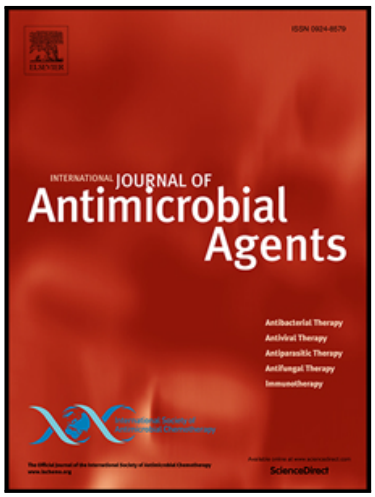

What is the optimal loading dose of broad-spectrum β-lactam antibiotics in septic patients? Results from a PK simulation modelling

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HIGHLIGHTS

- Standard loading doses of broad-spectrum β-lactams often result in insufficient drug concentrations for difficult-to-treat Gram negative pathogens
- Higher loading doses are needed to immediately obtain adequate drug concentrations
- These drug regimens should be validated in prospective studies

What is the optimal loading dose of broad-spectrum β-lactam antibiotics in septic patients? Results from a PK simulation modelling

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Running Title: Optimal First Dose of β-Lactams

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Abstract

Background: Optimal loading doses of β-lactams to rapidly achieve adequate drug concentrations in critically ill patients are unknown.

*Methods***:** Post-hoc analysis of a prospective study that evaluated broad-spectrum β-lactams (piperacillin, PIP; ceftazidime, CAZ; cefepime, FEP; meropenem, MEM) PKs in patients with sepsis or septic shock (n=88). Monte Carlo simulation was performed for 1000 virtual patients, using specific sets of covariates for various dosing regimens and different durations of administration. Pharmacodynamic (PD) targets were considered as drug concentrations exceeding at least 50% of the time above four times the minimal inhibitory concentration (T>4xMIC) of *Pseudomonas aeruginosa*, according to EUCAST criteria, for PIP, 70%T>4xMIC for CAZ and FEP and 40%T>4xMIC for MEM. The probability of target attainment (PTA) was derived by calculating the percentage of patients who attained the PK/PD target at each MIC. The optimal loading dose was defined as the one associated with the probability ≥90% to achieve the PD targets.

*Results***:** Our simulation model identified an optimal loading dose for PIP of 8g given as a 3-h infusion (PTA of 96.2%), for CAZ and FEP of 4g given as a 3-h infusion (PTA of 96.5%, and 98.4%, respectively), and for MEM of 2g given as a 30-min infusion (PTA of 93.4%), with the following antibiotic dose administered 6 hours thereafter, independently from the drug.

*Conclusions***:** Higher first dose of broad-spectrum β-lactams should be given to adequately treat less susceptible pathogens in septic patients. These findings need to be validated in a prospective study.

Keywords: β-lactams, loading dose, pharmacokinetics, sepsis

Introduction

Antimicrobial therapy is the cornerstone of therapies that are administered to critically ill patients with severe infections [1]. Antibiotics should be given as early as possible after infection recognition and adequately cover all potentially involved pathogens [2]. They should ensure not only an optimal clinical response for the individual patient but also avoid the development of subsequent antimicrobial resistance [3]. However, this is often challenging because, when initially faced with life-threatening infections, clinicians most often must administer antibiotics empirically and target less susceptible pathogens, such as *Pseudomonas aeruginosa* or *Acinetobacter baumannii*, which are associated with higher risk of therapeutic failure and increased mortality [1].

In this setting, several studies have shown that, because of significant changes in antibiotic pharmacokinetics (PKs), such as increased volume and distribution and augmented clearance, and the progressive increase of the minimal inhibitory concentration (MIC) of pathogens to the most common first-line drugs, including β-lactam antibiotics, standard regimens of antibiotics may result in insufficient drug concentrations to adequately treat such bacteria [4, 5]. Optimization of β-lactam antibiotic concentrations can be achieved by increasing daily drug dose or by continuous infusion [6]. Nevertheless, even when administering antibiotics in continuous infusion, up to 40% of patients may still have insufficient drug concentrations to cover less susceptible strains, which underlines the need for therapeutic drug monitoring (TDM) to rapidly adjust drug dosing [7].

As any delay in initiating adequate antibiotic therapy increases mortality in septic patients, it is imperative that adequate drug concentrations are achieved as soon as the first antibiotic dose is given. However, standard dosage regimens are based on PK studies performed in less severely ill patients or at the steady-state (e.g. 2 to 3 days after the onset of therapy). Therefore, it is not surprising that Taccone *et al.* found that serum concentrations after the first standard dose of broad-spectrum β-lactam antibiotics were insufficient to empirically cover less susceptible pathogens in many critically ill patients, in particular if treated with piperacillin-tazobactam (PIP), ceftazidime (CAZ) or cefepime (FEP) [4]. However, no particular recommendation was provided on how to adjust drug therapy in this setting.

Thus, using the Monte Carlo simulations (MCS) approach, which allows evaluating what would happen if various dosing regimens are given in virtual patients to achieve specific drug

levels, we aimed to identify the optimal loading dose of β-lactam antibiotics to treat patients with sepsis and septic shock.

Methods

Patients and drug assay

We analysed data coming from a previously published clinical study [4, 8]. Briefly, this study was conducted in the Intensive Care Units of four Belgian university hospitals (Hôpital Erasme, Cliniques Universitaires St-Luc and Universitair Ziekenhuis Brussels, in Brussels; Clinique St-Pierre in Ottignies) during the first hours of antibiotic therapy. The study was conducted according to the Declaration of Helsinki. Eighty-eight critically ill patients with severe sepsis or septic shock, as defined by standard definitions common at that time [9], were prospectively enrolled. All patients received a loading dose of PIP (4/0.5g), CAZ (2g), FEP (2g) or meropenem (MEM, 1g). Several blood samples were collected: before and 1, 1.5, 4.5, 6 or 8, and 24 hours after onset of the 0.5-h infusion. Total serum β-lactams concentrations were measured by high-performance liquid chromatography (HPLC) with diode array detection (DAD).

A total of 418 β-lactam antibiotics samples were collected. Ten patients were excluded from the present analysis for analytical and/or pre-analytical reasons (i.e. inappropriate sample storage or insufficient sample volume). Patients' demographic, hemodynamic and biological data were also collected [4].

Population PK modelling

PK analysis was carried out using the nonlinear mixed-effects modelling program NONMEM Version VI (double precision; ICON Development Solutions, LLC, Ellicott City, MD, USA), with Perl-speaks-NONMEM (PsN) toolkit and Xpose (Version 4) [10, 11]. The modelling process has been described in detail in a previous paper [8]. PK data were not adjusted for protein binding, as the four antibiotics under study show only low protein binding, especially when considering critically ill patients (due to lower serum protein levels and organ dysfunction). Briefly, the population modelling were performed using the first-order conditional estimation method with interaction (FOCEI) and included a body-weight dependence via allometric scaling [12, 13]. No patient-specific covariate was tested for influence on PK parameter estimates because of the small sized datasets for β-lactams [14, 15]. Only the renal function (assessed using the Cockcroft & Gault equation with a standard

creatinine clearance of 100 mL/min for a nominal 70-kg subject [16]) was considered as clinically relevant and therefore used as covariate for the β-lactam antibiotic clearance. Body weight (median: 70 kg; range: 38-125 kg) and creatinine clearance (median: 55 mL/min; range: 12-408 mL/min) were not found to be correlated (r=0.18). A two-compartment model with first-order elimination best fitted the β-lactam data. V1 (central volume of distribution) were 24 L for PIP and MEM, 20 L for CAZ and 18 L for FEP. CL (total body clearance) was 6.8 L/h for PIP, 3.5 L/h for CAZ, 4.5 L/h for FEP and 7.5 L/h for MEM. Goodness-of-fit plots included observed *vs*. predicted concentrations, conditional weighted residuals (CWRES) *vs*. predicted concentrations, and CWRES *vs*. time after dose; they did not reveal any obvious model misspecification [10, 11]. Bootstrap results were consistent with population parameter estimates and visual predictive check plots showed a substantial good overlap of the simulated concentrations with the observations, indicating suitable predictive performance of the population model for MCS simulations.

Monte Carlo Simulations (MCS)

MCS were performed using NONMEM. Based on the population PK model, serum concentrations in β-lactams were generated for 1000 virtual patients, using specific sets of covariates (body weight and renal function), for various dosing regimens: 4g, 6g or 8g of PIP administered as a 0.5-h, 2-h or 3-h infusion every 6h; 2g, 4g or 6g of CAZ and FEP administered as a 0.5-h, 2-h or 3-h infusion every 8h; 1g, 2g or 3g of MEM administered as a 0.5-h, 2-h or 3-h infusion every 8h. ~~PK data were not adjusted for protein binding, considering the low protein binding of the antibiotics that should therefore not influence the final conclusions of the MCS.~~

"Optimal" pharmacodynamic (PD) targets were considered for the studied antibiotics as follows: 50% the time above four times the minimal inhibitory concentration (T>4xMIC) for PIP, 70%T>4xMIC for CAZ and FEP, and 40%T>4xMIC for MEM [4]. Also, a "conservative" PD target of 100%T>4xMIC was investigated for each antibiotic, as secondary outcome. Since no MIC values would be available at first dose anyway, target MIC corresponded to the current clinical susceptibility breakpoints of EUCAST for *Pseudomonas* spp. (i.e. the highest MIC acceptable for a successful efficient empiric treatment): ≤ 16 mg/L for PIP, ≤ 8 mg/L for CAZ and FEP, ≤ 2 mg/L for MEM [17]. Target concentrations (TC; i.e. the drug concentration measured at 40% 50% or 70% for the different antibiotics) were measured for different MICs (from 0.25 to 256 mg/L).

The probability of target attainment (PTA) was derived by calculating the percentage of patients who attained TC exceeding 4xMIC of *Pseudomonas aeruginosa*. The optimal loading dose was defined when TC would result in PTA of at least 90% [18]. Maximal concentrations (C_{max}) and minimal concentrations (C_{min}) were also calculated for different drug regimens.

Results

Results of MCS were derived from population PK data of 78 critically ill septic patients treated with PIP (n=22), CAZ (n=18), FEP (n=19) or MEM (n=19). The proportion of simulated patients who attained the optimal PD targets at each TC for the four drugs are detailed in Supplemental Tables 1-4. PTA against *P. aeruginosa* are shown in Supplemental Figures 1-4.

The proportion of critically ill septic patients treated with PIP who attained the optimal PD target of at least 50%T>4xMIC during the standard dosing interval of 6h are shown in Figure 1, Table 1 and 2. A PIP loading dose of 8g given over 3-h infusion time was the only dosing strategy against *P. aeruginosa* (i.e. TC of 64 mg/L) able to achieve adequate drug concentrations in more than 90% of patients. However, if the dosing interval was above 6h, this loading dose would result in insufficient drug exposure in 27% (dosing interval of 8h) or 58% (dosing interval of 12h) of patients. A standard loading dose (4g given over 30 minutes) would provide adequate PIP levels for the following conditions: TCs of 8 mg/L (i.e. MIC of 2 mg/L) if the dosing interval is 6h; TC of 4 mg/L (i.e. MIC of 1 mg/L) if the dosing interval is 8h and TC of 2 mg/L (i.e. MIC of 0.5 mg/L) if the dosing interval is 12h (Supplemental Table 1).

Using the same approach, the optimal loading doses for CAZ and FEP against *P. aeruginosa* (i.e. 70%T>32 mg/L in > 90% patients) was 4g over a 3-h infusion time, provided that the dosing interval is not higher than 6h for CAZ and 8h for FEP (Figures 2 and 3 – Table 1 and 2). A standard loading dose (2g given over 30 minutes) would provide adequate CAZ levels for TCs of 8 mg/L (i.e. MIC of 2 mg/L) if the dosing interval is 6h; TC of 8 mg/L (i.e. MIC of 2 mg/L) if the dosing interval is 8h and TC of 4 mg/L (i.e. MIC of 1 mg/L) if the dosing interval is 12h (Supplemental Table 3). Similarly, a standard loading dose (2g given over 30 minutes) would provide adequate FEP levels for TCs of 16 mg/L (i.e. MIC of 4 mg/L) if the dosing interval is 6h; TC of 8 mg/L (i.e. MIC of 2 mg/L) if the dosing interval is 8h and TC of 4 mg/L (i.e. MIC of 1 mg/L) if the dosing interval is 12h (Supplemental Table 5).

The optimal loading dose for MEM against *P. aeruginosa* (i.e. 40%T>8 mg/L in > 90% patients) was 2g given over 30 minutes if the dosing interval is 6h, 2g given over a 3-h infusion if the dosing interval is 8h and 3g given over a 3-h infusion if the dosing interval is 12h (Figure 4 - Table 1 and 2). A standard loading dose (1g given over 30 minutes) would provide adequate MEM levels for TCs of 4 mg/L (i.e. MIC of 1 mg/L) if the dosing interval

is 6h; TC of 2 mg/L (i.e. MIC of 0.5 mg/L) if the dosing interval is 8h and TC of 1 mg/L (i.e. MIC of 0.25 mg/L) if the dosing interval is 12h (Supplemental Table 7).

If the "conservative" PD target was considered (i.e. 100%T>4xMIC), the dosing strategy of 8g (q6h) over 3-h infusion would achieve adequate PIP concentrations only in 42% of patients (Supplemental Table 5). In this setting, for CAZ and FEP, the dosing strategy of 6g given over 3-h infusion time every 6h would achieve adequate concentrations in 96% and 81% of patients, respectively (Supplemental Table 6 and 7). For MEM, no dosing strategy would provide adequate drug concentrations in case of "conservative" PD targets, except for very susceptible pathogens (Supplemental Table 8).

Estimated C_{max}, 1-h levels and C_{min} for the different drugs are shown in Supplemental Tables 9-11, respectively. As expected, C_{max} and 1-h levels increased as dose-regimens increased. On the other hand, C_{max} and 1-h levels decreased as the duration of infusion increased, averaging a decrease of 43% and 59%, respectively. An increase in the infusion duration from 0.5-h to 3-h lead to an average increase in C_{min} of 42% for PIP, 13% for CAZ, 24% for FEP, and 37% for MEM when considering the standard dosing interval (i.e. q6h for PIP and q8h for CAZ, FEP and MEM).

Discussion

In the present study, MCS, which has become a very popular technique to understand optimization of antibiotic dosing regimen, provided important information on rapid achievement of adequate β-lactam concentrations since the loading antibiotic dose. When the target pathogens are less susceptible Gram-negative pathogens, and according to the selected PD targets, we observed that the optimal loading dose should be 8g in 3-h for PIP, 4g in 3-h for CAZ and FEP, and 2g in 30-min for MEM. Moreover, the same antibiotic dose should be administered 6 hours thereafter, regardless of the drug. The use of a more conservative PD target (i.e. 100%T>4xMIC) was associated with the need of even higher drug regimen, which could not be feasible in all patients.

Most clinicians agree that a patient with obvious signs of severe infection, (e.g. septic shock) must be started on antibiotic therapy as soon as possible. Antibiotic treatment is therefore often initiated empirically, when pathogens and relative MICs are still unknown. Pathogens that frequently cause infections in the ICU and are associated with high mortality rates are *P. aeruginosa* and other non-fermenting Gram negative strains [19]. Our dosing strategy would be relevant when such pathogens are potentially responsible for the infection

needing treatment; in infections due to very susceptible strains, standard regimens would be sufficient to provide adequate β-lactams concentrations [4].

When performing the MCS, we aimed for a PD target of T>4xMIC of the pathogen at the end of the optimal period of time, corresponding to 70% of the dose interval for FEP/CAZ, 50% for PIP, and 40% for MEM, based on results from *in vitro*, *in vivo* and clinical studies [20-24]. Unbound MEM trough serum concentrations at 5 times the MIC of the infecting pathogen for patients with lower respiratory tract infections predicted microbiological and clinical success in a study analyzing data collected from 101 patients included in 4 different multicenter, randomized, open-label clinical trials [23]. Another study showed that FEP concentrations maintained at 4-6 times the MIC of the infecting pathogen accurately predicted microbiological success [24]. However, there is currently no consensus on optimal PK/PD targets for β-lactams in infected, critically ill patients because data is lacking on MIC or clinical outcome in different cohorts. Indeed, the clinical efficacy of different PK/PD targets has not been assessed in depth. In this study, we have therefore provided the results from our MCS for different PK/PD targets. Interestingly, our MCS highlights that the PTA of the more severe PD target of 100%T>4xMIC is very low for septic patients, even when high loading doses are administered over an extended infusion period.

In a previous study on the PKs of broad-spectrum β-lactams for severe sepsis or septic shock, volume of distribution of all 4 β-lactams was significantly increased when compared to non-critically ill patients or healthy subjects [4]. In order to optimize drug concentrations according to PK/PD targets, an increased loading dose is usually proposed in this setting. Indeed, as the VD of other hydrophilic antibiotics, such as amikacin, colistin, and vancomycin, is also increased in critically ill patients [25-27], higher than recommended loading doses have been proposed and clinical validation studies have confirmed the improvement of PK/PD target attainment for all 3 of these antibiotics [27-29]. The present study suggests the need for a higher loading dose of β-lactams in critically ill patients and claims further clinical validation in prospective studies.

As loading doses are increased, higher serum concentrations of β-lactam antibiotics are rapidly obtained which may improve clinical outcome but also increase the risk of drug toxicity. Overall, β-lactam antibiotics are considered to be very safe, with little risk of toxicity. However, neurotoxicity has been described in elderly patients and in patients with renal impairment or previous neurological disease [30]. This neurotoxicity seems to be

related to inhibition of the γ-aminobutyric acid (GABA-A) receptor. This receptor may induce neuronal hyper-excitability, depolarize the post-synaptic membrane and lower the threshold for seizure development [31]. In animal studies, neurotoxicity appears to be dose-dependent [30]. In a retrospective study on β-lactams TDM in 199 septic patients, elevated trough levels of broad-spectrum β -lactams were associated with neurological deterioration. A high C_{min} was identified as a predictive factor for neurological worsening in this patient population. More specifically, a C_{min} > 64 mg/L for CAZ and FEP, > 128 mg/L for PIP, and > 16 mg/L for MEM may increase the risk of drug toxicity. In another retrospective study on 64 courses of cefepime therapy during which trough concentrations were measured, a cut-off of ≥ 36 mg/L was identified to predict cefepime induced toxicity. Only half of these antibiotic courses were administered in the ICU, and trough concentrations were measured after a median duration of 5.4 days (3.0-8.0) and a median total dose of 24g (14-37.5) [33]. Neurotoxicity usually is expressed as myoclonus, hallucinations, confusion, and seizures. Whether neurotoxicity is responsible for an increase in mortality, remains to be determined, although some serious neurological complications have already been reported [34]. In our study, when giving a loading dose of 8g of PIP in 3-h, 4g of CAZ in 3-h, 4g of FEP in 3-h, or 2g of MEM in 30-min, the MCS showed that the median C_{max} was 150 mg/L, 97 mg/L, 95 mg/L, or 68 mg/L, and the median C_{min} was 51 mg/L, 46 mg/L, 27 mg/L, or 5 mg/L, respectively, when considering the standard dosing interval (i.e. q6h for PIP and q8h for CAZ, FEP and MEM). None of the trough concentrations exceeded reported thresholds of toxicity. Furthermore, the thresholds of neurotoxicity reported in the literature come from retrospective data in patients who received significantly longer antibiotic therapy than a single loading dose. The thresholds have not yet been validated prospectively, and there is currently no consensus on a specific beta-lactam concentration threshold for toxicity. Nevertheless, considering the high C_{max} levels obtained by MCS, further studies, incorporating real time TDM, are necessary to ensure that the loading doses do not cause neurotoxicity.

Our study has some limitations. First and most importantly, the suggested loading doses for β-lactams have not yet been validated in a prospective study. Second, only the total fraction of β-lactams was measured in the prospective PK study, despite that it is the unbound fraction of the antibiotic that is active. Third, suggested dosage regimens could not apply to patients receiving continuous infusions because our study focused on PD target attainment after a loading dose. It remains to be explored whether a continuous infusion after the loading

dose allows for more optimal PD target attainment at 24 hours and 48 hours of antibiotic therapy than intermittent drug regimens. Also, patients with extra-corporeal membrane oxygenation therapy (ECMO) could need even higher doses; as ECMO has been shown to increase the VD of hydrophilic drugs [35]; however a recent study showed similar PK characteristics and broad-spectrum β-lactam antibiotic concentrations between ECMO and non-ECMO matched critically ill patients [36]. Fourth, no dosage recommendations could be provided for PD targets of 100%T>4xMIC. Indeed, despite that certain authors advocate to rapidly attain this more stringent PK/PD target for patients with sepsis or septic shock, our simulations show that it is almost impossible to accomplish.

Conclusions

β-lactams are the most frequently prescribed antibiotics worldwide. They provide a broad-spectrum coverage of different pathogens, have rapid bactericidal activity, and low toxicity. Therefore, they are the recommended backbone of any empiric antibiotic therapy for sepsis or septic shock. Our study, using a MCS approach, is the first to provide new dosage suggestions for broad spectrum β-lactams in the early phase of sepsis. New "standard" doses for β-lactams in this condition should therefore be 4g in 3-h for CAZ and FEP, 8g in 3-h for PIP and 2g in 30-min for MEM.

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Declarations

Funding: No funding was provided for this study.

Competing Interests: The other authors declare that they have no competing interests.

Ethical Approval: The study protocol was approved by local Ethics Committees and informed consent was obtained from the patient or her/his legal representative.

Authors' contribution

FJ, PFL, TD, HS and FST conceived the study protocol. FST, FJ, TD, PFL, HS and ID participated to data collection. PW, ID and MH analyzed the data. ID, PW, MH, FJ and FST drafted the present manuscript. HS, PFL and HS critically revised the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

List of Abbreviations

CAZ = ceftazidime

CL = total body clearance

C_{max} = peak concentration

C_{min} = trough concentration

DAD = diode array detection

ECMO = extracorporeal membrane oxygenation

FEP = cefepime

HPLC = high-performance liquid chromatography

ICU = intensive care unit

MCS = Monte Carlo simulation

MEM = meropenem

MIC = minimal inhibitory concentration

PD = pharmacodynamic

PK = pharmacokinetic

PIP = piperacillin

PTA = probability of target attainment

TDM = therapeutic drug monitoring

VD = volume of distribution

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Table 1. Drug concentrations corresponding to the probability of target attainment (PTA) of at least 90% for different β-lactam regimens. Pharmacodynamic targets are 40%, 50% and 70% of the time above 4 times the minimal inhibitory concentration (MIC) for meropenem, piperacillin, and ceftazidime and cefepime. Target concentration (TC) is shown, together with MIC within brackets.

		Reachable TC for PTA of 90% (mg/L)		
β-lactam	Dosing regimen	0.5h-infusion	2h-infusion	3h-infusion
Piperacillin	4g q6h	8 (2)	16 (4)	32 (8)
	6g q6h	16 (4)	32 (8)	32 (8)
	8g q6h	16 (4)	32 (8)	64 (16)
Ceftazidime	2g q8h	8 (2)	8 (2)	8 (2)
	4g q8h	16 (4)	16 (4)	16 (4)
	6g q8h	32 (8)	32 (8)	32 (8)
Cefepime	2g q8h	4 (1)	4 (1)	8 (2)
	4g q8h	8 (2)	8 (2)	16 (4)
	6g q8h	8 (2)	16 (4)	16 (4)
Meropenem	2g q8h	2 (0.25)	4 (2)	8 (2)
	4g q8h	4 (1)	8 (2)	16 (4)
	6g q8h	8 (2)	16 (1)	16 (4)

Table 2. Percentage of patients with β-lactams concentrations of >4xMIC following target levels (i.e. 50% for piperacillin, 70% for ceftazidime and cefepime and 40% for meropenem) or following "conservative" targets (i.e. 100%T>4xMIC). Susceptibility breakpoints of EUCAST for *Pseudomonas* spp were used, i.e. 16 mg/L for piperacillin, 8 mg/L for ceftazidime and cefepime, and 2 mg/L for meropenem.

			% patients	
β-lactam	Daily regimen	Infusion time	**Target T ≥ 4xMIC**	**100%T ≥ 4xMIC**
Piperacillin	4g/6h	0.5h	26%	7%
		2h	41%	11%
		3h	65%	14%
	6g/6h	0.5h	50%	21%
		2h	67%	26%
		3h	88%	30%
	8g/6h	0.5h	65%	31%
		2h	81%	37%
		3h	96%	42%
Ceftazidime	2g/8h	0.5h	31%	17%
		2h	37%	22%
		3h	43%	24%
	4g/8h	0.5h	81%	64%
		2h	85%	70%
		3h	87%	74%
	6g/8h	0.5h	92%	82%
		2h	94%	85%
		3h	96%	87%
Cefepime	2g/8h	0.5h	13%	5%
		2h	17%	7%
		3h	21%	9%
	4g/8h	0.5h	52%	31%
		2h	61%	36%
		3h	69%	41%
	6g/8h	0.5h	72%	50%
		2h	79%	57%
		3h	85%	63%
Meropenem	1g/8h	0.5h	63%	15%
		2h	78%	19%
		3h	93%	23%
	2g/8h	0.5h	85%	38%
		2h	94%	45%
		3h	99%	50%
	3g/8h	0.5h	92%	52%
		2h	97%	58%
		3h	100%	63%

Figure Legends.

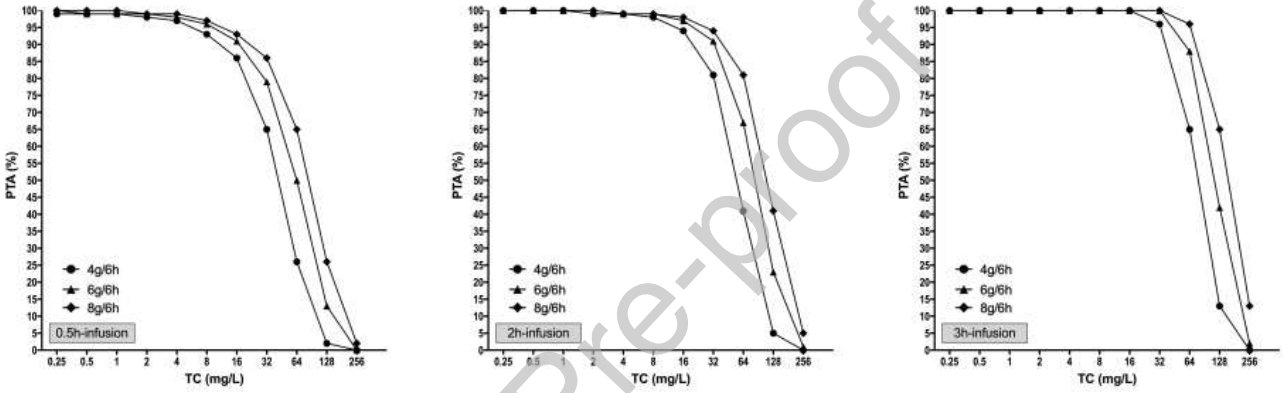

Figure 1. Probability of target attainment (PTA) for various dosing regimens of piperacillin (4g, 6g and 8g q6h), for a PK/PD target of 50%T> 4x MIC.

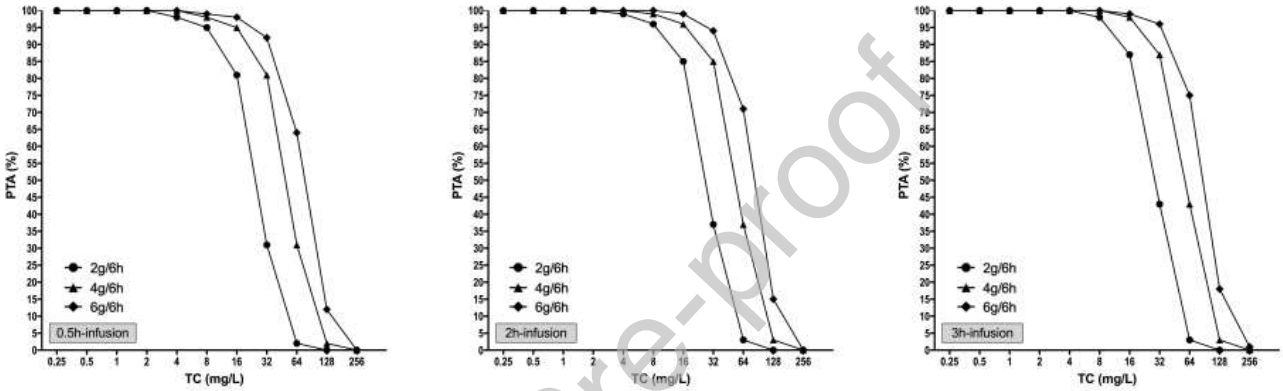

Figure 2. Probability of target attainment (PTA) for various dosing regimens of ceftazidime (2g, 4g and 6g q8h), for a PK/PD target of 70%T>4x MIC.

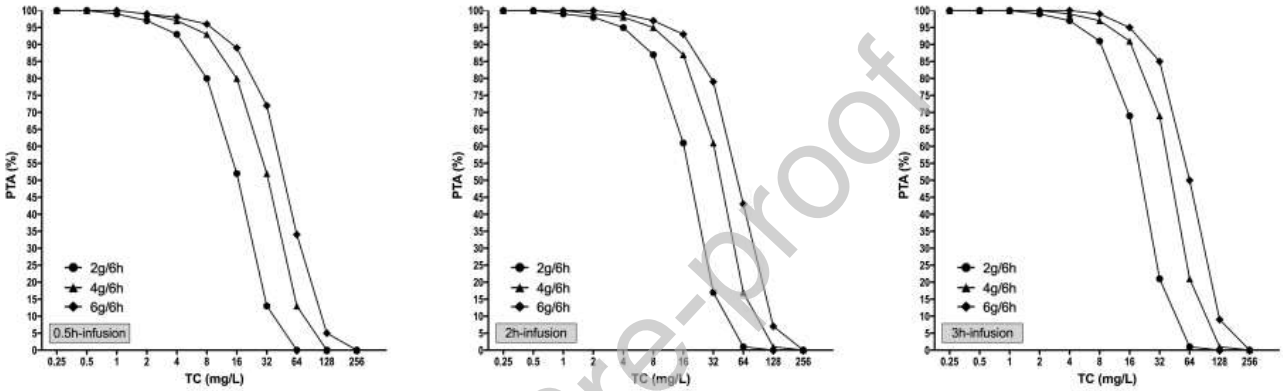

Figure 3. Probability of target attainment (PTA) for various dosing regimens of cefepime (2g, 4g and 6g q8h), for a PK/PD target of 70%T>MIC.

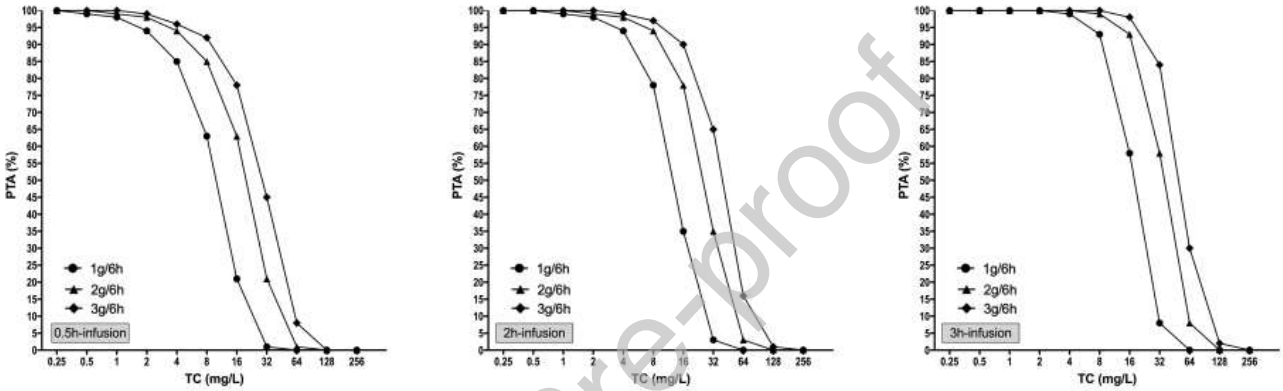

Figure 4. Probability of target attainment (PTA) for various dosing regimens of meropenem (1g, 2g and 3g q8h), for a PK/PD target of 40%T>MIC.