



Vancomycin therapeutic monitoring by measured trough concentration versus Bayesian-derived area under the curve in critically ill patients with cancer

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Abstract

The updated vancomycin guideline and recent studies suggested that trough concentrations may result in underestimation of the actual area under the curve (AUC), leading to excessive dosing and nephrotoxicity. With limited data available on critically ill cancer patients, this study aimed to compare the two methods in this patient population. This was a 5-year retrospective study on patients treated with vancomycin in the intensive care unit (ICU) of a comprehensive cancer center. The measured trough concentration was compared to Bayesian-derived AUC/minimum-inhibitory-concentration (MIC), considering MIC as 1. Trough concentrations of 15–20 mg/L and AUC of 400–600 mg h/L were considered the targeted goal. Multivariate analysis was performed to identify factors associated with an AUC below the targeted goal. During the study period, 316 patients were included. The mean age was 54 years \pm 16 (SD); most patients had solid tumors (75%), and 11% had neutropenia. A targeted goal AUC and trough were recorded in 128 (41%) patients and in 64 (20%) patients, respectively. Of the 128 patients with targeted goal AUC, 31 (24%) had targeted goal trough concentrations and 91 (71%) had trough concentrations below 15 mg/L. Furthermore, among the patients with targeted goal trough concentration ($n = 64$), 33 (52%) had higher than targeted goal AUC. Augmented renal clearance (ARC), defined as a calculated creatinine-clearance \geq 130 ml/min, was associated with an AUC below the targeted goal. In a cohort of critically ill patients with cancer, over two-thirds of the patients with a targeted goal Bayesian AUC/MIC had trough concentrations below the targeted goal. ARC was associated with AUC below the targeted goal.

KEYWORDS

area under curve, Bayes theorem, critical illness, drug monitoring, neoplasms, vancomycin

Abbreviations: AUC, area under the curve; CDSS, clinical decision support software; ICU, intensive care unit; IQRs, interquartile ranges; KDIGO, Kidney Disease: Improving Global Outcomes; MIC, minimum-inhibitory-concentration; TDM, Therapeutic drug monitoring.

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1 | INTRODUCTION

Therapeutic drug monitoring (TDM) is essential in patients receiving vancomycin to optimize therapy and minimize nephrotoxicity. Though the area under the curve to minimum inhibitory concentration (AUC/MIC) is considered the parameter that best predicts the clinical efficacy of vancomycin, a trough-based approach has historically been recommended for TDM.¹ Previous guidelines considered the trough as a surrogate marker for AUC/MIC and a more practical approach to assessing the appropriateness of vancomycin dosing.¹

Recently, the revised guidelines for TDM of vancomycin recommended against the use of trough concentrations to assess vancomycin dosing and instead recommended the use of the AUC/MIC approach.² This was based on recently published studies that demonstrated that the trough may not be the optimal surrogate for targeted goal AUC.^{3–6} Furthermore, studies demonstrated that the traditionally recommended trough concentrations of 15–20 mg/L generally achieve AUC/MIC that is higher than the recommended target of 400–600 mg h/L and have been associated with increased nephrotoxicity in adults and pediatrics.^{7–12} The guidelines also recommended the use of the Bayesian approach to estimate AUC as it allows clinicians to accurately estimate the AUC with limited pharmacokinetic sampling and without the need to reach steady state.²

Though the revised guidelines recommended vancomycin monitoring based on AUC/MIC rather than trough concentrations, most clinicians have not made the switch to the AUC-based monitoring. In a recent survey of 78 institutions, less than one-fourth performed AUC-based vancomycin monitoring, and only a few of those who were still conducting trough-based monitoring was planning to transition to AUC-based monitoring within the next year.¹³ Similar findings were reported in a survey of 364 critical care pharmacists in which over 80% of the pharmacists reported using vancomycin trough concentrations to assess exposure and to calculate further dosing.¹⁴ The most common barriers to implementing AUC-based monitoring were pharmacist and provider unfamiliarity, followed by training requirements, unclear benefit of AUC-based monitoring, time allocation, and cost of monitoring.^{13,14} Furthermore, the rationale behind the changes in the guidelines have been challenged.¹⁵ The evidence supporting the use of AUC/MIC rather than trough for pharmacokinetic monitoring was considered as insufficient and weak. In addition, recent clinical studies using human data suggested a high correlation between trough level and AUC ($R^2 = 0.88–0.95$).^{16–18} Others have also suggested that AUC-based dosing may be more important to certain subgroups of patients, which may help institutions focus their efforts on such groups, given the challenges faced with the widespread implementation of AUC-based TDM.¹⁹

With the expected pharmacokinetic alterations in critically ill adults with cancer due to the acuity of illness, neutropenic status, and underlying malignancy, coupled with limited data comparing AUC/MIC ratio and trough concentrations in this population, our

primary objective was to evaluate the Bayesian-derived AUC/MIC approach to trough-based therapeutic drug monitoring.²⁰ Secondary objectives included evaluating the pharmacokinetic parameters for vancomycin in this study population and identifying factors associated with AUC/MIC below the targeted goal.

2 | MATERIALS AND METHODS

This was a retrospective cohort study that included patients who were treated with vancomycin between January 2015 and August 2019 at the adult critical care unit at King Hussein Cancer Center in Jordan. The intensive care unit (ICU) has a closed-unit system and serves around 600 cancer patients per year admitted with oncology and non-oncology-related critical illnesses.²¹ The study protocol was approved by King Hussein Cancer Center Institutional Review Board (Reference Number: 19KHCC48). A waiver of informed consent was approved.

The pharmacy billing system was used to identify all patients who were prescribed vancomycin during the study period. Adult patients (≥ 18 years old), with stable kidney function, who received vancomycin during their ICU stay and had at least one steady-state vancomycin trough concentration, were included. Kidney function stability was determined based on the serum creatinine readings at 48 h before and up to the day of obtaining the trough concentration. Patients with acute kidney injury who had a change in their serum creatinine by more than or equal to 0.3 mg/dl as defined by Kidney Disease: Improving Global Outcomes (KDIGO) were excluded. A steady-state concentration was defined as a concentration measured after receiving at least three consecutive vancomycin doses within the same dosing regimen in the ICU. Those who received vancomycin but had no available steady-state trough concentrations in the ICU, as well as those on dialysis and admitted postoperatively for observation. For patients who had multiple ICU admissions that required vancomycin administration or those with multiple trough concentrations in the ICU, only the first steady-state concentration was included.

The computerized patient records system and the ICU database were used to obtain the patients' baseline characteristics and admission diagnosis, as well as the laboratory readings, and the need for mechanical ventilation or vasopressors.

The Bayesian-derived AUC and the pharmacokinetic parameters were calculated using a Bayesian clinical decision support software (CDSS) program, InsightRX, which utilizes a single measured vancomycin trough concentration. The pharmacokinetic model used for the software was that developed by Thomson et al, which has been reported to fit the reference AUC in critically ill patients.^{22,23} It is a bi-exponential elimination model based on general adult population who had at least one vancomycin concentration measurement. It includes weight and creatinine clearance as covariates.

Patient data entered on the CDSS for all patients included the age, date of first dose, single serum creatinine reading on day of measured vancomycin trough level, weight, height, MIC (assumed

to be 1), vancomycin doses since initiation of vancomycin, vancomycin administration dates and times and the ICU steady-state vancomycin trough concentration, along with any trough concentrations documented before that and the times the trough concentrations were obtained. The times for medication administration were assumed to be the hospital's standard medication administration times; for instance, twice daily dosing would be timed at 06:00 and 18:00 h.

The time the trough concentrations are obtained at our hospital is 30 min to 1 h prior to the administration of the next dose. When determining the Bayesian AUC, we assumed the trough to be taken 30 min prior to the administration time. However, we performed a sensitivity analysis to compare the Bayesian-derived AUC based on the assumption of a trough at 30 versus 60 min prior to the dose. Data calculated by and retrieved from the CDSS software were the Bayesian-AUC, volume of distribution, peak concentration, and clearance. Creatinine clearance was calculated using the Cockcroft-Gault equation. The weight used in the Cockcroft-Gault equation was the ideal body weight. In underweight patients, the actual weight was used and for obese patients, the adjusted body weight was used. A trough concentration of 15–20 mg/dl and an AUC range of 400–600 mg h/L were considered a targeted goal.

2.1 | Statistical analysis

Analyses were performed using JMP Pro v14.0 (SAS Institute). Categorical data were reported as counts and percentages, and continuous data as means and standard deviations or medians and interquartile ranges (IQRs). Categorical data were compared using the chi-square or Fisher's exact tests, while continuous data were compared using the Student's *t*-test. Statistical tests were two-tailed and a *p*-value of ≤ 0.05 was considered statistically significant. Univariate analysis logistic regression was performed to evaluate factors associated with an AUC below the targeted goal. Multivariate logistic regression was performed to identify factors that were significant in the univariate analysis and independently associated with AUC below the targeted goal.

3 | RESULTS

Over the study period, 1680 patients received vancomycin during their (ICU) stay, among whom 316 met the inclusion criteria. The mean age was 54 years ± 16 (SD), the majority of the patients had solid tumors (75%), 11% had neutropenia upon admission, and the most common ICU admission diagnoses were infectious and respiratory (74%). Most patients had good renal function with a mean baseline creatinine clearance of 134 ml/min ± 84.7 (SD) and received an average vancomycin dose of 30 mg/kg/day ± 4 (SD). Gram-positive cultures were reported in one-third of the patients but methicillin-resistant *Staphylococcus aureus* was observed in

only three patients. Blood was the most common site of infection (43%). ICU and hospital mortality were 31% and 48%, respectively. Table 1 outlines the baseline characteristics of the patients included in the study.

Of the 316 enrolled patients, a targeted goal AUC and trough were recorded in 128 (41%) and in 64 (20%) patients, respectively. Of the 128 patients with targeted goal AUC, 31 (24%) patients had measured targeted goal trough concentrations while 91 (71%) patients had measured trough concentrations below 15 mg/L. Furthermore, of the 64 patients with measured targeted goal trough concentration, 33 (52%) patients had higher than targeted goal AUC. Figure 1 demonstrates all ranges of the calculated AUC and the patients' measured trough concentrations.

In the sensitivity analysis, there was no significant difference in the mean AUC when the trough was assumed at 30 min or at 60 min before the dose. The mean AUC was 516 mg h/L ± 210 (SD) when the trough was assumed to be taken at 30 min before the dose versus a mean of 507 mg h/L ± 207 (SD) when the trough was assumed to be taken at 60 min prior to the dose.

A mean of 2 ± 1 (SD) trough concentrations was utilized to estimate the Bayesian pharmacokinetic parameters. The vancomycin calculated mean volume of distribution at steady state was 1.35 L/kg ± 0.36 (SD), clearance 4.60 L/h ± 2.66 (SD), and peak concentration 30.8 mg/L ± 7.99 (SD).

In the univariate analysis, age, height, type of malignancy, metastasis, Acute Physiology and Chronic Health Evaluation II (APACHE II), neutropenia, and thrombocytopenia upon admission, mechanical ventilation, and vasopressors while on vancomycin, baseline creatinine clearance, ICU vancomycin trough concentration, were significantly associated AUC below the targeted goal. However, in the multivariate analysis, only creatinine clearance ≥ 130 ml/min (OR 0.24; 95% CI, 0.09–0.63) was significant with vancomycin concentration below the targeted goal.

4 | DISCUSSION

In this study, we compared measured trough and Bayesian-derived AUC for vancomycin therapeutic monitoring in a relatively large sample of critically ill adult patients with cancer.²² This represents a patient population in whom the pharmacokinetics of vancomycin is not well studied despite the frequent use of vancomycin in critically ill cancer patients.²⁴ About two-third of the patients who had a targeted goal AUC of 400–600 had vancomycin concentration considered to be below the targeted goal (< 15 mg/L) in critically ill patients. Such patients would typically have their vancomycin doses increased unnecessarily. The findings of this study are important to demonstrate to clinicians the value of AUC/MIC dosing in the critically ill patient population and to address some of the controversy raised in the literature about such a dosing strategy.²⁰

In critically ill adult cancer patients with sepsis, vancomycin is among the most commonly utilized antibiotics.²⁴ The

TABLE 1 Patient baseline characteristics and study outcomes

Patient characteristic	All patients (n = 316)	AUC (<400) (n = 102)	AUC (≥400) (n = 214)	p-value
Age, mean ± SD, years	54 (16)	44 (14)	59 (14)	<.001
Gender, Male, n (%)	168 (53)	59 (58)	109 (51)	.250
Height, mean ± SD, cm	165 (8)	167 (8)	164 (9)	.006
Weight, mean ± SD, kg	70 (17)	71 (19)	70 (17)	.429
Source of admission, n (%)				
Emergency	156 (49)	49 (48)	107 (50)	.260
Floor	132 (42)	40 (39)	92 (43)	
Surgery	28 (9)	13 (13)	15 (7)	
Type of malignancy, n (%)				
Hematology	78 (25)	38 (37)	40 (19)	.001
Solid	238 (75)	64 (63)	174 (81)	
Metastasis, n (%)	157 (50)	39 (38)	118 (55)	.005
APACHE II upon admission, mean (SD)	20 (7)	19 (7)	21 (7)	.033
Admission diagnosis, n (%)				
Infectious	145 (46)	45 (44)	100 (47)	.240
Respiratory	89 (28)	28 (27)	61 (28)	
Neurological	29 (9)	12 (12)	17 (8)	
Cardiovascular	19 (6)	6 (6)	13 (6)	
Others	34 (11)	11 (11)	23 (11)	
Body mass index (BMI), mean (SD), kg/m ²	26 (7)	26 (7)	26 (6)	.770
Baseline creatinine clearance, mean (SD), ml/min	134 (85)	167 (58)	115 (50)	<.001
Mechanical ventilation upon admission, n (%)	122 (39)	36 (35)	86 (40)	.400
Mechanical ventilation while on vancomycin, n (%)	171 (54)	47 (46)	124 (58)	.048
Vasopressors upon admission, n (%)	108 (34)	28 (27)	80 (37)	.074
Vasopressors while on vancomycin, n (%)	142 (45)	36 (35)	106 (50)	.0151
Neutropenia upon admission, n (%)	35 (11)	21 (21)	14 (7)	<.001
Thrombocytopenia upon admission, n (%)	112 (35)	44 (43)	68 (32)	.050
Positive cultures, n (%)	227 (72)	69 (68)	158 (74)	.280
Empiric vancomycin dose, mean ± SD, mg/kg/day	30 (8)	29 (7)	31 (8)	.160
Duration of therapy, mean ± SD, days	8 (6)	8 (6)	8 (5)	.800
Vancomycin ICU steady-state trough concentration, mean (SD), mg/L	13 (6)	7 (2)	15 (6)	<.001
ICU length of stay, median (IQR), days	5 (3–10)	4 (3–11)	5 (3–10)	.240

pharmacokinetics of vancomycin in adult critically ill cancer patients could be altered by several factors such as neutropenia which may augment the clearance of vancomycin.^{25–27} This suggests that this special population may require higher than usual dosing regimens to ensure optimal therapeutic exposure. On the other hand, critically ill cancer patients frequently develop acute kidney injury with a reported incidence ranging from 15% to 60%.²⁸ Consequently, the use of the AUC approach for dosing vancomycin in this population may minimize the need for adjusting vancomycin to higher doses to achieve higher trough concentration and thus ensure a therapeutic exposure while minimizing adverse events.

The findings reported in this study are consistent with what others have reported in the literature for non-cancer and

non-critically ill patient populations.^{29–31} Neely et al. reported that among a diverse range of adults with normal renal function and targeted goal AUC of >400 mg h/L for an organism for which the vancomycin MIC is 1 mg/L, approximately 60% of the patients are expected to have a trough concentration below the suggested minimum target of 15 mg/L for serious infections based on simulation.³⁰ Neely et al. also reported in a prospective study conducted in general adult patients that 68% of enrolled patients with a Bayesian-derived AUC ≥400 mg h/L were associated with trough concentrations <15 mg/L.⁶ Furthermore, in a retrospective study of patients with a positive methicillin-resistant *Staphylococcus aureus* (MRSA) culture using an AUC calculation method, Hale et al. reported no significant association between attaining AUC/

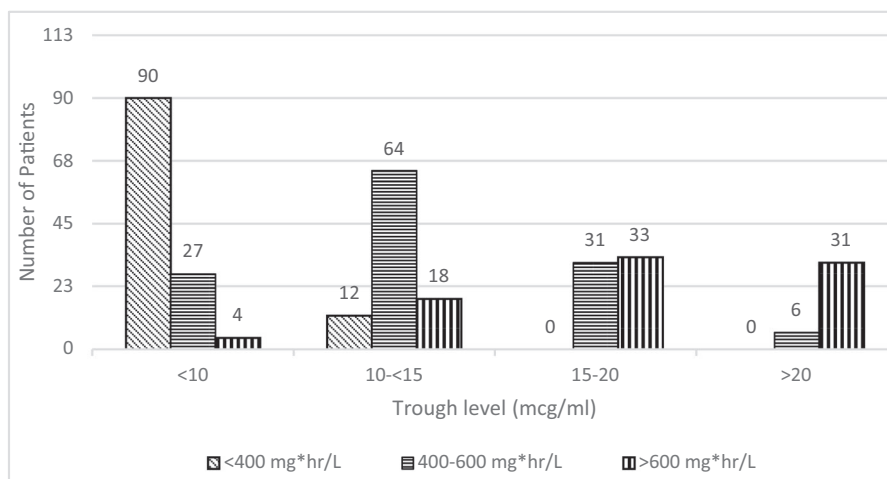


FIGURE 1 Comparison between measured vancomycin trough concentration and Bayesian-derived AUC/MIC

MIC \geq 400 and vancomycin troughs when comparing patients with troughs in range of 10–14.9 mg/L to those troughs of 15–20 mg/L ($p = .817$).³¹

An interesting finding of this study is the identification of factors that were significantly associated with AUC below the targeted goal. Augmented renal clearance (ARC), defined as a calculated creatinine clearance greater than or equal to 130 ml/min, was associated with AUC below the targeted goal. This finding is similar to what was published in a previous study by Baptista et al., who showed that patients with creatinine clearance greater than 130 ml/min had a significantly lower serum vancomycin concentration. However, Baptista et al monitored trough concentrations rather than AUCs.³² Given that ARC is common in critically ill patients with cancer, the association between ARC and vancomycin AUC is important when empirically initiating vancomycin therapy.³³

To our knowledge, no model has been validated in critically ill patients with cancer. The model that we used was the Thomson model, a two-compartment model that included 1,557 vancomycin concentration measurements with a median of three samples per patient from general population and showed a good fit in the critically ill patient population.^{22,23} In our study, only a single trough concentration was used in more than half of the patients. This may have resulted in pharmacokinetic parameters influenced by the model population estimates. In such a case, more than one concentration, such as peak concentration, would have been recommended but this data was not available.

This study has limitations. First, the nature of the study is retrospective and single-centered. Second, related to the Pharmacokinetic model used in the Bayesian analysis. Though the model is recommended in critically ill patients, it has not been evaluated in the critically ill patients with cancer. Third, we did not have the specific time of the trough concentrations. However, this was addressed through the sensitivity analysis that showed no significant difference between the sampling time drawn half an hour and 1 h before the dose.

5 | CONCLUSIONS

In a large cohort of critically ill patients with cancer, over two-thirds of the patients with targeted goal Bayesian AUC/MIC had trough concentration below the targeted goal. Augmented renal clearance was associated with AUC below the targeted goal. Future studies should be directed toward assessing the clinical implementation of targeting AUC/MIC.

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DISCLOSURE

The authors declare no conflicts of interest.

AUTHORS' CONTRIBUTIONS

Lama H. Nazer, Jennifer Le, and Aseel K. AbuSara contributed to the study conception and design. Material preparation and data collection were performed by Aseel K. AbuSara, Deema H. Abdelrahman, and Khader I. Habash. Data analysis was performed by Mohammad H. Alshaer and Aseel K. AbuSara. The first draft of the manuscript was written by Aseel K. AbuSara, Deema H. Abdelrahman, and Khader I. Habash, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL STATEMENT

The study protocol was approved by King Hussein Cancer Center Institutional Review Board (Reference Number: 19KHCC48). A waiver of informed consent was approved.

DATA AVAILABILITY STATEMENT

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

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