Towards a new era of vancomycin therapeutic monitoring : external evaluation of population pharmacokinetics models in pediatrics

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Introduction

- **Vancomycin:** Antibiotic used to treat severe Gram-positive bacterial infections
- **Therapeutic drug monitoring (TDM):** Part of routine clinical practice because of narrow therapeutic index and significant pharmacokinetic variability

Table 1. Main recommendations from previous and revised guidelines

Previous guidelines (2009)[1]	Revised guidelines (2020)[2]
$15 \leq C_{trough} \leq 20$ mg/L	$400 \leq AUC_{0\text{-}24}/MIC^a \leq 600$ (mg x h)/L

[a]Assuming MIC ≤ 1 mg/L - C_{trough}: Trough concentration - $AUC_{0\text{-}24}$: Area under the curve over 24 hours - MIC: Minimal inhibitory concentration

Objectives

- **Evaluate the predictive performance of vancomycin population pharmacokinetics (popPK) models in general pediatrics and validate the most predictive for CHU Sainte-Justine (CHUSJ) population**
- **Compare approaches of $AUC_{0\text{-}24}$ calculation (Bayesian versus traditional first-order equation[3]), Bayesian $AUC_{0\text{-}24}$ to corresponding trough and in terms of toxicty**

Methods

- **Literature reviews[4,5]:** Identification of pediatric popPK models up to December 31, 2021
- **Retrospective data collection:** Children who received intravenous vancomycin ≥ 48 hours in general pediatrics at CHUSJ between January 1, 2019 and December 31, 2020
- **Pharmacokinetic analyses (NONMEM, version 7.5)**
  1. **External evaluation (MAXEVAL=0):** Prediction error (PE) calculation

$$PE(\%) = \frac{(Concentration_{predicted} - Concentration_{observed})}{Concentration_{observed}} \times 100\%$$

  - **Acceptable predictive performance: Bias = Median PE ≤ ±20% AND Imprecision = Median |PE| ≤ 30%[6] on a population level**
  2. **Parameters re-estimation (MAXEVAL=9999):** If no model exhibits acceptable predictive performance and PE calculation de novo

- **$AUC_{0\text{-}24}$ calculation by Bayesian approach using previously validated model:**

$$Bayesian\ AUC_{0-24}\ (mg \times h/L) = \frac{Daily\ dose\ (mg)}{Predicted\ clearance\ (L/h)}$$

- **$AUC_{0\text{-}24}$ calculation by traditional first-order pharmacokinetic equation[3]:** Patient **ID282 (0.5 year old male weighing approximetaly 8.45kg)** was the only one with two vancomycin blood samples in the same therapeutic interval
- **Toxicity: Acute kidney injury (AKI)** defined as an **increase** in **serum creatinine ≥ 1.5-fold** from **baseline (Stage 1 – KDIGO)[7]**

Conclusion

- **External evaluation:** Key step towards clinical implementation of the latest guidelines[2]
- **De Cock[8]:** Validated for CHUSJ pediatric population after parameters re-estimation
- **Bayesian approach seems equivalent to traditional first-order equation and provides:**
  - **Faster attainment of therapeutic target and sampling flexibility (Ø steady-state)**
  - **Consideration of significant covariates to further guide dose optimization**
  - **Reduction of blood sampling for TDM of particular importance in pediatrics**
- **Poor correlation ($R^2 = 0.2955$)** between Bayesian $AUC_{0\text{-}24}$ and corresponding trough
- **Toxicity:** Slightly increased $AUC_{0\text{-}24}$ **(p = 0.3)** in patients experiencing nephrotoxicity

Perspectives

- The validated model[8] will be used to develop an initial dosing nomogram and may also be used in clinical practice for Bayesian adaptation

Results

Table 2. CHUSJ population characteristics

Characteristics (Units)	CHU Sainte-Justine
Number of patients (M/F)	74 (44/30)
Age (years)	3 [0-17]
Weight (kg)	13.3 [2.9-105.7]
Serum creatinine (µmol/L)	38.2 [18.5-73.0]
Number of blood samples	263
Number of blood samples/patients	3.55

Age, weight and serum creatinine = Median [range]

Figure 1. Predictive performance on population (a,b) and individual (c,d) levels

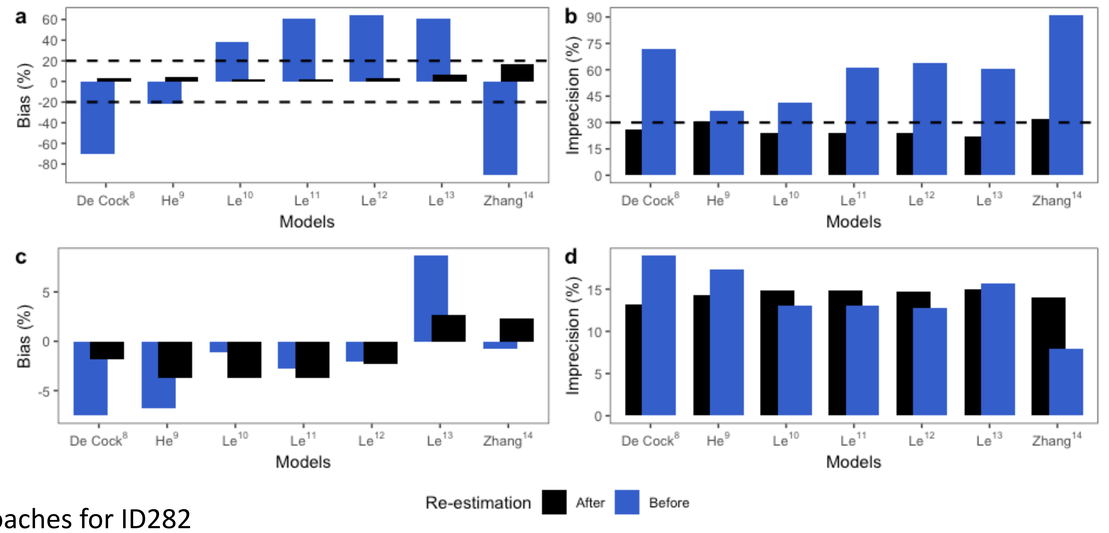


Table 3. Comparison of $AUC_{0\text{-}24}$ calculation approaches for ID282

Methods	$AUC_{0\text{-}24}$
Bayesian (De Cock[8])	632.8 mg*h/L
First-order equation[3]	616.2 mg*h/L

Daily dose = 780mg (130mg q4h) - CL (Predicted clearance) = 1.23 L/h - C_{2h} = 28.6 mg/L - C_{trough} = 13.8 mg/L

Figure 2. Bayesian $AUC_{0\text{-}24}$ against corresponding trough (30 min)

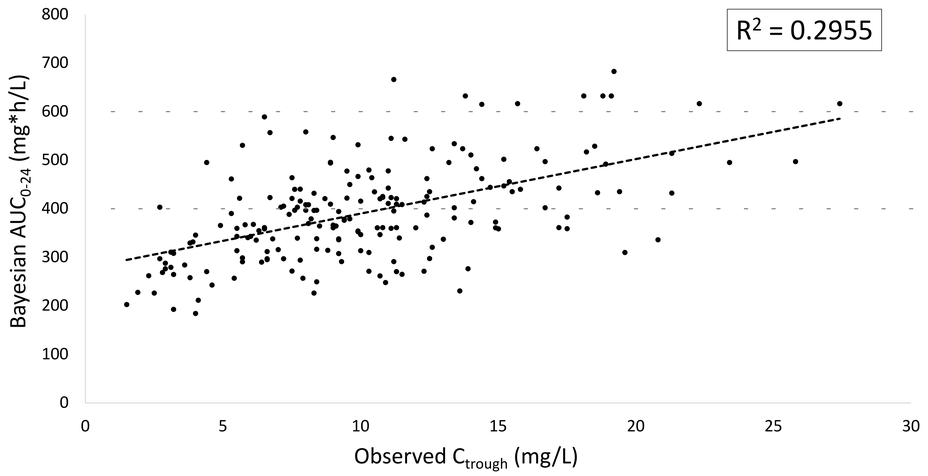
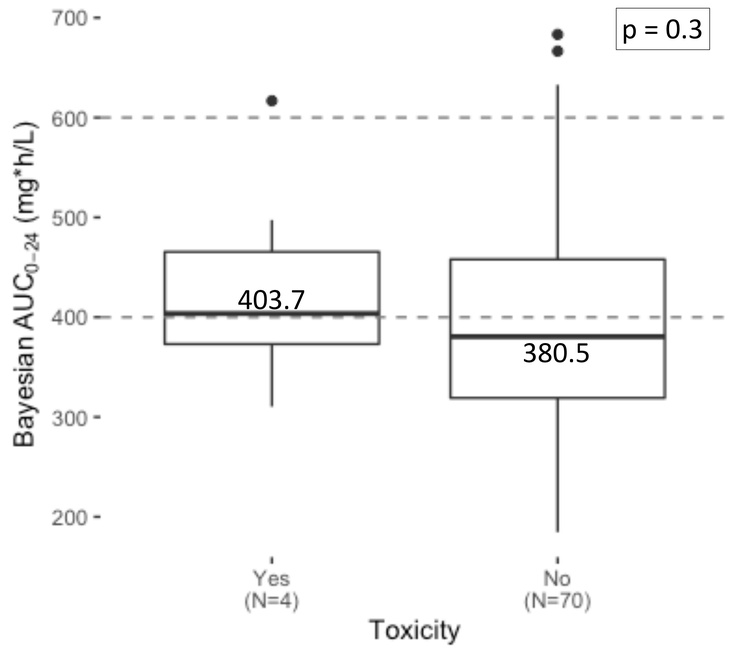


Figure 3. Bayesian $AUC_{0\text{-}24}$ with and without toxicity



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