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REVIEW

A narrative review of predictors for β-lactam antibiotic exposure during empirical treatment in critically ill patients

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ABSTRACT

Introduction: : Emerging studies suggest that antibiotic pharmacokinetics (PK) are difficult to predict in critically ill patients. The high intra- and inter-patient PK variability makes it challenging to accurately predict the appropriate dosage required for a given patient. Identifying patients at risk could help clinicians to consider more individualized dosing regimens and perform therapeutic drug monitoring. We provide an overview of relevant predictors associated with target (non-)attainment of β-lactam antibiotics in critically ill patients.

Areas covered: : This narrative review summarizes patient and clinical characteristics that can help to predict the attainment of target serum concentrations and to provide guidance on antimicrobial dose optimization. Literature was searched using Embase and Medline database, focusing on β-lactam antibiotics in critically ill patients.

Expert opinion: : Adequate concentration attainment can be anticipated in critically ill patients prior to initiating empiric β-lactam antibiotic therapy based on readily available demographic and clinical factors. Male gender, younger age, and augmented renal clearance were the most significant predictors for target non-attainment and should be considered in further investigations to develop dosing algorithms for optimal β-lactam therapy.

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B-lactam antibiotics; critically ill; predictors; risk factors; target attainment; therapeutic drug monitoring

1. Introduction

Severe bacterial infections are a major challenge in the intensive care unit (ICU) because of their high prevalence and mortality. Early adequate antimicrobial therapy improves the likelihood of clinical cure and survival rates [1–3]. However, dosage guidelines for most antibiotics are derived from pharmacokinetic (PK) studies in healthy volunteers, and do not consider the significant changes in PK and pathogen susceptibility that are common to the critically ill patient. For example, changes in drug clearance and/or volume of distribution can lead to significant changes in the plasma drug concentration [4,5], resulting in predetermined pharmacokinetic/pharmacodynamic (PK/PD) targets not being achieved and thus a higher treatment failure rate [6]. Furthermore, critically ill patients can undergo rapid physiological changes, such as altered fluid status, changes in serum albumin concentrations, end-organ dysfunction, systemic inflammatory response syndrome (SIRS), and microvascular failure [4,7]. These factors imply that antibiotic dosing in critically ill patients demands a thorough assessment and the need for an individualization from initiation of the therapy and during the course of treatment [8,9].

β-lactam antibiotics (penicillins, cephalosporins, monobactams, and carbapenems) are amongst the most commonly used antibiotics to treat severe infections in the ICU because of their broad spectrum, low likelihood of drug-drug interactions, and wide therapeutic range. These antibiotics display a time-dependent activity. The pharmacodynamic index associated best with a high probability of successful outcome is the percentage of time (T) of the dosing interval in which the unbound (free, f) serum antibiotic concentration remains above the minimum inhibitory concentration (% fT > MIC). For β-lactams, the fT > MIC value needed for bactericidal activity is between 40% and 70% in *in vitro* infection models [10,11], this has been confirmed in patients with nosocomial pneumonia for both ceftazidime and ceftobiprole [12,13]. However, clinical data suggest optimal efficacy is achieved at 100% fT > MIC in critically ill patients [14–17].

Achieving the high ICU targets is not easy, particularly when fixed conventional β-lactam dosing regimens are used. Although β-lactam antibiotics have a relatively wide therapeutic window, simply increasing the standard dosing for this group of antibiotics in all critically ill patients is not an optimal strategy, since high dosing regimens might result in trough levels associated with overexposure and

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Supplemental data for this article can be accessed here.

Article highlights

- This review provides an overview of important predictors for β-lactam target (non)-attainment in critically ill patients.
- Adequate target attainment can be anticipated in critically ill patients prior to initiating empiric β-lactam antibiotic therapy based on readily available demographic and clinical factors.
- Male gender, younger age, and augmented renal clearance are the most significant predictors for β-lactam target non-attainment.
- A higher daily dose of β-lactam antibiotics at the onset of treatment should be considered in the most critically ill patients and in those with preserved renal function or augmented renal clearance.

toxicity [18]. Looking at the current standard approach, dose adjustment and optimization is made only based on indication and adjusted for renal function. Moreover, appropriate antimicrobial therapy refers not only to a suitable drug choice in terms of spectrum of activity, but also to an adequate dosing regimen. Thus, it appears necessary to individualize β-lactam dosing regimens in critically ill patients. Accordingly, identifying patients at risk could guide clinicians to consider more individualized dosing regimens and incorporate therapeutic drug monitoring (TDM) when needed.

The purpose of this review is to examine recent evidence on relevant demographic and clinical characteristics predicting β-lactam exposure in critically ill patients and to provide dosing recommendations.

2. Methodology

A literature search was conducted in August 2020 without a restriction of the publication date. Two databases (Medline All Ovid and Embase) were searched to assess literature on risk factors to predict target concentration prior to initiating empiric β-lactam therapy in critically ill patients. The search was additionally limited to English-language articles. Detailed research terms can be found in supplementary **Table S1**.

2.1. Eligibility criteria and study selection

Studies reporting the relationship between patient or clinical variables and target (non-)attainment at the time of β-lactam antibiotics treatment initiation in critically ill patients were eligible for inclusion. Titles and abstracts were screened to identify relevant publications. Articles were excluded if they assessed pediatric patients, or were clinical cases, reviews, letters or editorials. Reference lists of eligible studies were searched for additional studies. The references from the database were imported into a reference manager (Endnote X9®).

2.2. Data extraction

We extracted the following data from each included study: author, year of publication, study antibiotics, number of participants, and the effect of the predictor on β-lactam target attainment. The estimates for the multivariate regressions examining the association of target attainment with predictor variables were extracted. For the effect size we have reported the odds ratios (ORs) and the 95% confidence intervals (95% CI). In studies in which the relationship with target non-attainment was investigated, the OR was converted to the inversed OR (1/OR).

3. Predictors for β-lactam exposure

3.1. Study selection

Figure 1 shows a flowchart of the selection process by which articles were identified. Using the search process described above, 839 studies remained once duplicates were removed. A total of 20 studies were included for the full-text assessment. Of these, 11 studies were found that met the inclusion criteria, representing 11 different β-lactam antibiotics (3 penicillins, 6 cephalosporins, and 3 carbapems) [16,19–28]. Only four studies were primarily designed to assess the relationship between drug concentrations or target attainment and risk factors [19,21,24,27]. Almost all studies were partly or fully performed in European hospitals (n = 10, 91%). Taken together, results suggest that β-lactam exposure is associated with a wide range of demographic and clinical characteristics (Figure 2). Details on the factors that predicted the achievement of the PK/PD targets (C_{min}> MIC, 50% (f)T > MIC, 100% (f)T > MIC, and 100% (f)T > 4× MIC are shown Table 1.

3.2. Demographic predictors

We found two demographic characteristics that can be used at the start of empirical antibiotic therapy to potentially increase the chance of target attainment. Firstly, male gender is significantly associated with target non-attainment [19,20,27]. On average, men have a larger volume of distribution (plasma volume and intra-/extracellular water) and a higher drug clearance, possibly explaining the observed effect of gender on drug exposure [29]. Furthermore, male gender is thought to offer an underlying physiological reserve to critically ill patients and contribute to target non-attainment by facilitating augmented renal clearance (ARC) [30]. Although gender is easy to implement in predictor models for target attainment, future studies should be designed with a primary focus on this topic to better understand the basic mechanisms of gender differences and the implications for clinical management.

Age is the second demographic predictor that was found to be significantly correlated with target attainment [20,27]. This association is related to the presence of reduced renal function, which is common in older patients.

3.3. Clinical predictors

We found various clinical characteristics that can be used at the start and during empirical antibiotic therapy to optimize target attainment. Evidence suggests that renal function is among the most important clinical factor to contribute to target non-attainment at the time of antibiotic initiation [16,19–25,27,28].

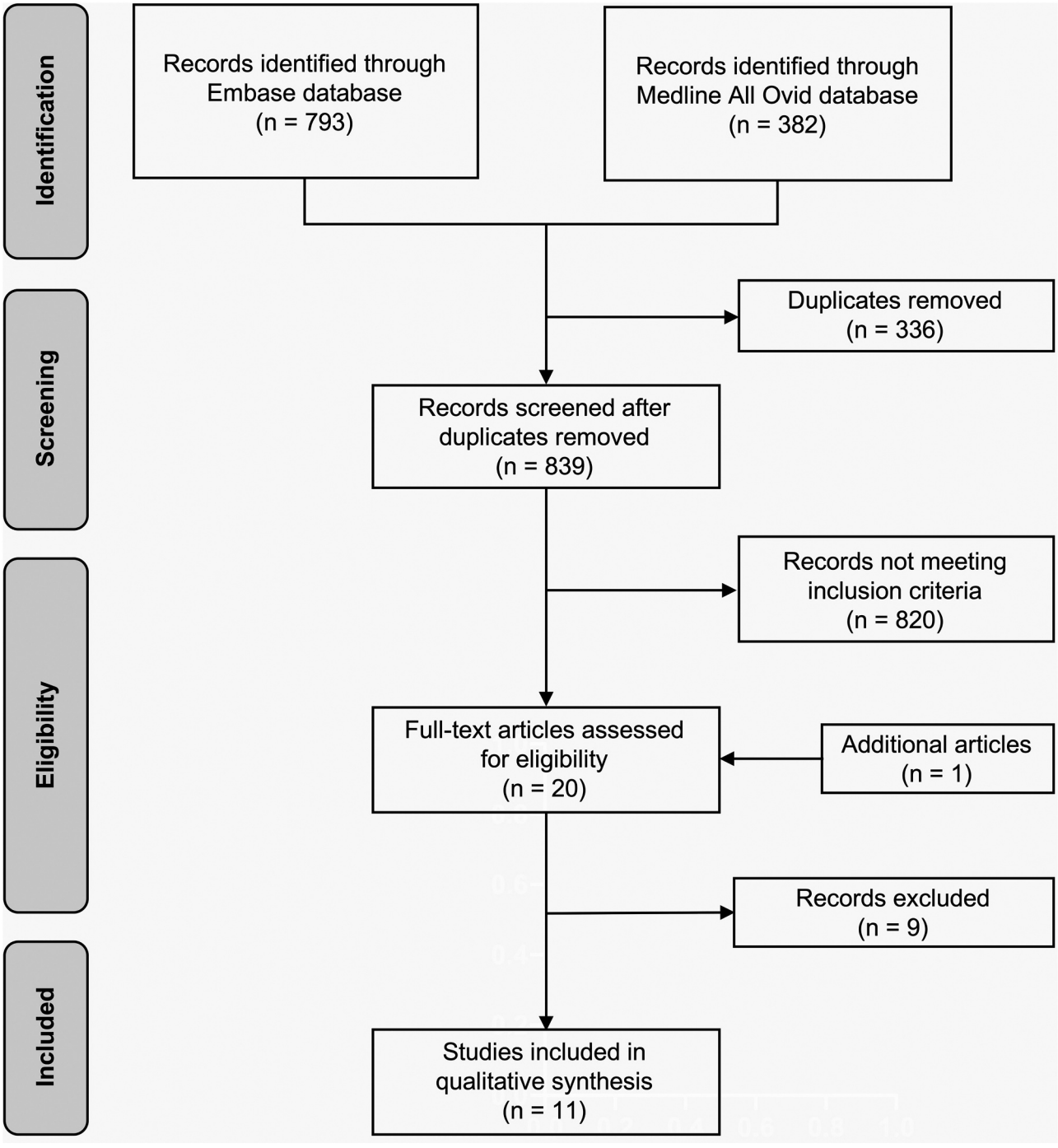

Figure 1. Flowchart of the search strategy and included articles.

Traditionally, renal function in critically ill patients has been routinely assessed with the objective of detecting renal impairment and adjusting drug doses. Nevertheless, ARC has also been identified in ICU patients [30,31]. As a result, patients with presumed 'normal' or increased renal function are at risk of target non-attainment [32]. The PK of critically ill patients can be significantly altered due to an increased cardiac output with resultant of increased renal blood flow and this may lead to ARC of solutes and drugs [33,34]. Furthermore, as β-lactam antibiotics are hydrophilic compounds and are predominantly cleared by the kidney, high renal function, as observed in ARC, contributes significantly to suboptimal target attainment [16]. Although there is no final consensus as to what defines ARC of drugs, a recent definition suggests ARC when the creatinine clearance (CLCr) exceeds 130 mL/min per 1.73 m^2 [35]. Udy et al. examined the CLCr and β-lactam trough concentrations of 58 intensive care unit (ICU) patients, CLCr values ≥130 mL/min/1.73 m^2 were

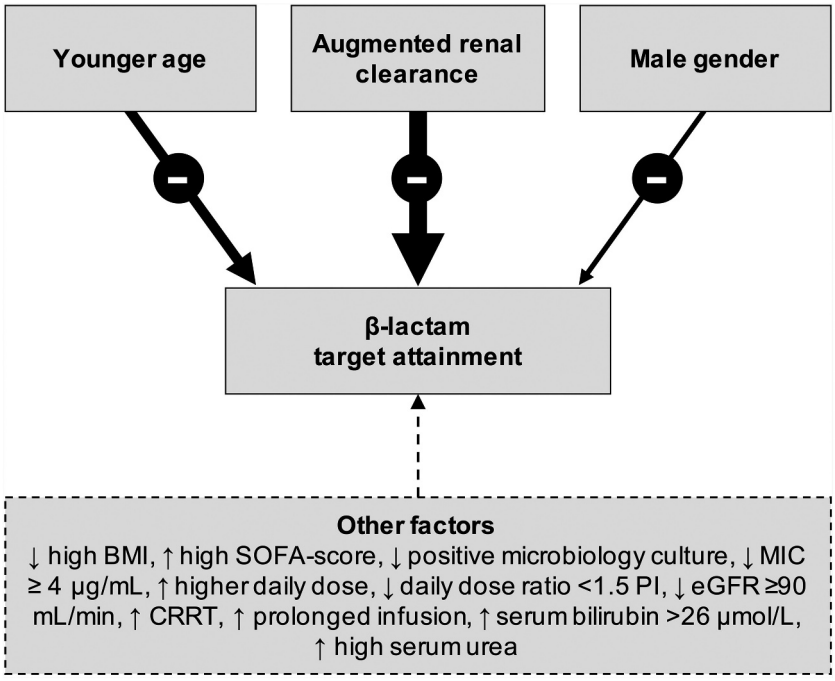

Figure 2. Demographic and clinical factors associated with β-lactam target attainment. The thickness of the arrow is a representation of the associated evidence. The up arrows indicate that the probability of target attainment increases, the down arrows indicate that the probability of target attainment decreases.

associated with trough concentrations less than the MIC of the antibiotic needed to inhibit the targeted micro-organism in 82% of patients [32]. Imani et al. assessed the performance of eGFR as an independent predictor for target non-attainment using a ROC curve and found an eGFR threshold value of ≥71.5 mL/min/1.73 m^2 had a sensitivity and specificity of 77% and 65%, respectively [27]. Furthermore, Carrié et al. reported that eGFR ≥170 mL/min were significantly associated with fT < 4× MIC [23]. The ability to rapidly predict the risk of target non-attainment in patients with ARC using available eGFR has considerable clinical value. Moreover, the emergence of ARC itself has been associated with a wide range of factors. One that has most consistently been linked to a high risk of ARC is younger age [30,36].

The use of renal replacement therapy (RRT) during β-lactam therapy also shows a strong and significant association with target attainment [19]. Not surprisingly, considering that β-lactam antibiotics are predominantly cleared via renal elimination. At the same time, these patients may be at risk for overexposure and toxicity due to the reduced elimination. Furthermore, in an obese patient cohort, RRT was identified as an independent risk factor for overdose and a protective factor for target attainment [26]. Predicting β-lactam concentrations during treatment with RRT (intermittent, prolonged or continuous) seem to be challenging, as both volume of distribution and total drug clearance are affected, and both parameters may be significantly disturbed during critical illness. In addition, it is important to realize that the effect of RRT on target attainment may be unpredictably affected by for example the type of membrane, device settings, and intensity.

Higher doses and prolonged infusions are also clear predictors for target attainment. Imani et al. found that prescribed daily antibiotic dose ≥ 1.5 times the product information (PI) recommendations were associated with better target attainment [27]. Higher total daily dose is associated with the achievement of 100% fT >4× MIC for piperacillin [20]. Moreover, Carrie et al. showed that in critically ill patients with ARC, higher than licensed dosing regimens of β-lactam antibiotics may be safe and effective in reducing the rate of therapeutic failure [37]. The total daily dose is not associated with achievement of 100% fT >MIC, because there was not a wide range of doses used in the studies, or alternatively, because the dose adjustments that were made for different levels of renal function prevented this being significant. However, in ARC patients, higher dosing than the licensed dosing regimens of β-lactam antibiotics may be safe and effective in reducing the rate of therapeutic failure [37]. Furthermore, the use of prolonged (extended or continuous) infusion is significantly associated with the achievement target attainment [20,24]. In dosing simulations studies, extended or continuous infusion has also been demonstrated to increase the changes of target attainment [38–41].

Obesity has previously been proposed to be a risk factor for altered β-lactam concentrations in both non-critically ill and critically ill patients [42–45]. High body mass index (BMI) was a significant risk factor for target non-attainment [19]. With the increased prevalence of obesity in Western societies and no dosing guidelines available for critically ill obese patients, ensuring adequate β-lactam therapeutic concentrations is considered to be a serious challenge for clinicians.

Table 1. Predictors for beta-lactam target non-attainment extracted from literature.

Predictors	*Study antibiotics (n of patients)*	*Effect on target attainment*	*OR (95%-CI), p-value*
Male gender	Meropenem (n = 80), piperacillin (n = 169)	↓[a]	0.26* (0.10–0.68), p = 0.006 [27]
	Amoxicillin (n = 9), cefotaxime (n = 93), ceftazidime (n = 5), ceftriaxone (n = 17), cefuroxime (n = 2), meropenem (n = 21)	↓[c]	0.32 (0.12–0.81) [19]
	Meropenem (n = 481), piperacillin (n = 919)	↓[c]	MER NS and 0.43 (0.28–0.64), p < 0.001 [20]
		↓[d]	0.36 (0.20–0.62), p < 0.001 and 0.29 (0.19–0.46), p < 0.001 [20]
Age	Meropenem (n = 80), piperacillin (n = 169)	↑[a]	1.03* (1.01–1.05), p = 0.015 [27]
	Meropenem (n = 481), piperacillin (n = 919)	↑[c]	1.04 (1.01–1.06), p = 0.002 and 1.02 (1.00–1.03), p = 0.012 [20]
		↑[d]	1.02 (1.00–1.04), p = 0.014 and PIP NS [20]
BMI	Amoxicillin (n = 9), cefotaxime (n = 93), ceftazidime (n = 5), ceftriaxone (n = 17), cefuroxime (n = 2), meropenem (n = 21)	↓[d]	0.91 (0.83–0.99) [19]
SOFA-score	Meropenem (n = 80), piperacillin (n = 169)	↑[c]	1.18* (1.05–1.32), p = 0.005 [27]
Positive microbiology culture	Meropenem (n = 80), piperacillin (n = 169)	↓[a]	3.23* (1.41–7.69), 0.006 [27]
MIC ≥ 4 µg/mL	Cefazolin (n = 10), cefepime (n = 6), cefotaxime (n = 2), ceftazidime (n = 10), piperacillin (n = 45), meropenem (n = 6)	↓[d]	0.18* (0.04–0.77) p = 0.02 [23]
Higher daily dose	Meropenem (n = 481), piperacillin (n = 919)	↑[d]	MER NS and 1.10 (1.02–1.20), p < 0.021 [20]
Daily dose ratio <1.5 PI	Meropenem (n = 80), piperacillin (n = 169)	↓[a]	0.15* (0.04–0.56), p = 0.004 [27]
Creatinine clearance mL/min	Amoxicillin (n = 71), ampicillin (n = 18), cefazolin (n = 10), cefepime (n = 13), ceftriaxone, doripenem (n = 13), meropenem (n = 78), piperacillin (n = 107)	↓[c]	0.99* (0.98–0.98), p < 0.001 [24]
	Meropenem (n = 17), piperacillin (n = 43)	↓[c]	0.892 (0.798–0.997), p = 0.045 [21]
	Meropenem (n = 48), piperacillin (n = 205)	↓[d]	0.988 (0.982–0.994), p = 0.001 [25]
eGFR ≥90 mL/min	Meropenem (n = 80), piperacillin (n = 169)	↓[a]	0.23* (0.10–0.51), p < 0.001 [27]
	Amoxicillin (n = 9), cefotaxime (n = 93), ceftazidime (n = 5), ceftriaxone (n = 17), cefuroxime (n = 2), meropenem (n = 21)	↓[d]	0.14 (0.03–0.49) [19]
	Cefotaxime (n = 38), meropenem (n = 24), piperacillin (n = 49)	↓[c]	0.008* (0.001–0.065), p < 0.001 [28]
CrCl ≤100 mL/min	Meropenem (n = 481), piperacillin (n = 919)	↑[c]	21.74 (6.02–76.92), p < 0.001 and 14.08 (7.41–27.08), p < 0.001 [20]
		↑[d]	20.83 (9.52–45.45), p < 0.001 and 166.6 (2.17–1000.0), p < 0.001 [20]
CrCl ≥130 mL/min	Cefepime (n = 2), imipenem (n = 54), meropenem (n = 11), piperacillin (n = 33)	↓[c]	0.30* (0.10-0.90), p < 0.05 [16]
CrCl ≥170 mL/min	Cefazolin (n = 10), cefepime (n = 6), cefotaxime (n = 2), ceftazidime (n = 10), piperacillin (n = 45), meropenem (n = 6)	↓[d]	0.10* (0.02–0.42), p = 0.001 [23]
	Piperacillin (n = 59)	↓[c]	NA [22]
CRRT	Amoxicillin [9], cefotaxime (93), ceftazidime [5], ceftriaxone [17], cefuroxime [2], meropenem [21]	↑[c]	6.54 (1.47–48.61) [19]
	Ceftazidime and cefepime (n = 12), meropenem (n = 37), piperacillin (n = 19)	↑[d]	16.67* (2.78–100.0), p = 0.002 [26]
Prolonged infusion (EI/CI vs IM)	Amoxicillin (n = 71), ampicillin (n = 18), cefazolin (n = 10), cefepime (n = 13), ceftriaxone, doripenem (n = 13), meropenem (n = 78), piperacillin (n = 107)	↑[b]	4.00* (0.02–8.33), p < 0.001 [27]
	Meropenem (n = 481), piperacillin (n = 919)	↑[c]	7.80 (3.72–16.38), p < 0.001 and 8.39 (5.35–13.17), p < 0.001 [20]
		↑[d]	7.31 (4.32–12.37), p < 0.001 and PIP NS [20]
Bilirubin >26 µmol/L	Cefotaxime (n = 38), meropenem (n = 24), piperacillin (n = 49)	↑[c]	4.76* (1.03–25.00), p = 0.045 [28]
Serum urea	Amoxicillin (n = 9), cefotaxime (n = 93), ceftazidime (n = 5), ceftriaxone (n = 17), cefuroxime (n = 2), meropenem (n = 21)	↑[c]	1.09 (1.03–1.17) [19]
		↑[d]	1.05 (1.00–1.10) [19]

Target attainment is defined as (a) C_{min} > MIC, (b) 50% T > MIC, (c) 100% T > MIC, or (d) 100% T > 4xMIC depending on the definition used in the study. The up arrows indicate that the probability of target attainment increases, the down arrows indicate that the probability of target attainment decreases.

* OR converted to the reversed OR (1/OR).

95%-CI: 95% confidence interval; CrCl: creatinine clearance; **CI**: continuous infusion; **CRRT**: continuous renal replacement therapy; **EI**: extended infusion; **IM**: intermittent; **eGFR**: estimated glomerular filtration rate; **MER**: meropenem; **MIC**: minimum inhibitory concentration; **NA**: not available; **NS**: not significant; **OR**: odds ratio; **PI**: product information; **PIP**: piperacillin; **SOFA**: sequential organ failure assessment.

Finally, there are several other significant but less prominent clinical predictors for target attainment. Target non-attainment is more frequently observed in patients with lower sequential organ failure assessment (SOFA) scores [27]. However, the presence of severe illness and especially the SIRS response, has also been shown to impact the volume of distribution for some antibiotics [46,47], making increased dosing and close monitoring necessary. Furthermore, positive microbiology cultures seem to be associated with target attainment [27]. Lastly, positive correlation was found between target attainment and high serum concentrations of bilirubin and urea [19,28].

3.4. Antimicrobial dosing strategies

For β-lactam antibiotics, an increase in %$fT > MIC$ can be achieved particularly by increasing the number of daily doses or by providing extended or continuous infusion. Furthermore, dosing individualization based on population PK models and patient factors known to influence antimicrobial PK increases the probability of achieving therapeutic drug exposure while at the same time avoiding toxic concentrations. However, optimizing antimicrobial therapy still represents a complex challenge given the wide and unpredictable variability of antibiotic concentrations in critically ill patients. Indeed, the complexity and dynamic nature of critically ill patients make associations of clinical variables and the considered risk of target non-attainment difficult to apply without supporting tools. To enable the practical application of significant relationships between risk factors and β-lactam exposure, and consequently target attainment, risk assessment tools could provide guidance. Ehmann et al. developed an easy-to-use tool, MeroRisk Calculator, for the risk assessment of target non-attainment based on the renal function [48].

3.4.1. Workflow for dose individualization

Refined dosing strategies for antimicrobials are necessary to enhance the probability of achieving drug concentrations that increase the likelihood of clinical success in critically ill patients [49]. A workflow involving several steps is proposed to achieve optimal dosing in these patients (Figure 3). Firstly, antibiotic selection must be based on both relevant patient and pathogen factors. Subsequently, the selection of the correct dosing regimen takes place using tools such as guideline and dosing nomograms. In addition, dose individualization in critically ill patients based dose simulations and patient factors increases the probability of achieving therapeutic drug exposures, while at the same time avoiding toxic concentrations. Pending the result TDM, a higher daily dose of β-lactam antibiotics at the onset of treatment should be considered, especially in the most critically ill patients and in those with preserved renal function. Particularly in the case of patients with ARC, evidence is building up regarding the clinical impact of ARC and the potential need for increased doses in critically ill

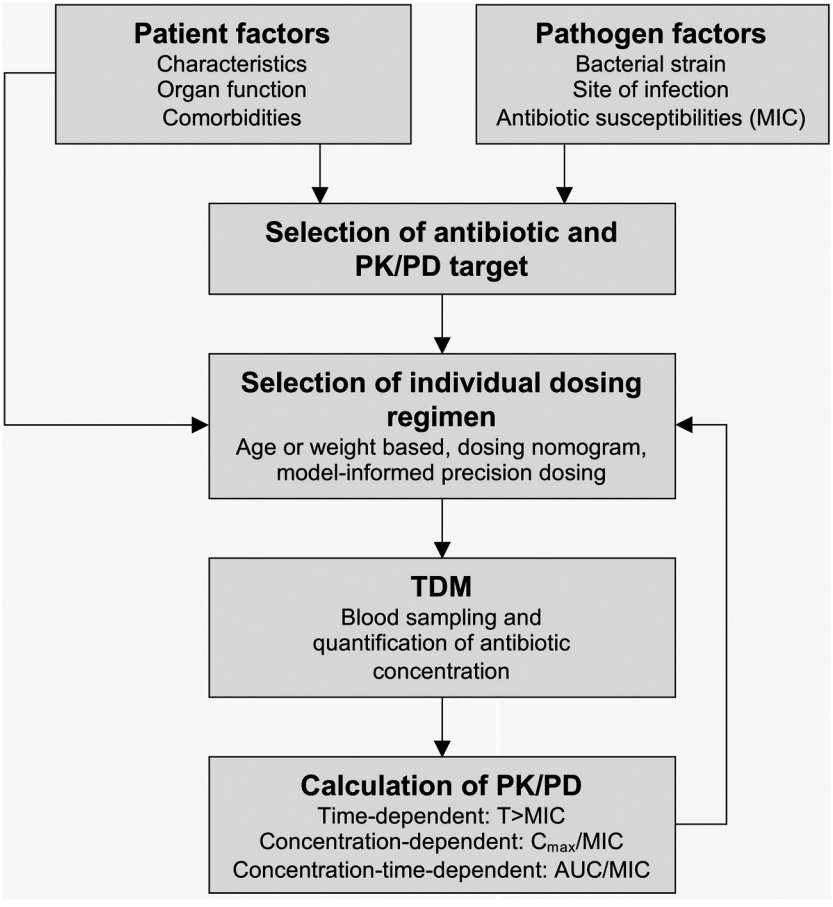

Figure 3. General steps to obtain antibiotic dose optimization (Modified form [54]).

patients [50–52]. Finally, appropriate PK models coupled to PD targets can be used to improve dosing regimens based on adaptive feedback through TDM.

AUC/MIC: the ratio of the area under the concentration–time curve to MIC; **C_{max}/MIC**: the ratio of maximum drug concentration to MIC; **MIC**: minimum inhibitory concentration; **PK/PD**: pharmacokinetic/pharmacodynamic; **T> MIC**: the duration of time that the drug concentration remains above the MIC during a dosing interval; **TDM**: Therapeutic drug monitoring.

3.4.2. Pharmacodynamic targets and outcome

The optimal pharmacodynamic target (PDT) is still not clearly defined for β-lactam antibiotics. The used PDTs in the included studies vary between 50% and 100% fT >MIC and 50–100% fT >4xMIC. However, 100% fT > MIC target attainment is reported in only 40% to 60% of critically ill patients treated with β-lactam antibiotics [5,19,53].

To maximize the probability of clinical efficacy in critically ill patients, unbound plasma concentration from one up to four times the MIC for 100% of the dosing interval (100% fT > 1–4× MIC) is recommended [54–59], although the correlation with improved clinical outcomes is not well established. Further increasing the exposure does not appear to increase the rate and extent of bacterial killing or positive clinical outcome [25,60].

For continuous infusions, a random concentration of at least 4xMIC is suggested. Toxicity of β-lactam antibiotics is rare, but can be serious. Neurotoxicity, especially convulsions, hallucinations, myoclonus and confusion, is described due to high concentrations of β-lactam antibiotics [61–65]. To avoid potentially toxic effects, dose reduction is arbitrarily recommended when the unbound trough levels exceeds 8–10xMIC [9,66,67].

There are two types of interventions commonly used to optimize beta-lactam exposure, which are modifying beta-lactam administration by increasing the duration of the infusion and/or TDM and adjusting the dose based on serum levels. However, the clinical impact on patient's prognosis using this strategy in critically ill patients is not yet fully demonstrated. The results from a multicenter randomized controlled trial investigating the effect of TDM of beta-lactams on clinical outcomes in critically ill patients are expected [68].

3.4.3. Prolonged infusion of β-lactams

Extended and continuous infusion of β-lactams is associated with better target attainment and cure rates in critically ill patients [69]. Recent meta-analyses have shown an association between extended infusion of β-lactams and lower mortality rates in critically ill patients with severe sepsis [70,71]. Especially for piperacillin-tazobactam and meropenem, extended or continuous infusion is strongly recommended based on high-quality evidence [71]. Prolonged infusion of β-lactams can facilitate in dose optimization in the critically ill patient are at risk for target non-attainment.

4. Conclusion

We provide an overview of evidence on factors associated β-lactam exposure in critically ill patients. Early identification of patients at risk when initiating empirical antibiotic therapy based on demographic and clinical risk factors has considerable clinical value. Based on the findings of this study, male gender, younger age, and augmented renal clearance are the most significant predictors for target non-attainment of β-lactam antibiotics. Furthermore, these factors could be considered when developing algorithms to help optimize antibiotics therapy.

5. Expert opinion

Patients admitted to the ICU represent a highly heterogeneous population ranging from young trauma patients to postsurgical patients and elderly medical patients. This heterogeneity is well known to result in high variability in PK parameters. B-lactam are hydrophilic antimicrobials, which experience increased volume of distribution, generally require a loading dose in patients with sepsis regardless of renal function. One should remind that patient's clinical condition may change rapidly during the ICU stay, toward either improvement or degradation, which may subsequently lead to altered PK parameters.

Identifying at-risk patients when initiating therapy is a first step in dose optimization. However, since PK parameters vary considerably in ICU patients during therapy, exposure should be monitored in this population. TDM combined with population PK models and dosing simulation can be used to interpret the complex and changing PK parameters in critically ill patients to improve target attainment. Yet, TDM of β-lactam antibiotics is not structurally performed due to the wide therapeutic window of these agents and the lack of concrete dose recommendations in relation to the measured drug levels. However, in recent years, the increasing resistance to β-lactam antibiotics and the association with low levels has increased the relevance of TDM with β-lactam antibiotics. β-lactam TDM is recommended after the onset of treatment, after any change in dosage, and in the event of a significant change in the patient's clinical condition [9,72].

In the present review some suggestions and solutions are offered based on the current knowledge. For the strong predictors regarding target attainment, we advise their integration into practice. Currently, the expansion of screening software provides an important tool to assist clinicians in the detection and management of under or overdosing. Yet, for demographic and clinical factors, and even for strongly substantiated associations, translation into clinical recommendations is still lacking in clinical practice. Our findings imply the need for dosing intensification in patients identified to be at risk of target non-attainment. Understanding which factors are responsible for the variability of β-lactam exposure would help predict and adjust the dosing strategy in each patient during the ICU stay and therefore optimize antimicrobial effectiveness. Thus, it appears possible to adjust the β-lactam dosage by taking into account demographic and clinical factors, until the plasma concentration data are available.

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Author contributions

Conception and design: AA, TE, RE, and BK. Analysis and interpretation of the data: AA. AA wrote the first draft of the manuscript. All authors contributed to subsequent drafts and gave final approval of the version to be published.

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