

# Higher Dosage of Ciprofloxacin Necessary in Critically Ill Patients: A New Dosing Algorithm Based on Renal Function and Pathogen Susceptibility

Emilie M. Gieling<sup>1,2,†</sup>, Eveline Wallenburg<sup>1,†</sup>, Tim Frenzel<sup>3</sup>, Dylan W. de Lange<sup>4</sup>, Jeroen A. Schouten<sup>3,5,6</sup>, Jaap ten Oever<sup>6,7</sup>, Eva Kolwijck<sup>6,8</sup>, David M. Burger<sup>1,6</sup>, Peter Pickkers<sup>3</sup>, Rob ter Heine<sup>1</sup> and Roger J. M. Brüggemann<sup>1,6,\*</sup>

The objective of the present study was to develop a dosing algorithm for ciprofloxacin based on both renal function and pathogen susceptibility in critically ill patients. In this observational prospective multicenter pharmacokinetic study, a total of 39 adult intensive care unit patients receiving ciprofloxacin were included. On two occasions a total of 531 samples of ciprofloxacin were collected. Renal function is a significant covariate on ciprofloxacin clearance. A dose of 400 mg every 12 hours was sufficient to reach the preestablished target of area under the curve (AUC) in relation to the minimum inhibitory concentration (MIC) ( $AUC/MIC > 125$ ) in patients with an estimated glomerular filtration rate (eGFR)  $< 130$  mL/min and an infection caused by a pathogen with an MIC  $\leq 0.125$  mg/L. For patients with infections caused by pathogens with an MIC  $\geq 0.5$  mg/L and eGFR  $> 100$  mL/min, doses up to 600 mg four times daily or more were estimated to be required. This study provides a new dosing algorithm for ciprofloxacin in critically ill patients. In order to achieve adequate target attainment, the dosing of ciprofloxacin should be based on renal function and the MIC of the causative pathogen. Higher doses than the standard licensed dose are necessary to obtain target attainment for less susceptible pathogens and patients with high renal clearance. In the setting of impaired renal function, a daily dose of 400 mg (which is currently recommended) will not result in adequate target attainment for less susceptible pathogens.

## Study Highlights

### WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ There exists great variability in ciprofloxacin clearance in critically ill patients. Currently, instructions for ciprofloxacin dose adjustments based on renal function are inconsistent. It remains unclear what dosage should be given in critically ill patients.

### WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study proposes a dosing algorithm for ciprofloxacin based on renal function and pathogen susceptibility in critically ill patients.

### WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ High ciprofloxacin dosages (i.e., up to 2,400 mg daily) are estimated to be required for patients with augmented renal clearance (estimated glomerular filtration rate  $> 130$  mL/min) and infections caused by pathogens with an MIC  $\geq 0.25$  mg/L.

### HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ We propose an essential change in the dosing algorithm of ciprofloxacin for critically ill patients based on renal function and pathogen susceptibility that could result in better treatment outcome of this vulnerable population.

<sup>1</sup>Department of Pharmacy, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands; <sup>2</sup>Department of Clinical Pharmacy, Division Laboratories, Pharmacy and Biomedical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands;

<sup>3</sup>Department of Intensive Care, Radboud University Medical Center, Nijmegen, The Netherlands; <sup>4</sup>Department of Intensive Care and Dutch Poisons Information Center, University Medical Center Utrecht, Utrecht, The Netherlands; <sup>5</sup>Department of Intensive Care, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands; <sup>6</sup>Radboud Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, The Netherlands; <sup>7</sup>Department of Internal Medicine, Radboud University Medical Center, Nijmegen, The Netherlands; <sup>8</sup>Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, The Netherlands. \*Correspondence: Roger J. M. Brüggemann ([roger.bruggemann@radboudumc.nl](mailto:roger.bruggemann@radboudumc.nl))

<sup>†</sup>These authors contributed equally to this work.

Received January 20, 2020; accepted March 29, 2020. doi:10.1002/cpt.1855

Ciprofloxacin is one of the most commonly prescribed antimicrobial drugs for patients admitted to the intensive care unit (ICU), used for both empirical and targeted therapy for a broad range of infections. Intravenous ciprofloxacin is typically administered in dosages of 400 mg twice daily. Ciprofloxacin is primarily eliminated (50–60%) by glomerular filtration and tubular secretion.<sup>1</sup> It is recommended that dose and/or frequency are reduced in the setting of impaired renal function.<sup>1,2</sup> Previous pharmacokinetic (PK) studies of ciprofloxacin in critically ill patients showed substantial variability in clearance, most likely driven by variation in renal function.<sup>3,4</sup> Correct estimation of renal function is difficult especially in critically ill patients with unstable renal function and altered muscle mass.<sup>5</sup> Despite its limitations, glomerular filtration rate (GFR)-calculations based on creatinine are currently the most-used method to estimate renal function to guide antimicrobial dosing. The use of combined renal function markers serum cystatin C and creatinine make the estimated GFR (eGFR) less dependent on changes in muscle mass.<sup>5</sup> This may result in an improved estimation of GFR and thus a better approximation of ciprofloxacin clearance.

The antimicrobial efficacy of ciprofloxacin is driven by the area under the curve (AUC) in relation to the minimum inhibitory concentration (MIC) of the causative microorganism (AUC/MIC). For ciprofloxacin, an AUC/MIC ratio of 125 has been found to be necessary for both microbiological clearance and clinical cure.<sup>6</sup> This might be easily reached with the licensed dose for pathogens with a low MIC, such as *Escherichia coli* with an epidemiological cutoff value of 0.064 mg/L.<sup>7</sup> Yet, for critically ill patients infected with pathogens with higher MICs such as *Pseudomonas aeruginosa*, higher dosages are required.<sup>5,8</sup> A maximum tolerated dose or maximum tolerated concentration is not defined for ciprofloxacin.

Considering the variability of ciprofloxacin clearance in critically ill patients and the conflicting instructions on dose adjustments based on renal function, it remains unclear what dosage should be given in critically ill patients. To resolve this issue we conducted a prospective observational PK study to propose a dosing algorithm for ciprofloxacin based on both renal function and MIC in critically ill patients.

## METHODS

All adult patients admitted to the ICU who were treated with ciprofloxacin intravenous therapy were eligible for inclusion in this prospective observational multicenter PK study. Patients were eligible if they had a central venous or arterial catheter. Dose and duration of ciprofloxacin therapy were determined by the attending physician. Demographic and biochemical data were collected from the medical charts of patients including age, sex, total body weight, height, diagnosis, drug dose history, and comedication. Biochemical data included serum creatinine, serum cystatin C, and urinary creatinine. Within 24 hours after start of ciprofloxacin therapy, two PK curves with eight timepoints each during a dosing interval were collected with an interval of 12–24 hours between the occasions. This study was evaluated by the local ethics committee and the need for a written informed consent was waived due to its observational nature.

Population PK analysis of ciprofloxacin was performed by nonlinear mixed-effect modeling using the software program NONMEM version 7.4 (Icon plc, Dublin, Ireland). We accounted for the impact of weight

on pharmacokinetics *a priori* by means of allometric scaling of the PK parameters to total body weight. We tested the following algorithms for eGFR as covariates for clearance of ciprofloxacin: Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration based on serum creatinine, based on serum cystatin C and on both serum creatinine and serum cystatin C and 24 hour urine creatinine clearance. Details of the pharmacokinetic analysis can be found in the **Supplementary material**. Model selection and diagnostics were performed in line with best practice.<sup>9</sup> The final model was used to perform Monte Carlo simulations to determine the probability of target attainment (PTA) with a target of AUC/MIC > 125 for various MICs (0.064–0.5 mg/L). We simulated 10,000 virtual patients for each dose group, using the demographics of 10,000 previous ICU patients at our clinic. From these simulations, we created a dosing algorithm of ciprofloxacin for different pathogen susceptibilities and different renal functions.

To define an upper limit of ciprofloxacin exposure that can be considered safe, we selected the 97.5th percentile of the AUC<sub>0–24h</sub> of 8,000 virtual ICU patients with normal renal function (eGFR > 60 mL/min) receiving 400 mg three times daily. A dosing regimen was considered successful if the PTA was ≥ 90% and the AUC<sub>0–24h</sub> was < 97.5th percentile.

## RESULTS

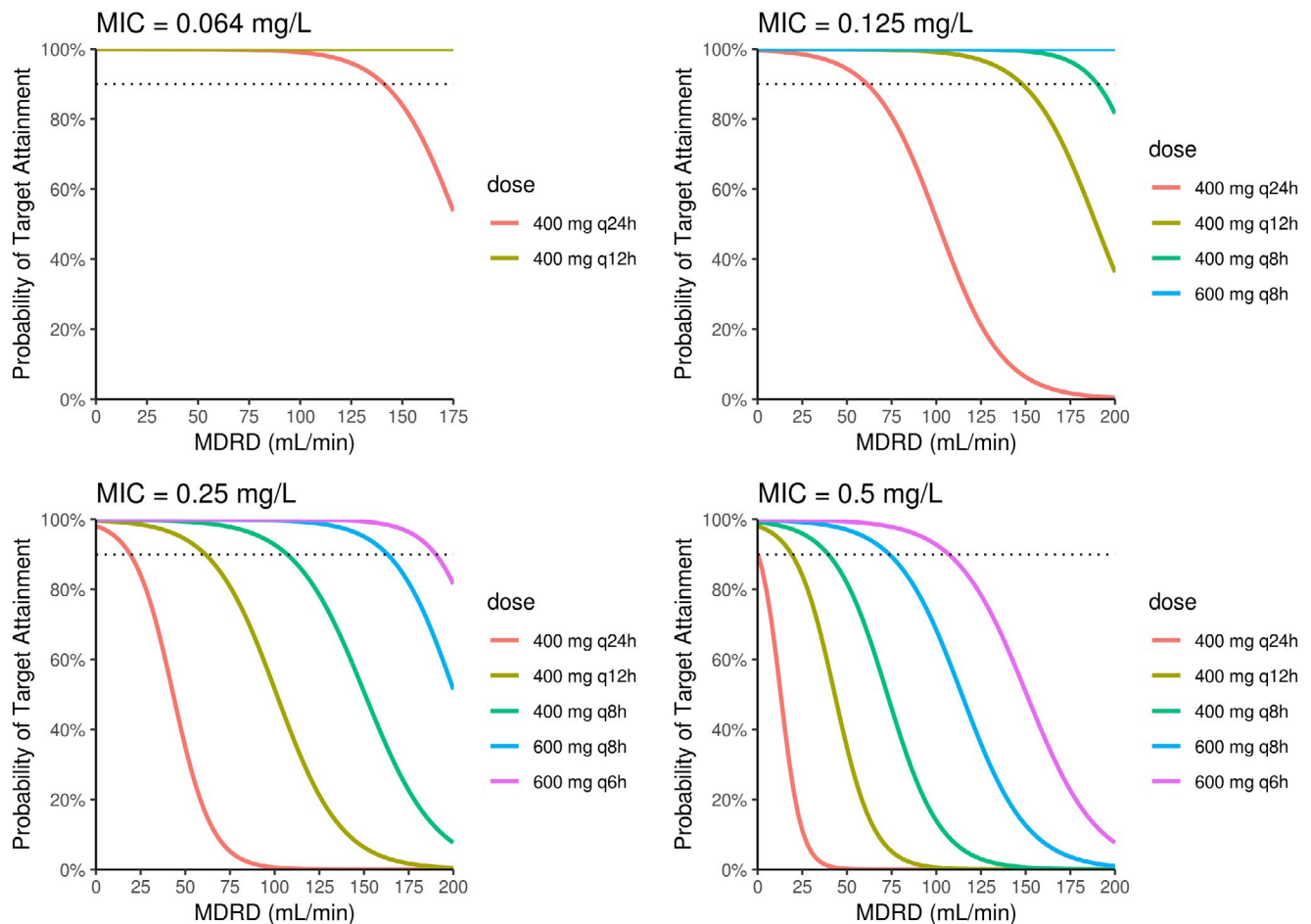
We included 39 patients with a total of 531 samples of ciprofloxacin; 21 males and 18 females with a median age of 68 (range 30–87) years. In this pharmacokinetic study, the majority of the patients (28/39) were treated with ciprofloxacin for pneumonia. The ciprofloxacin doses administered were 200 mg twice daily ( $n = 3$ ), 400 mg twice daily ( $n = 34$ ), or 400 mg three times daily ( $n = 2$ ). The median eGFR by MDRD was 78 (range 23–208) mL/min. The median AUC<sub>0–24h</sub> was 30.4 (range 14.5–103.5) mg\*h/L. A two-compartment linear model with MDRD as covariate on clearance provided the best fit.

**Figure 1** shows the PTAs of AUC/MIC > 125 for ciprofloxacin plotted against MDRD. The four different panels show the PTAs with different MICs (0.064–0.5 mg/L). All patients with an eGFR < 130 mL/min reached target attainment with a dose of 400 mg twice daily provided that the MIC of the pathogen was ≤ 0.125 mg/L. For patients with augmented renal clearance (eGFR > 130 mL/min) and infections caused by less susceptible pathogens, higher dosages than the maximum licensed dose of 1,200 mg daily were estimated to be necessary to obtain target attainment.

**Figure 2** shows the new dosing algorithm of ciprofloxacin. Our simulated upper safety limit of ciprofloxacin exposure is an AUC<sub>0–24h</sub> of 100 mg\*h/L. For infections caused by pathogens with an MIC < 0.5 mg/L, successful dosing regimens could be defined for the whole range of MDRDs. The dosing regimens needed to treat infections caused by pathogens with an MIC of 0.5 mg/L resulted in an AUC<sub>0–24h</sub> above our defined safe upper limit and are therefore not shown in the figure.

## DISCUSSION

In this hypothesis-generating study, we have proposed a dosing algorithm for ciprofloxacin for ICU patients, based on renal function and the MIC of the causative pathogen (**Figure 2**). We have demonstrated that renal function is a significant covariate on ciprofloxacin clearance. We found that MDRD, an eGFR based on serum creatinine, showed the best fit in our model as covariate on



**Figure 1** Probability of target attainment versus renal function by MDRD for different dosing regimens and four different minimum inhibitory concentrations. The dotted horizontal line indicates a probability of target attainment of 90%. MDRD, Modification of Diet in Renal Disease; MIC, minimum inhibitory concentration; q.8h., every 8 hours; q.12h., every 12 hours; q.24h., every 24 hours. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

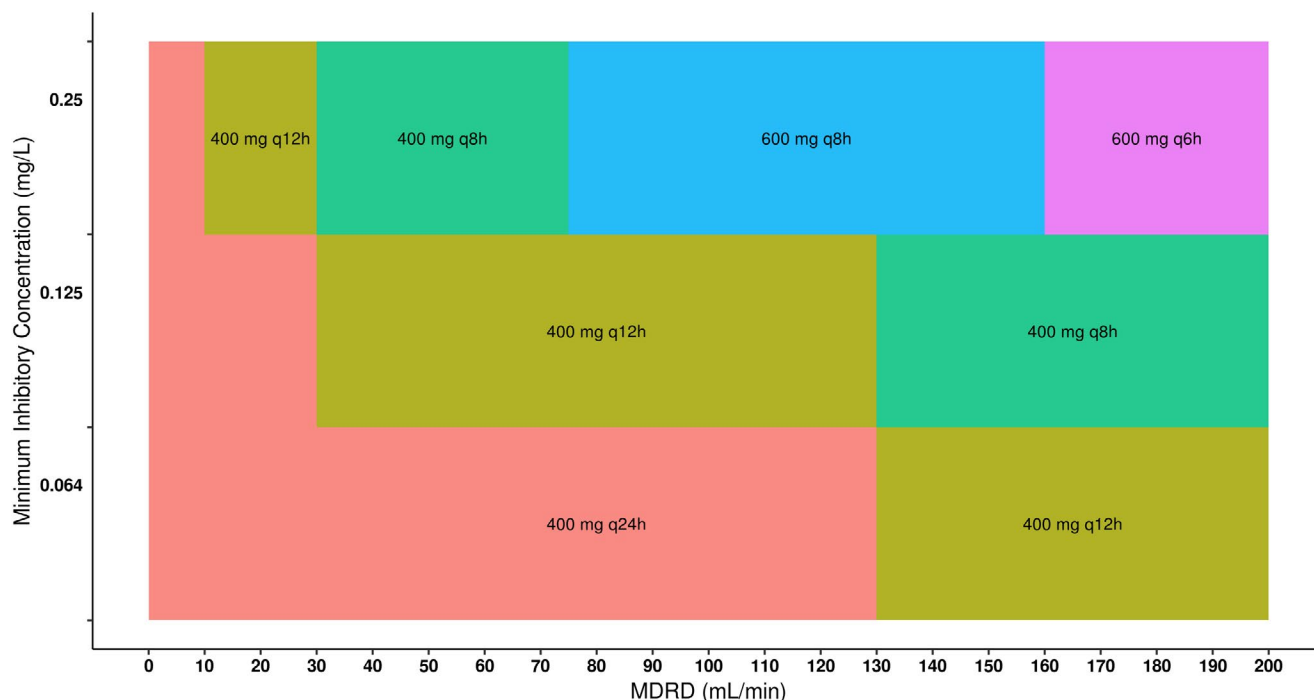
ciprofloxacin clearance. Adding serum cystatin C to the equation did not result in a better prediction of ciprofloxacin clearance. This was unexpected since serum creatinine is influenced by length of hospital stay, caused by muscle wasting in ICU patients and subsequent decreased creatinine production. Serum cystatin C-based eGFR is not influenced by length of stay, since serum cystatin C is not dependent on muscle mass or on age, sex, or race.<sup>5</sup> Although ciprofloxacin clearance was properly predicted by renal function, the study was not powered to detect which renal function estimation method had the best performance.

Body weight was also found to be a fundamental covariate on ciprofloxacin clearance. Yet, renal function is the main driver for clearance, and thus, systemic exposure. Body weight is already accounted for in the equation of MDRD, which is included as covariate on renal clearance. The nonrenal clearance of ciprofloxacin only accounts for a small part of the ciprofloxacin clearance. Therefore, we suggest that ciprofloxacin dosing should only be adjusted to eGFR and not on body weight.

To achieve adequate target attainment the dosing of ciprofloxacin should be based on renal function and the susceptibility of the causative pathogen. In the situation of empirical treatment,

the pathogen susceptibility is unknown and should be derived from epidemiological data. For our simulation, the highest MIC was 0.5 mg/L, which is the epidemiological cutoff value for *P. aeruginosa*.<sup>7</sup> To reach target attainment in this situation, predicted dosages up to 2,400 mg daily are required even for patients with normal renal function. These dosages are far higher than the licensed dosage of 1,200 mg daily. If more knowledge is gained about the safety and tolerability of higher ciprofloxacin doses, infections caused by pathogens with MIC  $\geq$  0.5 mg/L might be treatable as well. This encourages further investigations of efficacy and safety of high dose ciprofloxacin. Likewise, reducing the daily dose to 400 mg in case of renal impairment, as is currently recommended,<sup>1</sup> will not result in a desired PTA of  $>$  90% for less susceptible pathogens. In the provided simulations, the MIC is used as denominator. When deploying an MIC-based dosing strategy, assay variation of the susceptibility testing should be taken into account.<sup>10</sup>

The upper safety limit (AUC 100 mg $\cdot$ h/L) we defined is theoretical and might be conservative. Although treatment with ciprofloxacin is considered safe, with gastrointestinal adverse events as most common side effects, in 1–2% of the patients, more severe



**Figure 2** Dosing algorithm of ciprofloxacin based on renal function and minimum inhibitory concentrations. The dosing recommendations for infections caused by pathogens with a minimum inhibitory concentration of 0.5 mg/L are depicted in gray, because the corresponding area under the curve is above the defined upper safety limit ( $>100$  mg $\cdot$ h/L). MDRD, Modification of Diet in Renal Disease. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

adverse events might occur.<sup>11</sup> In a recent evaluation the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) reported on neuropsychiatric toxicities, tendinopathy long-term disability, and aortic aneurysms/dissections associated with fluoroquinolones.<sup>12</sup> Whether these toxicities are concentration dependent remains to be investigated, so currently there are no recommendations to the maximum exposure. Yet, dose reductions in renal impairment are still recommended to avoid possible toxicity, which we believe might result in insufficient exposure to reach target attainment. Indeed, in the treatment of children with cystic fibrosis with a pulmonary *P. aeruginosa* infection, doses higher than 1,200 mg daily are used. In these patients, a maximum daily dose of 2,000 mg intravenous is recommended and well-tolerated.<sup>13</sup> Because of higher clearance in children, the high dosages (30 mg/kg/daily) used in children with cystic fibrosis resulted in similar  $AUC_{0-24h}$  to adults using 1,200 mg daily.<sup>13</sup>

When aiming for a PTA of 90% in the setting of an infection with a pathogen MIC of 0.5 mg/L, therapeutic drug monitoring (TDM) can be considered to warrant that the  $AUC_{0-24h}$  of 62.5–100 mg $\cdot$ h/L is achieved (i.e.,  $AUC/MIC > 125$  with  $MIC = 0.5$ ). The rationale to perform TDM is supported by the relatively low interoccasion variability of 13.4%, considering the unstable critically ill patient population and the observed interindividual variability of 25.8%.

In conclusion, we provide a new dosing algorithm for ciprofloxacin in critically ill patients based on renal function and MIC. TDM might be considered to safeguard sufficiently high exposure in the setting of infections with a pathogen with a high MIC. In all settings, close observation of potential toxicity is recommended to learn more

on the upper limit associated with toxicity. There is an urgent need to clinically assess high-dose ciprofloxacin ( $>1,200$  mg/day) to allow treatment of less susceptible pathogens in the critically ill population.

#### SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website ([www.cpt-journal.com](http://www.cpt-journal.com)).

#### ACKNOWLEDGMENTS

Interim analysis of this work was presented at the 29<sup>th</sup> European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Amsterdam, the Netherlands 2019; poster 1962. We gratefully acknowledge Angela Colbers for her assistance in study design and data analysis.

#### CONFLICT OF INTEREST

The authors declared no competing interests for this work.

#### FUNDING

No funding was received for this work.

#### AUTHOR CONTRIBUTIONS

E.M.G., E.W., R.t.H., and R.J.M.B. wrote the manuscript. E.M.G., T.F., D.L., J.A.S., J.t.O., E.K., D.M.B., P.P., R.t.H., and R.J.M.B. designed the research. E.M.G., E.W., T.F., D.W.d.L., J.A.S., and P.P. performed the research. E.W., R.t.H., and R.J.M.B. analyzed the data.

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1. Summary of product characteristics Ciprofloxacin <[https://www.geneesmiddeleninformatiebank.nl/smpc/h30476\\_smpc.pdf](https://www.geneesmiddeleninformatiebank.nl/smpc/h30476_smpc.pdf)>. Accessed November 5, 2019.
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