Comparison of Vancomycin Clearance Between Augmented Renal Clearance and Normal Renal Function in Critically Ill Infants: A Population Pharmacokinetics Study

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Abstract

Augmented renal clearance presents as super-renal function with enhanced renal perfusion and glomerular hyperfiltration in many critically ill infants.

This study was to compare vancomycin clearance (CL) between critically ill infants with augmented renal clearance and with normal renal function and to optimize the vancomycin dosage. Data were retrospectively obtained from infants treated in intensive care units. Population pharmacokinetics analysis was conducted using nonlinear mixed-effects model software. A total of 66 critically ill infants were included: 47 infants with augmented renal clearance and 19 infants with normal renal function. The median doses of vancomycin for infants with augmented renal clearance and with normal renal function were 48 and 47 mg/kg/day (P > .05), respectively. The median CL in infants with augmented renal clearance was increased 1.96-fold compared with infants who had normal renal function (0.98 versus 0.5 L/h, P < .001). Simulations indicated that the recommended dosage of 60, 70, 80, and 100 mg/kg/day would be appropriate for infants with an estimated glomerular filtration rate (eGFR) of 130–149, 150–169, 170–189, 190–209, and >210 mL/min/1.73 m², respectively. Doses of 70 and 75 mg/kg/day were recommended for infants with augmented renal clearance and gestational ages of 27–32.9 and 33–39 weeks, respectively. Doses of 70, 75, 80, and 90 mg/kg/day were recommended for infants with augmented renal clearance and weights of 2.0–2.9, 3.0–3.9, 4.0–4.9, and 5.0–6.0 kg, respectively. In conclusion, the typical vancomycin dosage is insufficient for critically ill infants with augmented renal clearance. Premature infants and infants of low weight with augmented renal clearance need individualized dosing regimens to obtain an adequate area under the serum concentration time curve over 24 h/minimum inhibitory concentration ratio.

Keywords

augmented renal clearance, critically ill infant, normal renal function, population pharmacokinetics, vancomycin

Vancomycin is a glycopeptide antibiotic that is frequently used to treat methicillin-resistant Staphylococcus aureus (MRSA) infections in pediatrics. Vancomycin is mainly metabolized by the renal system and excreted in the urine as a prototype, and vancomycin pharmacokinetics (PK) is closely related to renal function. Augmented renal clearance is a pathological phenomenon in critically ill patients, which is characterized by increased creatinine clearance and the elimination of renal-eliminated drugs. The patient’s creatinine clearance in this state is greater than 130 mL/min/1.73 m². Young age, male sex, and less severe illness, trauma, and burns are generally considered to be risk factors for augmented renal clearance. Standard dosage regimens of renal clearance drugs are usually used for patients with normal renal function. However, typical dosages of drugs, including vancomycin, may not reach pharmacodynamic targets in the population with augmented renal clearance. Some studies have confirmed that augmented renal clearance increases the risk of subtherapeutic concentrations of vancomycin. The mechanism of augmented renal clearance has not yet been fully defined in critically ill patients. A common theme in critically ill patients with augmented renal clearance is aggressive fluid loading, the risk of capillary leak syndrome, and the subsequent expansion of the drug distribution volume. In addition, cytokines and inflammatory mediators are increased in critically ill infected patients. These endogenous substances promote changes in renal perfusion and glomerular filtration. It is necessary to evaluate the PK of critically ill groups.
Severe bacterial infections are a major challenge in the intensive care unit (ICU) because of their high prevalence and mortality. Early subtherapeutic concentrations of antibiotics may lead to treatment failure. Therefore, it is crucial that critically ill patients have sufficient antibiotics exposure in the early stages of infection. Vancomycin has a relatively narrow therapeutic window. When vancomycin exposure is insufficient, simply increasing the standard dose of vancomycin in all critically ill patients is not an optimal strategy because high-dose regimens may cause trough concentrations related to overexposure and toxicity. In the past, we used the vancomycin trough concentration ($C_{\text{min}}$) as a therapeutic target to optimize the vancomycin dosage regimen. However, some studies have reported that the $C_{\text{min}}$ was not associated with the success of infection treatment. The Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines recommend the area under the serum concentration time curve over 24 h/minimum inhibitory concentration ratio ($\frac{\text{AUC}_{0-24}}{\text{MIC}}$) > 400 as the ideal pharmacodynamic index to guide vancomycin dose adjustment.

Therefore, the purpose of this study was to compare the vancomycin CL in critically ill infants with augmented renal clearance and with normal renal function, and to optimize the dosage regimen for infants with augmented renal clearance using $\frac{\text{AUC}_{0-24}}{\text{MIC}}$.

**Methods**

**Patients and Data Collection**
This was a retrospective study, and the study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (no. 2017-KY-019). Infants who received intravenous vancomycin in the ICU to treat infection were enrolled. Plasma concentration data from January 2014 to June 2020 were retrospectively collected. The inclusion criteria were as follows: (1) age between 1 and 12 months and at least 1 recorded vancomycin $C_{\text{min}}$, (2) the infant’s estimated glomerular filtration rate (eGFR) was between 80 and 130 mL/min/m$^2$ or greater than 130 mL/min/m$^2$ throughout the vancomycin therapy period, and (3) the renal function status of infants with augmented renal clearance and with normal renal function did not change during vancomycin therapy. All infants had completed a course of vancomycin in the ICU. The exclusion criteria were as follows: (1) a history of hemodialysis, kidney transplantation, or continuous renal replacement treatment; and (2) infants with acute kidney injury. Each infant’s gestational age (GA), postnatal age (PNA), postmenstrual age (PMA), sex, weight (WT), height (HT), serum creatinine (Scr), and serum cystatin C (CysC) were collected. Mean values were calculated to replace the missing covariate values based on the covariate values of the day before and the day after. If the infant’s covariate was missing for three consecutive days, the infant was excluded. eGFR was calculated by the Schwartz formula based on Scr, as follows:

$$\text{eGFR} = \frac{(K \times HT)}{\text{Scr}},$$

where $K$ is 0.45 for infants aged <1 year, 0.55 for children aged <12 years and adolescent females, and 0.7 for adolescent males. HT is the height (cm) and Scr is the serum creatinine (mg/dL).

**Laboratory Assay**
In our hospital, the initial dose of vancomycin commonly used by clinicians for infants is 10 or 15 mg/kg/dose, divided into three or four doses. Blood samples were collected (2–3 mL) after the fourth dose of vancomycin was administered. The vancomycin dose was adjusted based on concentration and renal function. $C_{\text{min}}$ samples were collected just before the administration of the next dose, and peak concentrations ($C_{\text{max}}$) samples were collected 1 hour after administration. Vancomycin concentrations were measured by the enzyme multiplied immunoassay technique (EMIT) using an EMIT 2000 Vancomycin Assay Test Kit (Siemens Healthcare Diagnostic Inc., Newark, Delaware). The analytical instrument was a Siemens Via-E Drug Testing System with a quantitative limit of 2.0–50.0 mg/L. The coefficient of variation was <10% for both the intra- and inter-day assays. Samples with serum concentrations of >50 mg/L were diluted with EMIT 2000 Vancomycin Calibrators. Scr concentrations were measured by the enzymatic method using a Hitachi 7600 automatic biochemical analyzer (Hitachi Co., Ltd., Tokyo, Japan).

**Population Pharmacokinetics Analysis**
nonmem 7.3.0 (ICON Development Solutions, Ellicott City, Maryland) with the perl-speaks-nonmem and xpose packages for R were used to conduct the modeling process.

The PK parameters of vancomycin were estimated by first-order conditional estimation with an interaction method and compartment models. The base model was developed through the analysis of prior literature and visually evaluating the goodness-of-fit plot. One- and two-compartment models were compared. The interindividual variability (IIV) was described by the following exponential model:

$$\theta_i = \theta_{\text{pop}} \times e^{\eta_i},$$
where \( \theta_i \) is the individual PK parameter, \( \theta_{\text{pop}} \) is the typical value of the population pharmacokinetics (PopPK) parameter, and \( \eta_i \) is the random variable that is normally distributed with a mean of 0 and variance of \( \omega^2 \) in Equation 2.

For the covariant model, continuous covariates (GA, PNA, PMA, WT, HT, Scr, CysC, and eGFR) were evaluated by the following exponential function:

\[
\theta_i = \theta_{\text{pop}} \times \left( \frac{\text{COV}}{\text{COV}_{\text{median}}} \right)^\theta, \tag{3}
\]

where \( \text{COV}_{\text{median}} \) is the median value of the covariate in Equation 3. \( \theta \) is the estimated exponent of the vancomycin CL as power relationship for a typical subject. PMA and WT are important covariates for infants in most vancomycin PopPK studies. Therefore, the maturation function was used to evaluate PMA, and WT was added to the base model with allometric scaling on CL (exponent of 0.75) and volume of distribution (V) (exponent of 1). The equations are as follows:

\[
\theta_i = \theta_{\text{pop}} \times \frac{\text{PMA}^{\text{Hill}}}{\text{PMA}^{\text{Hill}} + \text{TM}_{50}^{\text{Hill}}}, \tag{4}
\]

\[
\theta_i = \theta_{\text{pop}} \times \left( \frac{\text{WT}}{70} \right)^{\text{power}}, \tag{5}
\]

where PMA is postmenstrual age (weeks), \( \text{TM}_{50} \) is the PMA when reaching 50% of adult PK parameters, and Hill is the coefficient with the slope of the maturation profile in Equation 4.

The covariates were selected in a forward-and-backward process. During forward selection, covariates were included in the base model if a reduction in objective function value (OFV) was greater than 3.84 (\( P < .05 \)). Individual covariates were then removed from the full model. If an OFV increased by greater than 10.83, which has a significant level of \( P \) value of less than .001, it was retained in the model.

Evaluation of the Final Model

The goodness-of-fit (GOF) plot, 1000 simulations prediction-corrected visual predictive check (pc-VPC), and normalized prediction distribution error (NPDE) were developed to evaluate the predictive performance of the final model. The 1000-times sampling bootstrap analysis was repeated to assess the robustness and repeatability of the final model.

Vancomycin CL, AUC\(_{0-24}\), and Dosage Optimization

Vancomycin CL in infants with augmented renal clearance and with normal renal function was calculated by the final model. The calculation formula of AUC\(_{0-24}\) is as follows:

\[
\text{AUC}_{0-24} = \frac{\text{vancomycin daily dose}}{\text{CL}}. \tag{6}
\]

Dosing recommendations based on the simulation were provided to obtain an AUC\(_{0-24}/\text{MIC}\) of between 400 and 700. The information for infants in the original data set was used to build a virtual data set. Monte Carlo simulation was used to simulate the 60 mg/kg/day for 2000 iterations. If the probability of obtaining AUC\(_{0-24}/\text{MIC}\) is insufficient, the daily dose will be increased.

Statistical Analysis

The categorical variables were summarized as frequencies and proportions, and the continuous variables were summarized as medians and means. In the univariate analysis, the \( \chi^2 \) test or Fisher’s exact test were used to compare the categorical variables. The continuous variables were compared with the Mann–Whitney \( U \)-test. \( P \) values of < .05 were considered statistically significant. Statistical analyses were performed using SPSS 19.0 (IBM, Armonk, New York).

Results

Patient Characteristics

A total of 66 infants treated in ICU were included in the analysis: 47 infants with augmented renal clearance (eGFR range: 130.7–547.0 mL/min/1.73 m\(^2\)) and 19 infants with normal renal function (eGFR range: 81.6–128.7 mL/min/1.73 m\(^2\)). The median GA and WT of infants with augmented renal clearance were 39.0 weeks (range: 28.5–41.3 weeks) and 6.0 kg (2.0–10.0 kg), respectively; the median GA and WT of infants with normal renal function were 39.0 weeks (range: 27.1–40.3 weeks) and 6.5 kg (range: 1.1–9.3 kg), respectively. The number of samples was 169, and 60.4% (102/169) of the samples were taken at \( C_{\text{min}} \) and 29.6% (67/169) of the samples were taken at \( C_{\text{max}} \). The characteristics of the infants are summarized in Table 1.

PopPK Analysis

A 1-compartment model with first-order elimination described the PK of vancomycin. An exponential model was used to describe the residual unexplained variability. The addition of WT with allometric scaling and PMA with maturation function to CL and V improved the fit, with a change in OFV of −53.44 and −12.09, respectively. The eGFR improved the fit with a change in OFV of −43.75. WT, eGFR, and PMA reduced the inter-individual variability of CL by 19%,
15.5%, and 4%, respectively. PK parameters estimated in the final model are shown in Table 2. The final model is presented below.

\[
CL (L/h) = 5.7 \times \left( \frac{WT}{70} \right)^{0.75} \times \left( \frac{eGFR}{168} \right)^{0.872} \times \frac{PMA^{3.97}}{PMA^{3.97+33.397}}, \tag{7}
\]

\[
V (L) = 54 \times \left( \frac{WT}{70} \right). \tag{8}
\]

**Evaluation of the Final Model**

Parameters estimated in the bootstrap analysis are described in Table 2, and the bootstrap minimization had a success rate of 99.7%. The range of all 95% confidence intervals included the PK parameters.

The GOF plot included: (1) population-predicted concentrations versus detected values, (2) individual predicted concentrations versus detected values, (3) conditional weighted residuals versus population-predicted concentrations, and (4) conditional weighted residuals versus time (Figure S1). The GOF plot showed good prediction performance, with the predicted values demonstrating good correlation with
the values detected. The pc-VPC plot of the simulation demonstrated that the 90% prediction interval included most of the detection values (Figure S2). The final model distribution was close to a normal distribution in the NPDE plot (Figure S3). The $P$ values for the Student’s $t$-test, Fisher’s test, and Shapiro–Wilk test were .617, .642, and .676, respectively.

Comparison of Vancomycin CL Between Augmented Renal Clearance and Normal Renal Function

The median CL of infants with augmented renal clearance was increased 1.96-fold compared with the median CL for infants with normal renal function; there was a statistical difference between the two groups (0.98 versus 0.5 L/h, $P < .001$). Compared against infants with augmented renal clearance, infants with normal renal function had a 1.55-fold (32.6 versus 21.0 mg/L, $P < .01$) increase in median $C_{\text{max}}$, a 1.97-fold (13.4 versus 6.8 mg/L, $P < .001$) increase in median $C_{\text{min}}$, and a 1.58-fold (517.2 versus 326.5, $P < .001$) increase in median $AUC_{0–4}/MIC$, respectively (Figure 1).

Dosage Optimization

Among all the infants included in this study, the MIC values were detected in just 17 infants and were all equal to 1 mg/L. In addition, most of the vancomycin MIC values in our hospital were equal to 1 mg/L. Therefore, the MIC values of all included infants were set to 1 mg/L in this study. The target $AUC_{0–24}/MIC$ values of infants with augmented renal clearance and with normal renal function were 29.8% (14/47) and 73.7% (14/19) ($P < .001$), respectively. The typical dosage was sufficient for infants with normal renal function. A simulation ($n = 2000$) was performed based on the median values for covariates that were included in the model stratified by the eGFR group for infants with augmented renal clearance. The simulations indicated that the recommended dosage of 60, 70, 80, 90, and 100 mg/kg/day would be appropriate in critically ill infants with eGFRs of 130–149, 150–169, 170–189, 190–209, and $>210$ mL/min/1.73 m², respectively. In addition, preterm infants and infants with low body weights with augmented renal clearance were simulated, and stratified by PMA and body weight. PNA was fixed at the median value, and GA was changed in the dose simulation of preterm infants. The recommended doses for infants with augmented renal clearance at GAs of 27–32.9 and 33–39 weeks were 70 and 75 mg/kg/day, respectively. The recommended doses for infants with augmented renal clearance and WTs of 2.0–2.9, 3.0–3.9, 4.0–4.9, and 5.0–6.0 kg were 70, 75, 80, and 90 mg/kg/day, respectively. The results are shown in Figure 2.

Discussion

We established a PopPK model to calculate the vancomycin CL in critically ill infants with augmented renal clearance. The results confirmed that the vancomycin CL was higher in infants with augmented renal clearance than in infants with normal renal function. The $C_{\text{min}}$ and $C_{\text{max}}$ values statistically differed between the two groups. Infants with augmented renal clearance exhibited rapid renal excretion function, which led to a need for higher dosage regimens in infants with augmented renal clearance to obtain the target pharmacodynamics value.

Vancomycin PopPK in patients with augmented renal clearance has been reported by some studies. Infants with augmented renal clearance and with normal renal function were included to establish a 1-compartment model, in which the typical values of vancomycin CL and V were 5.7 L/h and 54 L, respectively. The typical value of vancomycin CL was 6.32 L/h. The CL value in this study was lower than the value reported in the previous two studies, which may be because the data

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**Table 2. Population Parameter Estimates Based on the Final Population Model**

<table>
<thead>
<tr>
<th>Population Model</th>
<th>Final Estimates</th>
<th>RSE%</th>
<th>Bootstrap Estimates</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/h)</td>
<td>5.7</td>
<td>9</td>
<td>5.89</td>
<td>4.31–7.10</td>
</tr>
<tr>
<td>V (L)</td>
<td>54.0</td>
<td>9</td>
<td>54.2</td>
<td>43.90–64.00</td>
</tr>
<tr>
<td>Hill</td>
<td>3.97</td>
<td>44</td>
<td>3.86</td>
<td>1.00–5.62</td>
</tr>
<tr>
<td>TM50 (week)</td>
<td>33.3</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>$\theta_{\text{eGFR}}$</td>
<td>0.872</td>
<td>13</td>
<td>0.886</td>
<td>0.635–1.134</td>
</tr>
<tr>
<td>$\eta_{\text{CL}}$</td>
<td>31.7</td>
<td>33</td>
<td>30.0</td>
<td>19.40–41.0</td>
</tr>
<tr>
<td>$\eta_{V}$</td>
<td>32.8</td>
<td>37</td>
<td>32.2</td>
<td>17.10–45.7</td>
</tr>
<tr>
<td>Exponential error (%)</td>
<td>33.7</td>
<td>15</td>
<td>33.4</td>
<td>28.40–38.4</td>
</tr>
</tbody>
</table>

CI, confidence interval; CL, clearance; $\eta$, interindividual variability; eGFR, estimated glomerular filtration rate; RSE, relative standard error of the estimate; V, volume of distribution.
sets of patients with augmented renal clearance and normal renal function were not separated in our study. Children aged 1–18 years were included in the study conducted by He et al, for which the typical vancomycin CL value was 2.2 L/h; 64.6% (73/113) of the patients were older than 2 years of age and only 35.4% (40/113) of the patients were younger than 2 years of age in that study. Drug elimination and excretion are also affected in the pediatric population because of differences in liver and renal function. Neonates and infants are a special group, particularly critically ill patients, whose PK is changing rapidly as a result of increased cardiac output, with the resultant augmented renal clearance that may lead to an acceleration in the metabolism of solutes and drugs.

Traditionally, renal function has been routinely assessed in critically ill patients to monitor renal impairment and adjust drug dosages. Augmented renal clearance has been confirmed in critically ill patients. However, patients are at risk of drug sub-exposure if they are misdiagnosed as having normal or increased renal function. The vancomycin AUC₀–₂₄/MIC of patients with augmented renal clearance was 1.58-fold that of patients with normal renal function in our study. A similar study was reported by He et al, in which POPPK software was used to calculate vancomycin CL and AUC₀–₂₄/MIC in critically ill patients who were elderly. They found that vancomycin CL and AUC₀–₂₄/MIC had a statistical difference between patients with augmented renal clearance and patients with normal renal function. In addition, some of the β-lactam antibiotics cleared by the renal system may carry a risk of suboptimal target attainment in critically ill patients. Huttner et al reported that most of meropenem and imipenem concentrations were at undetectable or subthreshold levels in critically ill adult patients. Carrié et al reported that the treatment failure threshold of the conventional β-lactam antibiotics dosing regimen was higher than the highest dosing regimen used for adult patients with augmented renal clearance. The median values of vancomycin Cₘᵢₙ and AUC₀–₂₄/MIC were 6.8 mg/L.
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Figure 2. The probability of target attainment of simulated dosage: (a) simulated dosage based on estimated glomerular filtration rate, (b) simulated dosage based on postmenstrual age (postnatal age was fixed, stratified by gestational age), (c) simulated dosage based on weight. The red boxes indicate that the simulated dose was optimal to obtain the target AUC$_{0–24}$/MIC (400–700, MIC = 1 mg/L). AUC$_{0–24}$, area under the serum concentration time curve over 24 h; MIC, minimum inhibitory concentration.

and 326.5, respectively, implying that the C$_{\text{min}}$ and AUC$_{0–24}$/MIC values of patients with augmented renal clearance were not within the target range. It seems to be difficult to achieve the targeted therapeutic range with current conventional doses. Sridharan et al reported only 36.4% and 47.3% of the samples attained the recommended AUC$_{0–24}$ of >400 at the first dose and in steady state. Villanueva et al enrolled 70 adult patients with augmented renal clearance, only 15.71% of whom had vancomycin concentrations within the target therapeutic range (10–20 mg/L). Increasing the dose of vancomycin to obtain a target concentration or AUC$_{0–24}$/MIC may be a trend. However, excessive exposure can be associated with a risk of acute kidney injury. Several studies have confirmed that 700 was the upper threshold for AUC$_{0–24}$/MIC.

In our study, infants with normal renal function received vancomycin dosages that were lower than the
dosages recommended by the IDSA. However, most infants with normal renal function achieved the target $\text{AUC}_{0-24}/\text{MIC}$. With the lack of perspective and comparative data for pediatric patients, the empiric vancomycin dosage recommendation for pediatric patients was guided by adult patients with normal renal function (45–60 mg/kg/day) in the vancomycin consensus published by the IDSA in 2009. Recently, augmented renal clearance has been proposed in the therapy of vancomycin, and the data on dose adjustment of vancomycin in patients with augmented renal clearance are limited. Therefore, it is a challenge for clinical pharmacists to adjust vancomycin dose in critically ill infants with augmented renal clearance. Although in 2020 the updated IDSA vancomycin consensus added dosage recommendations for pediatric patients and neonates, the concept of augmented renal clearance was still not discussed. Vancomycin dosage recommendations of 60 mg/kg/day, or higher, have been recommended in pediatric patients by the Chinese Pharmacological Society. However, the guidelines mention that this was a weak recommendation, and the quality of evidence was very low. Vancomycin doses lower than the dose recommended by the IDSA have been observed in some studies of Chinese infants. The dosage of 60–80 mg/kg/day may not be needed for Chinese infants with normal renal function. The efficacy and safety of higher dosages should be further evaluated in Chinese infants with normal renal function.

The PK of critically ill patients is variable during therapy, and drug exposure should be considered in this population. The PopPK model and dose simulation can explain the complex and changing PK parameters to improve target achievement in critically ill patients. In our study, median doses of 50 and 47 mg/kg/day were provided for patients with augmented renal clearance and for patients with normal renal function, respectively. The current dosage regimen was insufficient in infants with augmented renal clearance. Dosage simulation results showed that 60–100 mg/kg/day achieved a high probability of attaining the target $\text{AUC}_{0-24}/\text{MIC}$.

A total of 63.8% (30/47) of the infants with augmented renal clearance had $C_{\text{min}}$ values that were less than 10 mg/L, and 90% (27/30) of these infants with augmented renal clearance had an $\text{AUC}_{0-24}/\text{MIC}$ value of less than 400. A $C_{\text{min}}$ value greater than 10 mg/L may not be needed in pediatric patients. Although the $C_{\text{min}}$ values of some infants were lower than 10 mg/L, they also achieved a positive outcome in the clinic. However, it does not mean that infants do not need to have an $\text{AUC}_{0-24}/\text{MIC}$ of greater than 400. The recommended target $\text{AUC}_{0-24}/\text{MIC}$ value for pediatric patients was greater than 400 in the IDSA consensus of vancomycin updated in 2020. Therefore, $\text{AUC}_{0-24}/\text{MIC}$ was selected as the target for optimizing the vancomycin dose, rather than $C_{\text{min}}$, in our study.

The recommended dose was higher than that for adult patients, which may be because of the higher vancomycin CL in children compared with adults. The IDSA has recommended 60–80 mg/kg/day for pediatric patients in the revised guidelines for vancomycin. Several studies demonstrated that doses higher than 60 mg/kg/day were necessary to obtain adequate exposure in pediatric patients. Data for pediatric patients with augmented renal clearance are limited, especially for critically ill patients. The current study suggested that a higher dose was necessary for pediatric patients with augmented renal clearance. Insufficient doses of vancomycin have a negative impact on clinical outcomes. Treatment failure increased 2-fold for patients who did not reach the target $\text{AUC}/\text{MIC}$ value in the first 2 days in the case of bloodstream infections caused by MRSA. We established a vancomycin PopPK model in infants with augmented renal clearance to optimize the dosing regimens. It is worth noting that renal function in certain patients may change over time, especially in neonates, in patients who are critically ill with sepsis, with cystic fibrosis, and with stem cell transplant, or in adults with brain injury. So, the timing of the course of vancomycin during a hospital stay may be important to consider when designing empiric regimens. Renal function status should be closely monitored to adjust the vancomycin dose in critically ill patients.

There were several limitations to this study. First, this was a single-center retrospective cohort study. The vancomycin dose, medication time, and sample collection time of critically ill patients were extracted from the electronic medical record system. This information may be biased, especially for the time of sample collection. Second, only peak and trough concentrations were used for modeling in this study. Third, our simulated dosage had a limited reference for infants with MIC > 1 mg/L. Fourth, our eGFR was calculated by the Schwartz formula. The Scr concentrations are insensitive for detecting mild-to-moderate reductions in GFR. In addition, age, sex, and muscle mass can affect Scr concentration. Finally, the pediatric population, including neonates, cystic fibrosis, stem cell transplant, and sepsis, is very vulnerable, and future study is needed in certain pediatric populations.

**Conclusion**

A vancomycin PopPK model was developed in this study to compare CL in critically ill infants with augmented renal clearance and with normal renal function. WT, eGFR, and PMA were included as significant covariates in the final model. The results
showed that critically ill infants with augmented renal clearance had higher vancomycin CL than critically ill infants with normal renal function. The typical dosages were sufficient for critically ill infants with normal renal function to achieve the target AU/C0–24/MIC. However, higher dosages were needed to obtain adequate exposure in critically ill infants with augmented renal clearance, especially in critically ill infants who were born preterm or had low birthweight.

Conflicts of Interest

The authors declare that they have no conflicts of interest to disclose.

Data Availability Statement

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

Author Contributions

J.-J.L. and T.-T.L. were involved in the conception and design of the study. G.-M.H. and Y.Q. collected the data for analysis. J.-J.L. and G.-M.H. provided the analysis of the population pharmacokinetic models. G.-M.H. wrote the first draft of the article, and all authors gave final approval to the article as published.

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References


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