Unraveling the drivers of antimicrobial pharmacokinetic variability in individuals with obesity and hospitalized patients with multimorbidity

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Part III

Antimicrobial pharmacokinetics in hospitalized patients with multimorbidity

CHAPTER 5

5

Pooled population pharmacokinetics analysis and dose recommendations for ciprofloxacin in Intensive Care Unit patients with obesity

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Abstract

Introduction: Recent studies have explored the influence of obesity and of critical illness on ciprofloxacin pharmacokinetics. However, variation across the subpopulation of individuals with obesity admitted to the ICU with varying renal function remains unexamined. This study aims to characterize ciprofloxacin pharmacokinetics in ICU patients with obesity and provide dose recommendations for this special population.

Methods: Individual patient data of 34 ICU patients with obesity (BMI >30kg/m^2) from 4 studies evaluating ciprofloxacin pharmacokinetics in ICU patients were pooled and combined with data from a study involving 10 individuals with obesity undergoing bariatric surgery. All samples were collected after intravenous administration. Non-linear mixed effects modelling and simulation were used to develop a population pharmacokinetic model and describe ciprofloxacin exposure in plasma. Model based dose evaluations were performed using a PK/PD target of AUC/MIC>125.

Results: The data from patients with BMI ranging from 30.2 – 58.1 were best described by a two-compartment model with first order elimination and a proportional error model. Inclusion of CKD-EPI as a covariate on clearance reduced inter-individual variability from 57.3% to 38.5% ($p<0.001$). Neither body weight nor ICU admission significantly influenced clearance or volume of distribution.

Conclusions: Renal function is a viable predictor for ciprofloxacin clearance in ICU patients with obesity, while critical illness and body weight do not significantly alter clearance. As such body weight and critical illness do not need to be accounted for when dosing ciprofloxacin in ICU patients with obesity. Individuals with CKD-EPI >60ml/min/1.73m^2 may require higher dosages for the treatment of pathogens with MIC ≥0.25mg/L.

Introduction

Ciprofloxacin is a fluoroquinolone used for empirical and targeted therapy of infections caused by a wide range of gram-negative pathogens in intensive care unit (ICU) patients. It is cleared by glomerular filtration, tubular secretion, trans-epithelial intestinal secretion and hepatic metabolism[1,2]. Enterobacterales, with minimal inhibitory concentrations (MIC) ranging from 0.064 – 0.25 mg/L are commonly targeted with ciprofloxacin[1]. The pharmacokinetic/pharmacodynamic (PK/PD) index that correlates best with clinical – and microbiological cure is the area under the curve (AUC) divided by the MIC[3]. There is a growing body of evidence that standard ciprofloxacin dosing regimens do not result in sufficient exposure to achieve a PK/PD target of AUC/MIC>125, especially for pathogens with MIC of 0.5 mg/L like P. *Aeruginosa*[4-7]. Guidelines currently recommend a dosing regimen of 400 mg q8h in ICU patients with extension of the dose interval for individuals with impaired renal function, with a maximum daily dose being 1600 mg[1,2,8].

Ciprofloxacin clearance and volume of distribution were found to be uninfluenced by body weight in (morbidly) obese individuals with body weights up to 212 kg undergoing bariatric surgery[9]. Previous studies in patients admitted to the ICU however show that renal function was associated with ciprofloxacin clearance albeit with considerable remaining variability[4-7,10]. It is therefore likely that dose modification is needed in obese ICU patients with varying renal function. The objective of this study was to characterize ciprofloxacin pharmacokinetics in ICU patients with obesity and varying renal function and explore dose optimization for this special population.

Materials & Methods

Patients and data

Data of total drug concentrations obtained in ICU patients with obesity (BMI ≥30kg/m2) treated with intravenous ciprofloxacin from 4 cohorts, all from university hospitals, were pooled[4-7]. Patients were excluded if they received renal replacement therapy or had Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) ≤20ml/min (without renal replacement therapy). Cohort 1 was a prospective observational study with 12 obese participants (147 samples) at Radboud University hospital (Nijmegen, the Netherlands)[6], Cohort 2 was a prospective observational study with 10 patients (86 samples) with obesity at Amsterdam UMC (Amsterdam, the Netherlands)[7], Cohort 3 was a prospective observational cohort with 4 participants (20 samples) with obesity at Erasmus University Hospital (Rotterdam, the Netherlands, NTR5632)[5], Cohort 4 was a prospective observational cohort with 8 participants (44 samples) with obesity at Copenhagen university hospital (Rigshospitalet, (Copenhagen, Denmark,

NCT02240277)[4]. The patients' data were simultaneously modelled with data from a cohort of 10 obese individuals undergoing bariatric surgery (106 samples) who received intravenous ciprofloxacin (NTR6058)[9].

Data on patient characteristics (sex, age, measures of body weight, height, BMI, serum creatinine, SOFA score and length of ICU stay at initiation of therapy) and ciprofloxacin treatment (dose, time and rate of administration) were collected. Estimated glomerular filtration rate was calculated using CKD-EPI, Modification of Diet in Renal Diseases (MDRD) and Cockcroft-Gault (CG)[11-13]. CKD-EPI and MDRD were de-indexed for body surface area (BSA) by multiplying the respective values by BSA/1.73. BSA was calculated using the Du Bois/ Du Bois formula[14].

Ethics

The local medical ethical committee Nijmegen provided a waiver for informed consent for participants in cohort 1 due to the observational nature of the study6. Participants in cohort 2 – 4 and the control group gave written informed consent for inclusion in the original studies[4,5,7,9]. All studies were conducted according to the Good Clinical Practices and the declaration of Helsinki[15,16]. Before sharing, all previously collected data was anonymized by the corresponding authors of the respective studies with ethics approval for data sharing provided where required in the local jurisdiction.

Pharmacokinetic analysis

All concentration-time data from the 4 cohorts and the control group were simultaneously analyzed by non-linear effects modelling using first-order conditional estimation with interaction (NONMEM; v7.4.0)[17].

A one- and two-compartment model with first-order elimination was tested to describe ciprofloxacin pharmacokinetics. Additive, proportional and combined residual error models were evaluated. Log-normal distribution of interindividual variability (IIV) was assumed. In the covariate analysis associations between model parameters and potential covariates (ICU admission, CKD-EPI, CKD-EPI$_{de\text{-}indexed}$, MDRD, MDRD$_{de\text{-}indexed}$, Sex, Age, TBW, LBW, ABW) were tested. Continuous covariates were implemented in the model using Equation (1) and (2), respectively. P_i and P_p represent the individual and population parameter estimates, Y represents the exponent for a power function and Z represents the slope of a linear covariate relationship. For dichotomous covariates different parameters were estimated for the respective subgroup. If multiple creatinine observations were available for an individual, renal function estimators were assessed as a time varying covariate with linear interpolation. Time varying covariates were analyzed by plotting conditional weighted residual (CWRES) versus the time varying covariate. Inter occasion variability was tested on clearance as this parameter is most

influential on ciprofloxacin exposure in plasma. An occasion was defined as 24 hours assuming dose adjustments are made on a daily basis.

$$P_i = P_p \times \left(\frac{COV}{COV_{standard}}\right)^Y \quad (1)$$

$$P_i = P_p \times \left(1 + Z \times (COV - COV_{standard})\right) \quad (2)$$

During model development, changes in objective function value (OFV), reduction in IIV and residual error, Goodness of Fit (GOF) and CWRES plots split for quantiles of covariates and diagnostic plots were used to compare models. Internal model validation was done using prediction corrected visual predictive check (pcVPC), normalized prediction distribution errors (NPDE) plots, GOF-plots, CWRES-plots and sampling importance resampling (SIR).

Exposure in plasma was simulated for 20.000 virtual ICU patients with obesity based on the final model. CKD-EPI was uniformly distributed between 20 and 120 ml/min/1.73m^2. The probability of target attainment (PTA) in the first 24 hours after initiation of therapy for pathogens with minimal inhibitory concentration (MIC) ranging from 0.064mg/L to 0.5mg/L was simulated using a pharmacokinetic/pharmacodynamic target of AUC/MIC>125, a PTA of 90% was considered acceptable since exposure is evaluated in the first 24 hours of therapy and consequently plasma concentration may increase during subsequent days of therapy[1,3]. Exposure for six different dosing regimens was investigated with daily intravenous doses ranging from 400 – 2400mg.

Results

Population characteristics

We included 44 individuals with obesity of which 34 were admitted to the ICU and 10 in the control group. We analyzed 403 samples of which 297 and 106 were collected in the ICU patients and the control group, respectively. In the ICU population 106 samples (36%), 125 samples (42%), 33 samples (11%) and 33 samples (11%) were collected on day 1, 2, 3 and >day 3 of initiation of ciprofloxacin therapy, respectively. Length of ICU stay (LOS) and SOFA score median (IQR) were 2 (1 – 3.5) days and 7.5 (6 – 10.5), respectively. Weight and renal function (assessed by CKD-EPI) ranged from 75 – 167 kg and 21-115 ml/min/1.73m^2 in the ICU patients and from 107 – 212 kg and 72 – 115ml/min/1.73m^2 in the control group. Further details on population characteristics are shown in Table 1. SOFA score was available for 28 patients (82%), all other data was complete for all patients.

Table 1: Baseline population demographics

	ICU patients with obesity (n=34)	Control group with obesity (n=10)
Age	58 (33 – 80)	50 (36 – 57)
Sex, male, n(%)	22 (65%)	5 (50%)
Weight (kg)	110 (75 – 167)	139 (107 – 212)
Lean body weight (kg)	69 (42 – 95)	67 (52 – 102)
Body surface area (m^2)	2.3 (1.7 – 2.8)	2.5 (2.1 – 3.2)
Body mass index (kg/m^2)	35.5 (30.2 – 54.5)	44.9 (38.5 – 58.1)
Number of days at ICU at initiation of therapy (median, IQR)	2 (1 – 3.5)	n.a.
SOFA score at initiation of therapy (median, IQR)[a]	7.5 (6 – 10.5)	n.a.
Serum creatinine (µmol/L)	119 (51 – 298)	76 (56 – 90)
CKD-EPI ($ml/min/1.73m^2$)	54 (21 – 115)	94 (72 – 115)
De-indexed CKD-EPI (ml/min)	75 (23 – 163)	134 (86 – 184)
MDRD ($ml/min/1.73m^2$)	49 (19 – 145)	86 (65 – 119)
De-indexed MDRD ($ml/min/1.73m^2$)	66 (22 – 108)	123 (78 – 191)
No of samples	297	106
Average no of samples per individual	8.7	10.6

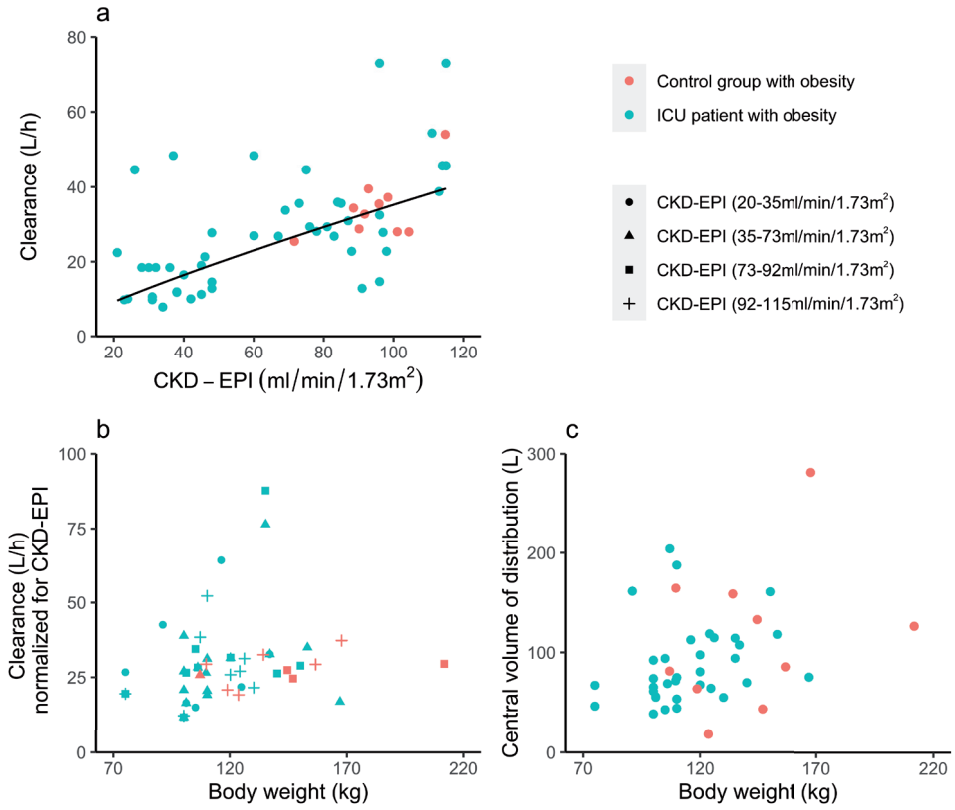
Data are shown as median (range) unless otherwise specified. Renal function was recorded at baseline. CKD-EPI: Chronic Kidney Disease Epidemiology collaboration, ICU: Intensive care unit. IQR: Interquartile range. MRD: Modification of diet in renal disease, SOFA: Sequential Organ Failure Assessment.
[a] based on data from 28 patients (82%)

Pharmacokinetic analysis

The data were best described by a two-compartment model with first-order elimination and a proportional error model. CKD-EPI was identified as a significant covariate on ciprofloxacin clearance as IIV reduced from 57.1% to 38.5% (dOFV -66.4, $p<0.001$). Individual values for clearance versus CKD-EPI for the base model are shown in Figure 1a. The different renal function estimators yielded a similar reduction of OFV and IIV on clearance, moreover diagnostic plots did not show pronounced differences. We implemented CKD-EPI in the final pharmacokinetic model as this parameter is most widely used in clinical practice. Our model could not be improved by inclusion of bodyweight as a covariate on clearance (exponent 0.136, dOFV -0.2, $p>0.05$, no improvement in GOF) or volume of distribution (exponent 0.8, dOFV -1.7, $p>0.05$, no improvement in GOF).

The GOF-plot, pcVPC (split for quantiles of CKD-EPI) and NPDE for the final model and diagnostic plots for renal function estimators of the base model are shown in Figure S1 – S4.

Figure 1



The individual values for clearance versus renal function (CKD-EPI) from the base model are shown in panel a. The black line indicates the covariate relation as implemented in the final model.
Individual values for clearance and volume of distribution versus total body weight for the final model are shown in panel b and c and indicate no statistically significant trend with bodyweight. The individual values for clearance in panel b are normalized for CKD-EPI at baseline (by $CL_{norm,\,i} = CL_i / (CKD_i$, *baseline* $/73)^{0.833}$*). The shape of the datapoints in panel b indicates the quantile of renal function at baseline.*

The model could not be improved by including a measure of bodyweight or (critical) illness (ICU admission, SOFA score, length of ICU stay) as a covariate on clearance or volume of distribution. Individual values of clearance (normalized for CKD-EPI) and volume of distribution versus total body weight for the final model are shown in Figure 1b and 1c illustrating there are no statistically significant trends with increasing body weight or ICU admission. The parameter estimates and SIR 95% confidence interval for the final model are presented in table 2. The model code and template for the dataset are provided in the supplementary material.

Table 2: Parameter estimates of the population pharmacokinetic model

Parameter	Base model (%RSE)	Final model (%RSE)	SIR 95% CI based on the final iteration of 5000 samples/ 1000 resamples
Fixed effects			
CL (L/h)	24.3 (8.3)		
$CL = CL_{CKD\text{-}EPI} * (CKD/73)^{X}$			
$CL_{CKD\text{-}EPI}$		27.1 (5.2)	24.5 – 29.9
X		0.833 (15.8)	0.616 – 1.05
V_c (L)	81.7 (14.4)	82.5 (14.1)	64.6 – 102.0
V_p (L)	121 (8.5)	115 (8.6)	98.7 – 133.5
Q (L/h)	60.2 (14.8)	59.1 (19)	51.7 – 70.9
Interindividual variability (%)[a,b]			
CL	57.1 (10.3)	38.5 (11.9)	31.3 – 45.2
V_c	64 (19.7)	65.9 (17.7)	42.1 – 76.6
V_p	44.8 (18.7)	38.3 (16.3)	27.0 – 49.0
Covariance $(CL/V_c)^c$		0.132	0.07 – 0.21
Residual variability (%)			
Proportional error [d]	16.8 (8.3)	16.3 (8.6)	14.9 – 18.1
OFV	-428.0	-494.4	

The parameter estimates are shown with the relative standard error. CI confidence interval, CL systemic clearance, CKD-EPI estimated glomerular function rate (ml/min/1.73m^2), OFV objective function value, Q intercompartmental clearance, RSE residual standard error, SIR sampling importance resampling, V_c central volume of distribution, V_p peripheral volume of distribution.

[a]: η-shrinkage of the final model: CL 3%, V_c 14%, V_p 28%

[b]: Calculated as: $\sqrt{(e^{\omega^2} - 1)}$

[c]: Correlation coefficient (RSE): 59.1% (18.7%)

[d]: ε-shrinkage: 11%

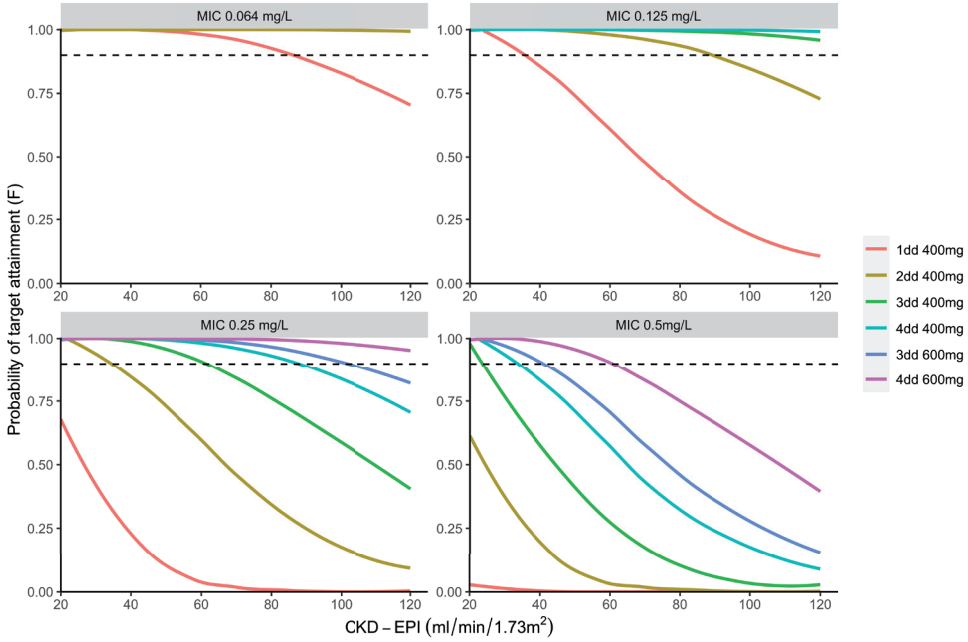
Model based dose evaluations

The probability of target attainment versus renal function for various dosing regimens split for pathogens with MIC ranging from 0.064mg/L to 0.5mg/L is shown in figure 2. This figure illustrates that the standard dosing regimen of ciprofloxacin 400mg q8h for individuals with CKD-EPI >30ml/min/1.73m^2 and with an increased dose interval of q12h for individuals with CKD-EPI <30 ml/min/1.73m^2 provides exposure in ICU patients with obesity that is sufficient to reach PTA >90% for all pathogens with MIC 0.064 – 0.125mg/L. For the treatment of pathogens with MIC 0.25mg/L, individuals with CKD-EPI >45ml/min/1.73m^2 fail to achieve this PK/PD target on day 1 of therapy although this target may be reached on day 2 of therapy as shown in Figure S5. A dosing regimen of

400mg ciprofloxacin q6h may provide PTA>90% for individuals with CKD-EPI 60 – 90ml/min/1.73m^2.

To evaluate safety of the simulated dosing regimens, the median and 90th percentile exposure versus renal function for the respective dosing regimens are shown in Figure S6, in which $AUC_{24\text{-}48h}$ is shown as highest exposure that will be attained during therapy. The median exposures for individuals with CKD-EPI 20-30ml/min/1.73m^2 receiving 400mg q12h, CKD-EPI 30-60ml/min/1.73m2 receiving 400mg q8h, and CKD-EPI 60-90 ml/min/1.73m2 receiving 400mg q6h are similar with 57 – 73 mg*h/L, 53 – 85 mg*h/L and 52 – 72 mg*h/L, respectively.

Figure 2



The probability of target attainment on the first day of therapy (using a target of AUC/MIC>125) versus renal function for various intravenous ciprofloxacin dosing regimens split for minimal inhibitory concentration (MIC) of the causative pathogen. The dashed line represents a target probability of target attainment of 90%.

Discussion

In this pooled pharmacokinetic analysis we show that CKD-EPI was the most important parameter for the prediction of ciprofloxacin clearance in individuals with obesity admitted to the ICU. Interestingly, both body weight and admission to the ICU did not influence the estimation of clearance and volume of distribution in this study and therefore dose adjustment solely based on body weight in ICU patients with obesity is not needed. Model based dose evaluation shows that current dosing regimens may not ensure target attainment for the treatment of pathogens with MIC ≥0.25mg/L in individuals with renal function >60 ml/min/1.73m^2.

To our knowledge this is the first study to evaluate ciprofloxacin exposure in a large cohort of individuals with obesity admitted to the ICU. A strength of our study is the use of pooled data from 4 university hospital ICU's in 2 countries which is an approach that could be used more widely, facilitating research in individuals with obesity in the ICU. The inclusion of a wide range in body weight and renal function allows discrimination of the predictive performance of renal function estimators at extreme bodyweight. In our study population of ICU patients with obesity the difference in predictive performance of MDRD and CKD-EPI was minimal and therefore the CKD-EPI was retained in the final model as this estimator of glomerular filtration rate is used most frequently in clinical practice. Our finding that clearance is correlated with renal function is consistent with previous studies on ciprofloxacin pharmacokinetics in the general ICU population[4,6,7].

ICU patients may initially be hemodynamically unstable, receive aggressive fluid resuscitation, have augmented renal clearance or acute kidney injury[18]. As a result, the potential influence of ICU admission on ciprofloxacin pharmacokinetics in individuals with obesity is expected to be most severe in the first 2 days of therapy. In our study 78% of all PK observation in ICU patients were collected within this critical period which is an important strength. In our study, ICU admission, SOFA score and Length of Stay at the ICU were not predictive for clearance although some patients with obesity admitted to the ICU showed high clearance despite a relatively low CKD-EPI. A possible explanation may be that creatinine is a late marker for changes in renal function. Initially, an increase in renal clearance may not yet be reflected in low serum creatinine.

Our study, which aimed at capturing the influence of body weight on ciprofloxacin pharmacokinetics in ICU patients with obesity, does not show improvement of the model after inclusion of body weight as a covariate. Therefore, fixed dosing in ICU patients with obesity with a dose modification based on renal function seems appropriate although previous studies on ciprofloxacin PK in ICU patients covering a narrower weight range assumed an influence of weight on clearance and volume of distribution by applying

a-priori allometric scaling which may result in higher dosages in ICU patients with obesity[6,7]. Moreover, a loading dose is not warranted in individuals with obesity as body weight was not associated with alterations in volume of distribution. Previously, Roberts *et al.* identified an association between body weight and volume of distribution in a study on ciprofloxacin pharmacokinetics in patients with septic shock for which a power-function with an exponent as low as 0.75 was found[4]. The finding that body weight is not correlated with clearance or volume of distribution in patients with obesity admitted to the ICU is consistent with our previous study in otherwise healthy individuals with obesity undergoing bariatric surgery[9].

Some limitations may apply to our results as individuals with obesity and severely impaired renal function (CKD-EPI <20ml/min/1.73m^2) or on renal replacement therapy were excluded from our study. Therefore, our results cannot be extrapolated to this population. Also, data on SOFA score are not complete which may hinder judgement of external validity of our results although SOFA score and length of ICU stay versus CWRES plots did not show any significant trend.

Ciprofloxacin treatment in patients admitted to the ICU usually consists of ciprofloxacin 400mg q8h with an increase in dosing interval to q12h for individuals with CKD-EPI <30ml/min/1.73m^2. Using this dosing approach, PTA is sufficient for the treatment of pathogens with MIC <0.25mg/L irrespective of renal function, body weight and ICU admittance. The results of our study do show that treatment of pathogens with MIC ≥0.25mg/L remains challenging, especially for individuals with CKD-EPI >60ml/min/1.73m^2 as increasingly higher dosages may be needed to achieve target attainment while experience with doses beyond 400mg q8h is limited. A need for ciprofloxacin doses beyond 1200mg/day in critically ill patients on the first day of therapy using a cut-off MIC of 1.0mg/L as was demonstrated by Roggeveen *et al.*[19]. The upper limit of safety for ciprofloxacin exposure is not well defined and it thus remains unclear if dosages beyond the current guidelines, which may be needed to achieve the PK/PD target for the treatment of pathogens with MIC ≥0.25mg/L in patients with CKD-EPI >60ml/min/1.73m^2 can be applied safely. Daily doses of up to 2000mg have been applied in children with cystic fibrosis although exposure remained relatively low as a result of increased clearance in this population[20].

A prospective clinical study testing renal function based dose individualization is needed to elucidate if doses beyond 1200mg/day lead to improved clinical outcomes in individuals with CKD-EPI >60ml/min/1.73m^2 as the AUC/MIC>125 PK/PD target is not extensively investigated.

Conclusions

Ciprofloxacin plasma concentration in individuals with obesity may be influenced by renal function but not by body weight or ICU admission. For pathogens with MIC 0.064mg/L – 0.125mg/L target attainment can be achieved with daily doses of 1200mg. The currently applied dosing regimens may not result in sufficient exposure for the treatment of pathogens with MIC ≥0.25mg/L in individuals with CKD-EPI >60ml/min/1.73m^2.

Disclosures

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References

1 EUCAST Ciprofloxacin: Rationale for EUCAST Clinical Breakpoints. [accessed 8-9-2023] https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Rationale_documents/Ciprofloxacin_Rationale_Document_2.0_20210101.pdf.

2 Ciprofloxacin prescribers information. [accessed 8-9-2023] https://www.accessdata.fda.gov/drugsatfda_docs/Label/2016/019537s086lbl.pdf

3 Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother. 1993;37(5):1073-81.

4 Roberts JA, Alobaid AS, Wallis SC, Perner A, Lipman J, Sjöval F. Defining optimal dosing of ciprofloxacin in patients with septic shock. J Antimicrob Chemother. 2019;74(6):1662-9.

5 Abdulla A, Rogouti O, Hunfeld NGM, Endeman H, Dijkstra A, van Gelder T, et al. Population pharmacokinetics and target attainment of ciprofloxacin in critically ill patients. Eur J Clin Pharmacol. 2020-7;76(7):957-67.

6 Gieling EM, Wallenburg E, Frenzel T, de Lange DW, Schouten JA, ten Oever J, et al. Higher Dosage of Ciprofloxacin Necessary in Critically Ill Patients: A New Dosing Algorithm Based on Renal Function and Pathogen Susceptibility. Clin Pharmacol Ther. 2020;108:770-4.

7 Guo T, Abdulla A, Koch BCP, van Hasselt JGC, Endeman H, Schouten JA, et al. Pooled Population Pharmacokinetic Analysis for Exploring Ciprofloxacin Pharmacokinetic Variability in Intensive Care Patients. Clin Pharmacokinet. 2022-6;61(6):869-79.

8 guideline for empirical antibacterial therapy of sepsis in adults [accessed 8-9-2023]. Available from: https://swab.nl/exec/file/download/144

9 van Rhee KP, Smit C, Wasmann RE, van der Linden PD, Wiezer R, van Dongen HPA, et al. Ciprofloxacin pharmacokinetics after oral and intravenous administration in (morbidly) obese and non-obese individuals; a prospective clinical study . Clinical pharmacokinetics. 2022;61:1167–75 .

10 van Zanten ARH, Polderman KH, van Geijlswijk IM, van der Meer GYG, Schouten MA, Girbes ARJ. Ciprofloxacin pharmacokinetics in critically ill patients: a prospective cohort study. J Crit Care. 2008-9;23(3):422-30.

11 Inker, L.E. et al. Chronic Kidney Disease Epidemiology Collaboration. New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race. N Engl J Med. 2021;385(19):1737-49.

12 Levey AS. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Annals Intern Med. 2006;145:247-54.

13 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

14 Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. Archives of Internal Medicine. 1916;17:863-71.

15 WMA. Declaration of Helsinki - Ethical principles for medical research involving human subjects WMA; 2013.

16 International Council for harmonization of technical requirements for pharmaceuticals for human use. Good clinical practice. 2016.

17 Beal S, Sheiner L, Boeckmann A. NONMEM Users Guide - Part IV. NONMEM Project Group University of California at San Francisco: 2018.

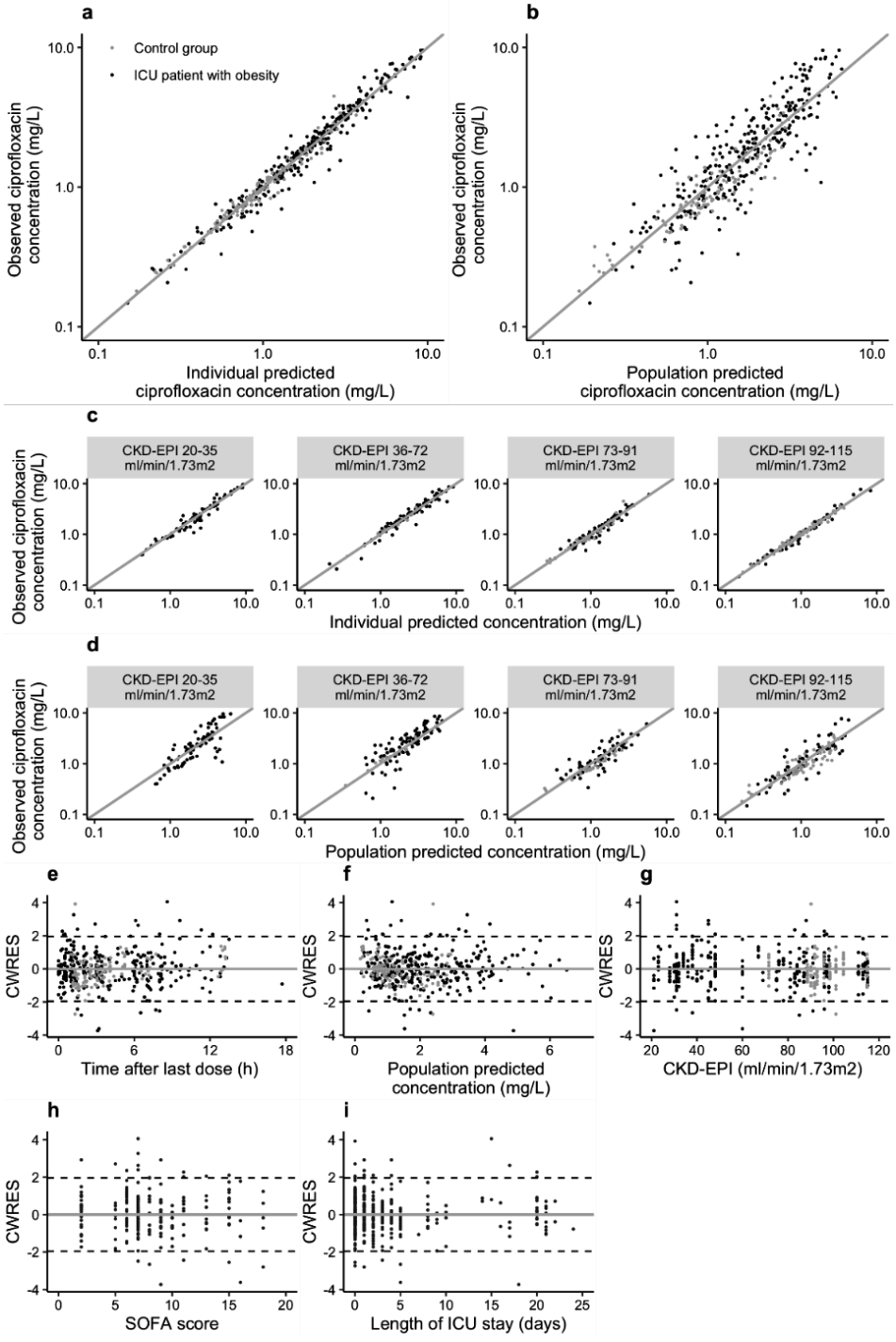
18 Alobaid A S, Hites M, Lipman J, Taccone F S, Roberts J A. Effect of obesity on the pharmacokinetics of antimicrobials in critically ill patients: a structured review. Int J Antimicrob Agents. 2016;47(4):259-68

19 Roggeveen L F, Guo T, Fleuren LM, Driessen R, Thoral P, van Hest RM et al. Right dose, right now: bedside, real-time, data-driven, and personalised antibiotic dosing in critically ill patients with sepsis or septical shock - a two-centre randomised clinical trial. Critical care. 2022;26:265.

20 Rubio T T, Miles M V, Lettieri J T, Kuhn R J, Echols R M, Church D A. Pharmacokinetic disposition of sequential intravenous/oral ciprofloxacin in pediatric cystic fibrosis patients with acute pulmonary exacerbation. Pediatr. Infect Dis. J.1997;16(1):112–117.

Supplementary material

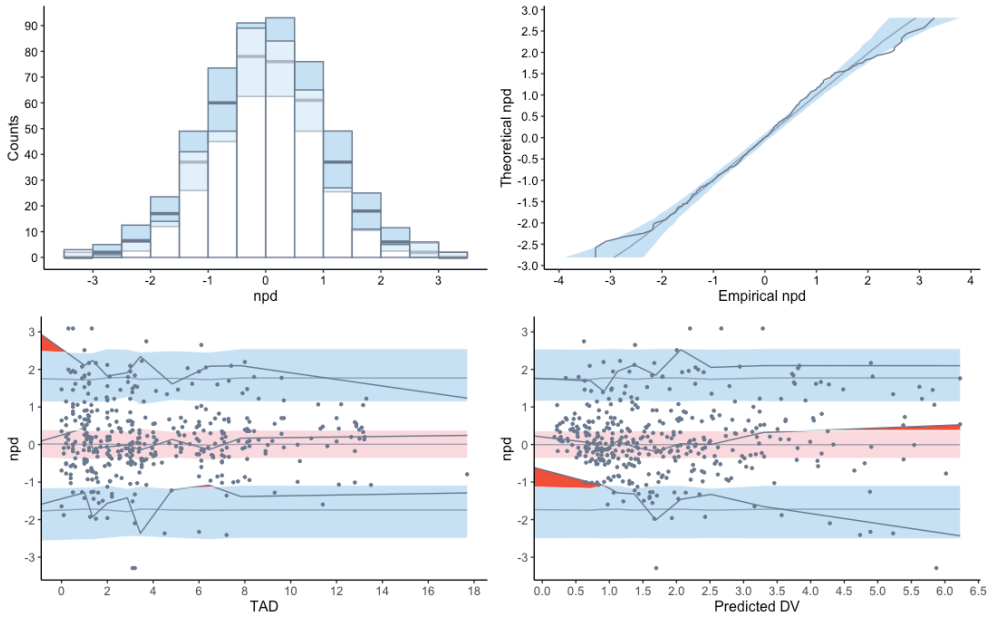
Figure S1: Diagnostic plots for the final pharmacokinetic model



Diagnostic plots of the final model for critically ill individuals with obesity (black dots) and the obese control group (grey dots). The grey line represents the line of identity and the dashed lines represent the 1.96, – 1.96 interval indicating the range within which 95% of the observations are expected to fall. CWRES: conditional weighted residuals CKD-EPI: chronic kidney disease epidemiology collaboration.

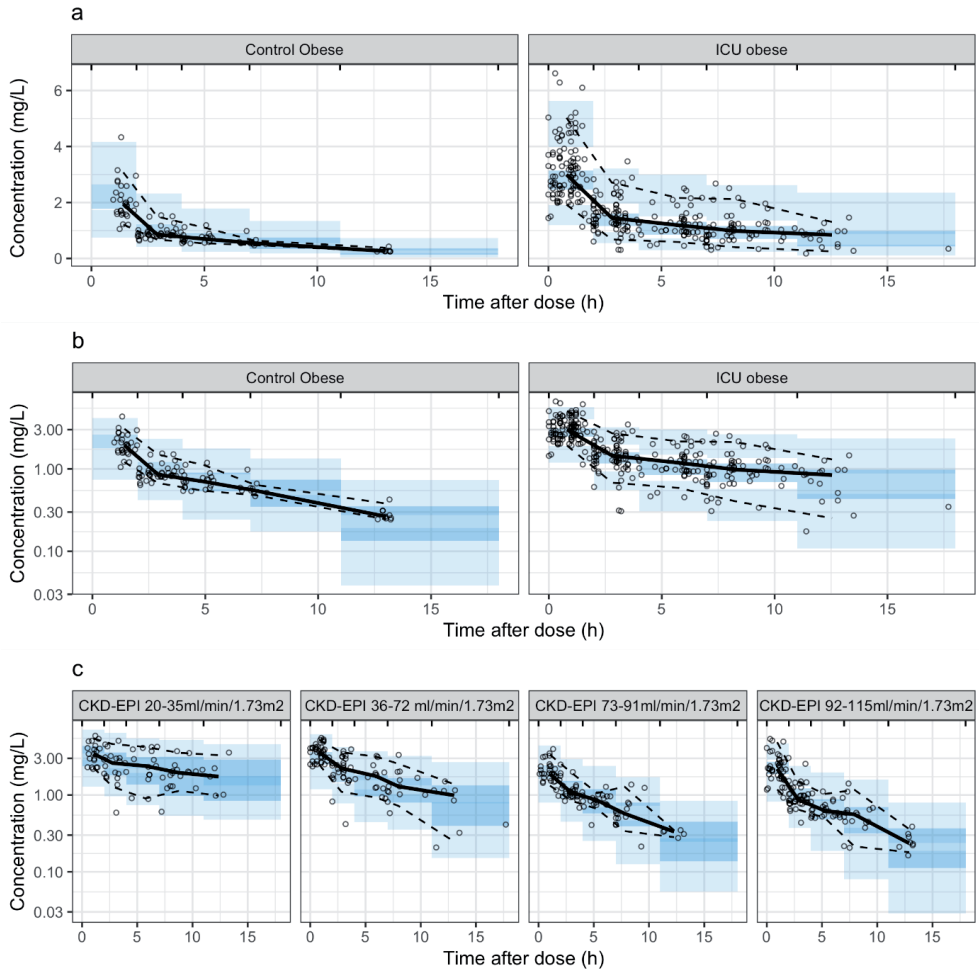
a) *Individual predicted concentration vs observed ciprofloxacin concentration*
b) *Population predicted concentration vs observed ciprofloxacin concentration*
c) *Individual predicted concentration vs observed ciprofloxacin concentration split for CKD*
d) *Population predicted concentration vs observed ciprofloxacin concentration split for CKD*
e) *Time after last dose versus CWRES*
f) *Population predicted ciprofloxacin concentrations versus CWRES*
g) *Renal function (estimated by CKD-EPI) versus CWRES*
h) *Sequential organ failure assessment (SOFA) score versus CWRES*
i) *Length of ICU stay (days) at start of therapy versus CWRES*

Figure S2: Normalized prediction distribution error of the final pharmacokinetic model



The NPDE shows no model misspecification as the data overlap the theoretical histogram (upper left panel), data points in the QQ plot follow the theoretical and are within the 95% confidence interval (upper right panel). Data points are scattered around the null line without a significant trend with time after dose (TAD) or predicted concentration (lower left and right panels).

Figure S3: Prediction corrected visual predictive check of the final pharmacokinetic model



Prediction corrected visual predictive check of the final model

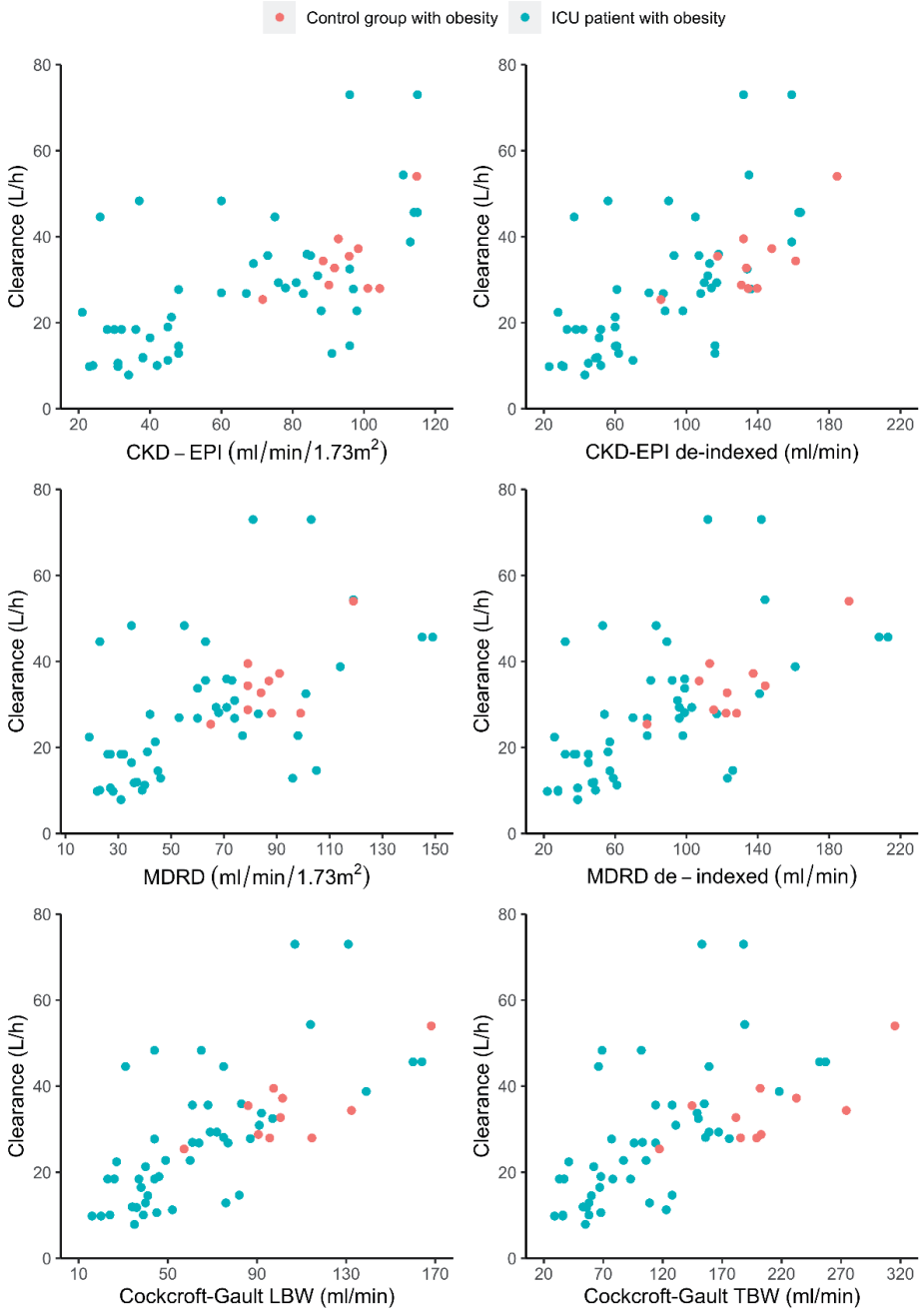
a) *stratified by subgroup on a linear scale*

b) *stratified by subgroup on a logarithmic scale*

c) *stratified by CKD-EPI on a logarithmic scale*

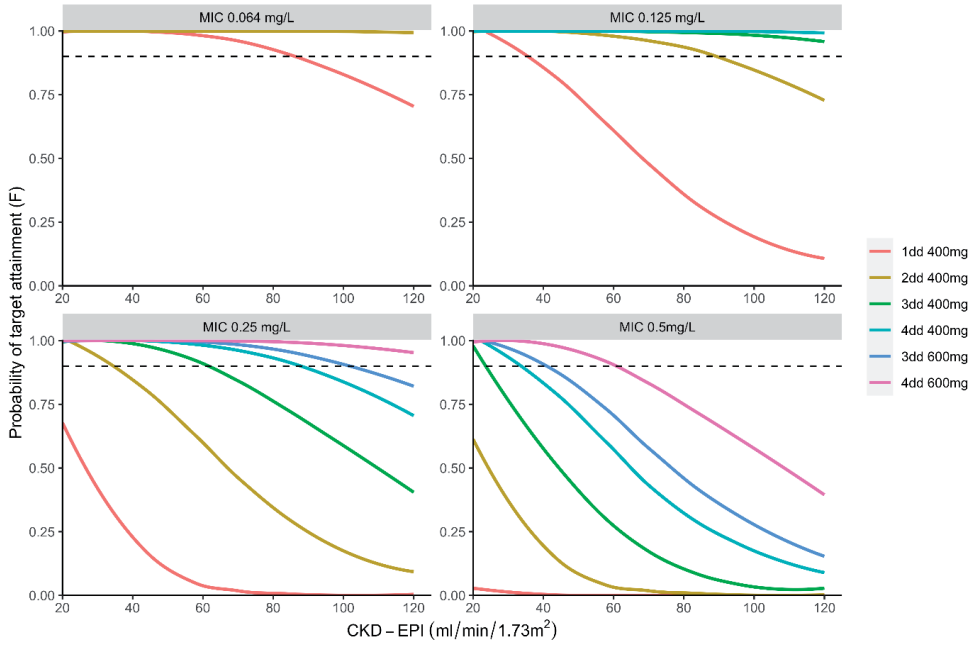
The observed data are shown as circles with the median and 2.5th and 97.5th percentile of the observed data shown as a solid black line and the upper and lower dashed lines, respecitvely. The blue areas represent the 95% confidence interval of the simulated median (dark blue) and 5th and 95th percentile (light blue) of the simulated concentrations based on 1000 simulations of the original dataset. Vertical lines at the top of the panels represent the bins.

Figure S4: Renal function estimators versus clearance for the base model



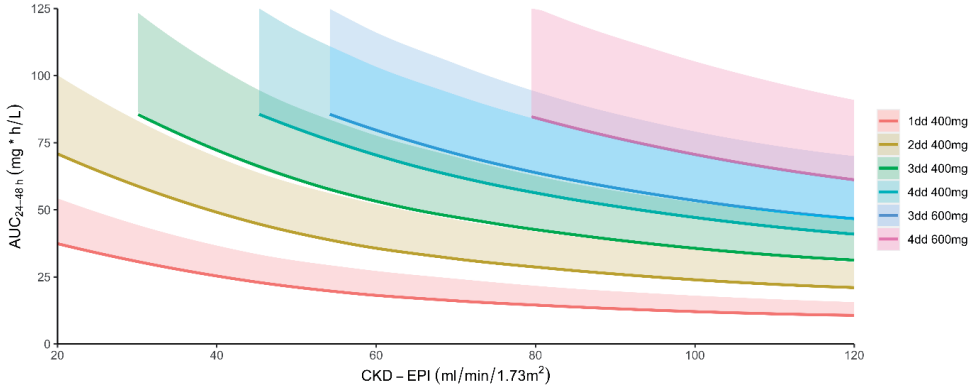
Mean individual values for clearance versus renal function estimators for the base model showing similar correlation for the renal function estimators. Patients admitted to the intensive care unit and the control group are shown in teal and red, respectively.

Figure S5: Probability of target attainment after the first day of therapy



The probability of target attainment after the first day of therapy (using a target of AUC/MIC>125) versus renal function for various intravenous ciprofloxacin dosing regimens split for minimal inhibitory concentration (MIC) of the causative pathogen. The dashed line represents a target probability of target attainment of 90%.

Figure S6: Median and 90th percentile exposure for the simulated dosing regimens for varying renal function



*Exposure versus renal function for the ciprofloxacin dosing regimens after the first day of therapy ($AUC_{24\text{-}48h}$) is shown as median (line) and median-90th percentile (shaded area). The shaded area is only plotted if the 90th percentile AUC is <125 mg*h/L which corresponds with the highest exposure reached after 3dd 400mg in an individual with CKD-EPI 30ml/min/1.72m^2.*
This reference exposure is not exceeded in ICU patients with obesity with CKD-EPI >46ml/min/1.73m^2, >55ml/min/1.73m^2 and >80ml/min/1.72m^2 after administration of 4dd 400mg, 3dd 600mg and 4dd 600mg, respectively.

NONMEM control stream for the final model

```
;; 1. Based on: run01
;; 2. Description: Ciprofloxacin PK in ICU patients with obesity
;; x1. Author: Koen van Rhee
;; 3. Label: Ciprofloxacin ICU
$PROBLEM Ciprofloxacin ICU
$INPUT ID TIME AMT RATE DV CMT EVID MDV CKD ICU
$DATA dataset.csv IGNORE=@

$SUBROUTINE ADVAN6 TOL9
$MODEL COMP=(CENT) COMP=(PERI)
$PK

; DISPOSITION MODEL
TVCL = THETA(1) * ((CKD/73)**THETA(5))
CL = TVCL * EXP(ETA(1))          ; CLEARANCE
V1 = THETA(2) * EXP(ETA(2))      ; CENTRAL VOLUME OF DISTRIBUTION
Q = THETA(3) * EXP(ETA(3))       ; INTERCOMPARTIMENTAL CLEARANCE
```

```
TVV2= THETA(4)
V2 = TVV2 * EXP(ETA(4))              ; PERIPHERAL VOLUME OF DISTRIBUTION
K12 = Q/V1
K21 = Q/V2
K10 = CL/V1                          ; ELIMINATION RATE CONSTANT

S1 = V1
S2 = V2

$DES
DADT(1)=-K12*A(1)+K21*A(2)-K10*A(1)
DADT(2)=K12*A(1)-K21*A(2)

$ERROR
IPRED = A(1)/S1 ; individual prediction
Y = IPRED + IPRED*EPS(1) + EPS(2)
IRES = DV-IPRED

$THETA
 27.1 ; CL
 82.5 ; V1
 59.1 ; Q
 115 ; V2
 0.833 ; CKD ON CL

$OMEGA BLOCK(2)
 0.138               ; IIV CL
 0.132 0.361         ; IIV V1
$OMEGA
 0 FIX               ; IIV Q
 0.137               ; IIV V2

$SIGMA
 0.0262 ; Proportional error PK
 0 FIX ; Additional error PK
$ESTIMATION METHOD=1 INTER MAXEVAL=999 NOABORT SIGL=9 NSIG=3 PRINT=5
POSTHOC
$COVARIANCE PRINT=E
$TABLE ID TIME DV MDV EVID IPRED ETAS(1:LAST) CWRES ONEHEADER NOPRINT
FILE=sdtab01
```