intercept.

The inverse of the estimated assay variance was used as the first estimate for weighting in the PK model. Weighting assumed that the total observation variance was proportional to assay variance, which

was determined on a between-day basis. The analysis was performed with adaptive gamma, a scalar that multiplies the polynomial described above and that is optimized with each cycle to produce the best approximation to the homoscedastic assumption.

Upon attaining convergence, Bayesian estimates for each patient were obtained using the "population of one" utility within BigNPAG. Mean, median, and modal values were used as measurements of the central tendency of the population parameter estimates and were evaluated in the maximum *a posteriori* probability (MAP) Bayesian analysis. Scatter plots were examined for individual patients and the overall population. Goodness of fit was assessed by regression with an observed versus predicted plot, coefficients of determination, and log-likelihood values. The predictive performance was based on the weighted mean bias and the bias-adjusted weighted mean precision.

AUC estimation. The MAP-Bayesian procedure within ADAPT V was used to estimate each patient's vancomycin 24-h area under the curve (AUC). The mean parameter vector and covariance matrix from each of the population pharmacokinetic vancomycin models (6, 16, 10, 17) was embedded in the PRIOR subroutine of ADAPT V (Bayesian prior). The MAP procedure in the standard two-stage module (STS) of ADAPT was then used to estimate the posterior conditional estimate of each patient's given PK parameters values after the dosing and drug concentrations were considered. With the Bayesian conditional posterior predicted PK parameters, the cumulative AUC was calculated for each patient. The 24-h AUC was calculated by subtracting the cumulative AUC at the beginning of the dosing interval for the intensive sampling period from the cumulative AUC at the end of the dosing interval for the intensive sampling period and multiplying the difference by the number of dosing intervals in a 24-h period (AUC_{FULL}). AUC_{FULL} was calculated with each population PK model (models 1 to 4) as a Bayesian prior to produce four different posterior conditional AUC estimates (model 1 to 4 AUC_{FULL} values).

Limited sampling AUC estimates. In order to estimate 24-h AUC with each limited sampling scheme, we used three PK data subsets: (i) peak and trough concentrations, (ii) midpoint and trough concentrations, and (iii) trough-only concentrations. For each patient, we produced three additional 24-h AUC estimates for each Bayesian prior: one from peak and trough data (AUC_{PT}), one from midpoint and trough data (AUC_{MT}), and one from single-trough data (AUC_{T}).

Data analysis plan. The goal of the analysis was to assess the ability of the 24-hour AUC estimates derived from data-depleted subsets (AUC_{T}, AUC_{PT}, and AUC_{MT}) to approximate the 24-h AUCs derived from the full data set (AUC_{FULL}). This comparison was conducted for each Bayesian prior. Ratios (AUC_{TEST}/AUC_{FULL}), mean prediction errors (i.e., $100 \times [AUC_{TEST} - AUC_{FULL}]/AUC_{FULL}$), and R^2 values were used as measures of bias and precision. Under the null hypothesis, the ratio of AUC derived from each of the data-depleted subsets to AUC_{FULL} (i.e., AUC_{T}/AUC_{FULL}, AUC_{PT}/AUC_{FULL}, and AUC_{MT}/AUC_{FULL}) was 1.

ACKNOWLEDGMENTS

This study was supported by a Society of Infectious Diseases Young Investigator grant.

J.J.C. designed the study, recruited patients, collected all study data, performed the modeling, simulation, and statistical analyses, and wrote the manuscript. B.L. and J.T. designed the study, recruited patients, and edited the manuscript. T.P.L. designed the study, assisted in the analysis of the data for the manuscript, and edited the manuscript.

REFERENCES

1. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, Kaplan SL, Karchmer AW, Levine DP, Murray BE, M JR, Talan DA, Chambers HF, Infectious Diseases Society of, A. 2011. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis 52:e18-55. https://doi.org/10.1093/cid/ciq146.
2. Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC, Craig WA, Billeter M, Dalovisio JR, Levine DP. 2009. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis 49: 325–327. https://doi.org/10.1086/600877.
3. Johannsson B, Beekmann SE, Srinivasan A, Hersh AL, Laxminarayan R, Polgreen PM. 2011. Improving antimicrobial stewardship: the evolution of programmatic strategies and barriers. Infect Control Hosp Epidemiol 32:367–374. https://doi.org/10.1086/658946.
4. Davis SL, Scheetz MH, Bosso JA, Goff DA, Rybak MJ. 2013. Adherence to the 2009 consensus guidelines for vancomycin dosing and monitoring practices: a cross-sectional survey of U.S. hospitals. Pharmacotherapy 33:1256–1263. https://doi.org/10.1002/phar.1327.
5. Neely MN, van Guilder MG, Yamada WM, Schumitzky A, Jelliffe RW. 2012. Accurate detection of outliers and subpopulations with Pmetrics, a nonparametric and parametric pharmacometric modeling and simulation package for R. Ther Drug Monit 34:467–476. https://doi.org/10.1097/FTD.0b013e31825c4ba6.
6. Neely MN, Youn G, Jones B, Jelliffe RW, Drusano GL, Rodvold KA, Lodise TP. 2014. Are vancomycin trough concentrations adequate for optimal dosing? Antimicrob Agents Chemother 58:309–316. https://doi.org/10.1128/AAC.01653-13.
7. Pai MP, Neely M, Rodvold KA, Lodise TP. 2014. Innovative approaches to optimizing the delivery of vancomycin in individual patients. Adv Drug Deliv Rev 77:50–57. https://doi.org/10.1016/j.addr.2014.05.016.
8. Tatarinova T, Neely M, Bartroff J, van Guilder M, Yamada W, Bayard D, Jelliffe R, Leary R, Chubatiuk A, Schumitzky A. 2013. Two general methods for population pharmacokinetic modeling: nonparametric adaptive grid and nonparametric Bayesian. J Pharmacokinet Pharmacodyn 40: 189–199. https://doi.org/10.1007/s10928-013-9302-8.
9. Patel N, Pai MP, Rodvold KA, Lomaestro B, Drusano GL, Lodise TP. 2011. Vancomycin: we can't get there from here. Clin Infect Dis 52:969–974. https://doi.org/10.1093/cid/cir078.
10. Rodvold KA, Blum RA, Fischer JH, Zokufa HZ, Rotschafer JC, Crossley KB, Riff LJ. 1988. Vancomycin pharmacokinetics in patients with various degrees of renal function. Antimicrob Agents Chemother 32:848–852. https://doi.org/10.1128/AAC.32.6.848.
11. Hurst AK, Yoshinaga MA, Mitani GH, Foo KA, Jelliffe RW, Harrison EC. 1990. Application of a Bayesian method to monitor and adjust vancomycin dosage regimens. Antimicrob Agents Chemother 34:1165–1171. https://doi.org/10.1128/AAC.34.6.1165.
12. Lodise TP, Drusano GL, Butterfield JM, Scoville J, Gotfried M, Rodvold KA. 2011. Penetration of vancomycin into epithelial lining fluid in healthy

volunteers. Antimicrob Agents Chemother 55:5507–5511. https://doi.org/10.1128/AAC.00712-11.
13. Grace E. 2012. Altered vancomycin pharmacokinetics in obese and morbidly obese patients: what we have learned over the past 30 years. J Antimicrob Chemother 67:1305–1310. https://doi.org/10.1093/jac/dks066.
14. Flegal KM, Kruszon-Moran D, Carroll MD, Fryar CD, Ogden CL. 2016. Trends in obesity among adults in the United States, 2005 to 2014. JAMA 315:2284–2291. https://doi.org/10.1001/jama.2016.6458.
15. Hong J, Krop LC, Johns T, Pai MP. 2015. Individualized vancomycin dosing in obese patients: a two-sample measurement approach improves target attainment. Pharmacotherapy 35:455–463. https://doi.org/10.1002/phar.1588.
16. Drusano GL, Ambrose PG, Bhavnani SM, Lodise TP, Rubino C, Forrest A, Louie A, Rodvold KA. 2007. Vancomycin dose recommendations for hospital-, ventilator- or health care-associated pneumonia and the attainment of vancomycin trough concentrations of 15 to 20 mg/liter: cognitive dissonance, abstr A-11. 45th Annual Meeting of the Infectious Diseases Society of America, San Diego, CA.
17. Vance-Bryan K, Guay DR, Gilliland SS, Rodvold KA, Rotschafer JC. 1993. Effect of obesity on vancomycin pharmacokinetic parameters as determined by using a Bayesian forecasting technique. Antimicrob Agents Chemother 37:436–440. https://doi.org/10.1128/AAC.37.3.436.
18. Rodvold KA, Garrison M, Rotschafer JC. 1989. Evaluation of a two-compartment Bayesian forecasting program for predicting vancomycin concentrations. Ther Drug Monit 11:269–275. https://doi.org/10.1097/00007691-198905000-00009.
19. Leary RH, Jelliffe R, Schumitzky A, Van Guilder M. 2001. An adaptive grid nonparametric approach to population pharmacokinetic/dynamic (PK/PD) population models, p 389–394. *In* 14th Institute of Electrical and Electronics Engineers Symposium on Computer-Based Medical Systems. IEEE, Bethesda, MD.