Vancomycin Initial Dosing in Adult Dialysis Patients in a Tertiary Care Hospital (VIDAD)

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Abstract

Introduction: Vancomycin is the drug of choice to treat methicillin-resistant *Staphylococcus aureus* infections in hospitalised patients. Guideline recommends a loading dose (LD) of vancomycin to rapidly achieve the targeted therapeutic concentration. However, in dialysis population there are conflicting opinions on whether LD is required.

Objective: The aims of the study were to identify the weight-based initial LD of vancomycin and time-to-first-sampling (TTFS) to achieve targeted serum vancomycin concentration (SVC) and the potential contributory factors affecting SVC at first sampling.

Methods: This was a prospective observational study conducted at a tertiary hospital over three months in 2016. All end-stage renal disease (ESRD) patients aged 18 years old and above, on dialysis and received intravenous vancomycin were included. Eligible patients were identified from the therapeutic drug monitoring (TDM) request forms. Demographic and clinical data were obtained from the medical records. Target SVC range was 15.0-20.0mg/L.

Results: Vancomycin dose prescribed ranged from 1,000-2,000mg with mean LD of 20.2 (standard deviation (SD) 5.8) mg/kg. This study found that the vancomycin TDM sampling was done either at TTFS less than 24 hours (49%) or 24-48 hours (51%). Only 18.4% of patients achieved the target SVC, while 65.3% were sub-therapeutic and 16.3% were above target. Factors that significantly influenced the SVC include LD ($p<0.001$) and TTFS ($p=0.003$). Target SVC was achieved in ESRD patients on dialysis when LD of 15.0-25.0mg/kg given and sampled at TTFS <24 hours. The linear regression equation describing the association is SVC = 0.616 (LD) - 0.213 (TTFS) + 7.487.

Conclusion: Weight-based LD and TTFS are important predictors that need to be considered when dosing vancomycin in dialysis patients to ensure its therapeutic effectiveness. LD of 20-25mg/kg is likely to achieve the target SVC at TTFS of 24 hours. The study findings may serve as a dosing guide of vancomycin in ESRD patients.

Keywords: vancomycin, dialysis, loading dose, TDM, sampling time

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Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections are common infections in hospitalised patients. The prevalence of MRSA infections in the hospitals worldwide are high and MRSA rates of more than 50% were reported in the Asian and American continent (1). Meanwhile, local data in Malaysia showed increasing trend of MRSA infections, with 17% in 1986 to 44.1% in 2007 (2,3). Although MRSA can cause infections in multiple sites of body, the major concern has always been MRSA bacteraemia. This is because it can often progress to complicated metastatic MRSA infection, such as infective endocarditis, septic arthritis, osteomyelitis and multifocal collections or abscesses (4,5). In addition, complicated MRSA infections were associated with poorer clinical outcomes (6). The risk of MRSA infections among haemodialysis patients was 45.2 per 1,000 population compared to 0.2-0.4 per 1,000 population among the general population. This means that the risk of MRSA infections among haemodialysis patients was 100-fold higher (7).

There are a few antibiotics with anti-MRSA activities, including vancomycin, daptomycin, linezolid,

ceftaroline, teicoplanin, trimethoprim-sulfamethoxazole, rifampicin and fusidic acid. Although the Infectious Diseases Society of America guidelines recommended the use of intravenous vancomycin or daptomycin to treat MRSA bacteraemia, vancomycin has remained as the drug of choice in Malaysia as it is readily available and cheaper (8). Therapeutic drug monitoring (TDM) of vancomycin is important to ensure that sufficient drug concentration is achieved in the body to provide good bactericidal effect (9). It is thus crucial to achieve the recommended vancomycin serum trough concentrations of 15–20mg/L for maximal efficacy (9). This will improve drug penetration and increase the probability of clinical success (9). Recent study found that the guidelines advocated the practice of giving a loading doses (LD) of vancomycin to rapidly attain the therapeutic concentrations. The LD of 15-20mg/kg in patients with normal renal function and 25-30mg/kg in seriously ill patients were recommended (4,9).

In the dialysis population, however, there are conflicting opinions on whether a loading dose is required. Matzke *et al.* suggested LD of 25mg/kg regardless of renal function (10). On the other hand, Matsumoto *et al.* found that a vancomycin loading dose is required to promptly achieve targeted serum vancomycin concentration (SVC) because vancomycin has markedly prolonged plasma half-life in patient with renal dysfunction. However, no recommendation for the exact loading dose in dialysis patients was given to date (11). This may lead to the variations in vancomycin dosing among dialysis patient, which may affect the clinical outcomes. The current practice in Hospital Kuala Lumpur (HKL) is to use a standard initial dosing of 1,000mg for all dialysis patients. Even though this one-size-fits-all dosing offers convenience of dosing, the effectiveness is questionable. An internal audit by HKL Pharmacy Department revealed that almost 50% of SVC taken after the initial dose were sub-therapeutic at lower than 15mg/L. It was also noted that the SVC varied substantially among dialysis patients who received this standard LD of 1,000mg (12).

Renal function shown by creatinine clearance and residual renal function is known to affect the SVC. This is because vancomycin is primarily excreted through the kidney and therefore, changes in renal function would affect its clearance, indirectly influencing the SVC. In addition, renal replacement therapies such as haemodialysis, sustained low-efficiency dialysis (SLED) and peritoneal dialysis (PD) were shown to affect the vancomycin clearance (13). The dialysability of a drug varies based on the molecular weight, protein binding, type of dialysis membrane and mode of dialysis. The lower the molecular weight and protein binding, the higher the dialysability of the drug (14). Since the protein binding properties of vancomycin is reduced further to 20% in renal impairment, its clearance via dialysis is increased especially in high flux membrane haemodialysis (14,15). In addition, dialyser membrane surface area and blow flow rate would also affect the extraction of vancomycin during the dialysis (14). El Nekidy *et al.* reported weight-based LD, age and time between administration of LD and dialysis as significant factors affecting SVC among end-stage renal disease (ESRD) patients on haemodialysis (16). Another study by Oyaert *et al.* found albumin to be a significant predictor of unbound vancomycin concentration, regardless of patient's renal function (17).

There is limited evidence on the optimal method of vancomycin initial dosing among ESRD patients on dialysis, especially in the local setting. Therefore, it is important to assess the initial dosing of vancomycin, attainments of target SVC and the factors influencing SVC among this population. The aims of this study were to identify the weight-based initial dose of vancomycin and time-to-first-sampling (TTFS) to achieve targeted serum vancomycin concentration (SVC) among ESRD patients on dialysis, and to determine the factors affecting SVC at first sampling.

Methods

This was a prospective observational study at the nephrology and general medical wards of HKL, a tertiary hospital with nephrology specialty. The study was conducted from December 2015 to February 2016. Hospitalised ESRD patients aged 18 years old and above who were undergoing dialysis and receiving intravenous vancomycin during the admission as an empirical and/or definitive treatment for any infection were included in the study. Patients who were critically ill and admitted to the intensive care units or high-dependency wards, renal transplant patients, those who require continuous renal replacement therapy or cycler peritoneal dialysis and those who received vancomycin therapy without sampling of serum vancomycin level following the initial dose were excluded.

Universal sampling method was applied where all patients fulfilling the inclusion and exclusion criteria during the study period were included in the study. Initially, eligible patients were identified from the vancomycin TDM request forms sent to the pharmacy. Then, the identified patients' medical records were screened. Information such as socio-demographic, co-morbidities, dialysis prescriptions, vancomycin dosing and administration records were collected. Subsequently, TTFS and SVC following the initial dose

of vancomycin were obtained from the TDM forms. Data were collected using a structured data collection form.

Data analyses were conducted using IBM® SPSS® Statistics Version 20. Weight-based initial dose or LD of vancomycin prescribed, pattern of TTFS and the resulting SVC were analysed descriptively. Categorical data were reported in frequency (n) and percentage (%), while continuous variables were reported as mean and standard deviation (SD). Multiple linear regression was applied to determine the factors affecting the SVC after initial dose of vancomycin on first TDM sampling. The variables were included in the initial simple linear regression analysis, where those with $p<0.25$ were selected to be included in the multiple linear regression model. Final results were presented as regression coefficient, b (95% confidence interval (CI)), where p-value of <0.05 indicates statistical significance.

This study was conducted as per ethical standards of the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia. Ethics approval was obtained from the MREC (NMRR-15-2428-25002) prior to the commencement of the study. Patient's privacy and confidentiality was protected throughout the data collection, analyses, interpretation and publication processes as there were no patient identifiable data included.

Results

Demographic and Clinical Characteristics

During the study period, there were a total of 49 patients fulfilling the eligibility criteria and included in the study. The demographic and clinical characteristics were described in Table 1. The mean age of patients was 57.3 (SD 13.9) years old, where majority were male (65.3%) and of Malay ethnicity (73.5%). Approximately 80-85% of them had diabetes mellitus and hypertension. The mean creatinine clearance was 10.8 (SD 4.1) mL/min, where mostly (67.3%) had poor residual renal function. Mostly, vancomycin was prescribed for bloodstream infections (87.8%) as definitive therapy for MRSA infections (69.4%).

Initial Dose of Vancomycin and SVC

Initial dose of vancomycin administered ranged from 1,000 to 2,000mg, in which majority of the patients (59%) received 1,000mg and 22% received 1,500mg. The overall mean initial dose and weight-based LD were 1,227.6 (SD 300.5) mg and 20.2 (SD 5.8) mg/kg respectively.

The overall mean TTFS was 26.2 (SD 12.8) hours, where the samples of 49% patients were taken at less than 24 hours while the others were taken between 24 to 48 hours after the initial dose of vancomycin. Meanwhile, the overall mean SVC was 14.11 (SD 7.11) mg/L. Only 18.4% of patients achieved the targeted SVC of 15.0-20.0 mg/L, while 65.3% had sub-therapeutic and 16.3% had supra-therapeutic levels. The patterns of TTFS and LD given according to the SVC range achieved were summarised in Table 2. Figure 1 showed the mean SVC according to the LD and TTFS. Based on Figure 1, the SVC increased as the LD increased, at both TTFS of <24 hours and 24-48 hours. Despite that, the SVC was not within the targeted range at TTFS 24-48hours for any LD. In contrast, LD of 15.0-25.0mg/kg could achieve SVC of 15.0-20.0mg/L at TTFS <24 hours.

Factors Affecting SVC

Haemodialysis was a common mode of dialysis (81.6%) among the study population, while other dialysis were PD and SLED. 53% of the patients had at least one dialysis session between the initial dose and TDM sampling as shown in Table 1. Majority of patients (44.9%) who had pre-TDM dialysis had sub-therapeutic SVC as shown in Table 2, However, this group of patients also received a lower LD.

The factors affecting SVC following the administration of the initial dose of vancomycin among ESRD patients on dialysis were shown in Table 3. Simple linear regression performed at the initial step found that variables such as LD, TTFS, initial dose, creatinine clearance, age, type and number of dialysis to have $p<0.25$. These variables were included in the multiple linear regression analysis. However, only LD and TTFS was found to be significant independent factors that affects SVC in this population as shown by the model. A significant model ($p<0.001$) with r^2 value of 0.346 found a linear relationship between LD, TTFS and the resulting SVC achieved. When the LD is increased by 1mg/kg, the SVC will increase by 0.616mg/L (95% CI 0.317, 0.916; $p<0.001$). Meanwhile, when the TTFS is delayed by an hour, the SVC will drop by 0.213mg/L (95% CI -0.349, -0.077; $p=0.003$).

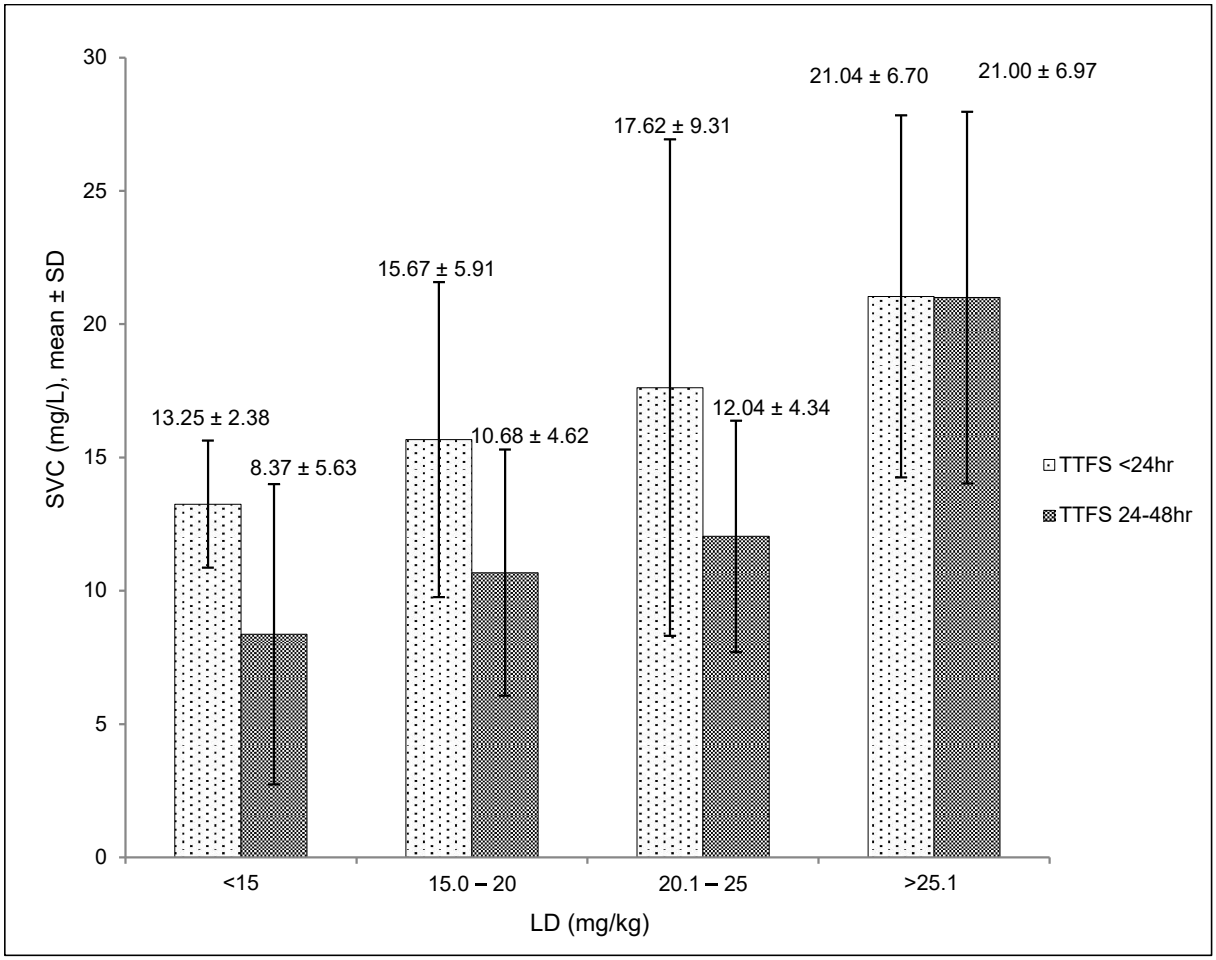
All the other variables; initial dose, creatinine clearance, age, albumin, residual renal function, type and number of dialysis were not significantly associated with the change in SVC. Based on the regression analysis, a linear equation showing the association between these factors were computed; SVC (mg/L) =

0.616 (LD in mg/kg) - 0.213 (TTFS in hours) + 7.487. Figure 2 showed the nomogram plotted based on the linear equation which can be used to predict the SVC. Based on the nomogram, a LD of 20-25 mg/kg and TTFS 24 hours after vancomycin administration would be able to produce an optimal initial SVC between 15.0 to 20.0 mg/L.

Table 1: Patient demographic and clinical characteristics (n=49)

Characteristics	Value
Age, year, mean (SD)	57.3 (13.9)
Age, year, n (%)	
≥ 60	27 (55.1)
< 60	22 (44.9)
Weight, kg, mean (SD)	62.7 (12.0)
Gender, n (%)	
Male	32 (65.3)
Female	17 (34.7)
Race, n (%)	
Malay	36 (73.5)
Chinese	2 (4.1)
Indian	9 (18.4)
Others	2 (4.1)
Comorbidities, n (%)	
Diabetes mellitus	42 (85.7)
Hypertension	41 (83.7)
Ischaemic Heart Disease	11 (22.4)
Heart failure	2 (4.1)
Malignancy	2 (4.1)
Serum creatinine, mg/L, mean (SD)	7.07 (3.23)
Creatinine clearance, mL/min, mean (SD)	10.8 (4.1)
Serum albumin, g/dL, mean (SD)	28.3 (6.2)
Residual renal function, n (%)	
≤100mL	33 (67.3)
>100mL	16 (32.7)
Type of dialysis, n (%)	
HD	40 (81.6)
PD	4 (8.2)
SLED	5 (10.2)
Number of dialysis session pre TDM, n (%)	
None	23 (46.9)
1 session	24 (49.0)
2 sessions	2 (4.1)
Indication of vancomycin, n (%)	
Empirical	15 (30.6)
Definitive	34 (69.4)
Site of infection, n (%)	
Bloodstream	43 (87.8)
Skin and soft tissue	2 (4.1)
Peritonitis	2 (4.1)
Urinary tract	1 (2.0)
Spine	1 (2.0)

Abbreviation: HD - haemodialysis, PD - peritoneal dialysis, SD – standard deviation, SLED - sustained low-efficiency dialysis, TDM – therapeutic drug monitoring



Abbreviation: LD - loading dose, TTFS - time-to-first-sampling, SVC - serum vancomycin concentration, SD – standard deviation

Figure 1: SVC according to LD and TTFS

Table 2: Vancomycin dosing according to the SVC (n=49)

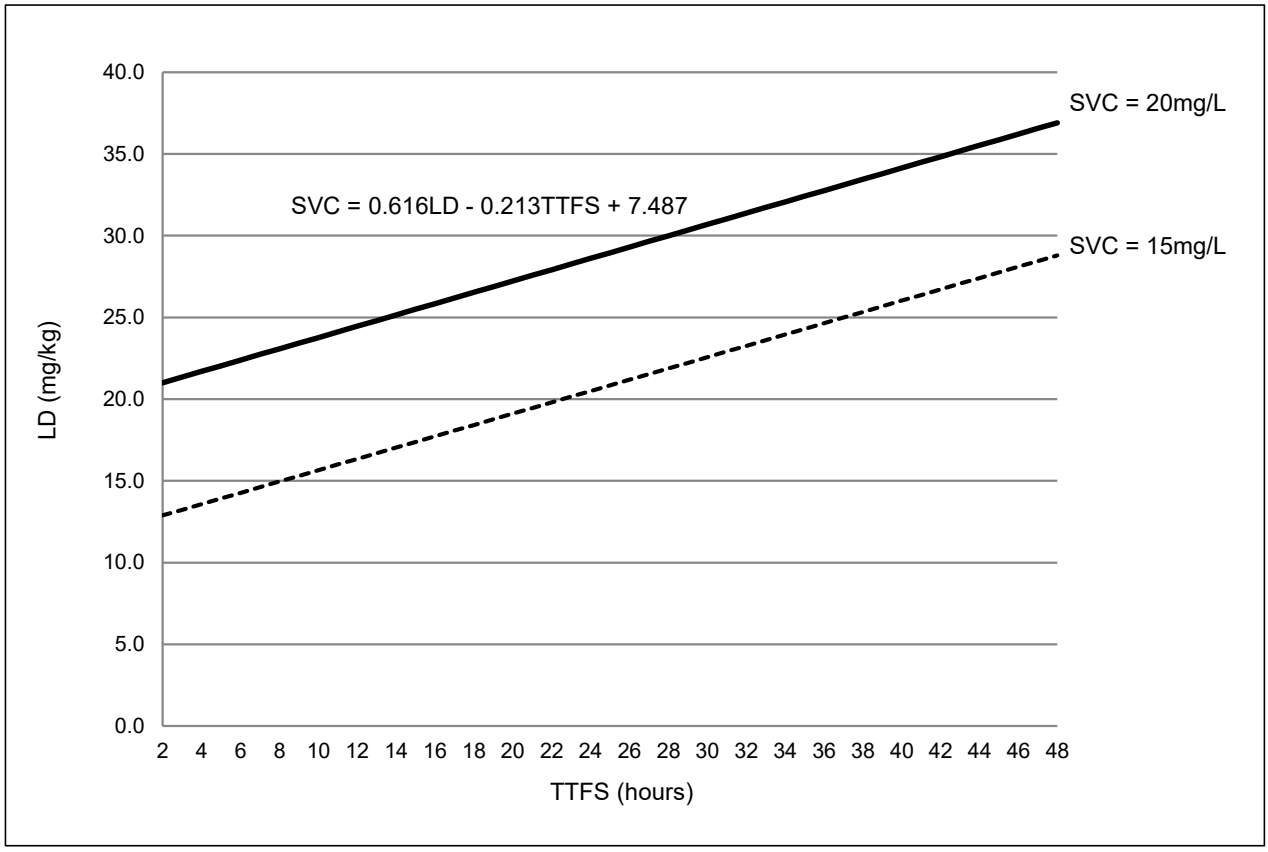
	SVC, mg/L		
	<15.0	15.0-20.0	>20.0
Total number of patients, n (%)	32 (65.3)	9 (18.4)	8 (16.3)
Number of patients who had dialysis prior to TDM, n (%)	22 (44.9)	1 (2.0)	3 (6.1)
SVC, mg/mL, mean (SD)	10.17 (3.5)	17.37 (1.6)	26.19 (6.2)
LD, mg/kg, mean (SD)	19.0 (5.4)	20.9 (4.3)	24.1 (7.4)
TTFS, hour, mean (SD)	28.5 (12.7)	22.5 (12.3)	21.2 (13.1)

Abbreviation: LD - loading dose, TDM – therapeutic drug monitoring, TTFS - time-to-first-sampling, SVC - serum vancomycin concentration, SD – standard deviation

Table 3: Factors affecting the SVC following initial dose of vancomycin among ESRF patients on dialysis (n=49)

Factors	Simple Linear Regression		Multiple Linear Regression	
	b^{ψ} (95% CI)	p-value	b^{ϵ} (95% CI)	p-value
LD	0.542 (0.218, 0.867)	0.002	0.616 (0.317, 0.916)	<0.001*
TTFS	-0.156 (-0.312, 0.000)	0.050	-0.213 (-0.349, -0.077)	0.003*
Initial dose	0.008 (0.002, 0.015)	0.012		
Number of dialysis session pre TDM	-3.442 (-6.913, 0.029)	0.052		
Creatinine clearance	-0.364 (-0.862, 0.134)	0.148		
Type of dialysis	-2.256 (-5.520, 1.007)	0.171		
Age	-0.093 (-0.240, 0.054)	0.209		
Albumin	0.049 (-0.289, 0.389)	0.771		
Residual renal function	0.007 (-3.033, 3.047)	0.996		

Abbreviation: ClCr – creatinine clearance, LD – loading dose, TDM – therapeutic drug monitoring, TTFS – time-to-first-sampling, SVC – serum vancomycin concentration, CI – confidence interval
Note: All variables except albumin and residual renal function were included in the multiple linear regression analysis.
b^{ψ} Crude regression coefficient; b^{ϵ} Adjusted regression coefficient; * p<0.05 denotes statistical significance.
Stepwise multiple linear regression method applied. Model assumptions are fulfilled.
Model is significant, p<0.001
No interactions and multi-collinearity detected
Coefficient of determination, r^2 = 0.346, constant = 7.487



Abbreviation: LD - loading dose, TTFS - time-to-first-sampling, SVC - serum vancomycin concentration

Figure 2: Nomogram predicting the LD and TTFS for SVC 15-20mg/L

Discussion

In this study, the initial vancomycin dose received by the patients ranged from 1,000mg to 2,000mg with LD 20.2 (SD 5.8) mg/kg. No specific weight-based calculations or dosing chart were used to determine the initial dose among our patients. El Nekidy *et al.* reported similar mean LD, although the range of the actual dose given was 1,000 – 3,000mg. This could be due to the higher mean weight of the patients included in their study compared to this study. In addition, El Nekidy *et al.* also used a pre-set dosing chart based on the body weight (LD 17.5mg/kg rounded to the nearest kilogram) to determine the initial dose (16).

There were equal proportion of TDM samples taken at <24 hours and 24-48 hours in this study, while the mean TTFS was closer to 24 hours. Similary, El Nekidy *et al.* and Brown *et al.* also reported mean sampling time between 23-29 hours (16, 18). Only a small proportion of patients in this study achieved the target SVC on the first TDM sampling, while majority had sub-therapeutic levels. However, El Nekidy *et al.* reported slightly higher proportion of patients with target SVC, while majority has supra-therapeutic levels (16).

This study also found that that weight-based LD and TTFS were significant predictors of SVC among ESRD patients on dialysis receiving vancomycin. Other studies also reported LD and sampling time or interval to be predictors of SVC (16,18-20). Our results also suggested that patients receiving a LD of 20-25mg/kg actual body weight of vancomycin with TTFS at 24 hours after vancomycin dose administration could achieve optimal initial SVC of 15.0-20.0 mg/L. El Nekidy *et al.* and Brown *et al.*, however, suggested a lower LD of 15-20 mg/kg of actual body weight and TTFS of 24 hours to achieve pre-haemodialysis SVC of 15.0-20.0mg/L (16,18). Barth *et al.*, on the other hand, suggested that vancomycin LD of 20mg/kg is more superior than a standard 1,000mg dosing to achieve the targeted pre-haemodialysis SVC of 10.0-25.0mg/L at TTFS 48 hours (19). On the other hand, Vandecasteele *et al.* proposed LD to be strategized as per the sampling interval, for example, 15mg/kg for one day interval, 25mg/kg for two days interval, and 35mg/kg for three days interval (20).

The optimal LD computed from this study are larger than others. This variation could be due to the differences in patient population studied, the type of dialysis and the presence of dialysis sessions between the LD and the first sampling of SVC. Studies by El Nekidy *et al.* and Brown *et al.* consist mostly of African Americans who may have different population pharmacokinetics compared to Asian population (16,18). Unlike the other studies which only included SVC taken pre-haemodialysis (16,18-20), our study included patients who had dialysis prior to SVC sampling and those who underwent SLED and PD. Given the fact that majority of the patients in this study were dialyzed using high flux dialyser, higher extent of removal of vancomycin resulted in higher requirement of LD (21).

Vancomycin has relatively low molecular weight of 1449 Dalton and dialysis using high flux dialyser made of membranes such as polysulfones, polyacrylonitrite and high efficiency cuprammonium rayon has been shown to effectively remove it (14,21). Apart from that, different mode of dialysis is shown to remove vancomycin to different extend. In the context of intermittent haemodialysis, supplementary dosing was generally proposed to achieve the target SVC. On the other hand, this was found to be not necessary for patients that were dialysed through PD (14). Removal rate by SLED however showed a 36% clearance over an eight-hours haemodialysis session (22). There were a small percentage of patients who underwent PD and SLED in this study, which may have contributed to variation in the results compared to the literatures.

Both El Nekidy *et al.* and Brown *et al.* did not study the effect of residual renal function on SVC but stated that as their study limitation instead. Pallota *et al.* suggested that the SVC of ESRD patient who have better residual renal function with creatinine clearance of 15mL/min would be double of that of a similar patient who is anuric. Thus, residual renal function has an impact towards SVC as it could influence vancomycin clearance and should be taken into consideration during dosing (15). Therefore, we included residual renal function in our analysis but found that it was not a significant predictor of SVC. This could be due to the majority of the study population had poor residual renal function as they were anuric or has urine output of ≤100mL. Hence, there was no significant predictive effect seen.

In addition to the factors suggested by this study, El Nekidy *et al.* and Brown *et al.* also found age to be another independent predictor of SVC in haemodialysis patient (16, 18). Our results did not find any significant correlation between age and SVC. Although the mean age of patients included in all three studies were similar, our study had equal proportion of elderly and non-elderly patients which is different from the other two studies. This may explain the lack of predictive value of age in our study. Aging is known to affect the pharmacokinetics of vancomycin, as study shown elderly haemodialysis subjects demonstrated 20% reduction in peak of concentration (Cmax), 23% reduction in systemic clearance and 45% higher volume of

distribution (Vd). This is attributed by higher tissue affinity in the elderly patients causing elevation of Vd (23).

In this study, the actual current weight was taken regardless of individual target dry weight. As vancomycin is a hydrophilic drug, weight differences between dry and wet body weights may influence the volume of distribution of vancomycin, and hence the SVC. Therefore, the time when the body weight measurement is taken (pre- or post-haemodialysis) is important assuming that all patients are dialysed up to their target dry weight. However, this was not taken into consideration in this study. In addition, three patients had their SVC taken within four hours post-dialysis. Since SVC taken within four hours of dialysis session might be inaccurate due to the incomplete distribution phase, the mean SVC reported could be affected (21).

Conclusion

Weight-based LD and TTFS are important factors that need to be taken into consideration when dosing vancomycin in ESRD patients on dialysis to ensure the achievement of therapeutic effectiveness of vancomycin. Vancomycin LD of 20-25mg/kg actual body weight is likely to yield desired SVC between 15.0-20.0 mg/L at TTFS of 24 hours. For future research, we recommend to investigate the significance of using dry and/or wet weight for dosing, type of dialysis and pre-dialysis vancomycin levels as the target SVC.

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Conflict of Interest Statement

No external funding was received and the authors declared no conflict of interest.

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