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REVIEW

Optimizing β-lactams treatment in critically-ill patients using pharmacokinetics/pharmacodynamics targets: are first conventional doses effective?

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ABSTRACT

Introduction: The pharmacokinetic/pharmacodynamic index determining β-lactam activity is the percentage of the dosing interval (%T) during which their free serum concentration remains above a critical threshold over the minimum inhibitory concentration (MIC). Regrettably, neither the value of %T nor that of the threshold are clearly defined for critically-ill patients.

Areas covered: We review and assess the targets proposed for β-lactams in critical illness by screening the literature since 1997. Depending on the study intention (clinical cure *vs*. suppression of resistance), targets proposed range from 20%T > 1xMIC to 100%T > 5xMIC. Assessment and comparative analysis of their respective clinical efficacy suggest that a value of 100%T > 4xMIC may be needed. Simulation studies, however, show that this target will not be reached at first dose for the majority of critically-ill patients if using the most commonly recommended doses.

Expert commentary: Considering that critically-ill patients are highly vulnerable and likely to experience antibiotic underexposure, and because effective initial treatment is a key determinant of clinical outcome, we support the use of a target of 100%T > 4xMIC, which could not only maximize efficacy but also minimize emergence of resistance. Clinical and microbiological studies are needed to test for the feasibility and effectiveness of reaching such a demanding target.

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B-lactams; critically-ill patients; PK/PD targets; first dose; maximal efficacy

1. Introduction

β-lactam antibiotics remain the mainstay of treatment for a variety of bacterial infections, especially when a gram-negative infection is suspected [1]. Optimal therapy, however, requires defining best doses, modes of administration and schedules. Critically-ill patients are challenging since common dosage recommendations are derived from pharmacokinetic (PK) data obtained in healthy volunteers or non-severely-ill patients. Yet, drug disposition in critical illness may be significantly altered, resulting in either accumulation and toxicity or decreased serum and tissue concentrations leading to subtherapeutic effects and risk of emergence of resistance [2]. Furthermore, hemodynamic instability results in unpredictable serum levels, making often empirical fixed-dose strategies inadequate [1,3,4]. Last, and even though the intrinsic pharmacological response of bacteria to an antibiotic should not be different between critically-ill and noncritically-ill patients, the former will undoubtedly need of and benefit from a more aggressive and rapidly effective treatment. This is all the more evident as we know that there is a strong association between lack of appropriate antibiotic therapy in critical illness and mortality [5–9]. Thus, continuous therapeutic drug monitoring (TDM) of an optimally administered antibiotic is probably the best tool to individualize its dosage in severely-ill patients and to improve clinical outcomes.

Although serum concentrations remain an imperfect proxy of what drives antibiotic activity at the site of infection, they are almost always accessible for clinicians, and most of the recommendations for optimizing β-lactams therapies are based on their measurement. Correct information on bacterial susceptibility is more problematic. Most often, it is only provided to the clinician by reference to predefined clinical breakpoints, with the causative organism being categorized as 'susceptible' or 'resistant' to the antibiotic of interest (i.e. when the minimal inhibitory concentration [MIC] of the antibiotic is either ≤ or > than the 'S' and 'R' breakpoints[1], respectively). Thus, the clinician will be triggered to select an MIC corresponding to the 'S' breakpoint as her/his target. More rarely, the actual value of the MIC is communicated, which would better allow for a real personalized adaptation of the dosing, assuming that this MIC truly describes the susceptibility of the causative organism.

The correct use of antibiotics will therefore be dependent on a clear understanding of the PK (serum concentrations) and pharmacodynamic (PD) (MIC) indices driving their activity and, perhaps more importantly today, minimizing the risk of emergence of resistance. Best target exposures in critically-ill

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patients remain, however, subject to controversies. In this paper, we review data relating to the rationale of the PK/PD indices driving the activity of β-lactams, and describe the targets favored by current authors for critically-ill patients. We focus on piperacillin/tazobactam, ceftazidime, cefepime, and meropenem since these are the most currently recommended broad-spectrum β-lactams in critical illness, and are the most frequently followed by TDM [10].

2. PK/PD indices: general considerations

In the conditions of their clinical use, β-lactams are essentially time-dependent antibiotics, and their antibacterial effects are related to the time during which the unbound (free) drug concentration remains above the minimum inhibitory concentration (MIC) of the infecting pathogen (*f*T>MIC) [11]. Therefore, the optimal dosage strategy for β-lactam antibiotics has long been to rapidly achieve the necessary target concentrations and maintain them during a sufficiently long period of time between successive drug administrations [5,12]. The necessary %T>MIC is (i) roughly similar for most organisms, except for *Staphylococci* (due to modest but significant persistent effects [13]), (ii) fairly constant over different dosing intervals [11], (iii) related to the free fraction of the drug [11,14], (iv) essentially similar across various sites of infection (e.g. blood, lung, peritoneum, soft tissue [15]), due to equilibrium between serum and the extracellular fluids, with the notable exception of the central nervous system and the urinary tract [11].

3. PK/PD targets: state of the art

Table 1 summarizes the key PK/PD targets of β-lactams suggested from animal studies of acute infections. Bacteriostasis requires a %*f*T>MIC of at least 20% for carbapenems, 30% for penicillins and 40% for cephalosporins, while maximal killing requires to add about 20 to these values [13,16]. While animal studies can provide useful information and may serve as general guidance for antibiotic activity assessment, the conditions of their performance (acute infections; 24-h treatments; initially healthy animals [even if made neutropenic]) are quite distinct from the situation encountered in the clinic with critically-ill patients. Thus, other targets have been proposed based on both *in vitro* and clinical studies, which can be summarized as follows.

(1) Infections are successfully treated with %*f*T>MIC varying from 45 to 100%

Table 1. Percentage of the dosing interval over which the unbound (free) drug concentration remains above the minimum inhibitory concentration (MIC) of the infecting pathogen (*f*T>MIC) for various β-lactams after bolus dosing in animal infection models [13,16].

	*f*T>MIC	
β-lactams	Bacteriostatic effect	Maximal bactericidal effect
Penicillins	30%	50%
Cephalosporins	35–40%[a]	60–70%[a]
Carbapenems	20%	40%

[a]40% and 70% have been used as targets for ceftazidime and cefepime in Figure 1.

The %*f*T>MIC associated with favorable microbiological and/or clinical outcomes varies between >45% (nosocomial pneumonia [17]), >53% (ventilator-associated pneumonia [18]), >54% (lower respiratory tract infections [19]), >68–74% (gram-negative bloodstream infections [20]), ≥83% (patients with high risk of morbidity and mortality [21]), and 100% (bacteremia and sepsis [22]). In parallel, achieving a %*f*T>MIC of 60% minimizes the risk of poor microbiological response [23], but a value of 100% has been advocated to avoid bacterial regrowth due to lack of post-antibiotic effect [24,25].

(2) Maximal killing may require free minimal drug concentrations at ≥4×MIC

3.1. *In vitro* data

While made under conditions that may seem quite remote from real clinical situations, *in vitro* studies allow to study the intrinsic pharmacological properties of the antibiotics and to fully assess conditions of success as well as failures. Thus, they provide basic information essential for a comprehensive analysis of desirable PK/PD targets. In this context, there are convincing *in vitro* data suggesting that maximal bacterial killing is achieved when the free serum β-lactam concentrations are maintained at 4–6×MIC [25–27]. *In vitro* studies with isolates from cystic fibrosis patients receiving ceftazidime confirm these data and show that these concentrations need to be maintained during the whole administration interval [26].

3.2. *Clinical data*

A limitation in clinical studies is the difficulty of assembling a large number of patients infected by poorly susceptible bacteria and treated with monotherapy. The clinicians will indeed quickly move to combined therapies, which makes the PK/PD analysis very difficult and uncertain. Given this *caveat*, a clinical study in patients with gram-negative infections clearly suggests that serum concentrations of cefepime need to be maintained around 4–6×MIC throughout the dosing interval (100%T > 4–6×MIC) for predictable microbiological success [28]. Consistent with these data, Li *et al*. identified a ratio of the free trough concentration of meropenem to the MIC (fC_{min}/MIC) of at least 5 as the most significant predictor of microbiological and clinical efficacy in patients with lower respiratory tract infections [19]. In parallel, Tam *et al*. have proposed to maintain a fC_{min}/MIC above 6 for meropenem in order to reduce the emergence of resistance of *P. aeruginosa* [29]. Even higher fC_{min}/MIC was suggested. Thus, a fC_{min}/MIC of 8 was reported to predict microbiological eradication in patients with infections caused by both extended spectrum β-lactamase (ESBL)- and non-ESBL-producing organisms treated with cefepime [30], while a fC_{min}/MIC of 12 was found to be a significant predictor of therapeutic success in patients with ventilator-associated pneumonia receiving ceftazidime or cefepime [18]. In a small series of case reports, Hayashi et al. suggested to adopt %*f*T >4–5×MIC of 50–100% for patients with severe infections [31]. In a recent paper, a fC_{min}/MIC <2.1 was reported to predict clinical failure in patients with gram-

negative bacterial pneumonia and various degrees of renal function [32]. While many of these studies had few points supporting the low end of T>MIC targets that would justify the high targets proposed, they globally show that the low targets deduced from short courses animal studies examining acute infections only (see Table 1) may clearly be insufficient.

(3) β-lactams administered by continuous infusion should have steady-state concentrations at 2–4×MIC

While maintaining steady-state concentrations above 2×MIC may be sufficient to achieve maximal bactericidal activity against some strains of *Pseudomonas aeruginosa* [33,34], *in vitro* data mimicking the continuous administration of ceftazidime have shown that steady-state concentrations of at least 4×MIC are necessary to fully protect against bacterial regrowth [27]. Other *in vitro* and *in vivo* animal studies have confirmed that continuous infusion is more effective than intermittent administration when concentrations are maintained at 4×MIC [16].

Thus, the magnitude and target of the %*f*T>MIC index that should be considered for β-lactams in patients remains debatable, especially when considering immunocompromised, critically-ill patients. These, indeed, have often been exposed to several previous antibiotic treatments, which may have caused a decreased susceptibility of colonizing bacteria that are often the starting point of the infection [35].

4. Achievement of PK/PD targets in critical illness

4.1. Literature review

4.1.1. Methods

We performed a systematic study of original articles published from January 2000 to October 2016 and available in PubMed[2] using the following search terms: 'piperacillin OR ceftazidime OR cefepime OR meropenem' in the paper title, and '(pharmacokinetics OR PK OR pharmacodynamics OR PD) AND MIC' in the text. Data from healthy subjects, pediatric and elderly patients, and non-critically ill patients were excluded. Key words used to search for critically-ill patients in the text included: 'critical,' 'severe,' 'critically-ill' or 'critically ill,' 'severely-ill' or 'severely ill,' 'intensive,' and 'ICU.' Papers in a language other than English or French, Editorial or Opinion Letter without research-based findings, case reports and reviews were excluded. Finally, only serum or plasma β-lactam concentrations were considered.

4.1.2. Results

Table 2 summarizes our research findings. A total of 230 papers were screened (60 for piperacillin, 39 for ceftazidme, 42 for cefepime, and 89 for meropenem), from which 64 papers meeting the criteria were retained in the analysis (21 for piperacillin, 9 for ceftazidime, 10 for cefepime, and 24 for meropenem). Targets proposed ranged from a %T > 1×MIC of 20% to a %T > 5×MIC of 100%. The most popular PK/PD targets for each antibiotic were: (i) 50%T>MIC for piperacillin (45% of cited targets), (ii) 100%T > 4–5×MIC for ceftazidime (78% of cited targets), (iii) 50–100%T>MIC for cefepime (25% of cited targets), and (iv) 40%T>MIC for meropenem (32% of cited targets). These targets were most often independent of the mode of administration (i.e. intermittent, extended, or continuous infusion). Regrettably, assessment and comparative analysis of the respective clinical efficacy associated with these targets were limited due to lack of clinical outcome data.

Importantly, any PK/PD target needs to be interpreted in view of the corresponding bacterial pathogen susceptibility. When reviewing papers, only 19% of the studies used actual MICs. Because MICs of the identified organisms were not available or known, antimicrobial susceptibility breakpoints rather than actual MICs have been frequently used as surrogates (39% of the studies used the EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints [with 52% targeting the clinical susceptible breakpoint ('S') for *Pseudomonas aeruginosa*]; 14% used the CLSI (Clinical and Laboratory Standards Institute) breakpoints [with 89% targeting the clinical 'S' breakpoint for *Pseudomonas aeruginosa*]).

4.2. Assessment of target attainment in real patients

For the purpose of this study, two targets with reasonable support for efficacy in critically-ill patients were selected. The first, advocated by an Australian group [95] and adopted by a majority of ICU performing β-lactam TDM as part of routine clinical care [10,96], was a %T > 1×MIC of 100% (primary target), considered as sufficient and reasonable for β-lactams when administered by intermittent infusion in ICU patients. According to their supporters, this should also allow reaching 4xMIC at 50%, 70%, and 40% of the dosing interval for piperacillin, ceftazidime and cefepime, and meropenem, respectively (maximal bactericidal effect; Table 1). A second, more demanding target, strongly advocated by a group in Houston [28,29], was 100%T > 4×MIC, considered essential in critical illness to ensure microbiological success.

4.2.1. Methods

First administration was examined as there is a general consensus that achieving efficient therapy as early as possible is a critical determinant in the therapeutic outcome [5]. We used data obtained from a published study in which serum levels of β-lactams were measured in critically-ill septic patients receiving a first dose of piperacillin (4 g [combined with 500 mg tazobactam]; n = 22), ceftazidime (2 g; n = 18), cefepime (2 g; n = 19), or meropenem (1 g; n = 19), each infused over 30 min in combination with amikacin (25 mg/kg) [97,98]. Monte Carlo simulations were performed (NONMEM version VI; ICON Development Solutions, LLC, Ellicott City, MD) based on the previously published population PK, including variability and error of estimates [98]. Simulated serum concentrations of each of the four β-lactams were generated for 1000 virtual patients. Since actual MICs are never available at first dose (although this dose needs to be as optimal as possible), we used the current EUCAST 'S' breakpoints for *Pseudomonas* spp. (2016-01-01, v 6.0; http://www.eucast.org; 16 mg/L for piperacillin, 8 mg/L for ceftazidime and cefepime, and 2 mg/L for meropenem). These would indeed correspond to the highest MIC considered acceptable for a successful efficient empiric treatment for bacteria reported as susceptible in epidemiological surveys. Total concentrations were used, as the four

Table 2. Original papers published from 2000 in critically-ill patients receiving intermittent, extended, or continuous infusion of β-lactam antibiotics, and their respective targets used or advocated for the appropriate pharmacokinetic/pharmacodynamic (PK/PD) index (q, interval of administration; *f*T>MIC, dosing interval over which the unbound (free) drug concentration remains above the minimum inhibitory concentration (MIC) of the infecting pathogen; $AUC_{0\text{-}24}$/MIC, area under the concentration-time curve for 24h of dosing to the MIC; fC_{min}/MIC, ratio of the free trough concentration to the MIC; LD, loading dose; inf., infusion).

β-lactams	Patients	Dosing regimens	PK/PD targets	MIC value	Reference
Piperacillin	Intensive care unit patients (*n* = 182)	- intermittent-bolus dosing - extended infusion - continuous infusion	-50%*f*T>MIC - 50%*f*T>4xMIC - 100%*f*T>MIC - 100%*f*T>4xMIC	- Actual MIC - EUCAST MIC_{90} values (for *Pseudomonas aeruginosa* (2 mg/L) if no pathogen formally identified)	[36]
	Critically-ill patients with multiple organ dysfunction syndrome receiving continuous venovenous hemodiafiltration (*n* = 19)	At the discretion of the treating physician	-50%*f*T>MIC - 100%*f*T>MIC	EUCAST 'S' breakpoint (8–16 mg/L)	[37]
	Patients with acute kidney injury due to septic shock (*n* = 10)	4g, 0.5-h inf. (single dose)	-50%*f*T>MIC - 100%*f*T>MIC	EUCAST 'S' breakpoints of 8 mg/L and 16 mg/L	[38]
	Critically-ill patients (*n* = 2)	4g q8h, 1-h inf.	100%*f*T>MIC	EUCAST 'S' breakpoint for *Pseudomonas aeruginosa* (MIC = 16 mg/L)	[39]
	Critically-ill patients with known or suspected septic shock (*n* = 15)	4g q8h, 0.05-h inf.	-50%*f*T>4×MIC - 100%*f*T>MIC	EUCAST 'S' breakpoint for *Pseudomonas aeruginosa* (MIC = 16 mg/L)	[40]
	Critically-ill patients undergoing continuous renal replacement therapy (*n* = 20)	4g q8h, 4-h inf.	50%T > 4xMIC	CLSI 'S' breakpoint for *Pseudomonas aeruginosa* (MIC = 16 mg/L)	[41]
	Febrile neutropenic patients with hematological malignancies (*n* = 32)	4g q8h, 0.5-h inf.	-100%*f*T>MIC - 50%*f*T>MIC	- Actual MIC (41%) - EUCAST 'S' breakpoint for *Pseudomonas aeruginosa* (MIC = 16 mg/L) (59%)	[42]
	Critically-ill patients with augmented creatinine clearance (*n* = 48)	4g q6h, 0.33-h inf.	-50%*f*T>MIC - 100%*f*T>MIC	EUCAST 'S' breakpoint for *Pseudomonas aeruginosa* (MIC = 16 mg/L)	[43]
	Trauma/surgical intensive care unit patients (*n* = 13)	3g or 4g, 0.5-h inf.	≥50%*f*T>MIC	EUCAST 'S' breakpoint for *Enterobacteriaceae* and *Pseudomonas aeruginosa* (MIC = 16 mg/L)	[44]
	Intensive care unit patients (*n* = 23)	• 4g, 0.5-h inf. (LD) followed by 4g q6h, 3-h inf. (*n* = 15) • 4g q6h, 0.5-h inf. (*n* = 8)	-100%*f*T>MIC - 50%*f*T>MIC - 100%*f*T>4×MIC	EUCAST 'S' breakpoint (MIC = 16 mg/L)	[45]
	Critically-ill patients with normal renal function (*n* = 11)	4g q6h, 3-h inf.	100%*f*T>MIC	EUCAST 'S' breakpoint for *Pseudomonas aeruginosa* (MIC = 16 mg/L)	[46]
	Critically-ill patients undergoing renal replacement therapy (*n* = 16)	4g q4h, 6h or 8h, 0.33-h inf.	100%*f*T>MIC		[47]
	Patients with cystic fibrosis-related acute pulmonary exacerbations (*n* = 9)	3g q8h, 4-h inf.	50%T>MIC		[48]
	Surgical intensive care patients with morbid obesity (*n* = 9)	4g q6h, 0.5-h inf.	50%*f*T>MIC	16 mg/L (CLSI 'S' breakpoint for *Pseudomonas aeruginosa*), 32 mg/L and 64 mg/L	[49]
	Critically-ill patients with normal renal function (*n* = 43)	4g, 0.5-h inf. (LD) followed by 4g q6h, 3-h inf.	-100%*f*T>MIC - 50%*f*T>MIC	EUCAST 'S' breakpoint for *Pseudomonas aeruginosa* (MIC = 16 mg/L)	[50]
	Patients with nosocomial infections (*n* = 11 with 7 ICU admissions)	3g q8h, 4-h inf.	50%*f*T>MIC	CLSI 'S' range for non-fermentative gram-negative pathogens	[51]
	Critically-ill patients with sepsis (*n* = 16)	• 4g q6h or 8h, 0.33-h inf. (*n* = 8) • 12g q24h, 24-h inf. (*n* = 8)	50%*f*T>MIC	2003 US MYSTIC (Meropenem Yearly Susceptibility Test Information Collection) database	[52]
	Hospitalized patients (*n* = 13 with 7 ICU hospitalizations)	4g q8h, 4-h inf.	50%*f*T>MIC	2004–2007 US MYSTIC database	[53]
	Intensive care unit patients (*n* = 7)	• 4g q8h, 0.25–33-h inf. • 4g, 0.25–0.33-h inf. (LD) followed by 8g q24h, 24-h inf	50%T>MIC	8 and 16 mg/L (surveillance German study data)	[54]
	Septic critically-ill patients (*n* = 40)	• 2g, 0.5-h inf. followed by 8g q24h, 24-h inf (*n* = 20) • 3g q6h, 0.5-h inf. (*n* = 20)		Actual MIC	[55]
	Patients with sepsis (*n* = 6)	4g, 0.17-h inf. (single dose)	35–70%T>MIC	Clinical isolates of *Pseudomonas aeruginosa* and *Staphylococcus aureus* with MIC of 4, 8 and 16 mg/L	[56]

(*Continued*)

Table 2. (Continued).

β-lactams	Patients	Dosing regimens	PK/PD targets	MIC value	Reference
Ceftazidime	Intensive care unit patients suffering from *Pseudomonas aeruginosa* nosocomial pneumonia (n = 72)	-–2g q8h, 0.5-h inf. (n = 22) - 6g q24h, 24-h inf. (n = 22) - 2g, 0.5-h inf. (LD) followed by 6g 24h, 24-h inf. (n = 28)	100%fT>4–5×MIC	EUCAST 'S' breakpoint for *Pseudomonas* spp. (MIC = 8 mg/L)	[57]
	Intensive care unit patients suffering from *Pseudomonas aeruginosa* nosocomial pneumonia (n = 72)	-–2g q8h, 0.5-h inf. (n = 22) - 6g q24h, 24-h inf. (n = 22) - 2g, 0.5-h inf. (LD) followed by 6g 24h, 24-h inf. (n = 28)	100%fT>4–5×MIC	EUCAST 'S' breakpoint for *Pseudomonas* spp. (MIC = 8 mg/L)	[58]
	Intensive care unit patients (n = 6)		60%T>MIC		[59]
	Febrile neutropenic patients with acute myeloid leukemia (n = 20)	1g (LD) following by 5g q24h, 24-h inf. on Day 1, and 6g q24h, 24-h inf. from Day 2	50%fT>4–5×MIC	'S' breakpoint for *Pseudomonas* spp. (MIC = 8 mg/L)	[60]
	Patients with severe nosocomial pneumonia (n = 16)	• 20 mg/kg, 0.5-h inf. (LD) followed by 60 mg/kg q24h, 0.5-h inf. (n = 8) • 20 mg/kg q8h, 0.5-h inf. (n = 8)	100%T > 5×MIC	4 mg/L (local ecology)	[61]
	Critically-ill patients with continuous venovenous hemofiltration (n = 12)	2g q8h, 0.5-h inf.	100%T > 4×MIC	Typical MIC of 4, 8, or 12 mg/L for important *Enterobacteriaceae* collected from Austrian ICU	[62]
	Intensive care unit patients with severe intra-abdominal infections (n = 18)	-–1.5g q8h, 0.5-h inf. (n = 6) - 1g, 0.5h- inf. (LD) followed by 4.5g q24h, 0.5-h inf. (n = 12)	100%T > 4×MIC	MIC_{90} for *Pseudomonas* at the institution (8 mg/L)	[63]
	Critically-ill trauma patients (n = 31)	-–2g q8h, 0.5-h inf. (n = 14) - 2g, 0.5-h inf. followed by 60 mg/kg q24h, 0.5-h inf. (n = 17)	100%T > 4–5×MIC	Actual MIC	[64]
	Patients with septicemic melioidosis (n = 21)	-–40 mg/kg q8h (n = 11) - 12 mg/kg (LD) followed by 4 mg/kg/h (n = 10)	100%T > 4×MIC	Actual MIC (with a median MIC of 2 mg/L)	[65]
Cefepime	Septic shock patients receiving continuous renal replacement therapy (n = 13)	2g q8h or 12h, 0.5-h inf.	-60%T>MIC - 100%T>MIC	- EUCAST 'S' breakpoint for *Pseudomonas aeruginosa* (MIC = 8 mg/L) - 16 mg/L	[66]
	Febrile neutropenic patients with hematological malignancies (n = 12)	2g q8h, 0.5-h inf.	-60%fT>MIC - 100%fT>MIC	- Actual MIC - CLSI and EUCAST highest MIC breakpoints of all susceptible organisms (8 mg/L)	[67]
	Patients with gram-negative pneumonia (n = 33)	-–2g q8h, 0.5-h inf. (n = 3) - 2g q12h, 0.5-h inf. (n = 16) - 1g q6h, 0.5-h inf. (n = 2) - 1g q8h, 0.5-h inf. (n = 3) - 1g q12h, 0.5-h inf. (n = 9)	100%fT>MIC	Actual MIC (MIC_{50} and MIC_{90} of the infecting pathogens: 4 mg/L and 8 mg/L, respectively)	[32]
	Hospitalized patients (n = 9 with 7 ICU hospitalizations)	1g q8h, 4-h inf.	60%fT>MIC	2005–2007 US MYSTIC database	[68]
	Intensive care unit patients with nosocomial pneumonia (n = 21)	2g q12h or 24h or 36h, 0.5-h inf.	50%T≥MIC	- Actual MIC - CLSI 'S' breakpoints for *Enterobacteriaceae, Pseudomonas aeruginosa* and *Staphylococcus aureus* (MIC≤8 mg/L), for *Haemophilus* spp. (MIC≤2 mg/L) and for *Streptococcus pneumoniae* and other streptococci (MIC≤1 mg/L)	[69]
	Critically-ill patients with ventilator-associated pneumonia (n = 32)	2g q8h, 0.5-h inf.	50%fT>MIC	'S', 'I' and 'R' breakpoints for *Pseudomonas aeruginosa* (MIC = 8, 16, 32 mg/L, respectively)	[70]
	Intensive care unit patients (n = 13)	2g q12h, 0.05-h inf.	65%fT>MIC	MIC distribution from Australian laboratories for *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Acinetobacter baumannii*	[71]
	Critically-ill patients with severe pneumonia (n = 41) or bacteremia (n = 9)	-–2g q12h - 4g q24h, 24-h inf.	100%T > 5×MIC	- Actual MIC - 4 mg/L ('French breakpoint')	[72]
	Critically-ill patients with sepsis and normal renal function (n = 13)	2g q12h 0.05-h inf.		4 mg/L (only for comparison purposes)	[73]

(*Continued*)

Table 2. (Continued).

β-lactams	Patients	Dosing regimens	PK/PD targets	MIC value	Reference
	Intensive care unit patients receiving continuous venovenous hemo(dia)filtration (n = 12)	1/2g q12/24h, 0.25–0.5-h inf.	-50%T>MIC - $AUC_{0\text{-}24}$/MIC≥100	- Actual MIC - CLSI 'S', 'I' and 'R' breakpoints for *Pseudomonas aeruginosa* (MIC = 8, 16, 32 mg/L respectively)	[74]
Meropenem	Intensive care unit patients (n = 34)	1g q12h or 8h, 0.5-h or 3-h inf.	-40%T>MIC - 100%T>MIC		[75]
	Intensive care unit patients (n = 182)	- intermittent-bolus dosing - extended infusion - continuous infusion	-50%*f*T>MIC - 50%*f*T>4×MIC - 100%*f*T>MIC - 100%*f*T>4×MIC	- Actual MIC - EUCAST MIC_{90} values (for *Pseudomonas aeruginosa* (2 mg/L) if no pathogen formally identified)	[36]
	Intensive care unit patients with *Klebsiella pneumoniae* infections (n = 27)	1g or 2g q8h or 12h, 3-h inf.	100%*f*T>4×MIC	EUCAST MIC values for *Klebsiella pneumoniae* (4–8 mg/L)	[76]
	Critically-ill patients with septic shock and continuous renal replacement therapy (n = 30)	At the discretion of the treating physician	-–40%*f*T>MIC - 100%*f*T>MIC - 100%*f*T>5×MIC	EUCAST 'S' (<2 mg/L) and 'R' breakpoints (2-4 mg/L)	[77]
	Critically-ill patients receiving continuous venovenous hemodialysis (n = 4)	0.5g or 1g q8h or 12h, 0.5-h inf.	40%T>MIC	MIC_{90} values against *Pseudomonas aeruginosa* isolates from respiratory tract infections and surgical site infections (4 mg/L and 16 mg/L, respectively)	[78]
	Overweight, obese and morbidly obese patients with stable and unstable kidney function (n = 375)	2g/day (median daily dose) q6h	100%T>MIC	2, 4, 8, 16 mg/L	[79]
	Critically-ill patients with severe sepsis or septic shock	1g q8h, 1-h inf.	-–40%*f*T>MIC - 80%*f*T>MIC		[80]
	Severely burned patients (n = 12)	1g q8h, 0.08-h inf.	-–40%T>MIC - 60%T>MIC - 80%T>MIC	EUCAST MIC distributions for *Escherichia coli, CoNS, Pseudomonas aeruginosa* and *Enterococcus faecalis*	[81]
	Critically-ill patients receiving renal replacement therapy (n = 5)	0.5g q8h, 0.05-h inf.	40%*f*T>MIC	Clinically relevant MIC of 2, 4, 8 and 16 mg/L	[82]
	Intensive care unit patients with severe nosocomial pneumonia (n = 55)	-–1g q8h, 0.5-h inf. (n = 30) - 1g q8h, 3-h inf. (n = 25)	-40%T>MIC - 40%T > 4×MIC - 54%T>MIC - 54%T > 4×MIC - 100%T>MIC - 100%T > 4×MIC	EUCAST breakpoints for *Pseudomonas* spp., *Acinetobacter* spp. and *Enterobacteriaceae* (susceptibility, intermediate and resistance thresholds of ≤2, 4–8 and .8 mg/L, respectively)	[83]
	Critically-ill patients (n = 10)	-–1g q8h, 0.5-h inf. - 0.5g q8h, 3-h inf.	40%T>MIC	CLSI breakpoint for *Pseudomonas aeruginosa*	[84]
	Intensive care unit patients (n = 10)	• 1g, 0.5-h inf. (LD) followed by 1g q8h, 3-h inf. (n = 5) • 1g q8h, 0.5-h inf. (n = 5)	-100%*f*T>MIC - 50%*f*T>MIC - 100%*f*T>4×MIC	EUCAST 'S' breakpoint (MIC = 16 mg/L)	[45]
	Critically-ill patients with ventilator-associated pneumonia (n = 9)	1g q8h, bolus, for 24h; then 1g q8h, 3-h inf., for 24h; then 2g q8h, 3-h inf., for 24h	-20%T>MIC - 40%T>MIC	- EUCAST breakpoints - MYSTIC database	[85]
	Intensive care unit patients with morbid obesity (n = 9)	0.5g or 1g q6h, 0.5-h inf.	-–40%*f*T>MIC - 54%*f*T>MIC	CLSI 'S' breakpoint for *Pseudomonas aeruginosa* (2mg/L)	[86]
	Critically-ill patients with normal renal function (n = 17)	1g, 0.5-h inf. (LD) followed by 1g q8h, 3-h inf.	-–100%*f*T>MIC - 50%*f*T>MIC	EUCAST 'S' breakpoint for *Pseudomonas aeruginosa* (MIC = 2 mg/L)	[50]
	Critically-ill patients with febrile neutropenia and bacteremia (n = 8)	1g q8h, 0.17-h inf., for 24h; then 1g q8h, 3-h inf., for 24h; then 2g q8h, 3-h inf., for 24h	-–40%T>MIC - 60%T>MIC - 80%T>MIC - 100%T>MIC	EUCAST MIC range for *Escherichia coli, Klebsiella* spp., *Pseudomonas aeruginosa* and *Acinetobacter* spp.	[87]

(*Continued*)

Table 2. (Continued).

β-lactams	Patients	Dosing regimens	PK/PD targets	MIC value	Reference
	Critically-ill patients (n = 26)	-–2g q8h, 3-h inf. (n = 11) - 2g q8h, 1-h inf. (n = 1) - 1g q8h, 1-h inf. (n = 3) - 1g q8h, 0.5-h inf. (n = 4) - 0.5g q8h, 0.5-h inf. (n = 2) - 0.5g q6h, 0.5-h inf. (n = 5)	40%*f*T>MIC	- EUCAST 'S' breakpoint for Gram negative organisms (<2 mg/L) - CLSI 'S' breakpoints for *Enterobacteriaceae* (<1 mg/L), *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (<4 mg/L)	[88]
	Patients from Burn Intensive Care Unit (n = 59)	-–1g q8h, 0.5-h inf. (n = 4) - 1g q12h, 0.5-h inf. (n = 18) - 0.5g q8h, 0.5-h inf. (n = 3) - 0.5g q12h, 0.5-h inf. (n = 34)	40%*f*T>MIC	MIC distribution of *P. aeruginosa* reported from Korean patients and the MYSTIC study	[89]
	Critically-ill patients with sepsis receiving high-volume continuous venovenous hemofiltration (n = 10)	1g q8h	100%T>MIC	MIC90 for *B. pseudomallei* (4 mg/L)	[90]
	Critically-ill patients undergoing continuous renal replacement therapy (n = 20)	0.5g or 1g or 2g q6h or 8h	100%T>MIC	NCCLS breakpoints	[91]
	Intensive care unit patients (n = 6)	-–1g q12h, 0.25–0.33-h inf. - 0.5g (LD) and 2g q24h, 24-h inf.		4 mg/L, 8mg/L and 16 mg/L to cover intermediately resistant strains of *Pseudomonas aeruginosa*	[54]
	Critically-ill patients receiving continuous veno-venous hemofiltration (n = 8)	0.5g q12h	40%T>MIC	4 mg/L (MIC for susceptible organisms); 8 mg/L (intermediately susceptible organisms)	[92]
	Critically-ill patients receiving continuous venovenous hemofiltration (n = 15)	0.5g or 1g q8h or 12h	75%T>MIC	4 mg/L (MIC for sensitive strains)	[93]
	Critically-ill patients with sepsis (n = 14)	1g q8h or 12h, 0.5-h inf.		Actual MIC	[94]

antibiotics under study show only low protein binding, especially when considering critically-ill patients due to lower serum protein levels and organ dysfunction (an actual measurement of the free fraction of piperacillin in the patients included in our analysis showed values around 92% [unpublished], confirming its lower protein in these patients compared to healthy subjects (see ref [99].).

4.2.2. Results

4.2.2.1. Reaching %t > 1×MIC of 100% with 4×MIC for 40–70% of the dosing interval.

Figure 1 shows the relationship between C_{min} (concentration at the end of the dosing interval) for each of the four antibiotics examined (abscissa) and the corresponding concentrations at 50% (piperacillin), 70% (ceftazidime and cefepime), and 40% (meropenem) of the dosing interval (ordinate) (as originally proposed; see Table 1). It clearly appears that reaching the first target proposed by the Australian investigators (%T > 1×MIC of 100% [95]) will be largely unsuccessful, since this will be obtained only for 56%, 87%, 63%, and 59% of patients for piperacillin, ceftazidime, cefepime, and meropenem, respectively. Moreover, only a small proportion of these patients (namely 46% for piperacillin, 35% for ceftazidime, and 20% for cefepime), will reach 4×MIC at 50% (piperacillin) or 70% (ceftazidime, cefepime) of the dosing interval (needed for a maximal bactericidal effect), but 94% will do it for meropenem.

4.2.2.2. Reaching 100%T>4×MIC.

As also illustrated in Figure 1, the percentage of patients reporting concentrations above 4×MIC for the entire standard dosing interval was even lower than for the previous targets, with only 7, 17, 5, and 15% of all patients reaching it for piperacillin, ceftazidime, cefepime, and meropenem, respectively.

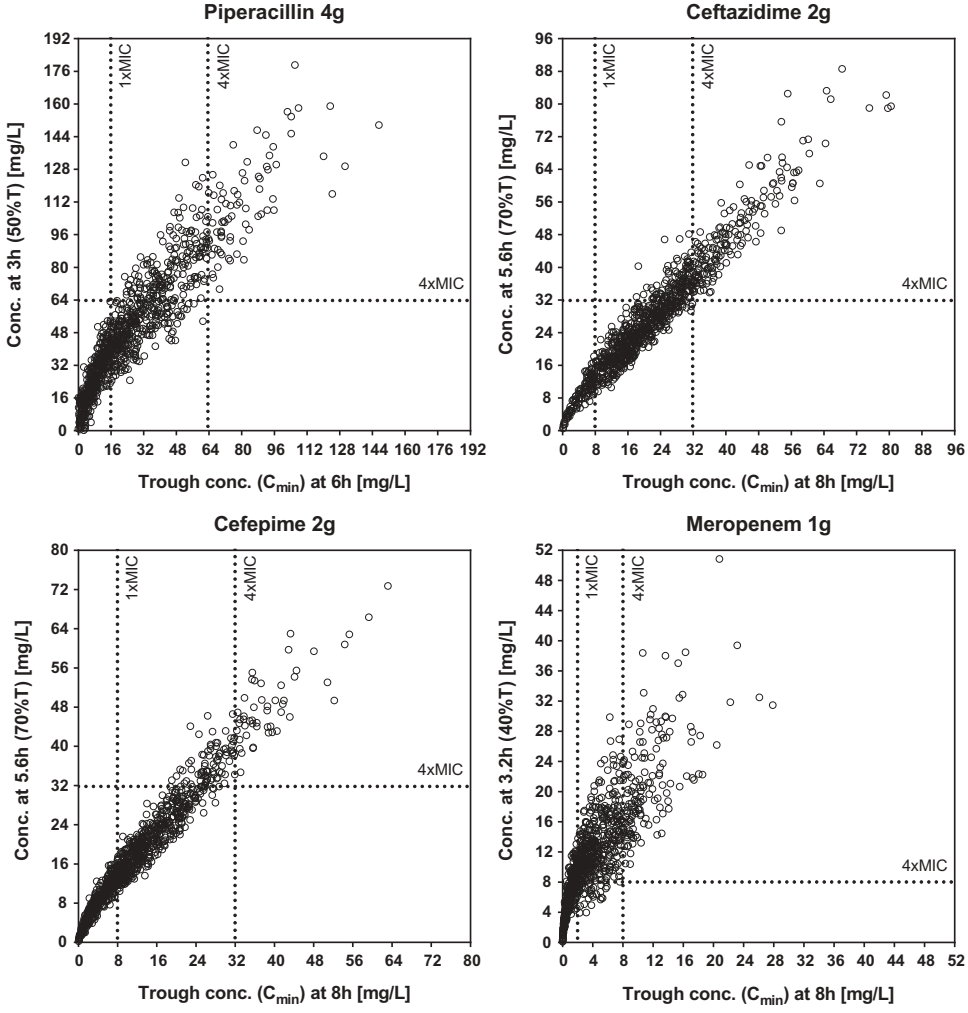

Figure 1. β-lactam serum concentrations assessed for a standard scenario of first dose of 1000 virtual critically-ill septic patients receiving a standard dose of piperacillin (4g), ceftazidime (2g), cefepime(2g) or meropenem (2g). The abscissa shows the through concentration (C_{min}) at the end of the corresponding standard dosing interval (piperacillin, 6h; ceftazidime, cefepime and meropenem, 8h each). The ordinate shows the concentration reached at 50% (piperacillin), 70% (ceftazidime and cefepime), or 40% (meropenem) of the dosing interval. The vertical dotted lines correspond to the proposed PD targets of 1x and 4xMIC (defined as the susceptibility breakpoint set by EUCAST for the corresponding antibiotics against *P. aeruginosa* (piperacillin, 16 mg/L; ceftazidime and cefepime, 8 mg/L; meropenem, 2 mg/L) at 50% (piperacillin), 70% (ceftazidime and cefepime), and 40% meropenem) of the dosing interval. Patients reaching the target of 100% T > 1xMIC advocated by the Asutralian group [95] (i.e. C_{min} > 1xMIC for the entire duration of the dosing interval) are those falling on the right of the 1xMIC vertical dotted line. Those reaching this target and for which the serum concentration also reaches 4xMIC at 50% (piperacillin), 70% (ceftazidime and cefepime) or 40% (meropenem) of the dosing interval (needed for maximal efficacy [95]; see also Table 1) are those falling above the horizontal 4xMIC dotted line. Patients reaching the more demanding target of 100%T > 4xMIC advocated by the Houston investigators [28,29] are those falling on the right of the vertical 4xMIC dotted line.

5. Expert commentary

To improve clinical outcomes, a prompt initiation of the right antibiotic therapy with the adequate doses is of paramount importance [5–9], the goal being to reach adequate values of the PK/PD targets (%*f*T>MIC and the C_{min}/MIC ratio) predicting clinical success and prevention of resistance emergence. The debate concerning the values of these targets is still very active, one of the major difficulty being that few *in vivo* studies were designed to evaluate endpoints in a true clinical context. The recent multinational DALI study ('Defining Antibiotic Levels in Intensive Care Patients;' 68 participating ICUs) showed, nevertheless, that clinical outcomes were better for %*f*T>1×MIC of 100%, compared to lower values, in severely ill patients [100]. Convincing *in vitro* data also suggest that microbiological success may be optimal when serum β-lactam concentrations are maintained above 4×MIC during the entire dosing interval [19,28–30]. Considering that ICU patients are severely vulnerable to suboptimal dosing and represent a source of selection of (multi)resistance to antibiotics, we propose to use the target of 100%T > 4×MIC [28,29], as this would allow for maximal bacterial killing [25–27], protect against bacterial regrowth [24,25,101], and ensure positive clinical outcome [100]. We show here that this target will be very difficult to reach, at least at first dose, for the four β-lactams mostly used to control gram-negative infections in critically-ill patients. Not reaching this target, however, may not only lead to poor clinical outcomes but also to emergence of resistance (already documented in clinical studies [102]). Larger initial doses may also be especially important when dealing with infections where local bacterial density is high (such as in pneumonia) because of impaired activity of β-lactams due to important defeating inoculum effects. Altogether, this could put increasing demands on β-lactams and seriously limit their clinical utility [103]. Since the successful clinical development of new antibiotics is becoming increasingly difficult and hazardous, major efforts are needed to optimize the dosages of currently available β-lactams using clearly defined targets for critically-ill patients. We, therefore, advocate that clinicians should use larger initial dosages in order to reach the desired target. While higher dosages carry an increased cost (in the absence of flat price policies), they will ensure therapeutic success, which it-self may be cost-saving. Alternatively, using extended or even continuous infusion may efficiently increase the %T>MIC while reducing the risk of toxicities associated with too high serum levels [104]. When interindividual PK variability is large, such as in critically-ill patients with comorbidities [1,3,4], maintaining the appropriate targets during therapy may, however, be difficult without TDM to personalize drug dosage and to correct for the insufficiencies of predictions based on population PK. Failure to move in this direction for critically-ill patients may not only make them the first victims of ineffective therapy but could create niches for selection of resistant organisms that may spread to other patients and environments.

6. Five-year view

Clinicians are increasingly faced with a major challenge in critically-ill patients by the necessity to reach two apparently contradicting goals, namely to rapidly prescribe the correct and appropriate antibiotic therapy while, at the same time, reduce the emergence of resistance and the overuse of antibiotics. We suggest that a target of 100%T > 4×MIC could achieve these goals, since a better efficacy may result in shorter treatment durations and avoid relapses, resulting in a global decrease of antibiotic use and protect against fast emergence of resistance. We, nevertheless, realize that this severe target has, so far, never been put to test in a comprehensive clinical trial. Thus, future research should first focus on confirming this PK/PD target along with clinical or microbiological success. A further step should be (i) to seek reducing the interindividual PK variability during therapy by using TDM (with rapid communication of the results to the clinician), and (ii) to measure microbiological outcomes (including eradication of bacteria, bacterial regrowth and development of antibiotic resistance).

The present paper highlights the significant need for additional research in the optimization of the β-lactam dosage for the treatment of critical illness. Now, more than ever, major efforts are needed to optimize clinical use of β-lactams in critically-ill patients.

However, a consensus on the optimal target of β-lactams along with a leverage effect of the PK/PD strategies in rationally optimizing β-lactam dosage regimens could be reasonably expected, for the upcoming years.

Key issues

- β-lactams are the cornerstone of antibiotic therapy in the critical care settings.
- They exhibit a time-dependent effect on bacterial killing, with minimal or no post-antibiotic effect. The pharmacokinetic/pharmacodynamic (PK/PD) index predicting best their clinical and microbiological efficacy is the time (T) for which the free serum concentration exceeds the minimal inhibitory concentration (MIC).
- Regrettably, the magnitude and targets of their PK/PD indices are not clearly defined, especially in critically ill patients where suboptimal dosing and increasing resistance rates remain major challenges for clinicians.
- The most conservative PK/PD targets are β-lactam concentrations maintained above 4x the MIC during 40–70% of the dosing interval (40–70%T > 4xMIC).
- While it is claimed that a %T > 1xMIC of 100% is likely sufficient to ensure a %T > 4xMIC of 40 to 70% for β-lactams in critical illness; the present results however invalidate this hypothesis for piperacillin, ceftazidime and cefepime at first dose.
- Convincing *in vitro* studies suggest, however, that larger drug exposures may be required in critically-ill patients, with a minimal β-lactam concentration/MIC ratio of at least 4 (100%T > 4xMIC), especially if considering the risk of emergence of resistance. Yet, this more demanding target is only reached for a limited proportion of patients at first dose when using the β-lactams studied here at their recommended dosages.
- Clinical and microbiological studies are urgently needed to test for the feasibility of reaching this demanding target and to assess its success in terms of efficiency in therapy and prevention of resistance.

Notes

1. According to the terminology of the European Committee for Antimicrobial Susceptibility Testing (EUCAST; see http://www.eucast.org) and used for inclusion in the Summary of Product Characteristics in Europe. The US Clinical and Laboratory Standard Institute (CLSI) and the US Food and Drug Administration (FDA) define as resistant an organism with an MIC ≥ to their corresponding 'R' breakpoint, which may be different from the 'R' EUCAST breakpoint.
2. Web version of the US National Library of Medicine – National Institutes of Health; available at https://www.ncbi.nlm.nih.gov/pubmed.

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•• **The authors claim that a target of 100%*f*T>MIC is likely to ensure a %*f*T>4×MIC of 40–70% (i.e. 100%*f*T>MIC ~ 40–70%*f*T>4×MIC).**
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