Towards precision dosing of vancomycin in critically ill patients: Predictive performance of pharmacometric models in Intensive Care Unit (ICU) patients

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Introduction

- Vancomycin dose selection is informed by target drug exposure
- Bayesian forecasting software can estimate vancomycin exposure (using a population pharmacokinetic (popPK) model) to facilitate personalised dosing[1]
- Several vancomycin popPK models exist[2]
- There is limited evidence to guide selection of the right popPK model for critically ill patients, who exhibit large pharmacokinetic variability, such as in the ICU[1, 2]

Aim

- To identify vancomycin popPK models with clinically acceptable predictive performance specifically in critically ill adult patients
- To identify the influence of clinical parameters, such as the number of vancomycin concentrations included for Bayesian forecasting, on predictive performance

Method

- Published vancomycin popPK models in critically ill adults were identified
- Vancomycin TDM data was collected from ICU adult patients (≥ 18 yrs) who received IV vancomycin (≥ 48 hrs) with ≥ 2 vancomycin concentrations available
  - Including: patient demographics, vancomycin dosing history and plasma concentrations
- Evaluated model performance to predict serum concentrations
  - ***a priori*** (no observed concentrations included)
  - **Bayesian** (concentration data & patient covariates)
- Predictive performance determined using relative bias (rBias, bias, eq 1) and relative root mean squared error

$$rBias = \frac{1}{N}\sum_{1}^{i}\frac{predicted_i - observed_i}{observed_i} \times 100 \quad (1)$$

$$rRMSE = \sqrt{\frac{1}{N}\sum_{1}^{i}\frac{(predicted_i - observed_i)^2}{(observed_i)^2}} \times 100 \quad (2)$$

where N is the number of vancomycin concentrations

- Models considered **clinically acceptable** if rBias was between ±20% and 95% CI included zero
- Models with a lower rRMSE were more precise and therefore more clinically appropriate
- The influence of clinical factors on model performance was assessed with multiple linear regression

Detailed Bayesian Forecasting Analysis

- Bayesian prediction of vancomycin concentrations in the 4th dosing interval were compared using different combinations of concentrations from the preceding 3 dosing intervals

Results

- 82 patients identified with 746 vancomycin concentrations; 648 (87%) were obtained in the ICU
- Median (range) number of concentrations per course of therapy was 6 (1–37)
- 12 models were evaluated

Overall Model Evaluation

- Accuracy of predicted concentrations improved with Bayesian forecasting compared to an *a priori* approach
- Goti model was the only clinically acceptable model using both *a priori* (3.4%) and Bayesian forecasting (1.5%) approaches (Fig. 1)
- 5 models were clinically acceptable in this Bayesian analysis: Buelga, Colin, Goti, Llopis-Salvia, Roberts (Fig. 1)

Detailed Bayesian Forecasting Analysis

- Colin model was biased using only the most recent vancomycin concentration
- Buelga model requires ≥ 4 concentrations to adequately predict vancomycin exposure (prolonged time to reach target)
- Goti model accurately predicts vancomycin drug exposure in both ICU and non-ICU patients, using only the most recent concentration (Fig. 2)
- The Roberts and Llopis-Salvia models underestimate the vancomycin concentrations more frequently than the Goti model

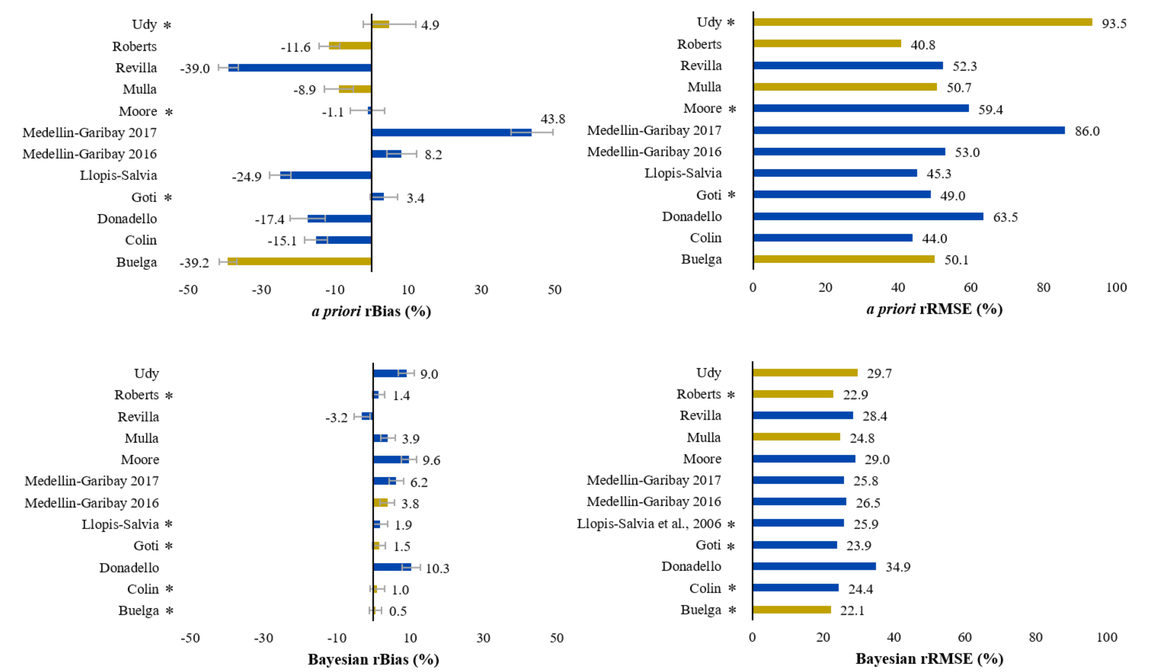

Figure 1: *Blue bars represent models developed with ICU patients; yellow bars represent models developed in heterogeneous patient cohorts. Errors bars are 95% CI. (*) Clinically acceptable model; ICU, Intensive Care Unit; rBias, relative bias (bias); rRMSE, relative root mean squared error (precision).*

Factors affecting predictive performance (Goti model)

- Vancomycin concentrations: model performance using all was not always better than only the most recent
- Dialysis status (perhaps not adequately represented by categorical covariate, e.g. due to variety of modalities)
- Sex (perhaps skewed by male-dominated population)
- SOFA score (severity of illness)

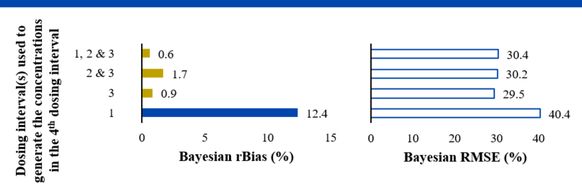

Figure 2: *Goti model performance in the 4th dosing interval when calculated using different combinations of concentrations in the preceding 3 dosing intervals. Yellow bars (vs blue) indicate scenarios where the bias was clinically acceptable;*

Conclusion

- The Goti, Llopis-Salvia and Roberts models are clinically appropriate to inform vancomycin dosing in critically ill patients using Bayesian forecasting
- Model performance improved with the use of (just one) recent vancomycin concentration(s)
- Roberts and Llopis-Salvia models less accurate than the Goti model in non-critically ill patient populations[2]
- Implementing the Goti model in Bayesian forecasting software could **simplify** and **streamline** dosing across **both ICU** and **non-ICU patients**, considering it is also the most accurate model in non-ICU patients[2]

References

1) Rybak et al. Am J Health Syst Pharm 2020 **2)** Broeker et al. Clin Microbiol Infect 2019