



Prediction of Vancomycin Levels Using Cystatin C in Overweight and Obese Patients: a Retrospective Cohort Study of Hospitalized Patients

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ABSTRACT The use of the kidney function biomarker cystatin C (cysC) can improve the accuracy of vancomycin dosing for target trough attainment in nonobese patients. It is unknown whether cysC can also improve vancomycin target trough attainment in overweight and obese patients. We conducted a retrospective observational study of overweight or obese hospitalized adults with stable renal function administered intravenous vancomycin between January 2011 and July 2019. Linear regression models were used to predict initial steady-state vancomycin troughs using several factors, including various cysC- and serum creatinine (SCr)-based estimates of kidney function. We compared the predicted proportion of patients within the target trough range (10 to 20 mg/liter) using the derived models to that observed from usual care. Of the 200 included patients, the mean trough level was 15 ± 6.3 mg/liter. The optimal model to predict the initial trough included both cysC and SCr ($R^2 = 0.48$) rather than either biomarker alone. This model predicted that 79% (95% confidence interval [CI], 73% to 85%) of troughs could be between 10 and 20 mg/liter compared to the 62% observed in clinical practice ($P < 0.001$), a 1.3-fold increase. This study is the first to examine the role of cysC in predicting vancomycin levels in an exclusively overweight or obese population. While dosing models based on cysC appear promising in this setting, prospective validation is needed.

KEYWORDS cystatin C, obesity, vancomycin

As the prevalence of adult obesity in the United States continues to rise, last reported at 40% in 2017 (1), the optimization of drug dosing and monitoring in obese patients has become increasingly important. Vancomycin, a hydrophilic renally eliminated glycopeptide antibiotic used for known or suspected Gram-positive infections, is a prototypical example of a medication that poses unique challenges in obesity. Pharmacokinetic differences in obese patients, including a disproportionate volume of distribution (V) relative to total body weight, and increased kidney-mediated drug clearance each contribute to poor vancomycin pharmacokinetic attainment relative to that observed in nonobese patients (2). Even tailored protocols for obese patients have resulted in as few as one-third of patients reaching their goals (3).

While the literature related to this issue has been dominated by studies exploring

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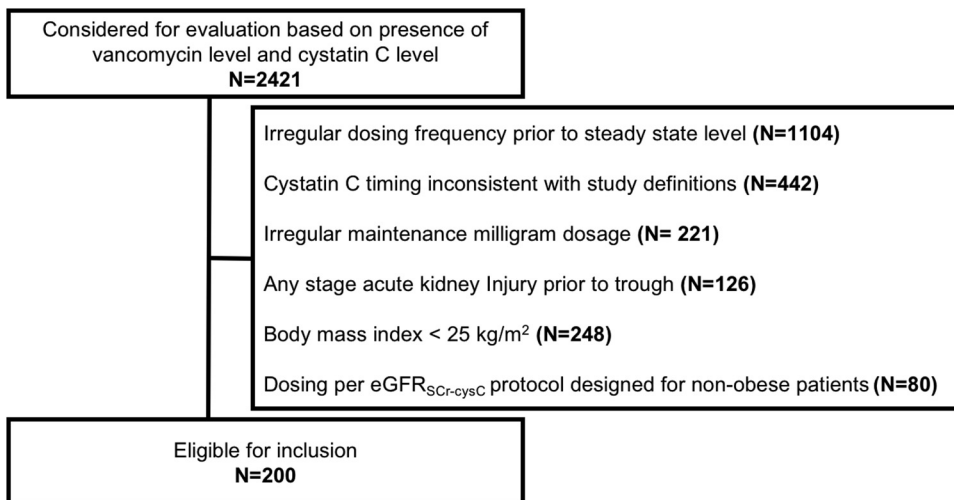


FIG 1 Inclusion of subjects (N, number of subjects).

the vancomycin volume of distribution and optimal patient weight for dose selection (actual, ideal, or adjusted), little attention is paid to the approach to estimating drug clearance (i.e., kidney function assessment) (3, 4). Kidney function assessment is inherently challenging in obese patients due to poor representation in derivation studies of estimated glomerular filtration rate (eGFR) equations (5). Reliance on serum creatinine (SCr), a by-product of skeletal muscle metabolism that traditionally has been used for medication dose adjustment, also contributes to suboptimal kidney function assessment in the obese (6–8). SCr has many nonrenal determinants that are incompletely accounted for in eGFR-estimating equations (9, 10). Specifically, reduced muscle mass often coexists with obesity, rendering SCr less informative for kidney function assessment in this population (11).

Cystatin C (cysC) has emerged as a viable adjunct or alternative to SCr for the prediction of medication clearance. cysC is a low-molecular-weight protein released from all nucleated cells that is freely filtered at the glomerulus and not systemically reabsorbed or actively secreted in the tubules (12). cysC in combination with SCr better predicts measured GFR than either biomarker alone (5).

Models incorporating cysC have been shown to improve the prediction of vancomycin trough levels compared to those using SCr alone (13–17). We previously demonstrated that an eGFR_{SCr-cysC}-based vancomycin dosing nomogram achieved a 2-fold increase in goal trough attainment compared to usual care with the Cockcroft-Gault estimated creatinine clearance (CG eCrCl) in nonobese critically ill patients (16). No studies to our knowledge have attempted to use cysC to predict vancomycin levels in overweight and obese patients. Algorithms using cysC in obese patients may provide an additional opportunity to optimize vancomycin dosing in this population with challenging pharmacokinetics. The overall goal of the study was to develop cysC-inclusive predictive models for vancomycin troughs in obese and overweight patients. Next, the impact of these models was assessed to determine expected vancomycin target trough achievement compared to the observed target trough achievement in routine practice. An exploratory secondary analysis examined the relationship of the observed and expected area under the curve (AUC) estimates.

RESULTS

Of the 2,421 subjects electronically screened with available serum vancomycin and cysC concentrations, 200 subjects met the inclusion criteria for the study (Fig. 1). The average body mass index (BMI) \pm the standard deviation (SD) was 33 ± 8 kg/m² (Table 1). The average eGFR_{cysC} and eGFR_{SCr} at vancomycin initiation \pm SD were 78 ± 36 ml/min and 102 ± 38 ml/min, respectively, with an intraindividual difference of -24 ml/

TABLE 1 Baseline characteristics ($n = 200$)^a

Parameter	Value
Mean age (yrs) \pm SD	59 \pm 17
No. (%) of male patients	119 (60)
No. (%) of Caucasian patients	198 (99)
Wt (kg) \pm SD	95 \pm 25
Mean body mass index (kg/m ²) \pm SD	33 \pm 8
No. (%) of patients with body mass index (kg/m ²) of:	
25–29.9	96 (48)
30–39.9	77 (39)
40–49.9	18 (9)
\geq 50	9 (4.5)
Mean Du Bois body surface area (m ²) \pm SD	2.0 \pm 0.3
No. (%) of patients in intensive care unit at initiation	121 (61)
Mean Charlson comorbidity index \pm SD	5.4 \pm 3.8
No. (%) of patients on systemic corticosteroids	34 (17)
No. (%) of patients with elevated CRP concentration	48 (24)
No. (%) of patients with low thyroxine concentration	1 (0.005)
No. (%) of patients with elevated thyroxine concentration	1 (0.005)
No. (%) of patients with cancer	68 (34)
Metastatic solid tumor	30 (15)
Renal parameters	
Median serum creatinine concentration (mg/dl) (interquartile range)	0.9 (0.6, 1.1)
Mean cystatin C concentration (mg/liter) \pm SD	1.3 \pm 0.5
Mean eGFR (ml/min) \pm SD	
Cockcroft-Gault ^b	108 \pm 64
CKD-EPI _{SCr}	102 \pm 38
CKD-EPI _{cysC}	78 \pm 36
CKD-EPI _{SCr-cysC}	89 \pm 36
Vancomycin	
No. (%) of patients with loading dose	99 (50)
Mean maintenance dose \pm SD	
Non-wt based (mg)	1,347 \pm 304
Wt based (actual) (mg/kg)	15 \pm 2.8
Wt based (adjusted) (mg/kg)	18 \pm 3.4
Wt based (ideal) (mg/kg)	22 \pm 6.8
No. (%) of patients with dosing interval of:	
8 h	25 (13)
12 h	139 (70)
24 h	36 (18)
Mean observed trough level (mg/liter) \pm SD	15 \pm 6.2
No. (%) of patients with observed trough level (mg/liter) of:	
<10	40 (20)
10–14.9	65 (32.5)
15–19.9	59 (29.5)
\geq 20	36 (18)
No. (%) of patients with trough level timing	
Before dose 4	142 (71)
Before dose 5 or later	58 (29)

^aAbbreviations: CKD-EPI eGFR, Chronic Kidney Disease Epidemiology Collaborative estimated glomerular filtration rate; cysC, cystatin C; SCr, serum creatinine.

^bUsing adjusted body weight.

min ($P < 0.001$). The mean trough level was 15 ± 6.3 mg/liter, with 62% of subjects with concentrations between 10 and 20 mg/liter. The application of a model derived primarily in nonobese patients (15) to a similarly composed subset of the current cohort resulted in a weak model fit ($R^2 = 0.38$) and poor calibration (see Fig. S1 in the supplemental material).

In the univariate analyses of possible features for a new model, BMI, creatinine, cysC, Cockcroft-Gault eCrCl (using ideal body weight and adjusted body weight), Chronic Kidney Disease Epidemiology Collaborative (CKD-EPI) eGFR_{SCr}, eGFR_{cysC}, and eGFR_{SCr-cysC}, total pretrough dose, and number of doses before the initial steady-state trough level

TABLE 2 Univariate predictors of vancomycin trough levels in milligrams per liter^a

Parameter	Beta value (SE)	P value
Demographic and anthropometric data		
Age (yr)	0.01 (0.03)	0.60
Male	-0.28 (0.90)	0.76
White race	5.41 (4.43)	0.22
Ht (cm)	-0.04 (0.03)	0.27
Wt (kg)	0.02 (0.02)	0.26
BMI (kg/m ²)	0.12 (0.05)	0.033
Kidney function markers		
Creatinine (mg/dl)	3.44 (1.13)	0.003
Cystatin C (mg/dl)	5.00 (0.81)	<0.001
Equations for estimated GFR (ml/min)		
Cockcroft-Gault (ideal body wt)	-0.01 (0.01)	0.11
Cockcroft-Gault (adjusted body wt)	-0.01 (0.01)	0.15
Cockcroft-Gault (total body wt)	-0.01 (0.01)	0.22
CKD-EPI _{SCr}	-0.03 (0.01)	0.014
CKD-EPI _{cysC}	-0.06 (0.01)	<0.001
CKD-EPI _{SCr-cysC}	-0.06 (0.01)	<0.001
Vancomycin parameters		
1st dose different than maintenance	0.86 (0.88)	0.33
No. of doses before level	1.46 (0.50)	0.004
Total pretrough dose (g)	1.11 (0.28)	<0.001
Interval		0.19
q8h	Reference	
q12h	-1.72 (1.36)	0.21
q24h	-2.16 (1.63)	0.19

^aAbbreviations: BMI, body mass index; CKD-EPI eGFR, Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate; cysC, cystatin C; q8h, every 8 h; SCr, serum creatinine; SE, standard error.

were each significantly associated with vancomycin trough levels (Table 2). A different first dose (i.e., loading dose) was not a significant predictor of the observed trough level in the univariate model beyond its contribution to pretrough total drug exposure.

Common features of the majority of the tested multivariate models included weight, dosing interval, milligram-per-kilogram dose using adjusted body weight, and number of doses before the trough (Table 3; Table S1). Model 3 (Fig. 2), which contained weight, SCr, cysC, dosing interval, number of doses before the trough, milligram-per-kilogram dose using adjusted body weight, age, and sex, was selected as the optimal model. Elevated C-reactive protein (CRP), abnormal thyroxine, any cancer, metastatic solid tumor, and corticosteroids were assessed for inclusion into model 3, and only abnormal thyroxine ($n = 2$ total; 1 subtherapeutic and 1 supratherapeutic) was significant ($P = 0.047$). This feature was ultimately not included in model 3, given the negligible improvement that it would offer (R^2 increase of 0.0076 compared to the more parsimonious model).

Compared to usual care, the model with the best performance (model 3 using cysC and SCr concentrations [$R^2 = 0.48$]) yielded a 1.3-fold increase in the percentage of subjects expected to achieve a vancomycin trough of between 10 and 20 mg/liter (79% [95% confidence interval {CI}, 73% to 85%] in the model versus 62% observed in usual care [$P < 0.001$]) (Fig. 3 and Table 3). The model fit was stronger in patients with a BMI of ≥ 40 kg/m² than in those with a BMI of < 40 kg/m² and in patients with an eGFR_{SCr-cysC} of < 60 ml/min than in those with an eGFR_{SCr-cysC} of ≥ 60 ml/min (Table 4). Cross-validation of model 3 achieved a mean R^2 value of 0.51 (range, 0.47 to 0.53).

In our exploratory secondary analysis, the mean eAUC_{observed} (defined in Table 5) \pm SD ranged from 575 ± 166 to 805 ± 198 mg \cdot h/liter (using V values of 0.7 mg/liter and 0.3 mg/liter total body weight, respectively). Using the expected trough from the model instead of the observed troughs, the mean eAUC_{expected} \pm SD had a range of 576 ± 122 to 808 ± 151 mg \cdot h/liter (Fig. S2). Compared to 11 to 49% of patients with an

TABLE 3 Predictive models for vancomycin trough levels in milligrams per liter^a

Model variable	Median beta value (95% CI)	P value	Model fit (R ²)	Target trough achievement (%) (95% CI)
Model 1			0.16	68 (62–74)
Intercept	–5.89			
Age, per 10 yrs	0.31 (–0.23, 0.84)	0.26		
Male	–1.28 (–3.02, 0.47)	0.15		
Wt, per 10 kg	0.11 (–0.25, 0.47)	0.55		
No. of doses prior to level	1.39 (0.44, 2.33)	0.005		
mg/kg dose (AdBW)	0.50 (0.25, 0.74)	<0.001		
Every-8-h interval	2.48 (–0.18, 5.14)	0.069		
Every-12-h interval	Reference			
Every-24-h interval	–3.08 (–5.51, –0.65)	0.014		
Serum creatinine	6.08 (3.53, 8.63)	<0.001		
Model 2			0.48	77 (71–83)
Intercept	–15.98	–15.98		
Age, per 10 yrs	0.22 (–0.20, 0.65)	0.22		
Male	–0.26 (–1.62, 1.09)	–0.26		
Wt, per 10 kg	0.04 (–0.24, 0.31)	0.04		
No. of doses prior to level	1.37 (0.62, 2.12)	1.37		
mg/kg dose (AdBW)	0.70 (0.50, 0.89)	0.70		
Every-8-h interval	4.60 (2.46, 6.74)	4.60		
Every-12-h interval	Reference			
Every-24-h interval	–8.39 (–10.54, –6.24)	–8.39		
Cystatin C	10.56 (8.86, 12.26)	10.56		
Model 3			0.48	79 (73–85)
Intercept	–16.13			
Age, per 10 yrs	0.22 (–0.21, 0.64)	0.32		
Male	–0.44 (–1.83, 0.95)	0.54		
Wt, per 10 kg	0.00 (–0.29, 0.29)	0.99		
No. of doses prior to level	1.36 (0.61, 2.11)	<0.001		
mg/kg dose (AdBW)	0.70 (0.50, 0.90)	<0.001		
Every-8-h interval	4.69 (2.55, 6.84)	<0.001		
Every-12-h interval	Reference			
Every-24-h interval	–8.56 (–10.73, –6.39)	<0.001		
Serum creatinine	1.19 (–1.02, 3.40)	0.29		
Cystatin C	10.15 (8.29, 12.01)	<0.001		
Model 4			0.09	63 (56–70)
Intercept	5.89			
No. of doses prior to level	1.33 (0.35, 2.31)	0.008		
mg/kg dose (AdBW)	0.36 (0.12, 0.61)	0.004		
Every-8-h interval	2.03 (–0.66, 4.72)	0.14		
Every-12-h interval	Reference			
Every-24-h interval	–1.26 (–3.59, 1.06)	0.29		
Cockcroft-Gault per 10 ml/min	–0.18 (–0.32, –0.03)	0.016		
Model 5			0.12	64 (57–71)
Intercept	9.06			
No. of doses prior to level	1.30 (0.34, 2.26)	0.009		
mg/kg dose (AdBW)	0.38 (0.13, 0.62)	0.003		
Every-8-h interval	2.71 (0.05, 5.38)	0.047		
Every-12-h interval	Reference			
Every-24-h interval	–2.34 (–4.72, 0.04)	0.055		
eGFR with CKD-EPI _{creatinine} per 10 ml/min	–0.49 (–0.74, –0.24)	<0.001		
Model 6			0.36	73 (67–79)
Intercept	11.37			
No. of doses prior to level	1.18 (0.36, 2.00)	0.005		
mg/kg dose (AdBW)	0.52 (0.31, 0.73)	<0.001		
Every-8-h interval	5.73 (3.35, 8.11)	<0.001		
Every-12-h interval	Reference			
Every-24-h interval	–5.42 (–7.53, –3.30)	<0.001		
eGFR with CKD-EPI _{cystatin C} per 10 ml/min	–1.19 (–1.43, –0.94)	<0.001		

(Continued on next page)

TABLE 3 (Continued)

Model variable	Median beta value (95% CI)	P value	Model fit (R^2)	Target trough achievement (%) (95% CI)
Model 7			0.31	72 (66–78)
Intercept	12.64			
No. of doses prior to level	1.19 (0.34, 2.04)	0.007		
mg/kg dose (AdBW)	0.48 (0.26, 0.70)	<0.001		
Every-8-h interval	5.30 (2.84, 7.77)	<0.001		
Every-12-h interval	Reference			
Every-24-h interval	−5.26 (−7.50, −3.04)	<0.001		
eGFR with CKD-EPI _{creatinine-cystatin C} per 10 ml/min	−1.12 (−1.38, −0.86)	<0.001		
Model 8			0.44	80 (74–86)
Intercept	−0.45			
Age, per 10 yrs	0.16 (−0.29, 0.61)	0.48		
Male	−1.56 (−3.01, −0.10)	0.037		
Wt, per 10 kg	−0.38 (−0.68, −0.08)	0.015		
Every-8-h interval	2.92 (0.61, 5.24)	0.014		
Every-12-h interval	Reference			
Every-24-h interval	−7.62 (−9.85, −5.39)	<0.001		
Cystatin C	10.18 (8.40, 11.96)	<0.001		
Steroid positive (yes vs no)	0.46 (−1.41, 2.32)	0.63		
CRP positive (yes vs no)	0.12 (−1.48, 1.72)	0.88		
T4 abnormal				
Normal	Reference			
Low	−2.74 (−12.50, 7.03)	0.58		
High	−9.36 (−18.90, 0.20)	0.056		
Metastatic solid tumor (yes vs no)	2.17 (−0.11, 4.44)	0.063		
Cancer (yes vs no)	−1.13 (−2.93, 0.67)	0.22		
First dose in ICU (yes vs no)	0.77 (−0.66, 2.21)	0.29		
Difference between baseline and trough SCr levels	5.61 (0.75, 10.48)	0.025		
Vancomycin total dose, per 1,000 g	1.49 (1.00, 1.99)	<0.001		
Model 9			0.49	79 (73–85)
Intercept	−16.18			
Age, per 10 yrs	0.20 (−0.23, 0.62)	0.37		
Male	−0.25 (−1.62, 1.12)	0.72		
Wt, per 10 kg	0.06 (−0.22, 0.34)	0.69		
No. of doses prior to level	1.40 (0.65, 2.16)	<0.001		
mg/kg dose (AdBW)	0.67 (0.47, 0.87)	<0.001		
Every-8-h interval	4.17 (1.91, 6.44)	<0.001		
Every-12-h interval	Reference			
Every-24-h interval	−8.36 (−10.51, −6.21)	<0.001		
Cystatin C	10.93 (9.19, 12.67)	<0.001		
Steroid positive (yes vs no)	0.03 (−1.76, 1.82)	0.97		
CRP positive (yes vs no)	−0.08 (−1.61, 1.45)	0.92		
T4 abnormal				
Normal	Reference			
Low	−2.88 (−12.22, 6.46)	0.55		
High	−7.85 (−16.98, 1.28)	0.093		
Metastatic solid tumor (yes vs no)	2.24 (0.07, 4.41)	0.044		
Cancer (yes vs no)	−0.72 (−2.44, 1.00)	0.42		
First dose in ICU (yes vs no)	0.47 (−0.91, 1.85)	0.50		
Difference between baseline and trough SCr levels	4.56 (−0.08, 9.19)	0.056		

^aAbbreviations: AdBW, adjusted body weight; CKD-EPI eGFR, Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate; CRP, C-reactive protein; ICU, intensive care unit; SCr, serum creatinine.

eAUC_{observed} of between 400 and 600 mg · h/liter, 7.5 to 56% of subjects would be expected to fall in the eAUC_{observed} target using the model.

DISCUSSION

In a cohort of 200 overweight and obese patients, 62% of patients were within the initial vancomycin trough target range of 10 to 20 mg/liter. A model derived in primarily nonobese patients to predict vancomycin trough levels from eGFR_{SCr-cysC} (15) demonstrated poor performance in the present study of overweight and obese patients. To determine whether cysC in conjunction with other clinically available data could be

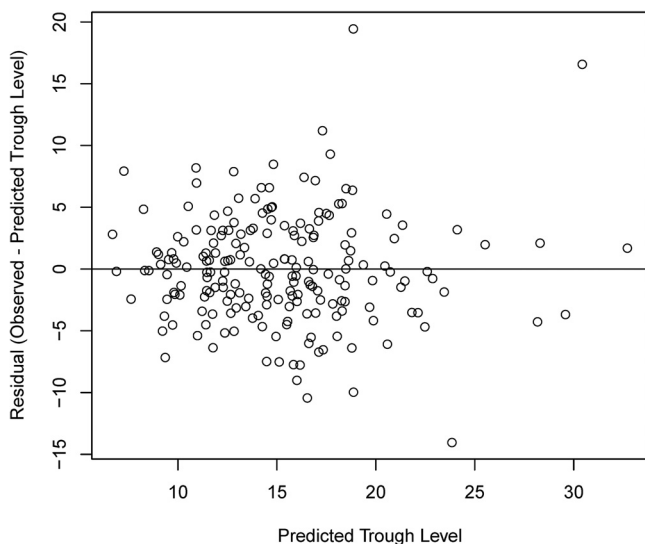


FIG 2 Residuals of model 3 in relation to the predicted trough level.

used to predict initial vancomycin trough levels in overweight or obese patient populations, we developed new models using the values for SCr and cysC or as part of the Cockcroft-Gault eCrCl and CKD-EPI eGFR equations. The optimal model used absolute concentrations of SCr and cysC and was expected to achieve target trough concentrations in 79% of cases compared to the 62% observed in clinical practice ($P < 0.001$). Model performance did not deteriorate at high BMI ranges ($\geq 40 \text{ kg/m}^2$) or low $eGFR_{\text{SCr-cysC}}$ ranges ($< 60 \text{ ml/min}$). From the model, a practical set of dosing guidelines tailored to overweight and obese patients could be developed. The present study addresses the unmet need to improve empiric vancomycin dosing precision in obese patients, a subpopulation associated with low rates of target attainment (3) and a correspondingly high risk of elevated trough levels and acute kidney injury (AKI) (4, 18, 19).

While cysC has been used to predict vancomycin levels in nonobese patients, overweight and obese patients warrant their own study due to unique pharmacokinetic differences in obesity (2) along with the known elevation of cysC in obesity indepen-



FIG 3 Distribution of observed versus expected troughs using model 3 ($n = 200$). Compared to usual care, model 3 is expected to achieve an improvement in the percentage of subjects achieving a vancomycin trough of between 10 and 20 mg/liter (79% in the model versus 62% observed in usual care; $P < 0.001$).

TABLE 4 Model 3 performance overall and across subgroups^a

Parameter	<i>R</i> ²	Observed % at 10–20 mg/liter	Expected % if model 3 used 10–20 mg/liter	<i>P</i> ^b
Overall	0.48	62	79	<0.001
BMI thresholds (kg/m ²)				
≥40 (<i>n</i> = 27)	0.54	59	85	0.62
<40 (<i>n</i> = 173)	0.45	62	77	<0.001
≥32 (<i>n</i> = 76)	0.68	63	80	0.99
<32 (<i>n</i> = 124)	0.41	61	77	<0.001
eGFR _{SCR-cysC} thresholds (ml/min)				
≥60 (<i>n</i> = 158)	0.4	63	76	<0.001
<60 (<i>n</i> = 42)	0.58	60	88	0.38

^aAbbreviations: BMI, body mass index; CKD-EPI eGFR, Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate; cysC, cystatin C; SCR, serum creatinine.

^b*P* values represent the association between the 10- to 20-mg/liter ranges for observed and expected trough levels.

dent of the GFR (20). In the present study, models using the eGFR (milliliters per minute) performed poorly relative to models using the absolute concentrations of cysC and SCR. Interestingly, model 2, which mirrored model 3 with the exception that it contained only cysC, had the same *R*², 0.48, as model 3. While model 3 was selected due to the assumption that SCR would nearly always be available in practice, the good performance of the cysC concentration as the lone kidney function surrogate in model 2 demonstrates the usefulness of cysC in this setting.

These findings are in contrast to a study of 173 nonobese patients that found that models with eGFR_{SCR-cysC} led to a superior prediction of vancomycin trough levels compared to models using absolute biomarker concentrations (15). The poor performance of GFR-estimating equations for the prediction of measured GFR in obese patients may help explain the suboptimal performance of those models seen for the prediction of vancomycin trough concentrations in the present study (21). We applied the generally accepted principle of reexpressing CKD-EPI eGFR values as milliliters per minute for drug dosing (20). This approach may lead to an overestimation of the eGFR due to disproportionate changes in the glomerular filtration rate with weight increases. In obese patients, a 2-fold increase in body weight results in only a 1.6-fold-higher mean GFR (21). The use of actual weight in GFR estimation equations or the use of a body surface area (BSA) correction could therefore overestimate kidney function. Our finding that eGFR with or without cysC poorly predicts vancomycin levels is consistent with known inaccuracies of eGFR at extremes of weight and reinforces the need to design dosing models specific for the overweight and obese population. The prospective validation of our developed model is warranted.

To our knowledge, no studies analyzing the role of cystatin C to predict vancomycin levels have analyzed common nonrenal factors of cysC, including malignancy, corticosteroids, abnormal thyroxine levels, or elevated CRP levels, as covariates in the model. Given that over two-thirds of hospitalized patients are known to have at least one nonrenal determinant of cysC (22), it is crucial that these factors are considered. We included information about corticosteroids, CRP, thyroxine, and malignancy in our models, noting that the nonrenal determinant of obesity was inherently included given the study cohort. The model with the highest *R*² value (model 9) included these factors, but they provided only a limited additional increase in the predictive performance relative to more parsimonious models and thus were excluded in our final determination. A study analyzing the use of cysC for aminoglycoside dosing had similar findings of the negligible impact of these factors (23). There remain many unanswered questions about the effects of nonrenal determinants of cysC in hospitalized patients, and additional studies are needed (22). While not the primary objective of this study, our results provide some reassurance that these factors are unlikely to lead to clinically significant changes in observed drug levels or target attainment.

Our study has various limitations that warrant discussion. Since this was a retrospective study, the timing of cysC and SCr values was not uniform relative to initiation and trough-level timing. We attempted to ensure that SCr and cysC collected at any time during the pretrough period were reflective of stable kidney function by excluding patients with any stage of AKI before the first trough. We also ensured that baseline laboratory measures were collected before the vancomycin trough but no earlier than 36 h before the start of therapy. Most patients had their first trough before the 4th dose, but some patients had their troughs collected at a later point. To account for this variability between patients, the number of doses before the level was included as a covariate within the model.

For feasibility reasons, this study was not restricted to microbiologically confirmed resistant Gram-positive infections (~10% of treated vancomycin patients [15, 16]). Thus, no conclusions can be drawn about the relationship between the trough level and efficacy, but it is presumed that improved rates of target attainment would offer clinical benefits. While pharmacokinetic target attainment is most critical for efficacy in patients with invasive Gram-positive infections, future application of the model developed in this study could improve safety in all obese patients empirically started on scheduled vancomycin given the known nephrotoxicity risks with supratherapeutic trough levels (4). We considered any trough of between 10 and 20 mg/liter within the target, as this approach has been taken by other studies in obese subjects that have resulted in similar vancomycin target attainment rates (3, 24). Notably, an obesity-tailored algorithm developed from our model could accommodate the traditionally high serum levels targeted in invasive infections (i.e., meningitis, endocarditis, and osteomyelitis) compared to less severe infections (i.e., cellulitis) (25). This approach was taken in a previous algorithm using cysC in nonobese critically ill patients by requiring the clinician to choose the trough goal of either 10 to 15 mg/liter or 15 to 20 mg/liter (16). Since new guideline recommendations discourage target troughs of >15 mg/liter due to the increased risk of nephrotoxicity (4), an algorithm developed from our model could target troughs of 15 mg/liter for invasive infections and slightly lower troughs for less serious infections.

We also acknowledge that the recently released vancomycin guidelines favor AUC-based monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections (4). However, these recommendations do not specifically include evidence in support of this approach for obese patients (4). Notably, troughs are typically necessary to calculate the AUC (26). Since we demonstrated that the addition of cysC to a model improves the accuracy and precision of trough predictions, it is possible that this, by extension, could improve the accuracy and precision of AUC calculations. The recently released vancomycin dosing and monitoring guidelines recommend a two-level method to calculate the AUC, but this was not feasible with the available data (4). Our exploratory secondary analysis to estimate the eAUC using a one-level trough approach provides preliminary data for future study (27). We acknowledge the limitations of using a single serum vancomycin level to estimate the AUC, especially owing to the variability in the vancomycin volume of distribution observed in the obese population, which is a critical parameter in the one-level AUC approach (3). Two plausible volumes of distribution were used (0.3 liters/kg and 0.7 liters/kg total body weight) to approximate a range of clinically relevant eAUC values (3, 4). Future studies could also consider varying the volume of distribution across the level of BMI. This analysis should be viewed as hypothesis generating and expanded upon by using more accurate methods to calculate the AUC, including a two-level equation-based approach or a one- to two-level approach using a Bayesian method validated in obese patients.

Conclusion. Obese patients have historically experienced low rates of vancomycin pharmacokinetic target attainment (3). cysC is a novel kidney biomarker that has been shown to improve vancomycin target attainment in populations of primarily nonobese patients (13). In an overweight and obese population, we found that the optimal model

TABLE 5 Study definitions^a

Term(s)	Definition
Steady-state vancomycin trough	Vancomycin trough collected no earlier than prior to the 4th dose
Trough target range	Vancomycin serum concn of 10–20 mg/liter
Observed trough	Steady-state vancomycin trough observed
Predicted trough	Steady-state vancomycin trough predicted from the best model
Residual	Observed trough – predicted trough
Expected trough	15 (median of goal range) + residual
eAUC _{observed} , eAUC _{expected}	Estimated (1-level) 24-h area under the curve using the equation
	$eAUC = \frac{\text{dose}(\text{mg}/\text{kg}) \times 24}{\ln \left(\frac{\text{trough} + \frac{\text{dose}(\text{mg}/\text{kg})}{V(\text{liters}/\text{kg})}}{\text{trough}} \right)} \times V(\text{liters}/\text{kg})$
	where the inputs include
	<ul style="list-style-type: none"> • observed trough for eAUC_{observed} or expected trough for eAUC_{expected} • dose (mg/kg), maintenance dose using total body wt • V (liters/kg), population estimate of the vol of distribution (estimated as 0.3 liters/kg or 0.7 liters/kg total body wt)

^aTroughs are in milligrams per liter, and areas under the curve are in milligrams per hour per liter. eAUC, estimated area under the curve.

included cysC and SCr absolute biomarker concentrations rather than the estimated GFR based on a standard equation. This study is the first to our knowledge to examine the role of cysC in predicting vancomycin levels in an exclusively overweight or obese population. While cysC appears promising in this setting, prospective validation is warranted.

MATERIALS AND METHODS

Settings and participants. This was an observational study of overweight and obese adults (≥ 18 years of age) who received intravenous vancomycin during hospitalization between 1 January 2011 and 13 July 2019, at Mayo Clinic—Rochester, a 2,059-bed academic medical center. The Mayo Clinic Institutional Review Board approved the study protocol, and the requirement for informed consent was waived. Rapid-turnaround (<3-h) cysC and SCr tests with eGFR reporting were available to be ordered by the care team without restriction throughout the study duration for kidney function assessment (22). cysC is used frequently across inpatient practice settings within our institution, with no specific protocols around use outside the above-mentioned eGFR_{SCr-cysC}-based vancomycin nomogram (22). Included individuals were those with a BMI of ≥ 25 kg/m², an available steady-state vancomycin trough concentration, and both SCr and cysC available before the first vancomycin trough and no earlier than 36 h before the first dose. Individuals with an inconsistent vancomycin dose (outside the first dose to allow for loading) or dosing interval were excluded. Also excluded were those with unstable kidney function defined as any stage of AKI during vancomycin therapy but before the drug level based on Kidney Disease Improving Global Outcomes (KDIGO) creatinine criteria (28). Individuals on renal replacement therapy or those who did not authorize the use of their medical records for research were excluded. Patients from the previous derivation and evaluation studies of the eGFR_{SCr-cysC}-based dosing nomogram were excluded (15, 16).

Throughout the study period, vancomycin dosing and monitoring were predominantly managed by pharmacists who were available on patient care units from 0700 to 2230. AUC-based vancomycin dosing was not used during the study period. Rather, doses were adjusted based on trough levels, collected just prior to the 4th dose. Guideline-recommended weight-based dose ranges were followed (25); however, adjusted body weight (0.4 correction factor) was used for dosing instead of total body weight if the BMI was ≥ 40 kg/m². The standard institutional protocol used eCrCl to estimate kidney function for dosing interval determination.

Definitions. Vancomycin parameters are defined in Table 5. The baseline SCr and cysC values for the study were determined by finding the value closest to that at vancomycin initiation that occurred no earlier than 36 h before vancomycin initiation and preceded the initial steady-state trough. An adequately timed steady-state trough level (Table 5) was defined as a trough level collected with a <25% deviation from the prescribed dosing interval and before the 4th or later dose of a regimen with a constant dosage and a constant interval. As an example, if the dosing interval was 12 h, any trough collected between 9 h and 12 h after the preceding dose would be a <25% deviation and considered acceptable. Any trough between 10 and 20 mg/liter was considered within the target trough range.

Data collection. All data were electronically abstracted from the Mayo Clinic Unified Data Platform (29), with 10% of data manually validated by a member of the study team (H. R. Teaford). Patient demographics (i.e., age, sex, race, height, and weight), level of care (intensive care unit [ICU]

versus general care), and comorbidity burden assessment using the Charlson comorbidity index were recorded. Other collected data included vancomycin dosing information (i.e., dose, interval, and duration), laboratory values (i.e., serum vancomycin levels, SCr, and cysC), and information about potential nonrenal confounders of cysC concentrations (i.e., steroid administrations, thyroxine levels, malignancy, and CRP values). The study goal was to make a parsimonious model of factors commonly used when selecting vancomycin doses or readily available nonrenal factors known to directly impact cysC concentrations.

Vancomycin levels were analyzed using the Syva Emit 2000 vancomycin assay (Siemens Healthcare Diagnostics, Inc., Newark, DE, USA). All observed levels in the cohort were detectable. Creatinine measurement was performed by using the standardized, isotope dilution mass spectrometry (IDMS)-traceable, Roche enzymatic creatinine assay (Roche, Basel, Switzerland). cysC was measured using a particle-enhanced turbidimetric assay (Gentian AS, Moss, Norway). This assay is traceable to the same internationally certified cysC reference material (ERM-DA471/IFCC) used to develop the cysC-based CKD-EPI equations (5).

Validation of the prior nonobese model in this obese cohort. To determine if a separate model for vancomycin troughs is needed in obese versus nonobese patients, our predictive model previously developed in nonobese patients (15) was assessed for its performance in the current cohort. Model features for this analysis included total vancomycin dose (grams), interval, and $eGFR_{SCr-cysC}$ (milliliters per minute) (see Table S2 in the supplemental material). To conform to the design of the nonobese study (15), only patients in the obesity data set who had their trough collected following exactly three doses were included in this validation analysis ($n = 142$).

Data analysis for new models tailored to overweight/obese populations. To develop clinically useful tools for drug dosing, linear regression models were fit for the outcome of the initial vancomycin trough concentration using only predictors available to clinicians at drug initiation. Features were selected *a priori* based upon previous studies (15, 16) and from an assessment of factors that can directly impact cysC levels (corticosteroids, malignancy, elevated CRP, and abnormal thyroxine). Kidney function was estimated in predictive models in several ways. Four previously validated estimation equations were tested, including the CG eCrCl (30) (computed with the actual, ideal, or adjusted [0.4 correction factor] body weights) and the three CKD-EPI eGFR equations ($eGFR_{SCr}$, $eGFR_{cysC}$, or $eGFR_{SCr-cysC}$) (5). The CKD-EPI equations were reexpressed in milliliters per minute by multiplying the result by the body surface area (BSA) derived from the Du Bois formula divided by 1.73 m² (5, 31). Models including eCrCl or eGFR did not include age and sex since these parameters are already included within the estimating equations. The values for SCr and cysC concentrations were also tested as predictors of the vancomycin trough, separate from the calculated eGFRs from these biomarkers. The other core variables tested for inclusion in models to predict trough concentrations were the number of doses prior to a level (i.e., 3 would indicate a trough prior to the 4th dose), the milligrams-per-kilogram maintenance dose using adjusted body weight, weight, the use of a loading dose, and the dosing interval (15, 16). Also, the presence of an elevated CRP level, abnormal thyroxine levels, or systemic (oral or intravenous) steroid administration in the 3 days prior to the cysC level was evaluated, as these factors have been described as non-GFR determinants of cysC in acutely ill hospitalized patients (22). The impact of the addition of these nonrenal determinants was assessed using the likelihood ratio test. Cross-validation was performed on the optimal model (see Appendix S1 in the supplemental material).

To evaluate the performance of models against a clinically useful reference standard, we sought to determine how well the models would predict vancomycin troughs within a target of 10 to 20 mg/liter compared to usual clinical practice. Model residuals were added to the median of the goal trough range (15 mg/liter) to determine the expected trough achievement with the new model, which was compared to the observed initial trough achievement in the cohort (Table 5). The performance of the optimal model was further tested at various BMI thresholds and eGFR cutoffs.

Given emerging recommendations that favor AUC-guided vancomycin monitoring rather than steady-state trough evaluation, we undertook an exploratory secondary analysis to relate observed and expected troughs to observed and expected estimated AUCs (eAUCs), respectively (4). Methods for calculating the vancomycin AUC traditionally require the use of a Bayesian pharmacokinetic model after attainment of one or two serum levels or the application of an equation-based methodology after obtaining two levels. During the study interval, trough-based monitoring was the standard of care, and thus, it was atypical to have multiple, appropriately timed vancomycin levels per patient to retrospectively calculate the AUC. Therefore, for this study, the AUC was estimated using the one-sample trough-only equation (27). Two population estimates of the volume of distribution (V) (0.3 liters/kg total body weight and 0.7 liters/kg total body weight) were used in the equation to provide an eAUC range due to the known variability of this parameter in obesity (2–4). Observed troughs were used to calculate the $eAUC_{observed}$ and the expected troughs from the optimal model were used to calculate the $eAUC_{expected}$ (Table 5). The proportions of obese patients within the target range of 400 to 600 mg · h/liter were numerically compared between the $eAUC_{observed}$ and the $eAUC_{expected}$.

All analyses were performed with JMP version 9 statistical software (SAS Institute, Inc., Cary, NC, USA) or R version 3.6.0 (2019; R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Data availability. Data are available upon request to the corresponding author. The ability to publish data to a public data repository is restricted due to the confidential nature of human subject data.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

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