

Do critically ill patients undergoing continuous renal replacement therapy require ceftaroline dosage adjustments? Ceftaroline PopPK model and dosage simulations with a probability of target attainment analysis based on retrospective data

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Introduction

Ceftaroline is a fifth-generation cephalosporin reserved for treating infections caused by resistant gram-positive and gram-negative bacteria [1]. Currently, no dosing standards have been recommended by The European Committee on Antimicrobial Susceptibility Testing or Stanford Health Care Antimicrobial Dosing Reference Guide for ceftaroline in patients undergoing continuous renal replacement therapy (CRRT) [2,3]. This study aimed to develop a preliminary population pharmacokinetic (PopPK) model and investigate dosages for CRRT intensive care unit (ICU) patients.

Methods

Pharmacokinetic and clinical data were obtained retrospectively from 4 articles describing ICU patients treated with 400-600 mg of ceftaroline in 1h infusion [4-7]. The data from the graphs were extracted using WebPlotDigitizer [8]. Ceftaroline concentration-time data were analysed using PopPK modelling according to the SAEM algorithm for non-linear mixed effects models implemented in the Monolix [9]. Model selection was based on goodness-of-fit criteria such as corrected Bayesian Information Criteria (BICc), the objective function value (OFV) defined as $-2 \times \text{Log Likelihood}$, the precision of the parameter estimates, and diagnostic plots. We assumed a priori a 2-compartment model with linear elimination [1]. Any clinical variables were examined as potential covariates using a stepwise covariate model procedure (SCM). We filled in the missing values for creatinine clearance (76/429 (17.71%)) with the median in the population. Simulations of dosing regimens were performed in Simulx [10]. We tested 200/300/400/600 mg in a 1h infusion every 12 hours (standard) and a 2h infusion every 8 hours (high dosage) [11]. For each combination, we simulated 2500 patients as 50 patients in a group replicated 50 times. For the probability of target attainment (PTA) analysis, we assumed $100\%fT_{>MIC}$ and $100\%fT_{>4 \times MIC}$ as standard and high PK/PD targets, respectively [12]. The $PTA \geq 90\%$ for MIC values up to 4 mg/L was considered an acceptable probability of success [13]. The free fraction of ceftaroline was calculated based on a percentage (~20%) of protein binding mentioned in SmPC [11].

Results

The study included 33 adult ICU patients (12 female, 21 male) and 296 plasma samples, of which 26 were from 4 CRRT patients. The median (range) of testing continuous covariates for age was 55.0 years (21.0 – 77.0), weight was 77.0 kg (49.0 – 111.8), creatinine clearance was 169.0 mL/min (58.3 – 309.0), and albumin level was 2.7 g/dL (2.0 – 3.2).

Table 1. Decrease in OFV related to added covariates

Model	-2×Log Likelihood	ΔOFV
Base structural model	1164.42	–
ClCr on Clpop	989.25	-175.17
ClCr + CRRT on Cl pop	982.95	-6.30
ClCr + CRRT on Cl pop & CRRT on V1 pop	967.40	-15.55

Table 2. Parameter estimations of the final model

Parameter	Value	Stochastic approximation		
		S.E.	R.S.E.(%)	
Fixed Effects				
Cl_pop	11.14	0.56	5	
beta_Cl_pop_ClCr	0.25	0.0006	0.24	
beta_Cl_pop_CRRT	-0.28	0.14	51.05	
V1_pop	20.25	1.17	5.77	
beta_V1_pop_CRRT	0.68	0.1	15.04	
Q_pop	7.36	1.63	22.18	
V2_pop	18.72	3.1	16.58	
Standard Deviation of the Random Effects				
	Value	C.V.(%)		
omega_Cl	0.24	23.94	0.035	14.83
omega_V1	0.048	4.84	0.027	56.26
omega_Q	0.36	37.04	0.12	33.87
omega_V2	0.7	78.92	0.17	24.06
Error Model Parameters				
a	0.11	0.027	24.75	
b	0.25	0.018	7.06	

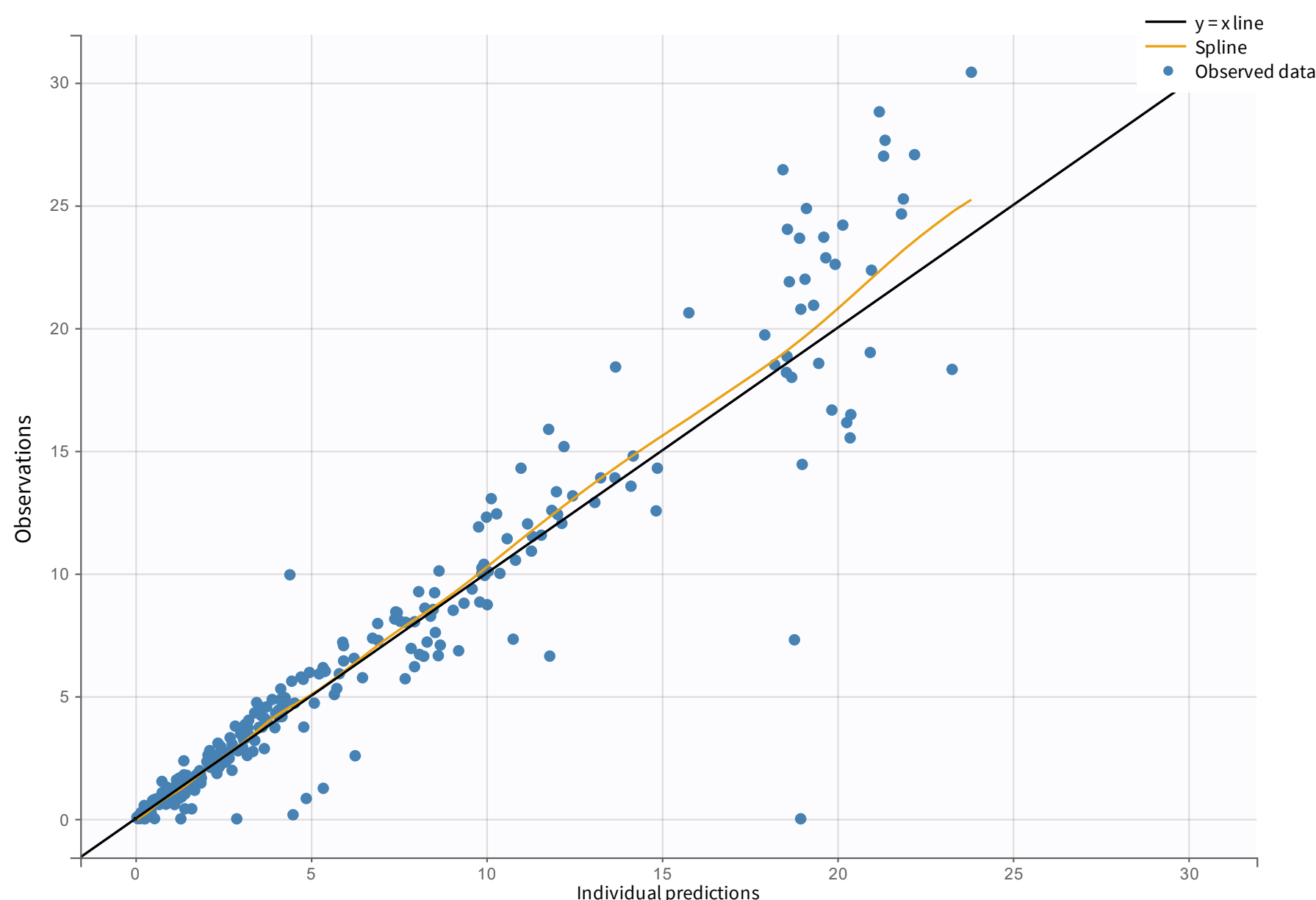


Figure 1. Observed vs. population-predicted concentrations

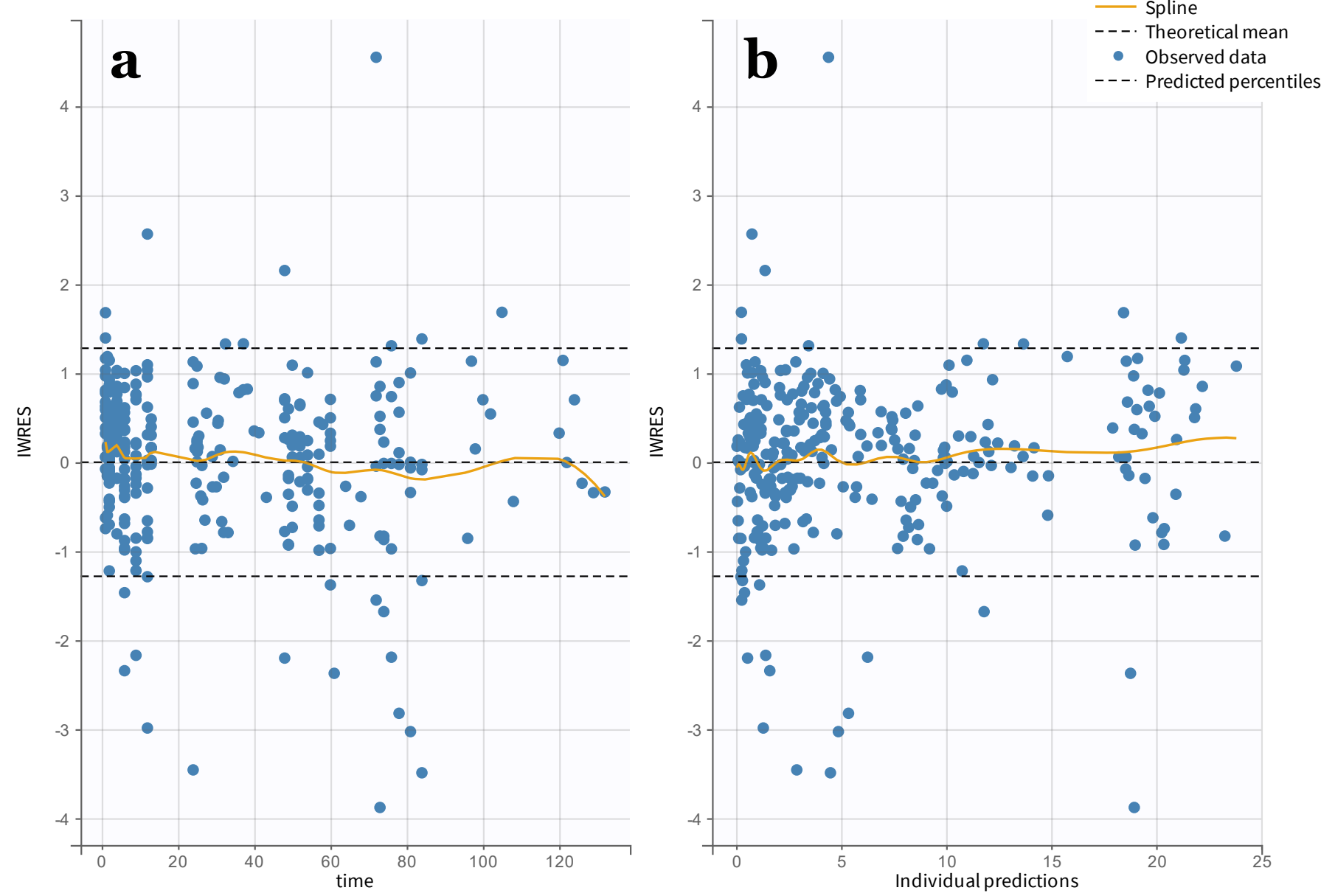


Figure 2. Individual weighted residual vs. time (a) and population-predicted concentrations (b)

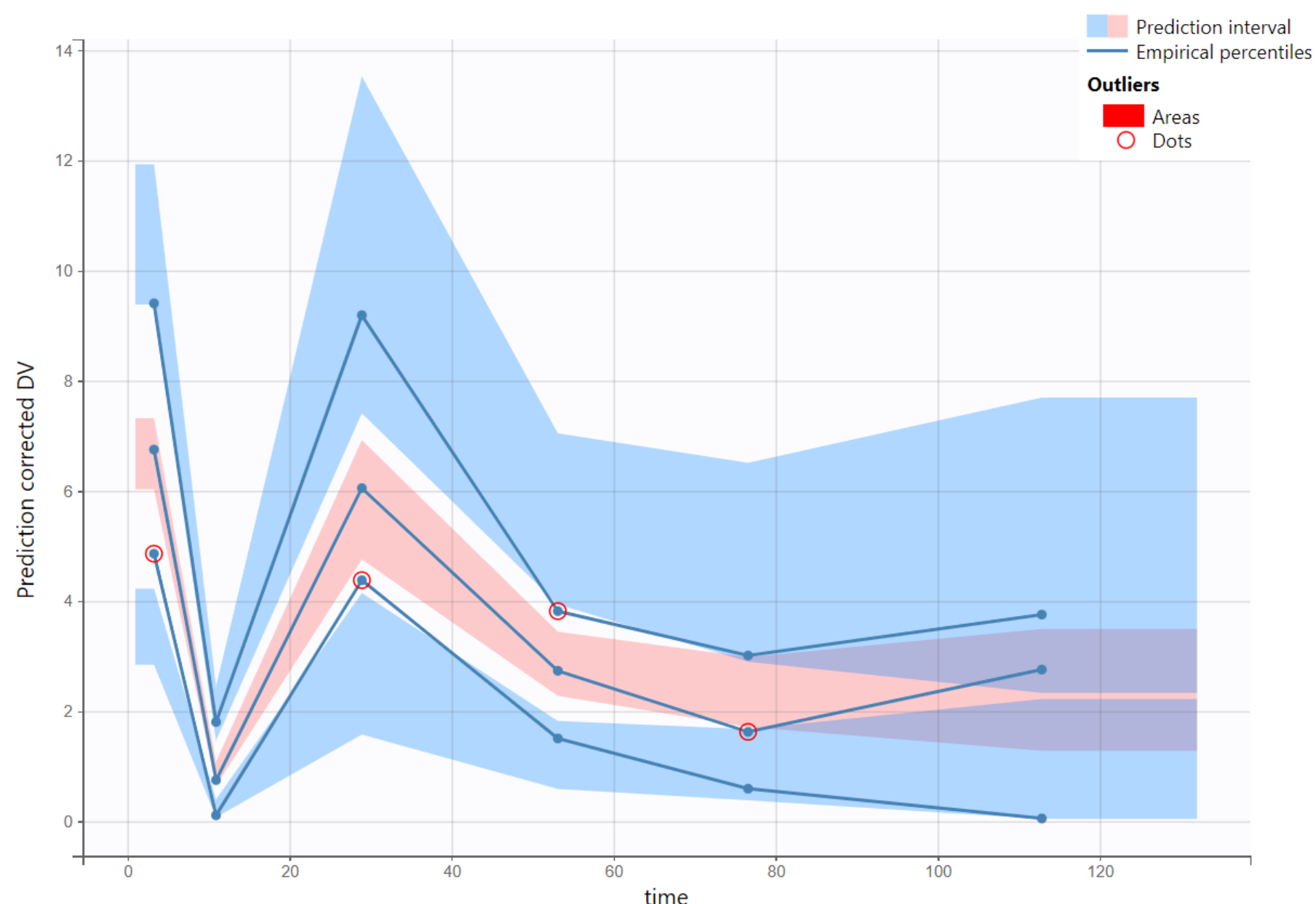


Figure 3. Prediction-corrected Visual Predictive Check

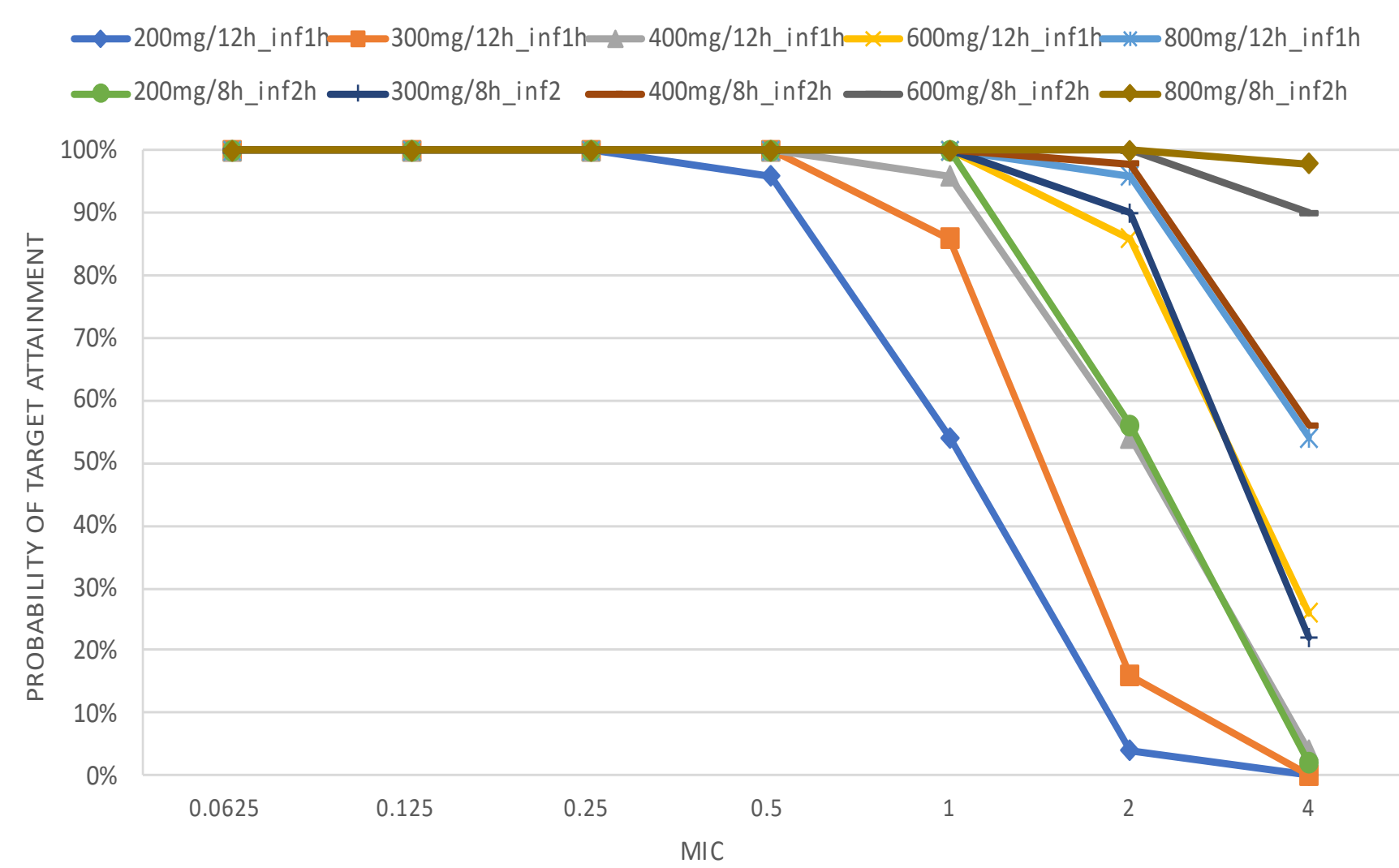


Figure 4. Probability of target attainment for standard PK/PD target ($100\%fT_{>MIC}$)

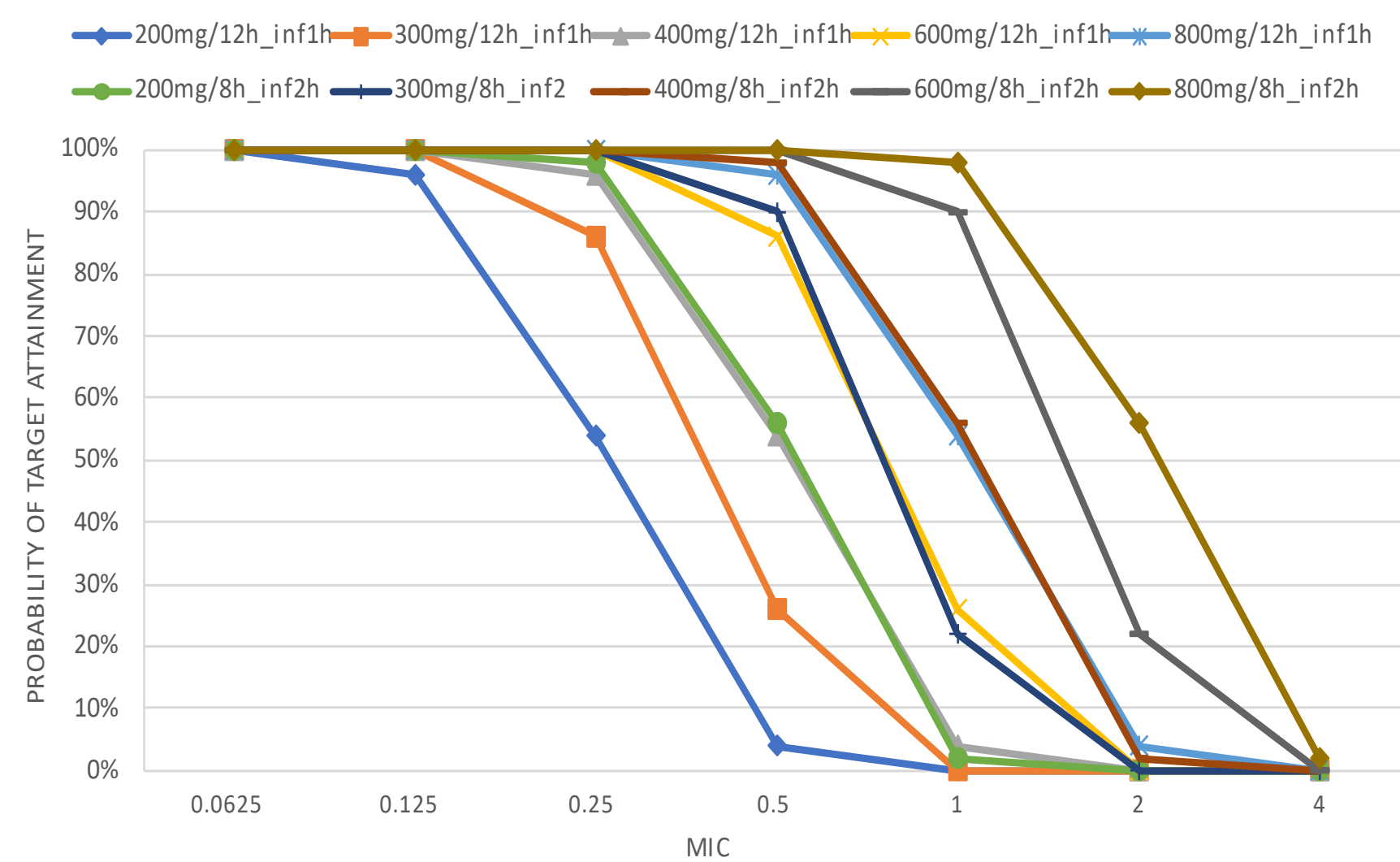


Figure 5. Probability of target attainment for high PK/PD target ($100\%fT_{>4 \times MIC}$)

Conclusions

CRRT affects the pharmacokinetics of ceftaroline, so dose adjustments are necessary. Doses approved to date are insufficient to achieve $PTA \geq 90\%$ for a high PK/PD target ($100\%fT_{>4 \times MIC}$) and $MIC \geq 2$ mg/L, which creates a need to consider higher total dosages or continuous infusion. Our results should be used with caution, given the scarce number of CRRT patients included in the model. Increasing the number of patients is a chance to integrate a total effluent flow rate during CRRT as a covariate, which may result in more precise dosage simulations and decreased model uncertainty.

References

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