RESEARCH LETTER

Using KeGFR for Vancomycin Dosing When Renal Clearance Is Acutely Changing: A Simulation Study in a Retrospective Cohort

To the Editor:

The glomerular filtration rate (GFR) is an important determinant of clearance for many commonly used antibiotics. In patients with fluctuating renal function, using the Cockroft-Gault creatinine clearance equation (CGeCrCl), Modification of Diet in Renal Disease (MDRD) estimated GFR, and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) estimated GFR for the purpose of antibiotic dosing is not ideal as these methods are applicable only when the serum creatinine (SCr) level is at a steady state. The kinetic estimated GFR (KeGFR) method has been studied in cohorts with acute kidney injury (AKI) and has been found to be reliable in predicting both the occurrence of and recovery from AKI earlier than the other methods.[1-5] Patients fall into discrepant antibiotic renal dosing categories when KeGFR is used compared with CGeCrCl, but whether KeGFR-based dosing is more likely to provide therapeutic antibiotic levels is not known.[6,7] Subtherapeutic vancomyin trough levels result in inadequate treatment and levels above the therapeutic range can lead to nephrotoxicity. We hypothesized that KeGFR-based vancomycin dosing is more likely to yield therapeutic vancomycin trough levels compared with CGeCrCl-based dosing in patients with fluctuating SCr levels.

From a retrospective cohort of 111 patients with methicillin-resistant *Staphylococcus aureus* bacteremia not on renal replacement therapy treated with at least 1 week of vancomycin, with SCr levels that varied by >5% during the treatment period, 38 patients who had trough levels measured before the second dose due to significantly impaired and fluctuating renal clearance as per hospital protocol formed the study group (Item S1, Fig S1). Predicted troughs using CGeCrCl, KeGFR, MDRD, and nonindexed MDRD were calculated using population pharmacokinetic equations (Item S2) and compared with the true (measured) troughs using Bland-Altman plots for agreement. The mean absolute error and the root mean squared error were calculated for each predicted trough. The dosing frequency was simulated using KeGFR and MDRD based on the hospital vancomycin dosing protocol and the likelihood of achieving the target trough (10-20 mg/L) was estimated empirically for each method (Table S1).

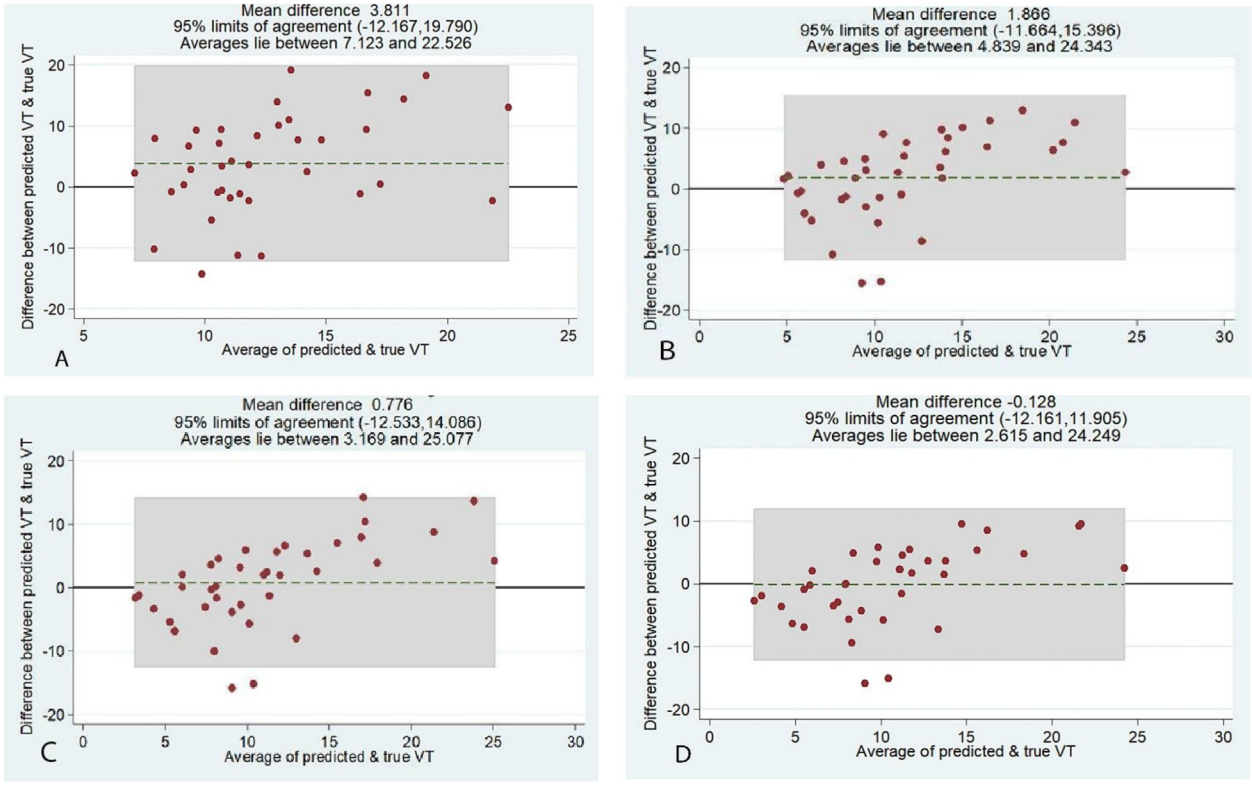

Figure 1. Bland-Altman plots for agreement between predicted vancomycin trough (VT) and true (measured) VT for the GFR-estimating methods. (A) Cockroft-Gault creatinine clearance equation; (B) MDRD eGFR nonindexed to body surface area; (C) MDRD eGFR indexed to body surface area; (D) KeGFR. Dotted lines represent biases (mean difference between the predicted VT and true VT). Shaded areas represent the upper and lower limits of agreement. KeGFR-predicted vancomycin troughs show the best agreement with measured levels. eGFR, estimated glomerular filtration rate; KeGFR, kinetic estimated GFR; MDRD, Modification of Diet in Renal Disease.

Table 1. Prediction Errors of the GFR-Estimating Methods for Vancomycin Trough Levels

eGFR Method Used for PVT	Mean AE (mg/L)	Median AE (mg/L)	RMSE (mg/L)
CGeCrCl	7.2	7.4	8.9
MDRDeGFR (nonindexed)	5.8	5.1	7.1
MDRDeGFR	5.3	4.0	6.8
KeGFR	4.9	4.0	6.1

AE, absolute error; CGeCrCl, Cockroft-Gault creatinine clearance equation; eGFR, estimated glomerular filtration rate; KeGFR, kinetic estimated GFR; MDRD, Modification of Diet in Renal Disease; PVT, predicted vancomycin trough; RMSE, root mean squared error.

Seventeen (45%) patients had subtherapeutic troughs. The median CGeCrCl was 23.3 mL/min (interquartile range, 14.3-30.3), 34% had AKI, and 79% had at least 5% variation in the SCr level.

KeGFR-predicted troughs showed the best agreement with measured troughs, with a mean difference (bias) of −0.128 (Bland-Altman plots). The mean difference was +3.81 for CGeCrCl-predicted troughs and +0.78 for MDRD-predicted troughs (Fig 1 and Fig S2). The mean absolute error and the root mean square error were the least for KeGFR (Table 1).

Table 2. Simulated Dose Frequency Table With Likelihood of Attainment of Therapeutic Range for Vancomycin Troughs

Patients	True Vancomycin Trough	Simulated Dosing Interval in Hours When KeGFR Is Used	Likelihood of Achieving Therapeutic Range When KeGFR Is Used	Simulated Dosing Interval in Hours When MDRD Is Used	Likelihood of Achieving Therapeutic Range When MDRD Is Used
1	4	24>12	High	24>12	High
2	4	48>12	High	48>12	High
3	5	96>48	High	96>48	High
4	6	48>24	High	Unchanged	Low
5	6	Unchanged	Unchanged	Unchanged	Unchanged
6	6	48>12	High	48>12	High
7	6	Unchanged	Unchanged	Unchanged	Unchanged
8	7	48>24	High	48>24	High
9	8	48>24	High	48>24	High
10	8	48>12	High	48>12	High
11	8	24>12	High	24>12	High
12	8	48>24	High	48>24	High
13	9	Unchanged	Unchanged	Unchanged	Unchanged
14	9	Unchanged	Unchanged	Unchanged	Unchanged
15	9	Unchanged	Unchanged	Unchanged	Unchanged
16	9	24>12	High	24>12	High
17	9	Unchanged	Unchanged	Unchanged	Unchanged
18	10	Unchanged	Unchanged	Unchanged	Unchanged
19	10	Unchanged	Unchanged	Unchanged	Unchanged
20	10	Unchanged	Unchanged	24>48	Low
21	11	48>24	Unknown	48>24	Unknown
22	11	96>48	Unknown	96>48	Unknown
23	11	Unchanged	Unchanged	Unchanged	Unchanged
24	11	Unchanged	Unchanged	Unchanged	Unchanged
25	12	Unchanged	Unchanged	Unchanged	Unchanged
26	12	Unchanged	Unchanged	Unchanged	Unchanged
27	12	Unchanged	Unchanged	Unchanged	Unchanged
28	13	Unchanged	Unchanged	Unchanged	Unchanged
29	13	Unchanged	Unchanged	Unchanged	Unchanged
30	13	Unchanged	Unchanged	Unchanged	Unchanged
31	13	Unchanged	Unchanged	Unchanged	Unchanged
32	16	Unchanged	Unchanged	Unchanged	Unchanged
33	17	48>96	Unknown	48>96	Unknown
34	17	Unchanged	Unchanged	24>48	Unknown
35	17	Unchanged	Unchanged	Unchanged	Unchanged
36	17	Unchanged	Unchanged	Unchanged	Unchanged
37	18	Unchanged	Unchanged	Unchanged	Unchanged
38	23	Unchanged	Unchanged	Unchanged	Unchanged

Please see Table S1 for rules followed for assignment of likelihood as high, low, or unchanged. Green font: increased likelihood of attaining the therapeutic range. Red font: unchanged or increased likelihood of not attaining the therapeutic range.
KeGFR, kinetic estimated GFR; MDRD, Modification of Diet in Renal Disease.

In the dose frequency simulation model, 11 of the 17 patients with troughs < 10 mg/L were likely to achieve the target levels when KeGFR was used, compared with 10 patients when MDRD was used and most of these patients required halving of their vancomycin dosing interval (eg, 48-24 hours). Two patients were likely to attain subtherapeutic levels when MDRD-based dosing was used (Table 2).

In this simulation study of acutely ill patients with fluctuating SCr levels of >5% with or without AKI, predicted vancomycin troughs showed better agreement with measured levels when KeGFR was used, compared with those when the traditional GFR estimation methods were used. Patients with subtherapeutic levels were more likely to reach therapeutic trough levels when KeGFR-based simulated dosing intervals were applied, requiring more frequent dosing.

Most patients on vancomycin therapy fail to attain therapeutic trough levels.[8,9] KeGFR can be calculated using 2 consecutive SCr levels. In a pharmacokinetic model, a KeGFR model for vancomycin clearance was ranked highest among other indexed and nonindexed test models, which included CKD-EPI, CGeCrCl, and MDRD, suggesting that KeGFR performed the best in estimating vancomycin clearance.[10] In patients with AKI, discordance in drug dosing categories was more likely than in those without AKI when KeGFR was compared with CGeCrCl and CKD-EPI.[7] In another study comparing KeGFR-predicted troughs with measured troughs in critically ill patients receiving vancomycin, KeGFR-predicted vancomycin troughs diverged the most from the measured vancomycin troughs compared with CGeCrCl.[11] However, the median SCr level in the study was 0.77 mg/dL, and only 14% of the patients had creatinine variability of >0.3 mg/dL, whereas in our cohort, the median creatinine level, incidence of AKI, and creatinine variability were significantly higher (Table S2). As KeGFR better reflects the true GFR when the SCr level is unsteady, KeGFR-based vancomycin dosing may be of use in patients with AKI (Item S3).

Although KeGFR performed better than CGeCrCl, it outperformed MDRD only marginally. It is possible that the creatinine levels were not "kinetic" enough to fully represent the dynamic changes in renal function (Item S4 and Table S3). The small study sample, retrospective nature of the data with potential errors in vancomycin infusion time, sample collection timing, and the use of pharmacokinetic equations before vancomycin reaching a steady state were study limitations. We intend to use KeGFR in a prospective simulation study in patients with AKI to assess the concordance of predicted with measured vancomycin troughs before conducting a randomized clinical trial.

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SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Figure S1: Patient Selection Flowchart.

Figure S2: B-A Plot for Agreement Between Predicted and True Troughs for Nonindexed KeGFR.

Item S1: Study Methodology Details.

Item S2: Methodolgy for Vancomycin Predicted Trough (PVT) Calculation.

Item S3: KeGFT: Its Potential Utility for Drug Dosing.

Item S4: Additional Notes: Discussion and Conclusion.

Table S1: Determination of Attainment of Therapeutic Range With Simulated Dosing Frequencies.

Table S2: Clinical Characteristics of the Whole Cohort and the Study Group.

Table S3: KeGFR Diverges Significantly From Estimates by MDRD and CGeCrC1 in AKI.

ARTICLE INFORMATION

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