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ORIGINAL RESEARCH

Are All Pharmacokinetic Equations Created Equal? A Comparative Analysis of Trapezoidal and Non-Trapezoidal Methods for Estimating Day 1 Area Under the Curve in Adult Hospitalized Patients with *Staphylococcus aureus* Bacteremia

Abdulwhab Shremo Msdi · Alireza Fakhri Ravari · Jacinda C. Abdul-Mutakabbir · Karen K. Tan

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ABSTRACT

Introduction: This study compared the calculated vancomycin area under the curve ($AUC_{0–24}$) using trapezoidal and non-trapezoidal first-order pharmacokinetic equations.

Methods: This retrospective observational study included adult patients with documented MRSA bacteremia who received ≥ 48 h of intravenous vancomycin and had two consecutive serum levels after the first dose. $AUC_{0–24}$ was calculated using trapezoidal and non-trapezoidal equations. Correlation and agreement between methods were assessed using Pearson's correlation coefficient (*r*) and Bland–Altman plots. Significant predictors ($p<0.05$) from simple linear regression were included in a multiple linear regression model to evaluate their impact on $AUC_{0–24}$ for both methods.

Results: Fifty-two patients were included. The median age was 63 years (interquartile range [IQR]: 50–73), and the median vancomycin clearance was 4 l/h (IQR: 2–6). Median vancomycin $AUC_{0\text{-}24}$ was 399 mg·h/l (IQR: 257–674) for the trapezoidal method and 572 mg·h/l (IQR: 466–807) for the non-trapezoidal method. There was a strong correlation between the methods ($r=0.87$ [95% CI, 0.79–1]; $P<0.01$),

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but Bland–Altman analysis showed poor agreement, with a bias of – 198 mg·h/l and 95% limits of agreement from – 482 to 86 mg·h/l. In multiple linear regression, total daily dose and vancomycin clearance were independent predictors of $AUC_{0–24}$ for both methods, with a stronger impact on non-trapezoidal AUC_{0-24} (adjusted $R^2 = 0.70$) than trapezoidal $AUC_{0–24}$ (adjusted $R^2 = 0.59$).

Conclusions: Trapezoidal and non-trapezoidal equations are not interchangeable for estimating vancomycin $AUC_{0–24}$. The trapezoidal method consistently results in lower $AUC_{0–24}$ estimates than the non-trapezoidal method.

Keywords: Pharmacokinetics; Vancomycin; Area under the curve; First-order pharmacokinetic equations

Key Summary Points

Why carry out this study?

Achieving the target vancomycin area under the curve (AUC) within the first 24 h of therapy ($AUC_{0–24}$) is associated with better outcomes for serious MRSA infections. Two methods, trapezoidal and non-trapezoidal, can estimate AUC. However, the 2020 vancomycin monitoring guidelines do not address which pharmacokinetic (PK) equation to use to estimate $AUC_{0–24}$. Furthermore, there is limited data directly comparing these methods on day 1 of therapy, especially in patients with confirmed MRSA infections.

This study used the trapezoidal and non-trapezoidal first-order pharmacokinetic equations to compare the calculated vancomycin AUC within 24 h of therapy in patients with confirmed MRSA infections.

What was learned from the study?

Our findings indicate a strong correlation ($r = 0.87$) between the two methods, but Bland–Altman analysis reveals significant discrepancies, with the trapezoidal method consistently producing lower $AUC_{0–24}$ estimates compared to the non-trapezoidal method. This is likely because the trapezoidal method does not account for additional doses administered within the first 24 h of therapy, which can impact dose adjustments and monitoring.

This study addresses key differences between two clinically relevant AUC estimation methodologies and aids in optimizing therapeutic drug monitoring and clinician decision-making regarding vancomycin monitoring during the early phase of therapy.

INTRODUCTION

The 2020 consensus guidelines for therapeutic monitoring of vancomycin recommend targeting a vancomycin area under the concentration–time curve (AUC) of 400–600 mg·h/l within the initial 24–48 h of therapy [1]. This approach is aimed to enhance vancomycin efficacy and mitigate toxicity in serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections [1]. Several studies have underscored the importance of optimizing vancomycin AUC within 24 h of therapy ($AUC_{0–24}$) [2, 3]. Notably, Lodise et al. found that achieving an $AUC_{0–24}$ threshold ≥ 521 mg·h/l was associated with a two-fold reduction in 30-day mortality in patients with MRSA bacteremia [2]. The use of either Bayesian software programs or first-order pharmacokinetic (PK) equations are endorsed by the vancomycin consensus guidelines to estimate vancomycin AUC [1]. Although Bayesian methods can utilize pre-steady state levels to estimate vancomycin $AUC_{0–24}$, the programs' accessibility and cost may hinder implementation efforts [4]. A 2019 survey conducted in U.S. academic medical centers revealed that the subset of surveyed

institutions using AUC-based monitoring utilize first-order PK equations instead of Bayesian programs as means for AUC estimation (67%; 12/18) [5].

Two different first-order PK equations (i.e., the trapezoidal and non-trapezoidal methods) have been validated and employed for estimating vancomycin AUC at steady state (AUC_{ss}) [1, 6, 7]. This approach offers simplicity, generalizability, and relies on fewer assumptions [1, 4, 8]. By utilizing two vancomycin levels, first-order PK equations can characterize the patient-specific vancomycin concentration–time profile, providing a true snapshot of the patient's vancomycin AUC [1, 6]. Additionally, both PK equations can be used without the need for additional software, thereby enhancing the accessibility of this method to institutions that may have limited access to these resources [4, 8]. Nonetheless, the consensus guidelines do not address which of the two PK equations to use for $AUC_{0–24}$ estimation. [1]. Of note, both trapezoidal and non-trapezoidal equations are listed in the vancomycin AUC dosing guideline, suggesting that both equations can be used when estimating $AUC_{0–24}$ and steady-state AUC [9].

The trapezoidal method computes the AUC for a specific dosing interval by summing the area of the trapezoid (infusion phase) and the integral of the mono-exponential curve (elimination phase) as described by Pai et al.'s Eq. 4 [6]. The resulting AUC is then adjusted for the number of doses per 24 h ($AUC \times \frac{24}{dosing\ interval}$) to provide the daily AUC (AUC_{24}). In contrast, the non-trapezoidal method estimates AUC_{24} directly by dividing the total daily dose of vancomycin by the calculated vancomycin clearance [10]. Notably, the trapezoidal method does not account for maintenance doses given within the 24-h therapy period. Consequently, these methods are likely not interchangeable for estimating vancomycin $AUC_{0–24}$ in patients who start a maintenance dose within 24 h of vancomycin therapy. Nonetheless, there is limited empirical evidence comparing these methods within the first 24 h of therapy, particularly in patients with confirmed MRSA infections.

Considering the documented importance of optimizing vancomycin AUC within 24 h of therapy in patients with serious MRSA infections, and limited studies investigating the use of first-order PK equations, this study aims to compare the calculated vancomycin $AUC_{0–24}$ using trapezoidal and non-trapezoidal PK equations in patients with MRSA bacteremia.

METHODS

Study Design and Setting

This was a retrospective cohort study of adult patients (aged ≥ 18 years) admitted to Loma Linda University Medical Center (LLUMC) between December 1, 2020 and December 31, 2023, who had an index blood culture positive for MRSA, received at least 48 h of intravenous vancomycin therapy, and had two consecutive serum vancomycin levels collected within 24 h of therapy. We excluded patients with an undetectable vancomycin serum level of < 4 mg/l and patients with serum levels collected within four hours of the loading dose (LD) administration. We also excluded those who received continuous infusion vancomycin, patients requiring kidney replacement therapy, pregnant patients, patients with vancomycin minimum inhibitory concentration (MIC) ≥ 2 mg/l, and patients with polymicrobial bacteremia.

Outcomes Data

The primary objective of this study was to compare the calculated vancomycin $AUC_{0–24}$ using first-order non-trapezoidal and trapezoidal PK equations based on two post-infusion vancomycin levels collected within 24 h of therapy.

Pharmacokinetic (PK) Analysis

At our institution, the vancomycin per pharmacy protocol recommends an LD of 20–25 mg/kg, followed by two consecutive serum concentrations (mg/l) [11]. The first level is drawn at least 4 h after the end of infusion to avoid the distribution phase, while the second level is drawn at least 6 h after the first level. These levels were then used to calculate the patient's

specific PK parameters, using Sawchuk–Zaske method, including volume of distribution (V), half-life ($T_{1/2}$), elimination rate constant (K_{el}), and vancomycin clearance (CL) within 24 h of therapy [12, 13]. Subsequently, we employed first-order trapezoidal and non-trapezoidal PK equations to calculate $AUC_{0–24}$, as detailed in the supplementary material (Table S1). Since $AUC_{0–24}$ is estimated following the initial dose, the vancomycin concentration is zero at the start of infusion. Therefore, a modified trapezoidal PK equation was used, wherein the area of a triangle substitutes for the area of a trapezoid to calculate the AUC during infusion [14, 15]. For improved readability, we will refer to the modified version of the trapezoidal PK equation as the trapezoidal method. Vancomycin plasma levels were measured using a Roche cobas® machine, with a limit of detection between 4 and 80 mcg/ml.

Data Collection and Definitions

Patient characteristics were recorded, including race/ethnicity, age, BMI, and comorbid conditions. Obesity was defined as having a BMI ≥ 30 kg/m^2. ICU admission and kidney function status were recorded within 24 h of therapy. Persistent MRSA bacteremia was defined as positive blood culture for ≥ 3 days, with day 1 being the initiation of active therapy. Thirty-day mortality was defined as death from any cause within 30 days of the index blood culture. The Cockcroft–Gault formula was used to estimate patients' CL_{CR}. Vancomycin-associated acute kidney injury (AKI) was defined as an increase in serum creatinine by either > 50% or 0.5 mg/dl from baseline for two or more consecutive occurrences [1]. Vancomycin treatment details were recorded, including dose, infusion duration, frequency, and serum levels. Study data were collected and managed using REDCap electronic data capture tools hosted at Loma Linda University Medical Center [16].

Data Analysis

Data were analyzed using IBM SPSS version 26 (IBM, Armonk, NY, USA) and R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). Normality tests were performed using the Shapiro–Wilk test on all continuous variables. Continuous variables were represented as median (interquartile range IQR: 25–75%). Categorical variables were represented by counts and percentages. Pearson correlation coefficient (r) was used to assess the correlations between $AUC_{0–24}$ values estimated by the non-trapezoidal and trapezoidal methods, with 95% confidence intervals and p values reported for r. Additionally, the Bland–Altman plot was used to evaluate the agreement and variability. Bias was measured as the mean difference, and the 95% Bland–Altman limits of agreement (LOA) was used to assess precision [17]. Overall clinical agreement was established if the bias between the two methods did not exceed a 20% threshold (± 100 mg·h/l), aligning with the recommended target range of AUC 400–600 mg·h/l and reported bias observed with different AUC estimation methodologies [1, 18, 19]. Predictive variables identified as significant (p value < 0.05) in simple linear regression were subsequently included in a multiple linear regression model to further investigate their impact on $AUC_{0–24}$ estimated by both methods. The goodness-of-fit for the multiple linear regression model was evaluated using adjusted R^2.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration. The LLUMC Institutional Review Board approved this study (#5,210,270) and the waiver of informed consent, given the minimal risk and retrospective nature of the study design.

RESULTS

A total of 193 patients were screened for eligibility, of which 80 adult patients with MRSA bacteremia received vancomycin for ≥ 48 h and had two consecutive vancomycin levels collected within 24 h of therapy available

Table 1 Baseline characteristics ($n = 52$)

Male, *n* (%)	**33 (63)**
Age (years), median (IQR)	63 (50, 73)
Hispanic, *n* (%)	25 (48)
Not Hispanic/Latino	27 (52)
Actual weight (kg), median (IQR)	75 (61, 86)
Height (cm), median (IQR)	169 (160, 177)
BMI, median (IQR)	26 (22, 31)
Obesity, *n* (%)	14 (27)
Scr, median (IQR)*	0.9 (0.8, 1.3)
CL_{CR}, median (IQR)	73 (47, 107)
White blood cells, median (IQR)	14 (10, 18)
Critically ill, *n* (%)	10 (19)
Concomitant pressor, (%)	2 (4)
Required intubation, *n* (%)	11 (21)
Steroid/immune suppressants	5 (10)
Diabetes, *n* (%)	14 (27)
Cerebrovascular disease, *n* (%)	11 (21)
Congestive heart disease, *n* (%)	10 (19)
Chronic pulmonary disease, *n* (%)	8 (15)
Chronic kidney disease (CKD), *n* (%)	8 (15)
Charlson Comorbidity Index, median (IQR)	4 (2, 6)
APACHE II score, median (IQR)	22 (20, 24)

BMI body mass index. **Scr* serum creatinine collected around the vancomycin first dose

for PK calculation. We excluded ten patients who received kidney replacement therapy, 15 patients who had polymicrobial bacteremia, and three patients with vancomycin MIC ≥ 2 mg/l. The final analysis included 52 patients.

The baseline characteristics are summarized in Table 1. The median age was 63 years (IQR: 50–73), and the median CL_{CR} was 73 ml/min (IQR: 47–107). Fifteen percent (8/52) had chronic kidney disease (CKD) at baseline, and 54% (28/52) had AKI on admission. Vancomycin patient-specific PK and outcome data are summarized in Table 2. All patients received a median vancomycin LD of 20 mg/kg (IQR: 18–21) and had two consecutive serum levels collected within 24 h. These levels were collected at least 4 h after the end of infusion to account for the distribution phase. The median duration between the LD and the first and second vancomycin levels was 7 h (IQR: 6–8) and 13 h (IQR: 12–15), respectively. The median total daily dose received on the first day of therapy was 2250 mg (IQR: 1750–3000).

Correlation and Agreement Between Day 1 Area Under the Curve Estimates by Trapezoidal Vs. Non-trapezoidal PK Equations

The median $AUC_{0–24}$, estimated using the trapezoidal method and the non-trapezoidal method, was 399 mg·h/l (IQR: 257–674) and 572 mg·h/l (IQR: 466–807), respectively. Using the trapezoidal method, 23% of AUC estimates (12/52) fell within the therapeutic range, compared to 50% (26/52) when using the non-trapezoidal method. A significant positive correlation was observed between the two methods ($r = 0.87$ [95% CI, 0.79–1]; $P < 0.01$) (Fig. 1). However, the Bland–Altman plot indicated a lack of agreement, demonstrating a bias (mean difference) of – 198 mg·h/l and 95% LOA ranging from – 482 to 86 mg·h/l (Fig. 2). In multiple linear regression (Table 3), CL_{CR}, total daily dose (TDD), Kel, and vancomycin CL explained 59% and 70% of the variance observed with trapezoidal $AUC_{0–24}$ ($R^2 = 0.59$) and non-trapezoidal $AUC_{0–24}$ ($R^2 = 0.7$), respectively. However, only TDD and vancomycin CL were significant predictors in both models ($P < 0.05$).

DISCUSSION

In this real-world cohort study, we compared two frequently utilized first-order PK equations

Table 2 Pharmacokinetic, exposure, and outcome data ($n = 52$)

Loading dose (LD) (mg), median (IQR)	1500 (1250, 1750)
LD (mg/kg), median (IQR)	20 (18, 21)
Two levels collected within 24 h after the LD, *n* (%)	52 (100)
Duration between LD & level 1 (h), median (IQR)	7 (6, 8)
Duration between LD & level 2 (h), median (IQR)	13 (12, 15)
Volume of distribution (V), (l/ABW) median (IQR)	0.85 (0.72, 1)
Vancomycin clearance (CL) (l/h), median (IQR)	4 (2, 6)
Elimination rate constant (K_{el}) (1/h), median (IQR)	0.06 (0.04, 0.09)
Half-life ($T_{1/2}$) (h), median (IQR)	12 (8, 19)
Total daily dose on day 1 of therapy (mg) median (IQR)	2250 (1750, 3000)
Trapezoidal AUC_{0-24}, median (mg/l·h)	399 (257, 674)
Non-trapezoidal AUC_{0-24}, median (mg/l·h)	572 (466, 807)
Persistent MRSA bacteremia, *n* (%)	8 (15)
30-day mortality, *n* (%)	7 (13)
Source	
Skin and soft tissue, *n* (%)	20 (38)
Respiratory, *n* (%)	14 (27)
Bone & joint, *n* (%)	8 (15)
Endocarditis, *n* (%)	7 (13)
Graft/device, *n* (%)	6 (12)
Primary bacteremia, *n* (%)	4 (8)
Intraabdominal, *n* (%)	1 (2)
Ears, nose, throat, *n* (%)	1 (2)
Source control indicated, *n* (%)	36 (69)
Source control attempted, n/N (%)	28/36 (78)
Patients with concomitant antimicrobial administered for ≥ 48 h ($n = 32$)*	
Piperacillin/tazobactam, *n* (%)	19 (37)
Cefepime, *n* (%)	9 (17)
Others, *n*^ (%)	12 (23)
Vancomycin used as the only anti-MRSA agent, *n* (%)	48 (92)
Vancomycin was used in combination for synergy, *n* (%)[a]	2 (4)
Alternative treatment agents (used instead of vancomycin), *n* (%)[b]	2 (4)
Length of hospital stay, days, median (IQR)	12 (8, 21)

AUC area under the curve. *Some patients received multiple agents. ^Others agent include: clindamycin, ceftriaxone, fluconazole, valganciclovir, acyclovir, cefazoline, metronidazole, and rifampin.[a]Vancomycin + cefazolin ($n = 2$).[b]Daptomycin ($n = 1$) and daptomycin/ceftaroline ($n = 1$)

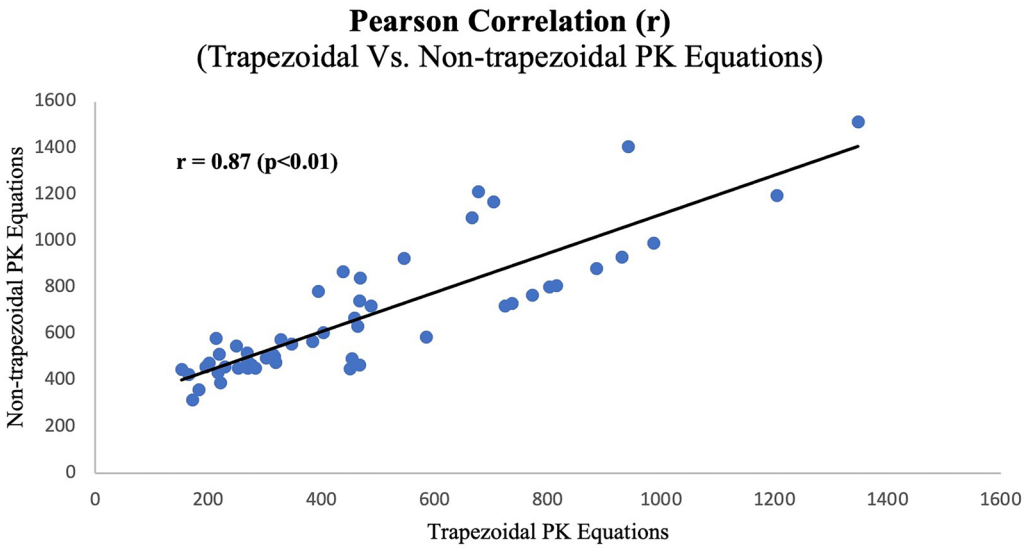

Fig. 1 Pearson correlation: trapezoidal vs. non-trapezoidal pharmacokinetic equations. Scatterplot of AUC_{0-24} estimations by trapezoidal and non-trapezoidal methods

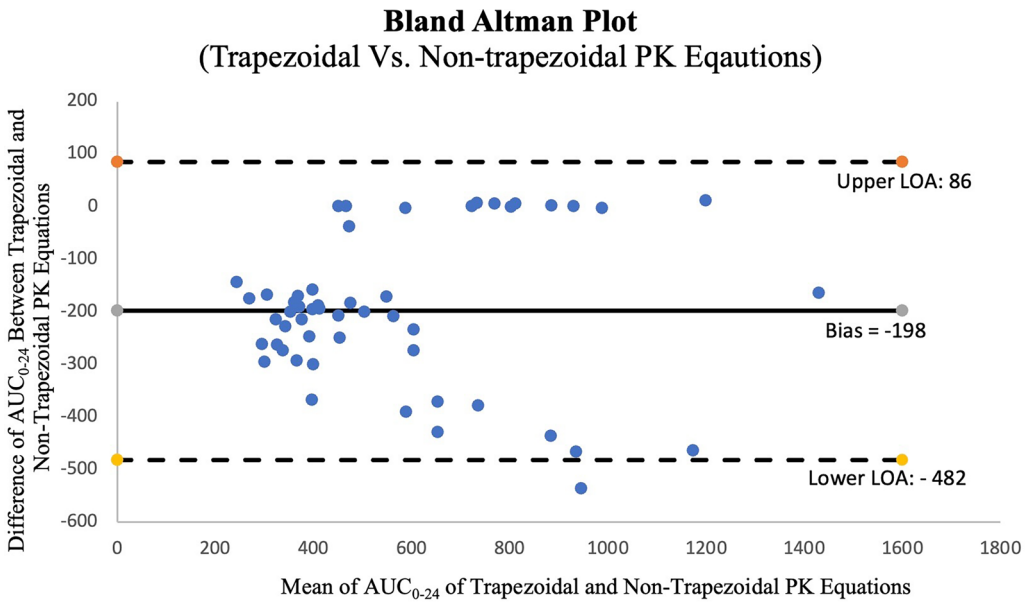

Fig. 2 Bland–Altman plot: Trapezoidal vs. non-trapezoidal pharmacokinetic equations. Bias and accuracy of AUC_{0-24} estimates by the two methods: a Bland–Altman plot analysis. *AUC* area under the curve

to estimate vancomycin AUC_{0-24} in patients with MRSA bacteremia. Despite a strong correlation between the two equations, the overall agreement between trapezoidal vs. non-trapezoidal was unsatisfactory, characterized by consistent bias and low precision.

The trapezoidal and non-trapezoidal methods are commonly used to estimate vancomycin AUC_{ss} [5]. However, to our knowledge, no studies have directly compared these methods to estimate AUC_{0-24}. In this study, AUC_{0-24} estimates derived using the trapezoidal method

Table 3 Multiple linear regression between patients' factors and AUC_{0-24} estimated by trapezoidal and non-trapezoidal methods

Variable*	Trapezoidal AUC_{0-24}		Non-trapezoidal AUC_{0-24}	
	p value	R^2	*p* value	R^2
CL_{CR}	0.76	0.59	0.87	0.7
Total daily dose	**0.03**		**< 0.01**	
K_{el}	**0.03**		0.49	
Vancomycin CL	**< 0.01**		**< 0.01**	

*Only variables with a *p* value < 0.05 were retained from the simple linear regression analysis. Trapezoidal AUC = 738.210 + (0.135 X CL_{CR}) + (0.128 X TDD) – (1833.909 X Ke) – (101.611 X CL) [$p < 0.01$]. Non-trapezoidal AUC = 711.538 + (0.063 X CL_{CR}) + (0.274 X TDD) – (482.867 X Ke) – (158.478 X CL) [$p < 0.01$]. *Bolded* variables are statistically significant (independently predict exposure). **Volume of distribution $p = 0.68$ in the simple linear regression

were, on average, 198 mg·h/l (95% LOA: – 482 to 86), lower than those obtained with the non-trapezoidal method. This discrepancy is likely clinically significant as it may lead to inappropriate dose adjustments. In our study, 50% (26/52) of the patients were classified as having a subtherapeutic AUC_{0-24} (< 400 mg·h/l). Upon closer inspection, we observed that the use of the trapezoidal equation resulted in a calculated AUC_{0-24} < 400 mg·h/l for all 26 patients. In contrast, when the non-trapezoidal method was employed, only three of 26 patients were classified as subtherapeutic AUC_{0-24}. Consequently, using the trapezoidal method to compute AUC_{0-24} in this cohort might prompt dose increases, thereby increasing the risk of overexposure and nephrotoxicity.

We employed multiple linear regression to identify factors predicting the AUC_{0-24}. Both the TDD and vancomycin CL were significant predictors of the AUC_{0-24} estimated by either method. However, the impact was stronger for the non-trapezoidal method ($R^2 = 0.70$) compared to the trapezoidal method ($R^2 = 0.59$). This is likely because the non-trapezoidal method directly integrates both variables into the AUC calculation ($AUC_{0-24} = \frac{TDD}{CL}$). Both methods use two post-infusion vancomycin levels collected within the same dosing interval and apply first-order PK equations, as the Sawchuk–Zaske method describes, to estimate the patient's specific PK parameters, such as K_{el} and V [12, 13]. However, inherent differences in the mathematical expressions used to calculate the AUC can potentially explain the discrepancy observed when estimating AUC_{0-24}.

It is crucial to note that accurate estimation of AUC_{24} using the trapezoidal method requires steady-state conditions and identical doses administered during each interval, neither of which are met when estimating AUC_{0-24} following a LD [6]. When applying the trapezoidal method on the first day of therapy, the AUC_{0-24} is computed by summing the time–concentration curve following a one-time LD [15]. Since the 24-h dosing correction factor will equal 1, the AUC estimated by this method only represents the exposure from the LD, not accounting for maintenance doses given within the first 24 h of therapy, as illustrated in Fig. 3. This results in a potential underestimation of AUC_{0-24} in patients who received more than one dose within 24 h of therapy. In contrast, the non-trapezoidal method uses vancomycin TDD and the patient's specific vancomycin CL to estimate AUC_{0-24} $\left(AUC = \frac{TDD}{CL}\right)$, capturing the true vancomycin exposure within the first 24 h of therapy (i.e., LD ± maintenance doses), as illustrated in Fig. 4 [10]. Evidently, in patients (27%; 14/52) who received a single dose within the first 24 h of therapy, both the trapezoidal and non-trapezoidal methods showed strong agreement, with a bias of 25 mg·h/l (95% LOA: – 36 to 112).

One advantage of the non-trapezoidal method is that it utilizes the same mathematical expressions initially employed to establish vancomycin AUC thresholds associated with significant clinical outcomes. The landmark trial by Moise et al. established AUC/MIC > 400 targets for patients with MRSA infections, utilizing TDD/CL to estimate vancomycin AUC [20]. Similarly, Holmes et al. applied this methodology to calculate AUC within 96 h of therapy, finding that AUC/MIC > 373 correlated with a 12% lower 30-day mortality in patients with MRSA bacteremia. Therefore, adopting the non-trapezoidal

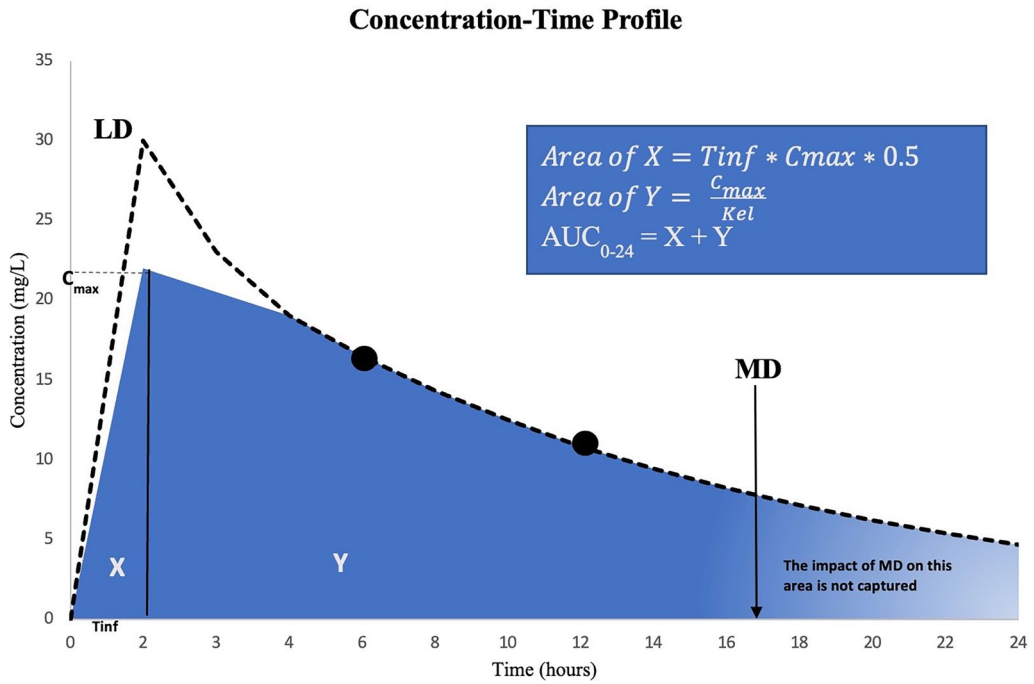

Fig. 3 Modified trapezoidal method. $AUC_{0–24}$ calculated using the modified trapezoidal method. *LD* loading dose, *MD* maintenance dose. *Cmax* extrapolated true peak at the end of infusion. *Tinf* duration of infusion. *Dark circle* measured levels at 6- and 12-h post-infusion. *Unshaded areas* areas not captured by first-order PK equations

method for AUC_{ss} estimation is expected to enhance consistency [21]. It is worth noting that both Moise et al. and Holmes et al. utilized a formula-based approach to estimate vancomycin CL, which could potentially increase interpatient variability [2]. However, in this study, the patient's specific levels were utilized to compute vancomycin CL, improving the accuracy and generalizability of AUC estimates.

This study has several limitations that warrant consideration. First, it is a retrospective observational study. Thus, causality cannot be established. While rich sampling is ideal for accurate AUC estimation, only two levels were available due to the retrospective nature of the data. However, a two-level AUC estimation is more representative of clinical practice, enhancing the external validity of our findings. Second, the findings are limited to $AUC_{0–24}$ calculations. At steady state, the trapezoidal and non-trapezoidal methods are expected to provide similar estimates [6, 7]. Third, we did not use a reference method for $AUC_{0–24}$ computation; however, the study aimed to describe the agreement between the two methods rather than establish one equation as the superior appropriate. Further research is necessary to compare the performance of both methods in estimating $AUC_{0–24}$ against a reference method. Fourth, for practical purposes, the AUC estimates using the trapezoidal method were calculated from zero to infinity rather than from zero to 24-h, due to the absence of a true trough level at 24 h. The true trapezoidal $AUC_{0–24}$ will be lower, which supports our conclusion that the trapezoidal method consistently result in lower $AUC_{0–24}$ estimates compared to non-trapezoidal method. Lastly, the study did not assess the impact of $AUC_{0–24}$ on clinical outcomes. In this study, only eight (15%) patients had persistent MRSA bacteremia, all of whom had a median $AUC_{0–24} > 450$ mg·h/l, regardless of the AUC estimation method. However, prospective studies designed specifically to evaluate the impact of AUC estimation methods on clinical outcomes are needed to confirm this observation.

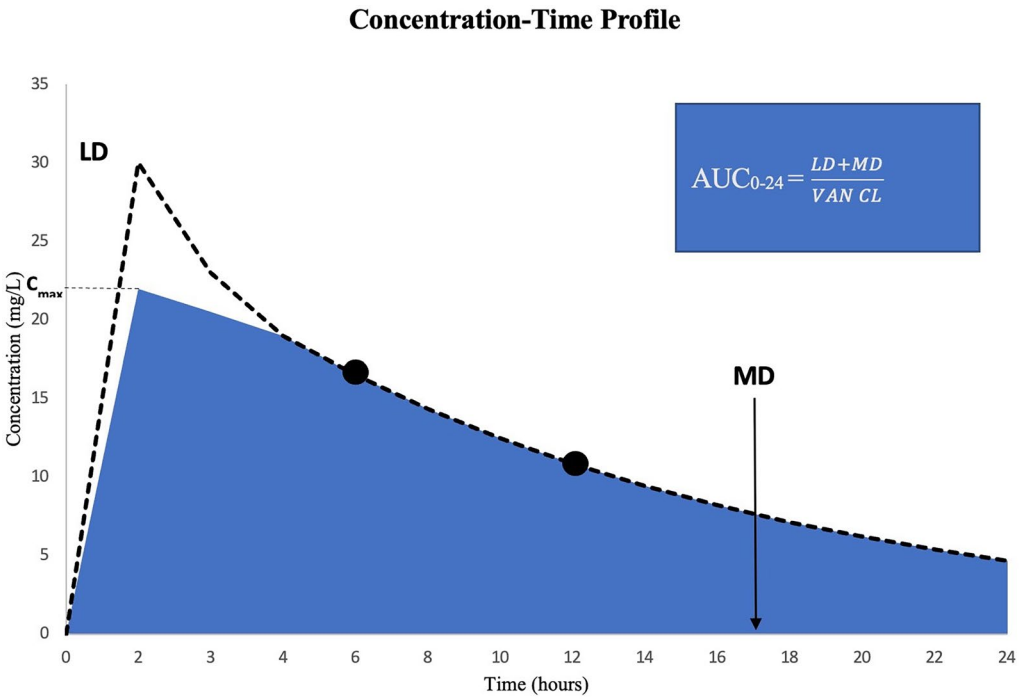

Fig. 4 Non-trapezoidal method. AUC_{0-24} calculated using the non-trapezoidal method. *LD* loading dose, *MD* maintenance dose. *Cmax* extrapolated true peak at the end of infusion. *Dark circle* measured levels at 6- and 12-h post-infusion. *Unshaded areas* areas not captured by first-order PK equations. *VAN CL* vancomycin clearance

CONCLUSIONS

Our findings contribute a more nuanced understanding of applying simple first-order PK equations to estimate vancomycin AUC_{0-24} in patients with MRSA bacteremia. When estimating AUC_{0-24} using two post-infusion levels, the trapezoidal method tends to produce lower AUC_{0-24} estimates than the non-trapezoidal method, primarily because it does not account for additional doses administered within the first 24 h of therapy. However, the two methods are likely interchangeable when estimating AUCss. Further research comparing both methods' AUC_{0-24} estimates to a reference method, utilizing rich sampling, is needed to validate these findings.

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Declarations

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Ethical Approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration. The LLUMC Institutional Review Board approved this study (#5210270) and the waiver of informed consent, given the minimal risk and retrospective nature of the study design.

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