Antibiotic dose optimization for specific patient populations

With focus on patients with renal impairment

de Vroom, S.L.

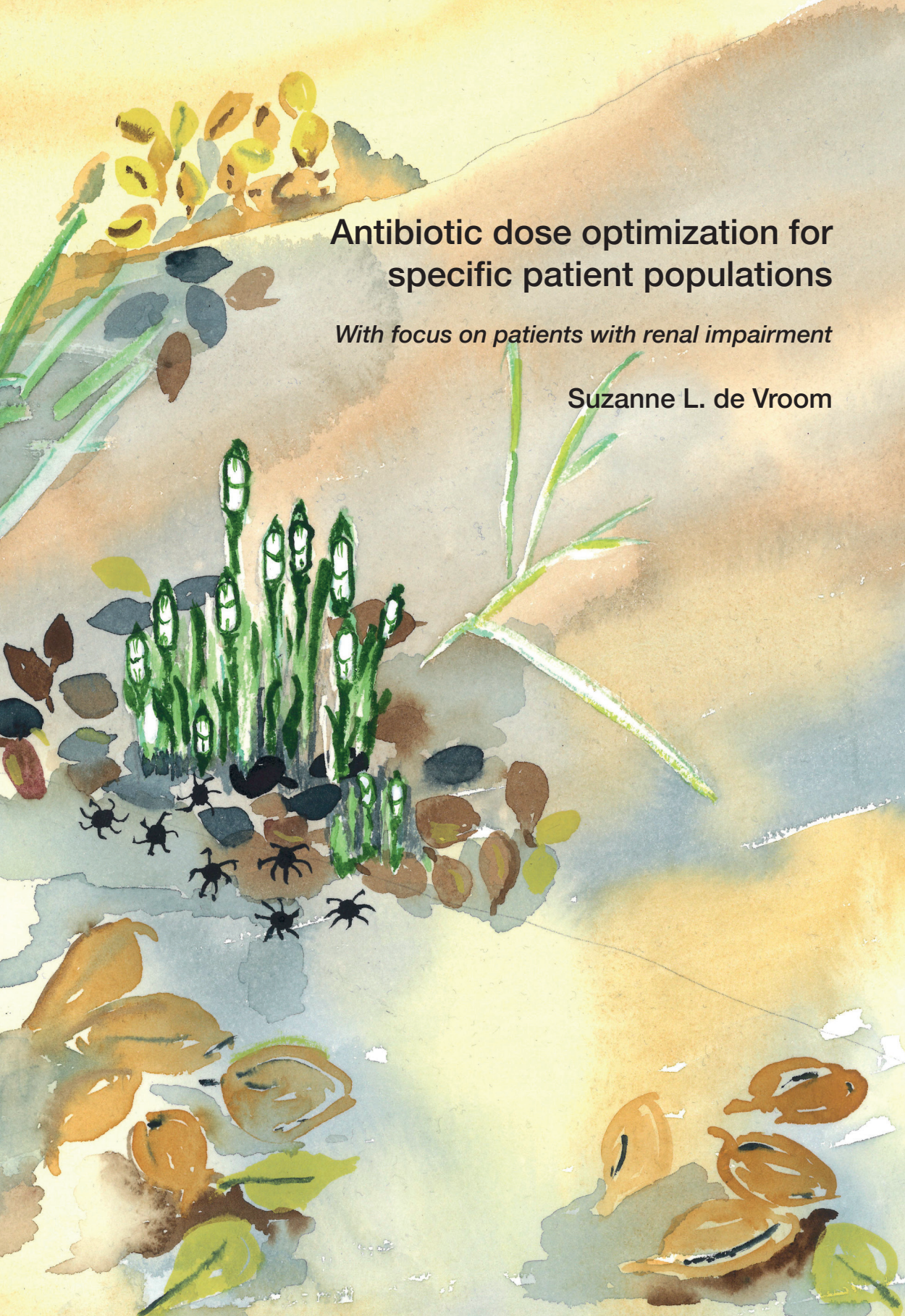
Publication date
2023

Document Version
Final published version

Antibiotic dose optimization for specific patient populations

With focus on patients with renal impairment

Suzanne L. de Vroom



Antibiotic dose optimization for specific patient populations

With focus on patients with renal impairment

Suzanne L. de Vroom

Antibiotic dose optimization for specific patient populations
Academic thesis, University of Amsterdam, the Netherlands

ISBN: 978 90 361 0707 5
Printing: Haveka, www.haveka.nl

Antibiotic dose optimization for specific patient populations
With focus on patients with renal impairment

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit van Amsterdam op
gezag van de Rector Magnificus prof. dr. ir. P.P.C.C. Verbeek
ten overstaan van een door het College voor Promoties ingestelde commissie, in het openbaar te
verdedigen in de Agnietenkapel op donderdag 25 mei 2023, te 16.00 uur

door Suzanne Luciana de Vroom geboren te Utrecht

Promotiecommissie

Promotores:	prof. dr. S.E. Geerlings	AMC-UvA
	prof. dr. R.A.A. Mathôt	AMC-UvA
Copromotores:	dr. R.M. van Hest	AMC-UvA
Overige leden:	prof. dr. J.M. Prins	AMC-UvA
	prof. dr. T. van Gelder	Universiteit Leiden
	prof. dr. M.A. van Agtmael	Vrije Universiteit Amsterdam
	prof. dr. F.J. Bemelman	AMC-UvA
	prof. dr. M.J. Kersten	AMC-UvA
	dr. C.E. Visser	AMC-UvA

Faculteit der Geneeskunde

Table of contents

Chapter 1

General introduction and outline of this thesis

''The greatest possibility of evil in self-medication is the use of too-small doses, so that, instead of clearing up the infection, the microbes are educated to resist penicillin''

— Sir Alexander Fleming, New York Times, 1945

Antibiotics

In September 1928 Alexander Fleming discovered the first antibiotic; penicillin. His discovery is assumed to be a serendipity; the Petri dish containing bacteria had been accidently infected by a mold of the penicillin species and no bacteria grew near it. When Ernst Boris Chain and Howard Florey were able to isolate penicillin a decade later, the widespread use of penicillin as treatment for bacterial infections was rapidly evolving. Treatment with antibiotics was urged by the outbreak of the Second World War, which was accompanied by many infectious diseases.[1]

By now, antibiotics are indispensable in healthcare both to treat and prevent bacterial infections. Many innovations in healthcare, such as organ transplantation, major surgeries and chemotherapy would not be possible without the use of effective antibiotics.[2]

Appropriate antibiotic use

Nowadays antimicrobial resistance presents a new threat to public health.[2] The incidence of antimicrobial resistance is rapidly increasing and infection-related mortality is expected to exceed ten million cases per year by 2050. Antimicrobial resistance is set to exceed current annual cancer-related deaths world-wide by 2050.[3] Misuse and overuse of antibiotics are the main drivers in the development of antimicrobial resistance.[4] Therefore, efforts are focused nowadays on appropriate use of antibiotics.

Appropriate antibiotic use is beneficial for patients' clinical outcome, leads to a decrease in antibiotic resistance rates and results in lowering of healthcare costs.[5-9] In general, quality indicators can be developed to measure quality of care. Nine of these quality indicators were developed and validated to define appropriate antibiotic use in the treatment of bacterial infections in hospitalized adult patients on general wards (Table 1).[10] One of these nine validated quality indicators is to adjust dose and dosing interval of systemic antibiotics to renal function.

Table 1. Quality indicators to monitor antibiotic use for all bacterial infections in hospitalized adult patients in non–intensive care unit departments[10]

Quality indicator
Empirical systemic antibiotic therapy should be prescribed according to the local guideline.
Before starting systemic antibiotic therapy, at least 2 sets of blood cultures should be taken.
When starting systemic antibiotic therapy, specimens for culture from suspected sites of infection should be taken as soon as possible, preferably before antibiotics are started.
Empirical antibiotics should be changed to pathogen-directed therapy if culture results become available.
Dose and dosing interval of systemic antibiotics should be adapted to renal function.
Systemic antibiotic therapy should be switched from intravenous to oral antibiotic therapy within 48–72 hours on the basis of the clinical condition and when oral treatment is adequate.
An antibiotic plan should be documented in the case notes at the start of systemic antibiotic treatment.
Therapeutic drug monitoring should be performed when the treatment duration is >3 days for aminoglycosides and >5 days for vancomycin.
Empirical antibiotic therapy for presumed bacterial infection should be discontinued based on the lack of clinical and/or microbiological evidence of infection. The maximum duration of empirical systemic antibiotic treatment should be 7 days.

Antibiotic dosing in patients with impaired renal function

Adequate antibiotic dosing is an indispensable goal of appropriate antibiotic use in clinical practice.[11-13] Underdosing increases the risk of treatment failure, while overdosing may lead to toxicity, both with negative effects on patients' outcome. Additionally, underdosing promotes the development of antimicrobial resistance due to subtherapeutic antibiotic concentrations.[14]

The kidney is the major route of elimination for many antibiotics, therefore, dosing of renally cleared antibiotics is often based on renal function. The aim of renal dose adjustment is to achieve antibiotic drug exposure equivalent to that in patients with adequate renal function receiving the regular dose, i.e., achieving *bioequivalence*, thereby preventing accumulation of the drug with risk for toxicity and maintaining efficacy.[15,16]

Antibiotic dose reduction for patients with impaired renal function is standard of care as incorporated in all clinical guidelines.[17-19] However, this dose reduction is often not applied in clinical practice and the question arises why this recommendation is not followed.[20] First, inconsistency exists between different guidelines in the cut-off value of renal function below which the dose per antibiotic should be reduced. Second, the degree of the dose reduction is inconsistent between clinical guidelines.[21] Third, significantly increased therapeutic failure and death were observed in patients with impaired renal function treated with recommended reduced doses of antibiotics and multiple antibiotics carry precautionary statements in their labelling for reduced clinical response in these patients.[22,23] Therefore, prescribers may fear therapeutic failure when reducing the dose.

In the Netherlands, already 1.7 million people show some degree of impaired renal function, making up about 10% of the total population. Due to aging of the population and an increase in the number of people with diabetes and hypertension, this will increase further.[24] Additionally, this number consists only of patients with chronic renal impairment, and does not include the number of patients with acute renal impairment. Approximately 20% of all hospital admissions are also associated with acute renal impairment.[25] However, as illustrated above uncertainty exists on adequate antibiotic dosing in this important patient population.

Antibiotic dosing in patients with mucositis

High dose chemotherapy is frequently used in patients with haematological malignancies, particularly prior to hematopoietic stem cell transplantation. Infections are a major cause of complications in patients receiving high dose chemotherapy and the most principal cause of non-malignancy-related deaths.[26] Therefore, most patients with haematological malignancies are at increased risk of infections, mostly because of the adverse effects of the treatment of the malignancy, like neutropenia due to treatment with chemotherapy, but also because of natural barrier disruption like mucositis and central venous catheter placement.[27] Therefore, anti-infective agents are administered as infection prophylaxis as standard of care.[28] Results have shown that infection prophylaxis is an effective and well-tolerated way to prevent febrile episodes and other relevant infection-related outcomes like microbiologically documented infections, bacteraemia and hospitalization.[29,30] Additionally, a substantial reduction in mortality was shown in patients using fluoroquinolone as antibiotic prophylaxis in comparison with patients using no prophylaxis, or using prophylaxis with other types of antibiotics.[31] Currently, anti-infective agents for the prophylaxis of bacterial infections, viral infections and fungal infections, among which *Pneumocystis jirovecii*, are prescribed as standard of care in these patients.

The efficacy of infection prophylaxis relies on adequate drug exposure, which is affected by dose, bioavailability and clearance.[32] In case of oral administration, the dose that reaches the systemic circulation is dependent of the administered dose and the bioavailability. Bioavailability reflects the combined process of absorption and first-pass effect.[33] However, patients treated with chemotherapy may face mucositis.[34,35] Mucositis means the loss of intestinal integrity and may affect the absorption of orally administered drugs.[36] Mucositis leads to a leak intestine and may affect absorption in two different ways:

1. The leak intestine leads to better absorption and therefore to higher exposure
2. The leak intestine leads to compromised absorption and therefore lower exposure

Depending on the dose and type of the chemotherapeutic agents, up to 40% of adult patients experience oral and/or gastro-intestinal (GI) mucositis.[36] Different studies have investigated the effect of mucositis on drug exposure and results are contradictory, besides only studies on anti-fungal prophylaxis are performed, studies on antibacterial prophylaxis are lacking at all.[37-40] For example, drug exposure and clinical outcome were not different between patients with and without mucositis receiving the anti-fungal agent isavuconazole. However, only patients with mucositis who were able to take oral isavuconazonium sulfate were included, indicating only mild mucositis was present in those patients.[37] Three other studies were performed on posaconazole.[38-40] The first study observed a reduced bioavailability of posaconazole in haematological patients with severe intestinal mucositis. However, this reduced bioavailability was not observed in patients with mild or moderate mucositis.[38] The second study observed no difference in drug exposure between patients with and without mucositis.[39] The third study did not observe statistically significant differences in posaconazole exposure in patients with and without mucositis or diarrhea.[40]

Regarding ciprofloxacin, only two small studies on its absorption in patients with haematological malignancies were performed, however nothing was mentioned about the presence or assessment of mucositis.[41,42] Besides, both studies were performed over 20 years ago, when infection prophylaxis in those patients was not even recommended as standard of care. Results were contradictory: one study showed adequate absorption and one study showed compromised absorption of ciprofloxacin.[41,42]

It is worrying that one study showed compromised absorption of ciprofloxacin in patients with haematological malignancies, while ciprofloxacin is administered orally as infection prophylaxis for decades to those patients. The administered dose for infection prophylaxis is the general dose that is used for patients with regular bacterial infections, without mucositis. Therefore, this dose may be inadequate for patients with mucositis, with concomitant risk of under- or overexposure.

To conclude, people with haematological malignancies are administered life-saving antibiotics with hardly any understanding of how mucositis impacts their absorption, bioavailability, drug exposure and thus efficacy of these antibiotics.

Pharmacokinetic/pharmacodynamic (PK/PD) target attainment

An innovative way to investigate adequate antibiotic dosing is through pharmacokinetic/pharmacodynamic (PK/PD) target attainment.[43,44]

Pharmacokinetics (PK) describe how the body processes the administered drug, resulting in drug exposure; both systemically and at the infection site. The stepwise process of drug entry in the body and departure from the body is regulated by complex physiologic processes. The four distinguished pharmacokinetic processes are:

- Absorption
- Distribution
- Metabolism
- Excretion

For systemic drug exposure this sum of processes visually ends up in the concentration-time curve, with area under this curve (AUC) being the most important parameter for drug exposure.[45]

Pharmacodynamics (PD) describe how the administered drug affects the body, and in the case of antibiotics, how the drug affects the infection causing microorganism. The primary pharmacodynamic property of antibiotics is commonly expressed as the minimal inhibitory concentration (MIC).[44] The MIC is the lowest concentration of an antibiotic that prevents visible growth of bacteria in vitro.[46]

Pharmacokinetics and pharmacodynamics are often studied together through PK/PD target attainment. PK/PD target attainment of an antibiotic determines the relationship between:

1. The administered antibiotic dose
2. Antibiotic drug exposure resulting from the administered antibiotic dose
3. A pre-specified target, involving the MIC, that needs to be attained (i.e., the antibiotic effect)

To investigate adequate antibiotic dosing for a specific patient population with infections caused by certain bacteria, more information about PK/PD target attainment is needed.

Investigating PK/PD target attainment has in some cases replaced the importance of the original antibiotic dose-finding studies.[47] The major advantage of PK/PD target attainment studies above dose-finding studies is the quantitative prediction of clinical and microbiological efficacy in relation to systemic drug exposure. Additionally, it allows extended mechanism-based models to improve antibiotic dosing. Nowadays almost all newly approved antibiotics include information about PK/PD

target attainment, however many 'old' antibiotics that were approved a long time ago, lack information about PK/PD target attainment.

Ciprofloxacin and ceftazidime

In this thesis we will investigate two antibiotics in clinical practice: ciprofloxacin and ceftazidime.

Ciprofloxacin is a fluoroquinolone antibiotic and is frequently prescribed both in inpatient and outpatient settings. The activity of ciprofloxacin mainly includes Gram-negative bacteria, of which *Enterobacteriaceae* and *Pseudomonas aeruginosa* are the most clinically relevant. Ciprofloxacin is used to treat a broad spectrum of infections, such as urinary tract infections, pneumonia, abdominal infections and skin and soft-tissue infections.[48]

Ceftazidime is a third-generation cephalosporin and is frequently used in hospitalized patients, due to the intravenous administration way. It covers a broad range of Gram-negative bacteria, including *Pseudomonas aeruginosa*. Ceftazidime is used to treat patients with different serious infections, such as patients with neutropenic fever, skin and soft-tissue infections or diabetic foot infections.[49]

In this thesis we investigate PK/PD target attainment of both ciprofloxacin and ceftazidime, therefore, the following part provides an overview of the evidence for both PK/PD targets.

Evidence for used PK/PD targets

Ciprofloxacin

The PK/PD target of ciprofloxacin that correlates best with clinical outcome is defined as the AUC/MIC ≥125, which has been established in two previous clinical studies.[50,51]

Forrest *et al.* observed significant higher clinical and microbiological cure for patients attaining an AUC/MIC ≥125, compared to patients attaining an AUC/MIC< 125 (80% and 82% versus 42% and 26% respectively).[50] Additionally, time to eradication, defined as the presence of negative cultures after the presence of positive cultures, was significantly shorter for patients with higher AUC/MIC values. For an AUC/MIC <125 time to eradication was >32 days, while this was 6.6 days for an AUC/MIC ≥125 and even 1.9 days for an AUC/MIC ≥250. Most patients were admitted to critical care units with moderate to severe infections, chiefly of the lower respiratory tract caused by different Gram-negative bacteria.[50]

Zelenitsky *et al.* showed that calculated cure rates of ≥90% were found when AUC/MIC were at least 86 based on unbound concentrations, or 123 based on total concentrations. All patients had a bacteraemia with *Pseudomonas aeruginosa*.[51]

Both studies were retrospective, single-centre studies and included 66, respectively 38 patients. The found AUC/MIC ≥123 by Zelenitsky *et al.*, is almost identical to the significant AUC/MIC breakpoint of 125 first proposed by Forrest *et al*. Later, Zelenitsky *et al*. showed even better clinical outcome at PK/PD targets of AUC/MIC ≥250.[52]

To conclude, clinical evidence on the PK/PD target of AUC/MIC ≥125 for ciprofloxacin is based on the clinical outcomes of patients from two retrospective studies, with a relatively small sample size, who often used concomitant other antibiotics and measured MIC values generally lower than MIC values that need to be covered for treatment with ciprofloxacin. So, there is a substantial risk for

coincidental findings. However, comparable AUC/MIC values across both studies were found, making the PK/PD target of AUC/MIC ≥125 currently the best existing.[50,51]

Ceftazidime

The PK/PD target of ceftazidime that correlates best with clinical outcome is defined as the percentage of time of a dosing interval the ceftazidime concentration is above the MIC (%T >MIC), conform other β-lactam antibiotics.

In vitro, bacteriostatic effect was observed at 30% to 40%T >MIC, whereas maximum killing was approached when levels were 60% to 70%T >MIC.[53] These results are comparable with PK/PD targets of other β-lactam antibiotics.

Three clinical studies on PK/PD target attainment of ceftazidime showed percentages of time above MIC ranging from approximately 50% to 100%.[54-56]

McKinnon *et al.* observed significantly greater clinical cure and bacteriological eradication in patients with T >MIC of 100% compared to patient with T >MIC of <100% (82% and 97% versus 33% and 44% respectively). Most patients were treated for complicated urinary tract infections and respiratory tract infections caused by different microorganisms.[54]

Muller *et al*. calculated a significant split value for 44.9%T >MIC, with an eradication rate of 90.2% above that value, and only 50% below that value.[55] Patients were treated for hospital acquired pneumonia, including ventilator associated pneumonia caused by different microorganisms.[55]

Finally, Mac Vane *et al*. observed that 53%T >MIC was significantly associated with microbiological success.[56] Patients were admitted to the ICU with ventilator associated pneumonia, again caused by different microorganisms.[56]

All studies were retrospective studies, McKinnon and Mac Vane performed both single-centre studies and included 76, respectively 73 patients, while Muller performed a multi-centre study and included 781 patients.[54-56]

To conclude, the percentage of the time that the concentration has to be above the MIC differs between the three clinical studies, yet the majority of the studies showed optimal clinical outcome at 50%T >MIC.[55,56] However, one might consider to use 100%T >MIC as a second target based on the study of McKinnon *et al*. that observed optimal outcome at that target.[54]

Aims and hypotheses of this thesis

This thesis contributes to answering the following questions:

1. Is the recommended dose reduction of renally cleared antibiotics for patients with impaired renal function adequate and validated in clinical practice?
2. Is the absorption of ciprofloxacin adequate after oral administration in patients with haematological malignancies and gastro-intestinal mucositis?

We hypothesize that the recommended dose reduction is mainly based on simulated and retrospective data and is not prospectively validated in clinical practice, with concomitant risk of under- or overexposure. Furthermore, we hypothesize that systemic drug exposure in patients with haematological malignancies and gastro-intestinal mucositis is changed compared to patients without mucositis. The rationale behind this hypothesis is that mucositis may mean the loss of intestinal integrity and thus may affect the absorption of orally administered drugs and therefore drug exposure.[36] Whether this could end up in enhanced absorption and higher exposure or in compromised absorption and therefore lower exposure of ciprofloxacin is currently unclear.

The ultimate goal is to strengthen the evidence underlying the quality indicator for appropriate antibiotic use on 'adjusting the dose to renal function' and provide evidence that adherence to that quality indicator actually leads to appropriate antibiotic use and therefore to improvement of patients' clinical outcome, decrease in antibiotic resistance rates and lowering of healthcare costs.[5-9] As such, this thesis tries to contribute to increasing physicians' confidence in the guideline-recommended dose reductions so that they will adhere better to these guidelines.

Outline of this thesis

In **Chapter 2**, we conduct a systematic review to summarize the available evidence on drug exposure or on PK/PD target attainment after dose reduction of all renally cleared antibiotics in patients with impaired renal function.

Subsequently, we investigate the adequacy of the currently recommended antibiotic dose reduction in real life clinical practice. A pre-requisite to investigate exposure to antibiotics in clinical practice is a validated method to measure concentrations of these antibiotics in body fluids. This is done by the development and validation of a liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay for the determination of ciprofloxacin plasma concentrations in **Chapter 3**.

This method is used in **Chapter 4** to investigate PK/PD target attainment of ciprofloxacin in patients with adequate and impaired renal function receiving regular and guideline-recommended reduced doses of ciprofloxacin. We investigate whether the guideline-recommended dose reduction of ciprofloxacin for patients with impaired renal function results in PK/PD target attainment and ciprofloxacin exposure similar to that in patients with adequate renal function receiving the regular dose.

Also, we investigate in **Chapter 5** whether the guideline-recommended dose reduction of ceftazidime for patients with impaired renal function results in PK/PD target attainment of ceftazidime and drug exposure similar to that in patients with adequate renal function receiving the regular dose.

Furthermore, to be able to fully investigate the adequacy of the administered antibiotic dose, one should investigate not only clearance (mainly determined by renal function in case of renally cleared antibiotics), but also that other pharmacokinetic parameter determining drug exposure: the bioavailability. In case of oral administration, bioavailability determines the amount of the drug that is being absorbed and thereby a large part of drug exposure.

Therefore, we investigate in **Chapter 6** ciprofloxacin pharmacokinetics after oral administration in patients with haematological malignancies and explore the impact of gastrointestinal-mucositis on oral bioavailability and clearance in order to assure adequate systemic exposure. To carefully monitor the effect of mucositis on oral bioavailability, and therefore absorption of ciprofloxacin, we assess the degree of gastrointestinal-mucositis by using the Daily Gut Score and measuring plasma citrulline and albumin.

In **Chapter 7** we discuss our findings and clinical implications regarding appropriate antibiotic use, in particular for patients with impaired renal function and haematological patients with mucositis. Methodological issues regarding the different executed studies are considered. Additionally, we provide directions for future research.

References

1. Gaynes R. The Discovery of Penicillin—New Insights After More Than 75 Years of Clinical Use. Emerg Infect Dis. 2017 May;23(5):849–53.
2. Aslam B, Wang W, Arshad MI, Khurshid M, Muzammil S, Rasool MH, Nisar MA, Alvi RF, Aslam MA, Qamar MU, Salamat MKF, Baloch Z. Antibiotic resistance: a rundown of a global crisis. Infect Drug Resist. 2018 Oct 10;11:1645-1658.
3. O'Neill J et al. Tackling drug-resistant infections globally: final report and recommendations. Government of the United Kingdom; 2016. Available on: https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf. Last accessed on January 20, 2023.
4. World Health Organiszation (WHO) - Antimicrobial resistance, 17 November 2021. Available on: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance. Last accessed on January 20, 2023.
5. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, Gould IM, Ramsay CR, Michie S. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2017 Feb 9;2(2):CD003543.
6. Schuts EC, Hulscher MEJL, Mouton JW, Verduin CM, Stuart JWTC, Overdiek HWPM, van der Linden PD, Natsch S, Hertogh CMPM, Wolfs TFW, Schouten JA, Kullberg BJ, Prins JM. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis. 2016 Jul;16(7):847-856.
7. van den Bosch CM, Hulscher ME, Akkermans RP, Wille J, Geerlings SE, Prins JM. Appropriate antibiotic use reduces length of hospital stay. J Antimicrob Chemother. 2017 Mar 1;72(3):923-932.
8. Spoorenberg V, Hulscher ME, Akkermans RP, Prins JM, Geerlings SE. Appropriate antibiotic use for patients with urinary tract infections reduces length of hospital stay. Clin Infect Dis. 2014 Jan;58(2):164-9.
9. McCabe C, Kirchner C, Zhang H, Daley J, Fisman DN. Guideline-concordant therapy and reduced mortality and length of stay in adults with community-acquired pneumonia: playing by the rules. Arch Intern Med. 2009 Sep 14;169(16):1525-31.
10. van den Bosch CM, Geerlings SE, Natsch S, Prins JM, Hulscher ME. Quality indicators to measure appropriate antibiotic use in hospitalized adults. Clin Infect Dis. 2015 Jan 15;60(2):281-91.
11. Polk R. Optimal use of modern antibiotics: emerging trends. Clin Infect Dis. 1999 Aug;29(2):264-74.
12. Joseph J, Rodvold KA. The role of carbapenems in the treatment of severe nosocomial respiratory tract infections. Expert Opin Pharmacother. 2008 Mar;9(4):561-75.
13. Ha DR, Haste NM, Gluckstein DP. The Role of Antibiotic Stewardship in Promoting Appropriate Antibiotic Use. Am J Lifestyle Med. 2017 Apr 4;13(4):376-383.
14. Pea F, Viale P. Bench-to-bedside review: Appropriate antibiotic therapy in severe sepsis and septic shock--does the dose matter? Crit Care. 2009;13(3):214.
15. Levison ME, Levison JH. Pharmacokinetics and pharmacodynamics of antibacterial agents. Infect Dis Clin North Am. 2009 Dec;23(4):791-815, vii.
16. Verbeeck RK, Musuamba FT. Pharmacokinetics and dosage adjustment in patients with renal dysfunction. Eur J Clin Pharmacol. 2009 Aug;65(8):757-73.
17. Stichting Werkgroep AntibioticaBeleid (SWAB) - Ciprofloxacine. Available on: https://adult.nl.antibiotica.app/nl/node/1240. Last accessed on 12 January 2023.
18. Farmacotherapeutisch Kompas (FK) - Ciprofloxacine. Available on: https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/c/ciprofloxacine. Last accessed on 12 January 2023.
19. KNMP Kennisbank – Ciprofloxacine. Available on: https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/S2078.html. Last accessed on 12 January 2023.

20. van Daalen FV, Prins JM, Opmeer BC, Boermeester MA, Visser CE, van Hest RM, Branger J, Mattsson E, van de Broek MFM, Roeleveld TC, Karimbeg AA, Haak EAF, van den Hout HC, van Agtmael MA, Hulscher MEJL, Geerlings SE. Effect of an antibiotic checklist on length of hospital stay and appropriate antibiotic use in adult patients treated with intravenous antibiotics: a stepped wedge cluster randomized trial. Clin Microbiol Infect. 2017 Jul;23(7):485.e1-485.e8.
21. Vidal L, Shavit M, Fraser A, Paul M, Leibovici L. Systematic comparison of four sources of drug information regarding adjustment of dose for renal function. BMJ. 2005 Jul 30;331(7511):263.
22. Crass RL, Rodvold KA, Mueller BA, Pai MP. Renal Dosing of Antibiotics: Are We Jumping the Gun? Clin Infect Dis. 2019 Apr 24;68(9):1596-1602.
23. Camargo MS, Mistro S, Oliveira MG, Passos LCS. Association between increased mortality rate and antibiotic dose adjustment in intensive care unit patients with renal impairment. Eur J Clin Pharmacol. 2019 Jan;75(1):119-126.
24. Nierstichting – Nierschade en nierfalen. Available on: https://nierstichting.nl/documents/399/FS1-Nierennierschade_en_nierfalen.22.pdf. Last accessed on January 13, 2023.
25. Argyropoulos A, Townley S, Upton PM, Dickinson S, Pollard AS. Identifying on admission patients likely to develop acute kidney injury in hospital. BMC Nephrol. 2019 Feb 14;20(1):56.
26. Gedik H, Simşek F, Kantürk A, Yildirmak T, Arica D, Aydin D, Demirel N, Yokuş O. Bloodstream infections in patients with hematological malignancies: which is more fatal - cancer or resistant pathogens? Ther Clin Risk Manag. 2014;10:743–752.
27. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. Cancer. 2004 Jan 15;100(2):228-37.
28. Mikulska M, Averbuch D, Tissot F, Cordonnier C, Akova M, Calandra T, Ceppi M, Bruzzi P, Viscoli C; European Conference on Infections in Leukemia (ECIL). Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines. J Infect. 2018 Jan;76(1):20-37.
29. Bucaneve G, Micozzi A, Menichetti F, Martino P, Dionisi MS, Martinelli G, Allione B, D'Antonio D, Buelli M, Nosari AM, Cilloni D, Zuffa E, Cantaffa R, Specchia G, Amadori S, Fabbiano F, Deliliers GL, Lauria F, Foà R, Del Favero A; Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) Infection Program. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med. 2005;353(10):977-87.
30. Cullen M, Steven N, Billingham L, Gaunt C, Hastings M, Simmonds P, Stuart N, Rea D, Bower M, Fernando I, Huddart R, Gollins S, Stanley A; Simple Investigation in Neutropenic Individuals of the Frequency of Infection after Chemotherapy +/- Antibiotic in a Number of Tumours (SIGNIFICANT) Trial Group. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. N Engl J Med. 2005 Sep 8;353(10):988-98.
31. Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Ann Intern Med. 2005 Jun 21;142(12 Pt 1):979-95.
32. Price G, Patel DA. Drug Bioavailability. [Updated 2022 Jun 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-
33. Rowland M, Tozer T. Clinical Pharmacokinetics. Concepts and Applications, 3rd Edition, Lea & Febiger, Philadelphia, London, 1995:14
34. Blijlevens NM, Donnely JP, de Pauw BE. Empirical therapy of febrile neutropenic patients with mucositis: challenge of risk-based therapy. Clinical Microbiology and Infection 2001; 7:47-52.
35. Peterson DE, Boers-Doets CB, Bensadoun RJ, Herrstedt J; ESMO Guidelines Committee. Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Ann Oncol. 2015 Sep;26 Suppl 5:v139-51.
36. Dahlgren D, Sjöblom M, Hellström PM, Lennernäs H. Chemotherapeutics-Induced Intestinal Mucositis: Pathophysiology and Potential Treatment Strategies. Front Pharmacol. 2021 May 4;12:681417.

37. Kovanda LL, Marty FM, Maertens J, Desai AV, Lademacher C, Engelhardt M, Lu Q, Hope WW. Impact of Mucositis on Absorption and Systemic Drug Exposure of Isavuconazole. Antimicrob Agents Chemother. 2017 May 24;61(6):e00101-17.
38. Jansen AME, Muilwijk EW, van der Velden WJFM, Maertens JA, Aerts R, Colbers A, Burger D, Verweij PE, Ter Heine R, Blijlevens NMA, Brüggemann RJM. Posaconazole bioavailability of the solid oral tablet is reduced during severe intestinal mucositis. Clin Microbiol Infect. 2022 Jul;28(7):1003-1009.
39. Bryant AM, Slain D, Cumpston A, Craig M. A post-marketing evaluation of posaconazole plasma concentrations in neutropenic patients with haematological malignancy receiving posaconazole prophylaxis. Int J Antimicrob Agents. 2011 Mar;37(3):266-9.
40. Pham AN, Bubalo JS, Lewis JS 2nd. Comparison of posaconazole serum concentrations from haematological cancer patients on posaconazole tablet and oral suspension for treatment and prevention of invasive fungal infections. Mycoses. 2016 Apr;59(4):226-233.
41. Gattis WA, Petros WP, Pickard WW, Drew RH, May DB, Hathorn JW. A prospective, open-label study of single-dose ciprofloxacin absorption after chemotherapy in patients with malignancy. Pharmacotherapy. 1997 Jul-Aug;17(4):836-40.
42. Smith GM, Leyland MJ, Farrell ID, Geddes AM. A clinical, microbiological and pharmacokinetic study of ciprofloxacin plus vancomycin as initial therapy of febrile episodes in neutropenic patients. J Antimicrob Chemother. 1988 May;21(5):647-55.
43. Kebriaei R, Berti AD. Editorial: Antibiotics Special Issue on Pharmacokinetic/Pharmacodynamic Models of Antibiotics. Antibiotics (Basel). 2022 Nov 3;11(11):1540.
44. Levison ME, Levison JH. Pharmacokinetics and pharmacodynamics of antibacterial agents. Infect Dis Clin North Am. 2009 Dec;23(4):791-815, vii.
45. Rowland M, Tozer T. Clinical Pharmacokinetics. Concepts and Applications, 3rd Edition, Lea & Febiger, Philadelphia, London, 1995:469-70
46. Mouton JW, Muller AE, Canton R, Giske CG, Kahlmeter G, Turnidge J. MIC-based dose adjustment: facts and fables. J Antimicrob Chemother. 2018 Mar 1;73(3):564-568.
47. Rodríguez-Gascón A, Solinís MÁ, Isla A. The Role of PK/PD Analysis in the Development and Evaluation of Antimicrobials. Pharmaceutics. 2021 Jun 3;13(6):833.
48. de Vroom SL, van Hest RM, van Daalen FV, Kuil SD, Mathôt RAA, Geerlings SE, Jager NGL. Pharmacokinetic/pharmacodynamic target attainment of ciprofloxacin in adult patients on general wards with adequate and impaired renal function. Int J Antimicrob Agents. 2020 Nov;56(5):1061-66.
49. Zieck SE, de Vroom SL, Mulder FP, van Twillert G, Mathôt RAA, Geerlings SE, van Hest RM. Pharmacokinetic/pharmacodynamic target attainment of ceftazidime in adult patients on general wards with different degrees of renal function: a prospective observational bicenter cohort study. Antibiotics. 2023; 12(3):469.
50. Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother. 1993 May;37(5):1073-81.
51. Zelenitsky SA, Harding GK, Sun S, Ubhi K, Ariano RE. Treatment and outcome of Pseudomonas aeruginosa bacteraemia: an antibiotic pharmacodynamic analysis. J Antimicrob Chemother. 2003 Oct;52(4):668-74.
52. Zelenitsky SA, Ariano RE. Support for higher ciprofloxacin AUC 24/MIC targets in treating Enterobacteriaceae bloodstream infection. J Antimicrob Chemother. 2010 Aug;65(8):1725-32.
53. Dhaese S, Van Vooren S, Boelens J, De Waele J. Therapeutic drug monitoring of β-lactam antibiotics in the ICU. Expert Rev Anti Infect Ther. 2020 Nov;18(11):1155-1164.
54. McKinnon PS, Paladino JA, Schentag JJ. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int J Antimicrob Agents. 2008 Apr;31(4):345-51.

55. Muller AE, Punt N, Mouton JW. Optimal exposures of ceftazidime predict the probability of microbiological and clinical outcome in the treatment of nosocomial pneumonia. J Antimicrob Chemother. 2013 Apr;68(4):900-6.
56. MacVane SH, Crandon JL, Nichols WW, Nicolau DP. In vivo efficacy of humanized exposures of Ceftazidime-Avibactam in comparison with Ceftazidime against contemporary Enterobacteriaceae isolates. Antimicrob Agents Chemother. 2014 Nov;58(11):6913-9.

Chapter 2

Does dose reduction of renally cleared antibiotics in patients with impaired renal function lead to adequate drug exposure? A systematic review

Suzanne L. de Vroom, Frederike V. van Daalen, Saskia E. Zieck, Ron A.A. Mathôt, Reinier M. van Hest and Suzanne E. Geerlings

Clin Microbiol Infect. 2021 Mar;27(3):352-363

Abstract

Background
There is inconsistency between many guidelines in the recommended dose reduction of renally cleared antibiotics in patients with impaired renal function.

Objectives
This systematic review summarizes the available evidence on the adequacy of the recommended dose reduction in terms of achieving sufficient antibiotic drug exposure or pharmacokinetic/ pharmacodynamic target attainment after treatment with these reduced doses.

Data sources
We systematically searched Ovid Medline and Embase from inception (respectively 1946 and 1947) through July 2019.

Study eligibility criteria
All studies reporting antibiotic drug exposure and/or pharmacokinetic/pharmacodynamic (PK/PD) target attainment after dose reduction of antibiotics in patients with impaired renal function.

Participants
Adult patients with or without infections.

Interventions
Administration of reduced doses of antibiotics (orally, intravenously or intramuscularly).

Methods
The reduced dose was considered adequate when the most relevant parameters of drug exposure or PK/PD target attainment in patients with impaired renal function were within a range of 80% to 125% of that in patients with adequate renal function receiving a regular dose (reference) or when PK/PD target attainment was attained in at least 90% of the patients with impaired renal function, regardless of the lack of a reference group.

Results
Twenty-seven of the 4202 identified studies were included. The quality of 15 of 27 studies was fair, and most studies were of β-lactams (12/27). Best evidence was available for meropenem: four studies were included, of which two studies were of good quality. Drug exposure for meropenem is 158% to 286% higher in patients with impaired renal function receiving reduced doses compared to patients with adequate renal function receiving regular doses. For all other antibiotics, a maximum of one good-quality study could be identified.

Conclusions
No good-quality evidence on the recommended dose reduction of renally cleared antibiotics in patients with impaired renal function is present, with the exception of meropenem.

Introduction

Adequate antibiotic drug exposure in patients treated for bacterial infections is of high importance because underexposure is associated with therapeutic failure and the development of antibiotic resistance, while overexposure may lead to toxicity.[1] Reducing the dose of renally cleared antibiotics for patients with impaired renal function is standard of care as incorporated in all clinical guidelines, aiming to prevent accumulation of the drug and to achieve antibiotic drug exposure equivalent to that in patients with adequate renal function receiving the regular dose.[2,3]

However, significantly increased therapeutic failure and death were observed in patients with impaired renal function treated with recommended reduced doses of antibiotics.[4] Additionally, multiple antibiotics recently approved by the US Food and Drug Administration (FDA) carry precautionary statements in their labeling for reduced clinical response in patients with impaired renal function.[5] In clinical practice, prescribers often do not apply recommended dose reductions for patients with impaired renal function because they worry about underexposure.[6] Particularly patients in the intensive care unit (ICU) are almost always treated with regular doses instead of recommended reduced doses because underexposure is a big problem in these patients.[7-9] Also, inconsistency exists between different guidelines in the cutoff value of renal function below which the dose per antibiotic should be reduced and in the degree of the dose reduction.[10]

The Summary of Product Characteristics (SmPC) is the cornerstone of most antibiotic prescribing guidelines. Although it is obligatory to provide dosing information for patients with impaired renal function in the SmPC, these dosing recommendations seem to be marginally studied because the efficacy and safety of the antibiotic for the general population are the first concern. Recommended dose reductions in the SmPC are mainly based on extrapolations from small studies, mostly ones investigating change in pharmacokinetic parameters after a single full, unadjusted dose is administered to patients with impaired renal function.

We wondered whether the recommended dose reduction of renally cleared antibiotics for patients with impaired renal function was adequate and whether they have been validated in clinical practice. Therefore, the aim of this systematic review was to summarize the available evidence on drug exposure or on pharmacokinetic/pharmacodynamic (PK/PD) target attainment after dose reduction of antibiotics in patients with impaired renal function.

Methods

This systematic review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42019120073) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[11]

Objectives

The primary objective was to investigate antibiotic drug exposure after dose reduction in patients with impaired renal function, with drug exposure defined as either antibiotic drug concentration, defined as a peak (Cmax) and/or trough concentration (Cmin); or antibiotic area under the concentration-time curve (AUC). Additionally, we calculated AUC when the exact measures of drug exposure were not reported (see the Supplementary Appendix for the formulas used).[12]

The secondary objective was PK/PD target attainment after dose reduction in patients with impaired renal function, which is defined further below and in the Supplementary Appendix.

Clinical outcome of patients with impaired renal function receiving a reduced dose of antibiotics was investigated as an exploratory objective.

Adequacy of reduced dose

The reduced dose was considered adequate when the most relevant parameters of drug exposure or PK/PD target attainment in patients with impaired renal function were within a range of 80% to 125% of that in patients with adequate renal function receiving a regular dose (the reference). This percentage is based on the bioequivalence rules of the FDA and the European Medicines Authority.[13,14] Additionally, it was considered adequate when PK/PD target attainment was attained in at least 90% of the patients with impaired renal function, regardless of the lack of a reference group.[15]

See the Supplementary Appendix for the process for defining adequacy of the reduced dose.

Search strategy and selection criteria

To identify relevant studies, we systematically searched Ovid Medline and Embase from inception (respectively 1946 and 1947) through July 2019 with the help of an experienced clinical librarian. For both databases, search terms for (a) all renally cleared antibiotics, (b) renal function and (c) parameters of drug exposure or PK/ PD target attainment were combined (see the Supplementary Appendix for the full search). Identified studies were imported into Rayyan, where duplicates were removed and the studies screened.[16] All titles and abstracts were screened for eligibility by one author (SdV), and 10% were independently screened by two other authors (FvD and SZ). A margin of difference of 2.5% between all screening authors was allowed to occur without the need to repeat the screening. Within-margin differences of opinion were resolved by discussion and, if necessary, discussed with a fourth and fifth author (SG and RvH). Full-text articles of potential eligible studies were retrieved, and all were assessed independently for eligibility by three authors (SdV, FvD and SZ). Additionally, reference lists of all included studies were screened manually to find additional studies.

Eligible studies reported antibiotic drug exposure (Cmax, Cmin or AUC) and/or PK/PD target attainment (T > MIC, Cmax/MIC or AUC/MIC) measured in clinical practice for adult patients with impaired renal function receiving a reduced dose. To be able to solely investigate the effect of dosing of antibiotics on the basis of renal function, studies also adjusting the dose on the basis of other factors than renal function, such as body weight or therapeutic drug monitoring, were excluded. Patients receiving renal replacement therapy were excluded because of altered pharmacokinetics.[17] Case series and case reports were excluded. Supplementary Table S1 provides the exact inclusion and exclusion criteria.

Data extraction and analysis

Data from included studies were extracted by one author (SdV) and fully checked for accuracy by two other authors (FvD and SZ) using a standardized prepiloted form. We extracted, if reported, data describing the basic characteristics of the study (Supplementary Table S2), data about drug exposure and/or PK/ PD target attainment (Table 1) and data for quality assessment (Table 2). Missing data of drug exposure and/or PK/PD target attainment were requested by contacting the authors of the study. All discrepancies of data extraction between authors were rectified by review of the full text by five authors (SdV, FvD, SZ, SG and RvH). If no summary measures but only individual data about drug exposure were reported, mean and standard deviation were calculated using IBM SPSS Statistics 25 software (IBM, White Plains, NY, USA). Data were analysed using descriptive statistics; no formal statistical tests were performed on the basis of the expected heterogeneity of the data. Data from figures were not extracted to prevent potential inaccuracy.

Quality assessment

Study quality was independently assessed by three authors (SdV, FvD and SZ) using an adjusted version of the Newcastle-Ottawa Quality Assessment Scale for nonrandomized control trials.[18] See the Supplementary Appendix for the exact quality assessment.

Results

Included studies

Our search yielded 4202 unique studies, and after screening of titles and abstracts, 409 studies were left for full-text screening. The inclusion criteria were met for 25 studies; additionally, two studies were identified by manually screening the reference lists. Ultimately 27 studies were included.[19-45] The main reason for exclusion of studies was that the administered dose of antibiotics was not reduced in patients with impaired renal function (Fig. 1).

Investigated antibiotics were β-lactams (12/27), fluoroquinolones (9/27), glycopeptides (4/27) and other antibiotics (2/27). Most studies were single-centre prospective cohort studies (15/27); 16 studies included patients with clinical infections, varying from patients with septic shock at the ICU to patients on general wards. The other 11 studies included patients with impaired renal function but without infections or did not explicitly specify the included patient population (Supplementary Table S2). Most studies administered multiple intravenous doses of antibiotics (17/27) (Supplementary Table S1, Table 1). The quality of most studies was fair (15/27) (Table 2).

Best evidence on dose reduction of antibiotics in patients with impaired renal function was available for meropenem.[19-22] Other frequently investigated antibiotics were imipenem/cilastatin, cefepime, ceftolozane/tazobactam, ciprofloxacin and teicoplanin; however, only one good-quality study per antibiotic was identified.[19-37]

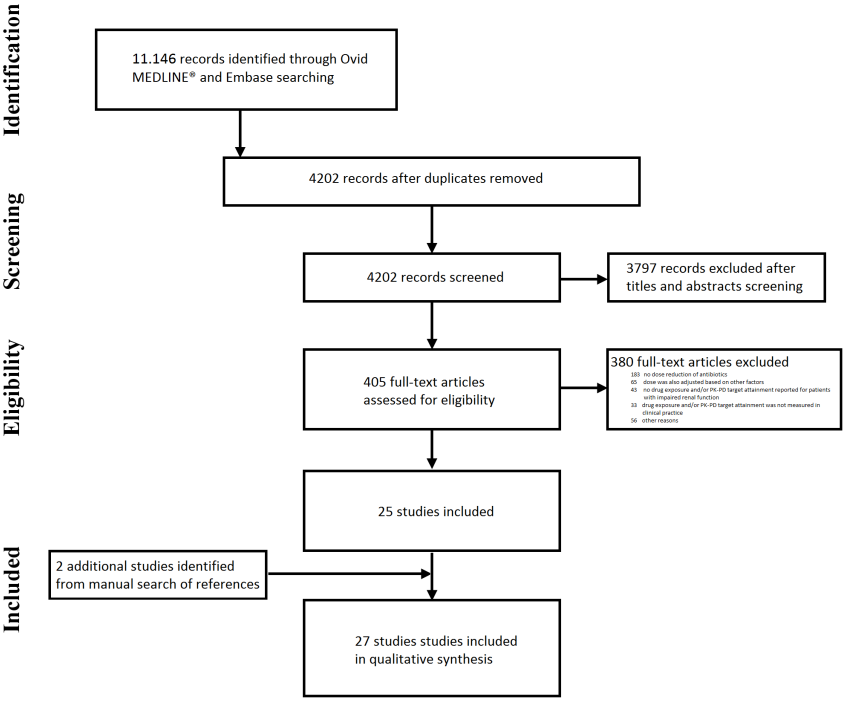


Fig. 1 Flow diagram of study selection process

Table 1 Drug exposure and PK/PD target attainment of individual studies

Study (year)	Renal function (ml/min)	Antibiotic dose (specified per renal function group)	Peak concentration (Cmax) (µg/mL)	Trough concentration (Cmin) (µg/mL)	AUC (µg·h/mL)	Within range 80%–125% compared to reference	Reduced dose seems adequate (A), too high (↑) or too low (↓)
MEROPENEM							
Del Bono (2017)[19]	Clcr ≥40	2 g q8 h	60.97 ± 27.92*		164.55 ± 102.22*	Reference	
	Clcr 10–39	2 g q12 h	48.99 ± 15.46*		339.27 ± 183.61*	>125% AUC *80%–125% Cmax*	↑
∗Calculated drug exposure.							
MEROPENEM							
Cheatham (2008)[20]	Clcr >60	500 mg q6 h	29.2 ± 9.8	2.4 ± 1.1	49.1 ± 11.7	Reference	
	Clcr 40–60	500 mg q8 h	33.2 ± 8.5	3.8 ± 2.7	86.2 ± 28.5	>125% Cmin >125% AUC *80%–125% Cmax*	↑/↑
	Clcr 10–39	500 mg q12 h	33.5 ± 4.7	4.9 ± 1.6	140.2 ± 25.0	>125% Cmin >125% AUC *80%–125% Cmax*	↑/↑
MEROPENEM							
Kitzes-Cohen (2002)[21]	Clcr >50	1 g q8 h	56.3 ± 19.1	3.3 ± 2.5	119.4 ± 32.6	Reference	
	Clcr <50	1 g q12 h	71.1 ± 5.1 p 0.1†	3.4 ± 1.8 p 0.9†	230.2 ± 43.3 p 0.0001†	80%–125% Cmin >125% AUC *>125% Cmax*	A/↑
†P value as reported by study.							
Study (year)	**Renal function (ml/min)**	**Antibiotic dose (specified per renal function group)**	**PK/PD target definition**	**MIC (µg/mL)**	**PK/PD target attainment (%)**	**Within range 80%–125% compared to reference**	**Reduced dose is adequate (A), too high (↑) or too low (↓)**
MEROPENEM, PK/PD target attainment							
Taccone (2010)[22]	Clcr >50	1 g q8 h (>80) 1 g q12 h (50–80)	% T > 4 × MIC	8	70%	Reference	
	Clcr <50	0.5 g q12 h (10–50) 0.5 g q24 h (<10)	% T > 4 × MIC	8	83%	80%–125% PK/PD	A
Study (year)	**Renal function (ml/min)**	**Antibiotic dose (specified per renal function group)**	**Peak concentration (Cmax) (µg/mL)**	**Trough concentration (Cmin) (µg/mL)**	**AUC (µg·h/mL)**	**Within range 80%–125% compared to reference**	**Reduced dose is adequate (A), too high (↑) or too low (↓)**
IMIPENEM/CILASTATIN							
Gibson (1985)[23]	Clcr ≥100	250 mg/250 mg			16.64*	No reference	Not applicable
	Clcr 30–100	250 mg/250 mg			29.34*		
	Clcr 29–10	250 mg/250 mg			48.20*		
	Clcr <10	250 mg/250 mg			73.97*		

⁎Calculated drug exposure, based on mean body weight of 73.2 kg, 86.6 kg, 76.5 kg and 71.3 kg (Clcr ≥ 100, 30–100, 10–29 and < 10 respectively).							
IMIPENEM/CILASTATIN							
Rogers (1985)[24]	GFR: 31–99	250/250 mg			32.1 ± 14.0	No reference	Not applicable
	GFR: 10–30	250/250 mg			55.0 ± 17.8		
IMIPENEM/CILASTATIN							
Verbist (1986)[25]	Clcr <15	500/500 mg q12 h			158 ± 32	No reference	Not applicable
Study (year)	**Renal function (ml/min)**	**Antibiotic dose (specified per renal function group)**	**Peak concentration (Cmax) (µg/mL)**	**Trough concentration (Cmin) (µg/mL)**	**AUC (µg·h/mL)**	**Within range 80%–125% compared to reference**	**Reduced dose is adequate (A), too high (↑) or too low (↓)**
CEFEPIME							
Lamoth (2010)[26]	Clcr >70	6 g/d		7 (2.1–21) (median, range)		Reference	Reference
	Clcr 40–70	4–6 g/d		20 (2.4–38) (median, range)		>125% Cmin	↑
	Clcr <40	2 g/d		11.4 (6.8–16) (median, range)		>125% Cmin	↑
CEFEPIME							
Tam (2003)[27]	Clcr ≥100	2 g q12 h	259 ± 287	3.3 ± 3.6	734 ± 344 (median ± range)	Reference	
	Clcr 60–100	2 g q12 h	167 ± 124	19.5 ± 21.5 p < 0.05 compared to Clcr>100†	1138 ± 540 (median ± range) p < 0.05 compared to Clcr>100†	>125% Cmin >125% AUC *<80% Cmax*	↑/↑
	Clcr 11–59	2 g q24 h (Clcr 30–59)	207 ± 295 No significant differences†	14.0 ± 11.5 p < 0.05 compared to Clcr>100†	845 ± 296 (median ± range)	>125% Cmin 80%–125% AUC *80%–125% Cmax*	↑/A
†P value as reported by study.							
Study (year)	**Renal function (ml/min)**	**Antibiotic dose (specified per renal function group)**	**PK/PD target definition**	**MIC (µg/mL)**	**PK/PD target attainment (%)**	**Within range 80%–125% compared to reference**	**Reduced dose is adequate (A), too high (↑) or too low (↓)**
CEFEPIME, PK/PD target attainment							
Taccone (2010)[22]	Clcr >50	2 g q8 h (>80) 2 g q12 h (50–80)	% T > 4 × MIC	32	14%	Reference	
	Clcr <50	1 g q12 h (10–50) 0.5 g q24 h (<10)	% T > 4 × MIC	32	17%	80%–125% PK/PD	A
Study (year)	**Renal function (ml/min)**	**Antibiotic dose (specified per renal function group)**	**Peak concentration (Cmax) (µg/mL)**	**Trough concentration (Cmin) (µg/mL)**	**AUC (µg·h/mL)**	**Within range 80%–125% compared to reference**	**Reduced dose is adequate (A), too high (↑) or too low (↓)**
CEFTOLOZANE/TAZOBACTAM							
Kakara (2019)[28]	Clcr >50	1000 mg/500 mg q8 h	69.7 (40.6%) (geometric mean, % geometric CV)		198 (43.7%) (geometric mean, % geometric CV)	Reference	

	Clcr 30–50	500 mg/250 mg q8 h	49.9 (28.6%) (geometric mean, % geometric CV)		184 (27.7%) (geometric mean, % geometric CV)	80%–125% AUC *<80% Cmax*	A
CEFTOLOZANE/TAZOBACTAM							
Wooley (2014)[29]	Clcr ≥90	1000/500 mg	72.8 (42–139) (median, range)		231 (161–311) (median, range)	Reference	
	Clcr 60–89	1000/500 mg	93.4 (75.8–141) (median, range)		315 (255–342) (median, range)	>125% AUC *>125% Cmax*	↑
	Clcr 30–59	1000/500 mg	84.5 (64–136) (median, range)		589 (306–900) (median, range)	>125% AUC *80%–125% Cmax*	↑
	Clcr 15–29	500/250 mg	47.0 (37.5–76.3) (median, range)		509 (429–762) (median, range)	>125% AUC *<80% Cmax*	↑
CEFTAROLINE FOSAMIL							
Riccobene (2014)[38]	Clcr >80	600 mg	28.4 ± 7.0		75.6 ± 9.7	Reference	
	Clcr >80	400 mg	14.8 ± 1.8		52.8 ± 10.5	—	
	Clcr 50–80	600 mg	28.2 ± 5.4		92.3 ± 25.3	80%–125% AUC *80%–125% Cmax*	A
	Clcr 30–50	600 mg	30.8 ± 4.9		114.8 ± 14.1	>125% AUC *80%–125% Cmax*	↑
	Clcr ≤30	400 mg	17.9 ± 2.9		113.3 ± 20.5	>125% AUC *<80% Cmax*	↑
Study (year)	**Renal function (ml/min)**	**Antibiotic dose (specified per renal function group)**	**PK/PD target definition**	**MIC (µg/mL)**	**PK/PD target attainment (%)**	**Within range 80%–125% compared to reference**	**Reduced dose is adequate (A), too high (↑) or too low (↓)**
CEFTAZIDIME, PK/PD target attainment							
Taccone (2010)[22]	Clcr >50	2 g q8 h (>80) 2 g q12 h (50–80)	% T > 4 × MIC	32	22%	Reference	
	Clcr <50	1 g q12 h (10–50) 0.5 g q24 h (<10)	% T > 4 × MIC	32	33%	80%–125% PK/PD	A
PIPERACILLIN/TAZOBACTAM, PK/PD target attainment							
Taccone (2010)[22]	Clcr >50	4 g q6 h	% T > 4 × MIC	64	15%	Reference	
	Clcr <50	4 g q8 h (10–50) 4 g q12 h (<10)	% T > 4 × MIC	64	71% p < 0.05 compared to Clcr >50†	>125% PK/PD	A *Better PK/PD target attainment*
†P value as reported by study.							
Study (year)	**Renal function (ml/min)**	**Antibiotic dose (specified per renal function group)**	**Peak concentration (Cmax) (µg/mL)**	**Trough concentration (Cmin) (µg/mL)**	**AUC (µg·h/mL)**	**Within range 80%–125% compared to reference**	**Reduced dose is adequate (A), too high (↑) or too low (↓)**
CIPROFLOXACIN							
Boelaert (1985)[30]	Clcr >60	250 mg	1523 ± 213 (µg/l)		1703 ± 405 (µg·h/l)	No reference	Not applicable
	Clcr <20	250 mg	1703 ± 405 (µg/l)		14,359 ± 3475 (µg·h/l)		
CIPROFLOXACIN							

Drusano (1987)[31]	Clcr >6.0 l/h	200 mg	6.30 ± 1.77	0.105 ± 0.026	7.46 (µg·h·1.73m2/mL)*	No reference	Not applicable
	Clcr 3.6–6.0 l/h	200 mg	4.14 ± 1.05	0.128 ± 0.064	9.51 (µg·h·1.73m2/mL)*		
	Clcr 0.6—3.6 l/h	200 mg	5.44 ± 0.82	0.268 ± 0.110	16.67 (µg·h·1.73m2/mL)*		
	Clcr <0.6 l/h	200 mg	5.39 ± 1.59	0.367 ± 0.060	16.24 (µg·h·1.73m2/mL)*		
∗Calculated drug exposure.							
CIPROFLOXACIN							
Macgowan (1994)[32]	Serum creat < 120 µmol/L	200 mg q12 h	1.5 ± 0.6	0.3 ± 0.3		No reference	Not applicable
	Serum creat > 120 µmol/L	200 mg q12 h	2.5 ± 1.3	0.6 ± 0.4			
CIPROFLOXACIN							
Shah (1996)[33]	Clcr >90	400 mg q8 h	4.33 (14) (geometric mean, % CV)		32.5 (18) (geometric mean, % CV)	Reference	
	Clcr 61–90	400 mg q8 h	5.86 (20) (geometric mean, % CV) p < 0.05 compared to Clcr>90†		50.4 (22) (geometric mean, % CV) p < 0.05 compared to Clcr>90†	>125% AUC >125% Cmax	↑/↑
	Clcr 31–60	400 mg q12 h	6.66 (29) (geometric mean, % CV) p < 0.05 compared to Clcr>90†		48.3 (24) (geometric mean, % CV) p < 0.05 compared to Clcr>90†	>125% AUC >125% Cmax	↑/↑
	Clcr <31	300 mg q12 h	6.03 (21) (geometric mean, % CV) p < 0.05 compared to Clcr>90†		66.3 (29) (geometric mean, % CV) p < 0.05 compared to Clcr>90†	>125% AUC >125% Cmax	↑/↑
†P value as reported by study.							
CIPROFLOXACIN							
Stoica (2015)[34]	eGFR <60	500 mg q12 h		1.35 ± 0.38		Reference	Not applicable
	<30 CKD 4	500 mg q24 h		1.36 ± 0.91		*80%–125% Cmin*	
	<30 CKD 5	500 mg q24 h		1.76 ± 1.80		*80%–125% Cmin*	
Study (year)	**Renal function (ml/min)**	**Antibiotic dose (specified per renal function group)**	**Peak concentration (Cmax) (µg/mL)**	**Trough concentration (Cmin) (µg/mL)**	**AUC (µg·h/mL)**	**Within range 80%–125% compared to reference**	**Reduced dose is adequate (A), too high (↑) or too low (↓)**
SPARFLOXACIN							
Dorr (1999)[39]	Clcr ≥50	400 mg loading dose day 1 + 200 mg q24 h	0.750 (29.3) (mean, % CV)		11.502 (32.2) (AUC0-t) (mean, % CV)	Reference	
	Clcr 30–49	400 mg loading dose day 1 + 200 mg q24 h	1.46 (17.2) (mean, % CV) p < 0.05 compared to Clcr ≥50†		25.397 (19.5) (AUC0-t) (mean, % CV) p < 0.05 compared to Clcr ≥50†	>125% AUC >125% Cmax	↑/↑
	Clcr 10–29	400 mg loading dose day 1 + 200 mg q48 h	0.800 (27.8) (mean, % CV)		19.2 (35.2) (AUC0-t) (mean, % CV) p < 0.05 compared to Clcr ≥50†	>125% AUC 80%–125% Cmax	↑/A
†P value as reported by study.							
PRULIFLOXACIN (ULIFLOXACIN ACTIVE COMPOUND)							

Tellone (2018)[42]	eGFR >80	600 mg q24 h	1.960 ± 0.992		9.829 ± 4.418	Reference	
	eGFR 50–80	600 mg q24 h	2.456 ± 1.242		14.879 ± 6.282	>125% AUC >125% Cmax	↑/↑
	eGFR 30–49	600 mg q24 h	1.801 ± 0.858		12.007 ± 5.702	80%–125% AUC 80%–125% Cmax	A/A
	eGFR <30	300 mg q24 h	1.554 ± 0.786		12.532 ± 5.921	>125% AUC <80% Cmax	↑/↓
GATIFLOXACIN							
Fish (2007)[40]	Clcr ≥40	400 mg q24 h	4.77 ± 0.76	1.08 ± 0.28	44.4 ± 9.2	Reference	
	Clcr <40	200 mg q24 h	2.85 ± 0.76 p < 0.0001 compared to Clcr ≥40†	1.20 ± 0.47	36.6 ± 3.4 p < 0.05 compared to Clcr ≥40†	80%–125% AUC 80%–125% Cmax	A/A
†P value as reported by study.							
Study (year)	**Renal function (ml/min)**	**Antibiotic dose (specified per renal function group)**	**PK/PD target definition**	**MIC (µg/mL)**	**PK/PD target attainment (%)**	**Within range 80%–125% compared to reference**	**Reduced dose is adequate (A), too high (↑) or too low (↓)**
GATIFLOXACIN, PK/PD target attainment							
Fish (2007)[40]	Clcr ≥40	400 mg q24 h	Cmax/MIC	0.25	11 ± 3 (ratios)	Reference	
				0.5	6 ± 2 (ratios)		
				1	3 ± 1 (ratios)		
				2	1 ± 0 (ratios)		
			AUC0–24/MIC	0.25	147 ± 13 (ratios)		
				0.5	73 ± 7 (ratios)		
				1	37 ± 3 (ratios)		
				2	18 ± 2 (ratios)		
	Clcr <40	200 mg q24 h	Cmax/MIC	0.25	19 ± 3 (ratios)	>125% PK/PD	A/A *Better PK/PD target attainment*
				0.5	10 ± 2 (ratios)		
				1	5 ± 1 (ratios)		
				2	2 ± 0 (ratios)		
			AUC0–24/MIC	0.25	178 ± 37 (ratios)	80%–125% PK/PD	
				0.5	89 ± 18 (ratios)		
				1	44 ± 9 (ratios)		
				2	22 ± 5 (ratios)		
LEVOFLOXACINE, PK/PD target attainment							
Kiem (2016)[41]	Clcr >50	500 mg q24 h	AUC/MIC >25/50/100	0.25	100%/100%/100%	Reference	
				0.5	100%/100%/81.25%		
				1	100/%81.25%/15.6%		
				2	62.5%/15.6%/0%		
				4	6.25%/0%/0%		
	Clcr 20–50	250 mg q24 h	AUC/MIC >25/50/100	0.25	100%/100%/100%	80%–125% PK/PD	A/A *Better PK/PD target attainment*
				0.5	100%/100%/83.3%	80%–125% PK/PD	
				1	100%/83.3%/33.3%	>125% PK/PD	
				2	83.3%/33.3%/0%	>125% PK/PD	
				4	33.3%/33.3%/0%	>125% PK/PD	

Study (year)	Renal function (ml/min)	Antibiotic dose (specified per renal function group)	Peak concentration (Cmax) (µg/mL)	Trough concentration (Cmin) (µg/mL)	AUC (µg·h/mL)	Within range 80%–125% compared to reference	Reduced dose is adequate (A), too high (↑) or too low (↓)
TEICOPLANIN							
Presterl (1993)[35]	Clcr 80–120	600 mg/d		5.0 ± 2.1*		Reference	
	Clcr <75	400 mg/d		5.0 ± 2.5*		80%–125% Cmin	A
∗Calculated drug exposure.							
TEICOPLANIN							
Ueda (2012)[36]	Clcr ≥50	Loading dose 400 mg q12 h for 2 days, followed by 400 mg q24 h		11.2 ± 2.5		Reference	
	Clcr <50	Loading dose 400 mg q12 h for 1 day, followed by 400 mg q24 h		11.4 ± 3.0		80%–125% Cmin	A
TEICOPLANIN							
Zhou (2018)[37]	Clcr ≥60	Loading dose: 400 mg q12 h for 3–6 times, after 400 mg/d		18.11 ± 6.37		Reference	
	Clcr 40–60	Loading dose: 400 mg q12 h for 3 times, after 400 mg/d		15.91 ± 4.94		80%–125% Cmin	A
	Clcr <40	Loading dose: 400 mg q12 h for 2 times, after 200 mg/d		17.06 ± 5.66		80%–125% Cmin	A
Study (year)	**Renal function (ml/min)**	**Antibiotic dose (specified per renal function group)**	**PK/PD target definition**	**MIC (µg/mL)**	**PK/PD target attainment (%)**	**Within range 80%–125% compared to reference**	**Reduced dose is adequate (A), too high (↑) or too low (↓)**
TEICOPLANIN, PK/PD target attainment							
Zhou (2018)[37]	Clcr ≥60	Loading dose: 400 mg q12 h for 3–6 times, after 400 mg/d	% > Cmin	10–30 15–30	88.89% 69.44%	Reference Reference	
	Clcr 40–60	Loading dose: 400 mg q12 h for 3 times, after 400 mg/d	% > Cmin	10–30 15–30	86.67% 66.67%	80%–125% PK/PD 80%–125% PK/PD	A/A
	Clcr <40	Loading dose: 400 mg q12 h	% > Cmin	10–30 15–30	88.23% 70.59%	80%–125% PK/PD	A/A

		for 2 times, after 200 mg/d				80%–125% PK/PD	
Study (year)	**Renal function (ml/min)**	**Antibiotic dose (specified per renal function group)**	**Peak concentration (Cmax) (μg/mL)**	**Trough concentration (Cmin) (μg/mL)**	**AUC (μg·h/mL)**	**Within range 80%–125% compared to reference**	**Reduced dose is adequate (A), too high (↑) or too low (↓)**
VANCOMYCIN							
Chung (2011)[43]	Clcr >60	1 g q12 h		12.5 ± 7	519	Reference	
	Clcr 30–60	1 g q24–48 h		16.7 ± 10	608	>125% Cmin 80%–125% AUC	↑/A
	Clcr <30	1 g q72–96 h		17.5 ± 19	563	>125% Cmin 80%–125% AUC	↑/A
TOBRAMYCIN							
Brogard (1982)[44]	Clcr ≥70	50 mg q8 h	4.3 ± 0.5	0.6 ± 0.1	18.2	—	
		75 mg q8 h	4.3 ± 0.3	1.0 ± 0.3	23.4	—	
		100 mg q8 h	4.4 ± 0.7	1.2 ± 0.1	29.0	Reference	
	Clcr <50	50 mg q24 h	6.0 ± 2.9*	2.7 ± 1.7*	34.32 ± 51.45*	>125% Cmin 80%–125% AUC *80%–125% Cmax*	↑/A
***Calculated drug exposure.**							
TELITHROMYCIN							
Shi (2004)[45]	Clcr >80	800 mg 1q24 h	2.07 (39) (mean, %CV)		12.44 (48) (mean, %CV)	Reference	
	Clcr 50–80	800 mg 1q24 h	2.56 (13) (mean, %CV)		16.00 (22) (mean, %CV)	80%–125% Cmax >125% AUC	A/↑
		600 mg 1q24 h	1.69 (37) (mean, %CV)		10.60 (52) (mean, %CV)	80%–125% Cmax 80%–125% AUC	A/A
		400 mg 1q24 h	1.00 (47) (mean, %CV)		4.96 (43) (mean, %CV)	<80% Cmax <80% AUC	↓/↓
	Clcr 30–49	800 mg 1q24 h	2.20 (48) (mean, %CV)		14.76 (41) (mean, %CV)	80%–125% Cmax 80%–125% AUC	A/A
		600 mg 1q24 h	1.46 (40) (mean, %CV)		10.01 (43) (mean, %CV)	<80% Cmax 80%–125% AUC	↓/A
		400 mg 1q24 h	1.01 (69) (mean, %CV)		5.48 (73) (mean, %CV)	<80% Cmax <80% AUC	↓/↓
	Clcr <30	800 mg 1q24 h	2.99 (40) (mean, %CV)		23.6 (29) (mean, %CV)	>125% Cmax >125% AUC	↑/↑
		600 mg 1q24 h	1.79 (32) (mean, %CV)		14.84 (60) (mean, %CV)	80%–125% Cmax 80%–125% AUC	A/A
		400 mg 1q24 h	1.17 (49) (mean, %CV)		6.89 (57) (mean, %CV)	<80% Cmax <80% AUC	↓/↓

Data are presented as mean ± SD unless otherwise stated. AUC, area under the concentration–time curve; Cl_{cr}, creatinine clearance; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic; CV, coefficient of variation.

Table 2 Quality assessment summary of individual studies

Study (year)	Selection				Comparability	Outcome	Total score (maximum 9)
	Representativeness of exposed cohort	Acertainment of exposure (1)	Ascertainment of exposure (2)	Sample size	Comparability of cohorts on basis of design or analysis	Assessment of outcome	
MEROPENEM							
Del Bono (2017)[19]	*	*	**	—	—	**	6: fair
Cheatham (2008)[20]	**	*	**	—	*	**	8: good
Kitzes-Cohen (2002)[21]	**	*	**	—	*	**	8: good
Taccone (2010)[22]	**	*	*	—	*	**	7: fair
IMIPENEM/CILASTATIN							
Gibson (1985)[23]	—	*	**	—	—	*	4: poor
Rogers (1985)[24]	**	—	**	—	—	**	6: fair
Verbist (1986)[25]	—	—	**	—	—	*	3: poor
CEPHALOSPORINS							
Lamoth (2010)[26]	*	*	**	—	*	**	7: fair
Tam (2003)[27]	**	*	**	*	*	*	8: good
Kakara (2019)[28]	*	*	**	—	*	**	7: fair
Wooley (2014)[29]	—	*	**	—	*	**	6: fair
Riccobene (2014)[38]	—	*	**	—	*	**	6: fair
CIPROFLOXACIN							
Boelaert (1985)[30]	—	—	**	—	—	*	3: poor
Drusano (1987)[31]	—	—	**	—	—	*	3: poor
MacGowan (1994)[32]	**	—	*	—	—	—	3: poor
Shah (1996)[33]	—	*	**	—	*	**	6: fair
Stoica (2015)[34]	**	*	*	—	*	**	7: fair
OTHER FLUOROQUINOLONES							
Dorr (1999)[39]	—	*	*	—	*	**	5: fair
Fish (2007)[40]	*	*	**	*	*	**	8: good
Kiem (2016)[41]	*	*	**	—	*	*	6: fair
Tellone (2018)[42]	—	*	*	—	*	**	5: fair
GLYCOPEPTIDES							
Presterl (1993)[35]	*	—	**	—	—	*	4: poor
Ueda (2012)[36]	*	*	**	—	—	—	4: poor
Zhou (2018)[37]	*	*	*	—	*	*	5: fair
Chung (2011)[43]	*	*	*	—	*	*	5: fair
OTHER ANTIBIOTICS							
Brogard (1982)[44]	—	—	**	—	—	—	2: poor
Shi (2004)[45]	—	*	**	—	*	**	6: fair

Exact definitions used for selection, comparability and outcome are provided in the Supplementary Appendix.

β-lactams

Meropenem

The best evidence on dose reduction of antibiotics in patients with impaired renal function was available for meropenem. Four studies were performed, all in patients with infections, of which two studied patients in the ICU. The quality of two studies was good and of the other two studies was fair (Supplementary Table S1, Table 2).

Three studies investigated drug exposure.[19-21] Two of these studies investigating trough concentrations showed 158% to 204% higher mean trough concentrations in patients with impaired renal function.[19,20] Mean AUCs were 170% to 286% higher in patients with impaired renal function in all three studies investigating AUC (Table 1).[19-21]

One study investigating PK/PD target attainment showed comparable target attainment (within 80-125%) between patients with impaired renal function and patients with adequate renal function (Table 1).[22]

Imipenem/cilastatin

Three studies investigated imipenem/cilastatin; however, none of the studies included an (external) reference group, so comparing drug exposure was not possible.[23-25]

Cefepime

Three studies investigated cefepime, all in patients with infections, of which one studied patients with febrile neutropenia and one patients in the ICU.[22,26,27] The quality of one study was good and of two studies was fair (Supplementary Table S1, Table 2). Mean and median trough concentrations were 163% to 591% higher in patients with impaired renal function in both studies that investigated drug exposure.[26,27] The one study investigating AUC showed higher median AUC in patients with creatinine clearance (Clcr) 60-100 mL/min at 155%, but comparable median AUC in patients with moderate to severe renal impairment (Clcr 11-59 mL/ min, 115%) (Table 1).[27]

One study investigating PK/PD target attainment showed comparable target attainment (within 80-125%) between patients with impaired renal function and patients with adequate renal function (Table 1).[22]

Ceftolozane/tazobactam

Two studies investigated ceftolozane/tazobactam, one multiple-dose study in patients with infections (administration of ceftolozane/tazobactam every 8 hours for 4-14 days) and one single-dose study in volunteers without infections.[28,29] The quality of both studies was fair (Supplementary Table S1, Table 2).

The multiple-dose study showed that the geometric mean AUC was comparable (within 80-125%) between patients with impaired and adequate renal function.[28] The single-dose study showed that the median AUC was 136% to 255% higher in patients with impaired renal function (ranges apply to patients belonging to different impaired renal function groups) (Table 1).[29] However, the cutoff

value of renal function below which a reduced dose was administered differed greatly; the multiple-dose study, which showed comparable AUC, administered reduced doses to patients with Clcr 30-50 mL/min, while the single-dose study only administered a reduced dose to patients with Clcr <30 mL/min, while patients with Clcr 30-50 mL/min received a regular dose (Table 1).

Fluoroquinolones

Ciprofloxacin

The most frequently investigated antibiotic was ciprofloxacin; however, only one of the five studies included an (external) reference group, so comparing drug exposure was only possible in one study.[33] The quality of this study was fair. Results showed that the geometric mean AUC and peak concentration were both higher in patients with impaired renal function, ranging from 149% to 204% (AUC) and from 135% to 154% (Cmax) among different impaired renal function groups (Table 1).

Glycopeptides

Teicoplanin

Three studies investigated teicoplanin, all in patients with infections.[35-37] The quality of one study was fair and of two studies was poor (Supplementary Table S1, Table 2). All three studies showed that the mean trough concentration was comparable (within 80-125%) between patients with impaired and adequate renal function. Additionally, PK/PD target attainment between both patient groups was comparable (within 80-125%) (Table 1).[37]

Other antibiotics

See the Supplementary Appendix for other antibiotics investigated by one sole study.[38-45]

Clinical outcome

One study showed significant longer time to resolution of symptoms in patients with impaired renal function receiving reduced doses of antibiotics.[20]

Discussion

No good-quality evidence on the recommended dose reduction of renally cleared antibiotics in patients with impaired renal function is available, with the exception of meropenem. Strikingly, these dosing recommendations are the standard of care as incorporated in all clinical guidelines and are applied globally on a daily basis. Because significantly increased failure of therapy and death were observed in patients with impaired renal function treated with these recommended reduced doses and because most prescribers do not even apply these dose reductions because they worry about underexposure, we question the adequacy of these dosing recommendations.[4-6]

The lack of evidence is caused by the absence of prospective validation of the recommended dose reduction of almost all renally cleared antibiotics. Current dosing recommendations are only based on extrapolations from studies reporting reduced renal clearance of a full antibiotic dose administered to patients with impaired renal function. Besides, the technical hurdles of drug monitoring (e.g. requirement of liquid chromatography-mass spectrometry) may have contributed substantially to this lack of evidence.

Remarkably, none of the studies used the same definition of renal impairment below which the dose was reduced, and most studies did not apply the same dose reduction for the same antibiotic. Although some heterogeneity is expected because the degree of renal clearance varies between antibiotics and consequently the influence of renal impairment, heterogeneity between studies investigating the same antibiotic is undesirable.

The adequacy of the recommended dose reduction has been questioned before because most recommendations would be based on studies performed in patients with chronic renal impairment.[5] This is in accordance with our results; when mentioned, most studies included only patients with chronic renal impairment. Because the measured renal function in patients with acute renal impairment may be worse than the actual renal function, the dose reduction for patients with acute renal impairment may be overestimated.

This review had some limitations. Firstly, only heterogeneous studies could be included, and only two studies performed a sample size calculation. Consequently, it was difficult to draw consistent conclusions about the adequacy of the recommended dose reduction of most antibiotics. Secondly, measures of clinical outcome were lacking in nearly all included studies. Although all studies reported drug exposure, only four studies related this to PK/PD target attainment, and only one sole study actually reported measures of clinical outcome. Although PK/PD target attainment is assumed to have an association with clinical outcome, this is also the subject of ongoing discussion because often no uniform PK/PD target ratios based on clinical evidence are available.[46] Thirdly, to provide unbiased evidence on renally based dosing of antibiotics, our inclusion criteria were rather strict, so we may consequently have missed some potentially relevant studies. Studies also adjusting doses for factors other than renal function (e.g. body weight or therapeutic drug monitoring) were excluded. This may have caused the striking lack of studies about glycopeptides and aminoglycosides: dosing of these antibiotics is often based on body weight and on therapeutic drug monitoring as well.

Further research should focus on prospective validation of current dosing recommendations of renally cleared antibiotics for patients with impaired renal function. It has to be assessed whether drug exposure (i.e. the unbound fraction, which represents the biologically active fraction) is comparable between patients with adequate renal function receiving regular doses and patients with impaired renal function receiving currently recommended reduced doses. Additionally, PK/PD

target attainment and ideally clinical efficacy should be comparable between both patient groups. We suggest that this be investigated separately for patients with acute and chronic renal impairment because renal clearance and drug exposure may not be interchangeable between both patient groups. We are currently performing studies to prospectively validate the recommended dose reduction of ciprofloxacin and ceftazidime in patients with impaired renal function (2019-005021-79 and NTR NL7864 respectively).[47]

Conclusions

No good-quality evidence from multiple studies is present showing that the recommended dose reductions of renally cleared antibiotics in patients with impaired renal function are adequate in terms of achieving comparable drug exposure as the regular dose in patients with adequate renal function. There is a need to prospectively validate the currently recommended dose reduction of renally cleared antibiotics.

Transparency declaration

RAAM reports grants from Baxter/Baxalta/Shire, grants from Bayer Schering Pharma, grants from CSL Behring, grants from Merck Sharp & Dohme and grants from Zeria, outside the submitted work. RMvH reports grants from Nordic Pharma, outside the submitted work. SEG reports grants from Nordic Pharma and grants from Vifor Pharma, outside the submitted work. The other authors report no conflicts of interest relevant to this review.

Acknowledgement

We thank Rene Spijker, information specialist of Cochrane Netherlands and the Amsterdam UMC University of Amsterdam Medical Library, for his help in developing the search strategy.

References

1. Pea F, Viale P. Bench-to-bedside review: Appropriate antibiotic therapy in severe sepsis and septic shock – does the dose matter? Crit Care, 2009;13(3):214.
2. Levison ME, Levison JH. Pharmacokinetics and Pharmacodynamics of Antibacterial Agents. Infect Dis Clin North Am, 2009;Dec 23(4):791–vii.
3. Verbeeck RK, Musuamba, FT. Pharmacokinetics and dosage adjustment in patients with renal dysfunction. Eur J Clin Pharmacol, 2009;65:757.
4. Camargo, M.S., Mistro, S., Oliveira, M.G. et al. Association between increased mortality rate and antibiotic dose adjustment in intensive care unit patients with renal impairment. Eur J Clin Pharmacol, 2019;75:119–126.
5. Crass RL, Rodvold KA, Mueller BA, Pai MP. Renal Dosing of Antibiotics: Are We Jumping the Gun? Clinical Infectious Diseases, 2019;68(9):1596–1602.
6. Van Daalen FV, Prins JM, Opmeer BC, Boermeester MA, Visser CE, van Hest RM *et al*. Effect of an antibiotic checklist on length of hospital stay and appropriate antibiotic use in adult patients treated with intravenous antibiotics: a stepped wedge cluster randomized trial. Clin Microbiol Infect, 2017;23(7):485.e1-e8.
7. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G *et al*. DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current β-Lactam Antibiotic Doses Sufficient for Critically Ill Patients?, Clinical Infectious Diseases, 2014;58(8):1072–83
8. Zoller, M., Maier, B., Hornuss, C. Neugebauer C, Döbbeler G, Nagel D *et al*. Variability of linezolid concentrations after standard dosing in critically ill patients: a prospective observational study. Crit Care, 2014;18:R148.
9. Udy AA, Varghese JM, Altukroni M, Briscoe S, McWhinney BS, Ungerer JP *et al*. Subtherapeutic Initial β-Lactam Concentrations in Select Critically Ill Patients. Chest, 2012;142(1):30-39.
10. Vidal L, Shavit M, Fraser A, Paul M, Leibovici L. Systematic comparison of four sources of drug information regarding adjustment of dose for renal function. BMJ, 2005;331:263.
11. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M *et al*. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev, 2015;4(1):1.
12. Rowland M, Tozer TN. Clinical Pharmacokinetics and Pharmacodynamics. Lippincott Williams And Wilkins, 2010:24.
13. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations. Available on: https://www.fda.gov/media/88254/download. Accessed 2019-12-02.
14. European Medicines Agency (EMA), Guideline on the investigation of bioequivalence, London 20 January 2010. Available on: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf. Accessed 2019-12-02.
15. Wang H, Zhang B, Ni Y, Kuti JL, Chen B, Chen M *et al*. Pharmacodynamic target attainment of seven antimicrobials against Gram-negative bacteria collected from China in 2003 and 2004. Int J Antimicrob Agents, 2007;30:452–7.
16. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid, A. Rayyan—a web and mobile app for systematic reviews. Syst Rev, 2016;5:210.
17. Pea F, Viale P, Pavan F, Furlanut M. Pharmacokinetic considerations for antimicrobial therapy in patients receiving renal replacement therapy. Clin Pharmacokinet, 2007;46(12):997-1038.
18. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M *et al*. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 2018-12-21.

19. Del Bono V, Giacobbe DR, Marchese A, Parisini A, Fucile C, Coppo E *et al*. Meropenem for treating KPC-producing Klebsiella pneumoniae bloodstream infections: Should we get to the PK/PD root of the paradox? Virulence, 2017:Jan2;8(1):66-73.
20. Cheatham SC, Kays MB, Smith DW, Wack MF, Sowinski KM. Steady-state pharmacokinetics and pharmacodynamics of meropenem in hospitalized patients. Pharmacotherapy, 2008;28(6):691-698.
21. Kitzes-Cohen R, Farin D, Piva G, De Myttenaere-Bursztein SA. Pharmacokinetics and pharmacodynamics of meropenem in critically ill patients. International Journal of Antimicrobial Agents, 2002;19:105-110.
22. Taccone FS, Laterre P, Dugernier T, Spapen H, Delattre I, Wiitebole X *et al*. Insufficient β-lactam concentrations in the early phase of severe sepsis and septic shock. Critical Care, 2010;14:R126.
23. Gibson TP, Demetriades JL, Bland JA. Imipenem/cilastatin: pharmacokinetic profile in renal insufficiency. Am J Med, 1985;Jun7;78(6A):54-61.
24. Rogers JD, Meisinger MA, Ferber F, Calandra GB, Demetriades JL, Bland JA. Pharmacokinetics of imipenem and cilastatin in volunteers. Rev Infect Dis, 1985;7Suppl3:S435-46.
25. Verbist L, Verpooten GA, Giuliano RA, Debroe ME, Buntix AP, Entwistle LA *et al*. Pharmacokinetics and tolerance after repeated doses of imipenem/cilastatin in patients with severe renal failure. J Antimicrob Chemother, 1986;18SupplE:115-20.
26. Lamoth F, Buclin T, Pascual A, Vora S, Bolay S, Decosterd LA *et al*. High cefepime plasma concentrations and neurological toxicity in febrile neutropenic patients with mild impairment of renal function. Antimicrobial Agents and Chemotherapy, 2010;54(10):4360–67.
27. Tam VH, McKinnon PS, Akins RL, Drusano GL, Rybak MJ. Pharmacokinetics and pharmacodynamics of cefepime in patients with various degrees of renal function. Antimicrobial Agents and Chemotherapy, 2003;47(6):1853-61.
28. Kakara M, Larson K, Feng H, Shiomi M, Yoshitsugu H, Rizk ML. Population pharmacokinetics of tazobactam/ceftolozane in Japanese patients with complicated urinary tract infection and complicated intra-abdominal infection. J Infect Chemother, 2019;2:182e191.
29. Wooley M, Miller B, Krishna G, Hershberger E, Chandorkar G. Impact of renal function on the pharmacokinetics and safety of ceftolozane-tazobactam. Antimicrobial Agents and Chemotherapy, 2014;58(4):2249-55.
30. Boelaert J, Valcke Y, Schurgers M, Daneels R, Rosseneu M, Rosseel MT *et al*. The pharmacokinetics of ciprofloxacin in patients with impaired renal function. Journal of Antimicrobial Chemotherapy, 1985;16:87-93.
31. Drusano GL, Weir M, Forrest A, Plaisance K, Emm T, Standiford HC. Pharmacokinetics of intravenously administered ciprofloxacin in patients with various degrees of renal function. Antimicrobial Agents and Chemotherapy, 1987;June:860-4.
32. Macgowan AP, White LO, Brown M, Lovering AM, McMullin CM, Reeves DS. Serum ciprofloxacin concentrations in patients with severe sepsis being treated with ciprofloxacin 200 mg iv bd irrespective or renal function. Journal of Antimicrobial Chemotherapy, 1994;33:1051-4.
33. Shah A, Lettieri J, Blum R, Millikin S, Sica D, Heller AH. Pharmacokinetics of intravenous ciprofloxacin in normal and renally impaired subjects. J Antimicrob Chemother, 1996;Jul38(1):103-16.
34. Stoica MC, Vari CE, Imre S, Vancea S, Dogaru MT, Carasca E *et al*. Correlations between the stages of kidney disease and the pharmacokinetic parameters of orally administered ciprofloxacin at patients with chronic kidney disease. Farmacia, 2015;63:5.
35. Presterl E, Graninger W, Georgopoulos A. The efficacy of teicoplanin in the treatment of endocarditis caused by Gram-positive bacteria. Journal of Antimicrobial Chemotherapy, 1993;31: 755-66.
36. Ueda T, Takesue Y, Nakajima K, Ichki K, Wada Y, Tsuchida T *et al*. Evaluation of teicoplanin dosing designs to achieve a new target trough concentration. J Infect Chemother, 2012;18:296–302.

37. Zhou L, Gao Y, Cao W. Retrospective analysis of relationships among the dose regimen, trough concentration, efficacy, and safety of teicoplanin in Chinese patients with moderate–severe Gram-positive infections. Infection and Drug Resistance, 2018;11:29–36.
38. Riccobene T, Jakate A, Rank D. A series of pharmacokinetic studies of ceftaroline fosamil in select populations: normal subjects, healthy elderly subjects, and subjects with renal impairment or end-stage renal disease requiring hemodialysis. The Journal of Clinical Pharmacology, 2014;54(7):742–52.
39. Dorr MB, Johnson RD, Jensen B, Magner D, Marbury T, Talbot GH. Pharmacokinetics of sparfloxacin in patients with renal impairment. Clinical Therapeutics, 1997;21:7.
40. Fish, DN. Evaluation of gatifloxacin pharmacokinetics and pharmacodynamics in severely ill adults in a medical Intensive Care Unit. International Journal of Antimicrobial Agents, 2007;29:715–23.
41. Kiem S, Ryu S, Lee Y, Schentag JJ, Kim Y, Kim H *et al*. Population pharmacokinetics of levofloxacin in Korean patients, Journal of Chemotherapy, 2016;28:4:308-13.
42. Tellone V, Coppola P, Ammendola M, Di Loreto G, Picollo R, Del Vecchio A *et al*. New Insights on the Pharmacokinetics of Ulifloxacin After Administration of Prulifloxacin in Patients with Mild, Moderate and Severe Renal Impairment. Drugs in R&D, 2018;18:237–45.
43. Chung J, Oh JM, Cho EM, Jang HJ, Hong SB, Lim CM *et al*. Optimal dose of vancomycin for treating methicillin-resistant Staphylococcus aureus pneumonia in critically ill patients. Anaesth Intensive Care, 2011;39(6):1030-7.
44. Brogard JM, Conraux C, Collard M, Lavillaureix J. Ototoxicity of tobramycin in humans – influence of renal impairment. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1982;20(9): 408-16.
45. Shi J, Montay G, Chapel S, Hardy P, Barrett JS, Sack M *et al*. Pharmacokinetics and safety of the ketolide telithromycin in patients with renal impairment. Journal of Clinical Pharmacology, 2004;44:234-44.
46. Heffernan AJ, Sime FB, Lipman J, Roberts JA. Individualising Therapy to Minimize Bacterial Multidrug Resistance. Drugs. 2018 Apr;78(6):621-641.
47. de Vroom SL, van Hest RM, van Daalen FV, Kuil SD, Mathôt RAA, Geerlings SE *et al.* Pharmacokinetic/pharmacodynamic target attainment of ciprofloxacin in adult patients on general wards with adequate and impaired renal function. Int J Antimicrob Agents. 2020 Nov;56(5):1061-66.

Supplementary Appendix

Methods

Objectives

Additionally, when the exact measures of drug exposure were not reported (i.e. Cmax, Cmin or AUC), but it was possible to calculate AUC based on other reported pharmacokinetic parameters, we used the following formulas to calculate AUC (dependent on the route of administration):

1) Intravenous administration: AUC = administered intravenous dose / total clearance[1]

2) Other routes of administration (i.e. oral or intramuscular administration): AUC = (administered dose * bioavailability) / total clearance

Adequacy of the reduced dose

Dosing of antibiotics is generally considered adequate when the relevant PK/PD target is attained:

1) For antibiotics with time-dependent killing (e.g. carbapenems, cephalosporins and penicillins), T >MIC is the relevant PK/PD target.[2] The most relevant parameter of drug exposure then is Cmin; when Cmin is still above MIC, it can be assumed that 100%T > MIC is attained. We also assessed AUC as relevant parameter, since Cmin also correlates with AUC.

2) For antibiotics with concentration-dependent killing (e.g. aminoglycosides and fluoroquinolones), Cmax/MIC and AUC/MIC are the relevant PK/PD targets and as such the most relevant parameters of drug exposure are Cmax for aminoglycosides and AUC and Cmax for fluoroquinolones.[2]

3) For antibiotics with time- and concentration-dependent killing (e.g. glycopeptides), AUC/MIC is the relevant PK/PD target and consequently the most relevant parameter of drug exposure is AUC.[2]

The reduced dose was considered adequate, when the most relevant parameter(s) of drug exposure in patients with impaired renal function were comparable to that in patients with adequate renal function receiving a regular dose (the reference). Comparable drug exposure was defined according to the general bioequivalence rules of the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), being a drug exposure in patients with impaired renal function receiving a reduced dose within a range of 80%-125% of the reference.[3,4] Drug exposure refers to the free unbound drug concentration, which represents the biologically active fraction. The comparability of drug exposure was independent of the measurement of free or total drug concentration. If patients with adequate renal function received different regular doses of the same antibiotic within one study, the drug exposure obtained with the highest regular dose was selected as the reference.

If studies did not include patients with adequate renal function receiving a regular dose, drug exposure in patients with impaired renal function was compared to drug exposure in an external reference group of patients with adequate renal function, referred to by the author(s) of the study. If also an external reference group was lacking, the adequacy of the reduced dose could not be defined in this study.

Additionally, when parameters of drug exposure were not reported, but PK/PD target attainment was, the reduced dose was considered adequate when PK/PD target attainment in patients with impaired renal function was comparable (within a range of 80%-125%) to PK/PD target attainment in patients with adequate renal function receiving regular doses, regardless of the actual (potentially low) percentages of target attainment; or when PK/PD target attainment was attained in at least 90% of the patients with impaired renal function, regardless of the lack of an (external) reference group.[5]

Search strategy and selection criteria

Eligible studies reported antibiotic drug exposure (Cmax, Cmin or AUC) and/or PK/PD target attainment (T > MIC, Cmax/MIC or AUC/MIC) for patients with impaired renal function receiving a reduced dose. Additionally, if it was not specifically mentioned that the dose was reduced, but the administered dose was already a reduced dose according to relevant clinical guidelines, the study was also eligible, since this provides insight in the adequacy of doses that are administered as reduced doses in real-life clinical practice.[6] To be able to solely investigate the effect of dosing of antibiotics based on renal function, studies also adjusting the dose based on other factors than renal function, such as bodyweight or therapeutic drug monitoring (TDM), were excluded. Patients on renal replacement therapy were excluded, because of altered pharmacokinetics.[7] Impaired renal function was based on the definition used by the authors of the original study and so could differ among studies. See for all inclusion and exclusion criteria Appendix Table S1.

Quality assessment

Study quality was independently assessed by three authors (SdV, FvD and SZ) using an adjusted version of the Newcastle-Ottawa Quality Assessment Scale for non-randomized control trials.[8] Six relevant items were scored of which three items could be scored with a maximum of two stars and three items with a maximum of one star. In total a maximum of 9 stars could be obtained. Study quality was assessed as good with ≥8 stars, fair with 5-7 stars and poor ≤4 stars.

Results

Other antibiotics

Other investigated antibiotics were one cephalosporins (ceftaroline fosamil), one penicillin (piperacillin/tazobactam), four fluoroquinolones (sparfloxacin, prulifloxacin, gatifloxacin and levofloxacin), one glycopeptide (vancomycin), one aminoglycoside (tobramycin) and one ketolide (telithromycin). The quality of most studies investigating these other antibiotics was fair (7/9) (Table 2) and all studies included a reference group. However, all these other antibiotics were only investigated by one sole study.

Full electronic search strategy from Ovid MEDLINE® 1946 to July 12, 2019*

1. exp Antibacterial agents/ or antibiotic*.ti,ab,kf. or (Aminoglycosides or amikacin or gentamicin or kanamycin or streptomycin or tobramycin or Carbapenems or ertapenem or imipenem or meropenem or Cephalosporins or cefaclor or cefalexin or cephalexin or cefalotin or cephalotinor cephalothin or cefamandole or cephamandole or cefazolin or cefazoline or cephazolin or cefixim* or cefotaxim* or cephotaxim* or ceftaroline or ceftazidim* or ceftibuten or ceftozolane or ceftriaxone or cefuroxime* or Quinolones or ciprofloxacin or levofloxacin or norfloxacin or ofloxacin or Glycopeptides or dalbavancin or teicoplanin or vancomycin or Macrolides or clarithromycin Penicillins or amoxicillin or penicillin or benzylpenicillinor flucloxacillin or piperacillin or colistin or Rifamycins or rifabutin or cotrimoxazole or trimethoprim or sulfamethoxazole or sulfadiazine or sulfametrol or Tetracyclines or minocycline or tetracycline or daptomycin or fosfomycin or doripenem or ethambutol or pyrazinamide).ti,ab,kf,rn.

2. (((renal or kidney) adj3 (disease* or impairment or function or dysfunction or insufficiency)) and (dose or dosage or mg)).ti,ab.

3. pharmacokinetics.fs. or exp pharmacokinetics/ or exp area under curve/ or exp absorption/ or half-life/ or
(Pharmacodynamic* or pharmacodynamic* or PK or PD or "pk/PD" or PPK or tmax or cmax or AUC or "area under the curve" or clearance or elimination or "volume of distribution" or "drug level" or absorption or half-life or "Therapeutic range" or "Drug exposure" or ((serum or plasma or blood) adj3 (concentration or level* or sample*))).ti,ab,kf. 4. 1 and 2 and 3

5. (exp animals/ not humans/) or (mice or mouse or rat or rats or guinea-pig* or dog).ti. or case reports.pt.

6. 4 not 5

*** Performed together with an experienced clinical librarian**

Full electronic search strategy from Embase 1947 to July 12, 2019*

1. exp antibiotic agent/ or antibiotic*.ti,ab,kw. or (Aminoglycosides or amikacin or gentamicin or kanamycin or streptomycin or tobramycin or Carbapenems or ertapenem or imipenem or meropenem or Cephalosporins or cefaclor or cefalexin or cephalexin or cefalotin or cephalotinor cephalothin or cefamandole or cephamandole or cefazolin or cefazoline or cephazolin or cefixim* or cefotaxim* or cephotaxim* or ceftaroline or ceftazidim* or ceftibuten or ceftozolane or ceftriaxone or cefuroxime* or Quinolones or ciprofloxacin or levofloxacin or norfloxacin or ofloxacin or Glycopeptides or dalbavancin or teicoplanin or vancomycin or Macrolides or clarithromycin Penicillins or amoxicillin or penicillin or benzylpenicillinor flucloxacillin or piperacillin or colistin or Rifamycins or rifabutin or cotrimoxazole or trimethoprim or sulfamethoxazole or sulfadiazine or sulfametrol or Tetracyclines or minocycline or tetracycline or daptomycin or fosfomycin or doripenem or ethambutol or pyrazinamide).ti,ab,kw,tn.

2. (((renal or kidney) adj3 (disease* or impairment or function or dysfunction or insufficiency)) and (dose or dosage or mg)).ti,ab.

3. exp pharmacokinetics/ or exp pharmacokinetic parameters/ or (Pharmacodynamic* or pharmacodynamic* or
PK or PD or "pk/PD" or PPK or tmax or cmax or AUC or "area under the curve" or clearance or elimination or "volume of distribution" or "drug level" or absorption or half-life or "Therapeutic range" or "Drug exposure" or ((serum or plasma or blood) adj3 (concentration or level* or sample*))).ti,ab,kw.

4. 1 and 2 and 3

5. case report/

6. (exp experimental organism/ or animal tissue/ or animal cell/ or exp animal disease/ or exp carnivore disease/ or exp bird/ or exp experimental animal welfare/ or exp animal husbandry/ or animal behavior/ or exp animal cell culture/ or exp mammalian disease/ or exp mammal/ or exp marine species/ or nonhuman/ or animal.hw.) not human/

7. 5 or 6

8. 4 not 7

9. limit 8 to (conference abstract or conference paper or "conference review")

10. 8 not 9

11. (canadian or elsevier or embase).cr.

12. 10 and 11

*** Performed together with an experienced clinical librarian**

Newcastle-Ottawa Quality Assessment Form for Cohort studies, adjusted version[8]

SELECTION

1) Representativeness of the Exposed Cohort

Is the exposed cohort representative for patients with infections in clinical practice?

**	Exposed cohort consists of patients with different kind of infections
*	Exposed cohort consists of patients with one specific or a couple of specific infections
-	Exposed cohort consists of patients without infections, (healthy) volunteers or the patient population is not described

2) Ascertainment of Exposure, impaired renal function (1)

How was impaired renal function ascertained?

*	Ascertainment of impaired renal function using a validated formula to calculate renal function
-	Ascertainment of impaired renal function using a non-validated formula to calculate renal function or no description of how renal function was calculated

3) Ascertainment of Exposure, dose reduction of antibiotics (2)

How was treatment with a reduced dose of antibiotics ascertained?

**	Ascertainment of treatment with a reduced dose of antibiotics in methods and confirmed in results section
*	Ascertainment of treatment with a reduced dose of antibiotics in methods, but not confirmed in results section
-	Ascertainment of treatment with a reduced dose of antibiotics in methods, but results showed that not all patients received the reduced dose, although it was stated in the method section

4) Sample size

Was the sample size justified and satisfactory?

*	The sample size was justified and satisfactory.
-	The sample size was not justified or not satisfactory.

COMPARABILITY

5) Comparability of Cohorts on the Basis of the Design or Analysis

Did the study compare drug exposure in patients with impaired renal function receiving reduced doses of antibiotics with patients with adequate renal function receiving regular doses?

*	Drug exposure in patients with impaired renal function receiving reduced doses of antibiotics was compared with patients with adequate renal function receiving regular doses
-	Only patients with impaired renal function receiving reduced doses were included or both patients with impaired and adequate renal function were included, but they were all treated with the same (reduced) dose of antibiotics

OUTCOME

6) Assessment of Outcome

How was drug exposure and/or PK/PD target attainment assessed, with regard to the method of 1) blood sample collection; 2) drug concentration measurement; and 3) calculation of drug exposure or pharmacokinetic parameters?

**	All three things are described and the methods used are validated
*	All three things are described, but it was not mentioned whether the methods that were used are validated
-	Not all three things are described

Table S1. Inclusion and exclusion criteria for studies

Inclusion criteria	Exclusion criteria
Antibiotic drug exposure (C_{max}, C_{min} or AUC) and/or PK/PD target attainment (C_{max} / MIC, AUC / MIC or T > MIC) are reported for patients with impaired renal function receiving a reduced dose of antibiotics	Drug exposure is simulated based on previously published pharmacokinetic models or simulated using experimental models (i.e. hollow fiber models)
Drug exposure or PK/PD target attainment is measured in clinical practice	Patients on renal replacement therapy[7]
Predominantly (>50%) adult patients (≥18 years) are included	The exact administered dose of antibiotics is not mentioned
Patients are treated orally (po), intravenously (iv) or intramuscularly (im) with antibiotics, as single or multiple doses	Not all patients with impaired renal function (100%) receive a reduced dose of antibiotics
Patients receive any kind of dose reduction of antibiotics, administered to patients with any degree of renal impairment as described in the study manuscript, or the administered dose was already a reduced dose according to relevant clinical guidelines[6]	Studies also adjusting the dose based on other factors than renal function, such as bodyweight or therapeutic drug monitoring (TDM)
	Paper is a case series or case report

Table S2: Basic characteristics of individual studies

β-Lactams: meropenem

Study (year)	Study population			Study Design	Multi or single-center, country	Antibiotic (iv/po/im)	Renal function * Clcr (ml/min), unless otherwise stated)	Number of patients per renal function group	Acute or chronic/stable renal impairment?
	Age (years) Mean ± SD	♂ (%)	Patient population as mentioned by authors						
Del Bono (2017)[9]	62 ± 13	63%	Hospitalized patients with KPC producing *Klebsiella* pneumoniae bloodstream infection	Prospective cohort	Single-center, Italy	Meropenem (iv)	Cl_{cr} ≥40	15	*Both*
							Cl_{cr} 10-39	3	
Cheatham (2008)[10]	46 ± 14.6	60%	Hospitalized patients with suspected or documented bacterial infections	Prospective cohort	Multicenter, USA	Meropenem (iv)	Cl_{cr} >60	8	Not reported
	64.4 ± 8.2						Cl_{cr} 40-60	8	
	74.8 ± 3.7						Cl_{cr} 10-39	4	
Kitzes-Cohen (2002)[11]	73.6 ± 9.7	65%	Critically ill patients with severe sepsis at the ICU	Prospective cohort	Single-center, Israel	Meropenem (iv)	Cl_{cr} >50	8	Not reported
	72.8 ± 6.2						Cl_{cr} <50	6	
	63 ± 13[a]	64%*				Meropenem (iv)	Cl_{cr} >50	10	*Both*

Taccone (2010)[12]			Patients with severe sepsis or septic shock at ICU	Prospective cohort	Multi-center, Belgium		Cl_{cr} <50	6	

*characteristics for total cohort (n=80), not explicitly for meropenem

β-Lactams: imipenem/cilastatatin

Study (year)	**Patients**			**Study Design**	**Setting, country**	**Antibiotic (iv/po/im)**	**Renal function** *** Clcr (ml/min), unless otherwise stated**	**N stratified per renal function group**	**Acute or stable renal impairment?**
	Age (years) Mean ± SD	♂ (%)	Study population as mentioned by authors						
Gibson (1985)[13]	73.2 ± 11.1	71%	Not specified	Prospective cohort	Single-center, USA	Imipenem / cilastatin (iv)	Cl_{cr} ≥100	7	Not reported
	86.6 ± 18.6	100%					Cl_{cr} 30-100	6	
	76.5 ± 11.1	100%					Cl_{cr} 29-10	6	
	71.3 ± 7.3	100%					Cl_{cr} <10	6	
Rogers (1985)[14]	NR	NR	Healthy volunteers, patients with renal insufficiency and patients with infections due to bacteria known or presumed to be susceptible to imipenem	Prospective cohort	Single-center, USA	Imipenem / cilastatin (iv)	GFR 31-99	14	Not reported
							GFR 10-30	15	
Verbist (1986)[15]	52.3 (32-66) (mean, range)	33%	Patients with severe but stable renal failure	Prospective cohort	Single-center, Belgium	Imipenem / cilastatin (iv)	Cl_{cr} <15	6	Stable

β-Lactams: cephalosporins

Study (year)	Patients			Study Design	Setting, country	Antibiotic (iv/po/im)	Renal function * Clcr (ml/min), unless otherwise stated	N stratified per renal function group	Acute or stable renal impairment?
	Age (years) Mean ± SD	♂ (%)	Study population as mentioned by authors						
Lamoth (2010)[16]	58 (32-78) (median, range)	53%	Patients on the general ward with febrile neutropenia	Retrospective cohort	Single-center, Switzerland	Cefepime (iv)	Cl_{cr} >70	15	Not reported
							Cl_{cr} 40-70	13	
							Cl_{cr} <40	2	
Tam (2003)[17]	39 ± 12	83%	Hospitalized patients with documented or suspected infections	Prospective cohort	Single-center, USA	Cefepime (iv)	Cl_{cr} ≥100	12	Stable
	57 ± 15	67%					Cl_{cr} 60-100	12	
	69 ± 14	58%					Cl_{cr} 11-59	12	
Taccone (2010)[12]	63 ± 13*	64%*	Patients with severe sepsis or septic shock at ICU	Prospective cohort	Multi-center, Belgium	Cefepime (iv)	Cl_{cr} >50	7	*Both*
							Cl_{cr} <50	12	
Kakara (2019)[18]	64.7 ± 15.7	49%	Japanese patients with cUTI and cIAI	Prospective cohort	Multi-center, Japan	Ceftolozane/tazobactam	Cl_{cr} >50	184	Not reported
							Cl_{cr} 30-50	16	
Wooley (2014)[19]	61.5 (7.1)	45%	Subjects with varying degrees of renal function	Prospective cohort	Single-center, Switzerland	Ceftolozane-tazobactam (iv)	Cl_{cr} ≥90	11	Stable
	72.3 (7.8)	33%					Cl_{cr} 60-89	6	
	65.6 (18.7)	43%					Cl_{cr} 30-59	7	
	66.2 (6.7)	17%					Cl_{cr} 15-29	6	
Riccobene (2014)[28]	34.7 (mean)	NR	Healthy adults	Prospective cohort	Single-center, USA	Ceftaroline Fosamil (iv)	Cl_{cr} >80	6	Not reported
	69.8 (mean)	NR					Cl_{cr} 50-80	6	
	49.6 (mean)	NR					Cl_{cr} 30-50	6	
	64.3 (mean)	83%					Cl_{cr} ≤30	6	
Taccone (2010)[12]	63 ± 13*	64%*	Patients with severe sepsis or septic shock at ICU	Prospective cohort	Multi-center, Belgium	Ceftazidime (iv)	Cl_{cr} >50	9	*Both*
							Cl_{cr} <50	9	

*characteristics for total cohort (n=80), not explicitly for cefepime
cUTI, complicated urinary tract infection; cIAI, complicated intra-abdominal infection

β-Lactams: penicillins

Study (year)	Patients			Study Design	Setting, country	Antibiotic (iv/po/im)	Renal function * Clcr (ml/min), unless otherwise stated	N stratified per renal function group	Acute or stable renal impairment?
	Age (years) Mean ± SD	♂ (%)	Study population as mentioned by authors						
Taccone (2010)[22]	63 ± 13*	64%*	Patients with severe sepsis or septic shock at ICU	Prospective cohort	Multi-center, Belgium	Piperacillin-tazobactam	Cl_{cr} >50	13	*Both*
							Cl_{cr} <50	14	

*characteristics for total cohort (n=80), not explicitly for piperacillin-tazobactam

Fluoroquinolones: ciprofloxacin

Study (year)	Patients			Study Design	Setting, country	Antibiotic (iv/po/im)	Renal function * Clcr (ml/min), unless otherwise stated	N stratified per renal function group	Acute or stable renal impairment?
	Age (years) Mean ± SD	♂ (%)	Study population as mentioned by authors						
Boelaert (1985)[20]	51 ± 9	Not reported	Patients, not specified	Prospective cohort	Not reported, Belgium	Ciprofloxacin (po)	Cl_{cr} >60	6	Chronic
	64 ± 4						Cl_{cr} <20	6	
Drusano (1987)[21]	28 (22-30) (median, range)	100%	Volunteers	Prospective cohort	Single-center, USA	Ciprofloxacin (iv)	Cl_{cr} >6.0 l/h	8	Not reported
	32 (27-48) (median, range)	100%					Cl_{cr} 3.6-6.0 l/h	5	
	44 (26-62) (median, range)	90%					Cl_{cr} 0.6 - 3.6 l/h	11	
	46 (33-55) (median, range)	100%					Cl_{cr} <0.6 l/h	8	
MacGowan (1994)[22]	47 (19-79) (mean, range)	81%	Severe infection requiring parenteral therapy and many of whom required intensive care	Not mentioned	Multi-center, UK	Ciprofloxacin (iv)	Serum creat < 120 µmol/L	3	Not reported
							Serum creat > 120 µmol/L	6	
Shah (1996)[23]	39.1 (32-46) (mean, range)	100%	Subjects	Prospective cohort	Multi-center, USA	Ciprofloxacin (iv)	Cl_{cr} >90	10	Not reported
	50.1 (28-68) (mean, range)	55%					Cl_{cr} 61-90	11	
	63.0 (32-64) (mean, range)	45%					Cl_{cr} 31-60	11	
	51.7 (32-64) (mean, range)	40%					Cl_{cr} <31	10	
Stoica (2015)[24]	65 ± 11.05 (average, not specified)	48%	Patients with chronic kidney disease associated with bacterial infections or clinical situations that required treatment with ciprofloxacin	Prospective cohort	Single-center, Romania	Ciprofloxacin (po)	eGFR (MDRD) <60, CKD 3‡	1	Stable
							<30, CKD 4‡	10	
							<30, CKD 5‡	6	

‡CKD, chronic kidney disease (CDK), 3, 4 or 5 not further specified by study

Fluoroquinolones: sparfloxacin, gatifloxacin, levofloxacin, prulifloxacin (ulifloxacin)

Study (year)	Patients			Study Design	Setting, country	Antibiotic (iv/po/im)	Renal function * Clcr (ml/min), unless otherwise stated	N stratified per renal function group	Acute or stable renal impairment?
	Age (years) Mean ± SD	♂ (%)	Study population as mentioned by authors						
Dorr (1999)[29]	52.6 (22-69) (mean, range)	43%	Healthy volunteers	Prospective cohort	Single-center, USA	Sparfloxacin (po)	Cl_{cr} ≥50	14	Stable
	54.4 (28-72) (mean, range)	50%					Cl_{cr} 30-49	8	
	50.8 (36-67) (mean, range)	38%					Cl_{cr} 10-29	8	
Fish (2007)[30]	54 ± 9	58%	ICU patients that required medical care with gatifloxacin	Prospective cohort	Single-center, USA	Gatifloxacin (iv)	Cl_{cr} ≥40	12	Stable
	45 ± 18	63%					Cl_{cr} <40	8	
Kiem (2016)[31]	52.1 ± 18.2	44%	Patients with acute infection who had/expected to have levofloxacine-susceptible pathogens, department of internal medicine	Prospective cohort	Single-center, Korea	Levofloxacin (iv)	Cl_{cr} >50	32	Not reported
	66.7 ± 14.1	66%					Cl_{cr} 20-50	6	
Tellone (2018)[32]	52.5 (21.0 - 70.0) (median, range)	50%	Subjects and patients with impaired renal function (no infection)	Prospective cohort	Multi-center, South Africa, Germany	Prulifloxacin (ulifloxacin active compound) (po)	eGFR >80	17	Not reported
	63.5 (52.0 – 69.0) (median, range)	37.5%					eGFR 50-80	8	
	69.5 (32.0 – 75.0) (median, range)	50%					eGFR 30-49	8	
	40.0 (22.0 – 69.0) (median, range)	50%					eGFR <30	8	

Glycopeptides: teicoplanin and vancomycin

Study (year)	Patients			Study Design	Setting, country	Antibiotic (iv/po/im)	Renal function * Clcr (ml/min), unless otherwise stated	N stratified per renal function group	Acute or chronic renal impairment?
	Age (years) Mean ± SD	♂ (%)	Study population as mentioned by authors						
Presterl (1993)[25]	46 (21-76) (mean, range)	85%	Gram positive endocarditis	Prospective cohort	Single-center, Austria	Teicoplanin (iv)	Cl_{cr} 80-120	10	Stable
							Cl_{cr} <75	8	
Ueda (2012)[26]	56.5 ± 15.1	74%	Patients with suspected or definitely diagnosed MRSA infection	Retrospective cohort	Single-center, Japan	Teicoplanin (iv)	Cl_{cr} ≥50 a	15	Both
	59.3 ± 15.2	79%					Cl_{cr} ≥50 b	4	
	74 ± 7.8	72%					Cl_{cr} <50	12	
Zhou (2018)[27]	78.17 ± 14.28	72%	Hospitalized patients with community acquired pneumoniae, confirmed by bacterial culture of drug-resistant Gram-positive bacterial infections	Retrospective cohort	Single-center, China	Teicoplanin (iv)	Cl_{cr} ≥60	36	Not reported
	82.53 ± 6.91	70%					Cl_{cr} 40-60	30	
	81.82 ± 13.06	76%					Cl_{cr} <40	17	
Chung (2011)[33]	62.7 ± 14	72%	Hospitalized patients with nosocomial pneumonia, ICU	Prospective cohort	Single-center, Korea	Vancomycin (iv)	Cl_{cr} >60	50	Not reported
							Cl_{cr} 30-60	53	
							Cl_{cr} <30	13	

Other antibiotics: tobramycin and telithromycin

Study (year)	Patients			Study Design	Setting, country	Antibiotic (iv/po/im)	Renal function * Clcr (ml/min), unless otherwise stated	N stratified per renal function group	Acute or chronic renal impairment?
	Age (years) Mean ± SD	♂ (%)	Study population as mentioned by authors						
Brogard (1982)[34]	Not reported	Not reported	Not reported	Prospective cohort	Not reported, France	Tobramycin (im)	Cl_{cr} ≥70	15	Not reported
							Cl_{cr} <50	10	
Shi (2004)[35]	57 ± 15	56%	Healthy subjects and patients with varying degrees of renal impairment	Prospective cohort	Multi-center, France, USA	Telithromycin (po)	Cl_{cr} >80	9	Not reported
	60 ± 10	50%					Cl_{cr} 50-80	8	
	61 ± 11	75%					Cl_{cr} 30-49	8	
	55 ± 17	67%					Cl_{cr} <30	8	

PRIMSA 2020 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3,4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5,6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8, Appendix Table 1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9, Table 2, Appendix
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Table 2, Appendix
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-13, Table 1, Appendix Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-13, Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-13, Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

References

1. Rowland M, Tozer TN. Clinical Pharmacokinetics and Pharmacodynamics. Lippincott Williams And Wilkins, 2010:24.
2. Onufrak NJ, Forrest A, Gonzalez D. Pharmacokinetic and Pharmacodynamic Principles of Anti-Infective Dosing. Clin Ther, 2016;38(9): 1930–1947.
3. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations. Available on: https://www.fda.gov/media/88254/download. Accessed 2019-12-02.
4. European Medicines Agency (EMA), Guideline on the investigation of bioequivalence, London 20 January 2010. Available on: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf. Accessed 2019-12-02.
5. Wang H, Zhang B, Ni Y, Kuti JL, *et al*. Pharmacodynamic target attainment of seven antimicrobials against Gram-negative bacteria collected from China in 2003 and 2004. Int J Antimicrob Agents, 2007; 30:452–457.
6. Richtlijnen SWAB. Available on: https://swab.nl/nl/richtlijnen-swab. Accessed 2020-04-20.
7. Pea F, Viale P, Pavan F, *et al*. Pharmacokinetic considerations for antimicrobial therapy in patients receiving renal replacement therapy. Clin Pharmacokinet, 2007 ; 46(12): 997-1038.
8. Wells GA, Shea B, O'Connell D, *et al*. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 2018-12-21.
9. Del Bono V, Giacobbe DR, Marchese A, Parisini A, Fucile C, Coppo E *et al*. Meropenem for treating KPC-producing Klebsiella pneumoniae bloodstream infections: Should we get to the PK/PD root of the paradox? Virulence, 2017:Jan2;8(1):66-73.
10. Cheatham SC, Kays MB, Smith DW, Wack MF, Sowinski KM. Steady-state pharmacokinetics and pharmacodynamics of meropenem in hospitalized patients. Pharmacotherapy, 2008;28(6):691-698.
11. Kitzes-Cohen R, Farin D, Piva G, De Myttenaere-Bursztein SA. Pharmacokinetics and pharmacodynamics of meropenem in critically ill patients. International Journal of Antimicrobial Agents, 2002;19:105-110.
12. Taccone FS, Laterre P, Dugernier T, Spapen H, Delattre I, Wiitebole X *et al*. Insufficient β-lactam concentrations in the early phase of severe sepsis and septic shock. Critical Care, 2010;14:R126.
13. Gibson TP, Demetriades JL, Bland JA. Imipenem/cilastatin: pharmacokinetic profile in renal insufficiency. Am J Med, 1985;Jun7;78(6A):54-61.
14. Rogers JD, Meisinger MA, Ferber F, Calandra GB, Demetriades JL, Bland JA. Pharmacokinetics of imipenem and cilastatin in volunteers. Rev Infect Dis, 1985;7Suppl3:S435-46.
15. Verbist L, Verpooten GA, Giuliano RA, Debroe ME, Buntix AP, Entwistle LA *et al*. Pharmacokinetics and tolerance after repeated doses of imipenem/cilastatin in patients with severe renal failure. J Antimicrob Chemother, 1986;18SupplE:115-20.
16. Lamoth F, Buclin T, Pascual A, Vora S, Bolay S, Decosterd LA *et al*. High cefepime plasma concentrations and neurological toxicity in febrile neutropenic patients with mild impairment of renal function. Antimicrobial Agents and Chemotherapy, 2010;54(10):4360–67.
17. Tam VH, McKinnon PS, Akins RL, Drusano GL, Rybak MJ. Pharmacokinetics and pharmacodynamics of cefepime in patients with various degrees of renal function. Antimicrobial Agents and Chemotherapy, 2003;47(6):1853-61.
18. Kakara M, Larson K, Feng H, Shiomi M, Yoshitsugu H, Rizk ML. Population pharmacokinetics of tazobactam/ceftolozane in Japanese patients with complicated urinary tract infection and complicated intra-abdominal infection. J Infect Chemother, 2019;2:182e191.
19. Wooley M, Miller B, Krishna G, Hershberger E, Chandorkar G. Impact of renal function on the pharmacokinetics and safety of ceftolozane-tazobactam. Antimicrobial Agents and Chemotherapy, 2014;58(4):2249-55.

20. Boelaert J, Valcke Y, Schurgers M, Daneels R, Rosseneu M, Rosseel MT *et al*. The pharmacokinetics of ciprofloxacin in patients with impaired renal function. Journal of Antimicrobial Chemotherapy, 1985;16:87-93.
21. Drusano GL, Weir M, Forrest A, Plaisance K, Emm T, Standiford HC. Pharmacokinetics of intravenously administered ciprofloxacin in patients with various degrees of renal function. Antimicrobial Agents and Chemotherapy, 1987;June:860-4.
22. Macgowan AP, White LO, Brown M, Lovering AM, McMullin CM, Reeves DS. Serum ciprofloxacin concentrations in patients with severe sepsis being treated with ciprofloxacin 200 mg iv bd irrespective or renal function. Journal of Antimicrobial Chemotherapy, 1994;33:1051-4.
23. Shah A, Lettieri J, Blum R, Millikin S, Sica D, Heller AH. Pharmacokinetics of intravenous ciprofloxacin in normal and renally impaired subjects. J Antimicrob Chemother, 1996;Jul38(1):103-16.
24. Stoica MC, Vari CE, Imre S, Vancea S, Dogaru MT, Carasca E *et al*. Correlations between the stages of kidney disease and the pharmacokinetic parameters of orally administered ciprofloxacin at patients with chronic kidney disease. Farmacia, 2015;63:5.
25. Presterl E, Graninger W, Georgopoulos A. The efficacy of teicoplanin in the treatment of endocarditis caused by Gram-positive bacteria. Journal of Antimicrobial Chemotherapy, 1993;31: 755-66.
26. Ueda T, Takesue Y, Nakajima K, Ichki K, Wada Y, Tsuchida T *et al*. Evaluation of teicoplanin dosing designs to achieve a new target trough concentration. J Infect Chemother, 2012;18:296–302.
27. Zhou L, Gao Y, Cao W. Retrospective analysis of relationships among the dose regimen, trough concentration, efficacy, and safety of teicoplanin in Chinese patients with moderate–severe Gram-positive infections. Infection and Drug Resistance, 2018;11:29–36.
28. Riccobene T, Jakate A, Rank D. A series of pharmacokinetic studies of ceftaroline fosamil in select populations: normal subjects, healthy elderly subjects, and subjects with renal impairment or end-stage renal disease requiring hemodialysis. The Journal of Clinical Pharmacology, 2014;54(7):742–52.
29. Dorr MB, Johnson RD, Jensen B, Magner D, Marbury T, Talbot GH. Pharmacokinetics of sparfloxacin in patients with renal impairment. Clinical Therapeutics, 1997;21:7.
30. Fish, DN. Evaluation of gatifloxacin pharmacokinetics and pharmacodynamics in severely ill adults in a medical Intensive Care Unit. International Journal of Antimicrobial Agents, 2007;29:715–23.
31. Kiem S, Ryu S, Lee Y, Schentag JJ, Kim Y, Kim H *et al*. Population pharmacokinetics of levofloxacin in Korean patients, Journal of Chemotherapy, 2016;28:4:308-13.
32. Tellone V, Coppola P, Ammendola M, Di Loreto G, Picollo R, Del Vecchio A *et al*. New Insights on the Pharmacokinetics of Ulifloxacin After Administration of Prulifloxacin in Patients with Mild, Moderate and Severe Renal Impairment. Drugs in R&D, 2018;18:237–45.
33. Chung J, Oh JM, Cho EM, Jang HJ, Hong SB, Lim CM *et al*. Optimal dose of vancomycin for treating methicillin-resistant Staphylococcus aureus pneumonia in critically ill patients. Anaesth Intensive Care, 2011;39(6):1030-7.
34. Brogard JM, Conraux C, Collard M, Lavillaureix J. Ototoxicity of tobramycin in humans – influence of renal impairment. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1982;20(9): 408-16.
35. Shi J, Montay G, Chapel S, Hardy P, Barrett JS, Sack M *et al*. Pharmacokinetics and safety of the ketolide telithromycin in patients with renal impairment. Journal of Clinical Pharmacology, 2004;44:234-44.

Chapter 3

Development and Validation of a Liquid Chromatography–Tandem Mass Spectrometry (LC-MS/MS) Assay for the Determination of Total and Unbound Ciprofloxacin Concentrations in Human Plasma

A Short Communication

Suzanne L. de Vroom, Marcel C. M. Pistorius, Yuma A. Bijleveld, Suzanne E. Geerlings, Ron A. A. Mathôt, Reinier M. van Hest and Nynke G. L. Jager

Ther Drug Monit. 2022 Aug 1;44(4):552-557

Abstract

Background
Although unbound ciprofloxacin is responsible for antibacterial effects, assays measuring the unbound drug plasma concentrations are scarce. This study aimed to develop and validate a rapid, reproducible, and sensitive liquid chromatography–tandem mass spectrometry assay for the determination of total and unbound ciprofloxacin plasma concentrations.

Methods
The determination of total ciprofloxacin concentrations required a 10 μL sample, while for unbound ciprofloxacin concentrations, it was 100 μL. Unbound ciprofloxacin was separated from protein-bound ciprofloxacin through ultrafiltration. A deuterated internal standard was used, and the sample preparation involved protein precipitation. The method was fully validated over a concentration range of 0.02–5.0 mg/L, according to the US Food and Drug Administration guidelines. In addition, its clinical application was demonstrated.

Results
The total run time was 1.5 minutes. For total ciprofloxacin plasma concentrations, the mean accuracy ranged from 94.5% to 105.0% across the validated range, the intraday imprecision was ≤7.6%, and the interday imprecision was ≤9.8%. For unbound ciprofloxacin plasma concentrations, the mean accuracy ranged from 92.8% to 102.1% across the validated range, the intraday imprecision was ≤7.0%, and the interday imprecision was ≤9.6%.
Ciprofloxacin in plasma and ultrafiltrate remained stable for at least 96 hours at room temperature, at least 4 years at -80°C, and at least 3 freeze/thaw cycles (-80°C), with a minimum interval of 24 hours.

Conclusions
The presented method is precise and accurate. It has been implemented in clinical care and research projects at a university hospital, permitting rapid determination of total and unbound ciprofloxacin.

Introduction

Fluoroquinolones are among the most commonly prescribed antibiotics worldwide that are used to treat a broad range of infections caused by Gram-negative bacteria.[1–4] Among fluoroquinolones, ciprofloxacin is the most widely used, and several studies on the pharmacokinetics (PK) and/or pharmacodynamics (PD) of this drug have been performed.[5–9] Attaining a PK/PD target of the area under the total concentration–time curve (AUC) over the minimum inhibitory concentration (MIC) $\geq$ 125 is associated with clinical and microbiological cure of relevant Gram-negative infections.[10,11] However, large interindividual variability in ciprofloxacin exposure has been described, with drug exposure often insufficient to attain efficacy targets.[5–9]

Therapeutic drug monitoring (TDM), where dosing is individualized based on measured drug concentrations, might prove beneficial for attaining efficacy targets and optimizing clinical outcomes. The Royal Dutch Pharmacists Association (KNMP) recommends TDM for patients with impaired renal function, and the routine use of TDM for all patients treated with ciprofloxacin is advocated in several reports.[6,9,12]

The unbound antibiotic concentration is solely responsible for the antibacterial effect of ciprofloxacin and thus relevant for predicting therapeutic efficacy.[13–15] A protein binding of approximately 70% has been reported for this drug.[12] Several assays determining total ciprofloxacin plasma concentrations through liquid chromatography–tandem mass spectrometry (LC-MS/MS) have been developed and validated.[16–20] To the best of our knowledge, only 1 report describing the measurement of unbound ciprofloxacin plasma concentrations has been previously published in the literature. However, the bioanalytical validation of this method is very limited.[21]

This study describes the development and validation of an LC-MS/MS assay for the determination of total and unbound ciprofloxacin plasma concentrations, which is feasible for clinical practice.

Materials and Methods

Chemicals and Reagents

Ciprofloxacin HCl and ammonium formate were purchased from Sigma-Aldrich (Steinheim, Germany) and the internal standard (IS) ciprofloxacin-*d*8 (purity ≥98%) from Toronto Research Chemicals (North York, ON, Canada). Acetonitrile (ACN) and methanol (MeOH), both hypergrade for LC-MS, and formic acid were purchased from Merck (Darmstadt, Germany). Water was purified and deionized by using ELGA PURELAB DV-25 (Veolia Water Technologies, Saint-Maurice, France).

Omniplasma (pooled human plasma) was obtained from Sanquin (Amsterdam, the Netherlands).

Instrumentation

A Shimadzu Nexera LC-30AD system (Kyoto, Japan) consisting of 2 binary HPLC pumps (LC-30AD) was used. The HPLC column was a Thermo Scientific Hypersil GOLD 50 x 2.1-mm column; particle size 1.9 μm. The mobile phase consisted of 0.1% vol/vol formic acid and 0.05% vol/vol ammonium formate (1.28g/mL) in ultrapure water [mobile phase A (A)] along with 0.1% vol/vol formic acid and 0.05% vol/vol ammonium formate (1.26g/mL) in acetonitrile [mobile phase B (B)]. The mobile phases were pumped through the HPLC column at 40^{o}C at a flow rate of 800 μL/min using the following gradient: initial condition 94/6 (vol/vol) A/B, 47/53 at 1 minute, 6/94 at 1.05 minutes, and 94/6 at 1.20–1.50 minutes.

An AB Sciex QTRAP 5500 System (AB Sciex, Framingham, MA) mass spectrometer was used, operating in the positive ionization mode. For quantification, multiple reaction monitoring chromatograms were acquired and processed by using the Analyst software (version 1.6, AB Sciex).

Ciprofloxacin and ciprofloxacin-*d*8 were analyzed as $[M+H]^+$, monitoring *m/z* = 332.1 → 231.1 and 340.1 → 235.1, respectively.

Preparation of Calibration Standards, QCs, and IS Solutions

Two independently prepared stock solutions containing 1.0 mg/mL ciprofloxacin in 0.1% vol/vol formic acid in ultrapure water were used for the calibration standards and QC samples, respectively.

Six calibration standards were freshly prepared before every run at concentrations of 0.020, 0.150, 0.500, 1.00, 2.50, and 5.00 mg/L. The calibration standards at 2.500 mg/L and 5.00 mg/L were prepared by diluting 25 and 50 μL of the stock solution, respectively, with 10 mL Omniplasma. For the remaining calibration standards, a working solution of 500 μL stock solution diluted to 10 mL with MeOH/ultrapure water (1:1, vol/vol) was prepared. The other calibration standards were prepared by further diluting the working solution with Omniplasma.

Four QC samples were prepared at concentrations of 0.020 mg/L [lower limit of quantification (LLOQ)], 0.150 mg/L (concentration of 3 x LLOQ, low), 2.00 mg/L (mid), and 5.00 mg/L (upper limit of quantification, high). QC high was prepared by diluting 50 μL of the stock solution with 10 mL Omniplasma. In addition, 500 μL of the stock solution was further diluted with ultrapure water to obtain 10 mL of working solution. Subsequently, the QC LLOQs and low-QC and mid-QC samples were prepared by further diluting 10 μL, 30 μL, and 400 μL of the working solution, respectively, with 10 mL Omniplasma.

For determination of unbound ciprofloxacin plasma concentrations, the QC LLOQ, low, mid, and high concentrations were prepared by using ultrafiltrate instead of Omniplasma (see further *Sample Preparation*). The procedure was identical to that described above.

For the IS solution, a stock solution of 0.250 mg/mL ciprofloxacin-*d*8 in 0.1% formic acid in ultrapure water was prepared. Subsequently, 200 µL of this solution was added to 500 mL ACN:MeOH:formic acid (419:79:2) to obtain an IS solution with a concentration of 100 mcg/L.

The stock solutions were stored at −80°C, while the IS solution was stored at −20°C.

Sample Preparation

For protein precipitation, 750 µL of IS solution was added to 10 µL of each calibration standard, QC, and patient sample.

Subsequently, the samples were vortexed and centrifuged at 2750*g* for 5 minutes at room temperature. An aliquot of the supernatant (0.5 µL) was injected for analysis.

Ultrafiltration was used to separate unbound ciprofloxacin from protein-bound ciprofloxacin in the plasma. At least 100 µL of sample was pipetted into a Nanosep 30 K Omega filtration cup (PALL Corporation, WA). After equilibration at 37°C for 30 minutes, the samples were centrifuged at 2750*g* and 37°C for 20 minutes. Further sample preparation was performed as described above.

Quantification

Drug concentrations of each sample were determined by relating the chromatographic peak areas of the analyte mass spectrometry response (unknown variable) to those derived from the IS mass spectrometry response (known variable), using multiple reaction monitoring for each sample separately. Patient samples were back-calculated using the calibration line according to their corresponding ratio of analyte/IS MS response.

Validation

The assay was validated according to the U.S. Food and Drug Administration (FDA) guidelines.[22]

Calibration Curve and Sensitivity

Six calibration standards ranging from 0.020 mg/L to 5.00 mg/L were freshly prepared in plasma (as described in *Preparation of Calibration Standards, QCs, and IS Solutions*) and analyzed in 6 different runs. Linear least-squares regression was applied (area ratio with the IS versus the nominal concentration), and the reciprocal of the squared concentration ($1/x^2$) was used as a weighting factor. Thereafter, the calibration curve parameters [slope, intercept fixed at zero, and correlation coefficient (R^2)] were calculated. The linearity of the calibration lines was deemed acceptable when $R^2 > 0.990$.

Deviations from the calculated concentrations should be within 85%–115% of the nominal concentrations. For the LLOQ, a deviation of 20% was permitted, but the response of the analyte had to be at least 5 times higher than that of the blank sample. Furthermore, at least 75% and a minimum of 6 nonzero calibrator levels should meet the above criteria in each validation run. The coefficient of variation (CV) was calculated as the ratio of the SD to the mean and should not exceed 15%. For the LLOQ, a CV of a maximum of 20% was permitted.

The QC samples in the ultrafiltrate (for the unbound ciprofloxacin plasma concentration) were quantified using the calibration curve in plasma.

Accuracy and Imprecision

The accuracy and precision of the method were assessed for the QC samples LLOQ, low, mid, and high, for both the total and unbound ciprofloxacin plasma concentrations. Intraday accuracy and imprecision were assessed in a single run in 6-fold. Similarly, interday accuracy and imprecision were assessed in 6 runs (including the aforementioned single run) analyzed on at least 2 different days.

The ratio of the determined value to the true value × 100% was used to calculate the accuracy. The accuracy should be within 85%–115%, except for the LLOQ, which should have an accuracy within 80%–120%. Coefficient of variation (CV) was used to calculate precision. The imprecision should not exceed 15% of the CV, except for the LLOQ, where the CV should not exceed 20%.

In addition, the feasibility of diluting plasma samples with concentrations above the upper limit of quantification (ULOQ) was tested using QC samples containing 10 times the concentration of the ULOQ sample. These samples were prepared 6-fold and analyzed after 10-fold dilution in Omniplasma.

Matrix Effects

To determine the matrix effects for total ciprofloxacin concentrations, the following samples were prepared in 6-fold: samples at low, mid, and high concentration levels in blank human plasma (1x), in patient samples (5x), and in ultrapure water (6x). These samples were processed to obtain the final extract according to the procedure described in *Sample preparation*.

The absolute matrix effect was determined by calculating the ratio of the peak area of the spiked sample response in the matrix (plasma) to the spiked sample response in ultrapure water.

The relative matrix effect was determined by calculating the ratio of the peak area of the spiked sample response to the IS response ratios in the matrix and in ultrapure water.

The matrix effects for unbound ciprofloxacin were investigated using ultrafiltrate instead of plasma. The procedure was identical to that described above for the total ciprofloxacin.

Carryover

Carryover was assessed by injecting a blank sample [ACN:MeOH, 82:16 (vol/vol)] (n = 6) after the QC high sample. The mean signal in the blank sample should be less than 20% of the peak area of the LLOQ and less than 5% of the IS of the LLOQ.

Selectivity and Specificity

Blank plasma samples from 5 different patients at the Amsterdam UMC not treated with ciprofloxacin—along with 1 blank Omniplasma sample—were used to assess the selectivity and specificity of the method. The samples were prepared according to the procedure described above (*Sample preparation*). The mean peak area of endogenous components in the 6 blank matrix samples should be less than 20% of the LLOQ for ciprofloxacin and less than 5% of the mean IS response.

Stability

The stability of ciprofloxacin and ciprofloxacin-*d*8 in the stock solutions was evaluated for 3 years at -80°C by comparing it with a freshly prepared stock solution.

The stability of ciprofloxacin in Omniplasma and ultrafiltrate was evaluated at room temperature, following storage at -80°C, and 3 freeze–thaw cycles. Two QC samples (low and high) were analyzed after 24 hours and 96 hours at room temperature (±20°C), after 3 months of storage at -80°C, and after 3 freeze (-80°C) and thaw cycles (±20°C) with minimum intervals of at least 24 hours. The autosampler stability was evaluated after 48 hours at 15°C. In addition, the stability of ciprofloxacin in Omniplasma was assessed after 4 years of storage at -80°C by comparing QC low and high with freshly prepared QC samples. All stability experiments were performed in triplicate. The QC stability samples were quantified based on a freshly prepared calibration curve.

Ciprofloxacin and ciprofloxacin-*d*8 are considered stable in stock and working solutions when 95%–105%, respectively, of the initial concentration is recovered and 85%– 115% for ciprofloxacin in the matrix.

Additional Validation Procedures to Improve Feasibility of the Method in Research and Clinical Practice

To ensure the applicability of the assay in clinical practice, accuracy and precision were tested using different collection tubes: (1) EDTA, (2) heparin, (3) heparin with gel, (4) citrate, and (5) serum, all purchased from Becton Dickinson (Plymouth, United Kingdom).

For each type of collection tube, low and high QCs were prepared in plasma or serum in duplicate from 3 different healthy volunteers.

An aliquot of 1.0 mL plasma or serum was pipetted out of each blood collection tube into Eppendorf Safe-Lock tubes, and stock or working solutions were added to prepare samples at QC high and low, respectively (*Preparation of Calibration Standards, QCs, and IS Solutions*). Subsequently, the Eppendorf tubes were vortexed at maximum speed for 1 minute and centrifuged at 2750*g* for 10 minutes.

This process was repeated for all 60 blood samples. For the heparin tubes with gel, 1.0 mL plasma was pipetted out of the serum tube into another empty heparin tube with gel, after which the aforementioned steps were repeated.

Total ciprofloxacin concentrations were quantified in all samples using a freshly prepared calibration curve in Omniplasma.

The accuracy and precision of the measurements in the different blood collection tubes were calculated. Acceptable levels of accuracy were 85%–115% and ±15% for imprecision.

Results

HPLC-MS/MS

The overall run time was 1.5 minutes while the retention time of ciprofloxacin and ciprofloxacin-*d*8 was 0.82 minutes. The chromatogram exhibited a small symmetrical peak with a baseline of 0.04 seconds.

Validation Results

Regression Models

Linear calibration curves were fitted to the observed area ratios (ciprofloxacin/ciprofloxacin-*d*8). The intercept was fixed at 0, with a mean slope of 0.9996 (n = 6, range 0.9992–0.9999). The mean coefficient of determination (R^2) was 0.9992 (range 0.9984–0.9999), which was above the acceptable limit of >0.990. All calculated concentrations of the calibration standards (n = 36) fell within ±15% of their nominal concentrations. The CV was <15% for all samples.

Accuracy and Imprecision

For total and unbound ciprofloxacin plasma concentrations, the mean accuracy ranged from 94.5%–105.0% and 92.8%–102.1%, respectively. The intraday imprecision was ≤7.6% and ≤7.0%, respectively, while the interday imprecision was ≤9.8% and ≤9.6%, respectively. The accuracy and imprecision of total ciprofloxacin concentrations above the upper limit of quantification were 97.4% and 2.4%, respectively, after a 10-fold dilution (Table 1).

Table 1. Assay Performance Data for Total and Unbound Ciprofloxacin (n = 6 per Run, n = 36 Total)

QC Level (Nominal Concentration)	Accuracy (%)	Intraday Imprecision (%)	Interday Imprecision (%)
Total ciprofloxacin plasma concentrations			
LLOQ	105.0	2.0	3.0
Low	94.5	4.9	6.4
Mid	100.2	4.1	3.6
High	99.5	7.6	9.8
>ULOQ (n = 5)	97.4	2.4	Not available
Unbound ciprofloxacin plasma concentrations			
LLOQ	101.7	5.3	7.4
Low	92.8	4.0	4.8
Mid	102.1	4.6	5.4
High	101.9	7.0	9.6

Matrix Effects

The absolute matrix effect was 4.0 for ciprofloxacin. The relative matrix effect was 1.0, and the coefficients of variation were below 3%.

Carryover

The peak area in the blank samples (n = 6) was less than 20% of the peak area of the LLOQ and less than 5% of the IS of the LLOQ and thus deemed acceptable.

Selectivity and Specificity

No interfering components were observed; the mean peak area of endogenous components was less than 20% of the peak area of the LLOQ and less than 5% of the mean peak area of the IS response.

Stability

Ciprofloxacin and ciprofloxacin-*d*8 in the stock solution remained stable for at least 3 years at -80°C.

Ciprofloxacin in plasma and in ultrafiltrate was stable for at least 96 hours at room temperature (±20°C) and for at least 3 months at -80°C. Autosampler stability was established for at least 48 hours. Ciprofloxacin in plasma and ultrafiltrate was stable for at least 3 freeze/thaw cycles (-80°C), with a minimum interval of 24 h. In addition, ciprofloxacin in Omniplasma remained stable for at least 4 years at -80°C.

Additional Validation Procedures for Application in Research and Clinical Practice

For total ciprofloxacin plasma concentrations, the accuracy ranged from 93% to 106% and the imprecision was ≤6.1% for all 5 types of blood collection tubes (Table 2). Thus, assay performance was adequate when samples were obtained in the following blood collection tubes and processed directly after sample collection: EDTA tubes, heparin tubes with and without gel, citrate tubes, and serum tubes.

Table 2. Accuracy and Imprecision of Blood Collection Tubes Containing Different Anticoagulants or Serum

Blood Collection Tube	Accuracy (%)		Imprecision (%)	
	Low QC (n = 3), (0.150 mg/L)	High QC (n = 3), (4.00 mg/L)	Low QC (n = 3), (0.150 mg/L)	High QC (n = 3), (4.00 mg/L)
EDTA tube	102.2	100.2	3.9	6.2
Heparin tube	98.6	95.0	4.1	5.7
Heparin gel tube	101.5	97.3	2.6	3.6
Citrate tube	100.1	97.9	3.2	4.0
Serum tube	103.4	102.0	2.8	2.5

Acceptable accuracy 85%–115% and acceptable imprecision ±15%.

Discussion

An LC-MS/MS assay was successfully developed and validated for the quantification of total and unbound ciprofloxacin concentrations in human plasma. This assay exhibited 4 major improvements over previously published assays:[16–21] (1) the validation of unbound ciprofloxacin quantification; (2) the LLOQ of 0.020 mg/L was substantially lower than the lowest LLOQ previously reported (0.050 mg/L);[20] (3) using only 10 µL of plasma volume, which was substantially lower than that previously reported (50 µL),[16] making this assay also suitable for concentration measurement in neonates and infants; and (4) demonstrating the usability of different types of blood collection tubes. This enables the use of residual material from blood samples collected for other purposes, which enables research on (unbound) ciprofloxacin PK/PD targets and postdetermination measurement in clinical practice.

This assay reliably facilitates the measurement of total and unbound ciprofloxacin concentrations in patient samples. Although currently the PK/PD target is determined for total concentrations, unbound ciprofloxacin is also pharmacologically active. This assay can be used to further explore the relationship between unbound ciprofloxacin concentrations and clinical outcomes.

This study had certain limitations. First, the measurement of unbound ciprofloxacin plasma concentrations was not validated for all blood collection tubes. Moreover, a matrix effect was observed; however, because the IS ciprofloxacin-*d*8 was able to effectively compensate for these effects, no negative consequence of this effect on assay performance is expected. Finally, the IS solution was stored at -20°C, whereas stability was assessed at -80°C.

Conclusions

The presented method is precise and accurate and has been implemented in clinical care and research projects at a university hospital, permitting fast determination of total and unbound ciprofloxacin. In addition, it can be used to improve antibiotic dosing in clinical practice by facilitating research on PK/PD targets using unbound ciprofloxacin plasma concentrations.

Author contributions

All authors contributed equally to this study.

Conflict of Interests

SEG has received grants from Nordic Pharma and Vifor Pharma outside of the submitted work; RAAM has received grants from Baxter/Baxalta/Shire, Bayer Schering Pharma, CSL Behring, Merck Sharp & Dohme, and Zeria outside of the submitted work; RMvH received grants from Nordic Pharma outside of the submitted work. All the other authors declare no competing interests.

Acknowledgements

The authors extend their thanks to Dennis van der Laan for assistance with sample analysis.

References

1. Linder JA, Huang ES, Steinman MA, et al. Fluoroquinolone prescribing in the United States: 1995 to 2002. *Am J Med*. 2005;118(3):259-268.
2. Mamdani M, McNeely D, Evans G, et al. Impact of a fluoroquinolone restriction policy in an elderly population. *Am J Med*. 2007;120(10):893-900.
3. Zhang Y, Steinman MA, Kaplan CM. Geographic variation in outpatient antibiotic prescribing among older adults. *Arch Intern Med*. 2012;172(19):1465-1471.
4. Sandoz B.V. Ciprofloxacine Sandoz 250/500/750 mg, filmomhulde tabletten RVG 25206-7-8 1.3.1.1 Summary of Product Characteristics.
https://www.geneesmiddeleninformatiebank.nl/smpc/h25207_smpc.pdf. Published November 2020. Accessed July 27, 2021.
5. de Vroom SL, van Hest RM, van Daalen FV. Pharmacokinetic/pharmacodynamic target attainment of ciprofloxacin in adult patients on general wards with adequate and impaired renal function. *Int J Antimicrob Agents*. 2020;56(5):1061-1066.
6. D Khachman, J Conil, B Georges, et al. Optimizing ciprofloxacin dosing in intensive care unit patients through the use of population pharmacokinetic–pharmacodynamic analysis and Monte Carlo simulations. *J Antimicrob Chemother*. 2011;66(8):1789-1809.
7. AR van Zanten, KH Polderman, IM van Geijlswijk, et al. Ciprofloxacin pharmacokinetics in critically ill patients: a prospective cohort study. *J Crit Care*. 2008;23(3):422-430.
8. P Kontou, K Chatzika, G Pitsiou, et al. Pharmacokinetics of ciprofloxacin and its penetration into bronchial secretions of mechanically ventilated patients with chronic obstructive pulmonary disease. *Antimicrob Agents Chemother*. 2011;55(9):4149-4153.
9. M Haeseker, L Stolk, F Nieman, et al. The ciprofloxacin target AUC:MIC ratio is not reached in hospitalized patients with the recommended dosing regimens. *Br J Clin Pharmacol*. 2013;75(1):180-185.
10. A Forrest, DE Nix, CH Ballow, et al. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob Agents Chemother.* 1993;37(5):1073-1081.
11. SA Zelenitsky, GK Harding, S Sun, et al. Treatment and outcome of Pseudomonas aeruginosa bacteraemia: an antibiotic pharmacodynamics analysis. *J Antimicrob Chemother*. 2003;52(4):668-674.
12. KNMP Kennisbank. Ciprofloxacine.
https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/S2078.html. Accessed July 20, 2021.
13. Liu P, Müller M, Derendorf H. Rational dosing of antibiotics: the use of plasma concentrations versus tissue concentrations. *Int J Antimicrob Agents*. 2002;19(4):285-290.
14. Roberts JA, Pea F, Lipman J. The Clinical Relevance of Plasma Protein Binding Changes. *Clin Pharmacokinet*. 2013;52(1):1–8.
15. Wong G, Briscoe S, Adnan S, et al. Protein binding of β-lactam antibiotics in critically ill patients: can we successfully predict unbound concentrations? *Antimicrob Agents Chemother*. 2013;57(12):6165-6170.
16. Barco S, Mesini A, Barbagallo L, et al. A liquid chromatography-tandem mass spectrometry platform for the routine therapeutic drug monitoring of 14 antibiotics: Application to critically ill pediatric patients. *J Pharm Biomed Anal*. 2020;186:113273.
17. El-bagary R, El-Zaher AA, Elkady E, et al. Simultaneous determination of ciprofloxacin hydrochloride and metronidazole in spiked human plasma by ultra performance liquid chromatography-tandem mass spectroscopy. *J of Applied Pharmaceutical Science*. 2016;6(3):41-47.
18. Kim H, Seo K, Kim H, et al. Simple and accurate quantitative analysis of 20 anti-tuberculosis drugs in human plasma using liquid chromatography–electrospray ionization–tandem mass spectrometry. *J Pharm Biomed Anal.* 2015;102:9-16.

19. Hösl J, Gessner A, El-Najjar N. Liquid chromatography-tandem mass spectrometry for the quantification of moxifloxacin, ciprofloxacin, daptomycin, caspofungin, and isavuconazole in human plasma, *J Pharm Biomed Anal*. 2018;157:92-99.
20. Paal M, Zoller M, Schuster C, et al. Simultaneous quantification of cefepime, meropenem, ciprofloxacin, moxifloxacin, linezolid and piperacillin in human serum using an isotope-dilution HPLC-MS/MS method. *J Pharm Biomed Anal*. 2018;152:102-110.
21. Mabelis NJ, Shudofsky KN, van Raaij JJ, et al. Therapeutic drug monitoring of protein unbound ciprofloxacin concentrations to avoid inadequate treatment of severe bacterial infections in critically ill patients. *J Appl Bioanal*. 2018;4(5):166-174.
22. US FDA. Guidance for Industry: Bioanalytical Method Validation. US Department of Health and Human Services, FDA, Center for Drug Evaluation and Research, Rockville, MD, USA (2018). https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf. Published May 2018. Accessed August 21, 2021.

Chapter 4

Pharmacokinetic/pharmacodynamic target attainment of ciprofloxacin in adult patients on general wards with adequate and impaired renal function

Suzanne L. de Vroom, Reinier M. van Hest, Frederike V. van Daalen, Sacha D. Kuil, Ron A.A. Mathôt, Suzanne E. Geerlings and Nynke G.L. Jager

Int J Antimicrob Agents. 2020 Nov;56(5):1061-1066

Abstract

Limited prospective data on pharmacokinetic/pharmacodynamic (PK/PD) target attainment of ciprofloxacin in patients with adequate and impaired renal function (eGFR <30 mL/min/1.73m^2) are available in the literature. We aimed to investigate whether the PK/PD target (AUC/MIC ≥125) is attained in patients with adequate and impaired renal function receiving regular and reduced ciprofloxacin doses.

This prospective observational cohort study included adult patients on general wards treated with ciprofloxacin. Three blood samples per patient were obtained for ciprofloxacin concentration measurement. Individual AUCs were calculated using a population PK model developed by non-linear mixed-effects modelling.

Forty patients were included, of whom eight had impaired renal function and were treated with a guideline-recommended reduced dose. Using the clinical breakpoint MIC of the most isolated bacteria (*Escherichia coli*, 0.25 mg/L), $AUC_{0–24}$/MIC ≥125 was attained in 13/32 (41%) patients with adequate renal function receiving regular doses and in 1/8 (13%) patients with impaired renal function receiving reduced doses. Median drug exposure ($AUC_{0–24}$) for patients with impaired renal function was 19.0 [interquartile range (IQR) 14.2–23.3] mg/L•h, which was statistically significantly lower than that for patients with adequate renal function [29.3 (IQR 25.0–36.0) mg/L•h] ($P < 0.01$).

$AUC_{0–24}$/MIC ≥125 is not attained in the majority of adult patients on general wards for clinically relevant bacteria with MICs at or just below the clinical breakpoint. The risk of not attaining the target appears to be highest in patients with impaired renal function receiving guideline-recommended reduced doses, as drug exposure is significantly lower in these patients.

Introduction

Early and adequate antibiotic treatment is associated with decreased mortality in hospitalised patients.[1] Underdosing can result in treatment failure and can promote the emergence of antimicrobial resistance, whilst overdosing may lead to potentially harmful side effects.[2]

The fluoroquinolone antibiotic ciprofloxacin is frequently prescribed both in inpatient and outpatient settings and its activity mainly includes Gram-negative bacteria, of which Enterobacterales and *Pseudomonas aeruginosa* are the most clinically relevant.[3]

Antibiotic dosing is generally considered to be optimal when the pharmacokinetic/pharmacodynamic (PK/PD) target is attained. For ciprofloxacin, this target is defined as the ratio of the area under the concentration–time curve (AUC) over the minimum inhibitory concentration (MIC), with the MIC being the lowest concentration of an antibiotic that prevents visible growth of bacteria in vitro.[4] Attaining the PK/PD target of AUC/MIC ≥125 for total ciprofloxacin exposure is associated with clinical and microbiological cure of lower respiratory tract infections, bacteraemia, wound and soft tissue infections, and complicated urinary tract infections, mainly caused by *P. aeruginosa* or other Gram-negative bacteria.[5,6] However, it has been shown that AUC/MIC ≥125 is often not attained in critically ill patients or in patients on general wards treated with recommended doses of ciprofloxacin (200–1500 mg/day).[7-10]

Ciprofloxacin is primarily eliminated renally. Therefore, dose reductions are recommended for patients with an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73m^2.[11-16] These dose reductions are based on extrapolations from small studies mostly investigating the PKs of ciprofloxacin after a single, full, unadjusted dose in volunteers with impaired renal function, but without an infection.[17-21] However, ciprofloxacin is also metabolised and partly excreted through the biliary system. This alternative elimination pathway may compensate for reduced elimination through the kidneys in patients with impaired renal function. Therefore, the correlation between eGFR and total clearance of ciprofloxacin might not be directly proportional.[22-24]

To the best of our knowledge, it has not been previously prospectively investigated whether the PK/PD target of AUC/MIC ≥125 is attained in patients on general wards with impaired renal function treated with the recommended reduced dose of ciprofloxacin. Therefore, the aim of this study was to investigate (i) whether the PK/PD target of ciprofloxacin (AUC/MIC ≥125) is attained in the first 24 h of treatment in adult patients on general wards with adequate and impaired renal function receiving regular and reduced doses of ciprofloxacin, respectively, and (ii) whether the guideline-recommended dose reduction of ciprofloxacin for patients with impaired renal function results in a drug exposure similar to the guideline-recommended regular dose in patients with adequate renal function.

Methods

Study design

All patients in this prospective observational cohort study (January–August 2018) were hospitalised on general surgical or non-surgical wards of the Amsterdam University Medical Centre (Amsterdam UMC), location Academic Medical Centre (AMC), the Netherlands.

Patients and data collection

Eligible patients were adults (age ≥18 years) treated with ciprofloxacin orally or intravenously based on a (suspected) bacterial infection (i.e. no prophylaxis) at the discretion of the treating physician while being hospitalised on a general ward. Eligibility was irrespective of renal function or administered dose. We excluded patients on renal replacement therapy and severely burned patients because of altered PKs such as increased volume of distribution and severely impaired clearance or, controversially, glomerular hyperfiltration.[25,26]

Regular doses of ciprofloxacin according to Dutch national guidelines were 500 mg orally (p.o.) or the intravenous (i.v.) equivalent of 400 mg every 12 h (q12h), based on an oral bioavailability rate of ciprofloxacin of 70–80%, irrespective of the kind of infection being treated.[14-16,27] Higher doses of ciprofloxacin (750 mg p.o. q12h or the i.v. equivalent of 400 mg every 8 h) were recommended for infections where penetration to the infection site may be difficult (e.g. osteomyelitis). Daily doses were halved in patients with impaired renal function (eGFR <30 mL/min/1.73m^2), either by reducing the dose per administration (250 mg p.o. or 200 mg i.v. q12h) or by doubling the dosing interval [500 mg p.o. or 400 mg i.v. every 24 h (q24h)][14-16]. The infusion time of ciprofloxacin was 400 mg/h.

Patient characteristics, concomitant use of other antibiotics, and data regarding dose and time of administration of ciprofloxacin were retrieved from the patient's electronic health record and independently checked by a second investigator. Additionally, information about the dosing regimen and time of administration of ciprofloxacin was checked with the responsible nurse and the patient. Laboratory measurements including eGFR, creatinine, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), and administration of co-medication influencing the oral absorption of ciprofloxacin were recorded during the whole course of treatment with ciprofloxacin. GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.[28,29]

Ethical considerations

This study was conducted in accordance with the Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki.[30,31] The research protocol was approved by the certified Medical Ethics Committee of the AMC, also known as an institutional review board, and registered at the Dutch Trial Register. All patients provided written informed consent; legally incompetent adults were excluded.

Procedures

We aimed to prospectively collect three venous heparin anticoagulated blood samples per patient by venipuncture, consisting of one trough concentration and two concentrations in the first 4 h of the

dosing interval. Therefore, the preferred sampling scheme was: (i) just before p.o. or i.v. administration, reflecting a trough concentration; (ii) 0–30 min after i.v. or 30–60 min after p.o. administration; and (iii) 1–4 h after p.o. and i.v. administration, the latter two aiming to capture the absorption and distribution phase of ciprofloxacin.

Additionally, waste material was collected to enrich the data set with more concentration–time data points. The date and time of all those samples were registered in the patient's electronic health record.

Ciprofloxacin concentration measurement

Collected blood samples were centrifuged immediately and plasma was stored at –80 °C at the clinical laboratory of the pharmacy department of the Amsterdam UMC, location AMC. Total and unbound ciprofloxacin plasma concentrations were analysed using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay within 3 months after sample collection. Detailed information on ciprofloxacin concentration measurement is available in the Appendix.

Minimum inhibitory concentration determination

Cultures were obtained for all patients. Bacteria were identified by Gram stain, colony morphology and matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDITOF/MS). MICs of clinically relevant bacteria were measured using a validated Etest (bioMérieux, Marcy-l'Étoile, France) if bacteria could be preserved. Detailed information on MIC measurement is available in the Appendix.

Outcomes

The primary outcome was the percentage of patients achieving an AUC/MIC ratio ≥125 in the first 24 h of ciprofloxacin treatment ($AUC_{0\text{-}24}$/MIC ≥125), first using the clinical breakpoint MIC of ciprofloxacin for the most frequently isolated bacteria, second using the epidemiological cut-off (ECOFF) value that distinguishes between bacteria with and without phenotypically expressed resistance mechanisms, both values according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST), and third using the actually measured MIC values.[32,33]

Secondary outcomes were the percentage of patients achieving AUC/MIC ≥125 after 24–48 h of treatment ($AUC_{24\text{-}48}$/MIC ≥125), drug exposure in the first 24 h (defined as $AUC_{0–24}$) and drug exposure after 24–48 h of treatment ($AUC_{24–48}$).

Clinical outcome was determined as an exploratory outcome and was defined according to the following individual parameters (not as a composite endpoint): 30-day and 3-month mortality after start of treatment with ciprofloxacin, admission to the intensive care unit, hospital length of stay, days of fever (≥38.5 °C) after start of treatment with ciprofloxacin, or switch to an antibiotic with more broad-spectrum activity within 48 h of treatment.

Sample size

Because no data were available in the literature on the percentage of patients with impaired renal function attaining AUC_{0-24}/MIC ≥125 to base the sample size calculation on, we based our sample size calculation on the second-best available data, namely detecting an association between renal function and total clearance of ciprofloxacin.

We used a stochastic simulation and estimation (SSE) procedure as implemented in Perl-speaks-NONMEM (PsN) v.3.5.3 software (Uppsala University, Uppsala, Sweden) for sample size calculation. With an SSE procedure, one can calculate how many patients need to be included, given a chosen blood sample collection scheme and an available population PK model, to detect an association between renal function and ciprofloxacin clearance. For this procedure, the population PK model reported by Cios et al. was used.[34]

The result was that with the inclusion of 20 patients, of whom 4 had an eGFR ≤30 mL/min/1.73m^2, it is possible to detect an association between renal function and total clearance of ciprofloxacin with a power of ≥95% at a significance level of 5%. This calculation is based on the collection of three samples per patient, including at least one trough sample, and that eGFR values in the patient population ranged between 15–115 mL/min/1.73m^2. Since this study was conducted in real-life clinical practice in patients with infections, in which collection and timing of blood samples can be challenging, we anticipated that we would not be able to obtain exactly three samples for every single patient (including at least one trough sample) and therefore decided to take a safety margin around the calculated sample size and aimed to include 40 patients including 8 with an eGFR ≤30 mL/min/1.73m^2.

Population pharmacokinetic data analysis for AUC calculation

To calculate the AUC for each individual patient, a PK model using the obtained ciprofloxacin concentration–time data was developed by means of non-linear mixed effects modelling (NONMEM) using the software package NONMEM v.7.3 (Icon Development Solutions, Ellicott City, MD, USA).

In short, first an integral structural compartmental population PK model for both intravenously and orally administered ciprofloxacin was developed. Second, a covariate analysis was performed in which patient demographics and pathophysiological factors (e.g. renal function) were tested for their association with the estimated clearance and volume of distribution parameters by univariate and subsequent multivariate analysis. This yielded the final model. Third and last, the robustness and validity of the final model was tested with respectively a bootstrap analysis and a visual predictive check using PsN v.3.5.3 software. Detailed information on methodological model building is available in the Appendix.

The AUC for individual patients was calculated by Bayesian estimation ('Posthoc' in the $ESTIMATION step of NONMEM software) using all available time points.[35-37]

Statistical analysis

Percentages of patients attaining and not attaining AUC/MIC ≥125 were calculated both for the group of patients with adequate renal function and the group of patients with impaired renal function (eGFR < 30 mL/min/1.73m^2). The Mann–Whitney *U*-test was used to compare drug exposure (AUC) between patients with adequate and impaired renal function. Differences were considered

statistically significant at a *P*-value of < 0.05. Parameters of clinical outcome were individually explored using descriptive statistics. Statistical analysis was performed using IBM SPSS Statistics v.25 (IBM Corp., Armonk, NY, USA).

Monte Carlo dosing simulations

Using the final population PK model, drug exposure in the first 24-h of treatment (AUC_{0-24}) following three different dosing regimens was predicted for patients with impaired renal function based on Monte Carlo simulations: (i) the guideline-recommended dose reduction (50% dose reduction, i.e. 500 mg p.o. or 400 mg i.v. q24h, or 250 mg p.o. or 200 mg i.v. q12h in the same ratio as in the observed data); (ii) a 25% dose reduction (i.e. 750 mg p.o. or 600 mg i.v. q24h); or (iii) a 12.5% dose reduction (i.e. 875 mg p.o. or 700 mg i.v. q24h). Additionally, AUC_{0-24} was predicted for patients with adequate renal function based on Monte Carlo simulations, following the regular dosing regimen (i.e. 1000 mg p.o. or 800 mg i.v. q24h, or 500 mg p.o. or 400 mg i.v. q12h in the same ratio as in the observed data). Simulations generated drug exposures for 8000 virtual patients with impaired renal function and 32 000 virtual patients with adequate renal function (in the same ratio as in the observed data, for all three dosing regimens). The distribution of eGFR values within the simulated groups of patients (patients with impaired and adequate renal function) was the same as for the observed distribution of eGFR values in both groups. Drug exposure was compared between patients with impaired renal function receiving one of the three different dose reduction regimens and patients with adequate renal function receiving the regular dosing regimen.

Additionally, the probability of PK/PD target attainment (AUC_{0-24}/MIC ≥125) at different MICs was predicted based on these simulated data.

Results

Patients and ciprofloxacin concentrations

A total of 40 patients were included, of which 28 patients were initially treated orally and 12 intravenously. Eight patients had an impaired renal function (eGFR < 30 mL/min/1.73m^2), all of which were treated with a recommended reduced dose of ciprofloxacin: in six patients the dose was halved (250 mg p.o. or 200 mg i.v. q12h) and in two patients the dose interval was doubled (500 mg p.o. or 400 mg i.v. q24h). Patients with adequate and impaired renal function were well balanced with respect to all patient characteristics, except for creatinine, eGFR and administered dose of ciprofloxacin (Table 1).

For the population PK model, 186 samples were available, of which 45 samples (24%) were collected within the first 48 h after the start of treatment with ciprofloxacin and 22 within the first 24 h. Most samples were collected after oral administration (*n* = 169; 91%). We collected 36 samples (19%) according to the predefined sampling scheme and the other 150 (81%) originated from waste material and as such contributed to random timing of sample collection. Sampling time as registered in the patient's electronic health record was used for the population PK model.

Of the 40 patients, 9 (23%) had less than three samples available owing to the patient declining additional venipunctures or failure to collect blood by venipuncture due to difficult venous access. Of the 186 samples, 2 resulted in a ciprofloxacin plasma concentration below the lower limit of quantitation (LLOQ); both were collected > 48 h after the end of treatment with ciprofloxacin. These samples were handled by using a value of 0.5 × LLOQ. Total and unbound plasma concentrations were determined in 186 and 127 samples, respectively. The mean fraction of unbound ciprofloxacin was 0.71 (95% confidence interval 0.69–0.73) and was independent of the total ciprofloxacin plasma concentration, indicating linear plasma protein binding (Fig. 1).

Table 1. Patient characteristics (*n* = 40) stratified by renal function

Characteristic	Adequate renal function (eGFR ≥30 mL/min/1.73m²) (*n* = 32)	Impaired renal function (eGFR <30 mL/min/1.73m²) (*n* = 8)
Female sex	10 (31%)	4 (50%)
Age (years)	67 (23–90)	69 (38–91)
Body mass index (kg/m²)	25 (18–53)	26 (20–38)
Creatinine (µmol/L)	93 (32–229)	257 (187–633)
eGFR (mL/min/1.73m²) [a]	70 (33–120)	20 (6–26)
Initial standard dose	32 (100%)	–
500 mg p.o. q12h	18 (56%)	
400 mg i.v. q12h	8 (25%)	
750 mg p.o. q12h	4 (13%)	
400 mg i.v. q8h	2 (6%)	
Initial reduced dose	–	8 (100%)
250 mg p.o. q12h		4 (50%)
200 mg i.v. q12h		2 (25%)
500 mg p.o. q24		2 (25%)
Infection site		
Urinary tract infection	12 (38%)	4 (50%)
Pneumonia	10 (31%)	–
Abdominal infection	5 (16%)	2 (25%)
Skin and soft-tissue infection	5 (16%)	2 (25%)
Co-morbidities	29 (91%)	7 (88%)
Cardiovascular	21 (66%)	4 (50%)
Diabetes mellitus	16 (50%)	5 (63%)
Immunosuppressive	8 (25%)	3 (38%)
Other	13 (41%)	5 (63%)
Concomitant use of other antibiotics		
β-Lactam	17 (53%)	2 (25%)
Clindamycin	2 (6%)	2 (25%)
Monotherapy	12 (38%)	3 (38%)
Other	1 (3%)	2 (25%)
Concomitant use of drugs possibly interfering with absorption of ciprofloxacin [b]	12 (38%)	4 (50%)

NOTE: Data are expressed as median (range) or *n* (%).
eGFR, estimated glomerular filtration rate; p.o., orally; q12h, every 12 h; i.v., intravenous; q8h, every 8 h; q24h, every 24 h.
All characteristics were determined at the start of treatment with ciprofloxacin.

[a] Estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[28,29]

[b] Drugs possibly interfering with the absorption of ciprofloxacin administered within 2 h before until 4 h after oral administration of ciprofloxacin: aluminium and magnesium antacids, sucralfate, calcium, bismuth, zinc and iron salts, and polymeric phosphate binders (all possibly leading to reduced absorption) and metoclopramide (possibly leading to faster absorption).

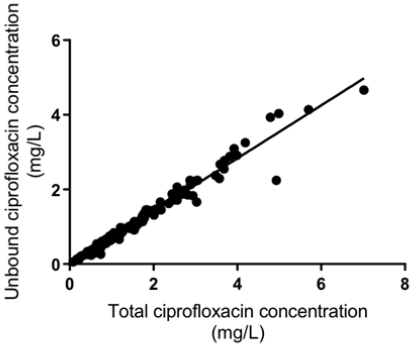


Fig. 1. Total and unbound ciprofloxacin plasma concentrations. The solid line represents the mean fraction of unbound ciprofloxacin; y = 0.71*x*; Pearson correlation coefficient, 0.98.

Minimum inhibitory concentration determination

Cultures were obtained from all patients; 22 (55%) of the 40 patients showed positive cultures, from which 24 clinically relevant bacteria were isolated. Of the 24 isolated bacteria, MICs could be measured by Etest for 7 bacteria; all bacteria showed MICs of ≤0.023 mg/L (Table 2).

Table 2. MICs of ciprofloxacin (clinical breakpoint and ECOFF according to EUCAST and measured MIC values) stratified by bacterial species[32,33]

Species	No. of times isolated (*n*)	Clinical breakpoint (mg/L)[32]	ECOFF (mg/L) [33]	MIC measured by Etest (mg/L)
Escherichia coli	7	0.25	0.064	0.012
				0.008
				0.023
				0.012
Pseudomonas aeruginosa	6	0.5	0.5	*
Enterobacter cloacae	3	0.25	0.125	0.023
				0.004
Klebsiella aerogenes	1	0.25	0.125	*
Klebsiella pneumoniae	1	0.25	0.125	*
Klebsiella oxytoca	1	0.25	0.125	*
Proteus mirabilis	1	0.25	0.064	*
Citrobacter freundii	1	0.25	– [a]	0.008
Morganella morganii	1	0.25	0.125	*
Serratia marcescens	1	0.25	– [a]	*
Acinetobacter baumannii	1	0.06	1.0	*

MIC, minimum inhibitory concentration; ECOFF, epidemiological cut-off value; EUCAST, European Committee on Antimicrobial Susceptibility Testing.

∗ Isolate(s) could not be preserved.

a – Data not provided.

Population pharmacokinetic analysis

Detailed information on the results of model development is available in the Appendix. In brief, a one-compartmental model provided the best fit. Between-patient variability could be estimated for volume of distribution and clearance. Residual variability was modelled with a proportional error model and was estimated to be 39%. Univariate analysis revealed that there was a statistically significant association between eGFR and clearance of ciprofloxacin (CL):

$$CL(L/h) = 21.1 \times (\text{eGFR}/70)^{0.277} \qquad \text{(A1)}$$

As observed in the visual predictive check, the final model was capable of predicting the individual observed concentration–time data without bias and was thus valid to be used for the AUC calculations (Appendix, Figs A.2–A.6).

Pharmacokinetic/pharmacodynamic target attainment

Using the clinical breakpoint MIC for the most frequently isolated bacteria, i.e. *Escherichia coli* (MIC = 0.25 mg/L), which is also the clinical breakpoint MIC of most other isolated bacteria in our study (Table 2), target attainment ($AUC_{0–24}$/MIC ≥125) was 41% (13/32) in patients with adequate renal function receiving a regular dose and 13% (1/8) in patients with impaired renal function receiving a reduced dose (Fig. 2). After 24–48 h of treatment with ciprofloxacin, target attainment ($AUC_{24–48}$/MIC

≥125) using this clinical breakpoint MIC (0.25 mg/L) improved from 41% to 72% for patients with adequate renal function. However, for patients with impaired renal function receiving a reduced dose, target attainment remained at 13%.

The PK/PD target of $AUC_{0–24}$/MIC ≥125 using the ECOFF value for the most frequently isolated bacteria, i.e. *E. coli* (ECOFF = 0.064 mg/L), was attained in 31 (97%) of the 32 patients with adequate renal function receiving a regular dose and in all 8 patients (100%) with impaired renal function receiving a reduced dose. However, $AUC_{0–24}$/MIC ≥125 using the ECOFF value for the second most frequently isolated bacteria, i.e. *P. aeruginosa* (ECOFF = 0.5 mg/L) was attained in none (0%) of the 32 patients with adequate renal function receiving a regular dose and in none (0%) of the 8 patients with impaired renal function receiving a reduced dose. Most other isolated bacteria had an ECOFF value of 0.125 mg/L (Table 2), which would result in target attainment of 94% in patients with adequate renal function receiving a regular dose and of 63% in patients with impaired renal function receiving a reduced dose (Fig. 2).

Using the actually measured MICs of the isolated bacteria (≤0.023 mg/L), $AUC_{0–24}$/MIC ≥125 was attained in all patients (Fig. 2).

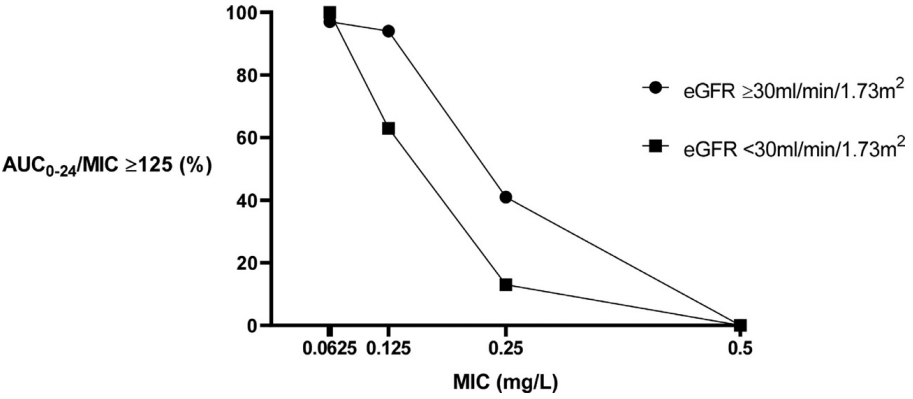


Fig. 2. Calculated percentage of patients attaining the pharmacokinetic/pharmacodynamic (PK/PD) target of AUC_{0-24}/MIC ≥125 at different MIC values (0.0625, 0.125, 0.25 and 0.5 mg/L) for patients with adequate renal function (eGFR ≥30 mL/min/1.73m^2, with most frequently prescribed ciprofloxacin dose of 500 mg p.o. q12h) and for patients with impaired renal function (eGFR <30 mL/min/1.73m^2, with most frequently presribed ciprofloxacin dose of 250 mg p.o. q12h). AUC_{0-24}/MIC, 24-h area under the concentration–time curve over the minimum inhibitory concentration; MIC, minimum inhibitory concentration; eGFR, estimated glomerular filtration rate; p.o., orally; q12h, every 12 h.

Drug exposure and clinical outcome

Median drug exposure in the first 24-h of treatment ($AUC_{0–24}$) for patients with impaired renal function receiving a reduced dose was 19.0 [interquartile range (IQR) 14.2–23.3] mg/L•h, which was statistically significantly lower than the median $AUC_{0–24}$ for patients with adequate renal function receiving a regular dose [29.3 (IQR 25.0–36.0) mg/L•h] ($P < 0.01$) (Fig. 3). Median drug exposure remained significantly lower for patients with impaired renal function after 24–48 h of treatment

[$AUC_{24–48}$ impaired renal function, 23.7 (IQR 17.7–28.2) mg/L•h, vs. $AUC_{24–48}$ adequate renal function, 37.9 (IQR 28.8–43.0) mg/L•h; $P < 0.01$].

When patients receiving higher doses of ciprofloxacin (1500 mg/day p.o. or 1200 mg/day i.v., $n = 6$) were excluded from this analysis, median drug exposure remained statistically significantly lower for patients with impaired renal function [$AUC_{0–24}$ impaired renal function, 19.0 (IQR 14.2–23.3) mg/L•h vs. $AUC_{0–24}$ adequate renal function, 29.1 (IQR 24.9–35.1) mg/L•h; $P < 0.01$]. No differences were observed for the individual parameters of clinical outcome between patients of the different renal function groups (Table 3).

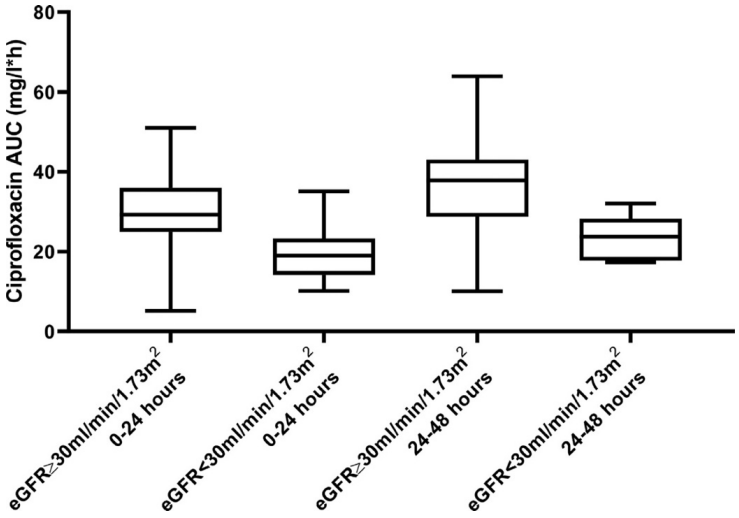


Fig. 3. Median ciprofloxacin exposure in the first 24-h (AUC_{0-24}) and 24–48 h (AUC_{24-48}) after treatment with ciprofloxacin for patients with adequate renal function (eGFR ≥30 mL/min/1.73m^2, with most frequently prescribed ciprofloxacin dose of 500 mg p.o. q12h) and for patients with impaired renal function (eGFR <30 mL/min/1.73m^2, with most frequently prescribed ciprofloxacin dose of 250 mg p.o. q12h). eGFR, estimated glomerular filtration rate; p.o., orally; q12h, every 12 h.

Table 3. Clinical outcome of patients ($n = 40$) stratified by function.

Outcome	Adequate renal function (eGFR ≥30 mL/min/1.73m²) (*n* = 32)	Impaired renal function (eGFR <30 mL/min/1.73m²) (*n* = 8)
30-day mortality after start of ciprofloxacin treatment (*n*)	0	0
3-month mortality after start of ciprofloxacin treatment (*n*)	1	0
Admission to ICU [*n* (%]	6 (19%)	2 (25%)
Hospital LOS after start of ciprofloxacin treatment (days) [median (range)]	8.5 (2–46)	4.5 (1–58)
Switch to antibiotic with more broad-spectrum activity (*n*)	0	1

NOTE: Data are expressed as median (range) or *n* (%). GFR, estimated glomerular filtration rate; ICU, intensive care unit; LOS, length of stay.

Monte Carlo dosing simulations

Of the three dosing regimens for patients with impaired renal function, a 25% dose reduction of the regular daily dose (i.e. 750 mg p.o. or 600 mg i.v. q24h, dosing regimen C) showed most equivalent drug exposure in the first 24-h of treatment [median $AUC_{0–24}$, 26.3 (IQR 19.2–34.5)] compared with patients with adequate renal function receiving a regular dose [median $AUC_{0–24}$, 25.3 (IQR 18.6–33.5)] (Fig. 4).

Additionally, with this 25% dose reduction (dosing regimen C), the probability of PK/PD target attainment ($AUC_{0–24}$/MIC ≥125) for patients with impaired renal function was almost equivalent to that in patients with adequate renal function receiving a regular dose, at all MIC values. For instance, using an MIC of 0.125 mg/L, the probability of PK/PD target attainment was 86% for patients with impaired renal function compared with 94% for patients with adequate renal function, and using an MIC of 0.25 mg/L the percentages were 34% and 41%, respectively (Fig. 5).

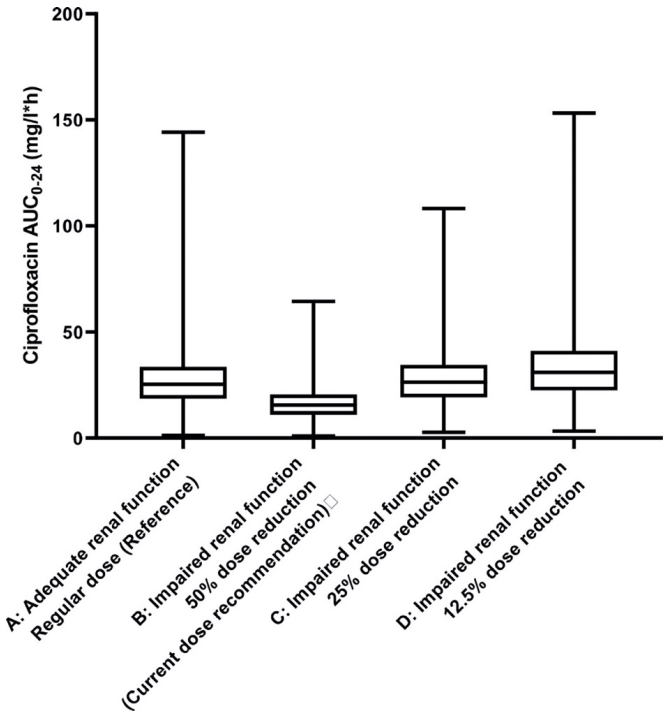


Fig. 4. Median ciprofloxacin exposure in the first 24-h of treatment (AUC_{0-24}) from 1000-subject Monte Carlo simulations for different dosing regimens: (A) patients with adequate renal function receiving a regular daily dose [1000 mg p.o. or 800 mg i.v. (median 25.3 (IQR 18.6–33.5) mg/L•h]; (B) patients with impaired renal function receiving the guideline-recommended dose reduction (50% dose reduction) [500 mg p.o. or 400 mg i.v. q24h (median 15.5 (IQR 11.0–20.5) mg/L•h]; (C) patients with impaired renal function receiving a 25% dose reduction [750 mg p.o. or 600 mg i.v. q24h (median 26.3 (IQR 19.2–34.5) mg/L•h]; and (D) patients with impaired renal function receiving a 12.5% dose reduction [875 mg p.o. or 700 mg i.v. q24h (median 30.9 (IQR 22.5–41.1) mg/L•h]. p.o., orally; i.v., intravenous; q24h, every 24 h; IQR, interquartile range.

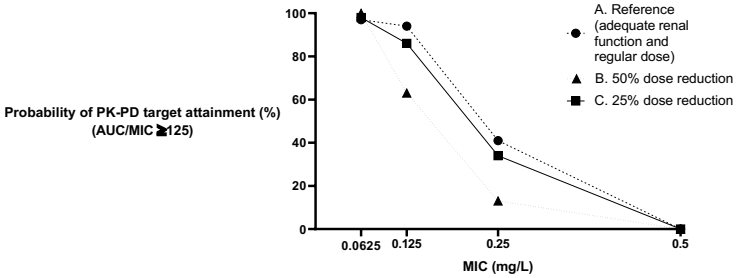


Fig. 5. Probability of pharmacokinetic/pharmacodynamic (PK/PD) target attainment of $AUC_{0\text{-}24}$/MIC ≥125 (%) for patients with impaired renal function (eGFR <30 mL/min/1.73m^2) from 1000-subject Monte Carlo simulations at different MIC values (0.0625, 0.125, 0.25 and 0.5 mg/L) for different dosing regimens: (A) reference [patients with adequate renal function receiving a regular dose (1000 mg p.o. or 800 mg i.v. q24h)]; (B) 50% dose reduction (500 mg p.o. or 400 mg i.v. q24h); and (C) 25% dose reduction (750 mg p.o. or 600 mg i.v. q24h). $AUC_{0\text{-}24}$/MIC, 24-h area under the concentration–time curve over the minimum inhibitory concentration; eGFR, estimated glomerular filtration rate; MIC, minimum inhibitory concentration; p.o., orally; i.v., intravenous; q24h, every 24 h.

Discussion

This study shows that the PK/PD efficacy target of $AUC_{0–24}$/MIC ≥125 is not attained in the majority of adult patients on general wards treated with current dosing regimens of ciprofloxacin (500–1500 mg/day p.o. or 400–1200 mg/day i.v.) for clinically relevant bacteria with MICs at or just below the clinical breakpoint (0.25 mg/L). For bacteria where the MIC was actually measured, all patients attained the PK/PD efficacy target because all measured MICs were far below the ECOFF value of relevant bacteria. The risk of not attaining the PK/PD target for clinically relevant bacteria with MICs at or just below the clinical breakpoint appears to be highest in patients with impaired renal function receiving a guideline-recommended reduced dose of ciprofloxacin.

After 24–48 h of treatment with ciprofloxacin, the percentage of patients with adequate renal function receiving a regular dose that attained the PK/PD target increased from 41% to 72%, indicating that steady-state was not reached within the first 24 h of treatment. Yet target attainment remained at only 13% for patients with impaired renal function receiving a reduced dose after 24–48 h of treatment, which further illustrates the low ciprofloxacin exposure in this subset of our population. In addition, our results show that ciprofloxacin exposure is not equivalent but is statistically significantly lower in patients with impaired renal function receiving a reduced dose compared with patients with adequate renal function receiving a regular dose. This is of importance since the rationale behind the guideline-recommended dose reduction of ciprofloxacin in patients with impaired renal function is to achieve drug exposure equivalent to exposure in patients with adequate renal function receiving a regular dose. To achieve equivalent drug exposure, we therefore postulate that the daily dose of ciprofloxacin should be reduced to 75% of the regular dose, instead of the currently recommended 50% dose reduction, as shown by the results of our Monte Carlo dosing simulations (Fig. 4). This is also supported by results of other studies which showed that non-renal clearance of ciprofloxacin increases in patients with impaired renal function to compensate for the reduced renal clearance.[22-24] Additionally, the results of our study showed that there was a non-linear association between renal function and ciprofloxacin clearance, indicating that the decrease in renal function is not directly proportional to the decrease in ciprofloxacin clearance (Appendix, Fig. A.1). Another reason why the current dose reduction in patients with impaired renal function may be too large might be that recommended dose reductions of antibiotics, including ciprofloxacin, are based on studies enrolling patients with chronic renal impairment in whom the decrease in ciprofloxacin clearance may not be representative for patients with acute renal impairment, who are often part of the patient population on general wards as also mentioned by Crass et al.[38] However, in our study only two (25%) of the eight patients with impaired renal function showed acute renal impairment at the start of treatment with ciprofloxacin, which resolved within 48 h in one patient.

Subsequently, one could argue that a loading dose of ciprofloxacin can improve the effect of ciprofloxacin treatment. Results show an improvement in PK/PD target attainment after 24– 48 h of treatment, indicating that steady-state is not reached in the first 24 h of treatment. By adding a loading dose, steady-state is likely to be reached within the first 24 h of treatment and PK/PD target attainment in this time period may improve accordingly. The need to increase the dose of ciprofloxacin was also concluded from three other European studies.[7,8,10] An important difference between these studies and our study is that these studies did not make a distinction between patients with adequate and impaired renal function receiving regular and reduced doses, respectively. Consequently, these studies could not show that patients with impaired renal function have an even greater risk of not attaining the PK/PD target compared with patients with adequate renal function. Of note, increasing the dose of ciprofloxacin for all patients might be controversial since the European Medicines Agency (EMA) has recently restricted the indications for ciprofloxacin

use following a review reporting disabling and potentially permanent side effects with fluoroquinolone use, such as tendonitis and tendon rupture, although those side effects were not reported to be dose-dependent.[39] We therefore suggest to only consider an increased daily dose when suboptimal treatment is suspected despite timely antibiotic treatment according to current guideline recommendations or in local settings with a relatively high level of antimicrobial drug resistance.[40] The latter was not the case in our study as we identified bacteria with much lower MICs than the ECOFF, in line with the fact that the majority of patients in clinical practice in the Netherlands are infected with susceptible strains of bacteria and thus attain $AUC_{0–24}$/MIC ≥125 with currently recommended dosing regimens.

Our final population PK model, specifically developed to fit our patient population, was valid for individual AUC calculations, and the PK parameter estimates were in line with other population PK models found in the literature.[34,41,42]

The biggest strength of this study is that it is innovative in both the methods used as well as the clinically relevant research questions that are answered. First, this is the first study in which a population PK model of orally and intravenously administered ciprofloxacin in patients admitted to general wards is developed and used for calculating target attainment and dosing simulations. Second, this is the first prospective study comparing PK/PD target attainment in patients with impaired renal function who receive an adjusted ciprofloxacin dose with a control group of patients with adequate renal function receiving regular doses. Nevertheless, limitations of this study should also be considered.

First, only 19% of all collected samples were obtained according to the predefined sampling scheme as a result of most patients declining additional venipunctures. Therefore, the majority of the samples originated from waste material. This is suboptimal since the time registration of the collection of waste material samples may be less accurate and may therefore contribute to the relatively high residual variability of the final population PK model of 39%. Additionally, only 24% of the samples was obtained within the first 48 h of treatment with ciprofloxacin, although our endpoints were $AUC_{0–24}$ and $AUC_{24–48}$. However, additional analysis showed that the AUC in our patient population was stable during the whole course of therapy with ciprofloxacin, which was confirmed by previously published data showing that ciprofloxacin PKs in mild-to-moderately ill patients were relatively stable and predictable.[43]

Second, MICs could only be measured with Etest for a small number of the isolated bacteria. Investigating AUC/MIC ≥125 based on measured MIC values rather than on clinical breakpoint MICs or ECOFF values, would generate a better prediction of target attainment for the local setting, but may on the other hand not be representative for settings with other susceptibility patterns. Additionally, measuring MICs in the same way as the original PD studies, where the efficacy target of AUC/MIC ≥125 was established using broth microdilution and macrodilution, would be more accurate.[5,6] However, other studies have shown that Etest results are as reliable as the results obtained by the standard antimicrobial susceptibility testing methods such as broth microdilution.[44]

Third, the efficacy target of $AUC_{0–24}$/MIC ≥125 is based on small studies performed in patients with moderate-to-severe infections, mainly lower respiratory tract or bloodstream infections.[5,6] This patient population may not be completely generalisable to our patient population consisting of patients on general wards with mostly urinary tract infections. Although attainment of lower PK/PD targets than AUC/MIC ≥125 may not necessarily translate into clinical failure in patients with less severe infections, we believe that one should not be aiming for less than optimal PK/PD targets. The targets we are aiming for were derived from seriously ill patients with more severe infections,

however they identify the optimal killing activity for infections caused by bacteria similar as in our patient population. Additionally, pursuing this PK/PD target is in line with another study investigating PK/PD target attainment of ciprofloxacin in patients on general wards.[10]

Fourth, different dosing regimens of ciprofloxacin were used for different kinds of infection. Although this leads to substantial heterogeneity of our patient population, it is representative of real-life clinical practice and promotes external validation of our study results. Moreover, when patients who received a higher dose of ciprofloxacin (1500 mg/day p.o. or 1200 mg/day i.v.) were excluded, the median $AUC_{0–24}$ remained statistically significantly lower for patients with impaired renal function receiving a reduced dose.

Fifth, ideally an association between PK/PD target attainment and clinical outcome would be investigated because the latter remains the most relevant outcome. However, this study was not powered to link PK/PD target attainment to clinical outcome and therefore we explored clinical outcome only in a descriptive way (Table 3).

Further research should focus on prospective validation of new dosing recommendations of ciprofloxacin for patients with impaired renal function to achieve drug exposure equivalent to patients with adequate renal function. Additionally, since target attainment of AUC/MIC ≥125 is associated with clinical and microbiological cure of Gram-negative infections, attainment of this target should be prospectively explored with the new recommended dosing regimen.[5,6]

To conclude, the PK/PD target of ciprofloxacin is not attained in the first 24 h of treatment in the majority of adult patients on general wards for clinically relevant bacteria with MICs at or just below the clinical breakpoint. The risk of not attaining the target appears to be the highest in patients with impaired renal function receiving a guideline-recommended reduced dose as drug exposure is significantly lower in this subgroup of patients compared with patients with adequate renal function receiving a regular dose. A dose reduction of 25% for patients with impaired renal function seems adequate to obtain a ciprofloxacin exposure equivalent to patients with adequate renal function. We are planning to conduct a study to prospectively validate a dose reduction of 25% for patients with impaired renal function.

Acknowledgments

The authors thank the patients who were willing to take part in this study, Marcel Pistorius and his colleagues from the Laboratory of Clinical Pharmacology for ciprofloxacin concentration measurement, Soemeja Hadid for preserving bacteria, and the staff of the clinical laboratory for identifying waste material of previously collected blood samples.

Funding

None.

Competing interests

RMvH has received grants from Nordic Pharma outside of the submitted work; RAAM has received grants from Baxter/Baxalta/Shire, Bayer Schering Pharma, CSL Behring, Merck Sharp & Dohme and Zeria outside of the submitted work; SEG has received grants from Nordic Pharma and Vifor Pharma outside of the submitted work. All other authors declare no competing interests.

Ethical approval

The research protocol was approved by the certified Medical Ethics Committee of the Academic Medical Centre (AMC) [METC 2017_242] and was registered at the Dutch Trial Register [NTR 6887].

References

1. MacArthur RD, Miller M, Albertson T, Panacek E, Johnson D, Teoh L, et al. Adequacy of early empiric antibiotic treatment and survival in severe sepsis: experience from the MONARCS trial. Clin Infect Dis 2004;38:284–8.
2. Pea F, review Viale PBench-to-bedside. appropriate antibiotic therapy in severe sepsis and septic shock—does the dose matter? Crit Care 2009;13:214.
3. Waller DG, Renwick AG, Hillier K. Medical pharmacology and therapeutics. Elsevier Limited; 2010. p. 595.
4. Mouton JW, Muller AE, Canton R, Giske CG, Kahlmeter G, Turnidge J. MIC-based dose adjustment: facts and fables. J Antimicrob Chemother 2018;73:564–8.
5. Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 1993;37:1073–81.
6. Zelenitsky SA, Harding GK, Sun S, Ubhi K, Ariano RE. Treatment and outcome of Pseudomonas aeruginosa bacteraemia: an antibiotic pharmacodynamics analysis. J Antimicrob Chemother 2003;52:668–74.
7. Khachman D, Conil J, Georges B, et al. Optimizing ciprofloxacin dosing in intensive care unit patients through the use of population pharmacokinetic–pharmacodynamic analysis and Monte Carlo simulations. J Antimicrob Chemother 2011;66:1789–809.
8. van Zanten AR, Polderman KH, van Geijlswijk IM, van der Meer GY, Schouten MA, Girbes AR. Ciprofloxacin pharmacokinetics in critically ill patients: a prospective cohort study. J Crit Care 2008;23:422–30.
9. Kontou P, Chatzika K, Pitsiou G, Stanopoulos I, Argyropoulou-Pataka P, Kioumis I. Pharmacokinetics of ciprofloxacin and its penetration into bronchial secretions of mechanically ventilated patients with chronic obstructive pulmonary disease. Antimicrob Agents Chemother 2011;55:4149–53.
10. Haeseker M, Stolk L, Nieman F, et al. The ciprofloxacin target AUC:MIC ratio is not reached in hospitalized patients with the recommended dosing regimens. Br J Clin Pharmacol 2013;75:180–5.
11. Ciprofloxacin Bayer – Article 30 referral – Annex I, II, III. https://www.ema.europa.eu/documents/referral/ciprofloxacin-bayer-article-30-referral-annex-iii- iii_en.pdf [accessed 31 December 2018].
12. Ashley C, Dunleavy A. The renal drug handbook. Radcliffe Publishing; 2014. p. 199.
13. CIPRO (ciprofloxacin hydrochloride) – FDA. https://www.accessdata.fda.gov/drugsatfda_docs/Label/2016/019537s086lbl.pdf [accessed 1 January 2019].
14. Ciprofloxacine I Farmacotherapeutisch Kompas. https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/c/ciprofloxacine [accessed 1 January 2019].
15. Ciprofloxacine I Stichting Werkgroep Antibiotica Beleid – SWAB (Nationaal). https://swabid.nl/node/1240 [accessed 1 January 2019].
16. KNMP Kennisbank – Antibacteriele middelen – Ciprofloxacine. https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/S2078.html [accessed 1 January 2019].
17. Gasser TC, Ebert SC, Graversen PH, Madsen PO. Ciprofloxacin pharmacokinetics in patients with normal and impaired renal function. Antimicrob Agents Chemother 1987;31:709–12.
18. Drusano GL, Weir M, Forrest A, Plaisance K, Emm T, Standiford HC. Pharmacokinetics of intravenously administered ciprofloxacin in patients with various degrees of renal function. Antimicrob Agents Chemother 1987;31:860–4.
19. Forrest A, Weir M, Plaisance KI, Drusano GL, Leslie J, Standiford HC. Relationships between renal function and disposition of oral ciprofloxacin. Antimicrob Agents Chemother 1988;32:1537–40.
20. Kowalsky SF, Echols M, Schwartz MT, Bailie GR, McCormick E. Pharmacokinetics of ciprofloxacin in subjects with varying degrees of renal function and undergoing hemodialysis or CAPD. Clin Nephrol 1993;39:53–8.

21. Singlas E, Taburet AM, Landru I, Albin H, Ryckelinck JP. Pharmacokinetics of ciprofloxacin tablets in renal failure; influence of haemodialysis. Eur J Clin Pharmacol 1987;31:589–93.
22. Rohwedder R, Bergan T, Thorsteinsson SB, Scholl H. Transintestinal elimination of ciprofloxacin. Chemotherapy 1990;36:77–84.
23. Dirksen MS, Vree TB. Pharmacokinetics of intravenously administered ciprofloxacin in intensive care patients with acute renal failure. Pharm Weekbl Sci 1986;8:35–9.
24. Boelaert J, Valcke Y, Schurgers M, et al. The pharmacokinetics of ciprofloxacin in patients with impaired renal function. J Antimicrob Chemother 1985;16:87–93.
25. Pea F, Viale P, Pavan F, Furlanut M. Pharmacokinetic considerations for antimicrobial therapy in patients receiving renal replacement therapy. Clin Pharmacokinet 2007;46:997–1038.
26. Blanchet B, Jullien V, Vinsonneau C, Tod M. Influence of burns on pharmacokinetics and pharmacodynamics of drugs used in the care of burn patients. Clin Pharmacokinet, 2008; 47(10): 635-654.
27. Dusano GL, Standiford HC, Plaisance K, Forrest A, Leslie J, Caldwell J. Absolute oral bioavailability of ciprofloxacin. Antimicrob Agents Chemother 1986;30:444–6.
28. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
29. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. Am J Kidney Dis 2010;55:622–7.
30. International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use. Good Clinical Practice. Current Step 4 version dated 9 November 2016. https://www.ich.org/fileadmin/Public_Web_Site/ ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf [accessed 16 July 2019].
31. WMA Declaration of Helsinki–Ethical Principles for Medical Research Involving Human Subjects October 2013, 30 July 2017. https:// www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principlesfor-medical-research-involving-human-subjects/ [accessed 16 July 2019].
32. European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters. Version 9.0, 2019. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/ Breakpoint_tables/v_9.0_Breakpoint_Tables.pdf [accessed 18 January 2019].
33. European Committee on Antimicrobial Susceptibility Testing (EUCAST). MIC and zone diameter distributions and ECOFFs, version 5.26. EUCAST; January 2019. http://www.eucast.org/mic_distributions_and_ecoffs/ [accessed 18 January 2019].
34. Cios A, Wyska E, Szymura-Oleksiak J, Grodzicki T. Population pharmacokinetic analysis of ciprofloxacin in the elderly patients with lower respiratory tract infections. Exp Gerontol 2014;57:107–13.
35. Zhao W, Elie V, Baudoin V, et al. Population pharmacokinetics and Bayesian estimator of mycophenolic acid in children with idiopathic nephrotic syndrome. Br J Clin Pharmacol 2010;69:358–66.
36. Yu ZC, Zhou PJ, Wang XH, et al. Population pharmacokinetics and Bayesian estimation of mycophenolic acid concentrations in Chinese adult renal transplant recipients. Acta Pharmacol Sin 2017;38:1566–79.
37. Eljebari H, Gaies E, Fradj NB, et al. Population pharmacokinetics and Bayesian estimation of cyclosporine in a Tunisian population of hematopoietic stem cell transplant recipient. Eur J Clin Pharmacol 2012;68:1517–24.
38. Crass RL, Rodvold KA, Mueller BA, Pai MP, Crass RL. Renal dosing of antibiotics: are we jumping the gun? Clin Infect Dis 2019;68:1596–602.
39. European Medicines Agency (EMA)Quinolone- and fluoroquinolone-containing medicinal products. EMA; 2019. https://www.ema.europa.eu/en/medicines/ human/referrals/quinolone-fluoroquinolone-containing-medicinal-products [accessed 11 July 2019].

40. Baudry-Simner PJ, Singh A, Karlowsky JA, Hoban DJ, Zhanel GG. Mechanisms of reduced susceptibility to ciprofloxacin in Escherichia coli isolates from Canadian hospitals. J Infect Dis Med Microbiol 2012;23 e60–4.
41. Rajagopalan P, Gastonguay MR. Population pharmacokinetics of ciprofloxacin in pediatric patients. J Clin Pharmacol 2003;43:698–710.
42. Thuo N, Ungphakorn W, Karisa J, et al. Dosing regimens of oral ciprofloxacin for children with severe malnutrition: a population pharmacokinetic study with Monte Carlo simulation. J Antimicrob Chemother 2011;66:2336–45.
43. Blotad SI, Peabc F, Lipmande J. The effect of pathophysiology on pharmacokinetics in the critically ill patient—concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev 2014;77:3–11.
44. Baker CN, Stocker SA, Culver DA, Thornsberry C. Comparison of the E test to agar dilution, broth microdilution, and agar diffusion susceptibility testing techniques by using a special challenge set of bacteria. J Clin Microbiol 1991;29:533–8.

Appendix

Methods

Ciprofloxacin concentration measurement

Total and unbound ciprofloxacin plasma concentrations were analyzed using liquid chromatography–mass spectrometry (LC-MS/MS), in the positive ionization mode, using a Shimadzu LC-30 Nexera (Nishinokyo-Kuwabaracho, Japan) coupled to a 5500 QTrap mass spectrometer (ABSciex, Framingham, Massachusetts, United States of America) within 3 months after sample collection. This method was fully validated according to the *Guidance for Industry, Bioanalytical Method Validation* of the Food and Drug Administration.[1]

To 10 µl of plasma, 750 µl of a mixture of acetonitrile / methanol / formic acid (419:79:2 v/v/v) containing the internal standard ciprofloxacin-*d8* was added. Subsequently, the samples were vortexed, centrifuged (2750 *g* for 5 minutes) and 0.5 µl of the supernatant was injected onto a Thermo Scientific Hypersil Gold (50 x 2.1 mm, 1.9 µm) chromatographic column.

Acetonitrile containing 5% buffer (1% ammonium formate / 2% formic acid) and ultra-pure water containing 5% buffer (1% ammonium formate / 2% formic acid), were used as mobile phases. The flow was 800 µl/min and the column-oven temperature was 40°C. Ciprofloxacin and ciprofloxacin-*d8* were analyzed as $[M+H]^+$, using the respective mass transitions of 332.1/231.1 and 340.1/235.1. This method was validated over a concentration range of 0.02 – 5.00 mg/L.

Additionally, for the measurement of the unbound ciprofloxacin plasma concentration, the samples were thawed, putted into a water bath of 37°C for 30 minutes and mixed after 15 minutes. At least 100 µl of the sample was pipetted into a Nanosep 30K centrifuge cup (PALL corporation, Washington, United States of America). The ultrafiltration method consisted of centrifuging these cups at 37°C for 20 minutes. The clean-up procedure was identical to the procedure used for the plasma samples (see above).

For the total ciprofloxacin plasma concentration, the accuracy ranged from 94.5% to 105.0% across the validated range, the intra-day precision was below 7.6% and the inter-day precision was below 9.8%. For the unbound ciprofloxacin plasma concentration, the accuracy ranged from 92.8% to 102% across the validated range, the intra-day precision was below 7.0% and the inter-day precisions was below 9.6%.

MIC determination

MIC measurement using E-test was fully validated according to The European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines.

Inocula were prepared in Phosphate-Buffered Saline from 24-hour growth on aerobic blood agar. Turbidity was adjusted to 0.5 MacFarland standard (Densichek, bioMérieux, Marcy-l'Étoile, France). Mueller-Hinton agar (bioMérieux, Marcy-l'Étoile, France) was used and results were interpreted after 18 hours aerobic incubation according to EUCAST guidelines.

Population Pharmacokinetic Analysis

We analyzed concentration-time data of total ciprofloxacin by means of the software package non-linear mixed effects modelling (NONMEM) (version 7.3; Icon Development Solutions, Ellicott City, Maryland). Pirana 2.9.4 was used as an interface for NONMEM, Xpose and R. The first order conditional estimation (FOCE) method with interaction was used throughout the data analysis. We developed an integrated model for orally and intravenously administered ciprofloxacin using the ADVAN6 subroutine in NONMEM. A stepwise approach was used for model building.

Structural Model

One- and two-compartment models were tested for both untransformed and logarithmically transformed data. PK parameters consisted of bioavailability (F), first order absorption rate constant (K_a), absorption lag time (T_{lag}), clearance (CL), central volume of distribution (V_1) and, in case of a two-compartment model, peripheral volume of distribution (V_2) and intercompartmental clearance (Q). BPV of V_1 and CL were modelled on an exponential scale.[2] The residual variability (i.e. the difference between analyzed ciprofloxacin concentrations and the corresponding ciprofloxacin concentrations predicted by the model) was modelled with additive or proportional models or a combination of both. Whether addition of a parameter to the model provided a better fit over the reduced model was evaluated by (1) the objective function value (OFV), obtained with the likelihood ratio test, where a drop of >3.84 units corresponds to a significance level of a p-value <0.05 in a Chi-squared distribution (with 1 degree of freedom), (2) the precision (relative standard error) of the estimated parameters (3) the magnitude of residual variability; (4) shrinkage of random parameters and (5) goodness of fit plots. Only 2 out of 186 analyzed concentrations were below the lower limit of quantification (LLOQ), therefore the concentrations <LLOQ were handled by imputing a value of 0.5*LLOQ.

Covariate model

Tested continuous covariate data were age, weight, creatinine, eGFR (calculated by CKD-EPI) and categorical covariate data were sex and the use of comedication influencing absorption of ciprofloxacin: aluminum and magnesium antacids, sucralfate, calcium-, bismuth-, zinc- and iron salts and polymeric phosphate binders. All covariates were screened for the significance of the association between the covariate and the PK parameter by univariate analysis, where continuous variables were modeled using a power function and the effect of a categorical variable was estimated by quantification of the fractional difference, relative to the reference category. A p-value of 0.05 obtained from the likelihood test, i.e. a decrease in OFV of >3.84 points, was used as a cut-off value for statistical significance. Furthermore, a reduction in BPV and residual variability, improvement of the goodness of fit plots, as well as biological plausibility of a covariate–PK parameter association was used as a criterion for covariate selection. All covariates selected during the univariate analysis subsequently entered an intermediate model for a backward elimination procedure (multivariate analysis). When exclusion of a covariate-PK parameter association resulted in an increase of the OFV of >6.63, ($p<0.01$, one degree of freedom) the association remained in the model. The resulting model was regarded as the final model.

Model Robustness and Predictive Performance

The robustness of the final popPK model was tested using a bootstrap analysis, in which the dataset was resampled and fitted to the model 1000 times. In addition, the model's capacity to predict the range of observed ciprofloxacin concentrations was tested by means of a visual predictive check (VPC). The bootstrap as well as the VPC analyses were performed using Perl-speaks-NONMEM version 3.5.3 software (PsN, Uppsala, Sweden).

Results

Population Pharmacokinetic Analysis

Structural Model

186 samples were obtained and included in the population pharmacokinetic analysis, of which 169 samples were obtained after oral administration and 17 samples after intravenous administration.

A one-compartmental model with first order elimination and first order absorption (in case of data from oral ciprofloxacin administration) and an absorption lag time, without logarithmic transformation of the data provided the best fit. F was fixed to 0.75, based on bioavailability data from Sweetman, as estimation of this parameter yielded highly unlikely values ($F<0.5$).[3] Since the vast majority of samples were collected more than 30 minutes after oral ciprofloxacin administration, T_{lag} could not be estimated precisely. Therefore, T_{lag} was fixed to a value 0.35 hour, based on data from Rajagopalan *et al*.[4] BPV could be estimated for V and CL. Residual variability was modeled with a proportional error model and was estimated to be 40%.

Covariate model

Hundred percent of covariate data was available. The univariate analysis revealed that there was a statistically significant association between eGFR and clearance (equation 1), with a decrease in OFV of 8.8 points.

$$CL\ (L/h) = 21.1 * (eGFR/70)^{0.277}$$ Equation 1 (Figure A.1)

With this association in the model, the BPV of CL decreased from 37.6% to 35.1% and the residual error decreased from 39.7% to 39.2%

Model robustness and predictive performance

As observed in the goodness of fit plots and VPC (Figure A.2.-A.6.) the final model was capable of predicting the observed concentration-time data without bias as the simulated data correspond well with the measured concentrations, as such showing the internal validity of the model. Also, the bootstrap estimations were similar (within ±15%) to the estimates from the final model (Table A.1).

Table A.1. Parameter Estimates of the Different Model Building Steps

Parameter	Structural model		Final model		Bootstrap (n=1000) of model with covariates	
	Estimate	RSE (%)	Estimate	RSE (%)	Estimate	95% CI
F (%)	Fixed 0.75		Fixed 0.75		Fixed 0.75	
K_a ($hour^{-1}$)	1.01	55.8	1.00	49.9	0.974	0.163-2.30
T_{lag} ($hour^{-1}$)	Fixed 0.35		Fixed 0.35		Fixed 0.35	
Cl (L/h)	20.3	9.0	21.1	8.5	20.8	17.4-24.8
V (L)	251	25.8	255	25.1	243	77.9-392
Between patient variability						
Cl (%CV)	37.6	18.1	35.1	17.3	33.5	16.6-47.1
V (%CV)	104.1	18.5	101.5	17.9	95.8	26.8-160.9
Residual variability						
Proportional error	0.397	9.0	0.392	9.2	0.392	0.318-0.467
Covariates						
eGFR (CKD-EPI) ($ml/min/1.73m^2$)	-	-	0.277	27.3	0.275	0.104 –0.464

Estimates are expressed as median, with relative standard error (RSE) or 95% confidence interval (95% CI).
Abbreviations: F, bioavailability; K_a, absorption rate constant; T_{lag} lag time; CL, clearance; V, volume of distribution; CV, coefficient of variation; eGFR (CKD-EPI), glomerular filtration rate estimated using the CKD-EPI formula.
Shrinkage for between patient variability in V and CL was 19.3% and 14.6% for the final model, respectively. Shrinkage in residual variability was 11.5%.

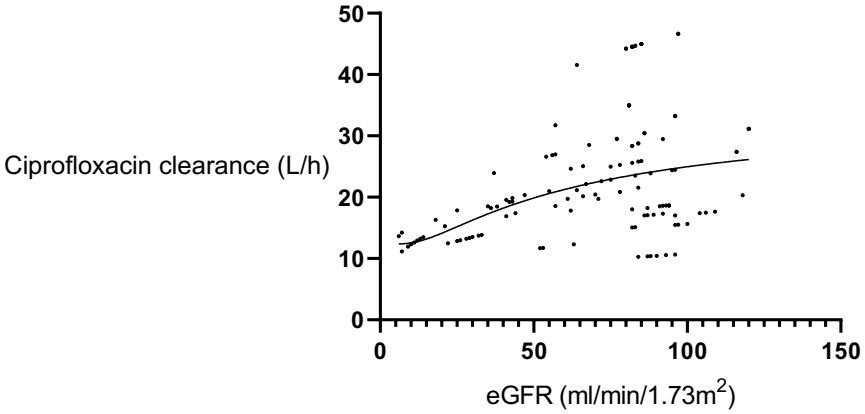


Fig. A.1. Ciprofloxacin clearance (CL) (L/h) plotted against eGFR (ml/min/1.73/m^2), using CL=21.1*(eGFR/70)$^{0.277}$

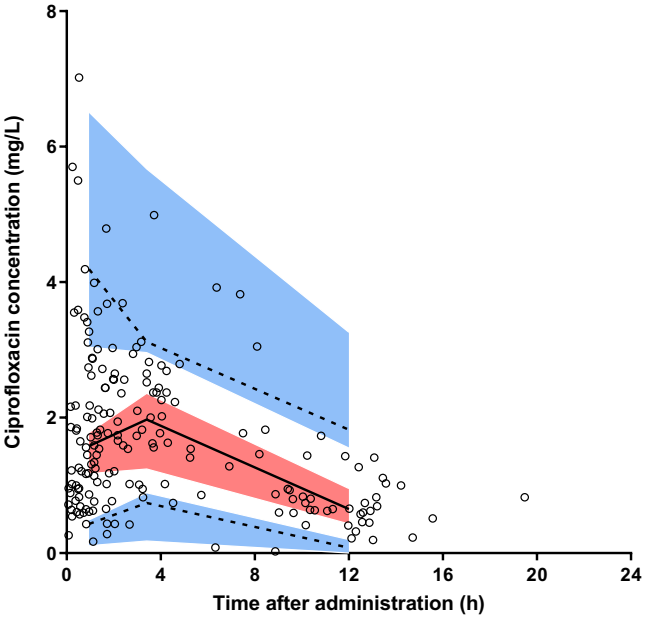


Fig. A.2. Observed ciprofloxacin concentration time-data and VPC of the final model. The dots are the observed concentrations. The solid line is the observed median concentration and the dashed lines are the 5th and 95th percentiles of the observed data. The red shaded area is the 95% confidence interval of the model-predicted median and the blue shaded areas are the 95% confidence intervals of the model-predicted 5th and 95th percentiles. The solid and dashed lines run within their respective shaded areas, thereby demonstrating adequate fit of the model.

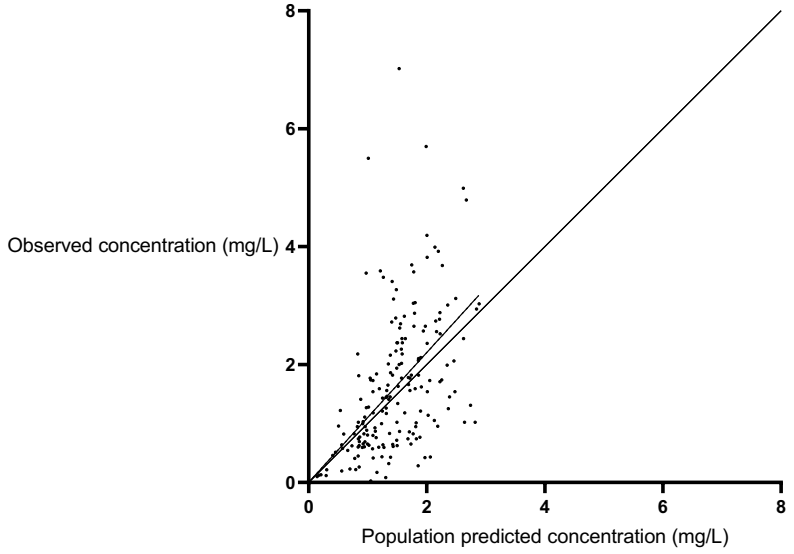


Fig. A.3. Observed concentrations versus population predicted concentrations. Each dot is a data point and the solid black line is the line of true identity.

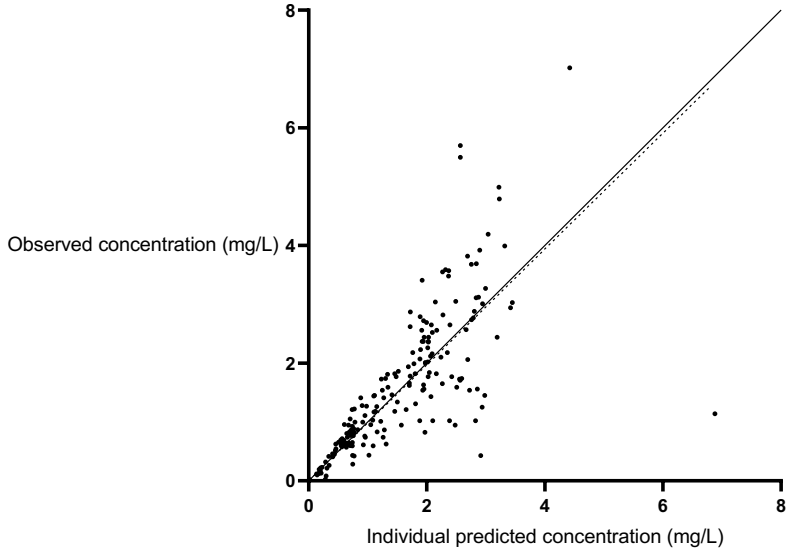


Fig. A.4. Observed concentrations versus individual predicted concentrations. Each dot is a data point and the solid black line is the line of true identity.

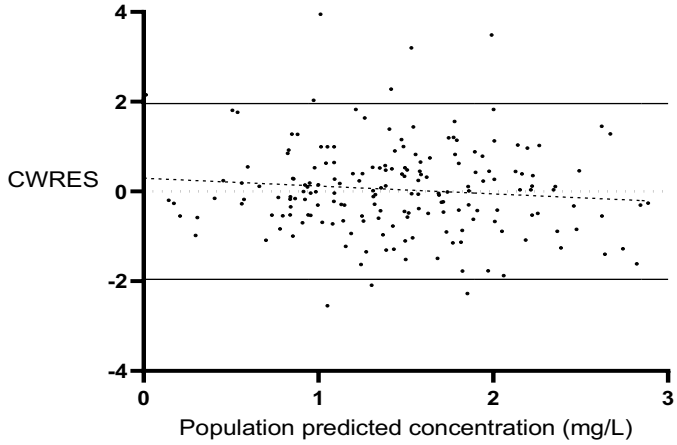


Fig. A.5. Conditional weighted residuals (CWRES) versus population predicted concentrations. Data are evenly distributed about zero, indicating no major bias in the residual error model.

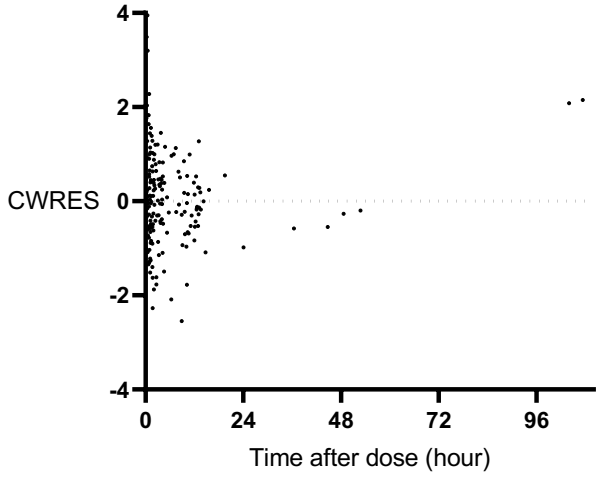


Fig. A.6. Conditional weighted residuals (CWRES) vs. time after dose. Data are evenly distributed about zero, indicating no major bias in the model.

References

1. FDA Guidance for Industry, Bioanalytical Method Validation 2011. Available at https://www.fda.gov/media/70858/download. Accessed 16 July 2019.
2. Bonate PL. Pharmacokinetic-Pharmacodynamic Modelling and Simulation (second edition). New York, USA: Springer, 2011.
3. Sweetman SC. Martindale: the complete drug reference (36th edition). London, Chicago: Pharmaceutical Press, 2009.
4. P Rajagopalan, M R. Gastonguay Population pharmacokinetics of ciprofloxacin in pediatric patients. J Clin Pharmacol 2003;43:698–710.

Chapter 5

Pharmacokinetic/pharmacodynamic target attainment of ceftazidime in adult patients on general wards with different degrees of renal function: a prospective observational bicenter cohort study

Suzanne L. de Vroom* and Saskia E. Zieck*, Frouke Ph. Mulder, Gitte van Twillert, Ron A.A. Mathôt, Suzanne E. Geerlings and Reinier M. van Hest

**These authors contributed equally to this work*

Antibiotics. 2023; 12(3):469

Abstract

No prospective evidence exists on the pharmacokinetic/pharmacodynamic (PK/PD) target attainment of ceftazidime in adult patients on general wards. We aimed to investigate whether the PK/PD target of ceftazidime (50% T > MIC) is attained in adult patients on general wards with adequate and impaired renal function receiving regular and guideline-recommended reduced doses of ceftazidime.

In this observational, prospective, bicenter cohort study, adult patients admitted to a general ward receiving ceftazidime as part of standard care were included. Three blood samples per patient within 72 h after start of treatment were collected. Data were analyzed with nonlinear mixed effects modeling. The primary endpoint was target attainment of 50% T > MIC during the first 24 h of treatment (50% $T_{0\text{-}24}$ > MIC).

Forty patients were included from whom 121 blood samples were obtained. All 25/25 patients with adequate renal function, 9/10 patients with moderately impaired renal function (eGFR 30–50 ml/min/1.73m^2) and 5/5 patients with severe impaired renal function (eGFR < 30 ml/min/1.73m^2) attained 50% $T_{0\text{-}24}$ > MIC when applying the clinical breakpoint MIC for *Pseudomonas Aeruginosa* of 8 mg/L.

Our results suggest ≥90% probability of the PK/PD target attainment of ceftazidime in patients on general wards with adequate and impaired renal function receiving regular and guideline-recommended reduced doses of ceftazidime for treatment of infections with *Pseudomonas aeruginosa* and all bacteria with lower MIC-values.

Introduction

Appropriate and early antibiotic treatment are primary determinants of mortality in patients with bacterial infections.[1-3] Antibiotic treatment is considered to be appropriate when the relevant pharmacokinetic/pharmacodynamic (PK/PD) target is attained. Optimal antibiotic dosing regimens aiming to attain those PK/PD targets are, therefore, of high importance to prevent treatment failure.[4,5]

The third-generation cephalosporin antibiotic ceftazidime is frequently administered to hospitalized patients with various infections caused by Gram-negative bacteria, particularly *Pseudomonas aeruginosa* (*P. aeruginosa*).[6] Ceftazidime exhibits, like other beta-lactams, time-dependent killing.[7-10] Therefore, successful treatment outcomes in terms of bacterial eradication and clinical cure is associated with the percentage of time of the dosing interval that the serum concentration remains above the minimum inhibitory concentration (T > MIC).[7-10] The MIC is defined as the lowest concentration of an antibiotic that prevents visible growth of bacteria in vitro.[11] For ceftazidime, the T > MIC value needed for bactericidal activity is reported to be between 30% and 100%. A target of 50% T > MIC is the most commonly used target and best associated with clinical efficacy in patients admitted to general wards.[7-10]

Ceftazidime shows low protein binding of 10% and is almost exclusively eliminated through the kidneys.[12,13] Consequently, a dose reduction is recommended for patients with impaired renal function.[12-14] However, physicians do not apply this dose reduction in half of all patients with impaired renal function, although a dose reduction is recommended by the applicable guideline.[15] A cause of this might be that currently advised dose reductions are merely based on extrapolations of small studies investigating a full, unadjusted, dose of ceftazidime.[16-20] Only one study investigated steady-state pharmacokinetics in patients with renal impairment receiving a reduced dose; however, only critically ill patients were included with concomitant use of furosemide.[20]

Although a variety of studies have been conducted to assess the PK/PD target attainment of ceftazidime in critically ill patients, we have not identified such studies in adult patients on general wards as these patients are likely to exhibit other pharmacokinetics compared to critically ill patients.[16-21] As such, no prospective evidence exists that currently guideline-recommended ceftazidime dosing regimens result in at least 50% T >MIC in adult patients on general wards, especially not in patients with renal impairment receiving a reduced dose of ceftazidime. Therefore, the aim of this study is to determine the probability of attaining the PK/PD target (PTA) of ceftazidime (50% T >MIC) in the first 24 h of treatment in adult patients on general wards with adequate and impaired renal function receiving regular and guideline-recommended reduced doses of ceftazidime.

Materials and Methods

Study design

This prospective, bicentre, observational cohort study was conducted between October 2019 and December 2021 on general wards at the Amsterdam UMC – location AMC (AMC); or Noordwest Ziekenhuisgroep – location Alkmaar (NWZ).

This study was performed according to the principles of the Declaration of Helsinki (October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).[29,30] The study was approved by the ethics committee of Amsterdam UMC – location AMC. Patients participating in this study all signed written informed consent before inclusion.

In- and exclusion criteria

Patients were eligible when meeting the following inclusion criteria: (1) adult patients (age ≥ 18 years); (2) admitted to a general ward of AMC or NWZ; and (3) receiving therapeutic dosages of ceftazidime as part of standard care prescribed by their attending physician and according to the current local guideline, which is adapted from the national antimicrobial guideline.[12-14] Patients were excluded if: (1) written informed consent was not obtained; (2) a patient was mentally incapacitated; or (3) patients with known altered pharmacokinetics compared to patients on general wards, i.e., patients in the ICU, patients undergoing renal replacement therapy, patients with cystic fibrosis and patients with severe burns.[31-33]

Sample size calculation

Since no data were available in the literature on the percentage of patients with impaired renal function attaining 50% $T_{0\text{-}24}$ > MIC to base the sample size calculation on, we based our sample size calculation on the second-best available data, namely detecting an association between renal function and clearance of ceftazidime. Detection of such an association is a prerequisite for analysing differences in target attainment of ceftazidime between populations with adequate and impaired renal function. A Stochastic Simulation and Estimation (SSE) procedure as implemented in the Pearl Speaks NONMEM software (version 3.5.3, Uppsala, Sweden) was applied for this purpose. In this Monte Carlo simulation procedure, the two-compartment population pharmacokinetic model as described by Delattre et al. was used.[34] A blood sample collection scheme of 3 samples per patient (1 trough and 2 random samples) within a total sample size of 40 patients was shown to have a power of ≥95% with an alpha level of 0.05 to detect an association between renal function and ceftazidime clearance. A total of 15 of the 40 patients needed to be included with an estimated glomerular filtration rate (eGFR) ≤ 50 ml/min/1.73m^2, of whom at least 5 had an eGFR < 30 ml/min/1.73m^2.

Study procedure

Dose and duration of ceftazidime treatment were determined by the discretion of the attending physician. The recommended dosing regimen for patients with adequate renal function varies between guidelines, but in general the dose is 500 mg every 12 h (q12h) to 2000 mg every 8 h (q8h) is recommended. In this study a dosing regimen of 2000 mg q8h was investigated in accordance with the local antimicrobial guidelines of the participating hospitals.[12-14] Based on (inter)national and local

guidelines, the dose of ceftazidime is adjusted when eGFR is 30–50 ml/min/1.73m^2 to 1000 mg q12h and when eGFR is below 30 ml/min/1.73m^2 to 1000 mg every 24 h (q24h).[12-14]

Demographic data, clinical data, laboratory data (e.g., serum creatinine and renal function expressed as eGFR (CKD-EPI)) of included patients, as well as the administration data of ceftazidime were derived from the electronic patient record and were stored anonymized in an online database subsumed into Castor EDC.

Preferably within 24 h but at least within 72 h after the start of ceftazidime treatment, three blood samples, one trough level and two random samples were prospectively collected in a vacutainer tube without anticoagulant for ceftazidime concentration measurement. Blood samples were immediately centrifuged at 3000x *g* after sample collection and the plasma was stored frozen at −80 °C until analysis. As part of the study protocol, waste material of samples obtained for standard care during ceftazidime treatment were, if available, collected from the Laboratory of Clinical Chemistry of the AMC and NWZ. Determination of total ceftazidime plasma concentration in the obtained blood samples was performed at the laboratory of the Department of Hospital Pharmacy & Clinical Pharmacology of the AMC, using a validated high-performance liquid chromatography tandem mass spectrometry (LC-MS/MS) method (LC30 Shimadzu, Kyoto, Japan; MS QTRAP 5500 system, SCIEX, Framington, Massachusets, United States of America). The method had a lower limit of quantification (LLOQ) of 0.1 mg/L and an upper limit of quantification (ULOQ) of 40 mg/L. In case concentrations above the ULOQ were measured, the sample was diluted and reanalyzed. In case concentrations below the LLOQ were measured, the ceftazidime concentration in the sample was set to a 0.5-fold lower concentration than the LLOQ for data analysis. The accuracy of the method at the LLOQ (0.1 mg/L) and ULOQ (40 mg/L) was 117% and 106%, respectively. The precision of the method at the LLOQ (0.1 mg/L) and ULOQ (40mg/L) were below 3.86% and 1.62%, respectively.

Study outcomes

The primary outcome of this study was target attainment defined as a ceftazidime concentration that exceeded the MIC during more than 50% (i.e., >12 h) of the first 24 h of IV treatment (50% $T_{0\text{-}24}$ > MIC). This parameter was subsequently used to calculate the probability of target attainment during the first 24 h of treatment, which was defined as the percentage of patients that attained 50% $T_{0\text{-}24}$ > MIC. The PTA was calculated for patients with adequate, moderately impaired and severely impaired renal function receiving regular and guideline-recommended reduced doses of ceftazidime. An MIC of 8 mg/L was considered most important, being the clinical breakpoint MIC of *P. aeruginosa* for ceftazidime and, therefore, the highest breakpoint of all ceftazidime-susceptible microorganisms and the microorganism that usually needs to be covered when treating with ceftazidime.[6] A PTA of ≥90% was considered adequate.

Secondary outcomes were target attainment of 50% T > MIC between 24 and 48 h of treatment (50% $T_{24\text{-}48}$ > MIC) and target attainment of 100% T > MIC during the first 24 h of treatment (100% $T_{0\text{-}24}$ > MIC), both for calculation of PTA for these targets. In this case, 100% $T_{0\text{-}24}$ > MIC was defined as 23.5 h of the first 24 h above the MIC given the infusion time of the first dose was 0.5 h; therefore, the ceftazidime concentration will be below the MIC for at least a part of this infusion time. A further secondary outcome was area under the concentration-time curve (AUC) at 24 h and 24–48 h after start of treatment ($AUC_{0\text{-}24}$ and $AUC_{24\text{-}48}$) to compare ceftazidime exposure. All primary and secondary outcomes were calculated for the three different renal function groups:

- Group I: adequate renal function; eGFR ≥ 50ml/min/1.73m^2 treated with regular doses of ceftazidime (2000 mg q8h).

- Group II: moderately impaired renal function: eGFR 30–49 ml/min/1.73m^2 treated with reduced doses of ceftazidime (1000 mg q12h).

- Group III: severely impaired renal function: eGFR 10–29 ml/min/1.73m^2 treated with reduced doses of ceftazidime (1000 mg q24h).

If a large proportion, defined as a percentage of 25% or a minimum of 10 patients, does not attain the primary outcome of 50% $T_{0\text{-}24}$ > MIC), we will explore whether or not attaining this target is associated with patients' clinical outcome.

Statistical Analysis & Pharmacokinetic model

The data in this study are presented as frequencies (categorical data) and median values (continuous data) with the interquartile range (IQR). Differences between groups were calculated for continuous values using the Kruskal–Wallis test and for categorical data using the Pearson Chi–square test with IBM-SPSS v28 (IBM corporation, Armonk, New York, USA). Differences were considered statistically significant at a *p*-value of <0.05.

A compartmental population pharmacokinetic model for ceftazidime was developed using non-linear mixed effects modelling (NONMEM) (v7.5 Icon Development Solutions, Ellicot City, Maryland, USA) to be able to calculate T > MIC and assess target attainment. The model was parameterized using the primary pharmacokinetic parameters volume of distribution (V) and clearance (CL). First a structural model was developed by testing one and two compartmental models as well as interpatient variability (IIV) and interoccasion variability (IOV) in the pharmacokinetic parameters. Afterwards, a covariate analysis was performed in which demographic and pathophysiological data of the included patients were tested for their association with CL and V with first a univariate analysis and subsequently a multivariate analysis with all statistically significantly associated covariates from the univariate analysis. This resulted in the final model. The following covariates were tested: serum creatinine, eGFR calculated with CKD-EPI formula, eGFR calculated with the Modification of Diet in Renal Disease (MDRD) formula, eGFR calculated with the Cockroft and Gault formula, BMI, age, ethnicity, admission to the orthopedic ward, admission to the hematology ward, fever yes/no ('yes' defined as body temperature > 38°C) and concomitant use of other antibiotics. The fit of the model was evaluated using goodness-of-fit plots, the objective function and precision of the parameter estimates. The robustness and internal validity of the model was tested with a bootstrap analysis (n = 1000) and a prediction corrected visual predictive check (VPC). The T > MIC for each individual patient was estimated using the empirical Bayesian estimates of the pharmacokinetic parameters from the final and internally validated model with which subsequently target attainment per patient could be assessed. Also, $AUC_{0\text{-}24}$ and $AUC_{24\text{-}48}$ for each individual patient was estimated using the empirical Bayesian estimates of the pharmacokinetic parameters from the final model.

Results

Patients and ceftazidime concentrations

Forty patients were included of which there were twenty-five patients with adequate renal function (eGFR ≥ 50 ml/min/1.73m^2), ten patients with moderate renal impairment (eGFR 30–49 ml/min/1.73m^2) and five patients with severe renal impairment (eGFR 10–29 ml/min/1.73m^2). All patients were treated with the guideline-recommended dose of ceftazidime based on their renal function (Table 1), except for one patient with severe renal impairment that was treated with 2000 mg q24h instead of the recommended 1000 mg q24h. We decided to keep this patient in the dataset for analysis of the primary outcome as this patients' ceftazidime level at 12 h after start of therapy was well above the worst-case MIC of 8 mg/L (namely 24.3 mg/L), making it highly likely that 50% T > MIC within the first 24 h of treatment would have been attained if 1000 mg would have been administered. Age, serum creatinine, eGFR and the department of admission differed significantly between the three renal function groups (Table 2).

Table 1. Guideline-recommended dose of ceftazidime

Renal function group	Guideline-recommended dose of ceftazidime
Adequate renal function (eGFR ≥ 50ml/min/1.73m^2, (n=25))	2000 mg q8h
Moderate renal impairment (eGFR ≥ 30-50 ml/min/1.73m^2, (n=10))	1000 mg q12h
Severe renal impairment (eGFR < 30 ml/min/1.73m^2, (n=5))	1000 mg q24h

q8h, every 8 h; q12h, every 12 h; q24h, every 24 h

A total of 121 samples were collected of which 52 samples (43%) were obtained within the first 24 h of treatment. Two samples were excluded. The first excluded sample was collected at the same time point in the same patient as another sample and, therefore, did not add additional information for population PK analysis. The second excluded sample was a sample with a ceftazidime concentration < lower limit of quantification (LLOQ) that followed a sample from the same patient that also already was <LLOQ. This left a total of 119 samples, of which 1 was <LLOQ and none > upper limit of quantification (ULOQ) for nonlinear mixed effects modeling (NONMEM). Five of these samples were obtained from waste material. From five patients (12.5%) only two samples per patient could be drawn.

Table 2. Baseline characteristics (n = 40) of the included patient population. Patients were classified according to their renal function expressed as eGFR (CKD-EPI) on the day of inclusion.

Variable*	Overall n = 40	eGFR[a] ≥50 ml/min/1.73m^2 n = 25	eGFR[a] ≥30-50 ml/min/1.73m^2 n = 10	eGFR[a] <30 ml/min/1.73m^2 n = 5
Female, n	17	9	6	2
Age, yrs	62.0 (47.0-72.0)	56.0 (40.5-68.5)	72.0 (69.8-86.0)	64.0 (41.5-73.0)
Weight, kg	79.6 (69.7-92.3)	80.0 (71.8-89.0)	78.5 (67.2-94.3)	71.7 (57.1-140.6)
Height, cm	175.5 (167.0-185.0)	180.0 (168.0-185.0)	171.5 (163.5-184.3)	167.0 (163.0-179.5)
BMI, kg/m^2	25.0 (22.0-29.0)	24.7 (21.3-27.8)	26.2 (23.7-31.4)	23.4 (21.3-46.5)
Ethnicity				
Caucasian	32	22	8	2
African American	4	1	2	1
Asian	3	1	0	2
Hispanic	1	1	0	0
Serum creatinine,	100.0 (67.3-135.3)	72.0 (59.5-92.5)	135 (118-162)	328.0 (217.5-430.0)
eGFR [a], ml/min/1.73m^2	73.5 (34.3-111.4)	102.8 (78.1-124.8)	34.3 (30.9-48.2)	18.6 (10.6-25.9)
Fever at start of treatment, yes	11	7	3	1
Department of admission				
Cardiology	1	1	0	0
Hematology	7	7	0	0
Infectious diseases	4	1	2	1
Internal medicine	5	1	3	1
Nephrology	2	0	0	2
Neurology	1	1	0	0
Oncology	1	1	0	0
Orthopedic	12	10	1	1
Respiratory medicine	4	1	3	0
Surgery	2	1	1	0
Urology	1	1	0	0
Concomitant other antibiotic use	27	19	6	2
Length of hospital stay [b]	10.0 (7-20.3)	11.0 (7.5-28.0)	12.0 (7.0-21.8)	10 (5.5-10.5)

*Variables are listed as median (interquartile range (IQR)). [a]eGFR = estimated glomerular filtration rate calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula. [b]Total length of hospital stay from day of admission to day of discharge.

Population pharmacokinetic analysis

A one-compartment model with first-order elimination best described the pharmacokinetics of ceftazidime (Table 3). The interpatient variability (IIV) of ceftazidime could be estimated for clearance (CL) and volume of distribution (V). During the multivariate analysis, a statistically significant association (p <0.01) was found between eGFR (CKD-EPI) and CL, which explained a large part of the IIV in CL: IIV CL dropped from 78.9% to 37.6% upon inclusion of this association. Furthermore, an association was found between the concomitant use of antibiotics and CL. This association also explained some IIV in CL as IIV CL decreased from 37.6% to 31.3% upon inclusion of this association (Table 3). There was no missing covariate data in the dataset.

The goodness of fit plots (GOF) (Supplementary Material Figure S1) and the prediction corrected visual predictive check (VPC) (Figure 1) show that the final model is able to adequately describe the observed ceftazidime concentrations and was, therefore, valid to be used to calculate individual T > MIC and AUC values. The NONMEM control stream of the final model can be found in Supplementary File S1.

Table 3. Parameter estimates of the structural, final model and bootstrap analysis.

Parameter	Structural model		Final model*		Bootstrap	
	Estimate	RSE (%) [shrinkage (%)]	Estimate	RSE (%) [shrinkage (%)]	Estimate	95% CI
CL (L/h)	4.50	11.7	3.74	9.80	3.74	3.03-4.41
V (L)	22.7	7.20	21.8	7.90	22.1	19.1-25.1
Interindividual variability						
CL (%CV)	78.9	20.3 (1.3)	31.3	29.6 (7)	31.1	22.6 -38.7
V (%CV)	40.5	64.7 (21)	40.2	61.8 (18)	40.9	10.0-59.2
Residual variability						
Proportional error (%)	19.2	15.0	18.6	15.9	18.7	13.9-23.6
Covariates						
eGFR (CKD-EPI) (ml/min/1.73m²) on CL	-	-	0.75	13.9	0.74	0.56-0.93
Concomitant antibiotic use on CL	-	-	1.56	12.4	1.57	1.20-1.94

*The equation of CL in the final model is: CL (L/h) = 3.74 x $(CKDEPI/76.86)^{0.75}$ x $1{,}56^{flag}$; flag = 0 in case of no concomitant antibiotic use and flag = 1 in case of concomitant antibiotic use. Abbreviations: CL = clearance in L/h, V = volume of distribution in L, RSE = relative standard error, 95%CI = 95% confidence interval; eGFR = estimated glomerular filtration rate, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration.

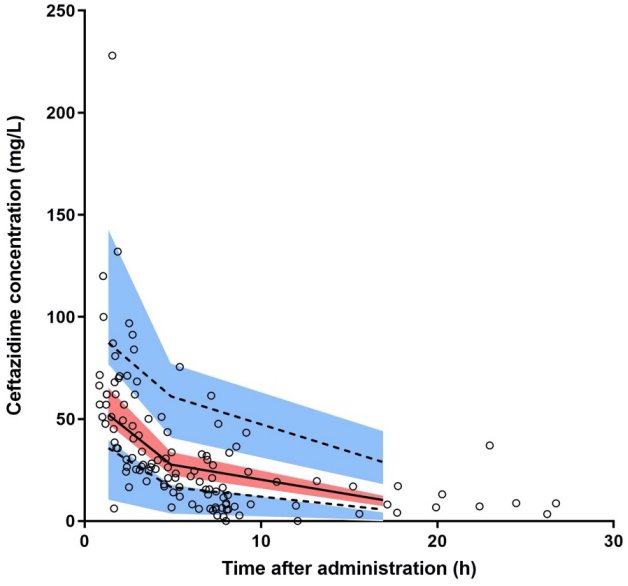


Figure 1. Prediction corrected visual predictive check of the final model. The dots represent the prediction corrected observed ceftazidime concentrations. The solid black line represents the observed median and the dashed black lines represent the 5th and 95th percentiles of the observed prediction-corrected data. The blue areas represent the 95% confidence interval of the model-predicted 5th and 95th percentiles. The red area represents the 95% confidence interval of the model-predicted median. The solid and upper dashed black lines run within their respective shaded areas, thus showing that the model adequately predicts the observed data. The lower dashed black line rises slightly above the blue shaded area at the end of the dosing interval, indicating a slight underestimation of the observed 5th percentile. Overall, this VPC demonstrates a sufficient fit of the final model.

Pharmacokinetic/pharmacodynamic target attainment

For an MIC of 8 mg/L, which is the clinical breakpoint of *P. aeruginosa*, the probability of PK/PD target attainment of 50% T > MIC within the first 24 h of treatment (the primary outcome) was 100% (25/25) in patients with adequate renal function receiving the regular dose, 90% (9/10) in patients with moderate renal impairment receiving a reduced dose and 100% (5/5) in patients with severe renal impairment receiving a reduced dose (Table 4). For the secondary outcomes, the patient with severe renal impairment due to receiving a significantly different dose (2000 mg q24h instead of 1000 mg q24h) was excluded. For an MIC of 8 mg/L PTA of 100% T_{0-24} > MIC was 24% (6/25) in patients with adequate renal function receiving the regular dose, 50% (5/10) in patients with moderate renal impairment receiving a reduced dose and 75% (3/4) in patients with severe renal impairment receiving a reduced dose (Table 5). For the secondary endpoint PTA of 50% T_{24-48} > MIC, a second patient was excluded, namely one patient with adequate renal function who received ceftazidime therapy during only the first 24 h of treatment. PTA of 50% T_{24-48} > MIC for an MIC of 8 mg/L was 100% (24/24) in patients with adequate renal function, 90% (9/10) in patients with moderate renal impairment and 100% (4/4) in patients with severe renal impairment (Table 6).

Table 4. Probability of PK/PD target attainment of 50% T > MIC for the the first 24 h of treatment based on the observed data in the different renal function groups using different MIC values of common Gram-negative bacteria susceptible for ceftazidime as listed in the EUCAST.

	PTA (50% T_{0-24} > MIC)						
MIC (mg/L)	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**
Renal function group							
Adequate renal function (eGFR ≥50ml/min/1.73m², (n=25))	100%	100%	100%	100%	100%	100%	100%
Moderate renal impairment (eGFR≥30-50 ml/min/1.73m², (n=10))	100%	100%	90%	90%	90%	90%	90%
Severe renal impairment (eGFR<30 ml/min/1.73m², (n=5))	100%	100%	100%	100%	100%	100%	100%

Table 5. Probability of PK/PD target attainment of 100% T > MIC for the first 24 h after the start of treatment based on the observed data in the different renal function groups using different MIC values of common Gram-negative bacteria susceptible for ceftazidime as listed in the EUCAST.

	PTA (100% T_{0-24} > MIC)						
MIC (mg/L)	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**
Renal function group							
Adequate renal function (eGFR ≥50ml/min/1.73m², (n=25))	100%	100%	100%	100%	56%	48%	24%
Moderate renal impairment (eGFR≥30-50 ml/min/1.73m², (n=10))	90%	90%	90%	90%	90%	80%	50%
Severe renal impairment (eGFR<30 ml/min/1.73m², (n=4))	100%	100%	100%	100%	100%	100%	75%

Table 6. Probability of PK/PD target attainment of 50% T > MIC for 24-48 h after the start of treatment based on the observed data in the different renal function groups using different MIC values of common Gram-negative bacteria susceptible for ceftazidime as listed in the EUCAST.

	PTA (50% T_{24-48} > MIC)						
MIC (mg/L)	**0.125**	**0.25**	**0.5**	**1**	**2**	**4**	**8**
Renal function group							
Adequate renal function (eGFR ≥50ml/min/1.73m², (n=24))	100%	100%	100%	100%	100%	100%	100%
Moderate renal impairment (eGFR≥30-50 ml/min/1.73m², (n=10))	90%	90%	90%	90%	90%	90%	90%
Severe renal impairment (eGFR<30 ml/min/1.73m², (n=4))	100%	100%	100%	100%	100%	100%	100%

Monte Carlo dosing simulations

The majority of the study population (n = 22, 55%) received more ceftazidime administrations during the first 24 h of treatment than prescribed due to the fact that follow-up administrations were planned during the routine time windows of nurses' administration rounds. This often resulted in drug administration early in the morning following the day of ceftazidime initiation. From that moment on, the dosing interval as prescribed was more accurately adhered to. As a consequence, the time above MIC in the first 24 h for these individuals is higher than when perfect dosing intervals of 8, 12 or 24 h (depending on renal function) would have been applied after the first dose. To examine the influence of this phenomenon on the PTA, the original dataset, but then with exact dosing intervals of q8h, q12h or q24h depending on the renal function, was simulated 1000 times by means of a Monte Carlo simulation with the final model. PTA of 50% $T_{0\text{-}24}$ > MIC remained high: 93%, 97% and 97% for patients with adequate, moderately impaired and severely impaired renal function, respectively (Figure 2). Similar PTA was found in the simulated patients when compared to the PTA as observed in the included patients indicating minimal bias in PTA of 50% $T_{0\text{-}24}$ > MIC due to the dose shift in our study population.

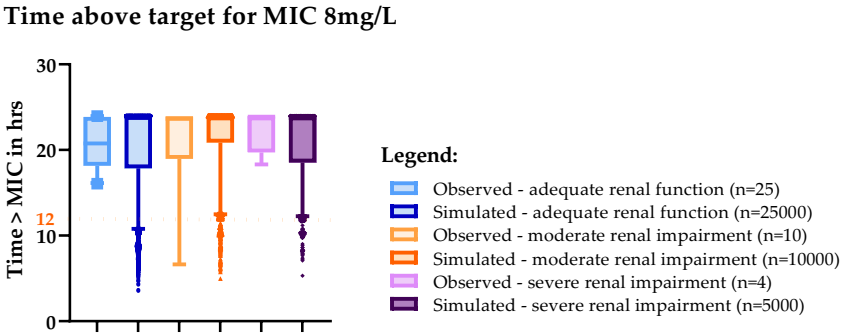


Figure 2. Boxplots of observed and simulated time above target for MIC 8 mg/L for patients with adequate, moderately impaired and severely impaired renal function within the first 24 h of treatment. Presented are the median (horizontal line within the box), the interquartile range (box) and the 5th and 95th percentile (whiskers). The target for 50% $T_{0\text{-}24}$ > MIC is presented as the orange dotted line at 12 h.

Drug exposure

No differences in median drug exposure in the first 24 h of treatment ($AUC_{0\text{-}24}$) and 24-48 h after start of treatment ($AUC_{24\text{-}48}$) were observed between patients with adequate renal function receiving regular doses and patients with moderately impaired and severely impaired renal function receiving the guideline-recommended reduced doses (p = 0.159 and p = 0.125) (Figure 3).

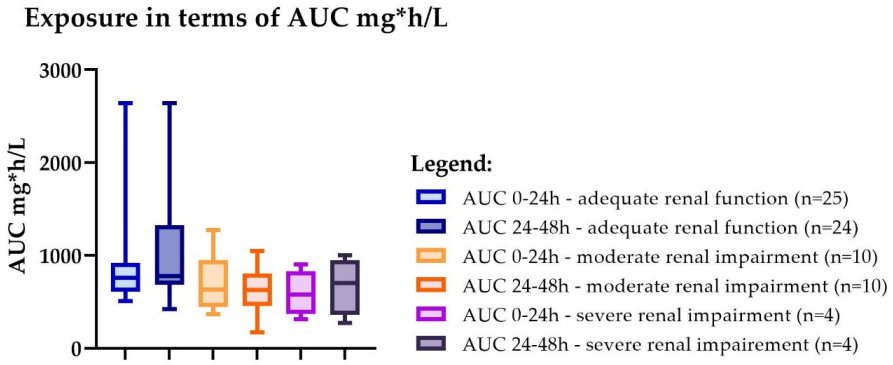


Figure 3. Exposure to ceftazidime in terms of AUC (mg*h/L) for the first 24 h of treatment (AUC_{0-24}) and the second 24 h of treatment (AUC_{24-48}) for different renal function groups. AUCs >1500 mg*h/L in the adequate renal function group were patients with eGFRs ranging between 51 and 77ml/min/1.73m^2.

Clinical outcome measure

Since only one out of 40 patients (2.5%) did not attain the primary outcome of 50% T_{0-24} > MIC for MIC values up to 8 mg/L, we did not explore clinical outcome in this study since a minimum of 25%, or 10 patients, not attaining the primary outcome was a prerequisite for exploring clinical outcome.

Discussion

This study shows that with the current dosing regimen of ceftazidime, the PTA of 50% T_{0-24} > MIC is attained in ≥90% of adult patients on general wards treated for clinically relevant bacteria with MICs ≤8 mg/L. Therefore, the current dosing regimen proves adequate treatment of infections caused by *P. aeruginosa*, which have a clinical breakpoint of 8 mg/L as defined by the EUCAST.[22]

No differences in PTA or drug exposure were observed between patients with adequate renal function receiving regular doses versus patients with moderately impaired and severely impaired renal function receiving the guideline-recommended reduced doses. This is in contradiction with the results from a comparable study with ciprofloxacin, which did show differences in drug exposure and PTA between patients with adequate renal function receiving regular doses and patients with impaired renal function receiving a 50% dose reduction.[23] This phenomenon may be explained by the fact that ceftazidime is eliminated exclusively through the kidneys, so no compensating pathways for excretion through the hepatic system exist as is the case for ciprofloxacin. Therefore, a gross dose reduction in case of renal impairment, as currently recommended and investigated in this study, seems appropriate.

One patient with moderate renal impairment showed a serum concentration of ceftazidime below the LLOQ at 8.02 h after ceftazidime administration. This was the only patient not attaining the PK/PD target. However, the PTA remained ≥90% within the moderate renal function group, which was defined as the minimum acceptable PTA.

In the present study, a one-compartment population PK model of ceftazidime was developed with associations between eGFR (CKD-EPI) and CL and between concomitant use of antibiotics and CL. This model could predict our observed data sufficiently well as seen in the visual predictive check (Figure 1). The association between the eGFR (CKD-EPI) and CL was as expected.[24,25] The statistically significant association between CL and the concomitant use of other antibiotics was unexpected. Although we could not find a physiological explanation for this association, we decided to retain this association within the final model as it gave a statistically significant drop of the objective function during the multivariate analysis (p <0.01), the corresponding parameter quantifying the effect of concomitant use of other antibiotics on CL was precisely estimated (Table 3) and it explained 16.8% IIV in CL. Nevertheless, it cannot be ruled out that the identification of this association is based on coincidence.

This is, to the best of our knowledge, the first prospective study measuring PK/PD target attainment of ceftazidime in real-life clinical practice in patients on general wards. The developed population PK model that was used for calculation of the outcome parameters T > MIC and AUC values showed low residual variability, indicating careful collection of study data. Additionally, this study was conducted in an academic medical center and a peripheral teaching hospital and included patients that were admitted to a broad variety of wards (e.g., cardiology, hematology, internal medicine, nephrology, orthopedic surgery and respiratory department), enhancing the representativeness of the included patient population.

Nevertheless, several limitations of this study should also be considered. First, a shift was observed in timepoint of drug administration in the morning following the day of ceftazidime initiation. As a result, more than half of our included patients (n = 22) received an additional antibiotic administration during the first 24 h of treatment than originally prescribed due to the fact that follow-up administrations are planned during the routine time windows of nurses' administration round. This is inherent to the observational design of this study and may well lead to a higher PTA

than when exact dosing intervals as prescribed would have been applied. However, Monte Carlo simulations were performed using exact dosing intervals. Results showed comparable PTA. Additionally, this dosing shift is representative for real-life clinical practice.

Second, one patient with severe renal impairment received a dose of 2000 mg q24h, that differed from the regular renal function-based dose adjustment within this group of 1000 mg q24h. Therefore, T > MIC is overestimated in this patient. Yet, the estimated concentration in this patient at t = 12 h after the first ceftazidime administration of 2000 mg was 24,3 mg/L, which makes it reasonable to assume that the concentration would also be >8 mg/L at t = 12 h if 1000 mg would have been administered, assuming that a factor two lower dose will grossly lead to a factor two lower concentration at the same time after the first administration. With this assumption, >50% $T_{0–24}$ > MIC would have been obtained with 1000 mg q24 h. We, therefore, decided not to exclude this patient from our analysis of the primary outcome. We did exclude this patient for all secondary outcomes because these are obviously overestimated with the higher dose and because no simple and reasonable assumption, as for the primary outcome, could be made with regard to AUC values and attainment of 100% $T_{0–24}$ > MIC if 1000 mg would have been administered, since a second dose of 2000 mg was already administered 18 h after the first one with an estimated trough level of 14 mg/L.

Third, the collected number of samples (121 of which 2 were excluded) is quite small, limiting the possibility to identify, e.g., a two-compartmental model or to identify more covariate associations.

Physicians are hesitant to adjust the dose of antibiotics in cases of renal impairment, probably due to fear of insufficient exposure.[26-28] For the antibiotic ciprofloxacin, our group has previously shown that this fear seems justified.[16] This research adds valuable evidence regarding the currently advised dosing regimen of ceftazidime used to treat patients with moderately impaired and severely impaired renal function admitted to general wards as we show that dose adjustment of ceftazidime in renal impairment results in adequate PTA and comparable exposure in comparison with patients with adequate renal function receiving 2000 mg q8h. Any potential fear among prescribers for underdosing thus appears to be unfounded.

Conclusions

In conclusion, the PTA of ceftazidime of 50% T_{0-24} > MIC is ≥90% in adult patients on general wards with adequate and impaired renal function receiving regular and guideline-recommended reduced doses of ceftazidime for the treatment of clinically relevant bacteria with MICs ≤8 mg/L. Therefore, the current dosing regimens for both patient categories are adequate for the treatment of infections caused by *P. aeruginosa*, which have a clinical breakpoint of 8 mg/L as defined by the EUCAST.[22]

Author Contributions

Conceptualization, S.E.Z., S.L.d.V., S.E.G., R.M.vH,; methodology, S.E.Z., S.L.d.V., S.E.G., R.M.vH, software, S.E.Z., R.M.v.H.; validation, S.E.Z., R.M.v.H; formal analysis, S.E.Z., R.M.v.H.; investigation, S.E.Z.; resources, R.M.v.H..; data curation, S.E.Z. .; writing—original draft preparation, S.E.Z., S.L.d.V.; writing—review and editing, S.E.Z., S.L.d.V, R.A.A.M., S.E.G., R.M.v.H, G.v.T., F.Ph.M. .; visualization, S.E.Z..; supervision, .; R.A.A.M., S.E.G., R.M.v.H. project administration, S.E.Z. and S.L.d.V.; funding acquisition, R.M.v.H. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review board of Amsterdam University Medical Centers (MEC2019_159 approved 24th of September 2019).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

Data available on request due to privacy restrictions.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Andersson, M.; Östholm-Balkhed, Å.; Fredrikson, M.; Holmbom, M.; Hällgren, A.; Berg, S.; Hanberger, H. Delay of appropriate antibiotic treatment is associated with high mortality in patients with community-onset sepsis in a Swedish setting. Eur. J. Clin. Microbiol. Infect. Dis. 2019, 38, 1223–1234.
2. Schuts, E.C.; Hulscher, M.E.J.L.; Mouton, J.W.; Verduin, C.M.; Stuart, J.W.T.C.; Overdiek, H.W.P.M.; van der Linden, P.D.; Natsch, S.; Hertogh, C.M.P.M.; Wolfs, T.F.W.; et al. Current evidence on hospital antimicrobial stewardship objectives: A systematic review and meta-analysis. Lancet Infect. Dis. 2016, 16, 847–856.
3. McCabe, C.; Kirchner, C.; Zhang, H.; Daley, J.; Fisman, D.N. Guideline-concordant therapy and reduced mortality and length of stay in adults with community-acquired pneumonia: Playing by the rules. Arch. Intern. Med. 2009, 169, 1525–1531.
4. Onufrak, N.J.; Forrest, A.; Gonzalez, D. Pharmacokinetic and Pharmacodynamic Principles of Anti-infective Dosing. Clin. Ther. 2016, 38, 1930–1947.
5. Nielsen, E.I.; Cars, O.; Friberg, L.E. Pharmacokinetic/pharmacodynamic (PK/PD) indices of antibiotics predicted by a semimechanistic PKPD model: A step toward model-based dose optimization. Antimicrob. Agents Chemother. 2011, 55, 4619–4630.
6. Arumugham, V.B.; Gujarathi, R.; Cascella, M. Third Generation Cephalosporins. In StatPearls; StatPearls Publishing: Tampa, FL, USA, 2022.
7. Dhaese, S.; Van Vooren, S.; Boelens, J.; De Waele, J. Therapeutic drug monitoring of β-lactam antibiotics in the ICU. Expert Rev. Anti Infect. Ther. 2020, 18, 1155–1164.
8. McKinnon, P.S.; Paladino, J.A.; Schentag, J.J. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int. J. Antimicrob. Agents 2008, 31, 345–351.
9. Muller, A.E.; Punt, N.; Mouton, J.W. Optimal exposures of ceftazidime predict the probability of microbiological and clinical outcome in the treatment of nosocomial pneumonia. J. Antimicrob. Chemother. 2013, 68, 900–906.
10. MacVane, S.H.; Crandon, J.L.; Nichols, W.W.; Nicolau, D.P. In vivo efficacy of humanized exposures of Ceftazidime-Avibactam in comparison with Ceftazidime against contemporary Enterobacteriaceae isolates. Antimicrob. Agents Chemother. 2014, 58, 6913–6919.
11. Mouton, J.W.; Muller, A.E.; Canton, R.; Giske, C.G.; Kahlmeter, G.; Turnidge, J. MIC-based dose adjustment: Facts and fables. J. Antimicrob. Chemother. 2018, 73, 564–568.
12. KNMP Kennisbank-Ceftazidime. Available online: https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/S1884.html (accessed on 13 January 2023).
13. Farmacotherapeutisch Kompas (FK)-Ceftazidime. Available online: https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/c/ceftazidim (accessed on 13 January 2023).
14. SWAB-Ceftazidime. Available online: https://adult.nl.antibiotica.app/en/node/1176 (accessed on 13 January 2023).
15. van Daalen, F.V.; Prins, J.M.; Opmeer, B.C.; Boermeester, M.A.; Visser, C.E.; van Hest, R.M.; Branger, J.; Mattsson, E.; van de Broek, M.F.M.; Roeleveld, T.C.; et al. Effect of an antibiotic checklist on length of hospital stay and appropriate antibiotic use in adult patients treated with intravenous antibiotics: A stepped wedge cluster randomized trial. Clin. Microbiol. Infect. 2017, 23, 485.e1–485.e8.
16. de Vroom, S.L.; van Daalen, F.V.; Zieck, S.E.; Mathôt, R.A.A.; van Hest, R.M.; Geerlings, S.E. Does dose reduction of renally cleared antibiotics in patients with impaired renal function lead to adequate drug exposure? A systematic review. Clin. Microbiol. Infect. 2021, 27, 352–363.
17. Welage, L.S.; Schultz, R.W.; Schentag, J.J. Pharmacokinetics of ceftazidime in patients with renal insufficiency. Antimicrob. Agents Chemother. 1984, 25, 201–204.

18. Leroy, A.; Leguy, F.; Borsa, F.; Spencer, G.R.; Fillastre, J.P.; Humbert, G. Pharmacokinetics of ceftazidime in normal and uremic subjects. Antimicrob. Agents Chemother. 1984, 25, 638–642.
19. Ackerman, B.H.; Ross, J.; Tofte, R.W.; Rotschafer, J.C. Effect of decreased renal function on the pharmacokinetics of ceftazidime. Antimicrob. Agents Chemother. 1984, 25, 785–786.
20. Walstad, R.A.; Dahl, K.; Hellum, K.B.; Thurmann-Nielsen, E. The pharmacokinetics of ceftazidime in patients with impaired renal function and concurrent frusemide therapy. Eur. J. Clin. Pharmacol. 1988, 35, 273–279.
21. Roberts, J.A.; Lipman, J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit. Care Med. 2009, 37, 840–851.
22. European Committee on Antimicrobial Susceptibility Testing (EUCAST). Clinical Breakpoints Table for Bacteria (v 11.0). Available online: https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_11.0_Breakpoint_Tables.xlsx (accessed on 17 March 2021).
23. de Vroom, S.L.; van Hest, R.M.; van Daalen, F.V.; Kuil, S.D.; Mathôt, R.A.A.; Geerlings, S.E.; Jager, N.G.L. Pharmacokinetic/pharmacodynamic target attainment of ciprofloxacin in adult patients on general wards with adequate and impaired renal function. Int. J. Antimicrob. Agents 2020, 56, 1061–1066.
24. Mazuski, J.E.; Gasink, L.B.; Armstrong, J.; Broadhurst, H.; Stone, G.G.; Rank, D.; Llorens, L.; Newell, P.; Pachl, J. Efficacy and Safety of Ceftazidime-Avibactam Plus Metronidazole Versus Meropenem in the Treatment of Complicated Intra-abdominal Infection: Results From a Randomized, Controlled, Double-Blind, Phase 3 Program. Clin. Infect. Dis. 2016, 62, 1380–1389.
25. Werumeus Buning, A.; Hodiamont, C.J.; Lechner, N.M.; Schokkin, M.; Elbers, P.W.G.; Juffermans, N.P.; Mathôt, R.A.A.; de Jong, M.D.; van Hest, R.M. Population Pharmacokinetics and Probability of Target Attainment of Different Dosing Regimens of Ceftazidime in Critically Ill Patients with a Proven or Suspected Pseudomonas aeruginosa Infection. Antibiotics 2021, 21, 612.
26. Vidal, L.; Shavit, M.; Fraser, A.; Paul, M.; Leibovici, L. Systematic comparison of four sources of drug information regarding adjustment of dose for renal function. BMJ 2005, 331, 263.
27. Crass, R.L.; Rodvold, K.A.; Mueller, B.A.; Pai, M.P. Renal Dosing of Antibiotics: Are We Jumping the Gun? Clin. Infect. Dis. 2019, 68, 1596–1602.
28. Camargo, M.S.; Mistro, S.; Oliveira, M.G.; Passos, L.C.S. Association between increased mortality rate and antibiotic dose adjustment in intensive care unit patients with renal impairment. Eur. J. Clin. Pharmacol. 2019, 75, 119–126.
29. WMA Declaration of Helsinki–Ethical Principles for Medical Research Involving Human Subjects, October 2013. Available online: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (accessed on 12 February 2023).
30. WMO Medical Research Involving Human Subjects Act. Available online: https://wetten.overheid.nl/BWBR0009408/2022-07-01 (accessed on 12 February 2023).
31. Gómez, C.M.H.; Cordingly, J.J.; Palazzo, M.G.A. Altered pharmacokinetics of ceftazidime in critically ill patients. Antimicrob. Agents Chemother. 1999, 43, 1798–1802.
32. Pruskowski, K.A. Pharmacokinetics and Pharmacodynamics of Antimicrobial Agents in Burn Patients. Surg. Infect. 2021, 22, 77–82.
33. Kercsmar, C.M.; Stern, R.C.; Reed, M.D.; Myers, C.M.; Murdell, D.; Blumer, J.L. Ceftazidime in cystic fibrosis: Pharmacokinetics and therapeutic response. J. Antimicrob. Chemother. 1983, 12, 289–295.
34. Delattre, I.K.; Hites, M.; Laterre, P.F.; Dugernier, T.; Spapen, H.; Wallemacq, P.E.; Jacobs, F.; Taccone, F.S. What is the optimal loading dose of broad-spectrum β-lactam antibiotics in septic patients? Results from pharmacokinetic simulation modelling. Int. J. Antimicrob. Agents 2020, 56, 106–113.

Supplementary Material

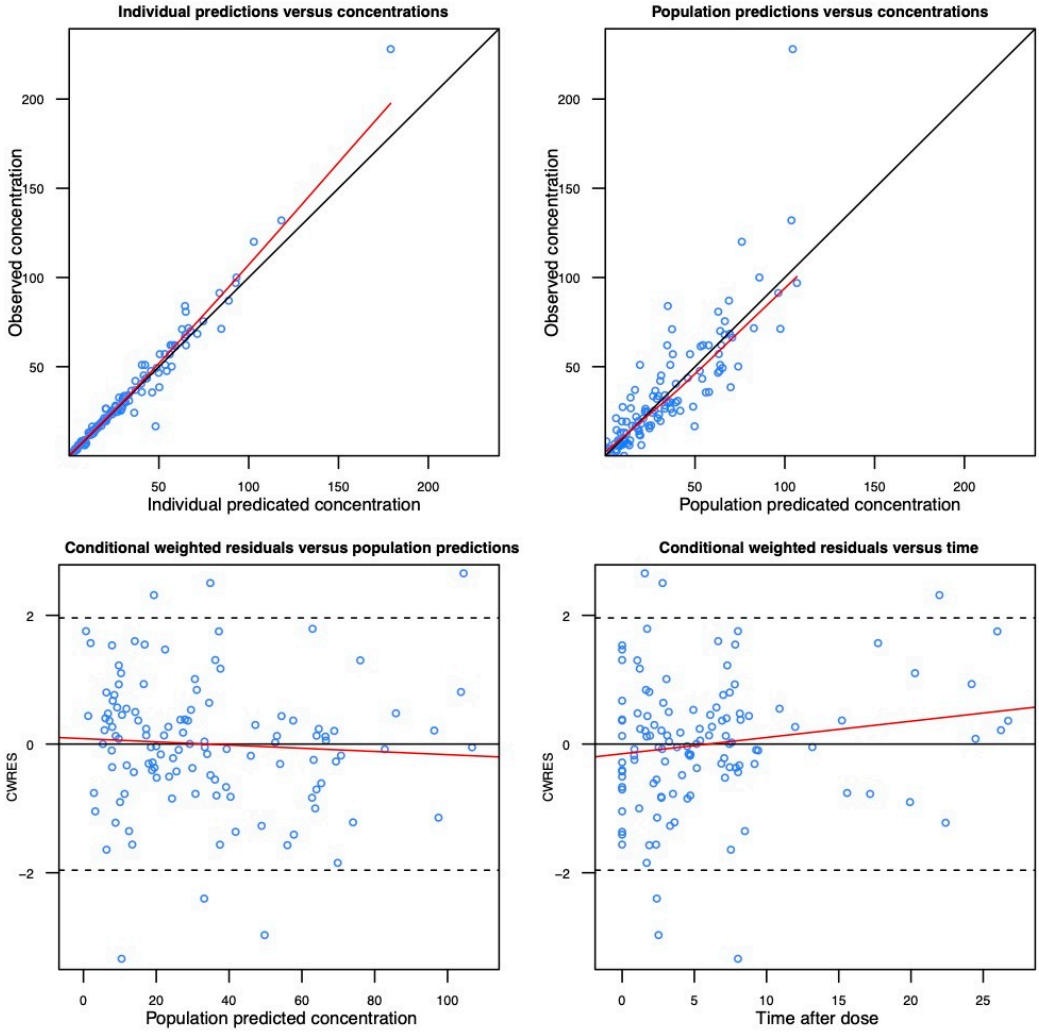


Figure S1. Goodness of fit plots of the final model. Individual predicted concentration versus (vs) observed concentration (left top), population predicted concentration vs observed concentration (right top), the conditional weighted residuals (CWRES) versus the population predicted concentration (left bottom) and CWRES versus the time after dose (right bottom). The data in the upper panels are evenly distributed around the line of identity (black solid line) and the data in the CWRES plots are evenly distributed around the x-axis both indicating no major bias in the final model.

Supplementary File S1

Results: NONMEM Control stream of the final model

```
PROBLEM PK model
$INPUT ID DROP DROP DROP TIME TAD INDTAT RATE AMT DV
DROP MDV
EVID WEIGHT IBW LBW HEIGHT BMI CREAT GENDER
ETHNICITY AGE CRGT
MDRD CKDEPI EGFRCAT OCC FEVER DEPTORT DEPTHEM
COMED
;-----------------------------------
$DATA Dataset_TTCefta.csv IGNORE=#
$SUBROUTINES ADVAN1 TRANS2
$PK
FLAG1=0
IF(COMED.EQ.1)FLAG1=1
TVCL=THETA(3)*(CKDEPI/76.85)**THETA(4)* THETA(6)**FLAG1
CL=TVCL*EXP(ETA(1))
V = THETA(5) * EXP(ETA(2))
S1 = V
$THETA
(0.186)  ;1 proportional error
(0 fix)  ;2 ADDITIVE ERROR
(3.74)   ;3 CL
(0.75) ;4 est exponent TVCL effect CKDEPI
 (21.8) ;5 V
(1.56) ;6 effect 127oncomitant AB$OMEGA
0.0936          ; IIV/BSV CL, fix to 0 to exclude
0.157           ; ETA V
$SIGMA
1 FIX   ;residual variability
$ERROR
IPRED = F
IRES = DV-IPRED
W = IPRED*THETA(1)+THETA(2)
IF (W.EQ.0) W = 1
IWRES = IRES/W
Y= IPRED+W*ERR(1)
$EST METHOD=1 INTERACTION
MAXEVAL=9999 SIG=3 PRINT=5 NOABORT POSTHOC
$COV PRINT=E UNCONDITIONAL
$TABLE ID TIME DV IPRED IWRES TAD AMT CWRES CL V ETA1
ETA2 CREAT
WEIGHT GENDER CKDEPI NOPRINT ONEHEADER
FILE=sdtab038
```

Chapter 6

Impact of mucositis on oral bioavailability and systemic exposure of ciprofloxacin Gram-negative infection prophylaxis in patients with haematological malignancies

Suzanne L. de Vroom* and Koen P. van Rhee*, Reinier M. van Hest, Paul D. van der Linden, Sanne H Tonino, Eva Molendijk, Ron A A Mathôt, Nicole M. A. Blijlevens, Catherijne A. J. Knibbe, Roger J. M. Brüggemann and Suzanne E. Geerlings

* These authors contributed equally to this work

J Antimicrob Chemother. 2022 Oct 28;77(11):3069-3076

Abstract

Background
Patients with haematological malignancies frequently endure neutropenia and gastrointestinal (GI)-mucositis after high-dose chemotherapy. In these patients, ciprofloxacin is used for Gram-negative infection prophylaxis.

Objectives
We investigate ciprofloxacin pharmacokinetics after oral administration in patients with haematological malignancies and explore the impact of GI-mucositis on oral bioavailability and clearance in order to assure adequate systemic exposure.

Methods
Adult haematological patients from two Dutch University Medical Centres received 500 mg twice daily oral ciprofloxacin for Gram-negative prophylaxis. The ciprofloxacin plasma concentrations were collected at various timepoints after oral ciprofloxacin administration and at various days after completion of chemotherapy. Data obtained after oral and intravenous ciprofloxacin administration in 28 healthy volunteers without mucositis served as a control group (391 samples). For haematological patients the degree of GI-mucositis was assessed using the Daily Gut Score (DGS), plasma citrulline and albumin. Data were analysed by non-linear mixed-effects modelling.

Results
In total, 250 blood samples were collected in 47 patients with a wide variety of haematological malignancies between 0–30 days after start of chemotherapy. Mucositis was generally mild [DGS median (IQR) 1 (1– 1) and citrulline 16 µmol/L (12–23)]. The time to C_{max} was slower in haematological patients compared with healthy volunteers although no association with the degree of mucositis (defined as DGS or citrulline) could be identified. Ciprofloxacin bioavailability and clearance were 60% and 33.2 L/h, respectively.

Conclusions
This study supports oral dosing of ciprofloxacin as Gram-negative infection prophylaxis in haematological patients with mild-to-moderate mucositis capable of oral intake.

Introduction

Fluoroquinolone prophylaxis reduces the relative risk of infection-related mortality in neutropenic patients with haematological malignancies by 68% while adverse effects and development of resistance are not significantly increased.[1-4] Of the fluoroquinolones, ciprofloxacin is the most frequently prescribed. It is typically administered orally in dosages of 500 mg twice daily and is rapidly and well absorbed from the gastrointestinal (GI) tract in healthy volunteers with a bioavailability of approximately 60%–80%. Ciprofloxacin is subject to glomerular filtration, tubular secretion, trans-epithelial intestinal secretion and hepatic metabolism.[5]

Patients with haematological malignancies treated with high-dose chemotherapy often encounter mucosal disruption of the GI-tract (GI-mucositis).[6,7] Mucositis affects oral absorption unpredictably in patients with haematological malignancies; for example, posaconazole bioavailability is reduced while isavuconazole bioavailability remains unaltered.[8,9] The gold standard method to diagnose mucositis is a biopsy from the small intestine. As this procedure is invasive and therefore not clinically feasible, clinical scores and biomarkers are used to assess severity of mucositis.[10-13] Several mucositis scores are available, although there are differences regarding the focus on oral- versus GI-mucositis. The Daily Gut Score (DGS) quantifies GI-mucositis by scoring the frequency, consistency and incontinence of faeces, nausea, vomiting, abdominal complaints and the ability for oral intake.[12] Nevertheless, the clinical assessment scale is subjective, based on symptoms that may not be specific for mucositis and could be influenced by analgesic agents.[14]

Both citrulline and albumin plasma concentrations are also used as biomarkers for mucositis, with citrulline being the most potent.[14] Citrulline is a non-protein amino acid almost exclusively produced by enterocytes of the small intestine. As mucositis develops, mucosal barrier integrity deteriorates which is associated with a reduced citrulline plasma concentration. Consequently, citrulline serves as a biomarker for GI-mucositis. Plasma citrulline <10 µmol/L is associated with severe mucositis, 10–30 µmol/L is associated with mild mucositis, while >30 µmol/L is considered normal.[13,15,16] Citrulline plasma concentration starts declining shortly after initiation of chemotherapy. The lowest values are observed 7–10 days after start of high-dose chemotherapy, after which citrulline levels rise to normal values around 21 days after high-dose chemotherapy.[13]

Besides mucositis, concomitant medication can also influence ciprofloxacin oral absorption. Prokinetic agents such as metoclopramide or clarithromycin increase gastric motility and augment oesophageal peristalsis, which can accelerate oral absorption.[17] Proton-pump inhibitors and antacids can delay gastric emptying by increasing gastric pH, while opioids may delay oral absorption as a result of reduced intestinal motility.[17] Bioavailability may be reduced by co-ingestion with Al^{2+}, Ca^{2+}, Fe^{2+} or Mg^{2+} ions.[5]

Ciprofloxacin pharmacokinetics in patients with chemotherapy for haematological malignancies showed conflicting results in three case-series (≤8 participants per series) as exposure was found to be unaltered or decreased.[18-20] Two studies did not report severity of mucositis at all, while one study only used clinical markers to describe severity of oral mucositis. Consequently, a knowledge gap remains regarding the influence of GI-mucositis on oral absorption and clearance of ciprofloxacin, risking underexposure and possibly higher infection-related mortality.

In a cohort of neutropenic patients treated for a wide variety of haematological malignancies leading to a high risk of mucositis, we investigated ciprofloxacin pharmacokinetics and evaluated whether mucositis influences oral bioavailability and clearance, in comparison with healthy volunteers.

Patients and methods

Data

Data from three cohorts consisting of only haematological patients were collected in two Dutch academic hospitals. Cohort 1 was a prospective observational cohort at the Amsterdam UMC, location Academic Medical Centre (Amsterdam UMC, location AMC). Patients were recruited between March 2019 and December 2020, *n* = 41 (NTR7520). Cohort 2 consisted of participants in a dense sampling study of micafungin pharmacokinetics (NCT02172768) who simultaneously received ciprofloxacin prophylaxis.[21] Cohort 3 consisted of participants in a dense sampling study of posaconazole pharmacokinetics (NCT02805946) who received ciprofloxacin prophylaxis.[8] Patients with concomitant use of ciprofloxacin on pharmacokinetic (PK)-sampling days of micafungin or posaconazole (*n* = 2 and 4 patients, respectively) were selected. Finally, to compare the impact of mucositis caused by high-dose chemotherapy on oral absorption, these data were compared with data from a previously performed dense-sampling pharmacokinetic study (*n* = 28 with 391 samples) after oral and intravenous ciprofloxacin administration in healthy volunteers and obese patients (NTR6058).[22]

Haematological patients receiving reduced-intensity conditioning regimens for allogeneic HSCT, first remission-induction chemotherapy for AML/myelodysplastic syndrome or CAR-T cell infusion for lymphoma and who received orally administered ciprofloxacin tablets (500 mg twice daily) for Gram-negative prophylaxis were eligible for inclusion if they were legally competent and at least 18 years of age. Exclusion criteria were admission to the ICU, receiving renal replacement therapy or patients unable to take oral medication due to progression or worsening of mucositis and patients with a previous ciprofloxacin treatment course for whom discontinuation lasted less than 48 h.

In Cohort 1, two samples were collected around 1–2 h after oral administration, one prior to administration and one random sample, all within 72 h around 7 days after initiation of chemotherapy. Additionally, leftover material from routine sampling at >7 days after initiation of chemotherapy was collected. Blood samples were centrifuged immediately and plasma was stored at −80°C at the clinical laboratory of the pharmacy department of the Amsterdam UMC, location AMC. In Cohorts 2 and 3 one trough concentration was collected daily with additional dense sampling (*t* = 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24 h) on two PK-days between day 1 and 15 after initiation of chemotherapy. Details of the sampling scheme and the schedule of the PK-days in relation to the start of chemotherapy are presented in Tables S1 and S2 (available as Supplementary data). Samples from Cohorts 2 and 3 were stored at −80°C at the clinical laboratory of the department of pharmacy at the Radboud university medical center, Nijmegen, until analysis.

Data on patient characteristics (sex, age, weight, height, BMI, diagnosis, current and previous treatment details, comorbidity), ciprofloxacin treatment (dose, date and time of administration), factors leading to reduced ciprofloxacin exposure (vomiting within 2 h after administration), interacting co-medication (ranitidine, Al^{2+}-, Ca^{2+}-, Fe^{2+}- or Mg^{2+}-containing drugs administered within 4 h before or 2 h after ciprofloxacin) and co-medication influencing the oral absorption process (prokinetic agents, proton pump inhibitors, opioids); serum creatinine, mucositis biomarkers (albumin, citrulline) and DGS were recorded over time. To estimate glomerular filtration rate (eGFR), both indexed and de-indexed Chronic Kidney Disease Epidemiology collaboration (CKD-EPI) and Modification of Diet in Renal Diseases (MDRD) were calculated.[23,24] De-indexing was done by multiplying the respective eGFR by 1.73/body surface area (BSA) (BSA was calculated using the du Bois-du Bois formula).[25]

A single citrulline plasma sample was drawn in Cohort 1, simultaneously with obtaining samples collected around 1–2 h after oral administration. In Cohort 3, citrulline plasma samples were collected daily. All citrulline samples were stored on ice and centrifuged within 2 h. Plasma was stored at −80°C until analysis. Plasma citrulline was not determined in Cohort 2 and the control group.

DGS was retrospectively scored based on data available in the electronic patient registry on every day of PK-sampling. For all six components of the DGS, patients could score 0–3 points, with 0 indicating no complaints and 3 indicating severe complaints with that component. GI-mucositis was scored as mild (1–6 points), moderate (7–12 points) or severe (>12 points).[12]

Ethics

The research protocol for Cohort 1 was approved by the certified Medical Ethics Committee of the Amsterdam UMC, location AMC (NL67783.018.18). All patients provided written informed consent. Participants in Cohorts 2, 3 and the control group provided written informed consent before inclusion in the respective studies (clinicaltrial.gov identifiers for Cohorts 2 and 3: NCT02172768, NCT02805946. Dutch trial registry number for the control group: NTR6058). The institutional review board permitted additional analysis on the previously collected samples from Cohorts 2 and 3 and waived informed consent. Additional clinical parameters were collected from the electronic patient registry if patients gave consent for inclusion in the Radboudumc Biobank Hematology.

The study was conducted in accordance with the Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki.[26,27]

Laboratory analysis

Total ciprofloxacin plasma concentrations were analysed using a validated LC-MS/MS assay at the Amsterdam UMC. The validated range of the analysis is 0.020–5.0 mg/L.[28] Citrulline samples were analysed using a validated UPLC MS/MS assay at the Clinical Chemistry laboratory of Canisius Wilhelmina Hospital, Nijmegen.[29]

Population PK analysis

Concentration–time data from haematological patients and healthy volunteers were analysed simultaneously by non-linear mixed-effects modelling using FOCE with interaction and the ADVAN6 subroutine (NONMEM; v7.4.0 with PsN; v4.7.1 and Pirana v2.9.7).[30,31] Bioavailability (F) and clearance (CL) are the pharmacokinetic parameters of primary interest as these drive systemic exposure (measured as AUC) after oral administration. Systemic exposure can be calculated as follows.

$$AUC = \frac{F * \text{Dose}}{CL} \qquad (1)$$

A previously developed PK-model for ciprofloxacin in healthy volunteers and obese patients with a two-compartment structure and transit compartments for oral absorption was used as a starting point.[22] For the group of haematological patients (Cohorts 1–3), all PK-parameters were estimated relative to the control group using Equation 2 with a correction factor significantly different from 1.0 indicating a difference in typical value between haematological patients and the control group for the respective parameter.

$$\theta_{haematological\ patient} = \theta_{healthy\ volunteer} * \theta_{correction\ factor} \quad (2)$$

The influence of covariates (age, sex, weight, BMI, CKD-EPI, MDRD, citrulline, albumin, DGS, days after chemotherapy) was tested for associations with model parameters. If multiple observations were available for one individual (creatinine, citrulline, albumin, DGS and days after chemotherapy) covariates were assessed as a time varying covariate with backward interpolation.

Continuous covariates were implemented in the model using exponential or linear relationships using Equation (3) and (4), respectively. P_i and P_p represent individual and population parameter estimates, X represents the exponent for a power function and Z represents the slope for the linear covariate relationship. For dichotomous covariates different parameters were estimated for the respective subgroup.

$$P_i = P_p \times \left(\frac{COV}{COV_{standard}}\right)^X \quad (3)$$

$$P_i = P_p \times (1 + Z \times (COV - COV_{standard})) \quad (4)$$

In the model building process, a change in objective function value (OFV), goodness-of-fit (GOF), conditional weighted residual plots, reduction in interindividual variability and individual fit plots were used to compare models. A *P* value of <0.05, representing a decrease of 3.84 in OFV with one degree of freedom was considered statistically significant for structural parameters. In the covariate analysis, a *P* value of <0.05 (OFV decrease >3.84) was considered statistically significant in the forward inclusion step while $P < 0.001$ (OFV increase >10.8) was considered statistically significant in the backward elimination. Internal model evaluation and validation was done using GOF-plots, CWRES-plots split for cohort- and time-dependent covariates, visual predictive check (VPC) and sampling importance resampling (SIR).

Continuous data are presented as mean ± SD and analysed by *t*-test when normally distributed or as median ± IQR and analysed by Mann–Whitney U-test when not normally distributed.

After development and internal validation of the pharmacokinetic model, simulations were performed with 2500 virtual individuals per cohort with interindividual variability. The ciprofloxacin exposure, measured as AUC in haematological patients was compared with healthy volunteers after the standard-of-care dosing regimen of twice daily oral administration of 500 mg.

Results

Subject characteristics

Data from 47 patients (19 men and 28 women) with a wide variety of haematological malignancies were included, from whom 250 ciprofloxacin plasma samples were available. The oral absorption phase was captured in detail with 82 plasma samples (33%) collected in the first 2 h after oral administration. Data from 28 healthy volunteers (14 men and 14 women) were included. Eight patients received semi-simultaneous oral and intravenous administration and 20 individuals received either oral or intravenous administration. In total 391 samples were collected in the control group, 178 after intravenous administration and 213 after oral administration. A detailed description of PK-data is provided in Table S2.

The majority of patients showed biochemically mild mucositis with the lowest observed citrulline (nadir) between 10–30 μmol/L (*n* = 32, 68%) and a DGS indicating clinically mild mucositis (*n* = 46, 98%). Clinically moderate mucositis (by DGS) was observed in one patient (2%) while biochemically severe mucositis (citrulline nadir ≤10 μmol/L) was observed in nine patients (19%). Of these nine patients, the DGS indicated clinically mild mucositis in eight patients and moderate mucositis in one patient. Samples were collected a median (IQR) of 6 (3–11) days after start of high-dose chemotherapy. In patients with multiple citrulline observations, a declining plasma citrulline was observed until 10 days after start of conditioning. Concomitant medication that could influence the oral absorption process was used by 29 haematological patients (62%) at the time of PK-sampling. Drugs delaying oral absorption were used by 26 patients (89%) while drugs accelerating oral absorption were used by 14 patients (48%). Details of patient characteristics including the use of concomitant medication potentially influencing oral absorption of ciprofloxacin are presented in Table 1.

Table 1. Population characteristics

Characteristic	Haematological patients (*n* = 47)	Control group (*n* = 28)
Age	53 (47–64)	40 (27–52)
Sex, male, *n* (%)	19 (40)	14 (50)
Weight (kg)	78 (69–90)	123 (84–149)
Citrulline nadir (µmol/L)[a]	16 (12–23)	ND
Citrulline nadir ≤10 µmol/L (*n*)	9	ND
Citrulline nadir 10–30 µmol/L (*n*)	32	ND
Citrulline nadir ≥30 µmol/L (*n*)	4	ND
Albumin nadir (g/L)	42 (26–50)	ND
Daily Gut Score	1 (1–1)	ND
Diagnosis		NA
Acute leukaemia	17	
Lymphoma	13	
Multiple myeloma	9	
Chronic leukaemia	3	
Other	5	
Treatment (*n*)		NA
Remission-induction	19	
Autologous SCT	16	
Allogeneic HSCT	10	
Other	2	
Relevant co-medication		
Reduced bioavailability		
Magnesium hydroxide	1	0
Delayed absorption		
Proton pump inhibitor	24	0
Esomeprazole	19	
Pantoprazole	3	
Omeprazole	2	
Opioid	7	0
Oxycodone	5	
Morphine	1	
Fentanyl	1	
Tramadol	1	
Accelerated absorption		
Metoclopramide	13	0
Metoprolol	1	0
Clarithromycin	1	0
Serum creatinine (µmol/L)	74 (62–89)	72 (64–80)
CKD-EPI (mL/min/1.73 m²)	97 (80–112)	134 (118–149)
CKD-EPI$^{b}_{\text{de-indexed}}$ (mL/min)	84 (68–105)	102 (95–109)
MDRD (mL/min/1.73 m²)	96 (78–121)	126 (110–154)
MDRD$^{b}_{\text{de-indexed}}$ (mL/min)	82 (66–115)	98 (90–108)

Data are presented as median (IQR) unless stated otherwise. For citrulline and albumin the lowest observed value is reported if multiple observations were available per patient. For serum creatinine and corresponding estimators of GFR the observation at baseline is reported. Daily Gut Score (DGS) 1 represents mild mucositis (1-6 points on the DGS) and 2 represents moderate mucositis (7-12 points on the DGS). HSCT, haematopoietic stem cell transplant, NA, not applicable; nadir, lowest observed value for an individual; ND: not determined; SCT, stem cell transplant.

[a]Citrulline plasma concentration was determined in 45 haematological patients.

[b]De-indexed by multiplying CKD-EPI or MDRD BSA/1.73

Pharmacokinetic analysis

The concentration–time profiles were best described by a two-compartment model with first order elimination and a transit compartment model for oral absorption with a correction factor of 2.07 (95% CI 1.4–2.5) on mean transit time for haematological patients, interindividual variability on clearance, volume of distribution and mean transit time and a proportional error model (for model structure, see Figure S1). Bioavailability and clearance were 60% and 33.2 L/h, respectively and were not significantly different between haematological patients and the control group. The degree of mucositis measured by DGS, citrulline and albumin plasma concentration as well as days after chemotherapy were investigated as potential drivers of the observed difference in the mean transit time between both groups, but evaluation of these parameters did not provide a better prediction of

the observed data. GOF-plots show the model adequately describes the observed data and conditional weighted residual plots indicate no model mis-specification as residuals were randomly spread against time after start of ciprofloxacin, predicted plasma concentration, plasma albumin, plasma citrulline and days after chemotherapy (Figure S2). The use of concomitant medication in the haematological patients showed no significant association with altered ciprofloxacin pharmacokinetics in haematological patients. Also, the predictive performance of citrulline plasma concentration as a biomarker for impaired oral absorption was not significantly different for patients receiving stem cell transplant compared with patients receiving other therapy (Figure S3). Clearance, bioavailability and volume of distribution were unaffected by mucositis. Total body weight and renal function also did not provide a statistically significant improvement of the fit when tested as covariates on these parameters. Internal model validity was confirmed using VPC stratified for haematological group and control group (Figure S4). Model parameters and their uncertainty based on SIR are shown in Table 2, the mean percentage error was −5.4%.

Table 2. Pharmacokinetic parameter estimates for the final model

Fixed effects	Estimate (%RSE)	SIR 95% CI
CL (L/h)	33.2 (6.9)	29.9–37.0
V_c (L)	69.0 (19.1)	50.7–92.8
V_p (L)	140 (10.6)	120–160
Q (L/h)	71.4 (13.4)	57.3–83.5
F	0.603 (8.5)	0.535–0.669
Ka (h^{-1})	1.35 (14.5)	1.08–1.70
MTT Control group (h)	0.317 (13.1)	0.230–0.369
Relative MTT	2.07 (14.8)	1.41–2.50
Haematological patients[a]		
NN (*n*)	10.9 (40.2)	6.51–15.8
Interindividual variability (%)[b]		
CL[c]	28.1 (12.8)	20.7–34.3
V_c[c]	86.7 (23.7)	55.9–134
MTT[c]	82.6 (13.2)	74.7–117
Residual error (%)[b]		
σ^d_{prop}	21.4 (5.9)	19.4–23.1

CL, clearance from the central compartment; F, bioavailability; Ka, absorption rate constant; MTT, mean transit time; NN, number of transit compartments; Q, intercompartmental clearance; RSE, relative standard error; SIR, sampling importance resampling based on 5000 samples and 1000 resamples; V_c, volume of distribution of the central compartment; V_p, volume of distribution of the peripheral compartment.
[a]Absolute MTT for haematological patients is 0.656 h (according to Eq. 1: 0.317 h*2.07 = 0.656 h).
[b]Calculated by $\sqrt{(e^{\omega^2} - 1)}$.
[c]η-Shrinkage: CL 5%, V_c 26%, MTT 26%.
[d]ϵ-Shrinkage: 11%.

Model-based dose evaluations

Using the final and internally validated model, exposure that can be expected upon the standard-of-care dosing regimen of twice daily oral ciprofloxacin administration of 500 mg was evaluated. The median (IQR) time to ciprofloxacin C_{max} was 1.5 (1.2–2.1) h for haematological patients and 1.2 (1.0–1.5) h for the control group as shown in Figure 1. In the first week of treatment, median (IQR) cumulative $AUC_{day\ 1\text{-}7}$ was 124 (105–149) mg·h/L for haematological patients and 123 (103–146) mg·h/L for healthy volunteers. In the second week of treatment, median (IQR) cumulative $AUC_{day\ 8\text{-}14}$ was 127 (107–154) mg·h/L for haematological patients and 126 (105–151) mg·h/L for healthy volunteers, as shown in Figure 2.

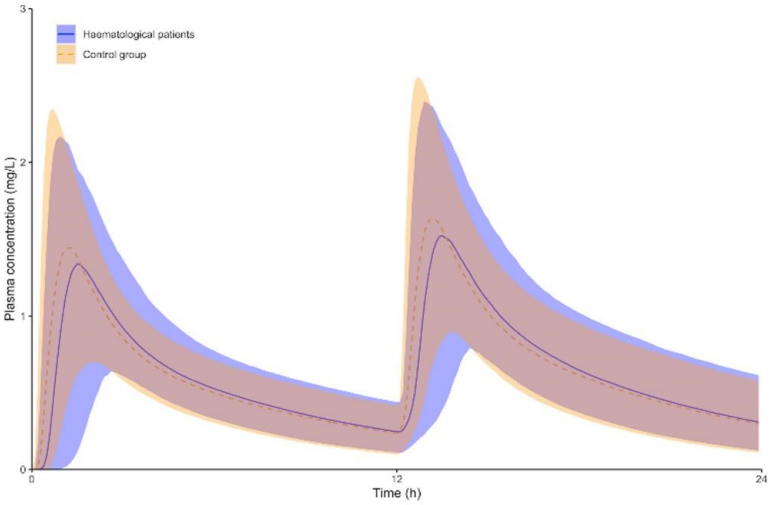


Figure 1. Concentration–time curve [median (solid line and dashed line) and 95% prediction interval (shaded areas)] for haematological patients (blue) and a control group of healthy volunteers (orange) after twice daily oral ciprofloxacin 500 mg. Data based on simulations with *n* = 2500 per subgroup. The median simulated time to ciprofloxacin C_{max} is 1.5 h for haematological patients and 1.2 h for the control group.

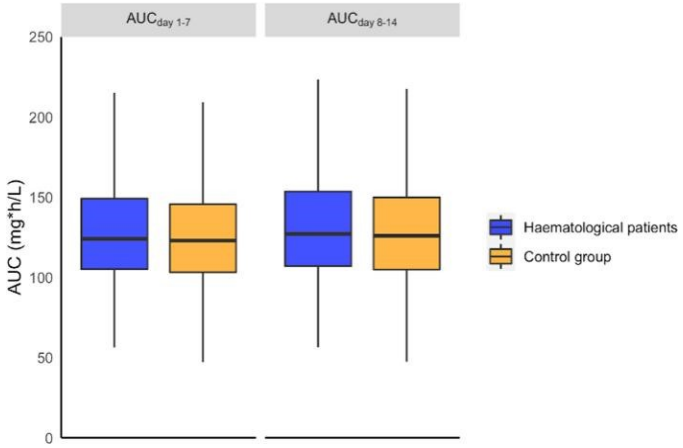


Figure 2. Boxplots illustrating similar cumulative systemic exposure in the first- and second week of therapy ($AUC_{day\ 1\text{-}7}$ left panel, $AUC_{day\ 8\text{-}14}$ right panel) for haematological patients (blue) and the control group of healthy volunteers (orange). Data are based on Monte Carlo simulations with *n* = 2500 per subgroup after the standard of care dosing regimen of 500 mg PO twice daily.

Discussion

Ciprofloxacin pharmacokinetics in patients with haematological malignancies and mild mucositis capable of oral intake and healthy volunteers is comparable. Oral absorption remains adequate during the whole chemotherapy treatment course, even in the second week after high-dose chemotherapy when mucositis is most severe. However, oral absorption was slower in haematological patients. Therefore, haematological patients with mild-to-moderate mucositis capable of oral intake can receive orally administered ciprofloxacin as Gram-negative infection prophylaxis.

We included 47 patients with a wide variety of haematological malignancies and a broad range in severity of underlying disease at different timepoints in their treatment course. The majority of participants capable of oral ciprofloxacin intake had clinically mild mucositis based on the DGS and as a result, few data on oral absorption and clearance of ciprofloxacin could be collected in patients with clinically moderate mucositis and no data were collected in patients with clinically severe mucositis. Patients unable to take oral medication due to progression or worsening of mucositis or developing fever were switched to intravenous therapy by their treating physician. There are no strict criteria for when to switch from oral to intravenous therapy. However, our results indicate that the clinical decision of the treating physician to switch patients from oral to intravenous therapy was at least not too late, as no underexposure was observed. The majority of haematological patients used concomitant medication that could accelerate or delay the oral absorption process. Although the use of concomitant medication delaying oral absorption may have contributed to the observed increased time to C_{max} in haematological patients compared with healthy volunteers, the use of delaying concomitant medication was not a statistically significant covariate. Most importantly, only one patient used concomitant medication that could decrease bioavailability. Therefore, it is unlikely that the absence of a correlation of mucositis with ciprofloxacin exposure is attributable to the use of concomitant medication.

In our study the degree of mucositis was assessed using the most adequate and feasible clinical scores and biomarkers. Haematological patients suffered from mild mucositis in the opinion of the treating physician and were capable of oral ciprofloxacin intake. DGS corresponded with mild-to-moderate mucositis while citrulline plasma concentration ranged from values corresponding with normal values to severe mucositis. A mucositis scoring mismatch was observed in nine patients (19%) as citrulline plasma concentration showed severe mucositis (nadir <10 µmol/L) while DGS suggested mild (n = 8) or moderate (n = 1) mucositis. Four of these patients did not switch to intravenous therapy at any time during their treatment course, indicating no development of clinically severe mucositis in the opinion of the attending physician. Nevertheless, uncertainty remains as to whether patients with mild mucositis according to the DGS actually showed mild mucositis in the small intestine. As patients were capable of oral intake and the physician judged mucositis to be generally mild, we chose to draw conclusions regarding mild-to-moderate mucositis despite citrulline plasma concentrations corresponding with severe mucositis. Observations in patients treated with intravenous antibiotics who were subsequently switched back to oral ciprofloxacin after clinical improvement were adequately described by our model. This may suggest ciprofloxacin oral absorption is not significantly altered in patients with a temporarily worsening in their clinical condition. The DGS was retrospectively scored based on data available in the electronic patient registry. Possibly, some components of the DGS may have been incompletely registered which could have led to an underestimation of mucositis severity using the DGS which is a limitation of our study. Also, citrulline was measured only once for participants in Cohort 1. An important strength of our

study is the comparison of ciprofloxacin PK data in haematological patients with data from 28 healthy individuals as a PK reference standard, to compensate for the lack of a formal PK/PD target for Gram-negative prophylaxis using ciprofloxacin.

Three previous case-series reported contradictory results on exposure of orally administered ciprofloxacin in patients with haematological malignancies.[18-20] Two studies found no difference in drug concentration between haematological patients with mucositis and data from the literature, although another study found a reduced drug concentration in patients with haematological malignancies.[18-20] Since these reports observed only 8, 6 and 5 patients, the external validity of the respective case-series is limited.[18-20] Moreover, two of the three case-series did not report severity of mucositis at all, while one study focused on severity of oral mucositis and, in contrast to our study, the role of biomarkers was not evaluated beforehand. In order to capture the severity of mucositis at the site of absorption, GI-mucositis scores and biomarkers were analysed concomitantly.

Ciprofloxacin is subject to OATP1 and OAT3 carrier-mediated absorption.[32] Disruption of the mucosa could negatively impact OATP1 and OAT3 carrier capacity but at the same time mucosal barrier function may be impaired. As a result, both an increased and decreased rate of absorption and bioavailability could be anticipated. Haematological patients showed an increased time to C_{max} although this was not associated with a significant alteration in bioavailability. Both active and passive processes play a role in ciprofloxacin absorption. Therefore, the slightly longer time to C_{max} in haematological patients could theoretically be caused by a negative impact on active absorption because of mucositis while the net-influence on bioavailability remains negligible.

In patients with severe mucositis treated with IV ciprofloxacin, further research may be needed to clarify whether destruction of the mucosa impacts the trans-epithelial intestinal secretion route of ciprofloxacin, as ciprofloxacin clearance could still be altered.

In conclusion, we found no significant influence of mild mucositis on ciprofloxacin bioavailability or clearance. This study supports oral dosing of ciprofloxacin 500 mg twice daily as Gram-negative infection prophylaxis in haematological patients with mild-to-moderate mucositis capable of oral intake.

Acknowledgements

The authors thank the patients who were willing to take part in this study, the nursing staff of the haematology departments for their help, Marcel Pistorius and his colleagues from the Laboratory of Clinical Pharmacology for ciprofloxacin concentration measurement, the staff of the clinical laboratory for identifying waste material of previously collected blood samples.

Funding

This research was funded by a research grant from Tergooi MC, Hilversum.

Transparency declarations

R.J.M.B. declares no interest with regards to this work. Outside of this work, he has served as 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 the Radboud University Medical Center. P.D.v.d.L. declares membership of the compliance committee of STIZON and is treasurer of the Dutch Working party on Antibiotic Policy (SWAB). The remaining authors have none to declare.

Author contributions

K.v.R. and S.d.V. wrote the manuscript; S.d.V., E.M. and K.v.R. collected the data. K.v.R. performed the data analysis under supervision of C.K., R.v.H. and R.J.M.B; R.v.H., P.v.d.L., S.H.T., E.M., R.A.A.M., N.M.A.B., C.A.J.K., R.A.A.M. and S.E.G. critically reviewed all versions of the manuscript. R.v.H., R.J.M.B. and S.E.G. supervised the final version of the manuscript.

References

1. Bucaneve G, Castagnola E, Viscoli C et al. Quinolone prophylaxis for bacterial infections in afebrile high risk neutropenic patients. Haematologica 2007; 5-12.
2. Cullen M, Steven N, Billingham L et al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. N Engl J Med 2005; 10: 988-98.
3. Gafter-Gvili A, Fraser AMD, Paul MPHM et al. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Ann Intern Med 2005; 12: 979-95.
4 Mikulska M, Averbuch D, Tissot F et al. Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines. J Infect 2018; 1: 20-37.
5. FDA. Ciprofloxacin prescribers information. 2016; Available at: https://www.accessdata.fda.gov/drugsatfda_docs/Label/2016/019537s086lbl.pdf
6. Blijlevens NM, Donnely JP, de Pauw BE. Empirical therapy of febrile neutropenic patients with mucositis: challenge of risk-based therapy. Clinical Microbiology and Infection 2001; 7:47-52.
7. Peterson DE, Boers-Doets CB, Bensadoun RJ et al. Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Annals of Oncology 2015; 26 :139-51.
8. Jansen AME, Muilwijk EW, van der Velden WJFM et al. Posaconazole bioavailability of the solid oral tablet is reduced during severe intestinal mucositis. Clinical Microbiology and Infection 2022; in press.
9. Kovanda LL, Marty FM, Maertens, J et al. Impact of Mucositis on Absorption and Systemic Drug Exposure of Isavuconazole. Antimicrob Agents Chemother 2017; 61: 1-10.
10. Blijlevens NM, Donnely JP, Naber AHJ et al. A randomised, double-blinded, placebo-controlled, pilot study of parenteral glutamine for allogeneic stem cell transplant patients. Supportive Care in Cancer 2005; 13: 790-6.
11. van Vliet MJ, Tissing WJE, Rings EHHM et al. Citrulline as a marker for chemotherapy induced mucosal barrier injury in pediatric patients. Pediatric Blood and Cancer 2009; 53: 1188-94.
12. Blijlevens NM, van't Land B, Donnelly JP et al. Measuring mucosal damage induced by cytotoxic therapy. Supportive Care in Cancer 2004; 12: 227-233.
13. van der Velden WJFM, Herbers AHE, Brüggemann RJM et al. Citrulline and albumin as biomarkers for gastrointestinal mucositis in recipients of hematopoietic SCT. Bone Marrow Transplant 2013; 48: 977-81.
14. Kuiken NNS, Rings EHHM, Blijlevens NMA et al. Biomarkers and non-invasive tests for gastrointestinal mucositis. Supportive Care in Cancer 2017; 25: 2933-2941.
15. Crenn P, Messing B, Cynober L. Citrulline as a biomarker of intestinal failure due to enterocyte mass reduction. Clinical Nutrition 2008; 27: 328-39.
16. Crenn P, Vahedi K, Lavergne-Slove K, et al. Plasma citrulline: A marker of enterocyte mass in villous atrophy-associated small bowel disease. Gastroenterology 2003; 124: 1210-9.
17. Parkman HP, Hasler WL, Fischer RS. American Gastroenterological Association technical review on the diagnosis and treatment of gastroparesis. Gastroenterology 2004; 127: 1592-1622.
18. Gattis WA, Petros WP, Pickard WW et al. A prospective, open-label study of single-dose ciprofloxacin absorption after chemotherapy in patients with malignancy. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy 1997; 17: 836-40.
19. Smith GM, Leyland MJ, Farrel ID et al. A clinical, microbiological and pharmacokinetic study of ciprofloxacin plus vancomycin as initial therapy of febrile episodes in neutropenic patients. J Antimicrob Chemother 1988; 21: 647-55.
20. Johnson EJ, MacGowan AP, Potter MN et al. Reduced absorption of oral ciprofloxacin after chemotherapy for haematological malignancy. J Antimicrob Chemother 1990; 25: 837-42.
21. Muilwijk EW, Maertens JA, van der Velden WJFM et al. Pharmacokinetics of extended dose intervals of micafungin in haematology patients: optimizing antifungal prophylaxis. Journal of antimicrobial chemotherapy 2018; 73: 3095-3101.

22. van Rhee KP, Smit C, Wasmann RE et al. Ciprofloxacin pharmacokinetics after oral and intravenous administration in (morbidly) obese and non-obese individuals; a prospective clinical study. Clinical pharmacokinetics 2022; in press.
23. Inker LA, Schmid CH, Tighiouart H et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012; 367: 20-9.
24. Levey AS, Coresh J, Greene T et al. 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.
25. 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: 863-871.
26. International Council for harmonization of technical requirements for pharmaceuticals for human use. Good clinical practice, 2016. https://ichgcp.net/
27. WMA. Declaration of Helsinki - Ethical principles for medical research involving human subjects. 2013. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
28. de Vroom SL, Pistorius MCM, Bijleveld YA et al. Development and Validation of a Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) Assay for the Determination of Total and Unbound Ciprofloxacin Concentrations in Human Plasma. Therapeutic drug monitoring 2022; in press.
29. Demacker PN, Beijers AM, van Daal H et al. Plasma citrulline measurement using UPLC tandem mass-spectrometry to determine small intestinal enterocyte pathology. Journal of Chromatography B 2009; 877: 387-92.
30. Beal S, Sheiner L, Boeckmann A. NONMEM Users Guide - Part IV. 2018.
31. Keizer RJ. Modeling and Simulation Workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose. CPT: Pharmacometrics and Systems Pharmacology 2013; 2: e50.
32. Arakawa H, Shirasaka Y, Haga M et al. Active intestinal absorption of fluoroquinolone antibacterial agent ciprofloxacin by organic anion transporting polypeptide, Oatp1a5. Biopharmaceutics and Drug Disposition 2012; 33: 332-41.

Supplementary data

Table S1. Study procedures and handling of samples

	Cohort I	**Cohort II**	**Cohort III**	**Control group**
Study acronym		MATADOR	PIRANA	AMIGO
Site	Amsterdam University Medical Center, Amsterdam	Radboud University Medical Center, Nijmegen	Radboud University Medical Center, Nijmegen	Radboud univserity Medical Center and st Antonius hospital
Design	Prospective observational cohort	Randomised open-label multiple-dose intervention study (micafungin)	Randomised open-label, multiple-dose, multiple-dose level intervention study (posaconazole)	Open-label prospective pharmacokinetic intervention study (ciprofloxacin)
Sampling scheme	2 peak samples, 1 trough sample, 1 random sample. All collected within 72 hours >7 days after conditioning. Additional scavenged sampling from left-over material from routine monitoring	Daily trough sample at 8:00 AM. Rich sampling on day 4 or 5 and day 8 at: t= 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24 after micafungin administration.	Daily trough sample at 8:00 AM. Rich sampling on day 7, 12 and 16 at: t= 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 18, 24 after posaconazole administration.	Dense sampling until 12 hours after administration with 11 samples after IV administration, 15 samples after PO administration and 17 samples after semi-simultaneous administration.
Handling of samples	Ciprofloxacin: centrifuged the same day Citrulline: stored on ice and centrifuged within 2 hours after collection	Ciprofloxacin: centrifuged the same day Citrulline: not studied	Ciprofloxacin: Centrifuged the same day Citrulline: stored on ice and centrifuged within 2 hours after collection	Ciprofloxacin: Centrifuged the same day
Storage of samples	-80°C until analysis	-80°C until analysis	-80°C until analysis	-80°C until analysis
Albumine monitoring	Routine care, 8:00 AM	Routine care, 8:00 AM	Routine care, 8:00 AM	Not studied
Citrulline monitoring	Obtained once, simultaneously with the first peak sample	Not studied	Daily at 8:00 AM	Not studied
DGS monitoring	Every PK day. Retrospectively collected from EPR	Every PK day. Retrospectively collected from EPR	Every PK day. Retrospectively collected from EPR	Not studied

DGS: Daily Gut Score, EPR: Electronic Patient Registry

Table S2. Description of pharmacokinetic data

	Cohort I	Cohort II	Cohort III	Control group	All haematological patients (Cohort 1,2,3)
Study acronym		MATADOR	PIRANA	AMIGO	
Patients (n)	41	2	4	28	47
Ciprofloxacin route of administration	PO	PO	PO	PO and IV	
Samples (n)	157	51	42	Total: 391 PO: 213 IV :178	250
Samples per patient (n)	3.8	25.5	10.3	PO: 7.6, IV: 6.4	5.3
Peak samples (n (%)) (0-2h after administration)	58 (37%)	15 (29%)	9 (21%)	PO: 92 (43%) IV: 45 (25%)	82 (33%)
Midway samples (n (%)) (2-10 h after administration)	41 (26%)	21 (41%)	10 (24%)	PO: 111 (52%) IV: 116 (65%)	72 (29%)
Trough samples (n (%)) (10-14h after administration)	54 (34%)	8 (16%)	10 (24%)	PO: 10 (5%) IV: 17 (10%)	72 (29%)
Wash-out samples (n (%)) (14-28h after administration)	4 (3%)	7 14%)	13 (31%)	PO: 0 (0%) IV: 0 (0%)	24 (10%)
Sampling at days after start of conditioning (median – IQR)	6 (3-12)	11 (7-15)	4 (1-7)	Not studied	6 (3-11)
Citrulline samples (n)	41	Not studied	24	Not studied	65
Albumin samples (n)	82	20	9	Not studied	111

IV: intravenous administration, PO: oral administration

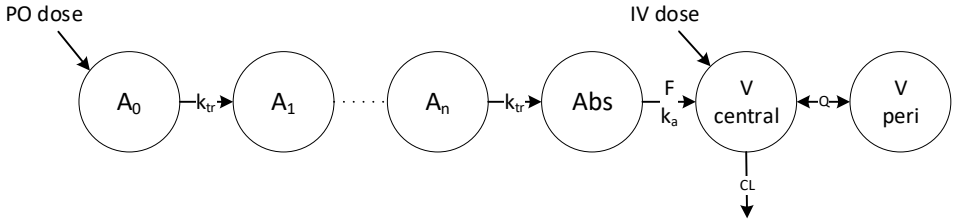


Figure S1. Structure of the pharmacokinetic model.
Abs: Absorption compartment, A_n: Transitcompartment (n), Cl: Clearance from the central compartment, F: Bioavailability, k_a: absorption rate constant, k_{tr}: transit rate constant, Q: Intercompartmental clearance, V central: Central volume of distribution, V peri: Peripheral volume of distribution.

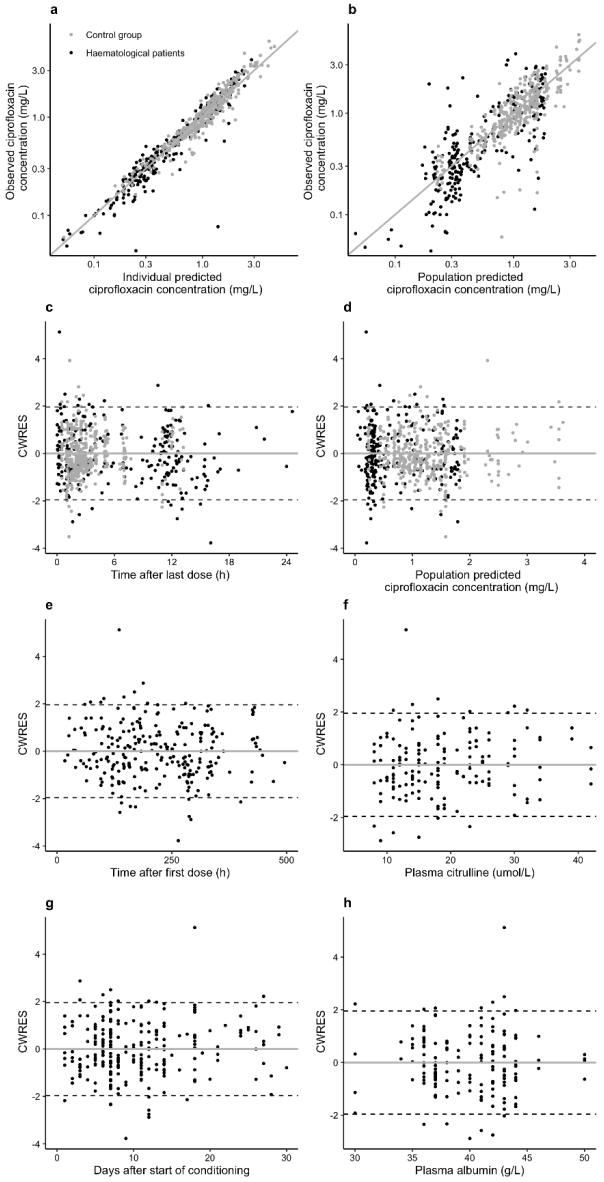


Figure S2. Diagnostic plots of the final pharmacokinetic model.
Diagnostic plots of the final model for haematological patients (black dots) and the control group (grey dots).
a: Individual predicted plasma concentrations versus observed plasma concentrations
b: Population predicted plasma concentrations versus observed plasma concentrations
c: CWRES versus time after last dose
d: CWRES versus Population prediction
e: CWRES versus time after first dose
f: CWRES versus Plasma citrulline
g: CWRES versus days after start of conditioning
h: CWRES versus plasma albumin
The grey line indicates the line of identity and the dashed lines indicate the range within 95% of the observations are expected to fall. For plots e, f, g and h only haematological patient data is presented.

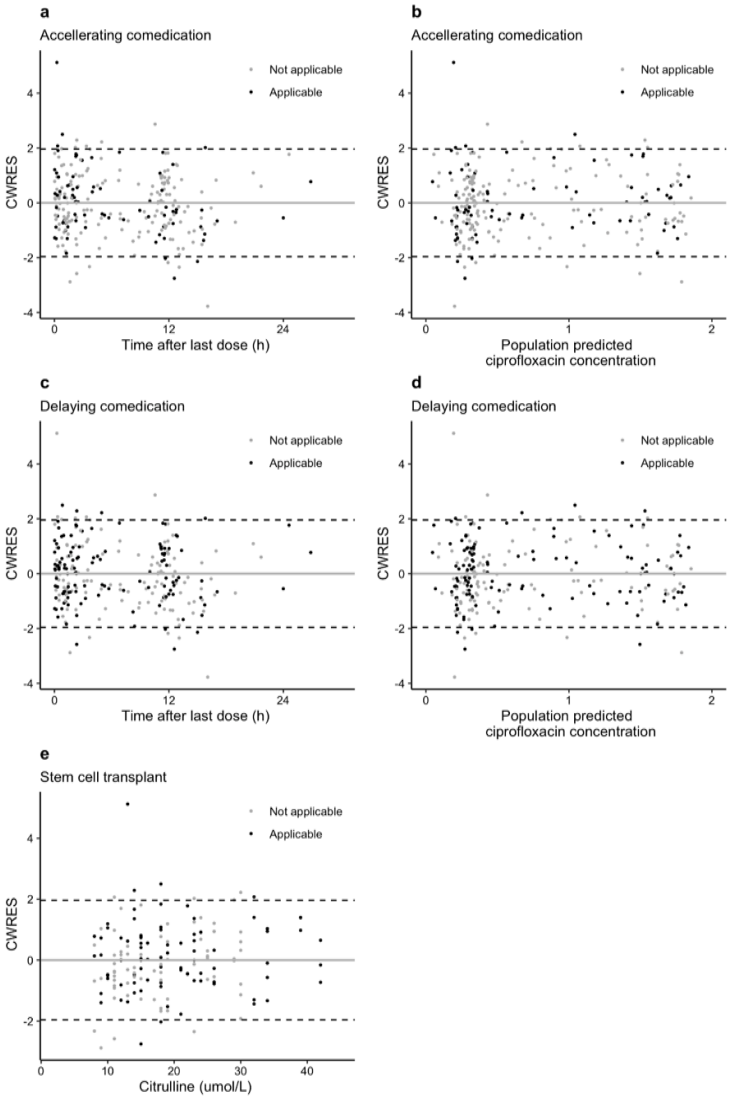


Figure S3. Diagnostic plots for concomitant medication use and stem cell transplant.
Conditional weighted residuals (CWRES) plots of the final model for potential covariates in haematological patients showing trends versus time (a, c, e), predicted plasma concentration (b, d, f) or citrulline plasma concentration (g). Black dots represent observations where the potential covariate is applicable, grey dots represent observation where the potential covariate is not applicable.
a: Use of comedication potentially accelerating oral absorption, residuals versus time after dose
b: Use of comedication potentially accelerating oral absorption, residuals versus PRED
c: Use of comedication potentially delaying oral absorption, CWRES versus time after dose
d: Use of comedication potentially delaying oral absorption, CWRES versus PRED
e: CWRES versus citrulline plasma concentration for patients receiving stem cell transplant
The grey line indicates the line of identity and the dashed lines indicate the range within 95% of the observations are expected to fall.

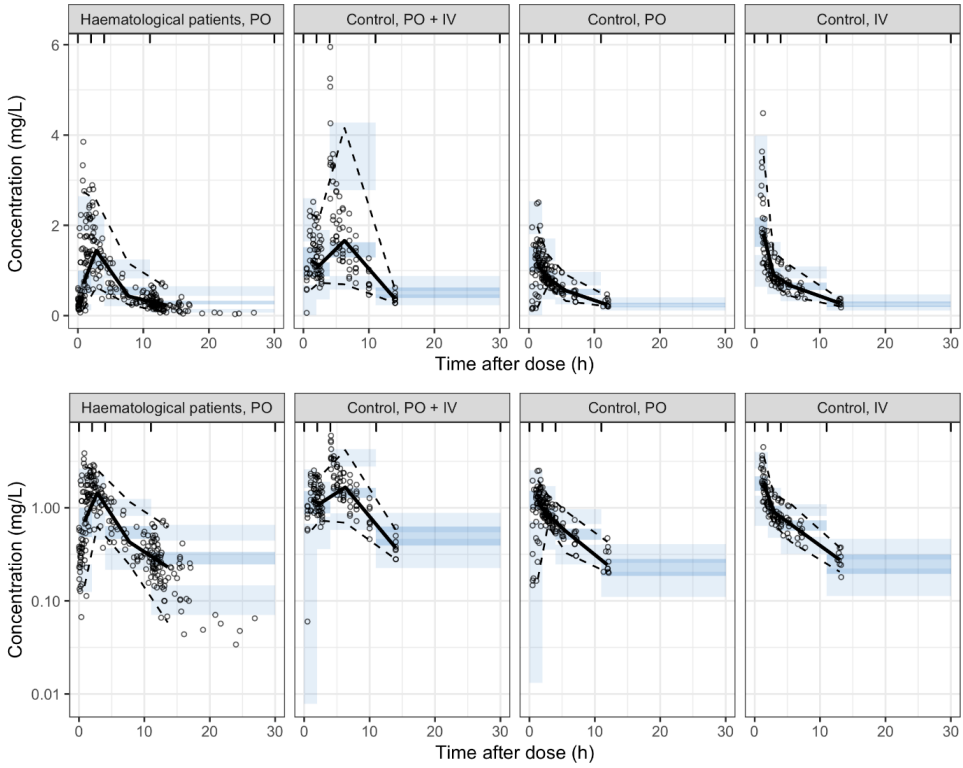


Figure S4. Visual Predictive Check of the final model.
Visual predictive check of the final model stratified by subgroup (Haematological patients n=47, control PO+IV n=8, Control PO n=10, Control IV n=10) on linear scale at the top and on logarithmic scale at the bottom. The observed data are shown as 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. PO represents 500 mg oral ciprofloxacin administration, PO+IV represents semi-simultaneous 500 mg oral administration followed by 400 mg IV infusion 3 hours after the oral administration, IV represents 400 mg ciprolfoxacin IV infusion.

Chapter 7

General discussion

General discussion

Appropriate antibiotic use is beneficial for patients' clinical outcome, leads to a decrease in antibiotic resistance rates and results in lowering of healthcare costs.[1-5] Quality indicators measure quality of care, such as appropriate antibiotic use. Such quality indicators have been defined for the measurement of appropriate antibiotic use in the treatment of bacterial infections in the hospital.[6] One of these nine validated quality indicators is to adjust the antibiotic dose to renal function. The antibiotic dose reduction for patients with impaired renal function is standard of care as incorporated in all clinical guidelines.[7-9] The aim of this dose reduction is to prevent accumulation of the drug, with risk for toxicity and thus patient harm, and to achieve antibiotic drug exposure equivalent to that in patients with adequate renal function receiving the regular dose, i.e., achieving bioequivalence.[10,11] However, this dose reduction is often not applied in clinical practice and the question arises why this recommendation is not followed.[12] First, inconsistency exists between different guidelines in the cut-off value of renal function below which the dose per antibiotic should be reduced.[13] Additionally, the degree of the dose reduction is inconsistent between clinical guidelines.[13] Second, prescribers may fear therapeutic failure when reducing the dose.[14,15]

The aim of this thesis was to investigate the adequacy of the guideline-recommended dose reduction of renally cleared antibiotics for patients with impaired renal function. We hypothesized that this dose reduction is mainly based on simulated and retrospective data and is not prospectively validated in clinical practice, with concomitant risk of under- or overexposure. Therefore, we systematically reviewed all literature ever published since the discovery of the first antibiotic in 1928 on antibiotic dose reduction (**Chapter 2**).[16] Additionally, the adequacy of the recommended dose reduction for ciprofloxacin and ceftazidime was prospectively investigated in clinical practice by measuring drug exposure (**Chapter 4 and 5**).[17,18] Furthermore, to be able to fully investigate the adequacy of the administered antibiotic dose, one should investigate not only clearance (mainly determined by renal function in case of renally cleared antibiotics), but also that other pharmacokinetic parameter determining drug exposure: the bioavailability. In case of oral administration, bioavailability determines the amount of the drug that is being absorbed and thereby a large part of drug exposure. Therefore, the absorption of oral ciprofloxacin was investigated in neutropenic patients with haematological malignancies and mucositis (**Chapter 6**).[19] We hypothesized that systemic drug exposure in these patients is changed compared to patients without mucositis. The rationale behind this hypothesis is that mucositis may mean the loss of intestinal integrity and thus may affect the absorption of orally administered drugs and therefore drug exposure. Whether this could end up in enhanced absorption and higher exposure or in compromised absorption and therefore lower exposure of ciprofloxacin was unclear.

A pre-requisite to investigate exposure to antibiotics in clinical practice is a validated method to measure concentrations of these antibiotics in body fluids. This was done by the development and validation of a liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay for the determination of ciprofloxacin plasma concentrations (**Chapter 3**).[20]

The ultimate goal was to strengthen the evidence underlying the quality indicator for appropriate antibiotic use on 'adjusting the dose to renal function' and provide evidence that adherence to that quality indicator actually leads to appropriate antibiotic use and therefore to improvement of patients' clinical outcome, decrease in antibiotic resistance rates and lowering of healthcare costs.

This discussion chapter includes a reflection of the main findings, clinical implications and methodological considerations of the results of this thesis. Finally, further steps and remaining

barriers for improving appropriate antibiotic use are discussed and directions for future research are provided.

Main findings

Adequacy of the guideline-recommended dose reduction of renally cleared antibiotics for patients with impaired renal function

Chapter 2 provides an overview of the available evidence on the guideline-recommended dose reduction of all renally cleared antibiotics for patients with impaired renal function. Although very broad inclusion criteria were applied, only 27 studies could be identified measuring drug exposure after dose reduction of renally cleared antibiotics. Most studies were about β-lactam antibiotics and best evidence was available for meropenem.

Meropenem is part of a special group of β-lactam antibiotics; the carbapenems, which are highly effective against Gram-negative and Gram-positive drug-resistant bacteria. As such, carbapenems are typically mentioned as antibiotics of last resort. The World Health Organisation (WHO) lists meropenem as an essential medicine.[21] Four studies on meropenem were included, of which two studies were of good quality. Drug exposure for meropenem is 158% to 286% higher in patients with impaired renal function receiving the guideline-recommended reduced dose compared to patients with adequate renal function receiving the regular dose. Therefore, the currently recommended dose of meropenem for patients with impaired renal function could be reduced even more.

Surprisingly, only one good-quality study for all other renally cleared antibiotics than meropenem, could be identified. It appears that guideline-recommended dose reductions are based on extrapolations from small studies, mostly ones investigating the change in pharmacokinetic parameters after a single full, unadjusted dose administered to patients with impaired renal function. Equivalence in drug exposure, PK/PD target attainment and/or clinical outcome between patients with impaired renal function receiving the guideline-recommended reduced dose and patients with adequate renal function receiving the regular dose have not been investigated for the vast majority of renally cleared antibiotics. Additionally, inconsistency exists between different studies in the cut-off value of renal function below which the dose per antibiotic should be reduced and in the degree of the dose reduction, even between studies investigating the same antibiotic. Therefore, it is not remarkable that inconsistency exists between guideline recommendations, since inconsistency already exists on the definition of impaired renal function on study level.

Liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay for the determination of total and unbound ciprofloxacin plasma concentrations

To be able to investigate the adequacy of currently used antibiotic doses one needs assays measuring antibiotic plasma concentrations. Surprisingly, assays measuring the unbound ciprofloxacin plasma concentrations are scarce, although unbound ciprofloxacin is responsible for antibacterial effects. Therefore, we developed a rapid, reproducible, and sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay for the determination of total and unbound ciprofloxacin concentrations in plasma, which is described in **Chapter 3**. The developed assay was precise, accurate, and fully validated according to the U.S. Food and Drug Administration guidelines.[22] Additionally, the use of different blood collection tubes for the measurement of ciprofloxacin plasma concentrations was validated. This facilitates the use of left-over material from samples already collected for routine clinical care in random blood collection tubes. The use of this so-called waste material enables performing PK/PD target attainment studies with minimal burden for the patient and in a sustainable way (one tube used for two purposes), as for example executed in **Chapter 4**, where 81% of all collected samples originated from waste material.

Pharmacokinetic/pharmacodynamic (PK/PD) target attainment of ciprofloxacin

In **Chapter 4** PK/PD target attainment of ciprofloxacin was investigated in patients with adequate and impaired renal function receiving regular and guideline-recommended reduced doses, in a prospective observational study. Thus, we attempted to prospectively validate the recommended 50% dose reduction of ciprofloxacin for patients with impaired renal function. The PK/PD efficacy target ($AUC_{0\text{-}24}$/MIC ≥125) is not attained in the majority of the patients, both for patients with adequate and impaired renal function, when applying the clinical breakpoint MIC for *Escherichia Coli* (*E. Coli*) of 0.25 mg/L. The risk of not attaining the target appears to be highest for patients with impaired renal function, as drug exposure is significantly lower in these patients. In conclusion, the results of the study show that the current dose reduction of ciprofloxacin in patients with impaired renal function is invalid. If one is aiming to attain the currently recommended PK/PD efficacy target, the dose of ciprofloxacin should be increased, particularly for patients with impaired renal function.

Pharmacokinetic/pharmacodynamic target attainment of ceftazidime

In **Chapter 5** PK/PD target attainment of ceftazidime was investigated in patients with adequate and impaired renal function receiving regular and guideline-recommended reduced doses, in a multi-centre prospective observational study. Thus, we attempted to prospectively validate the recommended dose reduction for patients with impaired renal function. No differences in drug exposure or PK/PD target attainment ($50\%T_{0\text{-}24}$ >MIC), when applying the clinical breakpoint MIC for *Pseudomonas Aeruginosa*, were observed between the different renal function groups. In conclusion, the guideline-recommended dose reduction of ceftazidime seems to be appropriate.

Impact of mucositis on absorption of ciprofloxacin

In **Chapter 6** the impact of gastro-intestinal (GI)-mucositis on absorption of orally administered ciprofloxacin was prospectively investigated in patients with haematological malignancies admitted to two academic medical centres. These patients frequently endure neutropenia and GI-mucositis after high-dose chemotherapy and therefore, ciprofloxacin is used as Gram-negative infection prophylaxis.[23,24] Mucositis means the loss of intestinal integrity and may affect the absorption of orally administered drugs and therefore drug exposure.[25,26] Whether this could lead to enhanced absorption and higher exposure or to compromised absorption and therefore lower exposure of ciprofloxacin was unclear. The results show that oral absorption remains adequate during the whole chemotherapy treatment course when the patient was capable of oral intake, which was based on the clinical decision of the treating physician, even in the second week after high-dose chemotherapy when mucositis is expected to be most severe.[25,26] Results indicate no risk of under- or overexposure of ciprofloxacin when the GI-tract is affected by mucositis.

Reflections on findings and clinical implications

Knowledge gap on the guideline-recommended antibiotic dose reduction

We have identified the lack of prospective validation studies on the guideline-recommended antibiotic dose reduction for patients with impaired renal function (**Chapter 2**).[16] Despite this lack of validation, these dose reductions are recommended globally on a daily basis. These dose reductions have different effects on antibiotic concentrations in clinical practice, depending on which antibiotic is prescribed.[16-18] For meropenem the dose does not seem to be reduced enough, leading to higher antibiotic concentrations in patients with impaired renal function and possibly leading to accumulation and toxicity-related problems (**Chapter 2**).[16] On the other hand, for ciprofloxacin the dose seems to be reduced too much, as we showed in our own patient population (**Chapter 4**), leading to lower antibiotic concentrations compared to patient with adequate renal function receiving the regular dose.[17] This may lead to worse clinical outcome and promoting antibiotic resistance due to subtherapeutic concentrations. For ceftazidime the dose seems to be adequate, since the PK/PD efficacy target is attained in most patients and antibiotic drug exposure is comparable between patients with adequate and impaired renal function receiving regular and reduced doses of ceftazidime (**Chapter 5**).[18]

Differences in pharmacokinetic properties of these antibiotics may explain the different effects on antibiotic concentrations, as illustrated in Table 1.[8,9,27-36] For instance, the degree of renal clearance in the total elimination is the highest for both ceftazidime and meropenem, up to 99% and 98%, respectively. For ciprofloxacin this varies between 66% and 75%. The rest is eliminated through the liver, bile and intestine. It may seem that all antibiotics that are excreted primarily and almost exclusively through the kidneys require a dose reduction as currently recommended, or even more, because no compensating mechanism of excretion through the liver and biliary system exists for these antibiotics. All antibiotics that are excreted primarily but not exclusively through the kidneys may require a dose reduction lower than currently recommended. The degree of dose reduction may be overestimated since the other elimination pathway may compensate for the reduced renal clearance. Interestingly, previous studies have actually shown that non-renal clearance of ciprofloxacin increases in patients with impaired renal function to compensate for the reduced renal clearance.[37-39] Additionally, the results of our study showed that there was a non-linear association between renal function and ciprofloxacin clearance, indicating that the decrease in renal function is not directly proportional to the decrease in ciprofloxacin clearance (Fig. 1) (**Chapter 4**).

For all renally cleared antibiotics, with the exception of meropenem, ciprofloxacin and ceftazidime, the effect of renal impairment on antibiotic concentrations in clinical practice remains unclear, since a lack of prospective validation exists for the dosing recommendations of all these other antibiotics.

Table 1. Pharmacokinetic parameters of meropenem, ciprofloxacin and ceftazidime[8,9,27-36]

Pharmacokinetic properties	Meropenem	Ciprofloxacin	Ceftazidime
Bioavailability	N.A.	70% - 80%[8,9]	N.A.
Volume of distribution	0.39 l/kg[27]	2 – 3 l/kg[8,9]	0.31 l/kg[29]
Metabolism	Hydrolysis of the β-lactam ring generating a microbiologically inactive metabolite[27,28]	Partially metabolized to at least four metabolites[8,9]	None[29]
Elimination route	98% urine 2% feces[27,28]	67% - 75% urine 25% - 33% feces[8,9]	99% urine 1% feces[29,30]
Half-life (T ½)	1 – 1.5 hours[27,28]	4 – 7 hours[8,9]	2 hours[29,30]
Plasma protein binding	2%[28]	20% – 30%[9]	10%[30]
PK/PD target	T > MIC[31]	AUC/MIC[31-33]	T > MIC[34-36]
Percentage of variability between patients in drug clearance that can be explained by GFR in the developed population PK models in Chapter 4 (ciprofloxacin) and Chapter 5 (ceftazidime)	*	12%[17]	73%[18]

N.A., not applicable, because of intravenous administration
*No clinical data on meropenem was collected in this thesis

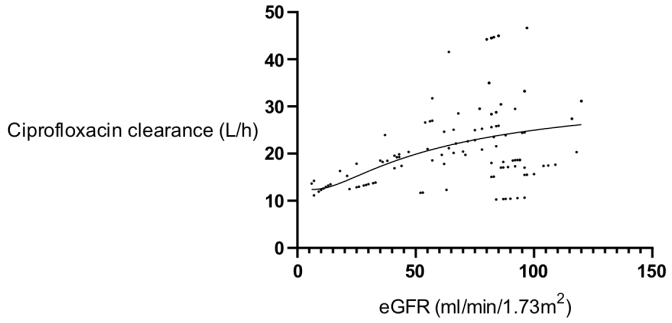


Fig. 1. Ciprofloxacin clearance against eGFR of individual patients. The solid line represents the estimated relationship according to [CL=21.1*(eGFR/70)$^{0.277}$][17]

Treatment failure of ciprofloxacin with the standard dosing regimen

Physicians should be aware of treatment failure of ciprofloxacin particularly in patients with impaired renal function receiving the recommended reduced dose and who are treated for infections caused by bacteria at or just below the susceptibility spectrum.

As seen in Fig. 2, the number of patients attaining the PK/PD efficacy target is dependent on the minimal inhibitory concentration (MIC) of the bacteria.[17] For low MIC values up to 0.0625 mg/L the vast majority of the patients attains the efficacy target. However, for higher MIC values from 0.125 mg/L to 0.25 mg/L many patients do not attain the PK/PD efficacy target.

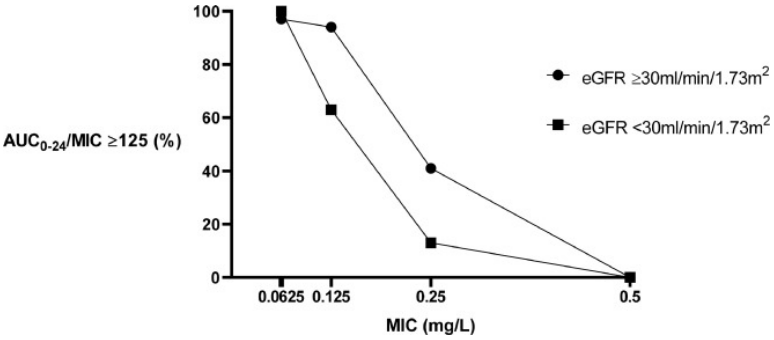


Fig. 2. Percentage of patients attaining the ciprofloxacin pharmacokinetic/pharmacodynamic (PK/PD) target of AUC_{0-24}/MIC ≥125 at different MIC values (0.0625, 0.125, 0.25 and 0.5 mg/L) for patients with adequate renal function (eGFR ≥30 mL/min/1.73m^2, with most frequently prescribed ciprofloxacin dose of 500 mg p.o. q12h) and for patients with impaired renal function (eGFR <30 mL/min/1.73m^2, with most frequently prescribed ciprofloxacin dose of 250 mg p.o. q12h).[17]
AUC_{0-24}/MIC, ratio of 24-h area under the concentration–time curve and the minimum inhibitory concentration (MIC); eGFR, estimated glomerular filtration rate; p.o., orally; q12h, every 12 h.

This is remarkable, since the MIC breakpoint of *E. Coli*, for which ciprofloxacin is one of the most important antibiotic treatments, is 0.25 mg/L.[40] This means that identified *E. Coli* bacteria with MIC values up to 0.25 mg/L are labelled as susceptible, which means that the treating physician assumes that ciprofloxacin in regular doses is adequate for the treatment of infections caused by *E. Coli*. However, results of our study have shown that the PK/PD efficacy target is often not attained for bacteria with an MIC > 0.0625 mg/L and physicians may be unaware of the possibility of treatment failure of that infection with the standard dosing regimen of ciprofloxacin.

Therefore, a discrepancy seems to exist between labelling of bacteria as susceptible with the standard dosing regimen of ciprofloxacin, as the PK/PD efficacy target for the treatment of that bacteria is frequently not attained. To overcome this discrepancy, three main options exist:

1. To lower current MIC breakpoints
2. To increase the dose
3. To use therapeutic drug monitoring

This will be explained in the following paragraphs.

Lower MIC breakpoints

The first possibility to reach more often the PK/PD efficacy target for the treatment of bacterial infections is to lower the MIC-value breakpoint of *Enterobacteriaceae* and label bacteria with MIC values of 0.25 mg/L as resistant (while currently labelled as sensitive).[40] Likewise, for example, *Pseudomonas aeruginosa* with an MIC-value breakpoint of 0.5 mg/L could be labelled as resistant (also currently labelled as sensitive).

This will cause more adequate PK/PD target attainment for bacteria being labelled as sensitive. However, more bacteria will be labelled as resistant for treatment with ciprofloxacin and infections

caused by those bacteria will then likely need other antibiotic treatment, possibly even with antibiotics of last resort.

The Clinical and Laboratory Standards Institute (CLSI), the other important global organization establishing interpretive criteria for in vitro susceptibility data, has lowered the MIC-value breakpoint as of 2019 of both *Enterobacteriaceae* and *Pseudomonas aeruginosa* (Table 2).[41] However, even with these revised breakpoints, *Enterobacteriaceae* and *Pseudomonas aeruginosa* with MIC values of 0.25 mg/L and 0.5 mg/L, respectively, are still labelled as sensitive. Therefore, we think revision of these breakpoints is an improvement, but the CLSI should consider to lower these breakpoints even more, while taking into account the PK/PD target attainment results of the treatment of ciprofloxacin.

Table 2. MIC breakpoints of ciprofloxacin of *Enterobacteriaceae* and *Pseudomonas aeruginosa* provided by the CLSI and EUCAST[40,41,43]

MIC-breakpoints of ciprofloxacin (mg/L)				
	2018 CLSI breakpoints (original)	2019 CLSI breakpoints (revised)	2019 EUCAST breakpoints	From 2020 EUCAST breakpoints*
Enterobacteriaceae	S ≤1; I: 2; R ≥4	S ≤0.25; I: 0.5; R ≥1	S ≤0.25; I: 0.26-0.5; R >0.5	S ≤0.25; I: 0.26-0.5; R >0.5
Pseudomonas aeruginosa	S ≤1; I: 2; R ≥4	S ≤0.5; I: 1; R ≥2	S ≤0.5; R >0.5	S ≤ 0.001; I 0.002-0.5; R >0.5

*Consistent in year 2020-2021, 2021-2022 and 2022-2023[40]
CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; S, susceptible, standard dosing regimen; I, susceptible, increased exposure; R, resistant

Increase the dose

The second possibility to reach more often the PK/PD efficacy target for the treatment of bacterial infections is to increase the standard dose of ciprofloxacin. This will lead to higher drug exposure, so that the likelihood increases that the PK/PD efficacy target is attained even for bacteria with MIC values up to the MIC breakpoint of 0.25 mg/L and 0.5 mg/L of *Enterobacteriaceae* and *Pseudomonas aeruginosa*, respectively.[40] As from 2019 EUCAST has redefined susceptibility testing categories: the old definition of 'I' being 'intermediate' is redefined to the new definition of 'I' being 'susceptible, increased exposure', which means a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dose.[42] Following this changed definition, EUCAST changed all *Pseudomonas aeruginosa* with an MIC up to 0.5 mg/L from 'S' to 'I': susceptible, increased exposure (Table 2) indicating to increase the standard dose of ciprofloxacin for infections caused by *Pseudomonas aeruginosa*.[43]

Therapeutic drug monitoring

The third possibility to reach more often the PK/PD efficacy target for the treatment of bacterial infections is therapeutic drug monitoring (TDM) of ciprofloxacin. TDM involves measuring the plasma drug concentration and adjusting the dose accordingly, aiming for a pre-specified target plasma concentration.[44] The target range of ciprofloxacin would be an exposure to attain at least the proposed PK/PD target of ciprofloxacin, which is an AUC/MIC ≥125.[32,33]

TDM is mainly used for drugs with a narrow therapeutic range and drugs with marked inter-individual pharmacokinetic variability.[44,45] Ciprofloxacin shows marked inter-individual pharmacokinetic variability; we observed a 35% inter-individual variability in clearance and 102% in volume of distribution (**Chapter 4**).[17] Remarkably, renal function as a covariate in the final model did not explain much inter-individual pharmacokinetic variability; the percentage inter-individual variability declines from 38% in the structural model (without covariate association) to 35% in the

final model (with covariate association), suggesting that inter-individual variability in clearance is mainly caused by other factors (**Chapter 4**).[17,46-49]

Increasing the dose can eventually be a solution to attain the established PK/PD target, but this should be closely monitored by TDM, not only to check whether the target indeed has been attained, but also because of multiple recent safety warnings on the use of ciprofloxacin. Although the direct association between drug exposure and adverse effects has not been established so far.[50-53] To conclude, regarding the higher doses needed to attain the established PK/PD target and the large inter-individual pharmacokinetic variability, TDM would be a useful way to reach more often the PK/PD target with ciprofloxacin. However, the biggest problem with TDM for ciprofloxacin is the disputable therapeutic range. We would recommend to aim for an exposure greater than AUC/MIC ≥125.[32,33] This target is based on the clinical outcomes of patients from two retrospective studies, with a relatively small sample size, who often used concomitant other antibiotics and measured MIC values generally lower than MIC values that need to be covered for treatment with ciprofloxacin.[32,33] However, comparable AUC/MIC values across both studies were found, making the PK/PD target of AUC/MIC ≥125 currently the best existing.[32,33] Nonetheless, the upper limit of the therapeutic range is not clear, since no association between plasma drug concentration and toxicity is known.

A pre-requisite for TDM is a rapid, reproducible, and sensitive analytical method to measure the plasma drug concentrations.[45] The unbound antibiotic concentration is the pharmacologically active compound and is responsible for the antibacterial effect.[54] Therefore, assays measuring the unbound plasma concentration are essential. We have developed and validated an assay for the measurement of unbound ciprofloxacin plasma concentration in **Chapter 3**, because it was not present yet.[20]

Overtreatment of intravenous infection prophylaxis

In clinical practice, patients unable to have oral intake, likely those with severe mucositis, are switched to intravenous (IV) therapy. Therefore, we included only patients that were able to take their medication orally (**Chapter 6**).[19] This is in line with real-life clinical practice, but we do not know how oral intake would have been if these patients were not switched to IV therapy. This switch is based on clinical decision of the treating physician.[19] Theoretically, these patients may be switched to IV therapy, while absorption may remain adequate. With the current results, we only know that this switch is not made too late, since absorption is adequate in all patients receiving oral prophylaxis. On the other hand, we do not know whether overtreatment of intravenous infection prophylaxis does exist in these patients.

Ideally in the context of research, we could investigate one treatment group according to standard practice and one group with only oral treatment, although the physicians would have switched to IV therapy already. However, we think this would be unethical in clinical practice, since we expect absorption is worse.[55] Additionally, these patients may not be capable to take oral medications due to other reasons, like pain or difficulty in swallowing.[56] To overcome this problem a nasogastric feeding tube can be used.[56]

Another study design could be to switch to IV therapy with ceftazidime as is currently done in routine clinical practice, to be sure that the patient receives adequate prophylaxis when the patient has severe mucositis and additionally administer one tablet of ciprofloxacin, whether or not using a nasogastric feeding tube, and afterwards measure the ciprofloxacin plasma concentration to get insight into the oral absorption of ciprofloxacin in these patients.

Absorption versus first-pass effect

We have shown that systemic exposure of ciprofloxacin is adequate in haematological patients with mild mucositis.[19] Systemic exposure after oral administration is the result of the administered dose, bioavailability (fraction of the dose that reaches the systemic circulation) and clearance.[57] Bioavailability reflects the combined process of absorption and first-pass effect.[58] We concluded that both are adequate, since exposure is adequate. However, the distinction between absorption and first-pass effect has not been taking into account.

Theoretically, the absorption could be reduced, but when the first-pass effect would be reduced as well as compensating mechanism, the net effect would be zero. On the other hand, the absorption could be increased and the first-pass effect could be increased as well and the net effect would be zero again. Previous studies indicated a first-pass effect of ciprofloxacin in the liver.[59] However, it remains unknown if this first-pass effect is a zero- or first-order kinetic process and so whether a higher absorption rate would be accompanied by a higher amount being metabolized per time unit during the first-pass of gastrointestinal and liver mucosa, as is the case of first order kinetics.[60]

Theoretically, we would like to measure the concentration of ciprofloxacin in both the vena porta and in the systemic circulation. However, this is not feasible for in vivo studies. Additionally, for clinical practice, the net effect that leads to systemic exposure is most important for the adequacy of the infection prophylaxis and not the pharmacological processes behind it.

Therefore, we think it is justified to conclude, based on systemic exposure, that absorption is adequate, although the first-pass effect has not been quantified.

Methodological considerations

Some overall limitations should be taken into account when looking at the findings described in this thesis.

PK/PD target attainment as surrogate endpoint

Pharmacokinetic/pharmacodynamic (PK/PD) target attainment is used as surrogate endpoint for clinical outcome. The used PK/PD targets have been established in previous clinical studies, in which they correlate with clinical and microbiological outcome, such as clinical success or time to eradication.[32-36] Nowadays, known PK/PD targets may help to optimize clinical outcome.[61] However, we want actual improvement of patients' clinical outcome in the end and not only attainment of PK/PD efficacy targets. The studies in this thesis did not show an association between PK/PD target attainment and clinical outcome, because this was not statistically tested.[17,18] Different reasons exist why we could not test or observe an association. First, our studies had a small sample size and therefore not enough power to observe an association between PK/PD target attainment and clinical outcome. Probably hundreds of patients would be needed to observe enough differences in clinical outcome, while only 40 patients were included. Second, a clear definition for clinical outcome is lacking. A wide range of possible endpoints exists: mortality, clinical cure, the need to switch antibiotics or add antibiotics to the initial treatment.[62,63] However, all of these endpoints suffer from drawbacks, such as the need of a large sample size, no consensual definitions, subjectivity of assessment and some are difficult to define, since switching or adding antibiotics may only be performed to ensure coverage of all pathogens.[62] Additionally, lack of consensus exists about which endpoint should be primary.[62] Third, most of the time no causative microorganism is being cultured and identified. In our study, 22 of the 40 patients showed positive cultures (55%) (**Chapter 4**).[17] For patients without a positive culture, we have assumed the most common causative microorganism for that specific infection, however, this may not be specific enough to investigate an association between clinical outcome and PK/PD target attainment. Fourth, clinical success in daily practice is dependent on many more factors than one antibiotic concentration only.[64,54] For example, many critically ill patients are treated with more than one antibiotic and for some infections, such as pyelonephritis or osteomyelitis, clinical success is also dependent on source control.[64]

An important limitation and common criticism of previously defined PK/PD targets is that associations with clinical outcome are susceptible to bias introduced by related, yet unidentified, variables.[66] For example, could the increased risk of death be related to critical illness in patients who can have expanded volumes of drug distribution due to high-volume suppletion during severe infections and therefore lower peak concentrations? In other words, does lower target attainment cause death or does another variable, such as critical illness and the total treatment of the infection, result independently in lower target attainment and higher mortality rates?

To overcome this limitation, we suggest to investigate PK/PD target attainment in different patient populations. By including different populations, the (unidentified) bias would be minimized. We suggest to include 1) patients with bacterial infections treated by the general practitioner (GP), 2) patients treated by a specialist at the outpatient clinic, 3) hospitalized patients and 4) critically ill patients admitted to the ICU. If comparable associations between PK/PD target attainment and clinical outcome are found, one could say that this correlation is consistent over different patient populations and independent of unidentified variables.

Also, we would suggest to develop and validate a general definition of clinical outcome. This will help to investigate the association between PK/PD target attainment and clinical outcome. Besides, a general definition of clinical outcome will facilitate comparison of study results on bacterial infections for other purposes as well.

Analysis of concentration-time data

Antibiotic exposure was investigated using nonlinear mixed-effects modelling (NONMEM).[17-19] First, a model is developed that best describes the concentration-time data, considering different co-variates. Afterwards, concentration-time curves can be simulated based on this model following different dosing regimens, again considering the individual patient characteristics.[17-19] Application of NONMEM analyses enables us to develop population pharmacokinetic (PK) models and subsequently simulate full concentration-time curves, based on sparse data sampling, i.e., three blood samples per patient.[67,68] Critics will argue that the golden standard for investigating concentration-time curves is actually measuring this curve based on rich sampling.[69] However, this leads to an enormous burden for the patient, since blood samples have to be taken very frequently. NONMEM provides reliable concentration-time curves, using sparse data sampling.[68] Besides, NONMEM enables the use of material already collected for routine clinical care, leading to even less burden for the patient. The use of waste material was validated for the measurement of ciprofloxacin plasma concentrations in different blood collection tubes used in everyday clinical practice (**Chapter 3**).[20] Therefore, we think that rich sampling is an outdated way of measuring concentration-time curves and advocate NONMEM being the new golden standard.

Renal function

Measurement and classification of renal function

Renal function is usually expressed as the glomerular filtration rate (GFR). In this thesis, renal function is estimated based on the CKD-EPI formula.[17-19] The CKD-EPI formula is a creatinine-based estimation equation and takes age, sex and ethnic origin into account.[70,71] The measurement of creatinine is relatively easy and is usually part of a routine lab report.[70] This enables the use for every day clinical practice and most hospitals therefore use creatinine-based estimation equation to estimate renal function. However, actually measuring the renal function using externally administered agents such as inulin is historically considered the golden standard.[72] Yet measuring inulin is expensive, rigorous and time consuming and therefore not useful for every day clinical practice, particularly not for large groups of patients receiving antibiotics in the hospital.[72] The estimated GFR provides an unbiased assessment of the measured GFR for the majority of people. Besides, the CKD-EPI formula is the most accurate method for estimating GFR at the moment and currently the most frequently used.[71] Therefore, using the CKD-EPI enables the extrapolation of study results to clinical practice.

Additionally, another pre-requisite for appropriate dosing recommendations for patients with impaired renal function is a clear classification of renal function groups to enable investigation of the appropriate dose for patients in those groups. We have identified the lack of a clear definition.[13,16] We would suggest to follow the classification of Chronic Kidney Disease (CKD) as illustrated in Table 3, which is endorsed by most national kidney associations (e.g., Dutch Kidney Foundation, UK Kidney

Association and American Kidney Fund).[73-75] Therefore, we think it would provide the most useful and practical classification of renal function groups per antibiotic.

Table 3. Classification of Chronic Kidney Disease[73-75]

Classification of Chronic Kidney Disease	eGFR (ml/min/1.73m²)
Stage 1	≥ 90
Stage 2	60 - 89
Stage 3a	45 - 59
Stage 3b	30 - 44
Stage 4	15 - 29
Stage 5	< 15

eGFR, estimated glomerular filtration rate

Acute versus chronic renal impairment

Approximately 20% of all hospital admissions are associated with acute renal impairment and approximately 33% of patients with chronic renal impairment in the hospital develop acute renal impairment during their time in hospital.[76] This usually resolves within 24-48 h after adequate intravenous resuscitation.[77] This short period of time during which renal function is impaired is one of the arguments for prescribers not to follow the guidelines on the recommended dose reduction in patients with impaired renal function.[14] The estimated renal function may lag behind on the actual renal function due to the fast recovery of renal function after volume resuscitation.[14] Another reason may be that most recommendations for dose reductions are from studies including patients with chronic renal impairment in whom the decrease in clearance may not be representative for patients with acute renal impairment.[14,16] Based on results of this thesis, we would recommend to treat patients with acute renal impairment who show an eGFR just below the limit where a dose reduction is recommended, with a full, regular antibiotic dose and to re-measure renal function the day after to confirm, or disprove, the expected improvement of renal function and act accordingly.

Scoring gastro-intestinal mucositis

Assessing the severity of mucositis is cumbersome as no golden standard for diagnosing or assessing gastro-intestinal (GI)-mucositis exists, despite the use of invasive biopsy of the GI-tract.[78] The Daily Gut Score (DGS) and daily mucositis score (DMS) are two clinical scoring systems developed to assess mucositis.[78,79] Additionally, citrulline and albumin levels are used as quantitative biomarkers of mucositis.[26,78,80] Citrulline is mainly produced by enterocytes of the small bowel and therefore a biomarker of remnant small bowel mass and function.[81] Single studies have shown the validity of these scoring systems, however complete validity is missing. We have used the DGS as a clinical scoring system and measured citrulline levels as quantitative biomarker in **Chapter 6**.[19] Contradictory results were obtained: nine patients showed severe mucositis based on citrulline levels, while only mild mucositis was predicted based on the DGS.[19] Additionally, when comparing both clinical scoring systems, completely different parameters are assessed: the DGS assesses defecation, abdominal pain and the ability to eat, while the DMS assesses local oral condition and the ability to swallow.[78,79] Therefore, both scoring systems seem to measure different parts of the GI-tract involved in mucositis and, therefore, do not meet the content validity or construct validity criteria.

Previous studies have shown that drug exposure or bioavailability is only reduced for patients with severe mucositis.[55] Patients with mild or moderate mucositis did not show reduced drug exposure or compromised bioavailability (**Chapter 6**).[82,83] We therefore think that complicated scoring systems of

mucositis that make a distinction between mild-, moderate- and severe mucositis are not necessary. In clinical practice only the distinction between severe and 'not severe' mucositis seems to be relevant for an effect on bioavailability or drug exposure. Additionally, the current clinical scoring systems are very time consuming and inconvenient for clinical practice. One scoring system even scores the amount of feces, which leads to an enormous hazard for patients and health care providers.[79] Additionally, the other scoring system of mucositis; the measurement of citrulline, is expensive and only available in a couple of hospitals in the Netherlands.

Our study has shown that ciprofloxacin exposure is adequate for patients treated orally.[19] The decision to treat patients orally or switch to intravenous (IV) therapy with ciprofloxacin or ceftazidime in case the patient develops the symptoms of an acute infection such as fever, is based on the clinical assessment of the treating physician.[19] Therefore, our results indicate that the physician is capable to select patients for oral treatment, since all of those patients showed adequate ciprofloxacin exposure. The adequateness of this clinical decision is endorsed by another study.[82] This study showed adequate isavuconazole exposure in patients with mucositis treated with the oral formulation. The decision to treat patients orally or switch to IV therapy was at the discretion of the site investigators.

None of these physicians or investigators used extended scoring systems or measured the citrulline levels on a daily basis.[82] We think no need for complicated scoring systems exists, as the treating physician seems to be perfectly capable of differentiating between patients that need to be treated orally or intravenously and to obtain adequate drug exposure. This is an example of excellent clinical decision making, without the need for complicated scoring systems or the measurement of biomarkers.

Representative patient samples

In **Chapter 4-6**, patients admitted to general wards of academic or regional hospitals in the Netherlands were included.[17-19] All patients showed signs of a bacterial infection or received antibiotic prophylaxis during high-dose chemotherapy. This results in a study population that is representative for everyday clinical practice with regard to patients admitted to general wards of hospitals. Therefore, our study results are transferable to every day clinical practice. However, other important patient populations such as nursing home patients, patients on the intensive care unit (ICU) and patients treated with ciprofloxacin by the general practitioner (GP) were excluded. Nonetheless, ciprofloxacin is prescribed frequently in these patients.[48,84,85] Changed pharmacokinetics and subsequently differences in drug exposure were reported for nursing home patients.[86] Additionally, it is well known that patients on the ICU face altered pharmacokinetics and altered drug exposure.[87] Therefore, we think that our studies have to be performed in other populations as well. Particularly in nursing home patients, patients on the ICU and patients treated with ciprofloxacin by the GP. These are big groups of patients treated with ciprofloxacin and they may face different pharmacokinetics compared to patients on general wards. This is substantiated by previous studies showing limited predictive value of internally validated population PK models for other populations, e.g., from different countries with different ethnic backgrounds and diets or with different degrees of illness.[88]

Implications for future research

Revisions of the recommended dose reduction of ciprofloxacin

Results of our study show that the PK/PD target of ciprofloxacin is not attained in the first 24 h of treatment in the majority of adult patients on general wards for clinically relevant bacteria with MIC values at or just below the clinical breakpoint (0.25 mg/L).[17] The risk of not attaining the PK/PD target seems to be highest in patients with impaired renal function (eGFR <30 ml/min/1.73m^2) receiving a guideline-recommended reduced dose of ciprofloxacin, as drug exposure is significantly lower in this subgroup of patients compared to patients with adequate renal function receiving a regular dose.[17] The rationale behind the guideline-recommended dose reduction of ciprofloxacin in patients with impaired renal function is to achieve equivalent antibiotic exposure, compared to patients with adequate renal function receiving a regular dose. However, the results show that drug exposure is not equivalent, but statistically significant lower in hospitalized patients with impaired renal function. To achieve equivalent drug exposure, the daily dose of ciprofloxacin for hospitalized patients with impaired renal function should be increased. Different dosing regimens of ciprofloxacin for patients with impaired renal function were simulated (**Chapter 4**).[17] Results of these simulations show that a daily dose of ciprofloxacin of 750 mg orally or 600 mg IV should lead to equivalent drug exposure, instead of the currently recommended daily dose of 500 mg orally or 400 mg IV. Increasing the daily dose for patients with impaired renal function is also supported by results of other studies that show that non-renal clearance of ciprofloxacin increases in patients with impaired renal function to compensate for the reduced renal clearance.[37-39]

Implementation of new dosing recommendations of ciprofloxacin

The appropriate way of implementation of new dosing recommendations remains subject of ongoing debate. Three options exist:

1. Implement the new dosing recommendations directly into current guidelines as the new standard of care. Other studies have also shown that current dosing recommendations of ciprofloxacin are suboptimal (**Chapter 4**), it would be unethical to treat patients with these dosing recommendations, although the new dosing recommendations have not been prospectively validated yet.[47-49]
2. Validation of the new dosing recommendations precedes implementation of the new dosing recommendations. First prospectively validate the new dosing recommendations and treat patients in between with the current standard of care, although this might be suboptimal.
3. A combination of both options: implement the new dosing recommendations directly and validate these while already being standard of care.

Currently, we are performing the CIPRO-3 study in which we investigate an alternative dose reduction of ciprofloxacin for patients with impaired renal function: a 25% dose reduction instead of the currently recommended 50% dose reduction (as described under option 2).[17] In the mean time in the 'NoordWest Ziekenhuisgroep' the new dosing recommendation of a 25% dose reduction of ciprofloxacin for patients with impaired renal function has already been implemented in the guidelines, while we are simultaneously validating these dosing recommendation by measuring plasma concentrations of ciprofloxacin and subsequently calculating antibiotic drug exposure (thus as described under option 3 above).

Validation of the recommended dose reduction of other renally cleared antibiotics

We have investigated and summarized the evidence on the validation of the recommend dose reduction of meropenem, ciprofloxacin and ceftazidime.[16-18] However, for all other antibiotics for which a dose reduction is standard of care for patients with impaired renal function this dose reduction has to be prospectively validated in clinical practice. We strongly recommended to start with antibiotics that do not have the kidneys as exclusive route of elimination, but also are partly eliminated by the liver, bile and intestine, such as ertapenem and piperacillin, since particularly for those antibiotics, concern exists on the adequacy of the recommended dose reduction.[18,89-91]

Currently we are performing a prospective observational study to investigate the recommended dose reduction and PK/PD target attainment of cefuroxime in patients admitted to general wards of 'Noordwest Ziekenhuisgroep'. This β-lactam antibiotic requires a dose reduction following current guidelines and has the kidneys as the main route of elimination.[92-94] Therefore, we hypothesize that the currently recommended dose reduction of cefuroxime for patients with impaired renal function is, like in ceftazidime and meropenem, adequate, when comparing drug exposure and PK/PD target attainment to that in patients with adequate renal function receiving the regular dose. However, for other antibiotics partly eliminated by the liver, bile and intestine, such as ertapenem and piperacillin we would hypothesize that the currently recommended dose reduction would not be adequate.

Mandatory information for elderly and patients with impaired renal function in the SmPC

Information to address the appropriate drug use in children is mandatory for SmPC approval. Information on appropriate drug use in elderly and patients with impaired renal function is only provided 'when clinically relevant differences' are known.[95]

Currently, in the Netherlands, the population consists of more than 3.5 million elderly (≥ 65 years), making up about 20% of the total population.[96] Additionally, 1.7 million people show some degree of impaired renal function, making up about 10% of the total population.[97] Due to aging of the population and an increase in the number of people with diabetes and hypertension, this will increase further.[97] Additionally, this number consists only of patients with chronic renal impairment, and does not include the number of patients with acute renal impairment. Approximately 20% of all hospital admissions are also associated with acute renal impairment.[98] These numbers emphasize the need for mandatory information in the SmPC on appropriate drug use in elderly and patients with impaired renal function even more.

It is well-known that pharmacokinetic parameters change in the elderly phase of life and during renal impairment.[99,100] In elderly, renal and hepatic clearance are reduced, while volume of distribution of lipid soluble drugs is increased, leading to prolongation of elimination half-life.[99] In patients with impaired renal function, renal clearance is reduced and volume of distribution may remain unchanged or can be increased.[100]

Based on the high number of elderly and patients with impaired renal function, together with the known altered pharmacokinetic parameters, we think it is justified to make information on appropriate drug use in elderly and patients with impaired renal function mandatory to include in de SmPC as well, before marketing authorization is approved.

We therefore suggest to investigate the (altered) pharmacokinetic parameters for both patient groups in phase II and III trials, define appropriate dosing recommendations based on these findings

and finally validate these dosing recommendations in real life clinical practice for elderly and patients with impaired renal function.

Revision of appropriate antibiotic use definition

Although the set of quality indicators defining appropriate antibiotic use was developed in a multidisciplinary international expert panel and tested and validated in clinical practice, we think revision may have to be considered.[6] It is incorrect to include a quality indicator on dose adjustment in renal impairment that is based on such sparse data with a low grade of evidence of the guideline recommendation on which the quality indicator is based.[16] Acceptance of this quality indicator would suggest that antibiotic dose adjustment when renal function is impaired, is appropriate, while in fact most dosing recommendations in renal impairment have never been prospectively validated in every-day clinical practice.[16]

Results on antibiotic resistance rates and healthcare costs

As mentioned in the first sentence of this discussion chapter, appropriate antibiotic use is beneficial for patients' clinical outcome, leads to a decrease in antibiotic resistance rates and results in lowering of healthcare costs.[1-5] In this thesis we have mainly focused on PK/PD target attainment, as a surrogate for patients' clinical outcome. However, the effect of appropriate antibiotic use for patients with impaired renal function on both antibiotic resistance rates and lowering of healthcare costs remains outside the scope of this thesis. Future research should focus on this effect as well, since it is as important as patients' clinical outcome.

Overall conclusion

Prospective validation in every-day clinical practice on the recommended dose reduction of most antibiotics in patients with impaired renal function is lacking (**Chapter 2**).[16] Additionally, a validated method to measure the pharmacologically active concentration of ciprofloxacin was lacking, which is a pre-requisite for investigating the adequate dose. We have validated a method for the measurement of unbound ciprofloxacin plasma concentration (**Chapter 3**).[20] Subsequently, we have prospectively validated the recommended dose reduction of ciprofloxacin and ceftazidime (**Chapter 4 and 5**).[17,18] Ceftazidime is dosed correctly, as the PK/PD efficacy target is attained in most patients and antibiotic drug exposure is comparable between patients with adequate and impaired renal function receiving regular and reduced doses of ceftazidime respectively.[18] However, for ciprofloxacin new dosing recommendations for patients with impaired renal function are warranted, as the PK/PD efficacy target is not attained in most patients and drug exposure is statistically significantly lower in patients with impaired renal function receiving reduced doses compared to patients with adequate renal function receiving regular doses.[17] Finally, we have validated the use of ciprofloxacin as infection prophylaxis in patients with haematological malignancies. Absorption and drug exposure remain adequate in patients with mild mucositis (**Chapter 6**).[19] Based on these results, we are performing a new study to investigate an alternative dose adjustment of ciprofloxacin for patients with impaired renal function: a 25% dose reduction instead of the currently recommended 50% dose reduction. Additionally, we are prospectively validating the currently recommended dose reduction of cefuroxime for patients with impaired renal function.

To conclude, we think that clinicians should follow the current guideline recommendations to reduce the dose of renally cleared antibiotics for patients with impaired renal function. Guideline deviation is not justified based on only the lack of prospective evidence for this recommendation. For ceftazidime we have shown that the recommended dose reduction is adequate. For ciprofloxacin this dose reduction seems inadequate, however prospective validation of revised dosing recommendations are warranted before implementing new dosing recommendations. In the meantime, we strongly advice clinicians to be cautious for treatment failure of antibiotics and to consider TDM when fearing underexposure after a dose reduction when treating patients with impaired renal function.

References

1. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, Gould IM, Ramsay CR, Michie S. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev*. 2017 Feb 9;2(2):CD003543.
2. Schuts EC, Hulscher MEJL, Mouton JW, Verduin CM, Stuart JWTC, Overdiek HWPM, van der Linden PD, Natsch S, Hertogh CMPM, Wolfs TFW, Schouten JA, Kullberg BJ, Prins JM. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis. 2016 Jul;16(7):847-856.
3. van den Bosch CM, Hulscher ME, Akkermans RP, Wille J, Geerlings SE, Prins JM. Appropriate antibiotic use reduces length of hospital stay. *J Antimicrob Chemother*. 2017 Mar 1;72(3):923-932.
4. Spoorenberg V, Hulscher ME, Akkermans RP, Prins JM, Geerlings SE. Appropriate antibiotic use for patients with urinary tract infections reduces length of hospital stay. *Clin Infect Dis*. 2014 Jan;58(2):164-9.
5. McCabe C, Kirchner C, Zhang H, Daley J, Fisman DN. Guideline-concordant therapy and reduced mortality and length of stay in adults with community-acquired pneumonia: playing by the rules. *Arch Intern Med*. 2009 Sep 14;169(16):1525-31.
6. van den Bosch CM, Geerlings SE, Natsch S, Prins JM, Hulscher ME. Quality indicators to measure appropriate antibiotic use in hospitalized adults. *Clin Infect Dis*. 2015 Jan 15;60(2):281-91.
7. Stichting Werkgroep AntibioticaBeleid (SWAB) - Ciprofloxacine. Available on: https://adult.nl.antibiotica.app/nl/node/1240. Last accessed on 12 January 2023.
8. Farmacotherapeutisch Kompas (FK) - Ciprofloxacine. Available on: https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/c/ciprofloxacine. Last accessed on 12 January 2023.
9. KNMP Kennisbank – Ciprofloxacine. Available on: https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/S2078.html. Last accessed on 12 January 2023.
10. Levison ME, Levison JH. Pharmacokinetics and pharmacodynamics of antibacterial agents. *Infect Dis Clin North Am*. 2009 Dec;23(4):791-815, vii.
11. Verbeeck RK, Musuamba FT. Pharmacokinetics and dosage adjustment in patients with renal dysfunction. *Eur J Clin Pharmacol*. 2009 Aug;65(8):757-73.
12. van Daalen FV, Prins JM, Opmeer BC, Boermeester MA, Visser CE, van Hest RM, Branger J, Mattsson E, van de Broek MFM, Roeleveld TC, Karimbeg AA, Haak EAF, van den Hout HC, van Agtmael MA, Hulscher MEJL, Geerlings SE. Effect of an antibiotic checklist on length of hospital stay and appropriate antibiotic use in adult patients treated with intravenous antibiotics: a stepped wedge cluster randomized trial. *Clin Microbiol Infect*. 2017 Jul;23(7):485.e1-485.e8.
13. Vidal L, Shavit M, Fraser A, Paul M, Leibovici L. Systematic comparison of four sources of drug information regarding adjustment of dose for renal function. *BMJ*. 2005 Jul 30;331(7511):263.
14. Crass RL, Rodvold KA, Mueller BA, Pai MP. Renal Dosing of Antibiotics: Are We Jumping the Gun? *Clin Infect Dis*. 2019 Apr 24;68(9):1596-1602.
15. Camargo MS, Mistro S, Oliveira MG, Passos LCS. Association between increased mortality rate and antibiotic dose adjustment in intensive care unit patients with renal impairment. *Eur J Clin Pharmacol*. 2019 Jan;75(1):119-126.
16. de Vroom SL, van Daalen FV, Zieck SE, Mathôt RAA, van Hest RM, Geerlings SE. Does dose reduction of renally cleared antibiotics in patients with impaired renal function lead to adequate drug exposure? A systematic review. *Clin Microbiol Infect*. 2021 Mar;27(3):352-363.
17. de Vroom SL, van Hest RM, van Daalen FV, Kuil SD, Mathôt RAA, Geerlings SE, Jager NGL. Pharmacokinetic/pharmacodynamic target attainment of ciprofloxacin in adult patients on general wards with adequate and impaired renal function. *Int J Antimicrob Agents*. 2020 Nov;56(5):1061-66.
18. Zieck SE, de Vroom SL, Mulder FP, van Twillert G, Mathôt RAA, Geerlings SE, van Hest RM. Pharmacokinetic/pharmacodynamic target attainment of ceftazidime in adult patients on general

wards with different degrees of renal function: a prospective observational bicenter cohort study. *Antibiotics.* 2023; 12(3):469.
19. de Vroom SL, van Rhee KP, van Hest RM, van der Linden PD, Tonino SH, Molendijk E, Mathôt RAA, Blijlevens NMA, Knibbe CAJ, Bruggemann RJM, Geerlings SE. Impact of mucositis on oral bioavailability and systemic exposure of ciprofloxacin Gram-negative infection prophylaxis in patients with haematological malignancies. *J Antimicrob Chemother*. 2022 Oct 28;77(11):3069-3076.
20. de Vroom SL, Pistorius MCM, Bijleveld YA, et al. Development and Validation of a Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) Assay for the Determination of Total and Unbound Ciprofloxacin Concentrations in Human Plasma. *Therapeutic Drug Monitoring*. 2022 Aug;44(4):552-557.
21. Armstrong T, Fenn SJ, Hardie KR. JMM Profile: Carbapenems: a broad-spectrum antibiotic. *J Med Microbiol*. 2021;70(12):001462.
22. US FDA. Guidance for Industry: Bioanalytical Method Validation. US Department of Health and Human Services, FDA, Center for Drug Evaluation and Research, Rockville, MD, USA (2001). Available on: https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf. Last accessed August 21, 2021.
23. Blijlevens NM, Donnelly JP, de Pauw BE. Empirical therapy of febrile neutropenic patients with mucositis: challenge of risk-based therapy. *Clin Microbiol Infect*. 2001;7 Suppl 4:47-52.
24. Peterson DE, Boers-Doets CB, Bensadoun RJ, Herrstedt J; ESMO Guidelines Committee. Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Ann Oncol*. 2015 Sep;26 Suppl 5:v139-51.
25. Crenn P, Messing B, Cynober L. Citrulline as a biomarker of intestinal failure due to enterocyte mass reduction. *Clin Nutr*. 2008 Jun;27(3):328-39.
26. van der Velden WJ, Herbers AH, Brüggemann RJ, Feuth T, Peter Donnelly J, Blijlevens NM. Citrulline and albumin as biomarkers for gastrointestinal mucositis in recipients of hematopoietic SCT. *Bone Marrow Transplant*. 2013 Jul;48(7):977-81.
27. Farmacotherapeutisch Kompas (FK) - Meropenem. Available on: https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/m/meropenem. Last accessed on January 13, 2023.
28. KNMP Kennisbank – Meropenem. Available on: https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/S2520.html. Last accessed on January 13, 2023.
29. Farmacotherapeutisch Kompas (FK) - Ceftazidime. Available on: https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/c/ceftazidim. Last accessed on January 13, 2023.
30. KNMP Kennisbank – Ceftazidime. Available on: https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/S1884.html. Last accessed on January 13, 2023.
31. Drusano GL. Prevention of resistance: a goal for dose selection for antimicrobial agents. *Clin Infect Dis*. 2003 Jan 15;36(Suppl 1):S42-50.
32. Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob Agents Chemother*. 1993 May;37(5):1073-81.
33. Zelenitsky SA, Harding GK, Sun S, Ubhi K, Ariano RE. Treatment and outcome of Pseudomonas aeruginosa bacteraemia: an antibiotic pharmacodynamic analysis. *J Antimicrob Chemother*. 2003 Oct;52(4):668-74.
34. McKinnon PS, Paladino JA, Schentag JJ. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. *Int J Antimicrob Agents*. 2008 Apr;31(4):345-51.
35. Muller AE, Punt N, Mouton JW. Optimal exposures of ceftazidime predict the probability of microbiological and clinical outcome in the treatment of nosocomial pneumonia. *J Antimicrob Chemother*. 2013 Apr;68(4):900-6.

36. MacVane SH, Crandon JL, Nichols WW, Nicolau DP. In vivo efficacy of humanized exposures of Ceftazidime-Avibactam in comparison with Ceftazidime against contemporary Enterobacteriaceae isolates. *Antimicrob Agents Chemother*. 2014 Nov;58(11):6913-9.
37. Rohwedder R, Bergan T, Thorsteinsson SB, Scholl H. Transintestinal elimination of ciprofloxacin. Chemotherapy 1990;36:77–84.
38. Dirksen MS, Vree TB. Pharmacokinetics of intravenously administered ciprofloxacin in intensive care patients with acute renal failure. Pharm Weekbl Sci 1986;8:35–9.
39. Boelaert J, Valcke Y, Schurgers M, Daneels R, Rosseneu M, Rosseel MT, Bogaert MG. The pharmacokinetics of ciprofloxacin in patients with impaired renal function. J Antimicrob Chemother. 1985 Jul;16(1):87-93.
40. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 12.0, 2022. http://www.eucast.org. Last accessed on December 26, 2022.
41. Van TT, Minejima E, Chiu CA, Butler-Wu SM. Don't Get Wound Up: Revised Fluoroquinolone Breakpoints for Enterobacteriaceae and Pseudomonas aeruginosa. *J Clin Microbiol*. 2019 Jun 25;57(7):e02072-18.
42. Gunnar Kahlmeter. EUCAST - To clinical colleagues: On recent changes in clinical microbiology susceptibility reports – new interpretation of susceptibility categories S, I and R. July 9, 2021. Available on: https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Guidance_documents/To_clinical_colleagues_on_recent_changes_in_clinical_microbiology_susceptibility_reports_9_July2021.pdf, Last accessed on December 26, 2022.
43. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 9.0, 2019. http://www.eucast.org. Last accessed on December 26, 2022.
44. Kang JS, Lee MH. Overview of therapeutic drug monitoring. *Korean J Intern Med*. 2009;24(1):1-10.
45. Ghiculescu R. Therapeutic drug monitoring: which drugs, why, when and how to do it. *Aust Prescr* 2008;31:42-4.
46. Guo T, Abdulla A, Koch BCP, van Hasselt JGC, Endeman H, Schouten JA, Elbers PWG, Brüggemann RJM, van Hest RM; Dutch Antibiotic PK/PD Collaborators. Pooled Population Pharmacokinetic Analysis for Exploring Ciprofloxacin Pharmacokinetic Variability in Intensive Care Patients. *Clin Pharmacokinet*. 2022 Jun;61(6):869-879.
47. Haeseker M, Stolk L, Nieman F, Hoebe C, Neef C, Bruggeman C, Verbon A. The ciprofloxacin target AUC : MIC ratio is not reached in hospitalized patients with the recommended dosing regimens. *Br J Clin Pharmaco*l. 2013 Jan;75(1):180-5.
48. van Zanten AR, Polderman KH, van Geijlswijk IM, van der Meer GY, Schouten MA, Girbes AR. Ciprofloxacin pharmacokinetics in critically ill patients: a prospective cohort study. *J Crit Care*. 23 (2008):422-430
49. Kontou P, Chatzika K, Pitsiou G, Stanopoulos I, Argyropoulou-Pataka P, Kioumis I. Pharmacokinetics of ciprofloxacin and its penetration into bronchial secretions of mechanically ventilated patients with chronic obstructive pulmonary disease. *Antimicrob Agents Chemother*, 55 (2011):4149-4153
50. FDA Drug Safety Communication. FDA advises restricting fluoroquinolone antibiotic use for certain uncomplicated infections; warns about disabling side effects that can occur together [05-12-2016]. Available on: https://www.fda.gov/media/97602/download. Last accessed on January 13, 2023.
51. FDA reinforces safety information about serious low blood sugar levels and mental health side effects with fluoroquinolone antibiotics; requires label changes. FDA Drug Safety Communication [07-10-2018]. Available on: https://www.fda.gov/drugs/drug-safety-and-availability/fda-reinforces-safety-information-about-serious-low-blood-sugar-levels-and-mental-health-side. Last accessed on January 13, 2023.

52. FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients. FDA Drug Safety Communication [12-20-2018]. Available on: https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-increased-risk-ruptures-or-tears-aorta-blood-vessel-fluoroquinolone-antibiotics. Last accessed on June 24, 2022
53. European Medicines Agency (EMA). Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics, March 11th 2019. Available on: https://www.ema.europa.eu/en/documents/referral/quinolone-fluoroquinolone-article-31-referral-disabling-potentially-permanent-side-effects-lead_en.pdf. Last accessed on January 13, 2023.
54. Liu P, Müller M, Derendorf H. Rational dosing of antibiotics: the use of plasma concentrations versus tissue concentrations. Int J *Antimicrob Agents*. 2002 Apr;19(4):285-90.
55. Jansen AME, Muilwijk EW, van der Velden WJFM, Maertens JA, Aerts R, Colbers A, Burger D, Verweij PE, Ter Heine R, Blijlevens NMA, Brüggemann RJM. Posaconazole bioavailability of the solid oral tablet is reduced during severe intestinal mucositis. *Clin Microbiol Infect*. 2022 Jul;28(7):1003-1009.
56. Lalla RV, Sonis ST, Peterson DE. Management of oral mucositis in patients who have cancer. *Dent Clin North Am*. 2008 Jan;52(1):61-77, viii.
57. Price G, Patel DA. Drug Bioavailability. [Updated 2022 Jun 23]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-
58. Rowland M, Tozer T. Clinical Pharmacokinetics. Concepts and Applications, 3rd Edition, Lea & Febiger, Philadelphia, London, 1995:14
59. Höffken G, Lode H, Prinzing C, Borner K, Koeppe P. Pharmacokinetics of ciprofloxacin after oral and parenteral administration. *Antimicrob Agents Chemother*. 1985;27(3):375-379.
60. Borowy CS, Ashurst JV. Physiology, Zero and First Order Kinetics. [Updated 2022 Sep 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-.
61. Hyatt JM, McKinnon PS, Zimmer GS, Schentag JJ. The importance of pharmacokinetic/pharmacodynamic surrogate markers to outcome. Focus on antibacterial agents. *Clin Pharmacokinet*. 1995 Feb;28(2):143-60.
62. Timsit JF, de Kraker MEA, Sommer H, Weiss E, Bettiol E, Wolkewitz M, Nikolakopoulos S, Wilson D, Harbarth S; COMBACTE-NET consortium. Appropriate endpoints for evaluation of new antibiotic therapies for severe infections: a perspective from COMBACTE's STAT-Net. *Intensive Care Med*. 2017 Jul;43(7):1002-1012.
63. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, Kaukonen KM, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Lipman J; DALI Study. DALI: defining antibiotic levels in intensive care unit patients: are current β-lactam antibiotic doses sufficient for critically ill patients? *Clin Infect Dis*. 2014 Apr;58(8):1072-83.
64. Bloos F, Rüddel H, Thomas-Rüddel D, Schwarzkopf D, Pausch C, Harbarth S, Schreiber T, Gründling M, Marshall J, Simon P, Levy MM, Weiss M, Weyland A, Gerlach H, Schürholz T, Engel C, Matthäus-Krämer C, Scheer C, Bach F, Riessen R, Poidinger B, Dey K, Weiler N, Meier-Hellmann A, Häberle HH, Wöbker G, Kaisers UX, Reinhart K; MEDUSA study group. Effect of a multifaceted educational intervention for anti-infectious measures on sepsis mortality: a cluster randomized trial. *Intensive Care Med*. 2017 Nov;43(11):1602-1612.
65. Tabah A, Lipman J, Barbier F, Buetti N, Timsit J-F, on behalf of the ESCMID Study Group for Infections in Critically Ill Patients—ESGCIP. Use of Antimicrobials for Bloodstream Infections in the Intensive Care Unit, a Clinically Oriented Review. *Antibiotics*. 2022;11(3):362.
66. Rodríguez-Gascón A, Solinís MÁ, Isla A. The Role of PK/PD Analysis in the Development and Evaluation of Antimicrobials. *Pharmaceutics*. 2021 Jun 3;13(6):833.
67. NONMEM Users Guide – Part V Introductory Guide, April 2011 by Boekman, Sheiner: 1
68. Heeremans EH, Proost JH, Eleveld DJ, Absalom AR, Struys MM. Population pharmacokinetics and pharmacodynamics in anesthesia, intensive care and pain medicine. *Curr Opin Anaesthesiol*. 2010 Aug;23(4):479-84.

69. Rowland M, Tozer T. Clinical Pharmacokinetics. Concepts and Applications, 3rd Edition, Lea & Febiger, Philadelphia, London, 1995:469-70
70. Traynor J, Mactier R, Geddes CC, Fox JG. How to measure renal function in clinical practice. *BMJ*. 2006 Oct 7;333(7571):733-7.
71. National Institute of Diabetes and Digestive and Kidney Diseases – Estimating Glomerular Filtration Rate. Available on: https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate/estimating. Accessed on January 15th 2023.
72. Sandilands EA, Dhaun N, Dear JW, Webb DJ. Measurement of renal function in patients with chronic kidney disease. *Br J Clin Pharmacol*. 2013 Oct;76(4):504-15.
73. Onderzoek en diagnose. Available on: https://nierstichting.nl/over-nieren/onderzoek-en-diagnose/. Last accessed on December 4, 2022.
74. Stages of kidney disease. Available on: https://www.kidneyfund.org/all-about-kidneys/stages-kidney-disease/. Last accessed on December 4, 2022.
75. CKD stages. Available on: https://ukkidney.org/health-professionals/information-resources/uk-eckd-guide/ckd-stages. Last accessed on December 4, 2022.
76. Argyropoulos A, Townley S, Upton PM, Dickinson S, Pollard AS. Identifying on admission patients likely to develop acute kidney injury in hospital. *BMC Nephrol*. 2019 Feb 14;20(1):56.
77. Palant CE, Patel SS, Chawla LS. Acute Kidney Injury Recovery. *Contrib Nephrol*. 2018;193:35-44.
78. Kuiken NSS, Rings EHHM, Blijlevens NMA, Tissing WJE. Biomarkers and non-invasive tests for gastrointestinal mucositis. *Support Care Cancer*. 2017 Sep;25(9):2933-2941.
79. Donnelly JP, Muus P, Schattenberg A, De Witte T, Horrevorts A, DePauw BE. A scheme for daily monitoring of oral mucositis in allogeneic BMT recipients. Bone Marrow Transplant. 1992 Jun;9(6):409-13.
80. Blijlevens NM, Lutgens LC, Schattenberg AV, Donnelly JP. Citrulline: a potentially simple quantitative marker of intestinal epithelial damage following myeloablative therapy. *Bone Marrow Transplant*. 2004 Aug;34(3):193-6.
81. Crenn P, Messing B, Cynober L. Citrulline as a biomarker of intestinal failure due to enterocyte mass reduction. *Clin Nutr*. 2008 Jun;27(3):328-39.
82. Kovanda LL, Marty FM, Maertens J, Desai AV, Lademacher C, Engelhardt M, Lu Q, Hope WW. Impact of Mucositis on Absorption and Systemic Drug Exposure of Isavuconazole. *Antimicrob Agents Chemother*. 2017 May 24;61(6):e00101-17.
83. Pham AN, Bubalo JS, Lewis JS 2nd. Comparison of posaconazole serum concentrations from haematological cancer patients on posaconazole tablet and oral suspension for treatment and prevention of invasive fungal infections. *Mycoses*. 2016 Apr;59(4):226-233.
84. Thompson ND, Stone ND, Brown CJ, et al. Antimicrobial Use in a Cohort of US Nursing Homes, 2017. *JAMA*. 2021;325(13):1286–1295.
85. NethMap 2022 - Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands, 3.1 Outpatient antibiotic use p. 32. Available on: https://swab.nl/en/exec/file/download/197. Last accessed on January 18, 2023.
86. Ahmed GF, Bathena SP, Brundage RC, Leppik IE, Conway JM, Schwartz JB, Birnbaum AK. Pharmacokinetics and Saturable Absorption of Gabapentin in Nursing Home Elderly Patients. *AAPS J*. 2017 Mar;19(2):551-556.
87. Smith BS, Yogaratnam D, Levasseur-Franklin KE, Forni A, Fong J. Introduction to drug pharmacokinetics in the critically ill patient. *Chest*. 2012 May;141(5):1327-1336.
88. Guo T, van Hest RM, Roggeveen LF, Fleuren LM, Thoral PJ, Bosman RJ, van der Voort PHJ, Girbes ARJ, Mathot RAA, Elbers PWG. External Evaluation of Population Pharmacokinetic Models of Vancomycin in Large Cohorts of Intensive Care Unit Patients. *Antimicrob Agents Chemother*. 2019 Apr 25;63(5):e02543-18.
89. Stichting Werkgroep AntibioticaBeleid (SWAB) - Ertapenem. Available on: https://adult.nl.antibiotica.app/nl/node/1379. Last accessed on January 30, 2023.

90. KNMP Kennisbank – Ertapenem. Available on: https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/S2899.html. Last accessed on January 13, 2023.
91. KNMP Kennisbank – Piperacillin. Available on: https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/S1876.html. Last accessed on January 13, 2023.
92. KNMP Kennisbank – Cefuroxime. Available on: https://kennisbank.knmp.nl/article/Informatorium_Medicamentorum/S1733.htm. Last accessed on January 13, 2023.
93. Stichting Werkgroep AntibioticaBeleid (SWAB) - Cefuroxime. Available on: https://adult.nl.antibiotica.app/node/1215. Last accessed on January 13, 2023.
94. Farmacotherapeutisch Kompas (FK) - cefuroxime. Available on: https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/c/cefuroxim__systemisch_. Last accessed on January 13, 2023.
95. European Medicines Agency (EMA) - Summary of product characteristics, p. 11,12. Available on: https://www.ema.europa.eu/en/documents/presentation/presentation-summary-product-characteristics_en.pdf. Last accessed on January 18, 2023.
96. CBS – Dashboard bevolking. Available on: https://www.cbs.nl/nl-nl/visualisaties/dashboard-bevolking/leeftijd/ouderen
97. Nierstichting – Nierschade en nierfalen. Available on: https://nierstichting.nl/documents/399/FS1-Nierennierschade_en_nierfalen.22.pdf. Last accessed on January 13, 2023.
98. Argyropoulos A, Townley S, Upton PM, Dickinson S, Pollard AS. Identifying on admission patients likely to develop acute kidney injury in hospital. *BMC Nephrol.* 2019 Feb 14;20(1):56.
99. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol*. 2004 Jan;57(1):6-14.
100. Roberts DM, Sevastos J, Carland JE, Stocker SL, Lea-Henry TN. Clinical Pharmacokinetics in Kidney Disease: Application to Rational Design of Dosing Regimens. *Clin J Am Soc Nephrol*. 2018 Aug 7;13(8):1254-1263.

Chapter 8

Summary in English

Summary in English

Appropriate antibiotic use is beneficial for patients' clinical outcome, leads to a decrease in antibiotic resistance rates and results in lowering of healthcare costs. Quality indicators measure quality of care, such as appropriate antibiotic use. Such quality indicators have been defined for the measurement of appropriate antibiotic use in the treatment of bacterial infections in the hospital. One of these nine validated quality indicators is to adjust the antibiotic dose to renal function. The antibiotic dose reduction for patients with impaired renal function is standard of care as incorporated in all clinical guidelines.

The aim of this dose reduction is to prevent accumulation of the drug, with risk for toxicity and thus patient harm, and to achieve antibiotic drug exposure equivalent to that in patients with adequate renal function receiving the regular dose, i.e., achieving bioequivalence. However, this dose reduction is often not applied in clinical practice and inconsistency exists between different guidelines in the extent of the recommended dose reduction and the renal function levels at which a dose reduction should be considered.

Currently, the level of evidence for the recommended antibiotic dose reduction for patients with impaired renal function is unclear. Additionally, it is unknown if this dose reduction leads to adequate drug exposure and PK/PD target attainment in clinical practice.

In this thesis we systematically reviewed all literature ever published since the discovery of the first antibiotic in 1928 on antibiotic dose reduction for patients with impaired renal function (**Chapter 2**). As a first step, a pre-requisite to investigate exposure to antibiotics in clinical practice is a validated method to measure concentrations of these antibiotics in body fluids. Therefore, we developed and validated a liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay for the determination of total and unbound ciprofloxacin plasma concentrations (**Chapter 3**). Thereafter, we prospectively investigated the adequacy of the recommended dose reduction for ciprofloxacin and ceftazidime in patients with impaired renal function, defined as equivalent drug exposure or PK/PD target attainment compared to that in patients with adequate renal function receiving the regular dose (**Chapter 4 and 5**). Finally, to be able to fully investigate the adequacy of the administered antibiotic dose, we also investigated that other pharmacokinetic parameter determining drug exposure: the bioavailability. In case of oral administration, bioavailability determines the amount of the drug that is being absorbed and thereby a large part of drug exposure. Therefore, we prospectively investigated the absorption of oral ciprofloxacin in neutropenic patients with haematological malignancies and mucositis (**Chapter 6**).

In **Chapter 2** we showed that no good-quality evidence on the recommended dose reduction of renally cleared antibiotics in patients with impaired renal function is present, with the exception of meropenem. We reviewed the literature to summarize the available evidence on the adequacy of the recommended dose reduction in terms of achieving equivalent drug exposure or pharmacokinetic/pharmacodynamic (PK/PD) target attainment compared to that in patients with adequate renal function receiving the regular dose. All studies reporting antibiotic drug exposure and/or PK/PD target attainment after dose reduction of antibiotics in patients with impaired renal function were included.

We included 27 studies, most studies with fair quality of evidence and most studies were of β-lactams. Best evidence was available for meropenem: four studies were included, of which two studies with good quality of evidence. Drug exposure for meropenem is 158% to 286% higher in patients with impaired renal function receiving reduced doses compared to patients with adequate

renal function receiving regular doses. For all other antibiotics, good-quality studies were scarce or studies were missing at all. For example, for ciprofloxacin, ceftazidime and piperacillin/tazobactam no good-quality studies were present, while for cefuroxime and amoxicillin/clavulanic acid studies were lacking at all. Therefore, it is unknown if this dose reduction leads to equivalent antibiotic drug exposure or PK/PD target attainment compared to patient with adequate renal function.

This result is striking, since the recommended dose reduction is standard of care for decades as incorporated in all clinical guidelines. Additionally, it is one of the quality indicators defining appropriate antibiotic use. Therefore, we have investigated the recommended dose reduction of two important antibiotics used in the hospital for which a dose reduction is standard of care in patients with impaired renal function: ciprofloxacin and ceftazidime (**Chapter 4 and 5**).

Before embarking on these studies, we first developed and validated a rapid, reproducible, and sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay for the determination of total and unbound ciprofloxacin plasma concentrations (**Chapter 3**), in order to be able to reliably assess ciprofloxacin exposure.

We fully validated the method over a concentration range of 0.02–5.0 mg/L, according to the U.S. Food and Drug Administration guidelines. The total run time was 1.5 minutes. For total ciprofloxacin plasma concentrations, the mean accuracy ranged from 94.5% to 105.0% across the validated range, the intraday imprecision was ≤7.6%, and the interday imprecision was ≤9.8%. For unbound ciprofloxacin plasma concentrations, the mean accuracy ranged from 92.8% to 102.1% across the validated range, the intraday imprecision was ≤7.0%, and the interday imprecision was ≤9.6%.

We have shown that the method is precise and accurate. Additionally, we have implemented the method in clinical care and research projects at a university hospital, permitting rapid determination of total and unbound ciprofloxacin.

In **Chapter 4** we showed that the PK/PD target of ciprofloxacin [area under the concentration-time curve/minimum inhibitory concentration (AUC/MIC) ≥125] is not attained in the majority of adult patients on general wards for clinically relevant bacteria with MICs at or just below the clinical breakpoint, regardless of renal function. However, the risk of not attaining the target appears to be highest for patients with impaired renal function receiving guideline-recommended reduced doses, as drug exposure is significantly lower in these patients compared to patients with adequate renal function receiving regular doses.

We performed a single-centre prospective observational cohort study including adult patients on general wards treated with ciprofloxacin. Three blood samples per patient were obtained for ciprofloxacin concentration measurement. Individual AUCs were calculated using a population pharmacokinetic (PK) model developed by non-linear mixed-effects modelling (NONMEM).

We included 40 patients, of whom eight had impaired renal function and were treated with a guideline-recommended reduced dose. Using the clinical breakpoint MIC of the most isolated bacteria (*Escherichia coli*, 0.25 mg/L), $AUC_{0\text{-}24}$/MIC ≥125 was attained in 13/32 (41%) patients with adequate renal function receiving regular doses and in 1/8 (13%) patients with impaired renal function receiving reduced doses. Median drug exposure ($AUC_{0\text{-}24}$) for patients with impaired renal function was 19.0 [interquartile range (IQR) 14.2-23.3] mg/L•h, which was statistically significantly lower than that for patients with adequate renal function [29.3 (IQR 25.0-36.0) mg/L•h] ($p < 0.01$).

In **Chapter 5** we showed that the PK/PD target of ceftazidime (50%T >MIC) is attained in the majority of adult patients on general wards for clinically relevant bacteria with MICs up to and including the breakpoint MIC of *Pseudomonas aeruginosa* (8 mg/L). We performed a multi-centre prospective observational cohort study including adult patients on general wards treated with ceftazidime. Three blood samples per patient were obtained for ceftazidime concentration measurement. Individual T>MIC and AUCs were calculated using a population PK model developed by NONMEM.

We included 40 patients, of whom 10 patients had moderately impaired renal function and 5 had severely impaired renal function, all patients with impaired renal function were treated with a guideline-recommended reduced dose. Using the clinical breakpoint MIC of the most important bacteria (*Pseudomonas aeruginosa* 8 mg/L), 50%$T_{0\text{-}24}$ >MIC was attained in all 25 patients with adequate renal function, in 9/10 (90%) patients with moderately impaired renal function and in all 5 patients with severely impaired renal function. No differences in drug exposure were observed between patients of the different renal function groups.

In **Chapter 6** we showed that oral dosing of ciprofloxacin as Gram-negative infection prophylaxis in haematological patients with mild-to-moderate gastro-intestinal (GI) mucositis capable of oral intake leads to adequate systemic drug exposure, since no differences in exposure were observed compared to healthy volunteers.

We performed a multi-centre prospective observational cohort study including adult patients with haematological malignancies receiving oral ciprofloxacin as Gram-negative prophylaxis to explore the impact of GI-mucositis on oral bioavailability and clearance in order to assure adequate systemic exposure with application of the currently used dose regimen.

We collected ciprofloxacin plasma concentrations at various timepoints after oral ciprofloxacin administration and at various days after completion of chemotherapy. Data obtained after oral and intravenous ciprofloxacin administration in 28 healthy volunteers without mucositis served as a control group. We assessed the degree of GI-mucositis for haematological patients using the Daily Gut Score (DGS), plasma citrulline and albumin. Data were analysed by NONMEM.

We included 47 patients with a wide variety of haematological malignancies between 0–30 days after start of chemotherapy. Mucositis was generally mild [DGS median (IQR) 1 (1–1) and citrulline 16 µmol/L (12–23)]. The time to C_{max} was longer in haematological patients compared with healthy volunteers, but no difference in systemic drug exposure was observed.

In **Chapter 7** we discussed our findings and clinical implications regarding appropriate antibiotic use, in particular for patients with impaired renal function and haematological patients with mucositis. Methodological issues regarding the different executed studies were considered. Additionally, we provided directions for future research.

Currently, we are performing a new study to investigate an alternative dose reduction of ciprofloxacin for patients with impaired renal function: a 25% dose reduction instead of the currently recommended 50% dose reduction. Additionally, we are prospectively validating the currently recommended dose reduction of cefuroxime for patients with impaired renal function.

Chapter 9

Summary in Dutch

Nederlandse samenvatting

Adequaat gebruik van antibiotica leidt tot betere klinische uitkomsten voor patiënten, tot minder ontwikkeling van resistente bacteriën en tot lagere zorgkosten. Verschillende kwaliteitsindicatoren meten adequaat antibiotica gebruik. Eén van deze kwaliteitsindicatoren betreft het aanpassen van de dosering van antibiotica aan de nierfunctie. In alle geldende (inter)nationale richtlijnen staat dan ook dat de dosering van antibiotica die voornamelijk door de nieren uit het lichaam worden uitgescheiden, moet worden verlaagd bij patiënten met een verminderde nierfunctie. Het voornaamste doel van deze verlaging is:

1) Het voorkomen van een te hoge concentratie antibiotica in het bloed en daarmee het voorkomen van toxiciteit en schade voor de patiënt.
2) Het bereiken van dezelfde blootstelling aan antibiotica vergeleken met de blootstelling in patiënten met een normale nierfunctie die de standaarddosering antibiotica krijgen, oftewel het bereiken van gelijkwaardigheid.

In de praktijk blijkt echter dat de dosering vaak niet wordt verlaagd voor patiënten met een verminderde nierfunctie. Artsen zouden bang zijn voor onderbehandeling van infecties met de verlaagde dosering. Daarnaast bestaat er onduidelijkheid binnen richtlijnen in de mate waarin aanbevolen wordt om de dosis te verlagen en vanaf welke nierfunctie dat van toepassing is. Momenteel is het wetenschappelijke bewijs voor gelijkwaardigheid van de aanbevolen dosisverlaging niet duidelijk. Daarnaast is het ook onduidelijk of deze dosisverlaging wel doeltreffend is.

In dit proefschrift hebben we systematisch alle literatuur geëvalueerd, die ooit gepubliceerd is sinds de ontdekking van het eerste antibioticum in 1928, over het verlagen van de dosering antibiotica bij patiënten met een verminderde nierfunctie (**Hoofdstuk 2**). Om de blootstelling aan antibiotica in de klinische praktijk te onderzoeken is een gevalideerde methode nodig om de concentratie van deze antibiotica in het bloed te meten. Daarom hebben we een meetmethode ontwikkeld en gevalideerd om de totale en de ongebonden (actieve) concentratie ciprofloxacine te meten in plasma (bloed) (**Hoofdstuk 3**). Vervolgens hebben we onderzocht of de huidige dosisverlaging van twee antibiotica (ciprofloxacine en ceftazidim) in patiënten met een verminderde nierfunctie gelijkwaardig en doeltreffend is in de klinische praktijk vergeleken met patiënten met een goede nierfunctie die de reguliere dosering kregen (**Hoofdstuk 4 en 5**). Tot slot hebben we, om de doeltreffendheid van de dosering antibiotica volledig te kunnen onderzoeken, ook de biologische beschikbaarheid onderzocht (de andere farmacokinetische parameter die de antibiotica blootstelling beïnvloedt). De biologische beschikbaarheid bestaat, bij orale toediening, voor een groot deel uit de absorptie van het geneesmiddel vanuit het maag-darmkanaal. Daarom hebben we de absorptie van orale ciprofloxacine onderzocht in patiënten met kwaadaardige bloedziekten en een ontstoken maag-darm slijmvlies (mucositis) (**Hoofdstuk 6**).

De term PK/PD target attainment komt veelvuldig in dit proefschrift terug. Het is een afkorting van pharmacokinetic/pharmacodynamic target attainment. Dit PK/PD target beschrijft de blootstelling aan antibiotica in relatie tot het remmen van de groei van bacteriën. Voor veel antibiotica is een optimaal PK/PD target bekend, waarbij de bacterie het meest doeltreffend wordt bestreden.

Voor ciprofloxacine is het PK/PD target de *area under the concentration-time curve* (AUC), een maat voor de totale blootstelling aan ciprofloxacine, gedeeld door de *minimum inhibitory concentration*

(MIC), de laagste concentratie van een antibioticum waarbij de verdere groei van bacteriën wordt geremd. Ciprofloxacine is doeltreffend als het PK/PD target van AUC/MIC ≥125 wordt behaald.

Voor ceftazidim is het PK/PD target het percentage tijd van een doseerinterval dat de concentratie boven de MIC blijft. Ceftazidim is doeltreffend als het gedurende 50% van de tijd van een doseerinterval boven de MIC blijft (50%T >MIC).

In **Hoofdstuk 2** hebben we laten zien dat slechts voor één antibioticum (meropenem) overtuigend onderzoek is gedaan naar de aanbevolen dosisverlaging van antibiotica voor patiënten met een verminderde nierfunctie.

We hebben systematisch alle literatuur geëvalueerd over de gelijkwaardigheid en doeltreffendheid van de dosisverlaging, uitgedrukt in gelijkwaardige antibiotica blootstelling of doeltreffendheid middels PK/PD target attainment na behandeling met deze verlaagde dosering. Alle onderzoeken die iets vermelden over antibiotica blootstelling of PK/PD target attainment na dosisverlaging van antibiotica bij patiënten met een verminderde nierfunctie werden geïncludeerd.

Uiteindelijk zijn 27 studies geïncludeerd, de meeste studies gingen over β-lactam antibiotica en hadden een matige studiekwaliteit. Het beste bewijs was beschikbaar voor meropenem: er werden vier studies geïncludeerd, waarvan twee studies met goede studiekwaliteit. De antibiotica concentraties voor patiënten met een verminderde nierfunctie die werden behandeld met een verlaagde dosering meropenem, zijn 158% tot 286% hoger, vergeleken met patiënten met een adequate nierfunctie, die werden behandeld met de standaarddosering. Voor alle andere antibiotica waren studies van goede kwaliteit schaars of ontbraken studies zelfs helemaal. Zo waren er voor ciprofloxacine, ceftazidim en piperacilline/tazobactam geen studies van goede kwaliteit en voor cefuroxim en augmentin ontbraken studies in zijn geheel. Zodoende blijkt de dosisverlaging voor patiënten met een verminderde nierfunctie onvoldoende te zijn onderzocht. Het is dan ook niet bekend of deze dosisverlaging leidt tot gelijkwaardige blootstelling aan antibiotica of tot doeltreffende PK/PD target attainment.

Dit resultaat is opvallend, aangezien de aanbevolen dosisverlaging al tientallen jaren standaardzorg is, zoals ook in alle richtlijnen staat. Bovendien is het één van de kwaliteitsindicatoren die adequaat antibioticagebruik meten. Daarom hebben we de aanbevolen dosisverlaging onderzocht van twee belangrijke antibiotica die in het ziekenhuis worden gebruikt en waarvoor een dosisverlaging standaardzorg is voor patiënten met een verminderde nierfunctie: ciprofloxacine en ceftazidim (**Hoofdstuk 4 en 5**).

Voordat we aan deze studies begonnen, hebben we eerst een snelle en nauwkeurige meetmethode ontwikkeld en gevalideerd om de totale en de ongebonden (actieve) concentratie ciprofloxacine te meten in plasma (bloed). Hiervoor is gebruikt gemaakt van de meetmethode liquid chromatography-tandem mass spectrometry (LC-MS/MS) (**Hoofdstuk 3).**

We hebben de methode volledig gevalideerd over een concentratierange van 0,02–5,0 mg/L, volgens de richtlijnen van de Amerikaanse Food and Drug Administration (FDA). De totale doorlooptijd van het systeem was 1,5 minuut. De meetmethode is nauwkeurig voor het meten van de totale concentratie ciprofloxacine, met een gemiddelde juistheid van 94,5% tot 105,0% binnen de gevalideerde concentratierange. De imprecisie binnen dezelfde dag was ≤7.6%, de imprecisie tussen verschillende dagen was ≤9.8%. Daarnaast is de meetmethode ook nauwkeurig voor het meten van

de ongebonden concentratie ciprofloxacine, met een gemiddelde juistheid van 92,8% tot 102,1% binnen de gevalideerde concentratierange. De imprecisie binnen dezelfde dag was ≤7,0%, de imprecisie tussen verschillende dagen was ≤9,6%.

Tot slot hebben we de meetmethode geïmplementeerd in zowel de klinische praktijk als binnen verschillende onderzoeksprojecten in een academisch ziekenhuis, waardoor een snelle bepaling van zowel de totale als de ongebonden concentratie ciprofloxacine in plasma mogelijk is.

In **Hoofdstuk 4** hebben we laten zien dat de huidige dosering ciprofloxacine niet doeltreffend is in de behandeling van infecties door de belangrijkste bacteriën, met MIC's op of net onder het klinische breekpunt voor de meerderheid van de volwassen patiënten op verpleegafdelingen, ongeacht hun nierfunctie.

We hebben een single-center cohortstudie uitgevoerd bij volwassen patiënten op de verpleegafdelingen, die werden behandeld voor een bacteriële infectie met ciprofloxacine. Patiënten met een normale nierfunctie kregen de standaarddosering ciprofloxacine en patiënten met een verminderde nierfunctie kregen de verlaagde dosering, conform de huidige (inter)nationale richtlijnen. Er werd per patiënt drie keer bloed afgenomen om de concentratie ciprofloxacine te meten. Vervolgens werd de blootstelling aan ciprofloxacine berekend door een populatie farmacokinetische model te maken met behulp van *non-linear mixed-effects modelling* (*NONMEM*).

We hebben 40 patiënten geïncludeerd, van wie er acht een verminderde nierfunctie hadden, deze werden allemaal behandeld met een door de richtlijn aanbevolen verlaagde dosering. Onze resultaten lieten zien dat in 13 van de 32 patiënten (41%) met een adequate nierfunctie het PK/PD target ($AUC_{0\text{-}24}$/MIC ≥125) wordt behaald en in slechts 1 van de 8 patiënten (13%) met een verminderde nierfunctie, bij een MIC-waarde van de belangrijkste bacterie waarbij ciprofloxacine veel wordt ingezet (*Escherichia coli*, breekpunt MIC 0,25 mg/L). Tevens was de mediane blootstelling aan ciprofloxacine significant lager in patiënten met een verminderde nierfunctie die de verlaagde dosering kregen [19.0, interquartile range (IQR) 14.2 – 23.3 mg/L•u], vergeleken met patiënten met een adequate nierfunctie die de standaarddosering kregen [29.3, IQR 25.0 – 36.0 mg/L•u ($p < 0.01$)]. Het risico dat het PK/PD target niet wordt behaald, en ciprofloxacine dus niet doeltreffend is, is het grootst voor patiënten met een verminderde nierfunctie die werden behandeld met de aanbevolen dosisverlaging, aangezien de blootstelling aan ciprofloxacine bij deze patiënten significant lager is.

Onze resultaten tonen dus aan dat de huidige dosering van ciprofloxacine te laag is voor voldoende doeltreffendheid en dat dit des te meer geldt voor patiënten met een verminderde nierfunctie, die de verlaagde dosering krijgen, omdat de dosering niet gelijkwaardig is. De dosering ciprofloxacine zou dus moeten worden verhoogd voor voldoende doeltreffendheid, voornamelijk bij patiënten met een verminderde nierfunctie.

In **Hoofdstuk 5** hebben we laten zien dat de huidige dosering ceftazidim wel doeltreffend is in de behandeling van infecties veroorzaakt door bacteriën met MIC's tot aan het klinische breekpunt van een veel voorkomende bacterie waar ceftazidim voor wordt voorgeschreven (*Pseudomonas aeruginosa*, breekpunt MIC 8 mg/L*)* voor volwassen patiënten op verpleegafdelingen.

We hebben een multi-center cohortstudie uitgevoerd in volwassen patiënten op verpleegafdelingen die werden behandeld voor een bacteriële infectie met ceftazidim. Patiënten met een normale nierfunctie kregen de standaarddosering ceftazidim en patiënten met een matig of ernstig

verminderde nierfunctie de verlaagde doseringen, conform de huidige (inter)nationale richtlijnen. Er werd per patiënt drie keer bloed afgenomen om de concentratie ceftazidim te meten. Vervolgens werd de blootstelling aan ceftazidim berekend door een populatie farmacokinetische model te maken met behulp van *NONMEM*.

We hebben 40 patiënten geïncludeerd, van wie tien patiënten met een matig verminderde nierfunctie en vijf met een ernstig verminderde nierfunctie. Alle patiënten met een verminderde nierfunctie werden behandeld met een door de richtlijn aanbevolen verlaagde dosering.

Onze resultaten lieten zien dat het PK/PD target ($50\%T_{0\text{-}24}$ >MIC) wordt behaald in vrijwel alle patiënten ongeacht de nierfunctiegroep bij de MIC-waarde van 8 mg/L. Het PK/PD target werd behaald in alle 25 patiënten met een adequate nierfunctie, in 9 van de 10 patiënten (90%) met een matig verminderde nierfunctie en in alle 5 patiënten met een ernstig gestoorde nierfunctie. Er werden geen verschillen in blootstelling aan ceftazidim waargenomen tussen de verschillende nierfunctiegroepen, de dosering is dus gelijkwaardig.

In **Hoofdstuk 6** hebben we laten zien dat orale toegediende ciprofloxacine goed wordt opgenomen uit het maag-darm kanaal bij patiënten met kwaadaardige bloedziekten en een mild tot matig ontstoken maag-darm slijmvlies (gastro-intestinale (GI) mucositis). De blootstelling aan ciprofloxacine in deze patiënten was gelijk aan die van gezonde vrijwilligers.

Patiënten met kwaadaardige bloedziekten worden vaak behandeld met zware chemotherapie, dit leidt tot 1) verlies van afweer (neutropenie) en 2) mucositis. Ter voorkoming van infecties door de neutropenie krijgen deze patiënten uit voorzorg antibiotica (profylaxe), namelijk ciprofloxacine. De absorptie van ciprofloxacine zou door mucositis ofwel enorm toegenomen kunnen zijn, met toxische spiegels tot gevolg, ofwel enorm afgenomen kunnen zijn, leidend tot te lage en mogelijk sub-therapeutische spiegels.

We hebben een multi-center cohortstudie uitgevoerd in volwassen patiënten op verpleegafdelingen met kwaadaardige bloedziekten, die oraal ciprofloxacine kregen als profylaxe. We hebben de impact van GI-mucositis op de biologische beschikbaarheid en klaring onderzocht, de twee farmacokinetische parameters die samen de blootstelling (ofwel de AUC) bepalen.

We hebben plasmaconcentraties van ciprofloxacine gemeten op verschillende tijdstippen na orale toediening van ciprofloxacine en op verschillende dagen na de chemotherapie. Deze data werd vergeleken met data van gezonde vrijwilligers zonder mucositis, die dienden als controlegroep.

De mate van GI-mucositis werd bepaald met de *Daily Gut Score* (DGS) en de citrulline en albumine concentratie in het bloed. Gegevens werden geanalyseerd met behulp van *NONMEM*.

We hebben 47 patiënten geïncludeerd met verschillende kwaadaardige bloedziekten tussen 0 en 30 dagen na de chemotherapie. Mucositis was over het algemeen mild [DGS mediaan (IQR) 1 (1–1) en citrulline 16 µmol/L (12–23)]. De tijd totdat de piekspiegel werd bereikt na ciprofloxacine inname was langer bij patiënten met kwaadaardige bloedziekten in vergelijking met de gezonde vrijwilligers, maar er werd geen verschil in blootstelling aan ciprofloxacine waargenomen.

Onze resultaten tonen dus aan dat orale toedieningen van ciprofloxacine goed worden opgenomen vanuit het maag-darm kanaal bij patiënten met kwaadaardige bloedziekten en mucositis, aangezien de blootstelling gelijk is aan die van gezonde vrijwilligers.

In **Hoofdstuk 7** bespreken we de bevindingen uit onze studies en hun klinische betekenis met betrekking tot het adequaat gebruik van antibiotica, in het bijzonder voor patiënten met een verminderde nierfunctie en patiënten met kwaadaardige bloedziekten met mucositis. Ook bespreken we de methodologische beperkingen van de uitgevoerde studies. Ten slotte doen we aanbevelingen voor de richting van toekomstig onderzoek.

Dit proefschrift kwam voort uit de vraag waarom de dosering van antibiotica vaak niet wordt verlaagd bij patiënten met een verminderde nierfunctie. Gebaseerd op het huidige gebrek aan bewijs voor deze aanbeveling, hebben artsen die terughoudend zijn met het verlagen van de dosering antibiotica gelijk (**Hoofdstuk 2**). Voortkomend uit dit gebrek aan bewijs hebben wij dit onderzocht voor twee belangrijke antibiotica: ciprofloxacine en ceftazidim (**Hoofdstuk 4 en 5**). Hieruit blijkt dat artsen die terughoudend zijn echter maar deels gelijk hebben: de dosisverlaging lijkt niet gelijkwaardig en doeltreffend voor ciprofloxacine, maar wel gelijkwaardig en doeltreffend voor ceftazidim. Om deze reden doen we momenteel de CIPRO-3-studie waarin we een alternatieve dosisverlaging van ciprofloxacine onderzoeken voor patiënten met een verminderde nierfunctie: een dosisverlaging van 25% in plaats van de momenteel aanbevolen dosisverlaging van 50%. Daarnaast onderzoeken we nog een derde antibioticum; cefuroxim, om meer bewijs te creëren rondom de noodzaak voor het verlagen van de dosering cefuroxim bij patiënten met een verminderde nierfunctie.

Appendices

Appendix I – List of publications

SL de Vroom, RM van Hest, FV van Daalen, SD Kuil, RAA Mathôt, SE Geerlings, NGL Jager.
Pharmacokinetic/pharmacodynamic target attainment of ciprofloxacin in adult patients on general wards with adequate and impaired renal function.
Int J Antimicrob Agents. 2020 Nov;56(5):106166. doi: 10.1016/j.ijantimicag.2020.106166. Epub 2020 Sep 14. PMID: 32941947.

SL de Vroom, FV van Daalen, SE Zieck, RAA Mathôt, RM van Hest, SE Geerlings.
Current evidence on dose reduction of antibiotics in patients with impaired renal function: a systematic review.
Clin Microbiol Infect. 2021 Mar;27(3):352-363. doi: 10.1016/j.cmi.2020.11.032. Epub 2020 Dec 5. PMID: 33290864.

SL de Vroom, MCM Pistorius, YA Bijleveld, SE Geerlings, RAA Mathôt, RM van Hest, NGL Jager.
Development and Validation of a Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) Assay for the Determination of Total and Unbound Ciprofloxacin Concentrations in Human Plasma.
Ther Drug Monit. 2022 Aug 1;44(4):552-557. doi: 10.1097/FTD.0000000000000969. PMID: 35094000.

SL de Vroom*, KP van Rhee*, RM van Hest, PD van der Linden, SH Tonino, E Molendijk, RAA Mathôt, NMA Blijlevens, CAJ Knibbe, RJM Bruggemann, SE Geerlings.
Impact of mucositis on oral bioavailability and systemic exposure of ciprofloxacin Gram-negative infection prophylaxis in patients with haematological malignancies.
J Antimicrob Chemother. 2022 Oct 28;77(11):3069-3076. doi: 10.1093/jac/dkac283. PMID: 35996887; PMCID: PMC9616544.

**These authors contributed equally to this work*

SL de Vroom*, SE Zieck*, FP Mulder, G van Twillert, RAA Mathôt, SE Geerlings, RM van Hest.
Pharmacokinetic/pharmacodynamic target attainment of ceftazidime in adult patients on general wards with different degrees of renal function: a prospective observational bicenter cohort study.
Antibiotics. 2023; 12(3):469

**These authors contributed equally to this work*

Other publications:

JC Teepen, **SL de Vroom**, FE van Leeuwen, WJ Tissing, LC Kremer, CM Ronckers.
Risk of subsequent gastrointestinal cancer among childhood cancer survivors: A systematic review.
Cancer Treat Rev. 2016 Feb;43:92-103. doi: 10.1016/j.ctrv.2015.12.002. Epub 2015 Dec 17. PMID: 26827697.

JC Teepen, **SL de Vroom**, FE van Leeuwen, WJ Tissing, LC Kremer, CM Ronckers.
A systematic review: Childhood cancer survivors and gastrointestinal cancer.
Cancer Treat Rev. 2017 Apr;55:210. doi: 10.1016/j.ctrv.2016.06.003. Epub 2016 Jun 7. PMID: 27342038.

CJ Hodiamont, AK van den Broek, **SL de Vroom**, JM Prins, RAA Mathôt, RM van Hest.
Clinical pharmacokinetics of gentamicin in various patient populations and consequences for optimal dosing for gram-negative infections - an updated review.

Clin Pharmacokinet. 2022 Aug;61(8):1075-1094. doi: 10.1007/s40262-022-01143-0. Epub 2022 Jun 27. PMID: 35754071; PMCID: PMC9349143.

Appendix II - Contributing authors

Yuma A Bijleveld
Department of Hospital Pharmacy, Division of Clinical Pharmacology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

Nicole M A Blijlevens
Department of Hematology, Radboud University Medical Center, Nijmegen, the Netherlands

Roger J M Brüggemann
Department of Pharmacy and Radboud Institute of Health Science, Radboud University Medical Center, Nijmegen, the Netherlands

Frederike V van Daalen
Department of Internal Medicine, Division of Infectious Diseases, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

Suzanne E Geerlings
Department of Internal Medicine, Division of Infectious Diseases, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

Reinier M van Hest
Department of Hospital Pharmacy, Division of Clinical Pharmacology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

Sacha D Kuil
Department of Medical Microbiology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

Nynke G L Jager
Department of Hospital Pharmacy, Division of Clinical Pharmacology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands
Department of Hospital Pharmacy, Division of Clinical Pharmacology, Radboud University Medical Center, Nijmegen, the Netherlands

Frouke Ph Mulder
Department of Hospital Pharmacy, Division of Clinical Pharmacology, Noordwest Ziekenhuisgroep, Alkmaar, the Netherlands

Catherijne A J Knibbe
Division of Systems Biomedicine and Pharmacology, Leiden Academic Centre for Drug Research, Leiden, the Netherlands
Department of Hospital Pharmacy, Division of Clinical Pharmacology, St. Antonius Hospital, Nieuwegein, the Netherlands

Paul D van der Linden
Department of Hospital Pharmacy, Division of Clinical Pharmacology, Tergooi MC, Hilversum, the Netherlands

Ron A A Mathôt
Department of Hospital Pharmacy, Division of Clinical Pharmacology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

Eva Molendijk
Department of Hematology, Radboud University Medical Center, Nijmegen, the Netherlands

Marcel C M Pistorius
Department of Hospital Pharmacy, Division of Clinical Pharmacology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

Koen P van Rhee
Department of Hospital Pharmacy, Division of Clinical Pharmacology, Tergooi MC, Hilversum, the Netherlands
Department of Hospital Pharmacy, Division of Clinical Pharmacology, St. Jansdal Hospital, Harderwijk, the Netherlands
Division of Systems Biomedicine and Pharmacology, Leiden Academic Centre for Drug Research, Leiden, the Netherlands

Sanne H Tonino
Department of Hematology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

Gitte van Twillert
Department of Internal Medicine, Division of Infectious Diseases, Noordwest Ziekenhuisgroep, Alkmaar, the Netherlands

Saskia E Zieck
Department of Hospital Pharmacy, Division of Clinical Pharmacology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands
Department of Hospital Pharmacy, Division of Clinical Pharmacology, Noordwest Ziekenhuisgroep, Alkmaar, the Netherlands

Appendix III - PhD portfolio

Name PhD student:	Suzanne de Vroom
PhD period:	Mei 2018 – July 2021
Names of PhD supervisors:	Prof. dr. S.E. Geerlings Prof. dr. R.A.A. Mathôt Dr. R.M. van Hest

General courses	**Year**	**ECTS**
E-BROK	2018	1.5
The AMC World of Science	2018	0.7
Practical Biostatistics	2018	1.4
Endnote	2019	0.1
Clinical Epidemiology 4: Systematic Reviews	2019	0.7
Oral presentation in English	2020	0.8
Scientific Writing in English for publication	2020	1.5

Specific courses	**Year**	**ECTS**
NONMEM	2018-2021	5.0
Infectious Diseases	2018	1.3

Seminars, workshops and master classes	**Year**	**ECTS**
APROVE Science Night	2019	0.1

Oral presentations	**Year**	**ECTS**
29th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), Amsterdam, the Netherlands	2019	0.5
FIGON Dutch Medicines Days, Leiden, the Netherlands	2019	0.5
Internistendagen, Utrecht, the Netherlands	2019	0.5

(Inter)national conferences	**Year**	**ECTS**
European Congress of Clinical Microbiology and Infectious diseases (ECCMID), Amsterdam, the Netherlands	2019	0.5
Infectious Diseases Symposium Amsterdam (IDSA), Amsterdam, the Netherlands	2019-2021	0.75
FIGON Dutch Medicines Days, Leiden, the Netherlands	2019	0.3

Other	**Year**	**ECTS**
Infectious Diseases and HIV weekly clinical meetings	2018-2021	2.0
Master Evidence Based Practice in Medicine, University of Amsterdam	2019-2021	90

Student supervision	**Year**	**ECTS**
Cheyenne Beverloo	2019	1.0

Bachelor thesis: The effect of ciprofloxacin on the QT/QTc interval.		
Franny Rensink Bachelor thesis: The clinical outcome of patients with an infection caused by a ciprofloxacin-resistant microorganism treated with ciprofloxacin.	2019	1.0
Saskia Zieck Onderzoek ter registratie tot Ziekenhuisapotheker: Pharmacokinetic/pharmacodynamic target attainment of ceftazidime in adult patients on general wards with different degrees of renal function: a prospective observational bicenter cohort study.	2019-2021	1.5
Tamara Rodenburg Master thesis: The association between ciprofloxacin plasma concentrations and its adverse drug reactions.	2021	1.5

Grants	**Year**
Stichting de Merel	2019
Amsterdams Universiteitsfonds	2020
NoordWest Ziekenhuisgroep (co-applicant)	2021

Total ECT	113.15