

Pharmacokinetics and Pharmacodynamics of Vancomycin in Severe COVID-19 Patients: a Preliminary Study in a Chinese Tertiary Hospital

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Abstract

Vancomycin plays an important role in the treatment of concurrent infections in severe coronavirus disease 2019 (COVID-19) patients. However, few is known about its pharmacokinetics (PK) in these patients. Here we performed therapeutic drug monitoring (TDM) of intravenous vancomycin with or without nasal administration in these patients. Drug dosage was adjusted depending on vancomycin concentration. A population PK model was developed using NONMEM software. Therapeutic effects, and vancomycin-related adverse events were monitored. A total of 63 samples from 8 patients were analyzed by ultra-performance liquid chromatography-tandem mass spectrometry. The mean trough and peak concentration were 13.79 ± 6.61 (4.63-34.2) mg/L (n=36) and 30.97 ± 9.71 (17-49.9) mg/L (n=27), respectively. 25.4% of serum vancomycin concentration was beyond optimal range. Dose adjustments were made for 3 patients. The PK of vancomycin was consistent with two-compartment model, with the clearance and distribution volume in the central compartment of 4.3 L/h and 2.0 L, respectively. The AUC_{0-24}/MIC of vancomycin was 848 ± 566 h. Target infection was clinically cured in all patients, and no vancomycin-associated nephrotoxicity was detected during the TDM process. In conclusion, the PK studies of vancomycin in COVID-19 patients are needed to optimize drug dosage. Based on our PK model, the clearance of vancomycin was 4.3 L/h.

Introduction

Since December 2019, a novel coronavirus disease (COVID-19) has been spreading rapidly all over the world, with nearly 3 million confirmed cases and 204 thousand deaths, till April 29, 2020 (<https://www.who.int/>). Secondary bacterial infections were observed in 31% of patients who required invasive mechanical ventilation and in 50% of non-survivors.¹ Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative *Staphylococci* (MRCNS) and *Enterococci* species are common nosocomial pathogens, which mainly cause ventilator-associated pneumonia (VAP).² Vancomycin 15 mg/kg IV per 8–12h with or without a loading dose was recommended for treating such infections.³ However, due to the narrow treatment window and personal difference, sub-optimal vancomycin concentrations were prevalent, leading to insufficient antibacterial potency or increased risk of acute kidney injury.⁴⁻⁷ Therefore, it is necessary to perform therapeutic drug monitoring (TDM) of vancomycin, so as to ensure its clinical effect while minimizing the occurrence of adverse reactions.⁸ For severe MRSA infection, the guidelines recommended a ratio of 24-hour area under the concentration time curve and minimum inhibitory concentration (AUC_{0-24}/MIC) of 400 to 600 in both adult and pediatric patients to maximize the clinical efficacy and minimize acute kidney injury (AKI) risk.⁹ Because AUCs are not routinely available in clinical practice, plasma or serum concentration is also used as substitute.¹⁰⁻¹³ The guidelines of the Chinese Pharmacological Society recommended a serum trough level of 10–15 mg/L in adult patients and 10–20 mg/L for serious MRSA infections.¹⁴ Furthermore, the peak concentration was expected to be less than 40 mg/L.¹⁵

Since the mass hospitalization of patients with COVID-19, including a high proportion relying on mechanical ventilation, it might increase vancomycin usage for treating hospital-acquired infections, especially ventilator-associated pneumonia (VAP). However, there was little knowledge about the pharmacokinetics of vancomycin in these patients. The decision of drug dosage relied on clinical experiences. Therefore, in this study, we performed TDM of vancomycin by ultra performance liquid chromatography/tandem mass spectrometry (UPLC-MS/MS) in COVID-19 patients. Doses were optimized according to drug concentration.

Results

Baseline Characteristic and Outcome of COVID-19 Patients

Among 368 patients hospitalized from Feb 11 to Mar 23, eight (2.17 %) received intravenous vancomycin treatment. TDM was conducted for all eight patients based on the clinical requirement (Table 1 and Table S1). The median age was 64.5 (57-81) years, including six males and two females (Table 1 and Table S1). Seven (87.5 %) patients had a clear etiology, including four cases with *Enterococcus faecium* pneumonia, and three with *Staphylococcus haemolyticus* bacteremia. The rest one received empirical vancomycin treatment for pneumonia. At baseline, each of them was on invasive mechanical ventilation. During the therapeutic process, 5 (62.5 %) were on Extracorporeal Membrane Oxygenation (ECMO), and 4 (50 %) were on hemodialysis. The baseline creatinine concentration and eGFR were 91.04 (31.67-188.67) $\mu\text{mol/L}$ and 92.33 (31.7-193.99) mL/min , respectively. Seven out of 8 have basic diseases. The initial vancomycin dosage was 1000 mg every 12 hours (1000 mg Q12 h) in six patients, 500mg per 8 hours (500 mg Q8 h) in one and 1000 mg every 24 h (1000 mg Qd) in the last patient. Five of them were also administered vancomycin through nasogastric tube feeding. The median treatment duration (including nasal administration) was 18.6 (5-39) days. All 7 culture confirmed infection turned negative after vancomycin treatment. Among patients who did not receive hemodialysis at baseline, 50 % (2/4) experienced AKI, including 1 initiated hemodialysis 4 days after vancomycin treatment.

Vancomycin Concentration Determination by UPLC-MS/MS

Vancomycin concentrations were detected by UPLC-MS/MS (supplement results). The ion channels of vancomycin and demethylvancomycin (IS) were m/z 725.5/144.2, and 718.4/144.2, respectively. As shown in Supplement Figure 1 (Figure S1), vancomycin and IS were eluted at about 1.7 min. The endogenous substances in the blank serum did not interfere with vancomycin and IS (Figure S1A and S1B). The compounds eluted from healthy donors (Figure S1C and S1D) were similar to those from COVID-19 patient's samples (Figure S1E and S1F). The calibration curve range was 1-100 mg/L, and met the clinical requirement.

TDM of Vancomycin in COVID-19 Patients

A total of 63 time spots were monitored, including 36 troughs and 27 peaks (Table S1). Out of the 36 trough samples, nine had concentrations less than 10 mg/L and 5 have concentrations greater than 20 mg/L. Of the 27 peak samples, seven had concentrations more than 40 mg/L, and 4 less than 20 mg/L. The mean trough concentration was 13.79 ± 6.61 (4.63-34.2) mg/L (n=36) and the peak concentration was 30.97 ± 9.71 (17-49.9) mg/L (n=27) (Figure 1A). For patients with available samples on peak or trough, 28.6 % (2/7) patients had at least one trough concentration less than 10 mg/L, and 80.0 % (4/5) of the patients had at least one peak concentration greater than 40mg/L. Of which, patient No.1 and 2 patients were continuously monitored for 16 days, and thus, more samples were collected from them than from the others, who had one to four samples (Table S1). For No.1, five samples showed trough concentrations beyond the normal range (10-20mg/L) and two samples showed higher peak concentration (>40 mg/L) (Figure 1B). For patient No.2, 10 samples (50 %) were out of normal range, including 7 at trough and 3 at peak (Figure 1C).

Furthermore, we examined the data from the first test of each patient, and found that 66.7% (4/6) of peak concentrations were higher than the upper limit of 40 mg/L with a mean of 37.19 (17-49.9) mg/L. Furthermore, 55.6% (5/9) of the trough concentrations were also beyond the recommended range (10-20 mg/L) with a mean of 15.59 (4.63-26.6) mg/L (Figure 1D).

Dose Adjustment Dependent on Drug Concentration

Four out of eight (50 %) patients had normal concentrations at the first detection; one (patient No. 5) had a little higher peak concentration (41.3 mg/L at peak (Table S1). Dose adjustment of intravenous vancomycin was made

for the other three (37.5%) patients (No.1, 2 and 4) according to their serum drug concentrations. After dose adjustments, the peak concentrations (27.37 (17.8-41.7) mg/L) were basically returned to normal range. Significant difference ($P < 0.05$) was detected in peak concentrations before and after dose adjustment (Figure 1E).

The curve of concentration for vancomycin, GFR, and creatinine from three patients with dose adjustments was shown in Figure 2. Figure 2A for Patient No.1, 2B for Patient No.2, 2C for Patient No.4. Patient No.1 (Figure 2A) was initiated with intravenous vancomycin at 1000 mg per 12 h to treat *Staphylococcus haemolyticus*. On day 5, at first detection, C_{trough} was 6.8 mg/L lower than 10 mg/L. The intravenous dose was then increased to 1000 mg Q8 h. He was also given nasal vancomycin at 250 mg Q12 h from day 7. C_{peak} was 47.7 and 41.9 mg/L on day 7 and day 8, respectively. Intravenous dose was decreased to 1000 mg Q12 h on day 8, and C_{trough} was 4.63 mg/L and 6.7 mg/L on day 11 and day 13, respectively. Intravenous dose was further adjusted to 500 mg Q6 h on day 13. Since then, optimal drug concentration was detected with 90% (9/10) of samples on trough spots and 100% (9/9) on peak spots. However, he met the criteria of grade 1 AKI on day 28 and then stopped intravenous vancomycin.

Patient No. 2 (Figure 2B) was initiated with intravenous vancomycin at 1000 mg Q12 h to treat *Enterococcus faecalis* bacteremia. He present with renal dysfunction and was on hemodialysis since baseline. At first detection on day3, C_{peak} was 33 mg/L and intravenous dose was adjusted to 1000mg Q8h according to improved eGFR. However, C_{peak} rised to 46.6 mg/L on day 4, then on the same day intravenous vancomycin was stopped. He also received nasal vancomycin from day 5 to day 39. From day 5 to day 12, C_{peak} and C_{trough} gradually returned to normal. He was given 1000mg Q24h of vancomycin intravenously on day 10 and stopped on day 12, when both C_{peak} and C_{trough} exceeded the expected range. From day 15 to day 33, C_{trough} was 5.9-13.1 mg/L and C_{peak} was 17.8-30.9 mg/L, although the patient was on nasal vancomycin alone.

Patient No.4 (Figure 2C) was initiated with intravenous vancomycin at 500mg Q8h to treat *Enterococcus faecium* pneumonia. On day 4 and 5, C_{trough} was 26.6 mg/L and 25.5 mg/L, respectively. After that, vancomycin administration was paused till day 10, when the patient was given intravenous vancomycin at 500mg Q8h and nasal vancomycin at 250mg Q6h. On day 12, C_{trough} and C_{peak} were 19.5 mg/L and 41.7 mg/L, respectively. Intravenous vancomycin was stopped on day 13, after the blood culture results were negative.

Population PK and pharmacokinetic / pharmacodynamic (PK/PD) analysis

The PK parameters of vancomycin were shown in Table 2. CL and Q were 4.3 L/h and 4.1 L/h, and V_1 and V_2 were 2.0 L and 56.7 L respectively. Half-life for distribution phase and elimination phase was 10 min and 19 h, respectively. Hemodialysis and serum creatinine level were covariates on the CL. Both of them were consistent with the power model. The CL in patients with hemodialysis decreased by 58% compared to those in patient without hemodialysis. IIV of CL was removed because it was close to zero after adding hemodialysis and serum creatinine level as the covariates. ECMO did not have significant effect on vancomycin PK parameters. As shown in Figure 3A, individual predictions were close to observations. The correlation coefficient reached 0.81. Most of conditional weighted residuals distributed evenly across zero horizontal line (Figure 3B), indicating that the model estimates were reliable and stable.

The AUC_{0-24} of vancomycin was shown in Table 1. The mean \pm SD were 622 ± 218 h·mg/L, and coefficient of variation was 35%. If the vancomycin dose was higher, or the drug was given more frequent, the AUC_{0-24} would increase. For example, in patient No.1, AUC_{0-24} changed from 871 to 740 h·mg/L when the dosage changed from 1g

Q8h IV+0.25g NS (day 5-7) to 1g Q12h IV+0.25g NS (day 8-11). The AUC_{0-24} changed from 596 to 945 h·mg/L when the dosage changed from 1g Q12h IV (day0-2) to 1g Q8h IV (day3) in patient No. 2.

AUC_{0-24}/MIC of vancomycin was shown in Table 1. The mean±SD was 848 ± 566 h·mg/L, and coefficient of variation was 67%. The maximum and minimum of AUC_{0-24}/MIC were 1738 and 244 h·mg/L, respectively. Although AUC_{0-24}/MIC for 3 patients was less than 400, the microbiological effects were all successful. There was no correlation between AUC_{0-24}/MIC and microbiological effect ($R^2 = 0.01$). AUC_{0-24} had a positive correlation with the grade of AKI. $AUC_{0-24} = 675$ h·mg/L was the best critical value for differentiating AKI occurrence. When $AUC_{0-24} \geq 675$ h·mg/L, 2 of 3 patients (67%) had AKI. Meanwhile, When $AUC_{0-24} < 675$ h·mg/L, only 1 of 5 patients (20%) had AKI ($p=0.19$).

Discussion

A previous study reported secondary infection in 15% of hospitalized patients with COVID-19.² Gram positive bacteria were the major pathogens in hospitalized (especially ventilated) patients. The rapid increase in hospitalization and ventilation, associated with COVID-19, highlighted the need for vancomycin usage in treating gram positive bacterial infections in these patients.¹ Rational usage of vancomycin relies on TDM, in order to maintain an optimal concentration, and reduce the risk of treatment failure, drug resistance, as well as renal injury. Here we presented pilot findings of TDM in patients with COVID-19.

Renal dysfunction, hemodialysis and ECMO usage were major factors that affected the PK of vancomycin.¹⁶ Among eight participants with COVID-19, six (except No.1 and 5) (75%) had at least one of these factors at baseline, implying the difficulty in the rationale of vancomycin usage among these patients. 25.4% (16/63) of serum concentration of vancomycin was beyond optimal range (< 10 mg/L at trough or > 40 mg/L at peak). After treatment, 60% (3/5) of patients with normal baseline renal function developed acute kidney injury. These highlighted the necessity of TDM for vancomycin treatment in patients with COVID-19.

Abnormal concentration especially for peak spots was more prevalent in samples at the beginning than after initiation of TDM (vs, $P < 0.05$). After dose adjustment in three patients with abnormal trough and/or peak concentrations, it returned to and maintained within the safe and effective range. Target infection was clinically cured in 7 of the patients (one is empirical treatment), and no vancomycin-associated nephrotoxicity was detected during TDM process. TDM could be a useful tool to guide the proper usage of vancomycin in patients with COVID-19.

Although vancomycin was generally considered to be nonabsorbable through gastral administration,¹⁷ there were a few case reports of 'red man syndrome',^{18,19} ototoxicity or encephalopathy related to oral vancomycin.^{19,20} In this work, we detected a distinct and stable serum concentration for 20 days in one patient during nasal vancomycin administration alone after stopping intravenous usage. This indicated that gastral vancomycin might be absorbed. Gastral vancomycin is often used to treat or prevent *Clostridium difficile* infection among ventilated patients, who might be numerous in the COVID-19 pandemic. Further study and special attention is needed to determine the potential toxicity and drug resistance induced by gastral vancomycin usage in COVID-19 patients, especially those who produce detectable serum concentrations.

AUC_{0-24}/MIC has been identified as the most suitable PK/PD index for the efficacy of vancomycin. For the MRSA infections, the recommended range of AUC_{0-24}/MIC in the guideline is between 400 and 600 assuming a MIC of 1 mg/L.⁹ The pathogens in the COVID-19 patients in this study were MRCNS and *Enterococci*. Although the average

AUC₀₋₂₄/MIC of No. 1, 2 and 5 patients was less than 400, microbiological clearance was still achieved in each of them. This was consistent with the results of a prospective study in Chinese adult subjects.²¹ The target value of AUC₀₋₂₄/MIC for clinical/ microbiological efficacy in Chinese adult patients may be between 200 and 300. Our study showed that AUC₀₋₂₄ with value 675 h·mg/L may be the critical value for differentiating AKI occurrence. This was similar to a report which showed that AUC₀₋₂₄≥650 h·mg/L was the cut point for AKI occurrence.²⁶

This study had certain limitations. First, being an observational study involving only 8 patients rather than a multicenter randomized controlled trial, the data of this study should be used cautiously when applying to larger populations and different settings. Second, we found considerable serum concentration in one patient during the period of nasal vancomycin administration alone. This data along with its clinical significance need to be further verified in larger cohorts. Third, vancomycin concentration was tested with the serum samples alone, which does not best represent the concentration in key organs such as the lung and kidney. Fourth, we did not test the covariates for basic disease and concomitant usage of drugs except for antibiotics. The fitting of PPK model might be improved if these data were analyzed additionally. Fifth, Last but not least, due to the small number of participants, this study did not find a correlation between AUC₀₋₂₄/MIC and efficacy in the COVID-19 patients.

Conclusions

Renal function, hemodialysis and ECMO usage were common in the COVID-19 patients, highlighting the need of TDM. An UPLC-MS/MS method was developed to quantify vancomycin concentration. Sixty-three serum samples were tested and 16 samples had a concentration beyond the expected range (<10 at trough and >40 mg/L at peak). TDM guided dosage adjustment in 37.5% of the patients, leading to an optimal concentration. All patients were cured and no vancomycin-associated nephrotoxicity was detected during the process of TDM. Considerable vancomycin concentrations were detected during sole nasal administration for 20 days, alerting the potential systemic risk during gastral usage of vancomycin. PK was consistent with two-compartment model, and CL was affected by hemodialysis and renal function. Most of the patients were infected with *Staphylococcus* or *Enterococcus* species and MIC₉₀ was 2 mg/L. Vancomycin AUC₀₋₂₄ had positive correlation with AKI occurrence, while AUC₀₋₂₄/MIC did not have correlation with the efficacy. It is necessary to perform randomized clinical trials to further justify the findings of the study and investigate best strategy of TDM for these patients.

Methods

Study Design and Patients

The study was performed in Shanghai Public Health Clinical Center (SPHCC, Shanghai, China), a designated hospital for COVID-19 patients. Laboratory confirmation of COVID-19 was made as previously reported.²⁷

The clinical management of COVID-19 was adherent to the Chinese management guideline for COVID-19 (version 6.0).²⁸ Gram-positive bacteria infection was diagnosed according to the guidelines.^{3,29} Cultures were carried out as described previously.³⁰⁻³² *Staphylococcus* species were cultured in LB medium³¹ and *Enterococcus* species were in BHI medium.³² Vancomycin usage (initial dosage, total duration of intravenous or nasal vancomycin) was decided by an expert panel of infectious disease and critical care, in adherence to the relevant guidelines.³ Data on serum drug concentrations were sent to the clinicians within 8 hours after blood collection. Doses were adjusted by a panel of experts, based on TDM and renal function data. Pathogen clearance was defined as negative conversion of

culture after treatment. Acute kidney injury (AKI) was defined and graded according to the KDIGO clinical practice guidelines.³³ Co-administration of nasal vancomycin to prevent *Clostridium difficile* colonitis was also recorded.

TDM of vancomycin was requested by the clinicians. The blood samples were collected within 0.5 h before the fourth continuous intravenous (IV) infusion of vancomycin (trough spot) and 0.5-1 h after infusion (peak spot). Similar time for NS administration was used. At each spot, 2 mL of blood was drawn into a non- anticoagulant tube, treated with acetonitrile (ACN) solution to inactivate the virus, and centrifuged. The volume of serum used for TDM was 50 μ L per test. The normal concentration range was set at 10-20 mg/L for the trough and 20-40 mg/L for the peak.¹⁰

The study protocol was reviewed and approved by the Ethics Commission of SPHCC (No. YJ-2020-S053-02), and all the procedures were performed in accordance with the recommendations of the Declaration of Helsinki on biomedical research involving human subjects. Informed consent was acquired from the patients or their surrogates.

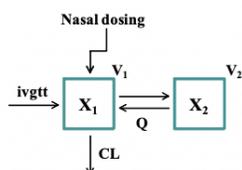
Measurement of Vancomycin Levels

Vancomycin concentrations were detected by UPLC-MS/MS as previously reported.¹⁰ The details are described in the supplementary material section. Briefly, fifty microliters of serum was precipitated with 360 μ L acetonitrile (ACN) solution (50 μ L 10% formic acid, 10 μ L demethylvancomycin (IS) (50mg/L) and 300 μ L ACN). The operations were carried out in the BSL-2 laboratory. After precipitation, the supernatant was sent to the analytical laboratory, diluted for 20-fold with 5% ACN solution, and detected by UPLC-MS/MS.

The UPLC system consisted of a Waters Acquity UPLC (Waters Corporation, Milford, USA) and an AB Sciex Triple Quad 5500 (AB SCIEX company, Boston, USA). Chromatographic separation of vancomycin and its IS was carried out on a Kinetex® 2.6 μ m Phenyl-Hexyl column 100 \AA (50 mm length x 3.0 mm internal diameter) (Phenomenex Company, USA). Chromatographic separation was performed using a mobile phase composed of 0.1% FA (A) and methanol containing 0.1% FA (B). The analytes were detected by multiple reaction monitoring (MRM) mode with ion pairs of m/z 725.5/144.2 for vancomycin and m/z 718.4/144.2 for IS. The line range was 1-100 mg/L.

Population PK (PPK) and pharmacokinetic / pharmacodynamic (PK/PD) analysis

PPK model was developed to describe the time profiles of vancomycin pharmacokinetic characters using NONMEM (Ver7.4, ICON Co. Ltd, USA), PsN (Ver4.7, Uppsala University) and Xpose software (Ver4.5, Uppsala University). The base model was two-compartment model as shown in follow:



The absorption of vancomycin was consistent with zero-order kinetics. X_1 and X_2 were drug amount in the central and peripheral compartment, respectively. CL was clearance from the central compartment, while Q was the inter-compartment clearance between the central and peripheral compartment. V_1 and V_2 were distribution volume in the central and peripheral compartment, respectively. Model equations for evaluation of candidate covariates are as follows:

$$\begin{cases} \frac{dX_1}{dt} = f_{ivgtt} + f_{Nasal} - \frac{CL}{V_1} X_1 - \frac{Q}{V_1} X_1 + \frac{Q}{V_2} X_2 \\ \frac{dX_2}{dt} = \frac{Q}{V_1} X_1 - \frac{Q}{V_2} X_2 \\ f_{ivgtt} = \begin{cases} AMT_{ivgtt} / D_{ivgtt} & t \leq D_{ivgtt} \\ 0 & t > D_{ivgtt} \end{cases} \\ f_{Nasal} = \begin{cases} AMT_{Nasal} / D_{Nasal} & t \leq D_{Nasal} \\ 0 & t > D_{Nasal} \end{cases} \\ C = \frac{X_1}{V_1} \end{cases}$$

f indicated input function. D_{Nasal} and D_{ivgtt} indicated the duration of drug in the absorption and infusion, respectively. AMT was drug dose, and C was vancomycin concentration in central compartment. Inter-subject variability (IIV) of CL was consistent with the exponential model, while IIV of other parameters were fixed as zero. The residual error model was consistent with the proportional model.

The following covariates were tested during development of the final PPK model: gender, age, serum creatinine, estimated glomerular filtration rate, urea nitrogen, alanine aminotransferase, direct bilirubin, body temperature, hemodialysis, extracorporeal membrane oxygenation (ECMO) and concurrent use of levofloxacin and/or carprofen. A fixed-effect model was developed using stepwise method. The covariate would be included in the model if the decrease of objective function value (OFV) was greater than 3.84 ($P < 0.05$) in the forward selection, or the increase of OFV was greater than 6.63 ($P < 0.01$) in the backward elimination. The type of covariate model tested included power model or linear model. Individual PK parameters of vancomycin were obtained using Bayesian feedback method.

The PPK model was simulated 100 times using the final estimates. Mean concentration was calculated using individual prediction data. The daily AUC_{0-24} was calculated using trapezoidal area method after the first dose each day. The average AUC_{0-24} was obtained according to $\text{sum}(AUC_{0-24}) / (\text{treatment duration-days without drug administration})$. The AUC_{0-24}/MIC was calculated as the ratio of mean AUC_{0-24} to MIC. These were performed using Matlab software (Ver7.0.1, Mathworks Co. Ltd, USA).

The correlation between AUC_{0-24}/MIC and the microbiological effect of vancomycin was analyzed. To analyze the relationship between AUC_{0-24} and AKI occurrence, logistic regression and cross tabulation were used to find the critical value which could differentiate the AKI occurrence with maximal probability.

Statistical Analysis

Graphpad Prime 5.0 (GraphPad Software, San Diego, California) was used to compare vancomycin concentrations, and create a scatter plot. The curve of concentration for vancomycin, estimated glomerular filtration rate (eGFR) and serum creatinine level were obtained by using OriginPro 70 software (OriginLab, Massachusetts, USA). The Student t test (and Nonparametric test) was used to compare the concentration levels. All tests were 2-tailed. A P value < 0.05 indicated statistical significance.

Declarations

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Author contributions

Lijun zhang originated, designed the study, conducted data analysis, and drafted the manuscript; Hongzhou Lu funded the research, and revised the manuscript; Lin Yin, Yuancheng Chen, Mingquan Guo, Zhaoqin Zhu, Menglu Gao, Jin Ke, Junjun Ping, and Yaru Xing contributed to sample detection and data collection; Tangkai Qi, Huichun Shi contributed to data collection, and drafted the manuscript; Yun Ling, Lin Wang, Yonghong Tao, Jing Zhang, Yaxin Fan, Shuibao Xu, Yili Li, Xianmin Meng and Wenhong Zhang contributed to data collection. All the authors proved the final version of this manuscript.

Competing Interest All authors declared no competing interests.

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Tables

Table 1 The clinical and experimental characters of 8 patients

No.	Age (Year)	Sex	Pathogen	MIC mg/L/site	Infection	ECMO	Hemodialysis on Baseline	Baseline Creatinine	Baseline eGFR	Initial Dose	Nasal feed vancomycin	Therapy duration (Total/IV/Pre.)*	Sub-optimal/total troughs	Overdose/total peaks	Trough/Cpeak	Adjust. dose	Pathogen Clearance	AKI	AUC ₀₋₂₄ (h-mg/L)	AUC ₀₋₂₄ /MIC (h)
1	64	M	<i>Staphylococcus haemolyticus</i>	2	Lung	Yes	No	71.77	101.39	1000mg Q12h	250mg Q6h	28/28/5	4/16	2/14	4.63-23.6/17-47.7	Yes	Yes	1	676	338
2	81	M	<i>Enterococcus faecalis</i>	2	Blood-stream	Yes	Yes	188.67	31.7	1000mg Q12h	250mg Q6h	39/5/3	5/13	3/9	5.9-34.2/21.8-49.9	Yes	Yes	NA	488	244
3	62	M	<i>Enterococcus faecium</i>	≤0.5	Lung	Yes	No	77.4	92	1000mg Q12h	No	25/25/4	0/1	0/0	6.15-18.8/NA	No	Yes	NA	456	912
4	75	M	<i>Enterococcus faecium</i>	≤0.5	Lung	Yes	Yes	85.62	80.13	500mg Q8h	250mg Q6h	17/13/4	0/3	1/1	19.5-26.6/41.7	Yes	Yes	3	869	1738
5	57	F	<i>Staphylococcus haemolyticus</i>	1	Blood-stream	No	No	46.88	107.93	1000mg Q12h	250mg Q6h	13/12/2	0/1	1/1	12.1/41.43	No	Yes	NA	370	370
6	70	M	<i>Staphylococcus haemolyticus</i>	1	Lung	No	Yes	79.82	88.09	1000mg Q12h	No	11/11/3	0/1	0/0	15.1/NA	No	Yes	NA	984	984
7	63	F	Emperical (NA)	NA	Lung	Yes	No	31.67	193.99	1000mg Q12h	125mg Q6h	11/10/6	0/1	0/1	14.3/34.8	No	NA	2	457	NA
8	65	M	<i>Enterococcus faecium</i>	≤0.5	Lung	No	Yes	146.48	43.37	1000mg Q12h	No	5/5/5	0/0	0/1	NA/24.6	No	Yes	NA	674	1349
Mean																			622	848
SD																			218	566

* Therapy duration (Total/IV/Pre.) represents the days for total vancomycin therapy / IV administration / the days before drug concentration detection, respectively

AKI: acute kidney injury

ECMO: Extracorporeal Membrane Oxygenation

NA: not available. For AKI data, it means AKI did not occur

SD: standard deviation

Table 2 Vancomycin PK parameters in the final PPK model

Parameter (Unit)	Explain	Value (RSE%)
CL (L/h)	Clearance from central compartment	4.33 (23.8%)
V_1 (L)	Distribution volume in central compartment	2.00 (62.3%)
Q (L/h)	Inter-compartment clearance between central and peripheral compartment	4.14 (68.4%)
V_2 (L)	Distribution volume in peripheral compartment	56.7 (36.3%)
D_1 (h)	Duration during drug absorption	1.90 (6.0%)
θ_{Hemo}	Impact factor of hemodialysis on the clearance	0.42 (13.5%)
θ_{Scr}	Impact factor of serum creatinine on the clearance	0.41 (20.5%)
ε (%)	Proportional residual error item	31.3 (5.7%)

RSE: relative standard error

Figures

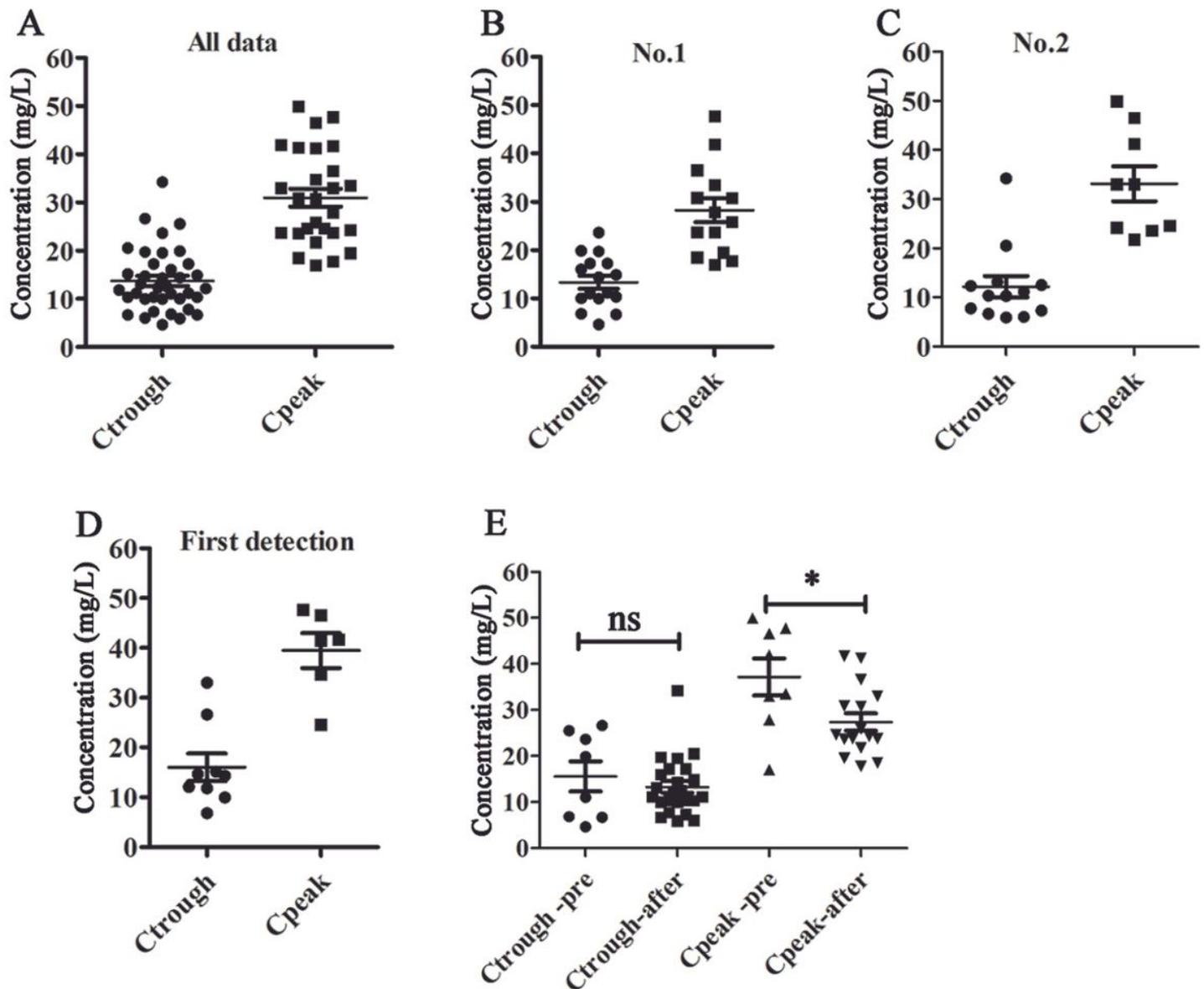


Figure 1

Monitoring of serum vancomycin concentration in COVID-19 patients A. All data from 8 patients. B and C. The data from patient No.1 and patient No.2, respectively. D. The data from the first detection of all patients. E. Comparison between the concentration before and after dose adjustments. P < 0.05 represents statistical difference. ns, no statistical difference. *, p < 0.05.

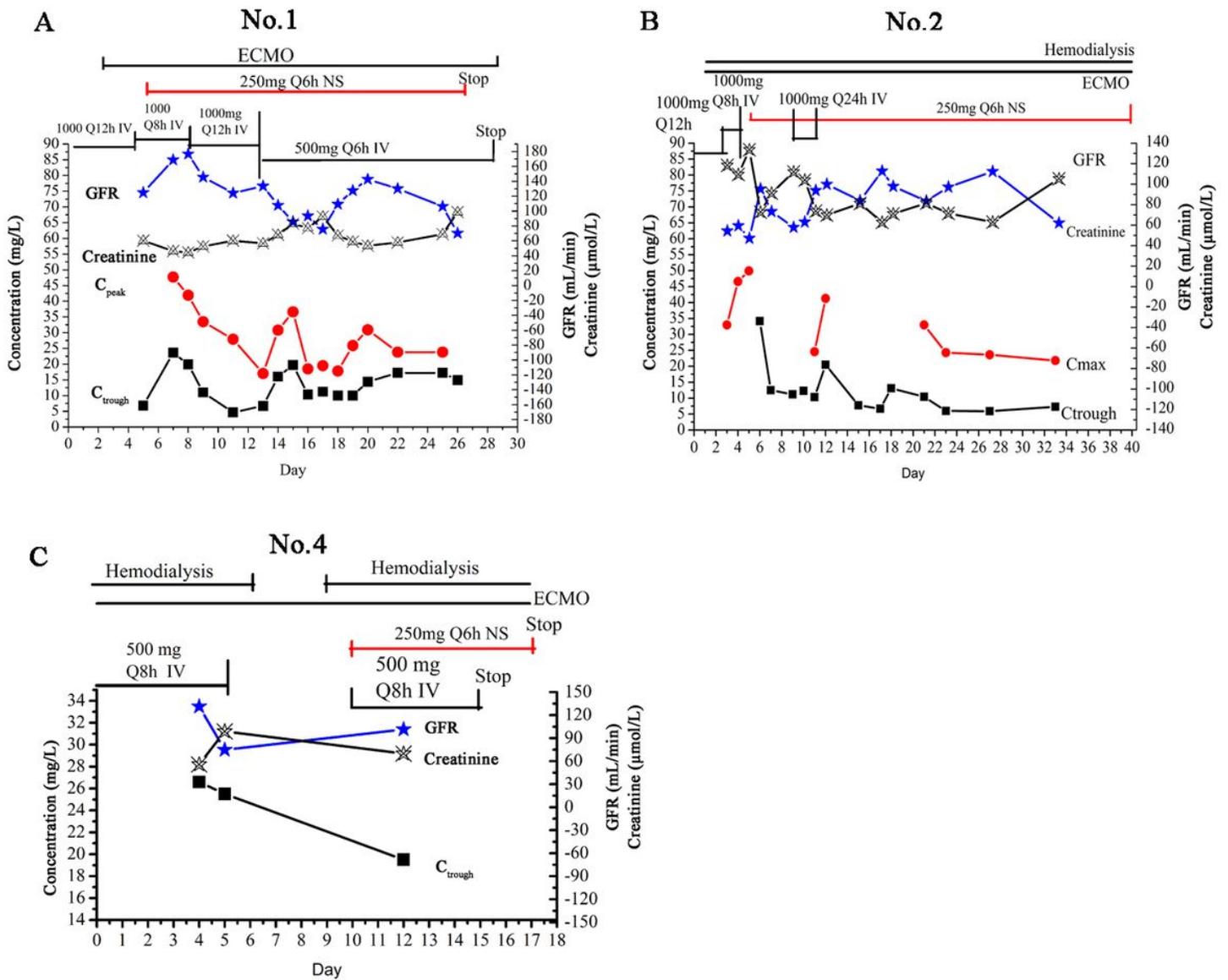


Figure 2

The curve of concentration for vancomycin, GFR, and creatinine from three patients with dose adjustments A. from No. 1; B. from No.2; C. from No.4. Intravenous administration (IV) shown in dosing and blank line; Nasal feed (NS) shown in dosing and red line. Square frame and blank curve: C_{trough} ; Circular dots and red line: C_{peak} ; Star and blue line: GFR; Star and blank line: Creatinine. The date giving loading dose was counted as day 0, and the data for vancomycin stopping as "stop". ECMO and Hemodialysis were shown from loading dose to drug stopping.

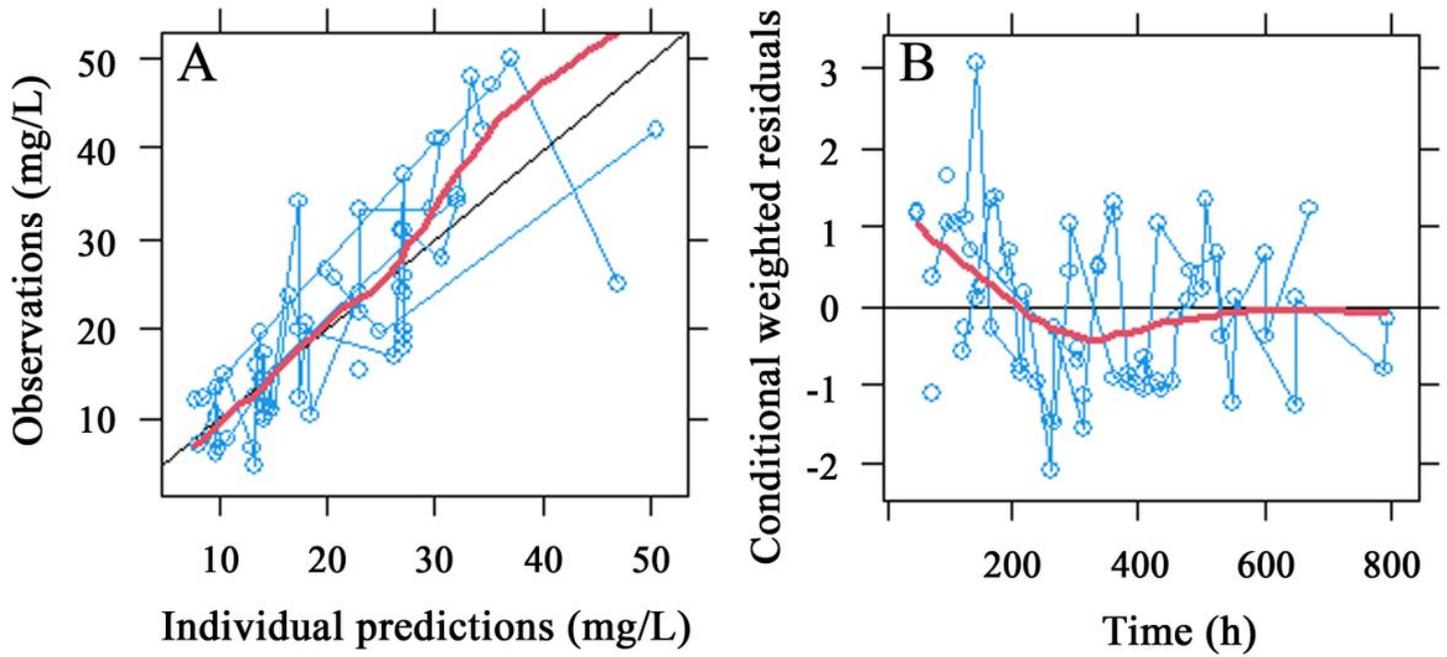


Figure 3

Diagnostic plot of final PPK model of vancomycin Circles means actual data. Red line means local weighted regression line, while blank line means unity line (A) or zero horizontal line (B).

Supplementary Files

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