



## Original Article



# Vancomycin Area under the Curve and Pharmacokinetic Parameters during the First 24 Hours of Treatment in Critically Ill Patients using Bayesian Forecasting

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## ABSTRACT

**Background:** Currently, the achievement of the target area under the curve (AUC)/minimum inhibitory concentration ratio during the first 24 - 48 h of treatment is associated with reduced 30-day mortality and greater microbiological eradication in patients with methicillin-resistant *Staphylococcus aureus* bacteremia. This study aimed to determine the AUC and pharmacokinetic parameters on the first day of vancomycin administration based on the Bayesian theorem to optimize the dosing regimen in critically ill patients.

**Materials and Methods:** This retrospective study included participants meeting the following criteria: 1) ≥18 years old; 2) receipt of at least one dose of vancomycin; 3) measurement of 2 vancomycin serum concentrations during the first 24 h of treatment; and 4) an intensive care unit admission, mechanical ventilator use, or an Acute Physiology and Chronic Health Evaluation II score >15 points. The AUC on day 1 of treatment and the estimated vancomycin pharmacokinetic parameters were measured using PrecisePK software based on the Bayesian theorem.

**Results:** We obtained 132 vancomycin concentrations from 66 patients. The vancomycin pharmacokinetic parameters were as follows: AUC<sub>0-24</sub>, 571.09 (± standard deviation [SD] 188.62) mg/L-h; clearance (CL), 2.97 (± SD 1.81) L/h; volume of distribution (Vd), 50.60 (± SD 13.91) L; elimination rate constant, 0.062 (± SD 0.039) h<sup>-1</sup>; and half-life, 18.19 (± SD 15.96) h. Focusing on the vancomycin loading dose, AUC<sub>0-24</sub> 400 - 600 was achieved in 41.7, 46.1, 44.4, and 26.3% of patients with loading doses of <20, 20 - 24.9, 25 - 30, and >30 mg/kg, respectively. Whereas AUC<sub>0-24</sub> ≥521 was achieved in 50, 50, 77.8, and 84.2% of patients with loading doses of <20, 20 - 24.9, 25 - 30, and >30 mg/kg, respectively. The CL of vancomycin was correlated with creatinine CL, whereas the Vd of vancomycin was significantly correlated with age and body weight.

**Conclusion:** This study revealed that the higher Vd and CL values on the first day of vancomycin therapy were found in critically ill patients. Additionally, a higher vancomycin loading dose (25 - 30 mg/kg) might be required to achieve target of AUC<sub>0-24</sub> during early phase of administration for critically ill patients.

**Keywords:** AUC; Clearance; Pharmacokinetic; Trough level; Volume of distribution

#### Conflict of Interest

No conflicts of interest.

#### Author Contributions

Conceptualization: MP, DC, WS. Data curation: KB, KS, ST, AU, WS. Formal analysis: KB, KS, ST, AU, WS. Funding acquisition: WS. Investigation: MP, WS. Methodology: WS. Project administration: WS. Resources: DC, WS. Software: WS. Supervision: MP, DC, WS. Validation: KB, KS, ST, AU, WS. Visualization: MP, WS. Writing - original draft: MP, WS. Writing - review & editing: MP, DC, KB, KS, ST, AU, WS.

## INTRODUCTION

*Staphylococcus aureus*, a Gram-positive coccus, is a major cause of various organ/system infections such as skin and soft tissue, bloodstream, bone and joint, respiratory tract, central nervous system, and endocardial infections [1]. At present, antibiotic resistance is increasing in *S. aureus*, especially methicillin-resistant *S. aureus* (MRSA) [2]. Meanwhile, glycopeptides, oxazolidinones, lipopeptides, and glycolipopeptides are the current therapeutic options for MRSA [3].

Vancomycin, a glycopeptide antibiotic, has been the first-line antibiotic against MRSA infections for several decades. However, serum vancomycin levels must be monitored in clinical practice to maximize its efficacy against MRSA infection and reduce its toxicity in patients [2]. An area under the curve (AUC)/minimum inhibitory concentration ratio (AUC) of 400 – 600 is desirable for vancomycin [4]. Recently, clinical practice guidelines indicated that the vancomycin AUC should be used to design vancomycin dosing regimens using the Bayesian theorem.

Bayesian-guided dosing is based on Bayes' theorem. Population pharmacokinetic variables, *e.g.*, drug clearance (CL) or the volume of distribution (Vd) of prior values (Bayesian prior), were recalculated using patients' pharmacokinetic parameter values and individual drug concentration data (conditional posterior) [5]. With vancomycin dose optimization using the Bayesian approach, vancomycin levels can be sampled in the early treatment period (first 24 – 48 h) to rapidly provide an appropriate vancomycin dosage. Conversely, to achieve vancomycin trough concentrations of 15 – 20 µg/mL, samples are collected at steady state, which may be too late to achieve favorable outcomes [4]. Lodise et al. examined the effect of early AUC target achievement during the first 24 – 48 h of treatment on clinical outcomes in patients with MRSA bacteremia. They found that patients with AUC  $\geq$ 521 during the first 24 h had a lower 30-day mortality rate and greater microbiological eradication. Moreover, from Poisson regression analyses, a decrease risk of failure of Classification and Regression Tree-derived (CART) AUC exposures was correlated with a decreased risk in failure [6].

Unfortunately, vancomycin pharmacokinetics remarkably differs between critically ill patients and other patient groups. Critically ill patients usually exhibit an increased volume of distribution and augmented renal clearance during the early period of sepsis. These conditions result in decreased vancomycin serum levels. Previous studies indicated that subtherapeutic vancomycin serum concentrations were achieved during the first 3 days of treatment, especially the first day [7, 8].

However, little research has investigated the vancomycin AUC during the first 24 h of treatment. Therefore, this study aimed to measure AUC and other pharmacokinetic parameters on the first day of vancomycin administration based on the Bayesian theorem to optimizing vancomycin dosing regimens for empirical therapy against MRSA infection in critically ill patients.

## MATERIALS AND METHODS

### 1. Study design and study participants

This retrospective study included critically ill patients who were treated with vancomycin at Phramongkutklo Hospital, a 1,200-bed university hospital located in Bangkok, Thailand,

between 2016 and 2018. The inclusion criteria were as follows: 1)  $\geq 18$  years old; 2) receipt of at least one dose of vancomycin; 3) two measurements of the vancomycin serum concentration during the first 24 h of treatment; and 4) intensive care unit admission, mechanical ventilator use, or an Acute Physiology and Chronic Health Evaluation (APACHE) II score exceeding 15 points.

The exclusion criteria were as follows: 1) receipt of hemodialysis, peritoneal dialysis, or continuous renal replacement therapy; and 2) unidentified sampling times for vancomycin or incomplete data for the vancomycin dosing regimen (dose, interval, and infusion time). The present study was approved by the ethics review committee of the Royal Thai Army Medical Department (approval no. Q039h/61\_Exp).

## 2. Patient data

Patient demographic data including age, gender, weight, height, ward, mechanical ventilator use, APACHE II scores, creatinine clearance (estimated using the Cockcroft–Gault formula), and comorbidity were gathered. Information on the vancomycin dosing regimen comprising the dose (mg), frequency per day (dosing interval), infusion time (minutes), and receipt of a loading dose (yes or no) was collected. The serum vancomycin levels ( $\mu\text{g/mL}$ ) were collected for the studied participants during the first 24 h of treatment at known sampling times.

## 3. Vancomycin assay

The total serum vancomycin concentrations were determined using a fluorescence immunoassay (VANC3, Cobas, Roche Diagnostics, IN, USA). The limit of detection (LOD) of this assay was 4 – 80  $\mu\text{g/mL}$ . The coefficient of variation for this assay was  $<10\%$ .

## 4. Pharmacokinetic parameter estimation

The AUC on day 1 ( $\text{AUC}_{0-24}$ ) of treatment and the estimated vancomycin pharmacokinetic parameters (CL,  $V_d$ , and half-life) were measured using PrecisePK software (Healthware Inc., San Diego, CA, USA) based on the Bayesian theorem. The one-compartment model and population parameters (Bayesian prior values) embedded in PrecisePK were used to estimate the Bayesian conditional posterior of patient pharmacokinetic parameters adjusted by individual vancomycin serum concentration (s).

## 5. Data analysis

Descriptive statistics for demographic data and pharmacokinetic parameters were used. The percentage of patients achieving the optimal  $\text{AUC}_{0-24}$  of 400 – 600 and of  $\geq 521$  was also determined. We compared the measured serum vancomycin concentrations with those predicted by Bayesian software program. We calculated mean error (ME) and root mean square error (RMSE) as following formula

$$\text{ME} = \sum_{i=1}^n \frac{(\text{Predicted value} - \text{Observed value})}{N}$$

$$\text{RMSE} = \sum_{i=1}^n \frac{\sqrt{(\text{Predicted value} - \text{Observed value})^2}}{\sqrt{N}}$$

Whereas Predicted value = Calculated vancomycin concentrations from Bayesian software  
 Observed value = Measured serum vancomycin concentrations  
 N = Number of samples

ME and RMSE were used to assess accuracy (bias) and precision of Bayesian software program, respectively.

The correlation between pharmacokinetic parameters (CL, Vd) and patient characteristics was analyzed using Pearson's correlation coefficient (r). We used linear regression to predict pharmacokinetic parameters according to patient characteristics.

## RESULTS

Over a 24-month period, we obtained 132 vancomycin concentrations from 66 patients (two measurements per patient) who received intravenous vancomycin and met the selection criteria. The mean ( $\pm$  standard deviation [SD]) patient age was 70.3 ( $\pm$  17.6) years. The general characteristics, pharmacokinetic values, and vancomycin concentrations are presented in **Table 1**.

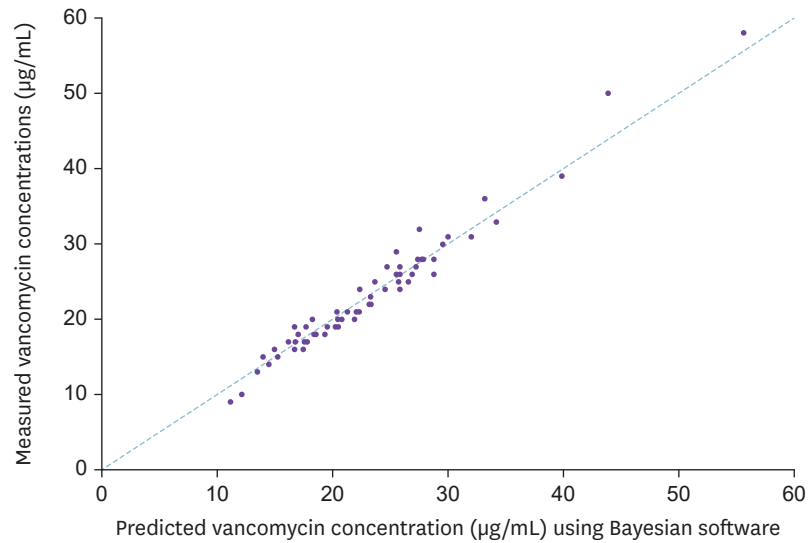
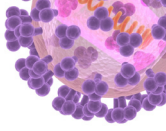
The estimated vancomycin pharmacokinetic parameters using Bayesian analysis were as follows:  $AUC_{0-24}$ , 571.09 ( $\pm$  SD 188.62) mg/L·h; CL, 2.97 ( $\pm$  SD 1.81) L/h; Vd, 50.60 ( $\pm$  SD 13.91) L; elimination rate constant, 0.062 ( $\pm$  SD 0.039)  $h^{-1}$ ; and half-life, 18.19 ( $\pm$  SD 15.96) h.

The accuracy (ME) of the first plasma sampling ( $C_1$ ) of vancomycin (measured during 3 - 5 h after end of infusion) and the second plasma sampling ( $C_2$ ) of vancomycin (measured 0.5 - 1 h before the next dose) was 0.034  $\mu$ g/mL and 0.137  $\mu$ g/mL, respectively. Whereas, the precision (RMSE) of the  $C_1$  and  $C_2$  was 0.194  $\mu$ g/mL and 0.176  $\mu$ g/mL, respectively. The relationship between measured vancomycin concentrations and predicted vancomycin concentrations from Bayesian software of  $C_1$  and  $C_2$  are presented in **Figure 1** and **2**, respectively.

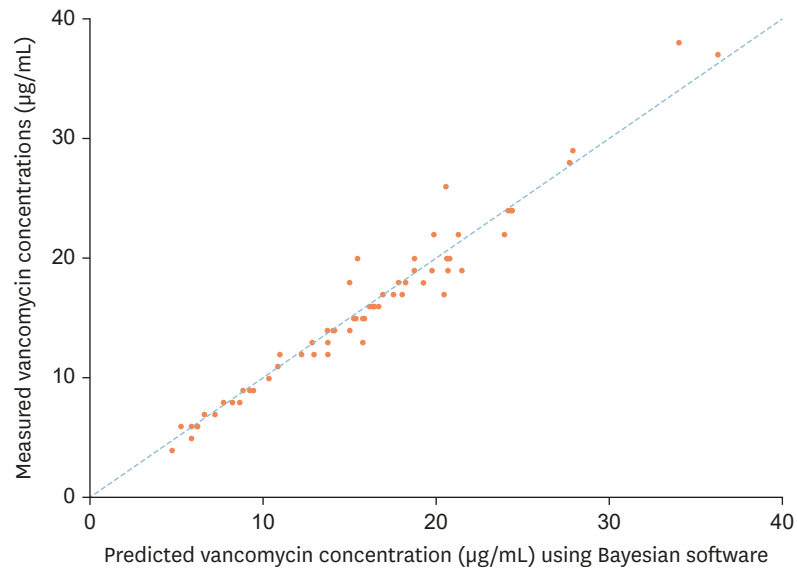
**Table 1.** The demographic data and vancomycin pharmacokinetic parameters for 66 clinically ill patients

Variables	Result
Age (yr), mean $\pm$ SD	70.3 $\pm$ 17.6
Male, number (%)	38 (57.6)
Height (cm), mean $\pm$ SD	161.7 $\pm$ 8.6
Body weight (kg), mean $\pm$ SD	60.8 $\pm$ 13.5
Body mass index ( $kg/m^2$ ), mean $\pm$ SD	23.2 $\pm$ 4.6
Creatinine clearance (mL/min), mean $\pm$ SD	51.07 $\pm$ 41.69
Indication of vancomycin treatment, number (%)	
Empirical therapy	56 (84.8)
Documented therapy	10 (15.2)
Intensive care unit admission, number (%)	43 (65.2)
Vancomycin dosing regimen	
Patients receiving loading dose ( $\geq 25$ mg/kg), number (%)	35 (53.0)
The first dose per body weight (mg/kg), mean $\pm$ SD	25.4 $\pm$ 6.7
Dose in the 1st day per body weight, mean $\pm$ SD	39.6 $\pm$ 11.9
Vancomycin pharmacokinetic parameters	
Ke ( $h^{-1}$ ), mean $\pm$ SD	0.062 $\pm$ 0.039
Half-life (h), mean $\pm$ SD	18.19 $\pm$ 15.96
Vd (L), mean $\pm$ SD	50.60 $\pm$ 13.91
Vd (L/kg), mean $\pm$ SD	0.85 $\pm$ 0.22
Clearance vancomycin (L/h) $\pm$ SD	2.97 $\pm$ 1.81
$AUC_{0-24}$ -hour/MIC (mg/L·h), mean $\pm$ SD during the first 24 hours	571.09 ( $\pm$ 188.62)

SD, standard deviation; Ke, elimination rate constant; Vd, volume of distribution; AUC, area under the curve; MIC, minimum inhibitory concentration.



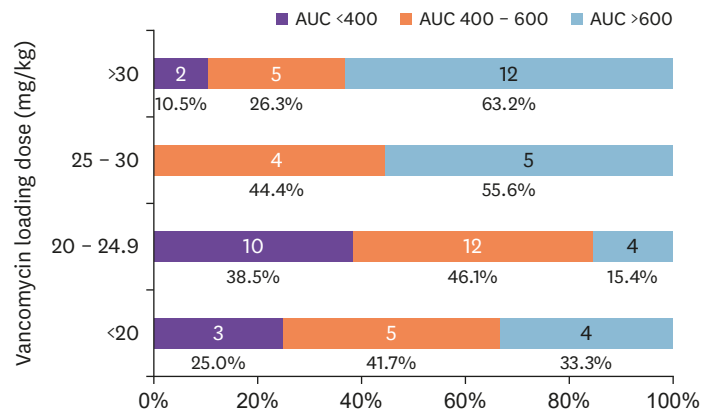
**Figure 1.** Diagnostic goodness of fit of the first plasma sampling (C1) (measured during 3 - 5 h after end of infusion) between the actually measured vancomycin serum levels and predicted vancomycin serum levels based on Bayesian analysis.



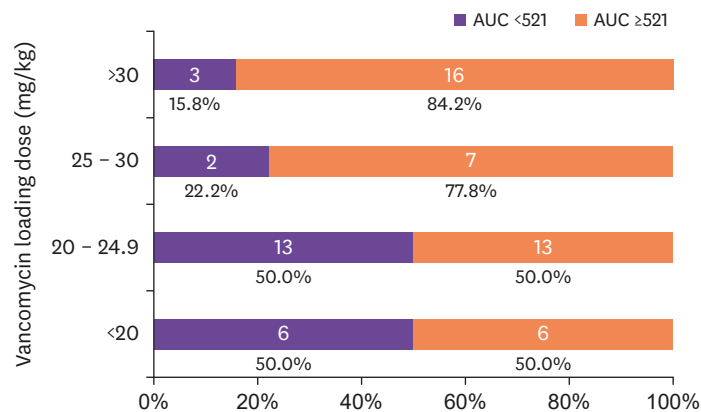
**Figure 2.** Diagnostic goodness of fit of the second plasma sampling (C2) (measured 0.5 - 1 h before the next dose) between the actually measured vancomycin serum levels and predicted vancomycin serum levels based on Bayesian analysis.

Focusing on  $AUC_{0-24}$  values,  $AUC_{0-24}$  400 - 600 on the first day of vancomycin treatment was observed in 26 of 66 patients (39.4%). Focusing on the vancomycin loading dose,  $AUC_{0-24}$  400 - 600 was achieved in 41.7, 46.1, 44.4, and 26.3% of patients with loading doses of <20, 20 - 24.9, 25 - 30, and >30 mg/kg, respectively (**Fig. 3**).

$AUC_{0-24} \geq 521$  on the first day of vancomycin treatment was observed in 42 of 66 patients (63.6%). Focusing on the vancomycin loading dose,  $AUC_{0-24} \geq 521$  was achieved in 50%, 50%, 77.8%, and 84.2% of patients who received loading doses of <20, 20 - 24.9, 25 - 30, and >30 mg/kg, respectively (**Fig. 4**).



**Figure 3.** The percentage of patients with AUC<sub>0-24</sub> of <400, 400 - 600, and >600 on the first day of vancomycin treatment at each loading dose. AUC, area under the curve.



**Figure 4.** The percentage of patients with AUC<sub>0-24</sub> ≥521 on the first day of vancomycin treatment at each loading dose. AUC, area under the curve.

The calculated vancomycin CL based on Bayesian analysis displayed a correlation with creatinine clearance ( $r = 0.75$ ,  $P < 0.001$ ). The predictive equation for vancomycin CL in relation to creatinine clearance was as follows: vancomycin CL (L/h) =  $0.549 \times$  creatinine clearance (L/h) + 1.283 ( $r = 0.75$ ,  $R^2 = 0.562$ ).

Meanwhile, the calculated Vd of vancomycin was significantly correlated with age ( $r = 0.469$ ) and body weight ( $r = 0.208$ ). The equation for Vd of vancomycin was as follows: Vd of vancomycin (L) =  $0.65 \times$  body weight (kg) +  $0.341 \times$  age (years) ( $r = 0.613$ ,  $R^2 = 0.376$ ).

## DISCUSSION

Previously, calculation of AUC in clinical practice was unrealistic due to needed multiple vancomycin serum concentrations. The previous guideline suggested trough concentration for vancomycin dosing adjustment [9]. Unfortunately, the recent studies revealed that trough level might not accurately predict for AUC value. Therefore, the Bayesian approach is raised for AUC calculation. The AUC based on Bayesian approach can be determined using one or two vancomycin plasma sample during the first 24 to 48 hours rather than at steady-state.

This early AUC calculation provides the benefit for critically ill patients rapidly achieving vancomycin target for a better clinical outcome. The AUC based on Bayesian theorem has been currently recommended for vancomycin monitoring in clinical practice [10].

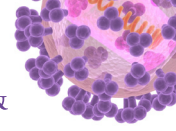
Recently, the American Society of Health-System Pharmacists (ASHP), Infectious Diseases Society of America (IDSA), Paediatric Infectious Diseases Society (PIDS), and Society of Infectious Diseases (SID) recommended that vancomycin AUC was a preferable variable for designing vancomycin dosing regimens using Bayesian software programs [10]. Moreover, this guideline has diminished the role of vancomycin minimum inhibitory concentration (MIC) determination due to 1) the vancomycin MIC<sub>90</sub> by broth microdilution method (BMD) in most settings is 1 mg/L or less, 2) the report of high degree of MIC variation and 3) MIC result for clinical judgment is usually not available during the first 72 hours of bacterial culture. Therefore, AUC values (assuming a MIC<sub>BMD</sub> of 1 mg/L) should be within 400 - 600 mg·h/L to optimized efficacy and minimize the risk of nephrotoxicity [10].

Despite the availability of several pharmacokinetic software packages, we used PrecisePK to estimate pharmacokinetic parameters and AUC in this study. However, Turner et al. studied the performance of Bayesian dose-optimizing software for predicting the vancomycin AUC in comparison with the reference AUC in 19 critically ill patients. PrecisePK gave the most accurate and least biased estimates among five Bayesian theorem software programs [11]. It is supported that vancomycin levels calculated Bayesian software gave a minor bias and precision in predicting the serum vancomycin concentrations among our participants.

Our report calculated the vancomycin AUC during first 24 h of treatment in critically ill adult patients based on Bayesian estimation from two samples per patient. This strategy is more accurate than measurements using only one sample. Neely et al. derived the AUC from trough-only and peak–trough concentrations with the full data set of vancomycin pharmacokinetics as the gold standard. They found that the peak–trough dataset underestimated the true AUCs compared with the full model by approximately 14%, whereas the trough-only data underestimated AUCs by approximately 23% [12].

The recent recommendation from 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 indicated that a loading dose of 20 - 35 mg/kg could achieve the AUC target in the first days of therapy. However, from our findings, only half of patients who received a loading dose of 20 - 24.9 mg/kg met the target of AUC<sub>0-24</sub> ≥521 and 10 out of 26 patients received a loading dose of 20 - 24.9 mg/kg met the target of AUC<sub>0-24</sub> <400. Conversely, vancomycin loading dose of 25 - 30 was appropriate in critically ill patients because of the high rate of achievement of AUC<sub>0-24</sub> ≥521 and AUC<sub>0-24</sub> 400 - 600. Our result was similar to that of previous research indicating that a vancomycin loading dose of 30 mg/kg followed by a maintenance dose of 20 mg/kg every 12 h had a probably of target attainment for the target AUC<sub>0-24</sub> of >90% [13]. Thus, we suggest that a higher dose than the recent recommendation might be appropriate for achieving better clinical outcomes. However, the suggested vancomycin dosing in this study based on pharmacokinetic (PK) parameters on day 1, it is reasonable use for early phase of critically ill condition. Thus, during recovery phase of sepsis, it has to use vancomycin monitoring levels guided-dosing regimen.

Vancomycin pharmacokinetic parameters were determined by using the one compartment model incorporated into PrecisePK software. It revealed that the Vd value in the studied



participants during the initial phase (Vd of 50.6 L) was similar to the value (Vd of 53.4 L) reported by Heffernan et al [14]. However, Roberts et al. reported lower value of Vd (37.4 L) in critically ill patients [15]. The patients in Heffernan et al. were conducted within 72 h of admission whereas Roberts et al. performed blood samples for vancomycin measurement taken every day [14, 15]. Thus, the Vd on the first day of vancomycin therapy and the subsequent phase to steady state might be different in the critically ill patients.

The vancomycin CL observed in this study (CL = 2.97 L/h) was lower than the result obtained from other studies. The values of vancomycin CL reported from the studies by Roberts et al. and Heffernan et al. were 4.58 L/h and 7.23 L/h, respectively [14, 15]. The lower value of vancomycin CL obtained from this study might result from the studied subjects having lesser renal function (mean value of creatinine CL 51.07 mL/min) as compared to patients in the studies of Roberts et al. (mean value of creatinine CL 90.7 mL/min) and Heffernan et al (median value of creatinine CL 107.0 mL/min) [14, 15].

It is fact that only unbound vancomycin is pharmacologically active and the critically ill patients usually have hypoalbuminemia, the free vancomycin concentration in plasma is concerned. Among critically ill patients, between the target of  $fAUC/MIC \geq 200$  for unbound vancomycin concentration and  $AUC/MIC \geq 400$  for total vancomycin levels, the target attainment rate was simply achieved when using pharmacokinetic/pharmacodynamic target based on unbound concentrations, when compared with total concentrations [16]. Thus, the impact of protein binding and role of unbound vancomycin concentrations for achievement of PK/pharmacodynamic (PD) indices has to be determined in critically ill population. Moreover, the two- or three-compartment model best described vancomycin concentration-time profile but the PrecisePK is based on one compartment model. Thus, the pharmacokinetic parameters in this study were used carefully.

In the present study, vancomycin CL had linear relationships with creatinine CL, whereas and the Vd was correlated with actual body weight. These correlations were also observed in several previous studies [17-19]. Surprisingly, patient age was also correlated with the Vd of vancomycin. This finding was similar to a study by Purwonugroho et al., who reported that the Vd was linearly related with age. We supposed that age directly influenced the volume of distribution and that age could be a surrogate of illness severity or comorbidity [17].

However, our study did not evaluate treatment efficacy against MSRA infections and nephrotoxicity according to the estimated vancomycin AUC during the first day [20]. The clinical benefit of the vancomycin AUC based on Bayesian estimation for MRSA treatment in the first day must be further studied.

This study revealed that higher vancomycin loading doses than recommended by recent practice guidelines (starting dose of 20 mg/kg) might be required to achieve  $AUC_{0-24} 400 - 600$  and  $AUC_{0-24} \geq 521$  on the first day of administration for critically ill patients. Moreover, the CL and Vd of vancomycin could be predicted using variables such as creatinine CL, body weight, and age. These factors must be incorporated to optimize the vancomycin dosing regimen for critically ill patients.



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## REFERENCES

1. Turner NA, Sharma-Kuinkel BK, Maskarinec SA, Eichenberger EM, Shah PP, Carugati M, Holland TL, Fowler VG Jr. Methicillin-resistant *Staphylococcus aureus*: an overview of basic and clinical research. *Nat Rev Microbiol* 2019;17:203-18.  
[PUBMED](#) | [CROSSREF](#)
2. Hassoun A, Linden PK, Friedman B. Incidence, prevalence, and management of MRSA bacteremia across patient populations-a review of recent developments in MRSA management and treatment. *Crit Care* 2017;21:211.  
[PUBMED](#) | [CROSSREF](#)
3. Vestergaard M, Frees D, Ingmer H. Antibiotic resistance and the MRSA problem. *Microbiol Spectr* 2019;7. doi: 10.1128/microbiolspec.GPP3-0057-2018.  
[PUBMED](#) | [CROSSREF](#)
4. Drennan PG, Begg EJ, Gardiner SJ, Kirkpatrick CMJ, Chambers ST. The dosing and monitoring of vancomycin: what is the best way forward? *Int J Antimicrob Agents* 2019;53:401-7.  
[PUBMED](#) | [CROSSREF](#)
5. Avent ML, Rogers BA. Optimising antimicrobial therapy through the use of Bayesian dosing programs. *Int J Clin Pharm* 2019;41:1121-30.  
[PUBMED](#) | [CROSSREF](#)
6. Lodise TP, Drusano GL, Zasowski E, Dihmess A, Lazariu V, Cosler L, McNutt LA. Vancomycin exposure in patients with methicillin-resistant *Staphylococcus aureus* bloodstream infections: how much is enough? *Clin Infect Dis* 2014;59:666-75.  
[PUBMED](#) | [CROSSREF](#)
7. Bakke V, Sporsen H, Von der Lippe E, Nordøy I, Lao Y, Nyrerød HC, Sandvik L, Hårvig KR, Bugge JF, Helset E. Vancomycin levels are frequently subtherapeutic in critically ill patients: a prospective observational study. *Acta Anaesthesiol Scand* 2017;61:627-35.  
[PUBMED](#) | [CROSSREF](#)
8. Baptista JP, Sousa E, Martins PJ, Pimentel JM. Augmented renal clearance in septic patients and implications for vancomycin optimisation. *Int J Antimicrob Agents* 2012;39:420-3.  
[PUBMED](#) | [CROSSREF](#)
9. Rybak M, Lomaestro B, Rotschafer JC, Moellering R Jr, Craig W, Billeter M, Dalovisio JR, Levine DP. 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. *Am J Health Syst Pharm* 2009;66:82-98.  
[PUBMED](#) | [CROSSREF](#)
10. Rybak MJ, Le J, Lodise TP, Levine DP, Bradley JS, Liu C, Mueller BA, Pai MP, Wong-Beringer A, Rotschafer JC, Rodvold KA, Maples HD, Lomaestro BM. 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. *Am J Health Syst Pharm* 2020;77:835-64.  
[PUBMED](#) | [CROSSREF](#)
11. Turner RB, Kojiro K, Shephard EA, Won R, Chang E, Chan D, Elbarbry F. Review and validation of bayesian dose-optimizing software and equations for calculation of the vancomycin area under the curve in critically ill patients. *Pharmacotherapy* 2018;38:1174-83.  
[PUBMED](#) | [CROSSREF](#)
12. Neely MN, Youn G, Jones B, Jelliffe RW, Drusano GL, Rodvold KA, Lodise TP. Are vancomycin trough concentrations adequate for optimal dosing? *Antimicrob Agents Chemother* 2014;58:309-16.  
[PUBMED](#) | [CROSSREF](#)
13. Katip Bpharm W, Jaruratanasirikul S, Pattharachayakul S, Wongpoowarak W, Jitsurong A. Initial dosage regimen of vancomycin for septic shock patients: a pharmacokinetic study and Monte Carlo simulation. *J Med Assoc Thai* 2014;97:1209-19.  
[PUBMED](#)

14. Heffernan AJ, Germano A, Sime FB, Roberts JA, Kimura E. Vancomycin population pharmacokinetics for adult patients with sepsis or septic shock: are current dosing regimens sufficient? *Eur J Clin Pharmacol* 2019;75:1219-26.  
[PUBMED](#) | [CROSSREF](#)
15. Roberts JA, Taccone FS, Udy AA, Vincent JL, Jacobs F, Lipman J. Vancomycin dosing in critically ill patients: robust methods for improved continuous-infusion regimens. *Antimicrob Agents Chemother* 2011;55:2704-9.  
[PUBMED](#) | [CROSSREF](#)
16. Smits A, Pauwels S, Oyaert M, Peersman N, Spriet I, Saegeman V, Allegaert K. Factors impacting unbound vancomycin concentrations in neonates and young infants. *Eur J Clin Microbiol Infect Dis* 2018;37:1503-10.  
[PUBMED](#) | [CROSSREF](#)
17. Purwonugroho TA, Chulavatnatol S, Preechagoon Y, Chindavijak B, Malathum K, Bunuparadah P. Population pharmacokinetics of vancomycin in Thai patients. *Sci World J* 2012;2012:762649.  
[PUBMED](#) | [CROSSREF](#)
18. Kovacevic T, Miljkovic B, Kovacevic P, Dragic S, Momcicevic D, Avram S, Jovanovic M, Vucicevic K. Population pharmacokinetic model of vancomycin based on therapeutic drug monitoring data in critically ill septic patients. *J Crit Care* 2020;55:116-21.  
[PUBMED](#) | [CROSSREF](#)
19. Tsai D, Stewart PC, Hewagama S, Krishnaswamy S, Wallis SC, Lipman J, Roberts JA. Optimised dosing of vancomycin in critically ill Indigenous Australian patients with severe sepsis. *Anaesth Intensive Care* 2018;46:374-80.  
[PUBMED](#) | [CROSSREF](#)
20. Chattaweelarp T, Changpradub D, Punyawudho B, Thunyaharn S, Santimaleeworagun W. Is early monitoring better? Impact of early vancomycin exposure on treatment outcomes and nephrotoxicity in patients with methicillin-resistant *Staphylococcus aureus* infections. *Antibiotics (Basel)* 2020;9:672.  
[PUBMED](#) | [CROSSREF](#)