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ORIGINAL RESEARCH

Characterizing Day 1 Area Under the Curve Following Vancomycin Loading Dose Administration in Adult Hospitalized Patients Using Non-Trapezoidal Linear Pharmacokinetic Equations: A Retrospective Observational Study

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ABSTRACT

Introduction: Methicillin-resistant *Staphylococcus aureus* (MRSA) infections are a serious threat to public health. Vancomycin (VAN) remains the primary treatment for these infections, and achieving the recommended area under the curve (AUC) target has been linked to improved clinical outcomes. The current VAN therapeutic monitoring guidelines recommend a loading dose (LD) of 20–35 mg/kg to rapidly attain targeted VAN exposures within 24 h of therapy. However, there is a paucity of data describing the impact of VAN LD on day 1 area under the curve ($AUC_{0–24}$). This study aims to employ pharmacokinetic (PK) equations to calculate and describe the $AUC_{0–24}$ following a VAN LD of 20 mg/kg.

Methods: This was a retrospective study of adult patients who were loaded with VAN 20 mg/kg, received ≥ 48 h of treatment, and had two consecutive serum VAN levels collected within 24 h. Linear, non-trapezoidal PK equations and two post-infusion VAN levels were used to calculate $AUC_{0–24}$. Therapeutic $AUC_{0–24}$ was defined as 400–600 mg/l*h.

Results: Among 123 included patients, the median age was 46 years (IQR 36, 62), 54% (67/123) of the patients had a body mass index (BMI) ≥ 30 kg/m^2 and 27% (33/123) were admitted to the intensive care unit (ICU). Following a LD of 20 mg/kg, 50% (61/123) of the patients met the therapeutic $AUC_{0–24}$, while 22% (27/123) of the patients were subtherapeutic, and 28% (35/123) were supratherapeutic. Compared with patients who achieved therapeutic

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$AUC_{0–24}$, patients with subtherapeutic $AUC_{0–24}$ were more likely to be younger (44 vs. 37 years old) and have a BMI ≥ 30 kg/m^2 (67 vs. 52%). In contrast, patients with supratherapeutic $AUC_{0–24}$ were more likely to be older (64 vs. 44 years old) and to have chronic kidney disease diagnosis (23 vs. 7%) when compared to patients who achieved a therapeutic $AUC_{0–24}$.

Conclusions: Only 50% of patients achieve the target AUC_{0-24} following a VAN 20 mg/kg LD, with younger, heavier patients underexposed and older patients with renal impairment overexposed, suggesting that different dosing strategies are needed for these populations.

Keywords: Area under the curve (AUC); Clearance; Loading dose; Pharmacokinetics; Volume of distribution; Vancomycin

Key Summary Points

Why carry out this study?

Appropriate vancomycin exposure within 24 h of therapy improves clinical outcomes for serious methicillin-resistant *Staphylococcus aureus* infections.

The utilization of a vancomycin loading dose facilitates the rapid attainment of therapeutic exposure; however, data describing the true effect of loading dose on day 1 area under the curve ($AUC_{0–24}$) estimated by non-Bayesian methods is scarce, especially in patients not admitted to the intensive care unit (ICU).

This study aims to employ linear non-trapezoidal (pharmacokinetic) PK equations to elucidate $AUC_{0–24}$ values following the administration of a fixed 20 mg/kg vancomycin loading dose in adult hospitalized patients.

What was learned from the study?

Following the vancomycin loading dose of 20 mg/kg, 50% (61/123) of the patients attained therapeutic $AUC_{0–24}$, however, the other half were either subtherapeutic (22%, (27/123)) or supratherapeutic (28%, (35/123)).

For most non-critically ill adult patients with good renal function, a 20 mg/kg vancomycin loading dose is adequate to achieve target vancomycin $AUC_{0–24}$; however, patient-specific characteristics, such as weight, age, and renal function can substantially affect vancomycin PK, necessitating further dose adjustment.

INTRODUCTION

Vancomycin (VAN) remains the primary treatment for serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections [1]; however, the efficacy of VAN can be impacted by inter-patient pharmacokinetic (PK) variability [1]. The 2020 therapeutic monitoring of vancomycin guidelines from the American Society of Health-System Pharmacy, Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists (ASHP/IDSA/PIDS/SIDP) highlight the importance of achieving therapeutic VAN levels within the initial 24 h for serious MRSA infections [2] and several studies have reported a correlation between day 1 VAN area under the curve ($AUC_{0–24}$) and improved clinical outcomes [3, 4]. Of note, Lodise et al. found that the risk of 30-day mortality was twice as high in patients with MRSA bacteremia who failed to achieve an $AUC_{0–24}$/MIC threshold of 521 or more [3].

VAN follows first-order elimination and is primarily cleared through the kidneys [5]. Depending on patients' renal function, the time needed to reach steady-state conditions can usually take 48–72 h, which can delay treatment optimization [5, 6]. To enhance the probability of target attainment within 24 h

of therapy, a one-time loading dose (LD) of 20–35 mg/kg is recommended by the 2020 ASHP/IDSA/PIDS/SIDP guidelines [2, 7]. Studies evaluating the impact of an LD on VAN AUC $_{0–24}$ have mainly focused on patients with critical illness and utilized Bayesian software for AUC estimation [8, 9]. However, the impact of VAN LD on $AUC_{0–24}$ in hospitalized patients, particularly with linear non-trapezoidal PK equations estimate of AUC, remains inadequately explored.

Linear non-trapezoidal PK equations, utilizing two VAN levels timed after LD administration, is an alternative approach for calculating $AUC_{0–24}$ [1, 6, 10–12]. This method was first proposed by Sawchuk-Zaske et al. to estimate PK parameters based on the first dose and has been utilized by several studies to calculate VAN patient-specific PK parameters during the first 24 h of therapy [11–14]. This approach is simple, relies on fewer assumptions, and provides a real-time snapshot of the AUC corresponding to the sampling interval [2, 10, 15]. In a single-center, retrospective cohort study comparing Bayesian two-concentration methods to first-order equations, the two-level PK method demonstrated excellent correlation ($r = 0.963$) and clinical decision agreement (87%) at steady-state conditions [16]. However, data providing a head-to-head comparison between non-trapezoidal PK equations and Bayesian $AUC_{0–24}$ estimates are lacking. Moreover, implementing the linear PK-equations is a practical and cost-effective method of calculating AUC [17]. This method can be achieved by integrating an Excel sheet-based formula into electronic medical records, thereby expanding the accessibility of this method to institutions that may have limited resources and lack funding to justify access to Bayesian software.

Given the reported clinical benefits of optimizing VAN AUC within the 24 h of therapy and the limited availability of data that utilize non-Bayesian methods to estimate $AUC_{0–24}$ following fixed LD, our study aims to use linear non-trapezoidal PK equations to elucidate $AUC_{0–24}$ values following the administration of a fixed 20 mg/kg VAN LD in adult hospitalized patients.

METHODS

Study Design and Setting

This was an IRB-approved, retrospective observational cohort study of adult patients (age 18 years or older) admitted to Loma Linda University Medical Center (LLUMC) from May 1, 2022, to December 31, 2022 who received at least 48 h of intravenous VAN therapy and had two consecutive serum levels collected within 24 h of the VAN LD. We excluded patients with an undetectable VAN serum level of < 4 mcg/ml, serum levels collected before 4 h from loading dose administration, and/or only one serum level collected following the loading dose. Additionally, we excluded those who received non-intravenous routes of VAN and continuous infusion VAN, patients requiring renal replacement, pregnant patients, and patients who had VAN minimum inhibitory concentration (MIC) ≥ 2 mcg/ml.

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.

Institutional Vancomycin Dosing and Monitoring Protocol

At our institution, the VAN per Pharmacy protocol recommends a LD of 20–25 mg/kg, followed by two consecutive serum concentrations (mcg/ml). 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 volume of distribution (V_d), half-life, elimination rate constant (Ke), and VAN clearance within 24 h of therapy. This protocol allows individualized PK dosing of

VAN, which another group validated previously [18]. Linear non-trapezoidal PK equations were used to calculate $AUC_{0–24}$, as detailed in the Supplementary Material (Table S1).

Data Collection and Definitions

Demographic information, including race/ethnicity, age, body mass index (BMI), and comorbid conditions were recorded. Obesity was defined as having a BMI ≥ 30 kg/m^2. The APACHE II scores and the Charlson Comorbidity Index were calculated. Intensive care unit (ICU) admission and renal function were recorded within 24 h of therapy. 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 [2]. VAN treatment details, including indication, dose, infusion duration, frequency, and serum levels, were recorded. Study data were collected and managed using REDCap electronic data capture tools hosted at Loma Linda University Medical Center [19, 20].

Outcomes Data

The primary objective of this study was to describe $AUC_{0–24}$ following the administration of a fixed 20 mg/kg VAN LD in adult hospitalized patients, using linear non-trapezoidal PK equations. Based on their calculated $AUC_{0–24}$, patients were categorized into one of the following groups: subtherapeutic $AUC_{0–24}$ (< 400 mg/l*h), therapeutic $AUC_{0–24}$ (400–600 mg/l*h), and supratherapeutic $AUC_{0–24}$ (> 600 mg/l*h). The secondary objective was to compare the characteristics of patients who achieved a therapeutic $AUC_{0–24}$ to those with either subtherapeutic or supratherapeutic VAN exposure.

Data Analysis

Data were analyzed using IBM SPSS version 26 (IBM, Armonk, NY, USA). Normality tests were performed using the Shapiro–Wilk test on all continuous variables. Continuous variables were represented by either mean (± standard deviation) or median (interquartile range IQR 25–75%) as appropriate. Categorical variables were represented by counts and percentages.

RESULTS

Patient Populations

A total of 260 patients who received VAN were screened for eligibility, out of which 154 patients received two or more days of VAN therapy and had two or more consecutive VAN levels available for PK calculation. Thirty-one patients who had an initial VAN concentration of < 4 mcg/ml were excluded due to the inability to calculate an accurate AUC. Interestingly, half of these excluded patients required admission to the ICU (52%, 16/31) and required vasopressor support (35%, 11/31) at VAN initiation. The final analysis included a total of 123 patients.

The baseline characteristics are summarized in Table 1. The median (IQR) age was 46 years (36, 62). Fifty-four percent (67/123) of the population were patients with obesity (BMI ≥ 30 kg/m^2), and 27% (33/123) required admission to the ICU on the day of VAN initiation. A total of 10% (12/123) of the patients had chronic kidney disease (CKD) documented at baseline. The majority of patients (80%, 100/123) had stable renal function on days 1 and 2 of VAN therapy, allowing for a more accurate calculation of the $AUC_{0–24}$. The leading indications for VAN treatment were skin and soft tissue (38%, 47/123) and pleuro-pulmonary infections (24%, 30/123) (Table 1). In terms of nephrotoxicity, 14% (17/12) of patients developed AKI during VAN treatment; however, only one case was attributed to VAN. Notably, the incidence of AKI was higher in patients who received vasopressors (36%; 8/22) than those who did not (8%; 9/101).

Pharmacokinetic Data

Table 2 summarizes VAN treatment and pharmacokinetic data. All patients received a median (IQR) LD of 20 mg/kg [19–22] and had two

Table 1 Baseline characteristics of the patients included in the study

Characteristic (*n* = 123)	Value
Demographic	
Male, *n* (%)	67 (54)
Age, year, median (IQR)	46 (36, 62)
White or Caucasian, *n* (%)	73 (59)
Hispanic, *n* (%)	36 (29)
Black or African American, *n* (%)	9 (7)
Asian, *n* (%)	3 (3)
Unknown, *n* (%)	2 (2)
BMI ≥ 30, *n* (%)	67 (54)
Scr, mg/dl, median (IQR)	0.8 (0.6, 1)
Creatinine clearance, ml/min, median (IQR)	116 (73, 156)
ICU admission, *n* (%)	33 (27)
Receipt of vasopressors, *n* (%)	22 (18)
Intubated, *n* (%)	17 (14)
Comorbidities	
Diabetes, *n* (%)	38 (31)
Moderate-to-severe renal disease (CKD), *n* (%)	12 (10)
Congestive heart disease, *n* (%)	12 (10)
Peripheral vascular disease (PVD), *n* (%)	6 (5)
Cardiovascular disease (CVD), *n* (%)	6 (5)
Charlson Comorbidity Index, median (IQR)	2 (0, 4)
Apache II, median (IQR)	22 (17, 28)
Indication	
Skin soft tissue infections, *n* (%)	47 (38)
Pleuro-pulmonary, *n* (%)	30 (24)
Bone and joints, *n* (%)	16 (13)
Intraabdominal, *n* (%)	10 (8)
Central nervous system *n* (%)	6 (5)
Head, neck, and sinus, *n* (%)	3 (2)
Genitourinary, *n*, (%)	2 (2)
Sepsis/empiric, *n* (%)	4 (3)
Microbiology	

Table 1 (continued)

Characteristic ($n = 123$)	Value
Staphylococcus aureus, *n* (%)	26 (21)
Coagulase-negative *Staphylococcus*, *n* (%)	16 (13)
Streptococcus spp., *n* (%)	12 (10)
Enterococcus spp., *n* (%)	9 (7)
Others*, *n* (%)	22 (18)
Empiric, *n* (%)	27 (22)

IQR interquartile range, *BMI* body mass index, *Scr* serum creatinine, *ICU* intensive care unit, *CKD* chronic kidney disease
*Others: *Brevibacterium*, *Campylobacter*, *Corynebacterium*, and Gram-negative rods

consecutive serum levels collected. All VAN levels were collected at least 4 h after the end of infusion, accounting for the distribution phase. The median duration between the first level and LD was 7 h [6, 8], and the median duration between the second level and LD was 13 h [12, 14]. Of the

Table 2 Treatment and pharmacokinetic data of the patients included in the study

Characteristics ($n = 123$)	Value
LD, mg, median (IQR)	1750 (1500, 2250)
LD mg/kg, median (IQR)	20 (19, 22)
Total vancomycin amount on day 1 mg, median (IQR)*	3000 (2250, 3500)
V_d, liter, median (IQR)	68 (53, 82)
V_d, l/kg, median (IQR)	0.76 (0.61, 0.93)
Ke, h^{-1} median (IQR)	0.08 (0.06, 0.11)
T 1/2, hours, median (IQR)	8 (6, 11)
VAN clearance, l/h, median (IQR)	6 (4, 8)
AUC on day 1 (AUC_{0-24}), mg/l*h, median (IQR)	525 (429, 618)
$AUC_{0-24} < 400$, *n* (%)	27 (22)
AUC_{0-24} 400–600, *n* (%)	61 (50)
$AUC_{0-24} > 600$, *n* (%)	35 (28)
AKI on admission, *n* (%)	23 (19)
AKI on treatment, *n* (%)	17 (14)
Concomitant nephrotoxic agents^, *n* (%)	5 (4)

*Including LD. ^Loop diuretic ($n = 2$), amphotericin B ($n = 1$), IV contrast ($n = 1$), vasopressors ($n = 1$). *VAN* vancomycin, *IQR* interquartile range, *LD* loading dose, *Vd* volume of distribution, *Ke* elimination rate constant, *T ½* elimination half-life, *AUC* area under the curve, *AKI* acute kidney injury

123 patients, only 50% (61/123) achieved therapeutic $AUC_{0–24}$ target (400–600 mg/l*h). Of the remaining patients, 22% (27/123) were subtherapeutic ($AUC_{0–24}$ < 400 mg/l*h), and 28% (35/123) were supratherapeutic ($AUC_{0–24}$ > 600 mg/l*h) (Fig. 1).

Comparison of Patients with Subtherapeutic $AUC_{0–24}$ ($AUC_{0–24}$ < 400 mg/l*h) vs. Therapeutic $AUC_{0–24}$

A total of 27 (22%, 27/123) patients had a calculated subtherapeutic $AUC_{0–24}$ < 400 mg/l*h. These patients were more likely to be younger (37 vs. 44 years old) and have a BMI ≥ 30 kg/m^2 (67 vs. 52%) compared to patients with therapeutic $AUC_{0–24}$. There were no other notable differences in comorbidities or requirement of an ICU admission between both arms. Patients in the subtherapeutic arm had larger Vd (0.86 vs. 0.75 l/kg) and faster VAN clearance (8 vs. 6 l/h) than patients in the therapeutic arm. The elimination rate constant was 33% higher in the subtherapeutic arm (0.12 vs. 0.09 1/h), resulting in a shorter half-life (6 vs. 8 h) in this population. The data are summarized in Table 3.

Comparison of Patients with Supratherapeutic $AUC_{0–24}$ ($AUC_{0–24}$ > 600 mg/l*h) vs. Therapeutic $AUC_{0–24}$

There were 35 (28%, 35/123) patients with a calculated $AUC_{0–24}$ > 600 mg/l*h. At baseline, these patients were more likely to be older (64 vs. 44 years old), and have known baseline CKD rates (23 vs. 7%). Otherwise, there were no appreciable differences in weight, ICU admission, and comorbidities between both arms. Patients in the supratherapeutic arm had slower VAN clearance (3 vs. 6 l/h) than patients with therapeutic $AUC_{0–24}$. As expected, the elimination rate constant was lower in the supratherapeutic arm (0.06 vs. 0.09 1/h), resulting in a longer half-life (13 vs. 8 h) in this population.

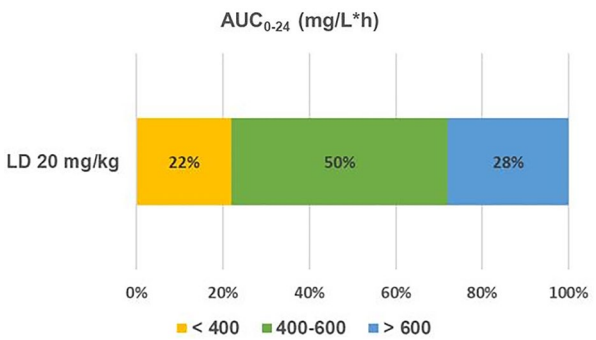

Fig. 1 Percentage of patients with $AUC_{0–24}$ < 400, 400–600, and > 600. *$AUC_{0–24}$* area under the curve on day 1 of therapy

DISCUSSION

In this study, we investigated the impact of a fixed VAN LD on the $AUC_{0–24}$ using a non-trapezoidal linear PK approach. We found that only 50% (61/123) of patients who received 20 mg/kg VAN LD achieved the target $AUC_{0–24}$ of 400–600 mg/l*h, while the remaining 50% (62/123) were either subtherapeutic or supratherapeutic.

Patients in the subtherapeutic cohort exhibited a faster Ke, increased VAN clearance, and larger Vd. These differences can potentially be attributed to the combined effects of younger age and increased body weight, impacting VAN PK [21–23]. Specifically, both youth and increased body weight are known to correlate with enhanced VAN clearance, as supported by existing literature [1, 21, 23, 24]. Our findings align with this observation, as VAN clearance in our cohort was higher than that reported in the general population (8 vs. 5 l/h) and more consistent with VAN clearance reported in younger patients with obesity (8 vs. 6–10 l/h) [5, 21, 25]. Conversely, since increased body weight and youth have opposing effects on VAN Vd, this parameter had less impact on VAN disposition in this young cohort with obesity [21–24]. It is essential to note that VAN Vd does not scale proportionally with actual body weight, underscoring the importance of limiting the LD to mitigate the risk of toxicity [2, 21, 22, 26]. Given that VAN clearance was the primary determinant of underexposure in this cohort, shortening the dosing interval of the maintenance dose rather than increasing the total LD may be a more prudent approach to optimize exposure

Table 3 Characteristics of patients with therapeutic vs. non-therapeutic day 1 AUC

Variable	AUC < 400 mg/l*h (subtherapeutic)	AUC 400–600 mg/l.h (therapeutic)	AUC > 600 mg/l*h (supratherapeutic)
Number of patients, *n*	27	61	35
Age, median, (IQR)	37 (29, 55)	44 (36, 57)	64 (42, 77)
Weight, kg, median, (IQR)	99 (72, 110)	88 (68, 113)	81 (63, 100)
Height, cm, median (IQR)	170 (155, 178)	170 (161, 178)	170 (158, 175)
BMI, median (IQR)	32 (24, 38)	30 (26, 37)	29 (24, 34)
BMI ≥ 30, *n* (%)	18 (67)	32 (52)	17 (49)
Scr, mg/dl, median (IQR)	0.70 (0.5, 0.8)	0.80 (0.6, 1)	1 (0.8, 1.5)
ICU admission, *n* (%)	6 (22)	16 (26)	11 (31)
LD, mg, median (IQR)	2000 (1500, 2250)	1750 (1250, 2250)	1750 (1250, 2000)
LD, mg/kg, median (IQR)	20 (19, 22)	20 (19, 22)	20 (19, 21)
Total VAN amount on day 1, mg, median (IQR)	3000 (2500, 3500)	3250 (2500, 3750)	2500 (2000, 3000)
Total VAN amount on day 1, mg/kg, median (IQR)	32 (29, 36)	34 (31, 40)	31 (25, 35)
V_d, L, median (IQR)	81 (48, 102)	68 (54, 79)	66 (52, 73)
V_d, L/kg, median (IQR)	0.86 (0.68, 0.98)	0.75 (0.61, 0.91)	0.69 (0.58, 0.89)
VAN clearance, L/h, median (IQR)	8 (7, 10)	6 (5, 8)	3 (2, 5)
K_e, 1/h, median, (IQR)	0.12 (0.09, 0.13)	0.09 (0.07, 0.12)	0.06 (0.03, 0.07)
Half-life, h, median (IQR)	6 (5, 8)	8 (6, 10)	13 (10, 21)
AUC_{0-24}, mg/l*h, median (IQR)	367 (350, 328)	520 (460, 544)	789 (658, 971)
AKI on admission, *n* (%)	1 (4)	10 (16)	12 (34)
AKI on treatment, *n* (%)	3 (11)	6 (10)	8 (23)

VAN vancomycin, *LD* loading dose, *BMI* body mass index, *Scr* serum creatinine, *ICU* intensive care unit, *CKD* chronic kidney disease, *Vd* volume of distribution, *Ke* elimination rate constant, AUC_{0-24} area under the curve on day 1 of therapy, *AKI* acute kidney injury

($Maintenancedose = Clearance \times Concentration \times Dosinginterval$) [5].

In the supratherapeutic cohort, patients exhibited lower Ke and VAN clearance, which can potentially be attributed to the combination of older age and poor renal function at baseline. The median age of these patients was 64 years old (IQR 42, 77), with 23% (8/35) of patients having CKD at baseline. Matzke et al. conducted a study investigating the relationship between changes in renal function and VAN PK across different age groups [27]. They employed linear PK equations to characterize VAN disposition after the first dose, similar to the methodology employed in this study. The authors reported a significant decrease in VAN clearance (2.4 l/h) and Ke (0.05 1/h) in patients aged between 46 and 66 years old and creatinine clearance (CrCl) between 40 and 87 ml/min. Similar to the results of these findings, our cohort's median (IQR) VAN

clearance and Ke were 3 l/h [2, 4] and 0.06 1/h (0.03, 0.07), respectively. The author concluded that reduced renal function was associated with a marked impact of VAN clearance, and dosage adjustment is warranted [27]. Since the Vd in this cohort was similar to values reported in the literature (0.7 l/kg), a change in LD is not required. Instead, extending the dosing interval may be a more effective solution to optimize exposure and minimize nephrotoxicity [5].

In our study, a 20 mg/kg LD resulted in a median $AUC_{0–24}$ of 525 mg/l*h, and achieved AUC > 400 mg/l*h in 78% (96/123) of the patients. Prior research by Hosiamont et al. and Pongchaidecha et al. proposed a higher LD of 25–30 mg/kg to optimize VAN $AUC_{0–24}$ [8, 9]. However, both studies focused on patients admitted to the ICU, where a higher LD might be warranted. A LD of 25–30 mg/kg resulted in $AUC_{0–24}$ > 600 mg/l*h in over 50% of patients in both studies [8, 9]. The majority of the patients included in our study did not require an ICU admission (73%, 90/123). Notably, our study excluded a small cohort of critically ill individuals with a subtherapeutic serum vancomycin concentration after receiving a LD of 20 mg/kg. It is unclear whether a higher dose of 25 mg/kg would have been more beneficial for these patients. Importantly, we observed a lower incidence of AKI compared to the findings reported by Hosiamount et al. (14 vs. 38%) [8]. Although the causation between VAN LD and nephrotoxicity remains uncertain, an $AUC_{0–48}$ > 650 mg/l*h was associated with an increased risk for AKI [28]. Future research should further explore the appropriate dose for the critically ill versus non-critically ill population. Otherwise, a 20 mg/kg LD appears sufficient to optimize VAN exposure without increasing the risk of nephrotoxicity in patients not admitted to the ICU.

Most studies evaluating the impact of a VAN LD on $AUC_{0–24}$ utilized Bayesian software to estimate $AUC_{0–24}$. While Bayesian software provides reliable AUC estimates, cost and clinical experience can limit their implementation [29]. According to a 2019 survey aimed at assessing VAN monitoring practices in academic medical centers in the U.S., 23% (18/78) of surveyed institutions performed AUC-based monitoring. Only 28% (5/18) of institutions have implemented Bayesian software, while 67% (12/18) used linear PK equations for AUC estimation [30]. Bayesian software can potentially underestimate the true AUC by 14% to 23%, depending on the PK model and sampling strategies [31]. In this study, we employed non-trapezoidal linear PK equations to calculate $AUC_{0–24}$. The main advantages of this method are simplicity, accessibility, and generalizability. Linear PK equations can be incorporated into electronic medical records and applied routinely in clinical practice [17]. By using timed post-distribution peak and trough levels to calculate patient-specific PK parameters (Vd and VAN clearance) and $AUC_{0–24}$, fewer assumptions were made, resulting in a more accurate estimation of the true AUC [1, 7, 11, 32].

For simplicity, we used VAN total daily dose (TDD) and calculated VAN total body clearance to estimate $AUC_{0–24}$ ($AUC = \frac{TDD}{VANclearance}$) [1, 11, 12, 14]. This approach captures the true $AUC_{0–24}$ associated with the total VAN dose administered within the initial 24 h of therapy (i.e., LD ± maintenance doses). Given that VAN disposition can be described using one-compartment mono-exponential equations, provided two levels are collected during the elimination phase, VAN clearance was determined using compartmental approaches ($VANclearance = K \times V$) [5, 33]. However, when applying one-compartment equations to drugs with two-compartment dispositions like VAN, drug loss during infusion (α-phase) is not fully accounted for, resulting in a slight underestimation of the true AUC [6]. Yet, intermittent infusion equations were used to account for most drug loss during infusion, which is likely insignificant as the median VAN half-life was five times longer than the infusion time [5, 7, 34]. Furthermore, 78% (96/123) of patients achieved an $AUC_{0–24}$ > 400 mg/l*h. Even if the true AUC was slightly higher than what was estimated by this approach, this finding does not alter the conclusion that a LD of 20 mg/kg would suffice to optimize VAN exposure within the initial 24 h of therapy for the majority of non-critically ill patients with good renal function.

This study has several strengths, including the use of the specific $AUC_{0–24}$ values for each patient allowing for minimal assumptions and improved internal validity as well as including patients with varying acuity of illness (27% of the patients were with critical illness) and PK profiles (50% of the patients were with obesity), thereby increasing the study's external validity. Despite the strengths of the study, this study has several limitations that warrant consideration. Firstly, due to the limited study period, our study did not include patients with a BMI below 18.5 kg/m^2. Although VAN dosing is weight-based and adjusts for differences in body weight, it has been suggested that VAN's Vd may not scale proportionally with actual body weight. Further investigation is needed to understand the impact of a 20 mg/kg LD of VAN on this population, as well as on other special populations not well represented in our study.

Secondly, the retrospective design of the study limited our ability to establish causality. Additionally, the small number of subtherapeutic and supratherapeutic patients prevented us from performing robust statistical analyses. Future studies with larger populations should aim to determine whether the variables identified in this study show significant correlations. Finally, the target AUC range of 400–600 mg*h/l is primarily validated in severe MRSA infections. In this study, only 26/123 patients (21%) had confirmed MRSA infection. However, this study focused on describing how fixed VAN LD affects $AUC_{0–24}$. The clinical implications of achieving the AUC target for non-MRSA infections require further investigations.

CONCLUSIONS

Ultimately, our findings offer additional insights into employing simple linear PK equations to estimate VAN $AUC_{0–24}$ following a fixed LD of 20 mg/kg. Based upon our linear PK calculations, non-critically ill patients with normal renal function are most likely to achieve a sufficient target $AUC_{0–24}$ with 20 mg/kg VAN LD. However, younger (< 40 years) patients with BMI ≥ 30 kg/m^2 are more likely to be subtherapeutic due to increased VAN clearance or/and Vd and may require an adjustment to the dosing frequency. A subset of patients who reside in the ICU may also be subject to subtherapeutic $AUC_{0–24}$, but further research is required to better characterize this population. Conversely, older patients with impaired renal function require closer monitoring, and a LD may not be necessary. With the results of this study, we aim to contribute to the nuanced understanding of the impact of patient-specific factors in optimizing VAN dosing within 24 h of therapy for the treatment of severe MRSA infections.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflicts of Interest. Jacinda Abdul-Mutakabbir is an Advisory Board member of Infectious Diseases and Therapy. Jacinda Abdul-Mutakabbir was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Jacinda Abdul-Mutakabbir received an honorarium from Shionogi, GSK, NovaVax, CSL Sequiris, Innoviva Specialty Therapeutics, and AbbVie. She has also received research support from CSL Sequiris. All other authors (Abdulwhab Shremo Msdi and Karen K. Tan) have no conflicts to report.

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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