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Vancomycin optimised dosing regimens for critically ill patients receiving renal replacement therapy

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Abstract

Background Optimal dosing of vancomycin in critically ill patients receiving renal replacement therapy (RRT) is uncertain due to high pharmacokinetic variability. We aimed to develop individualised vancomycin dosing recommendations that optimise efficacy while minimising toxicity.

Methods Prospective, international, pharmacokinetic study enrolling critically ill patients treated with vancomycin and various RRT modalities. A population pharmacokinetic model was developed, externally validated and applied to perform Monte Carlo dosing simulations. We calculated the probability of each dosing regimen to achieve the efficacy target against methicillin-resistant *Staphylococcus aureus* (ratio of the area under the concentration–time curve to the minimum inhibitory concentration ($AUC_{0\text{-}24\ h}$/MIC) ≥ 400) without exceeding the toxicity threshold ($AUC_{0\text{-}24\ h}$ ≥ 700 mg.h/L).

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Results We enrolled 65 critically ill patients from 6 countries receiving continuous RRT (50.8%) or sustained low-efficiency dialysis (49.2%). The model was developed using 1318 pre- and post-filter plasma and effluent concentrations and validated with a new dataset (19 critically ill patients, 124 pre-filter plasma concentrations), with 47.4% patients concomitantly treated with extracorporeal membrane oxygenation. Predictive performance was high (median prediction error = —13.4%). Simulations showed that dosing requirements were dependent on actual body weight and RRT intensity and duration ($p < 0.05$). An optimised dosing nomogram was subsequently developed considering these clinical characteristics.

Conclusions Actual body weight and RRT intensity and duration are the main determinants of vancomycin dosing requirements in critically ill patients treated with RRT. Efficacious, non-toxic dosing may be guided by the optimised nomogram.

Keywords Vancomycin, Renal replacement therapy, Intensity, Actual body weight, Dosing nomogram

Background

Severe acute kidney injury (AKI) that requires renal replacement therapy (RRT) is a major complication of sepsis in critically ill patients, and it is associated with mortality rates that can be up to 50% higher than those observed in non-septic patients with AKI [1, 2]. In this context, early, appropriate and optimally-dosed antibiotic therapy is crucial for improving patient outcomes [3]. Vancomycin is a frequently used antibiotic for the treatment of severe infections caused by methicillin-resistant *Staphylococcus aureus*. Belonging to the glycopeptide antibiotics, it is a large hydrophilic molecule that exhibits moderate and variable protein binding (40 – 55%), is eliminated primarily by the kidneys, and is significantly cleared with RRT [4]. With regards to efficacy, in vitro and observational clinical studies with *S. aureus* have related optimal activity to total exposure, quantified as the ratio of the area under the concentration–time curve over 24 h ($AUC_{0\text{-}24\,h}$) to the minimum inhibitory concentration (MIC) of the bacteria, with an optimal target for efficacy defined as $AUC_{0\text{-}24\,h}/MIC \geq 400$ [5, 6]. However, its use in clinical practice is limited by renal toxicity, for which it has a relative contraindication in patients with acute and acute-on-chronic renal failure [7]. Nevertheless, vancomycin has a clear role for treating severe Gram-positive infections; in such cases, the benefit-risk balance should be carefully evaluated, and dosing exquisitely adjusted to minimise toxicity while ensuring efficacy. For this reason, therapeutic drug monitoring (TDM) is strongly recommended by major clinical guidelines [5, 6]. Despite this, data from critically ill patients receiving different forms of RRT show that vancomycin exposure is subtherapeutic in over 50% of cases and supratherapeutic in 25%, owing to the drug's difficult-to-predict pharmacokinetics (PK) [8–10]. Consequently, universal dosing recommendations for vancomycin during RRT have not yet been successfully defined, making this one of the most difficult drugs to dose correctly in critically ill patients, particularly given that these patients may concomitantly be receiving other extracorporeal treatments such as extracorporeal membrane oxygenation (ECMO).

In this study, we aimed to describe the PK of vancomycin and its sources of variability in a large cohort of critically ill patients with AKI receiving RRT and externally validate the associated development model in a second cohort of patients. Using these data, we sought to develop generalizable dosing nomograms that optimise efficacy while minimising the likelihood of drug-associated toxicity.

Methods

The SaMpling Antibiotics in Renal Replacement Therapy (SMARRT) study was an international, prospective, observational PK study that included critically ill patients with AKI requiring RRT from 29 intensive care units (ICUs) in 14 countries across Europe, America and the Asia–Pacific region between December 2011 and March 2017.

Adult critically ill patients with a clinical indication for vancomycin and with severe AKI [11] receiving RRT with continuous veno-venous hemofiltration (CVVHF), hemodialysis (CVVHD), hemodiafiltration (CVVHDF) or intermittent sustained low-efficiency dialysis (SLED) for an expected duration of at least 4 days were included in the study. Exclusion criteria were imminent death, major bleeding, severe anaemia or thrombocytopenia, or treatment with vancomycin for more than 36 h within the 7 days before enrolment [12]. All patients or their legal representatives provided written informed consent before enrolment. To increase sample size and generalizability of the results, additional patient data were included from contemporary PK studies at participating sites with similar entry criteria and data collection methods [13, 14]. The SMARRT study was approved at the lead site by the Royal Brisbane and Woman's Hospital Human Ethics Research Committee (HREC/13/QRBW/1), and participating sites also obtained individual ethics approvals from their respective local committees. The study

protocol and the clinical results of this research have been published elsewhere [8, 12].

Antibiotic dosing, data collection and blood sampling

Vancomycin dosing and RRT settings were at the discretion of the treating clinical team. Demographic, clinical and analytical data were collected at ICU admission and on the days of sampling. Pharmacokinetic sampling was performed over a dosing interval on one or two occasions. The first occasion occurred on days 1—2 after commencing vancomycin, and the second occasion on days 3—6 of therapy. Plasma samples from pre- and post-filter RRT ports, as well as effluent fluid samples were collected using a rich sampling strategy (~10 samples from each port of the RRT circuit per patient). A detailed description of data and sample collection, handling and bioanalysis has been published elsewhere [12, 15] and is provided in the Supplementary Material.

Pharmacokinetic analysis

Individual $AUC_{0\text{-}24\ h}$ values for descriptive analysis of the included patients were obtained by non-compartmental analysis using Phoenix WinNonlin™ version 8.5.2.4 (Certara, Radnor, PA, USA). Population PK modelling and validation were performed using the non-linear mixed-effects modelling software Monolix 2024R1 (Lixoft SAS, Antony, France) [16]. A detailed description of model development and validation methodology is provided in the Supplementary Material.

An integrated population PK model was developed for total and unbound vancomycin pre-filter and post-filter plasma, and effluent concentrations [17]. One- and multi-compartment models with linear elimination were evaluated, and clearance (CL) was modelled as CL mediated by RRT (CL_{RRT}) and CL independent of RRT (CL body, CL_{body}). During the statistical analysis, the covariates sex, age, actual body weight, Sepsis-related Organ Failure Assessment (SOFA) [18] and Acute Physiology and Chronic Health disease Classification System (APACHE) II [19] severity scores, 24 h urine output, albumin plasma concentration, bilirubin plasma concentration, RRT settings including intensity (calculated as dialysate flow rate + replacement fluid flow rate), modality, blood flow, membrane surface in m^2, membrane type (brand and material) and transmembrane pressure at the begginning of the sampling period were tested for inclusion in the model. Of these covariates, those that clinically and significantly explained variability in CL and volume of distribution (V) were retained in the final model following a stepwise forward inclusion—backward elimination process.

Internal validation of the models was based on goodness-of-fit (GOF) plots, a prediction-corrected visual predictive check (pc-VPC) and non-parametric bootstrapping (n = 1000) [20, 21]. The a priori and a posteriori predictive performance of the PK model were assessed using data from patients receiving RRT who were not included in the model development process. Population predicted pre-filter plasma concentrations were obtained using the population PK model (a priori performance), and Bayesian forecasting was used to obtain individual predicted concentrations (a posteriori performance) [22]. Bias and precision were assessed by median (individual) prediction error (MPE, IMPE) and median (individual) absolute prediction error (MAPE, IMAPE) respectively. We also calculated F20 and F30, which indicate the percentages of MPE that fall within the ± 20% and ± 30% ranges respectively, representing a combined index of both accuracy and precision. The predictive performance of the model was considered excellent if MPE and MAPE ≤ ± 20%, and acceptable if MPE ≤ ± 20%, MAPE ≤ 30%, F20 ≥ 35%, and F30 ≥ 50% [23–25]. Furthermore, the population predictions were compared with the observed concentrations using the modified Bland–Altman plot [22].

Monte Carlo simulations and probability of target attainment for efficacy and toxicity

Monte Carlo simulations were performed with the final covariate model using the Simulx 2024R1 (Lixoft SAS) simulation software to generate 1000 PK profiles of total vancomycin pre-filter plasma concentrations for different dosing regimens.

For the simulations, it was assumed that RRT was initiated prior to the start of vancomycin therapy. Therefore, Days 1 and 2 were considered the initial treatment phase, while day 4 was assumed to represent steady state, accounting for the lowest CRRT intensity. *As per* current dosing recommendations for critically ill patients, an initial loading dose of vancomycin administered over a short infusion (≤ 2 h) was always simulated [6]. For CRRT, intermittent maintenance dosing was simulated to begin 12 h after the loading dose. For SLED, intermittent maintenance dosing was simulated to begin 12 h after the loading dose and during a SLED-off period (separated from the initiation of SLED by 12 h), reflecting clinical practice in the included studies [7] and in accordance with current recommendations. For both CRRT and SLED, continuous infusion was simulated to start immediately after the loading dose. A detailed description of the dosing simulations methodology by RRT modality and duration is provided in the Supplementary Material.

The pharmacokinetic/pharmacodynamic target associated with treatment success was defined taking into account 1) an efficacy target of $AUC_{0\text{-}24\ h}$/MIC ≥ 400 for *S. aureus* [6] and; 2) a toxicity threshold of $AUC_{0\text{-}24\ h}$ ≥ 700 mg.h/L in line with current clinical guidelines [6]. For each dosing regimen, we calculated

Table 1 Demographical and clinical characteristics of the patients included in the model development and model validation datasets

Variable	Model development dataset (n = 65) [13, 14]	Rich sampling validation dataset (n = 19) [30, 31]	TDM validation dataset (n = 27) [32]
Males (%)	41 (63.1%)	14 (73.7%)	20 (74.1%)
Age (years)	59.5 (49.8 – 74.2)	46 (35 – 53)	70.5 (60.5 – 79.5)
Body weight (kg)	82 (70—98.5)	80 (70 – 100)	78 (67.5 – 92)
APACHE II score at admission	28 (23 – 31)	17 (12 – 27.5)	n/a
Primary suspected or confirmed source of infection (number of episodes)[a]			
Respiratory	9	n/a	17
Abdominal	6	n/a	9
Urinary tract	6	n/a	4
Skin and soft tissue	2	n/a	2
Central venous catheter-related	2	n/a	0
Bone and joint	1	n/a	1
Cardiac	1	n/a	2
With concomitant bloodstream infection	7	n/a	n/a
Clinical and analytical variables (on the day of sampling occasion 1)			
SOFA score	10 (8 – 12)	12 (7 – 14.5)	14 (11 – 16)*
Use of vasopressors	58 (89.2%)	n/a	22 (81.5%)*
Mechanical ventilation	51 (78.5%)	n/a	23 (85.2%)*
Urine output (mL/24 h)	15 (0 – 40)	< 50 (qualitative data)	First 48 h: 500 (100 – 800) 48 – 96 h: 100 (14 – 305)
Urine output 0—499 mL/24 h (%)	51 (78.5%)	19 (100%)	First 48 h: 53.3% 48 – 96 h: 83.3%
Urine output ≥ 500 mL/24 h (%)	14 (21.5%)	0 (0%)	First 48 h: 46.7% 48 – 96 h: 16.7%
Serum creatinine (μmol/L)	300 (199.3 – 422.3)	161 (106 – 202)	154 (102.5 – 215.5)*
Serum albumin (g/L)	22 (20 – 26)	24 (22.5 – 28)	23 (19 – 29.3) *
Haematocrit (proportion)	0.26 (0.23 – 0.28)	0.26 (0.26 – 0.28)	n/a
Antibiotic daily dosing on the day of the study (mg)	Patients receiving CRRT: 2000 (1000 – 3000) Patients receiving SLED: 1000 (1000—1500)	Patients receiving CRRT: 2000 (1500 – 2000) Patients receiving SLED: 1000 (1000 – 1000)	1998.4 (1575.5 – 2128.8)
Day of sampling since vancomycin initiation	0 (0 – 1)	n/a (mostly first 24 h)	0 (0 – 1)
Administration of a loading dose	3 (5.2%) [c]	n/a	25 (92.6%)
$AUC_{0\text{-}24\ h}$/MIC on the first day of sampling [b]	Patients receiving CRRT: 523.6 (330.7 – 845.4) [d] Patients receiving SLED: 311.9 (263 – 414) [d]	No sufficient data	628.8 (490.8 – 724.2)
Subtherapeutic exposure ($AUC_{0\text{-}24\ h}$ /MIC < 400) on the first day of sampling	Patients receiving CRRT: 37.9%, $AUC_{0\text{-}24\ h}$/MIC: 316.2 (200.8 – 362.2) Patients receiving SLED: 71.4%, $AUC_{0\text{-}24\ h}$/MIC: 287.1 (246.1 – 343.0)	No sufficient data	9.6%
Supratherapeutic exposure ($AUC_{0\text{-}24\ h}$ /MIC > 700) on the first day of sampling	Patients receiving CRRT: 34.5%, $AUC_{0\text{-}24\ h}$/MIC: 883.2 (819.1 – 923.1) Patients receiving SLED: 4.7%, $AUC_{0\text{-}24\ h}$/MIC: 311.9 (only 1 subject)	No sufficient data	30.8%
RRT parameters			
RRT modality			
CVVHF	22 (33.9%)	0 (0%)	23 (85.2%)
CVVHD	5 (7.7%)	3 (15.8%)	4 (14.8%)
CVVHDF	6 (9.2%)	5 (26.3%)	0 (0%)

Table 1 (continued)

Variable	Model development dataset (n = 65) [13, 14]	Rich sampling validation dataset (n = 19) [30, 31]	TDM validation dataset (n = 27) [32]
SLED	32 (49.2%)	11 (57.9%)	0 (0%)
Concomitant ECMO	0 (0%)	9 (47.4%)	0 (0%)
Filter membrane type			n/a
Acrylonitrile & sodium methallyl sulfonate	2 (3.1%)	0 (0%)	n/a
Polyethersulfone	47 (72.3%)	0 (0%)	n/a
Polysulfone	16 (24.6%)	10 (52.6%)	n/a
Blend of polyarylethersulfone, polyvinylpyrrolidone, polyamide	0 (0%)	0 (0%)	n/a
Polyarylethysulfone	0 (0%)	0 (0%)	n/a
Unknown	0 (0%)	9 (47.4%)	n/a
Filter surface			
0.7 m^2	30 (46.2%)	0 (0%)	n/a
0.9 m^2	0 (0%)	0 (0%)	n/a
1 m^2	1 (1.5%)	0 (0%)	n/a
1.2 m^2	2 (3.1%)	0 (0%)	n/a
1.3 m^2	1 (1.5%)	7 (36.8%)	n/a
1.4 m^2	13 (20%)	3 (15.8%)	n/a
1.5 m^2	5 (7.7%)	0 (0%)	n/a
1.8 m^2	5 (7.7%)	0 (0%)	n/a
1.9 m^2	4 (6.2%)	0 (0%)	n/a
2 m^2	4 (6.2%)	0 (0%)	n/a
Unknown	0 (0%)	9 (47.4%)	n/a
Blood flow rate for SLED (mL/min)	200 (200 – 200)	300 (300 – 300)	Not applicable
Dialysate flow rate for SLED (mL/h)	18,000 (18,000 – 18,000)	21,000 (21,000 – 21,000)	Not applicable
Blood flow rate for CRRT (mL/min)	220 (175—250)	200 (200 – 250)	250 (200—250)*
Dialysate flow rate for CVVHD and CVVHDF (mL/h)	1700 (1000—2400)	n/a	2000 (2000 – 2400)*
Replacement fluid rate for CVVHF and CVVHDF (mL/h)	3000 (3000 – 6020)	n/a	2500 (1850 – 3000)*
RRT intensity for CRRT (mL/h) [e]	3000 (2400 – 5000)	1500 (1500 – 2738)	3000 (2200 – 3000)*
Duration for SLED (h)	8 (8 – 8)	8 (8 – 10)	Not applicable
ICU mortality	29 (44.6%) [d]	n/a	11 (44.5%)
28-days mortality	30 (46.2%) [d]	n/a	n/a

Continuous variables are summarised as median (quartile 1 (Q1) – quartile 3 (Q3)), discrete variables are described as absolute count (n, percentage (%)). APACHE II score: Acute physiology and chronic health evaluation II score, SOFA score: sepsis-related organ failure assessment score, RRT: renal replacement therapy, CRRT: continuous renal replacement therapy, CVVHF: continuous veno-venous hemofiltration, CVVHD: continuous veno-venous hemodialysis, CVVHDF continuous veno-venous hemodiafiltration, SLED: sustained low-efficiency dialysis, n/a: not available, ([a]): data available for 27 patients, ([b]): $AUC_{0\text{-}24\ h}$ have been calculated with non-compartmental analysis and MIC is generalised to 1 mg/L as recommended [6], ([c]): data available for 57 patients, ([d]): $AUC_{0\text{-}24\ h}$ was calculable with non-compartmental analysis in 51 patients, ([e]): RRT intensity calculated as dialysate flow rate + replacement fluid flow rate, (*): these patients were under a therapeutic drug monitoring program over several days; data marked with (*) correspond to the first sampling occasion

the probability of target attainment (PTA) assuming a conservative MIC of 1 mg/L given the described difficulties in *S. aureus* MIC measurement in clinical practice [6] and the potential impact of subtherapeutic exposure on the emergence or selection of heteroresistant subpopulations of *S. aureus* [26]. Although the epidemiological cut-off and the clinical breakpoint for vancomycin are 2 mg/L for *S. aureus*, [27, 28] we considered that vancomycin may not be an appropriate option for isolates with MIC > 1 mg/L in patients with severe AKI requiring RRT, because the $AUC_{0\text{-}24\ h}$ required to achieve an $AUC_{0\text{-}24\ h}$/MIC ≥ 400 would lead to an unnaceptably high risk of toxicity [29]. The optimal PTA for efficacy was defined as ≥ 90%. Based on these results, a dosing nomogram was developed including regimens that provided the highest joint likelihood of achieving effective and non-toxic exposures.

Results

A total of 65 patients comprising the model development dataset were enrolled from 10 ICUs in 6 countries. Of these, 27 patients were recruited under the SMARRT study protocol and 38 patients were included from contemporary studies with similar inclusion criteria [13, 14].

Most patients were male (63.1%), with a median age of 59.5 years, receiving invasive ventilation (78.5%) and vasoactive drugs (89.2%); most were treated with vancomycin for respiratory infections. With respect to RRT modalities, 50.8% of patients were receiving CRRT (33.9% CVVHF, 7.7% CVVHD and 9.2% CVVHDF), while 49.2% were receiving intermittent RRT as 8 h SLED sessions, with a wide range of intensities. The median daily vancomycin dose was 1000 mg, usually administered as 1—2 h short infusions (98.5%), and most patients did not receive a loading dose. Importantly, a high proportion of the enrolled patients exhibited an inappropriate vancomycin exposure at the first sampling occasion (most often corresponding to the first day of therapy); 53.7% had subtherapeutic exposures ($AUC_{0\text{-}24\ h}$/MIC < 400), while 19% had exposures in the range associated with toxicity ($AUC_{0\text{-}24\ h}$/MIC > 700). Underexposure predominantly occurred in patients not receiving a loading dose.

Table 2 Vancomycin population pharmacokinetic parameter estimates for the final model and bootstrap results

Parameter	Population estimate (RSE %) [Shrinkage %]	Median bootstrap estimates (95% CI)
Fixed effects		
V_c (L)	19.6 (8.9)	19.1 (13.7 -23.2)
CL_{RRT} (L/h)	1.2 (12.3)	1.3 (0.87—1.8)
CL_{body} (L/h)	0.67 (6.9)	0.66 (0.001—0.88)
V_p (L)	31.3 (6.8)	30.6 (25.8 – 39.7)
Q (L/h)	14.6 (10.4)	14.8 (11.1 -20.5)
$fu\ C_{pre}$	0.80 (1.5)	0.80 (0.77 – 0.83)
$fu\ C_{post}$	0.75 (1.3)	0.75 (0.73—0.77)
$\theta_{INTENSITY_CL_RRT}$	0.64 (18.4)	0.57 (0.37—0.88)
θ_{WEIGHT_Vc}	1.2 (25.6)	1.2 (0.64—1.7)
θ_{WEIGHT_Vp}	0.97 (23.9)	0.94 (0.45—1.6)
Random effects		
IIV on V_c	0.59 (12.3) [21.5]	0.57 (0.41—0.89)
IIV on CL_{RRT}	0.74 (15.7) [8.5]	0.65 (0.41 – 1)
IIV on V_p	0.48 (10.3) [10.4]	0.51 (0.37—0.66)
IIV on Q	0.62 (16) [26.8]	0.59 (0.31—0.96)
Residual error		
Proportional error C_{pre}	0.17 (3.3)	0.17 (0.14—0.2)
Proportional error C_{post}	0.10 (7.3)	0.10 (0.09—0.12)
Proportional error $C_{pre,\ unbound}$	0.14 (7.3)	0.13 (0.10—0.16)
Proportional error $C_{post,\ unbound}$	0.11 (7.7)	0.11 (0.09—0.13)
Proportional error C_{effl}	9.5 (7.8)	8.4 (4.5 -12.3)

V_c: volume of distribution of the central compartment, CL_{RRT}: CL mediated via RRT; CL_{body}: body CL; V_p: volume of distribution of the peripheral compartment; Q: intercompartmental clearance; fu: unbound fraction, $\theta_{INTENSITY_CL_RRT}$: effect of RRT intensity (L/h) on CL_{RRT}; $\theta_{INTENSITY_Vc}$: effect of RRT intensity on V_c; θ_{WEIGHT_Vc}: effect of body weight on V_c; θ_{WEIGHT_Vp}: effect of body weight on V_p; IIV: inter- individual variability reported as standard deviation of the random effects; C_{pre}: pre-filter plasma total vancomycin concentration; C_{post} – post-filter plasma total vancomycin concentration; $C_{pre,\ unbound}$: pre-filter plasma unbound vancomycin concentration;; $C_{post,\ unbound}$: post-filter plasma unbound vancomycin concentration C_{effl}: effluent vancomycin concentration; RSE: relative standard error; CI: confidence interval

Demographic and clinical characteristics of the enrolled patients are summarised in Table 1 and Tables A—B Supplementary Material.

Population PK modelling

The final population PK model was developed using 678 pre-filter plasma concentrations (119 unbound), 285 post-filter plasma concentrations (111 unbound) and 125 effluent fluid concentrations (total 1088 samples collected) from the 65 enrolled patients. The structural model that best described vancomycin PK was a two-compartment model with central and peripheral volumes of distribution (V_c and V_p respectively) and linear CL from the central compartment. Actual body weight and RRT intensity were the covariates that significantly influenced V_c, V_p (body weight) and CL_{RRT} (RRT intensity; $p < 0.05$), and explained their variability. The final population PK model is summarised in Table 2. Internal diagnostics (Table 2 and Figures A, B and C Supplementary Material) supported the adequacy of the model structure and parameter estimates.

Rich sampling validation

External validation was performed using a separate rich sampling cohort dataset comprising anuric critically ill patients receiving RRT enrolled in two prospective PK studies (rich sampling dataset, n = 19, 124 pre-filter plasma concentrations) [30, 31]. In this validation dataset, 11 patients receiving SLED were treated with notably higher intensities compared to the development dataset (21 L/min vs 18 L/min respectively), whereas those receiving CRRT were managed with lower intensities (1.5 L/min vs 3 L/min), predominantly using CVVHDF. Importantly, 9 patients (47.4%) were receiving ECMO concomitantly with CRRT [30]. Despite these differences in treatment characteristics, the results of the external validation with the rich sampling dataset were as follows: MPE (interquartile interval, IQI)—13.4% (IQI—42.7% to 9.4%), IMPE 2.3% (IQI—9.1% to 8.3%), MAPE 23.0% (IQI 11.3% to 44.0%) and IMAPE 8.6% (IQI 4.4% to 14.3%). Overall, 57.3% of observations were within 30% of the MPE (F30) and 43.5% within the 20% of the MPE (F20). These data suggest good a priori predictive performance for the model, consistent with the modified Bland–Altman plot (Fig. 1).

TDM validation

Additionally, we aimed to assess the predictive performance of the model using real-life TDM data from patients with sepsis treated with continuous infusion of vancomycin (TDM dataset, n = 27, 104 pre-filter plasma concentrations) [32]. These patients also differed notably from the development dataset, particularly in terms of residual urine output: 46.7% had urine

outputs ≥ 500 mL/24 h during the first 24 h of therapy, compared with 21.5% in the development dataset. For this TDM dataset, the external validation results were: MPE 81.9% (IQI 49.7% to 123.6%), IMPE 1.4% (IQI -4.0% to 11.1%), MAPE 81.9% (IQI 49.7% to 123.6%) and IMAPE 6.5% (IQI 2.8% to 13.3%). The a priori prediction was therefore not acceptable for the TDM dataset, with a consistent bias towards overestimation of total vancomycin concentrations. However, Bayesian forecasting (a posteriori prediction) markedly reduced individual prediction errors (IMPE and IMAPE) to < 10%, with the greatest improvement observed in the TDM dataset. Figures D and E in the Supplementary Material show the GOF plots for the a priori and a posteriori predictions for the external validation of both datasets.

Dosing simulations

Monte Carlo simulations were performed for the first 96 h (days 1 to 4) for different short (i.e. 1—2 h) and continuous infusion regimens that reflected usual prescriptions in the ICU [8]. Different actual body weights at admission, RRT intensities and SLED durations were tested, accounting for the covariates included in the model. The PTA for each dosing regimen at steady state are detailed in the Supplementary Material (Supplementary Spreadsheet Files 1—4). Dosing simulations indicate that, similar to patients not receiving RRT, the vancomycin loading dose in patients receiving RRT is primarily determined by body weight at admission and can be simplified using a weight stratification to 1500 mg for patients weighing 70—90 kg and 2000 mg for those weighing 90 – 120 kg. Maintenance dosing requirements depend largely on RRT intensity and, in the case of SLED, on the duration of therapy. Across all the tested body weights and RRT intensities and durations, the optimal daily dose achieved similar efficacy and toxicity targets whether the drug was administered as a continuous infusion or as a short (1-h) infusion, given once or twice daily; however, continuous infusion resulted in more stable drug concentrations over time. In all scenarios, achieving a favorable balance between efficacy and toxicity was challenging because of vancomycin's narrow therapeutic range. Table 3 provides the dosing nomogram for optimised vancomycin dosing in short and continuous infusion for the first 96 h of therapy stratified by actual body weight, RRT duration and intensity. Recommended dosing regimens are optimised for maximal joint efficacy and toxicity targets, prioritising a PTA for efficacy ≥ 90% given the severity of these infections.

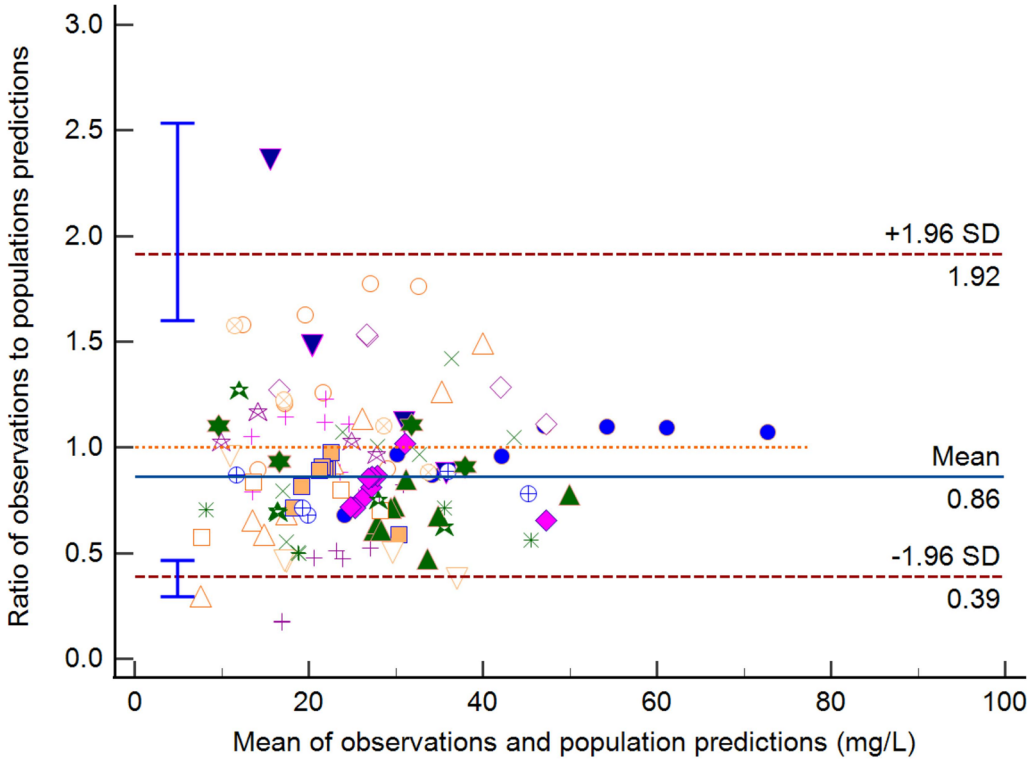


Fig. 1 Modified Bland–Altman plot of the ratio (mg/L) mean of vancomycin observed total concentrations to population predicted concentrations from the external validation using the rich sampling dataset. The solid blue line represents the mean difference (bias), and dashed red lines represent the superior and inferior 95% limits of agreement (with their exact 95% CI as solid vertical blue lines). The different symbols represent each individual patient

Discussion

To our knowledge, this represents the largest and most comprehensive prospective multicenter study of vancomycin PK in critically ill patients receiving RRT. The main findings are that vancomycin PK are highly variable in this population but can be largely explained by actual body weight and by the intensity and duration of RRT. Consequently, dosing requirements are primarily driven by these variables, irrespective of the specific RRT modality used. Across all tested scenarios, the most appropriate daily dose achieved comparable efficacy and toxicity targets when administered either as a continuous or an intermittent infusion, allowing clinicians to select the administration mode according to each individual patient's context. The novel nomograms provide optimised dosing recommendations stratified by body weight, RRT duration and intensity. Importantly, the external validation supports the use of these nomograms in oligoanuric patients receiving RRT and ECMO concomitantly.

Optimising vancomycin dosing is a priority in critically ill patients with AKI receiving RRT because of the delicate balance between achieving therapeutic exposure and avoiding toxicity, as well as the highly variable PK associated with fluctuating RRT settings and delivery in unstable patients. In fact, compelling evidence indicates that up to 50% of patients experience inadequate vancomycin exposure [8, 9]. Our findings are consistent with this literature, with around two-thirds of our cohort showing inadequate exposure on the sampling day (53.7% subtherapeutic and 19% toxic), most often corresponding to the first day of therapy. To address this challenge, several studies have investigated the PK of vancomycin in this population, identifying body weight and RRT intensity as the main predictors of V and CL, respectively, [4, 13, 14, 31–34] which is aligned with our findings. However, due to their small sample sizes and frequent reliance on limited TDM data, these studies were unable to develop comprehensive dosing recommendations tailored to these characteristics. In this context, the comparatively large sample size of our study and the rich sampling strategy across different sites of the RRT circuit provided sufficient data to identify and quantify the effects of a wide range of RRT intensities and body weights on vancomycin PK. This, in turn, enabled the development of dosing nomograms stratified by these factors, supporting individualised therapy across diverse clinical scenarios.

Importantly, urine output was not a significant predictor of vancomycin non-RRT CL, contrasting with previous findings that included patients with different degrees of urine output [33, 35, 36]. Most patients in our cohort were oligoanuric, with only 21.5% exhibiting urine outputs ≥ 500 mL/24 h. Furthermore, in some oligoanuric patients, urine output was recorded only

Table 3 Loading and maintenance dosing nomogram for vancomycin in critically ill patients receiving different modalities of RRT

RRT modality	RRT intensity	Recommended dosing regimen in continuous infusion	Recommended dosing regimen in short infusion (over 1 -2 h)
For all types of modality, time and settings: if starting a treatment, administer a 1500 mg loading dose over a 1 – 2 h infusion for patients weighing 70 – 90 kg or a 2000 mg loading dose over a 1 – 2 h infusion for patients weighing 90—120 kg For continuous infusion regimens: initiate the continuous infusion immediately after the loading dose at the recommended daily dose For short infusion regimens: administer the first maintenance dose 12 h after the loading dose For once-daily short infusion regimens in patients receiving SLED: Administer the daily dose early during the SLED-off period, at least 12 h before the next SLED session			
Continuous RRT	≤ 1.5 L/h	750 mg daily	750 mg once daily
	1.5—2 L/h	750 – 1000 mg daily	750 mg once daily—500 mg every 12 h
	2—3 L/h	1000 mg daily	500 mg every 12 h
	3—3.5 L/h	1000 – 1500 mg daily	500 mg – 750 mg every 12 h
	3.5—5 L/h	1500 mg daily	750 mg every 12 h
Short SLED (~ 6 h)	≤ 9 L/h	750 mg daily	750 mg once daily
	9—12 L/h		
	12—15 L/h		
	15—18 L/h	750—1000 mg daily	750 mg once daily—500 mg every 12 h
Medium SLED (~ 8 h)	≤ 9 L/h	750 mg daily	750 mg once daily
	9—12 L/h	750—1000 mg daily	750 mg once daily—500 mg every 12 h
	12—15 L/h	1000 mg daily	500 mg every 12 h
	15—18 L/h	1000 – 1500 mg daily	1000 – 1500 mg once daily (*)
Long SLED (~ 12 h)	≤ 9 L/h	1000 mg daily	500 mg every 12 h

Table 3 (continued)

RRT modality	RRT intensity	Recommended dosing regimen in continuous infusion	Recommended dosing regimen in short infusion (over 1 -2 h)
	9—12 L/h	1000 – 1500 mg daily	500 mg – 750 mg every 12 h
	12—18 L/h	1500 mg daily	750 mg every 12 h or 1500 mg once daily (*)

Dosing recommendations are stratified by total body weight and RRT modality, intensity and duration, and are designed to optimise exposure during the first 96 h of therapy

RRT: renal replacement therapy, SLED: sustained low efficiency dialysis. When a dose range is recommended, the choice should balance the benefit–risk of achieving adequate efficacy exposure against the risk of toxicity. Consider the lower dose for treating patients with low inoculum, less severe infections and high toxicity risk. The higher dose in a range will optimise the attainment of the efficacy target but is associated with a higher toxicity risk. (*): for longer SLED sessions using high intensity (i.e. 18 L/h), once-daily intermittent doses provide better target attainment than twice-daily doses

categorically as part of the SOFA score, [18] which may have limited the model's ability to accurately characterise its effect on non-RRT clearance. Consequently, it is plausible that the model consistently overestimated vancomycin concentrations in the external validation with the TDM dataset, as nearly 50% of those patients had urine outputs ≥ 500 mL/24 h. Nevertheless, when Bayesian forecasting was applied, i.e., when TDM data were incorporated, the model demonstrated sufficient flexibility to provide excellent individual predictions. Given that TDM is highly encouraged to guide vancomycin dosing in clinical practice, our external validation supports the potential integration of this model into model-informed precision dosing (MIPD) software capable of incorporating TDM data through Bayesian forecasting. This approach may enable accurate individualised dosing even in markedly different patient populations, such as those with preserved urine output.

Notably, the dosing simulations show that intermittent and continuous infusions have similar PTA for both efficacy and toxicity across the different scenarios, which is expected as both are primarily determined by the $AUC_{0\text{-}24\ h}$/MIC. However, continuous infusion offers the added advantage of providing more stable plasma concentrations even with intermittent RRT modalities, thereby facilitating TDM sampling and simplifying interpretation, as more constant concentrations can facilitate the estimation of $AUC_{0\text{-}24\ h}$ [6]. Such close monitoring is particularly important in patients with sepsis receiving RRT, where treatment with vancomycin has been associated with a three-fold increased risk of prolonged RRT dependence at ICU discharge [7]. In this context, continuous infusion may be advantageous for patients at higher risk of inadequate dosing and should be considered, for example, in those experiencing fluctuations in RRT intensity or recovering urine output.

This study has several strengths, including its prospective, multicenter design and the use of a rich sampling strategy from multiple sites of the RRT circuit. These factors enabled the development of a population PK model with robust predictive performance, which was externally validated using data from additional patients, supporting its potential implementation in clinical practice, including in patients concomitantly receiving ECMO. Furthermore, our dosing nomograms account for both efficacy and toxicity targets [6] and are based on easy to identify patient and treatment characteristics that facilitate implementation in clinical practice. The main limitations are that the PK model was developed primarily using data from oligoanuric patients, warranting caution when applying the nomogram to patients with significant urine output. In addition, our recommendations are based on plasma exposure, which may not fully reflect drug exposure at the site of infection. Finally, due to the observational nature of the study, the impact of optimised dosing on patient-centered outcomes remains uncertain and requires prospective evaluation.

In summary, vancomycin dosing requirements in critically ill patients treated with RRT are primarily driven by the key determinants of vancomycin PK in this population, namely body weight, and RRT intensity and duration. Our dosing nomogram enables individualised dose selection based on these characteristics and is designed to maximise efficacy while minimising the risk of toxic exposure. Although the probability of achieving optimal exposure is similar between continuous and intermittent infusion, continuous infusion provides more stable drug concentrations over time, which may simplify TDM.

Abbreviations

AKI	Acute kidney injury
APACHE II	Acute Physiology and Chronic Health Evaluation II
$AUC_{0\text{-}24\ h}$	Area under the concentration curve from 0 to 24 h
CI	Confidence interval
CL	Clearance
CL_{RRT}	CL mediated by RRT
CL_{body}	CL independent of RRT
C_{pre}	Pre-filter plasma total vancomycin concentration
C_{post}	Post-filter plasma total vancomycin
C_{effl}	Effluent vancomycin concentration
CRRT	Continuous renal replacement therapy
CVVHD	Continuous veno-venous hemodialysis
CVVHDF	Continuous veno-venous hemodialfiltration
CVVHF	Continuous veno-venous hemofiltration
ECMO	Extracorporeal membrane oxygenation
GOF	Goodness-of-fit
ICU	Intensive care unit
IIV	Interindividual variability
IMPE	Individual median prediction error
IMAPE	Individual median absolute prediction error
MIC	Minimum inhibitory concentration
MPE	Median prediction error

MAPE	Median absolute prediction error
pc-VPC	Prediction-corrected visual predictive check
PK	Pharmacokinetics
PTA	Probability of target attainment
Q	Intercompartmental clearance
RRT	Renal replacement therapy
RSE	Relative standard error
SLED	Sustained low-efficiency dialysis
SOFA	Sequential Organ Failure
TDM	Therapeutic drug monitoring
V	Volume of distribution
V_c	Central volume of distribution
V_p	Peripheral volume of distribution

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

Supplementary Material 5.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was designed and conducted following the declaration of Helsinki guidelines and received ethics approval from the Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/13/QRBW/1) as the lead site. All other participating sites also obtained individual HREC approval for the SMARRT study. All non-SMARRT-funded studies that contributed data also obtained individual HREC approval at each participating site. All patients or their legal representatives provided written informed consent before enrolment.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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