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Vancomycin area under the curves estimated with pharmacokinetic equations using trough-only data

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Abstract

What is known and objective: The revised vancomycin monitoring guidelines recommend targeting an area under the curve (AUC) of 400–600 mg*hr/L for serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections. An AUC can be measured by checking a peak and trough concentration at steady state; however, this requires obtaining an additional blood sample. The most practical way to perform AUC-guided dosing is by estimating an AUC from a steady-state trough. The purpose of this study was to compare AUCs estimated from trough-only data to AUCs calculated from peak and trough concentrations.

Methods: Steady-state peak and trough data were collected from an open-access clinical calculator VancoPK.com. Patients were included who had (1) peaks drawn ≥60 min after the end of infusion, (2) peak and trough levels drawn ≥4 h apart and (3) troughs drawn ≤4 h early or late. The population was randomized and divided into a model group and test group. A population equation for vancomycin volume of distribution (Vd) was derived and compared to other general adult Vd models. Accuracy and precision of estimated AUCs were measured with bias, root mean square error (RMSE) and Lin's concordance correlation.

Results and discussion: A total of 2,500 adult patients were included in the model group and 1,843 were included in the test group. The derived Vd equation, Vd (L) = 0.29(age) +0.33(total BW in kg) +11, produced accurate and precise AUC estimates from trough-only data. The mean actual AUC and estimated AUC were 504 and 503, respectively, with a correlation of 0.926. The RMSE between estimated and actual AUCs was 47.7, meaning that over 95% of estimated AUCs were within 100 points of actual AUCs with the study's Vd model. Other Vd models performed well for certain types of patients, depending on their body weight and age.

What is new and conclusion: There is limited evidence from large, robust populations regarding how to estimate Vd for general adult patients. Accuracy and precision of estimated AUCs depend on the applied population Vd model. The Vd model from the present study can be used for AUC-guided dosing with trough-only data which requires less blood work than peak-trough monitoring. AUC calculations are practical with the use of open-access websites.

KEYWORDS
area under the curve, clinical calculator, population pharmacokinetics, vancomycin, website

1 | WHAT IS KNOWN AND OBJECTIVE

When taken at face value, vancomycin troughs are poor surrogates of the area under the curve (AUC).[1] The revised vancomycin monitoring guidelines recommend targeting an AUC range of 400–600 mg*hr/L for serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections.[2] With a vancomycin minimum inhibitory concentration (MIC) of 1 mg/L, a daily AUC ≥400 is needed for efficacy while a daily AUC >650 may increase the risk of acute kidney injury.[3]

One of the preferred methods for AUC-guided dosing is by measuring a peak and trough when concentrations are at steady state. The levels can be used to calculate an elimination rate constant (Ke) and an apparent volume of distribution (Vd), which together equal vancomycin clearance (CLv). Equation (1).

$$CL_v\,(L/hr) = Vd \times Ke \tag{1}$$

At steady state, a snapshot of the daily AUC can be calculated from CLv based on a total daily dose (TDD). Equation (2).

$$AUC_{24} = \frac{TDD}{CL_v} \tag{2}$$

Although accurate, this method for AUC-guided dosing requires obtaining an additional blood sample at an appropriate time. One-compartment, first-order pharmacokinetic (PK) equations require peak levels to be drawn at least one hour after the end of infusion, and trough levels to be drawn at least 4 h after the peak level.[2]

Monitoring a trough near steady state is a practical way to estimate the AUC and provide AUC-guided dosing. This can be done by using Bayesian statistics or PK equations. The vancomycin guidelines define utilizing Bayesian software as a clinical option for some patients, but state that "more data are needed across different patient populations to confirm the viability of using trough-only data."[2] Bayesian software programmes produce very different results, and their use is often limited by costly subscriptions.[4]

The PK method uses analytical equations that produce consistent results; however, studies evaluating this approach for estimating AUCs have not been published previously. The primary issue of using trough-only data to estimate an AUC is that there is limited evidence for Vd models developed from large, robust populations. Most general adult Vd models are from studies that had fewer than 200 patients and had limited sampling of patients with extreme age or body weight.[5,6]

The following intermittent IV infusion equation was first described by Sawchuk and Zaske in 1976 (Equation 3).[7,8] When measuring a steady-state vancomycin level after distribution has finished, all variables in Equation 3 are known except for Vd and Ke.

$$C_{ss} = \frac{Dose\left(e^{-Ke(t-t_i)}\right)\left(1-e^{-Ke\times t_i}\right)}{t_i \times Ke \times Vd\left(1-e^{-Ke\times T}\right)} \tag{3}$$

The first step to solve this equation is to estimate Vd from a population model. Next, Ke must be determined so that the calculated level from the equation, Css, matches the level that was measured. Once Vd and Ke have been calculated, then Equation 1 can be used to estimate CLv, and Equation 2 can be used to estimate an AUC from a total daily dose.

Solving this equation by hand or with non-kinetics software like Excel is not practical, but there are open-access websites that use this method.[9,10] The purpose of this study was to compare the accuracy and precision of AUCs estimated from trough-only data to actual AUCs calculated from peak and trough concentrations.

2 | METHODS

Data were collected from the website VancoPK.com from June 2020 to May 2021. When users pressed the "calculate" button on the steady-state peak and trough calculator, the following data were gathered: the date and time, age, height, body weight, gender, serum creatinine, dose, dosing interval, infusion rate, steady-state peak and trough, and time from start of infusion to the peak and trough. Patient-specific Vd, Ke, CLv and AUC were calculated from the data using first-order, intermittent IV infusion equations.

Due to its simplicity and ease of clinical use, a one-compartment model was fit to the serum vancomycin concentrations.[2,8,11] Patients were included who had (1) peaks drawn ≥60 min after the end of infusion, (2) peak and trough levels drawn ≥4 h apart and (3) troughs drawn ≤4 h early or late. The detailed data gathered for each patient allowed for duplicate and test data to be identified and removed. This was done by using Excel's remove duplicate tool and by sorting the data by the different variables. Only one unique patient for every peak-trough couplet was allowed.

Multiple regression was used to identify significant patient variables for the Vd model. The population was randomized by a computer and divided into a model group and test group. Excel's solver tool was used to optimize the Vd equation's coefficients by minimizing the sum of squared differences between the actual and estimated AUCs.

Other population Vd models were identified by searching PubMed and reviewing pharmacokinetics textbooks. General adult Vd models were included that were derived from robust populations. Models derived from special populations such as burn patients, patients with haematological malignancies, or patients admitted to intensive care were excluded because they often have a larger mean Vd compared to general adult patients.[5,6]

To evaluate the Vd models, root mean square error (RMSE) was used as a measure of precision, and bias was used as a measure of accuracy. Lin's concordance correlation coefficient was used to measure the association between estimated AUCs with actual AUCs. Analysis was done using Microsoft Excel.

3 | RESULTS AND DISCUSSION

The adult Vd models identified for comparison are listed in Table 1. In general, vancomycin Vd ranges from about 0.5 to 1.0 L/kg, with an average of about 0.7 L/kg.[8,12,13] Out of the four models, the Tanaka model had the largest study population with 164 patients.[14]

A total of 4,343 patients were included in the present study, with 1,224 females and 3,119 males (Table 2). Many patients were excluded because their vancomycin levels were not drawn appropriately: 1,210 patients had peak levels drawn less than 60 min after the end of infusion, and 509 patients had peak and trough levels drawn less than 4 h apart.

Multiple regression analysis found that age and body weight were significant factors for estimating Vd ($p < 0.001$). Although most Vd models only include body weight, many studies have also identified age as a factor for predicting vancomycin Vd at steady state. This has been ascribed to changes in peripheral circulation and enhanced tissue binding of vancomycin in the elderly.[12,14–18]

TABLE 1 General adult Vd models included for comparison

	Vd Formulas (L)
Sanchez[14]	Vd = 0.283 × BW + 32.2 × (age/53.5)
Winter[13]	Vd = 0.70 L/kg
Tanaka[21]	Vd = 0.864 L/kg
Birt[22]	Vd = 0.54 L/kg

TABLE 3 Coefficients of the Vd equation

	Coefficients (±SD)	95% CI
Age	0.289 (0.015)	0.284–0.294
Body weight (kg)	0.334 (0.010)	0.33–0.338
Intercept	10.8 (1.0)	10.4–11.2

Coefficients in the Vd equation were determined by randomizing the total population, selecting 2,500 patients for a model group and optimizing the coefficients to reduce the square difference between actual and estimated AUCs. The process was repeated 30 times to find average coefficient values (Table 3). Equation (4).

$$Vd = 0.29\,(age) + 0.33\,(actual\ BW\ in\ kg) + 11 \quad (4)$$

The derived Vd equation reduced interindividual variability of Vd by 17.2% versus the population mean Vd of 61.1 L in the test group. The only other model to reduce variability was the Sanchez model which had a 13.5% reduction. Table 4 describes the accuracy and precision of AUCs estimated from the Vd models.

The Winter, Sanchez and study models all had low bias and strong correlation between actual and estimated AUCs for the overall test group (N = 1,843). They had a root mean square error (RMSE) of about 50, meaning that about 68% of estimated AUCs were within 50 points of actual AUCs. With an estimated AUC of 500, the actual AUC was within 400–600 about 95% of the time (Figure 1).

The Tanaka and Birt models had greater bias, weaker correlations and were less precise for the overall test group. Model performance was also evaluated by examining patients who had an extreme body mass index (BMI) (Table 5).

TABLE 2 Population characteristics (N = 4,343)

	Median	Mean	(±SD)	Range	Units
Age	64	61.8	(15.8)	18–100	years
Height	173	172	(10.8)	137–213	cm
Body weight	82	86	(27)	33–227	kg
BMI	27.5	29.1	(8.5)	13.1–84.4	kg/m^2
SCr	0.83	0.91	(0.37)	0.5–4.3	mg/dl
Dose	1000	1116	(315)	250–2500	mg
Dosing interval	12	14.7	(6.4)	6–72	hrs
Peak	26.5	27	(6.8)	12.1–51.7	mcg/ml
Trough	13.5	13.8	(4.6)	5–33	mcg/ml
CLcr	88.9	94.7	(41.3)	10.2–339	ml/min
Vd	57.2	60.8	(22.2)	16.2–173	L
Vd	0.68	0.74	(0.28)	0.20–2.55	L/kg
Ke	0.07	0.078	(0.04)	0.003–0.25	hr^{-1}
CLv	4.01	4.35	(2.07)	0.32–14.3	L/hr
AUC	499	504	(127)	184–1045	mg*hr/L

TABLE 4 Estimated AUCs compared to actual AUCs in the test group (*N* = 1,843)

Vd models	Mean trough-only AUC (±SD)	Bias	RMSE	Concordance correlation
Present study	503 (47.7)	1.6	47.7	0.926
Sanchez	495 (49.5)	9.6	50.4	0.918
Winter	500 (53.4)	4.6	53.5	0.909
Tanaka	470 (51.1)	34	61.4	0.882
Birt	544 (58.6)	−39.8	70.8	0.856

Note: Bias was calculated as the difference between the mean actual AUC of 504 and mean estimated AUCs; RMSE (root mean square error) was used as a measure of precision.

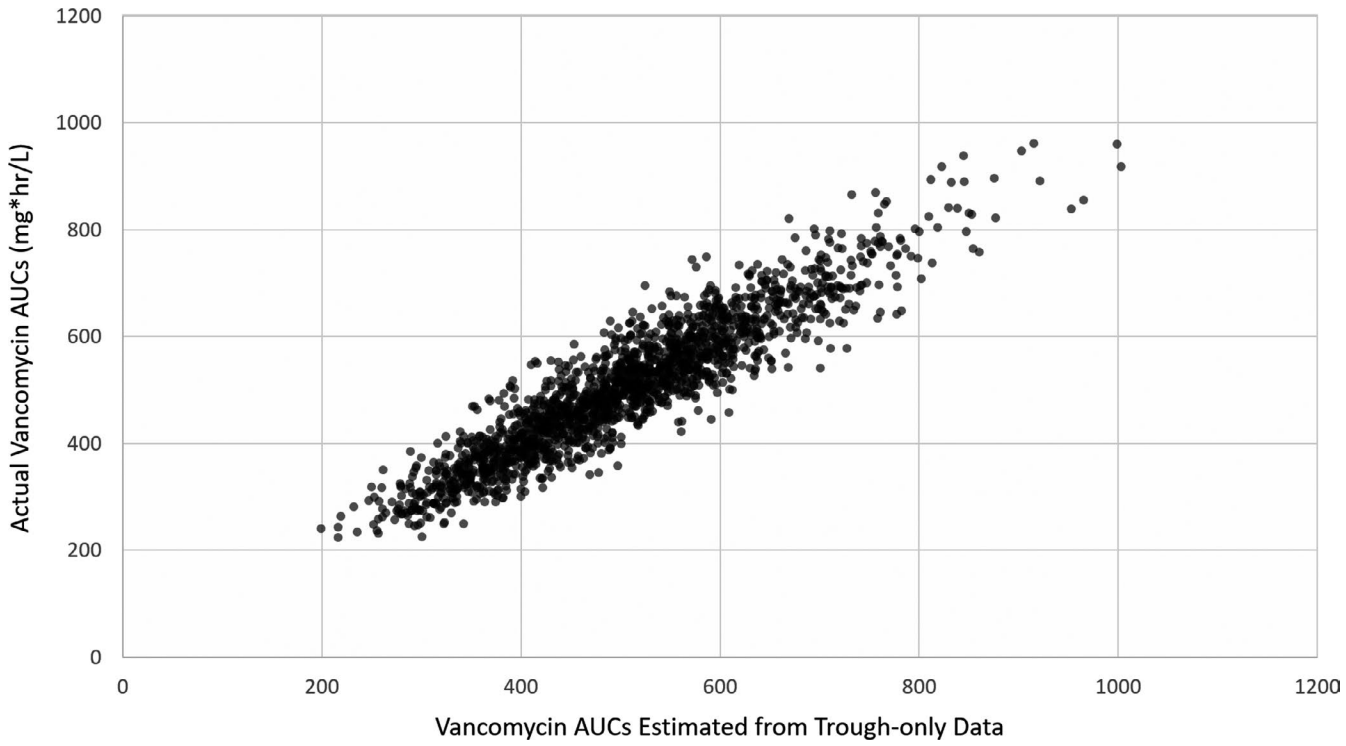

FIGURE 1 Actual AUCs compared to AUCs estimated from trough-only data (*N* = 1,843)

TABLE 5 Subgroup analysis of patients who had an extreme body mass index (BMI)

Vd models	BMI kg/m^2	Mean trough-only AUC (±SD)	Bias	RMSE	Concordance correlation
Present study	<20	502 (51.2)	1.6	51.1	0.927
	≥40	512 (39.2)	7.8	39.9	0.943
Sanchez	<20	493 (51.7)	10.4	52.5	0.924
	≥40	511 (39.7)	8.3	40.4	0.94
Winter	<20	538 (58.8)	−35	68.2	0.88
	≥40	478 (40.7)	42	58.4	0.884
Tanaka	<20	502 (56.2)	1.5	56.0	0.913
	≥40	455 (40.9)	64.3	76.2	0.816
Birt	<20	593 (64.7)	−89.8	110.5	0.747
	≥40	512 (41.7)	8.1	42.4	0.937

Note: The BMI <20 group had a mean actual AUC of 503 and a sample size of 150 patients; the BMI ≥40 group had a mean actual AUC of 520 and a sample size of 176 patients.

Only the Sanchez and study models had low bias and good precision for both extreme BMI groups. The Winter model is commonly used in clinical practice but may be ideally suited for patients who have normal body weight because increased bias and decreased precision were observed for both extreme BMI groups.

The Birt model, 0.54 L/kg, worked very well for the BMI ≥40 group who had a mean Vd of 0.54 L/kg. This finding is supported by a study from Adane et al.[19] who evaluated extremely obese patients and found a population Vd of 0.51 L/kg.

The Tanaka model, 0.864 L/kg, worked well for the low BMI group who had a mean Vd of 0.94 L/kg. This is supported by a study of Japanese adult patients who had a mean body weight of 55 kg and a population Vd of 1.1 L/kg.[20] Subgroup analysis of patients who had an extreme age is described in Table 6.

The Sanchez and study models were the most accurate and least-biased models for the younger age group. For the elderly group, the Tanaka and study models functioned well, followed by the Sanchez and Winter models which had somewhat greater bias and less precision.

For simplicity, trough-only data were the focus of this study, but the PK method can be applied to any steady-state level drawn ≥60 min after the end of infusion. Analysis of peak-only data resulted in

TABLE 6 Subgroup analysis of patients who had an extreme age

Vd models	Age	Mean trough-only AUC (±SD)	Bias	RMSE	Concordance correlation
Present study	18–40	492 (54.5)	1.8	54.4	0.924
	≥80	496 (45.9)	6.2	46.2	0.93
Sanchez	18–40	513 (55.8)	−18.7	58.7	0.915
	≥80	473 (45.5)	29	53.8	0.906
Winter	18–40	467 (56.6)	27.1	62.6	0.901
	≥80	520 (51.1)	−17.8	54.0	0.907
Tanaka	18–40	436 (54.7)	57.8	79.5	0.847
	≥80	490 (48.1)	12.5	49.6	0.918
Birt	18–40	513 (61.4)	−19.2	64.2	0.9
	≥80	566 (57.2)	−63.5	85.3	0.801

Note: The age 18–40 group had a mean actual AUC of 494 and a sample size of 216 patients; the age ≥80 group had a mean actual AUC of 502 and a sample size of 212 patients.

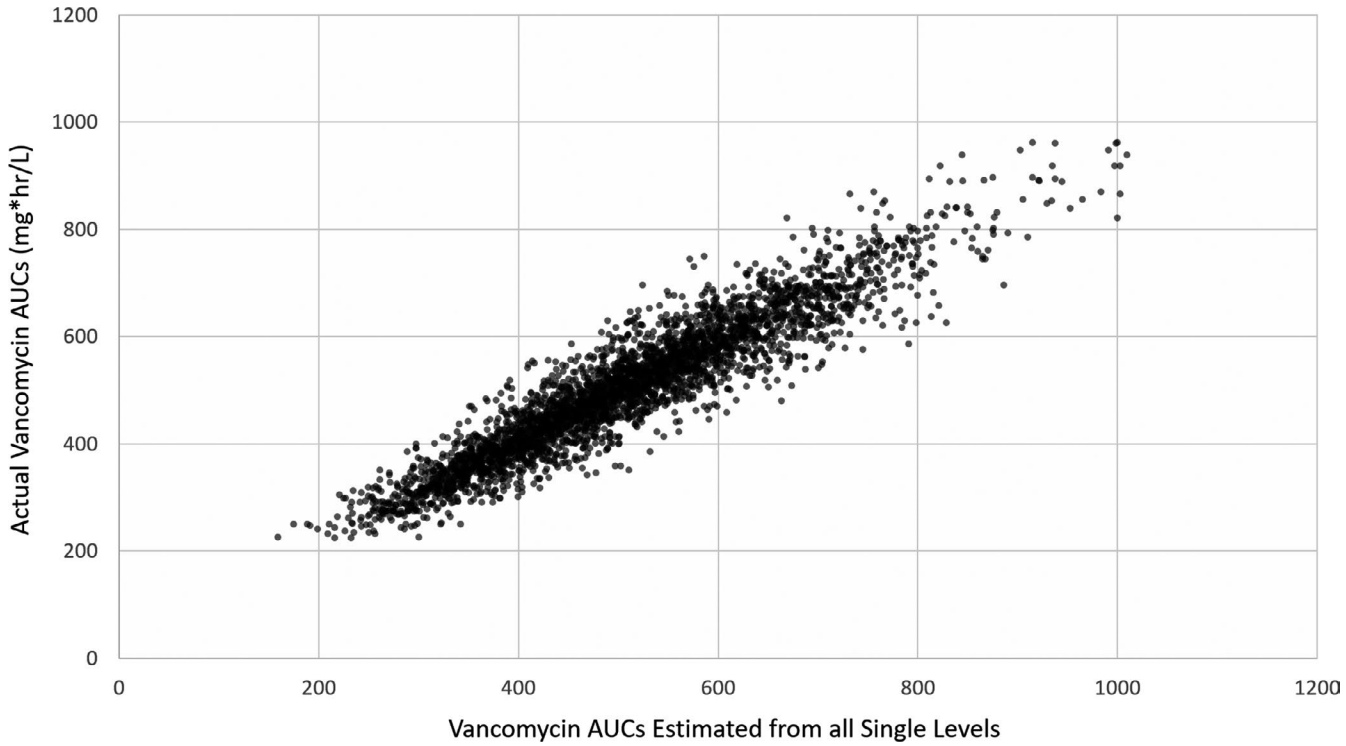

FIGURE 2 Actual AUCs compared to AUCs estimated from all 3,686 single levels in the test group (*N* = 1,843)

TABLE 7 Results from a validation group (*N* = 65, mean actual AUC = 492)

Vd models	Mean trough-only AUC (±SD)	Bias	RMSE	Concordance correlation
Present study	501 (35.9)	−9	36.7	0.936
Sanchez	489 (35.6)	2.9	35.5	0.939
Winter	498 (42.5)	−6	42.6	0.914
Tanaka	472 (40.6)	19.7	44.8	0.904
Birt	537 (46.9)	−45	64.7	0.828

essentially the same precision (RMSE) and correlation values as trough-only data. However, bias with trough-only data was nearly the opposite of peak-only data. For example, the Tanaka model in the test group had a trough-only bias of 34 and a peak-only bias of −32 (Figure 2).

Hospitals can validate Vd models by measuring peak and trough levels in their patient populations. For example, a quality improvement project was approved by the research service at the Central Texas Veterans Health Care System (N = 65). As in the present study, the Winter, Sanchez and study models performed very well overall. Greater precision of the estimated AUCs was observed in the validation group, which was probably due to the elderly, overweight population who generally have larger volumes of distribution (Table 7).

4 | WHAT IS NEW AND CONCLUSION

Vancomycin AUCs can be estimated from a single steady-state level with PK equations by using an estimated Vd. Accuracy and precision of the estimated AUCs depend on the applied Vd model. Until now, there has been limited evidence from large, robust populations regarding how to estimate Vd for general adult patients.

The Vd equation derived in this study, Vd = 0.29(age) +0.33(total BW in kg) +11, can be used to estimate an AUC with trough-only data for general adult patients. Other population Vd models can be used for certain types of patients, depending on their age and body weight. Monitoring one steady-state level requires less blood work and is more practical than peak-trough monitoring. The RMSE of the difference between the actual and estimated AUCs was about 50, meaning that about 68% of estimated AUCs were within 50 points of the actual AUCs. Dosage can be titrated to target an AUC near 500 to ensure that the actual AUC is within the recommended range of 400–600. Although AUC calculations are not practical by hand in a clinical setting, open-access website calculators are available.[9,10]

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

PATIENT CONSENT STATEMENT

N/a, the data were retrospective and did not contain any protected health information.

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