Clinical Application of Vancomycin PPK Model in Patients with Neutropenia

Xiangjun Fu
Hematological Department, Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University

Li Huang
Hematological Department, Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University

Li Guo
Hematological Department, Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University

Liangmo Lin (llm077@126.com)
Pharmacy Department, Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University

Research Article

Keywords: neutropenia, vancomycin, population pharmacokinetics (PPK) model

DOI: https://doi.org/10.21203/rs.3.rs-690254/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

**Background:** To explore the clinical application of a population pharmacokinetics (PPK) model of vancomycin in patients with hematological diseases who developed neutropenia.

**Methods:** Patients with neutropenia treated at the Department of Hematology in our hospital were included in the PPK model study. A nonlinear mixed effect modeling approach (NONMEM) was used to establish the PPK model of those patients. Monte Carlo simulation was also carried out. A total of 64 patients were divided into model group and non-model group for clinical application research. The model group was given the first dose of 1g q8h, and the non-model group was given 1g q12h as the empiric therapy; the follow-up dose adjustment was made according to the concentration results.

**Results:** This two-compartment model showed good stability and accuracy. The average concentrations in the model group and the non-model group were significantly different, i.e., 13.45±4.07 μg/ml, 60.71% reaching the target concentration vs. 9.85±3.76 μg/ml, 27.78% reaching the target concentration, respectively (all $P<0.05$). This suggested that for patients with neutropenia and CLCR≥90 ml/min/1.73m², the first dose of 1g q8h may help to reach the target concentration as soon as possible.

**Conclusions:** Our PPK model of vancomycin in patients with hematologic diseases who developed neutropenia can be used to realize the individualized application of vancomycin in this population.

**Background**

Vancomycin is the first-line drug in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infection that has been clinically used for a very long time. Because of its narrow therapeutic window and obvious individual differences in pharmacokinetics, there are many guidelines and expert consensuses that guide the clinical application of vancomycin in recent years [1–7]. With the development of quantitative pharmacology, numerous researches have shown clinical significance in optimizing the drug delivery scheme of vancomycin by using the PPK model, which could quickly help to improve the target rate of TDM [8–12]. The difference of pharmacokinetics was obvious in different pathological states. Over recent years, there has been an increasing interest in PPK of vancomycin in patients of different pathological states. However, there are only a few model studies on adult neutropenic patients.

More and more attention has been paid to the pharmacokinetics of vancomycin in patients with hematological tumors. Our previous research showed that vancomycin exposure was often inadequate in these populations. It is also mentioned in the guideline of vancomycin treatment drug monitoring of China revised in 2020 that neutropenic patients with fever are recommended to accept TDM, and the PPK model is helpful to realize the implementation of individualized drug delivery scheme. We had recently established a PPK model for patients with hematologic malignancy and neutropenia, and it showed good stability and prediction performance. In this paper, the clinical application of this PPK model was studied in order to promote the individualized application of vancomycin in this special population.
Methods

Determination of vancomycin concentration in serum

Vancomycin concentration in serum was tested by using the Siemens automatic drug concentration analyzer Viva-E. The quantitative range was 2.0 ~ 50.0 µg/ml. The time for trough concentration was 0.5 h before intravenous drip, and for peak, concentration was 0.5-1 h after intravenous drip. A 2ml venous blood was collected and centrifuged at 3500 rpm. The supernatant was taken for determination.

Establishment and validation of vancomycin PPK model in patients with neutropenia

Patients in the Department of Hematology of Hainan General Hospital from January 1, 2018, to January 1, 2020, were selected as the research subjects. The inclusion criteria were as follows: 1) diagnosed with hematological diseases; 2) ≥ 14 years old; 3) neutrophil deficiency during the study; 4) received intravenous vancomycin. The exclusion criteria were: 1)14 years old; 2) non-neutropenic state; 3) receiving any blood purification treatment; 4) incorrect sampling. The body weight (BW), age, creatinine (CR), white blood cell count (WBC), neutrophil count (ANC), hemoglobin (HGB), platelet count (PLT), serum total protein (TP), serum albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), vancomycin dosage (mg/d), administration time (h), serum concentration (µg/ml) of the patients were collected and recorded. The above indexes were measured on the same day or within 3 days before and after the monitoring of vancomycin serum concentration. Creatinine clearance rate (CLCR) was calculated using the CKD-EPI formula developed by the US chronic kidney disease epidemiology cooperative working group. This study was approved by the Medical Ethics Department of our hospital (approval number [2018]68), and all patients had informed consent.

The PPK model of the neutropenic population was established by the nonlinear mixed-effects model (NONMEM). The exponential model was used to describe the variation among individuals, and the residual variation was fitted by the additive model, proportional model, and mixed model. The fitting results of different error models were compared according to the objective function value (OFV), the goodness of fit graph, and the rationality of parameters. The basic model was established based on these same approaches. In the basic model, a stepwise regression method was used to add covariates and establish the final model. When the degree of freedom n = 1 and the decrease of OFV was more than 3.84 after adding a certain covariate, this covariate was kept in the final model. The covariates, which included age, gender, BW, creatinine, CLCR, WBC, ANC, HGB, PLT, TP, ALB, ALT, and AST, were eliminated one by one from the final model. When the degree of freedom n = 1 and the increase of OFV was more than 10.83, the covariate was saved. The final model was established following this approach.

The goodness of fit (GOF) and model predictive diagnostic chart (VPC) were drawn for model-based verification. The nonparametric bootstrap method was used for internal verification. In our study, the 95% confidence interval of population parameters and the estimated values of population parameters were obtained by 1000 times bootstrap method and were compared with the estimated values of the final model parameters. In addition, patients who were not included in the model group with the same entry
conditions in the same period were used for external verification. The prediction performance was judged by the prediction error (PE%) of the model. The median relative prediction error (MDPE) was used to evaluate the model's accuracy, and the median absolute prediction error (MAPE) was used to evaluate the precision of the model. Composite indexes $F_{20}$ and $F_{30}$ (PE% between ± 20% and ± 30% percentage) were used to evaluate the precision of the model. When MDPE $\leq$ ± 20%, MAPE $\leq$ ± 30%, $F_{20} \geq$ 35%, and $F_{30} \geq$ 50%, the prediction performance of the model was considered acceptable. The calculation formulas are shown in formulas 1 to 5.

$$PE\% = \frac{C_{\text{pred}} - C_{\text{obs}}}{C_{\text{obs}}} \times 100\% \quad \text{(Formula 1)}$$

$$\text{MDPE\%} = \text{Median} \left( \frac{C_{\text{pred}} - C_{\text{obs}}}{C_{\text{obs}}} \right) \times 100\% \quad \text{(Formula 2)}$$

$$\text{MAPE\%} = \text{Median} \left( \frac{|C_{\text{pred}} - C_{\text{obs}}|}{C_{\text{obs}}} \right) \times 100\% \quad \text{(Formula 3)}$$

$$F_{20\%} = \left( \frac{n_{\text{PE}\% \leq 20\%}}{n_{\text{obs}}} \right) \times 100\% \quad \text{(Formula 4)}$$

$$F_{30\%} = \left( \frac{n_{\text{PE}\% \leq 30\%}}{n_{\text{obs}}} \right) \times 100\% \quad \text{(Formula 5)}$$

**Monte Carlo Simulation Of PPK Model**

Based on the established PPK model, Monte Carlo simulation was used to simulate the steady-state trough concentration of neutropenic patients with different CLCR under different vancomycin administration schemes.

When CLCR was 30, 60, 90, 120 ml/min/1.73m$^2$, respectively, the following drug delivery schemes (including 1g q12h, 1g q8h, 0.5g q8h, 0.5g q6h) were simulated. One thousand sets of simulation data were generated for each combination of the dosing scheme and CLCR. If the vancomycin trough concentration was maintained at 10 ~ 20 µg/ml, it was considered that the scheme was feasible with this CLCR.

**Clinical Application Of PPK Model**

Patients with hematologic diseases accompanied by neutropenia and CLCR $\geq$ 90 ml/min/1.73m$^2$ were selected as the research subjects and were treated by intravenous vancomycin. The patients were randomly divided into two groups: the non-model administration group and the model administration group. The mean and standard rates of the first trough concentration of vancomycin in the two groups were compared.
Statistical analysis

NONMEM (icon development solutions, USA, version 7.3) software was used for model establishment and simulation. Perl speak NONMEM (PSN version 3.4.2) was used for model validation. R software (version 2.12.0) was used for statistical testing and drawing, and SPSS 19.0 was used for data analysis.

Results

Basic information of patients

A total of 77 patients, including 42 males and 35 females, were included in this PPK model study. One hundred nine trough concentrations and 43 peak concentrations were monitored. The primary diseases were 34 cases of acute myeloid leukemia, 16 cases of acute lymphoblastic leukemia, 10 cases of lymphoma, 5 cases of aplastic anemia, 5 cases of myelodysplastic syndrome, 4 cases of chronic myeloid leukemia, 2 cases of multiple myeloma, and 1 case of chronic monocytic leukemia. A total of 26 patients were included in the external validation. The basic information of patients is shown in Table 1.
Table 1
The basic information of enrolled patients

| Basic information of modeling patients | mean value ± sd | min | max |
|----------------------------------------|----------------|-----|-----|
| age (y)                                | 43.28 ± 15.88  | 17.00 | 83.00 |
| height (cm)                            | 162.57 ± 9.52  | 148.00 | 185.00 |
| body weight (kg)                       | 56.84 ± 11.09  | 33.00 | 83.50 |
| BMI (kg/m²)                            | 21.52 ± 3.63   | 14.67 | 31.87 |
| creatinine (µmol/L)                    | 53.66 ± 18.36  | 23.00 | 125.00 |
| CLCR (ml/min/1.73m²)                   | 118.78 ± 22.69 | 45.60 | 163.80 |
| WBC (10⁹/L)                            | 2.37 ± 8.37    | 0.01 | 66.74 |
| ANC (10⁹/L)                            | 0.19 ± 0.36    | 0.00 | 0.49 |
| HGB (g/L)                              | 66.71 ± 17.01  | 34.00 | 128.00 |
| PLT (10⁹/L)                            | 26.75 ± 23.68  | 1.00 | 138.00 |
| ALT (10⁹/L)                            | 40.03 ± 86.97  | 3.60 | 568.40 |
| AST (10⁹/L)                            | 21.82 ± 29.08  | 3.10 | 223.50 |
| TP (g/L)                               | 59.08 ± 8.41   | 34.20 | 78.10 |
| ALB (g/L)                              | 32.23 ± 6.34   | 17.90 | 59.40 |

| Basic information of external verification patients | mean value ± sd | min | max |
|------------------------------------------------------|----------------|-----|-----|
| age (y)                                              | 40.15 ± 16.20  | 20.00 | 68.00 |
| height (cm)                                          | 161.78 ± 9.66  | 153.00 | 172.00 |
| body weight (kg)                                     | 58.26 ± 8.39   | 49.00 | 76.00 |
| CLCR (ml/min/1.73m²)                                 | 118.92 ± 21.57 | 59.00 | 164.70 |

The Final Ppk Model And Verification Results

The final PPK model

One compartment model and a two-compartment model were used to fit the data. The OFV of the two-compartment model was lower than that of the one-compartment model. After considering the rationality
of the objective function value, the goodness of fit graph, and parameters, the two-compartment model was finally used as the basic model. The mixed model was used to describe the variation among individuals, and the OFV was 532.06. The estimated values of CL, V₁, Q, and V₂ were 6.43 L/h, 18.9 L, 19.5 L/h, and 37.1 L/h, respectively. Inter-individual variation of CL (ω²CL) was 0.0615, and the inter-individual variation of V₁ (ω²V₁) was 0.126. The stepwise regression method and stepwise elimination method were used to screen the covariates. Only CLCR was retained so that the final model was obtained. The formula for the final model was as follows:

\[
CL = 6.84 \times (BW/70)^{\theta_{BW_CL}} \times (CLCR/116)^{\theta_{CLCR_CL}} \times \exp(\eta_1)
\]

Formula 6

CL was the clearance rate, 6.84 in formula 6 was the typical value of Cl, BW was the bodyweight of patients. \(\eta_1\) represented the difference between the patient clearance rate and the typical value of the population.

\[
V_1 = 20.5 \times (BW/70)^{\theta_{BW_V1}} \times \exp(\eta_2)
\]

Formula 7

V₁ was the distribution volume of the central ventricle, and 20.5 in formula 7 was the typical value of V₁. \(\eta_2\) represented the difference between the apparent distribution volume of patients and the typical value of the population.

\[
Q = 15.2 \times (BW/70)^{\theta_{BW_Q}} \times \exp(\eta_3)
\]

Formula 8

Q was the clearance rate between rooms, 15.2 in formula 8 was the typical value of Q, \(\eta_3\) represented the difference between the parameters of patients' IVT and the typical values of the population.

\[
V_2 = 50 \times (BW/70)^{\theta_{BW_V2}} \times \exp(\eta_4)
\]

Formula 9

V₂ was the distribution volume of the peripheral ventricle. In formula 9, 50 was the typical value of V₂, \(\eta_4\) represented the difference between the distribution volume of the peripheral ventricle and the typical value of the population.

The parameters of the final model are shown in Table 2.
Table 2
The parameter and an estimated value of parameter variation of the final model

| parameter   | estimated value | RSE (%) | 95% CI       |
|-------------|----------------|---------|--------------|
| CL (L/h)    | 6.84           | 4.5     | (6.234, 7.446) |
| V1 (L)      | 20.5           | 17.3    | (13.562, 27.438) |
| Q (L/h)     | 15.2           | 23.4    | (8.242, 22.158) |
| V2 (L)      | 50             | 27.2    | (23.344, 76.656) |
| θ_{CLCR,CL} | 0.895          | 14.3    | (0.644, 1.146)  |
| η₁ (%)      | 17.8           | 15      | -            |
| η₂ (%)      | 33             | 35.8    | -            |

Model validation

The goodness of fit map (GOF) was drawn, including scatter plot of basic model observations (DV) and population predicted values (PRED), scatter plot of DV and individual predictive value (IPRED), scatter plot of DV and conditional weight residuals (CWRES), scatter plot of DV and time. According to DV and PRED scatter plots, the coincidence degree of the trend line and reference line was high; the distribution of scatter plot of predicted value and conditional weight residual and scatter plot of predicted value and time were symmetrical, and there was no obvious trend change, which indicated that the final model had a good predictive ability. The final model GOF and predictive diagnosis diagram are shown in Fig. 1 and Fig. 2.

The Bootstrap method was used to verify the final model. Repeated sampling 1000 times from the original data was performed in order to generate multiple sets of Bootstrap data. Then fitted the Bootstrap data and estimated the model parameters, summarized all the results of successful operation, and compared those with the final model parameters. There was no significant difference between the final model parameters and bootstrap median, and the success rate of convergence was 90%, indicating that the model was reliable. The validation results were shown in Table 3.
Table 3

The typical value of population and validation results of Bootstrap

| parameter | Final model estimated value | 95% CI       | Bootstrap median | 95% CI       |
|-----------|-----------------------------|--------------|-----------------|--------------|
| CL (L/h)  | 6.84                        | (6.221, 7.459) | 6.62            | (5.801, 7.211) |
| V1 (L)    | 20.5                        | (13.777, 27.223) | 21.00          | (12.545, 33.884) |
| Q (L/h)   | 15.2                        | (8.142, 22.276) | 14.17          | (8.339, 32.719) |
| V2 (L)    | 50                          | (22.168, 77.832) | 51.36         | (31.139, 184.524) |
| θ_{CLCR,CL} | 0.895                      | (0.642, 1.148) | 0.93           | (0.633, 1.388) |

The external validation results were: MDPE = −4.68%, MAPE = 18.74%, F₂₀ = 52.27%, F₃₀ = 68.18%, which showed that the prediction performance of the model was good.

Results Of Monte Carlo Simulation

According to Monte Carlo simulation, the predicted trough concentration of vancomycin in neutropenic patients with different CLCR under different administration regimens is shown in Fig. 3. When CLCR was 30 ml/min/1.73m², the recommended dosage regimen of vancomycin was 0.5g q8h; when CLCR was 60 ml/min/1.73m², the recommended dosage regimen was 1g q12h, 0.5g q6h or 0.5g q8h; when CLCR was ≥ 90 ml/min/1.73m², vancomycin 1g q8h could reach a satisfactory concentration.

Clinical Application Results Of The Ppk Model

As the CLCR of neutropenia patients was generally high [13, 14], the CLCR ≥ 90ml/ min /1.73m² was taken as the entry condition. A total of 64 adult patients with neutropenia, including 35 males and 29 females, were included in the clinical study. Among them, 28 were in the model group, and 36 were in the non-model group. All of them had a CLCR ≥ 90 ml/min/1.73m². The model group was given 1g q8h directly, while the non-model group was given 1g q12h based on the experience, after which the dosage regimen was adjusted after monitoring the concentration. After 48 h of administration, serum samples were collected 30 minutes before the next administration to monitor the first trough concentration, with 10 ~ 20 µg/ml being the target concentration. The average concentration in the model group was 13.45 ± 4.07 µg/ml; the compliance rate for the first time was 60.71%. The average concentration in the non-model group was 9.85 ± 3.76 µg/ml; the compliance rate for the first time was 27.78%. Independent sample t-test was used for age and CLCR between the two groups; Kruskal Wallis test was used for blood concentration, and Chi-square test was used for compliance rate. The results showed no significant difference between the two groups in age and CLCR. The mean and the rate of reaching the standard of the first blood concentration in the model group was higher than that in the non-model group. These
results suggested that for patients with neutropenia and CLCR ≥ 90 ml/ min /1.73m^2, the first dose of 1g q8h could be used to quickly reach the target concentration. The clinical application results are shown in Table 4.

**Table 4**

|                      | model group (n = 28) | non model group (n = 36) | p   | \( \chi^2 \) |
|----------------------|----------------------|--------------------------|-----|-------------|
| age (y)              | 41.68 ± 12.55        | 45.06 ± 11.92            | 0.345 | -          |
| CLCR (ml/min/1.73m^2)| 121.82 ± 15.88       | 123.01 ± 12.43           | 0.778 | -          |
| first concentration (µg/ml)| 13.45 ± 4.07      | 9.85 ± 3.76              | 0.002 | 9.650      |
| compliance rate (%)  | 60.71 (17/28)        | 27.78 (10/36)            | 0.008 | 7.005      |

**Introduction Of A Typical Case**

A 50-year-old female patient weighing 47kg, with a CLCR of 128.6 ml/min/1.73m^2 was diagnosed with acute myeloid leukemia. She developed neutropenia with fever after chemotherapy and was diagnosed with *Streptococcus bovis* infection in the blood. From February 18, 2021, she received 1g q12h of vancomycin. The first concentration of vancomycin was 6.0 µg/ml 48 h after the prescription. PPK model was used to predict that the concentration of 1 g q8h after adjustment was 11.8µg/ml, and the real measured concentration was 10.2 µg/ml. The prediction error was 13.56%. A week later, the blood culture showed that the pathogen was negative. If the patient had received 1g q8h at the first dose, this would have helped to quickly reach the target blood concentration and control the infection.

**Discussion**

The phenomenon of insufficient concentration of vancomycin is commonly found in patients with hematological diseases. Kergueris reported that the vancomycin elimination rate, which is constant in patients with neutropenia, was higher than that in the general population and had no significant correlation with serum creatinine and urine volume in such patients [15]. Michiel B. haeseker's study revealed that the clearance rate of vancomycin in patients with neutropenia was significantly higher than that in patients without neutropenia (CL = 67 ± 26ml/min vs. CL = 50 ± 22ml/min). They suggested that the average dose of vancomycin should be increased by one-third in neutropenic patients [16]. Choi et al used multiple logistic regression, which showed that neutropenia was the main cause of insufficient vancomycin exposure (OR = 1.75, p = 0.029) [17]. Our previous study revealed that the incidence of renal hyperfunction (ARC) in patients with hematologic diseases was 37.88%, while that in patients without hematologic diseases was only 21.56% (p = 0.001) [13]. Patients with neutropenia often have a severe infection and high mortality, thus requiring timely anti-infection treatment [18, 19]. Therefore, it is very important to make individual medication plans for vancomycin in this population.
In a meta-analysis conducted by Wang et al, which included 100 vancomycin PPK models, the median value of clearance (CL) in the PPK model for adults, the elderly, and children was 3.47 (0.0272 ~ 9.3200) L/h, 2.45 (2.025 ~ 4.230) L/h, and 1.20 (0.004 ~ 25.200) L/h, respectively [20]. The estimated CL value of neutropenia patients in this study was 6.84l/h, which was higher than that reported above. As shown by the results, such patients had a higher vancomycin clearance rate. According to the PPK model and Monte Carlo simulation, acute renal hyperfunction (ARC) is defined as CLCR ≥ 130 ml/min/1.73m$^2$ [14]. When the CLCR of neutrophil deficiency patients was ≥ 90 ml/min/1.73m$^2$, the initial regimen of 1g q8h helped to achieve sufficient drug exposure quickly. The CLCR value was lower than the definition of ARC, which should be considered in clinical practice. After long-term chemotherapy and other treatment, patients with hematological malignancies tend to lose weight gradually, which may affect the detection of serum creatinine. How to eliminate these effects needs to be further studied. In general, establishing the PPK model in line with the characteristics of patients with neutropenia has certain significance for optimizing the clinical application of vancomycin. The clinical application research of the model established in this study needs to be further researched to accumulate sufficient experience and promote the individualized application of vancomycin.

**Conclusions**

PPK models of vancomycin in adult patients with hematologic diseases and neutropenia are few. The model established in this study is helpful to promote the individualized application of vancomycin in this population.

**Abbreviations**

PPK  
Population pharmacokinetics  
NONMEM  
Nonlinear mixed effects model  
OFV  
Objective Function Value  
CLCR  
Creatinine clearance rate  
CL  
Clearance rate  
V  
Apparent distribution volume  
Q  
Inter ventricular transport rate

**Declarations**
Ethics approval and consent to participate

This study was approved by the Medical Ethics Department of Hainan General Hospital (approval number [2018]68), and all patients had informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by the General Projects of Hainan Natural Science Foundation (Experimental study of rituximab combined with cyclosporine in the treatment of chronic graft versus host disease with abnormal B cells and improvement of pulmonary fibrosis) [grant number 820MS137]; and the Hainan Health And Family Planning Industry Project (Individual application of vancomycin in intensive care patients based on NONMEM model and population pharmacokinetics) [grant number 20A200280].

Authors' contributions

XF contributed to experimental design, acquisition of data, analysis of data, and drafted the manuscript. LH contributed to acquisition of data and analysis of data. LG contributed to medical record management. LL contributed to experimental operation, and critically revised the manuscript. All authors have read and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Chen CH, Li GH. American Society of infectious diseases clinical practice guidelines for the treatment of methicillin - resistant Staphylococcus aureus infections in adults and children. Chinese Journal of infection and chemotherapy. 2011;11:428–34.

2. Matsumoto K, Takesue Y, Ohmagari N, Mochizuki T, Mikamo H, Seki M, et al. Practice guidelines for therapeutic drug monitoring of vancomycin: a consensus review of the Japanese Society of
Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring. J Infect Chemother. 2013;19:365–80.

3. Chen BY, Guan XT, He LX, Huang ZY. Chinese expert consensus on clinical application of vancomycin (2011 Edition). Chinese Journal of new drugs and clinical medicine. 2011;30:561–2.

4. Expert group on clinical dosage of vancomycin. Chinese expert consensus on clinical dosage of vancomycin. Chinese Journal of infectious diseases. 2012;30:641–6.

5. Chinese pharmacological society. Therapeutic drug monitoring of vancomycin: a guideline of the Division of Therapeutic Drug Monitoring. J Antimicrob Chemother. 2016:1–6.

6. Rybak MJ, Le J, Lodise TP, Levine DP, Bradley JS, Liu C, 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. Clin Infect Dis. 2020;71:1361–4.

7. He N, Su S, Zhai SD, Dong YL, He B. Interpretation of China vancomycin treatment drug monitoring Guide (2020 Update Edition). Journal of clinical drug therapy. 2021;19:12–6.

8. Liu T, Deng C, Cheng D, Zhou T, Lu H, Wei W, et al. Population pharmacokinetics of vancomycin in Chinese pediatric patients Int J Clin Pharmacol Ther. 2017;55:509–16.

9. Le J, Ny P, Capparelli E, Lane J, Ngu B, Muus R, et al. Pharmacodynamic Characteristics of Nephrotoxicity Associated With Vancomycin Use in Children. J Pediatric Infect Dis Soc. 2015;4:e109-16.

10. Mehrotra N, Tang L, Phelps SJ, Meibohm B. Evaluation of vancomycin dosing regimens in preterm and term neonates using Monte Carlo simulations. Pharmacotherapy. 2012;32:408–19.

11. Guo XZ, Lin RF, Lin WW. Development and application of individualized dose software of vancomycin based on group pharmacokinetic model. Chinese clinical pharmacology and therapeutics. 2021;26:30–9.

12. Gao YC, Jiao Z, Huang H, Xie C, Gao JJ, Zhang L. Development of decision support system for individual administration of vancomycin. Acta Pharmaceutica Sinica. 2018;53:104–8.

13. Fu XJ, Yang HB, Lin LM. Clinical characteristics and influencing factors of vancomycin concentration in patients with hematologic diseases. Chinese Journal of infection and chemotherapy. 2020;20:487–92.

14. Hirai K, Ihara S, Kinae A, Ikekaya K, Suzuki M, Hirano K, et al. Augmented Renal Clearance in Pediatric Patients With Febrile Neutropenia Associated With Vancomycin Clearance. Ther Drug Monit. 2016;38:393–7.

15. Kergueris MF, Le Normand Y, Jahan P, Milpied N. Application of USC*PACK clinical programs to vancomycin in neutropenic patients. Int J Biomed Comput. 1994;36:163–5.

16. Haeseker MB, Croes S, Neef C, Bruggeman CA, Stolk LM, Verbon A. Vancomycin dosing in neutropenic patients. PLoS One. 2014;9:e112008.
17. Choi MH, Choe YH, Lee SG, Jeong SH, Kim JH. Neutropenia is independently associated with sub-therapeutic serum concentration of vancomycin. Clin Chim Acta. 2017;465:106–11.

18. Chinese society of Hematology. Chinese Medical Association. Guidelines for clinical use of antibiotics in Chinese patients with neutropenia and fever (2020 Edition). Chinese Journal of Hematology. 2020;41:969–78.

19. Zhang L, Ye YJ, Yao YY. Study on neutropenia complicated with infection in patients with hematological malignancies Clinical research and practice. 2018;3:12–4.

20. Wang CH, Liu Y, Zhao SX, Zhang C. Systematic study on population pharmacokinetic model of vancomycin. Chinese Journal of clinical pharmacology. 2020;36:354–6.

Figures
Figure 1

Goodness-of-fit plots of final.
Figure 2

Visual predictive checks of the final model.
Figure 3

Trough concentrations of patients with different creatinine clearance under different dosage regimens.