Development of *a priori* dosing nomograms for daptomycin in patients at Swiss university hospitals

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Introduction

Daptomycin is used in the treatment of **infections** with **gram-positive bacteria** [1]. **Treatment efficacy** correlates with the **ratio** of **area under the curve (AUC) over minimum inhibitory concentration (MIC)**, and thus varies with the targeted organism's sensitivity to the drug [2]. An AUC/MIC > 800 is considered **bactericidal**, and 400 < AUC/MIC ≤ 800 is **bacteriostatic**. To minimize the risk of **rhabdomyolysis**, it is preferable to keep trough level **C_{24h} < 24 mg/L** [3]. The objectives were:

- Create a **pharmacometric model** for *a priori* and *a posteriori* **dose optimization**
- Generate **dosing nomograms** to guide clinicians without prompt access to a pharmacometric model

Methods

- **Retrospective** study of inpatients receiving **routine Therapeutic Drug Monitoring** (**TDM)** of their daptomycin treatment at the University Hospital Basel (UHBS) and Lausanne University Hospital (CHUV). TDM usually at 2h and 24h post-dose.
- Patient data were used to build a **population-based pharmacokinetic model** with **NONMEM** and to generate **dosing nomograms** with **Simulx.** The final model was used to simulate concentration time curves for different daily doses (2-14 mg/kg) at different renal functions and serum albumin concentration.

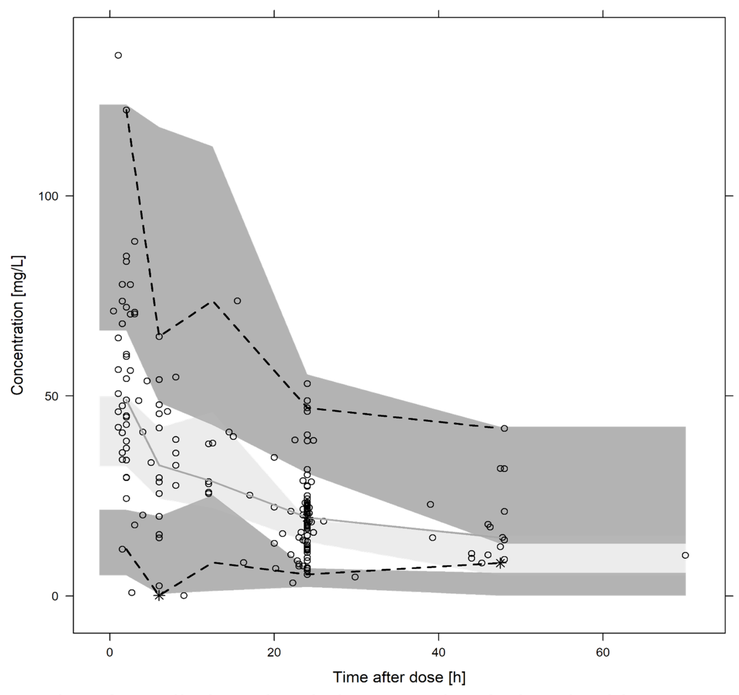

Figure 1: Visual predictive check (n=500 simulations) with 95% confidence intervals.

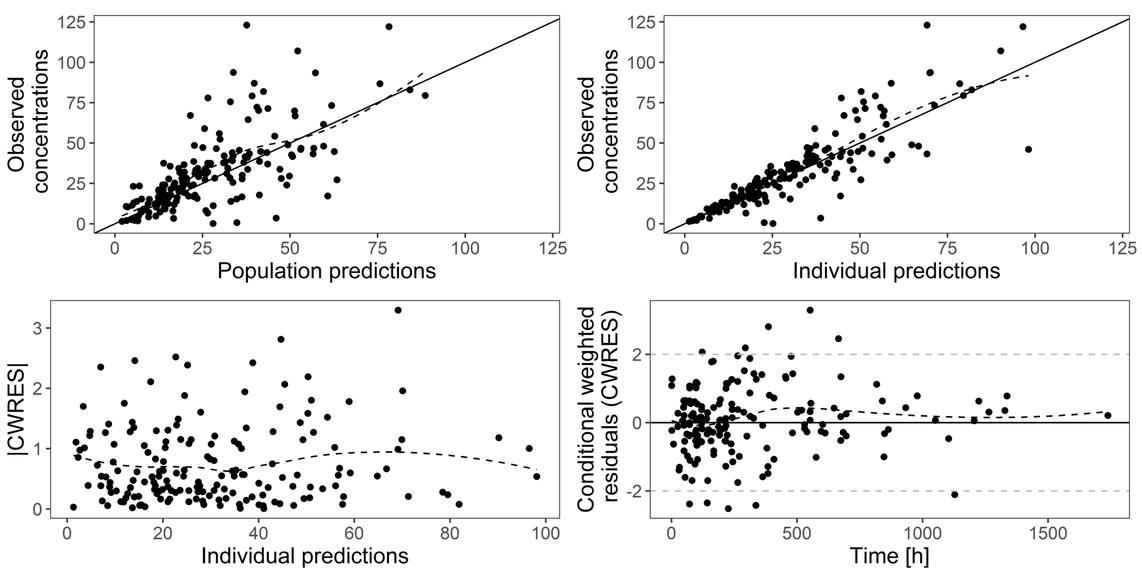

Figure 2: Basic goodness-of-fit plots for the final model

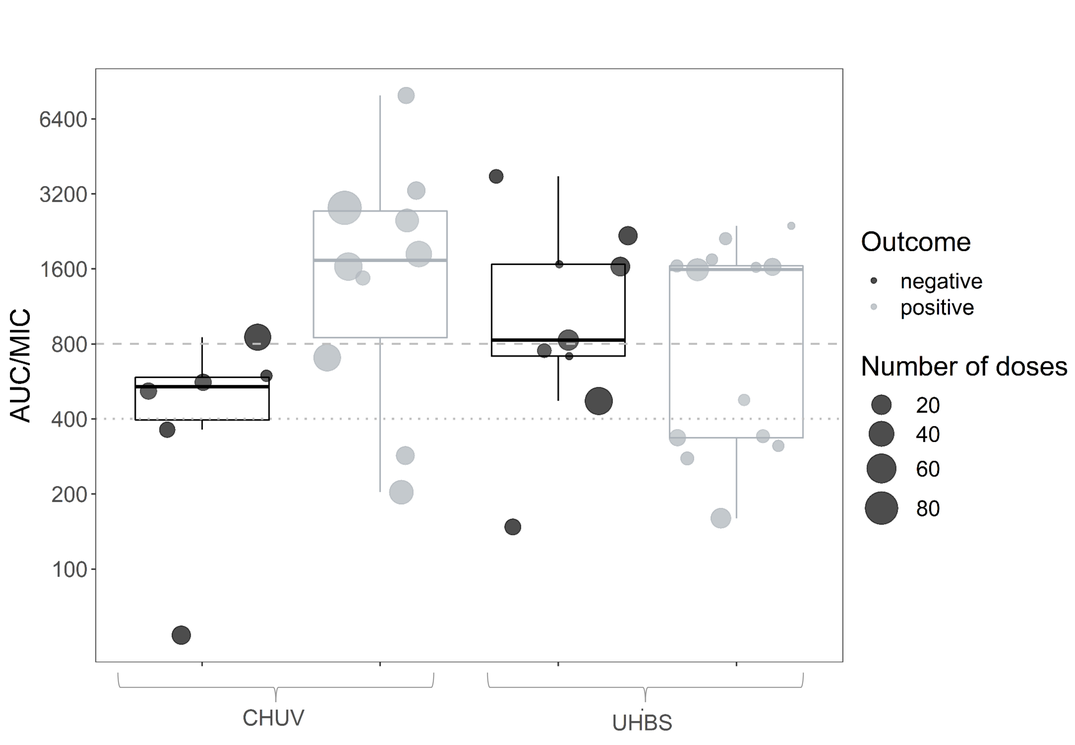

Figure 3: Individual patient outcomes (n=38) by hospital (CHUV or UHBS). Only patients with reported MIC for daptomycin are shown. Lines represent bactericidal (dashed) or bacteriostatic (dotted) AUC/MIC ratio.

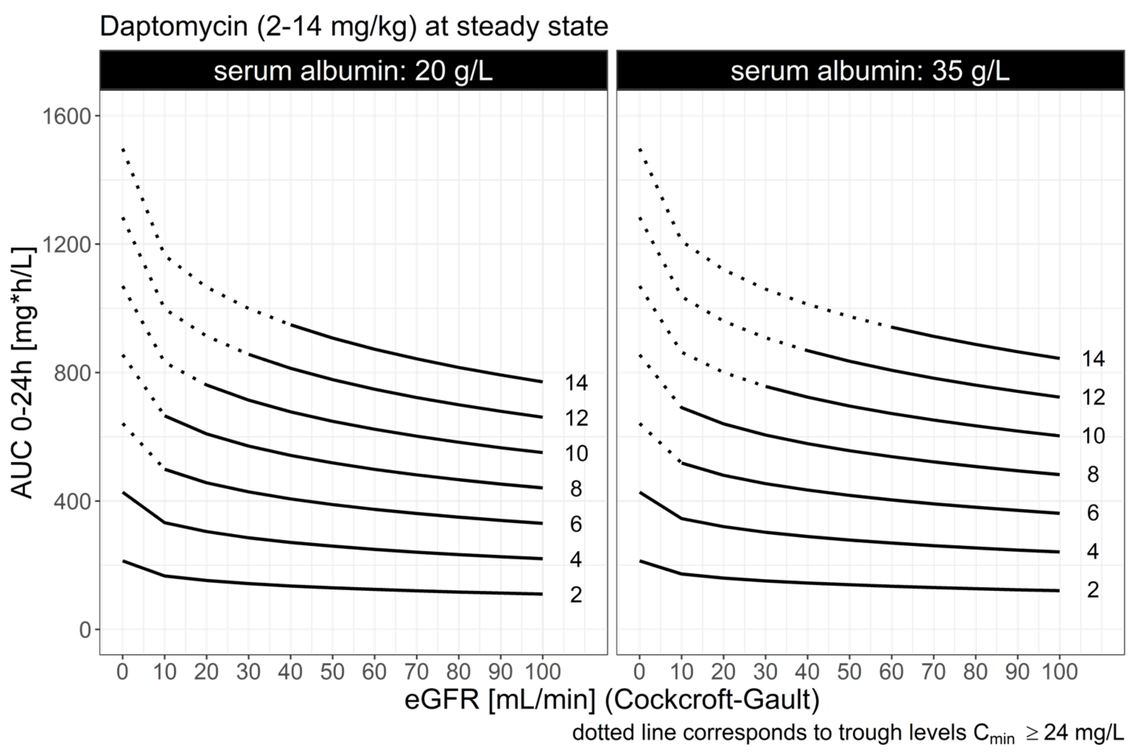

Figure 4: Daptomycin dosing nomograms for typical patients of the study population. Dose range of 2 to 14 mg/kg daptomycin. Serum albumin concentration 20 g/L (left) or 35 g/L (right).

Results

- Total of **58 patients** included (n=31 at UHBS, n=27 at CHUV), including **174 samples**.
- The final model is a **one-compartment model** with **linear elimination** (volume of distribution (Vd) 15.90 L (inter-individual variability (IIV): 40%) and clearance (CL) 0.79 L/h (IIV: 33%)). **Influential covariates on clearance**: **serum albumin concentration** and **renal function** (estimated by Cockcroft-Gault equation).
- **Dosing nomograms** were generated (Fig.4) by simulating concentration profiles at steady state for a broad range of doses and computing $AUC_{0\text{-}24h}$ for typical patients.

Conclusions

- Pharmacometric models can be used for initial *(a priori)* dose finding but involve specialist knowledge often not readily available at point-of-care.
- Dosing nomograms generated from simulation can help make **quicker informed decisions** for optimizing initial dosage, pending therapeutic monitoring when appropriate.

References: [1] Bidell et al., Pharmacotherapy, 2018. 38(12): p. 1205-1215. [2] European Committee on Antimicrobial Susceptibility Testing Steering, Clin Microbiol Infect, 2006. 12(6): p. 599-601. [3] Bhavnani et al., Clin Infect Dis, 2010. 50(12): p. 1568-74.