



Effects of continuous venovenous hemofiltration on vancomycin trough concentrations in critically ill children

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Background: Vancomycin trough concentrations are associated with clinical outcomes and drug adverse effects. This study investigates the effects of continuous venovenous hemofiltration (CVVH) on vancomycin trough concentrations in critically ill children with a vancomycin dosage of 40–60 mg/kg/day.

Methods: Children with steady-state vancomycin trough concentrations admitted to the pediatric intensive care unit (PICU) between January 2016 and December 2019 were retrospectively enrolled. Patients were divided into CVVH and non-CVVH groups according to treatment differences and renal function. Vancomycin trough concentrations were then compared between the groups, and risk factors for supratherapeutic trough concentrations (>20 mg/L) were analyzed with logistic regression.

Results: Of the 119 patients included, 35 were enrolled in the CVVH group and 84 in the non-CVVH group. Median vancomycin trough concentrations were significantly higher in the CVVH group than those in the non-CVVH group [14.9 (IQR =9.6–19.6) *vs.* 9.3 (IQR =7.0–13.4), $P<0.001$] and the proportion of therapeutic trough concentrations (10–20 mg/L) was similar between CVVH and non-CVVH groups (54.3% *vs.* 39.3%, $P=0.133$). However, CVVH therapy patients had a significantly higher proportion of supratherapeutic trough concentrations (20.0% *vs.* 1.2%, $P=0.001$) compared to the non-CVVH group. Multivariate analysis demonstrated that the Pediatric Risk of Mortality (PRISM) III score ≥ 28 (OR =13.7; 95% CI, 1.4–137.0; $P=0.026$) was an independent risk factor for supratherapeutic trough concentrations in critically ill patients.

Conclusions: CVVH therapy affects vancomycin trough concentrations and is associated with supratherapeutic concentrations with a 40–60 mg/kg/day vancomycin dosage. PRISM III scores ≥ 28 may serve as an independent risk factor for supratherapeutic trough concentrations in children receiving CVVH therapy.

Keywords: Vancomycin; continuous venovenous hemofiltration (CVVH); children; concentration

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Introduction

Vancomycin is a major glycopeptide antibiotic used in the treatment of most Gram-positive infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), and amoxicillin-resistant *enterococci* (1). It can be taken orally to treat pseudomembranous enterocolitis caused by *Clostridium difficile* (2). Vancomycin is currently recommended as an empirical antibiotic for pediatric patients with severe sepsis and is one of the most frequently used antibiotics in the intensive care unit (ICU) (3,4). Studies have indicated that nearly 30% of patients had sepsis either on admission to or during their ICU stay (5), and 21% of children with severe sepsis had acute kidney injury (AKI) and progress to requiring renal replacement therapy (6,7). Also, children with AKI and receiving continuous renal replacement therapy (CRRT) had high mortality (42–50%) (8,9). Continuous venovenous hemofiltration (CVVH) is a convective clearance CRRT modality that can remove middle molecular weight substances (500–5,000 Da) efficiently with a little impact on hemodynamics (10). As vancomycin has a molecular weight of 1445 Da, it can be excreted during CVVH therapy (1).

Vancomycin is bactericidal and exhibits time-dependent killing, which means that its antibacterial activity is pharmacokinetically dependent on the time that its serum concentration is above the minimum inhibitory concentration (MIC) (11). A pharmacodynamic study demonstrated that the area under the curve (AUC) ratio to the MIC ≥ 400 was an optimal predictor of vancomycin efficacy (12). However, in clinical practice, determining the AUC with the trapezoidal rule requires multiple serum concentrations, and it may be difficult for pediatricians to obtain multiple blood samples from children. Therefore, vancomycin trough concentrations have been regarded as surrogate measures for AUC/MIC (13). Reaching therapeutic trough concentrations is one of the most important factors in critically ill patients' successful treatment outcomes (14). Both the Infectious Diseases Society of America (IDSA) and the Japanese Society of Chemotherapy recommend a vancomycin trough concentration of 10–20 mg/L; 10–15 mg/L for uncomplicated infections and 15–20 mg/L for serious infections (including bacteremia, infective endocarditis, osteomyelitis, meningitis, and pneumonia) (13,15). The Chinese Pharmacological Society recommends 10–15 mg/L as the therapeutic trough concentration for adult patients and 10–20 mg/L for severe MRSA infections (16).

Lower vancomycin trough concentrations are associated with increased mortality and drug resistance, while higher concentrations can induce vancomycin-associated nephrotoxicity (17–20). Studies in both adults and children revealed that concentrations higher than 20 mg/L were associated with nephrotoxicity (17–19). Achieving the optimal vancomycin trough concentration without drug toxicity is undoubtedly important for critically ill patients receiving concurrent vancomycin and CVVH therapy. Some studies investigated CVVH therapy's effects on vancomycin trough concentrations in adult patients (21–23). A prospective observational study suggested that continuous infusion vancomycin (CIV) achieved target concentrations more rapidly and consistently when critically ill adult patients received CVVH treatment (23). Frazee *et al.* (21) demonstrated an inverse association between CVVH hemofiltration rates and serum vancomycin concentrations in adults; increases in hemofiltration rates significantly correlated with reductions in trough concentrations. While studies of adult patients provide important insight, few studies have explored the correlations between CVVH therapy and vancomycin trough concentrations in children. We conducted this retrospective study to investigate the effects of CVVH on vancomycin trough concentrations in critically ill children receiving vancomycin dosage of 40–60 mg/kg/day. We present the following article following the STROBE reporting checklist (available at: <http://dx.doi.org/10.21037/atm-20-4005>).

Methods

Study site and study population

This was a retrospective, observational cohort study conducted in the Children's Hospital of Chongqing Medical University, a 1,500-bed [40 pediatric intensive care unit (PICU) beds] tertiary teaching hospital in Chongqing, China, ranked among the top three domestic children's hospitals (rank list: <http://top100.imicams.ac.cn/home>). A total of 445 patients hospitalized in the PICU between January 2016 and December 2019 and receiving vancomycin therapy were retrospectively enrolled. The inclusion criteria were all of the following: (I) aged <18 years, (II) received vancomycin therapy with a dose of 40–60 mg/kg/day >48 hours, (III) either normal renal function or AKI (24), (IV) serum trough concentrations were obtained at steady-state conditions, 0.5±0.5 hour before the fourth or fifth dose (13), (V) if patients had >1 episode of vancomycin treatment, only the first episode was considered. The exclusion criteria included

any of the following: (I) patients with incomplete clinical information, (II) concomitant extracorporeal membrane oxygenation (ECMO) therapy (25), (III) the vancomycin trough concentration was measured before CVVH treatment, (IV) AKI without CVVH therapy. The study was conducted following the Declaration of Helsinki (as revised in 2013) and approved by the institutional review board of the Children's Hospital of Chongqing Medical University (Approval ID: 2020-191). Informed individual consent was waived owing to the retrospective design of the study.

Data collection

Trained staff extracted patient data from electronic medical records using a standard collection form. Along with demographic characteristics (age, sex, body weight), the source of infection, the severity of illness estimated by the Pediatric Risk of Mortality (PRISM) III scores (26), renal parameters (hemofiltration rates, blood flow rates, dialyzer used and urine output), vancomycin-related details (dose, frequency and duration, and concentrations), duration of hospital stay, duration of PICU stay, and clinical outcomes (survival/non-survival) were collected.

Classifications and definitions

Patients were divided into two subgroups: (I) a CVVH group in which patients received vancomycin and CVVH therapy concurrently due to AKI and (II) a Non-CVVH group in which patients with normal renal function received vancomycin therapy only. We defined AKI as urine output <0.5 mL/kg/h for 6 hours (24), and the source of infection was defined based on clinical records and laboratory or radiographic results. The severity of illness at the time of extracting serum vancomycin trough concentration samples was assessed by the PRISM III score (26), with a higher score indicating increasing severity. A vancomycin trough concentration between 10–20 mg/L was defined as a therapeutic trough concentration following IDSA guideline recommendations. A level <10 mg/L was defined as a subtherapeutic trough concentration and a level >20 mg/L as a supratherapeutic trough concentration (13).

Vancomycin therapy and trough concentrations

All eligible children received vancomycin (Vianex S.A., Athens, Greece) intravenously at an empiric dose of 40–60 mg/kg/day divided every 6 hours (a maximum daily

dose $<2,000$ mg) as recommended by pediatric references and drug instructions (27,28). The individualized initial daily dosage was determined by attending pediatric clinicians according to the severity of the disease and renal function. The dosage regimen was recommended by therapeutic drug monitoring (TDM), and the TDM target for the trough concentration was 10–20 mg/L (13). Vancomycin was infused in an appropriate normal saline (0.9%) intravenous injection for over 60 minutes, and its use was based on suspected or documented source(s) of Gram-positive cocci infections. Blood samples of approximately 2 mL were obtained at steady-state conditions 0.5 ± 0.5 hours before the fourth or fifth dose to determine the trough concentration (13). Trough concentration analysis was performed using the chemiluminescence immunoassay method (Abbott Laboratories, Chicago, IL, USA), which has an analytical range of 0.0–100.0 mg/L with a between-run coefficient of variation of $<15\%$ throughout the analytical range. A central laboratory was assigned to test all blood samples within 24 hours, and intra- and inter-batch quality control was performed following the China National Accreditation Service for Conformity Assessment standard.

CVVH procedures

All CVVH treatments were performed using a 0.7 m² high flux polysulfone membrane filter AEF-07 (Asahi Kasei Medical, Tokyo, Japan). A double-lumen catheter was inserted into either the internal jugular, femoral, or subclavian veins depending on clinical circumstances, and post-dilution performed using the CVVH system. The blood flow rate was 3–5 mL/kg/min, and the hemofiltration rate was 20–35 mL/kg/h for each patient. Sodium citrate was added to equipment to prevent blood coagulation.

Outcomes

The primary outcome was the effects of CVVH on vancomycin trough concentrations with a vancomycin dosage of 40–60 mg/kg/day, and the secondary outcome was risk factors for supratherapeutic trough concentrations in critically ill children.

Statistical analysis

Descriptive statistics were used to express the demographic data. The categorical variables were described as numbers (n) and percentages (%), while the median with inter-

quartile ranges (IQRs) was used to summarize non-normally distributed variables. Distribution of non-normally variables was assessed using the Mann-Whitney *U* test, and the chi-square or Fisher's exact test studied categorical data. Receiver operating characteristic analysis was employed to select the optimal cutoff point of PRISM III scores using the maximum Youden's index (29) and calculated sensitivity and specificity with 95% confidence intervals (CIs) for the optimal cutoff point. Univariate and multivariate logistic regression analyses were used to evaluate the correlation between possible factors and supratherapeutic trough concentrations, and odds ratios (ORs) and 95% CIs were calculated. For the logistic regression analysis, PRISM III scores were converted into categorical variables according to the optimal cutoff value as defined by receiver operating characteristic curve analysis, and a *P* value <0.05 (two-sided) was considered significant. IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

Enrollment

During the study period, 445 patients were evaluated for eligibility, and 161 were excluded for lacking available steady-state trough concentrations. A further 79 were excluded for receiving other vancomycin dosing regimens, 32 as they had AKI but did not receive CVVH therapy, 30 for having incomplete clinical information, 18 for having vancomycin trough concentrations measured before CVVH therapy, and six for receiving concomitant ECMO therapy. The remaining 119 patients were included in the study, of whom 35 received vancomycin and CVVH therapy simultaneously (*Figure 1*).

Basic characteristics and demographic data of CVVH and non-CVVH group patients

Basic characteristics and demographic data of CVVH and non-CVVH group patients are presented in *Table 1*. The median vancomycin trough concentrations and PRISM III scores in the CVVH group were significantly higher than those in the non-CVVH group [14.9 (IQR =9.6–19.6) *vs.* 9.3 (IQR =7.0–13.4), *P*<0.001; 28.0 (IQR =21.0–32.0) *vs.* 21.0 (IQR =15.0–24.0), *P*<0.001, respectively]. Of all enrolled patients, 27 had PRISM III scores \geq 28 and 70.4% (19/27) of these received CVVH therapies. Moreover, CVVH therapy patients had a significantly longer duration of PICU stay

[17.0 (IQR =10.0–32.0) *vs.* 13.0 (IQR =7.3–20.5) days, *P*=0.012] and hospital stay [39.0 (IQR =20.0–57.0) *vs.* 22.0 (IQR =15.0–34.0) days, *P*<0.001] when compared to non-CVVH groups. There were no remarkable differences in demographic data, initial vancomycin daily doses, duration of vancomycin therapy, infection sites, and mortality between the two groups (*P*>0.05).

Vancomycin trough concentrations in CVVH and non-CVVH groups

Figure 2 shows the distribution of vancomycin trough concentrations between CVVH and non-CVVH group patients. The proportion of therapeutic trough concentrations was similar between CVVH and non-CVVH groups (54.3% *vs.* 39.3%, *P*=0.133). However, CVVH therapy group patients had a significantly higher proportion of supratherapeutic trough concentrations than non-CVVH groups (20.0% *vs.* 1.2%, *P*=0.001) with current vancomycin dosing strategies. Also, 87.5% (7/8) of patients with supratherapeutic vancomycin trough concentrations were in the CVVH therapy group. As expected, our results showed a remarkably lower proportion of subtherapeutic trough concentrations in the CVVH therapy group when compared to non-CVVH groups (25.7% *vs.* 59.5%, *P*=0.001).

Risk factors for supratherapeutic trough concentrations

On bivariate analysis, CVVH therapy and PRISM III scores were related to supratherapeutic trough concentrations (*Table 2*). The receiver operating characteristic curve (0.87; 95% CI: 0.77–0.96) supported PRISM III scores could serve as a tool to screen supratherapeutic trough concentrations and PRISM III scores \geq 28 could be an optimal cutoff point with 87.5% sensitivity and 82.0% specificity. Further multivariate analysis revealed that a PRISM III score \geq 28 was the only independent risk factor for supratherapeutic trough concentrations in critically ill children (OR =13.7; 95% CI: 1.4–137.0; *P*=0.026) (*Table 3*).

Discussion

To the best of our knowledge, this is the first study to investigate the effects of CVVH therapy on vancomycin trough concentrations with a vancomycin dosage of 40–60 mg/kg/day. While our results showed CVVH and non-CVVH patients had a similar proportion of

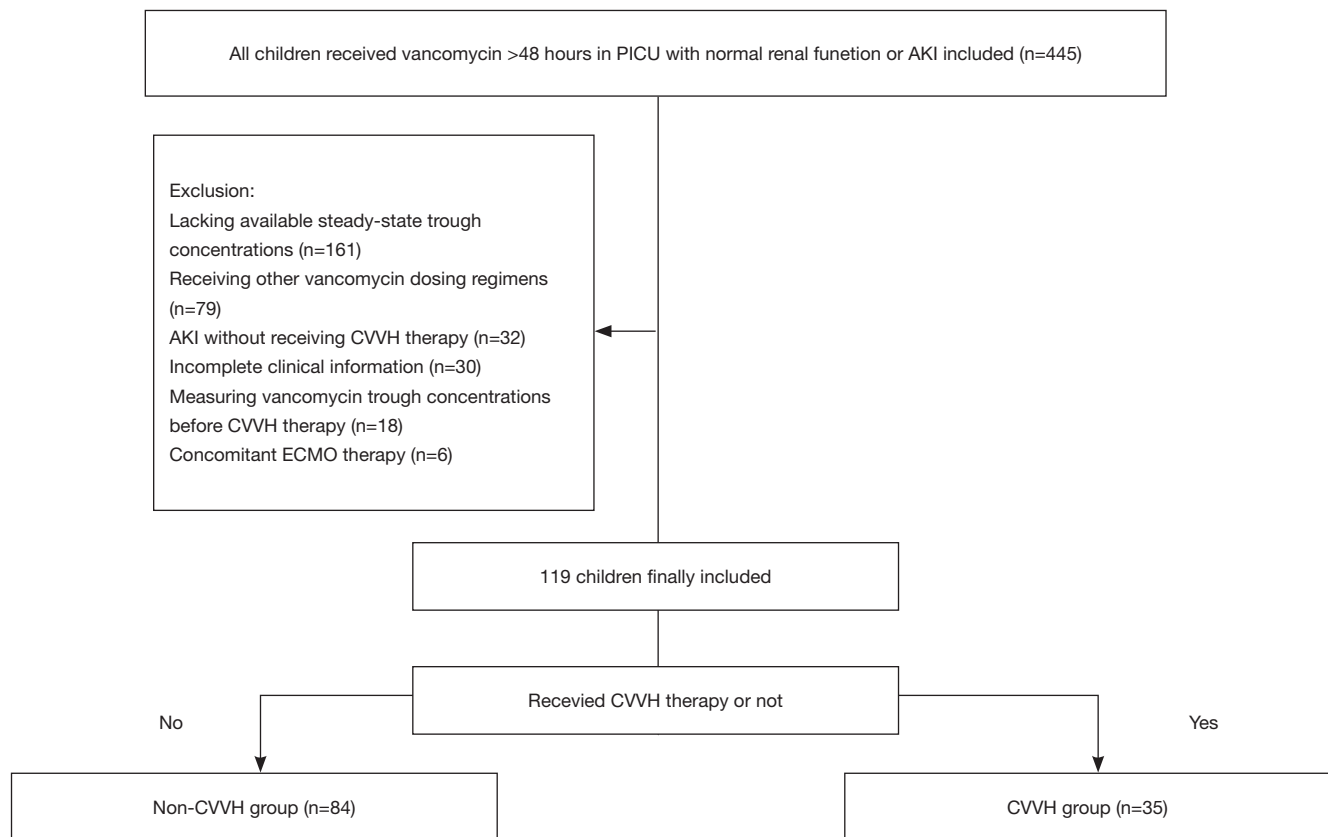


Figure 1 Flow chart of patient enrollment. PICU, pediatric intensive care unit; AKI, acute kidney injury; CVVH, continuous venovenous hemofiltration; ECMO, extracorporeal membrane oxygenation.

therapeutic trough concentrations, CVVH patients had a significantly higher proportion of supratherapeutic trough concentrations and a lower proportion of subtherapeutic trough concentrations when compared to the non-CVVH group. In contrast to our findings, Paciullo *et al.* (30) found CVVH therapy-induced subtherapeutic vancomycin concentrations in adult patients, and they recommended a higher vancomycin dosage for these patients. A possible explanation for this inconsistency could be in the significantly higher the average hemofiltration rate seen in the Paciullo study (56 mL/kg/h) in comparison to ours (20–35 mL/kg/h) as there is an inverse correlation between hemofiltration rates and vancomycin serum concentrations (21). In a prospective study, Li *et al.* (31) showed that CVVH clearance constituted 60–70% of total vancomycin clearance with a hemofiltration rate of 30–40 mL/kg/h.

Nevertheless, more than 80% of vancomycin is eliminated in the urine within 24 h after administering a

single dose in normal renal function patients (1). In this study, the hemofiltration rates of 20–35 mL/kg/h were lower than those in Li *et al.* (30–40 mL/kg/h) (31), leading to a lower percentage of vancomycin clearance. Therefore, vancomycin trough concentrations could be increased in CVVH therapy children due to vancomycin's reduced clearance.

Our results are consistent with recent studies, which showed that a dosage of 40–60 mg/kg/day was inadequate to reach therapeutic vancomycin concentrations and suggested critically ill children receive higher dosages (20,32). In our study's non-CVVH group, only 39.3% (33/84) of patients attained therapeutic vancomycin concentrations, and 60% (50/84) obtained subtherapeutic concentrations with the dosage of 40–60 mg/kg/day. However, our results also revealed CVVH therapy induced a higher proportion of supratherapeutic trough concentrations than non-CVVH therapy, which indicated that children receiving CVVH therapy might require lower vancomycin dosages

Table 1 Basic characteristics and demographic data of CVVH and non-CVVH therapy group patients

Variables	CVVH group (n=35)	Non-CVVH group (n=84)	P value
Demographics			
Age (months), median (IQR)	18.0 (8.5–80.0)	15.5 (5.4–70.3)	0.275
Male, n (%)	21 (60.0)	52 (61.9)	0.846
Body weight (kg), median (IQR)	12.0 (8.5–21.0)	10.3 (7.0–17.9)	0.086
Vancomycin therapy			
Initial daily dose (mg/kg/day), median (IQR)	40.0 (40.0–47.0)	40.0 (40.0–50.0)	0.498
Duration of therapy (days), median (IQR)	8.0 (5.0–11.0)	8.5 (6.0–12.0)	0.481
Trough concentrations (mg/L), median (IQR)	14.9 (9.6–19.6)	9.3 (7.0–13.4)	<0.001
PRISM III scores, median (IQR)	28.0 (21.0–32.0)	21.0 (15.0–24.0)	<0.001
Duration of hospital stay (days), median (IQR)	39.0 (20.0–57.0)	22.0 (15.0–34.0)	<0.001
Duration of PICU stay (days), median (IQR)	17.0 (10.0–32.0)	13.0 (7.3–20.5)	0.012
Infection site^a			
Respiratory system, n (%)	25 (71.4)	66 (78.6)	0.403
Bacteremia, n (%)	16 (45.7)	32 (38.1)	0.440
Nervous system, n (%)	8 (22.9)	14 (16.7)	0.428
Skin and soft tissue, n (%)	6 (17.1)	6 (7.1)	0.099
Alimentary system, n (%)	4 (11.4)	2 (2.4)	0.061
Cardiovascular system, n (%)	1 (2.9)	3 (3.6)	1.000
Unknown, n (%)	0 (0.0)	2 (2.4)	1.000
In hospital mortality, n (%)	13 (37.1)	34 (40.5)	0.735

^aThe total percentage may >100 due to a patient having multiple infectious sites. CVVH, continuous venovenous hemofiltration; IQR, interquartile range; PRISM, pediatric risk of mortality; PICU, pediatric intensive care unit.

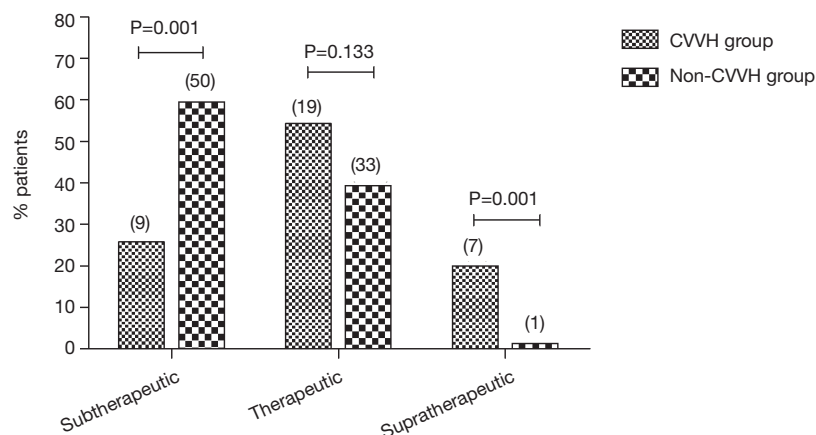


Figure 2 The distribution of vancomycin trough concentrations in CVVH and non-CVVH groups. The number in brackets above the columns reflects the total number of patients. CVVH, continuous venovenous hemofiltration.

Table 2 Basic characteristics between different vancomycin trough concentrations

Variables	Non-supratherapeutic (n=111)	Supratherapeutic (n=8)	P value
Age (months), median (IQR)	16.0 (6.0–72.0)	21.5 (11.3–41.0)	0.718
Male, n (%)	69 (62.2)	4 (50.0)	0.759
Body weight (kg), median (IQR)	11.0 (8.0–20.0)	11.0 (8.5–17.4)	0.886
CVVH therapy, n (%)	28 (25.2)	7 (87.5)	0.001
PRISM III scores, median (IQR)	21.0 (16.0–25.0)	29.5 (28.0–34.8)	0.001
Initial vancomycin daily dose (mg/kg/day), median (IQR)	40.0 (40.0–47.6)	51.0 (41.3–58.8)	0.053
Duration of vancomycin therapy (days), median (IQR)	8.0 (6.0–12.0)	7.5 (4.3–9.8)	0.171

CVVH, continuous venovenous hemofiltration; PRISM, pediatric risk of mortality; IQR, inter-quartile range.

Table 3 Logistic analysis of risk factors for supratherapeutic trough concentrations

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
CVVH therapy	20.8 (2.4–176.1)	0.005	6.6 (0.6–67.3)	0.111
PRISM III scores ≥ 28	31.9 (3.7–273.6)	0.002	13.7 (1.4–137.0)	0.026

CVVH, continuous venovenous hemofiltration; PRISM, pediatric risk of mortality; CI, confidence interval; OR, odds ratio.

to obtain therapeutic concentrations than non-CVVH therapy patients. Undoubtedly, higher vancomycin daily dosages caused higher trough concentrations. Although no significant differences in the initial vancomycin daily dosage were found between supratherapeutic and non-supratherapeutic groups ($P > 0.05$), the results showed the median initial vancomycin dosage of the supratherapeutic group was 51 mg/kg/day, which was higher than that in the non-supratherapeutic group (40 mg/kg/day). Therefore, caution should be applied when adjusting vancomycin dosages in children receiving vancomycin and CVVH therapy concurrently. Moreover, close monitoring of vancomycin trough concentrations is highly warranted in children receiving vancomycin and CVVH therapy simultaneously.

We found that PRISM III scores ≥ 28 increased the risk of reaching supratherapeutic trough concentrations nearly 13.7-fold. Higher PRISM III scores indicate more serious conditions (26), and critically ill patients usually have organ dysfunctions, multi-drug interactions, and other therapeutic interventions, which may impact antimicrobial pharmacokinetics (33). In this study, 27 patients had PRISM III scores ≥ 28 , and 19 (70.4%) had AKI and received CVVH therapy. We found that CVVH therapy was associated

with supratherapeutic trough concentrations. This may indicate multiple organ dysfunctions, and CVVH therapy increases the accumulation and decreases the elimination of drugs, leading to higher vancomycin trough concentrations in critically ill patients. It has been widely acknowledged that higher vancomycin trough concentrations increased the risk of nephrotoxicity and that a concentration of higher than 20 mg/L was an independent risk factor for nephrotoxicity both in children and adult patients (17–19). The present study results support the observation that vancomycin trough concentrations should be monitored closely in children with PRISM III scores ≥ 28 . There are several limitations to this study. Firstly, its retrospective design means that it was difficult to control all the variables to avoid biases. Secondly, this was a single-center study, and the findings may be affected by the utilization of different institutional CVVH practices, including but not limited to hemofiltration rates, flow rates of the blood, dialyzer selection, and pre/post-dilution fluid. Thirdly, the lack of microbiological outcomes prevented us from analyzing the effect of subtherapeutic trough concentrations, and finally, we failed to assess supratherapeutic trough concentration effects on nephrotoxicity because of a small sample size. A larger multicenter prospective study is needed in the future

to investigate the association between vancomycin trough concentration and its associated nephrotoxicity in pediatric patients receiving CVVH therapy to validate our results.

Conclusions

CVVH therapy affects vancomycin trough concentrations and is associated with supratherapeutic trough concentrations with a 40–60 mg/kg/day vancomycin dosage. PRISM III scores ≥ 28 may serve as an independent risk factor for supratherapeutic trough concentrations in CVVH therapy patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at: <http://dx.doi.org/10.21037/atm-20-4005>

Data Sharing Statement: Available at <http://dx.doi.org/10.21037/atm-20-4005>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at: <http://dx.doi.org/10.21037/atm-20-4005>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of the Children's Hospital of Chongqing Medical University (Approval ID: 2020-191) and individual consent for this retrospective analysis was waived.

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