The Adequacy of Vancomycin Fixed-loading Dose Regimen in CRBSI for Patients Receiving Haemodialysis in Hospital Melaka

Quak Chyi Ing[1], Chew Soo Piing[1], Nor Sa'adah Binti Harun[1], Ngan Su Kee[1], Tan Jhii Lien[1]

[1] Hospital Melaka, Melaka, Ministry of Health Malaysia

Abstract

Introduction: Catheter-related bloodstream infection (CRBSI) is the major cause of mortality in haemodialysis patients. Vancomycin is the first-line treatment for Methicillin Resistant *Staphylococcus aureus* (MRSA). Inadequacy of vancomycin loading dose during initial treatment has been speculated as the cause of delayed achievement of vancomycin level within therapeutic range.

Objective: This study aimed to identify whether the vancomycin fixed-loading dose regime can produce vancomycin level within therapeutic range (15-20µg/mL) and to determine the total duration of vancomycin treatment required to achieve negative MRSA blood culture.

Methods: This was retrospective, non-randomised and one-year descriptive study. Patients with end-stage renal failure undergoing high-flux haemodialysis who were prescribed with vancomycin to treat MRSA CRBSI were included. The vancomycin fixed-loading dose protocol used was IV vancomycin 1,000mg on Day 1 and 750mg on Day 2 with the first vancomycin level monitoring on Day 3 or Day 4 (pre-haemodialysis sample). Subjects were stratified into three groups based on the first vancomycin level which were therapeutic level (15-20µg/mL), subtherapeutic level (<15µg/mL) and supratherapeutic level (>20µg/mL). Demographic details, descriptive data on duration to clearance of blood culture and the total duration of vancomycin treatment were collected and analysed.

Results: A total of 34 subjects were included (58.8% male, mean age 53.5 (standard deviation 12.9) years). Of these, 41.2% (n=14) had subtherapeutic, 35.3% (n=12) had supratherapeutic and 23.5% (n=8) had therapeutic vancomycin level. There was no difference in the duration to obtain clearance of MRSA from blood culture (p=0.660) and duration of vancomycin treatment (p=0.155) among these three groups of subjects.

Conclusion: This study showed that vancomycin fixed-loading dose protocol was unable to achieve first vancomycin level within the therapeutic range. Further clinical studies to identify suitable dosing regimen of vancomycin such as weight-based regimen in local population is warranted.

Keywords: fixed-loading dose, vancomycin, catheter-related bloodstream infection, Methicillin Resistant *Staphylococcus aureus*, haemodialysis

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Corresponding author: Quak Chyi Ing
Department of Pharmacy, Hospital Melaka, Jalan Mufti Haji Khalil, 75400 Melaka.
Email: quakchyiing@moh.gov.my

Introduction

The prevalence of end-stage renal disease has been on an increasing trend and it is estimated to continue rising in the next decade. In 2010, around 2.6 million people received renal replacement therapy (RRT) worldwide, in which approximately 2 million people received dialysis (78%) and 0.6 million people received renal transplant. The number of people undergoing RRT was estimated to reach 5.4 million people by 2030 (1). In 2014, the total number of patients who required dialysis in Malaysia was 34,767 people and the annual death rate for patients with haemodialysis was 11.6% in year 2014 (2).

Catheter-related bloodstream infection (CRBSI) is common among end-stage renal failure (ESRF) patients undergoing haemodialysis via a catheter (3). With the incidence rate of 10% and mortality rate of 25%, CRBSI is a major complication resulting from long term use of catheter (4). The systemic progressions due to CRBSI include septic shock, multiorgan failure and deep-seated infection such as endocarditis and septic arthritis (5). One of the common pathogens found in CRBSI is staphylococcal species, with Methicillin Resistant *Staphylococcus aureus* (MRSA) being the emerging pathogen (6). Vancomycin is the first-line

treatment in CRBSI infection with MRSA (7). Trough level of vancomycin has been established to be within 15-20µg/mL to be able to achieve the area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio within 400 to 600 (8-9). The therapeutic range of AUC / MIC ratio is crucial to ensure adequate penetration of vancomycin into the infected sites and effective antibiotic exposure, hence improved clinical outcome and reduced mortality rate (10).

Vancomycin dosing in patients with ESRF who receive haemodialysis, however, is poorly defined currently with different approaches in initial loading dose being proposed for fast attainment of therapeutic vancomycin level (11). The delay in achieving therapeutic vancomycin level has been linked to the emergence of Vancomycin-intermediate *Staphylococcus aureus* (VISA) and Vancomycin-resistant *Staphylococcus aureus* (VRSA) infections, as well as treatment failure in MRSA bacteraemia from CRBSI (12).

The current protocol used in Hospital Melaka for CRBSI in haemodialysis patients is a fixed-loading dose of intravenous (IV) vancomycin 1,000mg on Day 1 followed by 750mg on Day 2. To ensure the clinical outcomes of our patients, it is highly crucial to investigate the effectiveness of this protocol. Therefore, our study aimed to identify whether the current vancomycin fixed-loading dose regime can produce vancomycin levels within the therapeutic range of 15-20µg/mL in ESRF patients receiving stable intermittent high-flux haemodialysis and to determine the total duration of vancomycin treatment required to achieve negative MRSA in blood culture.

Methods

This was a retrospective, non-randomised study conducted in Hospital Melaka, Malaysia. The study was approved by the Hospital Research Review Committee (HRRC) and the Ministry of Health (MOH) of Malaysia Medical Research & Ethics Committee (MREC). The study population involved of this study was admitted ESRF patients on regular high-flux haemodialysis who received vancomycin due to MRSA CRBSI during their stay in the hospital. The diagnosis of MRSA CRBSI was based on the blood culture from peripheral, red lumen, and blue lumen. Patients were excluded from the study if they did not complete the haemodialysis session while on vancomycin treatment and age below 18-years-old.

The vancomycin fixed-loading dose protocol used in Hospital Melaka was IV vancomycin 1,000mg on Day 1 followed by 750mg on Day 2. The first blood sampling for therapeutic drug monitoring (TDM) of vancomycin was conducted on Day 3 or Day 4 as pre-haemodialysis sample (Figure 1). The research team was alerted when patients were prescribed with vancomycin by the nephrologists and monitoring of serum vancomycin level was conducted for patients who were treated with vancomycin. The vancomycin was administered intravenously in normal saline and infused during the last hour of dialysis if the vancomycin dosing schedule fall on the haemodialysis day. The vancomycin serum concentrations were analysed in the Biochemistry Unit, Department of Pathology of Hospital Melaka using Viva-Pro E Siemens (immunoassay method). To evaluate this fixed-loading dose protocol, data on patient demographics, types of haemodialysis, duration of haemodialysis sessions, culture and sensitivity test data, dosing details of vancomycin, and serum concentration of vancomycin were collected using a pre-designed data collection form for the period of one year, from 1 December 2017 to 31 December 2018.

The sample size was calculated using Raosoft, an online calculator software for power analysis. All power analyses are assuming an alpha=0.05 with 95% power. From the calculation, the sample size required for this study was 30 patients. To cater for incomplete medical records, an additional 20% was added to the required sample sizes. The final sample size targeted was 36 patients.

The subjects were categorised into three groups based on their first TDM vancomycin level, which were subtherapeutic level (<15µg/mL), within therapeutic range (15-20µg/mL) and supratherapeutic level (>20µg/mL). The first blood culture monitoring was conducted after 3 days upon initiation of vancomycin treatment and repeated subsequently every 3 days until obtaining negative MRSA in the blood culture. These three groups of patients were compared in terms of duration to the clearance of blood culture from MRSA and the total duration of vancomycin treatment using one-way ANOVA test. Demographic data gathered were analysed using descriptive statistics in the form of frequency and percentages (mean ± SD or median ± IQR). All statistical analyses were performed using IBM Statistical Package for Social Science (IBM SPSS) programme version 22.0 and Microsoft Excel version 2013.

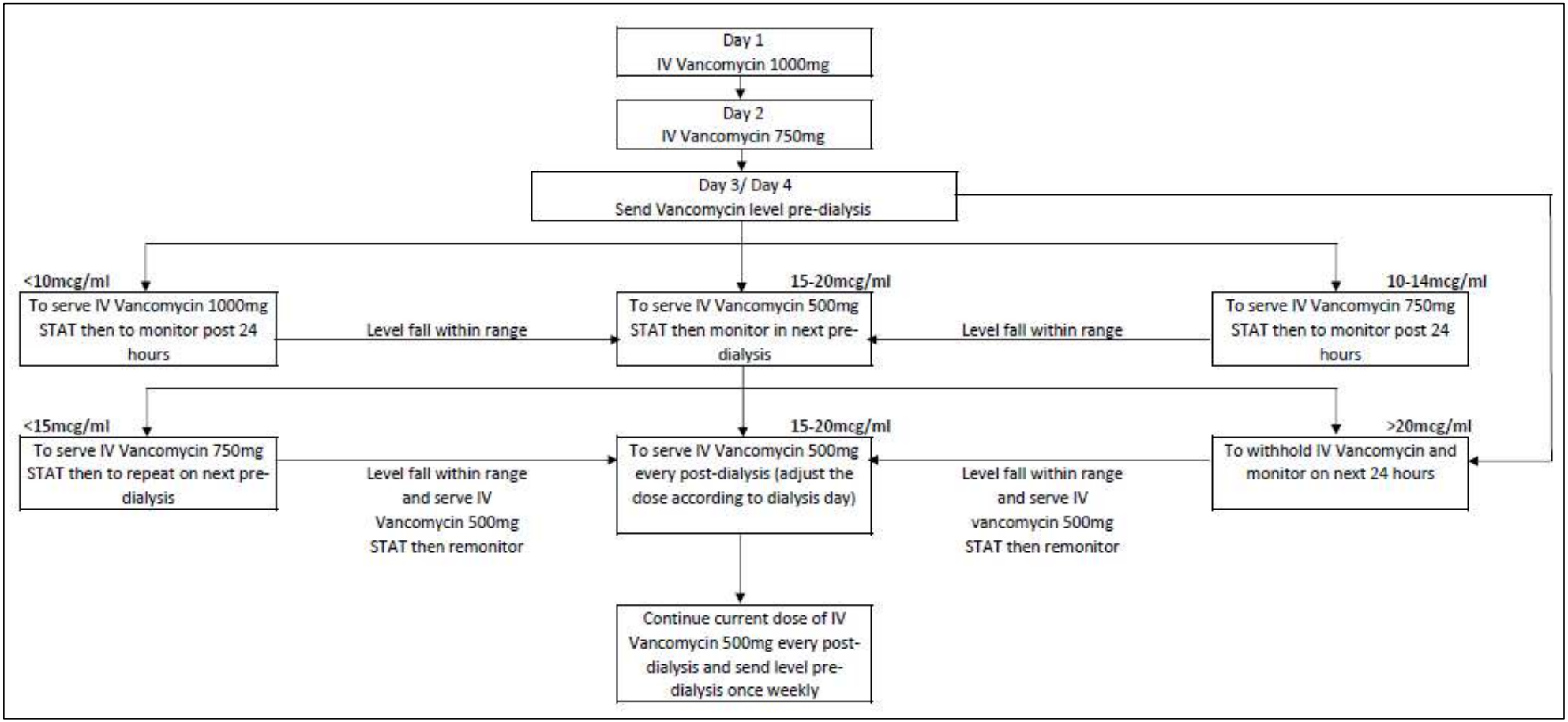

Figure 1: Vancomycin fixed-loading dose protocol in Hospital Melaka

Results

Thirty-four patients were included in this study instead of 36 targeted. The recorded adverse events of vancomycin were infusion-related side effects such as skin itchiness and redness if the rate of infusion was too fast. However, no patient was withdrawn from the study. The patient characteristics were shown in Table 1. The mean age of our patients was 53.5 (standard deviation (SD)12.9) years old, with 58.8% male patients. The common comorbidities of our patients were hypertension (88.2%) and diabetes (67.6%). In terms of the type of dialysis port used, most of the patients (61.8%) had internal jugular catheter (IJC) and femoral line(35.3%).

From the total of 34 patients, only eight (23.5%) patients achieved vancomycin level within the therapeutic range of 15-20µg/mL, 14 patients (41.2%) had subtherapeutic vancomycin level of <15µg/mL while 12 patients (35.3%) had supratherapeutic vancomycin level >20µg/mL. The mean duration for clearance of blood culture for the therapeutic range group was 12.9 (SD 6.5) days, subtherapeutic range group was 10 (SD 7.5) days and supratherapeutic range group was 10.4 (SD 10.2) days with no significant differences among these three groups (p =0.660).

The mean duration of vancomycin treatment for our patients who achieved therapeutic range 15-20µg/mL with the first TDM level was 25.8 (SD 19.8) days, group with subtherapeutic range was 32.7 (SD 14.4) days and group with supratherapeutic range was 20.9 (SD 12.4) days with no significant differences among these three groups (p =0.155) (Table 2).

Table 1: Patient demographics for vancomycin regimen in ESRF patients (n=34)

Variable	Value
Age, year, mean (SD)	53.5 (12.9)
Gender, n (%)	
Male	20 (58.8)
Female	14 (41.2)
Race, n (%)	
Malay	29 (85.3)
Chinese	4 (11.8)
Indian	1 (2.9)
Weight, kg, median (IQR)	63.5 (18)
Comorbidities, n (%)	
Hypertension	30 (88.2)
Diabetes	23 (67.6)
Dyslipedemia	4 (11.8)
Others *	21 (61.8)
Type of catheter, n (%)	
IJC	21 (61.8)
Femoral	12 (35.3)
FIstula	1 (2.9)

* liver cirrhosis, shoulder arthritis, gouty arthritis, young parkinsonism and glaucoma
Abbreviation: IJC - interjugular catheter; IQR - interquartile range; SD - standard deviation.

Table 2: Duration of vancomycin treatment and duration required to obtain first MRSA negative culture (n=34)

First vancomycin level	n (%)	Duration to MRSA negative culture, day, mean (SD)	F-statistic (df) [a]	P-value	Duration of vancomycin treatment, day, mean (SD)	F-statistic (df) [a]	P-value
<15µg/mL	14 (41.2)	12.9 (6.5)	0.421 (2,31)	0.660	32.7 (14.4)	1.983 (2,31)	0.155
15-20µg/mL	8 (23.5)	10.0 (7.5)			25.8 (19.8)		
>20µg/mL	12 (35.3)	10.4 (10.2)			20.9 (12.4)		

[a] One-way ANOVA

Discussion

Our analysis showed that 76.5% of the patients did not achieve first vancomycin level that was within the therapeutic range, with 41.2% had vancomycin level that was below while 35.3% was above the therapeutic range of 15-20µg/mL. This indicated that the current loading dose protocol was not able to attain targeted therapeutic vancomycin levels. The Infectious Diseases Society of America (IDSA) 2009 guidelines had established that the ideal duration for clearance of MRSA bacteraemia is 72 hours for the optimal clinical outcome. Therefore, vancomycin level needs to be within the therapeutic range on Day 3 or Day 4 as it is the surrogate marker for vancomycin exposure which translates to clinical progression, as therapeutic vancomycin level associates with better clinical outcome (7). In a study using a loading dose 1g, followed by a subsequent maintenance dose of 500mg or 1g, the targeted trough level of >15µg/mL was only 25.2% (13). Our study showed a similar result with only 23.5% of patients achieving the target range. The recent guideline suggested that weight-based vancomycin dosing appeared to be superior to fixed-dose dosing as the weght-based dosing considers patient's body size and may decrease the risk of subtherapeutic level on the first day of therapy (14). The National Antibiotic Guideline 2014 published by MOH Malaysia suggested vancomycin loading dose at 15-20mg/kg and then subsequently 500mg to 1000mg after each dialysis session (15). Furthermore, some studies demonstrated that the targeted vancomycin trough levels were more rapidly obtained by using a weight-based loading dose of 20mg/kg (11,16).

Our analysis showed that the first vancomycin level did not significantly affect the duration for clearance of MRSA from the blood culture and the total duration of vancomycin treatment. Factors that could have been significantly affecting these two clinical outcomes were the removal of the infected catheter or haemodialysis port, the involvement of deep-seated infection sites, and the presence of MRSA skin colonizer (17). However, our study showed that higher first vancomycin level did not associate with faster clearance of MRSA bacteraemia nor shorter duration of vancomycin treatment. Although the subtherapeutic level of vancomycin has not shown to affect clinical outcome, it is still important to maintain vancomycin trough at a minimum level of 10µg/mL to prevent treatment failure (8).

Vancomycin is a drug with high inter-individual and intra-individual variations in its pharmacokinetic parameters (18). Hence it is important to establish a loading dose protocol that is specific to the local population as an adaptation from other populations will not be suitable for drugs with a narrow therapeutic index. Vancomycin is substantially removed in patients who receive high-flux haemodialysis (19). Thus, the current fixed loading dose of vancomycin may not be suitable for patients undergoing high-flux haemodialysis in Hospital Melaka and more frequent dosing of vancomycin is needed to maintain the target serum concentrations.

The limitations of this study include the small sample size which might affect the significant effect of first vancomycin level on clinical outcomes. This study was also unable to determine whether the persistent subtherapeutic or supratherapeutic level of vancomycin will significantly affect the clinical outcomes. Nevertheless, the findings of this study would serve as a baseline to identify the best vancomycin initiation regimen for patients receiving haemodialysis. Further clinical studies can be carried out to identify other suitable dosing of vancomycin, such as the weight-based regimen, for patients undergoing haemodialysis with CRBSI.

Conclusion

Current vancomycin fixed-loading dose protocol for haemodialysis patients with MRSA induced CRBSI was unable to achieve therapeutic vancomycin level on Day 3 or Day 4 of vancomycin treatment. However, it was found that the first vancomycin level was not significantly associated with the clinical outcomes of CRBSI infection and the duration of vancomycin treatment.

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Conflict of interest statement

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References

1. Liyanage T, Ninomiya T, Jha V, et al. Worldwide access to treatment for end-stage kidney disease: A systematic review. *Lancet*. 2015;385(9981):1975-1982.
2. Malaysian Society of Nephrology. 22nd Report of the Malaysian Dialysis & Transplant Registry 2014. Kuala Lumpur: Malaysian Society of Nephrology; 2015.
3. Hoen B, Paul-Dauphin A, Hestin D, Kessler M. EPIBACDIAL: a multicenter prospective study of risk factors for bacteremia in chronic hemodialysis patients. *J Am Soc Nephrol*. 1998;9(5):869-876.
4. Fletcher S. Catheter-related bloodstream infection Authors. *Contin Educ Anaesth Crit Care Pain*. 2005;5(2):49-51.
5. Vandecasteele SJ, Boelaert JR, De Vriese AS. Staphylococcus aureus infections in hemodialysis: What a nephrologist should know. *Clin J Am Soc Nephrol* 2009;4(8):1388-1400.
6. Gafor AHA, Ping PC, Abidin AFZ, et al. Antibiogram for haemodialysis catheter related bloodstream infections. *Int J Nephrol* 2014;629459.
7. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection:2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009;49(1):1-45.
8. Rybak MJ, Lomaestro BM, Rotscahfer JC, et al. Vancomycin Therapeutic Guidelines: A Summary of Consensus Recommendations from the Infectious Diseases Society of America, the American Society of Health- System Pharmacists, and the Society of Infectious Diseases Pharmacists. *Clin Infect Dis* 2009;49(3):325-327.
9. Vandecasteele SJ, De Vriese AS. Recent changes in vancomycin use in renal failure. *Kidney Int* 2010;77:760-764.
10. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by Infectious Disease Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis* 2011;52(3):285-292.
11. Vandecasteele SJ, De Vriese AS. Vancomycin dosing in patients on intermittent hemodialysis. *Semin Dial* 2011;24:50-55.
12. Jung Y, KH S, Je C, et al. Area under the concentration-time curve to minimum inhibitory concentration ratio as a predictor of vancomycin treatment outcome in methicillin-resistant Staphylococcus aureus bacteraemia. *Int J Antimicrob Agents* 2014;43(2);179-183.
13. Pai AB, Pai MP. Vancomycin dosing in high flux hemodialysis: a limited sampling algorithm. *Am J Health Syst Pharm* 2004; 61:1812–1816.
14. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin: A revised consensus guideline and review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Disease Society and the Society of Infectious Disease Pharmacists. *ASHP* 2019.
15. National antibiotic guidleline 2014. 2nd ed. Ministry of Health of Malaysia: Pharmacy Practice & Development Division; 2014.
16. Barth RH, DeVincenzo N. Use of vancomycin in high-flux hemodialysis: experience with 130 courses of therapy. *Kidney Int* 1996; 50: 929–936.
17. Heil EL, Claeys KC, Mynatt RP, et al. Making the change to area under the curve-based vancomycin dosing. *Am J Health-Syst Pharm* 2018;75:e828-37.
18. Matzke GR, McGory RW, Halstenson Ce, et al. Pharmacokinetics of vancomycin in patients with various degrees of renal function. *Antimicrob Agents Chemother* 1984;25:433-437.
19. Quale JM, O'Halloran JJ, DeVincenzo N, Barth RH. Removal of vancomycin by high-flux 1578 hemodialysis membranes. *Antimicrob Agents Chemother* 1992;36(7):1424-1426.