

RESEARCH

Open Access



Impact of Vancomycin trough levels monitoring on uncomplicated *methicillin-resistant Staphylococcus aureus* bacteremia in chronic kidney disease on hemodialysis, retrospective cohort

Julian Felipe Ramirez-Osorio¹, Juan Esteban Velez-Hernandez^{1*}, Nathalia Fernandez-Castaño², David Felipe Rojas-Hernandez² and Fabian Jaimes^{1,3}

Abstract

Background CKD patients on hemodialysis (HD) with *Staphylococcus aureus* (SA) bacteremia present high morbidity, mortality and increased risk of MRSA. Vancomycin is the antibiotic of choice in these cases, it has a narrow therapeutic margin and inadequate dosage generates a risk of toxicity, therefore, the recommendation is to dosage it through serum levels.

Methods This is a retrospective cohort study in 3 hospitals of third level of complexity in the city of Medellin in which there were differences in the measurement and implementation of vancomycin₂₅ dosage based on trough levels (VL) in patients with chronic kidney disease on hemodialysis (CKD- HD) with uncomplicated bacteremia based infection by *methicillin-resistant Staphylococcus aureus* (MRSA). The primary outcome was the composite of hospital mortality, clinical response (fever, hemodynamic instability and altered consciousness), complications associated with bacteremia, or bacteriological response failure (positive cultures at first week follow-up) at 7 days. The composite variables were analyzed individually as secondary outcomes.

Results The main unadjusted outcome (OR 1.3, CI 0.6 - 2.7) and adjusted for age, Charlson index, loading dose, initial dose, dosing frequency and MIC to vancomycin (OR 1.2, CI 0.5 - 2.7). Regarding adjusted secondary outcomes: clinical response (OR 1.4 CI 0.3 - 5.8), death (OR 1.3 CI 0.3 - 4.6) and complications (OR 0.9, CI 0.37 - 2.2).

Conclusions We conclude that the measurement of trough levels in patients with HD-CKD does not modify the composite outcome. The main limitation is the sample size and type of study, randomized control trials may be required to confirm the results presented.

Keywords CKD-HD, Bacteremia, Vancomycin, Trough levels, MRSA

*Correspondence:

Juan Esteban Velez-Hernandez
juan.velez30@udea.edu.co

¹ Department of Internal Medicine, Hospital Alma Mater de Antioquia,
Carrera 77 B # 47 - 113, 050031 Medellin, Antioquia, Colombia

² University of Antioquia, Medellin, Colombia

³ IATERIA Journal, Medellin, Colombia



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Background

In Colombia, 6% of patients with CKD require renal replacement therapy (RRT) [1]. In patients with CKD-HD, bacteremia due to SA presents high morbidity, mortality and increased risk of MRSA [2]. Local studies have reported a mortality due to SA of 24-30% [3]. In a study conducted at the San Vicente Fundación Hospital of Medellín, SA bacteremias cases were collected retrospectively for 4 years (2012-2016) the results showed 43% of those infected were in RRT [2].

Vancomycin is the drug of choice for the treatment of MRSA bacteremia [2]. This antibiotic has a narrow therapeutic margin, and inadequate dosage poses a risk of toxicity [4] while underdosing predisposes to therapeutic failure and emergence of resistant microorganisms [5]. Its dosage should be based on the serum levels of the antibiotic and the minimum inhibitory concentration (MIC) of the microorganism, specifically for MRSA [6, 7].

Based on current evidence, the recommended PK/PD parameter for Vancomycin in MRSA infections is AUC/MIC with values between 400 to 700 [6]. In patients on hemodialysis, vancomycin trough levels (TL) are used as [8] surrogate marker for AUC/MIC > 400 [6, 7]. Maintaining pre-dialysis concentrations between 15 and 20 mg/L is considered optimal according to the 2020 IDSA guideline [4, 5]; in silico simulations have been conducted evaluating previous dosing models in HD patients [9] demonstrating low probability of attaining AUC/MIC > 400, also the authors developed a model predicting AUC/MIC 400-700 in 90% of patients with a proposed formula for modifying dosages with TL [10]. A retrospective cohort showed a decrease in mortality when target levels were achieved [7]. One study compared two dosing algorithms, both achieving similar TL, but without including clinical outcomes [11]. Despite the lack of clinical outcomes, the guideline by Rybak et al. [5] recommend dosing in CKD-HD patients based on TL.

Although there is a good correlation between the therapeutic levels of vancomycin and its therapeutic efficacy outside the setting of CKD-HD [12] the evidence to support this recommendation in this group of patients is limited [8, 11]. Additionally, this measurement strategy has not yet been compared in the literature with non-measurement of TL. Therefore, it is essential to understand the implications between measuring TL and non measuring TL related to clinical outcomes such as mortality and therapeutic failure. This study compares the results of patients who received dosing according to TL with those who did not, in terms of clinical and microbiological improvement, mortality and reduction of bacteremia related complications.

Methods

Study design

This is a retrospective cohort, data was collected from 3 third level hospitals in Medellín-Antioquia (Hospital Pablo Tobón Uribe [HPTU], Hospital San Vicente Fundación - Medellín [HUSVF], Hospital Alma Mater de Antioquia [HAMA]) with data from cultures with SA between January 2013 to January 2021 in HUSVF, January 2014 to January 2022 in HAMA and HPTU.

Participants

Inclusion criteria

Patients over 18 years of age with CKD on HD hospitalized for uncomplicated MRSA bacteremia treated with vancomycin. Exclusion criteria were defined as: bacteremia with another associated germ, treatment with antimicrobials different to vancomycin (as adjuvant or definitive therapy) after the diagnosis of MRSA bacteremia, initial cointervention with other antimicrobials effective against MRSA and complicated bacteremia in the first 48 h after the patient's admission. Cohorts of TL dosing and dosing without TL were assigned depending on the monitoring and if required dose modification in each individual patient. Institution #3 measures TL levels in all patients due to institutional protocol. In institutions #2 and #1 the dosing with TL levels is personalized and contingent upon the individual decisions of treating physicians.

Variables

The primary outcome was a composite at one-week follow-up, including hospital mortality, clinical response (fever > 38.2 C, hemodynamic instability [SBP < 90 MAP < 60] and altered consciousness [Glasgow < 15]), bacteremia-associated complications (endocarditis, abscesses, discitis, arthritis, empyema, among others) or bacteriological response failure (positive cultures at the end of the first week of follow-up). Secondary outcomes are the individual derivatives of the composite outcome. The quantitative variables used were: weight, TL measurements, cumulative dose, loading dose, initial dose in grams, antibiotic time since symptom onset, treatment duration and Charlson index. These were presented as means and standard deviations. As clarification, institutions do not measure AUC levels in CKD-HD patients. In cases where vancomycin was administered post-hemodialysis, TL levels were assessed prior to the dialysis session.

Databases

Initial database contained the cultures positive to SA, the data was filtered by MIC greater than or equal to 2 for oxacillin and blood cultures, then the medical records were reviewed individually and included depending on inclusion and exclusion criteria.

Bias

Measures done to avoid bias included: patients were admitted at the same time of the disease (suspected bacteremia, uncomplicated bacteremia in the first 48 h), knowing the heterogeneity of the sample as it was a cohort study, a multivariate analysis by logistic regression was performed. The assignment of the outcome was based on an exhaustive review of clinical histories by the principal investigators; if there were doubts between the assignment of outcomes, the specific case was discussed between the principal investigators.

Sample size

Sample size calculation was based in data of Young et al. and Mical et al. [11, 12] both studies in infections caused by MRSA and comparing vancomycin with teicoplanin or trimethoprim sulfamethoxazole. Assuming an outcome frequency of 40% in patients without use of VN, versus 30% in those with VN dosing of the antibiotic, with an exposed/not exposed ratio of 0.5, alpha error of 0.05 and beta error of 0.2; the calculated sample size was 852 patients: 284 with trough levels and 568 with conventional treatment.

Statistical analysis

Means and medians were calculated for quantitative variables; percentages were calculated for qualitative variables, both for the total cohort and for the cohort dosed by TL and without TL dosing. The unadjusted primary

outcome was initially performed by binomial logistic regression and then multivariate adjustment for age, Charlson index, loading dose, initial dose, dosing frequency and MIC to vancomycin. Secondary outcomes were assessed with and without adjustment in a similar manner through binomial logistic regression. The primary database was created in *Microsoft Excel version 16.71*. *Jamovi 2.3.25.0*. was used as statistical program.

Results

Patients

Clinical records of patients with positive cultures for SA were reviewed, being 10580 from hospital one, 391 from hospital two and 1135 from hospital three. The total number of patients included from each hospital was 21, 26 and 72, respectively, for a total of 119 patients. The main cause of exclusion was non-hemodialysis (7423 patients) and *methicillin-sensitive SA (MSSA)* (3768). The remaining variables were infrequent (causes of exclusion are specified in Fig. 1).

Descriptive data

Majority of patients were from hospital one $n=72$ (60.5%), 60 men (50%), mean age was 54.13 ± 17.35 years. Of the total number of infections, $n=104$ (87.4%) were catheter-associated bacteremia, most of them of community origin $n=81$ (68%). Of the clinical characteristics at admission, the most frequent was tachycardia $n=77$ (64%). Related to comorbidities, the most frequent was diabetes mellitus (DM) $n=59$ (49%). Median Charlson

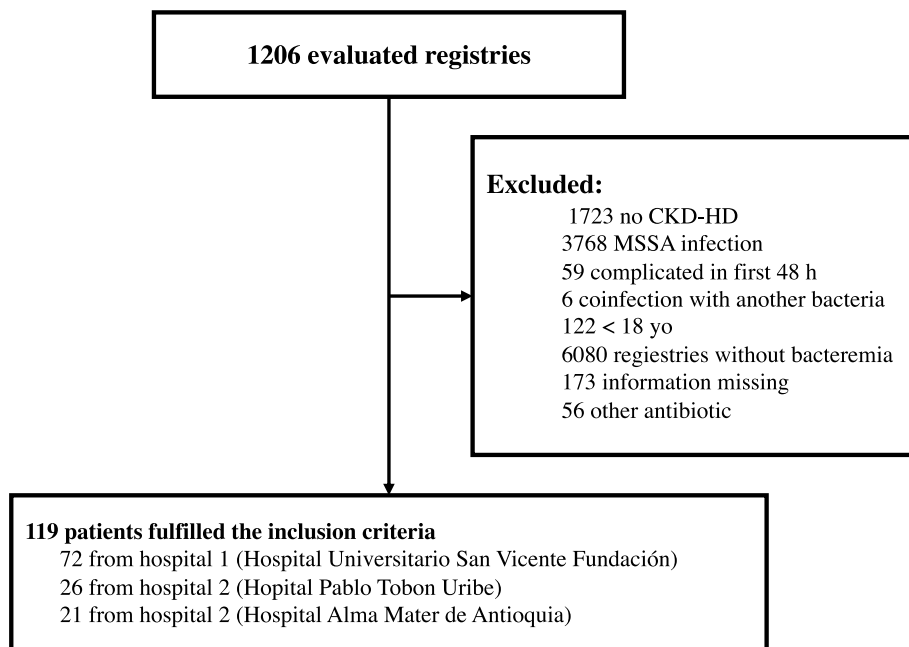


Fig. 1 Flowchart illustrating patient selection process

index was 5 (RIQ: 3 - 7). In patients with TL measurements, only $n=19$ (29.2%) were on target levels at the first measurement, most TL were supra-therapeutic $n=36$ (55.3%). Most frequent dosing interval was every 24 h $n=80$ (67%). Most received antibiotic co-intervention in the first 48 h $n=101$ (85%), mainly with piperacillin-tazobactam $n=66$ (55%). No patient in the cohort had MIC > 1, and most had MIC: 1 $n=73$ (61%). Of the included patients $n=65$ (54%) were dosed using at least one TL and $n=54$ (46%) were dosed without considering TL. Both cohorts are similar in their main characteristics, differences are observed in relation to the collection center as in hospital three all patients were dosed based on TL, while in hospital one the majority (60%) were dosed without TL. There was also a significant difference in onset of symptoms and the beginning of antibiotic therapy, being shorter in the group dosed based on TL. The main missing data in the cohort were follow-up cultures, at 72 h $N=39$ (32.7%) and at one week $N=38$ (31.2%) most being after negative cultures at 72 h. Individual patient characteristics are listed in Table 1.

Outcomes

Primary outcome in the entire cohort occurred $N=46$ (38%), in patients who were dosed with TL $N=27$ (41%) and in 19 (35%) of those who were not dosed with TL. The main complication was pulmonary septic emboli with $N=20$ (16%), followed by hospital mortality with $N=14$ (11%) and infective endocarditis with 12 (10%). The rest of the outcomes were infrequent and similar between groups as shown in Table 2.

An unadjusted OR of 1.3 (95% CI: 0.6 - 2.7) was found when comparing patients dosed based on TL to those who did not dose based on these levels. After adjusting for the main confounding variables (Charlson index, age, loading dose, initial dose in grams, dosing frequency and MIC to vancomycin), the adjusted OR was found to be 1.2 (95% CI: 0.56- 2.7). While demonstrating a higher proportion of the primary outcome in patients dosed with levels, the association was not statistically significant Table 3.

Other analysis

Secondary outcomes

Clinical instability in the adjusted analysis showed no significant association (OR 1.4, CI 0.3 - 5.8), an similarly, complications (OR 0.9, CI 0.4 - 2.2) and mortality (OR 1.3, CI 0.3-4.4) exhibited no statistical significance. There was a trend towards a higher proportion in the group of patients with VN measurement, except for complications.

As additional analysis, we compared the difference of the primary outcome in patients with TL in therapeutic

range (> 15 mg/L) with those who did not achieve these levels (< 15 mg/L) finding (OR 0.5, CI 0.1-2.5). We also calculated the odds for the primary outcome comparing those who dosed every 24 h with respect to those who used another dosing frequency, finding (OR 0.8, CI 0.3-2.2), other supplementary analysis are found in Table 3.

Discussion

Main findings

In the present study, no difference was found between the cohort dosed with and without TL, with a trend (without statistical significance) to a greater number of adverse outcomes (microbiological failure, clinical instability, complications and hospital mortality) in patients dosed with TL. Regarding safety, the main adverse effect (acute kidney injury) is not a variable to be considered in these patients.

Interpretation

There are few studies of MRSA bacteremia and CKD-HD. In the study of Valdés et al., 60% were associated with catheters and 88% of these were due to MRSA [13]. On the other hand, in the study by Cuervo et al. 15.6% of MRSA bacteremias were in HD patients and this subgroup, patients were more comorbid, had a higher MIC of vancomycin (60% had > 1.5 mg/L measured by E-test) and vancomycin was the definitive management in 83% of the cases [14]. In contrast to the above, the present study found that 88% of uncomplicated bacteremias were catheter-associated and 60% of isolates had a MIC of 1 to vancomycin by Vitek method®.

Regarding the dosing of vancomycin in HD, guidelines [5] recommends maintaining trough levels between 15-20 mg/l in order to guarantee efficacy [12]. Rambaran and collaborators in a retrospective cohort of patients with CKD-HD found that mortality was lower with TL between 15 to 29 mg/l OR 0.5 (95% CI 0.63 - 0.9), but did not compare the measurement of TL with not measuring them [8]. The study by Lobna et al. found that there was no difference in the achievement of target levels between measuring VN twice a week vs. measuring it before each HD session, without considering clinically relevant outcomes [11]. In silico studies with Monte Carlo simulations have predicted > 90% probability of target attainment (AUC/MIC 400-700) differentiating regimens according to intradialysis, postdialysis and if the dialysis is done with high flux or low flux membranes, being a start for proposing clinical studies in real world [10]. To our knowledge, this is the first study that compared a dosing group based on TL and another without measuring them, considering therapeutic efficacy in its outcomes.

This study suggests that, due to the erratic elimination of vancomycin in hemodialysis patients, a regular,

Table 1 Sociodemographic, clinical, laboratory, microbiologic and treatment characteristics

Sociodemographic variables	Full cohort <i>n</i> = 119 (%)	TL dosing <i>n</i> = 65 (%)	Dosing without TL <i>n</i> = 54 (%)
Hospital 1	72 (60.5)	29 (44.6)	43 (79.6)
Hospital 2	26 (21.8)	15 (23.1)	11 (20.7)
Hospital 3	21 (17.6)	21 (32.3)	0 (0.0)
Age years (Mean ± SD)	54.1 ± 17.3	53.2 ± 17.4	55.3 ± 17.4
Weight kg (Mean ± DE)	65.4 ± 19.7	66.4 ± 18.3	67.5 ± 16.4
Female	59 (49.6)	37 (56.9)	22 (40.7)
Male	60 (50.4)	28 (43.1)	32 (59.3)
Clinical variables			
Tachycardia ^a	77 (64)	41 (63.1)	33 (61.1)
Hypotension ^a	18 (15.1)	9 (13.8)	10 (18.5)
Fever ^a	71 (59.7)	43 (66.1)	28 (51.8)
Glasgow < 15	5 (4.2)	1 (1.5)	4 (7.4)
AMI	16 (13.4)	8 (12.3)	8 (14.8)
CHF	33 (27.7)	20 (30.7)	13 (24.0)
PAD	17 (14.3)	11 (16.9)	6 (11.1)
Stroke / TIA	10 (8.4)	4 (6.1)	6 (11.1)
COPD	11 (9.2)	6 (9.2)	5 (9.2)
Dementia	5 (4.2)	1 (1.5)	4 (7.4)
CTD	15 (12.6)	10 (15.4)	5 (9.2)
PUD	1 (0.8)	1 (1.5)	0 (0.0)
Hepatic disease	5 (4.2)	2 (3.0)	3 (5.5)
DM	59 (49.6)	33 (50.7)	26 (48.1)
Solid tumor	4 (3.3)	0 (0)	4 (7.3)
Leukemia / Lymphoma	6 (5.0)	2 (3.1)	4 (7.4)
AIDS	0 (0.0)	0 (0.0)	0 (0.0)
Charlson index IQR	5 (3 - 7)	5 (3 - 7)	6 (3-7)
Non steroidal immunosupresants	12 (10.8)	8 (12.3)	4 (7.4)
Past medical history of endocarditis	3 (2.5)	1 (1.5)	2 (3.7)
Mitral biologic valve	2 (1.7)	1 (1.5)	1 (1.8)
Catheter associated bacteremia	105 (88.2)	58 (89.2)	47 (87.0)
Community acquired bacteremia	81 (68.0)	47 (72.3)	34 (62.9)
Hospital acquired bacteremia	38 (31.9)	18 (27.7)	20 (37.0)
Catheter lock therapy	3 (2.5)	2 (3.1)	1 (1.8)
Permanent catheter	97 (81.5)	55 (84.6)	42 (77.7)
Femoral catheter	10 (8.4)	5 (7.7)	5 (9.2)
AB timing since symptom onset (hours, mean ± SD)	38.2 ± 38.2	33.2 ± 36.0	36.8 ± 41.1
Catheter retrieval since symptom onset (days, mean ± DE)	4.1 ± 3.0	3.6 ± 2.7	4.6 ± 3.3
Consolidation ^b AB with V	106 (89.0)	56 (86.1)	50 (92.6)
Daptomycin	9 (7.6)	7 (10.8)	2 (3.7)
AB consolidation with other medication	4 (3.4)	2 (3.1)	2 (3.7)
Vancomycin			
TL by por turbidimetry	12 (10.1)	12 (18.5)	N/A
TL by chemiluminescence	30 (25.2)	30 (46.1)	N/A
Unknown method	23 (19.3)	23 (35.4)	N/A
TL 1 (mg/L, media ± DE)	24.7 ± 13.8	24.7 ± 13.8	N/A
% TL < 15 mg/L	10 (8.4)	10 (15.4)	N/A
% TL 15–20 mg/L	19 (15.1)	19 (29.2)	N/A
% TL > 20 mg/L	36 (30.2)	36 (55.3)	N/A

Table 1 (continued)

Sociodemographic variables	Full cohort <i>n</i> = 119 (%)	TL dosing <i>n</i> = 65 (%)	Dosing without TL <i>n</i> = 54 (%)
Microbiológicos			
MIC < 0.5	44 (37.0)	25 (38.5)	19 (29.2)
MIC 1	73 (61.3)	39 (60.0)	34 (63.0)
Tratamiento			
Accumulated dose (g, mean ± SD)	8.6 ± 4.1	8.8 ± 3.9	8.5 ± 7.5
Loading dose (g, mean ± SD)	0.6 ± 0.2	0.5 ± 0.5	0.3 ± 0.5
No loading dose	73 (61.3)	33 (50.8)	40 (74.1)
Initial dose (g, mean ± SD)	0.66 ± 0.24	0.7 ± 0.2	0.6 ± 0.2
Frequency of initial dosage q 12 h	4 (3.4)	4 (6.1)	0 (0.0)
Frequency of initial dosage q24 h	80 (67.2)	34 (52.3)	46 (85.1)
Frequency of initial dosage q 48 h	29 (24.4)	22 (33.8)	7 (12.9)
Frequency of initial dosage q 72 h	4 (3.4)	3 (4.6)	1 (1.8)
AB cointerventions in the first 24–48 h	101 (85.0)	57 (87.7)	44 (81.4)
Didn't received cointervention	16 (13.4)	8 (12.3)	8 (14.8)
Cointervention with Piperacilina/tazobactam	66 (55.4)	38 (58.4)	28 (51.8)
Cointervention with Cefazolin	7 (5.8)	5 (7.6)	2 (3.7)
Cointervention with other antibiotic	28 (23.5)	14 (21.5)	14 (25.9)
Duration of treatment with V (days, mean ± SD)	16.81 ± 8.46	18.0 ± 9.5	15.4 ± 6.7

AMI Acute myocardial infarction, CHF Cardiac heart failure, PAD Peripheral artery disease, TIA Transient ischemic attack, COPD Chronic obstructive pulmonary disease, CTD Connective tissue disease, DM Diabetes mellitus, AIDS Acquired immunodeficiency syndrome, IQR Interquartile range, AB Antibiotic, V Vancomicina, TL Through level, SD Standar deviation

^a Tachycardia FC > 90. MAP < 60 o SAP < 90. T > 37.8

^b Patients that finished treatment with vancomycin or change to other AB after day 7

standard dosing schedule (the most frequent was every 24 h) is similar to level based dosing and suggests that adequate blood levels are achieved with this type of dosing.

Previous studies have shown that achieving TL above 15 is associated with better clinical outcomes, which is confirmed in the additional analysis of the study [5, 11, 12, 15].

Strengths and limitations

The strengths of this study include the design as a cohort because it provides information on the measurement of TL in CKD-HD and its performance in therapeutic efficacy in real life (without interference from the strict rules that limit the generalization of clinical trials). In addition, another strength is the exhaustive characterization of the population, since it evaluates demographic, clinical, microbiological and treatment variables (that have not been considered in similar studies). With respect to the comparison, to our knowledge this is the only study to date that questions the need for measurement of vancomycin TL in this population, comparing measurement vs. no measurement with respect to clinically relevant outcomes. We also emphasize the need for exploratory

analyses for TL > 15 mg/L and depending on the dosage form (12 h, 24 h and 72 h) as it is heterogeneous in this study.

The most common dosing schedule was every 24 h; the dosing recommendation in this population is after hemodialysis so we do not know if the results would be different with a higher proportion of patients dosed every 72 h.

The results of this study should be interpreted in the context of the limitations inherent to its design and the characteristics of the databases collected. Being a retrospective study, it is difficult to control for the risk of unmeasured confounding variables; logistic regression adjustment was performed for the main and secondary outcomes, for variables that could reasonably affect the proportion of the outcome. Also, the dose modification according to TL values was personalized and contingent upon the individual decisions of treating physicians in institution #1 and #2; is worth noting that certain factors influencing these decisions may be challenging to measure comprehensively.

It should be taken into account that the measurement TL could be a factor that increases the risk of bias due to indication (*selection bias*), the patients whom TL measurements are obtained may have factors (whether

Table 2 Clinical and microbiologic outcomes

Outcome variables	Full cohorts n = 119 (%)	TL dosing n = 65 (%)	Dosing without TL n = 54 (%)
Any complication	36 (30.2)	21 (32.3)	17 (31.5)
Lung septic embolism	20 (16.1)	10 (15.4)	10 (18.5)
Endocarditis	12 (10.1)	8 (12.5)	4 (7.4)
ST abscess	3 (2.5)	3 (4.6)	0 (0.0)
Ab abscess	1 (0.8)	1 (1.5)	0 (0.0)
B abscess	0 (0.00)	0 (0.0)	0 (0.0)
Discitis	2 (1.7)	1 (1.5)	1 (1.8)
Septic arthritis	1 (0.8)	1 (1.5)	0 (0.0)
OM	1 (0.8)	0 (0.0)	1 (1.8)
Empiema	2 (1.7)	0 (0.0)	2 (3.7)
Thromboflebitis	8 (6.7)	3 (4.6)	5 (9.25)
Meningitis	1 (0.8)	1 (1.5)	0 (0.0)
Hepatic abscess	1 (0.8)	1 (1.5)	0 (0.0)
Splenic abscess	1 (0.8)	1 (1.5)	0 (0.0)
Other complications	3 (2.5)	3 (4.6)	0 (0.0)
Possitive cultures at 72 h	30 (25.2)	19 (29.2)	11 (20.4)
Culture was not performed at 72 h	39 (32.7)	19 (29.3)	20 (37.0)
Possitive cultures end of the week	16 (13.4)	10 (15.4)	6 (11.1)
Culture was not performed at end of the week	38 (31.9)	24 (36.9)	22 (40.7)
Inhospital death	14 (11.8)	8 (12.3)	6 (11.1)
Hemodynamic instability*	12 (10.08)	7 (10.7)	5 (9.2)
Primary outcome	46 (38.6)	27 (41.5)	19 (35.18)

ST Soft tissue, Ab Abdominal, B Brain, OM Osteomyelitis. *Systolic arterial pressure <90 Median arterial pressure <60

Table 3 Primary and additional outcomes

Non adjusted outcome	OR	IC 95%	p
Primary outcome	1.3	(0.6 - 3.9)	0.4
Hemodynamic instability	1.8	(0.3 - 3.9)	0.8
Complications	1.0	(0.5 - 2.2)	0.8
Death	1.1	(0.4 - 3.5)	0.8
Adjusted otcomes			
Primary outcome	1.2	(0.3 - 2.7)	0.7
Hemodynamic instability	1.4	(0.3 - 5.8)	0.7
Complications	0.9	(0.3 - 2.2)	0.8
Death	1.1	(0.3 - 4.5)	0.7
Non adjusted additional outcomes			
First TL > 15 mg/L	0.6	(0.1 - 2.3)	0.4
Dosage q 12 h	0.6	(0.1 - 4.5)	0.6
Dosage q 24 h	1.1	(0.5 - 2.5)	0.7
Dosage q 72 h	1.6	(0.2 - 11.9)	0.6
Adjusted additional outcomes			
First TL > 15 mg/L	0.4	(0.1 - 2.4)	0.3
Dosage q 12 h	0.6	(0.1 - 5.0)	0.6
Dosage q 24 h	0.8	(0.3 - 2.2)	0.9
Dosage q 72 h	1.5	(0.1 - 13.2)	0.6

known or not) that make the clinician more prone to assess the vancomycin levels; for this reason, one of the institutions (hospital #3) was included, since by institutional protocol they measure TL in all patients who are prescribed vancomycin (regardless of their clinical condition). Regarding TL, it is important to highlight that in institution #3, since it is under institutional protocol, there is greater control over pre-analytical variables and staff training for sample collection, which cannot be assured in other institutions.

With respect to the sample size, it was calculated based on a clinical trial and an observational study [16, 17] with a similar composite outcome, the desired number being 852 patients. Due to inherent limitations of the databases, this objective was not achieved; it should be clarified that the search strategy (by means of cultures) reduces the probability of losing patients due to erroneous diagnostic classification.

Applicability and closure

It should be noted that the focus of this study was on patients with CKD-HD. While this group of patients is particularly vulnerable to infections and RRT-related complications, our findings may not be generalizable

to other patient groups. It is important to keep in mind that vancomycin dosing without requiring TL is an important finding, as it reduces the costs and complexity of dose administration; whether there are significant differences in therapeutic effectiveness is to be assessed in prospective randomized clinical trial-type studies.

Given that the MRSA bacteremia is a major public health problem worldwide, we recommend that additional clinical trials be conducted to evaluate the effectiveness and safety of vancomycin dosing according to TL's compared to no measurement in the ERC-HD population.

Abbreviations

AUC/MIC	Area under de curve to minimum inhibitory concentration
CKD	Chronic kidney disease
DM	Diabetes mellitus
HD	Hemodialysis
HAMA	Hospital Alma Mater de Antioquia
HPTU	Hospital Pablo Tobón Uribe
HUSV	Hospital Universitario San Vicente
MIC	Minimum inhibitory concentration
MRSA	Methicillin resistant staphylococcus aureus
MSSA	Methicillin susceptible staphylococcus aureus
SA	Staphylococcus aureus
TL	Trough levels
VL	Vancomycin trough levels

Authors' contributions

Ramirez Osorio, JF, and Velez Hernandez, JE, contributed equally to research design, data collection, writing, and manuscript review. Fernandez Castaño, N, and Rojas Hernandez, DF, were responsible for data collection and manuscript review before submission. Jaimes, F, provided essential methodological and epidemiological guidance, assisting with data processing and manuscript review.

Funding

This study is independent, not dependent on industry or third party funding.

Availability of data and materials

The raw data set was shared with the editors, also the tables, frequencies and ORs calculation from Jamovi 2.3.25.0[®]. For those interested in obtaining the study's raw data for academic purposes, please contact the corresponding author, Juan E. Velez-Hernandez at juan.velez30@udea.edu.co.

Declarations

Ethics approval and consent to participate

The research protocol was approved by the ethic committee of each hospital and the Institute for Medical Research of the University of Antioquia. The need for informed consent was waived by the Ethics committee of (Hospital Pablo Tobón Uribe [HPTU], Hospital San Vicente Fundación - Medellín [HUSV], Hospital Alma Mater de Antioquia [HAMA]). Patients personal data were protected during data collection and analysis.

Consent for publication

Non applicable.

Competing interests

The authors declare no competing interests.

References

1. Acuña Merchán L, María TD, Valbuena García AM, Soler LA, Valderrama F. Situación de la ERC, la HTA y la DM en Colombia. 2021. p. 79–333. Available from: <https://cuentadealtocosto.org/site/publicaciones/situacion-de-la-enfermedad-renal-cronica-la-hipertension-arterial-y-diabetes-mellitus-en-colombia-2020/?1680065218547>.
2. Hincapie C, Caraballo C, Tibađuza M, Garces D, Echeverri L, Jaimes F. Clinical and microbiological characterization of bacteremia by *Staphylococcus aureus*. *Acta Med Colomb*. 2018;43(4):200–6.
3. Alejandro J, Fernanda M, Andrés C, Alba Luz L, Alberto F. Mortalidad por estafilococemia: influencia de la resistencia a meticilina y lugar de adquisición de la infección, en una cohorte de pacientes de Medellín, Colombia. *Enfermedades Infecc y Microbiol*. 2020;40(1):420.
4. Vandecasteele SJ, De Vriese AS. Vancomycin Dosing in Patients on Intermittent Hemodialysis. *Semin Dial*. 2011;24(1):50–5.
5. Rybak MJ, Le J, Lodise TP, Levine DP, Bradley JS, Liu C, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric. *Am J Heal Pharm*. 2020;77(11):835–63.
6. Craig WA. Basic pharmacodynamics of antibacterials with clinical applications to the use of β -lactams, glycopeptides, and linezolid. *Infect Dis Clin North Am*. 2003;17(3):479–501.
7. Kullar R, Leonard SN, Davis SL, Delgado G, Pogue JM, Wahby KA, et al. Validation of the effectiveness of a vancomycin nomogram in achieving target trough concentrations of 15–20 mg/L suggested by the vancomycin consensus guidelines. *Pharmacotherapy*. 2011;31(5):441–8.
8. Rambaran KA, Alzghari SK, Seifert CF. Evaluation of factors which influence mortality in gram-positive bacteremia in hemodialysis patients. *Cureus*. 2018;10(7):e2917.
9. Zelenitsky SA, Ariano RE, McCrae ML, Vercaigne LM. Initial vancomycin dosing protocol to achieve therapeutic serum concentrations in patients undergoing hemodialysis. *Clin Infect Dis*. 2012;55(4):527–33.
10. Lewis SJ, Mueller BA. Evaluation and development of vancomycin dosing schemes to meet new AUC/MIC targets in intermittent hemodialysis using monte carlo simulation techniques. *J Clin Pharmacol*. 2021;61(2):211–23.
11. Mahmoud L, Chaabouni Y, Ghazzi H, Feriani H, Hakim A, Kharrat M, et al. Optimization of therapeutic drug monitoring of vancomycin in patients with chronic hemodialysis. *Clin Nephrol*. 2017;88(10):198–204.
12. Fu CF, Da Huang J, Wang JT, Lin SW, Wu CC. The ratio of pre-dialysis vancomycin trough serum concentration to minimum inhibitory concentration is associated with treatment outcomes in methicillin-resistant *Staphylococcus aureus* bacteremia. *PLoS One*. 2018;13(3):1–10. <https://doi.org/10.1371/journal.pone.0193585>.
13. Vento Valdés I, Toraño Peraza G, Del Sol González AC, Piquero Lazo EM. Bacteriemia relacionada con catéter por *Staphylococcus aureus* resistente a meticilina en pacientes con enfermedad renal crónica avanzada. *Rev Cubana Med Trop*. 2019;71(2):e427.
14. Cuervo G, Camoez M, Shaw E, Dominguez MÁ, Gasch O, Padilla B, et al. Methicillin-resistant *Staphylococcus aureus* (MRSA) catheter-related bacteraemia in haemodialysis patients. *BMC Infect Dis*. 2015;15(1):1–7. <https://doi.org/10.1186/s12879-015-1227-y>.
15. Soriano A, Marco F, Martínez JA, Pisos E, Almela M, Dimova VP, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2008;46(2):193–200.
16. Yoon YK, Park DW, Sohn JW, Kim HY, Kim YS, Lee CS, et al. Multicenter prospective observational study of the comparative efficacy and safety of vancomycin versus teicoplanin in patients with health care-Associated methicillin-resistant *staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother*. 2014;58(1):317–24.
17. Paul M, Bishara J, Yahav D, Goldberg E, Neuberger A, Ghanem-Zoubi N, et al. Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by methicillin resistant *Staphylococcus aureus*: randomised controlled trial. *BMJ*. 2015;350:h2219.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 5 September 2023 Accepted: 3 January 2024

Published online: 25 June 2024