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MAJOR ARTICLE

Big Data Bayesian Truths: No Vancomycin Trough Concentration Target Is Sufficiently Precise for Safety or Efficacy

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Introduction. Therapeutic drug monitoring is standard of care for vancomycin because of the known efficacy and safety exposure window (ie, area under the concentration-time curve [AUC] of 400–600 mg × 24 hours/L). Despite guideline recommendations, AUCs are infrequently calculated because of the perceived adequacy of trough (Cmin) concentrations. Yet, the percentage of real-world patients with goal measured vancomycin trough concentrations that achieve target vancomycin AUC remains unknown.

Methods. A large cohort of internationally represented adult patients treated with vancomycin in 2021 and 2022 and therapeutic drug monitoring performed had data anonymized via an electronic clearinghouse at DoseMe. Unique patients, dosing events, and measured Cmin were identified. Patient-individualized AUC was calculated using a Bayesian method with 4 validated models. For each dosing event, Cmin and AUC pairs were compared and categorized as "low," "target," and "high" using the therapeutic ranges for Cmin of 15–20 mg/L and AUC of 400–600 mg × 24 hours/L.

Results. In 2022, 17,711 adult patients from the European Union (4.9%), Australia (4.0%), and the United States (91.1%) had 26 769 measured trough levels obtained. Categorical disagreement between Cmin and AUC was 34.3%, with most disagreement (7959 Cmin levels, 30%) occurring with low Cmin but target AUC. Only 23% of paired Cmin and AUC were within range. AUC was variable for all trough categories (ie, low, target, and high).

Conclusions. These findings support AUC therapeutic drug monitoring and challenge Cmin as an adequate vancomycin AUC proxy. Because no trough concentration or range was sufficiently precise to ensure AUC targets, we suggest direct calculation of AUC.

Keywords. kidney injury; model informed precision dosing; precision dosing; therapeutic drug monitoring; therapeutic window.

BACKGROUND AND INTRODUCTION

Vancomycin, a mainstay antibiotic used in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections, requires therapeutic drug monitoring (TDM) for safety and efficacy. Previously, vancomycin therapeutic targets were based solely on trough concentrations. Specifically, the 2009 Infectious Diseases Society of America (IDSA) guidelines recommended the use of trough levels (targeting 15–20 mg/L) as a surrogate marker of the area under the concentration-time curve (AUC)/minimum inhibitory concentration (target 400 mg × hour/L) for individual dosing and monitoring [1]. More recently, because trough-based approaches resulted in increased kidney injury for both adults and pediatrics [1, 2], the 2020 IDSA guidelines [3] suggested targeting AUCs between 400 and 600 mg × hour/L for MRSA infections in both adults and pediatrics. Controversy exists on the predictive value of troughs for AUCs at the patient level, though projections suggest a high degree of interindividual variability between a measured trough concentration and the actual AUC value [4–6].

Because of the controversy of perceived benefit with AUC calculation, uptake has been modest by practitioners. Trough concentrations, as a single laboratory sample with no mathematical calculations, are perceived to be more easily obtained clinically. A Twitter (now X) survey on May 16, 2023, by author M.S. (@IDPharmacometrx) identified that 52% (518/997 respondents) used trough monitoring as their primary target for vancomycin TDM. Similarly, others have documented discomfort with the initiation of AUC-based guidance [7]. Most respondents (86.7% or 65/75) were uncomfortable changing

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Table 1. 2022 Patient Demographics

Characteristic	Overall, N = 17,711[a]	AU, N = 704[a]	EU, N = 870[a]	US, N = 16,137[a]
Sex				
F	7131 (40.26%)	306 (43.47%)	351 (40.34%)	6474 (40.12%)
M	10 580 (59.74%)	398 (56.53%)	519 (59.66%)	9663 (59.88%)
Age	62 [49,73] (18,95)	55 [40,69] (18,95)	68 [56,78] (19,95)	62 [49,73] (18,95)
Weight (kg)	81 [68,100] (30, 290)	84 [74,95] (40, 269)	72 [60,83] (40, 160)	82 [68,100] (30, 290)
Height (cm)	170 [163,180] (121, 210)	172 [165,180] (150, 197)	168 [160,175] (150, 197)	170 [163,180] (121, 210)
Unknown	5276	321	91	4864

Abbreviations: AU, Australia; EU, European Union; F, female; M, male; US, United States.

[a]N (%); median [25%,75%] (minimum, maximum).

vancomycin doses using AUC monitoring before the transition to an AUC vancomycin protocol, and only 42% of clinicians strongly agreed they were comfortable adjusting doses based on AUC a year later. Conversely, another survey found that 65.7% of respondents had a high awareness and positive perception of the updated IDSA guidelines in using AUC for dosing [8]. As such, there is much variability in practitioner awareness and willingness to employ AUC monitoring, and a significant number of practitioners still rely on trough monitoring. This study sought to use a large cohort of internationally represented patients to assess the relationship between measured vancomycin trough concentrations and precisely calculated AUCs.

METHODS

Patient Population and Data Collection

Adult patients from the United States, Australia, and the European Union treated with vancomycin between 2021 and 2022 and had TDM performed as part of [9] routine clinical care had data collected and anonymized via an electronic clearinghouse. All personally identifiable information, including names, dates of birth, and medical record numbers were removed, and date of treatment was anonymized. Additionally, the precision of geolocation data for the treatment locations was reduced to the continent level. Unique patients, dosing events, and trough concentrations (Cmin) were identified. Measured Cmin within 2 hours of the next scheduled dose were included. Patient-individualized AUC was calculated with a Bayesian method applied to 4 validated models [9–12] using DoseMeRx software (version 4.0.26 [v1.16.3], Brisbane, Australia). The individual model used for each patient was selected by the practitioner at the time of dosing. Patients without plasma concentrations, with hemodialysis, or with treatment duration shorter than 1 day were excluded. Summary statistics for patient demographics were calculated.

Data Analysis

Data were split into a primary analysis and 3 sensitivity analyses for confirmation. The primary analysis included 2022 data for patients that had trough levels measured within 2 hours of a vancomycin dose. We also performed the following sensitivity analyses to see if results were similar across years and if a more stringent time for trough impacted findings. The sensitivity analyses were: (1) 2021 data with measured troughs within 2 hours (compared to 2022 data with measured trough levels within 2 hours of a dose), (2) 2021 data with measured troughs within 0.5 hours (compared to 2022 data with measured trough levels within 2 hours of a dose), and (3) 2022 data with measured troughs within 0.5 hours (compared to 2021 data with measured troughs within 0.5 hours). In each analysis and for each dosing event, the paired Cmin and AUC24 were compared and categorically classified as "low," "target," and "high" based on predetermined thresholds (ie, 15–20 mg/L for trough and 400–600 mg × 24 hours/L for AUC).

A linear regression model was fitted in R version 4.2.3 using AUC by trough data to explore the relationship between trough concentrations and AUC. The adjusted R^2 was computed to assess the goodness of fit of the regression model. Furthermore, a 95% prediction interval was computed and plotted on the AUC by trough scatter plot to visualize the variability and uncertainty in the relationship (ie, what is the range of AUCs for any given interval trough concentration?). Inferential statistics for categorical analysis were analyzed with Pearson chi-squared test.

RESULTS

Primary Analysis

In the primary analysis completed for the year 2022, a total of 17 711 adult patients from the United States (91.1%), the European Union (4.9%), and Australia (4.0%) were included. Approximately 40% of the overall population was female. From these patients, 26 769 unique dosing events occurred with data available for paired-measured Cmin and AUC included. The median age was 62 years, and the median weight and height were 81 kg and 170 cm, respectively (Table 1). Most vancomycin AUCs were calculated by the Buelga Bayesian method at 79%, followed by the Sabourenkov model (13%) (Table 2). Of the total number of dosing events, 17 347

Table 2. 2022 Dose Outcome Summary

Characteristic	Overall, N = 26,769[a]	AU, N = 1,302[a]	EU, N = 2,879[a]	US, N = 22,588[a]
Model				
Adane	44 (0.16%)	43 (3.30%)	0 (0.00%)	1 (0.00%)
Buelga	21,210 (79.23%)	861 (66.13%)	2857 (99.24%)	17 492 (77.44%)
Goti	2003 (7.48%)	275 (21.12%)	20 (0.69%)	1708 (7.56%)
Sabourenkov	3512 (13.12%)	123 (9.45%)	2 (0.07%)	3387 (14.99%)
Trough level	13.8 [10.4,17.7] (0.8, 80.0)	16.0 [12.5,20.0] (3.0, 50.0)	16.6 [13.0,20.0] (1.5, 80.0)	13.4 [10.2,17.1] (0.8, 71.6)
Cmin	13.2 [10.3,16.6] (0.4, 52.4)	15.1 [12.0,19.2] (3.3, 46.2)	16.8 [13.4,20.5] (2.3, 52.4)	12.7 [10.0,15.9] (0.4, 50.6)
AUC24	442 [369,524] (85, 1405)	494 [424,582] (108, 1310)	529 [445,616] (120, 1405)	432 [361,506] (85, 1367)

Abbreviations: AU, Australia; AUC, area under the curve; Cmin, perceived adequacy of trough concentrations; EU, European Union; US, United States.
[a]N (%); median [25%, 75%] (minimum, maximum).

Table 3. 2022 Measured Troughs Within 2 Hours of Dose vs AUC24 Outcome Categories

	AUC24 Status			
	High	In Range	Low	*P*[a]
Trough status	…	…	…	<.001
High	2089 (7.8%)	1544 (5.8%)	37 (0.1%)	
In range	674 (2.5%)	6498 (24.3%)	420 (1.6%)	
Low	169 (0.6%)	6578 (24.6%)	8760 (32.7%)	

Abbreviation: AUC, area under the curve.
[a]Pearson chi-squared test.

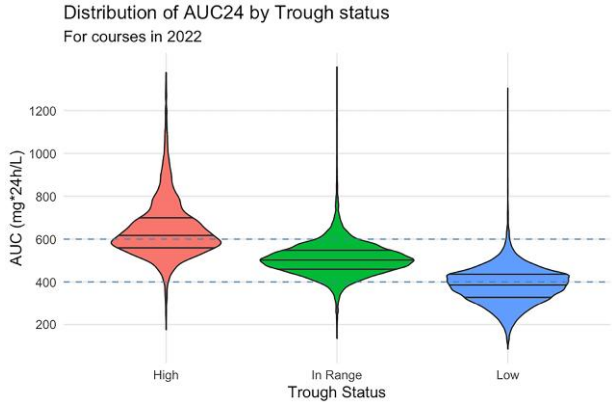

Figure 1. 2022 Violin plot of Cmin versus AUC24 categories. AUC, area under the curve; Cmin, perceived adequacy of trough concentrations.

events (64.8%) had matching Cmin and AUC, whereas the remaining 9422 events (35.2%) had categorical discordance between the Cmin and AUC status (Table 3). Most of the categorical disagreement occurred with events that had a low Cmin but AUC at target (6578 dosing events, 25%). Only 6498 (24%) of paired Cmin and AUC were simultaneously at target per the 2020 IDSA guidelines for MRSA infection ($P < .001$). AUC was highly variable for all trough categories (ie, low, target, and high; Figure 1).

The AUC by Cmin linear regression result was as follows: AUC24 = 185.32+ (18.65 × Cmin) with an adjusted $R^2 = 0.667$. From this equation, the predicted AUC and 95% confidence interval (CI) for the mean at Cmin = 12 mg/L was 409.13 (95% CI, 408.1–410.1) mg × 24 hours/L. However, the 95% prediction interval for the individual was 260.0 to 558.3 mg × 24 hours/L, highlighting the variability and uncertainty in the relationship between trough concentrations and AUC (Figure 2) at the individual level versus the population mean.

Sensitivity Analyses

In the sensitivity analysis for patients who had measured troughs within 2 hours of a dose in the year 2021, 20,874 unique dosing events occurred with data for paired and measured Cmin and AUC. Of the total number of unique doses, 13 477 events (64.6%) had matching Cmin and AUC, whereas the remaining 7397 events (35.4%) had categorical discordance between the Cmin and AUC status (Table 4). The majority of the categorical disagreement occurred with a low Cmin but AUC at target (25%). In comparing the measured troughs obtained within 2 hours of a dose for both 2022 and 2021 (sensitivity analysis 1), the overall percentage of categorical discordance decreased marginally by 0.2% (from 35.4% in 2021 to 35.2% in 2022). The overall percentage of categorical agreement increased marginally by 0.2% (from 64.6% in 2021 to 64.8% in 2022). All individual Cmin and AUC pairs had marginal differences (Table 5), but the largest individual pairing difference was for Cmin and AUC both at target with an increase in 0.7% (from 23.6% in 2021 to 24.3% in 2022).

When restricting trough levels to those measured within 0.5 hours of the next dose in 2021, 8651 unique dosing events occurred with data for paired and measured Cmin and AUC. Of the total number of unique doses, 5260 events (60.8%) had matching Cmin and AUC, whereas the remaining 3391 events (39.2%) had categorical discordance between the Cmin and AUC status (Table 6). The majority of the categorical disagreement occurred with a low Cmin but AUC at target (26.5%). In

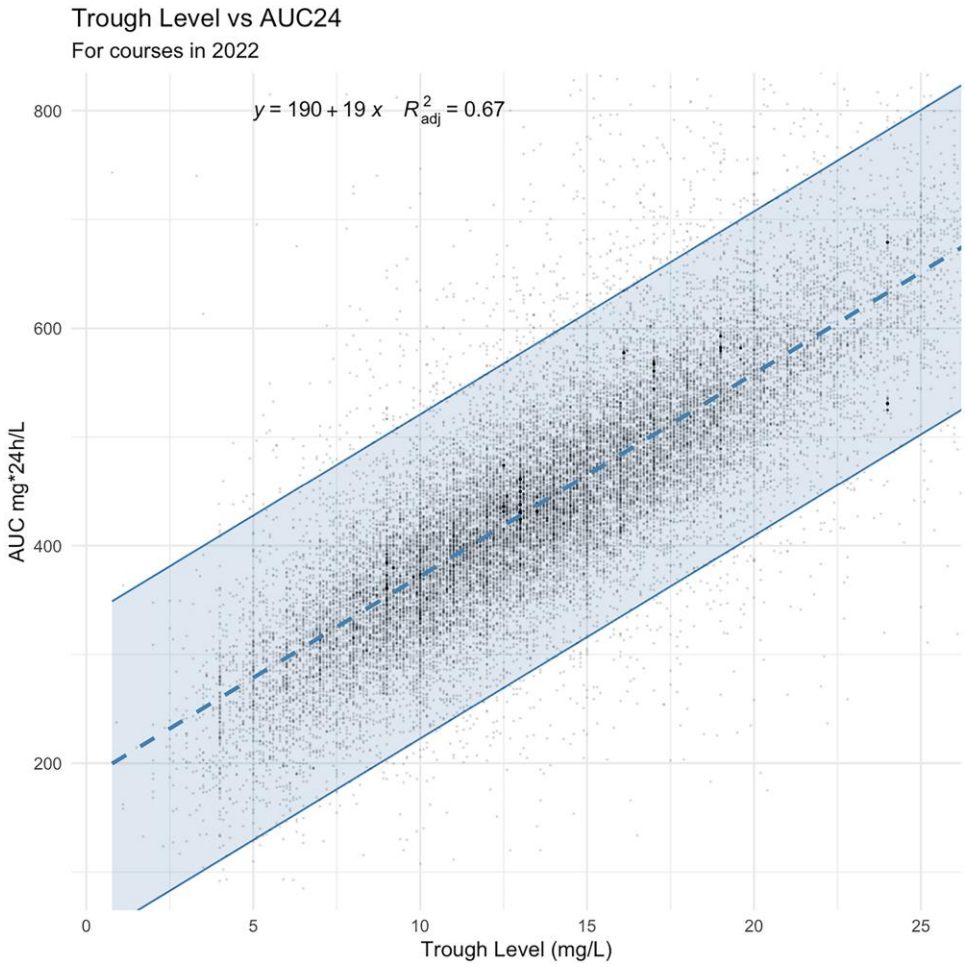

Figure 2. 2022 Prediction interval for AUC at incremental measured Cmin concentrations. AUC, area under the curve; Cmin, perceived adequacy of trough concentrations.

Table 4. 2021 Measured Troughs Within 2 Hours of a Dose vs AUC24 Outcome Categories

	AUC24 Status			
	High	In Range	Low	*P*[a]
Trough status	…	…	…	<.001
High	1708 (8.2%)	1077 (5.2%)	36 (0.2%)	
In range	619 (2.9%)	4919 (23.6%)	318 (1.5%)	
Low	129 (0.6%)	5218 (25%)	6850 (32.8%)	

Abbreviation: AUC, area under the curve.

[a]Pearson chi-squared test.

Table 5. Percentage Difference for 2022 vs 2021 Measured Troughs Within 2 Hours

	AUC24 Status		
	High	In Range	Low
Trough status			
High	−0.4%	0.6%	−0.1%
In range	−0.4%	0.7%	0.1%
Low	0%	−0.4%	0.1%

Abbreviation: AUC, area under the curve.

comparing the measured troughs obtained within 2 hours in 2022 versus measured troughs obtained within 0.5 hours in 2021 (sensitivity analysis 2), the overall percentage of categorical discordance decreased by 4% (from 39.2% in 2021 to 35.2% in 2022). The overall percentage of categorical agreement increased by 4% (from 60.8% in 2021 to 64.8% in 2022). There were variable differences in the individual Cmin and AUC pairings (Table 7). The largest difference was for Cmin and AUC both at low concentrations which increased by 4.7% (from 28% in 2021 to 32.7% in 2022).

Data were also obtained for measured troughs within 0.5 hours of the next dose in 2022. A total of 9985 unique dosing events occurred with data for paired and measured Cmin and AUC. Of the total number of unique doses, 5998 events

Table 6. 2021 Measured Troughs Within 0.5 Hours of Dose vs AUC24 Outcome Categories

	AUC24 Status			
	High	In Range	Low	P^a
Trough status	…	…	…	<.001
High	907 (10.5%)	475 (5.5%)	22 (0.3%)	
In range	379 (4.4%)	1928 (22.3%)	132 (1.5%)	
Low	89 (1%)	2294 (26.5%)	2425 (28%)	

Abbreviation: AUC, area under the curve.

[a]Pearson chi-squared test.

Table 8. 2022 Measured Troughs Within 0.5 Hours of Dose vs AUC24 Outcome Categories

	AUC24 Status			
	High	In Range	Low	P^a
Trough status	…	…	…	<.001
High	1017 (10.2%)	664 (6.6%)	13 (0.1%)	
In range	376 (3.8%)	2372 (23.8%)	132 (1.3%)	
Low	108 (1.1%)	2694 (27%)	2609 (26.1%)	

Abbreviation: AUC, area under the curve.

[a]Pearson chi-squared test.

Table 7. Percentage Difference for 2022 Measured Troughs Within 2 Hours vs 2021 Measured Troughs Within 0.5 Hours

	AUC24 Status		
	High	In Range	Low
Trough status			
High	−2.7%	0.3%	−0.2%
In range	−1.9%	2%	0.1%
Low	−0.4%	−1.9%	4.7%

Abbreviation: AUC, area under the curve.

Table 9. Percentage Difference for 2022 vs 2021 Measured Troughs Within 0.5 Hours

	AUC24 Status		
	High	In Range	Low
Trough status			
High	−0.3%	1.1%	−0.2%
In range	−0.6%	1.5%	−0.2%
Low	0.1%	0.5%	−1.9%

Abbreviation: AUC, area under the curve.

(60.1%) had matching Cmin and AUC, whereas the remaining 3987 events (39.9%) had categorical discordance between the Cmin and AUC status (Table 8). The majority of the categorical disagreement occurred with a low Cmin but AUC at target (27%). In comparing the measured troughs obtained within 0.5 hours of a dose for both 2022 and 2021 (sensitivity analysis 3), the overall percentage of categorical discordance marginally increased by 0.7% (from 39.2% in 2021 to 39.9% in 2022). The overall percentage of categorical agreement marginally decreased by 0.7% (from 60.8% in 2021 to 60.1% in 2022). Individual Cmin and AUC pairings were variable (Table 9), and the largest difference was for Cmin and AUC both at low concentrations, which decreased by 1.9% (from 28% in 2021 to 26.1% in 2022). The individual Cmin and AUC pairing that had the most difference in categorical disagreement was a high Cmin but in range AUC (1.1% increase from 2021 to 2022).

DISCUSSION

Our findings suggest that real-world vancomycin trough concentrations do not correlate well with an individual's vancomycin AUC. For any given measured vancomycin trough concentration, a large range of AUCs is possible. For instance, the 95% prediction interval for a trough that is exactly 15 mg/L is 369–578 mg/L × 24 hours, whereas a trough that is exactly 10 mg/L is 254–463 mg/L × 24 hours. Notably, 95% CIs for the mean are less meaningful at the individual patient level, whereas the prediction interval (Figure 2) provides the 95% range of AUCs that can be expected for any individual patient with a measured trough concentration. Ranges spanning 200 mg/L × 24 hours for any given trough concentration are not sufficiently precise for clinical care of the individual, and results at the individual level are critically important. Our results agree with previous studies that have shown there is a discordance between the trough concentrations and the AUC levels of vancomycin through simulation [6]. This analysis, however, is the first to use real-world patients with highly precise estimates of vancomycin AUC exposures and measured trough concentrations.

Previous research has clearly identified that vancomycin AUC is the driver of vancomycin-induced kidney injury, both in animal studies [13] and clinical studies [14, 15]. The contemporary vancomycin-monitoring guidelines [3] thus focus on AUC targets for patient safety. It has been demonstrated that AUCs >600 are associated with the highest kidney injury [16, 17]; however, toxicity is a direct function of exposure and increasing risk exists for each increasing amount of exposure [18]. To this end, multiple studies have previously shown that using vancomycin AUC targets rather than trough targets results in less kidney injury for patients [19–21]. Presumably, the reason that AUC target strategies lessen kidney injury is that (1) patients receive less vancomycin with these strategies [22] and (2) troughs are imprecise estimates of AUC, as we have shown here. Indeed, the maintenance of trough concentrations between in the 15–20 mg/L range results in greater

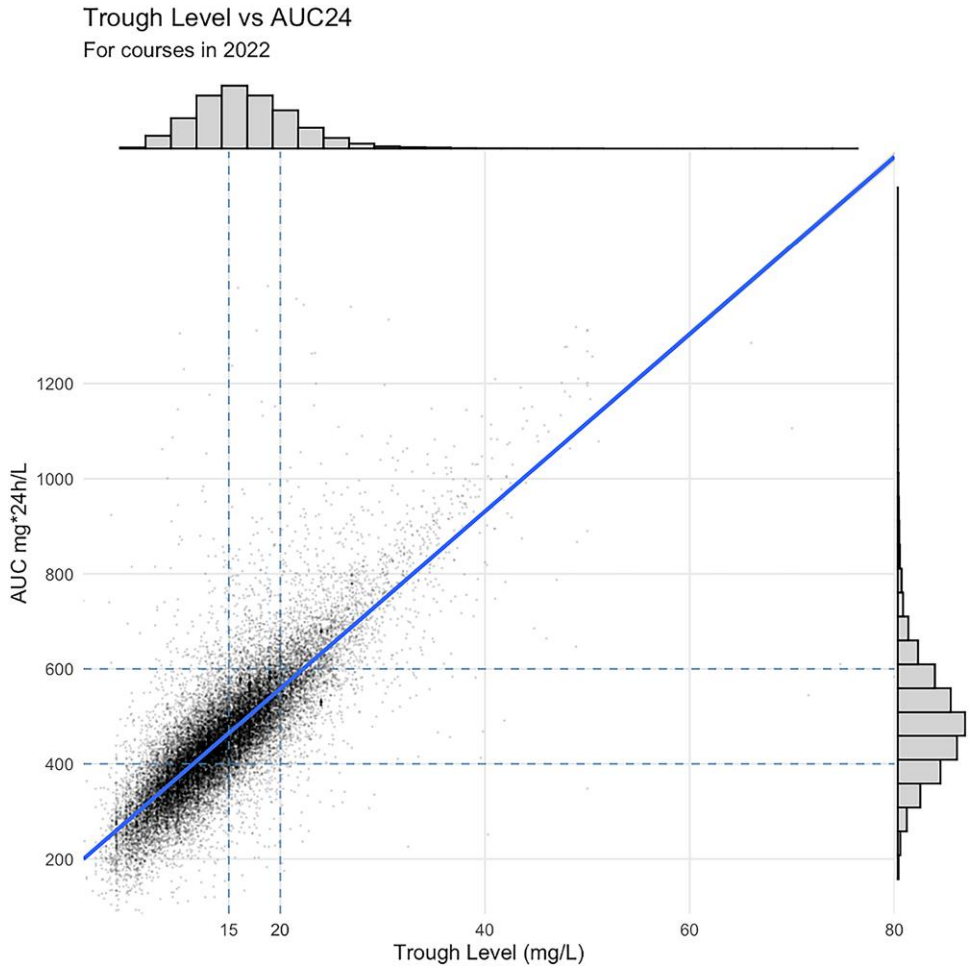

Figure 3. 2022 Scatter plot with marginal histograms, vancomycin AUC versus Cmin. AUC, area under the curve; Cmin, perceived adequacy of trough concentrations.

acute kidney injury [2]. In our data, an exact trough of 20 mg/L resulted in a 95% prediction interval range AUC of 483–692 mg/L × 24 hours. This trough target was initially selected because population models suggested a higher probability of achieving an AUC/minimum inhibitory concentration ratio > 400 for *S. aureus* isolates [23–25].

The use of vancomycin trough concentrations as a surrogate for AUC has been a longstanding topic of debate [5, 26, 27]. The argument for using trough concentrations rather than AUC is that troughs are suggested to correspond to reasonably precise AUCs and that obtaining a trough concentration is perceived as simple, convenient, and inexpensive. Some have suggested that AUC calculations are more time consuming and can require more than a single concentration if Bayesian-based software is not used.

In our analysis, we categorically selected a goal trough range of 15–20 mg/L and an AUC range of 400–600 mg/L × 24 hours as the points for comparison but any categorical comparison could be made. For these categories, we found that the categorical disagreement between Cmin and AUC was 35.6%, with most disagreement (6578 dosing events, 25%) occurring within the low Cmin but with AUC at target category. It is notable that only 64.8% of paired Cmin and AUC dosing events were in direct agreement whether it be both at target, high, or low. Perhaps more important than any single categorical comparison, our data demonstrate relatively high variability at the individual level. Often, however, arguments are made based on measures of central tendency (eg, mean relationships) though these are less relevant to the individual patient). Based on the regression equation (ie, AUC24 = 185.32+ [18.65 × Cmin]), the 95% CI for the AUC based on a mean trough of 12 mg/L ranges from 408.1 to 410.1 mg/L × 24 hours, which is a narrow interval for the confidence level surrounding the mean. However, the 95% prediction interval for a trough of 12 mg/L is AUC is 260.0 to 558.3 mg × 24 hours/L. That is, for the individual patient, a trough of 12 mg/L is expected to result in AUCs that range from 260.0 to 558.3 mg/L × 24 hours in 95% of cases. Thus, trough concentration monitoring may be appropriate if clinicians are able to maintain troughs within a range of ±1 mg/L; however, this is far from clinically feasible.

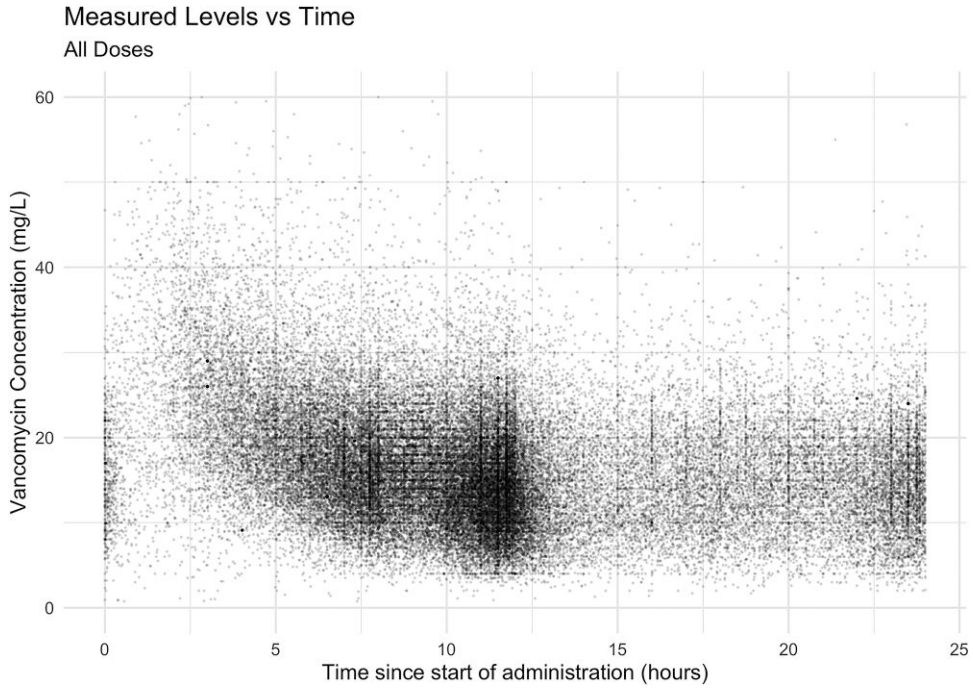

Figure 4. 2022 Time after dose for all doses given.

Our results from this analysis show that there remains a large number of instances with high discordance between the Cmin and the AUC (Figure 3).

Estimates for AUC were provided from 4 validated models, which were selected and used by individual practitioners at the time of Bayesian AUC calculation. These models include Buelga et al [9], Sabourenkov et al [12], Goti et al [11], and Adane et al [10]. The Buelga model [9] is a 1-compartment first-order elimination model with total body weight (TBW) and creatinine clearance as covariates. It includes noncritically ill patients, making it well equipped for the patients represented in this analysis. The Sabourenkov model [12] is a 1-compartment 0-order absorption model with ideal body weight modifying the volume of distribution (Vd), and creatinine clearance (CrCl) modifying clearance (CL) as covariates. This model was developed from and validated with obese patients from all 3 body mass index classes, making it well-equipped to dose all 3 body mass index classes with low bias. The Goti model [11] is a 2-compartment 0-order absorption model with TBW and hemodialysis status modifying Vd, as well as CrCl based on TBW and hemodialysis status modifying CL as covariates. The fourth and final model used is Adane [10]. This is a 1-compartment, 0-order absorption model. TBW and CrCl normalized to body surface area are modifiers for the Vd and CL, respectively. The patient cohort is inclusive of class III obesity patients.

Our analysis is subject to several limitations. First, our study population was largely from the United States but we did have representation from the European Union and Australia. Second, we used DoseMeRx software for this analysis and Bayesian posteriors for the AUC. It is extremely likely that completing the analysis with a different software program would produce slightly different results (depending on the pharmacokinetic model used); yet, it is unlikely that different software would demonstrate low variability between trough and AUC. Third, we restricted our primary analysis to a single year of data (ie, 2022). We did this to hold time-relevant changes in medicine constant and because we had an extremely large number of dosing events available within a single year (ie, ~27 000 unique events). Our sensitivity analysis revealed similar relationships when considering the year 2021. Fourth, because this analysis uses a Bayesian calculation on mostly trough concentrations, it is possible the AUC may not match the "true" AUC as measured in richly sampled situations. However, we believe our estimate of the AUC is clinically accurate. To assess if we were subjected to bias from only including trough concentrations, we investigated the times at which a concentration was drawn after a dose was given. This can be seen in our time after dose plot for samples obtained in 2022 (Figure 4). As can be visually appreciated, much of our data are obtained around 12 hours (trough); however, a large number of samples are obtained throughout the dosing interval. Thus, our model was derived from many concentrations that were not troughs alone. We also performed a subanalysis in which we restricted the analyzed 2022 data to patients with at least 2 measurements

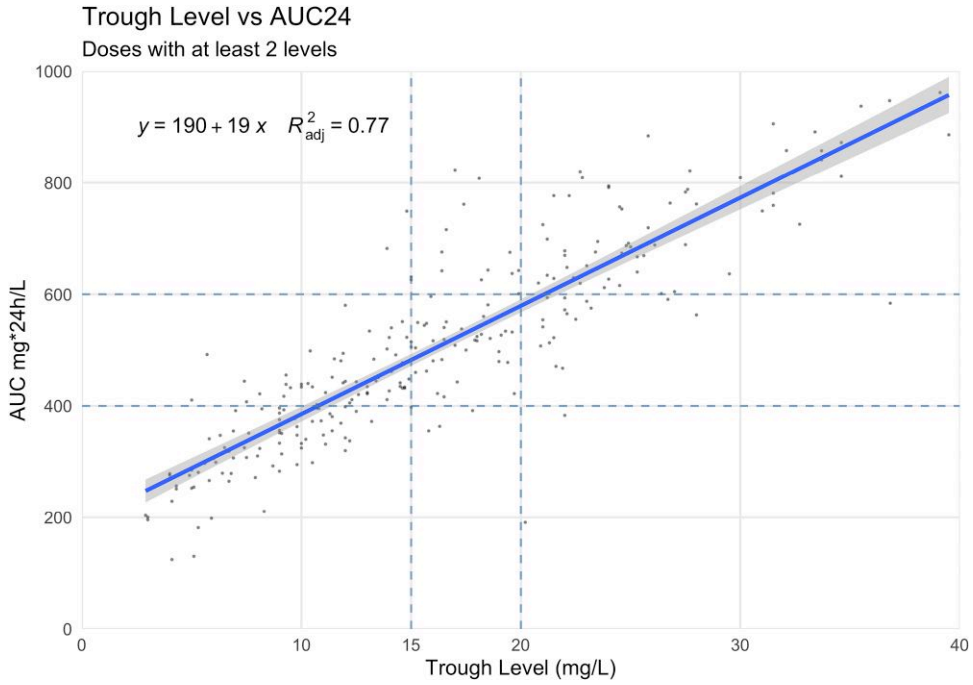

Figure 5. Trough level versus AUC24 for doses with at least 2 concentrations drawn on a single time curve. AUC, area under the curve.

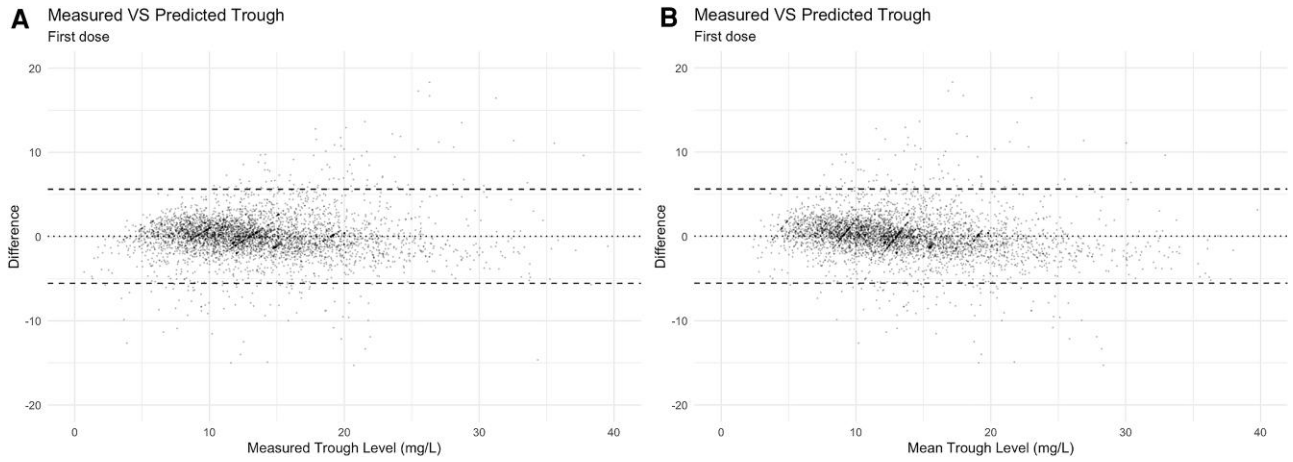

Figure 6. Bias assessment plots for the first dose only. *A*, Difference of measured—predicted versus measured trough for the first dose. *B*, Difference of measured—predicted versus measured mean of measured and predicted trough for the first dose.

during the same dosing interval to understand if single concentrations resulted in bias. We then compared the relationship between model predicted trough and AUC over 24 hours in only patients that had 2 concentrations drawn on a single time curve (Figure 5). When compared to the full dataset (Figure 2), results are isometric. We then sought to see if measured trough concentrations were well predicted. For this, we created modified Bland Altman plots (ie, the residual [the difference of the measured trough within 0.5 hours of the next dose minus the predicted trough]) versus measured trough and Bland Altman plots (ie, residual of the measured and predicted values vs the average of the measured and predicted values) for both first dose (Figure 6) and steady state (Figure 7). These plots demonstrate low bias between measured and predicted concentrations used to calculate the AUC. Finally, we are not the first to look at these relationships [6]. Our analysis is unique in that we have paired actual trough data (not simulated) and we interrogated a large multinational database.

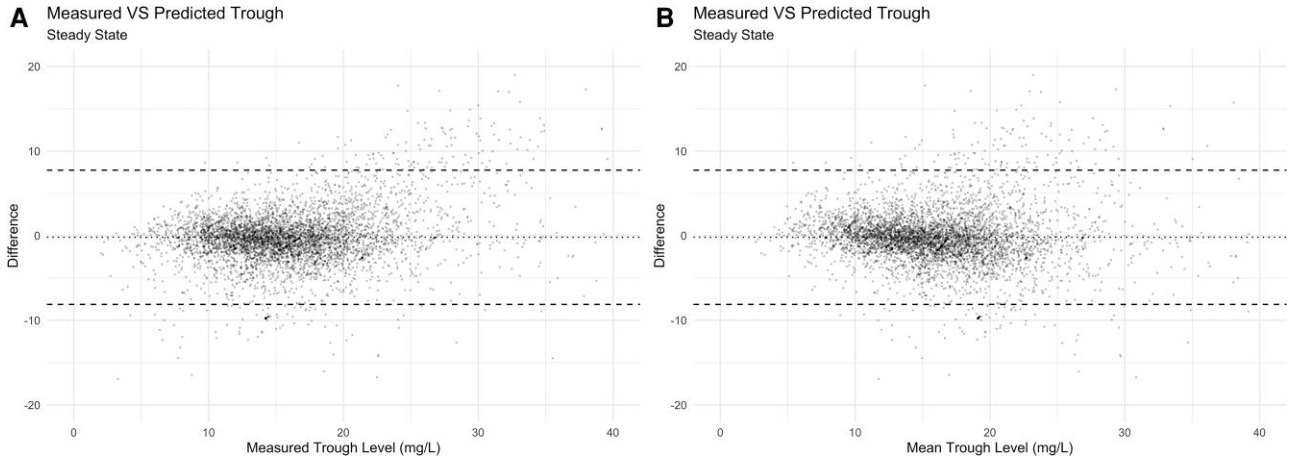

Figure 7. Bias assessment plots at steady state. *A*, Difference of measured—predicted versus measured trough at steady state. *B*, Difference of measured—predicted versus mean of measured and predicted trough at steady state.

These results are important as AUC best links to toxicity outcomes in many clinical studies [14, 28] as well as animal outcomes [29, 30]. The animal studies provide especially convincing evidence given that there are no other clinical confounders.

CONCLUSIONS

Trough concentrations resulted in frequent misclassification of AUC category, with troughs <15 mg/L frequently resulting in AUCs > 400 mg × 24 hours/L. No clinically used range of trough concentrations resulted in sufficiently precise vancomycin AUCs. These findings support AUC TDM and challenge the historic use of Cmin as an adequate proxy for vancomycin AUC. These findings have important clinical implications as low Cmin often compels clinicians to increase doses, and unnecessarily high AUCs have clearly been linked to increased kidney injury.

Notes

Author Contributions. J.S., S.R., P.S., and M.S. wrote the manuscript; S.R., P.S., and M.S. designed the research; S.R., P.S., and M.S. performed the research; S.R., P.S., and M.S. analyzed the data; S.R., P.S., and M.S. contributed new reagents/analytical tools.

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Patient consent. Our study does not include factors necessitating patient consent. The Midwestern University institutional review board determined that analysis of deidentified data in this project did not meet the definition of human subjects' research as defined in 45 CFR 46.102.

Potential conflicts of interest. M.S. serves on the advisory board for DoseMe. S.R. and P.S. are employees of DoseMe. J.S. has no relevant conflicts of interest.

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