

Total and unbound flucloxacillin population pharmacokinetics in patients with *Staphylococcus aureus* bloodstream infection

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Introduction

Target attainment of flucloxacillin in patients with *Staphylococcus aureus* bloodstream infections (BSI) is challenging due to the high inter-individual variability in pharmacokinetics, particularly in critically ill patients.

Although flucloxacillin is **highly protein-bound**, in a clinical setting it is the total concentration which is usually measured, with an **assumed unbound fraction of 5%**. Especially in **critically ill patients** with altered renal function and hypoalbuminemia, this might lead to **supratherapeutic levels**. A population pharmacokinetic (popPK) model can be used to optimize and individualize antibiotic dosing. The objective of this study was to develop a **flucloxacillin popPK model** for precision dosing, and to retroactively assess target attainment in patients with BSI.

Results

We included **178 total and unbound flucloxacillin concentrations of 49 patients, where 47% were critically ill**. The majority of patients (69%) were treated with flucloxacillin 12g qd. We found that the unbound fraction was higher compared to literature (5%) at 11.5% and 16.7% for non-critical and critically ill patients, respectively. A **one-compartment model with linear elimination** best described the concentration profiles. We improved model performance by incorporating the estimated glomerular filtration rate according to the Cockcroft-Gault equation (eGFR-GC), and albumin as covariates (Table 1). Dosing simulations revealed better target attainment for continuous compared to intermittent bolus infusion (Figure 1).

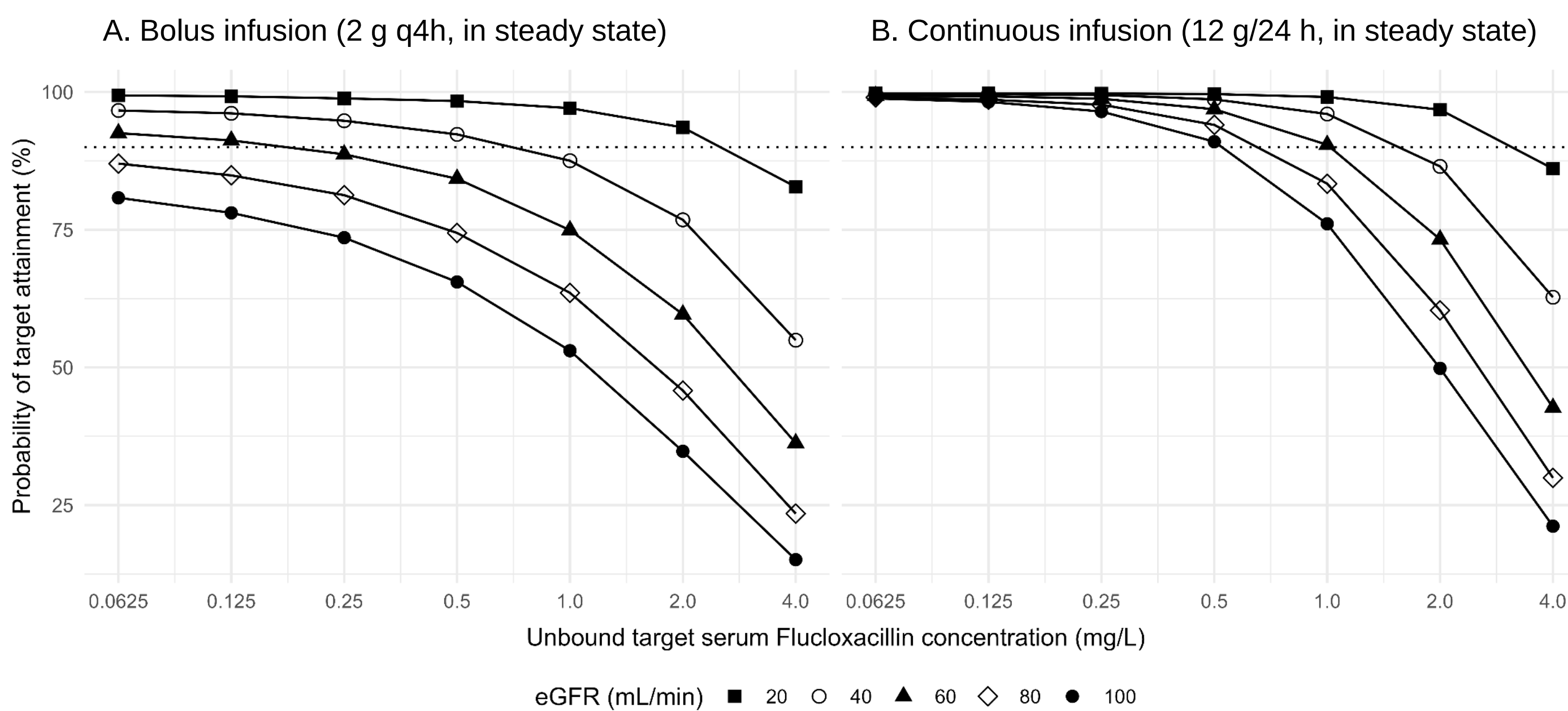


Figure 1: Probability of target attainment for flucloxacillin for different eGFRs and target unbound serum concentrations based on Monte Carlo dosing simulations.

Methods

We included hospitalized, adult, critically and non-critically ill patients with confirmed BSI in this single-centre, prospective, observational pharmacokinetic cohort study conducted at the University Hospital Basel, Switzerland. We measured both **mid-dose and trough level of total and unbound flucloxacillin concentrations following intermittent bolus administration** using HPLC-MS. We developed and validated a popPK model for total and unbound serum flucloxacillin, considering different models for protein binding. We used **Monte Carlo dosing simulations** to assess and compare target attainment (100% fT>MIC) for intermittent bolus and continuous infusion.

Conclusions

The base structural model underlying all analyses uses a **one compartment with linear elimination**, while other authors have proposed more elaborate configurations [1-3]. We believe this is due to the nature of flucloxacillin dosing schedules (short intervals of 2-8h), which do not capture slow elimination from deep compartments.

The identification of **eGFR-GC as one of the informative covariates** is plausible as flucloxacillin is **mainly eliminated by the kidneys** [4].

Serum albumin was the other informative covariate and was mainly responsible for the **determination of the ratio of unbound and total flucloxacillin concentration**. Preference should be given to measuring unbound flucloxacillin concentrations, as the actual unbound fractions may significantly exceed those calculated using an assumed fraction of 5%.

Other studies [5, 6] also showed potential **improvements in target attainment by using continuous infusions over intermittent bolus infusions**. Additionally, continuous infusion reduces peak concentrations and thus might decrease the risk of toxicity.

	Final joint model Estimate [%RSE]	Bootstrap analysis Median [95% CI]
Fixed effects		
$CL_{pop} \cdot I_{h-1}$	66.1 [11.6]	65.7 [50.7-83.8]
$V_{pop} \cdot I$	217.4 [12.3]	222.7 [168.8-286.2]
kd_{pop}	6.0 [8.2]	6.0 [5.0-7.2]
GFR_{CL}	1.1 [13.7]	1.1 [0.9-1.4]
$Albumin_{kb}$	1.6 [15.3]	1.6 [1.1-2.2]
Inter-individual variability (IIV)		
CL_{IIV}	0.7 [12.8]	0.7 [0.5-0.9]
V_{IIV}	0.6 [22.4]	0.6 [0.3-0.8]
kb_{IIV}	0.5 [13.2]	0.5 [0.3-0.6]
Inter-occasional variability (IOV)		
CL_{IOV}	0.3 [13.4]	0.3 [0.2-0.4]
V_{IOV}	0.5 [21.3]	0.4 [0.20-0.7]
kb_{IOV}	0.06 [141.6]	0.1 [0.05-0.2]
Residual proportional error		
Constant (a)		
Unbound	0.06 [26.0]	0.06 [0.0002-0.08]
Total	0.9 [29.3]	0.8 [0.01-1.2]
Proportional (b)		
Unbound	0.26 [11.09]	0.3 [0.2-0.3]
Total	0.12 [21.32]	0.1 [0.04-0.2]
Covariate Relationships		
CL	$CL_{pop} * \left(\frac{GFR}{70}\right)^{GFR_{CL}}$	
kb	$kb_{pop} * \left(\frac{Albumin}{20}\right)^{Albumin_{kb}}$	
Protein binding	$C_{bound} = kb \times C_{unbound}$ $C_{total} = C_{unbound} + C_{bound}$	

Table 1: Population parameter estimates.

CI: confidence interval; CL_{pop} : clearance; V_{pop} : volume of distribution; kb_{pop} : dissociation constant; GFR_{CL} : exponent for the allometrically scaled estimated glomerular filtration rate on clearance covariate; $Albumin_{kb}$: exponent for the allometrically scaled albumin on kb covariate; RSE: relative standard error [%RSE = 100 * (standard error/parameter estimate)].