Population pharmacokinetics and dosing nomograms of daptomycin at a Swiss university hospital

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Introduction

The lipopeptide antibiotic daptomycin is primarily used in the treatment of **systemic infections with gram-positive bacteria**. It is primarily **eliminated unchanged via the kidneys**. The efficacy correlates with the ratio of area under the curve (AUC) over minimum inhibitory concentration (MIC), and thus varies with an organism's sensitivity to the drug. An **AUC:MIC > 800** is considered **bactericidal**, and a ratio of 400 - 800 bacteriostatic [1]. Some practitioners prefer to keep **C_{24h} < 24 mg/L** to minimize risk of **rhabdomyolysis** [2]. Current practice at the University Hospital Basel (UHBS) is to determine these values with a variation of Begg's method [3].

Objectives

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

Patients and Methods

Samples were collected retrospectively from measurements made during **routine daptomycin TDM from January 2014 until December 2017** at the UHBS. Available covariates included demographic data, chemistry and hematology labs, infection specific data (type, site, organism, MIC where available), and clinical outcome at time of discharge from the hospital. Population pharmacokinetic analysis and simulations were carried out using NONMEM (Version 7.4.3).

Results and Discussion

A total of **32 patients** were enrolled, totaling **111 samples** from 1-7 different occasions. The final model was a **one-compartment model with linear elimination** (Vd 13.9 L (IIV: 31%), CL 0.48 L/h (IIV: 36%)) and a proportional residual error (0.24). Diagnostic plots are given in Figures 1 and 2. These results are in agreement with previous reports (e.g. [4]). Estimated glomerular filtration rate was positively and **serum albumin** negatively correlated with CL. **ICU patients** had an added CL of 0.3 L/h.

We generated **dosing nomograms** by simulating profiles at steady state for a broad range of doses (2-14 mg/kg), and computing $AUC_{0\text{-}24h}$ and C_{24h} (Figure 3). Given that daptomycin is often administered when there may not be enough time to wait for a dose recommendation, nomograms **could help make more informed decisions**. They are interpretable by non-pharmacometricians and familiar to clinicians. They can convey the practical aspects of the often multidimensional relationships captured by pharmacometric models more intuitively than a set of differential equations.

Conclusions

The model presented here describes the collected data well and can be used in model-based TDM. Nomograms are easily created and are potentially useful for communication and deployment.

References
[1] Clin Microbiol Infect, 2006. 12(6): 599-601, [2] Clin Infect Dis, 2010. 50(12): 1568-74, [3] Br J Clin Pharmacol, 1995. 39(6): 605-9, [4] Int J Antimicrob Agents, 2013. 42(3): 250-5

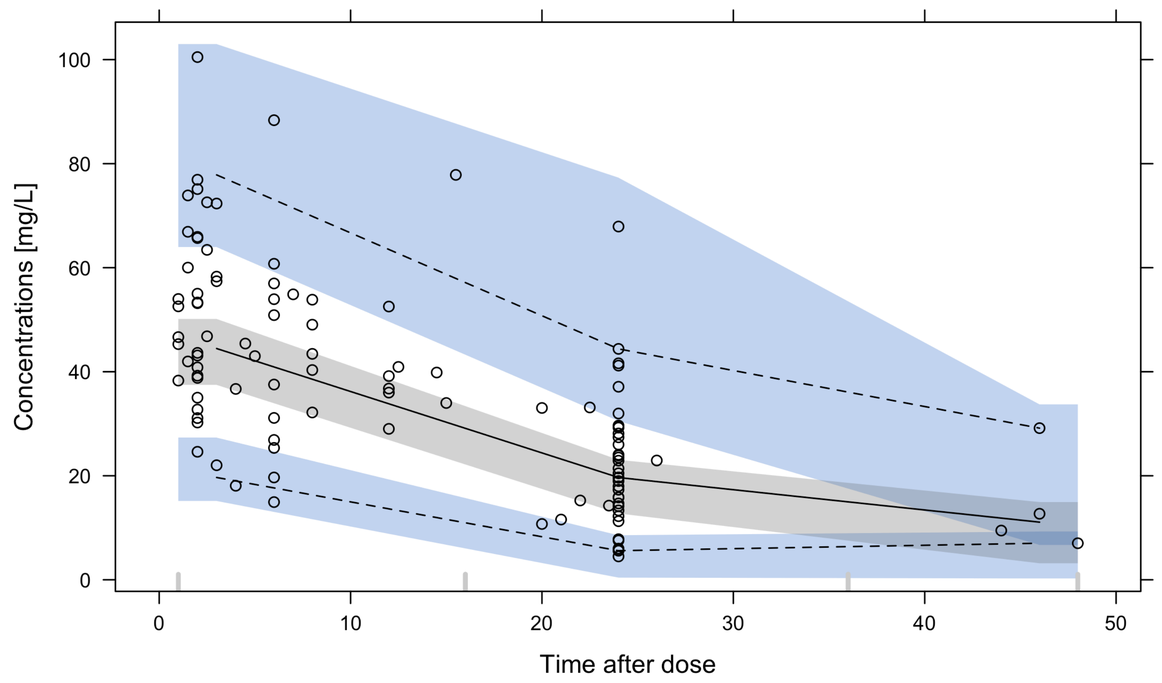

Figure 1 - Prediction corrected visual predictive check of the final model (n=500 simulations)

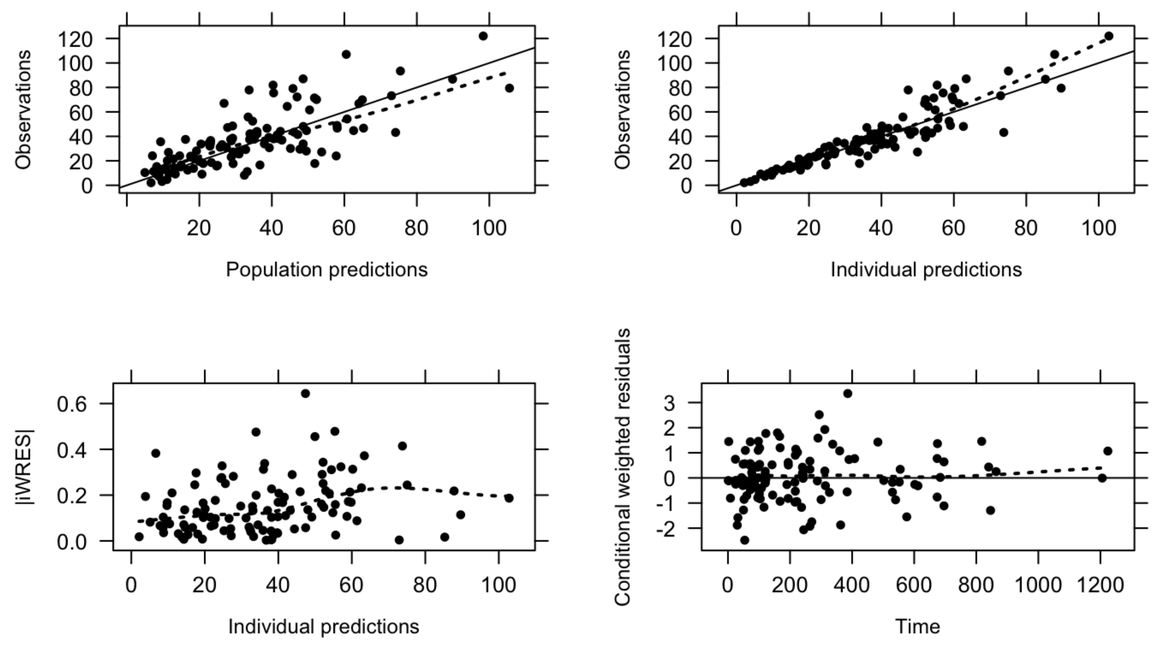

Figure 2 - Basic goodness-of-fit plots for the final model

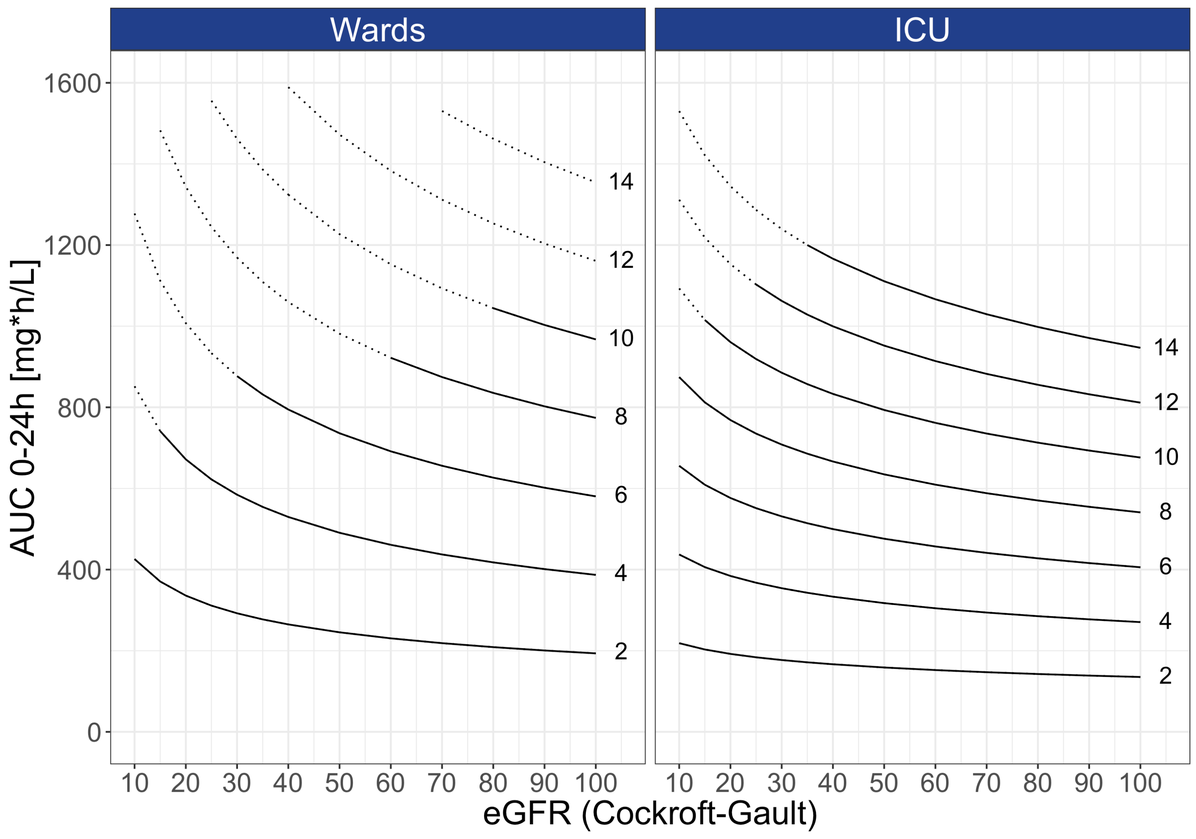

Figure 3 - Dosing nomograms for a typical patient (serum albumin: 20 g/L) from simulated data (dose range 2-14 mg/kg). Dotted lines indicate C_{24h} > 24 mg/L.

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