Title: Limited sampling on model-informed precision dosing of daptomycin for rapidly achieving target area under the concentration–time curve: A simulation study

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Abstract (350 ≤ 350word)

Background: Daptomycin, a first-line treatment for bloodstream infections caused by methicillin-resistant *Staphylococcus aureus*, carries a risk of exposure-dependent muscle toxicity. Although the area under the concentration-time curve (AUC) is expected to assess efficacy and safety comprehensively, the optimal model-informed precision dosing strategy for daptomycin AUC remains uncertain. This simulation study aims to identify efficient limited sampling strategies using Bayesian forecasting to rapidly achieve the target AUC range for daptomycin.

Methods: We generated a virtual population of 1,000 individuals using two validated population pharmacokinetic models identified though a systematic literature search from pharmacokinetic studies (model 1, various background patients; model 2, kidney transplant recipients). AUC for each blood sampling point was evaluated using the probability of achieving a ratio of estimated/reference AUC on the second day ($AUC_{24–48}$) and at steady state (AUC_{ss}) in the 0.8–1.2 range. Daptomycin was administered at 6 mg/kg every 24 hours for creatinine clearance ≥ 30 mL/min and every 48 hours for < 30 mL/min.

Results: In model 1, the Bayesian posterior probability of achieving the $AUC_{24–48}$ range increased from 50.7% (*a priori* probability) to 59.4% with one-point trough sampling at 24 hours, and further to 73.8% with two-point sampling at 7 and 24 hours after the first dose. Those for AUC_{ss} rose from 48.9% (*a priori* probability) to 61.9% with one-point trough sampling at 24 hours, and further to 69.7% with two-point sampling at 7 and 24 hours after the first dose. Additionally, it reached 81.5% for AUC_{ss} with two-point sampling on the third day while 63.5% and 67.8 % with one-point trough sampling on the third and fourth days. Model 2 produced results similar to those of model 1. Three-point or more rich sampling did not enhance the probabilities in either model.

Conclusions: These results suggest that two-point sampling during the first dosing interval accelerates rapidly achieving target $AUC_{24–48}$ and AUC_{ss} range. Resampling two points on the third day or later may support dosing decisions with high predictive accuracy for AUC_{ss}.