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Vancomycin administration and AUC/MIC in patients with acute kidney injury on hemodialysis (HD): randomized clinical trial

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The pharmacokinetics and pharmacodynamics (PK/PD) of vancomycin change during HD, increasing the risk of subtherapeutic concentrations. The aim of this study was to evaluate during and after the conventional and prolonged hemodialysis sessions to identify the possible risk of the patient remaining without adequate antimicrobial coverage during therapy. Randomized, non-blind clinical trial, including critically ill adults with septic AKI on conventional (4 h) and prolonged HD (6 and 10 h) and using vancomycin for at least 72 h. Sessions were analyzed and randomized into three groups (G): control (C), dose of 15 mg/kg after session), intervention (I) 2 h (dose of 7.5 mg/kg in the second hour and 7.5 mg/kg after) and IG continuous infusion (dose of 30 mg/kg in 24 h). Of the 316 patients recruited, 87 were randomized, and 174 HD sessions were monitored. For the analysis, 28 sessions belonged to the CG, 47 to the 2-hour IG, and 31 to the continuous IG. The groups were similar in age, weight, severity scores, use of nephrotoxins, sérum albumin, Kt/V, HD modality, ultrafiltration, and intradialytic intercurrences. The intervention groups showed a higher therapeutic concentration frequency than the control group ($p < 0.002$). The initial concentration was identified as a risk factor (OR 1.16, $p = 0.001$) for a non-therapeutic vancomycin concentration in the logistic regression. In contrast, the 2-hour IG was identified as a protective factor (OR 0.24, $p = 0.04$). Administration of vancomycin during dialysis proved to be a protective factor against concentrations outside the therapeutic target. Further studies are needed to suggest more appropriate doses of vancomycin for patients with AKI on dialysis therapy and to assess the impact of these results on clinical outcomes.

Keywords Acute kidney injury, Dialysis, Pharmacokinetics, Sepsis, Vancomycin

Sepsis is a life-threatening organ dysfunction caused by an unregulated host response to an infection[1–4]. Gram-positive bacteria infections correspond to approximately a quarter of nosocomial infections[5,6].

Vancomycin is a glycopeptide antimicrobial with a molecular weight of 1450 Da, bactericidal action, acting by inhibiting cell wall synthesis. The drug is not metabolized, and its excretion is 80–90% renal[7–9]. The bactericidal activity of vancomycin is considered concentration-time-dependent[7,8,10]. Due to its pharmacodynamics, a ratio of the area under the curve to the minimum inhibitory concentration (AUC/MIC) between 400 and 600 mg·h/L is recommended for MRSA with a MIC of 1 mg/L[11].

However, there is great concern in critically ill patients due to changes in their pharmacokinetics related to drug distribution, metabolism, and elimination[8,9,12,13], which can lead to subtherapeutic concentrations and the selection of resistant mutants. Regarding safety, emphasis has been given to the main side effect of the medication: nephrotoxicity, which can worsen the clinical picture and contribute to unfavorable outcomes[7,10–13].

This situation can get worse when the patient needs acute kidney replacement therapy (AKRT) in about 50% of critically ill patients with acute kidney injury (AKI) associated with sepsis[3,14,15]. In general, drugs primarily eliminated by the kidneys, with small molecular weight, a small volume of distribution, and little protein binding, can be removed by dialysis. In critically ill patients, as there is a decrease in the binding of drugs to proteins,

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despite the increase in the volume of distribution, there is a more significant elimination of them since there is a greater free fraction to be removed.

When using a high-flux membrane, vancomycin is dialyzed substantially, with rates varying between 30 and 46%[7,16–19], with a rebound effect of 16 to 36% at the end of the session, with a duration between 3 and 6 h, resulting from drug recirculation from protein binding sites (redistribution phase). Keeping the pre-dialysis vancomycin concentration between 15 and 20 mg/L seems reasonable to reach the AUC/MIC target between 400 and 600 mg·h/L, even though based on scarce data in the literature[11].

Because of the many determinants involved in the serum concentration of antimicrobials in critically ill patients with AKI undergoing dialysis therapy, further studies are justified to establish specific protocols for administering antimicrobials from the *in vivo-in vitro* correlation provided by PK/PD modeling.

This study aimed to evaluate during and after the conventional and prolonged hemodialysis sessions to identify the possible risk of the patient remaining without adequate antimicrobial coverage during therapy.

Materials and methods

Study design

A single-center, non-blind, randomized clinical trial compared different ways of administering the antimicrobial vancomycin to critically ill patients with AKI undergoing hemodialysis (HD) therapy.

The local institutional ethics committee obtained ethical approval, and the trial was prospectively registered in ReBEC on april/2019 (RBR-5rcknr) and conducted under the Declaration of Helsinki.

All participants provided written informed consent, were at least 18 years of age, were admitted to the intensive care units of the Clinics Hospital of Botucatu Medical School between May/2019 and May/2021, with sepsis criteria identified by the SOFA score[1], using vancomycin for at least 72 h to reach its steady state[11], with a diagnosis of AKI according to KDIGO[3] and in AKRT (after the second dialysis session), and under modalities of HD, conventional and prolonged. Patients on chronic dialysis, kidney transplant recipients, pregnant women, and those whose dialysis sessions were interrupted for clinical or technical reasons were excluded.

The prescription of vancomycin followed a protocol instituted by the institution's Commission of Control of Infections Related to Health Assistance. It was administered in an initial dose of 25 mg/kg and 15 mg/kg/day after the hemodialysis session. The infusion time was 1 h. The trough concentrations/pre-dialysis between 15 and 20 mg/L were considered therapeutic[11].

All HD sessions were carried out by nursing technicians on the team, under the responsibility of the service nurse and physician. The prescription was performed according to the degree of hemodynamic instability: for patients with norepinephrine doses below 0.3mcg/kg/min, conventional intermittent HD (CIHD); norepinephrine doses between 0.3 and 0.6mcg/kg/min, prolonged intermittent HD (PIHD) for 6 h; norepinephrine doses above 0.6mcg/kg/min, PIHD for 10 h.

The patients were then submitted to a process of block randomization through the website Randomization.com (http://www.randomization.com) and allocated in 3 groups, according to the maintenance dose: Control Group: administration of vancomycin after the end of the HD session, in a single dose of 15 mg/kg for 1 h; Intervention Group 2 h: administration of 7.5 mg/kg of vancomycin in the 2nd hour of the HD session for 1 h, with another 7.5 mg/kg administered at the end of the procedure for 1 h; Intervention Group continuous infusion: administration of 30 mg/kg of vancomycin in a continuous infusion pump, for 24 h.

Proportion machines (Fresenius 4008) and high-flux polysulphone HD membranes (FX 60, FX 80, or FX 100), with surface areas of 1.6, 1.8, and 2.0 m^2, respectively, were used in CIHD and PIHD sessions. The CIHD sessions were carried out with a blood flow of 300 mL/min and a dialysate flow of 500 mL/min for 4 h. The PIHD session was carried out with a blood flow of 200 mL/min and a dialysate flow of 300 mL/min for 6–10 h.

During the sessions, patients were anticoagulated with 50 to 100 UI/kg of heparin in a bolus and 500–1000 UI/hour in the remaining hours. When anticoagulation was contraindicated, the system was cleaned with 50 to 100 mL of 0.9% sodium chloride every 30 min. Concentrations of bicarbonate (28–36 mEq/L), potassium (1–4 mEq/L), sodium (135–142 mEq/L), and calcium (2.5–3.5 mEq/L) in the dialysis bath were adjusted according to the patient's requirements and examinations. The ultrafiltration rate (UF) did not exceed 5 ± 3 mL/kg/hour[20].

Data were collected during routine care and extracted from electronic medical records. This information included demographic data, weight, height, calculated body mass index [Weight/(height)^2][21], comorbidities, the reason for hospitalization, infectious focus, APACHE II score[22], AKI prognostic score[23], diuresis, use of vasoactive drugs, use of loop diuretics, use of nephrotoxic drugs or those that present toxicity synergism (piperacillin-tazobactam, aminoglycosides, amphotericin B), laboratory data [serum urea pre and post-dialysis, serum albumin, serum hematocrit, serum C-reactive protein, culture results, minimum inhibitory concentration for vancomycin (a value of 1 mg/L was assigned for unknown results)[11], serum concentration of vancomycin before the start of the session], dialysis data [session time, ultrafiltration, received Kt/V[24], use of heparin, complications during the session (such as system coagulation or hypotension)]. The follow-up time was during the entire period of hospitalization until the clinical outcome and always by the same team.

The last administration of vancomycin was 24 h ago, after the previous hemodialysis session. Serial collection of blood samples (2mL each) was performed through the central venous catheter and dialysis effluent (2mL each) by the dialysis nursing team to determine serum and effluent concentrations of vancomycin before starting dialysis (T0), after 2 h (T2), at its end (Tfinal) and before the next session of HD (Fig. 1) were used to calculate the AUC/MIC24hours and the clearance of vancomycin by the therapy. AUC was determined using the trapezoidal method until the last non-zero time point. This procedure was performed twice per patient in two consecutive days with hemodialysis sessions.

The collected material was transferred to vacuum collection tubes (10 mL) containing Benton Dickinson gel and kept in styrofoam with a plate or refrigerator until the last collection day, when they were sent to the laboratory for separation and storage. The collection tubes with the material were duly identified with the patient's

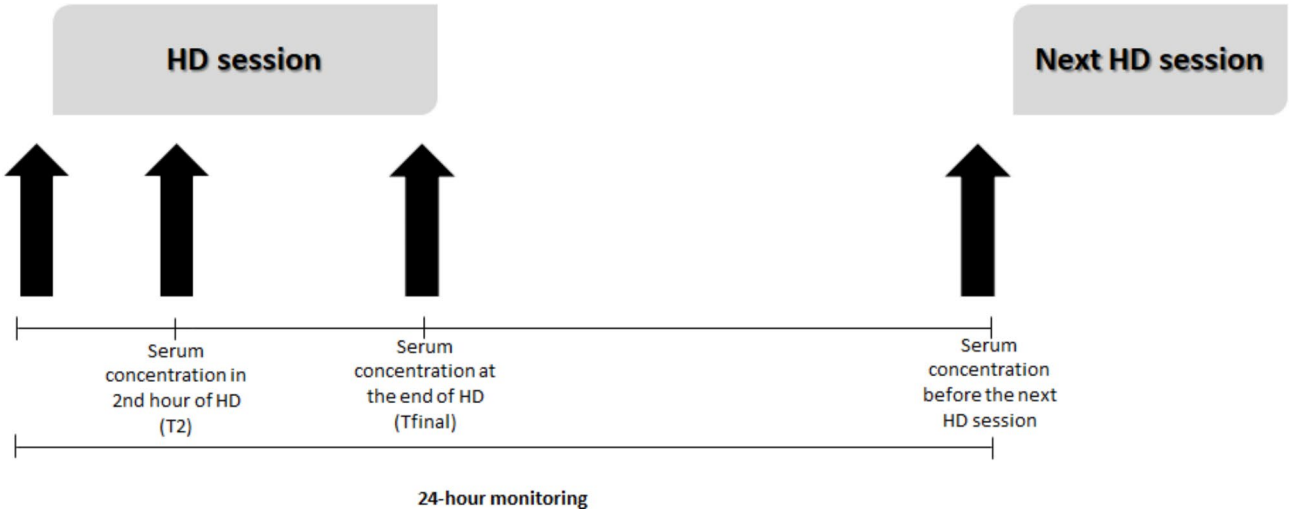

Fig. 1. Study protocol: serial collection of blood samples.

Pharmacokinetic	Formula
Distribution volume (L)	$\mathrm{DV} = \frac{\text{vancomycin dose (mg)}}{\text{vancomycin concentration (mg/L)}}$
Dialytic clearance of vancomycin (L/h)	$\mathrm{Cl\ vancomycin} = \frac{(\text{initial} - \text{final concentration}) \times \mathrm{QD}}{\text{initial concentration} \times \mathrm{t}}$
Half-life time	$\mathrm{T}^1/_2\ \mathrm{life} = \frac{0.693 \times \mathrm{DV}}{\mathrm{Cl}}$
% reduction in vancomycin	$\%\ \mathrm{red} = \frac{(\text{pre C HD} - \text{final C HD}) \times 100}{\text{pre C HD}}$

Table 1. Formulas used for Vancomycin pharmacokinetic calculations[19,27,28]. DV: distribution volume; Cl: *Clearance*; QD: dialysate flux (L/h); t: time in hours); T½ life: Half-life time; pre C HD: concentration of vancomycin pre hemodialysis; final C HD: concentration of vancomycin at the end of hemodialysis.

allocation number, and in the sequential order of the collections performed for each investigated patient, being sent for separation of the serum in a centrifuge (3000 g, 20 min), transfer of the serum to tubes of Eppendorf (2mL), duly identified and reserved to contain the biological matrix/serum. The matrices were packaged in cardboard boxes provided by the Analytical Laboratory and stored in a freezer (−80º C) with temperature control on a shelf reserved for the study protocol.

The quantification of vancomycin in the biological matrix was performed using a homogeneous enzyme Immunoassay (*Enzyme Multiplied Immunoassay Technique*- EMIT)[25]. Based on these results, the serum concentration of vancomycin at different times during dialysis was used to calculate pharmacokinetic data, as shown in Table 1. AUC was determined using the trapezoidal method up to the last non-zero time point[26].

Outcomes related to the therapeutic monitoring of vancomycin were evaluated for monitored dialysis sessions. Therapeutic concentrations were those between 15 and 20 mg/L before the HD session or with AUC/MIC24 hours between 400 and 600 mg·h/L.

Statistical analysis

Based on the study by Freitas et al.[29], the sample size was calculated using GPower 3.1 software, and considering non-independent samples, 27 sessions were necessary for each group (81 sessions). According to the study protocol, each patient had two monitored sessions. Therefore, at least 14 patients per group (42 patients) were required for an alpha error of 0.05 and a study power of 80%. Data were entered into an electronic spreadsheet, possible typing errors were checked, and their analysis was performed using the statistical program IBM SPSS 20 or Sigma Stat 3.5.

Data were expressed as means, standard deviation, median, and interquartile in descriptive statistics. Data were initially analyzed for distribution (Shapiro-Wilk normality W test). For continuous variables, the measures of central tendency were used: mean and standard deviation for those with normal distribution and median and interquartile for those with non-normal distribution. Frequency measures were used for categorical variables.

HD sessions were compared between dialysis modalities (CIHD and PIHD 6 and 10 h), control and intervention groups (2 h and continuous infusion), and later between AUC/MIC in therapeutic concentration. For continuous parametric variables, Student's t-test and ANOVA were used, and for non-parametric variables, the Mann-Whitney and Kruskall-Wallis tests were used, with Tuckey's post-test. The Chi-Square Test was used to compare categorical variables between groups.

A multivariate analysis was conducted using logistic regression models, calculating Odds Ratios (OR). All independent variables associated with the outcomes with $p \leq 0.20$, were included in the model. Statistical significance was set at $p < 0.05$.

Results

A total of 316 patients who used vancomycin in the ICU were recruited. However, only 87 could be included in the study (Fig. 2) and were randomized into three groups: control ($n = 28$, 56 HD sessions to be analyzed), 2-hour intervention ($n = 30$, 60 HD sessions to be analyzed), and continuous infusion intervention ($n = 29$, 58 HD sessions to be analyzed), as shown in Fig. 2. During follow-up, 28 patients were considered ineligible, and 12 dialysis sessions were withdrawn from the analysis due to technical interruption.

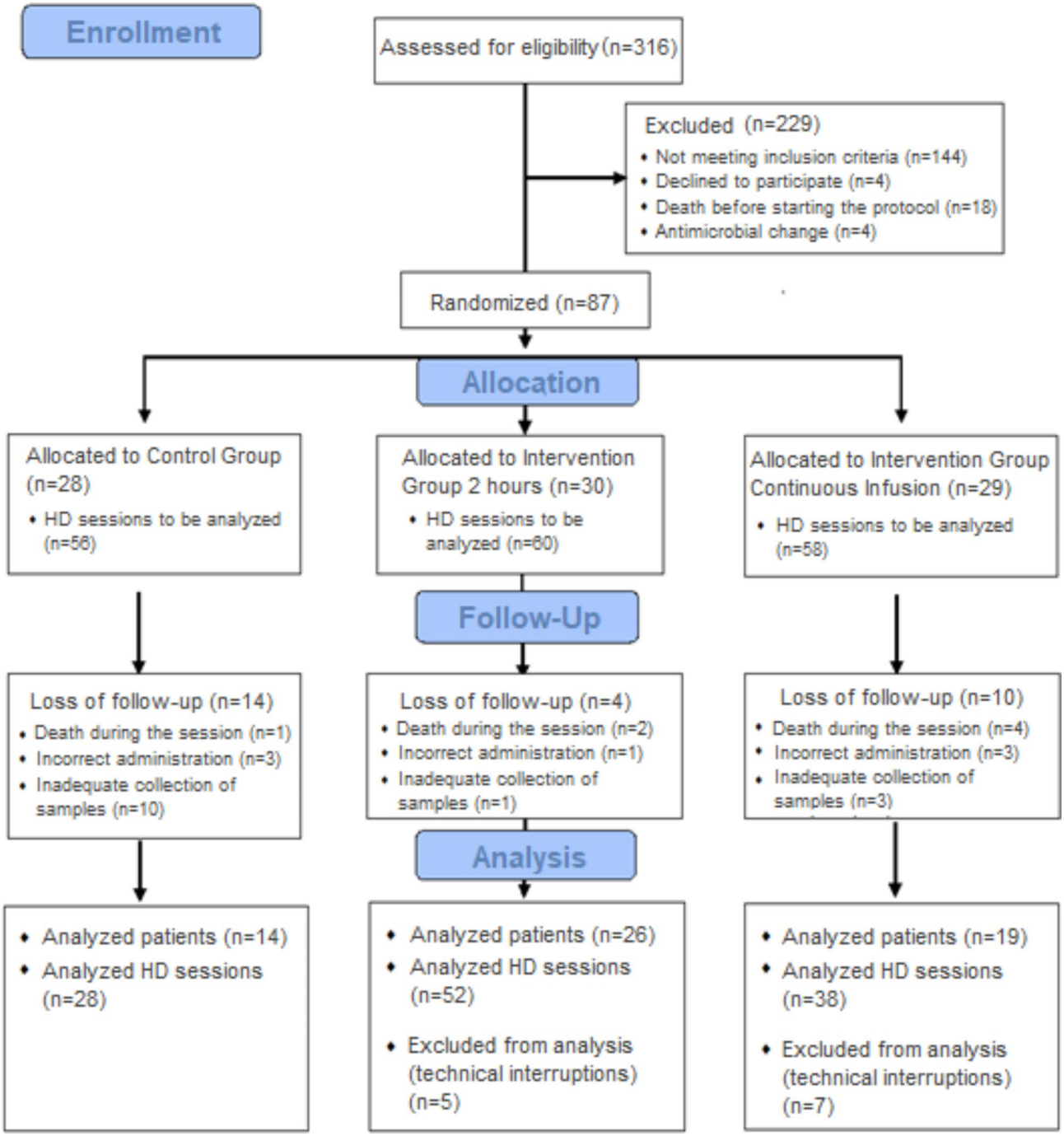

Fig. 2. Patient enrollment flowchart.Adapted from CONSORT 2010 Flow Diagram, available at http://www.consort-statement.org/.

Baseline characteristics

Among the 59 patients analyzed, there was a predominance of males (69.5%), aged 61 ± 11 years, and BMI of 26.23 (23.53–31.89). The main comorbidities were smoking (49%), systemic arterial hypertension (44.1%), and cardiovascular disease (27.1%). The patients' severity was assessed using the APACHE II prognostic score, with a mean of 31 ± 6, and the prognosis of AKI using the ATN-ISS score, with a mean of 0.79 ± 0.14. Their median diuresis was 150 (50–500) mL.

Admissions were predominantly due to infection (64.4%), followed by surgical (20.3%) and cardiovascular (18.6%) admissions. The main focus of infection under treatment was the lung (72.9%), with 64.4% of the patients having a positive culture. Of these, 23.7% detected a Gram-positive microorganism (14% with Staphylococcus aureus, 86% with negative Staphylococcus coagulase).

Of the 59 patients analyzed, 14 were allocated to the control group and 45 to the intervention groups (26 to the 2-hour protocol and 19 to the continuous infusion protocol). The median number of days of vancomycin use was 6 (5–10) days. The groups had no significant differences regarding clinical characteristics (age, BMI, comorbidities, baseline renal function, diuresis, use of diuretics or other nephrotoxic drugs) and laboratory characteristics (albumin, hematocrit, C-reactive protein).

Hemodialysis sessions

We analyzed 106 HD sessions, 61 (57.5%) CIHD and 45 (42.5%) PIHD, 34 for 6 h (32.1%), and 11 (10.4%) for 10 h. The groups were similar regarding intradialytic complications (hypotension and coagulation), received Kt/V, ultrafiltration, drug distribution volume, and initial and final vancomycin plasma concentrations.

Of the 106 HD sessions, 28 belonged to the control group, 47 sessions to the intervention group 2-hour, and 31 sessions to the intervention group continuous infusion. There was no difference between the groups regarding HD modality, Kt/V, ultrafiltration, intradialytic intercurrences (system coagulation or hypotension), or diuretics use. The continuous infusion intervention group received a higher daily dose of vancomycin compared to the other groups ($p < 0.0001$) and higher serum concentrations at times T0, T2, and Tfinal ($p < 0.0001$). The control group had a higher frequency of subtherapeutic serum concentrations at the end of HD and higher dialysis clearance ($p = 0.04$), as described in Table 2.

Table 3 shows the factors related to therapeutic and non-therapeutic vancomycin concentrations (AUC/MIC ratio between 400 and 600 mg·h/L and below 400 mg·h/L or above 600 mg·h/L, respectively). The intervention groups showed a higher therapeutic concentration frequency than the control group ($p < 0.002$). Smaller volume of distribution, a higher daily dose of vancomycin, and higher serum concentrations of vancomycin at T0, T2, and Tfinal were associated with AUC/MIC at the therapeutic concentration ($p < 0.0001$, $p = 0.001$, $p < 0.0001$, $p < 0.0001$ and $p < 0.0001$, respectively). There was no difference between the groups regarding HD modality, Kt/V, ultrafiltration, intradialytic intercurrences (system coagulation or hypotension), diuretic use, or serum concentration measured before the beginning of the HD session.

Variables	All of sessions ($N = 106$)	Control group ($N = 28$)	Intervention group 2 h ($n = 47$)	Intervention group continuous infusion ($n = 31$)	p-value
HD MODALITIES					0.06
CIHD (%)	61 (57.5)	17 (56.7)	23 (51.5)	21 (67.7)	
PIHD 6 h (%)	34 (32.1)	9 (30)	20 (44.4)	5 (16.1)	
PIHD 10 h (%)	11 (10.4)	4 (13.3)	2 (4.4)	5 (16.1)	
System coagulation (%)	20 (18.9)	8 (26.7)	7 (15.6)	5 (16.1)	0.43
Hypotension (%)	34 (32.1)	11 (36.7)	15 (33.3)	8 (25.8)	0.64
Diuretic (%)	37 (34.9)	15 (50)	12 (26.7)	10 (32.3)	0.1
Ultrafiltraion (ml)	2500 (1500–2800)	2500 (2000–3000)	2500 (0–2800)	2000 (1700–2500)	0.17
Received Kt/v	0.91 ± 0.3	0.9 ± 0.25	0.9 ± 0.31	0.93 ± 0.33	0.89
Distribution volume (l/kg)	**0.74 ± 0.37**	**0.83 ± 0.4[b]**	**0.6 ± 0.32[a]**	**0.85 ± 0.37[b]**	**0.006**
Daily dose of vancomycin (mg)	**1200 (1000–1500)**	**1050 (900–1250)[b]**	**1110 (900–1260)[b]**	**1800 (1350–2300)[a]**	**< 0.0001**
T0 concentration (mg/l)	**26.21 ± 9.33**	**19.51 ± 5.41[c]**	**27.08 ± 9.84[b]**	**31.43 ± 7.75[a]**	**< 0.0001**
T2 concentration (mg/l)	**20.84 ± 7.62**	**14.22 ± 4.05[c]**	**21.36 ± 6.52[b]**	**26.49 ± 6.91[a]**	**< 0.0001**
T final concentration (mg/l)	**16.91 (12.41–21.9)**	**11.14 (8.9–13.59)[c]**	**16.26 (13.71–20.5)[b]**	**23.37 (20.67–25.36)[a]**	**< 0.0001**
Dialytic clearance (L/h)	**1.78 ± 1.15**	**2.09 ± 1.4[b]**	**1.84 ± 1.05[b]**	**1.38 ± 0.91[a]**	**0.04**
Reduction in 2 h (%)	**19.6 ± 13**	**25.35 ± 13.43[a]**	**18.58 ± 13.95[b]**	**15.5 ± 8.94[b]**	**0.009**
Total reduction (%)	**33.04 ± 14.72**	**39.9 ± 15.65[b]**	**35.1 ± 13.61[b]**	**23.42 ± 10.06[a]**	**< 0.0001**
Half life time (h)	**52.52 ± 39.3**	**32 ± 27.4[b]**	**27.08 ± 25.64[b]**	**82.29 ± 66.21[a]**	**0.002**

Table 2. Dialytic and Pharmacokineti/Pharmacodynamic characteristics in all of sessions and in the control and intervention groups (2 h and continuous infusion). a: significantly different from b; c: significantly different from a and b; ab: similar to a and b. CIHD: conventional intermittent hemodialysis; PIHD: prolongated intermittent hemodialysis; HD: hemodialysis; T0: initial time; T2: second hour; Tfinal: end of the session; AUC/MIC: area under the curve/minimum inhibitory concentration.

Variables	All of sessions ($N=106$)	AUC/MIC in non-therapeutic concentration ($N=82$)	AUC/MIC in therapeutic concentration ($n=24$)	p-value
HD modalities				0.4
CIHD (%)	61 (57.5)	48 (58.5)	13 (54.2)	
PIHD 6 h (%)	34 (32.1)	24 (29.3)	10 (41.7)	
PIHD 10 h (%)	11 (10.4)	10 (12.2)	1 (4.2)	
Group				**0.002**
Control (%)	**28 (26.5)**	**30 (36.6)**	**0 (0)[a]**	
Intervention 2 h (%)	**47 (44.3)**	**31 (37.8)**	**14 (58.3)[b]**	
Intervention continuous infusion (%)	**31 (29.2)**	**21 (25.6)**	**10 (41.7)[b]**	
System coagulation (%)	20 (18.9)	18 (22)	2 (8.3)	0.23
Hypotension (%)	34 (32.1)	27 (32.9)	7 (29.2)	0.72
Diuretic (%)	37 (34.9)	30 (36.6)	7 (29.2)	0.5
Previous concentration of vancomycin (mg/l)	23.42 (18.73–27.6)	23.01 (17.6–26.19)	25.6 (21.92–29.9)	0.11
Ultrafiltration (ml)	2500 (1500–2800)	2500 (1500–3000)	2250 (1000–2500)	0.62
Kt/v	0.91 ± 0.3	0.9 ± 0.31	0.93 ± 0.25	0.66
Distribution volume (l/kg)	**0.74 ± 0.37**	**0.81 ± 0.38**	**0.5 ± 0.21**	**< 0.0001**
Daily dose of vancomycin (mg)	**1200 (1000–1500)**	**1150 (900–1275)**	**1500 (1200–1800)**	**0.001**
T0 concentration (mg/l)	**26.21 ± 9.33**	**23.29 ± 8.16**	**36.15 ± 5.37**	**< 0.0001**
T2 concentration (mg/l)	**20.84 ± 7.62**	**18.98 ± 7.36**	**27.19 ± 4.41**	**< 0.0001**
T final concentration (mg/l)	**16.91 (12.41–21.9)**	**14.36 (10.83–20.28)**	**23.35 (20.17–24.98)**	**< 0.0001**
Dialytic clearance (L/h)	1.78 ± 1.15	1.77 ± 1.21	1.8 ± 0.91	0.89
Reduction in 2 h (%)	19.6 ± 13	18.45 ± 12.32	25.53 ± 14.69	0.09
Total reduction (%)	33.04 ± 14.72	32.38 ± 14.69	35.3 ± 14.92	0.39
Half life time (h)	52.52 ± 39.3	56.76 ± 43.15	31.8 ± 26.16	0.16

Table 3. Characteristics associated with the prescription of Vancomycin and its pharmacodynamics and pharmacokinetics in the general population about therapeutic concentration (AUC/MIC between 400 and 600 mg·h/L) and non-therapeutic (AUC/MIC less than 400 mg·h/L or greater than 600 mg·h/L) of the antimicrobial. a: significantly different from b. AUC/MIC: area under the curve/minimum inhibitory concentration; HD: hemodialysis; CIHD: conventional intermittent hemodialysis; PIHD: prolongated intermittent hemodialysis; T0: initial time; T2: second hour; Tfinal: end of the session.

Variables	OR	Confidence interval	p-value
Daily dose of vancomycin	1.001	1.000–1.002	0.12
Subtherapeutic concentration at the end of HD	5.734	0.563–58.391	0.14
T0 concentration	**1.163**	**1.061–1.275**	**0,001**
Intervention group 2 h	**0.239**	**0.058–0.978**	**0,04**

Table 4. Binary logistic regression of variables associated with non-therapeutic concentration (AUC/MIC less than 400 mg·h/L or greater than 600 mg·h/L) of Vancomycin. AUC/MIC: area under the curve/minimum inhibitory concentration; OR: Odds Ratio; HD: hemodialysis; T0: initial time.

When the two groups were analyzed using binary logistic regression, the initial concentration variable was identified as a risk factor for a non-therapeutic concentration (AUC/MIC less than 400 mg·h/L or greater than 600 mg·h/ L) of vancomycin (OR 1.16, $p=0.001$). In contrast, the 2-hour intervention group was identified as a protective factor (OR 0.24, $p=0.04$), as shown in Table 4.

Discussion

Considering that critically ill patients with sepsis who have AKI and require AKRT have high mortality and, combined with pharmacokinetic changes in this population, removing vancomycin by hemodialysis can lead to subtherapeutic concentrations, leading to the selection of resistant mutants and higher mortality.

This non-blinded randomized clinical trial aimed to compare different vancomycin administration protocols to assess serum concentrations and AUC/MIC from PK/PD during hemodialysis sessions. Were analyzed 106 sessions (57.5% CIHD and 42.5% PIHD) with similar groups. The half-life was shorter in the group that underwent the CIHD session. The half-life time is directly proportional to the volume of distribution and inversely proportional to the dialytic clearance, justifying the lower value found in this modality.

Of the 106 HD sessions, 28 belonged to the control group, 47 sessions to the intervention group 2 h, and 31 sessions to the intervention group continuous infusion. The last one received a higher daily dose of vancomycin

than the other groups and higher serum concentrations at times T0, T2, and Tfinal, justified by the clinical protocol for administering vancomycin at higher doses.

The control group had a higher frequency of subtherapeutic serum concentrations at the end of HD (86.7% of the sessions). A study by Freitas et al.[29], evaluating the removal of vancomycin by different dialysis methods with high-flux membranes based on pharmacokinetic-pharmacodynamic modeling (PK/PD) in critically ill patients with AKI, identified that 46.34% of patients had lower AUC/MIC than 400, with 84.2% of patients on PIHD and 15.8% on CIHD. Dialysis clearance was more significant in the first two hours of therapy. In logistic regression, PIHD was a risk factor for AUC/MIC lower than 400 mg·h/L (OR = 11.59, $p = 0.033$).

According to the most current guideline on the use of vancomycin[11], maintaining the pre-dialysis concentration between 15 and 20 mg/L seems to be reasonable to reach the AUC/MIC target between 400 and 600 mg·h/L since data confirming this association for patients on hemodialysis are scarce in the literature, with information extrapolated from the non-dialysis population[30]. Most studies on antimicrobial doses in critically ill patients on dialysis have been performed in people treated by continuous therapy[31–33].

On the other hand, PIHD is still the main dialysis method used in developing countries. Most studies on antimicrobials in HD have been performed in patients with chronic kidney disease (CKD) receiving HD three times a week. PIHD consists of a hybrid method with characteristics of CIHD and continuous HD. Studies addressing antimicrobial dosage are even scarcer in this type of HD[34,35], often with inadequate dosage leading to subtherapeutic concentrations[36–38].

Nephrotoxicity is associated with more extended hospital stays, costs, and mortality[39], a significant concern for healthcare teams. In our study, both intervention groups, 2 h and continuous infusion, showed higher AUC/MIC at 24 h compared to the control group.

When assessing the variables related to therapeutic (AUC/MIC ratio between 400 and 600 mg·h/L) and non-therapeutic concentrations of vancomycin (below 400 mg·h/L or above 600 mg·h/L), the intervention groups showed a higher frequency of therapeutic concentration compared to the control group. A smaller volume of distribution, a higher daily dose of vancomycin, and higher serum concentrations of vancomycin both at the beginning and end of the session were associated with AUC/MIC at a therapeutic level. In logistic regression, the initial concentration variable was identified as a risk factor for a non-therapeutic concentration (AUC/MIC less than 400 mg·h/L or greater than 600 mg·h/L) of vancomycin (OR 1.16, $p = 0.001$). In contrast, the intervention group 2 h was identified as a protective factor (OR 0.24, $p = 0.04$).

This study has some limitations. Data analysis at a single academic center limits its generalizability. Assistant physicians, Nursing staff, patients, and family members knew which vancomycin administration scheme had been randomized, making blinding impossible. However, this was the first clinical study with a randomized design that evaluated the AUC/MIC ratio during both conventional and prolonged hemodialysis sessions in septic patients with AKI under different vancomycin administration regimens.

Our results suggest that administering vancomycin during dialysis proved to be a protective factor against concentrations outside the therapeutic target. Further studies are needed to suggest more appropriate doses of vancomycin for patients with AKI on dialysis therapy and to assess the impact of these results on clinical outcomes.

Data availability

No datasets were generated or analysed during the current study.

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Author contributions

All authors were involved in study design and concept. W.Z and D.P. analyzed the data. W.Z. drafted the manuscript; all authors reviewed and edited the manuscript and approved the final version.

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Competing interests

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