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Population Pharmacokinetic Analysis of Factors Influencing Vancomycin Trough Levels in Non-Critical Care Patients in Saudi Arabia

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ABSTRACT

Vancomycin is a primary therapy for methicillin-resistant Staphylococcus aureus infections, but its pharmacokinetics show considerable variability, particularly among older adults. Data on factors affecting vancomycin pharmacokinetics in Saudi adult patients are scarce. This study aimed to develop a population pharmacokinetic (Pop-PK) model for vancomycin in medical ward patients and to identify patient-specific factors influencing trough concentrations.We conducted a retrospective multicenter study including patients aged 40 years or older admitted to medical wards in the Eastern Province of Saudi Arabia and treated with vancomycin from January to December 2022. Non-linear mixed-effects modeling (Monolix) was used to construct the Pop-PK model, with the base model chosen based on the Akaike information criterion. Covariates analyzed were age, sex, body weight, C-reactive protein (CRP), serum creatinine, creatinine clearance (CrCl), and albumin. Covariates were retained in the final model if $P < 0.05$ using stepwise addition. Model adequacy was evaluated with visual predictive checks, and simulations using Simulx assessed the impact of the significant covariates on vancomycin trough levels.Data from 124 patients encompassing 172 vancomycin trough measurements were included. The final Pop-PK model followed a one-compartment structure with linear elimination. CrCl and CRP were identified as the significant covariates, reducing between-subject variability in clearance from 173% to 81%. Simulations suggested that higher CRP and lower CrCl were associated with elevated vancomycin trough concentrations.Considerable variability exists in vancomycin trough levels among patients, and this study highlights the influence of renal function and systemic inflammation, reflected by CrCl and CRP, on vancomycin pharmacokinetics in non-critical medical ward patients.

Keywords: Medical care patients, Vancomycin trough concentration, Population pharmacokinetics, Creatinine clearance, C-reactive protein

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Introduction

Vancomycin is a frontline antibiotic for treating severe infections caused by resistant Gram-positive bacteria, particularly methicillin-resistant Staphylococcus aureus (MRSA) [1, 2]. Because of its narrow therapeutic window, monitoring drug levels is essential to prevent adverse effects and achieve effective therapy [3]. Guidelines from multiple professional bodies recommend standardized approaches for vancomycin therapeutic drug monitoring (TDM) [4]. Traditionally, a trough concentration of 10–20 mg/L has been considered appropriate [5, 6], while more recent consensus guidelines advocate targeting a 24-hour area under the concentration-time curve (AUC24) of 400–600 mg·h/L to optimize efficacy and reduce toxicity, assuming a minimum inhibitory concentration (MIC) of 1 mg/L [7].

Vancomycin pharmacokinetics (PK) vary widely among different patient groups, including older adults, oncology patients, and individuals with impaired renal function [8–10]. As vancomycin is almost entirely eliminated via the kidneys, its clearance (CL) depends heavily on creatinine clearance (CrCl), making renal function the principal determinant of PK variability [11]. Reported CL values for vancomycin range from 0.334 to 8.75 L/h, and the

volume of distribution (V) spans 7.12–154 L for one-compartment models and 29.2–501.8 L for two-compartment models, with between-subject variability (BSV) reported up to 77% for V and 99% for CL [2].

Antimicrobial resistance is a key contributor to treatment failures in infectious diseases [12]. To improve therapy, particularly in critically ill patients, population pharmacokinetic (Pop-PK) modeling has been employed to predict drug exposure based on patient characteristics and the infecting pathogen, supporting individualized dosing strategies [13]. Pop-PK modeling and simulation are particularly valuable for optimizing vancomycin dosing by quantifying inter- and intra-individual PK variability. Previous Pop-PK studies have identified renal function as a major determinant of vancomycin exposure [8, 10, 14–18], emphasizing the importance of monitoring both renal parameters and vancomycin trough levels.

Ethnic differences can also influence drug PK via genetic variation, metabolic differences, and protein-binding variations [19]. However, since vancomycin is predominantly renally cleared, observed differences in trough concentrations across ethnic groups are likely due to polymorphisms in renal drug transporters rather than metabolic enzymes [17].

Despite existing Pop-PK studies, no model has specifically evaluated vancomycin PK in adult patients admitted to medical wards. This study, therefore, aims to develop a Pop-PK model for vancomycin in Saudi adults and to identify patient-specific factors that could guide dose optimization.

Materials and Methods

Study design and patient selection

This retrospective, multicenter Pop-PK study was conducted in the Eastern Province of Saudi Arabia, including patients admitted to the medical wards of Al-Mana General Hospital (AGH) in Al-Khobar, Qatif Central Hospital (QCH), and Dammam Medical Complex (DMC) between January 1 and December 31, 2022. Adult patients aged 40 years and above who received systemic vancomycin and had documented trough concentrations were eligible. Exclusion criteria were admission to emergency, intensive care, or surgical wards; chronic kidney disease; pregnancy; age below 40 years; or absence of documented trough concentrations. Data were retrieved from electronic medical records.

The age cutoff of 40 years was chosen to assess age-related changes in comorbidities and polypharmacy, which may influence vancomycin PK [20]. For patients with multiple admissions during the study period, only data from the first encounter were analyzed.

Data collection

Collected data included demographics (age, sex, body weight), co-administered medications, previous vancomycin doses, and laboratory results from hematology and biochemistry panels. Creatinine clearance (CrCl) was calculated using the Cockcroft-Gault equation [21]. Vancomycin dosing details, including dose, timing, and duration, as well as TDM data (sampling time and plasma concentrations), were recorded.

For graphical comparison, vancomycin doses were normalized to 500 mg, though actual doses were used for Pop-PK modeling.

Vancomycin measurement

Plasma concentrations were measured using enzyme-multiplied immunoassay technique (EMIT) per manufacturer instructions [22]. The assay range was 2–50 mg/L (1.3–34 µmol/L), with intra- and inter-day variability below 10%.

Population pharmacokinetic modeling

Pop-PK modeling was conducted using non-linear mixed-effects modeling with the stochastic approximation expectation-maximization (SAEM) algorithm in Monolix software (version 2023, Lixoft) [23, 24]. PK parameters were assumed to follow a log-normal distribution, with exponential random effects employed to capture between-subject variability.

$$\theta i = \theta pop.\, e^{\eta i} \eta i \sim N(O, \omega_\theta^2)\ [23] \quad (1)$$

For the ith individual, the PK parameter (θi) was expressed as a function of the population mean parameter (θpop) and an independent random effect (ηi), which had a mean of zero and variance ω^2. Model development followed a three-stage approach: first, a structural base model was established to best fit the data without covariates; second, a covariate model was built by assessing patient-specific characteristics for statistical significance; finally, the model was evaluated and validated [23–25].

Base model development

The structural base model for vancomycin was developed by testing one-, two-, and three-compartment models, incorporating either infusion or bolus administration, with or without absorption lag time, and assuming linear or nonlinear elimination. Parameters estimated included clearance (CL), central and peripheral compartment volumes (V1 and V2), and inter-compartmental clearance (Q). Residual variability was modeled using constant, proportional, or combined error structures. Model selection was guided by multiple criteria, including lower Akaike information criterion (AIC), objective function value (OFV; equivalent to −2 log-likelihood, −2LL), relative standard error (RSE) of parameter estimates, physiological plausibility, and goodness-of-fit (GOF) plots such as observed vs. predicted concentrations, residuals, and visual predictive checks (VPC). Outliers were identified visually and through conditional weighted residuals (CWRES), with values outside −6 to +6 considered extreme; these were excluded and the model refitted [23, 24].

Covariate model development

Following base model selection, potential covariates were evaluated, including age, sex, body weight, number of prior vancomycin doses, serum creatinine, albumin, CrCl, and C-reactive protein (CRP). All covariates were treated as continuous variables, except sex, which was categorical. Model comparison used changes in OFV (−2LL). Covariates were retained if they significantly reduced OFV by ≥3.84 (χ^2, $P < 0.05$) or increased OFV by ≥10.83 (χ^2, $P < 0.001$) during stepwise deletion. Final covariate selection was confirmed using the Wald test (stochastic approximation) with a significance threshold of $P < 0.05$ [23–25].

Model evaluation

GOF plots were examined to assess model performance, including individual and population predictions compared to observed concentrations. VPC plots were generated using 1000 simulated datasets to illustrate the 10th, 50th, and 90th percentiles of observed data over time, evaluating predictive performance. Convergence robustness was tested using Monolix, performing five estimation runs with varying initial fixed effects and random seeds [23–25].

Simulation of vancomycin exposure

Monte Carlo simulations were conducted using Simulx (version 2023) with the final covariate-incorporated Pop-PK model. A virtual cohort of 1000 patients was generated and stratified into nine groups based on CRP levels (low: 20 mg/dL, normal: 80 mg/dL, high: 180 mg/dL) and CrCl (normal: 90 mL/min, moderately reduced: 60 mL/min, severely reduced: 30 mL/min). Trough concentrations were simulated 48 hours after administration of 1 g vancomycin every 12 hours.

Statistical analysis

All analyses outside Pop-PK modeling were performed using SPSS (version 26). Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR). Graphs were produced using R or derived from Monolix/Simulx outputs.

Ethical considerations

The study received ethical approval from the Mohammed Al Mana College for Medical Science IRB (SR/Rp/79, 17/2/2022), Qatif Central Hospital IRB (QCH-SRECO 19/2022, 8/6/2022), and Dammam Medical Complex IRB (PH-26, 1/11/2023). Informed consent was waived due to the retrospective nature of the study, and all patient data were de-identified to maintain confidentiality.

Results and Discussion

Patient demographics

The study included 124 patients receiving vancomycin doses ranging from 500 to 1750 mg **(Table 1).** The median age was 79 years, with most patients aged 60–89. Males comprised 59% of the cohort, with a mean body weight of 72 ± 20 kg. The average CrCl was 61 ± 48 mL/min, and 35% of patients had CrCl ≤30 mL/min.

Table 1. Characteristics of the patients (n = 124)

Characteristics	
Age, median (IQR)	79 (50–86)
Age groups	n (%)
40–49 years	8 (7%)
50–59 years	8 (7%)
60–69 years	42 (33%)
70–79 years	31 (25%)
80–89 years	26 (21%)
90–99 years	9 (7%)
Sex	n (%)
Male	73 (59%)
Female	51 (41%)
Body weight in kg, mean (±SD)	72 (± 20)
Serum albumin level (g/L), mean (± SD)	29.5 (± 8)
Serum creatinine level (mg/dL), mean (± SD)	183 (±171)
C-reactive protein level (mg/dL), mean (± SD)	80.6 (± 32.5)
CrCl (mL/min), mean (± SD)	61.1 (± 48.2)
CrCl (mL/min)	n (%)
> 120 mL/min	17 (14%)
120–91 mL/min	21 (17%)
90–61 mL/min	14 (11%)
60–31 mL/min	28 (23%)
≤ 30 mL/min	44 (35%)
Vancomycin doses	n (%)
500 mg	31 (25%)
750 mg	20 (15%)
850 mg	2 (2%)
1000 mg	50 (40%)
1200 mg	1 (1%)
1250 mg	11 (9%)
1500 mg	7 (6%)
1750 mg	2 (2%)

Abbreviations: IQR, interquartile range; SD, standard deviation; kg, kilogram; g, gram; mL, milliliter; min, minute.

Vancomycin trough concentrations

A total of 172 vancomycin trough measurements were obtained from 124 patients. As shown in **Figure 1**, there was considerable variability in trough levels across the cohort. Concentrations varied widely, with some patients reaching approximately 20 µg/mL, whereas others had much lower levels, falling below 5 µg/mL.

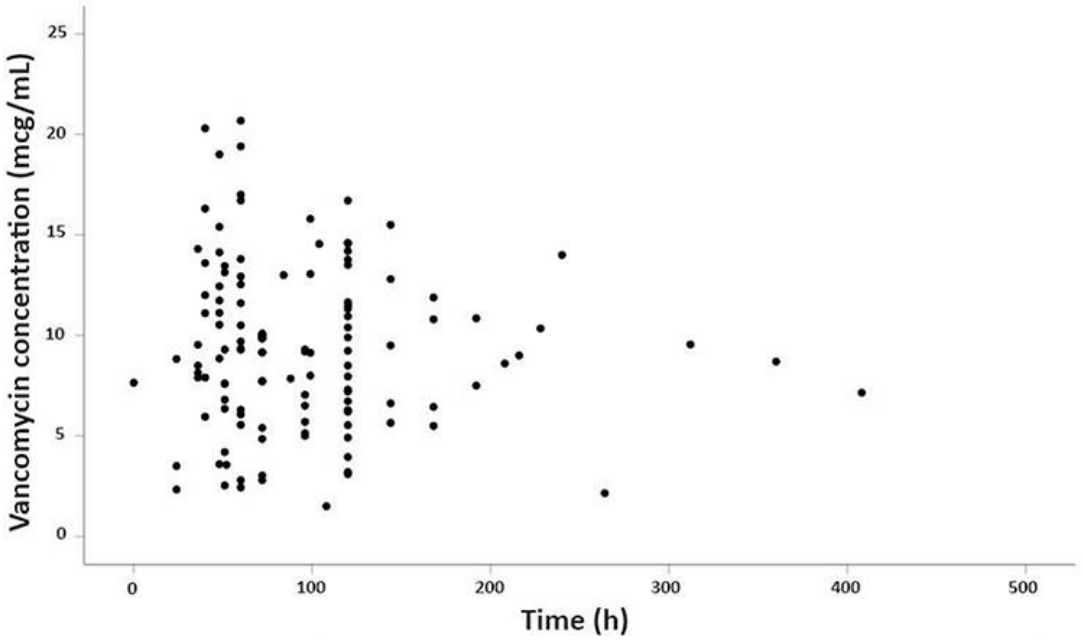


Figure 1. Individual vancomycin trough concentrations for each patient over time, with doses normalized to 500 mg.

Subsequent analyses explored associations between patient characteristics and vancomycin-related parameters, summarized in **Figure 2**. The results showed that higher CRP levels were positively associated with older age (r = 0.49) and higher albumin levels (r = 0.36), but inversely associated with CrCl (r = −0.25). Additionally, body weight demonstrated a positive correlation with CrCl (r = 0.54) and a negative correlation with CRP levels (r = −0.35).

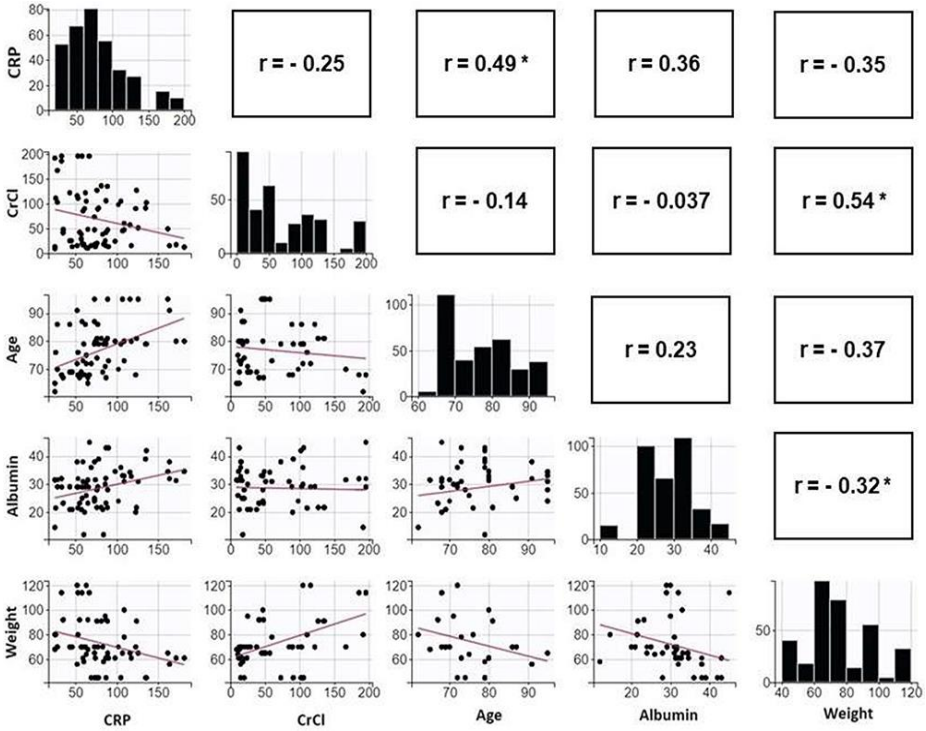


Figure 2. Correlation matrix of patients' clinical characteristics. * indicates P < 0.05.
Abbreviations: CRP, C-reactive protein; CrCl, creatinine clearance

Population pharmacokinetic parameters of vancomycin

The base model development revealed that vancomycin pharmacokinetics were best represented by a one-compartment model with linear elimination, administered via infusion and without absorption delay. This model selection was supported by goodness-of-fit plots and demonstrated a substantial reduction in the Akaike information criterion (AIC) compared to models assuming bolus administration, lag-time absorption, two- or three-compartment distribution, or nonlinear elimination. Residual variability was best captured using a proportional error model with a coefficient (b) of 0.4 **(Table 2).**

Table 2. Population pharmacokinetic model estimates for vancomycin

Parameter	Base Model		Final Model	
	Population	RSE (%)	Population	RSE (%)
V (L)	224.37	9.48	193.65	7.41
CL (L/h)	0.0035	240	3.52	62.5
CRP effect on CL	–	–	− 0.05	28
CrCl effect on CL	–	–	0.0088	48.4
Omega V	0.37	29.6	0.33	17.2
Omega Cl	1.73	28	0.81	44
Residual error, b (%)	0.38	17.4	0.3	13.7

Abbreviations: RSE, relative standard error; V, volume of distribution; CrCl, creatinine clearance; CL, clearance; CRP, C-reactive protein; L, liter; h, hour; Ω, inter-individual variability expressed as standard deviation.

All potential covariates were evaluated using a univariate stepwise approach. Only CrCl and CRP produced a significant reduction in the objective function value (OFV) in the final model **(Table 3)**, leading to a marked decrease in between-subject variability (BSV) for clearance from 173% to 81% **(Table 2)**. The final population PK parameter estimates for vancomycin are presented in **Table 3**, with a volume of distribution (V) of 224.4 L and clearance (CL) of 3.52 L/h. Shrinkage values for all estimated parameters ranged from 1.9% to 14.9%, and the condition number of the final model was 36.91, indicating model stability.

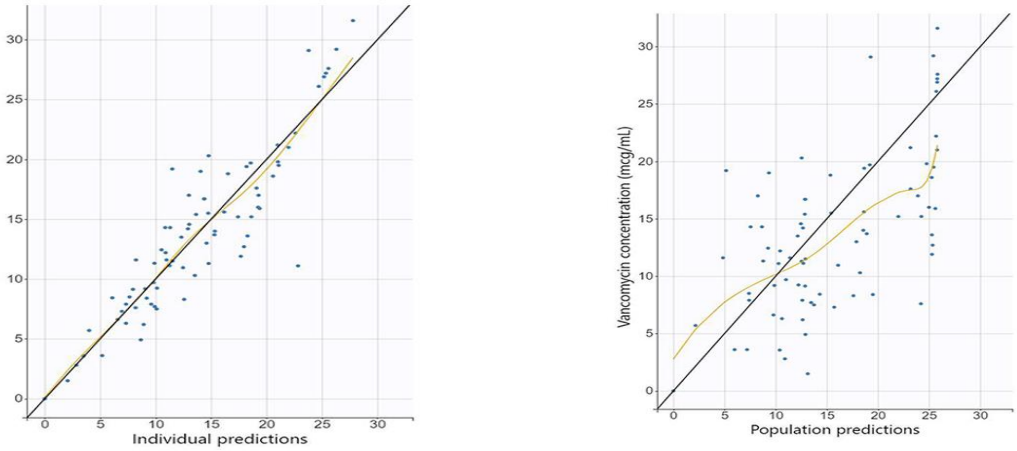
Table 3. Change in Objective Function Value (−2LL) for the Base and the Final Model

Parameter	OFV (−2LL)	Difference	P-value
Base model	377.5		
CrCl effect on CL	368.5	13	< 0.001
CRP effect on CL	366.5	11.2	< 0.001
Covariates model	355.3		

Abbreviations: CrCl, creatinine clearance; CRP, C-reactive protein; CL, clearance.

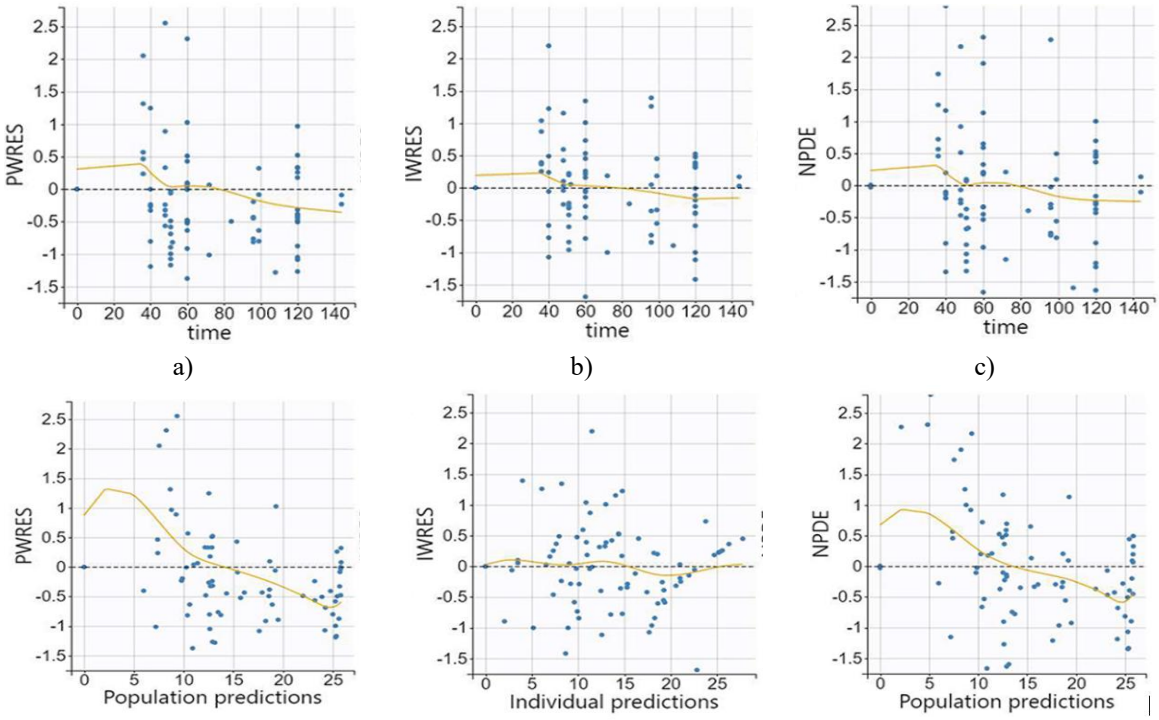
Model evaluation

Assessment of parameter precision using relative standard error (RSE, **Table 2**) indicated that the majority of PK parameters were reliably estimated, with the exception of clearance (CL), which showed higher uncertainty at 62.5%. Goodness-of-fit (GOF) diagnostic plots for the final covariate-inclusive model are shown in **Figures 3 and 4**, illustrating that the model adequately reproduces the observed vancomycin trough concentrations. Although **Figure 3** suggested a few potential outliers in the population-predicted concentrations, the residual analysis **(Figure 4)** confirmed that all conditional weighted residuals remained within the pre-specified ±6 range, indicating that these apparent deviations did not compromise the overall model fit.



a) b)

Figure 3. Goodness-of-fit (GOF) plots comparing predicted and observed vancomycin concentrations from the final model. (a) Observed concentrations versus individual predicted concentrations. (b) Observed concentrations versus population-predicted concentrations. The yellow line indicates the model-based spline fit.



a) b) c)

d) e) f)

Figure 4. Diagnostic goodness-of-fit (GOF) plots of residuals from the final vancomycin model. The upper panels display residuals over time: left, population residuals; center, individual residuals; right, normalized prediction distribution errors (NPDE). The lower panels show residuals versus predictions: left, population residuals against population-predicted concentrations; center, individual residuals versus individual predictions; right, NPDE versus population predictions.

The visual predictive check (VPC) further demonstrated strong agreement between the simulated percentile ranges from the final model and the observed vancomycin data **(Figure 5),** indicating reliable predictive performance. Specifically, the 10th, 50th, and 90th percentiles of observed trough concentrations fell within the 90% confidence intervals derived from simulations. The mean predicted concentrations closely aligned with those from the covariate model, confirming both the accuracy and stability of the final model.

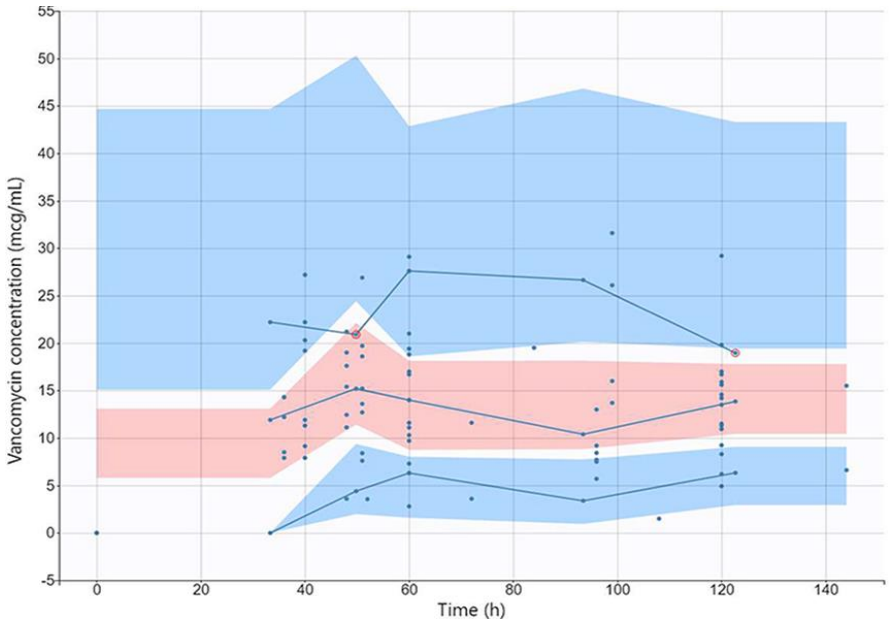


Figure 5. Visual predictive check (VPC) illustrating vancomycin concentrations over time based on 1000 Monte Carlo simulations. Solid blue lines indicate the 10th, 50th, and 90th percentiles of observed concentrations, while the shaded areas represent the 90% confidence intervals of the corresponding simulated percentiles. Blue circles denote individual observed concentrations.

Simulation of vancomycin trough concentrations

Monte Carlo simulations examining vancomycin exposure across patient subgroups are presented in **Figure 6**. When CrCl was held constant, higher CRP levels were associated with elevated simulated trough concentrations, demonstrating the impact of CRP on vancomycin clearance.

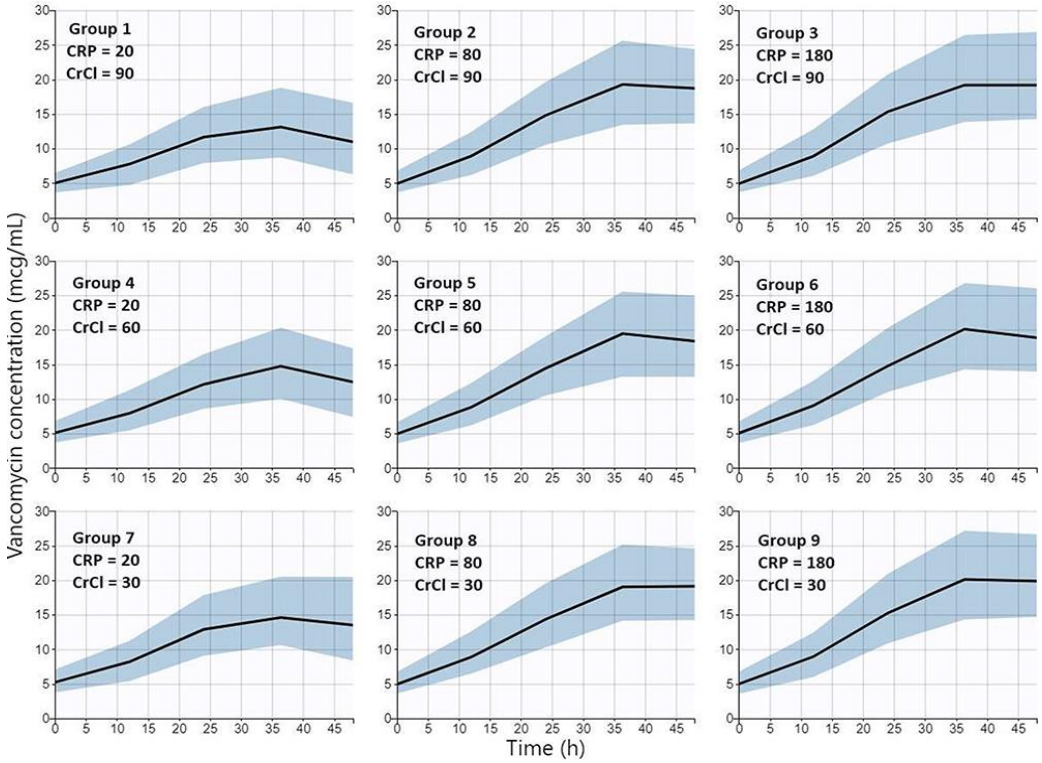


Figure 6. The simulated vancomycin trough levels produced by Simulx following a twice-daily 1 g dosing regimen, with CRP concentrations reported in mg/dL and CrCl values in mL/min.

A population pharmacokinetic (Pop-PK) model for vancomycin was developed to characterize its pharmacokinetics in adult patients admitted to medical wards in the Eastern region of Saudi Arabia. The results indicate that vancomycin PK is best described by a one-compartment model with linear elimination, which aligns with certain previously reported models [15, 26] but contrasts with other studies suggesting two- or three-compartment models [10, 16, 27]. This discrepancy may stem from the retrospective study design, which collected blood samples solely for routine trough concentration monitoring as part of therapeutic drug monitoring (TDM), limiting insight into the absorption and distribution phases. Nevertheless, the base model was selected based on the lowest AIC values compared to other candidate models and validated through residual error statistics and goodness-of-fit plots.

Inflammation plays a critical role in altering drug pharmacokinetics by increasing plasma drug concentrations and elevating the risk of overdose and adverse drug reactions (ADRs) [28]. A major finding of this study is that CRP, a marker of inflammation, significantly affects vancomycin PK (**Figure 6)**, (groups 1–3). Inflammatory processes are known to downregulate drug-metabolizing enzymes (DMEs) and transporters, affecting both metabolism and clearance [27]. Additionally, inflammation can suppress receptor activation, potentially reducing drug efficacy even in the presence of elevated plasma concentrations [29]. Elevated pro-inflammatory cytokines also contribute to variability in non-renal clearance, particularly in patients with renal impairment [30]. Jalusic *et al*. previously highlighted the effect of inflammation on vancomycin PK and recommended dosing adjustments based on inflammatory status [27], which is particularly relevant for older patients and those with impaired renal function, as inflammation can further decrease vancomycin clearance, leading to higher trough levels and increased toxicity risk. Our final simulated model supports this recommendation, emphasizing the need to consider inflammation when prescribing vancomycin.

Inflammation increases vascular permeability, facilitating immune cell migration into the interstitium, a key process in pathogen clearance [30]. Recent studies indicate that acute inflammation and tissue injury enhance vancomycin penetration into lung tissue [29]. The hydrophilic nature of vancomycin, combined with increased vascular permeability, may explain the observed higher volume of distribution. However, the retrospective design limited precise characterization of the early distribution phase, which may contribute to elevated trough concentrations associated with higher CRP levels, as vancomycin initially moves out of circulation and later equilibrates between interstitial and plasma compartments. This should be considered when evaluating the impact of inflammation on vancomycin distribution.

Simulations across different patient groups demonstrated that vancomycin concentrations rise with increasing CRP levels. It should be noted that CRP measurements were taken at the time of trough sampling and may not represent the inflammatory state at the initiation of therapy. In patients responding to treatment, inflammation decreases over time, normalizing DME and transporter expression and consequently reducing plasma drug concentrations [28]. Conversely, persistent inflammation in non-responding patients maintains suppressed DME and transporter activity, sustaining high plasma drug levels, which is particularly critical when treating drug-resistant infections, as uncontrolled infection further elevates inflammatory markers, increasing ADR risk.

Creatinine clearance (CrCl) has been repeatedly identified as a significant covariate influencing vancomycin clearance, consistent with prior models across various patient cohorts [12, 14, 26, 27]. In line with these findings, our final model confirmed that reduced CrCl is associated with higher vancomycin trough concentrations. Given vancomycin's hydrophilic nature, renal filtration is the primary elimination route [9]. The substantial variability observed in vancomycin trough concentrations in this study underscores the necessity for careful therapeutic monitoring to minimize overdose risk.

Several patient factors that may affect the results were not addressed, including specific vancomycin indications, therapeutic targets, bacterial culture results, drug susceptibility, and clinical outcomes, representing study limitations. Only CRP was used as an inflammatory biomarker due to its rapid response; however, CRP has been linked effectively to vancomycin PK/PD [31]. Nonetheless, CRP alone may not fully reflect inflammatory status, and additional markers such as erythrocyte sedimentation rate, procalcitonin, plasma viscosity, leukocyte counts and differentiation, and pro-inflammatory cytokines (IL-1, IL-6, TNF-α) should be considered [32]. Most patients had some degree of renal impairment, limiting generalizability to similar populations, and findings may not apply to patients with augmented renal clearance, such as those in critical care settings [33]. Prospective studies with larger cohorts and comprehensive patient data are warranted.

The use of vancomycin in combination with other antibiotics, especially for MRSA infections, is of growing interest [34, 35]. Recent literature suggests that combining vancomycin with beta-lactams can enhance treatment

efficacy through synergistic effects [35, 36]. However, the influence of inflammation on vancomycin PK in combination therapy remains to be explored, as elevated inflammatory markers may alter the PK of both vancomycin and co-administered antibiotics, potentially necessitating dose adjustments. Future research should evaluate the interactions between vancomycin and other antibiotics under varying inflammatory conditions to optimize individualized treatment regimens.

Conclusion

A one-compartment model with linear elimination accurately described vancomycin trough concentrations. The considerable between-subject variability (BSV) in clearance (81%) reflected the high variability observed in actual vancomycin trough levels. The final model identified creatinine clearance (CrCl) and CRP as significant covariates, with higher CRP levels or lower CrCl values associated with increased vancomycin trough concentrations and reduced clearance. These findings can guide clinical practice by emphasizing critical patient factors to consider when adjusting vancomycin dosing, thereby optimizing efficacy and reducing the risk of adverse drug reactions (ADRs).

Key points

1. The large between-subject variability in clearance mirrored the substantial variability observed in vancomycin trough concentrations.
2. CrCl and CRP were significant covariates in the final model, with elevated CRP or reduced CrCl linked to higher vancomycin trough levels and altered clearance.

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Conflict of Interest: None

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Ethics Statement: None

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