

A population PK model predicting bone concentrations for cefuroxime in PJI patients: Considering target-site concentrations

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AIMS

- To describe the relationship between the plasma and bone cefuroxime concentrations in patients with prosthetic joint infection (PJI) with a population pharmacokinetic (popPK) model
- To identify covariates for target site exposure of cefuroxime in PJI patients

Fig. 1 Model evaluation

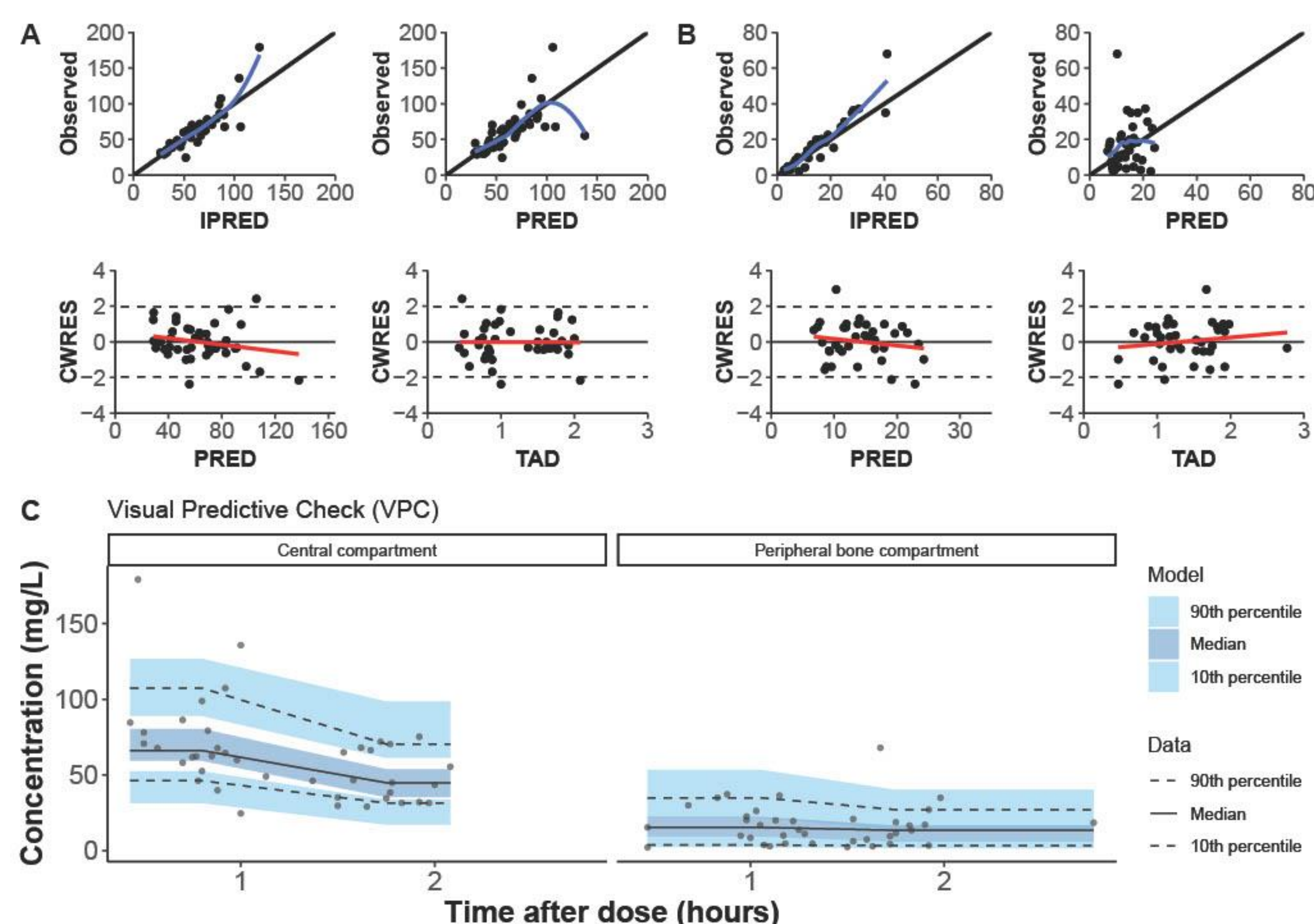


Fig. 1 Diagnostic plots of the final popPK model of cefuroxime. **A)** GOF-plot of plasma samples. (I)PRED: (individual) predicted concentrations in mg/L. CWRES: conditional weighted residuals. **B)** GOF-plot of bone samples **C)** Visual Predictive Check (VPC) based on 1000 simulations and stratified for plasma and bone compartment

CONCLUSION

- Adequate cefuroxime concentrations after 1 hour of administration with rapid clearance from bone
- A single dose 1500 mg cefuroxime was inadequate for ECOFF values of 4 mg/L especially in PJI patients with eGFR >80 mL/min

Fig. 2 Simulations

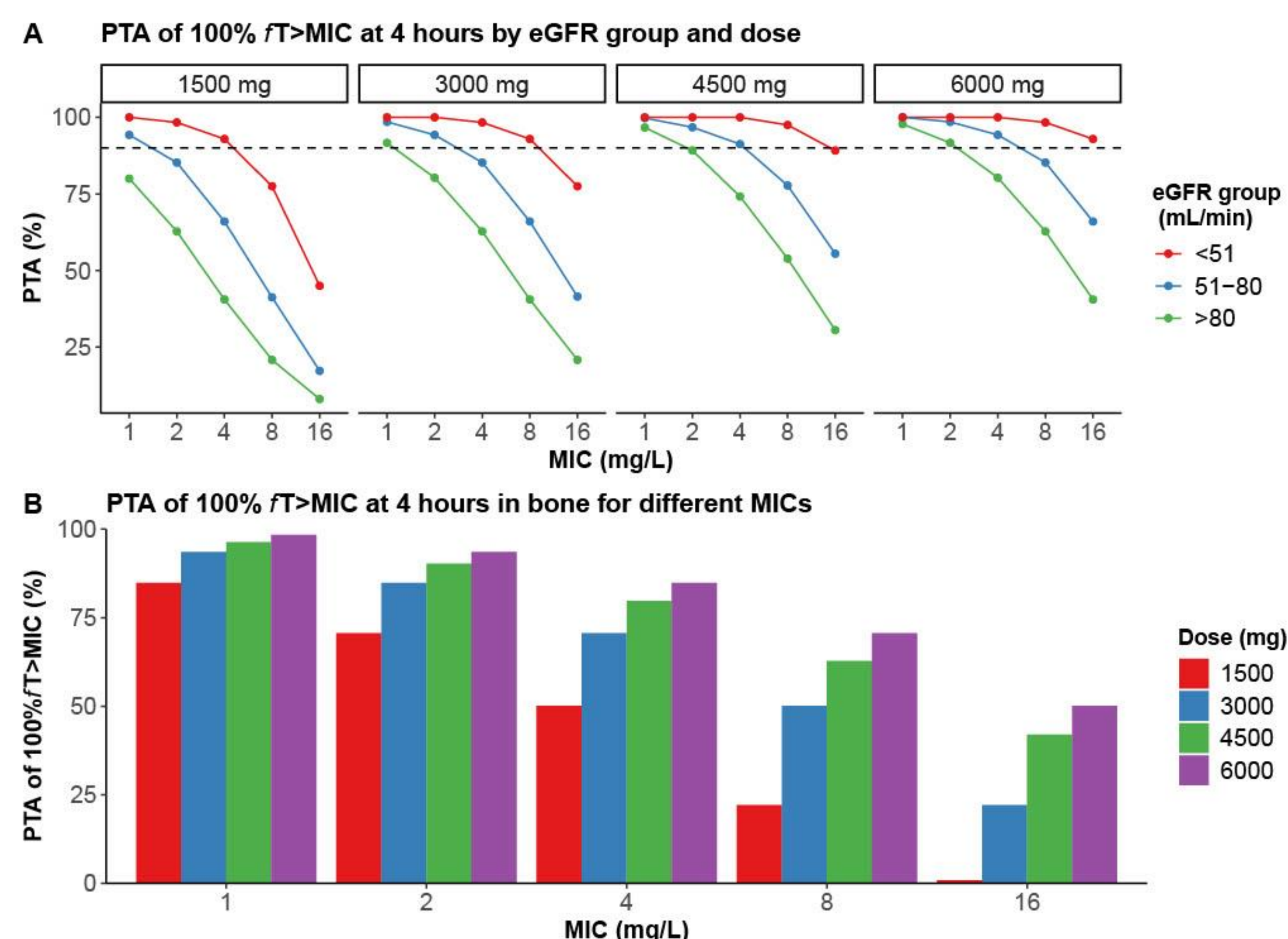


Fig. 2 Simulations of 100% $fT > MIC$ of probability of target attainment (PTA) at 4 hours after start IV bolus: **A)** Stratified for different dose and estimated glomerular filtration rate (eGFR) and different minimal inhibitory concentrations (MIC) on the x-axis. **B)** Stratified for different doses and MIC

INTRODUCTION

PJI are a common reason for revisions in patients that underwent total hip or knee arthroplasty (THA/TKP). To prevent PJI, cefuroxime is given as a prophylaxis peri-operatively and to treat PJI after microbiological confirmation of cefuroxime coverage. However, prophylactic target site coverage is unknown. Therefore, based on target site concentrations a popPK model will be able to describe prophylactic coverage of cefuroxime during knee/hip revisions.

METHODS

PJI patients undergoing one- or two-stage revision, >18 years, and treated with antibiotics, like cefuroxime, were included in the ASTERICS study. At 30-60 and 90-120 minutes after start of IV bolus plasma and bone samples were taken during revision surgery. Using methods described by Bahmany et al. [1-2], cefuroxime plasma and bone concentrations were quantified. With nonlinear mixed effect modelling (NONMEM, V7.5), a popPK model was built. Monte Carlo simulations were run to assess probability of target attainment (PTA) and different dosing regimens.

RESULTS

A total of 25 patients were included with a total of 44 plasma and 38 bone samples. A two-compartment model best described the plasma and bone compartment (fig. 1). Allometric scaling was applied *a priori* and interindividual variability on clearance (CL) and the rate constant from the second to first compartment (k_{21}) was estimated. eGFR was the only significant covariate on CL. The PTA of patients with an eGFR >80 mL/min at 4 hours with an epidemiological cut-off (ECOFF) value of 4 mg/L with a 1500 mg dose is <50% (fig. 2a). Simulations showed (fig. 2b) that 1500 mg IV bolus of cefuroxime reach a PTA at 4 hours of 50% for the ECOFF value of 4 mg/L.

DISCUSSION

Local PD-targets are unknown and make translation to treatment difficult. A single dose of 1500 mg cefuroxime is insufficient to maintain adequate concentrations at target site during surgery. No differentiation between cortical and cancellous bone was possible. External validation of the model is required.

References

- Bahmany S et al. 2022;219:114904. doi:10.1016/j.jpba.2022.114904
- Bahmany S et al. 2024;1241:124169. doi:10.1016/j.jchro.2024.124169

