Towards precision dosing of vancomycin in critically ill patients: An evaluation of the predictive performance of pharmacometric models in ICU patients.

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Background: Vancomycin dose recommendations depend on appropriate population pharmacokinetic models. These models have not been adequately assessed in critically ill patients, whom exhibit large pharmacokinetic variability. This study evaluated the predictive performance of these models in Intensive Care Unit (ICU) patients and identified factors influencing model performance.

Methods: Retrospective data from ICU adult patients administered vancomycin were used to evaluate the performance of the models to predict serum concentrations *a priori* (no observed concentrations included) or with Bayesian forecasting (using concentration data). Predictive performance was determined using relative bias (rBias, bias) and relative root mean squared error (rRMSE, precision). Models were considered clinically acceptable if rBias was between -20% and 20%, and 95% confidence intervals included zero. Models were compared with rRMSE, no threshold was employed. The influence of clinical factors on model performance was assessed with multiple linear regression.

Results: Data from 81 patients were used to evaluate 12 vancomycin models. The Goti model was the only clinically acceptable model with a satisfactory a priori (rBias 3.4%) and Bayesian forecasting (rBias1.5%) result. Bayesian forecasting was superior to a priori prediction, improving with the use of more recent concentrations. Four models were clinically acceptable with Bayesian forecasting. Renal replacement therapy status ($p<0.001$) and sex ($p<0.007$) significantly influenced the performance of the Goti model.

Conclusions: Similar to studies in heterogeneous patients, the Goti model was the most accurate model in ICU adults. This model is recommended for dose prediction software when dosing vancomycin in heterogeneous and critically ill patients.

Key words: vancomycin, critically ill, therapeutic drug monitoring, population pharmacokinetic models, predictive performance