

Do critically ill patients undergoing continuous renal replacement therapy require levofloxacin dosage adjustments? Levofloxacin PopPK model and dosage simulations based on retrospective data and developed using open-source R packages.

Arkadiusz Adamiszak^{1,2}, Agnieszka Bienert¹

¹Department of Pharmacology, Poznan University of Medical Sciences, Poland

²Doctoral School, Poznan University of Medical Sciences, Poland



Introduction

Levofloxacin is a third-generation fluoroquinolone with a broad spectrum, including gram-positive and -negative bacteria [1]. Currently, no dosing standards have been recommended by The European Committee on Antimicrobial Susceptibility Testing (EUCAST), and the doses proposed in the Stanford Health Care Antimicrobial Dosing Reference Guide seem to be insufficient for critically ill patients undergoing continuous renal replacement therapy (CRRT) [2,3]. This study aimed to develop a preliminary levofloxacin population pharmacokinetic (PopPK) model and investigate dosages for CRRT and non-CRRT intensive care unit (ICU) patients.

Methods

- Data were obtained retrospectively from 3 articles [4–6]
- PK data were extracted using WebPlotDigitizer [7]
- Critically ill adults were treated with 125 – 500 mg of levofloxacin per 24 – 48h in 0.5 – 1h infusions,
- PopPK modeling, SAEM algorithm, **nlmixr2** [8]
- Model selection was based on goodness-of-fit criteria:
 - Bayesian Information Criteria (BIC)
 - the objective function value (OFV) defined as $-2 \times \text{Log Likelihood}$
 - the precision of the parameter estimates (RSE%)
 - diagnostic plots
- One- and two-compartment models with linear elimination were tested
- Any available clinical variables were examined as potential covariates using a stepwise covariate model procedure (SCM)
- Simulations were performed in **rxode2** [9] and **posologyr** [10]
- Tested doses: 250/500/750/1000 mg in a 1h infusion every 24 (standard) and 12 (high) hours [2]
- For each combination, 2500 patients, as 50 patients in a group replicated 50 times, were simulated,
- PK/PD target = $fAUC_{0-24}/MIC \geq 80$ [11,12]
- The probability of target attainment (PTA) $\geq 90\%$ for MIC values between 0.0625 – 8 mg/L [11]
- The free fraction of levofloxacin was calculated based on a percentage (~35%) of protein binding from SmPC [13]

Results

We included 25 ICU adults and 77 plasma samples, of which 32 were from 16 CRRT patients. The median (range) of testing covariates for age was 57.0 years (23.0 – 76.0), and for weight was 95.6 kg (60.0 – 189.0) For CRRT patients, we tested creatinine clearance (ClCr) estimated by the Cockcroft-Gault formula (median = 77.7 mL/min and range = 55.0 – 235.0 mL/min) and creatinine serum (median = 1.0 mg/dL and range = 0.7 – 1.6 mg/dL) on non-CRRT patients' clearance ($CL_{non-CRRT}$). For CRRT patients, we tested the influence of blood flow rate (median = 9 L/h and range 5.4 – 12.0 L/h) and effluent flow rate (median = 1.5 and range 0.84 – 2.38 L/h) on CRRT patients' clearance (CL_{CRRT}).

Table 1. Decrease in OFV related to added covariates		
Model	$-2 \times \text{Log Likelihood}$	ΔOFV
2-compartment model with $CL_{non-CRRT}$ or CL_{CRRT}	149.91	–
2-compartment model with $CL_{non-CRRT}$ or CL_{CRRT} + ClCr on $CL_{non-CRRT}$	117.93	–31.98
2-compartment model with $CL_{non-CRRT}$ or CL_{CRRT} + ClCr on $CL_{non-CRRT}$ + CRRT on CL_{CRRT} (Final model)	108.62	–9.31

Table 2. Parameter estimations of the final model	
Parameters	Mean Estimate (%RSE)
	Final Model Estimates
$CL_{non-CRRT}$ (L/h)	4.51 (6.63)
ClCr on $CL_{non-CRRT}$	1.22
IIV on $CL_{non-CRRT}$ (CV%)	18.03
CL_{CRRT} (L/h)	2.23 (7.77)
IIV on CL_{CRRT} (CV%)	29.69
V_c (L)	35.01 (24.70)
IIV on V_c (CV%)	79.91
Q (L/h)	42.10 (22.49)
CRRT on Q	1.63
IIV on Q (CV%)	13.89
V_p (L)	46.46 (16.82)
IIV on V_p (CV%)	51.27
Proportional residual error (CV%)	7.72

$CL_{non-CRRT}$: non-CRRT patients clearance; CL_{CRRT} : CRRT patients clearance; ClCr, creatinine clearance; CRRT, continuous renal replacement therapy; CV%, coefficient of variation calculated as $\sqrt{\exp(\omega^2)} - 1 \times 100\%$; IIV, interindividual variability; V_c , central compartment volume; V_p , peripheral compartment volume; Q, inter-compartmental clearance

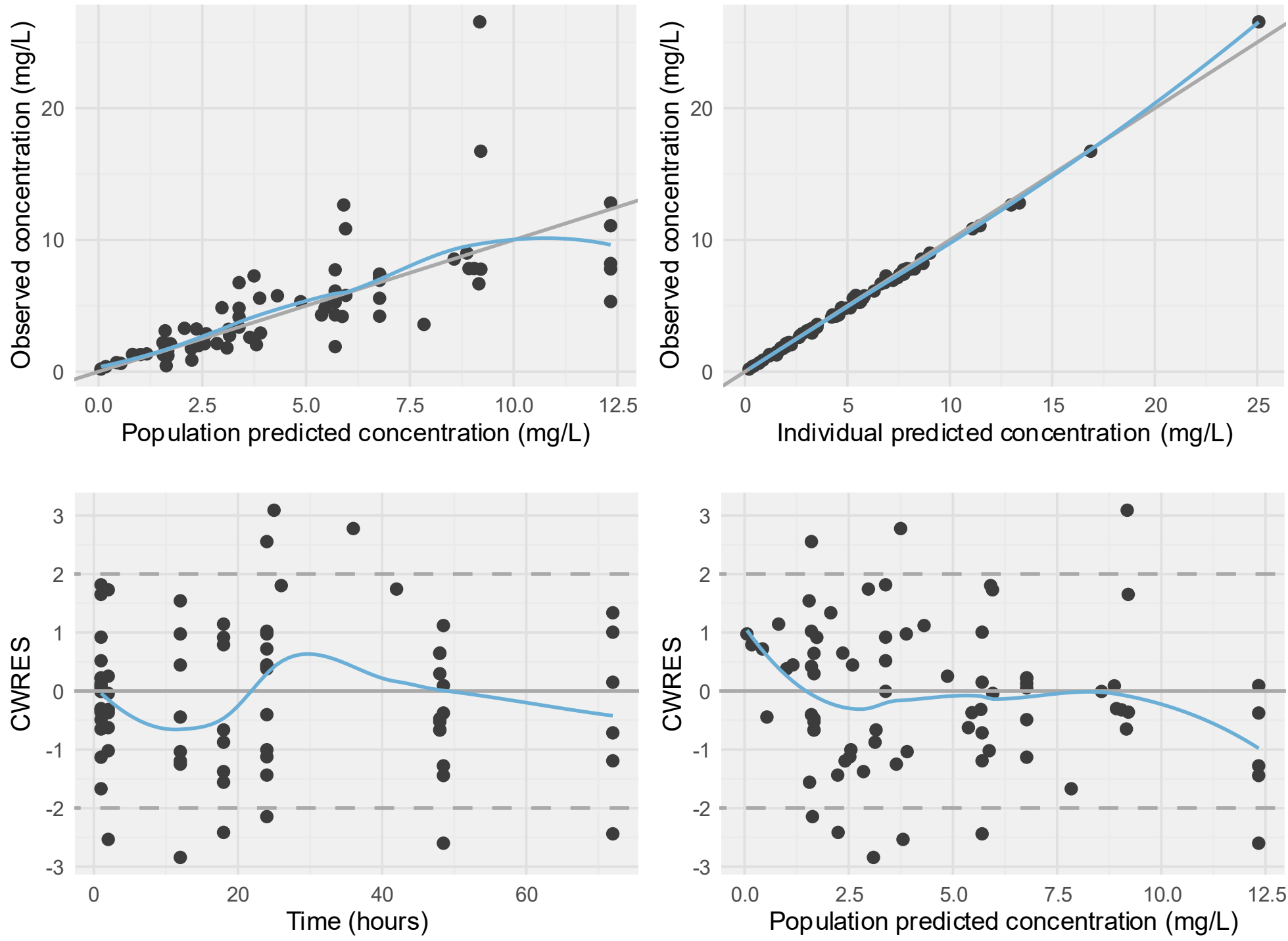


Figure 1. Goodness-of-fit plots of the final model. Concentration versus population predictions (Top left). Concentration versus individual predictions (Top right). Conditional weighted residuals versus time (Bottom left). Conditional weighted residuals (CWRES) versus population predictions (Bottom right).

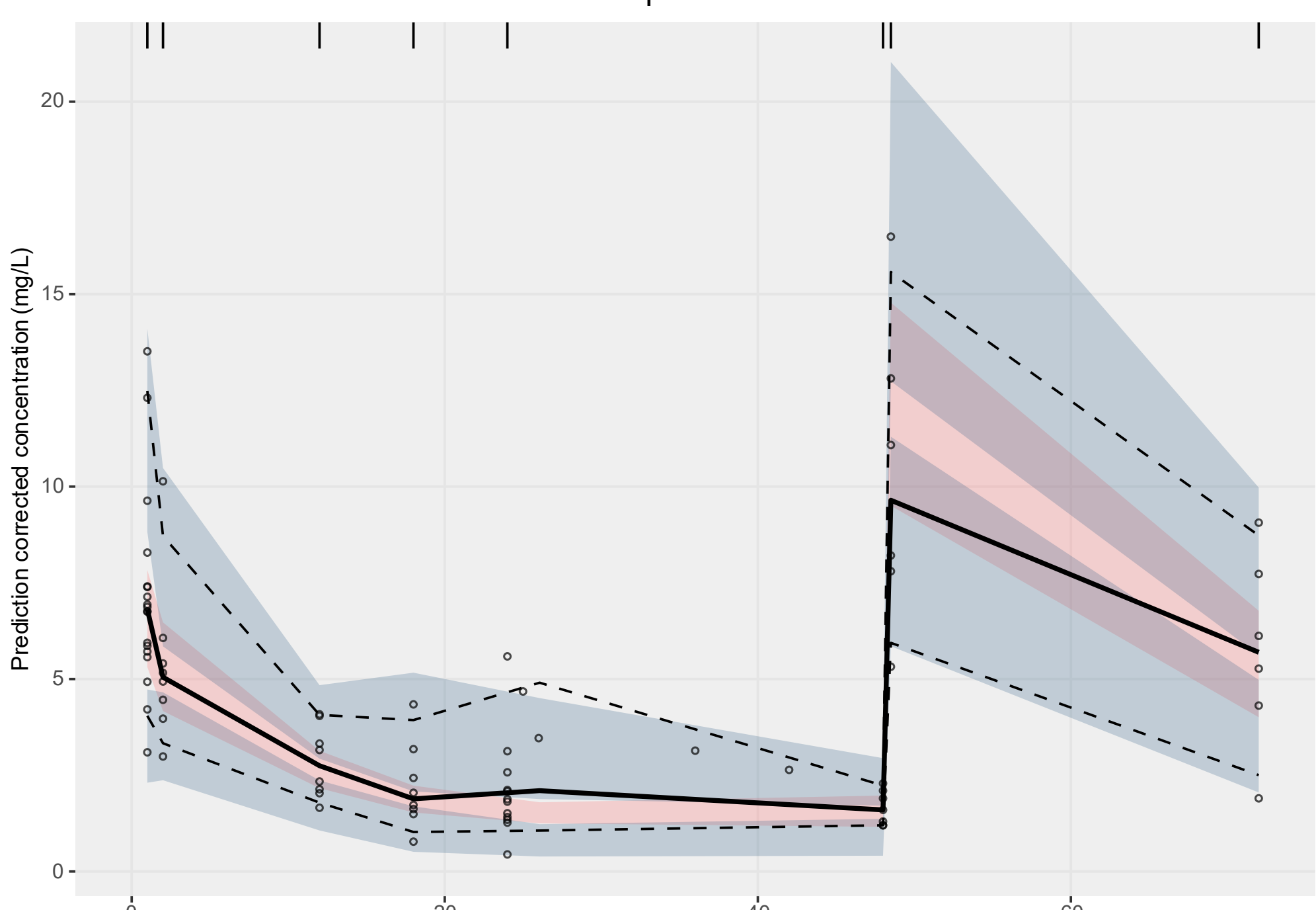


Figure 2. Prediction-corrected Visual Predictive Check

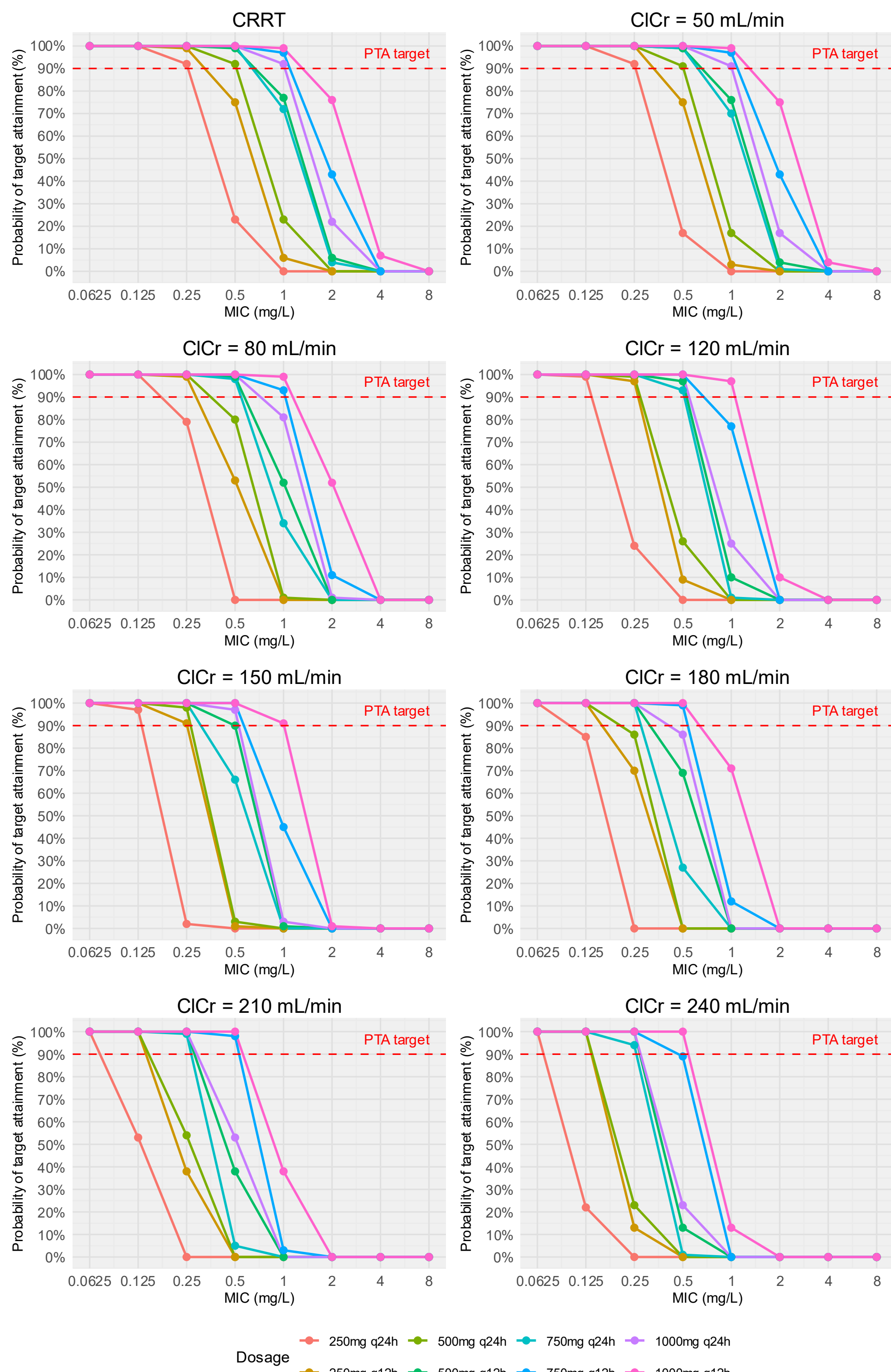


Figure 3. Probability of target attainment for $fAUC_{0-24}/MIC \geq 80$ PKPD target and 1h infusions

Conclusions

- There is a need to establish levofloxacin doses for CRRT and increased ClCr patients
- $MIC \geq 2$ mg/L should be considered resistance
- Higher than registered doses increase the risk of side effects and toxicity, which should be taken into account
- Our results should be used with caution, given the scarce number of patients and concentrations
- It is worth considering measuring effluent and plasma concentrations after CRRT in order to provide a mechanistic view of renal replacement therapy processes

References

- [1] Podder, V. et al. in StatPearls (StatPearls Publishing, 2025)
- [2] EUCAST Clinical breakpoints and dosages 2024 (v 14.0) (https://www.eucast.org/clinical_breakpoints)
- [3] Stanford Antimicrobial Safety & Sustainability Program (<https://med.stanford.edu/bugsanddrugs/guidebook.html>)
- [4] Sánchez Navarro, A. et al. Clin Pharmacokinet 44, 627–635 (2005)
- [5] Guenter, S. G. et al. Pharmacotherapy 22, 175–183 (2002)
- [6] Malone, R. S. et al. Antimicrob Agents Chemother 45, 2949–2954 (2001)
- [7] Rohatgi, A. WebPlotDigitizer User Manual Version 4.6 (2022)
- [8] Fidler, M. et al. (2024) NlmiXr2
- [9] Fidler, M. L. et al. (2025) Rxode2
- [10] Leven, C. et al. (2025) Posologyr
- [11] Setiawan, E. et al. Sci Rep 12, 8930 (2022)
- [12] Roberts, J. A. et al. Antimicrob Agents Chemother 60, 1459–1463 (2016)
- [13] Tavanic (SmPC)

