ORIGINAL ARTICLE

Maximizing Vancomycin Efficacy Through Optimal Dosing Strategy: A Comparison of Trough Concentration and Area Under the Curve-based Strategies for Achieving Therapeutic Levels

Ong Bee Yean

Department of Pharmacy, Hospital Enche' Besar Hajjah Khalsom, KM 5, Jalan Kota Tinggi, 86000 Kluang, Johor, Malaysia

ABSTRACT

Introduction: The transition from trough-guided dosing to an area under the concentration-time curve (AUC)-guided dosing strategy was implemented to enhance treatment response and minimize unnecessary vancomycin exposure. This study compared the achievement of therapeutic targets, total daily dose of vancomycin required to reach the target, and the incidence of vancomycin-associated nephrotoxicity between the two dosing strategies. **Materials and methods:** This prospective cohort study involved 40 adult patients with methicillin-resistant *Staphylococcus aureus* infection who received intermittent intravenous vancomycin using an AUC-guided dosing strategy. The retrospective comparison group consisted of 65 patients who received vancomycin with a trough-guided dosing approach. Daily AUC was calculated using two-point serum vancomycin concentrations and first-order pharmacokinetic equations. **Results:** In the trough-guided dosing group, only 13 (20%) of 65 initial trough levels were therapeutic, compared to 17 (42.5%) of 40 initial AUC values in the AUC-guided dosing group (p= 0.013). The AUC-guided dosing group required a significantly lower mean daily vancomycin dose (2085.94 ± 958.01 mg) to achieve therapeutic goals compared to the trough-guided dosing group (2669.05 ± 1034.58 mg, p= 0.016). Nephrotoxicity occurred in 16.9% of trough-guided patients and 5% of AUC-guided patients (p= 0.072). **Conclusion:** Compared to trough-guided dosing, AUC-guided dosing with two-point sampling improved therapeutic target attainment and resulted in lower mean daily vancomycin doses. Although the reduction in nephrotoxicity incidence was not statistically significant, this study provides valuable evidence supporting the transition to AUC-guided dosing for optimizing vancomycin dosage.
Malaysian Journal of Medicine and Health Sciences (2024) 20(6): 270-277. doi:10.47836/mjmhs20.6.35

Keywords: Vancomycin, Therapeutic drug monitoring, Pharmacokinetics, Area under curve, Methicillin-resistant *Staphylococcus aureus*

Corresponding Author:
Ong Bee Yean, MMedSc
Email: ongbeeyean@gmail.com
Tel : +607-7787000

INTRODUCTION

Vancomycin, an antibiotic classified as a glycopeptide, is employed in the treatment of Gram-positive bacterial infection (1). Despite being introduced over half a century ago, the optimal dosing strategy remains undefined, leading to potential nephrotoxicity in patients (2).

Several guideline bodies have recommended maintaining vancomycin concentration between 15 and 20 mg/L, particularly in complicated infections attributed to methicillin-resistant *Staphylococcus aureus* (MRSA), such as bacteremia, endocarditis, osteomyelitis, meningitis, and nosocomial pneumonia (3). Trough concentrations between 15 and 20 mg/L are recommended to enhance the probability of reaching the daily area under the concentration-time curve (AUC24) goal of 400 mg.hour/L (4). However, an earlier prospective multicenter trial in South Carolina, United States showed that a vancomycin trough concentration of more than 15 mg/L appears to be associated with a three-fold risk of nephrotoxicity (5). Thereafter, the endorsement for vancomycin dosing strategies targeting trough concentrations of 15 to 20 mg/L has been withdrawn, citing a lack of efficacy evidence and an elevated risk of nephrotoxicity (6).

Recent consensus guidelines no longer support trough monitoring as a surrogate for optimal dosage and safety. Instead, they advocate AUC-based dosing for most infections, targeting AUC24 to minimum inhibitory concentration (MIC) ratios of 400 to 600 mg.hour/L, under the assumption of a MIC value of 1 mg/L for clinical effectiveness (7). Recent evidence has also shown that the AUC-guided dosing provides better exposure estimates than the vancomycin trough concentration (8). Additionally, AUC24 nomograms have shown effective achievement of the AUC24 targets, ensuring a minimum of 400 mg.hour/L, even with more conservative troughs ranging from 10 to 15 mg/L (6). Therefore, adhering strictly to the prior recommendation of maintaining vancomycin trough concentration between 15 and 20 mg/L is often unnecessary to reach the AUC24 target. Concerns arise as our hospital practices administering vancomycin at doses aiming for trough concentrations of 15 mg/L or higher, potentially leading to overexposure and an elevated risk of nephrotoxicity (4). To address this, our hospital switched to AUC-guided dosing in April 2022. This study aimed to compare therapeutic target achievement after the switch and assess its impact on vancomycin-associated nephrotoxicity as part of our vancomycin-per-pharmacy protocol.

MATERIALS AND METHODS

Study Design and Setting

This prospective cohort study was conducted over 1 year from May 2022 to April 2023 at the Pharmacy Department of Hospital Enche' Besar Hajjah Khalsom, Kluang. An AUC-guided vancomycin dosing protocol was implemented hospital-wide on 1st April 2022, utilizing two-point sampling (peak and trough) and first-order pharmacokinetic equations. The pre-implementation retrospective comparison cohort comprised patients whose vancomycin dosage was adjusted based on a trough-guided dosing approach between 1st April 2021 and 31st March 2022. The post-implementation group included patients who received the dose of vancomycin as part of an AUC-guided dosing strategy between 1st May 2022 and 30th April 2023.

Estimation of Sample Size

The sample size was determined using Power and Sample Size Calculation version 3.1.2. Based on the previous study (9), the rate of attainment of therapeutic trough levels among the trough-guided dosing group was 0.19. If the true attainment rate for AUC-based dosing subjects was 0.70, we would have to study 18 AUC-guided dosing subjects and 18 trough-guided dosing subjects to reject the null hypothesis, assuming the attainment rates of both groups were equal, with a power of 0.80 and an alpha of 0.05. Accounting for an estimated attrition rate of 20%, the designated sample size was 23 patients per group.

Study Population and Sampling

This study recruited hospitalized patients who received an intermittent intravenous infusion of vancomycin to treat susceptible pathogens and who underwent therapeutic drug monitoring (TDM) in the hospital during the pre- or post-implementation phase of the AUC-guided dosing strategy. All eligible patients were enrolled in the study until the required sample size was reached. Patients aged 18 years or older were eligible for inclusion if they had at least one trough concentration measured after receiving a minimum of three doses of intravenous vancomycin in the pre-implementation group, and if they had at least one calculated AUC value in the post-implementation group. Patients with acute kidney injury (AKI), chronic kidney disease (CKD), or end-stage renal failure (ESRF) who were receiving renal replacement therapy before starting vancomycin therapy were excluded from the study. AKI was characterized as either an elevation in serum creatinine (SCr) concentration of at least 0.3 mg/dl within 48 hours or 50% of baseline within 7 days, a decrease in creatinine clearance by 25 to 50%, or urine output below 0.5 ml/kg/hour for six consecutive hours (10,11,12). We excluded patients who had no SCr measured before or during the receipt of vancomycin, or who had no trough levels measured before the onset of nephrotoxicity (for patients experiencing nephrotoxicity). Patients allergic to vancomycin or receiving a single dose of vancomycin and patients whose planned duration of treatment was less than 3 days were excluded from the study.

Study Outcomes

The primary outcome was the achievement of therapeutic AUC values of 400 to 600 mg.hour/L in the post-implementation group or therapeutic trough levels of 10 - 20 mg/L in the pre-implementation group. Secondary outcomes included the differences in total daily dose and rates of vancomycin-associated nephrotoxicity between conventional trough-guided dosing and AUC-guided dosing, as well as an assessment of the characteristics of patients who experienced nephrotoxicity. Vancomycin-associated nephrotoxicity was characterized by a rise in SCr of at least 44.2 umol/L or 50% from baseline, sustained for a minimum of two consecutive days after receiving vancomycin up to 72 hours following the last dose, and primarily attributed to vancomycin rather than another cause (12,13). Patients with an isolated, documented increase in SCr that resolved within 24 hours of retesting were not classified as nephrotoxicity.

Dosing Strategies

Our hospital guidelines recommended different dosing regimens for vancomycin depending on the indication and the target trough concentration. During the pre-implementation phase, the recommended target trough level at the steady-state was 10 to 20 mg/L for susceptible uncomplicated infections (for instance, cellulitis, urinary tract infection, and uncomplicated skin and soft tissue infections), and 15 to 20 mg/L for complicated infections or susceptible pathogens with an MIC of at least 1 mg/L (for instances, bacteremia, endocarditis, osteomyelitis, meningitis and pneumonia). Per institutional protocol, steady-state trough levels were drawn within 30 minutes prior to the fourth dose of vancomycin, and again every

3 to 4 days or in case of significant alterations in renal function.

In the post-implementation phase, the target AUC24 for most infections was 400 to 600 mg.hour/L, including all sources of bacteremia, endocarditis, bone or joint infection, necrotizing fasciitis, pneumonia, skin and soft tissue infections, unknown sources of sepsis and as empirical therapy. At the estimated steady state, we utilized both peak and trough concentrations to compute the AUC24 using 2-point serum vancomycin concentrations and first-order pharmacokinetic equations (Table I) (14). The vancomycin regimen was then adjusted to achieve the desired AUC24. Vancomycin peak concentrations were collected one hour post-infusion to account for drug distribution. The secondary outcome involved comparing the recommended dose based on trough concentration with the prescribed dose needed to reach a target AUC24 of 400 to 600 mg.hour/L. The serum vancomycin concentrations were analyzed with a particle-enhanced turbidimetric inhibition immunoassay (PETINIA).

Table I: First-order Pharmacokinetic Equations

Variable	Equation
Elimination rate constant, Ke (h^{-1})	ln Cpost – ln Cpre / Δt , where Cpost is the measured peak, Cpre is the measured trough, Δt is the difference in time between these two concentrations
Concentration at start of infusion, Csoi (mg/L)	Cpost x $e^{Ket'}$, where t' is the interval between "start of infusion" and post-sampling time
Concentration at the end of dosing interval, Ctrough or Ct (mg/L)	Cpre x $e^{-Ket''}$, where t" is the interval between trough concentration and dosing time
Area under the concentration-time curve per dose, $AUC_{per\ dose}$ (mg.hour/L)	Csoi - Ct / Ke
Daily area under the concentration-time curve, AUC_{24} (mg.hour/L)	$AUC_{per\ dose}$ x number of dose per day

Data Collection and Measurement Tools
The process of data collection is depicted in Fig. 1. Data were obtained from patients' electronic pharmacy records - the Pharmacy Information System (PhIS), the TDM Request Form, and the HC Lab. Data variables included age, gender, height, weight, body mass index, Intensive Care Unit (ICU) stay, culture results, renal profile before and during vancomycin treatment, occurrence of nephrotoxicity, as well as vancomycin indication and dosing regimens including dose, frequency, serum concentration data and calculated AUC values. In patients who developed nephrotoxicity, initial troughs or AUC24, baseline SCr, vancomycin treatment days at which nephrotoxicity occurred, duration of treatment with vancomycin, and concomitant use of nephrotoxic medications including aminoglycosides, piperacillin/tazobactam, intravenous frusemide, inotropes and others were determined. All the data were recorded in the self-designed data collection form.

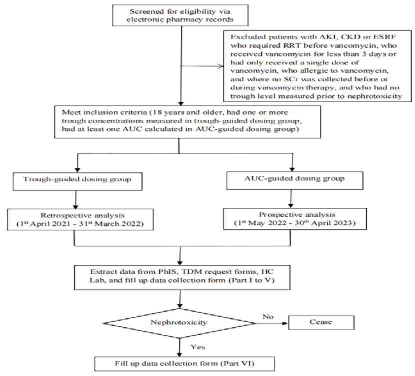

Figure 1: Flowchart of data collection process. AKI = acute kidney injury; CKD = chronic kidney disease; ESRF = end-stage renal failure; RRT = renal replacement therapy; SCr = serum creatinine; AUC = area under the concentration-time curve; PhIS = Pharmacy Information System

Data Analysis
Statistical analyses were conducted utilizing SPSS software version 26.0. Before conducting the data analysis, normality tests were performed to assess data distributions. Categorical variables were expressed as numbers and percentages, while continuous variables were reported using either mean and standard deviation (SD) or median and interquartile range, as appropriate. The differences between groups including the rate of achieving therapeutic targets and the incidence of vancomycin-associated nephrotoxicity were evaluated using the Pearson Chi-square test. A two independent-sample t-test was employed to compare the total daily doses between the trough-guided and AUC-guided dosing strategies. Additionally, patient characteristics with and without vancomycin-associated nephrotoxicity were assessed using the Pearson Chi-square test and two independent-sample t-test, respectively. In all analyses, a p-value of less than 0.05 (two-tailed) was deemed to be statistically significant.

Ethical Clearance
This study was approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR ID-22-00055-IKE). The authorization to gather data was granted by the director of Hospital Enche' Besar Khalsom, Kluang.

RESULTS

Patient Characteristics
Throughout the study period, 189 MRSA patients were considered for potential eligibility. Of these, 84 patients were excluded - 29 were under 18 years of age, 54 had AKI, CKD, or ESRF, and one patient had received only a single dose of vancomycin. Although the calculated sample size was 23 patients per group, due to a higher number of eligible patients, we included all remaining eligible patients in the study. Out of the remaining 105 patients, 65 were assigned to the trough-guided dosing group, while 40 were allocated to the AUC-guided dosing

group. Baseline characteristics are detailed in Table II. Apart from the culture source, there were generally no substantial discrepancies observed between the groups in terms of demographic and clinical characteristics.

Table II: Baseline demographic and clinical characteristics of the study patients

Characteristics	Trough-guided Dosing Group (n=65)	AUC-guided Dosing Group (n=40)	P value
Age (years)	46.98 ± 19.06	47.05 ± 14.96	0.984
Age > 65 years	12 (18.5)	6 (15.0)	0.792
Gender			
Male	47 (72.3)	28 (70.0)	0.827
Female	18 (27.7)	12 (30.0)	
Body weight (kg)	69.70 ± 15.32	73.50 (14.99)	0.216
Intensive Care Unit stay	5 (7.7)	0 (0)	0.154
Serum creatinine (μmol/L)	74.91 ± 38.71	100.02 ± 73.44	0.051
Creatinine clearance (ml/min)	123.05 ± 67.64	108.69 ± 59.90	0.273
Source of culture			
Blood	24 (36.9)	7 (17.5)	
Tissue	27 (41.5)	27 (67.5)	0.048
Bone	6 (9.2)	3 (7.5)	
Swab	4 (6.2)	3 (7.5)	
Tracheal aspirate	2 (3.1)	0 (0)	
Others	2 (3.1)	0 (0)	
Indication for vancomycin therapy			
Bacteremia	24 (36.9)	7 (17.5)	0.055
Bone/ joint infection	18 (27.7)	10 (25.0)	
Skin & soft tissue infection	18 (27.7)	21 (52.5)	
Others	5 (7.7)	2 (5.0)	
Minimum Inhibitory Concentration of vancomycin (mg/L)			
Less than 1	34 (52.3)	16 (40.0)	
1	25 (38.5)	19 (47.5)	0.467
More than 1	6 (9.2)	5 (12.5)	
Days to first vancomycin serum level	2.55 ± 0.66	2.35 ± 0.48	0.072

Data are presented as mean ± standard deviation or number (percentage) of patients. n = number

Attainment of Therapeutic Target

Table III shows that only 20% (13 out of 65) of the initial trough levels were within the therapeutic range in the trough-guided dosing group, while 42.5% (17 out of 40) of the initial AUC values were therapeutic in the AUC-guided dosing group ($p < 0.05$). Subtherapeutic levels were more common in the trough-guided dosing group (64.6%) than in the AUC-guided dosing group (25%), with a significant difference of $p < 0.001$. On the other hand, the AUC-guided dosing group had a higher proportion of patients (32.5%) with supratherapeutic initial AUC values compared to the trough-guided dosing group (15.4%, $P < 0.05$). The relationship between initial AUC levels and initial trough levels in the AUC-guided dosing group was examined using Pearson Chi-square analysis. The analysis revealed a significant association between the two variables ($p < 0.001$). Specifically, of the observed AUC values ranging from 400 to 600 mg.hour/L, 37.5% corresponded to trough levels below 10 mg/L, 31.2% corresponded to trough levels between 10 and less than 15 mg/L, and 31.2% corresponded to trough levels between 15 and 20 mg/L (Table IV). These findings highlight the variability in trough levels that can correspond to therapeutic AUC ranges, underscoring the limitations of using trough levels alone for vancomycin dosing.

Table III: Initial trough and AUC values and their attainment rates in two vancomycin dosing strategies

Characteristics	Trough-guided Dosing Group (n=65)	AUC-guided Dosing Group (n=40)	P value
Initial trough concentration (mg/L)	12.63 ± 7.14	13.00 ± 6.36	0.782
Initial area under the concentration-time curve (AUC)			
AUC value (mg.hour/L)	NA	523.47±172.05	NA
Initial peak concentration (mg/L)	NA	27.97 ± 8.93	NA
Total initial vancomycin daily dose (mg)	2224.62 ± 646.88	2037.50 ± 785.59	0.188
Attainment of therapeutic initial target level			
Subtherapeutic	42 (64.6)	10 (25.0)	0.000
Within target range	13 (20.0)†	17 (42.5)	0.013
Supratherapeutic	10 (15.4)	13 (32.5)	0.039

Data are presented as mean ± standard deviation or number (percentage) of patients. n = number
†Refers to initial trough levels of 10 to 20 mg/L for susceptible uncomplicated infections (for instances, cellulitis, urinary tract infection, and uncomplicated skin and soft tissue infections) and 15 to 20 mg/L for complicated infections or susceptible pathogens with a minimum inhibitory concentration (MIC) of at least 1 mg/L (for instances, bacteremia, endocarditis, osteomyelitis, meningitis and pneumonia).
Refers to initial AUC values of 400 to 600 mg.hour/L for all sources of bacteremia, endocarditis, bone or joint infection, necrotizing fascilitis, pneumonia, skin and soft tissue infections, unknown sources of sepsis and as empirical therapy

Table IV: Association between initial AUC values and initial trough concentrations in AUC-guided dosing group

Initial AUC Values (mg. hour/L)	Initial Trough Concentration (mg/L) , n (%)			
	< 10	10 to < 15	15 to 20	> 20
< 400	10 (100.0)	0 (0)	0 (0)	0 (0)
400 to 600	6 (37.5)	5 (31.2)	5 (31.2)	0 (0)
> 600	1 (7.1)	4 (28.6)	2 (14.3)	7 (50.0)

Significant at P< 0.001 using Pearson Chi-square test. AUC = area under the concentration-time curve; n = number; % = percentage

Total Daily Dose to Reach Therapeutic Target Levels

Table V displays that six patients receiving trough-guided dosing and five patients receiving AUC-guided dosing were excluded from the analysis because they did not undergo repeat therapeutic monitoring of serum vancomycin concentrations, despite having initial subtherapeutic trough levels or AUC values. The group following AUC-guided dosing had a significantly higher percentage of achieving target levels at the first or subsequent therapeutic monitoring of serum vancomycin concentrations compared to the trough-guided dosing group (91.4% versus 71.2%, $P < 0.05$). The mean total daily dose required to achieve target therapeutic levels was also significantly lower in the AUC-guided dosing group compared to the trough-guided dosing group (28.30 ± 12.34 mg/kg/day versus 38.73 ± 13.26 mg/kg/day, P = 0.001). More than half of the AUC-guided dosing patients (53.1%) achieved target AUC without dose adjustment, while the majority of trough-guided patients (59.5%) required a single adjustment ($p < 0.05$).

Table V: Total daily dose, number of days and dosage adjustments to reach target therapeutic levels

Characteristics	Trough-guided Dosing Group (n=59)†	AUC-guided Dosing Group (n=35)	P value
Achieve target levels			
Yes	42 (71.2)	32 (91.4)	0.020
No	17 (28.8)	3 (8.6)	
Total daily dose required (mg/day)	2669.05 ± 1034.58	2085.94 ± 958.01	0.016
Total daily dose per body weight (mg/kg/day)	38.73 ± 13.26	28.30 ± 12.34	0.001
Number of dosage adjustments			
No adjustment	12 (28.6)	17 (53.1)	0.049
Once	25 (59.5)	10 (31.2)	
Twice	2 (4.8)	4 (12.5)	
Thrice	3 (7.1)	1 (3.1)	
Number of days to reach first target level	6.10 ± 3.75	5.78 ± 4.32	0.739

Data are presented as mean ± standard deviation or number (percentage) of patients. n = number
†Six patients were excluded from the analysis (four discharged at their own risk, two transferred to a state hospital)
Five patients were excluded from the analysis (two stopped treatment, one discharged at his own risk, two transferred to state hospital)

Vancomycin-associated Nephrotoxicity

Nephrotoxicity occurred in 2 (5%) of patients in the AUC-guided dosing group, typically occurring around day 4 of vancomycin therapy. This rate was lower compared to the trough-guided dosing group, where 11 patients (16.9%) experienced nephrotoxicity, typically around day 9.91 ± 6.67 of vancomycin therapy ($p = 0.072$) (Table VI). Older patients in the trough-guided dosing group, with a mean age of 59.27 ± 14.93 years, were significantly associated with vancomycin-associated nephrotoxicity ($p<0.05$). In contrast, higher initial trough concentrations were significantly associated with more cases of nephrotoxicity in the AUC-guided dosing group (22.32 ± 2.18 mg/L versus 12.26 ± 6.06 mg/L, $p < 0.05$).

Table VI: Incidence of vancomycin-associated nephrotoxicity and characteristics of patients with nephrotoxicity

Table VI: Incidence of vancomycin-associated nephrotoxicity and characteristics of patients with nephrotoxicity. (CONT.)

Characteristics	Trough-guided Dosing Group (n=65)			AUC-guided Dosing Group (n=40)		
	Nephrotoxicity (n=11)	No nephrotoxicity (n=54)	P value	Nephrotoxicity (n=2)	No nephrotoxicity (n=38)	P value
Age (years)	59.27 ± 14.93	44.48 ±18.95	0.018	37.00 ± 11.31	47.48 ± 15.05	0.336
Day of vancomycin therapy	9.91 ± 6.67	-	-	4.00 ± 0.00	-	-
Baseline SCr (μmol/L)	63.64 ± 14.83	77.20 ± 41.67	0.067	88.50 ± 31.82	100.63 ± 75.17	0.823
Initial trough (mg/L)	15.02 ± 8.48	12.17 ± 6.85	0.230	22.32 ± 2.18	12.26 ± 6.06	0.026
Initial AUC (mg.hour/L)	-	-	-	747.82 ± 200.39	509.43 ± 165.06	0.055
Duration of vancomycin therapy (days)	13.27 ± 10.26	11.09 ± 6.03	0.341	14.00 ± 0.00	12.03 ± 6.80	0.687
Concomitant use of nephrotoxic agents	2 (18.2)	6 (11.1)	0.614	1 (50.0)	4 (10.5)	0.237

CONTINUE

Data are presented as mean ± standard deviation or number (percentage) of patients.
n = number; SCr = serum creatinine; AUC = area under the concentration-time curve

DISCUSSION

In this study, the higher percentage of patients achieving therapeutic AUC values in the AUC-guided dosing group indicates improved dose optimization and a greater likelihood of attaining the desired drug exposure compared to trough-guided dosing. Additionally, the lower mean total daily dose required in the AUC-guided dosing group and the lower incidence of vancomycin-associated nephrotoxicity imply that the AUC-guided dosing strategy may provide a more efficient and potentially safer approach to vancomycin therapy.

While trough concentration is commonly used as a proxy for AUC24/MIC, our study reveals its limitations in accurately guiding vancomycin therapy. Specifically, our findings show that in 68.7% of cases, AUCs of 400 to 600 mg.hour/L were achieved despite trough concentrations being below 15 mg/L. This indicates that relying solely on trough concentrations, particularly targeting the 15 to 20 mg/L range, may result in excessive dosing (9,12,15). Moreover, our study demonstrates that AUC-guided dosing improved the likelihood of achieving therapeutic target levels and reduced the risk of both subtherapeutic and supratherapeutic exposures. This finding aligns with the notion that AUC-guided dosing allows for more precise and efficient dosing compared to trough-guided dosing. Notably, previous

research by Neely et al. (9) and Meng et al. (12) have also noted similar benefits associated with AUC-guided dosing.
In addition to the higher success rate in achieving target levels, the AUC-guided dosing group also required a significantly lower mean total daily dose of vancomycin compared to the trough-guided dosing group. This suggests that AUC-guided dosing allows for more efficient dosing, potentially reducing the risk of drug-related adverse effects and unnecessary drug exposure. These observations are consistent with the findings of a retrospective quasi-experimental study that investigated the impact of transitioning from trough concentration-guided dosing to AUC-guided dosing approach on vancomycin-associated nephrotoxicity (4). The study revealed decreased trough concentrations, reduced nephrotoxicity, and the utilization of lower doses, as clinicians were no longer exclusively pursuing the aggressive goal of maintaining trough concentrations at 15 to 20 mg/L in all patients with MRSA infections (4).

The observations concerning dose adjustments in both study groups provide valuable insights into the dosing strategies employed. In our study, it was observed that a larger percentage of patients in the AUC-guided dosing group (53.1%) achieved the target AUC without requiring any dose adjustment. This indicates that initial dosing decisions based on AUC values were effective in achieving the desired drug exposure in a significant number of patients. On the other hand, the majority of trough-guided dosing patients (59.5%) required at least one dose adjustment to reach the target levels. This highlights the limitations of relying solely on trough concentrations as a dosing guide, as it may result in suboptimal drug exposure in a substantial number of patients. These findings underscore the potential advantages of AUC-guided dosing over trough-guided dosing in terms of dose optimization, reducing the need for dose adjustments, and improving the overall effectiveness of vancomycin therapy.

Using the AUC-guided dosing approach has been significantly associated with a decrease of approximately 47% in the odds of experiencing AKI compared to trough-guided dosing, as demonstrated in a recent meta-analysis comprising 57 primary studies evaluating vancomycin-associated nephrotoxicity in adult patients (16). Consistent with these findings, we also observed a lower incidence of vancomycin-associated nephrotoxicity in the AUC-guided dosing group. However, unlike the meta-analysis findings, the association between AUC-guided dosing and reduced nephrotoxicity was not confirmed conclusively in our study, as the difference between the two dosing strategy groups did not reach statistical significance. This discrepancy may be explained by several factors, including variations in study populations, differences in therapeutic targets, dosing strategies, definitions of nephrotoxicity, and the duration of nephrotoxicity studied between the meta-analysis and our study. It is possible that the variability in patient characteristics and comorbidities in our study, as well as differences in vancomycin dosing protocols between institutions, may have influenced the outcomes. Additionally, the sample size of our study might have limited our ability to detect smaller differences between the two dosing approaches. Furthermore, nephrotoxicity is a complex outcome that can be influenced by various factors, and our study may not have accounted for all potential confounders that could impact the risk of nephrotoxicity.

Age was identified as a significant factor linked to vancomycin-associated nephrotoxicity in the group that followed trough-guided dosing in this study, consistent with previous research by Hall et al. (17) and Higashi et al. (18). However, Carreno et al. (19) reported no differences in the risk of nephrotoxicity between younger and older adults. These mixed findings underscore the necessity for additional research to gain a deeper understanding of how age contributes as a risk factor in vancomycin therapy. On the other hand, numerous observations in the literature consistently highlight an increased risk of nephrotoxicity when targeting the typical trough concentration range of 15 to 20 mg/L for vancomycin therapy (5,20). Our study further supports this association, as patients who experienced vancomycin-associated nephrotoxicity had elevated initial trough concentrations and initial AUC values compared to those without nephrotoxicity. However, our study did not find any statistically significant disparities in trough concentrations and AUC values between the two groups.

Strengths of this study include its comparative design, allowing for a direct comparison between AUC-guided dosing and trough-guided dosing. The real-world application of the study's results adds practical relevance in clinical settings, and its findings are consistent with existing literature, supporting the benefits of AUC-guided dosing in optimizing vancomycin therapy and reducing nephrotoxicity risk. However, several limitations should be acknowledged. The retrospective design of the trough-guided dosing group introduces inherent biases and data collection limitations, potentially affecting result reliability. Additionally, the specific definition of nephrotoxicity may vary from other studies, making direct comparisons challenging. While the sample size collected was larger than required, it may still be considered modest, possibly underrepresenting certain subgroups. Lastly, clinical outcomes and treatment efficacy were not assessed in this study, warranting future comprehensive analyses to understand AUC-guided dosing's impact on patient outcomes and treatment effectiveness.

CONCLUSION

In conclusion, our study supports the benefits of AUC-guided dosing in optimizing vancomycin therapy. Although the reduction in nephrotoxicity incidence was not statistically significant, implementing individualized dosing strategies based on AUC values shows promise in enhancing patient outcomes during vancomycin treatment. Further research with larger sample sizes and comprehensive clinical outcomes assessment is needed to validate these findings and gain deeper insights into the clinical impact of AUC-guided dosing.

ACKNOWLEDGEMENT

The author wishes to express gratitude to the Director-General of Health Malaysia for authorizing the publication of this article. The authors did not receive any financial assistance from funding organizations and have affirmed that there are no conflicts of interest associated with this work.

REFERENCES

1. Zonozi R, Wu A, Shin JI, Secora A, Coresh J, Inker LA, et al. Elevated vancomycin trough levels in a tertiary health system: frequency, risk factors, and prognosis. Mayo Clin Proc. 2019;94(1):17-26. doi: 10.1016/j.mayocp.2018.08.034.
2. Ryan WS, Francis CSB. Use AUC to optimize vancomycin dosing. Pharmacy Times. 2019 Apr 4 [cited 2023 Apr 24];8(2). Available from: https://www.pharmacytimes.com/view/use-auc-to-optimize-vancomycin-dosing
3. Martin JH, Norris R, Barras M, Roberts J, Morris R, Doogue M, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society Of Infectious Diseases Pharmacists. Clin Biochem Rev. 2010 [cited 2023 Apr 5];31(1):21-4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2826264/
4. Finch NA, Zasowski EJ, Murray KP, Mynatt RP, Zhao JJ, Yost R, et al. A quasi-experiment to study the impact of vancomycin area under the concentration-time curve-guided dosing on vancomycin-associated nephrotoxicity. Antimicrob Agents Chemother. 2017;61(12):e01293-17. doi: 10.1128/AAC.01293-17.
5. Bosso JA, Nappi J, Rudisill C, Wellein M, Bookstaver PB, Swindler J, et al. Relationship between vancomycin trough concentrations and nephrotoxicity: a prospective multicenter trial. Antimicrob Agents Chemother. 2011;55(12):5475-9. doi: 10.1128/AAC.00168-11.
6. Lines J, Burchette J, Kullab SM, Lewis P. Evaluation of a trough-only extrapolated area under the curve vancomycin dosing method on clinical outcomes. Int J Clin Pharm. 2021;43(1), 263-9. doi: 10.1007/s11096-020-01157-3.
7. Rybak MJ, Le J, Lodise TP, Levine DP, Bradley JS, Liu C, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised Consensus Guideline and Review by the American Society of Health-system Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis. 2020;71(6), 1361-1364. doi: 10.1093/cid/ciaa303.
8. Lee BV, Fong G, Bolaris M, Neely M, Minejima E, Kang A, et al. Cost-benefit analysis comparing trough, two-level AUC and Bayesian AUC dosing for vancomycin. Clin Microbiol Infect. 2021;27(9):1346.e1-1346.e7. doi: 10.1016/j.cmi.2020.11.008.
9. Neely MN, Kato L, Youn G, Kraler L, Bayard D, van Guilder M, et al. Prospective trial on the use of trough concentration versus area under the curve to determine therapeutic vancomycin dosing. Antimicrob Agents Chemother. 2018;62(2):e02042-17. doi: 10.1128/AAC.02042-17.
10. Davies SW, Efird JT, Guidry CA, Dietch ZC, Willis RN, Shah PM, et al. Vancomycin-associated nephrotoxicity: the obesity factor. Surg Infect (Larchmt). 2015;16(6):684-93. doi: 10.1089/sur.2014.198.
11. Minejima E, Choi J, Beringer P, Lou M, Tse E, Wong-Beringer A. Applying new diagnostic criteria for acute kidney injury to facilitate early identification of nephrotoxicity in vancomycin-treated patients. Antimicrob Agents Chemother. 2011; 55(7):3278-83. doi: 10.1128/AAC.00173-11.
12. Meng L, Wong T, Huang S, Mui E, Nguyen V, Espinosa G, et al. Conversion from vancomycin trough concentration-guided dosing to area under the curve-guided dosing using two sample measurements in adults: implementation at an Academic Medical Center. Pharmacotherapy. 2019;39(4):433-42. doi: 10.1002/phar.2234.
13. Prabaker KK, Tran TP, Pratummas T, Goetz MB, Graber CJ. Elevated vancomycin trough is not associated with nephrotoxicity among inpatient veterans. J Hosp Med. 2012;7(2):91-7. doi: 10.1002/jhm.946.
14. Pai MP, Neely M, Rodvold KA, Lodise TP. Innovative approaches to optimizing the delivery of vancomycin in individual patients. Adv Drug Deliv Rev.2014;77:50–7. doi: 10.1016/j.addr.2014.05.016.
15. Neely MN, Youn G, Jones B, Jelliffe RW, Drusano GL, Rodvold KA, et al. Are vancomycin trough concentrations adequate for optimal dosing? Antimicrob Agents Chemother. 2014;58(1):309–16. doi: 10.1128/AAC.01653-13.
16. Lim AS, Foo SHW, Benjamin Seng JJ, Magdeline Ng TT, Chng HT, Han Z. Area-under-curve-guided versus trough-guided monitoring of vancomycin and its impact on nephrotoxicity:

a systematic review and meta-analysis. Ther Drug Monit. 2023; 45(4):519-32. doi: 10.1097/FTD.0000000000001075.

17. Hall RG 2nd, Hazlewood KA, Brouse SD, Giuliano CA, Haase KK, Frei CR, et al. Empiric guideline-recommended weight-based vancomycin dosing and nephrotoxicity rates in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: a retrospective cohort study. BMC Pharmacol Toxicol. 2013;14:12. doi: 10.1186/2050-6511-14-12.
18. Higashi T, Tsukamoto H, Kodawara T, Igarashi T, Watanabe K, Yano R, et al. Evaluation of risk factors for nephrotoxicity associated with high-dose vancomycin in Japanese patients. Pharmazie. 2021;76(2):114-8. doi: 10.1691/ph.2021.0138.
19. Carreno JJ, Jaworski A, Kenney RM, Davis SL. Comparative incidence of nephrotoxicity by age group among adult patients receiving vancomycin. Infect Dis Ther. 2013;2(2): 201–8. doi: 10.1007/s40121-013-0022-6.
20. Barriere SL, Stryjewski ME, Corey GR, Genter FC, Rubinstein E. Effect of vancomycin serum trough levels on outcomes in patients with nosocomial pneumonia due to *Staphylococcus aureus*: a retrospective, post hoc, subgroup analysis of the Phase 3 ATTAIN studies. BMC Infect Dis. 2014;14:183. doi: 10.1186/1471-2334-14-183.