INTRODUCTION

Vancomycin is a major glycopeptide antibiotic widely used to treat methicillin-resistant \textit{Staphylococcus aureus} (MRSA), methicillin-resistant coagulase-negative \textit{Staphylococcus} species, and amoxicillin-resistant enterococci infections.\textsuperscript{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 inhibitory concentration (MIC) is commonly used to assess the pharmacokinetic efficacy of vancomycin. The relationship between vancomycin area under the concentration-time curve (AUC) and trough concentration, age, dose, and renal function has been extensively studied in adults. However, limited data are available in critically ill pediatric patients, especially those with augmented renal clearance (ARC).

The AUC/MIC ratio is an important parameter for assessing the pharmacodynamic efficacy of vancomycin. A ratio of \( \frac{AUC_{24}}{MIC} \) of 400 is considered as the benchmark for achieving durable bactericidal effects against MRSA.\textsuperscript{2,3} Additionally, the relationship between the trough concentration and the AUC/MIC ratio is crucial for ensuring optimal vancomycin dosing in critically ill patients, especially those with ARC.

In this study, we aimed to evaluate the pharmacokinetic parameters of vancomycin in Chinese critically ill pediatric patients and to explore the relationship between the trough concentration and the AUC/MIC ratio. We also sought to determine the AUC values that correlate with the trough concentration and to assess the impact of age, dose, and renal function on vancomycin pharmacokinetics.

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, \( \frac{AUC_{24}}{MIC} \) ≥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-hour intervals, and 6.63 mg/L for 8-hour 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
inhibitory concentration (AUC24/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.\textsuperscript{2–4} Monitoring the vancomycin serum steady-state trough concentration as a surrogate is recommended by clinical treatment guidelines, and to achieve the target AUC24/MIC ≥400, the 2009 IDSA guidelines recommend targeting trough concentrations of 15–20 mg/L in both adult and pediatric patients.\textsuperscript{5} However, there was a lack of efficacy and safety data for this recommendation for pediatric patients.\textsuperscript{5,6} Studies have shown that a much lower trough concentration is sufficient to achieve AUC24/MIC ≥400 in children.\textsuperscript{6–11} Therefore, the 2020 guideline from the Chinese Pharmacological Society recommends 5–15 mg/L as the therapeutic trough concentration in pediatric patients or neonates.\textsuperscript{9}

In guideline updated in 2020 from IDSA, AUC-guided dosing and monitoring utilizing first-order PK equations or Bayesian software programs are recommended.\textsuperscript{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.\textsuperscript{10,11} In addition, it requires Bayesian software tools and personnel training in order to implement into clinical practice.\textsuperscript{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.\textsuperscript{13–15} Thus, we monitored the two concentrations (peak, trough) routinely, calculated AUC24 through two-concentration analytic equations to manage vancomycin dosing in clinical practice.\textsuperscript{14}

The objectives of this study were to better understand pediatric age, dose, and trough concentration-associated differences in AUC24 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 antibiotics with MICs, were obtained from electronic medical records. Estimated glomerular filtration rate (eGFR) was assessed using the equation: eGFR = 40.7 x (height/SCr)\textsuperscript{0.64} x (30/BUN)\textsuperscript{0.202} according to the guidelines recommended (BUN, blood urea nitrogen in mg/dl; height in meters; SCr, serum creatinine in mg/dl).\textsuperscript{14,17} Patients with an eGFR <50 mL/min/1.73 m\textsuperscript{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\textsuperscript{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\textsuperscript{2}.\textsuperscript{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.\textsuperscript{19}

2.2 | Vancomycin concentration and PK parameters

Vancomycin concentrations were determined by high-performance liquid chromatography, as described previously.\textsuperscript{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.\textsuperscript{21} PK parameters were derived using a one-compartment model with first-order elimination. The elimination rate constant (k\textsubscript{e}) was calculated by the Sawchuk-Zaske method,\textsuperscript{22} using the peak (C1) and trough (C2) concentrations obtained consecutively.

\[ K_e = \frac{\ln C_1}{t} \]

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

\[ \text{AUC}_1 = \frac{t' \times C_{eo1} + C_t}{2} + \frac{C_{eo1} - C_t}{K_e} \]

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. AUC24 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. 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.

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

- Pediatric patients hospitalized in pediatric intensive care unit or neonatal intensive care unit (≤14 years)
- Intravenous vancomycin for longer than 48 hours
- Measured vancomycin serum trough, peak concentration within 48 - 96 hours of vancomycin therapy initiation.
- June, 2013 - Sep. 2020 (n = 571)

| 101 Exclusions: |
|-----------------|
| 5 Gestational age < 37 weeks |
| 43 inappropriate sampling time |
| 40 enrolled more than once |
| 11 renal replacement therapy |
| 2 laboratory errors |

Enrolled population (n = 470)
**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 (67.10)         |
| 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 m², 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<sub>24</sub>, mg h/L, Median (IQR): 342 (255, 455)

Note: AUC<sub>24</sub>, area under the time-concentration curve over 24 h; eGFR, estimated glomerular filtration rate; IQR, interquartile range.

AUC<sub>24</sub> was dependent on renal function, as it increased with elevated serum creatinine and urea, and decreased with an elevation in eGFR 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<sub>24</sub>. There was no correlation between AUC<sub>24</sub> 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 m². 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<sub>1/2</sub> (2.76 ± 1.28 vs. 3.27 ± 1.97, p = 0.026) h, lower concentrations, and lower AUC<sub>24</sub> values were observed in children with ARC compared to those without ARC (Table 4). AUC<sub>24</sub> < 400 was more common in patients with ARC, and none of them achieved supratherapeutic AUC<sub>24</sub> values (>600) regardless of dosage.

**3.3 | Association between trough vancomycin concentration and AUC<sub>24</sub>**

Significant correlations were observed between the trough vancomycin concentration and AUC<sub>24</sub> 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<sub>24</sub> 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<sub>24</sub> 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). 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<sub>1/2</sub> 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). 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<sub>1/2</sub> of 6–10 h in neonates, 4 h in infants, and 2.2–3 h in older children have been reported.26 Similar t<sub>1/2</sub> in children older than 1 month, but a much shorter t<sub>1/2</sub> in neonates were observed in the present study, may be due to changes in Vd and/or drug.
clearance in critically ill neonates. Six of 10 (60%) in the neonatal group achieved AUC$_{24}$/MIC $\geq 400$, 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 $\geq 400$ 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.

### 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                           | 4.41 ± 2.46       | 3.27 ± 1.80           | 2.95 ± 1.96         | 2.89 ± 1.46          | .003   |
| Mean ± SD (IQR)                       | (2.95, 5.06)      | (1.99, 3.98)          | (1.95, 3.31)        | (2.05, 3.40)         |        |
| 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$^b$ |
|---------------------------------------|----------------|----------------|
|                                       | <1 month (n = 10) | ≥1 month (n = 267) | ≥1 month (n = 119) | p value$^c$ |
| 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.
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, and 2020 Chinese guidelines.

Approximately 90% of vancomycin is eliminated by the kidneys, therefore the renal function has a great effect on PK of vancomycin. 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. A total of 27.3% of patients manifested ARC in the present study, which was similar to that (20%–65%) reported in other literature. 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, 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. 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 for 12-h intervals, and 5.93 mg/L for 24-h intervals.

| Parameter                  | 40 mg/kg/d | 60 mg/kg/d |
|----------------------------|------------|------------|
| eGFR, ml/min               | 50–130     | 50–130     |
| (n = 180)                  | (n = 80)   | (n = 86)   |
| Vancomycin concentration   |            |            |
| Trough, mg/L               | 8.8 ± 5.5  | 10.2 ± 6.6 |
| Mean ± SD (IQR)            | (4.8, 11.2)| (5.6, 12.7)|
| Peak, mg/L                 | 21.7 ± 10.7| 24.9 ± 10.3|
| Mean ± SD (IQR)            | (15.3, 26.8)| (18.8, 28.0)|
| Vancomycin AUC$_{24}$, mg h/L| 386 ± 180  | 459 ± 185  |
| Mean ± SD (IQR)            | (260, 469) | (341, 517) |
| AUC$_{24}$/MIC, count (%)  | <.001      | <.001      |
| <400                       | 114 (63.3)| 36 (41.9)  |
| =400–600                   | 46 (25.6)| 38 (44.2)  |
| >600                       | 20 (11.1)| 12 (14.0)  |

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).

*Included patients at dose of 35–45 mg/kg/d.

*Included patients at dose of 55–65 mg/kg/d.
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 $AUC_{24}/MIC \geq 400$ 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.

**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 $AUC_{24}$.
5 | CONCLUSION

Individualized dosing is needed in critically ill neonates and children. Vancomycin trough concentration that related to the AUC\textsubscript{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\textsubscript{24}. However, the dosage regimen of 60 mg/kg/day was not enough for producing AUC\textsubscript{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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