Journal of Critical Care 54 (2019) 77–82

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Optimal vancomycin dosing regimens for critically ill patients with acute kidney injury during continuous renal replacement therapy: A Monte Carlo simulation study

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ARTICLE INFO

Keywords:
vancomycin
continuous renal replacement therapy
Monte Carlo simulations
critically ill
acute kidney injury

ABSTRACT

Purpose: This study aims to determine the optimal vancomycin dosing in critically ill patients with acute kidney injury receiving continuous renal replacement therapy (CRRT) using Monte Carlo simulation.
Methods: A one compartment pharmacokinetic model was conducted to define vancomycin deposition for the initial 48 hours of therapy. Pharmacokinetic parameters were gathered from previously published studies. The AUC_{24}/MIC ratio of at least 400 and an average of $AUC_{0\text{-}24}$ at > 700 mg h/L were utilized to evaluate efficacy and nephrotoxicity, respectively. The doses achieved at least 90% of the probability of target attainment (PTA) with the lowest risk of nephrotoxicity defined as the optimal dose.
Results: The regimens of 1.75 grams every 24 hours and 1.5 grams loading followed by 500 mg every 8 hours were recommended for empirical therapy of an MRSA infection with expected MIC ≤1 mg/L, and definite therapy with actual MIC of 1 mg/L. The probabilities of nephrotoxic results from these regimens were 35%.
Conclusions: A higher dose of vancomycin than the current literature-based recommendation was needed in CRRT patients.

1. Introduction

Acute kidney injury (AKI) is a complication that occurs frequently in critically ill patients. Nearly 50% of AKI cases are caused by sepsis and consequently require initiation of continuous renal replacement therapy (CRRT) [1,2]. Previous research indicates that early use of appropriate antibiotics is important in the management of sepsis [3,4]. Thus, choosing the appropriate antibiotic with optimal dosing is crucial.

The factors shown to affect antibiotic concentration in critically ill patients undergoing CRRT are as follows; the increased volume of distribution (Vd), the decreased plasma protein binding, and the increased drugs clearance by CRRT extracorporeal clearance [5]. These variables may lead to inadequate blood concentration and contribute to adverse clinical outcomes. Vancomycin is a first-line agent for methicillin-resistance *Staphylococcus aureus* (MRSA) infection. Because of its hydrophilic property and medium molecule size (MW), vancomycin is potentially removed by CRRT clearance [6,7]. The recommended doses of vancomycin from available clinical resources for patients receiving CRRT varied; either 1 g every 96 h, 1.5 g every 24 h, or 750 mg every 12 h has been recommended [8-13]. However, some previous studies

Abbreviations: AKI, Acute kidney injury; AUC/MIC ratio, The area under the plasma concentration-time curves over MIC; CL, Clearance; CL_{HD}, Transmembrane clearance in hemodialysis; CL_{HF}, Transmembrane clearance in hemofiltration; CL_{NR}, Non-renal clearance; CLSI, Clinical Laboratory Standards Institute; CRRT, Continuous renal replacement therapy; CVVH, Continuous venovenous hemofiltration; CVVHD, Continuous venovenous hemodialysis; g, Gram; h, Hour; ISN, International Society of Nephrology; k, Elimination rate constant; KDIGO, Kidney Disease: Improving Global Outcomes; kg, Kilogram; L, Liter; LD, Loading dose; mg, Milligram; MIC, Minimum inhibitory concentration; mL, Milliliter; PTA, Probability of target attainment; Q, Every; Q_{blood}, Blood flow rate; Q_d, Dialysate flow rate; Q_{plasma}, Plasma flow rate; $Q_{replacement}$, Replacement fluid flow rate; Q_{uf}, Ultrafiltrate flow rate; r^2, Population-specific correlation; SA, Saturation coefficient; SC, Sieving coefficient; SD, Standard deviation; SEA-AKI, Southeast Asia entitled The Epidemiology and Prognostic Factors for Mortality in Intensive Care Unit Patients with Acute Kidney Injury in Southeast Asia; Vd, Volume of distribution.

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https://doi.org/10.1016/j.jcrc.2019.07.008
0883-9441/

show that these current dosing regimens of vancomycin are not adequate to produce clinical efficacy against MRSA infections [14,15].

Regarding vancomycin-related nephrotoxicity, several studies have reported the relationship between AUC_{0-24} levels and vancomycin-related nephrotoxicity. Zasowski et al. found the highest predictive performance of AUC for nephrotoxicity at daily AUC values between 600 and 800 mg·h/L [16]. Additionally, the results from the Mogle et al. study reveal that the vancomycin related nephrotoxicity increased from 9.3% in the patients with an AUC_{0-24} < 710 mg·h/L to 66.7% in those with an AUC_{0-24} at ≥710 mg·h/L [17]. Although AUC_{0-24} level thresholds between 563 and 1300 mg·h/L were reported, most study results indicated that an AUC_{0-24} level threshold at >700 mg·h/L was associated with nephrotoxicity [16-20].

The optimal vancomycin dosing regimens for critically ill, AKI patients during CRRT remain unclear. This study aims to use the Monte Carlo simulation to (i) evaluate the currently recommended dosing regimens of vancomycin in critically ill patients receiving CRRT and (ii) determine the optimal dosing of vancomycin in these patients receiving CRRT in 3 different modalities and 3 effluent rates.

2. Method

A compartment pharmacokinetic model of vancomycin deposition for the first 48 h of the initial therapy for critically ill patients receiving uninterrupted CRRT was developed. The pharmacokinetic parameters incorporated into the model to perform on a group of 5000 virtual patients include: body weight, volume of distribution (Vd), non-renal clearance values (CL_{NR}), and sieving coefficient (SC) or saturation coefficient (SA). Body weights were obtained from an international database of the International Society of Nephrology (ISN). The ISN funded the prospective multicenter observational ongoing study of AKI epidemiology in Southeast Asia: The Epidemiology and prognostic Factors for Mortality in Intensive Care Unit Patients with Acute Kidney injury in Southeast Asia (SEA-AKI) [21]. The lower limit was set at ≥40 kg to represent that the virtual patients are adults. The necessary pharmacokinetic parameters were derived from 7 published vancomycin pharmacokinetics studies in critically ill patients with acute kidney injury (AKI) receiving CRRT [8,13,22-26]. The correlation (r^2) between body weight and V_d or CL_{NR} were incorporated in the model to generate a realistic virtual patient. The pharmacokinetic simulation parameters are shown in Table 1.

The total drug clearance (CL_{TOTAL}) was calculated from the sum of patient's clearance (non-renal; CL_{NR} and renal clearance; CL_R) and CRRT extracorporeal clearance (CL_{CRRT}) using the following equation:

$$CL_{TOTAL}(L/h) = (CL_{NR} + CL_R) + CL_{CRRT}.$$

Most AKI patients have no urine output; therefore, the renal clearance of these patients was assumed as 0 mL/min. Thus, only the sum of non-renal clearance and CRRT clearance was calculated to define the total drug clearance in this study. The CRRT clearance was calculated using the following equations depending on the different modalities [27]:

$$CL_{HF(pre)}\ (L/h) = SC * Q_{uf} * \left[Q_{plasma}/(Q_{plasma} + Q_{replacement})\right].$$

$$CL_{HF(post)}\ (L/h) = SC * Q_{uf}.$$

$$CL_{HD}\ (L/h) = SA * Q_{d.}$$

where $CL_{HF(pre)}$ is extracorporeal clearance in hemofiltration with predilution technique (pre-dilution CVVH); $CL_{HF(post)}$ is extracorporeal clearance in hemofiltration with post-dilution technique (post-dilution CVVH); CL_{HD} is extracorporeal clearance in hemodialysis (CVVHD); Q_{uf} is ultrafiltrate flow rate; Q_{plasma} is plasma flow rate ($Q_{plasma} = Q_{blood}$*(1-hematocrit)); hematocrit is 30% and Q_{blood} was set at 200 mL/min; $Q_{replacement}$ is replacement fluid flow rate ($Q_{replacement} = Q_{uf}$); Q_d is dialysate flow rate. SC is the ratio of drug concentration in the ultrafiltrate to plasma; SA is the ratio of drug concentration in the dialysate to plasma. The elimination rate constant (k) was calculated as the total of vancomycin clearance (CL_{TOTAL}) divided by volume of distribution (V_d).

Table 1
Virtual patient characteristics compared with input pharmacokinetic parameters from published vancomycin studies.

Pharmacokinetic parameters	Literature-based values (mean ± SD (range limits)) ($N = 38$)	Simulation-based values (mean ± SD (range limits)) ($N = 5000$)
Weight (kg)	60.72 ± 14.5 (40–230)	61.72 ± 13.78 (40–146.80)
V_d (L/kg)	0.57 ± 0.26 (0.17–1.37)	0.75 ± 0.40 (0.12–2.84)
CL_{NR} (mL/min)	24.86 ± 22.59 (0.00–84.28)	22.29 ± 15.88 (1.31–84.29)
SC	0.73 ± 0.1 (0.43–0.89)	0.72 ± 0.1 (0.44–0.89)
SA	0.71 ± 0.142 (0–1)	0.70 ± 0.1 (0.36–1.00)

Effluent flow rates of 20–25 mL/kg/h were used in the models based on Kidney Disease: Improving Global Outcomes (KDIGO) recommendation [28]. Because higher effluent flow rate might be used in real practice especially in septic patients or aggressive fluid removal remain necessary [29,30], the effluent flow rate of 35 mL/kg/h was also applied in the simulations.

A 2-hour infusion time was set in our pharmacokinetic model to evaluate all of the vancomycin dosing regimens. An average of AUC_{0-24} at >700 mg·h/L, calculated by the total 48-h AUC divided by 2, was used to evaluate vancomycin-related nephrotoxicity.

2.1. Monte Carlo simulations

Following a previously published method [31,32], simulations of 5000 virtual patients were conducted for each dosage regimen using the Oracle Crystal Ball Classroom Edition to create the drug concentration-time profile. The area under the plasma concentration-time curves (AUC) was calculated using the trapezoidal rule. An AUC/MIC ratio ≥ 400 was a pre-specified PD target which has been advocated as a target to achieve clinical outcomes in terms of ventilator associated *S. aureus* pneumonia infection [33]. According to The Clinical and Laboratory Standards Institute (CLSI), the vancomycin MIC breakpoint of susceptible MRSA isolate was ≤2 mg/L. Moreover, attaining AUC/MIC ≥400 for pathogens with MIC >2 mg/L will require a minimum AUC of 800 which is associated with vancomycin nephrotoxicity. Consequently, MIC distribution of 1, 1.5 and 2 mg/L were selected and utilized in this study. The probability of target attainment (PTA) which describes the proportion of patients that attain each pre-specified PD target was calculated. Recommended dosing regimens were considered adequate when 90% of the virtual patients achieved the PD target over the 48-h period. The dose that achieved at least 90% of the PTA with the lowest risk of nephrotoxicity was defined as the optimal vancomycin dosing regimens for each CRRT modality and each effluent flow rate. To provide more useful data in clinical practice, the PTA sensitivity analysis of selected vancomycin dosing regimens with various effluent flow rates in CRRT was done. The simulation CRRT clearance of three different modalities of CRRT and effluent flow rate are shown in Table 2.

3. Results

The simulation CRRT clearance of three different modalities of CRRT and flow rate are shown in Table 2. The PTAs from the simulations of the standard literature-based vancomycin dosing regimens and the probability of developing nephrotoxicity from selected vancomycin dosing regimens are shown in Tables 3 and 4, respectively. All literature-based doses achieved <90% of the PTA target regardless of CRRT

Table 2
The simulation CRRT clearance of three different modalities of CRRT and effluent flow rates.

Effluent rates (mL/kg/h)	CVVH (pre-hemofilter dilution) (mean ± SD	CVVH (post-hemofilter dilution) (mean ± SD	CVVHD (mean ± SD)
20 mL/kg/h	0.77 ± 0.17 L/h	0.88 ± 0.23 L/h	0.86 ± 0.25 L/h
25 mL/kg/h	0.93 ± 0.20 L/h	1.10 ± 0.28 L/h	1.08 ± 0.31 L/h
35 mL/kg/h	1.23 ± 0.26 L/h	1.55 ± 0.40 L/h	1.51 ± 0.43 L/h

CVVH continuous venovenous hemofiltration, *CVVHD* continuous venovenous hemodialysis.

modality, effluent rate or selected MRSA MIC. The two highest literature-based recommended doses of 1.5 g every 24 hours [12] and 750 mg every 12 hours [13] achieved the highest PTA of 84% and 76%, respectively, among all selected CRRT modality and an effluent rate for an MRSA MIC of 1 mg/L. Considering efficacy and the risk of nephrotoxicity, optimal vancomycin dose depends on effluent rate and MRSA MIC. For an effluent rate of 20 mL/kg/h and MRSA MIC = 1 mg/L, a regimen of 1.75 grams every 24 hours would be the optimal dose for all three CRRT modalities since it achieved PTA of >90%. However, this regimen resulted in $AUC_{0\text{-}24\ h}$ >700 in 43-46% of simulated patients among three CRRT modalities. For effluent rate of 25 mL/kg/h and MRSA MIC = 1 mg/L, a regimen of 1.75 grams every 24 hours was the optimal dose for pre-dilution CVVH modality, whereas the regimen of 1.5 grams loading, then 500 mg every 8 hours was optimum for post-dilution-CVVH and CVVHD modalities. The probabilities of nephrotoxic results from those regimens mentioned above for an effluent rate of 25 mL/kg/h were about 40–43%. In a higher effluent flow rate of 35 mL/kg/h and MRSA MIC = 1 mg/L, the optimal dose for pre-dilution CVVH modality was 1.5 g loading, then 500 mg every 8 h. The regimen of 2 grams every 24 hours was preferred for post-dilution CVVH as well as CVVHD modalities. The probabilities of nephrotoxic results from those regimens mentioned above for effluent rate of 35 mL/kg/h were 35–37%. Results of the sensitivity analysis of these selected dosing regimens are shown in Table 5.

The dosing regimens for an MRSA infection with vancomycin MIC of 1.5 mg/L were (i) 2.75 grams loading, then 2.5 g every 24 h for pre-dilution CVVH and (ii) 1.5 g every 12 h for post-dilution CVVH and CVVHD modalities with KDIGO recommended effluent flow rates (20–25 mL/kg/h). The dosing regimens of 2.75 g every 24 h and 3 g loading followed by 2.75 g every 24 h were the doses that achieved at least 90% PTA for pre-dilution CVVH, post-dilution CVVH and CVVHD modalities, with a higher effluent flow rate of 35 mL/kg/h. The probability of nephrotoxic was almost 80% with these dosing regimens (Supplemental Table 1 and 2).

Total daily doses of 3.5–4 g/day are required to achieve at least 90% PTA for an MRSA infection with vancomycin MICs of 2 mg/L. These high doses result in a nephrotoxic risk as high as ≥90% (Supplemental Table 1 and 2).

A summary of recommended vancomycin dosing regimens for AKI patients receiving three different CRRT modalities, effluent rates, and MIC of 1 mg/L is shown in Supplemental Table 3. Regarding actual MIC <1 mg/L, the lower dose was preferred as shown in Fig. 1.

4. Discussion

This study revealed that the current literature-based dosing regimens are not adequate to attain AUC/MIC ≥400, especially those with vancomycin MIC ≥1 mg/L. The highest literature-based dosing regimen in our study was 1.5 g/day or approximately 25.4 ± 5.26 mg/kg/day, which was higher than the Wilson and Berns study. They reported the mean vancomycin dose of 14 ± 8.03 mg/kg/day which was insufficient to achieve the therapeutic concentration of ≥15 mg/L in surgical intensive care (SICU) patients undergoing CRRT [15]. The average body weight of 87.3 ± 25.1 kg was used in their study while ours was 60.72 ± 14.5 kg. Therefore, their mean vancomycin dose per kilogram was lower than ours when considering the same fixed-dosing regimens. However, the selected vancomycin doses from both studies were not sufficient to achieve pharmacokinetic and/or pharmacodynamic target. It could be explained through pharmacokinetic alternation in critically ill patients. First, the Vd from simulation was 0.75 ± 0.40 L/kg, slightly higher than those of normal population (0.4-1 L/kg) [33]. Vasodilation

Table 3
PTA of all recommended vancomycin dosing regimens for MRSA infections in three CRRT modalities with different effluent rates and various MICs.

Vancomycin dosing regimens	Pre-dilution CVVH					Post-dilution CVVH					CVVHD				
	Effluent rates (mL/kg/h)	AUC_{0-24} (mg.h/L)	PTA (%) MIC (mg/L)			Effluent rates (mL/kg/h)	AUC_{0-24} (mg.h/L)	PTA (%) MIC (mg/L)			Effluent rates (mL/kg/h)	AUC_{0-24} (mg.h/L)	PTA (%) MIC (mg/L)		
			1	1.5	2			1	1.5	2			1	1.5	2
1 g Q24H[a]	20	404.84	46.04	9.60	1.24	20	392.98	42.84	7.92	0.74	20	393.51	42.68	8.14	0.86
	25	388.56	42.08	6.84	0.62	25	365.15	34.36	4.22	0.30	25	371.42	35.96	5.46	0.40
	35	351.52	31.00	2.34	0.00	35	322.90	20.86	1.00	0.04	35	327.09	21.80	1.36	0.06
500 mg Q12 H[a]	20	364.67	34.08	4.80	0.48	20	350.90	30.28	3.54	0.28	20	357.22	32.46	4.06	0.48
	25	344.30	28.34	2.54	0.02	25	328.93	22.80	1.62	0.12	25	331.94	23.48	1.88	0.12
	35	317.21	19.34	0.70	0.02	35	293.07	11.66	0.36	0.00	35	297.78	13.58	0.40	0.02
1.5 g Q24H[a]	20	608.51	84.26	45.78	17.32	20	587.76	82.42	42.24	14.26	20	591.91	82.38	43.66	15.08
	25	583.58	82.34	42.02	13.14	25	549.55	78.26	35.68	9.18	25	557.15	79.22	36.00	10.46
	35	528.26	77.88	29.70	6.20	35	482.17	67.82	19.62	2.84	35	484.28	67.84	20.58	3.40
750 mg Q12 H[a]	20	546.04	76.32	33.78	10.00	20	523.79	73.60	29.46	7.56	20	529.51	73.14	30.52	8.94
	25	519.39	73.66	28.44	7.18	25	497.49	69.62	24.38	4.84	25	503.39	69.04	25.44	5.90
	35	471.43	65.88	18.04	2.40	35	439.39	56.30	12.26	1.16	35	446.14	58.14	13.98	1.68
1.75 g Q24H	20	706.84	**92.90**	62.88	30.20	20	690.95	**90.86**	60.00	29.08	20	693.45	**91.14**	61.10	28.44
	25	671.27	**90.02**	57.16	26.00	25	638.52	88.62	52.34	21.74	25	648.61	89.64	52.82	22.12
	35	619.06	88.06	49.14	16.92	35	556.99	81.80	36.18	8.50	35	569.46	82.94	39.68	9.96
2 g Q24H	20	812.10	96.04	75.30	46.30	20	782.11	95.70	72.28	41.68	20	793.59	96.18	73.06	43.92
	25	771.12	95.88	72.36	40.12	25	728.27	94.30	67.46	34.16	25	743.23	94.68	68.38	36.06
	35	695.55	93.74	63.18	28.80	35	643.45	**90.68**	54.18	20.64	35	650.11	**90.54**	55.68	21.58
1.5 g LD then	20	751.33	94.14	68.24	36.82	20	727.70	93.9	65.82	34.18	20	732.75	93.98	66.30	34.60
500 mg Q8H	25	712.22	93.8	64.16	32.06	25	678.63	**92.14**	59.52	26.32	25	685.66	**92.58**	60.00	27.18
	35	651.23	**90.92**	56.26	21.54	35	594.19	87.24	44.28	12.52	35	601.71	87.10	45.08	14.48

PTA probability of target attainment, *CVVH* continuous venovenous hemofiltration, *CVVHD* continuous venovenous hemodialysis, *LD* loading dose. Bold indicates the recommended doses for the MRSA infections with vancomycin MIC less than or equal to 1 mg/L.

[a] Literature based regimens.

Table 4
The probability of developing nephrotoxicity from selected vancomycin dosing regimens.

Vancomycin dosing regimens	Pre-dilution CVVH		Post-dilution CVVH		CVVHD	
	Effluent rates (mL/kg/h)	Probability of AUC_{0-24} > 700 mg.h/L (%)	Effluent rates (mL/kg/h)	Probability of AUC_{0-24} > 700 mg.h/L (%)	Effluent rate (mL/kg/h)	Probability of AUC_{0-24} > 700 mg.h/L (%)
750 mg Q12 H[a]	20	19.36	20	15.84	20	17.22
	25	14.42	25	11.8	25	12.88
	35	7.20	35	4.18	35	5.00
1.5 g Q24H[a]	20	29.26	20	26.18	20	27.10
	25	24.30	25	18.88	25	20.54
	35	13.92	35	7.82	35	9.14
1.75 g Q24H[a]	20	45.46	20	43.28	20	43.22
	25	40.02	25	34.62	25	35.76
	35	31.22	35	18.82	35	21.62
2 g Q24H	20	61.10	20	56.94	20	58.40
	25	55.70	25	49.66	25	51.56
	35	44.68	35	35.78	35	36.02
1.5 g LD then 500 mg Q8H	20	51.90	20	49.24	20	50.26
	25	48.02	25	41.2	25	42.02
	35	36.78	35	25.4	35	26.58

CVVH continuous venovenous hemofiltration, *CVVHD* continuous venovenous hemodialysis, *LD* loading dose.
[a] Literature based regimens.

and capillary leakage, as well as aggressive fluid resuscitation in acute phase of sepsis led to an increased Vd. Consequently, it lowered vancomycin concentration. Secondly, some current literature-based dosing regimens were derived from pharmacokinetic studies performed in patients with end stage renal disease [9]. Macias et al. reported the mean non-renal clearance of vancomycin in early course of acute renal failure was approximately 16.2 mL/min [8]. This value was higher than those of patients with chronic renal failure undergoing dialysis (5–6 mL/min) [34]. Hence, AKI patients seemed to be more at risk to sub-therapeutic regimens compared to those with end stage renal disease when the same vancomycin regimen was prescribed in AKI patients receiving CRRT. In this study, the CL_{NR} from studies in critically ill patients receiving CRRT which incorporated to the pharmacokinetic model was 22.29 ± 15.88 mL/min. It was higher than of the previously reported values [8]. Thus, this may be the major factor contributing to sub-therapeutic drug concentration.

The CRRT related-factors (including the improvement of CRRT machines, surface area and type of hemofilters, as well as uninterrupted CRRT) cause current CRRT drug clearance to be higher than in the past. Lastly, because of the current emergence of drug-resistance pathogens, we often required using higher dosing regimens to overcome MRSA infection with higher vancomycin MIC.

The main factors of drug elimination by CRRT are sieving or saturation coefficient (SC or SA) and effluent flow rate. The effluent flow rate was calculated from the sum of replacement fluid (pre- and post-hemofilter), dialysis fluid, and net fluid removal rates [27]. In high effluent flow rate settings, the drug clearance by CRRT was higher when compared to low effluent flow rates for all type CRRT modality (Table 2 and Table 3). Because of the dilution effect from replacement fluid in pre-dilution CVVH modality, drug removal by CRRT was less in pre-dilution CVVH than in post-dilution CVVH modality. Therefore, the optimum dosing regimens of the pre-dilution CVVH was slightly lower than the post-dilution CVVH (Table 5). Due to the minor difference between SA and SC values used in our simulation, 0.70 ± 0.1 and 0.72 ± 0.1 respectively, the difference of drug clearance in CVVHD and post-dilution CVVH modality were insignificant.

Based on our simulations, the optimal dosing regimen on the first day of therapy for MRSA infections with vancomycin MIC of 1 mg/L was 1.75–2.5 g/day or approximately 28–40 mg/kg/day. The vancomycin dosing of 1.5–2 g/day was recommended as the maintenance therapy depending on effluent flow rates (20–35 mL/kg/h). In clinical application, we recommended these dosing regimens for empirical therapy of MRSA infections with expected vancomycin MIC ≤1 mg/L. After the culture, susceptibility profile and actual MIC are available, dose adjustment should be done based on actual MIC. The dose lower than our recommendation should be considered in regards to actual MIC <1 mg/L. However, our recommended doses were slightly higher when compared with previous studies, which range from 1 g every 48 h to750 mg every 12 h [8,13,22,25,35]. To compare with these studies, the pharmacokinetic parameters, e.g. the non-renal clearance and the CRRT clearance, were lower than ours [8,13,22,25,35]. The mean sieving coefficient of 0.66 ± 0.08 was reported in the Davies et al. study which is lower than that which was used in our simulation [35]. Moreover, the volume of distribution was only 0.38 ± 0.18 L/kg in one study [13]. Consequently, those recommendations of vancomycin dosing regimens were lower than our recommendations.

Covajes et al. reported that most patients with adequate vancomycin concentration received a median daily dose of 25 mg/kg. This study was conducted in patients undergoing 2 modalities of CRRT, CVVH and CVVHDF with effluent flow rates 20–40 mg/kg/h [36]. Wilson and

Table 5
The average AUC_{0-24} and PTA Sensitivity Analyses of recommended vancomycin dosing recommendation with various effluent flow rates in CRRT.

AUC/MIC ≥400 Actual MIC of 1 mg/L						
CRRT Modalities	CVVH (pre-hemofilter dilution)		CVVH (post-hemofilter dilution)		CVVHD	
Effluent rates (mL/kg/h)	1.75 g Q24H		1.5 g LD then 500 mg Q8H		1.5 g LD then 500 mg Q8H	
	% PTA	AUC (mg·h/L)	% PTA	AUC (mg·h/L)	% PTA	AUC (mg·h/L)
10 mL/kg/h	94.12	808.60 ± 317.09	96.12	847.16 ± 321.64	96.38	847.19 ± 321.40
15 mL/kg/h	93.54	761.95 ± 282.56	94.70	771.55 ± 278.93	95.20	786.68 ± 290.17
20 mL/kg/h	92.90	706.84 ± 244.15	93.90	727.70 ± 247.95	93.98	732.75 ± 732.75
25 mL/kg/h	90.02	671.27 ± 230.60	92.14	678.63 ± 219.21	92.58	685.66 ± 685.66
35 mL/kg/h	88.06	619.06 ± 191.39	87.24163.76	594.19 ± 174.90	87.10	601.71 ± 601.71
40 mL/kg/h	86.22	590.44 ± 177.41	84.72	567.10 ± 163.76	84.14	574.38 ± 174.96

CVVH continuous venovenous hemofiltration, *CVVHD* continuous venovenous hemodialysis, *LD* loading dose.

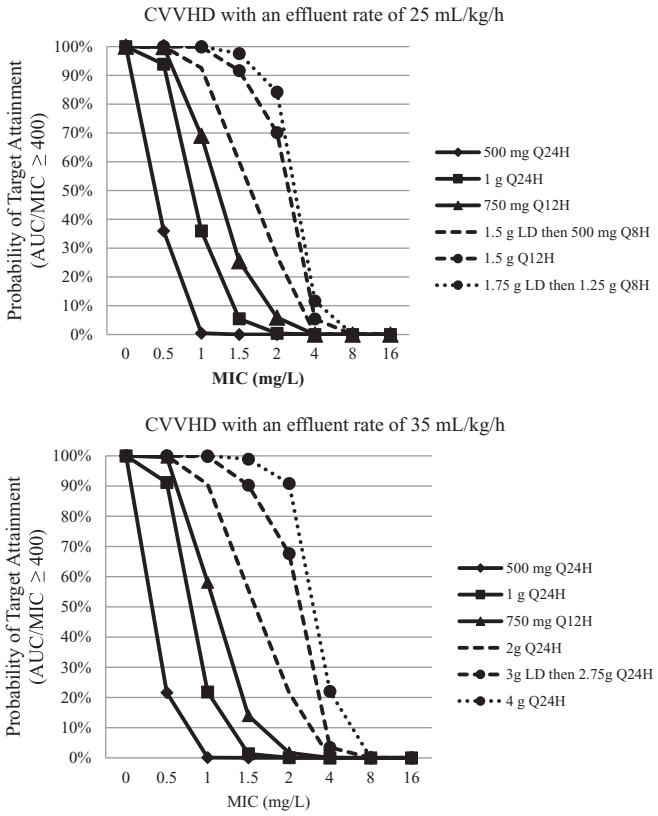

Fig. 1. PTA results of vancomycin dosing regimens at different MICs in CVVHD with 25 and 35 mL/kg/h effluent rates for treatment of MRSA infection (AUC/MIC ≥400) in virtual patients for the first 48 h.

Berns recommended an initial dose of 20 mg/kg of vancomycin, followed by only 15 mg/kg every 24 h while a patient was on CVVHD with a blood flow rate of 300 mL/min and dialysate flow rate of 2–3 L/h [15]. Except for the different effluent flow rates from ours, the other pharmacokinetic parameters were not reported. However, all of studies mentioned above used the plasma vancomycin concentrations of 5–30 mg/L as pharmacokinetics target to determine the optimal doses [13,15,22,25,35,36], while our study used AUC/MIC ≥400.

The Infectious Disease Society of America (IDSA) recommends using alternative drugs for the treatment of MRSA, such as high-dose daptomycin in combination with other susceptible agents if the vancomycin MIC is 2 mg/L, particularly in septic or critically ill patients [37]. Our results demonstrated that the nephrotoxic risk is as high as 80% with the regimens of 3–4 g/day for treatment of MRSA isolates having MIC of 1.5–2 mg/L (Table 4). These results aligned with previous reported that high doses of vancomycin (≥ 4 g/day) is associated with nephrotoxicity [38]. Consequently, we strongly suggest using our recommended vancomycin recommendations, especially for MRSA infection with an expected or actual MIC of 1 mg/L. Alternative antimicrobial agents would be considered when higher MIC is a major concern.

There were some limitations in our study. First, we developed the pharmacokinetic model for adult anuric AKI patients undergoing uninterrupted CRRT for at least 48 h. In addition, the virtual patients were constructed, using the pharmacokinetic data from the previous literature. Thus, both patient and CRRT characteristics, such as anuric patients, similar effluent flow rate and uninterrupted CRRT setting, should be taken into account when determining the vancomycin dosage in real practice to avoid over- or under-therapeutic drug concentration. In the case of CRRT being interrupted before 48 h (e.g. circuit clothing or the patient developing hemodynamic instability while on CRRT [which possibly occurred in real clinical practice]) the lower dose than our recommendation should be considered. Secondly, our simulation dosing regimens were fixed-dose regimens. The mean body weight in our study was 60.72 kg; therefore, the optimal dose is approximately 28–40 mg/kg/day for MRSA infections with vancomycin MIC of 1 mg/L. Using these fixed-dose regimens, 1.75–2.5 g/day, in patients of extreme weight were not recommended. Individualized dosing based on the patient's body weight must be considered. Third, given that we only used the AUC_{0-24} at >700 mg·h/L to determine the risk of nephrotoxicity, other independent risk factors, e.g., the concomitant nephrotoxic agents or the duration of vancomycin therapy, were not applied in our models. Additionally, our evaluated nephrotoxic threshold was extrapolated from the previous studies in which patients undergoing CRRT or having preexisting renal impairment were excluded. Due to limiting data of vancomycin-related nephrotoxicity in these populations, close monitoring is still necessary for clinical situations.

5. Conclusion

The current literature-based dosing regimens are not adequate to attain AUC/MIC ≥400 in critically ill patients with AKI receiving CRRT. With the effluent flow rate of 25 mL/kg/h, the dosing regimens of 1.75 g every 24 h (pre- dilution CVVH) and 1.5 g loading followed by 500 mg every 8 h (post-dilution CVVH and CVVHD) were recommended for empirical therapy of an MRSA infection with expected MIC ≤1 mg/L, and definite therapy of an MRSA infection with actual MIC of 1 mg/L. In higher effluent flow rate setting (35 mL/kg/h), a higher dose of vancomycin was required to achieve the target goal when compared to low effluent flow rates. Clinical validation of the recommendation is absolutely warranted.

Funding

This study was supported by the funding from the Siam University. The funding source had no role in the study design, the collection, analysis and interpretation of data, the writing of the article, and the decision to submit it for publication.

Declaration of Competing Interests

The authors have declared that no competing interests exist.

Acknowledgements

We would like to thank Associate Professor Dr. Wibul Wongpoowarak for his great advice in our simulation, and Thipsuda Dulyaphakorn and Supamas Punthanitisarn for proofreading the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.07.008.

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