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ORIGINAL RESEARCH

Population Pharmacokinetics and Dosing Optimization of Norvancomycin for Chinese Patients with Community-Acquired Pneumonia

Yaqian Li[1], Xiaodan Jiao[2], Guozhu Sun[3], Fuxu Wang[4], Xikun Wu[1], Weichong Dong[1], Wenpeng Lu[3], Zhiyong Zhang[1], Yadong Yuan[2], Zhiqing Zhang[1]

[1]Department of Pharmacy, The Second Hospital of Hebei Medical University, Shijiazhuang, 050000, People's Republic of China; [2]Department of Respiratory and Critical Care Medicine, The Second Hospital of Hebei Medical University, Shijiazhuang, 050000, People's Republic of China; [3]Department of Neurosurgery, The Second Hospital of Hebei Medical University, Shijiazhuang, 050000, People's Republic of China; [4]Department of Hematology, The Second Hospital of Hebei Medical University, Shijiazhuang, 050000, People's Republic of China

Correspondence: Zhiqing Zhang, Department of Pharmacy, The Second Hospital of Hebei Medical University, 215 hepingxi Road, Shijiazhuang, Hebei Province, 050000, People's Republic of China, Email 26500007@hebmu.edu.cn; Yadong Yuan, Department of Respiratory and Critical Care Medicine, The Second Hospital of Hebei Medical University, 215 hepingxi Road, Shijiazhuang, Hebei Province, 050000, People's Republic of China, Email yuanyd1108@163.com

Purpose: Determining the optimal dosage of norvancomycin (NVCM) for Chinese patients with community-acquired pneumonia (CAP) caused by gram-positive cocci remains uncertain. This research aimed to identify influential factors affecting NVCM pharmacokinetics and explore optimal dosage regimens via population pharmacokinetic (PPK) analysis.

Patients and Methods: A prospective analysis was conducted at the Second Hospital of Hebei Medical University (Shijiazhuang, China). CAP patients aged ≥18 years and receiving intravenous NVCM were enrolled. Each patient underwent the collection of 3–8 blood samples for analysis during the treatment. Nonlinear mixed effect model (NONMEM) software was used to develop PPK models, while Monte Carlo simulations were employed to optimize dose regimens. Pharmacokinetic-pharmacodynamic (PK/PD) breakpoint was defined as daily area under the concentration on the second day of therapy to minimum inhibitory concentration ratio ($AUC_{24\text{-}48h}$/MIC) ≥361, and a steady-state AUC to MIC radio ($AUC_{ss,24h}$/MIC) ≥361.

Results: A prospective PPK analysis of 231 NVCM concentrations was performed in 34 patients. A two-compartment model with first-order elimination adequately described the pharmacokinetics. The population typical clearance (CL) of NVCM was 3.15 L/h, and the central volume of distribution was 12.3 L. Notably, CL exhibited significant correlations with age and serum creatinine (Scr) levels. For mild or moderate CAP patients, the recommended doses were 400–800 mg every 12 h to achieve the target exposure with $AUC_{ss,24h}$/MIC ≥361. For community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) pneumonia, the suggested dosage regimen was 600–800 mg every 8 h, which could achieve the target exposure preferably within the initial 24 to 48 h.

Conclusion: Age and Scr levels significantly influenced the pharmacokinetic parameters of NVCM in CAP patients. Our model-informed precision dosing approach may help for early optimization of NVCM exposure. Further prospective studies with larger samples will be needed.

Keywords: norvancomycin, population pharmacokinetics, community-acquired pneumonia, dosing optimization

Introduction

Community-acquired pneumonia (CAP) presents a significant public health concern both in China and globally.[1] Epidemiological surveys in Chinese adults have identified *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* as predominant pathogens, with others such as *Staphylococcus aureus, Chlamydia pneumoniae*, and *Haemophilus influenzae* also commonly implicated.[2–6] Treatment duration typically ranges from 5 to 7 days for mild or moderate CAP, and 10 to 14 days for severe CAP or cases with extrapulmonary complications. However, infections involving *Staphylococcus aureus* may necessitate extended treatment periods of 14 to 21 days.[7–9]

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Recently, a few cases of community-acquired methicillin-resistant *S. aureus* (CA-MRSA) pneumonia have emerged in China,[10,11] posing a significant challenge due to its high mortality rate of 41.1%.[12] Therefore, it is crucial to enhance treatment efficacy and reduce the duration of therapy for severe pneumonia.

Currently, vancomycin (VCM), linezolid, and norvancomycin (NVCM) are the primary empiric antibiotic therapies for gram-positive cocci pulmonary infections.[1] NVCM, a glycopeptide antimicrobial agent developed independently by the North China Pharmaceutical Group Corporation, exhibits a molecular structure distinct from that of vancomycin due to the absence of one methyl group.[13] In China, NVCM has become a standard treatment for infections associated with antibiotic-resistant gram-positive bacteria such as MRSA, owing to its similar antibiotic activity and spectrum to VCM.[13,14] 24-h area under the concentration–time curve to minimum inhibitory concentration ratio (AUC_{24h}/MIC) of 361 was considered as pharmacokinetics/pharmacodynamics (PK/PD) efficacy index of NVCM for staphylococcal infection.[13] Current guidelines for the diagnosis and treatment of CAP recommend a standard dose of 800 mg every 12 h (q12h).[1]

Optimal antimicrobial dosing should consider the pharmacokinetics within the target population, the relationship between drug exposure and outcomes and the vulnerability of the pathogens involved.[15] In typical adults, standard dose evaluations of antimicrobials often rely on a "normal" dosage, overlooking the significant impact of underlying diseases on drug exposure in clinical scenarios. Recent data highlights a concerning decline in the efficacy of NVCM and other similar antibiotics against MRSA infections due to increasing minimum inhibitory concentration (MIC) levels.[16–18] Conventional dosage of NVCM in clinical practice contributes to prolonged pneumonia treatments and the emergence of drug-resistant bacterial strains.[1,19] These findings emphasize the need for population pharmacokinetic (PPK) models and personalized dosage regimens, since there are limited PPK/PD studies of NVCM in pneumonia patients, and the optimal dosing regimen of NVCM in severe pneumonia has not been determined. Therefore, optimizing the NVCM dosage regimens for adult patients with mild (or moderate) and severe pneumonia is essential, based on a defined PK/PD breakpoint.

This prospective study aimed to construct a PPK model, comprehensively assess the pharmacokinetic characteristics and variations of NVCM, and determine optimized dosage regimens of NVCM in Chinese adult patients with mild (or moderate) and severe pneumonia.

Materials and Methods

Study Design

This prospective, single-center, open-label observational study was conducted at the Second Hospital of Hebei Medical University between November 2020 and March 2022 (Shijiazhuang, China). The experimental protocols were carried out, and written informed consent was obtained in accordance with the ethical standards established by the 1964 Declaration of Helsinki. The study was registered with the Chinese Clinical Trial Registry (registration number: ChiCTR2000039794, the date of registration: 2020–11-23) and approved by the Ethics Committee of the Second Hospital of Hebei Medical University (2020EC07-05-2).

Patient Cohort and Data Acquisition

Patients

This research included hospitalized patients aged ≥18 years who were diagnosed with CAP. All enrolled patients presented suspected or confirmed pulmonary infections attributable to gram-positive bacteria. NVCM therapy was administered via intravenous infusion, with concurrent monitoring of serum NVCM concentrations. Pregnant individuals and those undergoing renal replacement therapy were excluded from the analysis. Demographic features, along with laboratory and clinical examination data, were acquired for all enrolled patients. In addition, information related to NVCM treatment was collected from each enrolled patient, including the dosing information (eg, dosage regimen, date, time, and duration), serum concentrations, sampling time, and concomitant medications.

Dosage Regimen and Sampling

To treat pulmonary infections, NVCM (400 mg/bottle; North China Pharmaceutical Group Corporation, Shijiazhuang, China) was administered intravenously at a dose of 800 mg every 12 h for 1 h via a syringe pump. Serum samples (3 mL)

were collected at the baseline (0.5 h before administration) and 0.5–1.5 h after the first dose of NVCM was finished. We repeated the serum sampling at the second, third, fourth, and the last day of NVCM treatment.

Assay of Serum NVCM and Creatinine

NVCM concentrations were determined by a high performance liquid chromatography (HPLC) method using the 2489 ultraviolet detector system (e2695, Waters Corp., MA, USA). A Diamonsil C_{18} column (150 mm × 4.6 mm, 5 μm) was used, and the detection wavelength was 236 nm. The calibration curve ranged from 0.25 to 100 μg/mL. The limit of detection for the analysis of NVCM was 0.05 μg/mL. Serum samples were processed by protein precipitation, and vancomycin was used as internal standard.[20] Serum creatinine (Scr) concentrations were measured by an enzymatic method using a Creatinine Test Kit (Creatinine plus ver.2 (CREP2), Roche Diagnostics GmbH, Germany).

PPK Modeling

Basic Model

PPK analysis was conducted using the nonlinear mixed effects modeling software NONMEM (version 7.5.0, ICON Development Solutions, MD, USA). Employing first-order conditional estimation method (FOCE-I) with an interaction option to estimate the pharmacokinetic parameters.

The compartmental model of NVCM was preliminarily established by an exploratory analysis of blood sample data. One- or two-compartment models were determined based on the principle of minimizing the objective function value (OFV) and visual inspection of the routine diagnostic plots of the model.

Interindividual variability in PK parameters was assessed by the following exponential model:

$P_i = TV(P) \times e^{\eta_i}$

where P_i denotes the parameter value of the *i*th subject; TV(P) represents the typical parameter value in the population; and η_i signifies the variability between subjects, assuming to adhere to a normal distribution with the mean and variance of 0 and ω^2, respectively.

The residual variability model selection was considered by OFV and visual inspection of the routine diagnostic plots. And the models are expressed as follows:

Additive error model: $C_{obs} = C_{pred} + \varepsilon_1$

Proportional error model: $C_{obs} = C_{pred} x(1+ \varepsilon_1)$

Exponential error model: $C_{obs} = C_{pred} x e^{\varepsilon 1}$

Combined error model: $C_{obs} = C_{pred} x (1+ \varepsilon_1)+\varepsilon_2$

where C_{obs} is the observed concentration of subjects, C_{pred} is the simulated concentration of subjects, ε_1 and ε_2 are proportional and additive residual variabilities, respectively, which are all assumed to follow a normal distribution with a mean of 0 and variance of σ^2.

Evaluation of Covariate

Demographic information, including sex, age, weight, and physiological characteristics (hepatic and renal function) of patients were evaluated as possible covariates. Stepwise covariate modeling and likelihood ratio tests were used to assess the effect of each variable.

Covariate selection was conducted through forward inclusion and backward elimination procedure. During forward inclusion, a covariate was deemed significant if a reduction in the OFV surpassed 3.84 with $P < 0.05$ (chi-squared distribution). All significant covariates were integrated into the whole model. Subsequently, backward elimination was performed, removing a covariate from the whole model if its removal resulted in an increase in the OFV of less than 6.64 ($P < 0.01$, chi-squared distribution). This process led to the derivation of the final PPK model.

Model Evaluation and Verification

The stability of the final model was examined through the bootstrap approach, implemented using the Perl-speaks-NONMEM (PsN, v.5.2.6; http://uupharmacometrics.github.io/PsN/) module.[21] The acquired dataset was replicated via iterative sampling. A 1000-times resampling bootstrap procedure was employed to assess the reliability of the final

model. The values (median, 95% confidence interval (CI)) obtained from the bootstrap procedure were compared with the estimated parameters of the final model.

The model was verified based on goodness-of-fit (GOF) plots and statistical criteria. Initially, GOF plots, comprising observed (DV) versus individual prediction (IPRED), DV versus population prediction (PRED), conditional weighted residuals (CWRES) versus time, and CWRES versus PRED, were employed for diagnostic purposes.[22] Line of identity was incorporated into the DV-IPRED and the DV-PRED plots. The proximity of the data points to the unit line indicated the quality of the fit of the final model.

Additionally, normalized prediction distribution errors (NPDE) and visual predictive check (VPC) were used to verify the predictive performance of the final model.[23] For the VPC, the 5/50/95th percentiles of the simulated data were processed using the RStudio environment (v.4.3.3, http://www.rstudio.com/). For the NPDE, we used an NPDE R package for model validation, and the results were presented graphically by using density histogram and quantile–quantile plot (Q-Q plot). The analysis was based on 1000 simulations of the dataset.

Dosing Optimization

Analysis of the Initial Dosage Regimen

The established PPK model was used to simulate individual PK parameters ($AUC_{0\text{-}24h}$, $AUC_{24\text{-}48h}$, $AUC_{48\text{-}72h}$, and $AUC_{ss,24h}$) by Bayesian feedback method. Simulated prediction data were generated based on a dose of 800 mg administered every 12 h, an infusion duration of 1 h, and a dense sampling interval of 0.1 h. PK parameters were calculated as follows:

$$AUC_{t1-t2} = \delta t \times \frac{c1 + c2}{2}, \delta t = t2 - t1$$

$AUC_{ss,24h}$ i = initial daily dose/CL_i

The target AUC was defined based on the PK-PD breakpoint of NVCM in *Staphylococcus aureus*, with an AUC_{24h}/MIC ratio of 361.[13] According to previous literature,[16] *Staphylococcus aureus*, including MRSA, typically exhibits MIC values within the range of 0.25–1 mg/L. In our study, MIC values of 0.5 and 1 mg/L were assumed, representing the more frequently observed MIC values for NVCM. The probability of target attainment (PTA) of the initial dosage regimen was calculated and defined as the number of qualified patients divided by the number of total patients.

Dosing Simulations

Monte Carlo simulations were carried out for different subgroups according to the covariates obtained from the final model. According to the instructions, the total daily dose of NVCM ranging from 800 to 2400 mg, divided into 2–3 intravenous doses, with each dose not exceeding 1000 mg, aimed at minimizing the risk of nephrotoxicity. Randomly generated sample simulation data includes dosing frequencies of q8h, q12h, and q24h, and preset single doses of 200, 400, 600, and 800 mg. A total of 5000 simulations were performed using the RStudio mrgsolve package, and the PK profiles were estimated for each simulated patient.

The first set of simulations was performed, and the optimal dosage was defined as the one that maximized the proportion of simulated patients with $AUC_{ss,24h}$/MIC ≥361. According to the 2020 Infectious Diseases Society of America (IDSA) guidelines and others,[24–28] achieving targeted exposure within the first 24–48 h of therapy is crucial. Considering that an alternative goal of initial therapy may be to maximize the effect early in some patients with severe CAP, a second set of simulations was performed to identify the dosage that maximized the proportion of patients achieve $AUC_{24\text{-}48h}$/MIC over 361. To achieve the target AUC/MIC in approximately 90% of the patients, the PTA ≥ 90% was considered as acceptable.

Results

Patient Characteristics

Initially, 46 patients were assessed for eligibility. Subsequently, four patients withdrew from the study, while 2 excluded due to a treatment duration of NVCM less than 72 h. Additionally, 6 patients were excluded due to missing serum

samples. Consequently, 34 patients were included in the final analysis, comprising 23 from the Department of Respiratory and Critical Care Medicine, 6 from the Department of Neurosurgery, and 5 from the Department of Hematology. Serum NVCM concentration monitoring was conducted in all patients, including 17 males, with an average age of 54.8 years. Each patient underwent the collection of 3–8 blood samples for analysis and a total of 231 NVCM concentrations were available. A total of 115 (49.8%) NVCM samples were measured as peak concentrations and 116 (50.2%) were trough concentrations. Patient characteristics are summarized in Table 1.

Finally, 10 bacterial strains were isolated from the alveolar lavage fluid or sputum culture of 34 enrolled patients. These strains were identified as methicillin-sensitive *S. aureus* (4), *S. epidermidis* (2) and MRSA (4). The results from susceptibility testing with five anti-bacterial agents, including norvancomycin, showed that all of the 10 Staphylococcus isolates were susceptible to both norvancomycin and vancomycin. And the MICs of the norvancomycin against the 10 strains of MRSA or Staphylococcus were 1 mg/L or lower. The supplement table we provide also details the information on bacterial culture results and blood sampling.

PPK Modeling

In total, 231 NVCM concentrations were available for PPK modeling. The data conformed better to a two-compartment model (OFV = 513.504) with first-order elimination, as opposed to a one-compartment model (OFV = 585.283). Interindividual variability in PK parameters was best described by an exponential model. And the residual variability was fitted to a combined error model.

Following the establishment of the two-compartment model, the impacts of various covariates on PK parameters were explored. The covariates examined were age, sex, weight (WT), height, C-reactive protein (CRP), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), Scr, direct bilirubin (DBIL), and creatinine clearance (CLcr).

During the forward inclusion, height, age, and Scr were added to build the initial model, with a significant decrease in OFV exceeding 3.84 ($P < 0.05$). Furthermore, inappropriate covariates were excluded using backward elimination. Age and Scr on CL ($\Delta OFV = -23.95$) were retained as influential covariates in the final model. Parameter estimates for the final model and bootstrap validation are summarized in Table 2. The bootstrap statistical analysis (n = 1000) showed that

Table 1 Baseline Characteristics of Patients (n = 34)

Parameters	Mean	SD	Median	Min	Max
Age (y)	54.91	15.66	57.50	27.00	80.00
Height (cm)	165.94	6.76	165.00	153.00	185.00
WT (kg)	64.75	11.24	64.00	46.00	90.00
BMI (kg/m2)	23.50	3.72	23.48	16.07	30.42
CRP (mg/L)	99.97	77.02	99.97	1.59	235.20
ALT (U/L)	28.43	21.76	20.40	3.40	88.00
AST (U/L)	28.52	19.76	21.55	6.80	87.90
ALP (U/L)	90.09	30.02	81.50	50.00	187.00
TBIL (μmol/L)	12.47	12.09	11.05	2.63	73.30
DBIL (μmol/L)	7.15	11.43	5.00	1.17	68.70
Urea (mmol/L)	4.60	3.15	3.58	1.14	17.50
Scr (μmol/L)	64.09	21.77	59.00	26.00	130.00
CLcr (mL/min) [a]	107.57	41.06	102.93	35.61	195.17
Cmax (μg/mL)	10.70	6.96	8.80	0.36	30.37
Cmin (μg/mL)	36.87	16.68	33.52	6.88	93.61

Notes: [a] CLcr (mL/min) was calculated by the Cockcroft-Gault formula.
Abbreviations: SD, standard deviation; WT, weight; BMI, body mass index; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TBIL, total bilirubin; DBIL, direct bilirubin; Scr, serum creatinine; Cmax, peak concentrations; Cmin, trough concentrations; CLcr, creatinine clearance.

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Table 2 Population Pharmacokinetic Parameter Estimates for the Final Model and Bootstrap Validation

Parameters	Final model estimates	RSE (%)	Bootstrap (N=1000)	
			Median	95% CI
CL (L/h)	3.15	8.2	3.13	2.69 ~ 3.58
V1 (L)	12.3	7.4	12.3	10.3 ~ 14.5
V2 (L)	115	18.6	113	74.3 ~ 180.5
Q (L/h)	5.21	7.2	5.17	4.17 ~ 6.03
Scr effect on CL	−0.00886	22.2	−0.00901	−0.016 ~ −0.004
Age effect on CL	−0.426	39.9	−0.426	−0.765 ~ −0.003
IIV of CL	0.0803	17.1	0.0671	0.033 ~ 0.115
IIV of V1	0.0424	46.4	0.0381	0.005 ~ 0.106
IIV of V2	0.996	22.6	0.898	0.271 ~ 1.88
IIV of Q	0.0968	25.2	0.0952	0.019 ~ 0.239
RV (proportional)	0.0401	9.5	0.0390	0.028 ~ 0.053

Abbreviations: CL, clearance; V1, central volume; V2, peripheral volume; Q, intercompartment clearance; Scr, serum creatinine; IIV, interindividual variability (variance value); RV, residual variability (variance value); RSE, relative standard error; CI, confidence interval.

the parameters derived from the final PPK model closely resembled the mean bootstrap estimates. The respective parameter values fell within the 95% CI, underscoring a robust fit. The final model and typical PK parameters are shown in the following equations:

$$CL\ (L/h) = 3.15x\ (Age/57.5)^{-0.425} xe^{((Scr-59)\ x\ (-0.00886))}\ xe^{\eta CL}$$

$$V1\ (L) = 12.3xe^{\eta V1}$$

$$V2\ (L) = 115xe^{\eta V2}$$

$$Q\ (L/h) = 5.21xe^{\eta Q}$$

The routine diagnostic GOF plots are shown in Figure 1. Both the PRED and IPRED concentrations aligned well with observed concentrations, distributed evenly on either side of the line of identity. The CWRES values ranged from −2 to 2, indicating adherence to the acceptable GOF criteria for the final model.

The VPC outcomes for the final model showed that 93.1% (215/231) of the observed data points fell within the 90% CI of the corresponding percentiles of the predicted data. This suggests that the final model accurately predicted the observed concentrations, thus reflecting its reliability. Visual inspection and statistical tests of the NPDE results based on 1000 simulations show that the final model has good predictive performance. The model is shown to accurately describe typical trends as well as the variability in the populations. The density histogram and scatter plot versus time are shown in Figure 2.

Dosing Optimization

The PTA at different MIC levels for the initial dosage regimen is shown in Figure 3. When the MIC was set to 1 mg/L, only 29.41% of the patients could achieve the target concentration on the second day of administration ($AUC_{24\text{-}48h}$: 341.87 ± 109.10 mg·h/L, Mean ± SD), and 76.47% patients could achieve the target value after the plasma concentration reached a steady state ($AUC_{ss,\ 24h}$: 505.63 ± 162.11 mg·h/L, Mean ± SD). According to previous literature,[16] a MIC of 1 mg/L was more frequently observed, indicating that the majority of patients were at risk of underdosing. When the MIC was set to 0.5 mg/L, the target AUC/MIC was achieved at the initial dose ($AUC_{24\text{-}48h}$: 683.74 ± 218.20 mg·h/L, $AUC_{ss,\ 24h}$: 1011.26 ± 324.22 mg·h/L, Mean ± SD), indicating a risk of overdose.

Based on the covariate selected in the final population pharmacokinetic model, age and Scr were the most important covariates implemented in CL. Thus, various subgroups (Age: 18–64, 65–80 years; Scr: <60, 60 – <133, 133 – <178 μmol/L) were divided. Dosage regimens with different doses (200, 400, 600, and 800 mg) and frequencies (q8h,

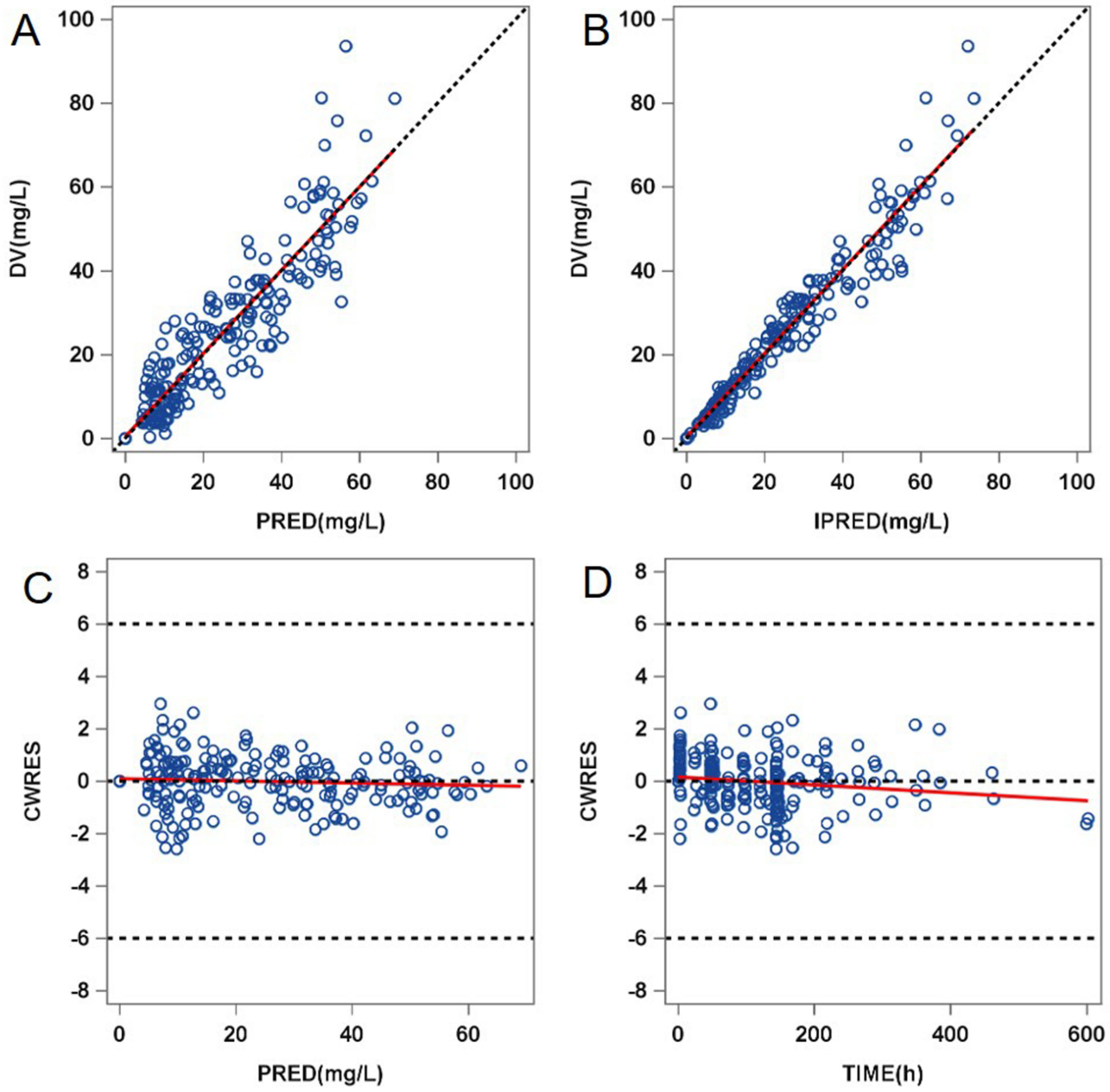

Figure 1 Goodness-of-fit plots for final model (**A-D**).
Notes: (**A**) population prediction (PRED) versus observed (DV). (**B**) individual prediction (IPRED) versus DV. (**C**) conditional weighted residuals (CWRES) versus PRED. (**D**) CWRES versus time. Points are individual data. Dashed lines in the middle represent the line of identity (**A** and **B**) or the line at zero (**C** and **D**). Red solid lines represent the linear regression line.

q12h, q24h) were simulated according to different subgroups. Fraction of patients achieving the $AUC_{24\text{-}48h}$ and $AUC_{ss,24h}$ target for different dosage regimens in each subgroup are shown in Figure 4.

The final tailored doses for patients are summarized in Table 3. For mild or moderate pneumonia caused by gram-positive cocci, the recommended dosage regimen was 400–800 mg q12h when the target PK/PD breakpoint was set as $AUC_{ss,24h}$/MIC ≥361 and MIC was assumed as 1 mg/L. For severe pneumonia-like CA-MRSA pneumonia, NVCM-targeted exposure should be achieved early during the course of therapy, preferably within the first 24–48 h, and the recommended dosage regimen was 600–800 mg q8h when the target PK/PD breakpoint was set as $AUC_{24\text{-}48h}$/MIC. Furthermore, when the MIC was assumed as 0.5 mg/L, the recommended dose of administration was significantly reduced compared with the dose of 800 mg q12h in previous guidelines, as shown in Table 3.

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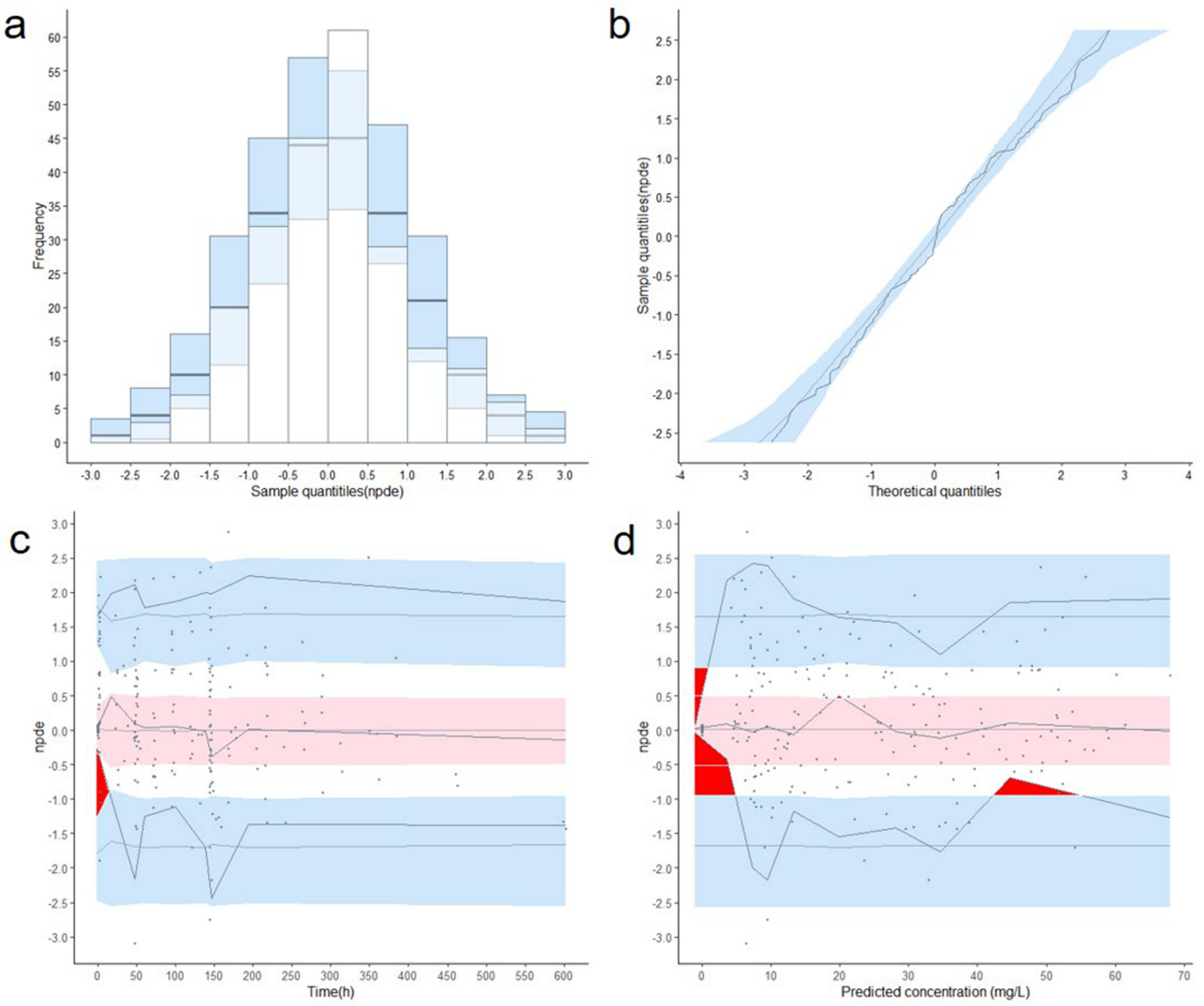

Figure 2 Normalized prediction distribution errors (NPDE).
Notes: (**a**) histogram of NPDE with the density of the standard normal distribution; (**b**) quantile–quantile plot of NPDE. (**c**) scatterplot of NPDE versus time; (**d**) scatterplot of NPDE versus predicted concentration.

Discussion

Overall, 85.9% of NVCM is excreted through the kidneys, making renal function a crucial factor in its pharmacokinetics. Renal parameters, such as Scr, urea, and CLcr, are used to evaluate the renal function. Numerous studies on population pharmacokinetic models for NVCM and VCM in adults have demonstrated that CLcr is a key covariate affecting pharmacokinetics.[13,29] Our study identified age and Scr as the most important covariates regulating CL parameter in patients with pulmonary infections. In the final population model of NVCM developed by other researchers,[13] the typical value of CL in the population was 2.54 L/h, which is close to our finding of 3.15 L/h. Their study included CLcr as a covariate for CL, but the majority of the dataset (60%) consisted of patients with various gram-positive bacterial infections, including skin and bloodstream infections, with the remaining 40% of the modeled dataset coming from healthy volunteers. Thus, extrapolation to patients with CAP was limited, as the pharmacokinetics within the target population may change. The typical value of the volume of peripheral distribution (V_2) in their study was 21 L, which is lower to our finding of 115 L, indicating increased V_2 was observed in patients with pneumonia. Further studies are needed to confirm our results.

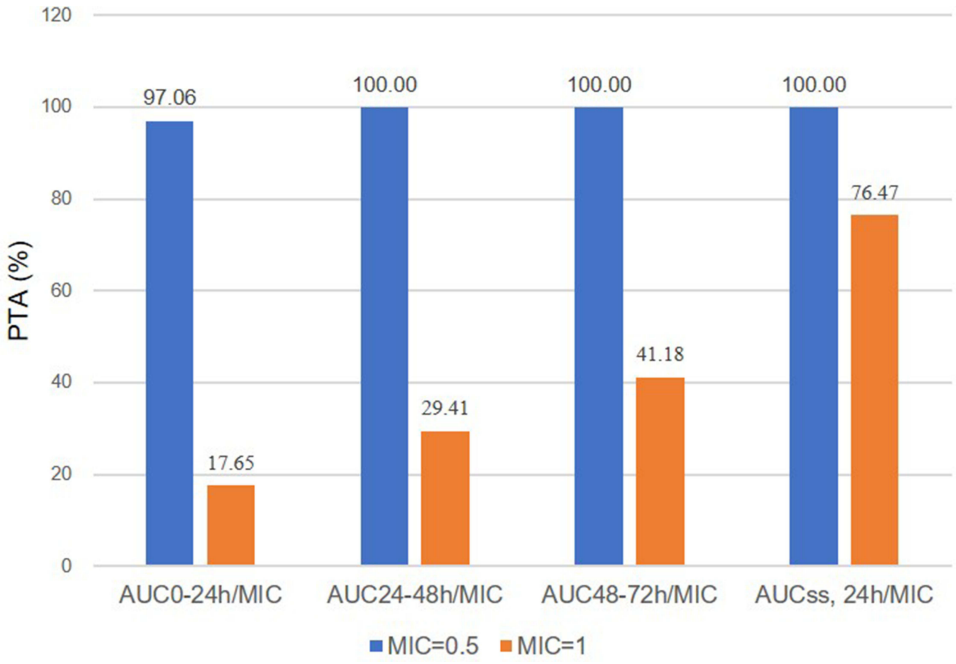

Figure 3 Probability of target attainment (PTA) in initial dosage regimen (800 mg every 12 h).
Notes: The 24-h area under the concentration–time curve to minimum inhibitory concentration ratio (AUC24h/MIC) target is 361. $AUC_{0\text{-}24h}$, $AUC_{24\text{-}48h}$ and $AUC_{48\text{-}72h}$ correspond to the AUC estimated during the first, second, and third days of therapy. $AUC_{ss,24h}$ correspond to AUC of steady-state.

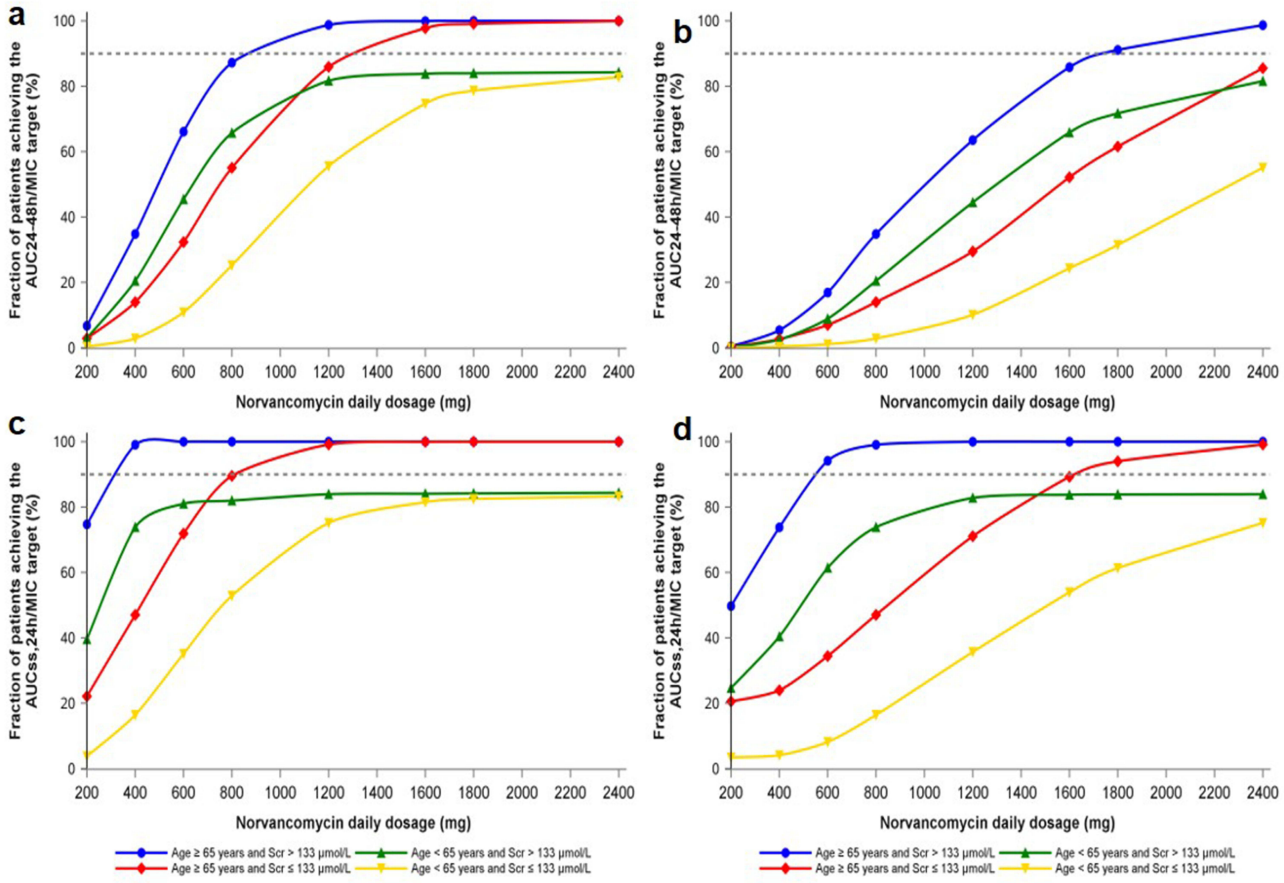

Figure 4 Fraction of patients achieving the AUC/MIC target in each subgroup.
Notes: (**a**) target exposure was set as $AUC_{24\text{-}48h}$/MIC = 361, MIC = 0.5mg/L. (**b**) target exposure was set as $AUC_{24\text{-}48h}$/MIC = 361, MIC = 1mg/L. (**c**) target exposure was set as $AUC_{ss,24h}$/MIC = 361, MIC = 0.5mg/L. (**d**) target exposure was set as $AUC_{ss,24h}$/MIC = 361, MIC = 1mg/L.

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Table 3 Tailored Dose of NVCM in Adults with Pneumonia

MIC (mg/L)	Age (Year)	Scr (umol/L)	Dose (mg, Target: $AUC_{24\text{-}48h}$/MIC≥361)			Dose (mg, Target: $AUC_{ss,24h}$/MIC≥361)		
			Q8h	Q12h	Q24h	Q8h	Q12h	Q24h
0.5	18–64	<60	400–600	600–800	–	400	400–600	–
		60-<133	400	600	–	–	400	–
		133-<178	–	400	800	–	200	400
	65–80	<60	400	600	–	–	400	800
		60-<133	400	–	–	200	–	–
		133-<178	–	400	800	–	200	400
1	18–64	<60	800	–	–	600–800	800	–
		60-<133	800	–	–	400	600	–
		133-<178	600	800	–	–	400	600–800
	65–80	<60	800	–	–	600	800	–
		60-<133	600–800	–	–	400	400–600	–
		133-<178	600	800	–	–	400	600

According to the 2020 VCM guidelines developed by IDSA and others,[28,30] achieving targeted VCM exposure within the first 24–48 h of therapy is crucial (Grade A-II). Early treatment is also appropriate for NVCM, owing to its similar molecular structure, antibiotic activity, and spectrum to VCM. The current recommended dose of NVCM is 800 mg every 12 h, which poses a high risk of underdosing in the target population. Assuming an MIC of 1 mg/L, only 29.41% of the patients in our study achieved the target value within the first 24–48 h after administration. Therefore, to ensure early and appropriate therapy, the dose of NVCM should be increased in patients with severe pulmonary infections. Bayesian-derived AUC monitoring is suitable in such cases as it allows early assessment of AUC target attainment without requiring steady-state serum drug concentrations.

According to the final tailored dose for patients, higher doses (600–800 mg every 8 h) are required if the PK/PD target was $AUC_{24\text{-}48h}$/MIC ≥361. Assuming an MIC of 1 mg/L, the recommended dosage regimen was 400–800 mg q12 h when the target PK/PD breakpoint was set as $AUC_{ss,24h} \geq 361$ mg·h/L for mild or moderate CAP. With increasing age and Scr levels, the dose was gradually reduced from 800 mg to 400 mg every 12 h. Patients with abnormal renal function were not included in the model, so extrapolation to those with renal insufficiency or failure is limited. Prospective studies with larger sample sizes are warranted to verify the safety and efficacy of the recommended dose.

With an increase in the MIC of NVCM against MRSA infections, a higher AUC is required to obtain similar efficacy. Consequently, increasing the daily NVCM dosage is necessary to mitigate the risk of therapeutic failure. However, the PK parameters and safety profile of these higher NVCM dosages remain undetermined. Dosing simulations have been premised on the assumption of linear pharmacokinetics. Nonetheless, extrapolating the dosage regimen beyond the observed range may lead to nonlinear pharmacokinetics, which warrants further investigation. Additionally, when administering higher NVCM doses, it is crucial to be aware of infusion-related adverse events, such as "red man syndrome". To mitigate these risks, a slow infusion rate of at least 2 hours is recommended. Therefore, it is prudent to use regimens similar to those employed in routine clinical practice and adjust doses empirically. TDM should be conducted, with dose adjustments made as necessary.

This research has several strengths. First, the prospective collection of blood specimens enhances the accuracy of model outcomes compared to retrospective studies. Second, the PK/PD targets, namely, $AUC_{24\text{-}48h}$/MIC and $AUC_{ss,24h}$/MIC ≥361, provide guidance for early and appropriate therapy. Third, recommending dosage regimens tailored to various

subgroups categorized by age and Scr levels improves the clinical relevance of the findings. Clinicians could consider these covariates when selecting the optimal initial NVCM dose regimen. We also employed a graphical approach to recommend doses for achieving the desired probability of meeting the PK/PD efficacy target. Additionally, the established population pharmacokinetic model allows for precise adjustment of NVCM dosage when combined with TDM results, thereby facilitating individualized drug administration in future work.

Nevertheless, the research also has some limitations. The sample size was relatively small, external validation was not conducted, limiting the generalizability of the conclusions to similar clinical contexts. The number of patients with mild to moderate renal insufficiency was so small, which restricts extrapolation to individuals with renal insufficiency or failure. And the proposed method of adjusting administration dose and interval according to Scr value should be carefully considered. We included patients with confirmed or suspected Gram-positive cocci pneumonia, but not all bacteriological evidence was available, and pharmacokinetics of antibiotics in different pathogens may vary.

Conclusion

In summary, we successfully established a two-compartment PPK model of NVCM in Chinese patients with CAP. Notably, age and Scr emerged as covariates influencing NVCM pharmacokinetic parameters, and we proposed dosage regimens tailored for different subgroups based on these covariate levels. Our findings suggest that the conventional dosage regimen may not be optimal for adult patients. Higher doses may be necessary to achieve targeted exposure within the first 24–48 h of treatment initiation. To further elucidate the clinical safety and efficacy of this optimized dosage regimen, prospective studies with larger samples are warranted.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

This study was carried out in the Second Hospital of Hebei Medical University. The experimental protocols were carried out, and written informed consent was obtained in accordance with the ethical standards established by the 1964 Declaration of Helsinki. The study was registered with the Chinese Clinical Trial Registry (registration number: ChiCTR2000039794, the date of registration: 2020-11-23) and approved by the Ethics Committee of the Second Hospital of Hebei Medical University (2020EC07-05-2).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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