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Comparison of Race-Based and Non–Race-Based Equations for Kidney Function Estimation in Critically Ill Thai Patients for Vancomycin Dosing

Sirima Sitaruno, PharmD[1], Wichai Santimaleeworagun, PhD[2], Sutthiporn Pattharachayakul, PharmD[1], Kenneth C. DeBacker, BS[3], Veerapong Vattanavanit, MD[4], Wanrada Binyala, PharmD[5], and Manjunath P. Pai, PharmD, FCP[3]

Abstract

Empiric antibiotic dosing frequently relies on an estimate of kidney function based on age, serum creatinine, sex, and race (on occasion). New non–race-based estimated glomerular filtration rate (eGFR) equations have been published, but their role in supporting dosing is not known. Here, we report on a population pharmacokinetic model of vancomycin that serves as a useful probe substrate of eGFR in critically ill Thai patients. Data were obtained from medical records during a 10-year period. A nonlinear mixed-effects modeling approach was conducted to estimate vancomycin parameters. Data from 208 critically ill patients (58.2% men and 36.0% septic shock) with 398 vancomycin concentrations were collected. Twenty-three covariates including 12 kidney function estimates were tested and ranked on the basis of the model performance. The median (min, max) age, weight, and serum creatinine was 69 (18, 97) years, 60.0 (27, 120) kg, and 1.53 (0.18, 7.15) mg/dL, respectively. The best base model was a 1-compartment linear elimination with zero-order input and proportional error model. A Thai-specific eGFR equation not indexed to body surface area model best predicted vancomycin clearance (CL). The typical value for volume of distribution and CL was 67.5 L and 1.22 L/h, respectively. A loading dose of 2000 mg followed by maintenance dose regimens based on eGFR is suggested. The Thai GFR not indexed to BSA model best predicts vancomycin CL and dosing in the critically ill Thai population. A 5% to 10% absolute gain in the vancomycin probability of target attainment is expected with the use of this population-specific eGFR equation.

Keywords

critically ill patient, kidney function estimation, population pharmacokinetic, Thai, vancomycin

Early effective antimicrobial therapy is a crucial strategy for lowering morbidity and mortality associated with septic shock.[1] Empirical antibiotic dosing in patients with septic shock should be based on pharmacokinetic/pharmacodynamic (PK/PD) principles for improving treatment outcomes.[1] Septic shock alters antibiotic PK that can lead to subtherapeutic concentrations and also increased risk of antimicrobial toxicity.[1,2]

Vancomycin is commonly administered empirically to patients with septic shock to ensure coverage against methicillin-resistant *Staphylococcus aureus*.[1,3–5] Currently, an area under the concentration-time curve over minimum inhibitory concentration determined by broth microdilution (AUC/MIC_{BMD}) ratio of 400 to 600 is recommended as the optimal PK/PD index target to sustain efficacy and minimize nephrotoxicity risk.[5] The PK of vancomycin in critically ill patients is distinct from other populations, with empirical dosing recommendations of vancomycin that suggest the need for high doses and close monitoring.[6–9]

[1]Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla, Thailand
[2]Department of Pharmacy, Faculty of Pharmacy, Silpakorn University, Nakhon Prathom, Thailand
[3]Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor, Michigan, USA
[4]Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand
[5]Pharmacy Department, Songklanagarind Hospital, Hat Yai, Songkhla, Thailand

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Corresponding Author:
Sirima Sitaruno, PharmD, Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand
Email: sirima@pharmacy.psu.ac.th

Body weight and an estimate of kidney function is the basis for vancomycin maintenance dose selection. Estimated creatinine clearance (eCrCL) using the Cockcroft-Gault (CG) equation has consistently been identified as a covariate of vancomycin clearance (CL) in critically ill patients and is commonly used for vancomycin dose adjustment.[6,7,9,10] The eCrCL in milliliters per minute is based on age, body weight, serum creatinine (SCr), and sex, while the other estimated glomerular filtration rate (eGFR) equations including the Modification of Diet in Renal Disease (MDRD) equation and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is based on age, SCr, sex, and race and reported in milliliters per minute per 1.73 m^2.[11,12] The original MDRD equation for race was imprecise and so was reexpressed with a Thai racial factor correction equation to improve the kidney function estimation in the Thai population.[13] However, the relevance of this Thai race factor on drug dosing for kidney function has not been evaluated. Recently, a new creatinine-based eGFR equation has been published to address the potential for systemic racism in medicine. While discussions have focused on Black and non-Black populations, less attention has been drawn to unique Asian populations such as the Thai.[14] A systematic evaluation of vancomycin CL prediction using eCrCL and eGFR equations, body surface area (BSA) indexed and unindexed values, and inclusion and exclusion of race has not been performed.[15]

The objectives of this study were to rank the performance of race-based and non–race-based equations for kidney function estimation as covariates and to evaluate the influence of covariates on PK parameters of vancomycin in critically ill Thai patients. We also quantify the marginal loss and gain with the use of alternate eGFR equations for vancomycin dosing in critically ill Thai patients.

Methods

Study Design and Study Population

This retrospective population PK study was conducted at Songklanagarind Hospital, a tertiary care university hospital located in Songkhla, Thailand. The study was approved by the human research ethics committee of the Faculty of Medicine, Prince of Songkla University. Data of all patients fulfilling the inclusion criteria during August 2011 to July 2021 were obtained.

Thai patients >18 years of age who were admitted in the intensive care unit (ICU) or met critically ill patient criteria[16] and received intravenous vancomycin and measurement of serum vancomycin concentrations during the course of vancomycin treatment were enrolled. Patients were excluded if they (1) were pregnant, (2) had incomplete or missing vancomycin dosing or concentration time information, (3) were on extracorporeal membrane oxygenation, and (4) were on renal replacement therapies during vancomycin measurement.

The intravenous vancomycin orders, administration times, serum concentration, and collection times were collected. Concentrations collected ≤4 hours after dosing and ≤2 hours before dosing were defined as peak and trough values, respectively; otherwise, concentrations were classified as midpoint values. Patient demographics, vasopressor information, Sequential Organ Failure Assessment score, 24-hour fluid balance, pathogen and site of infection, and laboratory information on the first day of vancomycin measurement were also collected. Patients were defined as having septic shock if they had sepsis-induced hypotension refractory to adequate fluid resuscitation and required vasopressor administration.[17]

Kidney Function Estimates

The eCLCr was based on the CG equation using total body weight (TBW) or adjusted body weight in patients with a body mass index (BMI) >23.0 kg/m^2.[18–20] The eGFR was calculated by (1) 4-variable MDRD using an isotope dilution mass spectrometry (IDMS) traceable equation,[11] (2) 2009 CKD-EPI creatinine equation,[12] (3) 2021 CKD-EPI creatinine equation,[14] (4) Thai eGFR equation,[13] and (5) reexpressed MDRD with Thai racial factor correction.[13] The specific equations used for these eGFR estimates are provided in Table S1. The eGFR and eCrCL for drug dosing were calculated on a single-point measurement of SCr on the first day of vancomycin measurement and were transformed into either milliliters per minute or BSA-indexed as milliliters per minute per 1.73 m^2 units for all equations. Therefore, we evaluated 12 kidney function estimates from 6 equations.

Vancomycin Assays

During this 10-year study period, serum vancomycin concentrations were measured by 4 assays. The AxSYM (Abbott Laboratories, Abbott Park, Illinois), VITROS Chemistry Products VANC Reagent (Ortho-Clinical Diagnostics, Raritan, New Jersey), VANC2 cobas c system (Roche Diagnostics, Indianapolis, Indiana), and VANC3 cobas c system (Roche Diagnostics) with the measurement range of 2.04 to 90.65 μg/mL, 5.00 to 50.00 μg/mL, 1.7 to 80.00 μg/mL, and 4.0 to 80.0 μg/mL were used during the study period. The impact of measurement method was included as a potential confounder in the covariate model development process.

Pharmacokinetic and Statistical Analyses

Data analysis processes were conducted at the College of Pharmacy, University of Michigan, Ann Arbor,

Michigan. Data management was performed by EpiData 3.1 (EpiData Association, Odense, Denmark). Pharmacokinetic analyses were performed by Monolix2020R1, and compared with Sycomore2020R1 (Lixoft SAS, Antony, France). Population parameter estimation was derived using the stochastic approximation expectation maximization algorithm. One-, 2- and 3-compartment models with zero-order, linear clearance were first tested as the base model. The proportional, constant, combined1, and combined2 error models were tested to determine proper observation models of residual variability. Vancomycin parameters were estimated on the basis of a log-normal distribution.

Once the base model was defined, the influence of covariates on vancomycin parameters was determined by stepwise forward selection approach. The 23 covariates including 12 kidney function estimates, SCr, age, sex, BSA, TBW, BMI, Sequential Organ Failure Assessment score, septic shock status, vasopressor dose as norepinephrine equivalents (NEs), 24-hour fluid balance, and vancomycin assays were evaluated for their impact on vancomycin PK parameters. Continuous covariates were normalized to the data set's median value before inclusion in the model for testing. The models of each covariate on vancomycin parameters were ranked on the basis of the greatest to smallest change in Akaike information criterion (AIC) relative to the base model. Automatic covariate building using the conditional sampling use for stepwise approach based on correlation tests was also used to identify correlations between individual parameters and covariates for developing the final model.[21]

Model discrimination was based on change in AIC (Δ AIC), precision of parameter estimates, and goodness-of-fit plots between models. The nonparametric bootstrap technique including 1000 bootstrap replicates was performed by R package Rsmlx (R speaks Monolix; R Foundation for Statistical Computing, Vienna, Austria) to assess the precision of the final model parameter estimates. Group comparisons were made using Pearson's chi-squared test with results presented as frequencies with percentages, means with standard deviations, and medians with interquartile ranges (IQRs), respectively. Descriptive statistical analyses and graphs were produced using Stata version 17 (StataCorp LLC, College Station, Texas).

Dose Regimen Optimization by Monte Carlo Simulation

The probability of target attainment (PTA) of AUC/MIC_{BMD} ratio of 400 to 600 served as the basis for defining optimal vancomycin dose regimen. AUC/MIC_{BMD} ratio >650 indicated an increased risk of nephrotoxicity.[22] The modal vancomycin minimum inhibitory concentration (MIC) is 1 mg/L at our institutions, and so the AUC from time 0 to 24 hours ($AUC_{0\text{-}24}$) and 24 to 48 hours ($AUC_{24\text{-}48}$) were used to evaluate the loading dose (LD) and maintenance doses (MDs), respectively. Monte Carlo simulations of 1000 critically ill patients by Simulx2020R1 (Lixoft SAS) was conducted to estimate PK/PD index ratio and PTA of clinical effectiveness and nephrotoxicity. The LDs of 1000, 1500, 2000, and 2500 mg with an infusion rate of 1000 mg/h were simulated. Once the optimal LD was identified, MDs of 750 and 1000 mg infused at 500 mg/h after the LD every 8, 12, 24, and 48 hours as intermittent infusion (II) were simulated to predict $AUC_{24\text{-}48}$. The optimal time to start the MD after receiving the LD for the II regimen was also determined. Simulations of 500, 1000, 2000, 4000, and 6000 mg continuous infusion over 48 hours or ≈10, 21, 42, 83, and 125 mg/h following the end of LD infusion were also tested.

Results

Study Population

Table 1 summarizes the population demographics, laboratory data, pathogen information, kidney function, and initial dose of vancomycin. A total of 208 critically ill patients including 75 patients with septic shock were enrolled. The majority of patients were men, on a mechanical ventilator, admitted to the medical ICU, and had a BMI <23 kg/m^2. The median (min, max) age was 69 (18, 97) years. Norepinephrine was used in 50 (66.7%) patients with septic shock with median (IQR) NEs of 0.14 (0.08-0.41) μg/kg/min. Half of the patients received vancomycin as empiric therapy for bloodstream, skin and soft tissue, and respiratory tract infections. Infection secondary to *Enterococcus* spp. was the primary pathogen cultured in this study with an MIC_{50} of 1 mg/L based on data from 11 isolates. Kidney function estimates were reported by eCrCL using CG equation and eGFR using 2009 CKD-EPI and Thai eGFR equation. The median (IQR) eCrCL for the population was 33.6 (15.1-56.8) mL/min. The median (IQR) eGFR using 2009 CKD-EPI and Thai GFR was 43.5 (20.4-83.4) and 52.0 (30.0-80.5). The overall population kidney function estimates stratified by septic shock presence is included in Table S2. Table S3 provides a comparison of eGFR strata based on CKD staging among the Thai GFR, the CKD-EPI 2009, and 2021 CKD-EPI equation. The 2009 and 2021 CKD-EPI equations illustrated similarity in this classification; however, a lower proportion of eGFR <15 mL/min/1.73 m^2 population was observed when calculated with the Thai GFR equation. The initial dose of vancomycin was ≈20 mg/kg. The MD was given at an intermittent infusion rate of 500 mg/h. Most patients

Table 1. Demographic, Anthropometric, and Laboratory Variables of Study Population

	N (%) or Median (IQR)		
Variable	Overall (n = 208)	Septic Shock (n = 75)	Without Shock (n = 133)
Sex, male	121 (58.2)	41 (54.7)	80 (60.2)
Age, y	69.0 (54.0 to 78.0)	69.0 (54.5 to 77.5)	69.0 (54.0 to 78.0)
Height, cm	162.5 (154.0 to 170.0)	163.0 (153.0 to 167.5)	162.0 (155.0 to 170.0)
TBW, kg	60.0 (50.0 to 67.6)	58.4 (50.0 to 68.3)	60.0 (50.0 to 66.0)
BMI, kg/m^2	22.5 (19.6 to 24.4)	22.6 (20.4 to 26.2)	22.5 (19.4 to 24.2)
<18.5 kg/m^2	36 (17.3)	12 (16.0)	24 (18.0)
18.5-22.9 kg/m^2	86 (41.3)	29 (38.7)	57 (42.9)
23-30 kg/m^2	73 (35.1)	27 (36.0)	46 (34.6)
≥ 30 kg/m^2	13 (6.3)	7 (9.3)	6 (4.5)
BSA, m^2	1.6 (1.5 to 1.8)	1.6 (1.5 to 1.8)	1.6 (1.5 to 1.8)
Setting			
°Medical ICU, %	124 (59.6)	51 (68.0)	73 (54.9)
°Surgical ICU, %	78 (37.5)	23 (30.7)	55 (41.4)
°Other, %	6 (2.9)	1 (1.3)	5 (3.8)
°Mechanical ventilation, %	165 (79.3)	68 (90.7)	97 (72.9)
NEs, µg/kg/min [a]	NA	0.14 (0.08 to 0.41)	NA
SOFA score	6 (4 to 11)	12 (9 to 15)	4 (3 to 6)
Albumin, g/dL[b]	2.60 (2.10 to 3.00)	2.40 (1.90 to 2.90)	2.70 (2.30 to 3.10)
Lactate, mmol/L[b]	2.05 (1.23 to 3.78)	2.80 (1.58 to 4.83)	1.45 (1.20 to 2.25)
24-hour fluid balance, mL	802.50 (–91.25 to 1753.50)	1935.00 (924.00 to 2752.00)	400.00 (–285.00 to 1105.00)
Indication of vancomycin			
°Empirical therapy, %	115 (55.3)	56 (74.7)	59 (44.4)
°Pathogen specific therapy, %	93 (44.7)	19 (25.3)	74 (55.6)
°*Enterococcus faecium*	45 (48.4)	12 (63.2)	33 (44.6)
°MRSA	19 (20.4)	3 (15.8)	16 (21.6)
°MRSE	12 (12.9)	1 (5.3)	11 (14.9)
°*Enterococcus faecalis*	5 (5.4)	0 (0)	5 (6.8)
°*Corynebacterium* spp.	3 (3.2)	1 (5.3)	2 (2.7)
°*Staphylococcus hemolyticus*	3 (3.2)	1 (5.3)	2 (2.7)
°Other	6 (6.5)	1 (5.3)	5 (6.8)
Site of infection			
°Bloodstream infection	53 (25.5)	20 (26.7)	33 (24.8)
°Skin and soft tissue infection	39 (18.8)	14 (18.7)	25 (18.8)
°Respiratory tract infection	35 (16.8)	17 (22.7)	18 (13.5)
°Intra-abdominal infections	23 (11.1)	7 (9.3)	16 (12.0)
°Urinary tract infection	23 (11.1)	7 (9.3)	16 (12.0)
°Central nervous system infection	20 (9.6)	1 (1.3)	19 (14.3)
°Infective endocarditis	13 (6.3)	9 (12.0)	4 (3.0)
°Bone or joint infection	2 (1.1)	0 (0)	2 (1.5)
MIC, mg/L			
°Total specimen	11	5	6
°MIC_{50} (min-max)	1 (0.02 to 2)	1 (0.02 to 2)	1 (0.5 to 1.5)
BUN, mg/dL[b]	37.40 (20.8 to 60.0)	31.29 (17.3 to 47.3)	31.00 (16.0 to 52.8)
SCr, mg/dL[b]	1.53 (0.89 to 2.65)	1.85 (1.43 to 3.14)	1.27 (0.74 to 2.33)
eGFR, mL/min/$1.73m^2$			
°2009 CKD-EPI	43.5 (20.4 to 83.4)	30.9 (17.1 to 48.5)	51.4 (23.1 to 98.4)
°Thai GFR	52.0 (30.0 to 80.5)	39.4 (27.9 to 56.6)	58.7 (33.2 to 108.1)
eCrCL, mL/min	33.6 (15.1 to 56.8)	24.7 (14.2 to 43.8)	37.4 (17.3 to 71.3)
Initial dose of vancomycin, mg	1000 (1000 to 1500)	1000 (1000 to 2000)	1000 (1000 to 1500)
Initial dose of vancomycin, mg/kg	20.0 (15.6 to 27.4)	21.7 (15.3 to 30.3)	19.6 (15.6 to 25)

BMI, body mass index; BSA, body surface area; BUN, blood urea nitrogen; CKD-EPI, Chronic Kidney Disease Epidemiology equation; eCrCL, estimated creatinine clearance using Cockcroft–Gault equation; eGFR, estimated glomerular filtration rate using 2009 Chronic Kidney Disease Epidemiology creatinine equation and Thai glomerular filtration rate equations; ICU, intensive care unit; IQR, interquartile range; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis;* NEs, norepinephrine equivalents; SCr, serum creatinine; SOFA, Sequential Organ Failure Assessment; TBW, total body weight.

[a] Norepinephrine equivalents = norepinephrine dose in µg/kg/min + epinephrine dose in µg/kg/min + dopamine dose in µg/kg/min divided by 100.

[b] Normal ranges: albumin, 3.5–5.2 g/dL; lactate, 0.5-1.6 mmol/L; BUN, 6-20 mg/dL; SCr, 0.67-1.17 mg/dL.

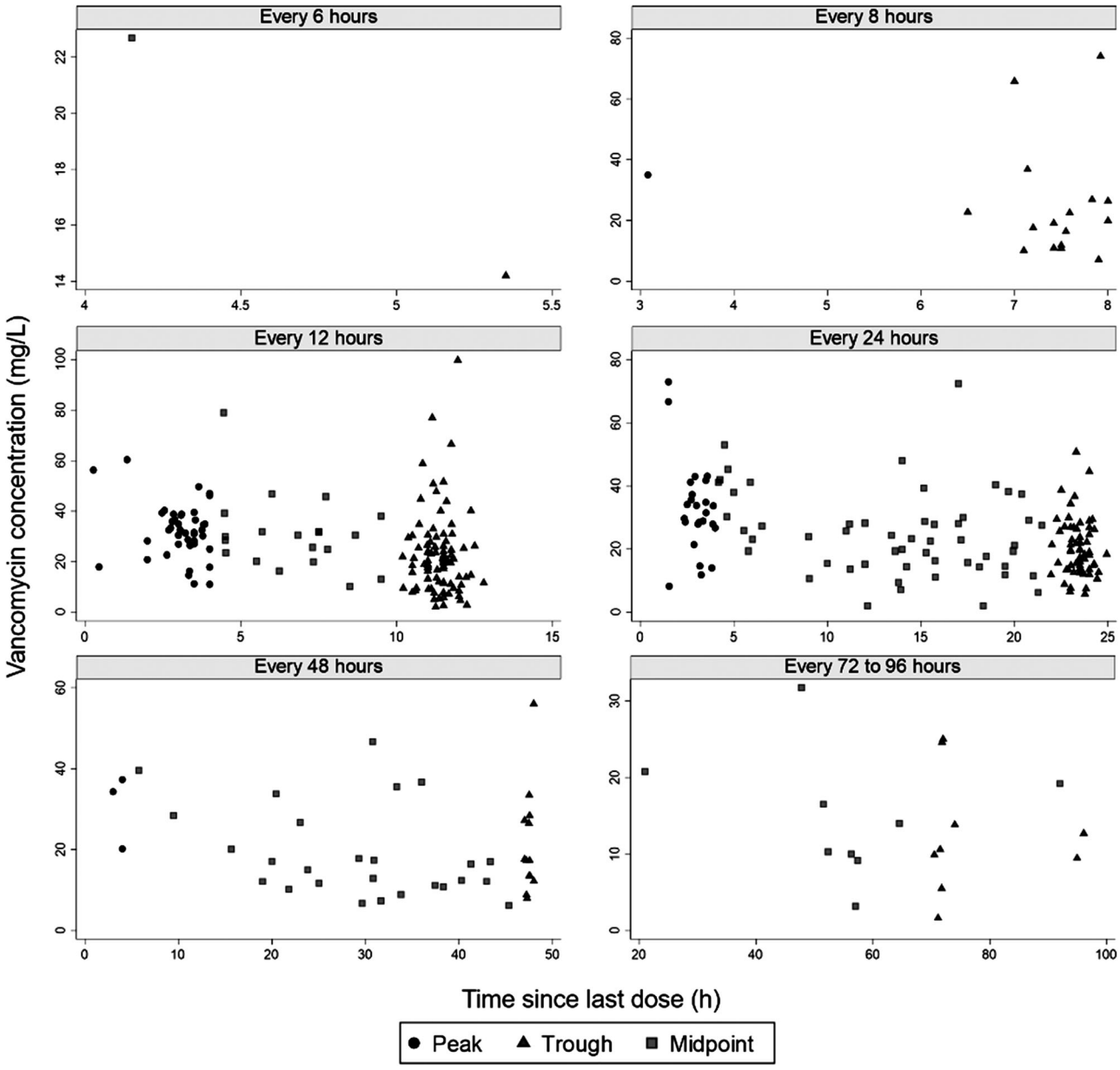

Figure 1. Observed vancomycin concentrations as peak, midpoint, and trough values by dosing interval from time to last dose.

(n = 136) received 1000 mg as the typical LD, and 22% received 2000 mg as the LD at a rate of 1000 mg/h.

Observed Vancomycin Concentration Profile

In total, 398 vancomycin concentrations with a mean (min, max) of 1.9 (1, 7) concentrations per patient were available for population PK analysis. The lower limit of quantification was observed in 3 samples that were imputed as lower limit of quantification/2. The median (IQR) time to vancomycin measurement was 3.0 (1.5-6.8) days. The distribution of vancomycin concentrations for patients treated every 6 hours, every 8 hours, every 12 hours, every 24 hours, every 48 hours, every 72 hours, and every 96-hours was 2 (0.5%), 17 (4.3%), 155 (38.9%), 142 (35.7%), 42 (10.6%), 14 (3.5%), and 4 (1.0%), respectively. The dosing interval for 22 (5.53%) concentrations could not be ascertained. Based on collection at time since last vancomycin infusion, the vancomycin concentrations were classified to be peak (74 samples; 18.6%), midpoint (111 samples; 27.9%), and trough (193 samples; 48.5%). Figure 1 illustrates the measured vancomycin concentration against the time since last dose categorized by dosing interval for clarity.

Table 2. Covariate Ranking Based on the AIC for Vancomycin Clearance and Volume of Distribution Relative to the Base Model

Covariates on CL	AIC	Δ AIC	Covariates on V_d	AIC	Δ AIC
Base model	2985.5		Base model	2985.5	
Thai GFR, mL/min	2780.0	–205.4	2021 CKD-EPI, mL/min	2975.1	–10.4
2009 CKD-EPI, mL/min	2788.7	–196.8	2009 CKD-EPI, mL/min	2977.6	–7.9
eCrCL, mL/min	2789.8	–195.7	2021 CKD-EPI, mL/min/1.73 m^2	2977.6	–7.9
MDRD4-IDMS, mL/min	2796.3	–189.2			
MDRD with Thai racial factor correction, mL/min	2796.5	–188.9	MDRD with Thai racial factor correction, mL/min	2978.7	–6.8
2021 CKD-EPI, mL/min	2798.0	–187.5	MDRD4-IDMS, mL/min	2978.9	–6.6
Thai GFR, mL/min/1.73 m^2	2798.2	–187.3	Thai GFR, mL/min	2979.5	–6.0
eCrCL, mL/min/1.73 m^2	2806.6	–178.9	2009 CKD-EPI, mL/min/1.73 m^2	2980.4	–5.1
2009 CKD-EPI, mL/min/1.73 m^2	2807.6	–177.9	NEs	2980.5	–5.0
			Sex	2980.6	–4.8
2021 CKD-EPI, mL/min/1.73 m^2	2814.6	–170.9	MDRD with Thai racial factor correction, mL/min/1.73 m^2	2981.5	–4.0
MDRD with Thai racial factor correction,mL/min/1.73 m^2	2817.4	–168.1	SCr	2981.5	–4.0
MDRD4-IDMS, mL/min/1.73 m^2	2817.5	–168.0	SOFA score	2982.5	–3.0
SCr	2852.6	–132.9	Thai GFR, mL/min/1.73 m^2	2982.8	–2.7
Age	2947.5	–38.0	MDRD4-IDMS, mL/min/1.73 m^2	2983.1	–2.4
SOFA score	2955.4	–30.1	eCrCL, mL/min	2983.2	–2.3
Septic shock	2975.6	–9.9	TBW	2983.8	–1.7
NEs	2978.9	–6.6	Age	2984.0	–1.5
BSA	2979.4	–6.1	eCrCL, mL/min/1.73 m^2	2984.1	–1.3
TBW	2981.9	–3.6	24-h fluid balance	2984.6	–0.9
Sex	2983.2	–2.2	Septic shock	2985.2	–0.3
24-h fluid balance	2986.2	0.7	BSA	2985.9	0.4
BMI	2988.0	2.6	BMI	2986.8	1.3
Vancomycin assays	2991.4	5.9	Vancomycin assays	2987.7	2.2

AIC, Akaike information criterion which is Δ AIC was difference of AIC to base model; BMI, body mass index; BSA, body surface area; CKD-EPI, Chronic Kidney Disease Epidemiology equation; CL, clearance; eCrCL, estimated creatinine clearance calculated by Cockcroft-Gault (CG) equation; MDRD4-IDMS, 4-variable Modification of Diet in Renal Disease using an isotope dilution mass spectrometry traceable equation; MDRD with Thai racial factor correction, reexpressed Modification of Diet in Renal Disease with Thai racial factor correction; NEs, norepinephrine equivalents; SCr, serum creatinine; SOFA, Sequential Organ Failure Assessment; TBW, total body weight; Thai GFR, Thai glomerular filtration rate equations; V_d, volume of distribution.

Pharmacokinetic Analysis

The best base model was a 1-compartment linear model with zero-order input and a proportional error model. The estimates of volume of distribution (V_d) and CL of the base model were 66.5 L and 1.48 L/h, respectively. As expected from the sparse data per patient, 2- and 3-compartment model structures did not improve AIC and had higher relative standard error for fixed effects. The influence of individual covariate on vancomycin PK parameters is shown in Table 2. The kidney function estimates had substantial impact on vancomycin CL. Kidney function estimates that were not indexed to BSA performed better (lower AIC) than those indexed to BSA at 1.73 m^2. The Thai GFR model (mL/min) had the lowest AIC (Δ AIC = –205.4). Septic shock status was found to influence CL (Δ AIC = -9.9) but not impact V_d (Δ AIC = –0.3).

The automated covariate model-building algorithm selected eGFR not indexed to BSA from the Thai GFR as the covariate of CL, and age, TBW, NEs, and eGFR calculated by 2021 CKD-EPI equation as the covariates of V_d. This overly parameterized model had a high relative standard error for the V_d parameter estimate and could not be supported by data contributed per patient. This led us to stepwise comparison of 1 covariate at a time on CL and V_d. The final model that best described vancomycin CL of our population was eGFR calculated by Thai GFR (mL/min) normalized to 40 mL/min and was used in simulation for dose regimen optimization. The 2009 CKD-EPI creatinine (mL/min) equation and eCrCL (mL/min) were the next best models. The 2021 CKD-EPI creatinine (mL/min) equation will likely be incorporated by laboratories in the United States to avoid the potential for systemic racism in medicine[23]; therefore, we ran dosing simulations to compare PK/PD index targets of these 3 alternate models to the Thai GFR (mL/min) equation final model.

Table 3. Pharmacokinetic Parameters of Final Vancomycin Population Model and Bootstrap

	Final Model[a]		Bootstrap of Final Model	
	Estimate	%RSE	Estimate	95%CI
Fixed-effect parameter				
°CL, L/h	1.22	4.46	1.23	1.09-1.33
°V_d, L	67.46	4.63	66.51	61.05-75.66
°θ1	1.01	5.61	1.00	0.90-1.15
Interindividual variability				
°On CL	0.41	6.97	0.39	0.24-0.49
°On V_d	0.38	11.1	0.41	0.34-0.48
Residual variability				
°Proportional	0.21	5.32	0.21	0.16-0.27

CL, clearance; RSE, relative standard error; V_d, volume of distribution; θ1, reflecting the influence of estimated glomerular filtration rate on CL

[a] Final model: $CL = 1.22 \times (eGFR/40)^{1.01} \times e^{\eta i}$, where eGFR is calculated by the Thai GFR equation not indexed to BSA (mL/min) and $\Gamma]_i$ represents the random effects.

The parameter estimates of Thai GFR not indexed to BSA final models and bootstrap analysis are presented in Table 3. Vancomycin parameter estimates from the final model were contained within 95%CIs from 1000 bootstrap replicates. The goodness-of-fit plots showed good agreement between observed and model-predicted concentrations. The majority of population weighted residual vs time after dose and predicted concentration lay within 2 standard deviations, similar to the normalized prediction distribution errors (Figures 2 and 3). Estimated log-likelihood and information criteria, distribution of the individual parameters, and visual predictive check of final PK models are presented in Table S4 and Figures S1 and S2.

Dose Regimen Optimization

Parameter estimates from the Thai GFR not indexed to BSA final models were used in simulations to predict optimal vancomycin doses for our population. Monte Carlo simulation was conducted to identify dose regimens for each eGFR category as follows: 15 to 30, 30 to 45, 45 to 60, 60 to 90, 90 to 120, and 120 to 150 mL/min. The $AUC_{0\text{-}24}/MIC_{BMD}$ $\geq$400 and $\geq$650 were used to benchmark efficacy and toxicity of the LD for each eGFR group (Table S5). Higher LDs were associated with PTAs that were likely to achieve $AUC_{0\text{-}24}/MIC_{BMD}$ $\geq$400, but also exceed 650. Based on the simulations, an LD of 2000 mg of vancomycin was identified as the pragmatic option when weighing these probabilities across eGFR group.

The PTAs achieving the target of $AUC_{24\text{-}48}/MIC_{BMD}$ simulated from Thai GFR not indexed to BSA models of MD regimens are included in Table S6. PTAs achieving $AUC_{0\text{-}24}/MIC_{BMD}$ target at various MD start time after the LD is shown in Table S7. Table 4 summarizes the suggested vancomycin dose regimens for each eGFR group based on Thai GFR compared to CG, 2009 CKD-EPI, and 2021 CKD-EPI equations.

As expected, the lower eGFR groups should receive lower doses and longer dosing intervals to maintain PK/PD efficacy and safety targets. The PTAs to were comparable for intermittent and continuous infusion regimens based on the expected daily dose. A statistically significant difference in PTAs to achieve $AUC_{24\text{-}48}/MIC_{BMD}$ of 400 to 600 was noted when the Thai GFR equation model was compared to the other alternate kidney function models (P <.05). This difference was greatest when compared to eCrCL, where an ≈10% absolute difference in PTA is expected. In contrast, a 5% to 7% difference in PTA is expected when comparing Thai GFR to the 2 alternate CKD-EPI models.

Discussion

Bacterial infections are common in critically ill patients, requiring the administration of antibiotic therapy in more than half of admitted patients.[24] Serious infections can lead to septic shock in 5.9% to 16.1% of ICU admissions with a high (40%) probability of mortality.[25,26] Rapid initiation of effective antimicrobial therapy is therefore a crucial strategy for lowering morbidity and mortality associated with septic shock. Fluid resuscitation and vasopressors are also administered alongside antimicrobials to manage hypotension. Previous studies have suggested that patients with septic shock can have a higher vancomycin V_d and altered CL that may be augmented early on or reduced due to acute kidney injury. As expected, these temporal shifts in physiology and PK are complex to capture. Most population PK of vancomycin models have linked kidney function estimates to CL and body weight to V_d. In this analysis, we focused on identifying the optimal kidney function estimation equation to predict vancomycin CL by specifically comparing race-based to non–race-based equations. As a secondary aim, we

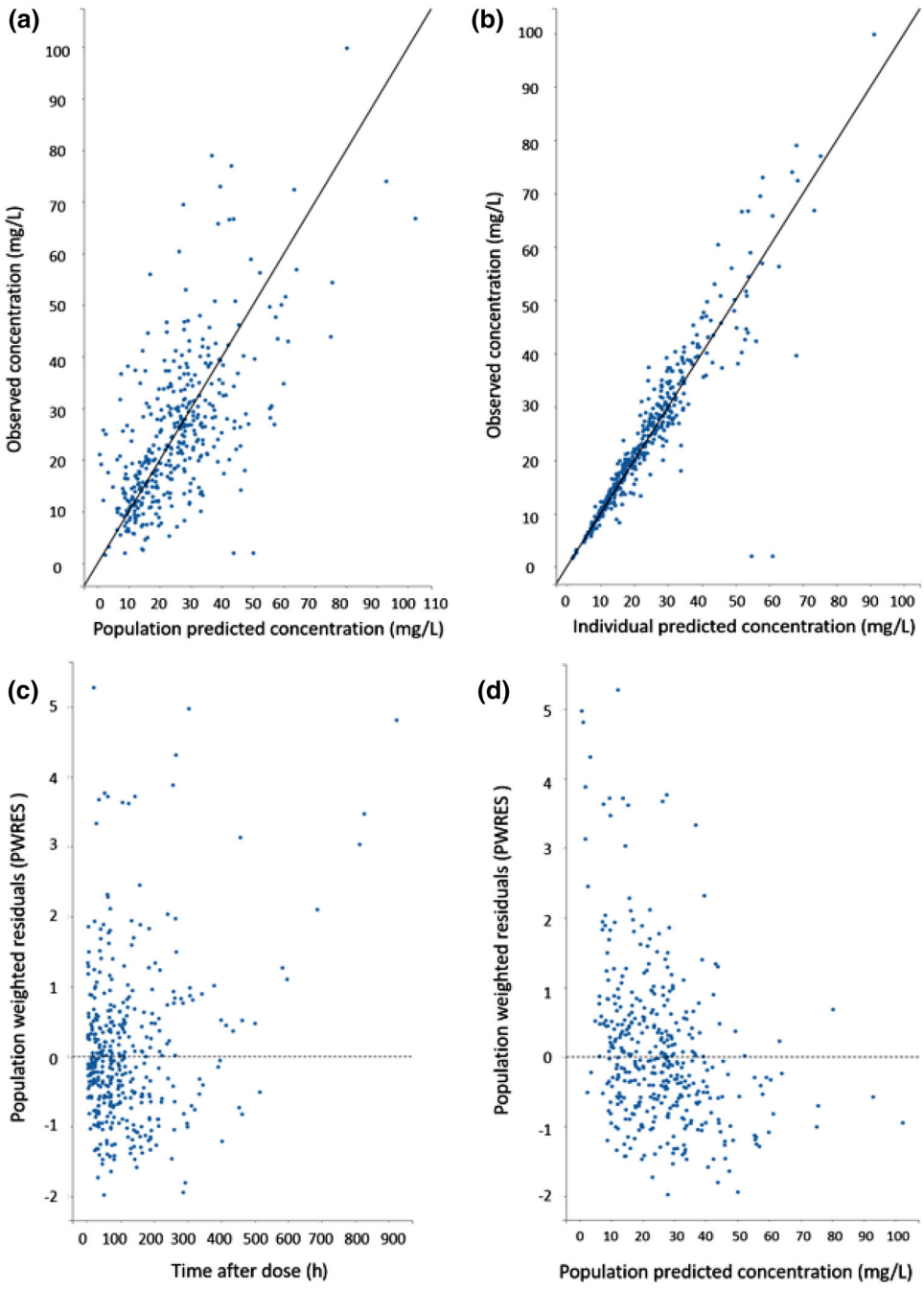

Figure 2. The goodness-of-fit plots of the Thai GFR equation final vancomycin model. (a) observed concentration versus population predicted concentration; (b) observed concentration vs individual predicted concentration; (c) population weighted residuals vs time after dose; and (d) population weighted residuals (PWRES) vs population predicted concentration.

tested the potential of other critical care patient factors as covariates of V_d.

Our analyses show in relative terms that covariates had a smaller effect on the interindividual variability of V_d compared to CL. While weight is often used to predict V_d, we show that this covariate does not improve the model. In contrast, the model for CL is substantially improved by eGFR and in standard units (mL/min) compared to BSA scaled values (mL/min/1.73 m^2). We show that the race-based Thai GFR equation is the best model to predict vancomycin CL in Thai critically ill patients. As a reference model, Thai GFR had 8.6-, 9.7-, and 17.9-point differences in AIC compared to the 2009 CKD-EPI, CG, and 2021 CKD-EPI equations, respectively, resulting in distinct probabilities of PTAs of vancomycin in this simulated study. As with previous

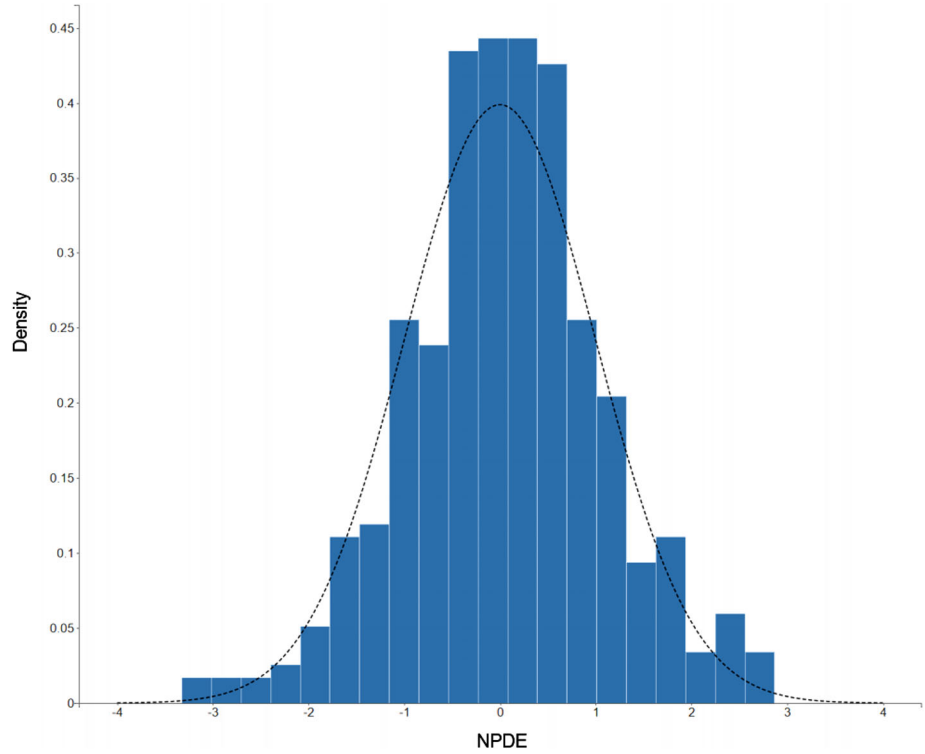

Figure 3. Histogram of the normalized prediction distribution errors (NPDE) of the Thai GFR equation final vancomycin model with the theoretical distribution (dashed line).

vancomycin population PK models, pragmatic dosing regimens are predicted to achieve the AUC/MIC_{BMD} target in 40% to 50% of cases with II. This reinforces the need for therapeutic drug monitoring to achieve the optimal exposure target. Our approach is relatively unique in the literature, given that we compared the "best" model to potential alternatives that fit conventional approaches. A 5% to 10% difference in the PTA is expected and needs clinical confirmation. This expected improvement is based on comparisons of PTAs at the same dosage regimen using different equations for kidney function. It is possible that the optimal dosage regimen may be different if a different equation of kidney function was used during simulation, and clinical confirmation is needed to evaluate which regimen is ultimately optimal. While race is a social construct, our findings suggest that there may be a loss of precision when the population origin is not factored. While we did not test genetic ancestry, our population is expected to be more homogenous than that of other multicultural societies.

As noted, the purpose of our analysis was to clarify the distinction between race-based and non–race-based eGFR functions. We did not intend to generate a new vancomycin population PK model but rather use this drug as a test case. Regardless, our model is consistent with the literature. Heffernan and colleagues[6] most recently evaluated the PK of vancomycin in 27 patients with sepsis and septic shock. This analysis included sample collections at 1 hour after infusion and within 30 minutes of the next dose. The evaluated population was a median (IQR) 37 (26-49.3) years and 75 (65.5-84.8) kg. This analysis only identified eCrCL (Jelliffe equation) as a covariate of CL and did not identify any covariates of V_d. Similar to most models, the final population model only accounted for 43.9% of the interindividual variability. Similar to our findings, these investigators did not identify a relationship between weight or illness severity on vancomycin PK. A similar small study (n = 16) with more intensively sampled study (peak, 2 random, trough concentrations) of obese patients in sepsis and septic shock was recently reported. This population had a median weight of 113 kg and median age of 62 years. This model also identified no covariate relationship of weight to V_d and only eCrCL was predictive of vancomycin CL.[27] As a final point of reproducibility, Katip and colleagues[7] also show through intensive sampled and noncompartmental analysis in 12 patients with septic shock that V_d does not increase. Our study includes a larger sample size and a population median age of 69 years and median weight of 60 kg and confirms these findings in contradiction to clinical convention.

Our study has the limitations expected from a retrospective analysis, lengthy data collection period, and reliance on multiple assay methods to quantify

Table 4. Comparison of the Probability of Target Attainment ($AUC_{24\text{-}48}/MIC_{BMD}$ 400-600) by Kidney Function Equation for Each eGFR Group and Intermittent Infusion Dose or Continuous Infusion Rate

eGFR, mL/min	Suggested MD Regimens[a]	PTAs to Achieve $AUC_{24\text{-}48}/MIC_{BMD}$ 400-600, %						
		Thai GFR	2009 CKD-EPI	*P* Value[b]	2021 CKD-EPI	*P* Value[b]	eCrCL	*P* Value[b]
15-29	1000 mg every 48 h	52.8	42.7	.000	43.0	.000	35.7	.000
	10 mg/h	46.1	48.2	.347	49.9	.089	47.2	.622
30-44	750 mg every 24 h	45.3	51.5	.006	49.2	.081	48.0	.226
	10 mg/h	50.0	40.5	.000	40.2	.000	32.2	.000
45-59	750 mg every 24 h	51.7	42.3	.000	42.5	.000	36.5	.000
	21 mg/h	48.4	38.3	.000	40.2	.000	30.9	.000
60-89	1000 mg every 24 h	44.7	35.3	.000	36.2	.000	30.1	.000
	42 mg/h	46.2	42.6	.105	43.0	.150	39.0	.001
90-119	750 mg every 12 h	43.5	38.4	.020	38.7	.029	34.9	.000
	42 mg/h	34.6	27.1	.000	29.2	.010	23.1	.000
120-150	1000 mg every 12 h	43.2	42.0	.587	39.6	.102	39.7	.112
	83 mg/h	41.0	37.5	.109	37.7	.131	36.7	.049

$AUC_{24\text{-}48}/MIC_{BMD}$, area under the curve during 24-48 hours over minimum inhibitory concentration determined by broth microdilution ratio; CKD-EPI, Chronic Kidney Disease Epidemiology creatinine equation; eCrCL, estimated creatinine clearance calculated by Cockcroft–Gault equation; eGFR, estimated glomerular filtration rate; MD, maintenance dose; PTAs, probability of target attainments assuming a vancomycin MIC_{BMD} of 1 mg/L; Thai GFR, Thai glomerular filtration rate equations.

[a] Intermittent infusion regimens: after the loading dose (LD) of 2000 mg is infused, the first maintenance dose should be administered as follows: 24-48 h after LD for every-48-h regimen; 12-24 hours after LD for every-24-h regimen; and 8-12 h after LD for every-12-h regimen.

Continuous infusion regimens: the maintenance doses are suggested to initial at the end of 2000-mg LD infusion.

[b] Pearson's chi-squared test.

vancomycin. Our data could not support development of a time-varying V_d or CL model, so our prediction of LD and MD assume no change over time in V_d and CL. Central to this limitation is the recognition that eGFR and eCrCL equations are based on the assumption of homeostasis in creatinine production and elimination that allows for translation of a single steady-state measurement of SCr to CL. This assumption may be false in many patients with acute infections.[15] Studies have shown that alternate kinetic functions of eGFR such as the Chen model and Chiou model are better than time-invariant models of vancomycin CL.[15,28,29] We did not have the data available to us in this study to explore this major point. This key limitation is also not addressed in drug development when building population PK models in patients with critical illness and is a major caveat that impacts interpretation of kidney function–based dose adjustment in this population.[30,31] Our simulations are also based on infusing vancomycin MD at 500 mg/h that is half the typical rate of that in the United States. We acknowledge these limitations with the rigor and detailed disclosure of our analysis. Our approach and findings are relevant to drug development because they add granularity on the impact of race-based and non–race-based eGFR on drug dosing considerations. Future studies should assess the marginal cost associated with a 5% to 10% difference in PTA or work to build consensus on what is clinically meaningful. While our findings remain to be reproduced for other drug products that are adjusted for kidney function, our approach provides a valuable template to tease out these differences. Additional work in this domain is encouraged to demonstrate that elimination of the race factors does not negatively harm drug-dosing decisions. These works will support international harmonization on kidney function estimation for both CKD staging and drug dosing and aid global drug development.

Conclusions

Models of eGFR are better than eCrCL as predictors of vancomycin CL. The race-based ThaiGFR model performs best when the eGFR value is in milliliters per minute and not indexed to BSA. Both race-based and non–race-based models of eGFR generate comparable dosing regimens for this representative kidney function adjusted compound. Body weight may not serve as a reliable covariate of vancomycin V_d in critically ill patients in this study and confirms several recent findings. A fixed loading dose followed by maintenance doses of vancomycin by eGFR is suggested by our model.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Data Sharing Statement

Data sharing of representative data sets and analysis code can be made available upon request to the corresponding author (sirima@pharmacy.psu.ac.th).

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Supplemental Information

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