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ORIGINAL ARTICLE

The relationship between vancomycin AUC/MIC and trough concentration, age, dose, renal function in Chinese critically ill pediatric patients

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Abstract

To assess the pharmacokinetic parameters of vancomycin in Chinese critically ill pediatric patients, children treated with vancomycin, hospitalized in the intensive care unit were included. Samples to determine peak and trough serum concentrations were obtained on the third day of treatment. Half-life was significantly longer in neonates and showed a decreasing trend in infants and children. In patients aged ≥1 month, AUC_{24}/MIC ≥400 was achieved in 31.8% at the dose of 40 mg/kg/d, and in 48.7% at the dose of 60 mg/kg/d with an assumed MIC of 1 mg/L. Augmented renal clearance (ARC) was present in 27.3% of children, which was associated with higher vancomycin clearance and lower AUC values. A good correlation was observed between trough concentration and AUC_{24}, and the trough concentration that correlated with AUC_{24} of 400 were varied according to the dosage regimens, 8.42 mg/L for 6-hintervals, and 6.63 mg/L for 8-h intervals. To conclude, vancomycin trough concentration that related to the AUC_{24} of 400 was much lower in critically ill children than that in adults. The dosage of 60 mg/kg/day did not enough for producing AUC_{24} in the range of 400–600 mg h/L in critically ill children, especially in those with ARC.

KEYWORDS
area under the concentration-time curve, pediatric patients, pharmacokinetics, trough concentration, vancomycin

1 | INTRODUCTION

Vancomycin is a major glycopeptide antibiotic widely used to treat methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative *Staphylococcus* species, and amoxicillin-resistant enterococci infections.[1] Although vancomycin is primarily characterized by time-dependent killing, a ratio of the 24-h area under the concentration-time curve to the minimum

Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant Staphylococcus aureus; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; PK, pharmacokinetic; PD, pharmacodynamics.

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inhibitory concentration (AUC_{24}/MIC) of ≥400 mg h/L has been established as the pharmacokinetic/pharmacodynamics (PK/PD) index that is, most predictive of a successful outcome in invasive MRSA infections.[2–4] Monitoring the vancomycin serum steady-state trough concentration as a surrogate is recommended by clinical treatment guidelines, and to achieve the target AUC_{24}/MIC ≥400, the 2009 IDSA guidelines recommend targeting trough concentrations of 15–20 mg/L in both adult and pediatric patients.[2] However, there was a lack of efficacy and safety data for this recommendation for pediatric patients.[5,6] Studies have shown that a much lower trough concentration is sufficient to achieve AUC_{24}/MIC ≥400 in children.[6–8] Therefore, the 2020 guideline from the Chinese Pharmacological Society recommends 5–15 mg/L as the therapeutic trough concentration in pediatric patients or neonates.[9]

In guideline updated in 2020 from IDSA, AUC-guided dosing and monitoring utilizing first-order PK equations or Bayesian software programs are recommended.[3] However, there is an issue that Bayesian approach requires a precise understanding of population modeling, and PK data for vancomycin in Chinese children have rarely been reported.[10,11] In addition, it requires Bayesian software tools and personnel training in order to implement into clinical practice.[12] AUC estimates calculated from two vancomycin levels have shown good precision and accuracy when compared with AUC estimates derived from Bayesian software using a single vancomycin level.[13–15] Thus, we monitored the two concentrations (peak, trough) routinely, calculated AUC_{24} through two-concentration analytic equations to manage vancomycin dosing in clinical practice.[14]

The objectives of this study were to better understand pediatric age, dose, and trough concentration-associated differences in AUC_{24} derived from two-point pharmacokinetics in Chinese critically ill pediatric patients in a real-world setting.

2 | MATERIALS AND METHODS

2.1 | Study design and patient population

This was a retrospective cohort study performed at Xinhua Hospital in Shanghai between June 2013 and September 2020. Pediatric patients who received intravenous vancomycin and had at least two vancomycin serum concentrations obtained in pediatric intensive care unit (PICU) or neonatal intensive care unit (NICU) were screened. The final inclusion criteria were (1) 14 years of age or younger, (2) vancomycin therapy for longer than 48 h, and (3) measurement of both vancomycin peak concentration (1 h after the end of infusion) and trough concentration (0–30 min prior to next dose) within 48–96 h of vancomycin therapy initiation. The exclusion criteria were (1) gestational age <37 weeks, (2) having inappropriate sampling time, (3) ongoing renal replacement therapy, and (4) values out of the detection limit or with laboratory errors. For individuals who met inclusion criteria multiple times, we retained data from the first course of vancomycin, so that an individual patient would only be included once in the analysis.

Age, sex, weight, height, serum creatinine, blood urea nitrogen, serum albumin, vancomycin dosage, infusion, and measurement time, measured concentrations, indications for vancomycin, cultures, and antibiograms with MICs, were obtained from electronic medical records. Estimated glomerular filtration rate (eGFR) was assessed using the equation: $eGFR = 40.7 \times (height/SCr)^{0.64} \times (30/BUN)^{0.202}$ according to the guidelines recommended (BUN, blood urea nitrogen in mg/dl; height in meters; SCr, serum creatinine in mg/dl).[16,17] Patients with an eGFR <50 mL/min/1.73 m^2 standardized were also included, but the correlation analysis of AUC and age was restricted to patients with an eGFR ≥50 mL/min/1.73 m^2 as renal function might act as a confounding factor. Augmented renal clearance (ARC) was defined by a GFR of >130 ml/min/1.73 m^2.[18]

The study has been approved by the Ethics Committee of Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (XHEC-D-2021-036). The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies.[19]

2.2 | Vancomycin concentration and PK parameters

Vancomycin concentrations were determined by high-performance liquid chromatography, as described previously.[20] The linear range for the assay was 2.0–100 mg/L, the lower detection limit was 1 mg/L, and intra- and inter-day precision and accuracy values were both within 15%. The vancomycin MIC was determined by Etest (Bio-Merieux). For the calculation of AUC/MIC, we assumed the MIC values to be 1 mg/L, considering that MIC declined for vancomycin from 2008 to 2018 in Shanghai.[21] PK parameters were derived using a one-compartment model with first-order elimination. The elimination rate constant (k_e) was calculated by the Sawchuk–Zaske method,[22] using the peak (C1) and trough (C2) concentrations obtained consecutively.

$$K_e = \frac{\mathrm{Ln}\frac{C1}{C2}}{t}$$

where t is the difference in time between these two concentrations. k_e was then used to calculate the elimination half-life ($t1/2 = k_e/0.693$) and AUC for one dosing interval using a widely used equation.[14]

$$AUC_1 = \frac{t' \times Ceoi' + Ct}{2} + \frac{Ceoi' - Ct}{K_e}$$

where Ceoi and Ct are the theoretical (i.e., not measured) concentrations at the end of infusion and at the end of the dosing interval, respectively, calculated by the formula for first-order pharmacokinetics. t' is the infusion time. AUC_{24} is equal to AUC1 multiplied by daily dose frequency. Vancomycin clearance (CL) was calculated from daily

vancomycin dose/AUC_{24}, and volume of distribution (Vd) was derived from CL/k_e.

2.3 | Statistical analysis

Statistical comparisons were made using Fisher's exact test, Mann–Whitney *U* test, and Kruskal–Wallis H test, where appropriate. Spearman's correlation test was employed to assess the association between renal function and AUC_{24}, and between trough concentration and AUC_{24}. A receiver operating characteristic (ROC) curve was used to assess the ability of trough vancomycin concentration to predict AUC_{24}. The cutoff value was 400 mg h/L, as suggested by guideline.[3,9] The optimal threshold was assessed by identifying the closest point in the curve to the coordinates (0, 1). The 95% confidence interval (CI) was used wherever appropriate. SPSS 26.0 (IBM Corp.) and Microsoft Excel (Microsoft Corp.) software was used for statistical analysis. A p value of <.05 was considered statistically significant.

3 | RESULTS

3.1 | Patient population

A total of 571 subjects were screened and 101 excluded (Figure 1). The remaining 470 patients were included in the study. Demographic and clinical characteristics are shown in Table 1. Approximately 60% of the patients were male, and the median age of the cohort was 1.0 years. Twenty-four were in neonates, 215 were aged 1 month to <2 years, 122 were aged 2 to <6 years, and 109 were aged 6–14 years. Twenty-nine patients (6.2%) were admitted to neonatal intensive care unit (NICU), and 441 patients (93.8%) were admitted to pediatric intensive care unit (PICU).

The median duration of vancomycin therapy was 11 (IQR: 8–17) days. Two hundred and forty patients (51.0%) had positive culture of gram-positive pathogens. Most isolates were *Staphylococcus* ($n = 177$), of which 66.7% ($n = 118$) were coagulase-negative *Staphylococcus*, and the rest were *Staphylococcus aureus* ($n = 59$, 33.3%). Among *Staphylococcus aureus*, MRSA accounted for 69.5% ($n = 41$), and vancomycin MICs were ≤0.5 mg/L in 36.6% ($n = 15$), and 1.0 mg/L in 63.4% ($n = 26$). In addition to *Staphylococcus*, the most common pathogen was *Enterococcus* ($n = 43$), followed by *Streptococcus* ($n = 35$).

3.2 | Effect of age, vancomycin daily dose and renal function on AUC_{24}

We divided the enrolled patients into different groups according to their age, and a summary of the PK parameters is provided in Table 2 (those with renal dysfunction were not included). Assessment of PK parameters revealed no significant differences between subgroups except for a significantly higher $t_{1/2}$ of vancomycin in neonates compared to all other age groups. It seemed that the AUC of the neonatal group was similar to that of other age groups, but it was due to a smaller daily dose. If we compared them at the same daily dose of 40 mg/kg (Table 3), higher serum concentration, and higher AUC_{24} values were observed in neonates. As for children older than 1 month, 58 of 119 (48.7%) achieved AUC_{24}/MIC ≥400 at the daily dose of 60 mg/kg. Although the proportion was significantly higher than that of the 40 mg/kg/d group (48.7% vs. 30.7%, $p < .01$), it was still not satisfactory.

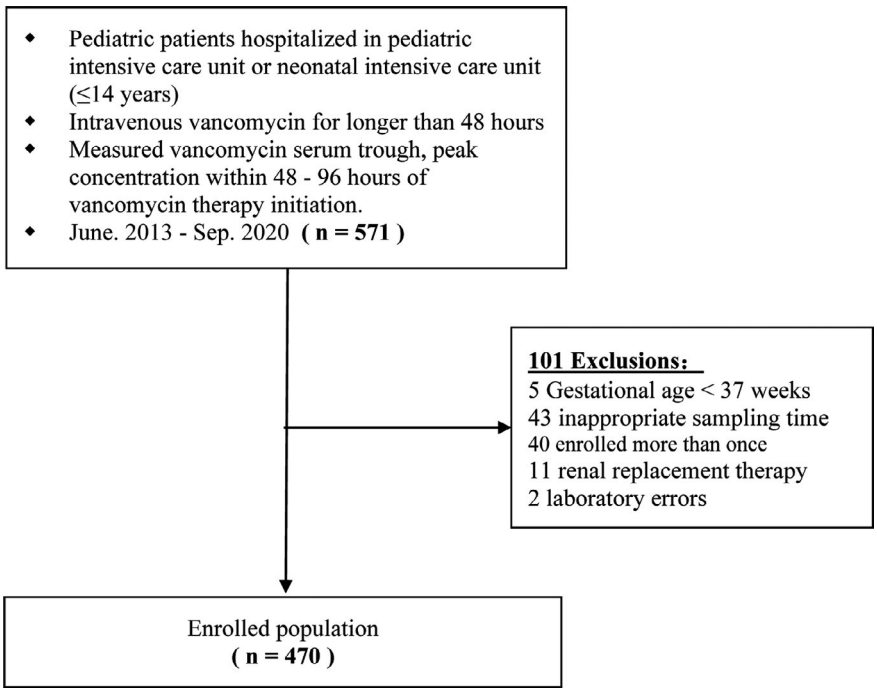

FIGURE 1 Flow diagram of patient selection, with inclusion and exclusion criteria

TABLE 1 Baseline characteristics and vancomycin regimens

Characteristic	Patients (n = 470)
Male, count (%)	289 (61.5)
Female, count (%)	181 (38.5)
Age, years, Median (IQR)	1.0 (0.5, 5.0)
Weight, kg, Median (IQR)	11.4 (7.0, 19.0)
Height, cm, Median (IQR)	80 (67, 110)
Serum creatinine, μmol/L, Median (IQR)	24.7 (19.1, 33.0)
Blood urea nitrogen, mmol/L, Median (IQR)	3.3 (2.2, 4.5)
eGFR, ml/min/1.73 m^2, Median (IQR)	105.4 (87.3,132.8)
Serum albumin, g/L, Median (IQR)	36.1 (31.4, 40.6)
Vancomycin dose (mg/kg/d), Median (IQR)	40.0 (40.0, 57.1)
Indication for vancomycin	
Sepsis, count (%)	224 (47.7)
Respiratory infection, count (%)	219 (46.6)
Central nervous system infection, count (%)	155 (33.0)
Gastro-Intestinal Infections, count (%)	55 (11.7)
Skin and soft tissue infection, count (%)	38 (8.1)
Bone and joint infections, count (%)	34 (7.2)
Urinary tract infection, count (%)	17 (3.6)
Fever of unknown origin, count (%)	13 (2.8)
Other, count (%)	5 (1.1)
Vancomycin administration	
10–15 mg/kg, 4 times/day, 1 h infusion, count (%)	263 (56.0%)
10–15 mg/kg, 4 times/day, 2–4 h infusion, count (%)	70 (14.9%)
10–20 mg/kg, 3 times/day, 1 h infusion, count (%)	110 (23.4%)
10–15 mg/kg, 3 times/day, 2–4 h infusion, count (%)	18 (3.8%)
10–20 mg/kg, 2 times/day, 1 h infusion, count (%)	9 (1.9%)
Vancomycin concentration, mg/L	
Trough, Median (IQR)	6.9 (4.5, 10.7)
Peak, Median (IQR)	19.3 (14.9, 25.7)
Vancomycin AUC_{24}, mg h/L, Median (IQR)	342 (255, 455)

Note: AUC_{24}, area under the time-concentration curve over 24 h; eGFR, estimated glomerular filtration rate; IQR, interquartile range.

AUC_{24} was dependent on renal function, as it increased with elevated serum creatinine and urea, and decreased with an elevation in GFR at both the daily dose of 40 mg/kg ($p < .001$ for creatinine, urea, and GFR; with Spearman's rank correlation coefficient: $R = 0.46$, 0.39, and −0.56, respectively), and 60 mg/kg/d ($p < .001$ for creatinine, urea, and GFR; with $R = 0.40$, 0.45, and −0.54, respectively). Figure 2 shows plots and correlations between GFR and AUC_{24}. There was no correlation between AUC_{24} and serum albumin.

ARC was present in 121 of 444 (27.3%) patients, and those patients had a mean ± SD GFR of 156.9 ± 27.2 ml/min/1.73 m^2. PK parameters for vancomycin were significantly different in patients with ARC. Significantly higher CL (0.19 ± 0.09 vs. 0.13 ± 0.05, $p < .001$) L/kg/h, larger Vd (0.72 ± 0.39 vs. 0.56 ± 0.29, $p < .001$) L/kg, shorter $t_{1/2}$ (2.76 ± 1.28 vs. 3.27 ± 1.97, $p = 0.026$) h, lower concentrations, and lower AUC_{24} values were observed in children with ARC compared to those without ARC (Table 4). $AUC_{24} < 400$ was more common in patients with ARC, and none of them achieved supratherapeutic AUC_{24} values (>600) regardless of dosage.

3.3 | Association between trough vancomycin concentration and AUC_{24}

Significant correlations were observed between the trough vancomycin concentration and AUC_{24} at 6-h intervals (Spearman's rank correlation coefficient: $R = 0.80$; 95% CI 0.76–0.84; $p < .001$) and at 8-h intervals ($R = 0.81$, 95% CI 0.74–0.86, $p < .001$) (Figures 3A and 4A). The ROC curve analysis indicated that trough concentration was a good predictor of AUC_{24} at 6-h intervals (0.90, 95% CI 0.86–0.93, $p < .001$), and at 8-h intervals (0.89, 95% CI 0.83–0.95, $p < .001$) (Figures 3B and 4B). The cutoff trough concentration was observed to be 8.42 mg/L for a sensitivity of 85.0% and a (1 − specificity) value of 18.7% at 6-h intervals, and 6.63 mg/L for a sensitivity of 87.5% and a (1 − specificity) value of 20.7% at 8-h intervals.

4 | DISCUSSION

In this study, we evaluated the pharmacokinetics of vancomycin in Chinese critically ill pediatric patients by enrolling children admitted to intensive care unit who needed vancomycin for their treatment. We included neonates to assess the effect of age on the pharmacokinetics of vancomycin, and children with renal insufficiency to assess the correlation between trough concentration and AUC_{24} in a real-world clinical setting. In other studies, those two populations were usually excluded or studied separately.[23–25]

Critical care patients have unique PK parameters. The value of vancomycin Vd observed in this study (0.62 ± 0.27 L/kg for neonates, and 0.61 ± 0.33 L/kg for ≥1 month), was similar to the values that have been reported (0.55 ± 0.10 L/kg).[8] However, the value of CL observed in this study was a little lower (0.11 ± 0.06 L/kg/h for neonates, and 0.15 ± 0.07 L/kg/h for ≥1 month) than the value reported (0.16 ± 0.01 L/kg/h), resulting in a little longer $t_{1/2}$ of vancomycin observed (4.41 ± 2.45 h for neonates, and 3.09 ± 1.78 h for ≥1 month) than the value reported (2.65 ± 1.12 h).[8] The ages of the patient populations were slightly different, for the patients in our study were much younger [1.0 (0.5, 5.0) vs. 6.3 (3.3–10.8), respectively)].

Vancomycin $t_{1/2}$ of 6–10 h in neonates, 4 h in infants, and 2.2–3 h in older children have been reported.[26] Similar $t_{1/2}$ in children older than 1 month, but a much shorter $t_{1/2}$ in neonates were observed in the present study, may be due to changes in Vd and/or drug

TABLE 2 Pharmacokinetic data of children of different ages

Parameter	<1 month ($n = 20$)	1–23 months ($n = 209$)	2–5 years ($n = 122$)	6–14 years ($n = 105$)	*p* value
Male, count (%)	12 (60.0)	128 (61.2)	70 (57.4)	71 (67.6)	.464
Vancomycin dose, mg/kg/d	38.5 ± 10.3	45.4 ± 9.4	46.2 ± 9.6	44.0 ± 11.3	.023
Mean ± SD (IQR)	(30.9, 44.0)	(40.0, 55.8)	(40.0, 59.7)	(38.5, 57.1)	
Vancomycin concentration					
Trough, mg/L	9.2 ± 5.0	8.8 ± 6.0	7.7 ± 5.8	7.2 ± 4.6	.026
Mean ± SD (IQR)	(5.9, 11.7)	(4.6, 11.2)	(4.3, 9.3)	(3.6, 9.5)	
Peak, mg/L	24.9 ± 13.0	20.8 ± 9.3	19.5 ± 8.7	21.5 ± 11.6	.189
Mean ± SD (IQR)	(18.6, 25.9)	(15.2, 25.3)	(13.6, 25.2)	(14.0, 23.8)	
Vancomycin AUC_{24}, mg h/L	409 ± 202	378 ± 169	350 ± 170	360 ± 178	.227
Mean ± SD (IQR)	(273, 472)	(262, 460)	(241, 420)	(238, 440)	
$t_{1/2}$, h Mean ± SD (IQR)	4.41 ± 2.46 (2.95, 5.06)	3.27 ± 1.80 (1.99, 3.98)	2.95 ± 1.96 (1.95, 3.31)	2.89 ± 1.46 (2.05, 3.40)	.003
Vd, L/kg	0.62 ± 0.27	0.61 ± 0.33	0.63 ± 0.35	0.57 ± 0.29	.780
Mean ± SD (IQR)	(0.43, 0.80)	(0.38, 0.73)	(0.39, 0.76)	(0.37, 0.72)	
CL, L/kg/h	0.11 ± 0.06	0.14 ± 0.07	0.16 ± 0.08	0.15 ± 0.07	.818
Mean ± SD (IQR)	0.07, 0.14)	(0.10, 0.18)	(0.10, 0.20)	(0.10, 0.19)	

Note: AUC_{24}, area under the time-concentration curve over 24 h; IQR, interquartile range; $t_{1/2}$, elimination half-life; CL clearance; Vd, volume of distribution.

TABLE 3 Vancomycin serum concentration and AUC_{24} in children with different daily doses

Parameter	40 mg/kg/d[a]		60 mg/kg/d[b]	*p* value[c]
	<1 month ($n = 10$)	≥1 month ($n = 267$)	≥1 month ($n = 119$)	
Vancomycin concentration				
Trough, mg/L	11.7 ± 6.2	8.4 ± 6.2	10.5 ± 12.8	.066, .098
Mean ± SD (IQR)	(8.0, 16.7)	(4.4, 10.4)	(4.9, 11.3)	
Peak, mg/L	28.9 ± 17.0	20.2 ± 10.5	24.6 ± 14.7	.050, <.001
Mean ± SD (IQR)	(18.2, 33.5)	(12.9, 25.1)	(17.2, 27.9)	
Vancomycin AUC_{24}, mg/h/L	487 ± 255	363 ± 189	455 ± 318	.074, <.001
Mean ± SD (IQR)	(288, 604)	(230, 438)	(303, 489)	
AUC_{24}/MIC, count (%)				.051, .002
<400	4 (40.0)	185 (69.3)	61 (51.3)	
=400–600	3 (30.0)	57 (21.3)	44 (37.0)	
>600	3 (30.0)	25 (9.4)	14 (11.8)	

Note: IQR, interquartile range; AUC_{24}, area under the time-concentration curve over 24 h; MIC, minimum inhibitory concentration (assuming 1 mg/L).

[a]Included patients at dose of 35–45 mg/kg/d.

[b]Included patients at dose of 55–65 mg/kg/d.

[c]For comparison of <1 month vs. ≥1 month at dose of 40, and 40 mg/kg/d vs. 60 mg/kg/d aged ≥1 month, respectively.

clearance in critically ill neonates. Six of 10 (60%) in the neonatal group achieved AUC_{24}/MIC ≥400, much higher than old children at the daily dose of 40 mg/kg/d, while 3 of 10 (30%) in the neonatal group with supratherapeutic AUC_{24} values (>600) at the same dose, indicating that monitoring of vancomycin AUC exposure is of necessity for the prominent increasing renal function that occurs over the first several weeks of life.

For the patients older than 1 month, the recommended AUC_{24}/MIC ≥400 was attained in only 34.3% of critically ill children in our study, which can be largely attributed to the doses that were too low. In the population we studied, only 8.7% of them had positive culture of MRSA, and MIC of 36.6% MRSA isolates was less than 0.5 mg/L, thus clinicians tend to use lower doses empirically because of the concern about nephrotoxicity

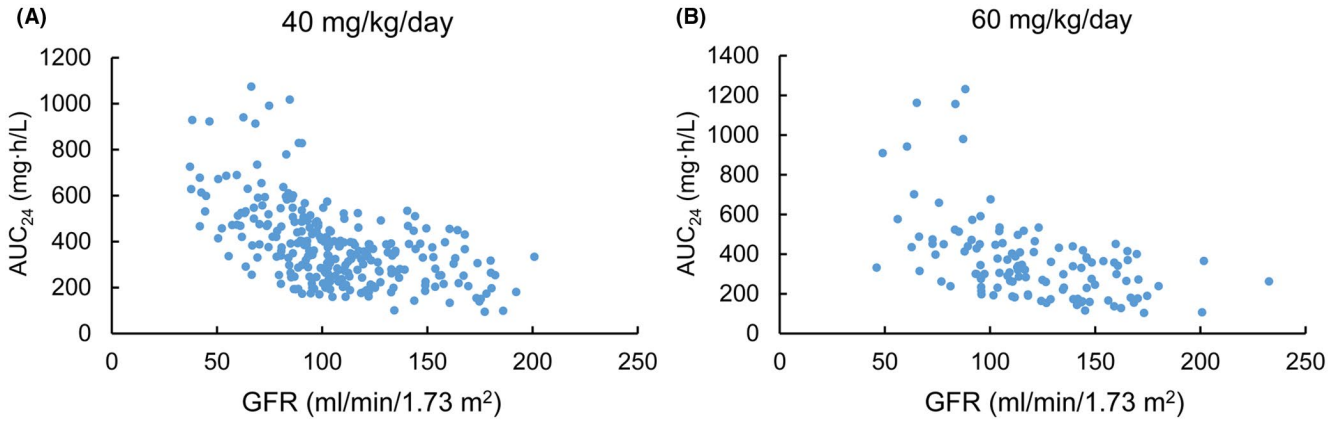

FIGURE 2 Correlation between GFR and AUC_{24} of vancomycin. (A) 40 mg/kg/day group. (B) 60 mg/kg/day group

TABLE 4 Vancomycin serum concentration and AUC_{24} in children with different renal function

Parameter	40 mg/kg/d[a]			60 mg/kg/d[b]		
	eGFR, ml/min 50–130 (*n* = 180)	eGFR, ml/min >130 (*n* = 80)	*p* value	eGFR, ml/min 50–130 (*n* = 86)	eGFR, ml/min >130 (*n* = 29)	*p* value
Vancomycin concentration						
Trough, mg/L	8.8 ± 5.5	5.8 ± 3.3	<.001	10.2 ± 6.6	6.3 ± 3.0	.002
Mean ± SD (IQR)	(4.8, 11.2)	(3.2, 7.7)		(5.6, 12.7)	(4.0, 8.2)	
Peak, mg/L	21.7 ± 10.7	15.2 ± 6.6	<.001	24.9 ± 10.3	18.5 ± 6.5	<.001
Mean ± SD (IQR)	(15.3, 26.8)	(10.1, 18.7)		(18.8, 28.0)	(13.5, 21.4)	
Vancomycin AUC_{24}, mg h/L	386 ± 180	268 ± 104	<.001	459 ± 185	323 ± 93	<.001
Mean ± SD (IQR)	(260, 469)	(180, 339)		(341, 517)	(252, 384)	
AUC_{24}/MIC, count (%)			<.001			.001
<400	114 (63.3)	70 (87.5)		36 (41.9)	23 (79.3)	
=400–600	46 (25.6)	10 (12.5)		38 (44.2)	6 (20.7)	
>600	20 (11.1)	0 (0)		12 (14.0)	0 (0)	

Note: AUC_{24}, area under the time–concentration curve over 24 h; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MIC, minimum inhibitory concentration (assuming 1 mg/L).

[a]Included patients at dose of 35–45 mg/kg/d.

[b]Included patients at dose of 55–65 mg/kg/d.

of vancomycin. However, in 60 mg/kg/d group, 48.7% of patients achieved AUC_{24}/MIC ≥400, suggesting that a more aggressive approach to vancomycin dosing is necessary in critically ill children with suspected serious MRSA infections. This is consistent with the recommendation in the 2020 IDSA guidelines,[3] and 2020 Chinese guidelines.[9]

Approximately 90% of vancomycin is eliminated by the kidneys, therefore the renal function has a great effect on PK of vancomycin.[27] ARC children have a higher glomerular filtration rate, which means higher vancomycin clearance, resulting in a shorter $t_{1/2}$, lower serum concentration, and smaller AUC_{24}, which leads to insufficient therapy, and an increased risk of treatment failure.[28–30] A total of 27.3% of patients manifested ARC in the present study, which was similar to that (20%–65%) reported in other literature.[29] Only one-sixth of ARC children included in our study achieved optimal AUC_{24} at a dose of 60 mg/kg/d. Thus, when the patient demonstrates ARC, monitoring of renal function is needed, and an increased vancomycin dosage would be considered in order to maintain therapeutic AUC_{24}. According to our results, a daily dose of more than 60 mg/kg/d is needed for pediatric patients if they have ARC and invasive MRSA infections.

A systematic review revealed that trough concentrations of 6–10 mg/L were appropriate for achieving AUC_{24} ≥ 400 in most general hospitalized pediatric patients,[6] and a prospective observational study of critically ill children showed a trough concentration of 7 mg/L has corresponded to an AUC_{24} of 400.[31] Consistent with previous studies, our observed results showed trough vancomycin concentration is a good predictor of AUC_{24}, and the values of trough concentration that correlated with AUC_{24} of 400 were varied according to the vancomycin dosage regimens, 8.42 mg/L for 6-h intervals, 6.63 mg/L

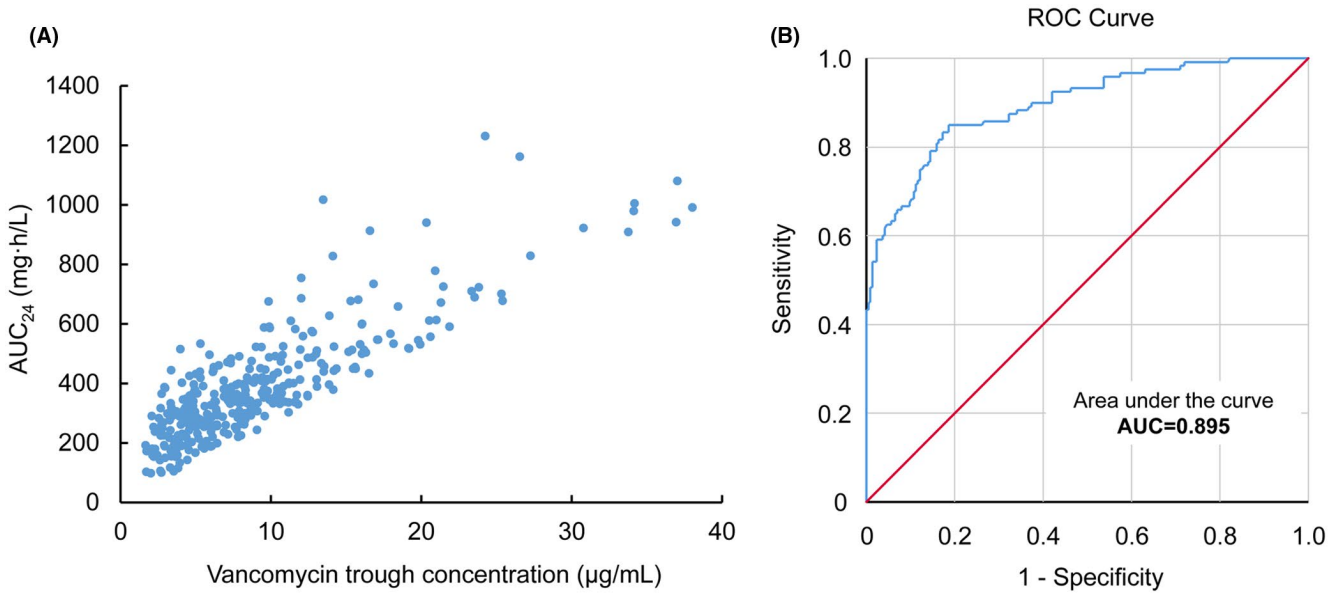

FIGURE 3 Correlation between trough concentration and AUC_{24} of vancomycin in children receiving a 6-h dosing interval regimen. (A) Dot plot of trough concentration and AUC_{24}. (B) Receiver operating characteristic curve of the trough concentration versus AUC_{24}

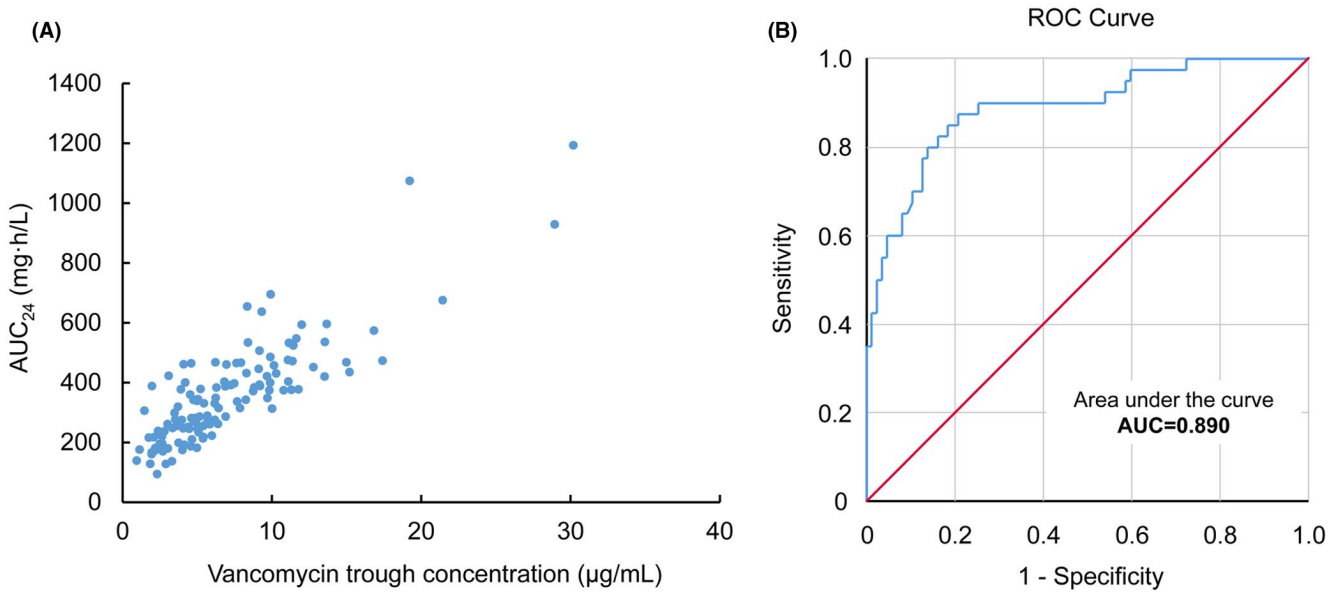

FIGURE 4 Correlation between trough concentration and AUC_{24} of vancomycin in children receiving a 8-h dosing interval regimen. (A) Dot plot of trough concentration and AUC_{24}. (B) Receiver operating characteristic curve of the trough concentration versus AUC_{24}

for 8-h intervals. This is easy to follow that, under the same daily dose and AUC, the value of trough concentration varies with different dosing intervals. Desired vancomycin trough concentration to achieve AUC_{24}/MIC ≥400 under an 8-h interval dosing schedule has rarely been reported in the literature, as the dosing regimen is currently used by fewer institutions in pediatric patients. However, an 8-h interval dosing regimen is recommended in children older than 7 days in 2020 Chinese guidelines, and in children older than 12 years in guidelines from IDSA, therefore our study provides very valuable data.

A few limitations need to be addressed. First, there are limitations inherent to the single-center, retrospective study design. Due to the diversity of the patient population, and in only 8.7% of patients, was MRSA isolated, we did not report associated clinical outcomes or treatment failures. Second, the sample size was relatively small when we stratified the groups into different age and dose categories. Also, there might be a certain deviation between the actual PK parameters and the values calculated by the peak and trough concentrations.

5 | CONCLUSION

Individualized dosing is needed in critically ill neonates and children. Vancomycin trough concentration that related to the AUC_{24} of 400 was much lower in critically ill children than the target trough concentration in adults, and varied depending on vancomycin dosing interval. Increasing the vancomycin daily dose from 40 to 60 mg/kg led to a significant increase in AUC_{24}. However, the dosage regimen of 60 mg/kg/day was not enough for producing AUC_{24} in the range of 400–600 mg h/L in critically ill children, especially in those with ARC. Additional studies of clinical outcomes and vancomycin PK and PD parameters in critically ill pediatric patients are needed to modify current vancomycin dosing recommendations.

DISCLOSURE

The authors declare no conflict of interest.

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ETHICAL APPROVAL

Our research was approved by the ethics committee of Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (Approval No. XHEC-D-2021-036). The study data have been fully de-identified and confidential information of patients has been deleted, and consequently the study was deemed exempt from informed consent by study participants.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Hartman S, Brüggemann R, Orriëns L, Dia N, Schreuder M, de Wildt S. Pharmacokinetics and target attainment of antibiotics in critically Ill children: a systematic review of current literature. *Clin Pharmacokinet*. 2020;59(2):173-205. https://doi.org/10.1007/s40262-019-00813-w
2. Rybak MJ, Lomaestro BM, Rotscahfer JC, et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. *Clin Infect Dis*. 2009;49(3):325-327. https://doi.org/10.1086/600877
3. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2020;77(11):835-864. https://doi.org/10.1093/ajhp/zxaa036
4. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children: executive summary. *Clin Infect Dis*. 2011;52(3):285-292. https://doi.org/10.1093/cid/cir034
5. Álvarez R, López Cortés L, Molina J, Cisneros J, Pachón J. Optimizing the clinical use of vancomycin. *Antimicrob Agents Chemother*. 2016;60(5):2601-2609. https://doi.org/10.1128/aac.03147-14
6. Tkachuk S, Collins K, Ensom M. The relationship between vancomycin trough concentrations and AUC/MIC ratios in pediatric patients: a qualitative systematic review. *Paediatr Drugs*. 2018;20(2):153-164. https://doi.org/10.1007/s40272-018-0282-4
7. Sridharan K, Al Daylami A, Ajjawi R, Al-Ajooz H, Veeramuthu S. Clinical pharmacokinetics of vancomycin in critically Ill children. *Eur J Drug Metab Pharmacokinet*. 2019;44(6):807-816. https://doi.org/10.1007/s13318-019-00568-6
8. Issaranggoon Na Ayuthaya S, Katip W, Oberdorfer P, Lucksiri A. Correlation of the vancomycin 24-h area under the concentration-time curve (AUC24) and trough serum concentration in children with severe infection: a clinical pharmacokinetic study. *Int J Infect Dis*. 2020;92:151-159. https://doi.org/10.1016/j.ijid.2019.12.036
9. He N, Su S, Ye Z, et al. Evidence-based guideline for therapeutic drug monitoring of vancomycin: 2020 update by the division of therapeutic drug monitoring, Chinese pharmacological society. *Clin Infect Dis*. 2020;71(4):S363-S371. https://doi.org/10.1093/cid/ciaa1536
10. Weng X, Zhu C, Duan L, et al. Vancomycin in neonatal sepsis: predictive performance of a Chinese neonatal population pharmacokinetic model and clinical efficacy evaluation. *Eur J Hosp Pharm*. 2021. https://doi.org/10.1136/ejhpharm-2020-002479
11. Liu T, Deng C, Cheng D, et al. Population pharmacokinetics of vancomycin in Chinese pediatric patients. *Int J Clin Pharmacol Ther*. 2017;55(6):509-516. https://doi.org/10.5414/CP202835
12. Jorgensen S, Spellberg B, Shorr A, Wright W. Should therapeutic drug monitoring based on the vancomycin area under the concentration-time curve be standard for serious methicillin-resistant staphylococcus aureus infections?-no. *Clin Infec Dis*. 2021;72(9):1502–1506. https://doi.org/10.1093/cid/ciaa1743
13. Turner RB, Kojiro K, Shephard EA, et al. Review and validation of Bayesian dose-optimizing software and equations for calculation of the vancomycin area under the curve in critically Ill patients. *Pharmacotherapy*. 2018;38(12):1174-1183. https://doi.org/10.1002/phar.2191
14. Pai MP, Neely M, Rodvold KA, Lodise TP. Innovative approaches to optimizing the delivery of vancomycin in individual patients. *Adv Drug Deliv Rev*. 2014;77:50-57. https://doi.org/10.1016/j.addr.2014.05.016
15. Meng L, Wong T, Huang S, et al. Conversion from vancomycin trough concentration-guided dosing to area under the curve-guided dosing using two sample measurements in adults: implementation at an academic medical center. *Pharmacotherapy*. 2019;39(4):433-442. https://doi.org/10.1002/phar.2234
16. Schwartz GJ, Muñoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol*. 2009;20(3):629-637. https://doi.org/10.1681/ASN.2008030287
17. Outcomes IG, (KDIGO) CKD work group. KDIGO. Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2012;2013(3):1-150.
18. Cook A, Hatton-Kolpek J. Augmented renal clearance. *Pharmacotherapy*. 2019;39(3):346-354. https://doi.org/10.1002/phar.2231
19. Tveden-Nyborg P, Bergmann TK, Jessen N, Simonsen U, Lykkesfeldt J. BCPT policy for experimental and clinical studies. *Basic Clin Pharmacol Toxicol*. 2021;128(1):4-8. https://doi.org/10.1111/bcpt.13492
20. Liu Y, Yin Y, Liu X-Z, et al. Retrospective analysis of vancomycin nephrotoxicity in elderly chinese patients. *Pharmacology*. 2015;95:279-284. https://doi.org/10.1159/000381783

21. Jian Y, Lv H, Liu J, et al. Dynamic changes of staphylococcus aureus susceptibility to vancomycin, teicoplanin, and linezolid in a central teaching hospital in Shanghai, China, 2008–2018. *Front Microbiol*. 2020;11:908. https://doi.org/10.3389/fmicb.2020.00908
22. Sawchuk R, Zaske D. Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions: gentamicin in burn patients. *J Pharmacokinet Biopharm*. 1976;4(2):183-195. https://doi.org/10.1007/bf01086153
23. Chen Y, Wu D, Dong M, et al. Population pharmacokinetics of vancomycin and AUC-guided dosing in Chinese neonates and young infants. *Eur J Clin Pharmacol*. 2018;74(7):921-930. https://doi.org/10.1007/s00228-018-2454-0
24. Sosnin N, Curtis N, Cranswick N, Chiletti R, Gwee A. Vancomycin is commonly under-dosed in critically ill children and neonates. *Br J Clin Pharmacol*. 2019;85(11):2591-2598. https://doi.org/10.1111/bcp.14084
25. Zhang H, Wang Y, Gao P, et al. Pharmacokinetic characteristics and clinical outcomes of vancomycin in young children with various degrees of renal function. *J Clin Pharmacol*. 2016;56(6):740-748. https://doi.org/10.1002/jcph.653
26. Broome L, So TY. An evaluation of initial vancomycin dosing in infants, children, and adolescents. *Int J Pediatr*. 2011;2011:1-4. https://doi.org/10.1155/2011/470364
27. Sinha Ray A, Haikal A, Hammoud K, Yu A. Vancomycin and the risk of AKI: a systematic review and meta-analysis. *Clin J Am Soc Nephrol*. 2016;11(12):2132-2140. https://doi.org/10.2215/cjn.05920616
28. Lv C-L, Lu J-J, Chen M, et al. Vancomycin population pharmacokinetics and dosing recommendations in haematologic malignancy with augmented renal clearance children. *J Clin Pharm Ther*. 2020;45(6):1278-1287. https://doi.org/10.1111/jcpt.13206
29. Bilbao-Meseguer I, Rodríguez-Gascón A, Barrasa H, Isla A, Solinís M. Augmented renal clearance in critically Ill patients: a systematic review. *Clin Pharmacokinet*. 2018;57(9):1107-1121. https://doi.org/10.1007/s40262-018-0636-7
30. Udy A, Roberts J, Lipman J. Implications of augmented renal clearance in critically ill patients. *Nat Rev Nephrol*. 2011;7(9):539-543. https://doi.org/10.1038/nrneph.2011.92
31. De Cock PAJG, Desmet S, De Jaeger A, et al. Impact of vancomycin protein binding on target attainment in critically ill children: back to the drawing board? *J Antimicrob Chemother*. 2017;72(3):801-804. https://doi.org/10.1093/jac/dkw495

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