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## Vancomycin dosage optimization during the first 24-hour treatment of Methicillin resistant *Staphylococcus aureus* in critically ill patients using Monte Carlo simulation method

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## Introduction

Vancomycin, a glycopeptide antibiotic, has been used for a half decade to treat the penicillin non-susceptible Gram positive bacteria. Nowsday, vancomycin remains the first-line treatment for methicillin resistant *Staphylococcus aureus* (MRSA) infections.<sup>(1)</sup> However, the serum vancomycin concentrations were complex and varied upon patient conditions. <sup>(2)</sup> Especially critically ill patients, they treated with high-volume resuscitation and increasing vascular permeability due to sepsis process. del Mar Fernández et al. found that critically ill patients had an increased volume of distribution (Vd) up to 1.68 L/kg.<sup>(3)</sup> Additionally, The early period of sepsis often present a hypermetabolic condition (namely, augmented renal clearance; ARC) leading to increased renal blood flow and decreased serum level of renally eliminated drugs. Baptista et al. showed that ARC was strongly associated with subtherapeutic vancomycin serum concentrations during first 3 days of treatment.<sup>(4)</sup>

Use of the vancomycin loading dose at 25 to 30 mg/kg is a strategy to achieve effective concentrations from the first-treatment dose avoiding treatment failure in critical patients.<sup>(5)</sup> Bakke et al. revealed that vancomycin trough serum concentrations among critically ill patients were often not reached within therapeutic range (15–20  $\mu$ g/L) during the first three days of vancomycin administration, especially the first day of treatment.<sup>(6)</sup> The sub-level of vancocomycin due to low dose administration directly affects patient outcome. The recent study showed that the median time to resolution of systemic inflammatory response syndrome was 109 h in the vancomycin <20 mg/kg group compared to 67 h in the ≥20 mg/kg group.<sup>(7)</sup> Similar to the previous study, each hour of delay in appropriate antimicrobial administration was associated with an average decrease in survival of 7.6% among septic shock patients. Thus, loading doses of vancomycin is quite important due to the high mortality seen with these population. However, there is scant published study investigating the effect of vancomycin dosing on achieving pharmacokinetic/pharmacodynamic target during the first 24-hour treatment of MRSA in Thailand. Therefore, the aim of the present study was to predict optimal vancomycin dosing regimens for empirical and documented therapy against MRSA infection using Monte Carlo simulation in critically ill patients.

## Methods

#### Pharmacokinetic parameters of vancomycin

Monte Carlo simulation was conducted using the pharmacokinetic parameters of vancomycin in 12 septic shock patients from a previous Thai study.<sup>(8)</sup> The two-compartment model was chosen to predict vancomycin concentration-time profile. The vancomycin pharmacokinetic parameters included vancomycin clearance (CLvan) (L/h) = 3.34 ( $\pm$ 1.39), the central volume of distribution (Vc) (L) = 8.53 ( $\pm$ 1.50), the elimination rate constant ( $k_e$ I) ( $h^{-1}$ ) = 0.37 ( $\pm$ 1.67), the intercompartmental transfer rate constant from compartment 1 to compartment 2 ( $k_{12}$ ) ( $h^{-1}$ ) = 2.39 ( $\pm$ 1.60) and the intercompartmental transfer rate constant

from compartment 2 to compartment 1 ( $k_{21}$ ) ( $h^{-1}$ ) = 0.67 (±1.30). In this study, we calculated the probabilities of target attainment (PTA) to reach target of the area under the concentration–time curve over minimum inhibitory concentration (AUC/MIC) and to determine a trough vancomycin concentration ( $C_{trough}$ ) of <15 µg/mL, 15-20µg/mL, >20–35 µg/mL, and >35 µg/mL at the first day of vancomycin administration.

#### Susceptibility data for MRSA isolates

104 non-duplicated MRSA isolates from Chaoprayayomraj Hospital located Central Thailand during 2014 were collected. These data were incorporated to calculate the cumulative fraction of response (CFR). CFR was calculated by the cumulative fraction of proportional bacteria of each vamcomycin MIC multiplied by PTA of each vancomycin MIC. The CFR was the probability of drug dose covering a specified bacterial population. The MRSA vancomycin susceptibility data were determined using an Epsilometer test (E-test) (Thermo Fisher Scientific) in accordance with CLSI 2017.<sup>(9)</sup>

The present study was considered from the Institutional Review Board approval, Faculty of Pharmacy, Silpakorn University (approval No. 1/2558) and Chaoprayayomraj Hospital (approval No. YM 014/2558).

#### Pharmacokinetic/Pharmacodynamic index

The ratio of vancomycin AUC and minimum inhibitory concentration (AUC/MIC)  $\geq$ 400 is a target value of Pharmacokinetic/Pharmacodynamic index. This study also evaluated the PTA to reach a trough vancomycin concentration (C<sub>trough</sub>) of <15 µg/mL, 15-20µg/mL, >20–35 µg/mL, and >35 µg/mL.

Vancomycin dosing regimen that reached above 90% of PTA and CFR was considered as the optimal dosage for documented therapy and empirical therapy, respectively.

# Results

#### Demographic data

With the susceptibility data among 104 non-duplicated MRSA isolates, one hundred and two strains were isolated from sputum. The remaining isolates were obtained by hemocultue. The MIC range, MIC50, and MIC90 for vancomycin against studied MRSA isolates were 0.5-2.0  $\mu$ g/mL, 1  $\mu$ g/mL, and 2  $\mu$ g/ mL, respectively.

#### Probabilities of target attainment

The PTA in the first day of treatment for the vancomycin regimens at specific MICs with targets of AUC/MIC  $\geq$  400 is shown in Table 1. Among critically ill patients, for MRSA with a MIC of 1.0 µg/mL, all vancomycin doses reached the PTA nearly 100%. However, only a vancomycin dosage of 2.5 g loading followed by 1 g q 8 h covered for isolates with a MIC of 2.0 µg/mL.

## Cumulative fraction of response

Using a CFR >90%, only two regimens were reached to targets of AUC/MIC  $\ge$  400 including 2.0 g loading followed by 1 g q 8 h and 2.5 g loading followed by 1 g q 8 h at Day 1 of treatment and at steady state. (Figure 1).

## The trough vancomycin concentrations

With the vancomycin regimen of 1.5 g loading followed by 1 g q 12 h, the proportion of trough serum concentrations sub-therapeutic level (<15  $\mu$ g/mL) was 31.95 % at day 1 of treatment. However, all maintain dose regimens of every 8 h that generated C<sub>trough</sub>>35  $\mu$ g/mL, were approximately a half of patients.

**Table 1.** The percentage of probability target attainment (PTA) at Day 1 of treatment for the different vancomycin regimens at specific vancomycin MICs (μg/mL) with targets of AUC/MIC ≥400

Vancomycin dosing regimen	Percentage of PTA in each MIC levels				
	0.25	0.5	1.0	1.5	2.0
1.5 g loading followed by 1 g q 12 h	100	100	95.11	68.91	40.2
1.5 g loading followed by 1.25 g q 12 h	100	100	97.35	75.47	47.53
1.5 g loading followed by 1 g q 8 h	100	100	99.7	89.99	67.92
2.0 g loading followed by 1 g q 12 h	100	100	99.22	85.59	61.72
2.0 g loading followed by 1.25 g q 12 h	100	100	99.49	88.85	67.01
2.0 g loading followed by 1 g q 8 h	100	100	99.98	96.42	81.61
2.5 g loading followed by 1 g q 12 h	100	100	99.85	93.66	75.47
2.5 g loading followed by 1.25 g q 12 h	100	100	99.97	95.78	80.06
2.5 g loading followed by 1 g q 8 h	100	100	99.98	98.71	90.16



Figure 1. The cumulative fraction of response (CFR) achieving an area under the curve (AUC)/minimal inhibitory concentration (MIC) ≥400 at the first day of treatment and at the steady state and the percentage of trough vancomycin concentrations (Ctrough) for each dosing regimen in simulated patients.

#### Discussion

Recently, Lodise et al revealed the significant AUC/MIC target at the first day was associated with an increased risk of failure. AUC/MIC0-24 archiving target gave reduced risk of 30-day mortality (RR 0.39; 95%CI 0.19-0.80). This effect also decreased the risk of mortality at the second day (AUC/MIC24-48) of therapy (RR 0.41; 0.21-0.82). These findings establish the critical importance of daily AUC/MIC ratios during the first 2 days of therapy.<sup>(10)</sup> The benefit of early reaching target also found in Casapao et al study. An AUC/MIC met target during first 24 hour was independently associated with failure (adjusted odds ratio, 2.3; 95%CI, 1.01-5.37).<sup>(11)</sup>

In this study, vancomycin loading dose of 2.0-2.5 g followed by 1 g every 8 h was appropriate to be recommended dose in critically ill patients. These vancomycin regimens met the target AUC/MIC regardless at initial therapy or at the steady state. Similarly, Álvarez et al. study indicated that 92% of patients with loading dose based on population pharmacokinetic parameters of the critically ill patient could reach optimal AUC<sub>0-24</sub>  $\geq$ 400.<sup>(12)</sup> Additionally, we found that approximately one third of simulated patient receiving loading dose of 1.5 g with 1 g every 12 h had the sub-therapeutic level (<15 µg/mL). This unwanted target was noted in the recent study showing less than 40% of the patients attained therapeutic Ctrough during the initial therapy.<sup>(6)</sup> Unfortunately, patients who reached a subtherapeutic level at the first vancomycin measurement had a significant correlation with in-hospital mortality.<sup>(13)</sup>

Even, we suggested that vancomycin loading dose of 2.0-2.5 g followed by maintain dose every 8 h seems to be optimal regimen. The risk of nephrotoxicity due to high Ctrough is cautious. All of vancomycin dose of every 8 h administration revealing Ctrough above 35  $\mu$ g/mL was at least a half of simulated patients. This vancomycin trough concentration was significantly associated with acute kidney injury<sup>(14)</sup>. Thus, after initially high dose used in critical patients, the vancomycin therapeutic drug monitoring and renal function assessment are important process for treatment optimization with less nephrotoxicity.

In the same way, for prevention of nephrotoxicity, our result indicated that a maintain dose of 1.25 g every 12 h might be an alternative regimen as closing to our target CFR at the steady state except during initial therapy. Thus, vancomycin loading dose of 2.0-2.5 g followed by maintain dose every 8 h is recommended at Day 1 of treatment. This dosing regimen gave more than 90% of simulated patients with Ctrough  $\geq$ 15 µg/mL. The vancomycin maintain dose at 1.25 g every 12 h was then suggested to reach target CFR at steady state.

However, our study has some limitations. 1) Owing to pharmacokinetic parameter obtained from Katip et al study, the percentage of probability target attainment in each vancomycin MIC could be apply in patients with more than 18 years of age and with septic shock. 2) The size of our sample dictates the information of vancomycin dosing regimen. Thus, the larger sample size is more coverage of the vancomycin MIC distribution in MRSA population. 3) The MRSA isolates in this study seem to be high MIC value which might be dissimilar when taken from other settings. Around forty percent of studied MRSA isolates had vancomycin MIC at 2  $\mu$ g/mL. Our situation of vancomycin susceptibility need the higher vancomycin dosing regimen. Thus, the other setting with different condition, could be applied from PTA at specific vancomycin MICs. For instance, among pathogens with a MIC of 0.5  $\mu$ g/mL, all dosage regimens achieved the PTA target.

However, only a vancomycin dosage of 1 g intravenous three times a day that covered for isolates with a vancomycin MIC of 2  $\mu$ g/mL.

# Conclusion

The administration of the loading calculated from simulated patients at the beginning of therapy is a strategy to obtain therapeutic Ctrough range and AUC/MIC in critically ill patients. This study demonstrated that loading dose of 2.0-2.5 g with maintain dose 1 g every 8 h gave the target AUC/MIC  $\geq$ 400 at the first day of vancomycin administration. At the steady state, maintain doses of 1.25 every 12 h or 1 g every 12 h also met the target AUC/MIC. However, above vancomycin regimens might be the risk of nephrotoxicity. Practically, the vancomycin therapeutic drug monitoring and renal function assessment are important issues for favourable patient outcome with minimized nephrotoxicity.

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