Title: External evaluation of intravenous vancomycin population pharmacokinetics models in adults receiving high-flux intermittent hemodialysis

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Background: Intravenous (IV) vancomycin remains a mainstay of antimicrobial therapy for patients undergoing chronic hemodialysis (HD), given the increased risk of hospital-acquired infection caused by methicillin resistant organisms. Despite recent guidelines endorsing the use of populational pharmacokinetic (popPK) models for IV vancomycin TDM, dosing recommendations remain ill-defined for patients undergoing HD. Considering the variability of HD practices among centers and the specificity of their settings between patients, the proposed dosing regimens may not be applicable to all patients. The objective of this study is to perform an external evaluation of published popPK models developed for adults undergoing intermittent high-flux HD in a multicentered retrospective cohort in North America.

Methods: A literature search was conducted in the Embase/Pubmed database to identify relevant popPK models. Data collection was performed retrospectively in two healthcare centers in Quebec (Canada) to include all eligible patients receiving IV vancomycin and undergoing intermittent high-flux HD between January 1st 2019 and December 31st 2022. Model performance was assessed through prediction and simulation-based diagnostics performed with *NONMEM* (v7.5; ICON Development Solutions), *Microsoft Excel* (v16.69.1; Microsoft Office) and *R Studio* (v1.4; Posit Software).

Results: A total of 2386 vancomycin concentrations were collected from 274 patients and 476 antibiotic courses. The median age and weight (range) in the study population were 65 years (19-94) and 78.1 kg (37.8-204.4). Four vancomycin popPK models were selected for evaluation. All models showed inadequate predictive performance. Nonetheless, the model by Bae and al. showed the best performance for populational prediction with a median predictive error (MDPE) of 16.3% and median absolute predictive error (MDAPE) of 34.7%, whereas the model by Goti and al. was the best performing for individual prediction with a MDPE of -1.4% and MDAPE of 16.2%. When considering only vancomycin concentrations drawn between HD sessions, the two other models exhibited comparable performance.

Conclusions: Although these models offer different and interesting approaches to describe the effect of intermittent HD on vancomycin pharmacokinetics, their predictive performance proved to be subpar in our population. Further studies are required to adjust existing models or develop new models, while considering the timing of HD sessions and the presence of residual diuresis.

Keywords: vancomycin, population pharmacokinetic, pharmacokinetics, dialysis