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ORIGINAL ARTICLE

Comparison of the mathematical equation and trapezoidal approach for 24 h area under the plasma concentration-time curve calculation in patients who received intravenous vancomycin in an acute care setting

Pimonrat Chanapiwat[1] | Taniya Paiboonvong[2] | Pinyo Rattanaumpawan[3] | Preecha Montakantikul[4]

[1]Department of Pharmacy, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[2]Department of Pharmacy Practice, College of Pharmacy, Rangsit University, Pathum Thani, Thailand

[3]Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[4]Division of Clinical Pharmacy, Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand

Correspondence
Preecha Montakantikul, Division of Clinical Pharmacy, Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand.
Email: preecha.mon@mahidol.ac.th

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Abstract

The current recommendation for therapeutic monitoring of vancomycin has recently suggested AUC-guided dosing in patients with serious methicillin-resistant *Staphylococcus aureus* infections. The study objective was to evaluate mathematical equations and trapezoidal methods for calculating the 24 h area under the plasma vancomycin concentration-time curve (AUC24). The analysis of plasma vancomycin concentrations was performed in 20 adult patients treated with intravenous vancomycin. For each patient, AUC24 was estimated using two methods including, equation and trapezoidal calculation. The AUC24 from two methods was analyzed for correlation. The correlation between the equation and trapezoidal methods was strong. The coefficient of determination (R^2) values was greater than .99. The two plasma vancomycin concentrations to achieve the highest correlation were concentration at 2.5 to 3 h after starting the infusion and concentration at 1 h before the next dose. Moreover, the AUC24 calculation from trapezoidal and equation methods showed that 19 out of 20 patients (95%) had AUC24 of more than 400 mg·h/L, and more than 50% in this group had AUC24/MIC greater than 600. Of those patients with AUC-trapezoidal >600, 15.38% of patients had trough under 15 mg/L, 15.38% of patients had trough in the range 15 to 20 mg/L and 69.23% of patients had trough more than 20 mg/L. The results of AUC-equation were similar to those of the AUC-trapezoidal method. Our study confirmed that the AUC monitoring is more appropriate than the trough vancomycin concentration. Given these considerations, the AUC-equation method is better and more practical to use in part of a point-of-care treatment, especially in the part of the Bayesian program is not available. The best sampling time point of the peak concentration was 0.5–1 h after 2-h infusion.

KEYWORDS
area under curve, equation method, monitoring, vancomycin

Abbreviations: AUC, area under the plasma concentration-time curve; BMD, broth microdilution; MRSA, Methicillin-resistant *Staphylococcus aureus*; TBW, total body weight.

1 | INTRODUCTION

Vancomycin is an antimicrobial agent for the treatment of Gram-positive bacterial infections and is the drug of choice for Methicillin-resistant *Staphylococcus aureus* (MRSA) infection.[1] Vancomycin is also used for infections caused by Methicillin-susceptible organisms in patients who are allergic to penicillins or cephalosporins. The vancomycin treatment target is the ratio of the 24-h area under the plasma concentration-time curve (AUC) to the minimum inhibitory concentration (MIC).[2] The current recommendation for therapeutic monitoring of vancomycin in patients with serious MRSA infections has recently suggested AUC-guided dosing and monitoring. The use of vancomycin trough concentrations of 15–20 mg/L as a surrogate marker for the target AUC 400 mg·h/L is no longer recommended. The new vancomycin consensus guidelines have recommended AUC/MIC of 400–600 mg·h/L, assuming a broth microdilution (BMD) MIC of 1 mg/L to achieve clinical efficacy and safety.[3] Some studies support the 2020 guidelines by which some patients who had trough concentration in target level of 15–20 mg/L may not achieve the AUC target of ≥400, and more than half of patients may achieve the target despite their trough concentration was below 15 mg/L.[4] Therefore, AUC-guided dosing is preferred over trough-guided dosing. However, AUC-trapezoidal calculation is not feasible in clinical practice since multiple samples are required from an individual patient.

Pai et al recently proposed methods for AUC calculation based on mathematical equations using 2-point concentrations by measuring a peak concentration (C_p) after the end of infusion, and a trough concentration (C_T) before the next dose within the same dosing interval.[5] Regarding vancomycin pharmacokinetics, it was best described by a two-compartment model, showing an alpha-distribution phase of 0.5 to 1 h after a 1-h infusion in patients who have normal creatinine clearance. This has important implications for C_p sampling drawn after finishing the distribution phase to use a first-order, one-compartment PK equation to estimate AUC. Thus, the C_p sampling has been generally suggested to be taken approximately 1 to 2 h after the end of infusion. This approach has been advocated by the revised guideline recommendation likewise Bayesian-estimated AUC using the one-trough concentration sampling.[3] Although the Bayesian approach is preferred to estimate AUC values, this tool is limited for many institutions. Therefore, this study aimed to evaluate the correlation between two methods for the calculation of AUC for utilization in the Thai population and to identify the appropriate peak sampling time for the best correlation.

2 | MATERIALS AND METHODS

The study was conducted at Siriraj Hospital, Mahidol University, Bangkok, Thailand from October 2016 to August 2017. The research protocol was approved by the Institutional Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (certification of approval number 288/2016). Patients were included in the study if they were 18 years of age or older, and received intravenous vancomycin for at least 72 h adjusted by his/her renal clearance function. Exclusion criteria included end-stage renal disease, undergoing dialysis or continuous renal replacement therapy, pregnancy or breastfeeding, serum albumin below 2 g/dl, having an active cancer disease, receiving chemotherapy, and a history of allergy to vancomycin. All eligible patients provided informed consent. Patients received 25 to 30 mg/kg of total body weight (TBW) of loading dose vancomycin, then followed by 15 to 20 mg/kg of TBW every 8, 12, 24, or 72 h adjusted by individual renal function. The infusion time is based on a rate of no more than 10–15 mg/min to avoid infusion-related reactions.

Seven blood samples were taken from each patient for measurement of vancomycin concentrations at the steady state in the same interval dosing. Blood samples for peak and trough concentrations were collected at 0.5 and 1 h after the end of infusion ($C_{2.5}$ and C_3), and 1 h before the next dose (C_T), respectively. The infusion time was 1 and 2 h for doses of 500 mg and 750–1500 mg, respectively. According to the dosing interval of vancomycin, the serial plasma concentrations were collected as follows: The patients who had received vancomycin dosing interval of 8 h, had blood samples taken at 0, 2, 2.5, 3, 4, 6, and 7 h after starting the infusion. The patients who had received vancomycin dosing intervals of 12 h had blood samples taken at 0, 2, 2.5, 3, 4, 8, and 11 h after starting the infusion. The patients who had received vancomycin dosing intervals of 24 h had blood samples taken at 0, 2, 2.5, 3, 11, 17, and 23 h after starting the infusion. The patients who received vancomycin dosing intervals of 48 h had blood samples taken at 0, 2, 2.5, 3, 11, 30, and 47 h after starting the infusion. The patients who received vancomycin dosing intervals of 72 h had blood samples taken at 0, 2, 2.5, 3, 11, 47, and 71 h after starting the infusion. The blood samples collected by time and dosing interval are shown in supplement section.

All vancomycin concentrations were analyzed by Chemiluminescence Microparticle Immunoassay (CMIA; TDx, Abbott Laboratories). The minimum quantifiable vancomycin concentration was 0.24 mg/L. Seven vancomycin concentrations of each patient were then calculated for the AUC value. There were two methods for vancomycin AUC calculation. The first method was the "trapezoidal method" which requires all concentrations for calculation (AUC-trapezoidal). The second method requires only two vancomycin concentrations for AUC calculation (equation method). The equation method was derived from a mathematical model comprised of two equations.[5] The two equations are equations A and B (supplement) and the AUCs that were calculated from equations A and B were called "AUC-equation A" and "AUC-equation B," respectively. The calculation of AUC from the equation method used two of the seven vancomycin levels and alternatingly switched the pair of levels until all was done. Vancomycin AUC24 of dose interval was calculated as follows; 8-h interval by multiplying by 3 (AUC8 × 3), 48-h interval, or 72-h interval by dividing by 2 (AUC48/2) or 3 (AUC72/3), respectively. The data analysis was demonstrated as mean and standard deviation (SD) if data were normally distributed. For non-normal distributions, data were presented as the median and interquartile range (IQR). The relationship between the equation method and the trapezoidal method was

analyzed using correlation analysis as well as regression analysis. The association of two continuous variables was presented as the coefficient of determination (R^2). Data were analyzed by SPSS statistic 18.

3 | RESULTS

Twenty adult patients were enrolled in this study (6 males and 14 females) with a mean age of 63.75 ± 18.44 years, a mean total body weight (TBW) of 58.88 ± 12.99 kg, and a mean creatinine clearance of 71.09 ± 37.33 ml/min. All patients received a loading dose with a mean loading dose of 25.67 ± 2.08 mg/kg of TBW and a mean maintenance dose of 16.37 ± 5.07 mg/kg of TBW. All patients received vancomycin with a median dosing interval of 12 h (range 8–48 h), and no patient received a vancomycin dosing interval of 72 h. The baseline characteristics, trough vancomycin concentrations, and AUC-trapezoidal of each patient are shown in Table 1. There were 5 (25%), 6 (30%), and 9 (45%) patients who had trough vancomycin concentrations of <15, 15 to 20, and >20 mg/L, respectively. The correlation of trapezoidal AUCs has shown a strong relationship with the equation method when AUC-equation A and B were performed from concentrations at 2.5 h ($C_{2.5}$) and 1 h before true trough (C_T), or 3 h (C_3), and 1 h before true trough (C_T) as shown in Figure 1. The median (IQR) of calculated AUC-trapezoidal was 664.60 (203.22) mg·h/L while the median (IQR) of AUC-equation A and AUC equation B were 697.25 (202.99) mg·h/L and 663.89 (211.91) mg·h/L, respectively. For AUC-equation A, the best correlation to AUC-trapezoidal was from C_3 and C_T of vancomycin concentrations (R^2 = .9932) while AUC-equation B had found the best correlation to AUC-trapezoidal when calculated from $C_{2.5}$ and C_T (R^2 = .9961). The calculated AUCs from equation methods tended to over-predict when compared with a trapezoidal method as presented in Table 2. A median (IQR) of AUC-equation A to AUC trapezoidal and AUC-equation B to AUC trapezoidal ratio were 1.04 (0.05) and 1.04 (0.08), respectively. In addition, we also found a good correlation (R^2 = .970 in Eq-A, and R^2 = .978 in Eq-B) among the patients with abnormal renal function (dosing interval 24–48 h).

For the calculated AUCs from trapezoidal and equation methods, 19 out of 20 patients (95%) had AUC24 of more than 400 mg·h/L. We categorized patients into three groups by trough concentrations of <15, 15 to 20, and >20 mg/L which are represented in Figure 2. For AUC-trapezoidal (Figure 2A), 20%, 40%, and 40% of patients in the first group had AUC24/MIC of <400, 400 to 600, and >600, respectively. In the second group, 0%, 66.67%, and 33.33% had AUC24/MIC of <400, 400 to 600, and >600, respectively. Lastly, all patients (100%) in the third group with trough concentrations over 20 mg/L had AUC24/MIC of >600. Likewise, the results of the AUC-equation method were similar to the AUC-trapezoidal method (Figure 2B,C).

4 | DISCUSSION

Using AUC for vancomycin monitoring was not practical due to the difficulty of techniques and calculation. Even though the Bayesian method is widely used in the western country, there is no generally validated program in Thailand. This study aimed to compare methods for AUC calculation, mathematical equations, and trapezoidal approaches using correlation. We found a relatively strong correlation between the two approaches. The highest R^2 were .9932 and .9961 of AUC-equation A (C_3–C_T) and B ($C_{2.5}$–C_T), respectively. Our results were similar to the study of Pai et al, which compared the equation method with the Bayesian method. The result demonstrated that R^2 values were .987 for AUC from equation A and .971 for AUC from equation B method.[5] However, their study used the Bayesian method that the AUCs were determined from predicted population pharmacokinetic parameters, which was a different method for AUC calculation from our study. Interestingly, we tested C_P–C_T pairs that included C_P values after starting the infusion at 2.5 and 3 h (0.5 and 1 h after the end of 2-h infusion) and C_T (1 h before the next dose) to clarify the best-correlated sampling time (results are shown in Table 2 and Figure 1). This may differ from Pai et al. that tested C_P between 1 and 3 h after the end of infusion. We found that the C_P at 0.5 to 1 h after the end of 2-h infusion showed the best correlation, compared to the C_P at 1.75 to 3 h after 1.5-h infusion as Pai et al. with the Bayesian approach. Nonetheless, our analysis showed that the trough concentration did not always correspond to vancomycin AUC24. All of our patients who had the trough range of 15 to 20 mg/L achieved the target AUC24/MIC over 400. On the contrary, patients who had a trough below 15 mg/L achieved the target AUC24/MIC over 400 in up to 80%. Most of the patients in our study had normal renal function (most of the dosing regimens were 1000 mg every 12 h). The patient who had abnormal renal function was a small group (7 patients), which did not result in a different correlation compared to the group with normal renal function.

Our findings are consistent with several previous studies that reported that the trough concentrations did not correlate well with the AUC.[4,6,7] The study of Hale et al showed that patients who had trough concentrations <15 or 15–20 mg/L achieved AUC24/MIC ≥400 in 50% and 45% of those patients, respectively.[4] Similar to Bel et al., the significant correlation between AUC24 and trough was moderate (R^2 = .51), which 30% and 95% of patients with a trough concentration <15 and over 15 mg/L had the AUC24/MIC ≥400.[6] The study by Neely et al. found that 68% of patients with a trough concentration <15 mg/L had AUC ≥400 mg·h/L.[7] Furthermore, Finch et al. showed that AUC-guided dosing can reduce nephrotoxicity incidence (40%) due to decreased vancomycin exposure. Of those, AUC24 > 400 mg·h/L, but the troughs were less than the trough-guided dosing group (p < .001).[8] Considering obese patients, we found that 50% of patients who had BMI > 25 with trough in ranged 15–20 mg/L had AUC > 600 mg·h/L. Consistent with a recent study in obese patients, vancomycin monitoring with AUC24 was associated with a decreased risk of acute kidney injury (AKI) when compared with trough monitoring (OR 0.61; 95% CI, 0.42–0.89; p = .010).[9] These also supported the 2020 guidelines that recommend AUC-guided dosing instead of trough concentration.

In addition, the AUC thresholds for nephrotoxicity are varied, but more previous evidence showed that nephrotoxicity increased

TABLE 1 The baseline characteristics, trough vancomycin concentrations, and AUC-trapezoidal of each patient.

Patients	Age (years)	Total body weight (kg)	Scr (mg/dl)	CrCL (ml/min)	Albumin (g/dl)	Dosing interval (h)	Maintenance dose (mg/kg/dose)	Trough vancomycin (mg/L)	AUC-Trapezoidal (mg·h/L)	AUC_{Trap} 24 (mg·h/L)
1	31	40	0.36	142.98	2.5	8	25.00	22.16	267.47	802.40
2	45	57.7	0.55	117.66	2.8	12	17.33	21.11	461.53	923.06
3	93	56	0.81	45.13	2.7	24	17.86	7.98	367.78	367.78
4	87	60.1	0.60	52.25	2.3	12	16.64	23.80	365.17	730.33
5	70	60	0.49	82.94	2.3	12	13.33	22.38	363.69	727.39
6	81	47.5	1.76	18.74	2.8	48	21.05	20.15	1399.14	699.57
7	65	59	0.81	75.87	4.1	12	25.42	13.86	332.33	664.66
8	78	70	0.64	57.30	2.3	24	10.71	19.89	565.53	565.53
9	41	71	1.00	90.26	3.1	12	17.61	14.82	330.82	661.64
10	52	48	1.39	42.21	3.0	24	10.42	16.43	513.32	513.32
11	58	90	0.92	78.98	3.4	12	7.50	21.42	308.63	617.27
12	62	68	1.35	33.55	2.6	24	11.03	12.24	461.62	461.62
13	66	79	0.74	105.22	3.2	12	15.19	17.08	289.46	578.93
14	38	47	0.68	83.23	2.1	12	10.64	17.61	333.37	666.75
15	63	51.2	0.74	61.54	3.0	12	19.53	26.46	479.68	959.37
16	66	68	0.33	156.99	3.1	8	14.71	20.12	221.51	664.53
17	38	43	0.82	63.15	2.8	12	23.26	20.14	366.67	733.34
18	75	50	0.78	49.19	2.4	12	20.00	19.26	333.52	667.03
19	93	59	0.88	34.49	2.1	24	12.71	15.49	461.70	461.70
20	73	43	1.13	30.10	2.2	48	17.44	10.60	805.59	402.79
Mean ± SD	63.75 ± 18.44	58.38 ± 12.99	0.84 ± 0.35	71.09 ± 37.33	2.74 ± 0.50	12 (8–48)[a]	16.37 ± 5.07	18.15 ± 4.63	451.42 ± 257.60	643.45 ± 155.47

Abbreviations: AUC_{Trap}24, the 24-h area under the plasma concentration-time curve was calculated from the trapezoidal method from the 1st dose in the given dosing interval; CrCL, creatinine clearance by Cockcorft-Gault method; dl, deciliter; h, hour; kg, kilogram; mg, milligram; ml, milliliter; min, minute; Scr, serum creatinine; SD, standard deviation.

[a]Median(range).

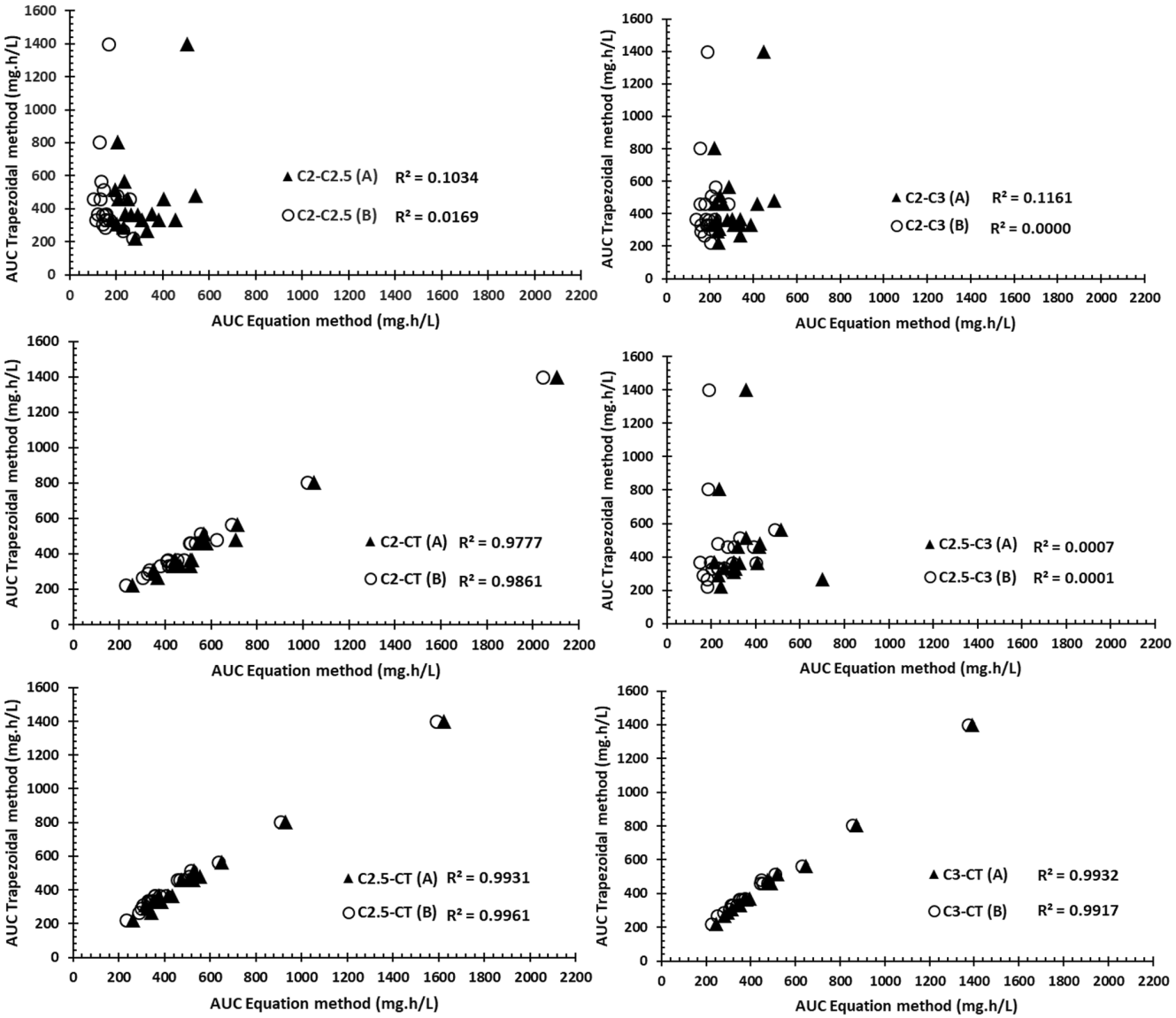
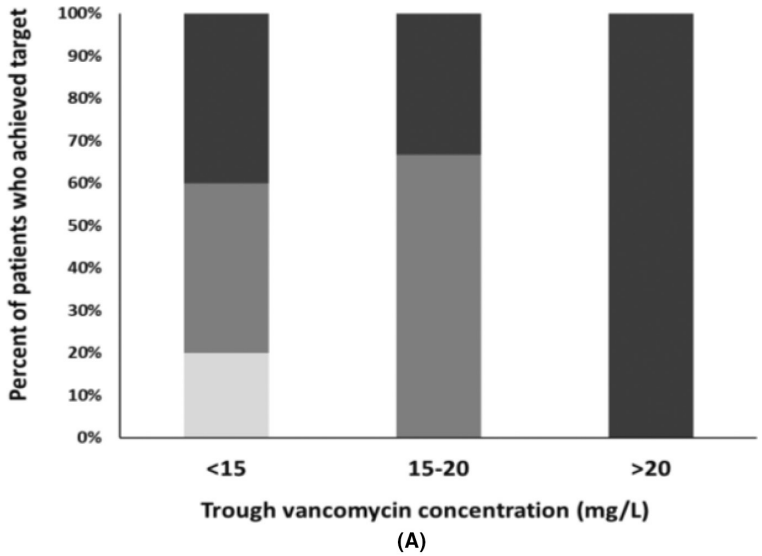


FIGURE 1 Correlation between calculated AUC (mg·h/L) by Method 1 (trapezoidal method) and Method 2 (equation method; AUC-equation A method (▲), AUC-equation B method (○) classification by pair of serum vancomycin concentrations were brought to determine AUC from equations A and B. C_2: vancomycin concentration at the end of infusion, $C_{2.5}$: vancomycin concentration at 2.5 h after starting the infusion, C_3: vancomycin concentration at 3 h after starting the infusion and C_T: vancomycin concentration before the true trough concentration 1 h, R^2: the coefficient of determination.

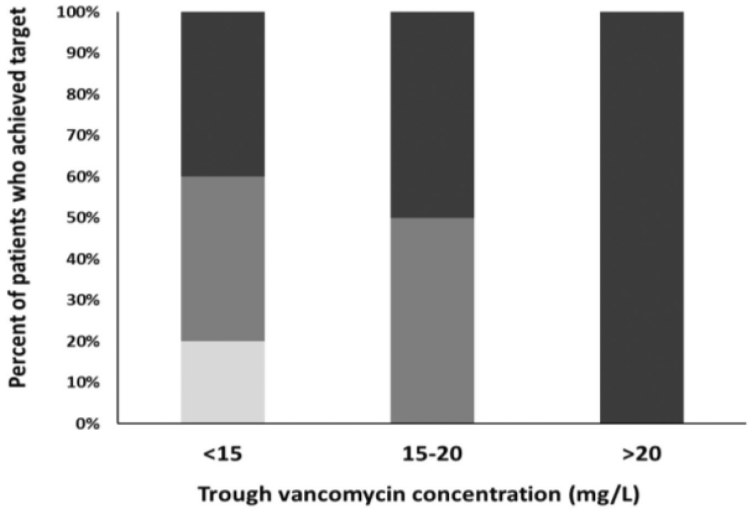
TABLE 2 Median (Interquartile range, IQR) area under the curve (AUC) values, the ratio of calculated AUC to reference AUC values, and coefficient of determination (R^2) for the trapezoidal method and equation-method from all patients.

AUC methods	Concentration for calculation	AUC_{24} (mg·h/L)	Ratio of calculated AUC_{24} to reference AUC_{24}	R^2
Trapezoidal	All	664.60 (203.22)	Reference	Reference
Equation A	$C_{2.5}$–C_T	732.23 (251.06)	1.13 (0.12)	0.9931
	C_3–C_T	697.25 (202.99)	1.04 (0.05)	0.9932
Equation B	$C_{2.5}$–C_T	663.89 (211.91)	1.04 (0.08)	0.9961
	C_3–C_T	632.65 (178.46)	0.98 (0.05)	0.9917

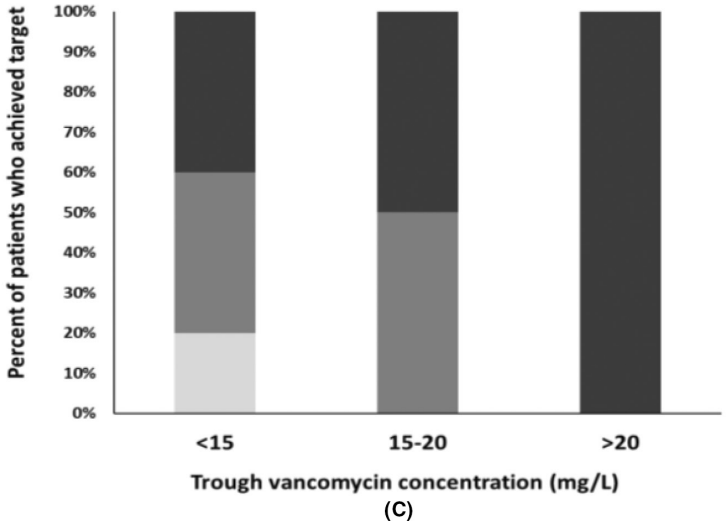
Abbreviations: $C_{2.5}$, vancomycin concentration at 2.5 h after starting the infusion; C_3, vancomycin concentration at 3 h after starting the infusion; C_T, vancomycin concentration before the true trough concentration 1 h; R^2, the coefficient of determination.



(A)



(B)



(C)

FIGURE 2 Distribution of AUC24/MIC values (MIC = 1 mg/L) according to various groups of trough vancomycin concentrations. AUCs24 were calculated from the trapezoidal method (A), equation A method (B), and equation B method (C). (■ AUC/MIC >600, ■ AUC/MIC 400–600, ■ AUC/MIC <400).

in patients with AUC > 600 mg·h/L.[10–16] A meta-analysis reported that the incidence of AKI in AUC-guided monitoring was lower than in trough-guided monitoring (OR 0.54, 95% CI 0.28–1.01).[17] Implement AUC-based dosing protocol using two concentrations can improve the therapeutic vancomycin target and reduce nephrotoxicity.[7,13,14] As mentioned above, our results found that patients who had AUC24/MIC >600 were not only from patients who had higher trough concentrations but also from trough under 15 mg/L or in the target range. Consequently, if we managed vancomycin monitoring by trough concentration, we need to increase the vancomycin dose in patients with troughs under 15 mg/L to achieve the target goal. The patients are undeniably taking risk of nephrotoxicity from AUC24/MIC >600.

To the best of our knowledge, monitoring the AUC of vancomycin to keep the target at 400 to 600 mg/L is by far the better approach for maximizing efficacy and minimizing nephrotoxicity. Additionally, the AUC-based dosing protocol with multidisciplinary team (MT) supports significantly improved adherence with the protocol, associated with a lower 30-day mortality rate and a trend toward reduction in nephrotoxicity.[18] We suggested calculating AUC from peak and trough vancomycin concentrations obtained during the elimination phase of vancomycin (C_P is 0.5 or 1 h at the end of 2-h infusion and C_T is 1 h before the next dose) that showed the best correlation with the AUC trapezoidal method. Our study supports current recommendations of the AUC-based monitoring to the target values of 400–600 mg·h/L using two-point pharmacokinetics calculation.

Limitations of our study were moderate sample size, and the use of the trapezoidal method as a reference for AUC calculation instead of the Bayesian method. Additionally, our AUCs were calculated from serial blood sampling of vancomycin concentrations in the same dose for each patient. Moreover, our study did not evaluate clinical outcomes or nephrotoxicity in all patients.

5 | CONCLUSIONS

Individualized AUC monitoring is more appropriate than the trough vancomycin concentration. The optimal method for the determination of AUC24 is the AUC-equation method because it uses only two serum vancomycin concentrations for calculation and is more practical to use in part of the point-of-care treatment, especially in a country where the Bayesian program is not widely used. The best sampling time point of the peak concentration was 0.5 to 1 h after 2-h infusion. Further studies need to evaluate clinical outcomes in patients with AUC monitoring by the equation method.

AUTHOR CONTRIBUTIONS

Pimonrat Chanapiwat was involved in the investigation, data collection, initial data analysis, and drafting of the manuscript. Taniya Paiboonvong reviewed and edited the final manuscript. Pinyo Rattanaumpawan is involved in the investigation, project administration, grant acquisition, and supervision of the study. Preecha Montakantikul conceptualized the study design, performed the final analysis, and finished the final manuscript. All authors have read and agreed to the published version of the manuscript.

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DISCLOSURE

PR received a research grant and speaker honorarium from Siam Pharmaceutical Company. All other authors declare no conflict of interest. The sponsors did not involve in the manuscript preparation process.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed for this study are available from the corresponding author upon request.

ETHICS STATEMENT

The study protocol was approved by the Siriraj Research Ethic Committee (certification of approval number 288/2016).

ORCID

Pimonrat Chanapiwat https://orcid.org/0000-0003-4564-7900
Taniya Paiboonvong https://orcid.org/0000-0001-6193-6433
Pinyo Rattanaumpawan https://orcid.org/0000-0002-2964-6732
Preecha Montakantikul https://orcid.org/0000-0001-6782-2939

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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