Original article

Bayesian approach to AUC-guided vancomycin monitoring in Intensive Care Unit and Poison Control Department

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Abstract

Objectives: To compare AUC_{24} values between three vancomycin AUC estimation methods, including Bayesian two-concentration, Bayesian one-concentration, and first-order equations. **Materials and methods:** A cross-sectional, retrospective study of 67 medical records of adult patients who received vancomycin therapy drug monitoring based on AUC at the Intensive Care Unit - Poison Control Department, Nguyen Tri Phuong Hospital, from July 2023 to April 2024. **Results:** There was high agreement between Bayesian two-concentration and one-concentration methods (r = 0.974, clinical agreement 91%), and Bayesian two-concentration method and first-order equations (r = 0.968, clinical agreement 83.6%) with a variability of 95% LOA -150.5 to 98.9 (MD = -25.8 mg.h/L) and 95% LOA -99.3 to 175.8 (MD = 38.3 mg.h/L), respectively. The Bayesian one-concentration and first-order equations had lower agreement than the other comparisons (r = 0.927, clinical agreement 80.6%), showing significant variability with 95% LOA -144.4 to 272.5 (MD = 64 mg.h/L). **Conclusion:** The Bayesian two-concentration and one-concentration methods demonstrated the highest agreement. The methods which had significant differences need to be considered for their interchangeability in clinical practice.

Keywords: *AUC; Bayesian; ICU; TDM; vancomycin.*

1. INTRODUCTION

Vancomycin is a glycopeptide antibiotic used to treat Gram-positive bacterial infections, especially methicillin-resistant *Staphylococcus aureus* (MRSA). Vancomycin therapy carries risks of side effects such as nephrotoxicity and ototoxicity [1]. Its efficacy is predicted by the ratio of the area under the serum drug concentration-versus-time curve to the minimum inhibitory concentration (AUC/MIC), with a narrow therapeutic range [2, 3]. However, special pathophysiological conditions in patients with severe infections can change the pharmacokinetics/pharmacodynamics (PK/PD) of vancomycin, affecting the treatment effectiveness and increasing the risk of toxicity [4]. Therefore, therapeutic drug monitoring (TDM) can optimise vancomycin use in clinical practice [3].

In the past, calculating AUC by the linear-trapezoid rule could be challenging, as this approach required multiple concentrations within the same dosing interval. Previous guidelines suggested using trough concentration as a surrogate for the AUC/MIC ratio [2]. However, trough values might not be an optimal choice in TDM vancomycin [5]. The 2020 consensus guidelines recommended targeting an AUC/MIC ratio of 400 to 600 (assuming a vancomycin MIC of 1 mg/L) for serious MRSA infections [3]. There are innovative approaches to estimate AUC of vancomycin. One approach uses a Bayesian software program to estimate real-time AUC with one or two vancomycin concentrations samples. Another approach calculates AUC values through both peak and trough concentrations at a steady state by first-order PK analytic equations [6].

Since 2019, Nguyen Tri Phuong Hospital has applied TDM vancomycin by trough concentration. According to updated guidelines, the hospital has implemented TDM vancomycin based on AUC/MIC in the Intensive Care Unit - Poison Control Department since 2023. However, there was a lack of available data to assess which approach was appropriate for clinical settings, especially for the cohort of seriously ill patients. This study aimed to compare AUC_{24} values estimated by three approaches, including Bayesian one-concentration, Bayesian two-concentration, and first-order equations, for their overall agreement and variability.

2. SUBJECTS AND METHODS

2.1. Subjects

Patient data

This was a retrospective study of adult patients

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who received vancomycin for more than three doses and had at least two concentration samples for AUC_{24} estimation, based on the local TDM guideline at the Intensive Care Unit - Poison Control Department, Nguyen Tri Phuong Hospital, from July 2023 to April 2024. According to common procedures at the hospital, patient clinical data were collected from hospital electronic health records. Patients were excluded if they were under 18 years old, required renal replacement therapy, had a MIC value for vancomycin over 1 µg/ml, or had an incorrect sampling time.

Pharmacokinetic data

The pharmacokinetic data used in the vancomycin TDM process were implemented according to the local guidelines. Two vancomycin concentrations at steady state in the first TDM occasion were used to estimate AUC_{24}. The peak concentration was drawn 1 to 2 hours after the end of infusion, and the trough concentration was drawn 30 minutes to 1 hour before the next dose. AUC_{24} values estimated by different methods were compared at the same dosing time. The clinical pharmacist documented patient's clinical data, PK parameters, and vancomycin dosing history, then suggested appropriate sampling times on a vancomycin TDM indication form. Subsequently, the actual sample collection time was retrieved from the electronic health record and/or confirmed with the physician or nurse.

Vancomycin TDM process

A clinical pharmacist entered patient clinical data and trough value into the software to obtain AUC estimation by Bayesian one-concentration ($AUC_{Bayesian1}$), followed by input of the peak concentration value to AUC estimation by Bayesian two-concentration ($AUC_{Bayesian2}$). Clinical pharmacist adjusted vancomycin dose based on Bayesian results from PrecisionPK® software and suggested it to physicians.

2.2. Methods

AUC_{24} values were estimated by three methods in the first TDM occasion.

2.2.1. AUC estimation by first-order PK analytic equations (AUC_{PK})

AUC value calculated based on the Sawchuk-Zaske method with the equations as follows(7):

$$AUC = \frac{(C_{max} + C_{min})}{2} + \frac{(C_{max} - C_{min})}{k_e}$$

In which:

$$k_e = \frac{ln\frac{C_{peak}}{C_{trough}}}{\Delta t}\ ;\ C_{max} = \frac{C_{peak}}{e^{-kt}};\ t = \text{infusion time}$$

C_{max} (true peak) and C_{min} (true trough) were back-extrapolated from C_{peak} and C_{trough}. As in a single dosing interval, the AUC value must be multiplied by the dosing frequency to calculate the total $AUC_{0\text{-}24}$ [7].

2.2.2. AUC estimation by Bayesian methods

AUC values were estimated by PrecisionPK® software using a pharmacokinetic model of Rodvold et al(8). Patient clinical data and vancomycin TDM data (therapeutic target, dosage history, serum drug level) were entered into the software to estimate individual PK parameters and AUC_{24} values using Bayesian approach. The Bayesian one-concentration method estimates AUC_{24} using only the trough value, while the Bayesian two-concentration method utilises both the trough and peak values.

2.2.3. Evaluation of agreement between three AUC estimation methods

This study applied a similar approach to Olney et al (9) to compare AUC_{24} values. Clinical agreement between AUC estimation methods was assessed by classifying AUC_{24} values: subtherapeutic (AUC_{24} < 400 mg.h/L), therapeutic (AUC_{24} 400 - 600 mg.h /L) or supratherapeutic levels (AUC_{24} > 600 mg.h/L).

2.2.4. Statistical analysis

The data were entered and processed using Microsoft Excel and IBM SPSS Statistics version 26.0. Qualitative variables were presented as percentages. Quantitative variables were presented as mean ± standard deviation (SD) for normally distributed data, or as median with interquartile range (25th and 75th percentiles) for non-normally distributed data. The correlation between vancomycin AUC estimation methods was evaluated using Pearson's correlation coefficient (r), with a p-value < 0.05 considered statistically significant. Agreement and variability were assessed using the mean difference (MD) and the 95% limits of agreement (LOA) based on Bland-Altman plots, with LOA = MD ± 1.96 SD.

2.3. Research ethics

The study was approved by the Ethics Council in Biomedical Research of Nguyen Tri Phuong Hospital, code number 1041/NTP-HDDD, on May 31, 2024.

3. RESULTS

3.1. Characteristics of patients and vancomycin TDM

Among 97 adult patients who received TDM vancomycin by AUC at the Intensive Care Unit - Poison Control Department of Nguyen Tri Phuong Hospital, 67 patients were included in the final. A total of 30 patients were excluded from the study, including 12 patients requiring renal replacement therapy, 2 patients with a vancomycin MIC exceeding 1 mg/L, and 16 patients having incorrect sample collection

times. The mean age of patients was 65.2 ± 16.3 years, and male gender accounted for 41.8%. The median BMI was 22.2 (20.3, 25.4) kg/m^2. The median baseline serum creatinine was 105.8 (72.9, 147.7) µmol/L, and the mean creatinine clearance was 46.1 ± 23.4 mL/min. The patients prescribed vancomycin were primarily diagnosed with pneumonia, accounting for a high proportion (37.3%). There were 64.2% of patients who were indicated a loading dose of vancomycin. The median total daily dose was 2000 (1500, 2000) mg. Baseline characteristics and dosing data of the patients are described in detail in Table 1.

Table 1. Characteristics of patients and vancomycin TDM

Patient characteristics (N = 67)	
Age (years), mean ± SD	65.2 ± 16.3
Male gender, n (%)	28 (41.8)
BMI (kg/m^2), median (Q1, Q3)	22.2 (20.3, 25.4)
Baseline serum creatinine (µmol/L), median (Q1, Q3)	105.8 (72.9, 147.7)
Creatinine clearance (mL/min), mean ± SD	46.1 ± 23.4
CrCl classification, n (%)	
CrCl ≤ 30 mL/min	17 (25.4)
30 < CrCl ≤ 60 mL/min	36 (53.7)
60 < CrCl ≤ 90 mL/min	10 (14.9)
90 < CrCl ≤ 130 mL/min	4 (6.0)
CrCl > 130 mL/min	0 (0.0)
ARCTIC score, n (%)	
High ARC risk	15 (22.4)
Low ARC risk	52 (77.6)
ICU length of stay (days), median (Q1, Q3)	10 (7, 18)
Infections, n (%)	
Skin and soft tissue infection	17 (25.4)
Bacteremia	17 (25.4)
Pneumonia	25 (37.3)
Meningitis	1 (1.5)
Urinary tract infection	1 (1.5)
Musculoskeletal infection	3 (4.5)
Others	3 (4.5)
Vancomycin TDM characteristics	
Loading dose, n (%)	43 (64.2)
Total daily dose (mg), median (Q1, Q3)	2000 (1500, 2000)
Vancomycin treatment duration (days), median (Q1, Q3)	7 (4, 11)
Dosing interval, n (%)	
8 hours	1 (1.5)
12 hours	59 (88.1)
24 hours	7 (10.4)
Total vancomycin blood samples	151
1st TDM occasion	134
2nd TDM occasion	17
AUC_{PK} (mg.h/L), mean ± SD	669.4 ± 279.6
$AUC_{Bayesian1}$ (mg.h/L), mean ± SD	733.4 ± 276.0
$AUC_{Bayesian2}$ (mg.h/L), mean ± SD	707.6 ± 278.7

3.2. Evaluation of agreement between AUC estimation methods

Between Bayesian two-concentration and first-order pharmacokinetic equation

The Bayesian two-concentration method and the first-order pharmacokinetic equation method were highly correlated with r = 0.968 (p < 0.001) (Figure 1). Based on the Bland-Altman plot, the MD was 38.3 mg.h/L, the difference was statistically significant (p < 0.001) and 95% LOA was -99.3 to 175.8 mg.h/L (Figure 1). The clinical agreement between $AUC_{Bayesian2}$ and AUC_{PK} was 83.6% (Table 2). Among patients with AUC_{PK} results lower than the target (< 400 mg.h/L), there were 6 patients with $AUC_{Bayesian2}$ results reaching the target (400 - 600 mg.h/L). In the group of patients whose AUC_{PK} results were classified as supratherapeutic, 2 patients had therapeutic $AUC_{Bayesian2}$ values.

Table 2. Clinical categories of AUC_{24} values between Bayesian 2-concentration method and Linear method

		Linear			
Bayesian 2-concentration	**AUC_{24} (mg.h/L)**	**Subtherapeutic**	**Therapeutic**	**Supratherapeutic**	**Total**
	Subtherapeutic	6	0	0	6
	Therapeutic	6	15	2	23
	Supratherapeutic	0	3	35	38
	Total	12	18	37	67
Total agreement (%) = 56/67 = 83.6%					

Between Bayesian one-concentration and first-order pharmacokinetic equation

There was a high correlation between Bayesian one-concentration method and the first-order pharmacokinetic equation method with r = 0.927 (p < 0.001) (Figure 1). Based on the Bland-Altman plot, the MD was 64 mg.h/L, the difference was statistically significant (p < 0.001) and 95% LOA was -144.4 to 272.5 mg.h/L (Figure 1). The clinical agreement between $AUC_{Bayesian2}$ and AUC_{PK} was 80.6% (Table 3). Out of the patients with subtherapeutic AUC_{PK} levels, 6 had $AUC_{Bayesian2}$ results within the target range (400 – 600 mg.h/L). Conversely, among those with supratherapeutic AUC_{PK} levels, only 1 patient had $AUC_{Bayesian2}$ classified as therapeutic.

Table 3. Clinical categories of AUC_{24} values between the Bayesian 1-concentration method and Linear method

		Linear			
Bayesian 1-concentration	**AUC_{24} (mg.h/L)**	**Subtherapeutic**	**Therapeutic**	**Supratherapeutic**	**Total**
	Subtherapeutic	6	1	0	7
	Therapeutic	6	12	1	19
	Supratherapeutic	0	5	36	41
	Total	12	18	37	67
Total agreement (%) = 54/67 = 80.6%					

Between Bayesian two-concentration and Bayesian one-concentration

The Bayesian one-concentration and Bayesian two-concentration had excellent correlation with r = 0.974 (p < 0.001) (Figure 1). Based on the Bland-Altman plot, the two methods have a low average difference, in which $AUC_{Bayesian2}$ was lower than $AUC_{Bayesian1}$. The MD was -25.8 mg.h/L, the difference was statistically significant (p < 0.001) and 95% LOA was -150.5 to 98.9 (Figure 1). The clinical agreement between $AUC_{Bayesian2}$ and AUC_{PK} was the highest among comparisons at 91% (Table 4). For patients with $AUC_{Bayesian1}$ levels below 400 mg·h/L, $AUC_{Bayesian2}$ measurements reached the therapeutic range (400 – 600 mg·h/L) in 2 cases. In contrast, among individuals with supratherapeutic $AUC_{Bayesian1}$ levels, therapeutic $AUC_{Bayesian2}$ values were observed in 3 patients.

Table 4. Clinical categories of AUC_{24} values between Bayesian 2-concentration method and Bayesian 1-concentration method

Bayesian 2-concentration	Bayesian 1-concentration			
AUC_{24} (mg.h/L)	Subtherapeutic	Therapeutic	Supratherapeutic	Total
Subtherapeutic	5	1	0	6
Therapeutic	2	18	3	23
Supratherapeutic	0	0	38	38
Total	7	19	41	67
Total agreement (%) = 61/67 = 91.0%				

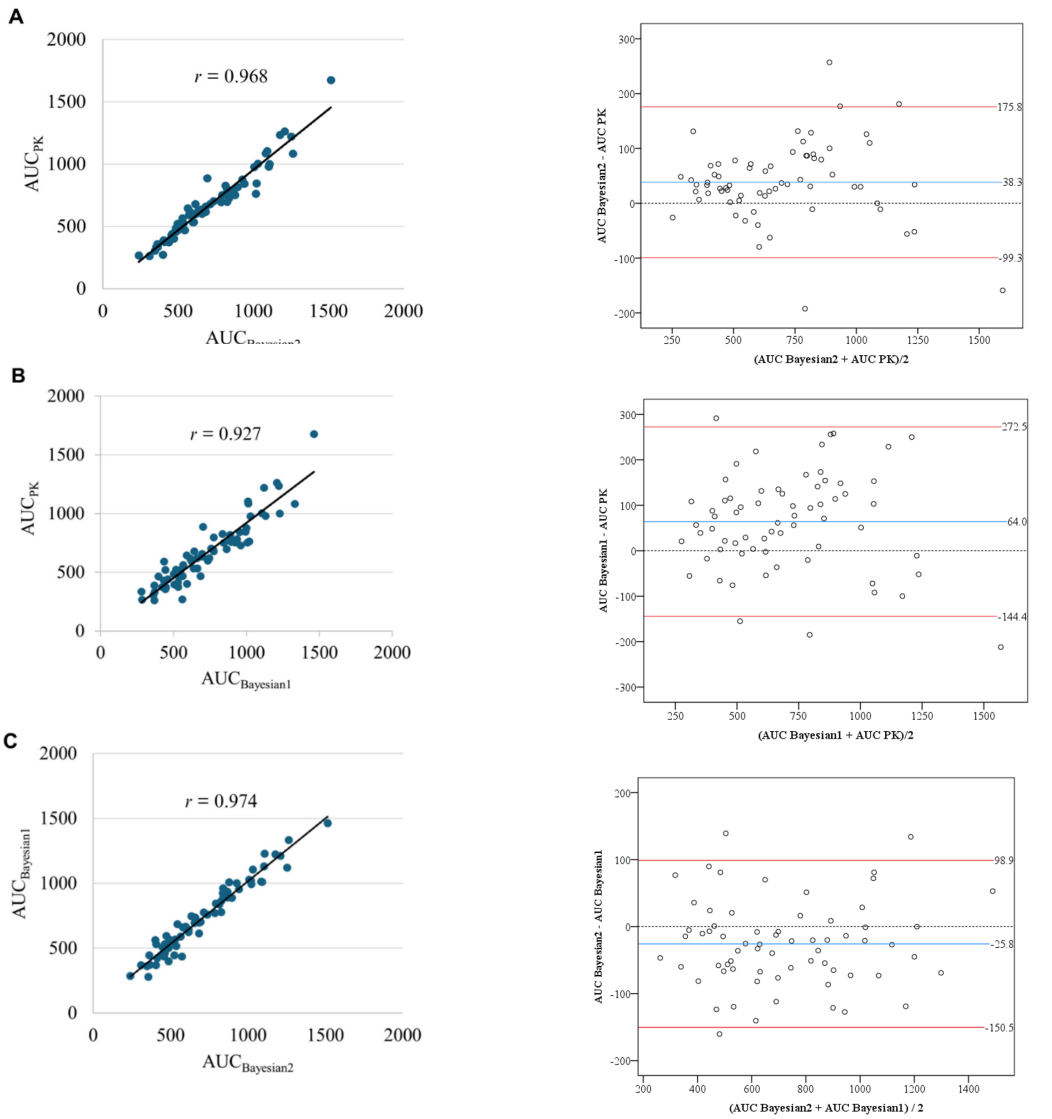

Figure 1: Correlation between AUC methods and the comparison via Bland-Altman plotting

– : Mean Difference – : 95% Limits of Agreement

A: Bayesian 2-concentration method versus Linear method

B: Bayesian 1-concentration method versus Linear method

C: Bayesian 2-concentration method versus Bayesian 1-concentration method

4. DISCUSSION

In our study, the average AUC values of all methods exceeded the therapeutic threshold. Among the three methods, Bayesian one-concentration method had the highest average AUC values and pharmacokinetic equation method had the lowest. Bayesian AUC results tend to be higher than those calculated using linear method, due to the characteristics of the research cohort undergoing ICU care had poor and changeable kidney function. Unlike the linear method, the Bayesian software is embedded with a PK model and can integrate evolving patient-specific PK parameters, making it more accurate if the patients have physiologic changes [6].

When comparing AUC estimation methods in pairs, they were all statistically different ($p < 0.001$). The mean difference in estimated AUC_{24} between these methods showed considerable variability. Based on the Bland-Altman plots in Figure 1, there was no proportional bias. The significant differences might be caused by random errors and were independent of the scale values, as evidenced by the scattered data points.

However, our study recorded high correlation results corresponding to clinical agreement. Bayesian one and two concentrations methods had the highest correlation (r = 0.974; 91.0% clinical agreement), followed by Bayesian two-concentration and linear (r = 0.968; 83.6% clinical agreement), and finally the Bayesian one-concentration linear (r = 0.927; 80.6% clinical agreement). Similarly, in the study by Olney KB et al [9], the level of correlation and agreement were in the order of Bayesian two-concentration and one-concentration (r = 0.931; 88.5% agreement); the Bayesian two-concentration and linear (r = 0.963; 87.4% agreement); the Bayesian one-concentration and linear (r = 0.823; 76.8% agreement). When comparing methods, it is important to consider the implications of discrepancies between AUC estimation methods in clinical decision-making. When one method predicts an AUC_{24} above the therapeutic range while the other estimates it within or below the therapeutic range, the risk of nephrotoxicity must be taken into account. In cases where AUC_{24} > 600 mg.h/L, misclassifying AUC_{24} as within or below the therapeutic range may fail to adjust the dose or even an increase in the subsequent dose, leading to elevated vancomycin exposure and a heightened risk of nephrotoxicity [10]. Conversely, therapeutic efficacy must be considered if one method predicts a subtherapeutic AUC_{24} while the other estimates it to be therapeutic or supratherapeutic. The consequences of inconsistency between AUC estimation methods may compel clinicians to maintain or reduce the dose, despite suboptimal vancomycin exposure, thereby increasing the risk of treatment failure and mortality [11].

In addition, Nguyen Tri Phuong Hospital's internal guideline recommended measuring two vancomycin concentrations in critically ill patients [12]. Therefore, the study also evaluated the possibility of interchangeability between Bayesian one-concentration and two-concentration. The two approaches showed the strongest agreement (91%) and no proportional bias. The study by Covington et al [13] also demonstrated a high overall agreement (87%) between AUC estimated by Bayesian one versus two concentrations. Although they observed a proportional bias at higher AUC_{24} values, they concluded that a trough-only approach could be reasonably applied to obese patients. In the hospital setting of our study, Nguyen Tri Phuong Hospital had already applied TDM vancomycin using trough concentrations. Therefore, trough-only monitoring might be more advantageous for healthcare professionals than both trough and peak concentrations. However, due to the results of this study, the interchangeable use of the methods needs further consideration.

4. CONCLUSIONS

AUC values estimated by the Bayesian one-concentration tended to exceed Bayesian two-concentration and the first-order pharmacokinetic equation. All comparisons had high correlation and acceptable clinical agreements, but there were significant differences. The Bayesian two-concentration and one-concentration methods demonstrated the highest clinical agreement. However, the three compared methods had significant variability, so their interchangeability in clinical practice needs to be carefully considered.

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