CRITICAL CARE

COMMENTARY

Antibiotics for the critically ill: more than just selecting appropriate initial therapy

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See related research by Carlier *et al.*, http://ccforum.com/content/17/3/R84

Abstract

Critically ill patients with infection provide a number of challenges to clinicians in terms of optimizing their antimicrobial treatment. Of foremost importance, initial antibiotic treatment should be selected as to provide coverage for the causative pathogens. However, the administration of those antibiotics (dosing, interval of administration, duration of infusion, route of administration) should be prescribed in a manner to ensure optimal drug delivery to the site of infection. This is a challenge given the characteristics of many infected critically ill patients (shock, elevated cardiac output in the resuscitated state, supranormal creatinine clearance, increased volume of distribution). Intensive care unit practitioners should utilize treatment strategies that strive to deliver antibiotics in an individualized manner aimed at attaining desired pharmacokinetic/pharmacodynamic targets. The goal of such a treatment strategy is to maximize the likelihood of curing the infection and allowing the critically ill patient the best opportunity for recovery. Effective implementation of antimicrobial optimization delivery strategies will likely require a multi-disciplinary approach including intensivists, pharmacists, and infectious disease specialists.

In this issue of *Critical Care*, Carlier and colleagues describe pharmacokinetic/pharmacodynamic (PK/PD) target attainment in critically ill patients receiving meropenem or piperacillin/tazobactam as extended infusions [1]. These investigators found that 48% of patients did not achieve the desired PK/PD target (100% time that the free antibiotic fraction exceeds the minimum inhibitory concentration (MIC)), of which almost 80% had a measured creatinine clearance (CrCl) >130 ml/minute. More worrisome was the observation that 37% of patients with CrCl >130 ml/minute did not achieve the minimum PK/PD target (50% time that the free antibiotic fraction exceeds the MIC). These investigators concluded that patients not attaining PK/PD targets may be at risk for treatment failure without upward antibiotic dose titration. The findings from this study suggest that we should add inadequate antibiotic dosing to the list of antibiotic treatment characteristics that can adversely impact the outcomes of infected critically ill patients. This is an important issue when one considers that antibiotic use is often viewed as a variable expense in the hospital setting that can be manipulated to achieve cost savings. Such an attitude is flawed with the understanding that the most cost-effective approach to treating serious infections is the approach that is most likely to achieve rapid clinical success.

The most recent Surviving Sepsis Campaign Guidelines recommend that broad-spectrum antibiotics be administered within the first hour of recognition of septic shock, with one or more agents that have activity against the likely causative pathogens, and that the duration of therapy typically be between 7 and 10 days [2]. These recommendations are based on studies demonstrating that the timing of appropriate antibiotic therapy, defined as an antimicrobial regimen demonstrating *in vitro* activity against the isolated organism(s) responsible for the infection, is critical in determining the outcomes of such patients [3-5]. However, even if an appropriate initial therapy with an active antibiotic regimen is administered, patient outcomes may not be optimized due to inadequate drug concentration delivery to the site of infection. This is important for both concentration-dependent antibiotics as well as for antibiotics whose efficacy is based on the achieved dosing interval time that the antibiotic concentration is above the MIC of the pathogen. Moreover, many prescribers of antimicrobial therapy in the hospitalized patient are unaware that drug delivery targets are not met given that therapeutic drug monitoring is not routinely performed for most antibiotic classes.

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Recent randomized trials of inadequately dosed antibiotics (ceftobiprole and tigecycline) for patients with nosocomial pneumonia have demonstrated greater treatment failures and mortality for the inadequately dosed antibiotics compared to more optimally dosed comparators [6-8]. The usual rationale for selecting such doses for investigational antibiotics is to minimize any drug-related toxicity. This is highlighted by the current dosing of tigecycline that is half of the originally considered dosing due to greater rates of nausea and vomiting at the higher doses (the higher doses being more likely to achieve desired drug concentration PK/PD targets). Additionally, the results from two meta-analyses and a recent clinical trial found that the use of prolonged infusions of beta-lactam antibiotics achieved similar clinical results compared to similar or higher dosed intermittent infusion antibiotic therapy [9-11]. However, in one of the meta-analyses, a trend towards benefit among patients receiving intermittent infusion antibiotics possibly explained by the use of higher antibiotic doses was observed [10]. For fair balance it should be noted that another recent meta-analysis showed that prolonged or continuous infusion of pipercillin-tazobactam or carbapenems was associated with lower mortality, although these results were primarily from nonrandomized studies [12].

The influence of CrCl on outcomes among patients with severe infections also seems to be an important determinant of clinical outcome, in large part by influencing antibiotic elimination and achieved drug concentration targets at the infection site. Elevated CrCl has been shown to be an important predictor of subtherapeutic beta-lactam concentrations [13,14]. The use of prolonged antibiotic infusions has been proposed as a strategy to achieve appropriate targeted antibiotic blood concentrations in patients with augmented renal clearance [15]. The potential detrimental influence of augmented CrCl on the outcomes of critically ill patients with infections has been demonstrated in several randomized trials. Kollef and colleagues [16] found that patients with CrCl ≥150 ml/minute had greater clinical cure rates for VAP with 10 days of imipenem compared to 7 days of meropenem despite administering meropenem as a prolonged infusion. In a trial of nosocomial pneumonia, ceftobiprole dosed at 500 mg every 8 hours was clinically inferior and associated with greater mortality compared to ceftazidime dosed at 2 grams every 8 hours plus linezolid dosed at 600 mg every 12 hours [8]. In this trial, increased CrCl was found to be associated with a greater risk of mortality, suggesting that under-dosing of antibiotics may be most detrimental in patients with normal or augmented CrCl. This may also explain the hesitation among intensivists to use the currently approved dosing regimen of ceftaroline (600 mg every 12 hours) in critically ill patients as it has not been rigorously evaluated in that population.

Carbapenem antibiotics and beta-lactams represent the most common antibiotics currently prescribed in critically ill patients. However, there is no routine therapeutic drug monitoring available for these agents as exists for aminoglycosides and vancomycin. This creates uncertainty for many clinicians prescribing antibiotics, especially when patient-specific conditions such as renal function, volume status, and hemodynamics are changing. Therefore, intensivists must carefully consider how antibiotics are delivered in terms of dose, interval of administration, and duration of infusion in order to optimize PK/PD target attainment. The duration of therapy must also be carefully considered in that longer durations of treatment for optimal success may be necessary for difficult to treat pathogens such as *Pseudomonas* or *Acinetobacter* species [16]. A recent example of new methods for achieving such targets is the use of advanced aerosol delivery systems that hold the promise of exceeding therapeutic targets in the lung with antibiotics such as colistin, aminoglycosides, and fosfomycin that cannot be accomplished with parenteral administration.

Conclusion

Carlier and colleagues must be commended for their study highlighting the relationship between elevated CrCl and inability to attain PK/PD targets for prescribed antibiotics despite the use of prolonged infusions. This is an important finding given the increasing use of prolonged antibiotic infusions and suggests that clinicians should carefully evaluate the presence of elevated CrCl when making decisions regarding antibiotic dosing. From a practical standpoint, the use of an antibiotic loading dose along with the prolonged antibiotic infusion should be considered in patients with elevated CrCl to allow for more rapid attainment of the desired antibiotic concentration at the infection site. Moreover, maximal recommended doses of antibiotics should be prescribed in critically ill patients, especially in the presence of elevated CrCl, as suggested by Arnold and colleagues [11] regardless of whether or not prolonged infusions are employed (for example, cefepime 2 grams every 8 hours, pipercillin-tazobactam 4.5 grams every 6 hours, meropenem 1 gram every 8 hours). Future studies are needed that address the issue of antibiotic dosing optimization in the presence or absence of elevated CrCl. Such studies also need to carefully consider the influence of confounding factors, such as the MIC of the targeted pathogens and the patient's drug volume of distribution, that can also influence the optimization of antibiotic dosing.

Abbreviations

CrCl, creatinine clearance; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic.

Competing interests

The author declares that they have no competing interests.

Author's contribution
MHK was solely responsible for the development and writing of this article.

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Meropenem and piperacillin/tazobactam prescribing in critically ill patients: does augmented renal clearance affect pharmacokinetic/pharmacodynamic target attainment when extended infusions are used?

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Abstract

Introduction: Correct antibiotic dosing remains a challenge for the clinician. The aim of this study was to assess the influence of augmented renal clearance on pharmacokinetic/pharmacodynamic target attainment in critically ill patients receiving meropenem or piperacillin/tazobactam, administered as an extended infusion.

Methods : This was a prospective, observational, pharmacokinetic study executed at the medical and surgical intensive care unit at a large academic medical center. Elegible patients were adult patients without renal dysfunction receiving meropenem or piperacillin/tazobactam as an extended infusion. Serial blood samples were collected to describe the antibiotic pharmacokinetics. Urine samples were taken from a 24-hour collection to measure creatinine clearance. Relevant data were drawn from the electronic patient file and the intensive care information system.

Results: We obtained data from 61 patients and observed extensive pharmacokinetic variability. Forty-eight percent of the patients did not achieve the desired pharmacokinetic/pharmacodynamic target (100 % $fT_{>MIC}$), of which almost 80 % had a measured creatinine clearance > 130 mL/min. Multivariate logistic regression demonstrated that high creatinine clearance was an independent predictor of not achieving the pharmacokinetic/pharmacodynamic target. Seven out of nineteen patients (37 %) displaying a creatinine clearance > 130 ml/min did not achieve the minimum pharmacokinetic/pharmacodynamic target of 50 % $fT_{>MIC}$.

Conclusions: In this large patient cohort, we observed significant variability in pharmacokinetic/pharmacodynamic target attainment in critically ill patients. A large proportion of the patients without renal dysfunction, most of whom displayed a creatinine clearance > 130 mL/min, did not achieve the desired pharmacokinetic/pharmacodynamic target, even with the use of alternative administration methods. Consequently, these patients may be at risk for treatment failure without dose up-titration.

Introduction

Infection is a well recognized but persisting problem in critical care medicine. Sepsis alone is the leading cause of mortality in non-cardiac intensive care units, with up to 30 % of patients dying within one month of diagnosis [1, 2]. Adequate antibiotic therapy is one of the mainstays in treatment, with the emphasis on timely administration and appropriateness of the spectrum [3]. Optimizing antibiotic exposure is highly important as well, however, this is proving to be a greater challenge with recent data showing that antibiotic concentrations in critically ill patients are highly variable, unpredictable and commonly sub-optimal [4-7].

Antibiotic dosing regimens are usually determined in healthy adults with normal physiology or non-critically ill hospitalized patients. Both the volume of distribution and clearance are the key determinants of the pharmacokinetics of a drug. Unfortunately, pathophysiological changes in critically ill patients have profound effect on both [8].

One of these pathophysiological changes is the development of augmented renal clearance (ARC). This is a phenomenon in which renal elimination of circulating molecules – including antibiotics - is enhanced. This, in turn, may lead to sub therapeutic concentrations of time-dependent antibiotics such as β-lactam antibiotics, potentially causing therapeutic failure and selection of antibiotic-resistant pathogens. Critically ill patients are at risk for ARC, because of their pathophysiological disturbances, as well as the clinical interventions administered [9, 10]. The incidence of ARC in critically ill patients is high and varies between 30 and 85 % depending on the studied population and the definition of ARC [11-13].

One study has demonstrated the relationship between renal clearance and low antibiotic concentrations [14], but the relationship between renal clearance and β-lactam pharmacokinetic/pharmacodynamic characteristics has not been evaluated in a large cohort of patients. However, various pharmacokinetic modeling and simulation studies have suggested that

using extended infusions will prevent low antibiotic exposure. However, this has never been tested in a large cohort of relevant patients with ARC. Therefore, the aim of this study was to assess the influence of renal clearance on pharmacokinetic/pharmacodynamic (PK/PD) target attainment when the antibiotic was administered as an extended infusion. Both the minimum target (50 % $fT_{>MIC}$), as well as the target of 100 % $fT_{>MIC}$ which is considered to have higher bactericidal activity [15] were calculated. Notably this study enrolled patients without renal dysfunction, defined as an estimated glomerular filtration rate (eGFR) assessed by the MDRD equation of <80mL/min.

Materials and methods

Inclusion and exclusion criteria

The data used for this analysis were collected in two separate studies performed in the medical and surgical ICU of Ghent University Hospital, a tertiary care hospital with a total of 50 adult ICU beds. Both studies were approved by the Ethics Committee of the Ghent University Hospital (study 1: registration number 2009/543, study 2: 2010/814). Written informed consent was obtained from the patient or his/her legal representative.

Adult patients receiving either meropenem (Meronem®, AstraZeneca) or piperacillin/tazobactam (Tazocin®, Pfizer) were included if they did not meet exclusion criteria which included renal dysfunction (defined as an estimated glomerular filtration rate (eGFR) assessed by the MDRD equation of <80mL/min/1.73 m^2), absence of an arterial catheter or absence of informed consent.

Antibiotic administration

Patients received a loading dose (1g meropenem or 4.5 g piperacillin/tazobactam) administered over 30 minutes, followed immediately by the first extended infusion dose of either antibiotic (1g

meropenem or 4.5 g piperacillin/tazobactam) every 6h for piperacillin/tazobactam and every 8 hours for meropenem. Extended infusion doses were administered over 3 hours using a syringe pump via a central venous catheter.

Sampling and β-lactam assay

The sampling strategy and β-lactam assay used was different in the studies that contributed patients for this analysis. Twenty patients were included in the first study, and forty-one in the second.

Study 1 (20 patients)

Eight serial plasma concentrations were obtained from each patient between 24-48 hours after the initiation of therapy at baseline and after 1, 1.5, 3, 3.5, 4, 6 and 8 hours for meropenem; at baseline and after 1, 1.5, 3, 3.5, 4, 5 and 6 hours for piperacillin. For each sample, 5mL of blood was collected in heparin anticoagulant tubes without separator gel, via the arterial catheter. Specimens were centrifuged at 3000 rpm for 10 min within 30 minutes of sampling, and then frozen at minus 80°C. They were shipped to the Burns, Trauma & Critical Care Research Centre of the University of Queensland, Australia for analysis by a specialized carrier.

The samples were analysed at the Burns Trauma and Critical Care Research Centre, University of Queensland. The plasma concentrations of meropenem and piperacillin were determined by validated high performance liquid chromatography (HPLC) methods based on a published procedure that has been optimized for each drug [16]. Sample preparation was by protein precipitation with acetonitrile and a wash step with dichloromethane. Separations were performed on a Waters X-bridge C18 column (2.1 x 30 mm, 2.5 µm) with an acetonitrile: phosphate buffer mobile phase (pH 2.5 for meropenem, pH 3 for piperacillin). Detection was by UV at 304 nm (meropenem) or 210 nm (piperacillin). The meropenem assay was linear from 0.2 to 100 mg/L with an imprecision and inaccuracy <7% at high, medium and low concentrations. The piperacillin assay was linear from 0.5 to 500 mg/L with an imprecision and inaccuracy <10% at high, medium and low

concentrations. Observed concentrations were corrected for protein binding (piperacillin 30%; meropenem 2%).

Study 2 (41 patients)

Two plasma samples were obtained per patient (mid-dose and trough), after administration of at least 3 doses, to ensure steady-state. For each sample, 5 mL of blood was collected in heparin-anticoagulant tubes without separator gel, via the arterial catheter. The samples were then sent to the core laboratory of the Dept of Laboratory Medicine at the Ghent University Hospital, where they were centrifuged and frozen immediately upon arrival at minus 20°C and were analyzed on the same day.

These samples were analysed at the toxicology laboratory of the Dept of Laboratory Medicine at the Ghent University hospital. The plasma concentrations of meropenem and piperacillin were determined by validated ultra high performance liquid chromatography coupled to tandem mass spectrometry (UPLC-MS/MS). Samples were deproteinized using acetonitrile. After centrifugation, a portion of the supernatant was diluted and injected on a Waters BEH C18 column (1.7 µm, 100 mm x 2.1 mm) kept at 50 °C and a gradient elution of water and acetonitrile, both containing 0.1 % formic acid. Compounds were detected with a Waters Acquity TQD mass spectrometer operating in positive electrospray ionization using a compound specific MRM method. The assay was linear from 2 to 80 mg/L for meropenem, and from 4 to 250 mg/L for piperacillin with an imprecision and inaccuracy < 15 % at high, medium and low concentrations. Observed concentrations were corrected for protein binding (piperacillin 30%; meropenem 2%).

It should be highlighted that the samples in Study 1 and Study 2 were analysed using different assays in two different laboratories. Although a formal inter laboratory validation was not undertaken, both methods have been independently validated according to FDA guidelines.

Furthermore, both laboratories monitor the quality of their analysis by using internal quality controls at 3 levels.

Pharmacodynamic analysis

Depending on the study and number of samples available, different methods were used to calculate the $fT_{>MIC}$. When enough samples were available, the $fT_{>MIC}$ was calculated by observing the time during the dosing interval that the log-linear least squares regression analysis intersected the target MICs for *Pseudomonas aeruginosa* (16 mg/L for piperacillin and 2 mg/L for meropenem based on EUCAST breakpoints [17].

In the case when only two concentrations were available per patient, another approach was used. One concentration (C_1) was taken halfway through the dosing interval, the second sample was a trough concentration (C_2). Using these two concentrations, it is possible to calculate the elimination constant (equation 1).

Equation 1 : $C_2 = C_1 - e^{k \cdot t}$

Assuming one compartmental first order kinetics, this is sufficient to calculate the time within the dosing interval where the concentration reaches or drops beneath a certain threshold. In order to investigate if these two approaches are comparable, the $fT_{>MIC}$ for the samples from the first study was calculated using the pharmacodynamic analysis used for the second study. This was performed for validation purpose only and was not used for the analyses.

Measurement of creatinine clearance and calculation of estimates

To calculate a reliable creatinine clearance, urine samples were taken from a 24-hour collection. Creatinine was measured in both serum/plasma and urine using the rate blanked, compensated and uncompensated Jaffe technique, respectively (Modular P and Cobas 6000, Roche Diagnostics GmbH, Mannheim, Germany). The creatinine clearance was calculated as follows :

24 hour creatinine clearance = U_v x U_{cr}/(1440 x S_{cr}), where U_v is the urinary volume (mL), U_{cr} the urinary creatinine concentration (µmol/L) and S_{cr} the serum creatinine concentration (µmol/L).For assessment of ARC a cut-off of creatinine clearance ≥ 130 mL/min-was used [14].

Statistical analysis

The statistical analysis was performed using the statistical software package IBM-SPSS statistics version 20.0 (IBM Corp, New York USA). Data are expressed as median values with interquartile ranges (IQR) for continuous variables, numbers and percentages for categorical variables. In order to identify important covariates, multivariate logistic regression analyses (single step, forced entry) were conducted with target attainment 100 % $fT_{>MIC}$ and target attainment 50 % $fT_{>MIC}$ as dependent variable using the variables which gave a p-value of <0.10 in the univariate analysis. In the case of covariates which were closely related (such as weight, height and BMI), the one with the most significant p-value was chosen. Goodness of fit was assessed by the Hosmer-Lemeshow statistic. A receiver operator characteristic (ROC) curve was constructed to examine the sensitivity and specificity.

All tests were two-tailed, and $p<0.05$ was considered statistically significant.

Results

Patients

Sixty-one patients were included in the analysis. Patient characteristics on the day of study, and the comparison between the patients who did and did not reach the PK/PD target of both 100% $fT_{>MIC}$ and 50%$fT_{>MIC}$ are shown in Table 1. The median (IQR) creatinine clearance from all patients included in the study was 125 (93-173) mL/min ranging from 55 to 310 mL/min.

Validation of the pharmacodynamic analyses

It was found that the results for both methods used for determination of $fT_{>MIC}$ were comparable.

Creatinine clearance and PK target attainment

Sixty-one patients were included in the study. One patient was excluded from the analyses since no urine was collected, as a result of which the creatinine clearance could not be calculated. Six patients treated with meropenem had a trough concentration which was lower than the lower limit of quantification (2 mg/L), which is also the breakpoint MIC of *Pseudomonas aeruginosa*. This implies that these patients did not reach the desired target of 100 % $fT_{>MIC}$, but the exact % $fT_{>MIC}$ could not be calculated, as this is not possible using only one sample. Two patients treated with piperacillin/tazobactam could also not be used for this analysis, because only the trough concentration was available, which is not enough to calculate the exact % $fT_{>MIC}$. These eight patients were included in the analysis using the PK/PD target of 100 % $fT_{>MIC}$, but could not be entered in the analysis using the PK/PD target of 50 % $fT_{>MIC}$.

Target 100 % $fT_{>MIC}$

Only 33 out of 60 patients (55%), for whom both creatinine clearance and trough concentrations were available, reached the PK/PD target of 100% $fT_{>MIC}$. Patients who did not attain the predefined PK target (100%$fT_{>MIC}$) were younger, had a higher creatinine clearance and a higher weight (Table 1). Twenty-nine patients (48 %) had ARC, of which 22 (76 %) did not reach the PK target of 100%$fT_{>MIC}$.

Figure 1 illustrates the $fT_{>MIC}$ for the patients with and without ARC. The mean $fT_{>MIC}$ in patients with and without ARC is shown in Figure 2 and was 61% vs. 94% in patients with and without ARC respectively ($p<0.001$).

The results of the multivariate logistic regression are shown in Table 2. As the antibiotic administered was not significantly different between the groups who did and did not achieve the PK/PD target, this was not included in the multivariate analysis (p=0.264). Contrary to creatinine clearance and weight, age was not found to be significant in the multivariate analysis. The area under the ROC-curve was 0.86 (Figure 3a), with a sensitivity of 81% and a specificity of 81% for predicting target attainment at 50 % probability.

As an illustration of the impact of an increase in creatinine clearance, the probability of achieving the PK/PD target of 100% $fT_{>MIC}$ was plotted according to the creatinine clearance using the logistic model for a patient aged 55 years, weighing 75 kg (Figure 4).

Target 50 % $fT_{>MIC}$

Using the data from these 52 patients for whom both creatinine clearance and $fT_{>MIC}$ were available, we found that out of 19 patients displaying ARC, 7 (37 %) did not achieve the lower PK/PD target of 50 % $fT_{>MIC}$(p = 0.002) (Table 1)

The results of the multivariate logistic regression analysis are shown in Table 3. As the antibiotic administered was not significantly different between the groups who did and did not achieve the PK/PD target, this was not included in the multivariate analysis (p=0.515). The area under the ROC- curve was 0.99, with a sensitivity of 95 % and a specificity of 100% for predicting target attainment at 50 % probability (Figure 3b). Only creatinine clearance was found to be significant in the multivariate analysis.

Discussion

In this large observational PK study, using clinical data from 61 critically ill patients with normal to increased renal function treated with meropenem or piperacillin/tazobactam, we found that ARC

was associated with a higher risk of not achieving different PK/PD-targets in critically ill patients, even when administering these drugs by extended infusion. This calls into question the present approach to antibiotic dosing in these patients and supports use of more aggressive dosing strategies to minimize the likelihood of clinical failure.

In patients with apparent normal renal function, the relationship between creatinine clearance and low target attainment may not come as a surprise as previous studies have already demonstrated the correlation between creatinine clearance and clearance of β-lactam antibiotics [18-26]. However, to the best of our knowledge, this study is the first to report the association between creatinine clearance and the lack of attainment of different PK/PD targets including the lower target of 50 % $fT_{>MIC}$ in patients with apparent normal renal function receiving antibiotic therapy administered as an extended infusion. Using trough antibiotic concentrations, Udy et al have demonstrated the association between subtherapeutic β-lactam concentrations and creatinine clearance in select critically ill patients [14]. In the current study we could also investigate other targets as we were able to use data from the entire antibiotic infusion, including the lower PK-target of 50 % $fT_{>MIC}$. We found that - even when the dose was administered as an extended infusion - up to 37% of the patients with ARC did not achieve this minimum PK/PD target - and may thus be at risk for treatment failure.

Controversy exists in contemporary literature which PK target should be aimed for in critically ill patients, as it is not clear which PK/PD target is associated with highest probability of reaching clinical cure. Studies have shown that - depending on the antibiotic - 40 to 70% $fT_{>MIC}$ is necessary to treat infections [27]. However, recent research has shown that achieving higher targets may be associated with a higher probability of reaching clinical cure. In order to maximize the effect of β-lactam antibiotics, it may therefore be necessary to increase the $f_{T>MIC}$ to 100 % or even maintaining the concentration four to five times the MIC for the entire dosage duration [28-30].

Nevertheless, irrespective of the PK/PD target considered relevant, increasing creatinine clearance is associated with lower target attainments.

Although ARC is a relatively new concept in intensive care medicine, its relevance should not be underestimated. The incidence in critically ill patients is high [11-13]. Implications for therapy with renally excreted drugs are considerable. Case reports have shown that some patients require up to 6, 8 or even 12 g meropenem per day to reach adequate serum concentrations [31, 32]. The effects of renal clearance are important not only for β-lactam antibiotics, but have also already been described for other antibiotics, such as vancomycin [14, 33].

This study has a number of limitations. First of all, this study did not look at clinical outcomes as the data were drawn from PK studies. Logically, clinical cure and mortality should be investigated in future validation studies of altered antibiotic dosing, although these studies should be even larger than the present study. Secondly, we have described renal function at inclusion using the MDRD which has been shown to underpredict glomerular filtration rate in some critically ill patients [34, 35]. Moreover this study was only a snapshot, and might not be representative for the entire course of treatment as creatinine clearance varies in the course of the disease. Also, this study is a single-center study, which only included patients with apparent normal renal function, which limits extrapolation of these finding to all ICU patients. Finally, we have measured total drug concentrations with correction for protein binding based on literature. This is an oversimplification, but our data show that this approach is acceptable for these two antibiotics, although is not for more highly protein bound drugs.

The findings from this study suggest that an even more sophisticated method of optimization may be necessary in selected patients - patient-tailored antibiotic therapy – which is the adaptation of antibiotic therapy to the need of the individual patient in order to maximize efficacy and minimize toxicity through therapeutic drug monitoring and dose adaptation. Unfortunately, TDM of β-lactam antibiotics is currently challenging with long turn-around times,

expensive equipment, logistical problems related to the instability of the antibiotics in the samples and the need for well-trained personnel. Efforts to overcome these limitations, and clinical studies to assess utility in the clinical setting are urgently needed [36].

Conclusions

In conclusion, this study has demonstrated that in critical care patients receiving meropenem or piperacillin/tazobactam as an extended infusion, creatinine clearance is a key factor in the probability of PK/PD target attainment – irrespective if this is 50 or 100% $f_{T>MIC}$. This study, which excluded patients with renal dysfunction, demonstrated that a specific subset of patients is at risk for PK/PD target non-attainment, more specifically those patients with increased creatinine clearances, even if the dose is administered as an extended infusion, which improves the $f_{T>MIC}$. By means of multivariate logistic regression, it was found that a high creatinine clearance was an independent predictor of not achieving the PK/PD target, implying that without dose up-titration, these patients are at risk of treatment failure, even when extended infusions are used.

Key messages

- Antibiotic concentrations vary greatly in intensive care patients with normal kidney function.
- The pharmacokinetic/pharmacodynamic target attainment is dependent on kidney function .
- Patients with augmented renal clearance have a high probability of target non attainment, even with the use of an extended infusion strategy.

Abbreviations

ARC : augmented renal clearance; BSA : body surface area; BMI : body mass index; eGFR : estimated glomerular filtration rate; $\%fT_{>MIC}$: % time which the free fraction exceeds the minimal inhibitory concentration (MIC); HPLC : high pressure liquid chromatography; k_e : elimination constant; MDRD : modification of diet in renal disease; PK/PD : pharmacokinetic/pharmacodynamic; ROC : receiver operator characteristic; UPLC-MS/MS : Ultra high performance liquid chromatography coupled to tandem mass spectrometry.

Competing interests

Dr. Lipman is a consultant to AstraZeneca and Janssen-Cilag and has received honoraria from AstraZeneca, Janssens-Cilag, and Wyeth, Australia. Astra-Zeneca provides an annual donation to the Burns, Trauma and Critical Care Research Center. Dr Roberts has previously consulted for Astra-Zeneca, Janssen-Cilag and Johnson and Johnson. The other authors have no conflicts of interest to declare.

Authors' contributions

As principal investigator, MC had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design were performed by JDW. JDW, EH, PDP, JDC carried out the coordination of the study. SW, VS and AV were responsible for the laboratory analysis of the samples. Drafting of the manuscript was executed by MC and JDW. Critical revision of the manuscript for important intellectual content was done by JR and JL. All authors read and approved the final manuscript.

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Figure 1. Histogram *% f*$T_{>MIC}$ for patients with and without augmented renal clearance (ARC).

Figure 2. Mean *% f*$T_{>MIC}$ for patients with and without augmented renal clearance (ARC) with 95 % confidence interval.

Figure 3. ROC curves of the binary logistic model. a : ROC curve for the logistic model with attainment of 100 % *f*$T_{>MIC}$ as dependent variable. **b**: ROC curve for the logistic model with attainment of 50 % *f*$T_{>MIC}$ as dependent variable.

Figure 4. Predicted probability of 100 % *f*$T_{>MIC}$ target attainment in function of the creatinine clearance for a patient 55 years, weighing 75 kg.

Table 1. Patient characteristics and comparison between patients who did and did not achieve the PK/PD target of 100 % $fT_{>MIC}$ and 50 % $fT_{>MIC}$. .

Variable	All patients (n= 60)	PK/PD target (100 % $fT_{>MIC}$) achieved (n= 33/60) (55%)	PK/PD target (100 % $fT_{>MIC}$) not achieved (n=27/60) (45 %)	p-value	PK/PD Target (50 % $fT_{>MIC}$) achieved (n= 43/52) (86 %)	PK/PD target (50 % $fT_{>MIC}$) not achieved (n=7/52) (14 %)	p-value
Male gender (n, %)	51 (85%)	28 (84%)	23 (85%)	0.721	36 (84 %)	7 (100%)	0.330
Age (years)	56 (48-67)	61 (53–73)	51(30-60)	0.016	60 (52-72)	48 (25-67)	0.054
Weight (kg)	78 (69-90)	75 (65-81)	83 (75-90)	0.014	75 (66-85)	85 (75-90)	0.041
Height (m)	1.75 (1.70-1.80)	1.75 (1.67-1.79)	179 (1.72-1.80)	0.170	1.74 (1.68-1.80)	1.79 (1.75-1.80)	0.098
BMI	25 (22-28)	24 (22-27)	25 (24-29)	0.084	24 (22-27)	25 (25-28)	0.188
SOFA at the day of study	5 (3-7)	5 (2-8)	5 (3-6)	0.693	5 (3-8)	4 (2-6)	0.358
Serum creatinine concentration (μmol/L)	54 (43-75)	53 (44-79)	56 (41 - 64)	0.623	57 (44-76)	54 (38-59)	0.306
Creatinine clearance (mL/min)		104 (87-123)	165 (138-208)	<0.001	106 (91-143)	215 (190-246)	<0.001
Antibiotic used				0.24			0.515
Meropenem (n, %)	17 (30%)	7/17 (41%)	10/17 (59%)		9/11 (82 %)	2/11 (18 %)	
Piperacillin (n, %)	43 (70%)	25/43 (58%)	18/43 (42%)		33/41 (80 %)	8/41 (20 %)	

Data are reported as median (interquartile range). SOFA – Sequential Organ Failure Assessment.

Table 2. Multivariate regression model with attainment of 100 % $fT_{>MIC}$ as dependent variable.

	attainment of 100 % $fT_{>MIC}$ as dependent variable				
	B	p-value	Exp(B)	95% C.I.for Exp(B)	
				Lower	Upper
Creatinine clearance (ml/min)	-0.028	0.002	0.972	0.955	0.990
Weight (kg)	-0.040	0.114	0.961	0.915	1.010
Age (years)	0.020	0.331	1.020	0.980	1.063
Constant	5.788	0.033	326.34		

Table 3. Multivariate regression model with attainment of 50 % $fT_{>MIC}$ as dependent variable.

	attainment of 50 % $fT_{>MIC}$ as dependent variable				
	B	p-value	Exp(B)	95% C.I.for Exp(B)	
				Lower	Upper
Creatinine clearance (ml/min)	-0.114	0.045	0.892	0.798	0.997
Weight (kg)	-0.035	0.616	0.965	0.841	1.108
Age (years)	0.005	0.906	1.005	0.926	1.096
Constant	24.07	0.07	2.8×10^{10}		

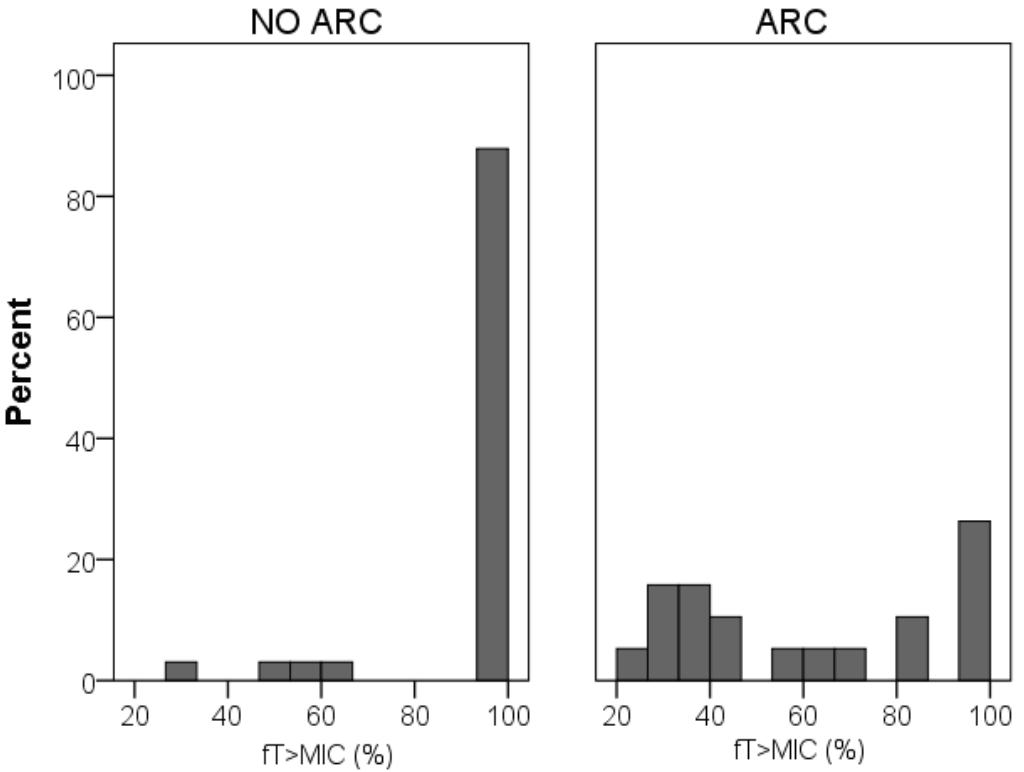


Figure 1

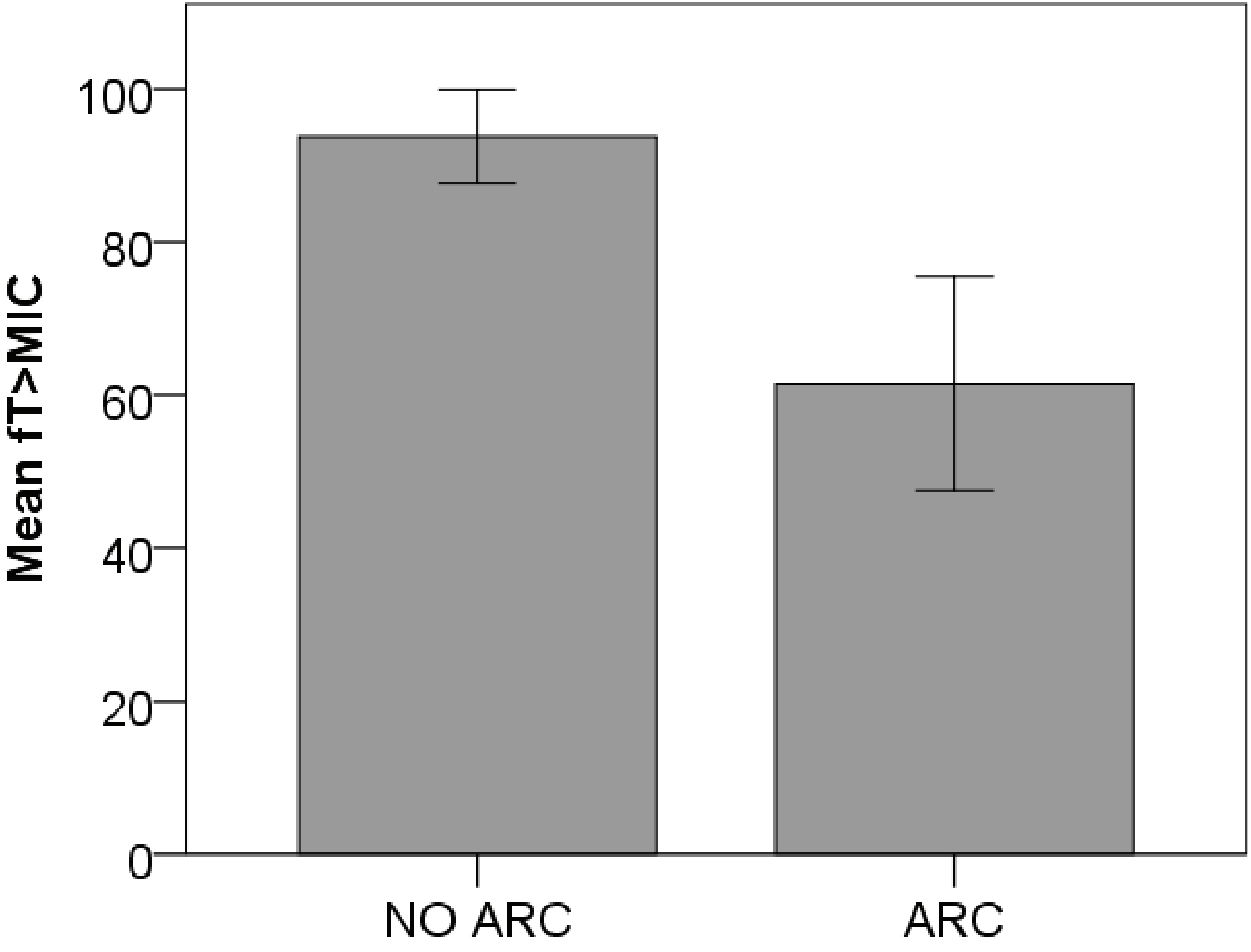
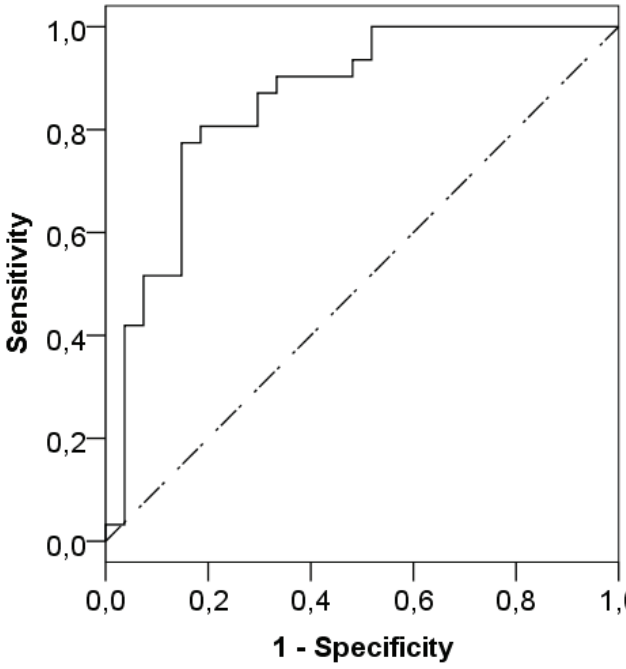


Figure 2

a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b

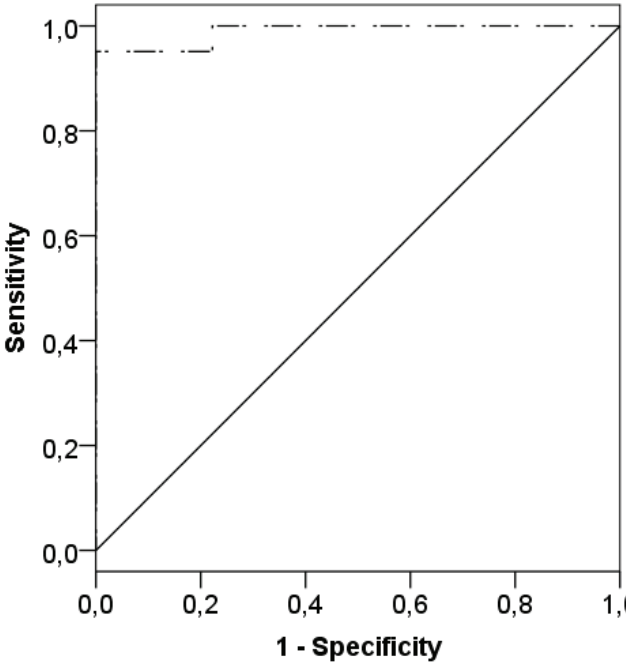
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Figure 3

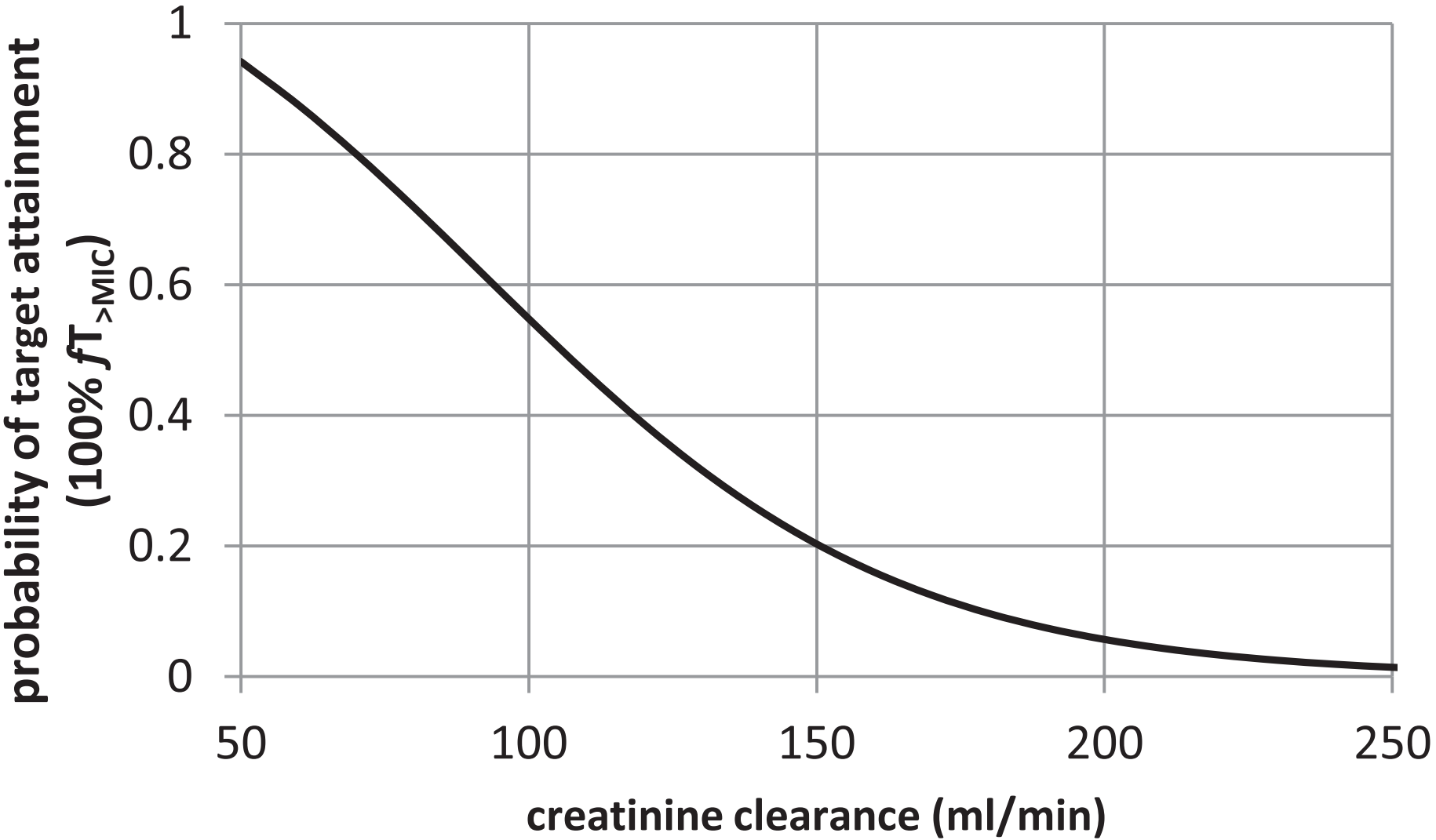
probability of target attainment
(100% $fT_{>MIC}$)
1
0.8
0.6
0.4
0.2
0
50
100
150
200
250
creatinine clearance (ml/min)

Figure 4