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Research Article

Evaluation on therapeutic monitoring of vancomycin using the 2020 consensus guideline at one teaching hospital at Ho Chi Minh City

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ABSTRACT

According to the 2020 vancomycin updated consensus guideline, the ratio of 24-hour area under the concentration-time curve to minimum inhibitory concentration (AUC_{24}/MIC) was considered a better surrogate marker of efficacy than trough concentration (C_{trough}) in serious MRSA infections. This study aimed to investigate the implementation of vancomycin therapeutic drug monitoring following the updated guideline and determine the association between different ranges of C_{trough} and the attainment of AUC_{24}/MIC target among patients treated at University Medical Center Ho Chi Minh City (UMC HCMC). A cross-sectional study was conducted among hospitalized adult patients receiving intravenous vancomycin for severe infections at UMC HCMC from May 2020 to Aril 2021. AUC_{24} was estimated using first-order pharmacokinetic equation with Sawchuk-Zaske model. Linear regression analysis was used to estimate C_{trough} and AUC_{24} correlation. Ninety-five patients, including 27 patients in ICU group and 68 patients in non-ICU group, were enrolled in the study. The volume of distribution in ICU and non-ICU groups were 1.08 ± 0.36 L/kg and 0.95 ± 0.36 L/kg, respectively. Vancomycin clearance in ICU was lower than that in non-ICU (3.56 (IQR 1.38; 19.8) L/h vs. 6.07 (IQR 2.30; 13.3) L/h, $p < 0.001$). The mean C_{trough} was 10.9 ± 5.4 mg/L and the mean AUC_{24}/MIC was 412.3 ± 176.2. The proportions of patients achieving an AUC_{24} within the targeted range in the C_{trough} < 15 mg/L group and C_{trough} 15 – 20 mg/L group were 35.1% and 70.0%, respectively. Nephrotoxicity occurred in 10.5% of patients. Logistic regression analyses suggested the association between CrCL < 50 mg/L and the possibility of achieving AUC_{24}/MIC target (OR = 2.712; 95% CI 1.093 – 6.726; p = 0.031). Our findings indicate that an AUC_{24}/MIC-based dosing strategy may help limit unnecessary vancomycin exposure, providing valuable data to inform updates to the current vancomycin therapeutic drug monitoring guideline at UMC HCMC.

Keywords:
vancomycin, pharmacokinetics, therapeutic drug monitoring, pharmacodynamics, infectious diseases

1. INTRODUCTION

Vancomycin is a glycopeptide antibiotic commonly used as the first-line therapy for severe infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Therapeutic drug monitoring during vancomycin treatment is essential to optimize clinical efficacy and minimize the risk of nephrotoxicity. The first 2009 vancomycin therapeutic drug monitoring guideline recommended using a trough concentration (C_{trough}) value of 15–20 mg/L as a surrogate pharmacokinetic/pharmacodynamic parameter for a 24-hour area under the concentration-time curve (AUC_{24}) in clinical practice[1]. However, this approach has been criticized, as C_{trough} tends to underestimate AUC_{24} by approximately 25%[2]

The 2020 revised consensus guideline has favored AUC-guided monitoring to optimize vancomycin dosing instead of C_{trough} target because recently updated data found that C_{trough} was not well correlated with efficacy and particularly nephrotoxicity[3]. Additionally, *in vitro* and *in vivo* assessments of pharmacokinetic/pharmacodynamic

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models in MRSA infections have demonstrated that bactericidal activity is achieved when AUC_{24}/MIC reaches 400 or greater[4,5,6]. Besides, the risk of acute kidney injury increases when AUC_{24} exceeds 650 - 1300 mg.h/L[7] Therefore, the target AUC_{24} to minimum inhibitory concentration (AUC_{24}/MIC) of 400-600 (assuming a vancomycin MIC is 1 mg/L) is recommended by the 2020 guideline. The AUC_{24} can be estimated using two methods, the Bayesian method with at least one measured concentration and first-order pharmacokinetic equations namely Sawchuk-Zaske method with two vancomycin concentrations at steady state[3].

At University Medical Center Ho Chi Minh City (UMC HCMC), a local therapeutic protocol based on the 2020 consensus guideline has not yet been established. Therefore, we conducted this study to investigate the implementation of vancomycin therapeutic drug monitoring following the updated guideline and determine the association between different ranges of C_{trough} and the attainment of AUC_{24}/MIC target among patients treated at University Medical Center Ho Chi Minh City.

2. MATERIALS AND METHODS

2.1. Study population

Adult inpatients admitted to UMC HCMC from 1 May 2020 to 30 April 2021 and treated with intravenous vancomycin for serious infections including bacteremia, pneumonia, endocarditis, central nervous system infection, and bone and joint infection were included in this study. These patients underwent AUC-guided vancomycin therapeutic drug monitoring, with two steady-state vancomycin concentrations measured to estimate the AUC[24]

Patients were excluded if they received vancomycin for less than 72 hours, were administered the drug via continuous infusion, or had conditions that could significantly alter vancomycin pharmacokinetics, such as pregnancy, renal replacement therapy, severe vomiting, severe diarrhea, cystic fibrosis, edema, or ascites. The sample size was determined based on sample sizes used in previous vancomycin pharmacokinetic/pharmacodynamics studies, with the range of 95 to 123 cases[5,8,9,10]. All data were extracted from the hospital's electronic medical record system.

2.2. Method

A descriptive cross-sectional study was conducted to provide information on pathogens isolated, vancomycin use, vancomycin pharmacokinetic profiles, therapeutic drug monitoring of vancomycin, and nephrotoxicity.

Implementation of therapeutic drug monitoring vancomycin

The initial vancomycin loading and maintenance dose were determined by the clinical physicians based on the package insert of vancomycin and the previous local protocol of therapeutic drug monitoring vancomycin. Two vancomycin concentrations were collected at steady state, typically after 4-5 doses had been administered. These included post-distributional peak concentration measured 1-2 hours after the end of infusion, and a trough concentration collected 30 minutes prior to the next dose.

These two levels of concentrations were used to calculate an elimination rate constant (ke), true peak concentration (C_{peak}), true trough concentration (C_{trough}), volume of distribution (V_d), and vancomycin clearance (CL_{vanco}). AUC_{24} was then estimated using first-order pharmacokinetic equations by clinical pharmacists, with a target range of 400-600 mg.h/L as recommended by the 2020 consensus guideline[3]. The pharmacokinetic parameters were calculated after the first vancomycin therapeutic drug monitoring during the entire treatment course with the following equations[11]

- $k_e = \ln\frac{measured\ peak}{measured\ trough} / (T2-T1)\ (h^{-1})$;
- C_{peak} = measured peak × $e^{ke\times(T1-Tinf)}$ (mg/L);
- C_{trough} = measured trough × $e^{-ke\times(Tau-T2)}$ (mg/L);
- $V_d = \frac{Dose/Tinf*(1-e^{-ke*Tinf})}{ke*(C_{peak}-(C_{trough}*e^{-ke*Tinf})}$ (L);
- $CL_{vanco} = k_e * V_d$ (L/h);
- $AUC_{24} = (\frac{C_{peak}+C_{trough}}{2} \times Tinf + \frac{C_{peak}-C_{trough}}{ke}) \times \frac{24}{Tau}$

(mg.h/L), in which T1: time from the start of vancomycin infusion to measurement of peak concentration (hours); T2: time from the start of vancomycin infusion to measurement of trough concentration (hours); Tau: dosing interval (hours); Tinf: duration of vancomycin infusion (hours); Vd: volume of distribution; CL_{vanco}: vancomycin clearance

When the specific vancomycin MIC was not available, a standardized MIC of 1 mg/L was assumed in the following cases: empirical vancomycin usage before microbiological identification, identification of other Gram-positive bacteria besides MRSA, MRSA infections without available susceptibility data to vancomycin. This assumption was based on recommendations from the 2020 updated consensus guidelines, which advise using a 1 mg/L MIC when the

exact value is unknown. This standardized MIC value was further supported by the hospital's resistance surveillance data, which found that the majority of MRSA isolates had a vancomycin MIC of 1 mg/L[3]

Any subsequent vancomycin dose adjustments, if required, were determined using the initial maintenance dose, the calculated AUC_{24}, and the target AUC_{24}/MIC range of 400-600. The equation used was that AUC_{24} is proportional to the total daily vancomycin dose. Vancomycin serum concentrations were measured using a fluorescence polarization immunoassay method.

Nephrotoxicity

Nephrotoxicity events that occurred during the course of vancomycin therapy were recorded and classified based on the RIFLE (Risk, Injury, Failure, Lost of kidney function, and End-stage kidney disease) classification for assessing the severity of acute kidney injury.

Statistical analysis

All data analysis was performed using RStudio version 4.1.0 software. Descriptive statistics were calculated using Student's t-test for continuous data and Chi-squared or Fisher's exact test for categorical variables. A p-value of less than 0.05 was considered a statistically significant difference. Linear regression analysis was used to estimate the correlation between C_{trough} and AUC_{24}/MIC.

Logistic regression analysis was generated to analyze the probability of attaining an AUC_{24}/MIC target of 400 - 600 of independent variables, including age, sex, renal dysfunction with creatinine clearance (CrCL) less than 50 mL/min according to the vancomycin product labeling threshold for dose adjustment, body mass index, Charlson comorbidity index, administration of a loading dose (yes/no), and empirical antimicrobial therapy (yes/no).

3. RESULTS AND DISCUSSION

3.1. Results

Characteristics of the study population

Over the study period from 1 May 2020 to 30 April 2021, a total of 95 patients were enrolled and categorized into an intensive care unit (ICU, n = 27) group and non-ICU group (n = 68). Compared to the non-ICU group, patients in ICU group had a lower creatinine clearance, as well as a higher mean age and Charlson comorbidity index. However, no statistically significant differences were observed between ICU and non-ICU groups with respect to body weight or gender distribution.

Concomitant infections were common, with 54.7% of patients presenting with bacterial co-infections. The three most prevalent infections were bacteremia (n = 46), pneumonia (n = 40), and central nervous system infections (n = 32). Additionally, 46.3% of patients required mechanical ventilation. The three most frequently documented comorbid diseases were cardiovascular diseases (63.0%), diabetes mellitus (44.4%), and cerebrovascular diseases (29.6%). The two most commonly co-administered nephrotoxic medicines were furosemide (33.7%) and angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists (25.3%). The detailed baseline characteristics of the study population are presented in Table 1.

Pathogens isolated and vancomycin minimal inhibitory concentrations

Of 95 medical records collected, microbiological testing was performed in 94 cases (98.9%). A total of 366 specimens were analyzed, with 101 specimens (27.6%) yielding positive test results. Gram-positive bacteria accounted for 43.6% of the isolated pathogens. Among the positive bacterial isolates, MRSA (40.9%) and Methicillin-resistant Coagulase Negative Staphylococcus (MR-CNS) (20.5%) were the most prevalent Gram-positive organisms.

Vancomycin minimal inhibitory concentrations (MICs) were reported in 21 patient medical profiles. The most common vancomycin MIC observed was 1 mg/L, accounting for 61.9% of the isolates with available MIC data. One case exhibited a vancomycin MIC of 1.5 mg/L, and two cases had a vancomycin MIC of 2.0 mg/L. The distribution of vancomycin MIC values of these 21 cases is presented in Table 2.

Characteristics of vancomycin therapy

All patients were administered vancomycin via intermittent intravenous infusion. The proportion of patients using a loading dose was 34.7%, with a mean loading dose of 23.6 ± 2.9 mg/kg. When comparing the ICU and non-ICU groups, the mean loading doses (22.8 ± 2.2 mg/kg vs. 24.0 ± 3.2 mg/kg, p = 0.262) and mean maintenance doses (33.4 ± 12.9 mg/kg vs. 36.1 ± 10.4 mg/kg, p = 0.157) were not statistically different. However, the duration of vancomycin treatment was significantly longer in non-ICU group compared to the ICU group (14 days [IQR:10.0 ;19.0] vs. 11 days [IQR: 3.7; 20.7], p = 0.012). The detailed characteristics of vancomycin therapy are presented in Table 3.

Vancomycin pharmacokinetic parameters

The vancomycin pharmacokinetic parameters for the overall study population are presented in Table 3.

When comparing the ICU and non-ICU groups, there was no significant difference in the mean volume of distribution of vancomycin, which was 1.08 ± 0.36 L/kg and 0.95 ± 0.36 L/kg, respectively. However, vancomycin clearance was significantly lower in the ICU group compared to the non-ICU group, at 3.56 [IQR: 1.38; 19.8] L/h and 6.07 [IQR: 2.30; 13.3] L/h, respectively ($p < 0.001$).

Correspondingly, the mean vancomycin half-life was significantly longer in the ICU group compared to the non-ICU group (13.50 ± 8.95 hours vs. 7.00 ± 4.66 hours, respectively, $p < 0.001$)

Further analysis revealed a poor linear correlation of the relationship between vancomycin clearance and creatinine clearance, with an R-squared of 0.113. The following equation described this association: CL_{vanco} (mL/min/kg) = 1.019 x CrCL (mL/min/kg) + 0.581, $p < 0.05$.

Vancomycin therapeutic drug monitoring

The majority of peak and trough vancomycin concentrations were collected around the fourth dose or fifth dose, with 28.4% at the fourth dose, 23.2% at the fifth dose, and 42.1% after the fifth dose. Approximately 80% of peak concentrations were collected one hour after the end of the vancomycin infusion, and 95.8% of trough concentrations were collected 30 minutes prior to the next dose.

The mean AUC_{24} and C_{trough} for the overall study population were 409.1 ± 150.8 mg.h/L and 9.5 ± 5.1 mg/L, respectively. However, the mean AUC_{24} and C_{trough} were significantly higher in the ICU group compared to the non-ICU group (503.3 ± 121.5 mg.h/L vs. 371.8 ± 142.9 mg.h/L, $p < 0.001$ and 14.2 ± 5.0 mg/L vs. 8.9 ± 4.7 mg /L, $p < 0.001$, respectively).

Linear regression analysis demonstrated a positive correlation between C_{trough} and AUC24/MIC, with an R-squared of 0.67 (Figure 1). However, when stratifying by $C_{trough} \leq 15$ mg/L and $C_{trough} > 15$ mg/L, the R-squared differed substantially, being 0.61 for $C_{trough} \leq 15$ mg/L and 0.17 for $C_{trough} > 15$ mg/L

In the $C_{trough} < 15$ mg/L group, 35.1% of patients achieved the target AUC_{24}/MIC of 400 to 600 whereas 70.0% of patients in the C_{trough} 15 – 20 group achieved this AUC_{24}/MIC target. Notably, the majority (61.7%) of patients who reached the AUC24/MIC ≥ 400 had a $C_{trough} < 15$ mg/L. Importantly, all patients with a $C_{trough} \geq 15$ mg/L (n = 18) were able to achieve an AUC_{24}/MIC ≥ 400 The detailed association between AUC_{24} and C_{trough} is presented in Table 4

Clinical outcomes between different C_{trough} and AUC_{24}/MIC groups

Clinical outcomes were documented as success or failure. The determination of these outcomes was obtained from electronic medical records at the end of treatment, based on the physician's clinical assessment. The study reported that eighty patients (84.21%) were successfully treated in the hospital profiles. We analyzed the clinical outcomes of different C_{trough} and AUC_{24}/MIC groups. The results showed no significant association between clinical outcomes and the possibility of attaining C_{trough} target (15 – 20 mg/L) or AUC_{24}/MIC target (400 – 600) (Table 5).

Nephrotoxicity

In this study, acute kidney injury events were documented in 10.5% of the study population. Of the overall study population, 4.2% were classified as the Risk group, 4.2% were categorized as the Injury group, and 2.1% was Failure group based on the RIFLE staging system.

Factors associated with the probability of attaining an AUC_{24}/MIC target

The study found that 36.8% of patients achieved the target AUC_{24}/MIC of 400-600.When comparing the dosing approaches, the probability of attaining the AUC_{24} target was numerically higher in the loading dose group compared to the non-loading dose group (63.6% vs. 41.9%, p=0.072).

Using a univariable logistic regression model, the only factor found to be associated with the likelihood of achieving the AUC_{24}/MIC target was a creatinine clearance (CrCL) less than 50 mL/min (OR = 2.712, 95% CI 1.093–6.726, p = 0.031). The detailed results are presented in Table 6.

Table 1. Baseline characteristics of the study population

Characteristics	ICU (N = 27)	Non – ICU (N = 68)	P-value
Age (years), mean (SD)	78.15 (20.3)	58.79 (14.4)	0.001
Male sex, n (%)	13 (48.1%)	41 (60.3%)	0.396
Weight (kg), mean (SD)	57.3 (15.0)	60.4 (13.5)	0.347
Charlson comorbidity index (score), median [IQR]	5.0 [0,0; 7.0]	2.55 [0,0; 7.0]	<0.001
Baseline creatinine clearance (mL/min), mean (SD)	48.1 (31.2)	76.3 (26.1)	<0.001
Infectious diseases diagnosed, n (%)			
Bacteremia	12 (44.4%)	34 (50.0%)	0.625
Respiratory infection and pneumonia	20 (74.1%)	20 (29.4%)	<0.001
Central nervous system infection	4 (14.8%)	28 (41.2%)	0.014
Bone and joint infection	0 (0%)	9 (13.2%)	0.042
Others	12 (44.4%)	16 (23.5%)	0.044
Comorbid diseases, n (%)			
Cardiovascular diseases	17 (63.0%)	48 (70.6%)	0.471
Cerebrovascular diseases	8 (29.6%)	27 (39.7%)	0.358
Diabetes mellitus	12 (44.4%)	16 (23.5%)	0.044
Gastroenterology and hematology diseases	4 (14.8%)	27 (39.7%)	0.02
Others	21 (77.8%)	48 (70.6%)	0.478
Concomitant nephrotoxic medications, n (%)			
Furosemide	14 (51.1%)	19 (27.9%)	0.027
ACEIs/ARB	2 (7.4%)	22 (32.4%)	0.012
NSAIDs	2 (7.4%)	9 (13.2%)	0.342
Antibiotics	27 (100%)	61 (89.7%)	0.088
Others	4 (14.8%)	11 (16.2%)	0.571

ACEis: angiotensin-converting enzyme inhibitors, ARB: angiotensin II receptor antagonists, NSAIDs: non-steroidal anti-inflammatory drugs, SD: standard deviation, IQR: interquartile range

Table 2. Distribution of MIC values of vancomycin in the study population (N = 21)*

MIC value (mg/L)	n (%)
MIC = 0,5	**5 (23.8)**
MRSA	1 (4.8)
MS-CNS	2 (9.5)
Enterococcus spp.	1 (4.8)
Streptococus spp.	1 (8.8)
MIC = 1	**13 (61.9)**
MRSA	7 (33.3)
MSSA	2 (9.5%)
MR-CNS	4 (19.0)
MIC = 1,5	**1 (4.8)**
MRSA	1 (4.8)
MIC = 2	**2 (9.5)**
MRSA	1 (4.8)
MR-CNS	1 (4.8)

* MIC values were available for 21 patients.
MIC: mimimal inhibitory concentration; MRSA: Methicillin-resistant Staphylococcus aureus, MSSA: Methicillin-sensitive Staphylococcus aureus, MR-CNS: Methicillin-resistant Coagulase Negative Staphylococcus

Table 3. Characteristics of vancomycin use and pharmacokinetic parameters of vancomycin estimated in the study population

Variables	ICU (N = 27)	Non-ICU (N = 68)	P-value
Using loading dose, n (%)	13 (48.1%)	32 (47.1%)	1
Loading dose (mg/kg), mean (SD)	18.3 (4.3)	18.60 (5.8)	0.879
Maintenance dose (mg/kg), mean (SD)	33.4 (12.9)	36.1 (10.4)	0.157
Duration of vancomycin treatment (days), median [IQR]	11.0 [3.7; 20.7]	14.0 [10.0; 19.0]	0.012
V_d (L/kg), mean (SD)	1.08 (0.36)	0.95 (0.36)	0.121
CL_{vanco} (L/h), median [IQR]	3.56 [1.38; 19.8]	6.07 [2.30; 13.3]	< 0.001

Variables	ICU (N = 27)	Non-ICU (N = 68)	P-value
$T_{1/2}$ (hours), mean (SD)	13.50 (8.95)	7.00 (4.66)	< 0.001
AUC_{24} (mg.h/L), mean (SD)	503.3 (121.5)	371.8 (142.9)	< 0.001
C_{trough} (mg/L), mean (SD)	14.2 (5.0)	8.9 (4.7)	< 0.001

Vd = volume of distribution (L/kg), T1/2 = half-life (hours), CLvanco = vancomycin clearance (L/h)

Table 4. The association between AUC_{24}/MIC and C_{trough} in the study population

C_{trough} (mg/L)	**AUC/MIC n (%)**			**P-value**
	< 400	**400 – 600**	**> 600**	
< 15 (n = 77)	48 (62.3)	27 (35.1)	2 (2.6)	< 0.001
15 – 20 (n = 10)	0 (0.0)	7(70.0)	3 (30.0)	
> 20 (n = 8)	0 (0.0)	1 (12.5)	7 (87.5)	

Table 5. The association between clinical outcomes and PK/PD target attainment in the study population

		Outcome		P-value
		Success	Failure	
C_{trough} target attainment (15 – 20 mg/L)	Yes	8 (8.4%)	2 (2.1%)	0.493
	No	72 (75.8%)	13 (13.7%)	
AUC_{24} /MIC target attainment (400 – 600)	Yes	29 (30.5%)	6 (6.3%)	0.782
	No	51 (53.7%)	9 (9.5%)	

Table 6. Univariate logistic regression analyzing the association of independent factors and the likelihood of attaining AUC_{24}/MIC target of 400 – 600 mg.h/L in the study population

Variable	**Odds Ratio**	**95% Confidential interval**	**P-value**
Age	1.026	0.999– 1.053	0.056
Gender (male)	1.227	0.527 – 2.860	0.635
BMI	1.012	0.915 – 1.120	0.814
CrCL < 50 mL/min	**2.712**	**1.093 – 6.726**	**0.031**
Charlson comorbidity index	1.180	0.965 – 1.444	0.107
Empiric antimicrobial therapy	0.917	0.375 – 2.239	0.849
Loading dose	0.517	0.220 – 1.213	0.130

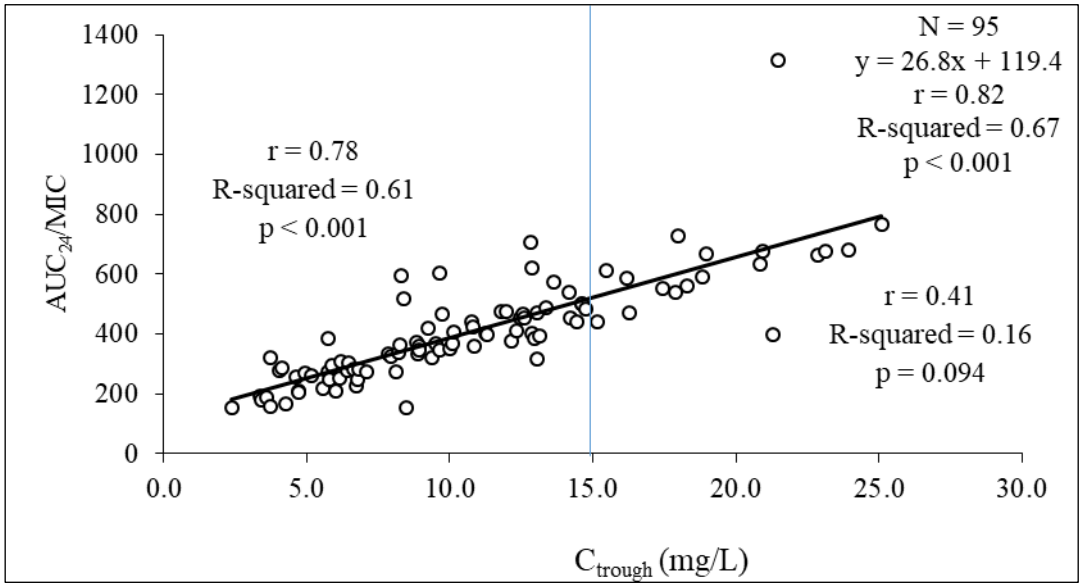

Figure 1. Linear correlation between AUC_{24}/MIC and C_{trough} of vancomycin in the study population

3.3. Discussion

Vancomycin has long been an effective first-line therapeutic agent for infections caused by Gram-positive pathogens. However, the narrow therapeutic window of vancomycin has brought significant challenges, with issues such as nephrotoxicity necessitating careful therapeutic drug monitoring during treatment. Prior to 2020, the 2009 vancomycin guidelines identified C_{trough} as the primary pharmacokinetic marker used as a surrogate for efficacy and safety. However, accumulating evidence of toxicity associated with the C_{trough}-based approach led to the release of updated guidelines in 2020. The most notable change in the 2020 guidelines was the shift from relying on C_{trough} to instead using AUC_{24}/MIC. This change was implemented to reduce the unnecessary dose escalation and ultimately mitigate the risk of vancomycin-induced nephrotoxicity.

This study provides the real-world application of the 2020 updated vancomycin therapeutic drug monitoring guidelines in Vietnam, providing insight into vancomycin therapy at UMC HCMC. These findings include medication use, pharmacokinetic profiles of vancomycin in both ICU and non-ICU patient populations, therapeutic drug monitoring practices, the association between AUC_{24}/MIC and C_{trough}, and associated nephrotoxicity. Importantly, the data generated from this study were utilized as initial resources for updating local vancomycin therapeutic drug monitoring protocols at our hospital.

In general, there were differences in therapeutic regimens as well as vancomycin pharmacokinetic parameters between patients in ICU and non-ICU groups. These differences were affected by a wide range of factors. In our study, age and Charlson comorbidity index were found to be higher in ICU patient group compared to the non-ICU group. In contrast, the ICU group had lower creatinine clearance compared to the non-ICU group. These differences, along with other disparities between the groups, could contribute to the differences in pharmacokinetic characteristics as well as the probability of achieving treatment efficacy.

Hypertension was the most common comorbid disease in our study, observed in 52.6% of the study population. The median Charlson Comorbidity Index in this study was 3.0 [2.0; 4.3], which was higher than the mean Charlson Comorbidity Index reported in previous studies in Vietnam for vancomycin monitoring. Such difference might be due to our inclusion criteria, which focused on severe infectious patients treated with vancomycin.

Determining the accurate vancomycin MIC is critical for guiding appropriate treatment of severe MRSA infections. The broth microdilution (BMD) method is considered the gold standard for vancomycin MIC testing[3]. When the MIC_{BMD} is > 1 mg/L, achieving the target AUC_{24}/MIC of ≥ 400 with conventional vancomycin dosing becomes challenging, while increasing the dose risks toxicity. Due to limited hospital resources, the current study utilized an automated testing system to assess vancomycin MIC, which has been demonstrated to correlate well with the BMD method. The results showed that the majority of MRSA isolates (80%) had a vancomycin MIC ≤ 1 mg/L, consistent with previous literature reporting a narrow range of vancomycin MIC values among MRSA, with a BMD MIC_{90} ≤ 1 in most situations. This is one of the reasons for assuming a vancomycin MIC of 1 mg/L in cases where the specific MIC value is unavailable. Importantly, the study also identified several MRSA strains with higher vancomycin MICs of 1.5 mg/L and 2 mg/L. This emergence of MRSA with MIC > 1 mg/L had not been previously reported at our hospital and may represent an alarming sign of increasing antibiotic resistance. In such cases, consideration of alternative antibiotic regimens would be an appropriate approach to ensure treatment efficacy while mitigating toxicity risks.

In terms of vancomycin therapy, our study showed a low rate of patients administered with loading doses. However, among patients receiving loading doses, the mean dosage strictly followed the revised consensus guideline (20-35 mg/kg based on actual body weight)[3]. The proportion of patients achieving AUC_{24} of > 400 mg.h/L in those receiving a loading dose was higher than those without a loading dose. Similar results were seen in the study by Rosini et al. on 99 patients admitted to the Emergency Department, where a C_{trough} of 15-20 mg/L was achieved more frequently among patients who received a loading dose than those who did not (34% vs. 3%)[12]. While these findings suggest potential benefits of vancomycin loading dose, the literature on this practice remains limited due to small sample sizes, heterogeneous populations, and variable dosing practices. Accordingly, the 2020 revised guideline recommended this strategy in critically ill patients with serious MRSA infections who require rapid attainment of the concentration target[3,13]

The mean vancomycin daily maintenance dose in our study was slightly lower than the recommended dosing regimen of 15-20 mg/kg/dose every 8 to 12 hours for patients with normal kidney function[3]. This was more commonly observed in non-ICU group patients, which may have contributed to the low percentage of these patients reaching the target AUC_{24} > 400 mg.h/L. Despite the longstanding clinical utilization of vancomycin therapeutic drug monitoring, its application appears more established in departments with clinical pharmacists on duty. Physicians may still favor a conventional fixed-dose approach of 1 g twice daily, irrespective of patient-specific factors like weight and renal function. This can lead to more conservative

indications in terms of initial dosing in clinical practice.

Consequently, the initial maintenance dose prescribed was likely lower than it should have been, and dose adjustment is often made after receiving the therapeutic drug monitoring results. These findings underscore the need to optimize initial vancomycin dosing strategies to reliably achieve the target AUC_{24} from the outset, rather than relying solely on post-hoc therapeutic drug monitoring-guided dose modifications. Proactive dose selection algorithms accounting for patients characteristics may help clinicians ensure rapid attainment of the desired vancomycin exposure.

Regarding the duration of vancomycin therapy, the study observed a longer duration of vancomycin therapy in non-ICU group compared to the ICU group. This difference may be attributed to the higher prevalence of bone and joint infections, typically requiring 2 to 4 weeks of vancomycin therapy, in the non-ICU group, at 13.2%. In contrast, the ICU patients were more commonly infected with multidrug-resistant Gram-negative bacteria. For these patients, the initial empiric vancomycin therapy would typically be discontinued and de-escalated to Gram-negative targeted antibiotics, such as carbapenems, aminoglycosides, or colistin, based on microbiology results.

It is essential to use the appropriate initial antimicrobial dosage to increase the likelihood of early optimal exposure to antibiotics for patients[14]. To this end, conducting pharmacokinetic studies is important to determine the value of V_d and CL_{vanco}. However, there is considerable variability in these pharmacokinetic parameters among studies, likely due to discrepancies in the targeted population (ICU or non-ICU) and the wide range of kidney functions[15]. In our research, di profiles and AUC_{24} were calculated using first-order pharmacokinetic equations with two vancomycin levels at steady state, usually after administration of the initial 4 - 5 first doses. The results showed that the mean V_d value estimated in this study was not significantly different between the ICU and non-ICU patient groups, and was likely similar to Vd values reported in previous studies. Specifically, Matzke et al. observed V_d of 0.72 ± 0.35, 0.89 ± 0.31, and 0.90 ± 0.21 L/kg in groups with CrCL > 60, 10 - 60, and <10 mL/min, respectively[16]. Similarly, Bauer et al. reported an average V_d of 0.7 L/kg (range 0.5 - 1.0 L/kg) for vancomycin in non-obese adults with normal renal function[11]. However, V_d values have been established with high variability across studies, which may be attributed to the differences in pharmacokinetic models, and study population.

Regarding clearance of vancomycin, it is mainly eliminated through the kidney and has been demonstrated to highly correlate with CrCL[11]. This relationship permits the estimation of the vancomycin clearance, which is an important variable in calculating the initial empiric maintenance dose. We found that vancomycin clearance increased in proportion with CrCL and proposed a correlating equation between the two variables of CL_{vanco} (mL/min/kg) = 1.019 x CrCL + 0.58. Meanwhile, according to Bauer et al., the equation was CL_{vanco} (mL/min/kg) = 0.695 x CrCL + 0.05[11]. These differences could be explained by population averages, small sample size, retrospective observational study design, and sparse sampling strategy in our study. It requires more extensive analysis from intensive data to explore more precisely the covariate factors that could estimate vancomycin clearance in specific populations.

To estimate the AUC_{24}, the revised vancomycin guideline recommended using either Bayesian approach with at least one concentration or the first-order PK equations with two concentrations at steady-state[3]. Our study used the latter approach to estimate AUC_{24}[3]. The possibility of AUC_{24}/MIC target attainment in our study was 36.8%, which was found to be smaller than that of the study by Clark et al. (96.3%). This large discrepancy might be due to differences in daily dose (about 2500 mg in Clark's study vs. about 2000 mg in our study) and baseline CrCL (80 (47 – 120) mL/min in Clark's study vs. 66.3 ± 33.6 mL/min in our study)[17]

By contrast, our result showed a higher proportion of patients meeting the AUC_{24}/MIC of ≥ 400when compared with Hale's study (49.5% vs. 42%), with a higher weight-based daily dose (35.3 ± 11.9 mg/kg/day vs. 26.3 ± 9.4 mg/kg/day) and the lower CrCL (66.3 ± 33.6 mL/min vs. 102.0 (IQR 74.5 – 120.0) mL/min)[18].

Given the modest AUC_{24} target attainment rate and lower mean AUC_{24} value observed in our study, it would be important to focus on optimizing the empiric maintenance dose to help patients reach the target of AUC_{24} more quickly as above discussion.

The study findings indicate that the mean C_{trough} and AUC_{24} /MIC were significantly higher in ICU group compared to the non-ICU group. This can be attributed to the lower baseline vancomycin clearance observed in the critically ill patients, despite both groups receiving equivalent loading and maintenance doses. Typically, patients with reduced baseline CrCL would be expected to receive lower vancomycin maintenance doses. However, in this study, the ICU patients with severe sepsis or septic shock received more aggressive dosing regimens in order to expedite the achievement of target concentrations within the initial 24 to 48 hours of therapy. In contrast, the non-ICU group, who exhibited better baseline renal function, were administered lower maintenance doses than typically recommended. This resulted in AUC_{24} and C_{trough} values in the non-ICU group that remained below the desired target thresholds. These findings highlight the requirement to individualize vancomycin dosing strategies based on patient-specific factors, such as renal function and weight, rather than utilizing a one-size-fits-all approach to improve the likelihood of attaining the target AUC_{24}/MIC across diverse patient populations.

As regards the implementation of vancomycin therapeutic drug monitoring, the 2009 guideline recommended using C_{trough} as a simple surrogate marker for AUC_{24}, with a desirable C_{trough} target of 15 - 20 mg/L to ensure AUC_{24}/MIC target of 400-600[1]. However, the updated 2020 consensus guideline now emphasizes the use of AUC_{24}/MIC instead of C_{trough} for a wide range of reasons. First, the AUC_{24} represents the entire vancomycin exposure during the dosing interval and is considered a more appropriate pharmacokinetic/pharmacodynamic indice for this concentration-dependent antibiotic. Specifically, the AUC_{24} depends on all parameters of the 2-compartment pharmacokinetic model, whereas C_{trough} depends primarily on drug clearance and less on drug distribution[20].This is expected from a pharmacokinetic standpoint since C_{trough} represents just a single point throughout the concentration-time profile and this concentration at the end of the dosing interval does not accurately represent the overall drug exposure as AUC_{24} does[3]. Additionally, unlike AUC_{24}/MIC, C_{trough}-guided monitoring does not take into account the MIC of the pathogen, rendering its measurement less useful when taken alone as a surrogate for treatment success, especially in patients infected with organisms having vancomycin MIC ≥ 2 mg/L, which has been demonstrated to lead to poor microbiological and clinical outcomes[21].

In the current study, linear regression analysis demonstrated a strong positive correlation between, C_{trough} and AUC_{24}/MIC, with an R-squared value of 0.67. This is consistent with findings from Clark's study, which reported an R-squared of 0.73[17]. However, a study by Ben Kamel in 95 elderly patients found a weaker correlation between C_{trough} and AUC_{24}, with an R-squared value of only 0.51, potentially due to altered pharmacokinetic patterns in that study population[19]. Importantly, subgroup analyses demonstrated that a stronger positive correlation with an R-squared of 0.61 was found in the group of patients with C_{trough} < 15 mg/L compared to the group with C_{trough} ≥ 15 mg/L. Interestingly, our analysis showed that a high proportion of patients (37.7%) with C_{trough} < 15 mg/L were still able to attain the AUC_{24} target of ≥ 400 mg.h/L. The higher percentage was observed in Neely'study, which reported that among patients with normal renal function and a therapeutic of AUC_{24} of ≥ 400 mg.h/L, approximately 60% are expected to have a trough concentration below the suggested minimum target of 15 mg/L[2]. These findings suggest that relying solely on C_{trough} to guide dose adjustment, as per the 2009 guideline, could result in unnecessarily increased doses and greater vancomycin exposure, thereby potentially increasing the risk of vancomycin-induced nephrotoxicity.

Results from the logistic regression model in this study suggested that lower clearance creatinine (CrCL < 50 mL/min) was an independent factor associated with an increased likelihood of AUC_{24}/MIC target attainment. This finding is entirely reasonable, as vancomycin is primarily eliminated by the kidney. Patients with impaired renal function have prolonged half-life, leading to an increase in vancomycin exposure. In contrast, augmented renal clearance, defined as having CrCL >130 mL/min is also a significant concern in ICU group which is treated with renal excreted antibiotics like vancomycin or aminoglycosides, resulting in reduced serum drug concentration and suboptimal drug exposure[11].The optimal drug concentrations are therefore unlikely to be achieved. In such situations, using the maximum permitted dose, prolonged or continuous infusion, or switching to alternative antibiotics may be necessary to achieve optimal drug concentrations. Although maintenance dose and loading dose are generally thought to have an essential effect on AUC_{24} target attainment, our study did not show a statistically significant relationship between these variables AUC_{24}/MIC target attainment. BMI and age were analyzed as continuous independent variables in the logistic regression model and no association with the likelihood of AUC_{24}/MIC target was found for all other variables except for CrCL < 50 mL/min.

Regarding clinical outcomes, we found no significant difference in the rates of treatment success among different groups of patients categorized by the levels of C_{trough} or AUC_{24}/MIC. This result might be due to the fact that in this study, we only assessed the first occasion of vancomycin therapeutic drug monitoring from the initial peak and trough concentrations, which may not have reflected the entirety of the vancomycin treatment course. Additionally, the treatment outcomes might also have been influenced by numerous important factors such as patient comorbidities and the appropriateness of concomitant antibiotics for Gram-negative microorganisms.

In addition to therapeutic efficacy, safety is one of the most important concerns when utilizing vancomycin, which needs to be monitored closely throughout the treatment course. Factors that increase the risk of vancomycin-associated renal impairment include high trough concentrations, high dosages, concurrent use of other nephrotoxic agents, prolonged vancomycin use, and elevated drug exposure. In the current study, the rate of acute kidney injury according to the RIFLE classification was 10.5%, of which the risk (R) and injury (I) levels accounted for the highest proportion (4.2%). Similar acute kidney injury incidence rates have been recorded in other studies, which drives the suggestion that therapeutic drug monitoring according to AUC_{24}/MIC could help reduce the incidence of acute kidney injury events compared to therapeutic drug monitoring according to C_{trough}[22,23].However, in this study, the limited number of acute kidney injury cases and the inherent drawback of observational studies preclude the ability to definitively conclude the specific causes of acute kidney injury in the context of vancomycin therapy, such as concomitant medications, infection severity, and patients comorbidities.

Limitations

The major limitations of our study included a small sample size, a study design undedicated to PK analysis, and a sparse sampling strategy. Moreover, we did not assess the association between AUC_{24} value and vancomycin-induced nephrotoxicity. Lastly, we only evaluated the probability of attaining AUC_{24}/MIC target with the initial maintenance dosing regimens and calculated the vancomycin pharmacokinetic parameters at this time. Our study results are preliminary and require further confirmation by extensive studies with larger sample sizes and more pertinent study designs to assess the effect of these variables on AUC_{24}/MIC target attainment and clinical outcomes.

4. CONCLUSION

This study was one of the first studies in Vietnam to estimate the AUC_{24}/MIC of vancomycin following the release of the 2020 revised consensus guideline for vancomycin therapeutic drug monitoring.

Our findings indicate that an AUC_{24}/MIC-based dosing strategy may help limit unnecessary vancomycin exposure, providing valuable data to inform updates to the current vancomycin therapeutic drug monitoring guideline at UMC HCMC and other Vietnamese hospitals.

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Conflict of interest

We declare that there is no conflict of interest in conducting and publishing this article.

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Ethics approval

The research was reviewed and approved by the Ethical Committee of the University of Medicine and Pharmacy at Ho Chi Minh City under decision number 333/HĐĐĐ-ĐHYD on 4th May 2020.

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