The adequacy of vancomycin initial dosing in CRBSI for hemodialysis patients in a specialized district hospital of Malaysia

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Abstract

Background: Catheter-related bloodstream infections (CRBSIs) are a common complication in hemodialysis (HD) patients with central venous catheters (CVCs), and are often caused by Methicillin-Resistant Staphylococcus aureus (MRSA). Vancomycin is the preferred first-line treatment for MRSA-related CRBSI. At Hospital Pakar Sultanah Fatimah (HPSF), the current protocol for CRBSI in HD patients involves a weight-based intravenous (IV) vancomycin loading dose (LD) of 25 mg/kg, followed by therapeutic drug monitoring (TDM) within 48 hours post-administration. This study evaluates the adequacy of the initial dosing regimen in achieving the target serum vancomycin concentration (SVC) of 15–20 mcg/ml.

Methods: A retrospective cross-sectional study was conducted among hospitalized HD patients receiving IV vancomycin from July 1, 2022, to July 31, 2023. Data were collected from TDM request orders in the Pharmacy Information System (PhIS). The primary outcomes analyzed were the proportion of patients achieving the target SVC and factors influencing vancomycin pharmacokinetics. Multiple linear regression was used to assess associations between SVC and variables such as time-to-first-sampling (TTFS), age, and initial vancomycin dose.

Results: A total of 106 TDM samples were analyzed. The mean vancomycin LD was 1568.2 mg (SD 303.6), with a mean TTFS of 41.2 hours (SD 11.8). Only 32.1% of patients achieved the target SVC, while 56.6% had subtherapeutic levels and 11.3% had supratherapeutic levels. Multiple linear regression identified TTFS ($p=0.003$), age ($p=0.002$), and initial dose ($p=0.004$) as significant predictors of SVC.

Conclusion: The current vancomycin dosing protocol at HPSF does not consistently achieve therapeutic SVC in HD patients with CRBSI. Increasing the LD to 25–35 mg/kg and optimizing TTFS within 24–48 hours may improve target attainment. Further studies are needed to validate these findings and refine vancomycin dosing strategies in HD patients.

Keywords: vancomycin, catheter-related bloodstream infections, hemodialysis, therapeutic drug monitoring, dosing adequacy, Methicillin-Resistant Staphylococcus aureus (MRSA)

Introduction

End-stage renal disease (ESRD), which marks the most severe and irreversible stage of chronic kidney disease (CKD), has emerged as a pressing global public health concern. This is largely due to its steadily increasing incidence worldwide, its strong association with high mortality rates, and the substantial financial burden it places on healthcare systems (Eknoyan et al., 2004). In Malaysia, hemodialysis (HD) is the preferred treatment modality for ESRD. The prevalence of ESRD patients undergoing dialysis has increased dramatically, from 7,837 in 2001 to nearly 23,000 in 2010 (NRR, 2011). By 2014, the total number of patients requiring dialysis in Malaysia had risen to 34,767, and the annual mortality rate among hemodialysis patients was 11.6% (NRR, 2015).

One of the major complications in HD patients with central venous catheters (CVCs) is catheter-related bloodstream infections (CRBSIs) (Gahlot et al., 2014; Shingarev et al., 2013). It is estimated that up to 80% of HD patients begin dialysis with a CVC as their initial vascular access, rather than with a more permanent access — either an arteriovenous fistula (AVF) or an arteriovenous graft (AVG). Among those starting with a CVC, non-tunneled catheters are often used, particularly in developing countries. These are temporary devices inserted into a central vein, and are intended for short-term use before the permanent vascular access is set, or in emergency or unplanned dialysis. In contrast with tunneled catheters, non-tunneled CVCs do not pass under the skin before entering the vein. Without the subcutaneous tunnel, the exit site is more exposed and prone to contamination because the catheter emerges from the body (Allon, 2004; Haddadin et al., 2022). This lack of a protective tunnel allows

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bacteria easier access to the bloodstream, significantly elevating the probability of CRBSIs — infections which not only cause a direct threat to patient safety but also lead to prolonged hospitalizations, increased use of antibiotics, and higher rates of complications, all of which contribute substantially to greater morbidity and increase the healthcare burden (Allon, 2004; Gahlot et al., 2014; Zimlichman et al., 2013).

Among the most commonly isolated pathogens in CRBSI cases are *staphylococcal* species, with Methicillin-Resistant *Staphylococcus aureus* (MRSA) emerging as a prevalent concern (Abdul Gafor et al., 2014; Gahlot et al., 2014, Haddadin et al., 2022). Vancomycin is frequently used as the first-line treatment for MRSA-related CRBSI (Mermel et al., 2009). Determining the adequate vancomycin initial dosing in HD patients is complex because they often have altered pharmacokinetics, including reduced renal clearance and variable drug removal depending on the dialysis modality and membrane used. Because of the limited clinical data specific to the HD population, as well as the lack of standardized guidelines for vancomycin dosing and therapeutic drug monitoring (TDM) in HD patients, there is significant variability in vancomycin dosing regimens across healthcare institutions (Rybak et al., 2020).

The mechanism of HD involves diffusion and ultrafiltration, which facilitate the movement of solutes across a semi-permeable membrane (Oshvandi et al., 2014). Dialyzers are categorized into two major types: high-flux and low-flux. At Hospital Pakar Sultanah Fatimah (HPSF), in Muar, Johor, Malaysia, HD procedures are conducted using low-flux dialyzers. These dialyzers, characterized by an ultrafiltration rate of <15 mL/mmHg/h, are primarily effective in removing small solutes through diffusion but have minimal clearance of middle-sized solutes, which are considered more toxic and difficult to eliminate by diffusion alone (Abe et al., 2022).

Currently, HPSF follows a weight-based vancomycin dosing protocol for CRBSI treatment in HD patients. This protocol consists of an intravenous (IV) loading dose of 25 mg/kg (rounded up to the nearest 250 mg), followed by TDM within 48 hours post-administration to assess drug levels. To optimize clinical outcomes, it is crucial to evaluate the effectiveness of this protocol. This study aimed to assess the adequacy of the initial vancomycin dosing and the time-to-first-sampling (TTFS) in achieving the target serum vancomycin concentration (SVC) of 15–20 mcg/mL.

Methods

This cross-sectional retrospective study was conducted among HD patients at HPSF from July 1, 2022, to July 31, 2023. The study included hospitalized ESRD patients aged 18 years and above who were undergoing HD and who received intravenous vancomycin during admission as either empirical or definitive treatment for an infection.

A universal sampling method was applied, where eligible patients were identified through vancomycin Therapeutic Drug Monitoring (TDM) request orders in the Pharmacy Information System (PhIS). The medical records of these patients were reviewed to collect socio-demographic data, comorbidities, dialysis prescriptions, vancomycin dosing, and administration records. Additionally, TTFS and SVC following the initial vancomycin dose were retrieved from the TDM order in PhIS.

In this study, TTFS was defined as the TDM sampling time occurring 36–48 hours after the vancomycin loading dose, while a TDM request was defined as a TDM test order placed by a prescriber via PhIS. Doctors were reminded by pharmacist working at the time to draw blood for the SVC after the initial dose of vancomycin was administered.

Data analysis was performed using IBM SPSS Version 26. The weight-based initial vancomycin loading dose, TTFS patterns, and resulting SVC were analyzed descriptively. Categorical data were presented as frequencies (n) and percentages (%), whereas continuous data were reported as mean and standard deviation (SD).

To determine factors influencing SVC after the initial vancomycin dose at first TDM sampling, multiple linear regression analysis was conducted. Initially, simple linear regression was performed for all variables, and those with $p < 0.25$ were subsequently included in the multiple linear regression model. The regression results were expressed as regression coefficients (β) with 95% confidence intervals (CI), and statistical significance was set at $p < 0.05$.

This study was approved by the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia, with registration number NMRR ID-24-02412-PBR. Patient privacy and confidentiality were strictly maintained throughout data collection, analysis, and publication by ensuring that no patient identifiers were included.

Results

A total of 106 TDM samples were included in this study. The demographic and clinical characteristics of the patients are presented in Table 1. The mean age of patients whose TDM samples were analyzed was 56.3 years (SD 12.7). The distribution of male (52.8%) and female (47.2%) patients was nearly equal. The majority of patients were younger than 60 years old and of Malay ethnicity (85.8%).Most patients received vancomycin as a definitive treatment (93.4%), with only 6.6% receiving it empirically.

Table 1. Patient Demographic and Clinical Characteristics (n = 106 TDM samples)

Characteristics	Value
Age, year, mean (SD)	56.3 (12.7)
Age, year, n (%)	
≥ 60	46 (43.4)
<60	60 (56.6)
Weight, kg, mean (SD)	67.4 (14.6)
Gender, n (%)	
Male	56(52.8)
Female	50(47.2)
Race, n (%)	
Malay	91(85.8)
Chinese	13(12.3)
Indian	2(1.9)
Indication of vancomycin, n (%)	
Empirical	7 (6.6)
Definitive	99 (93.4)

A fixed vancomycin loading dose (LD) of 25 mg/kg resulted in a mean initial dose of 1568.25 mg (SD 303.6), with a mean patient weight of 67.4 kg (SD 14.6). The overall mean TTFS was 41.2 hours (SD 13.3), with most TDM samples (85.8%) taken between 24 to 48 hours post-dose.

From 106 TDM samples, only 32.1% achieved the targeted SVC (15.0–20.0 mcg/mL), while 56.6% had subtherapeutic levels (<15.0 mcg/mL) and 11.3% had supratherapeutic levels (>20.0 mcg/mL) (Table 2).

With a fixed LD of 25 mg/kg, the mean SVC in the target range was 16.9 mcg/mL (SD 1.4), while the mean SVC in the supratherapeutic group was 24.3 mcg/mL (SD 4.1). While the mean TTFS was comparable across subtherapeutic, target, and supratherapeutic group, more than half (56%) of samples taken 24–48 hours post-dose exhibited subtherapeutic SVC.

Table 2. Vancomycin Dosing According to SVC

	SVC, mcg/ml		
	<15.0	**15.0-20.0**	**>20.0**
Total number of patients, n (%)	60 (56.6)	34 (32.1)	12 (11.3)
SVC, mcg/ml, mean (SD)	10.8 (3.3)	16.9 (1.4)	24.3 (4.1)
Initial dose, mg, mean (SD)	1694.4 (265.5)	1481.6 (283.4)	1644.1 (375.7)
Overall TTFS, hour, mean (SD)	41.2 (13.3)	38.5 (8.8)	39.2 (11.7)
TTFS 24 to 48 hours, n (%)	51 (56.0)	30 (33.0)	10 (11.0)
TTFS > 48 hours, n (%)	9 (60.0)	4 (26.7)	2 (13.3)

Abbreviations: TDM – Therapeutic Drug Monitoring, SVC – Serum Vancomycin Concentration, SD – Standard Deviation, TTFS – Time to First Sampling

Table 3 shows factors that significantly influenced the SVC following the administration of vancomycin initial dose. Simple linear regression was conducted to see the individual effect of each factor on the SVC. The results show that only age and TTFS had a statistically significant effect on SVC, while initial dose showed a slight positive effect. The three factors were then included in the multiple linear regression; all three show a significant effect on SVC: TTFS (p=0.003), age (p= 0.002) and initial dose of vancomycin (p= 0.004), where the association shown in model SVC = 18.809 - 0.132 (TTFS) - 0.125 (Age) + 0.005(Dose).

Table 3. Factors affecting the SVC following initial dose of vancomycin among ESRD patients on dialysis

Factors	Simple Linear Regression		Multiple Linear Regression	
	Regression coefficient (95% CI)	**p-value**	**Regression coefficient (95% CI)**	**p-value**
Age	-0.113(-0.194,-0.033)	0.006	-0.125 (-0.202, -0.049)	0.002
TTFS	-0.203 (-0.180,-0.006)	0.037	-0.132 (-0.218, -0.047)	0.003
Initial Dose	0.003 (0.000, 0.006)	0.087	0.005 (0.002, 0.008)	0.004
Weight	0.037(-0.035,0.109)	0.309		
No of dialysis	-0.212(-1.926,1.502)	0.807		

Note: p<0.05 denotes statistical significance. Stepwise multiple linear regression method applied. Model assumptions are fulfilled. Model is significant , p<0.001. No interactions or multicolinearity detected. Coefficient of determination r2 = 0.182, constant = 18.809

Discussion

The results of this study suggest that the current vancomycin dosing protocol at HPSF does not consistently achieve therapeutic SVC in HD patients with CRBSI. The finding that only 32.1% of patients reached the target SVC range highlights the need for a dosing adjustment. The high proportion (56.6%) of patients with subtherapeutic SVC indicates that the standard LD of 25 mg/kg (rounded up to the nearest 250 mg) may be insufficient for most patients, leading to inadequate bacterial eradication and potential treatment failure.

This issue has been similarly reported in previous studies. For example, Rybak et al. found that standard vancomycin dosing in HD patients often resulted in subtherapeutic SVC levels, and recommended an increased LD of 20–35 mg/kg to improve outcomes (Rybak et al., 2020). Additionally, a study by Rosini et. al reported that a 30 mg/kg loading dose of vancomycin resulted in a higher percentage of therapeutic levels at 12

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hours compared to the standard 15 mg/kg dose, without an increase in nephrotoxicity or adverse events (Rosini et al., 2015). Achieving therapeutic drug concentrations rapidly at the early treatment is essential for optimizing clinical outcomes, as it helps reduce the risk of treatment failure and prevents the persistence of bacteria, which could lead to prolonged infection and potential complications (Bruniera et al., 2015). Abdul Gafor et al. further highlighted that inadequate vancomycin exposure was associated with prolonged infection resolution times, reinforcing the need for individualized dosing strategies (Abdul Gafor et al., 2014).

A supratherapeutic level of vancomycin in HD patients is associated with several significant adverse events, primarily ototoxicity, Red Man syndrome, and neurotoxicity due to impaired renal clearance and altered pharmacokinetics. These adverse outcomes underscore the importance of individualized dosing and rigorous monitoring of vancomycin levels in the HD population. (Crețu et al., 2025). Although 11.3% of patients in our study had supratherapeutic levels, this is of less concern in the HD setting. Vancomycin is typically administered post-dialysis, and approximately 30% of the drug is removed during a single dialysis session. A study by Ariano et al. demonstrated that supratherapeutic pre-dialysis vancomycin levels were often mitigated by dialysis, preventing significant toxicity while maintaining therapeutic efficacy (Ariano et al., 2005).

Similarly, Petejova et al. reported that low-flux HD removed considerable amounts of vancomycin in critically ill septic patients with acute kidney injury (AKI), reducing toxicity risks; this finding supports the argument that supratherapeutic levels do not necessarily translate to increased adverse effects in dialysis patients (Petejova et al., 2012). Slight elevations in pre-dialysis vancomycin levels should therefore not be overemphasized, as post-dialysis drug removal often brings levels back into the therapeutic range.

The mean initial dose of 1568.2 mg (25 mg/kg) in our study was insufficient for many patients, particularly older individuals and those with delayed TDM sampling. The regression analysis showed a positive association between initial dose and SVC levels, suggesting that increasing the LD to 25–35 mg/kg may improve therapeutic outcomes. This is supported by recent guidelines recommending higher initial doses in HD patients to account for reduced drug clearance (Abdul Gafor et al., 2014).

A critical factor influencing SVC was TTFS, which had a significant negative correlation ($p=0.003$) with SVC levels. Our study found that an optimal TTFS within 24–48 hours post-administration is necessary to accurately assess vancomycin levels and guide subsequent dosing. Delayed sampling beyond 48 hours was associated with greater fluctuations in SVC, which may lead to inappropriate dose modifications.

Age also played a significant role in vancomycin pharmacokinetics, with older patients exhibiting lower SVCs ($p=0.002$). This finding aligns with previous studies that suggest age-related changes in renal function and altered drug distribution can impact vancomycin clearance, necessitating dose adjustments in elderly patients. Furthermore, the initial vancomycin dose demonstrated a mild positive correlation with SVC ($p=0.004$), indicating that higher loading doses could improve target attainment.

Compared with prior research, our study supports the recommendations of Rybak et al., which suggested that an increased LD of 20–35 mg/kg may be necessary to achieve target vancomycin levels in HD patients (Rybak et al., 2020). Similarly, Mermel et al. emphasized the importance of precise TDM sampling, reinforcing our conclusion that optimizing TTFS is crucial for therapeutic success (Mermel et al., 2009).

The variability in SVC observed in our study suggests that a fixed dosing strategy may not be ideal for all patients. Instead, individualized dosing models incorporating patient-specific pharmacokinetic parameters, weight, and dialysis efficiency may yield better therapeutic outcomes. Implementing a revised protocol with an increased LD (25–35 mg/kg) and standardized TTFS within 24–48 hours post-dose could enhance the achievement of target SVC and reduce the risk of treatment failure or toxicity.

Conclusion

The current vancomycin dosing protocol at HPSF is suboptimal in achieving therapeutic SVC in HD patients with CRBSI. An increase in the LD to 25–35 mg/kg and optimized TTFS may enhance vancomycin efficacy. Further prospective studies are needed to validate these findings and refine dosing recommendations for improved clinical outcomes.

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