Vancomycin therapeutic drug monitoring in patients on continuous renal replacement therapy: a retrospective study

Yuyan Liu [ID], Li Jiang, Ran Lou [ID],
Meiping Wang and Quan Si

Abstract

Objectives: This study aimed to investigate vancomycin therapeutic drug monitoring (TDM) in patients on continuous renal replacement therapy (CRRT) and explore the risk factors for exceeding the target concentration.

Methods: This retrospective study enrolled patients aged ≥ 18 years who were admitted to the intensive care unit and treated with ≥ 3 intravenous vancomycin doses during CRRT, and who underwent vancomycin TDM. Demographic and other information were collected. Multivariate logistic regression was used assess the risk factors for exceeding the target concentration.

Results: Sixty-nine patients were included, and 40.6% patients underwent TDM. Additionally, 14.5% of patients reached the optimal concentration, and 87.5% of patients who exceeded the target received a daily dose adjustment. The cumulative dose of vancomycin and serum albumin were risk factors for exceeding the target concentration in patients on CRRT.

Conclusions: Patients on CRRT did not meet the optimal vancomycin management; $<50\%$ of the patients routinely received vancomycin TDM, and $<15\%$ achieved the optimal concentration. Fewer patients in the subtherapeutic group received a daily dose adjustment than those who exceeded the target concentration. Cumulative vancomycin and serum albumin doses before TDM were the risk factors for exceeding the target concentration in CRRT patients.

Department of Critical Care Medicine, Xuanwu Hospital, Capital Medical University, Beijing 10053, China

Corresponding author:
Li Jiang, Department of Critical Care Medicine, Xuanwu Hospital, Capital Medical University, 45 Changchun Street, Xicheng District, Beijing 100053, China.
Email: jianglipaper@sina.com

Introduction

The Infectious Diseases Society of America (IDSA) indicates that the clinical efficacy of severe methicillin-resistant *Staphylococcus aureus* (MRSA) infection is closely related to the vancomycin trough concentration. To confirm the efficacy and safety, a loading dose that is based on the actual body weight should be administered, and trough concentrations should be obtained before the fourth or fifth dose under steady-state conditions. The subsequent dosage adjustment should be administered on the basis of the actual trough concentration to achieve the optimal target of 15 to 20 mg/L.[1]

When patients on continuous renal replacement therapy (CRRT) receive vancomycin for sepsis, vancomycin clearance becomes complex. CRRT parameters[2–6] and patient conditions[7] may affect vancomycin pharmacokinetics (PK)/pharmacodynamics (PD). For example, continuous venovenous hemodiafiltration (CVVHDF) clearance of vancomycin was 1.3- to 7.2-times greater than that of other types of CRRT.[3] Additionally, severe hypoalbuminemia influenced the half-life of vancomycin in older patients.[7] Inappropriate therapeutic drug monitoring (TDM) time points and nonalternative daily doses may lead to a trough concentration that does not achieve the optimal target and contributes to adverse clinical outcomes.[8] Previous studies showed that the vancomycin trough concentration in CRRT patients has a wide variability.[9–13]

The purpose of this study was to investigate vancomycin TDM in patients on CRRT and explore the risk factors of vancomycin trough concentrations that exceeded the target.

Methods

Study design and data collection

This retrospective observational study was performed at the Department of Critical Care, a general intensive care unit (ICU) with 24 beds in a tertiary hospital in Beijing from 1 January 2014 to 31 December 2019. Because this was a retrospective study, the requirement for patient consent was waived by the ethics committee at Fuxing Hospital, Capital Medical University (approval notice number: 2013FXHEC-KY018).

The inclusion criteria were as follows: age ≥18 years; admitted to ICU; received CRRT; and treated with ≥3 doses intravenous vancomycin during CRRT. The exclusion criterion was patients who did not receive TDM.

Sex, age, body mass index (BMI), comorbidities, creatinine clearance (calculated using the Cockcroft–Gault formula), serum albumin level before TDM, Acute Physiology and Chronic Health Evaluation II (APACHE II), survival at day 28, infection sites, and etiology were collected. The following vancomycin parameters were recorded: daily dose, intermittent or continuous infusion, TDM time point (TDM before the fourth or fifth dose of vancomycin), trough concentration, and alternative therapy. The following CRRT parameters were recorded: mode (continuous venovenous hemofiltration [CVVH] or continuous venovenous hemodiafiltration [CVVHDF]), blood flow rate (mL/minute), dose (mL/kg/hour) in the CRRT effluent volume, duration (hours; including cumulative CRRT working hours, which is the CRRT machine run time from the first vancomycin dose administered for TDM from which the circuit priming time is subtracted), and the cumulative dose (L/kg; the product of duration and dose [duration was unchanged]).

The enrolled patients were divided into the following two groups on the basis of a trough concentration of 20 mg/L: nonexceeding target group and exceeding target group.

Vancomycin hydrochloride injection was manufactured by of Eli Lilly Japan KK,

Seishin (Kobe, Japan). Each bottle contained 0.5 g of vancomycin. The CVVH was performed using Prismaflex with the PRISMAFLEX ST150 SET filter (Deerfield, IL, USA). The CVVHDF was performed using a Multifiltrate, and the filter was Fresenius AV600S (Fresenius, Bad Homburg, Germany). An Abbott ARCHITECT i1000 immunoassay analyzer (Abbott, Abbott Park, IL, USA) with a quality control box and standard curve box administered fluorescence polarization immunoassay were used for the vancomycin TDM.

Statistical analysis

Continuous data were presented as the mean ± standard deviation (SD) or as the median and interquartile range (IQR). Categorical data were presented as the number and percentage. A Student's t-test and the Mann–Whitney U test were used to compare continuous data. The Chi-square test and Fisher's exact test were used to compare categorical data. Multivariate logistic regression was used to analyze the risk factors associated with a vancomycin trough concentration that exceeded the target. Additionally, a P value <0.05 was considered to be statistically significant. Statistical analyses were conducted using SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Study population and characteristics

Four hundred eighty-seven patients who were admitted to the ICU and underwent CRRT were enrolled into our study. Among them, 119 patients were treated with vancomycin and 69 patients received TDM (Figure 1).

Among these 69 patients who received TDM, the median age was 77.0 (56.0, 83.5) years, 35 (50.7%) were men, and the median BMI was 22.9 (20.6, 26.7) kg/m^2. Most patients had comorbidities (63, 91.3%), and 42 (60.7%) patients had died at day 28 in the ICU.

Among all of the included patients, 43 (62.3%) patients had pneumonia, ten (14.5%) patients had a bloodstream infection, 13 (18.8%) patients had an abdominal infection, and three (4.3%) patients had a urinary tract infection. Among all the included patients, 27 (39.1%) patients had MRSA.

Vancomycin TDM and daily dose adjustment

All included patients received vancomycin by intermittent infusion, and each infusion time was greater than 1 hour.

More patients received vancomycin TDM in 2018 and 2019 than those in 2014 to 2017 (75.0% versus 48.0%, $P = 0.004$). There were five (7.2%) patients who received TDM before the third dose, and 28 (40.6%) patients who received TDM before the fourth or fifth dose. There were 36 (52.2%) patients who received TDM after the fifth dose. Fourteen (20.3%) patients were administered a loading dose.

Ten (14.5%) patients achieved the optimal concentration of 15 to 20 mg/L. A subtherapeutic concentration (<15 mg/L) was observed in 27 (39.1%) patients, and 32 (46.4%) patients had a concentration >20 mg/L.

Thirty-nine (66.1%) patients received a daily dose adjustment. Among them, 11 patients with a concentration <15 mg/L and 28 patients with a concentration >20 mg/L received alternative therapy for their daily dose (40.7% versus 87.5%, $P < 0.001$).

CRRT parameters

There were 50 (72.5%) patients who underwent CVVH and 29 (27.5%) patients who
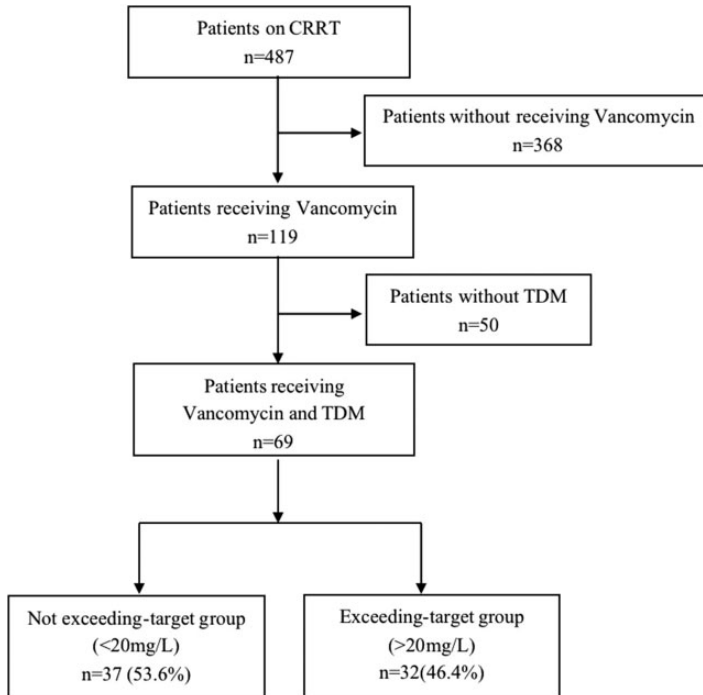
Figure 1. Flowchart of patient inclusion in the study.

underwent CVVHDF. Among all included patients, the blood flow rate was 120 (120, 150) mL/minute. The therapeutic dose was 26.7 (25.0, 30.0) mL/kg/hour. The CRRT duration was 46.0 (34.0, 67.0) hours, and the cumulative dose was 1.17 (0.91, 1.74) L/kg.

Risk factors for a vancomycin concentration exceeding the optimal target in patients on CRRT

The exceeding target group seemed to have a lower BMI and received a higher cumulative dose of vancomycin before TDM compared with that of the nonexceeding group (Tables 1 and 2).

The cumulative dose of vancomycin (odds ratio [OR]: 1.505, 95% confidence interval [CI]: 1.066–2.125) and serum albumin (OR: 1.204, 95%CI: 1.001–1.449) were the risk factors for a concentration exceeding the optimal target. The cumulative

CRRT dose (OR: 0.264, 95%CI: 0.091–0.767) and BMI (OR: 0.816, 95%CI: 0.683–0.976) (Table 3) could reduce the risk of the concentration exceeding the optimal target.

Discussion

In our study, patients on CRRT did not achieve optimal vancomycin management. Fewer than half of the patients on CRRT routinely received vancomycin TDM, and less than 15% of these patients achieved the optimal concentration. On the basis of the trough concentration, fewer patients in the subtherapeutic group (which included patients whose vancomycin trough concentration was less than 15 mg/L) received an daily dose adjustment than those in the exceeding target group. The cumulative dose of vancomycin and serum albumin before TDM were risk factors for the

Table 1. Demographics, baseline, and comorbidities.

	Total (n = 69)	Nonexceeding target (n = 37)	Exceeding target (n = 32)	P-value
Sex (male), n (%)	35 (50.7)	20 (54.1)	15 (46.9)	0.552
Age (years)	77.0 (56.0,83.5)	73.0 (50.0,81.5)	78.0 (65.0,85.0)	0.253
BMI (kg/m^2)	22.9 (20.6,26.7)	23.9 (21.7,27.3)	21.7 (19.5,25.6)	0.015
APACHE II	23.8 ± 8.1	22.9 ± 8.5	25.0 ± 7.4	0.310
Dead at 28-day, n (%)	42 (60.9)	25 (67.6)	17 (53.1)	0.220
Creatinine clearance (mL/minute)	14.7 (10.3, 24.5)	17.2 (11.3,27.9)	14.2 (9.1,19.7)	0.108
Serum albumin (g/L)	24.0 ± 5.0	23.9 ± 5.3	24.2 ± 4.6	0.813
Comorbidities, n (%)				
Cardiovascular diseases	56 (81.2)	28 (75.7)	28 (87.5)	0.236
Respiratory diseases	5 (7.2)	4 (10.8)	1 (3.1)	0.363
Endocrine diseases	28 (40.6)	14 (37.8)	14 (43.8)	0.618
Cerebrovascular diseases	30 (43.5)	14 (37.8)	16 (50.0)	0.309
Chronic renal diseases	30 (43.5)	14 (37.8)	16 (50.0)	0.309
Immunological diseases	7 (10.1)	6 (16.2)	1 (3.1)	0.113
Malignancy	12 (17.4)	6 (16.2)	6 (18.8)	0.782

BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II.

Table 2. Vancomycin therapy and CRRT parameters.

	Total (n = 69)	Nonexceeding target (n = 37)	Exceeding target (n = 32)	P-value
Loading dose, n (%)	14	9 (24.3)	5 (15.6)	0.370
Cumulative dose before TDM (g)	3.5 (2.0,6.0)	3.0 (1.8,3.8)	4.3 (3.0,7.8)	0.002
Time point of TDM	5.0 (2.0,8.0)	4.0 (3.0,7.0)	5.0 (4.0,9.8)	0.211
CRRT mode, n (%)				0.129
CVVH	50 (72.5)	24 (64.9)	26 (81.2)	
CVVHDF	19 (27.5)	13 (35.1)	6 (18.8)	
Blood flow rate (mL/minute)	120 (120,150)	120 (120,150)	120 (120,143)	0.365
Duration (hours)	46.0 (34.0,67.0)	46.0 (34.0,78.0)	40.0 (30.0,58.0)	0.101
Dose (mL/kg/hour)	26.7 (25.0,30.0)	25.5 (24.0,30.0)	29.9 (25.0,30.5)	0.079
Cumulative dose (L/kg)	1.17 (0.91,1.74)	1.38 (0.92,1.92)	1.14 (0.87,1.64)	0.189

CRRT, continuous renal replacement therapy; TDM, therapeutic drug monitoring; CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration.

concentration exceeding the optimal target in patients on CRRT.

Vancomycin clinical efficacy is closely related to its trough concentration. To confirm the efficacy and safety, a dose regimen on the basis of a trough concentration target of 15 to 20 mg/L is recommended by IDSA. Providing a loading dose on the basis of the actual body weight rather than on the basis of the empirical dose is recommended to attain the optimal concentration as soon as possible. When obese patients receive vancomycin for infection, the loading dose should be increased,[14] while in our study, fewer patients received a loading dose.

The previous dose regimen was based on vancomycin TDM. The study performed by Ye et al. showed that nearly 50% of

Table 3. The risk factors for the vancomycin concentration exceeding the target in patients on CRRT.

Variables	OR (95%CI)	*P*-value
BMI	0.816 (0.683–0.976)	0.026
Creatinine clearance	0.941 (0.884–1.000)	0.051
Serum albumin	1.204 (1.001–1.449)	0.049
Cumulative dose before TDM	1.505 (1.066–2.125)	0.020
CRRT mode	3.031 (0.601–15.274)	0.179
CRRT cumulative dose	0.264 (0.091–0.767)	0.014

CRRT, continuous renal replacement therapy; BMI, body mass index; TDM, therapeutic drug monitoring OR, odds ratio; CI, confidence interval.

patients received TDM and that the TDM group had a significantly higher rate of clinical efficacy and a significantly decreased risk of nephrotoxicity compared with those without TDM.[15] Some studies[16–19] with a small sample size showed that 10% to 60% of patients received vancomycin TDM, which was a large variation. Vancomycin clearance is complex in patients on CRRT, which means that physician should monitor vancomycin trough concentration particularly in CRRT patients.

Vancomycin will reach a stable trough concentration after the third or fourth dose, so TDM should be performed before the fourth or fifth dose. Additionally, the daily dose should be adjusted on the basis of the measured trough concentration. Van Der Heggen et al. showed that delayed sampling occurred in 16% of adults,[20] while over half of the patients received vancomycin TDM later than recommended in our study. In many tertiary hospitals in China, vancomycin TDM is only available on weekdays during working hours, and thus, TDM and the daily dose adjustment may be delayed, which may lead to a concentration that exceeds the optimal target. Therefore, balancing the supply and demand in the pharmacology and clinical departments seems to be important. Moreover, the clinical department should provide supervision for vancomycin TDM and improve its

awareness to prevent a missed test resulting from human-related issues.

There were only 14.5% patients whose TDM met the optimal target range of 15 to 20 mg/L in our study. Al-Maqbali et al. showed that the vancomycin therapeutic level was not achieved in 16.8% of patients, and 47.5% of them had high vancomycin levels (>20 mg/L),[8] which was consistent with our study results. Subtherapeutic concentrations were measured by Van Der Heggen in 68% of adults in their study, showing that it is common for vancomycin TDM to not meet the optimal target.[20] When patients on CRRT receive vancomycin for sepsis, vancomycin clearance is complex and trough concentrations may be uncertain. Subtherapeutic concentrations may lead to inadequate drug efficacy and supertherapeutic concentrations may aggravate renal failure. Thus, vancomycin TDM should be carefully monitored in CRRT patients, but few studies have focused on them. The purpose of our study was to highlight the vancomycin regimen in CRRT patients.

Bakke et al. studied 245 patients who received vancomycin. When the concentration was not within the target concentration range, only 46.2% of patients received an adjustment.[21] Clinicians in our study were watching more carefully for supertherapeutic concentrations because more patients

(87.5% versus 40.7%) in this group received a daily dose adjustment. When excessive serum levels were observed, clinicians decreased the daily dose and provided extra vancomycin if subtherapeutic concentrations occurred.

Hypoproteinemia may increase vancomycin clearance by CRRT. Vancomycin shows approximately 55% protein binding, and only free drug can be cleared by CRRT.[20,22] When patients with hypoproteinemia receive vancomycin, the increasing amount of free drug can be cleared more easily by CRRT, leading to concentrations that do not meeting the target.

Different CRRT modes and doses will affect vancomycin clearance.[23–25] The adequacy of CRRT can decrease the occurrence of excessive concentration.[26–28] Some studies showed that a higher CRRT dose was closely related to subtherapeutic concentrations.[13,29,30] In our study, a lower cumulative CRRT dose led to the supertherapeutic vancomycin concentrations.

Additionally, some studies showed that other factors influenced the vancomycin concentration. Lin et al.[31] and Covajes et al.[32] suggested that when patients are undergoing CRRT, it was easier to achieve and maintain the target concentration with continuous vancomycin infusion compared with intermittent infusion.

Our study results showed that patients on CRRT did not meet optimal vancomycin management. The physician should administer TDM at the correct time point, and the individualized drug regimen should be administrated on the basis of the trough concentration results.[33–36]

Our study had some limitations. This was a retrospective study at a single center, and although the observation time was extended, the number of patients who met the inclusion criteria was small. Thus, selection bias might exist. Additionally, we did not exclusively analyze medications such as exogenous albumin, diuretics, and citrate anticoagulation.

Conclusions

Patients on CRRT did not meet optimal vancomycin management requirements. Fewer than half of the patients routinely received vancomycin TDM, and less than 15% of them achieved the optimal concentration. On the basis of the trough concentration, fewer patients in the subtherapeutic target group received a daily dose adjustment compared with those in the group that exceeded the target. The cumulative dose of vancomycin and serum albumin before TDM were risk factors for a concentration exceeding the target in patients on CRRT.

Author contributions

YL and LJ designed the study. YL performed data collection. YL and LJ analyzed data and drafted the manuscript. YL and LJ were in charge of overall direction and planning and contributed to reviewing and editing the manuscript. All authors contributed to editing the manuscript for important intellectual content and approved the final manuscript.

Additional data

There are no additional data.

Declaration of conflicting interest

The author declares that there is no conflict of interest.

Ethics approval

The Ethics Committee at Fuxing Hospital, Capital Medical University approved the present

study (Approval Notice Number: 2013FXHEC-KY018) and waived the requirement for patient consent because of its retrospective nature.

Research checklist

This paper is not associated with any research checklist.

Statement

Study participants or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

ORCID iDs

Yuyan Liu https://orcid.org/0000-0001-6571-2082
Ran Lou https://orcid.org/0000-0002-7437-0528

References

1. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health-Syst Pharm* 2009; 66: 82–98.
2. Joy MS, Matzke GR, Frye RF, et al. Determinants of vancomycin clearance by continuous venovenous hemofiltration and continuous venovenous hemodialysis. *Am J Kidney Dis* 1998; 31: 1019–1027.
3. DelDot ME, Lipman J and Tett SE. Vancomycin pharmacokinetics in critically ill patients receiving continuous venovenous haemodiafiltration. *Br J Clin Pharmacol* 2004; 58: 259–268.
4. Wilson FP and Berns JS. Vancomycin levels are frequently subtherapeutic during continuous venovenous hemodialysis (CVVHD). *Clin Nephrol* 2012; 77: 329–331.
5. Körtge A, Majcher-Peszynska J, Heskamp B, et al. Antibiotics removal by continuous venovenous hemofiltration with a novel asymmetric triacetate membrane hemofilter: an in vitro study. *Blood Purif* 2021; 50: 899–905.
6. Ackerman BH, Taylor EH, Olsen KM, et al. Vancomycin serum protein binding determination by ultrafiltration. *Drug Intell Clin Pharm* 1988; 22: 300–303.
7. Mizuno T, Mizokami F, Fukami K, et al. The influence of severe hypoalbuminemia on the half-life of vancomycin in elderly patients with methicillin-resistant Staphylococcus aureus hospital-acquired pneumonia. *Clin Interv Aging* 2013; 8: 1323–1328.
8. Al-Maqbali JS, Shukri ZA, Sabahi NA, et al. Vancomycin therapeutic drug monitoring (TDM) and its association with clinical outcomes: a retrospective cohort. *J Infect Public Health* 2022; 15: 589–593.
9. Li L, Li X, Xia Y, et al. Recommendation of antimicrobial dosing optimization during continuous renal replacement therapy. *Front Pharmacol* 2020; 11: 786.
10. Roberts JA, Joynt GM, Lee A, et al. The effect of renal replacement therapy and antibiotic dose on antibiotic concentrations in critically ill patients: data from the multinational SMARRT study. *Clin Infect Dis* 2021; 72: 1369–1378.
11. Trotman RL, Williamson JC, Shoemaker DM, et al. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. *Clin Infect Dis* 2005; 41: 1159–1166.
12. Wahby KA, Cunmuljaj L, Mouabbi K, et al. Evaluation of dosing strategies and trough concentrations of vancomycin in patients undergoing continuous venovenous hemofiltration. *Pharmacotherapy* 2021; 41: 554–561.
13. Petejova N, Martinek A, Zahalkova J, et al. Vancomycin pharmacokinetics during high-volume continuous venovenous hemofiltration in critically ill septic patients. *Biomed*

Pap Med Fac Univ Palacky Olomouc Czech Repub 2014; 158: 65–72.

14. Smit C, Wasmann RE, Goulooze SC, et al. Population pharmacokinetics of vancomycin in obesity: finding the optimal dose for (morbidly) obese individuals. *Br J Clin Pharmacol* 2020; 86: 303–317.

15. Ye ZK, Tang HL and Zhai SD. Benefits of therapeutic drug monitoring of vancomycin: a systematic review and meta-analysis. *PLoS ONE* 2013; 8: e77169.

16. Chu Y, Wang Z, Shen J, et al. Evaluation of vancomycin monitoring in our hospital based on the "China vancomycin therapeutic drug monitoring guidelines". *China Pharmacovigilance* 2017; 14: 54–57.

17. Li B, Cui X, Wang Y, et al. Monitoring and analysis of blood concentration of vancomycin in 73 Cases. *Chinese Journal of Clinical Pharmacology* 2015; 31: 128–130.

18. Yu Z, Zhao H, Yu Q, et al. Monitoring and analysis of vancomycin blood concentration in Peking University People's Hospital in 2015. *Abstract Collection of Papers of National Academic Annual Conference on Therapeutic Drug Monitoring* 2016; 1: 43.

19. Yan Y. Analysis of vancomycin concentration of 119 cases of vancomycin in our hospital. *Electronic Journal of Clinical Medicine Literature* 2018; 5: 12–13.

20. Van Der Heggen T, Buyle FM, Claus B, et al. Vancomycin dosing and therapeutic drug monitoring practices: guidelines versus real-life. *Int J Clin Pharm* 2021; 43: 1394–1403.

21. Bakke V, Sporsem H, Von der Lippe E, et al. Vancomycin levels are frequently subtherapeutic in critically ill patients: a prospective observational study. *Acta Anaesthesiol Scand* 2017; 61: 627–635.

22. Chen J, Li S, Wang Q, et al. Optimizing antimicrobial dosing for critically ill patients with MRSA infections: a new paradigm for improving efficacy during continuous renal replacement therapy. *Pharmaceutics* 2022; 14: 842.

23. Kirwan M, Munshi R, O'Keefe H, et al. Exploring population pharmacokinetic models in patients treated with vancomycin during continuous venovenous haemodiafiltration (CVVHDF). *Crit Care* 2021; 25: 443.

24. Lewis SJ and Mueller BA. Development of a vancomycin dosing approach for critically ill patients receiving hybrid hemodialysis using Monte Carlo simulation. *SAGE Open Med* 2018; 6: 1–10.

25. Yamazaki S, Tatebe M, Fujiyoshi M, et al. Population pharmacokinetics of vancomycin under continuous renal replacement therapy using a polymethylmethacrylate hemofilter. *Ther Drug Monit* 2020; 42: 452–459.

26. Böhler J, Donauer J and Keller F. Pharmacokinetic principles during continuous renal replacement therapy: drugs and dosage. *Kidney Int Suppl* 1999; 56: S24–S28.

27. Omrani AS, Mously A, Cabaluna MP, et al. Vancomycin therapy in critically ill patients on continuous renal replacement therapy: are we doing enough? *Saudi Pharm J* 2015; 23: 327–329.

28. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012; 120: c179–c184.

29. Frazee EN, Kuper PJ, Schramm GE, et al. Effect of continuous venovenous hemofiltration dose on achievement of adequate vancomycin trough concentrations. *Antimicrob Agents Chemother* 2012; 56: 6181–6185.

30. Roberts DM, Liu X, Roberts JA, et al. A multicenter study on the effect of continuous hemodiafiltration intensity on antibiotic pharmacokinetics. *Crit Care* 2015; 19: 84.

31. Lin H, Bukovskaya Y, De Moya M, et al. Vancomycin continuous infusion versus intermittent infusion during continuous venovenous hemofiltration: slow and steady may win the race. *Ann Intensive Care* 2015; 5: 10.

32. Covajes C, Scolletta S, Penaccini L, et al. Continuous infusion of vancomycin in septic patients receiving continuous renal replacement therapy. *Int J Antimicrob Agents* 2013; 41: 261–266.

33. Charoensareerat T, Chaijamorn W, Boonpeng A, et al. Optimal vancomycin dosing regimens for critically ill patients with acute kidney injury during continuous renal replacement therapy: a Monte Carlo

simulation study. *J Crit Care* 2019; 54: 77–82.

34. Beumier M, Roberts JA, Kabtouri H, et al. A new regimen for continuous infusion of vancomycin during continuous renal replacement therapy. *J Antimicrob Chemother* 2013; 68: 2859–2865.

35. Oda K, Jono H, Kamohara H, et al. Development of vancomycin dose individualization strategy by Bayesian prediction in patients receiving continuous renal replacement therapy. *Pharm Res* 2020; 37: 108.

36. Chen J, Huang X, Lin Z, et al. Case report: monitoring vancomycin concentrations and pharmacokinetic parameters in continuous veno-venous hemofiltration patients to guide individualized dosage regimens: a case analysis. *Front Pharmacol* 2021; 12: 763575.