Population Pharmacokinetics of Vancomycin in Critically ill Patients Undergoing Continuous Renal Replacement Therapy

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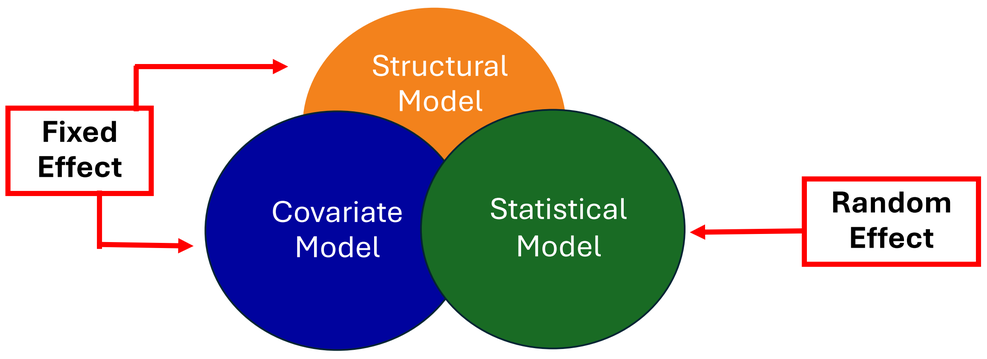
INTRODUCTION

- Vancomycin is a glycopeptide antibiotic commonly used to treat serious Gram-positive infections, particularly methicillin-resistant *Staphylococcus aureus* (MRSA).
- AKI is highly prevalent among critically ill patients in ICU, These patients often present with multiple physiological disturbances such as altered fluid status, hypoalbuminemia, and reduced organ perfusion that further complicate drug disposition. As a result, pharmacokinetic profiles in critically ill patients can differ significantly from those in the general population.
- Recent advances in CRRT membranes, such as the oXiris membrane, offer enhanced adsorption capabilities for cytokines and endotoxins. However, these membranes may also adsorb drug molecules. In vitro studies suggest that vancomycin can be adsorbed by these membranes by approximately 20%. Despite this, their impact on vancomycin pharmacokinetics has not been fully evaluated in vivo, and previous population pharmacokinetic (PopPK) studies have not included membrane adsorptive properties as a covariate.
- This study aims to develop a PopPK model of vancomycin in critically ill patients undergoing CRRT, with a specific focus on assessing the influence of adsorptive membranes on drug clearance.

METHOD

- This was a single-center, retrospective study conducted at Ramathibodi Hospital, Bangkok, Thailand.
- Electronic medical records were reviewed for patients admitted to the intensive care unit (ICU) between January 1, 2014, and December 31, 2024. Patients were eligible for inclusion if they met all the following criteria: Age ≥18 years, diagnosis of AKI treated with CRRT CVVHDF mode, received intravenous vancomycin and at least one vancomycin serum concentration measured during the CRRT period.
- Patients were excluded if they had ESKD with a history of HD, PD or KT , or if vancomycin was administered via a non-intravenous route.

Composition of Population Modeling Development



- The population pharmacokinetic (PopPK) model was developed using nonlinear mixed-effects modeling with MonolixSuite software (version 2024R1, Lixoft, Antony, France), which employs the stochastic approximation expectation-maximization (SAEM) algorithm. Initially, structural models were developed to describe vancomycin pharmacokinetics. Model selection was based on goodness-of-fit (GOF) plots, log-likelihood value, Akaike Information Criterion (AIC), the precision of parameter estimates expressed as relative standard error (RSE, %), and physiological plausibility.

Covariates Evaluated for Influence on Vancomycin Pharmacokinetics

Age | Sex | Body Weight | Serum Albumin | urine volume | AST ALT | Effluent Flow Rate | Use of Adsorptive membranes (oXiris or CytoSorb)

- Model performance was assessed using goodness-of-fit (GOF) plots, visual predictive checks (VPC), and nonparametric bootstrap analysis. A total of 1,000 bootstrap datasets were generated by resampling the original data with replacement. The final model was refitted to each dataset to estimate the distribution of pharmacokinetic parameters.

RESULT

- The final cohort included 116 of vancomycin concentrations from 51 critically ill patients were included in the PopPK model development. The mean patient age was 66.3 ± 16.2 years, the mean body weight was 64.0 ± 17.2 kg., mean serum albumin was 25.82 g/L and residual urine volume was 156.82 ml/day.
- In this study, 45% of patients received treatment with an adsorptive membrane, (21 patient received oXiris membranes and 1 patient received Cytosorb membranes)

Table 1. Final population pharmacokinetic model estimates and bootstrap analysis

Parameter	Final model[a]		Bootstrap analysis Median (95%CI)
	Estimate	RSE (%)	
V_{pop} (L/kg)	0.47	5.57	0.47 (0.41 to 0.54)
$\delta_{V, MM=1}$	- 0.18	51.1	-0.17 (-0.40 to 0.041)
CL_{pop} (L/h/kg)	0.079	22.2	0.076 (0.049 to 0.12)
$\theta_{CL, BW}$	- 0.0094	19.7	-0.01(-0.014 to -0.0054)
$\theta_{CL, age}$	- 0.0046	42.9	-0.0051 (-0.0098 to – 0.0011)
Inter-individual variability (IIV)			
IIV V (%)	0.15	15.58	0.19 (0.069 to 0.30)
IIV CL (%)	0.24	24.32	0.20 (0.14 to 0.26)
Residual variability			
σ (%)	0.13	10.6	0.11 (0.044 to 0.15)

[a] The final model was as follows: CL (L/h/kg) = $0.079 \cdot e^{-0.0094 \cdot BW\ (kg) - 0.0046\ Age\ (years)}$, V (L/kg) = $0.46 \cdot e^{-0.18 \cdot [MM=1]}$, Where: adsorptive membrane use (1 = yes, 0 = no)

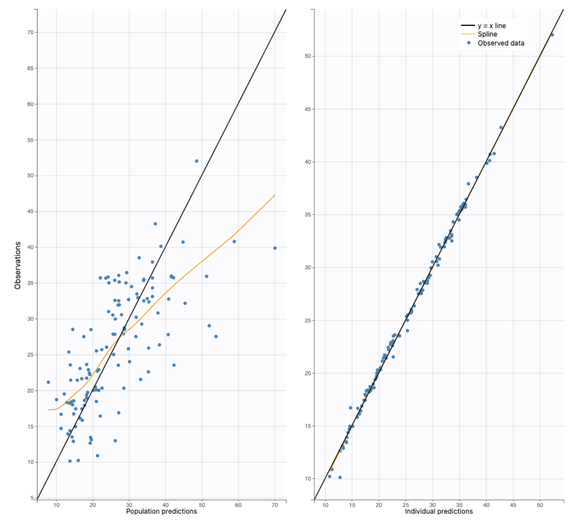


Figure 1: Goodness-of-Fit (GOF) plots for the final PopPK model. The left panel shows observed vancomycin concentrations versus population predictions, while the right panel shows observed concentrations versus individual predictions. The black line represents the line of identity (y = x), the yellow spline indicates the trend of the data, and the dotted lines in the right panel represent the 95% prediction interval.

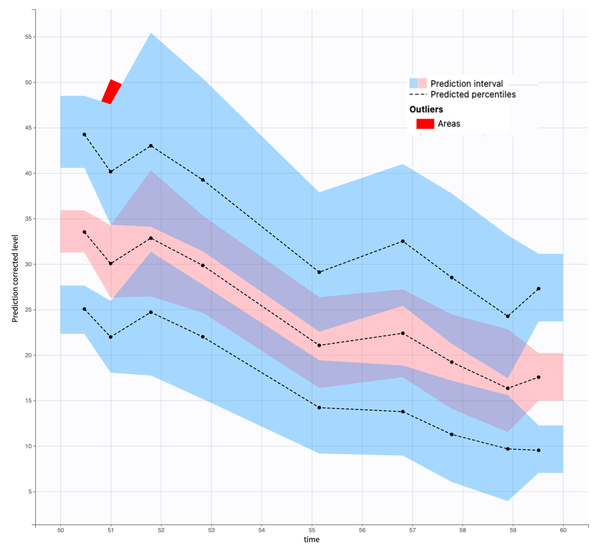


Figure 2: Prediction-corrected visual predictive check (pcVPC) for vancomycin concentration over time. The dashed lines represent the 10th, 50th, and 90th percentiles of the observed data. The shaded regions indicate the 90% confidence intervals around the 10th, 50th, and 90th percentiles of the simulated data. Red shaded area highlights regions with notable deviation.

CONCLUSION

- This is the first study to demonstrate that using adsorptive membranes may significantly impact the pharmacokinetic parameters of vancomycin in critically ill patients undergoing CRRT. Individualized vancomycin dosing in this population should consider membrane type, along with patient-specific factors such as body weight and age, to optimize therapeutic outcomes.

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