Clinical Therapeutics 47 (2025) e1–e7

Contents lists available at ScienceDirect

Clinical Therapeutics

journal homepage: www.elsevier.com/locate/clinthera

Original Research

Vancomycin Dosing in Patients on Intermittent Hemodialysis—A Retrospective Study

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ARTICLE INFO

Key words:
Dosing protocol
Hemodialysis
Loading dose
Vancomycin

ABSTRACT

Purpose: To determine the incidence of therapeutic target attainment using a three-times per week protocol for vancomycin therapy given during the last hour of intermittent hemodialysis (HD).

Methods: A single-center retrospective cohort study was conducted of patient medical records in a remote dialysis center from January 2017 to July 2023. Adult patients with chronic kidney disease stage 5 on ≥3 months of intermittent HD who had received a course of vancomycin therapy with ≥1 serum vancomycin concentration recorded were included. Demographic and dosing data were collected. Clinician adherence with the dosing protocol and attainment of the therapeutic target (trough concentration within 15–20 mg/L) following the loading and maintenance doses were assessed. Factors associated with target nonattainment following the loading dose were analyzed, and the 48- and 72-h maintenance dosing intervals were analyzed for target nonattainment.

Findings: A total of 98 vancomycin courses (67 patients) were available for analysis. Only 38% of the loading doses were prescribed as per protocol. Following the loading dose, 25% of trough concentrations achieved the therapeutic target concentration (15–20 mg/L), 25% returned a supra-therapeutic concentration (>20 mg/L) and 50% were sub-therapeutic (<15 mg/L). When compared with those achieving target, sub-therapeutic concentrations were associated with a lower loading dose (median 16.6 vs 20.0 mg/kg, $P < 0.002$), and supra-therapeutic concentrations had a shorter dosing interval between the loading dose and first maintenance dose (median 31.5 vs 39.0 h, $P = 0.06$). Of the 201 maintenance trough concentrations collected, 65% were therapeutic, 21% were sub-therapeutic and 14% were supra-therapeutic, with an overall median trough concentration of 17.3 mg/L. As the treatment duration increased, an increase was seen in the number of dose adjustments required to achieve the target trough concentration. The 48-h dosing interval was associated with more supra-therapeutic concentrations and the 72-h interval was associated with more sub-therapeutic concentrations (df = 2, $P = 0.022$).

Implications: We have identified a high rate of target nonattainment for HD patients on a three times a week vancomycin dosing regimen. We recommend a loading dose of 20 to 25 mg/kg irrespective of the indication and a better-defined dosing interval after the loading dose. A higher maintenance dose should be prescribed when the time to next dialysis session is 72 h. Further pharmacokinetic studies are needed to assess factors influencing target concentration attainment following the maintenance doses and to determine an optimal dosing regimen.

Introduction

Staphylococcus aureus (*S. aureus*) infection is one of the leading causes of mortality in patients receiving intermittent hemodialysis (HD).[1] This is mainly due to immunosuppression associated with chronic kidney disease (CKD) and is potentiated by the increased risk of bacteremia and localized skin and soft tissue infection from the ongoing requirement for direct vascular access.[1–4] Patients receiving HD have a 100-fold higher risk of infection with methicillin-resistant *S. aureus* (MRSA) compared with the general population, which is associated with longer hospitalizations and higher mortality rates if optimal treatment is not received.[5,6] Over the past decade, a growing incidence of MRSA isolates has been recorded in Central Australia, with MRSA comprising 50% of all *S. aureus* isolates.[7–9] Noncommunicable diseases and demographics that con-

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https://doi.org/10.1016/j.clinthera.2025.01.001
Accepted 3 January 2025

tribute to the higher incidence of MRSA infection in remote communities include a higher prevalence of diabetes, alcohol use, chronic renal failure, and socioeconomic disadvantage, in particular, crowded living.[8–10]

The Northern Territory has the highest incidence and prevalence of patients with end-stage renal disease (ESRD) requiring HD in the country.[11,12] The increased risk of ESRD in this population is multideterminant and includes restricted access to healthcare in remote areas, a higher chronic disease burden (particularly diabetes) and Indigenous ethnicity which carries a higher genetic predisposition at birth for developing CKD later in life.[13,14]

Vancomycin is a glycopeptide, Gram-positive bactericidal antibiotic commonly used in the treatment of MRSA infections worldwide and is frequently used in Central Australia in HD patients.[15–18] Vancomycin is 90% renally cleared which presents a challenge when dosing in HD patients due to the altered pharmacokinetic parameters and the variations in HD modalities. The accepted pharmacodynamic target for therapeutic drug monitoring in HD has been extrapolated from the recommendations for patients with normal renal function and is defined as a 24-h area under the concentration-time curve to minimum inhibitory concentration ($AUC_{0–24}$:MIC) of 400 to 600 mg.h/L.[15,19] This is logistically difficult to attain in clinical settings and a serum pre-HD trough concentration of 15 to 20 mg/L is widely accepted as a surrogate target.[15,19]

Current evidence highlights a strong association between vancomycin concentrations and clinical outcomes when treating infections.[15,18] Despite numerous studies, recommendations for vancomycin dosing in HD patients remain conflicting. Studies that evaluate existing vancomycin protocols are limited by small sample sizes, variations in therapeutic dose targets, variations in dosing strategies, inconsistencies in HD modalities, and heterogeneity of HD regimes.[20–26] This places HD patients at risk of receiving suboptimal loading doses and/or maintenance doses which can result in therapeutic target nonattainment and an increased risk of toxicity, or treatment failure with the development of vancomycin resistance.[15,21,27] Enhanced dosing guidelines, tailored to individual patient characteristics and dialysis schedules, could improve therapeutic target attainment in HD patients by addressing risk factors associated with target nonattainment. The aim of this study was to assess the rate of target concentration attainment of a protocolized three times weekly vancomycin dosing regimen in a remote dialysis center. Adherence to the protocol and factors impacting on therapeutic target attainment was also assessed.

Participants and Methods

Study Design

A single-center, retrospective cohort study was conducted in a remote Central Australian dialysis center. Ethics approval was obtained from the Northern Territory Human Research Ethics Committee (project code: HREC 2022-4485).

Participants

Patients who had received a course of vancomycin between January 2017 and July 2023 were identified from the electronic medication management application system. Episodes were included if the patients were aged over 18 years, had CKD stage 5 requiring intermittent HD (defined as three times a week) for at least 3 months, had received ≥1 vancomycin dose, had ≥1 serum vancomycin trough concentration recorded, and had not received a course of vancomycin in the previous 14 days. A total of 95 patients (comprising 135 vancomycin courses) who received HD at the study site were identified. Of the 135 courses, 29 vancomycin administration charts were unable to be located and were excluded, three were excluded due to the infection type not documented, three were excluded due to the loading dose not documented and two were excluded due to not receiving dialysis for at least 3 months. Three courses had a first trough concentration documented >3 days since the loading dose and were included for the analysis of the maintenance dosing only.

Table I
Nomogram for maintenance dose.

Trough vancomycin concentration (mg/L)	Next vancomycin dose (mg)
<5	2000
5–15	1500
15–20 (therapeutic target)	1000
20–25	500
>25	0
Result unavailable	Contact infectious diseases or renal registrar for advice

Procedure

A search for "vancomycin paper chart" on the electronic medication chart was conducted as this indicates the patients were receiving vancomycin therapy and would have a paper-based vancomycin administration chart in their written patient records. Written medical records and electronic records were searched to collect patient demographic information, vancomycin medication orders, and trough vancomycin concentration-time data. Demographic data collected included age, gender, actual weight, years on dialysis, ethnicity, type of infection, and vancomycin treatment duration. Vancomycin therapy data collected included the loading dose, date and time of loading dose, all trough concentrations recorded for the duration of vancomycin treatment, whether the dose was given as per protocol, date and time of trough concentrations taken and the date and time of doses administered. The standardized dialysis duration at the study site is 4 h. When assessing target trough attainment rates, trough concentrations that had more than 3 days lapse since the loading or maintenance dose, and less than 2 days between maintenance doses were excluded from analysis. This is because it is anticipated that the three times a week dialysis schedule will include two sessions with 48 h between them and one session with 72 h between them.

A vancomycin trough concentration was defined as a sample collected within 30 min prior to initiation of HD which aligns with existing guidelines and practices which recommend predialysis sampling.[15] This is reflective of standard nursing practice at the dialysis site. The target (therapeutic) vancomycin concentration was defined as a trough concentration of 15 to 20 mg/L.[15,19] A trough concentration <15 mg/L was deemed sub-therapeutic, and >20 mg/L deemed supra-therapeutic.[15,19] Dose adjustments were defined as a trough concentration being sub-therapeutic or supra-therapeutic, warranting a subsequent dose of more than, or less than 1000 mg, respectively. All patients received high-flux dialysis with dialyzers used being one of: FX80, FX100, or FX120 (Fresenius Medical Care, Hesse, Germany).

The dialysis center utilized a fixed dose protocol for the administration of vancomycin in HD. The recommended loading dose was 25 mg/kg for proven or suspected MRSA bacteremia (rounded to the closest 250 mg and capped at 2000 mg) and 1000 mg for all other indications unless specified by the infectious diseases team. The loading dose was prescribed by a medical officer and given irrespective of the time to the next dialysis session which could vary from 12 h up to 3 days to maintain the patient's regular dialysis schedule. The maintenance dose was determined by a routinely taken predialysis vancomycin concentration, where nursing staff followed the dosing nomogram (**Table I**) and administered the recommended dose over the last hour of HD.

Data Analysis

Data were analyzed using R (version 4.3.0). Results were reported as *n* (%) and median (interquartile range). Where appropriate, a chi-

Table II
Characteristics of the study population.*

Characteristic	Overall episodes (n = 98)
Number of patients	67
Age years, median (IQR)	50 (44–60)
Sex, female, n (%)	75 (77%)
Ethnic background Indigenous Australian, n (%)	100 (100%)
Time on dialysis (years) (IQR)	3 (2–4)
Body weight (kg), median (IQR)	76 (70–90)
Vancomycin duration (days), median (IQR)	6.5 (3–12)
Total number of vancomycin doses given, median (IQR)	4 (3–5)
Infection type, n (%)	
Skin and soft tissue	53 (54%)
Suspected or proven bacteremia	29 (30%)
Other	16 (16%)

IQR = interquartile range; kg = kilograms.
* Characteristics are described per treatment course at the initial prescription for vancomycin.

squared test was used to test between-group differences for categorical variables, and a Wilcoxon test was used to test for non-normally distributed continuous variables. Statistical significance was set at a P value of <0.05.

Results

Patient Demographics

A total of 98 vancomycin courses, comprising 442 vancomycin doses and 296 trough concentrations, were obtained from 67 patients. The demographic characteristics of the patients at the start of each treatment course are summarized in **Table II**. Whilst ethnicity was not targeted during data collection, all patients were incidentally Indigenous Australians with a median (IQR) age of 50 (44–60) years, and the majority were female (77%). Patients received a median of four doses of vancomycin and the primary indication was skin and soft tissue infections, followed by bacteremia.

Target Concentration Attainment Following the Loading Dose

Following administration of the loading dose, 95 vancomycin trough concentrations were available for analysis. Overall, 25% achieved the target trough concentration, 50% were sub-therapeutic and 25% were supra-therapeutic. Factors associated with sub-therapeutic and supra-therapeutic vancomycin trough concentrations following the loading dose are shown in **Table III**. There was a trend indicating that the time interval between the loading dose and first trough taken was longer in those who achieved a therapeutic target trough concentration compared with those with a supra-therapeutic trough concentration (median 40.5 vs 31.5 h, P = 0.06). There was a higher weight-based loading dose given in those who achieved a therapeutic target trough concentration compared to those with a sub-therapeutic trough concentration (median 20 vs 16.6 mg/kg, P = 0.002).

Target Concentration Attainment for Maintenance Dosing

A total of 201 maintenance trough concentrations were available for analysis. Of these, 65% fell within the target therapeutic range, 21% were sub-therapeutic and 14% were supra-therapeutic. **Figure 1** shows the rates of target attainment for patients with a 48- and a 72-h dialysis window. A similar incidence of target attainment was achieved between the 48-h interval and 72-h interval. However, more sub-therapeutic concentrations occurred using the 72-h dosing interval, and more supra-therapeutic concentrations occurred in the 48-h dosing interval (df=2, P = 0.022). The median vancomycin trough concentration for the maintenance doses was 17.3 mg/L (IQR 15.3–19.0). **Figure 2** illustrates the median trough concentrations attained over the course of vancomycin treatment.

The number of dose adjustments required for varying treatment durations is shown in **Table IV**. For treatment courses lasting up to 14 days, 21% of courses did not require any dose adjustments and most required 1 to 2 dose adjustments. For treatment courses longer than 14 days, there was an increase in the number of dose adjustments required with most courses requiring between 3 and 7 dose adjustments.

Adherence to the Protocol

The protocol recommended loading dose was 25 mg/kg stat (capped at 2000 mg) for proven or suspected MRSA bacteremia and 1000 mg stat for all other indications. Overall, 62% of loading doses were not prescribed per protocol. Prescriber adherence to the loading dose protocol for both proven or suspected MRSA bacteremia and all other indications and the resultant trough concentration is summarized in **Table V**. Of the 59 loading doses not prescribed per protocol, 17 indications were for proven or suspected MRSA bacteremia and were prescribed a dose less than the recommended 25 mg/kg.

When adherent to the 1000 mg flat dose, 12% achieved the therapeutic target, compared with 29% when nonadherent (P = 0.204). A trend was seen with a higher incidence of subtherapeutic cases when the protocol was followed, compared to when doses exceeding 1000 mg were prescribed (76% vs 40%, P = 0.065).

Of the 369 maintenance doses administered, 368 (99.7%) adhered to the dosing protocol. However, the one nonadherent dose was omitted without the reason documented.

Discussion

To the best of our knowledge, this is the largest study to assess therapeutic target attainment of vancomycin therapy in patients receiving HD in remote Central Australia. The study found a higher proportion of protocol adherence with the maintenance doses when compared with the loading doses. Following the administration of a 1000 mg loading dose, few patients achieved a therapeutic target trough concentration of 15 to 20 mg/L. The incidence of target attainment was associated with weight-based dosing and the time interval to the first trough concentration taken. When maintenance doses were given in accordance with the dosing nomogram, a third of the resulting trough concentrations did not achieve the therapeutic target. There was an increased frequency of dose adjustments needed to achieve the therapeutic target as the treatment duration increased.

Target Trough Attainment Following the Loading Dose

Assessing the effectiveness of the loading dose protocol was difficult due to the low protocol adherence rate (38%). A quarter of patients achieved a target trough concentration of 15 to 20 mg/L following the loading dose when the protocol was adhered to, with most achieving a sub-therapeutic concentration and a smaller number achieving a supra-therapeutic concentration. For patients without proven or suspected MRSA bacteremia, about three-quarters of those prescribed a 1000 mg loading dose achieved a sub-therapeutic trough concentration. This indicates that a flat dose prescription of 1000 mg is inadequate as a loading dose and is supported by the greater number of patients who achieved the target trough concentration when a dose >1000 mg was prescribed. These findings align with a published audit of this protocol by Jeremiah et al. in 2014, which reported that a 25 mg/kg loading dose was necessary for rapid target attainment.[28] This study found that patient weight influenced target attainment following the loading dose as those who achieved the target trough concentration received a median calculated weight-based dose of 20 mg/kg, whereas those who achieved a sub-therapeutic concentration received a lower median weight-based dose of 17 mg/kg. These findings are in line with numerous guidelines and

Table III
Factors affecting the vancomycin trough concentration following the loading dose.

	Achieved target (15–20) $n = 24$	Sub-therapeutic concentration (<15) $n = 47$	Supra-therapeutic concentration (>20) $n = 24$
Age, median (IQR)	49 (45–51)	52 (45–61)	47.5 (41–49)
Sex, female, *n* (%)	17 (71%)	35 (74%)	23 (96%)
Years on dialysis, median (IQR)	3.0 (2–6)	3.0 (2–5.5)	2.5 (1–4)
Weight, kg, median (IQR)	76 (72 –80)	75 (65–85)	77 (70–87)
Time since last dose, h, median (IQR)	40.50 (24–40)	39 (19–37)	31.5 (15–43)[†]
Loading dose, mg/kg, median (IQR)	20 (17–21)	17 (13–19)[*]	21 (19–22)

[*] $P = 0.002$ compared to achieved target group.
[†] 0.06 compared to achieved target group.

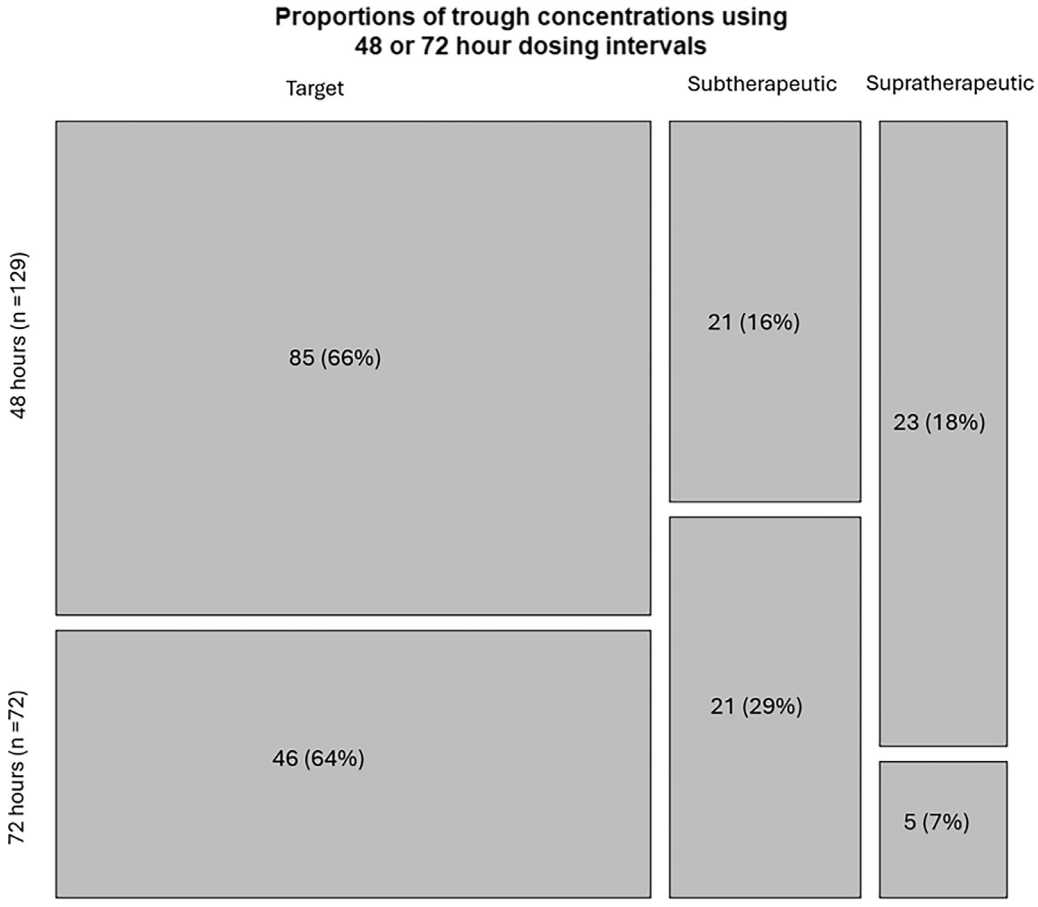

Figure 1. Proportions of maintenance trough concentrations attained with 48- or 72-h dosing intervals.

Table IV
Number of persons requiring dose adjustments over a treatment course.

Treatment course (days)	Number of dose adjustments required							
	0	1	2	3	4	5	6	7
1–7 ($n = 55$)	11 (20%)	34 (62%)	10 (18%)	-	-	-	-	-
8–14 ($n = 23$)	5 (22%)	8 (35%)	6 (26)	4 (17%)	-	-	-	-
15–21 ($n = 11$)	1 (9%)	4 (37%)	0 (0%)	2 (18%)	1 (9%)	2 (18%)	1 (9%)	-
22+ ($n = 6$)	-	-	-	1 (17%)	2 (33%)	2 (33%)	-	1 (17%)

published protocols which recommend a loading dose between 20 and 35 mg/kg (dependent on high/low flux dialysis and timing of administration) to more rapidly achieve a target trough of 15 to 20 mg/L.[29–32] Fixed-loading doses were recommended in the literature prior to 2009 when the target trough concentration range was 5 to 20 mg/L.[23,33] Based on our findings, we recommend a standardized loading dose of 20 to 25 mg/kg (nonintradialytic) irrespective of the indication.

This study found that those with an initial supra-therapeutic concentration had a shorter time interval between the loading dose and the first trough taken, and those who achieved the therapeutic target had a median dose interval of 41 h. This suggests that the time to first sample is associated with the probability of target attainment, which the protocol does not incorporate. Other researchers have also suggested that the dosing interval following the loading dose be a predictor of ther-

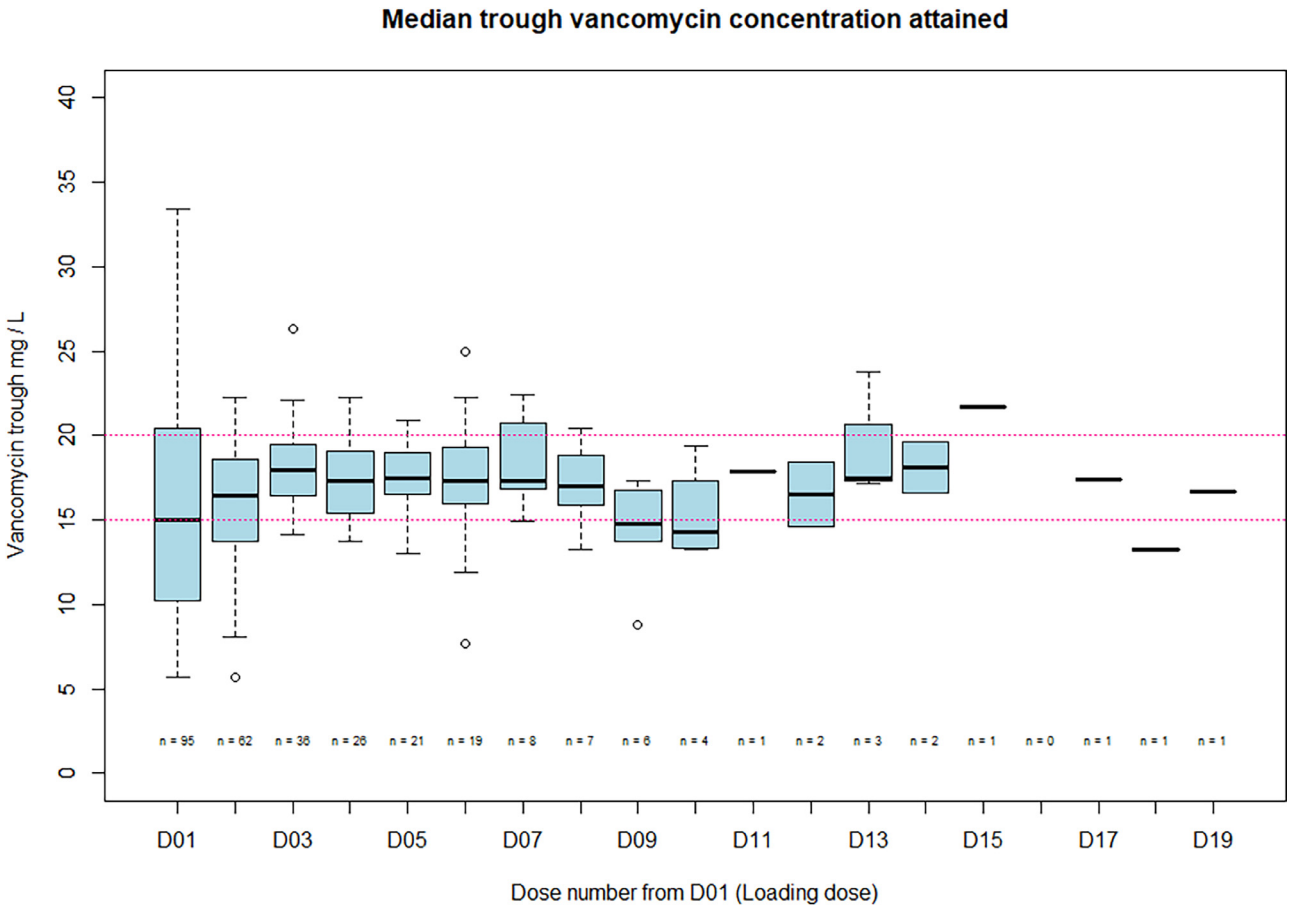

Figure 2. Median trough vancomycin concentrations following each dose of vancomycin.

Table V
Adherence with the loading dose protocol and subsequent trough concentration achieved.

	Proven or suspected MRSA bacteremia (n = 28)			All other indications (n = 67)		
	Adherent with LD protocol (n = 11)	Nonadherent with LD protocol (n = 17)	P value	Adherent with LD protocol (n = 25)	Nonadherent with LD protocol (n = 42)	P value
Patients who achieved therapeutic target (15–20 mg/L), n (%)	3 (28%)	6 (35%)	0.890	3 (12%)	12 (29%)	0.204
Therapeutic target, median (IQR)	16.10 (15.47–16.32)	15.75 (15.47–16.32)	0.905	18.30 (17.00–17.67)	17.30 (16.85–18.60)	0.945
Patients with sub-therapeutic concentrations (<15 mg/L), n (%)	4 (36%)	7 (41%)	1.000	19 (76%)	17 (40%)	0.065
Sub-therapeutic concentrations, median (<15 mg/L) (IQR).	9.70 (8.98–11.05)	7.40 (6.40–13.25)	0.507	10.10 (8.30–11.90)	10.60 (8.30–12.40)	0.476
Supra-therapeutic concentrations cases (>20 mg/L), n (%)	4 (36%)	4 (24%)	0.839	3 (12%)	13 (31%)	1.00
Supra-therapeutic concentrations, median (IQR)	27.45 (26.18–28.43)	24.85 (23.77–25.98)	0.486	30.50 (27.70–31.60)	27.80 (23.00–28.90)	0.501

IQR = interquartile range; LD = loading dose; MRSA = methicillin-resistant *Staphylococcus aureus*.

apeutic target attainment.[25,34] A pharmacokinetic study is needed to quantify the optimal loading dose incorporating weight-based dosing, time to next dose, and other potential covariates.

Maintenance Dosing

Two-thirds of the postmaintenance dose trough concentrations fell within the target therapeutic range, which is higher than what was reported in other studies (ranging from 35% to 37%), considering the use of different dosing strategies in those studies.[31,35] Jeremiah et al. reported a target therapeutic attainment rate of 54.5% using this nomogram, although this study only included 28 treatment courses.[36] In our study, 21% of patients achieved sub-therapeutic trough concentrations, aligning with a recent systematic review that found 20% to 30% of trough concentrations were sub-therapeutic when nonweight based initial maintenance dosing was used.[37]

We found that the therapeutic concentration was not reliably maintained once achieved, with most patients requiring several dose adjustments over their treatment course (see **Table IV**). The requirement for dose adjustments is undesirable as it signifies an incidence of supra-therapeutic or sub-therapeutic concentrations. When comparing the 48- and 72-h time intervals, a larger proportion achieved a sub-therapeutic

concentration in the 72-h interval whereas a larger proportion achieved a supra-therapeutic concentration in the 48-h interval. Reasons for the dose adjustments observed could be attributed to the dosing nomogram only considering the previous trough concentration to guide dosing and does not consider the previous dose administered and time until the next dialysis session.[25] It may also be attributed to the varying residual renal function seen in different patients, which the dosing nomogram does not take into consideration.

At the time of writing, all published dosing recommendations include an initial maintenance weight-based approach either as mg/kg or dose-banding.[15,38,39] Adjusting subsequent doses using a percentage of the previously administered dose may reduce the trough concentrations falling outside of the target range.[35,40,41] Ables et al. suggested administering an additional 250 mg for the 3-day inter-dialytic interval,[40] with others recommending a 25% to 30% dose increase.[38,40] Whether these dosing strategies can reduce the requirement for maintenance dose adjustment requires validation. All protocols recommend sustaining the previous dose if the target trough concentration was achieved, which differs from the protocol used by our dialysis center as all concentrations which are within the therapeutic range warrant a dose of 1000 mg irrespective of the previous dose required to achieve target. No recently published protocols by other institutions or consensus guidelines employ the dosing nomogram used by Central Australia to achieve a target trough concentration of 15 to 20 mg/L, however, one older study which aimed to achieve a target trough concentration of 10 to 20 mg/L used this approach.[42] An improved dosing protocol should include the time to next dialysis, utilizing a slightly higher dose when the time interval is 72 h.

Adherence to Protocol

Substantial low adherence to the loading dose protocol was observed, however reasons for nonadherence were not assessed. Nonadherent doses prescribed by nephrologists or infectious diseases physicians may be attributed to the consideration of extremes of body weight, time until next dialysis session, or residual renal function. The nursing-led maintenance dosing nomogram to adjust the vancomycin dose ensured timely administration of vancomycin during HD.

Strengths and Limitations

This study demonstrates several strengths and limitations that are important for contextualizing its findings. One notable strength is the unintentional inclusion of 100% Australian Indigenous patients, which adds to the limited body of research in this population who are largely susceptible to ESRD. Additionally, the study's longitudinal design spanning from 2017 to 2023 captured the complete treatment journey of each patient, providing a comprehensive view over a considerable period. However, the study also has several limitations that should be acknowledged. Firstly, being a single-center study may limit the generalizability of findings to the broader population and requires further validation through multicenter studies or larger sample sizes. The risk of selection bias in this study is mitigated by the unique demography of the Australian remote study site which serves a vast, diverse population (catchment area of over 1.6 million km^2), with centralized care provided by the same nephrology team across all dialysis sites. This ensures consistency in clinical practices and enhances the representativeness of our sample. Secondly, the retrospective nature of the study introduces the potential for missing data or transcription errors in patient records, which could affect the accuracy and reliability of the results. Thirdly, the study did not quantify residual renal function or vancomycin clearance by the dialyzer, which could have provided additional insights into treatment efficacy and outcomes. Residual renal function in ESRD, though not specifically analyzed in this study due to the retrospective nature of the dataset and the unavailability at the time of vancomycin administration, has a minimal impact on vancomycin clearance. Similarly, while we did not analyze variability in vancomycin clearance between different dialyzer types, all patients in our cohort were treated with a consistent dialysis protocol at a single-center, using similar high-flux dialyzers. Based on available manufacturer-reported performance data, differences in clearances between the dialyzer models are unlikely to significantly influence vancomycin clearance. Finally, data on infection severity, comorbidities, and concomitant medications were not uniformly available, which precluded their inclusion as confounding factors in the analysis. While comorbidities and concomitant medications may influence vancomycin pharmacokinetics in other populations, their impact in this cohort of patients with ESRD is expected to be minimal, as dialysis clearance is the primary determinant of vancomycin levels. Infection severity may be a confounding factor as severe infection such as sepsis may influence vancomycin concentrations through changes in the volume of distribution. Standardized severity scores were not uniformly available in our data set, limiting our ability to account for this factor, especially in a retrospective nature. Nonetheless, we have specified that all patients were being treated with active infection.

Future Direction

The focus of this study was to evaluate the clinical application of a local dosing protocol in the context of real-world practice. Future research is needed to develop clinical guidelines using population-based pharmacokinetic techniques to optimize vancomycin dosing. These guidelines should address factors linked to target nonattainment, such as weight-based dosing, time-to-next-dose considerations for loading doses, and dosing intervals for maintenance therapy.

Conclusion

The findings show the vancomycin dosing protocol does not consistently achieve the vancomycin target trough concentration following the loading dose or reliably maintain the target trough concentrations following the maintenance doses. Adherence to the loading dose protocol was suboptimal, although adherence did not improve target trough concentration attainment with most achieving a sub-therapeutic trough concentration. We recommend a loading dose of 20 to 25 mg/kg for all indications, and the time between the loading dose and first maintenance dose should also be considered, especially for those with residual renal function. When determining the next maintenance dose, we recommend that a higher adjusted dose be administered for the 72-h maintenance dose interval than the 48-h interval. Further pharmacokinetic modelling studies are needed to determine the optimal dosing strategies and determine the factors that influence target attainment.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JM was funded by an Australian Defence Force grant to cover the tuition fees associated with the Master of Clinical Pharmacy degree at the University of Tasmania, Australia. This research project and manuscript was completed as part of this degree. The funding body had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

CRediT authorship contribution statement

Jacqueline Martin: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Colin M. Curtain:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization. **Mohammed S.**

Salahudeen: Writing – review & editing, Supervision. **Sonja Janson:** Writing – review & editing. **Sachin Kodgire:** Writing – review & editing. **Danny Tsai:** Writing – review & editing, Visualization, Supervision, Methodology, Data curation, Conceptualization.

Acknowledgments

The authors would like to thank the nephrologists at the dialysis center for their support and administrative staff at the dialysis center for their assistance.

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