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Abstract

Recent studies have explored the influence of obesity and critical illness on ciprofloxacin pharmacokinetics. However, variation across the subpopulation of individuals with obesity admitted to the intensive care unit (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. Individual patient data of 34 ICU patients with obesity (BMI >30 kg/m^2) from four 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 modeling and simulation were used to develop a population pharmacokinetic model and describe ciprofloxacin exposure in plasma. Model-based dose evaluations were performed using a pharmacokinetic/pharmacodynamic target of AUC/MIC >125. The data from patients with BMI ranging from 30.2 to 58.1 were best described by a two-compartment model with first-order elimination and a proportional error model. The inclusion of Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) as a covariate on clearance reduced inter-individual variability from 57.3% to 38.5% ($P < .001$). Neither body weight nor ICU admission significantly influenced clearance or volume of distribution. 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 >60 mL/min/1.73 m^2 may require higher dosages for the treatment of pathogens with minimal inhibitory concentration ≥ 0.25 mg/L.

Keywords

ciprofloxacin, dosing, ICU patients, obesity, pharmacokinetics

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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 (MICs) ranging from 0.064 to 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 *Pseudomonas aeruginosa*.[4–7] Guidelines currently recommend a dosing regimen of 400 mg q8h in ICU patients with an extension of the dosing 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 and Methods

Patients and Data

Data of total drug concentrations obtained in ICU patients with obesity (BMI $\geq$ 30 kg/m^2) treated with intravenous ciprofloxacin from four 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) $\leq$ 20 mL/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] and 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 modeled 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, Sequential Organ Failure Assessment [SOFA] score, and length of ICU stay at the initiation of therapy) and ciprofloxacin treatment (dose, time, and rate of administration) were collected. The 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 study.[6] Participants in cohorts 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 were 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 four cohorts and the control group were simultaneously analyzed by non-linear effects modeling 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$_{\text{de-indexed}}$, MDRD, MDRD$_{\text{de-indexed}}$, Sex, Age, Total body weight, Lean Body Weight[18], Adjusted Body Weight[19]) were tested. Continuous covariates were implemented in the model using Equations (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 h assuming dose adjustments are made on a daily basis.

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

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

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/1.73 m^2. The probability of target attainment (PTA) in the first 24 h after initiation of therapy for pathogens with minimal inhibitory concentration (MIC) ranging from 0.064 to 0.5 mg/L was simulated using a PK/PD target of AUC/MIC > 125; a PTA of 90% was considered acceptable since exposure is evaluated in the first 24 h 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 to 2400 mg.

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 days 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 to 167 kg and 21 to 115 mL/min/1.73 m^2 in the ICU patients and from 107 to 212 kg and 72 to 115 mL/min/1.73 m^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 were complete for all patients.

Table 1. Baseline Population Demographics of Patients with Obesity

	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/1.73 m^2)	54 (21-115)	94 (72-115)
De-indexed CKD-EPI (ml/min)	75 (23-163)	134 (86-184)
MDRD (mL/min/1.73 m^2)	49 (19-145)	86 (65-119)
De-indexed MDRD (mL/min/1.73 m^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.
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; ICU, intensive care unit; MDRD, 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, $P < .001$). 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 PK model as this parameter is most widely used in clinical practice. Our model could not be improved by the inclusion of body weight as a covariate on clearance (exponent 0.136, dOFV −0.2, $P > .05$, no improvement in GOF) or volume of distribution (exponent 0.8, dOFV −1.7, $P > .05$, no improvement in GOF).

The GOF-plot, pcVPC (split for quantiles of CKD-EPI), and NPDE for the final model and diagnostic

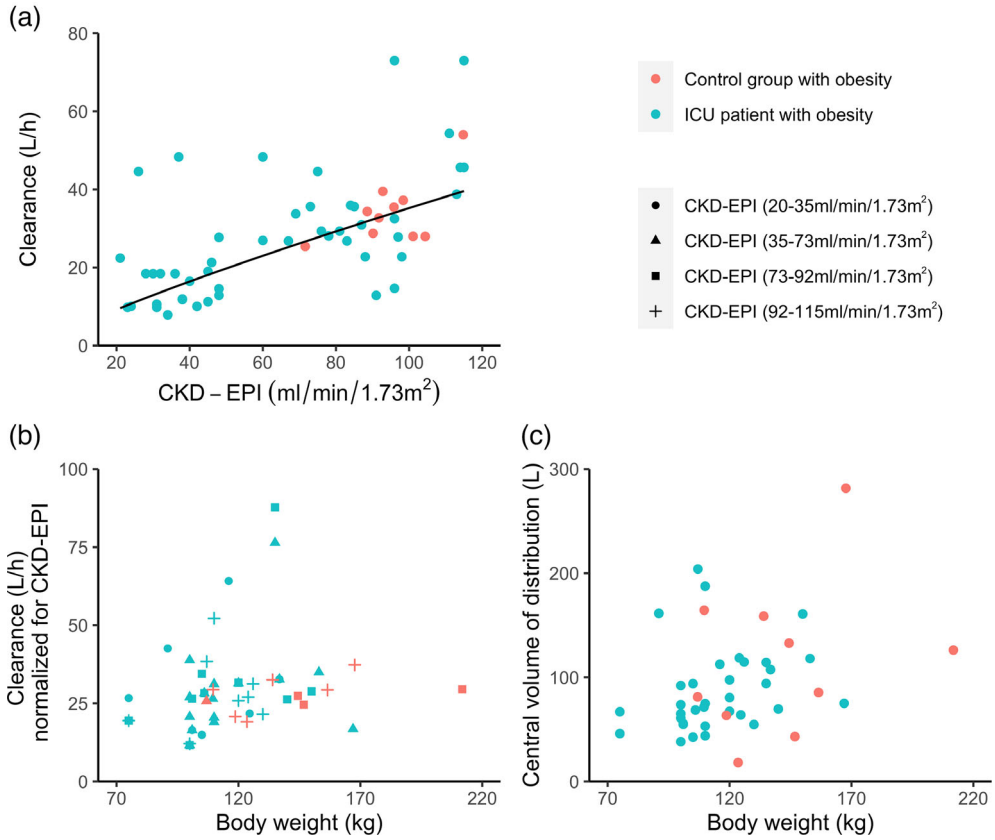

Figure 1. The individual values for clearance versus renal function (CKD-EPI) from the base model are shown in panel (a). The black line indicates the covariate relation as implemented in the final model. Individual values for clearance and volume of distribution versus total body weight for the final model are shown in panels (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 data points in panel (b) indicates the quantile of renal function at baseline.

plots for renal function estimators of the base model are shown in Figures S1–S4.

The model could not be improved by including a measure of body weight 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,c 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 materials.

Model-Based Dose Evaluations

The probability of target attainment versus renal function for various dosing regimens split for pathogens with MIC ranging from 0.064 to 0.5 mg/L is shown in Figure 2. This figure illustrates that the standard dosing regimen of ciprofloxacin 400 mg q8h for individuals with CKD-EPI >30 mL/min/1.73 m^2, with an increased dose interval of q12h for individuals with CKD-EPI <30 mL/min/1.73 m^2, provides exposure in ICU patients with obesity that is sufficient to reach PTA >90% for all pathogens with MIC 0.064-0.125 mg/L. For the treatment of pathogens with MIC 0.25 mg/L, individuals with CKD-EPI >45 mL/min/1.73 m^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 400 mg ciprofloxacin q6h may provide PTA >90% for individuals with CKD-EPI 60-90 mL/min/1.73 m^2.

To evaluate the 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 the highest exposure that will be attained during therapy. The median exposures for individuals with CKD-EPI 20-30 mL/min/1.73 m^2 receiving 400 mg q12h, CKD-EPI 30-60 mL/min/1.73 m^2 receiving 400 mg q8h, and CKD-EPI 60-90 mL/min/1.73 m^2 receiving 400 mg q6h are similar with 57-73, 53-85, and 52-72 mg*h/L, respectively.

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/1.73 m^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%.

Discussion

In this pooled PK 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 $\geq$0.25 mg/L in individuals with renal function $>$60 mL/min/1.73 m^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 four university hospital ICUs in two countries, which is an approach that could be used more widely to facilitate research on 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 body weight. 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 have acute kidney injury.[20] 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 observations 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 in the model after the inclusion of body weight as a covariate. Therefore, fixed dosing in ICU patients with obesity

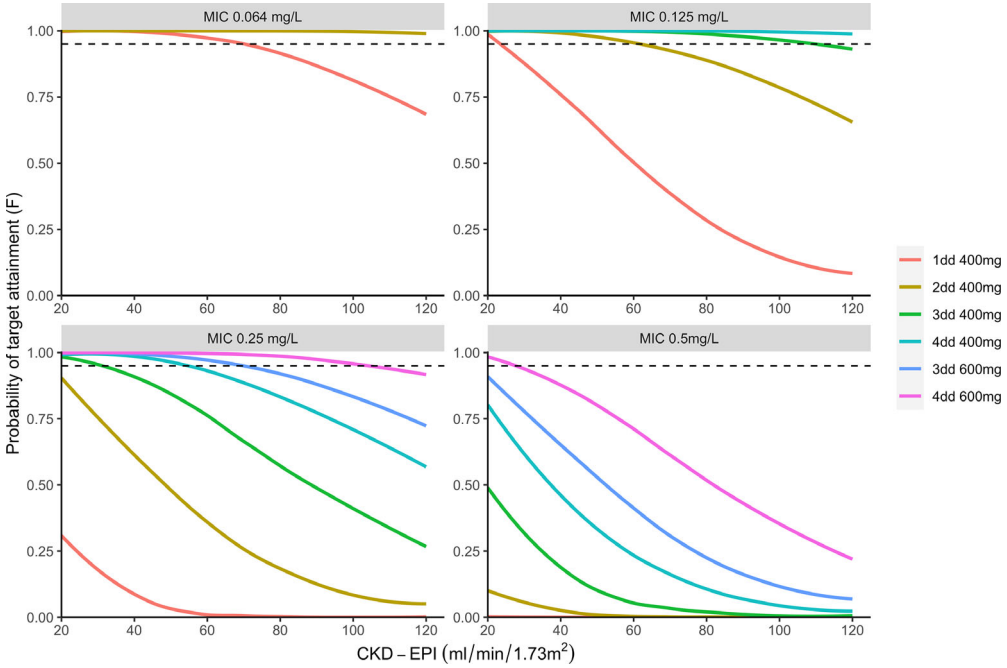

Figure 2. The probability of target attainment on the first day of therapy (using a target of AUC/MIC>125) versus renal function for various intravenous ciprofloxacin dosing regimens split for minimal inhibitory concentration (MIC) of the causative pathogen. The dashed line represents a target probability of target attainment of 90%.

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 the 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 <20 mL/min/1.73 m^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 the judgment of the 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 400 mg q8h with an increase in dosing interval to q12h for individuals with CKD-EPI <30 mL/min/1.73 m^2. Using this dosing approach, PTA is sufficient for the treatment of pathogens with MIC <0.25 mg/L irrespective of renal function, body weight, and ICU admittance. The results of our study do show that treatment of pathogens with MIC ≥0.25 mg/L remains challenging, especially for individuals with CKD-EPI >60 mL/min/1.73 m^2 as increasingly higher dosages may be needed to achieve target attainment while experience with doses beyond 400 mg q8h is limited. A need for ciprofloxacin doses beyond 1200 mg/day in critically ill patients on the first day of therapy using a cut-off MIC of 1.0 mg/L was demonstrated by Roggeveen *et al.*[21] The upper limit of safety for ciprofloxacin exposure is not well defined, and it thus remains unclear if dosages beyond the current guidelines that may be needed to achieve the PK/PD target for the treatment of pathogens with MIC ≥0.25 mg/L in patients with CKD-EPI >60 mL/min/1.73 m^2 can be applied safely. Daily doses of up to 2000 mg have been applied in children with cystic fibrosis although exposure remained relatively low as a result of increased clearance in this population.[22]

A prospective clinical study testing renal function-based dose individualization is needed to elucidate if doses beyond 1200 mg/day lead to improved clinical outcomes in individuals with CKD-EPI >60

mL/min/1.73 m^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 0.064-0.125 mg/L, target attainment can be achieved with daily doses of 1200 mg. The currently applied dosing regimens may not result in sufficient exposure for the treatment of pathogens with MIC ≥0.25 mg/L in individuals with CKD-EPI >60 mL/min/1.73 m^2.

Author Contributions

Conceptualization: CK, RB, PvdL, and KvR. Data preparation: AA, RvH, KvR, FS, JR, PE, and RB. Data analysis: KvR, supervised by CK, RB, and PvdL. Writing original draft: KvR. Writing—review and editing: All authors. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

RJMB declares no interest with regard to this work. Outside of this work, he has served as a consultant to and has received unrestricted research grants from Astellas Pharma Inc., F2G, Gilead Sciences, Merck Sharpe and Dohme Corp., Mundipharma Inc., and Pfizer Inc. All payments were invoiced by Radboud University Medical Center. PDvdL declares membership of the compliance committee of STIZON and is treasurer of the Dutch Working Party on Antibiotic Policy (SWAB). JAR would like to acknowledge funding from the Australian National Health and Medical Research Council for a Centre of Research Excellence (APP2007007) and an Investigator Grant (APP2009736) as well as an Advancing Queensland Clinical Fellowship.

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Data Availability Statement

Data from the pooled studies are available at reasonable request from the respective corresponding authors.

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Supplemental Information

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