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ORIGINAL RESEARCH ARTICLE

Concordance of Vancomycin Population-Predicted Pharmacokinetics with Patient-Specific Pharmacokinetics in Adult Hospitalized Patients: A Case Series

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Abstract

Background Vancomycin empiric therapy is commonly dosed using clinical algorithms adapted from population-predicted pharmacokinetic parameters. However, precise dosing of vancomycin can be designed using patient-specific pharmacokinetic calculations.

Objective The objective of this study is to assess the correlational fit between vancomycin population-predicted and patient-specific pharmacokinetic parameters [elimination rate constant (K_e) and half-life ($t_{1/2}$)] in a case series of adult hospitalized patients.

Methods This is a single-center case series of hospitalized adult patients who received vancomycin, had creatinine clearance calculation for derivation of population-predicted pharmacokinetic parameters, and had two vancomycin concentrations for calculation of patient-specific pharmacokinetic parameters. The primary objective of this case series is to evaluate the correlation between population-predicted and patient-specific pharmacokinetic parameters. The secondary objectives of this study are to evaluate the mean bias and precision between the population-predicted and patient-specific pharmacokinetic parameters and to assess the correlation between population-predicted and patient-specific pharmacokinetic parameters in special population subgroups (obese patients with body mass index ≥ 30 kg/m^2 and patients with renal dysfunction). All correlation analyses were performed on the population-predicted pharmacokinetics using diverse methods of estimating renal function (Salazar–Corcoran and Cockcroft–Gault methods using either ideal, actual, or adjusted body weights). All significance testing was set at an α of < 0.05. IBM SPSS Statistics version 25 and SAS version 9.4 were used to conduct all statistical analyses.

Results A total of 30 patients were included in the study; 33.3% (10/30) of the patients were obese and 56.7% (17/30) had renal dysfunction. In all patients in the study, the calculated population-predicted K_e and $t_{1/2}$ using all four creatinine clearance estimation methods were each significantly correlated with patient-specific K_e and $t_{1/2}$ (all Pearson correlation coefficients [r]: $> +0.7$, $p < 0.001$). The population-predicted K_e and $t_{1/2}$ calculated using Cockcroft–Gault creatinine clearance using adjusted body weight showed the strongest association with patient-specific K_e and $t_{1/2}$. In the subgroup analyses, all the population-predicted K_e and $t_{1/2}$ using four creatinine clearance estimation methods were each significantly correlated with patient-specific K_e and $t_{1/2}$. The exception was the population-predicted $t_{1/2}$ derived from Cockcroft–Gault creatinine clearance using actual body weight that did not show a significant correlation with patient-specific $t_{1/2}$ in obese patients.

Conclusions In this case series, population-predicted pharmacokinetic parameters were strongly correlated with patient-specific pharmacokinetic parameters. The vancomycin population-predicted pharmacokinetic formula can be used safely to predict a patient's vancomycin pharmacokinetic disposition and can be maintained as an empiric dosing strategy in various hospitalized adult patients.

1 Introduction

Vancomycin is a glycopeptide antibiotic used in the treatment of Gram-positive aerobic and anaerobic bacteria such as *Enterococcus*, *Staphylococcus*, *Streptococcus*, and *Clostridium*. Since the 1950s, this antibiotic has served as the first-line therapy for methicillin-resistant *Staphylococcus aureus* strains and ampicillin-resistant *Enterococcus* species [1].

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Key Points

This study found a strong association between patient-specific and population-based pharmacokinetic parameters that guide the initial dosing of vancomycin in most hospitals.

Our study findings show that in hospitalized patients who cannot have patient-specific pharmacokinetic parameters calculated, clinical algorithms based on population-predicted pharmacokinetic parameters can be used for vancomycin dosing.

Vancomycin empiric dose selection is weight based and the selection of dosing frequency is often adapted from population-predicted pharmacokinetic parameter estimates and/or using patient-specific pharmacokinetic parameters when two vancomycin concentrations are obtained [1, 2]. Matzke et al. have proposed the most common population-predicted pharmacokinetic elimination rate constant (K_e) used in the calculation of half-life ($t_{1/2}$) and clearance for vancomycin elimination [2]. This equation ($K_e = [0.00083 \times$ creatinine clearance (CrCl)$] + 0.0044$) is used routinely in many hospitals to develop clinical algorithms for selecting initial vancomycin dose frequency [2]. Alternatively, after two vancomycin concentrations are obtained, the patient-specific pharmacokinetic K_e can be calculated using a patient's vancomycin concentrations and can inform more precise selection of vancomycin dose frequency.

In a recent study, using the Matzke population-predicted K_e formula $= 0.00083 \times \text{CrCl} + 0.0044$ [2], Oswalt et al. found that population and patient-specific K_e and half-life were similar in 158 patients with acute brain injury. More specifically, the study found statistically significant differences between the mean population-predicted and patient-specific K_e and $t_{1/2}$; however, these were negligible clinical differences with a mean K_e difference of 0.0211 h^{-1} and a mean $t_{1/2}$ difference of 1.01 h [3]. The study authors concluded that population-predicted pharmacokinetics may be an accurate empiric dosing strategy for selecting vancomycin dose frequency given the small clinical difference between population-predicted and patient-specific K_e. Additionally, Murphy and colleagues evaluated seven methods for estimating vancomycin pharmacokinetic parameters (K_e, volume of distribution, and vancomycin clearance) and concluded that these methods varied widely in their ability to predict vancomycin concentrations with measured vancomycin concentrations. The authors noted that the seven methods were not reliable to replace therapeutic monitoring of vancomycin concentrations [4]. However, the authors found that out of all the seven methods for estimating vancomycin pharmacokinetic parameters, the Matzke method had the least bias and best precision compared with the other six methods assessed [2, 4].

Previous studies have shown that factors such as age, renal function, and body weight influence vancomycin clearance and modulate vancomycin pharmacokinetics [5–9]. Various studies have looked at several equations used in estimating CrCl in obese patients with evolving divergent findings on the best equations and body weight to use [10–15]. The Salazar–Corcoran (S–C) equation had been proposed as the best method for estimating CrCl in obese patients with a body mass index ≥ 30 kg/m^2 and this finding was corroborated by the study by Spinler et al. [10, 11]. However, more recent studies have been testing the use of the Cockcroft–Gault (C–G) equation to estimate CrCl [12] using ideal body weight, actual body weight, lean body weight, and 40% adjusted body weight [adjusted body weight = ideal body weight $+ 0.4 \times$ (actual body weight − ideal body weight)] [13–15]. Initially, using lean body weight in the C–G equation was promising [14]; however, using the 40% adjusted body weight in the C–G equation has emerged as the least biased and most accurate method for calculating the C–G CrCl [15].

The primary objective of this case series is to evaluate the correlation between patient-specific vs population-predicted vancomycin pharmacokinetic parameters (K_e and $t_{1/2}$) in a case series of hospitalized patients at an academic medical center. We aim for findings from this study to contribute to the literature and influence clinicians' confidence on the use of population-predicted vancomycin pharmacokinetics K_e and $t_{1/2}$ when obtaining patient-specific K_e and $t_{1/2}$ is impractical or impossible.

2 Methods

2.1 Study Design and Patient Population

This is a single-center case series of patients who received vancomycin pharmacokinetic monitoring at University Medical Center, New Orleans, Louisiana from 1 July, 2018 to 30 May, 2019. This study was approved by the Institutional Review Board of Xavier University of Louisiana and the University Medical Center Research Review Committee. The target sample size proposed for this case series is approximately 20–40 patients based on a priori estimates on the number of patients who will meet inclusion criteria over the specified study timeframe.

All patients who were 18 years of age and older and received vancomycin therapy were included in the study. Patients were included if they were on the vancomycin monitoring list serviced by the primary investigator, had serum creatinine for calculation of population-predicted pharmacokinetic parameters, and had two vancomycin

concentrations for calculation of patient-specific pharmacokinetic parameters. Patients were included if their vancomycin concentrations and serum creatinine were obtained within a 1-day period. Patients were excluded if vancomycin doses were given in between the two vancomycin concentrations.

2.2 Data Collection

The following demographic and clinical variables were collected on patients: age, sex, race, height, actual body weight (ABW), ideal body weight (IBW), adjusted body weight (AdjBW), body mass index, serum creatinine, C–G CrCl using IBW (C–G CrCl-IBW), C–G CrCl using ABW (C–G CrCl-ABW), C–G CrCl using AdjBW (C–G CrCl-AdjBW), S–C CrCl using ABW (S–C CrCl-ABW), first serum vancomycin concentration during elimination phase, second serum vancomycin concentration during elimination phase, hours apart between vancomycin concentrations for patient-specific pharmacokinetics, and time from last vancomycin dose to first serum vancomycin concentration during elimination phase. In addition, the following predictor variables were collected: K_e using C–G CrCl-IBW, K_e using C–G CrCl-ABW, K_e using C–G CrCl-AdjBW, K_e using S–C CrCl ABW, $t_{1/2}$ using C–G CrCl-IBW, $t_{1/2}$ using C–G CrCl-ABW, $t_{1/2}$ using C–G CrCl-AdjBW, and $t_{1/2}$ using S–C CrCl-ABW. Collected outcome variables were patient-specific K_e and patient-specific $t_{1/2}$. All diagnoses were supported with a documented physician diagnosis and confirmed on the electronic medical record using the definition criteria below. Acute kidney injury was defined, based on the Kidney Disease: Improving Global Outcomes guideline, as an increase in serum creatinine by ≥ 0.3 mg/dL within 48 h; or an increase in serum creatinine to ≥ 1.5 times the baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume < 0.5 mL/kg/h for 6 h [16]. Chronic kidney disease was defined, based on the Kidney Disease: Improving Global Outcomes guideline, as the presence of either kidney damage or decreased kidney function for 3 or more months, irrespective of cause [17]. The chronic kidney disease definition accounted for: duration—duration ≥ 3 months, predicted on documentation or inference; function – glomerular filtration rate < 60 mL/min/1.73 m^2 (glomerular filtration rate categories G3a–G5); and damage—kidney damage, as defined by structural abnormalities or functional abnormalities other than decreased glomerular filtration rate such as albuminuria (albumin excretion rate ≥ 30 mg/24 h; albumin-to-creatinine ratio ≥ 30 mg/g [≥ 3 mg/mmol]), urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, and history of kidney transplantation. End-stage renal disease was defined as chronic kidney failure in which a person's kidneys cease functioning on a permanent basis leading to the need for a regular course of long-term dialysis or a kidney transplant to maintain life. [18].

Weight was calculated using one of the following equations:

$$\text{Actual body weight (ABW) for male and female patients} = \text{Measured weight using weighing scale}$$

$$\text{Ideal body weight (IBW)for male patients} = 50 + 2.3\ (\text{height in inches} > 60\ \text{inches})$$

$$\text{Ideal body weight (IBW) for female patients} = 45.5 + 2.3\ (\text{height in inches} > 60\ \text{inches})$$

$$\text{Adjusted body weight for male patients} = \text{IBW for male patients} + 0.4\ (\text{ABW} - \text{IBW for male patients})$$

$$\text{Adjusted body weight for female patients} = \text{IBW for female patients} + 0.4\ (\text{ABW} - \text{IBW for female patients})$$

where weight is in kilograms, and height is in inches.

Creatinine clearance was calculated using one of the following equations:

$$\text{Cockcroft}-\text{Gault}\ (C-G)\ \text{equation for male patients} = \frac{(140 - \text{age})\ (\text{weight})}{(72)\ (\text{serum creatinine})}$$

$$\text{Cockcroft}-\text{Gault (C}-\text{G)equation for female patients} = \frac{(140 - \text{age})\ (\text{weight})}{(72)\ (\text{serum creatinine})} \times 0.85$$

$$\text{Salazar}-\text{Corcoran (S}-\text{C) equation for male patients} = \frac{(137 - \text{Age})\ (0.285 \times \text{weight}) + \left(12.1 \times \text{height}^2\right)}{(51)\ (\text{serum creatinine})}$$

$$\text{Salazar}-\text{Corcoran (S}-C\text{) equation for female patients} = \frac{(146 - \text{Age})\ (0.287 \times \text{weight}) + \left(9.74 \times \text{height}^2\right)}{(60)\ (\text{serum creatinine})}$$

where age is in years, weight is in kilograms, height is in meters, and serum creatinine is in milligram (mg)/deciliter (dL). Weight is either actual body weight (ABW), ideal body weight (IBW), or adjusted body weight (AdjBW) for the C–G equation and weight is actual body weight (ABW) for the S–C equation.

Population-predicted pharmacokinetic parameters were calculated using the following equations [2]:

$$K_e = (0.00083 \times CrCl) + 0.0044$$

$$t_{1/2} = \frac{0.693}{K_e},$$

where K_e is the first-order elimination rate constant, CrCl is the creatinine clearance in mL/min based on the C–G equation or S–C equation, and $t_{1/2}$ is the half-life.

Patient-specific pharmacokinetic parameters were calculated using the following equations [19]:

$$K_e = \frac{\ln\left(\frac{C1}{C2}\right)}{\text{time hours between } C1 \text{ and } C2}$$

$$t_{1/2} = \frac{0.693}{K_e},$$

where K_e is the first-order elimination rate constant, $C1$ is the first vancomycin concentration drawn at least 2 h after vancomycin is fully administered to ensure vancomycin post-administration distribution phase is complete [20], $C2$ is the second vancomycin concentration drawn after $C1$, and $t_{1/2}$ is the half-life. Vancomycin doses were not given in between $C1$ and $C2$.

The default vancomycin infusion durations were 1 h for vancomycin ≤ 1000 mg, 1.5 h for vancomycin 1250–1500 mg, 2 h for vancomycin 1750–2000 mg, and 3 h for vancomycin 2250–3000 mg. Data on whether vancomycin concentration was collected at steady state were assessed. Steady-state concentration was defined as a vancomycin concentration obtained prior to the fourth maintenance dose for patients with normal renal function and prior to the third dose for patients with renal dysfunction (acute kidney injury, chronic kidney disease, and end-stage renal disease); consistent with our hospital protocol [21].

2.3 Study Objectives

The primary objective of this study is to evaluate the correlation between population-predicted and patient-specific pharmacokinetic parameters (K_e and $t_{1/2}$). The secondary objectives of this study is to evaluate the mean bias and precision between the population-predicted and patient-specific pharmacokinetic parameters (K_e and $t_{1/2}$) in select adult medicine patients. A subgroup analysis was performed to assess the correlation between population-predicted and patient-specific pharmacokinetic parameters (K_e and $t_{1/2}$) in special populations—obese patients with a body mass index ≥ 30 kg/m^2 and patients with renal dysfunction (acute kidney injury, chronic kidney disease, and end-stage renal disease). All correlation analyses were performed on the population-predicted pharmacokinetics using diverse methods of estimating renal function (S–C and C–G methods using either ideal, actual, and adjusted body weights).

2.4 Statistical Analyses

Descriptive statistics were used to describe the study demographic characteristics. Simple linear regression analysis was performed to assess the Pearson correlation coefficient (r) and the unstandardized coefficient (β) ± standard error between population-predicted and patient-specific pharmacokinetic parameters: K_e and $t_{1/2}$. The Student's t test was used to compare mean differences between the population-predicted and patient-specific pharmacokinetic parameters (K_e and $t_{1/2}$) in patients. An F-test is used to test if the ratio of the two precision estimates between the two groups is different. All significance testing was set at an α of < 0.05. IBM SPSS Statistics version 25 and SAS version 9.4 were used to conduct all statistical analyses.

3 Results

A total of 30 patients were included in the study. 33.3% (10/30) of the patients were obese and 56.7% (17/30) of the patients had renal dysfunction (11 had acute kidney injury, 1 had chronic kidney disease, 3 had both acute kidney injury and chronic kidney disease, and 2 had end-stage renal disease). Of the 30 patients, 23 patients (76.7%) were at steady state when the vancomycin concentration was drawn, six patients did not reach steady state when the vancomycin concentration was drawn, and for 1 patient, we could not decide whether the patients was at steady state because the patient received the vancomycin dose at an outside hospital and had no documented record of the vancomycin doses received at the outside hospital. Out of the 23 patients who were at steady state, only four were counted as reaching steady state prior to the third dose as the patients had renal dysfunction. Seven patients were hospitalized in the intensive care unit and 23 patients were admitted in non-intensive care unit inpatient settings when the vancomycin concentration was drawn. Tables 1, 2, and 3 provide information on our hospital's vancomycin protocol and patients' baseline information.

Tables 4 and 5 show the relationship between the population-predicted pharmacokinetic parameters (K_e and $t_{1/2}$) and patient-specific pharmacokinetic parameters (K_e and $t_{1/2}$) in all patients. All the calculated population-predicted K_e and $t_{1/2}$ using all four CrCl estimation methods were each significantly correlated with patient specific K_e and $t_{1/2}$; with the population-predicted K_e and $t_{1/2}$ calculated using C–G CrCl-AdjBW showing the strongest association with patient-specific K_e and $t_{1/2}$. Figures 1, 2, 3 and 4 provide a

simple linear regression graph of the relationship between the patient-specific K_e and population-predicted K_e calculated using different methods for estimating CrCl.

When evaluating the mean difference in bias between the population-predicted parameter; K_e (Table 6), there was no significant mean difference between the patient-specific K_e and population-predicted K_e calculated using C–G CrCl-IBW and C–G CrCl-AdjBW. The mean patient-specific K_e was significantly different from the population-predicted K_e calculated using C–G CrCl-ABW and S–C CrCl-ABW; however, the mean differences observed were small at 0.018 h^{-1} and 0.016 h^{-1}, respectively. There were no significant differences in precision between any of the population-predicted K_e and the patient-specific K_e. Table 7 shows the $t_{1/2}$ calculation derived from the K_e from Table 6. All population-predicted $t_{1/2}$ were significantly different from patient-specific $t_{1/2}$. Likewise, the precision of all the population-predicted $t_{1/2}$ were smaller than the patient-specific K_e.

Tables 8 and 9 show the relationship between the population-predicted K_e and $t_{1/2}$ and patient-specific K_e and $t_{1/2}$ in obese patients. All the population-predicted K_e using different CrCl methods were significantly correlated with patient-specific K_e. The population-predicted $t_{1/2}$ was significantly correlated with patient-specific $t_{1/2}$ using three different CrCl methods with the population-predicted $t_{1/2}$ derived from C–G CrCl-ABW not showing a strong correlation with patient-specific $t_{1/2}$. The population-predicted K_e and $t_{1/2}$ calculated using C–G CrCl-IBW showed the strongest association with patient-specific K_e and $t_{1/2}$ in obese patients. Among patients with renal dysfunction (Tables 10 and 11), all the population-predicted K_e and $t_{1/2}$ were significantly correlated with patient-specific K_e and $t_{1/2}$. The population-predicted K_e using C–G CrCl-ABW had the strongest correlation to the patient-specific K_e, while the population-predicted $t_{1/2}$ using C–G CrCl-AdjBW had the strongest correlation to the patient-specific $t_{1/2}$ in patients with renal dysfunction.

4 Discussion

To our knowledge, this is the first study examining the correlation between vancomycin population-predicted and patient-specific pharmacokinetic parameters. This study noted that regardless of the CrCl method used, the Matzke population-predicted K_e was reliable and strongly correlated to the patient-specific K_e. Our study findings were consistent with findings from the Oswalt et al. and Murphy et al. studies [3, 4]. The Oswalt study found small, clinically negligible differences between the population-predicted and patient-specific pharmacokinetics and concluded that using

Table 1 Vancomycin dosing guide protocol used at the University Medical Center, New Orleans [21]

University Medical Center New Orleans protocol for goal vancomycin trough of 15–20 mcg/mL Serious infections: bacteremia, endocarditis, osteomyelitis, meningitis, and pneumonia	
Actual body weight (kg)	Vancomycin dose range (mg)
50–64	750–1000
65–94	1000–1250
≥ 95	1500
CrCl (mL/min)	Dosing interval (h)
30–49	24
50–79	12–24
≥ 80	8–12
University Medical Center New Orleans protocol for goal vancomycin trough of 10–15 mcg/mL Mild infections: urinary tract and skin and soft-tissue infections	
Actual body weight (kg)	Vancomycin dose range (mg)
50–64	500–1000
65–94	750–1000
≥ 95	1000–1250
CrCl (mL/min)	Dosing interval (h)
30–49	24
50–79	12–24
≥ 80	8–12

CrCl creatinine clearance

Table 2 Baseline characteristics

Baseline characteristics ($N=30$)	
Mean age (years) ± SD [range]	48.9 ± 14.01 [26–76]
Sex, *n* (%)	Male: 20 (66.7) Female: 10 (33.3)
Race, *n* (%)	Whites: 12 (40) Black/African-Americans: 14 (46.7) Others: 4 (13.3)
Mean height (cm) ± SD	172.51 ± 11.04
Mean actual body weight (kg) ± SD	85.85 ± 24.93
Mean ideal body weight (kg) ± SD	66.82 ± 11.60
Mean body mass index (kg/m^2) ± SD	28.70 ± 7.32
Mean body mass index in obese patients (kg/m^2) ± SD [$n=10$]	37.23 ± 5.82
Mean serum creatinine (mg/dL) ± SD	2.29 ± 2.06
Median serum creatinine (mg/dL) [range]	1.47 [0.57–8.69]
Mean serum creatinine (mg/dL) in patients with renal dysfunction ± SD [$n=17$]	3.38 ± 2.18
Mean initial vancomycin dose (mg) ± SD	1258.3 ± 350.39
Mean initial vancomycin dose per weight (mg/kg) ± SD	15.1 ± 4.01
Mean current vancomycin dose at the day vancomycin concentration was drawn (mg) ± SD	1225 ± 355.68
Mean current vancomycin dose per weight at the day vancomycin concentration was drawn (mg/kg) ± SD	14.5 ± 3.30
Mean initial vancomycin dosing interval (h) ± SD ($N=25$)	14.1 ± 5.90
Median initial vancomycin dosing interval (h) [range] ($N=25$)	12 [8–24]
Mean current vancomycin dosing interval at the day vancomycin concentration was drawn (h) ± SD ($N=25$)	14.8 ± 6.83
Median current vancomycin dosing interval at the day vancomycin concentration was drawn (h) [range] ($N=25$)	12 [8–24]
Mean time from vancomycin administration to C1 levels (h) ± SD	13.10 ± 6.54
Mean time between C1 and C2 levels (h) ± SD	13.11 ± 7.31
Percent of patient with steady-state vancomycin concentration ordered, *n* (%)	23 (76.7)

SD standard deviation

Table 3 Infections treated in all patients

Infections ($N=30$)		
Methicillin-resistant infections, *n* (%)	Methicillin-resistant *Staphylococcus aureus*	14 (46.7)
	Methicillin-resistant *Staphylococcus epidermidis*	1 (3.3)
	Non-methicillin-resistant infections	15 (50)
Organ system infections, *n* (%)	Osteomyelitis	8 (26.7)
	Surgical-site infections	2 (6.7)
	Central nervous system	2 (6.7)
	Endocarditis[a]	4 (13.3)
	Bacteremia only	4 (13.3)
	Skin and soft-tissue infections	5 (16.7)
	Sepsis	3 (10)
	Pneumonia	1 (3.3)
	Spontaneous bacterial peritonitis	1 (3.3)
Definitive vs. empiric infections	Definitive (organism isolated)	16 (53.3)
	Empiric (no organism isolated)	14 (46.7)

[a]Note three of the four patients with endocarditis had bacteremia

Table 4 Relationship between population-predicted elimination rate constant (K_e) and patient-specific K_e in all patients ($n = 30$)

Predictor variables	Patient-specific K_e outcome variable		
	r	β ± SE	*P* value
K_e using C–G CrCl-IBW (h^{-1})	0.718	0.916 ± 0.168	< 0.001
K_e using C–G CrCl-ABW (h^{-1})	0.711	0.732 ± 0.137	< 0.001
K_e using C–G CrCl-AdjBW (h^{-1})	0.729	0.867 ± 0.154	< 0.001
K_e using S–C CrCl-ABW (h^{-1})	0.725	0.784 ± 0.141	< 0.001

ABW actual body weight, *AdjBW* adjusted body weight, *CG* Cockcroft–Gault, *CrCl* creatinine clearance, *IBW* ideal body weight, *S–C* Salazar–Corcoran, *SE* standard error

Table 5 Relationship between population-predicted half-life ($t_{1/2}$) and patient-specific $t_{1/2}$ in all patients ($n = 30$)

Predictor variables	Patient-specific $t_{1/2}$ outcome variable		
	r	β ± SE	*P* value
$t_{1/2}$ using C–G CrCl-IBW (h)	0.767	1.255 ± 0.198	< 0.001
$t_{1/2}$ using C–G CrCl-ABW (h)	0.752	1.293 ± 0.214	< 0.001
$t_{1/2}$ using C–G CrCl-AdjBW (h)	0.773	1.315 ± 0.204	< 0.001
$t_{1/2}$ using S–C CrCl-ABW (h)	0.761	1.419 ± 0.228	< 0.001

ABW actual body weight, *AdjBW* adjusted body weight, *CG* Cockcroft–Gault, *CrCl* creatinine clearance, *IBW* ideal body weight, *S–C* Salazar–Corcoran, *SE* standard error

population-predicted pharmacokinetics may be an accurate empiric dosing strategy for determining vancomycin dosing frequency in patients with acute brain injury. [3] Similar to the Oswalt et al. study, our study found two small and clinically negligible significant differences between patient-specific and population-predicted pharmacokinetics using C–G CrCl-ABW and S–C CrCl-ABW, while there was no significant bias between patient-specific and two population-predicted pharmacokinetics using C–G CrCl-IBW and C–G CrCl-AdjBW. The Murphy et al. study also noted that the Matzke population-predicted pharmacokinetic parameter (which was used in our study) performed best compared with the other six methods evaluated in their study.

In our study, we observed that regardless of the CrCl estimation method used, the population-predicted K_e was significantly correlated with patient-specific K_e. However, population-predicted K_e using C–G CrCl-AdjBW had the strongest correlation with patient-specific K_e in all patients in our case series. In the subgroup analyses of special populations, population-predicted K_e using C–G CrCl-IBW had the strongest correlation with patient-specific K_e in obese patients and the population-predicted K_e using C–G CrCl-ABW had the strongest correlation in patients with renal dysfunction. This slightly stronger favoring of the C–G CrCl-IBW as the best method for calculating population-predicted K_e is somewhat inconsistent with other studies, which have previously reported that the C–G CrCl-IBW underestimates CrCl in obese patients [14, 22]. This finding of the better performance of the C–G CrCl-IBW for the calculation of population-predicted K_e in obese patients should be interpreted cautiously given the limitations of our small study. The S–C equation was also not the best method in obese patients as supported by prior studies [10, 11]. The population-predicted K_e using C–G CrCl-ABW had the best correlation to patient-specific K_e in patients with renal dysfunction. The assessment of the correlation between patient-specific and population-predicted pharmacokinetics in patients with renal dysfunction was an exploratory subgroup analysis in our case series. It is worth noting that two methods, not used in our case series, have been previously proposed for calculating CrCl in patients with renal dysfunction, although these methods are dated and need validation in a larger population [23, 24].

Our study has some strengths and limitations. The strength of this study is that it evaluated a mix of adult patients that is

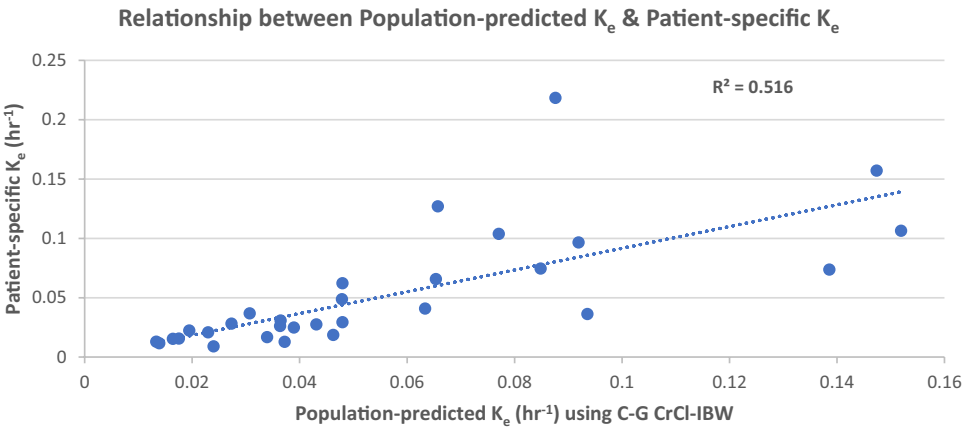

Fig. 1 Relationship between population-predicted elimination rate constant (K_e) using Cockcroft–Gault creatinine clearance-ideal body weight (C–G CrCl-IBW) and patient-specific K_e ($r = 0.718$; coefficient of determination [R^2] = 0.516; $n = 30$)

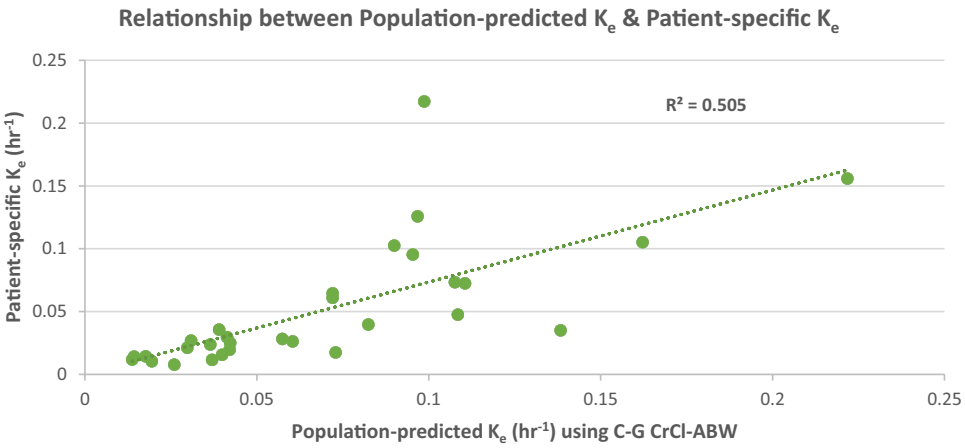

Fig. 2 Relationship between population-predicted elimination rate constant (K_e) using Cockcroft–Gault creatinine clearance-actual body weight (C–G CrCl-ABW) and patient-specific K_e ($r=0.711$; $R^2=0.505$; $n=30$)

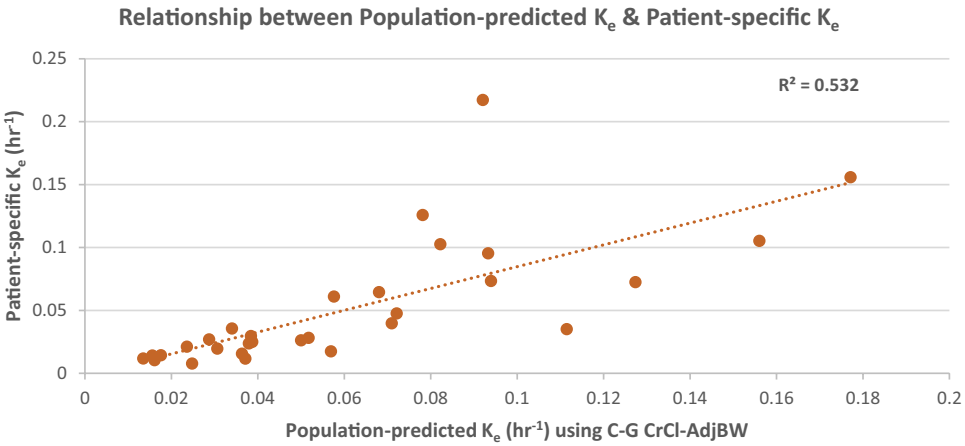

Fig. 3 Relationship between population-predicted elimination rate constant (K_e) using Cockcroft–Gault creatinine clearance-adjusted body weight (C–G CrCl-AdjBW) and patient-specific K_e ($r=0.729$; $R^2=0.532$; $n=30$)

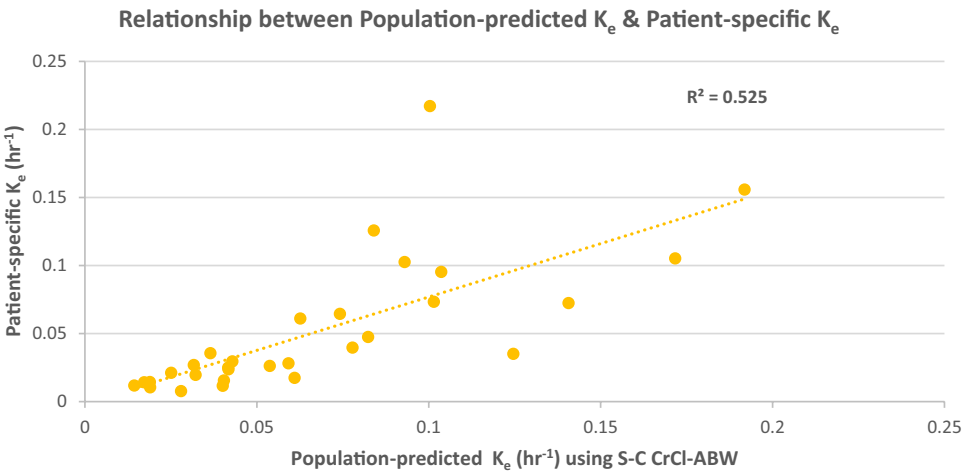

Fig. 4 Relationship between population-predicted elimination rate constant (K_e) using Salazar–Corcoran creatinine clearance-actual body weight (S–C CrCl-ABW) and patient-specific K_e ($r=0.725$; $R^2=0.525$; $n=30$)

similar to patients encountered in real-life clinical settings, with different infections, comorbid status (obesity, renal dysfunction), and vancomycin concentrations obtained pre- and post-steady state. The study limitations include that this is a single-center study, which reduces the external validity and generalizability of our study. The study sample size is small ($N=30$); although the risk of a type 2 statistical error is low as the study sufficiently identified a significant correlation between population-predicted and patient-specific pharmacokinetic parameters (K_e and $t_{1/2}$). There is a risk of selection bias in our study given that patients with renal dysfunction may have been oversampled as this population typically requires multiple vancomycin concentrations to help in the selection of an appropriately individualized vancomycin dose

Table 6 Mean bias and precision between population-predicted elimination rate constant (K_e) and patient-specific K_e in all patients ($n = 30$)

Outcome	Predictor variables	Population-predicted K_e	Patient-specific K_e	Mean difference/ratio	*P* value
Bias	K_e using C–G CrCl-IBW (h^{-1})	0.0557	0.0511	0.0046	0.474
	K_e using C–G CrCl-ABW (h^{-1})	0.0693		0.0182	0.012
	K_e using C–G CrCl-AdjBW (h^{-1})	0.0611		0.0100	0.120
	K_e using S–C CrCl-ABW (h^{-1})	0.0671		0.0160	0.019
Precision	K_e using C–G CrCl-IBW (h^{-1})	0.0387	0.0494	1.629	0.195
	K_e using C–G CrCl-ABW (h^{-1})	0.0480		1.059	0.877
	K_e using C–G CrCl-AdjBW (h^{-1})	0.0416		1.410	0.358
	K_e using S–C CrCl-ABW (h^{-1})	0.0456		1.174	0.673

ABW actual body weight, *AdjBW* adjusted body weight, *CG* Cockcroft–Gault, *CrCl* creatinine clearance, *IBW* ideal body weight, *S–C* Salazar–Corcoran

Table 7 Mean bias and precision difference between population-predicted half-life ($t_{1/2}$) and patient-specific $t_{1/2}$ in all patients ($n = 30$)

Outcome	Predictor variables	Population-predicted $t_{1/2}$	Patient-specific $t_{1/2}$	Mean difference/ratio	*P* value
Bias	$t_{1/2}$ using C–G CrCl-IBW (h)	19.38	27.71	−8.33	0.003
	$t_{1/2}$ using C–G CrCl-ABW (h)	16.31		−11.41	< 0.001
	$t_{1/2}$ using C–G CrCl-AdjBW (h)	17.83		−9.89	0.001
	$t_{1/2}$ using S–C CrCl-ABW (h)	16.26		−11.45	< 0.001
Precision	$t_{1/2}$ using C–G CrCl-IBW (h)	13.20	21.60	2.68	0.010
	$t_{1/2}$ using C–G CrCl-ABW (h)	12.57		2.95	0.005
	$t_{1/2}$ using C–G CrCl-AdjBW (h)	12.69		2.90	<0.001
	$t_{1/2}$ using S–C CrCl-ABW (h)	11.59		3.47	0.001

ABW actual body weight, *AdjBW* adjusted body weight, *CG* Cockcroft–Gault, *CrCl* creatinine clearance, *IBW* ideal body weight, *S–C* Salazar–Corcoran

Table 8 Relationship between population-predicted elimination rate constant (K_e) and patient-specific K_e in obese patients ($n = 10$)

Predictor variables	Patient-specific K_e outcome variable		
	r	β ± SE	*P* value
K_e using C–G CrCl-IBW (h^{-1})	0.772	0.962 ± 0.280	0.009
K_e using C–G CrCl-ABW (h^{-1})	0.752	0.624 ± 0.193	0.012
K_e using C–G CrCl-AdjBW (h^{-1})	0.766	0.800 ± 0.237	0.010
K_e using S–C CrCl-ABW (h^{-1})	0.754	0.717 ± 0.221	0.012

ABW actual body weight, *AdjBW* adjusted body weight, *CG* Cockcroft–Gault, *CrCl* creatinine clearance, *IBW* ideal body weight, *S–C* Salazar–Corcoran, *SE* standard error

Table 9 Relationship between population-predicted half-life ($t_{1/2}$) and patient-specific $t_{1/2}$ in obese patients ($n = 10$)

Predictor variables	Patient-specific $t_{1/2}$ outcome variable		
	r	β ± SE	*P* value
$t_{1/2}$ using C–G CrCl-IBW (h)	0.657	0.839 ± 0.340	0.039
$t_{1/2}$ using C–G CrCl-ABW (h)	0.602	1.176 ± 0.551	0.066
$t_{1/2}$ using C–G CrCl-AdjBW (h)	0.637	0.998 ± 0.427	0.048
$t_{1/2}$ using S–C CrCl-ABW (h)	0.640	1.052 ± 0.446	0.046

ABW actual body weight, *AdjBW* adjusted body weight, *CG* Cockcroft–Gault, *CrCl* creatinine clearance, *IBW* ideal body weight, *S–C* Salazar–Corcoran, *SE* standard error

frequency. The equations used in this study for measuring CrCl provide CrCl estimates compared to 24-h urine collection and these equations do not account for rapid changes in CrCl among patients with renal dysfunction. Additionally, we acknowledge that not assessing the area under the curve to minimum inhibitory concentration is a limitation of our study as emerging evidence is pointing to this measure as a better pharmacokinetic/pharmacodynamic marker for monitoring vancomycin efficacy while ensuring patient safety and guiding vancomycin dose optimization [25–29].

Table 10 Relationship between population-predicted elimination rate constant (K_e) and patient-specific K_e in patients with renal dysfunction ($n = 17$)

Predictor variables	Patient-specific K_e outcome variable		
	r	β ± SE	*P* value
K_e using C–G CrCl-IBW (h^{-1})	0.691	0.680 ± 0.184	0.002
K_e using C–G CrCl-ABW (h^{-1})	0.785	0.545 ± 0.111	< 0.001
K_e using C–G CrCl-AdjBW (h^{-1})	0.749	0.643 ± 0.147	0.001
K_e using S–C CrCl-ABW (h^{-1})	0.744	0.587 ± 0.136	0.001

ABW actual body weight, *AdjBW* adjusted body weight, *CG* Cockcroft–Gault, *CrCl* creatinine clearance, *IBW* ideal body weight, *S–C* Salazar–Corcoran, *SE* standard error

Table 11 Relationship between population-predicted half-life ($t_{1/2}$) and patient-specific $t_{1/2}$ in patients with renal dysfunction ($n = 17$)

Predictor variables	Patient-specific $t_{1/2}$ outcome variable		
	r	β ± SE	*P* value
$t_{1/2}$ using C–G CrCl-IBW (h)	0.593	0.988 ± 0.347	0.012
$t_{1/2}$ using C–G CrCl-ABW (h)	0.604	0.995 ± 0.340	0.010
$t_{1/2}$ using C–G CrCl-AdjBW (h)	0.615	1.048 ± 0.347	0.009
$t_{1/2}$ using S–C CrCl-ABW (h)	0.591	1.108 ± 0.390	0.012

ABW actual body weight, *AdjBW* adjusted body weight, *CG* Cockcroft–Gault, *CrCl* creatinine clearance, *IBW* ideal body weight, *S–C* Salazar–Corcoran, *SE* standard error

5 Conclusions

The study found that regardless of the CrCl estimation method used, population-predicted K_e was significantly correlated with patient-specific K_e. Population-predicted K_e using C–G CrCl-AdjBW had the strongest correlation with patient-specific K_e in all patients. Among special populations assessed, population-predicted K_e using C–G CrCl-IBW had the strongest correlation with patient-specific K_e in obese patients and population-predicted K_e using C–G CrCl-ABW had the strongest correlation in patients with renal dysfunction. The vancomycin population-predicted pharmacokinetic formula can be used safely to estimate a patient's vancomycin pharmacokinetics in hospitalized adult patients.

Compliance with Ethical Standards

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Conflict of interest IfeanyiChukwu O. Onor, Alison Neuliep, Kieu Anh Tran, Jennifer Lambert, Christopher J. Gillard, Fatima Brakta, Michael C. Ezebuenyi, Kirbie St. James, John I. Okogbaa, and Robbie A. Beyl have no conflicts of interest that are relevant to the content of this article.

Ethics Approval The Institutional Review Board of the Xavier University of Louisiana and the University Medical Center Research Review Committee reviewed and approved this study protocol in accordance with the ethical standards set forth in the 1964 Declaration of Helsinki.

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