PHARMACOTHERAPY

ORIGINAL RESEARCH ARTICLES

Modeling Kinetic Glomerular Filtration Rate in Adults with Stable and Unstable Kidney Function: Vancomycin as the Motivating Example

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Background Equations used to estimate kidney function for drug dosing rely on the assumption of homeostasis to translate a single-point measurement of serum creatinine into clearance (CL). Our objective was to rank order the performance of alternate kidney function equations as predictors of drug CL in stable and unstable patients.

Methods Data were extracted from medical records at a single center for all adult patients treated with vancomycin over a 5-year period for population pharmacokinetic analysis. This analysis focused on comparison of nine kidney function equations as covariates of vancomycin CL. Both body surface area (BSA) indexed (ml/min/1.73 m^2) and unindexed units (ml/min) of kidney function were tested, as time-varying and time-invariant covariates of vancomycin CL.

Results The final data set consisted of 2640 patients (62% male, 81% white) with 6628 concentration measurements. The median (5th, 95th percentile) of measurements per patient, age, weight, body mass index (BMI) was 2 (1, 7) concentrations, 61.5 (28, 83) years, 90.0 (56.7, 147) kg, and 30.0 (20.7, 48.0) kg/m^2. Unstable kidney function was documented in 43.6% of patients, primarily as acute kidney injury (AKI) on admission with improvement (19.4%) and AKI during the admission (17.4%). Models based on time-varying kidney function estimates performed better than as time-invariant. Kidney function estimated by the Chen method was ranked higher than other estimation methods.

Conclusions A time-varying kinetic estimated glomerular filtration rate method not indexed to BSA was identified as the highest ranked covariate model of vancomycin CL.

Key Words creatinine clearance, pharmacokinetics, unstable, glomerular filtration rate, antibiotic.

(Pharmacotherapy 2020;40(9):872–879) doi: 10.1002/phar.2442

One in seven individuals in the United States are estimated to have chronic kidney disease (CKD), which by definition develops over several years and can progress to end-stage kidney disease requiring dialysis or transplantation.[1] In contrast, acute kidney injury (AKI) is the sudden and temporary loss of kidney function typically caused by shock, blood or fluid loss, heart failure, nephrotoxic drugs, allergic reactions, injuries, or major surgeries.[2] Drug dosing is adjusted for kidney function impairment typically when a significant portion (> 30%) of the drug is eliminated in urine or if the safety profile is altered.[3] In clinical practice, accurate measurement of kidney function through administration of an exogenous biomarker is not feasible and so requires estimation using endogenous biomarkers such as serum creatinine and cystatin C.[3] Currently, the staging of CKD relies on estimated glomerular filtration rate (eGFR), while drug-dosing adjustment relies on either

Conflict of interest: The authors have declared no conflicts of interest for this article.

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estimated creatinine clearance (eCrCL) or eGFR.[3] The eGFR and eCrCL equations for drug dosing rely on a single-point measurement of serum creatinine. The Modification of Diet in Renal Disease (MDRD) equation and Chronic Kidney Disease–Epidemiology (CKD-EPI) equations are the predominant eGFR methods in adults.[4–6] The Cockcroft-Gault (CG) equation is the predominant method for eCrCL.[7] Although cystatin C improves the precision of kidney function estimation with a modified CKD-EPI function, it is not a widely accessible assay and not included in any product label to guide drug dosing.[8]

Translation of a single-point measurement of serum creatinine into clearance (CL) is based on the assumption of homeostasis, i.e., production or systemic input of creatinine and the rate of creatinine elimination is constant and equivalent.[9] A corollary to this estimation method occurs with continuous infusion drug dosing, where the rate of infusion (Ro) divided by the steady-state concentration (Css) equals clearance (CL). While this assumption may be reasonable in healthy individuals and patients with CKD, it is not for patients with AKI. Two key equations that predate the CG equation, commonly known as the Jelliffe method and Chiou method, were developed in the 1970s and overcome this limitation of single-point assessment by relying on a moving-average method.[10–12] These methods rely on a creatinine volume of distribution estimate of 0.6 L/kg based on ideal body weight (IBW) and estimates of creatinine production based on age, IBW, and gender. A kinetic eGFR method (Chen equation) was introduced in 2013 that is also a moving-average method, which transforms the CKD-EPI results with a weighted maximum change in serum creatinine of 1.5 mg/dl.[13] Recently, use of these dynamic models of kidney function have been shown to be useful for drug-dosing considerations in patients with unstable kidney function.[14, 15] Five decades have transpired since the original introduction of the first eCrCL equation for patients with unstable kidney function.[10–12] The prevalence of obesity is projected to approach 50% in the next decade, and life expectancy increased by an average of 9 years in the United States.[16, 17] Serum creatinine assay methods have also become traceable to an isotopic dilution mass spectrometry standard to reduce variability.[6] Based on these changes in demography and analytical methods, we undertook a reappraisal of existing kidney function equations as covariates of drug CL. Our primary objective was to compare eGFR and eCrCL as covariates of drug CL to rank order the performance of these equations in patients with stable and unstable kidney function. We relied on vancomycin CL as the benchmark for drug clearance because it is primarily eliminated unchanged in urine and undergoes routine monitoring.[18]

Methods

Ethics

This was a retrospective study conducted across the Michigan Medicine enterprise. Institutional review board approval was obtained from the University of Michigan prior to the collection of any patient data.

Design and Study Population

Data were retrospectively obtained from Data-Direct, a self-service clinical database developed and maintained by the University of Michigan. The query time-frame was a 5-year period between January 2015 and December 2019. Subject records were queried if the following criteria were satisfied: (i) patients greater than 18 years of age, (ii) therapy with intravenous vancomycin during the study period, and (iii) measurement of vancomycin concentrations during the course of therapy. Data queried included patient demographics, intravenous vancomycin drug orders and administration times, and laboratory information. Data were password protected and stored on a secure platform maintained by the university. Data manipulation was accomplished using the Python programming language and environment (Python Software Foundation, Wilmington, DE). Subjects were excluded if they met any of the following criteria: (i) incomplete or missing vancomycin dosing or concentration-time information, (ii) lack of documentation or non-physiologically plausible height and/or weight, and (iii) renal replacement therapy (including hemodialysis and continuous renal replacement therapy).

Descriptive Group Stratification

Previous studies have demonstrated varying levels of performance of eCrCL formulas when the serum creatinine is rising versus declining.[19, 20] As a consequence, we categorized

patients in groups to inform the generalizability of our findings. The four groups were: (i) Stable, if the Scr on admission (admScr) was within 20% of the minimum recorded SCr (minSCr) and the maximum recorded Scr (maxScr) was < 1.5-fold of the minSCr; (ii) Declining, if the admSCr was ≥ 1.5-fold of the minSCr and the admScr was within 20% of maxSCr; (iii) Rising, if the maxScr was ≥ 1.5-fold of the admSCr and admScr was within 20% of the minSCr; and (iv) Mixed, individuals with a mixture of stable, rising, and declining profiles. These definitions were based on expected variations of SCr and the Acute Kidney Injury Network criteria for staging SCr changes.[21]

Kidney Function Estimates

Alternative body size scalars including IBW, adjusted body weight (adjBW), and BSA using Mosteller's adaptation were computed as previously described.[22] We calculated eCrCL using the CG equation with total body weight (TBW), IBW, adjBW, and a dosing weight (DW).[7] The DW was based on the principle for use of IBW or TBW if TBW < IBW or adjBW if TBW > 1.25 × IBW. The eCrCL was also estimated using the Jelliffe equation, Chiou equation, and the Chen equation.[11–13] The eGFR was estimated using the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations.[4, 5] The CKD-EPI equation served as the baseline estimate for the Chen equation. Given that these equations generate estimates of kidney function in either ml/minute or BSA-indexed as ml/minute/1.73 m^2 (denoted as Equation$_{BSA}$), we transformed each estimate into both units for all equations. In total, we evaluated 9 equations (18 estimates) for kidney function.

Pharmacokinetic and Statistical Analyses

Pharmacokinetic analyses were performed using Monolix2019R2, and Sycomore2019R2 (Monolix Suite2019R2, Antony, France: Lixoft SAS, 2019). For population PK analysis, the stochastic approximation expectation maximization (SAEM) algorithm was used within Monolix2019R2 and individual vancomycin dosing and concentration time data. The base model was a 1-compartment, zero order input and linear clearance parameterized model structure was selected given the common clinical application of this model and reliance on primarily trough sampled data. The initial volume of distribution (V_d) was based on 0.7 L/kg and fixed to the median weight but included random effects for estimation of inter-individual variability (IIV). The base model was subsequently modified by testing each kidney function estimate as a covariate of CL. Parameters were estimated based on a log-normal distribution. This was tested as a time-invariant covariate, which fixes the kidney function estimate to the first estimated value for each subject and as a time-varying covariate that tests the covariate as a regressor function. This regressor function was set as a simple linear model, typical of the current practice of transforming eCrCL to an estimate of vancomycin CL. Model discrimination was based on the Akaike Information Criterion (AIC), goodness of fit plots, and changes to the residual standard error between models. Models were ranked based on the greatest to smallest change in AIC relative to the base model. Model comparisons were performed using Sycomore2019R2 within the Monolix suite. Nonparametric distribution error checks were performed with each model run through an efficient pipeline process within Monolix2019R2. Descriptive statistical analyses and graphs were produced using Stata version 16 (StataCorp LLC, College Station, TX).

Results

Study Population

A total of 2640 adult patients were identified based on the inclusion and exclusion criteria. Table 1 summarizes the population demographics, body size profile for the entire population as well as by SCr descriptive groups. The majority of patients were male, and the race distribution was 81% white and 13.5% black, which is consistent with the demography of Michigan. The median [min, max] age was 62 [18, 103] years; 75%, 25%, and 7% of the population were over the ages of 50, 70, and 80 years, respectively. The average height was approximately 172 cm with a range of approximately 122–213 cm. The median [min, max] weight was 95 [38, 298] kg with 35% of the population ≥ 100 kg. The median [min, max] body mass index (BMI) was 30.0 [16.5, 99.2] kg/m^2, 50.1% met the definition of obesity (≥ 30 kg/m^2), and 15.5% met the definition of morbid obesity (≥ 40 kg/m^2). The estimated kidney function was reported based on eCrCL and eGFR using the CG_DW and CKD-

Table 1. Demographic, Anthropometric, and Laboratory Variables on Admission for Patients based on Serum Creatinine Over Time Categorization

Variable	Stable (n=1489)	Unstable			Total (n=2640)
		Declining (n=511)	Rising (n=460)	Mixed (n=180)	
Gender (male)	63%	59%	63%	56%	62%
Race					
White	81.8%	80.4%	81.7%	75.6%	81.1%
Black	13.0%	14.5%	12.6%	17.2%	13.5%
Other	5.2%	5.1%	5.7%	7.2%	5.4%
Age (yrs)	61 (16)	58 (15)	58 (16)	56 (17)	59 (16)
Height (cm)	172 (11)	171 (11)	172 (11)	172 (11)	172 (11)
Weight (kg)	94.0 (28.1)	93.4 (28.3)	94.2 (25.9)	94.0 (33.2)	93.9 (28.1)
BMI (kg/m^2)	31.7 (8.8)	31.7 (8.9)	31.9 (8.5)	32.0 (11.4)	31.7 (9.0)
BSA (m^2)	2.10 (0.34)	2.09 (0.34)	2.10 (0.31)	2.09 (0.37)	2.10 (0.34)
SCr (mg/dl)	1.65 (0.96)	1.92 (0.92)	1.15 (0.57)	1.48 (0.92)	1.60 (0.92)
BUN (mg/dl)	36 (23)	44 (26)	26 (16)	33 (21)	36 (23)
Albumin (g/L)	3.2 (0.6)	3.1 (0.7)	3.1 (0.7)	3.2 (0.7)	3.2 (0.6)
eCrCL (ml/min)	63 (39)	52 (31)	88 (53)	74 (44)	66 (43)
eGFR (ml/min/1.73 m^2)	56 (31)	46 (27)	75 (33)	64 (33)	58 (32)

Mean (standard deviation) or percent values at admission.
BMI = body mass index; BSA = body surface area; BUN = blood urea nitrogen; eCrCL = estimated creatinine clearance using Cockcroft-Gault equation with dosing weight; eGFR = estimate glomerular filtration rate using the chronic kidney disease epidemiology equation; SCr = serum creatinine.

EPI equations from the admission SCr. The median [min, max] eGFR was 51 [8, 209] ml/minute/1.73 m^2, and 18%, 23%, 17%, 19%, 19%, and 4% of the population met the incremental CKD staging definitions of > 90, 60–89, 45–59, 30–44, 15–29, and < 15 ml/minute/1.73 m^2, respectively, based on admission SCr. Figure 1 illustrates the fractional change in SCr over time based on stable, declining, rising, and mixed group categorizations. When considering only patients categorized as having stable SCr (n=1489), 61% met the definition of Stage 3a CKD or higher (<60 ml/min/1.73 m^2) comparable to a rate of 59% when considering the entire population without this stability categorization.

Observed Concentration Profile

A total of 6628 vancomycin concentrations were measured and included in the analyses with a median [5th, 95th percentile] of 2 [1, 7] samples per patient. The mean (SD) initial dose was 1264 (323) mg or 14 (3.9) mg/kg. Patients were on multiple dosing regimens. Therefore, Figure 2 includes the distribution of concentrations for patients managed with every 12-hour, every 24-hour, every 48-hour, and every 72-hour regimens. Figure 2 illustrates the measured vancomycin concentration against the time since last dose. As shown, the majority of concentrations collected were > 4 hours from dosing and so represent mid-point and trough measurements.

Pharmacokinetic Analysis

The median [IQR] V_d and CL was 73.2 [60.5, 98.2] L and 0.59 [0.44, 0.85] L/hour for the base model. A two-compartment model structure was also evaluated but did not improve upon the model fit and had a higher AIC. Table 2 provides a summary of the AIC values for the base model (covariate unstructured model) along with the models that incorporated kidney function estimates. As shown, the time-varying models of kidney function had lower AIC values with a median [min, max] difference of −158 [−99, −196] points. Table 2 is organized by highest to lowest reduction in AIC relative to the base model. Kidney function estimates that were not indexed to BSA performed better than those indexed to BSA at 1.73 m^2. The Chen model and Chiou model performed better than all other tested models under both time-varying and time-invariant conditions. Overall, the Chen method applied as a time-varying covariate had the lowest AIC value of all the tested models. To ensure that this rank order was not altered in stable versus unstable patients, we tested this as a binary covariate. The previous rank order was maintained and the AICs for the Chen and Chiou models were 50,198 and 50,213, confirming that the Chen model was the best ranked model. The stability status of any given patient is not consistently knowable a priori and so this stability factor was not incorporated into the final model. Bootstrap analysis with 1000

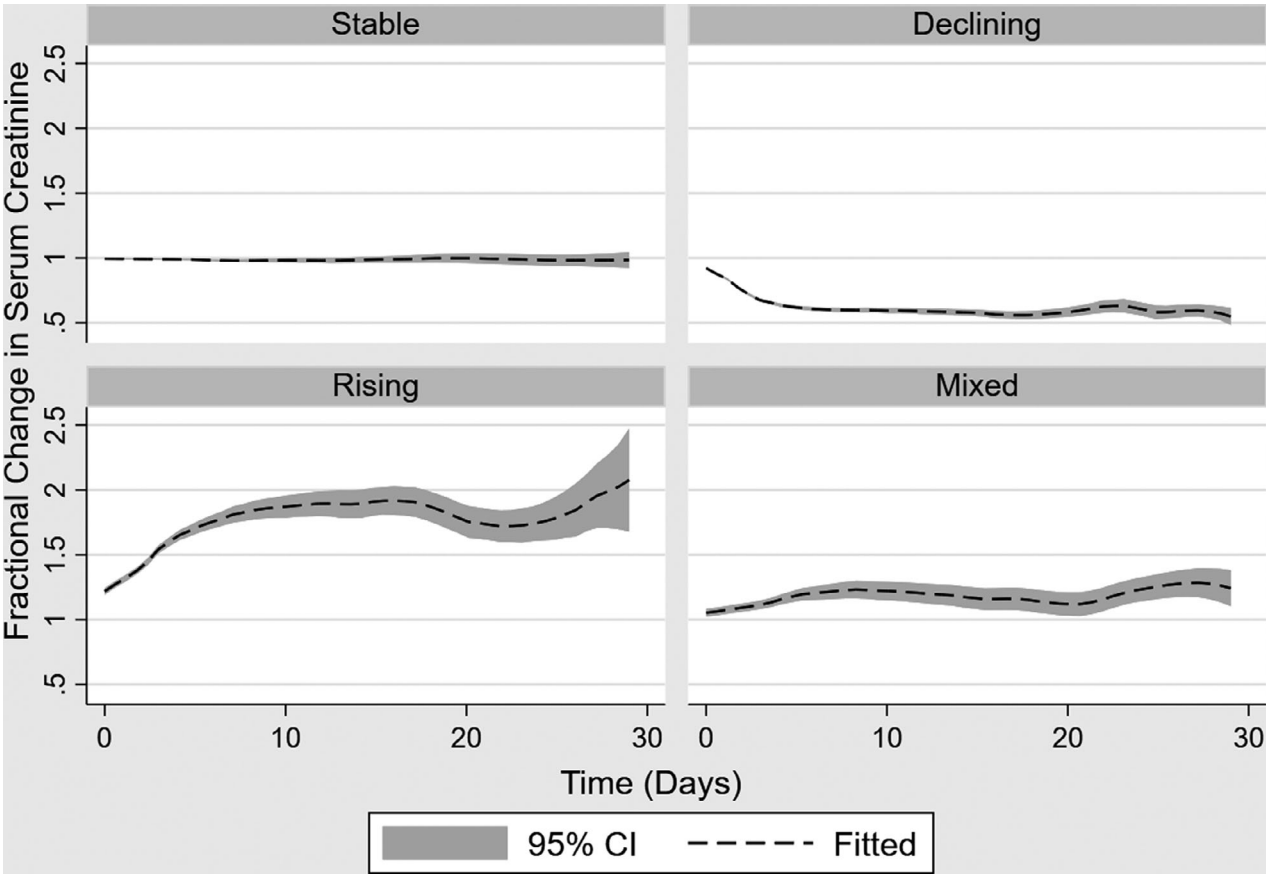

Figure 1. Local polynomial fitted with 95% confidence interval (CI) plot of the fractional change in serum creatinine (weighted to the minimum observed serum creatinine) over time.

bootstrap replicates to obtain 95% confidence intervals for all pharmacokinetic parameters are included in Table 3. The final model provided reasonable internal validity based on NPDE analysis that showed a majority of values within a normal distribution ranging from −2 to 2.

Discussion

Drug dosing based on kidney function is performed routinely in hospitalized patients often using eCrCL based on the CG equation.[3] Electronic health records (EHR) automatically report the eGFR using the MDRD or CKD-EPI equation that is also based on SCr.[6] Although there is much controversy on the selection and interchangeability of these equations for drug dosing, an often overlooked issue is their applicability in patients who are acutely ill. Homeostasis in the generation and elimination of creatinine is required for the use of a single point measurement to be translated into eCrCL or eGFR, which is not consistently the case.[10] We have previously demonstrated in a large cohort of hospitalized patients with infections that AKI is present on admission in 17.5% of cases, and in over half of these cases, kidney function improves.[23] Similarly, the current investigation 511 (19.3%) had elevated SCr that declined during the admission. Overall, in this cohort of vancomycin-treated patients, 43.6% of patients were classified as having unstable kidney function, implying that commonly applied equations that use single-point measurement of SCr may be less reliable for drug dosing.

Two researchers[10, 11] pioneered the first approach to estimation of kidney function in acutely ill and unstable patients. The underlying principles behind this equation was on empirical grounds that required an estimate of creatinine production based on age, gender, and ideal body weight (to reflect skeletal muscle mass).[10, 11] These estimates for creatinine production were based on the data and a V_d estimate of 0.6 L/kg.[24] More contemporary estimates of creatinine production also rely on age, gender, and skeletal

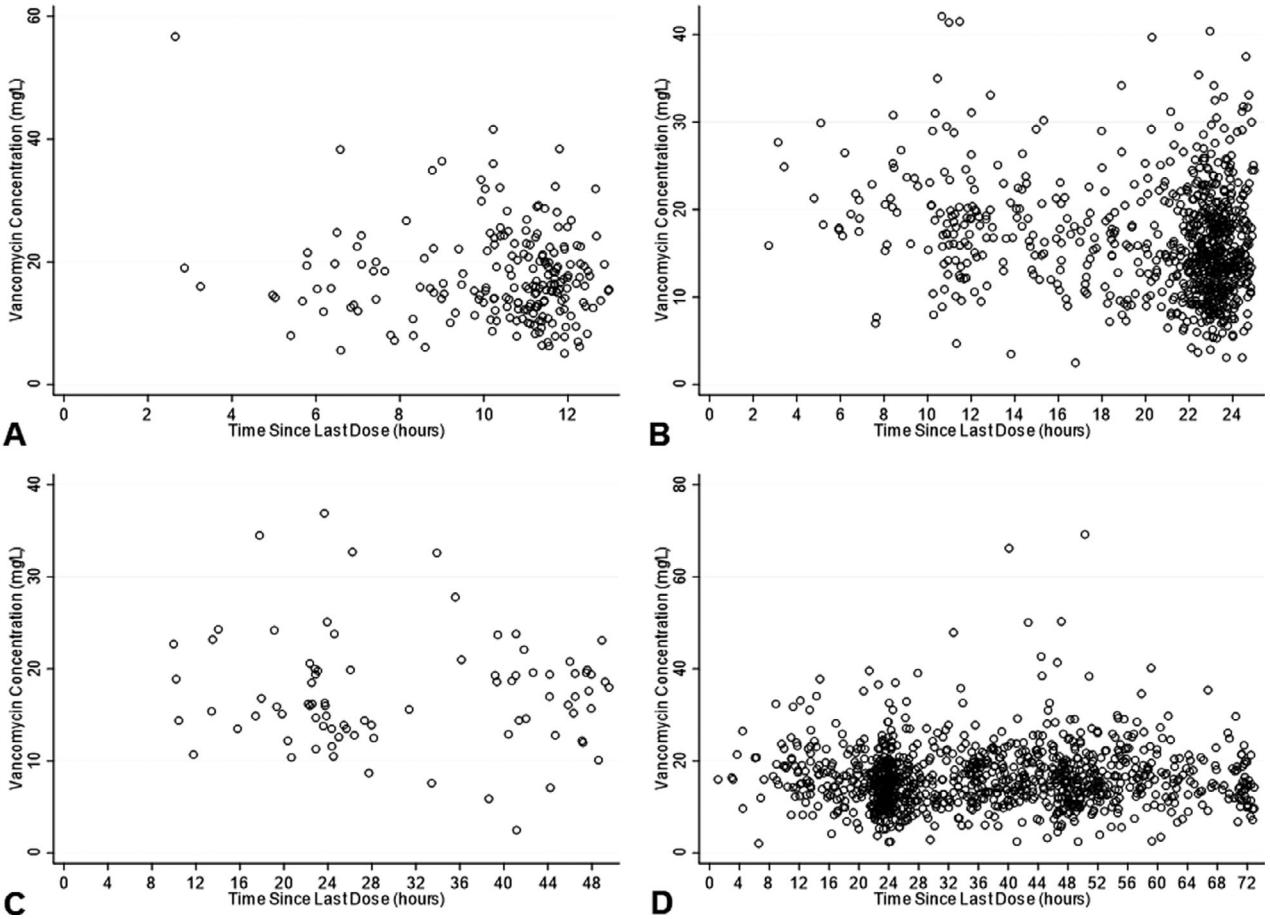

Figure 2. Vancomycin concentrations over the time since last dose stratified by (A) every 12 hr regimen (B) every 24 hr regimen (C) every 48 hr regimen, and (D) every 72 hr regimen.

muscle mass.[25] These principles were later extended to include a small component of nonrenal clearance of creatinine in patients with unstable kidney function.[12] Modeling and simulation exercises using these approaches have nicely demonstrated the time lag between changes in SCr and shifts in kidney function.[26] However, forecasting this time lag is not easy to accomplish in clinical practice as it is dependent on the baseline SCr and an assumption of constant production that also may not be correct in acutely ill patients.[26] The simplest approach undertaken by these methods includes a moving average approach that includes the average of two sequential SCr measurements and the time difference between these measurements.[10–12] Recently, this approach was extended by incorporating a fractional change in eGFR reliant to the maximum expected change in SCr per day of 1.5 mg/dl per day.[13] Details regarding the derivation of this formula and practical use are included in the original publication.[13] Recently, this equation has been applied in practice to illustrate its potential utility for drug dosing in patients with AKI.[14] Furthermore, extended covariate models using the CKD-EPI equation in patients with unstable kidney function have been explored in population PK models of vancomycin.[15] These developments led us to interrogate current kidney function equations in a large cohort of patients treated with vancomycin.

We specifically sought to compare eGFR and eCrCL as covariates of drug clearance in order to rank order the performance of these equations in patients with stable and unstable kidney function. These models were constructed as time-invariant implying use of the initial measurement for the entire time-course. We also tested a time-varying covariate structure and demonstrated that this extension improved the model fit. Our large cohort of subjects supports generalizability of our findings through inclusion of a wide range of age (18–103 yrs), weight

Table 2. Summary of the Akaike Information Criterion (AIC) for each of the Tested Kidney Function Estimated and Compared to the Baseline Model by Largest to Smallest Change in AIC (ΔAIC)

Time-Invariant			Time-Varying		
Model	AIC	ΔAIC	Model	AIC	ΔAIC
Base model	50,530		Base model	50,530	
Chiou (ml/min)	50,388	−142	Chen (ml/min)	50,209	−321
Chen (ml/min)	50,405	−125	Chiou (ml/min)	50,222	−308
CG_TBW (ml/min)	50,415	−115	CG_TBW (ml/min)	50,236	−294
Jelliffe (ml/min)	50,424	−106	Jelliffe (ml/min)	50,250	−280
CKD-EPI (ml/min)	50,430	−100	CG_DW_{BSA} (ml/min/1.73 m^2)	50,352	−178
CG_DW (ml/min)	50,434	−96	CKD-EPI (ml/min)	50,255	−275
$Chiou_{BSA}$ (ml/min/1.73 m^2)	50,438	−92	MDRD (ml/min)	50,265	−265
CG_AdjBW (ml/min)	50,439	−91	CG_DW (ml/min)	50,266	−264
MDRD (ml/min)	50,454	−76	CG_AdjBW (ml/min)	50,276	−254
CG_TBW_{BSA} (ml/min/1.73 m^2)	50,466	−64	Chiou (ml/min)	50,297	−233
$Chen_{BSA}$ (ml/min/1.73 m^2)	50,467	−63	Chen (ml/min)	50,298	−232
CG_IBW (ml/min)	50,473	−57	CG_TBW_{BSA} (ml/min/1.73 m^2)	50,314	−216
$Jelliffe_{BSA}$ (ml/min/1.73 m^2)	50,477	−53	$Jelliffe_{BSA}$ (ml/min/1.73 m^2)	50,326	−204
CG_DW_{BSA} (ml/min/1.73 m^2)	50,489	−41	CG_IBW (ml/min)	50,330	−200
$CKD\text{-}EPI_{BSA}$ (ml/min/1.73 m^2)	50,491	−39	$CKD\text{-}EPI_{BSA}$ (ml/min/1.73 m^2)	50,342	−188
CG_AdjBW_{BSA} (ml/min/1.73 m^2)	50,493	−37	$MDRD_{BSA}$ (ml/min/1.73 m^2)	50,357	−173
$MDRD_{BSA}$ (ml/min/1.73 m^2)	50,502	−28	CG_AdjBW_{BSA} (ml/min/1.73 m^2)	50,360	−170
CG_IBW_{BSA} (ml/min/1.73 m^2)	50,515	−15	CG_IBW_{BSA} (ml/min/1.73 m^2)	50,416	−114

Models labeled by name of author, Chiou, Chen, Jelliffe. A subscript of BSA to denote body surface area indexed values.
CG_AdjBW, Cockcroft-Gault equation using adjusted body weight; CG_DW, Cockcroft-Gault equation using dosing weight; CG_IBW, Cockcroft-Gault equation using ideal body weight; CG_TBW, Cockcroft-Gault equation using total body weight; CKD-EPI, chronic kidney disease epidemiology equation; MDRD, modification of diet in renal disease equation.

Table 3. Parameter Estimates of the Final Model and Bootstrap Analysis of Parameter Estimates

		Bootstrap of Final Model	
Parameter	Final Model	Estimate	95% CI
V_d (L)	66.4 (fixed)		
CL (L/h)			
θ_1	1.03	1.03	1.02–1.05
θ_2	0.737	0.758	0.657–0.863
θ_3	−1.63	−1.69	−1.83 to −1.57
IIV			
θ_1	1.82	1.80	1.64–1.96
θ_2	1.24	1.21	1.12–1.30
θ_3	1.32	1.28	1.18–1.36
Residual variability			
Additional	0.76	0.76	0.73–0.79

CL = clearance; V_d = volume of distribution; For the final model, $CL = \exp(\theta_1 + \theta_2 \times (eGFR/100)) - \theta_3$, where eGFR is the estimated glomerular filtration rate using the Chen equation in ml/min.[13]

(38–103 kg), and BMI (16.5–99.2 kg/m^2). These contemporary age and body size distributions far exceed the populations used to derive prior formulas for kidney function in unstable patients. Despite the largely empiric grounds for their construct, the Chiou equation and Jelliffe equation also performed well in this cohort of patients. The Chen equation ultimately was associated with the lowest AIC and selected as the final model. Paramount to this rank order was our demonstration that estimates of kidney function in absolute units performed better than those indexed to BSA. The underlying limitation and source of error with this indexation has been reviewed.[27]

Our findings have important implications for practice given that kidney function is routinely estimated for drug dosing.[3] We selected the CKD-EPI equation as the baseline estimate for the Chen formula for multiple reasons: (i) a prior study has demonstrated this equation to be better than others tested for estimation of vancomycin CL[14]; (ii) eGFR is automatically outputted in the EHR when SCr is measured and is based on the MDRD or CKD-EPI equation; (iii) the CKD-EPI equation permits estimation across the kidney function spectrum, while the accuracy of the MDRD equation is best for patients with an eGFR < 60 ml/minute/1.73 m^2; (iv) a small modification to the existing EHR output would be needed with use of the Chen formula allowing for improved implementation of future automated dosing protocols; and (v) harmonization of future drug-dosing labels is needed given current inconsistencies.[15,28] Undoubtedly, additional studies are necessary to overcome the limitations of our current analysis before broad application. Increasing measurement of both a peak and trough concentration when dosing vancomycin will allow for reevaluation of our findings by not fixing V_d.[18] Although multiple

samples were measured in patients especially among those with extended dosing intervals, few samples were collected 2–4 hours post infusion. This was our primary reason for having fixed but random effects for V_d. Our findings for kidney function performance may or may not extend to other drugs that are dose adjusted for renal impairment or recovery and requires further study before broad implementation. Finally, our intent was not to develop a new model of vancomycin CL but rather to compare existing renal function models as covariates of drug CL. Therapeutic drug monitoring is widely available for vancomycin and will be the more reliable approach to dosing this agent in patients with unstable kidney function.

Conclusion

A kinetic eGFR estimate based on the Chen equation was ranked above other tested models for estimation of vancomycin CL in patients with stable and unstable kidney function. Use of a time-varying covariate structure was superior to a time-invariant one. Estimates of eGFR perform better in absolute rather than BSA indexed values when estimating drug CL.

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