

Title:

Towards Model-Informed Precision Dosing for Daptomycin: An External Evaluation of Pharmacokinetic Models in Elderly Patients

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Background

Daptomycin exhibits large inter-individual pharmacokinetic variability, with efficacy and safety linked to exposure metrics. Population pharmacokinetic (PopPK) models enable model-informed precision dosing (MIPD), but their external predictive performance and clinical transferability in elderly patients remain unevaluated.

Methods

Published daptomycin PopPK models were identified from a prior systematic review and re-implemented. External validation was conducted using an independent elderly cohort with routine therapeutic drug monitoring (TDM). Predictive performance was assessed under three scenarios: a priori prediction and two Bayesian forecasting scenarios with increasing TDM information. Model evaluation integrated prediction errors, simulation-based diagnostics, and exposure metrics. A Bayesian AUC calculator was developed based on the best-performing model.

Results

External validation included 119 elderly patients (308 plasma concentrations). A priori predictive performance varied widely; models developed in populations most similar to the external cohort showed the greatest transferability. Bayesian updating consistently improved accuracy and precision, with median absolute prediction error decreasing from 61.94% (a priori) to 52.29% (after one TDM pair) and further to 46.86% (after two TDM pairs). The

Takahashi model demonstrated the best overall performance and was selected to develop a Bayesian AUC calculator, implemented as a freely accessible Shiny web application (https://mipdshinyapp.shinyapps.io/Daptomycin_AUC_Cal/).

Conclusions

This study established a clinical decision support system for individualized daptomycin therapy in elderly patients, spanning model evaluation, external validation, and tool implementation. Bayesian updating incorporating TDM data markedly enhanced individual exposure prediction, providing a feasible pharmaceutical informatics solution for precision antimicrobial therapy.

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