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MAJOR ARTICLE

Optimizing the Use of Beta-Lactam Antibiotics in Clinical Practice: A Test of Time

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Despite their limitations, the pharmacokinetics (PK) and pharmacodynamics (PD) indices form the basis for our current understanding regarding antibiotic development, selection, and dose optimization. Application of PK-PD in medicine has been associated with better clinical outcome, suppression of resistance, and optimization of antibiotic consumption. Beta-lactam antibiotics remain the cornerstone for empirical and directed therapy in many patients. The percentage of time of the dosing interval that the free (unbound) drug concentration remains above the minimal inhibitory concentration (MIC) (%fT > MIC) has been considered the PK-PD index that best predicts the relationship between antibiotic exposure and killing for the beta-lactam antibiotics. Time dependence of beta-lactam antibiotics has its origin in the acylation process of the serine active site of penicillin-binding proteins, which subsequently results in bacteriostatic and bactericidal effects during the dosing interval. To enhance the likelihood of target attainment, higher doses, and prolonged infusion strategies, with/or without loading doses, have been applied to compensate for subtherapeutic levels of antibiotics related to PK-PD changes, especially in the early phase of severe sepsis. To minimize resistance and maximize clinical outcome, empirical therapy with a meropenem loading dose followed by high-dose-prolonged infusion should be considered in patients with high inoculum infections presenting as severe (Gram negative) sepsis. Subsequent de-escalation and dosing of beta-lactam antibiotics should be considered as an individualized dynamic process that requires dose adjustments throughout the time course of the disease process mediated by clinical parameters that indirectly assess PK-PD alterations.

Keywords. acylation; inoculum effect; loading dose; PK/PD; resistance suppression.

INTRODUCTION

Based on in vitro and in vivo experiments with rodents, Eagle et al [1], and decades later Craig [2], were among the first to postulate that the relationship between antibiotic exposure and microbiological effects can be separated in antibiotics that show time-dependent and concentration-dependent killing effects [1, 2]. Multiple reviews have since been published regarding this topic describing the 3 principal pharmacokinetics-pharmacodynamics (PK-PD indices): (1) time-dependent antibiotics, the percentage of time of the dosing interval that the free (unbound) antibiotic concentration remains above the minimal inhibitory concentration (MIC) (%fT > MIC); (2) concentration-dependent antibiotics, the maximum concentration of the antibiotic divided by MIC (C_{max}/MIC); and (3) time-concentration-dependent antibiotics, the area under the curve in 24 hours divided by the MIC (AUC24h/MIC) [3–6].

Although the application of PK-PD is widely considered as the basis for our current understanding regarding antibiotic development, selection, and dose optimization, various limitations are increasingly being recognized. The traditional PK-PD models represent the concentration of the antibiotic at the beginning and at the end of the dosing interval (PK) and rely on a standardized MIC value (determined in vitro) representing the PD component. As a consequence, these models lack a description of bacterial growth dynamics as a function of time [7–9]. In addition, PK changes due to changes in renal function, serum albumin, and/or type of administration will affect the PK curve of the model [10]. Although several authors have reported about PK changes in critically ill patients over more than 30 years ago [11, 12], it was not until 2010 when Taccone et al [13] published their results of a study with 80 patients showing insufficient levels of beta-lactam antibiotics in the early phase of severe sepsis and septic shock. Subsequently, in 2011, Gonçalves-Pereira and Póvoa [14] published a systematic review of the pharmacokinetics of beta-lactams in which the authors reported significant PK heterogeneity in critically ill patients with an up to 2-fold increase in volume of distribution (Vd) and drug clearance. In 2014, Roberts et al [15] published their results of the DALI

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(Defining Antibiotic Levels in Intensive Care Unit Patients) study. In this multicenter seminal study, which included 384 critically ill patients, 16% of the 248 patients treated with beta-lactam antibiotics did not achieve the minimal PK-PD target (defined as 50% fT > MIC) [15]. In addition, insufficient antibiotic levels have been reported in patients with hemodialysis [16], extracorporeal membrane oxygenation [17], obesity [18], severe burns [19], and pediatric patients [20]. From the available literature it may be concluded that alterations in Vd, renal function, and/or serum albumin together with antibiotic losses are among the main risk factors for subtherapeutic levels of antibiotics. These PK alterations have major consequences for the appropriate dosing of antibiotics, especially the time-dependent beta-lactams. Furthermore, high-inoculum infections and/or infections due to bacteria with higher MIC values will complicate the use of certain beta-lactam antibiotics and reduce the necessary time above the MIC, potentially affecting its efficacy. Different from other PK-PD reviews on beta-lactam antibiotics, this article will focus on the molecular mechanism of action of beta-lactam antibiotics and how to achieve dose optimization especially in high-inoculum infections with severe sepsis.

METHODS

Search Strategy and Selection Criteria

Combinations of the key words "PK", "PD", "Dose", "Augmented Renal Clearance", "Hypoalbuminemia", "Post Antibiotic Effect", "Inoculum effect", "Acylation", "Deacylation", "Penicillin Binding Proteins", "Prolonged and continuous Infusion", "Loading doses", "Toxicity" and "Suppression of resistance" were used for multiple searches in PubMed and relevant articles in English published from 1980 until 2023 including randomized controlled trials (RCTs), meta-analysis, observational studies, and reviews that were selected for this article. In addition, one relevant publication from 1953 was included in the manuscript that was considered an essential pioneer publication introducing the topic.

Time Dependence of Beta-Lactams and Acylation of Penicillin-Binding Proteins

Penicillin-binding proteins (PBPs) are membrane-bound molecules in bacteria with enzymatic activity involved in cross-linking reactions of peptidoglycan precursor molecules [21]. It has been shown that a time-dependent chemical reaction named acylation of the serine active site of the PBP is necessary to achieve inhibition of bacterial growth [22]. Williamson et al [23] were the pioneers that studied the association between inhibition of cell wall synthesis and acylation of the PBPs in *Streptococcus pneumoniae*. Their experiments showed that inhibition of peptidoglycan incorporation is always preceded by inhibition of protein synthesis and growth. Furthermore, they concluded that the degree of acylation of 1 or more PBPs beyond a threshold value is necessary to inhibit peptidoglycan incorporation [23]. From the available evidence, it can be carefully concluded that a minimal antibiotic concentration and degree of acylation of the PBPs is necessary to inhibit bacterial growth, which depends on the PBP affinity and varies among the different beta-lactams. As the percentage of acylated PBPs increases, bactericidal effects can be observed, but once the saturation of PBPs is maximum, increased killing rates are unlikely to occur. During the dosing interval, acylation of PBPs occurs in a time-dependent manner, which requires a minimal antibiotic concentration to occur but can hardly be accelerated by increasing the dose [24].

The Post-Antibiotic Effect

The post-antibiotic effect (PAE) is defined as a period that bacterial growth is inhibited after the antibiotic concentration falls below the minimal inhibitory concentration. The PAE has been observed in experiments with different antibiotics and can be seen in Gram-positive as well as Gram-negative bacteria, indicating that different mechanisms underlie this phenomenon [25].

It is interesting to note that among the beta-lactams, only carbapenems have shown a PAE for Gram-negative bacteria and may explain a shorter %fT > MIC for optimal bactericidal activity compared with other beta-lactam antibiotics [5, 26]. When PAE occurs with beta-lactam antibiotics, it is possibly related to prolonged or irreversible acylation of PBPs [27]. Vice versa, the relatively slow deacylation reaction of PBPs can occur over time and could result in reactivation of the enzymatic activity of the PBPs [28] (Figure 1).

Acylation of Penicillin-Binding Proteins and Pharmacokinetics-Pharmacodynamics Changes in the Critically Ill Patient

Independent of the condition of the patient, beta-lactam antibiotics will always require a minimal free drug concentration (superior to the MIC) to initiate and maintain the acylation process of the PBPs for a minimal period of time during the dosing interval, which depends on the affinity for the PBP of the beta-lactam being used. Physiological changes in the critically ill patient will cause important alterations of the PK parameters. In addition, changes in PD should be considered: relatively more resistant bacteria can be observed in the critically ill patient in the intensive care unit (ICU), reflected as an increased MIC value of the antibiotic for the microorganism. The PK-PD changes in critically ill patients greatly affect the 2 aforementioned requirements with the risk of underdosing, as will be discussed next.

Volume of Distribution

More than 30 years ago, there were publications suggesting that in the critically ill patient, there are important physiological alterations and changes in PK that could lead to underexposure

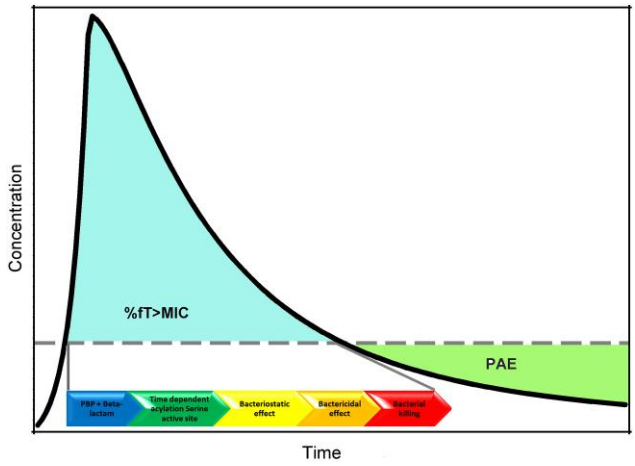

Figure 1. The basic pharmacokinetics-pharmacodynamics model. The shaded area above the dashed line represents the time above the minimal inhibitory concentration (MIC) (%fT > MIC) during which the time-dependent acylation reaction of penicillin-binding protein (PBP) occurs. As more PBP proteins are being acylated during the dosing interval, sequentially bacteriostatic and bacterial kill can be observed. When the concentration falls below the MIC (shaded area below the dashed line), meropenem is the only beta-lactam antibiotic that will show a post-antibiotic effect (PAE) of a maximum of a few hours in Gram-negative bacteria. Meropenem has a relatively high affinity for the serine active site of the PBP compared with other beta-lactams, and its PAE could be related to the prolonged acylation of the PBP.

of antibiotics. One of the most important PK changes is increased Vd, which can lead to subtherapeutic levels of antibiotics [14, 29, 30]. The systemic inflammatory response syndrome, particularly in patients with severe sepsis and septic shock, results in endothelial damage and capillary leakage with subsequent extravasation of fluid and plasma proteins into the interstitial space creating interstitial edema and oncotic pressure. To compensate for this loss of circulating volume, fluid resuscitation is being used that increases the Vd even further, especially in the early critical phase of the disease process [30, 31].

Hypoalbuminemia

Yet another important physiological change is hypoalbuminemia, which is expected to affect the PK of highly protein bound antibiotics. Low levels of albumin are frequently observed in critically ill patients and will increase the Vd of the antibiotic because the unbound fraction will be able to pass the vascular compartments and membranes more easily into the interstitial compartment. Although the unbound fraction of antibiotics at the site of infection is considered to be clinically relevant, it is also more efficiently eliminated by the kidneys with the possible risk of antibiotic underexposure [32].

Augmented Renal Clearance

Another important physiological change that occurs in critically ill patients is augmented renal clearance (ARC). Augmented renal clearance can be described as the augmented elimination of renally cleared medicines in critically ill patients. Augmented renal clearance is defined as a creatinine clearance of more than 130 mL/min/1.73 m^2. The mechanisms underlying ARC are complex and seem to be related to changes in the cardiovascular system (increased cardiac output, vasodilation), which occur in patients with severe inflammatory response syndrome (SIRS) and sepsis. These changes together with the effects of intravenous fluids and vasoactive medications result in increased renal blood flow and consequently ARC. Despite the fact that ARC has been linked to subtherapeutic levels of antibiotics, it is infrequently considered in ICUs. The hydrophilic classes of antibiotics such as beta-lactams are expected to be affected by ARC [33]. Taken together, PK changes such as ARC and Vd will greatly complicate adequate dosing of antibiotics [31] and challenge the critical PBP acylation process in the case of beta-lactams.

Inoculum Effect

The inoculum effect is important in severe infections and can be defined as reduced antimicrobial activity (reflected as a relatively higher MIC value) at inocula above those utilized for susceptibility testing. A recent review of the existing literature revealed that especially cephalosporins and beta-lactam/beta-lactamase inhibitor combinations consistently showed inoculum effects in vitro, whereas carbapenems were less susceptible to an inoculum effect, and a few animal studies confirmed these pharmacodynamic effects in vivo [34]. (Figure 2).

Strategies for Optimizing Time Above the Minimal Inhibitory Concentration

Considering that the time a beta-lactam concentration remains above the MIC is crucial for the acylation process of PBPs (%fT > MIC), and several strategies have been studied to maximize time above the MIC: increased doses (eg, 2 g q 8 hours versus 1 g q 8 hours), increasing the dosing frequency (eg, q 6 hours versus q 8 hours), prolonged versus continuous infusion of the beta-lactam (eg, infusion over 3 hours versus continuous infusion over 24 hours), or a combination of these [35]. MacVane et al [36] reported a 50% increase of time above the MIC when higher doses were infused over a prolonged period of time. Multiple clinical trials have been performed to compare the effects of prolonged/continuous infusion versus traditional intermittent infusion. A meta-analysis of studies performed before 2015 failed to show a clear clinical benefit for prolonged infusion [37].

It became clear that the heterogeneity of patient populations, type of antibiotic regimen used, disease severity, study design, and the type of PK-PD analysis applied are important issues to be considered when it comes to design of clinical trials with profound effects on study outcome [38]. Subsequent meta-analyses with more recent studies showed a clear

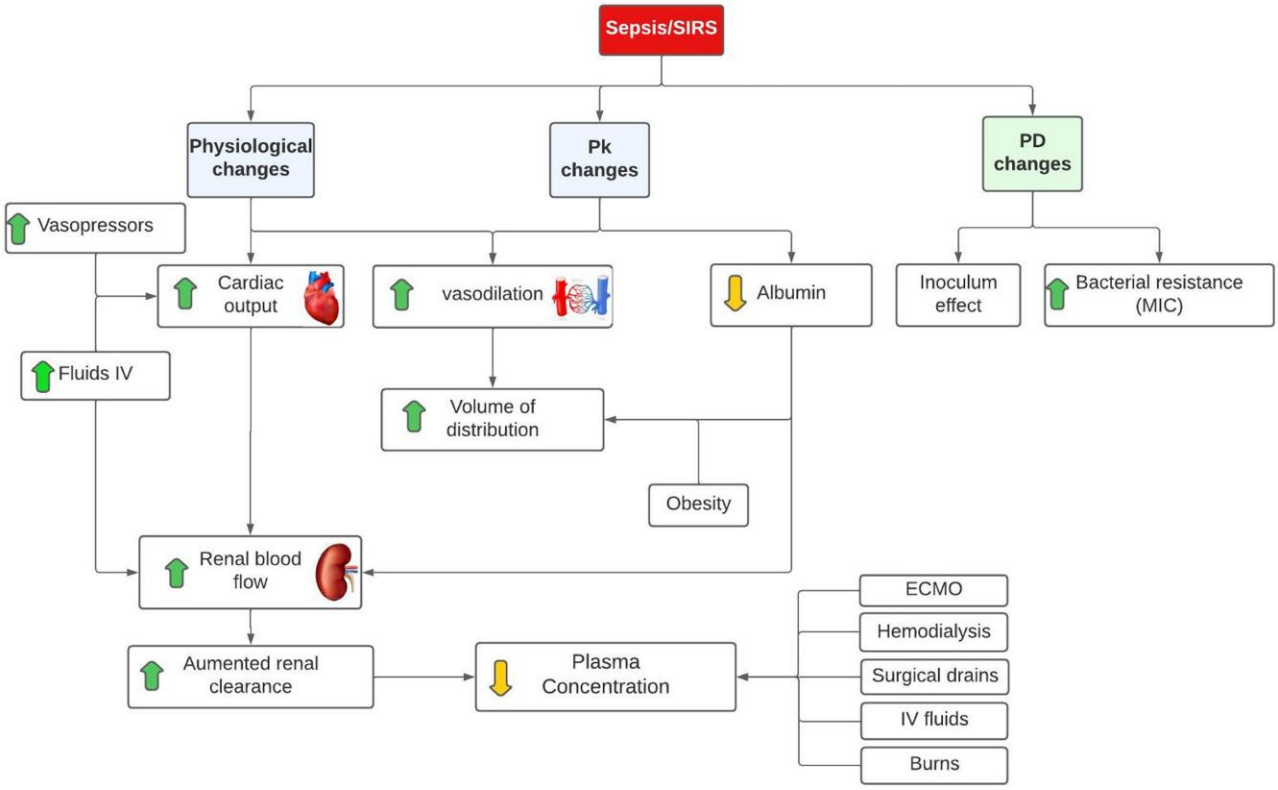

Figure 2. Pharmacokinetics (PK) changes related to physiological changes and pharmacodynamics (PD) changes in the critically ill patient ultimately resulting in low plasma concentration and relatively more resistant bacteria, respectively. EMCO, extracorporeal membrane oxygenation; IV, intravenous; MIC, minimal inhibitory concentration; SIRS, severe inflammatory response syndrome.

tendency in favor of prolonged infusion compared with intermittent infusion with better clinical outcome and less mortality [39–42]. From the available trials, we can carefully conclude that prolonged or continuous infusion will probably only benefit critically ill patients (eg, Acute Physiologic Assessment and Chronic Health Evaluation [APACHE] scores >16) and/or those with infections caused by more resistant bacteria reflected by higher MIC values [43, 44].

Concepts of Resistance Suppression

Not only should the time above the MIC be considered, but evidence also suggests that the margin above the MIC matters when it comes to suppression of resistance. Antibiotic concentrations close to the minimal inhibitory concentration have been linked to the growth of (hetero) resistant subpopulations and higher concentrations with resistance suppression. As a consequence, some experts argue that antibiotic concentrations should be maintained during the dosing interval just above the so-called "mutation prevention concentration": the antibiotic concentration associated with maximum suppression of resistance. Considering both T > MIC and the mutation prevention concentration, new PK-PD targets have been proposed, which generally implies higher doses compared with the traditional dosing [5, 45, 46]. Some experts recommend a PK-PD target for beta-lactam antibiotics of 100%T > 4×MIC, which could not only maximize efficacy but also minimize emergence of resistance [47].

A different PK-PD index (C_{min}/MIC) has been reported to describe the correlation between antibiotic exposure and resistance suppression as shown by experiments done by Tam et al [48]. Drug exposures expressed as C_{min}/MIC do not have the limitation of the so called "ceiling effect" compared with the %T > MIC, which is bounded from above 100% [48].

The hypothesis of maintaining antibiotic concentrations during the dosing interval just above the mutation prevention concentration by using prolonged or continuous infusion has been challenged. Felton et al [49] reported that the C_{min}/MIC ratio targets for different PD endpoints (bacterial stasis, bacterial killing, and the suppression of resistance) were dependent on the type of infusion used as well as the inoculum: C_{min}/MIC ratios were significantly higher in the extended infusion group compared with the intermittent infusion group. In addition, higher inocula were associated with progressive growth of resistant subpopulations (independent of the type of infusion used), demonstrating the complex dynamic nature of PK-PD indices [49].

The PK/PD index is a static representation of a dynamic process. As a consequence, factors that affect the PK curve (eg, type of infusion, renal insufficiency, augmented renal clearance, hypoalbuminemia, etc) will likely result in different PK-PD targets. In addition, the MIC derived from in vitro representing the PD line is inaccurate when resistance suppression is being considered. Indeed, other factors such as the type of pathogen involved, inoculum, and the duration of therapy are important factors to be considered [9, 45, 46, 50] as well as the acylation reaction of the PBPs in the case of beta-lactam antibiotics.

The Clinical and Microbiological Impact of Loading Doses

Although frequently used when dosing vancomycin or colistin, there is accumulating evidence that loading doses of beta-lactam antibiotics should also be considered, especially in critically ill patients [51, 52]. Several types of loading dose strategies have been studied. For example, the administration of a relatively high first antibiotic dose in a prolonged versus short period of time or a normal (maintenance) dose in a relatively short period of time. Regardless of the strategy used, the loading dose has the potential advantage of rapidly reaching PK-PD targets. Once above the MIC, the acylation of PBPs can begin and antimicrobial effects can be achieved in the shortest time period possible. In comparison, when only high doses (without a loading dose) are being used, it will probably take more time to reach target concentrations at the site of infection, potentially affecting clinical outcome as well as bacterial resistance, especially in high-inoculum infections [53].

Gonçalves-Pereira and Póvoa [14] reported PK heterogeneity with an up to 2-fold increase in Vd, which at least partly explains why double maintenance doses of beta-lactam antibiotics are being used in critically ill patients. Optimal loading doses of beta-lactam antibiotics and the moment to start prolonged infusion still have to be defined, but they are likely to be individualized. Delattre et al [54] performed a post hoc analysis of a prospective study with piperacillin-tazobactam, cefepime, and meropenem in 88 patients with sepsis or septic shock using Monte Carlo simulations with different regimens and durations of administration. The PD targets were defined as concentrations exceeding at least 50% of time above 4 times the MIC (T > 4×MIC) of *Pseudomonas aeruginosa* (EUCAST criterion). The optimal loading dose was defined as at least 90% probability to achieve PD targets. Delattre et al [54] reported an optimal loading dose for piperacillin-tazobactam of 8 g given as a 3-hour infusion, cefepime of 4 g given as a 3-hour infusion, and meropenem of 2 g given as a 30-minute infusion. Regardless of the antibiotic used, Delattre et al [54] stated that the following antibiotic dose should be administered at least 6 hours after the loading dose. It is interesting to note that despite the high initial loading doses used, none of the trough concentrations exceeded reported thresholds of toxicity [54].

Liebchen et al [55] reported on the optimal loading dose of meropenem before continuous infusion in critically ill patients using a previously evaluated pharmacokinetic model of critically ill patients. Maintenance doses administered as continuous infusion of 1.5–6 g/24 h with preceding loading doses (administered in 30 minutes) of 0.15–2 g were investigated. Various scenarios using individual covariates (albumin concentration, body weight and renal clearance) were simulated. If all 3 covariates showed extreme values ("worst-case scenario"), a loading dose of 0.5 g was necessary to achieve PK-PD targets. Liebchen et al [55] recommended the administration of a loading dose of 0.5 g meropenem over 30 minutes immediately followed by continuous infusion. It is interesting to note that a higher loading dose did not lead to further improvements of target attainment (%fT > MIC) [55]. Wu et al [56] published a subgroup meta-analysis analyzing the efficacy of a loading dose followed by continuous or prolonged infusion of beta-lactams compared with intermittent infusion in critically ill patients. The meta-analysis included 18 RCTs and 13 non-RCTs. Of particular interest, Wu et al [56] reported that subgroup analyses revealed that a loading dose significantly increased clinical cure rate in the loading dose group (relative risk, 1.44; 95% confidence interval, 1.22–1.69), which remained significant after adjustments for beta-lactam type. In addition, a significant decrease in overall mortality and better clinical outcome was observed in the carbapenem group. Wu et al [56] concluded that continuous/prolonged infusion with prior loading dose may significantly improve clinical outcome in critically ill patients and recommend empirical treatment with a carbapenem starting with a loading dose followed by prolonged infusion [56].

A Paradigm Shift: Dynamic Individualized Dosing Versus Static Standardized Dosing

In the critical initial phase of severe sepsis, attention is frequently focused on the timely administration of an appropriate antibiotic but not on dose optimization. Administration of higher doses and prolonged infusion strategies are common practice in some institutions. However, a loading dose of beta-lactam antibiotics is infrequently applied, and some experts recommend a loading dose to be standard practice [51, 52]. Without a loading dose, administration of a beta-lactam antibiotic in the early phase of severe sepsis might result in delay of achieving adequate concentrations above the MIC sufficient to initiate/maintain the acylation reaction of PBPs and achieve target attainment (Figure 3).

Administration of a loading dose, subsequently followed by continuous/prolonged infusion, is likely to optimize clinical and microbiological outcome in patients who are critically ill [57]. Vice versa, clinical trials with prolonged/continuous infusion and/or with higher doses in the noncritically ill patient and/or with infections due to bacteria with low MICs was not associated with improved outcome. These findings indicate

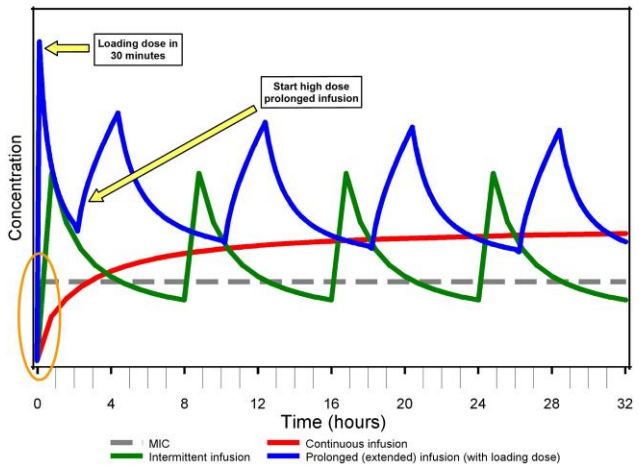

Figure 3. Basic pharmacokinetics-pharmacodynamics model with different modes of administration. Compared with traditional intermittent (lower alternating line) and continuous infusion without loading dose (steadily rising line), delay is to be expected in reaching rapid target attainment in the early phase of severe sepsis and/or shock (ellipse at lower left). Target concentrations can be rapidly achieved by administration of a loading dose (1–2 grams in 30 minutes), followed within 1–2 hours by high-dose prolonged infusion (upper alterating line). Note that time above the minimal inhibitory concentration (MIC) is 100% and a multiple of MIC, maximizing the time to acylate penicillin-binding proteins and suppress resistance.

that standard conventional dosing in the noncritically ill patient resulted in sufficient time above the MIC to achieve acylation of PBPs, and that higher doses probably will not improve clinical outcome resulting in unnecessary antibiotic consumption. Bearing in mind the time-dependent acylation process of the PBPs and considering the important PK-PD changes observed in critically ill patients, the concept of "compensation for losses and/or higher MIC" should be applied: higher doses barely accelerate the acylation reaction but should be considered to compensate for the antibiotic losses secondary to the PK-PD changes, especially in the early phase of severe sepsis. Considering the aforementioned aspects, the concept of individualized and dynamic dosing should be applied. Several articles have been published in the last few years, highlighting the importance of population PK modeling using simulation programs (eg, Monte Carlo and Bayesian simulations) and therapeutic drug monitoring (TDM) for dose optimization. However, this is unavailable in many low- and middle-income countries [58, 59]. The PK changes seem to be correlated and proportional with illness severity [60], which requires higher initial doses during the early course of the disease. Subsequently, with clinical improvement, dose reduction should be considered. To avoid unnecessary renal, hepatic, and or neurotoxicity, dose and antibiotic de-escalation adjustments should be considered after 48–72 hours based on renal clearance, body weight, serum albumin levels, hemodynamic, respiratory, and infectious disease parameters together with microbiology results. Uncertainty remains regarding the optimal amount of loading dose, the moment to start continuous/prolonged infusion, and the risk of toxicities. At present, there are no studies that directly compare outcomes of prolonged versus continuous infusion. Although the time above the MIC is maximum with continuous infusion, it requires the permanent use of a (central) line and therefore complicates vascular access in the critically ill patient. Consequently, a second line is likely to be needed that increases the risk for line-related sepsis. Furthermore, this modality asks for additional educational training, special infusion pumps, and infusion bags that are relatively more expensive [38, 43, 44]. Therefore, prolonged infusion of beta-lactam antibiotics seems to be a more practical approach in most institutions globally.

Toxicodynamic Considerations

McDonald et al [61] published a retrospective review of critically ill patients who received higher than licensed doses of either meropenem (3–6 g/day) or piperacillin-tazobactam (16 g–2 g/day) guided by TDM. McDonald et al [61] reported no significant differences in toxicities between the high-dose and licensed-dose groups. However, the effect of loading doses was not studied [61].

A clear dose-toxicity relationship still remains to be proven and studies have revealed inconsistent results [62]. In the beta-lactam family, neurotoxicity due to cefepime seems to be clinically most relevant [50, 62, 63], making it a less suitable candidate for high-dose and/or prolonged-infusion strategies, especially in the setting of renal insufficiency. The available evidence shows that the risk of subtherapeutic levels in the early phase of severe sepsis outweighs the risk of toxicity due to the use of loading doses, higher than conventional maintenance doses, and/or prolonged infusion strategies. Various meta-analyses about prolonged infusion (with or without prior loading doses), compared with traditional intermittent dosing, reported about the safety of these procedures because there were no significantly more adverse events between the 2 groups [39, 41, 42]. In addition, if toxicity occurs, it will probably be of short duration and reversible when beta-lactam antibiotics are being considered.

Clinical Assessment of the "Pharmacokinetics-Pharmacodynamics Status"

In absence of TDM and/or dosing simulation software, dynamic personalized dosing should be based on daily assessment of the "PK-PD status", which can be estimated indirectly by hemodynamic, respiratory, renal, and infectious disease parameters. An example of a hemodynamic parameter is the use of a vasopressor agent: when used, it indirectly reflects ongoing sepsis and PK alterations with a high volume of distribution. Respiratory parameters including respiratory frequency, FiO_2/PEEP (fraction of inspired oxygen/positive end-expiratory pressure) on the ventilator, and arterial blood gas analyses can provide information about

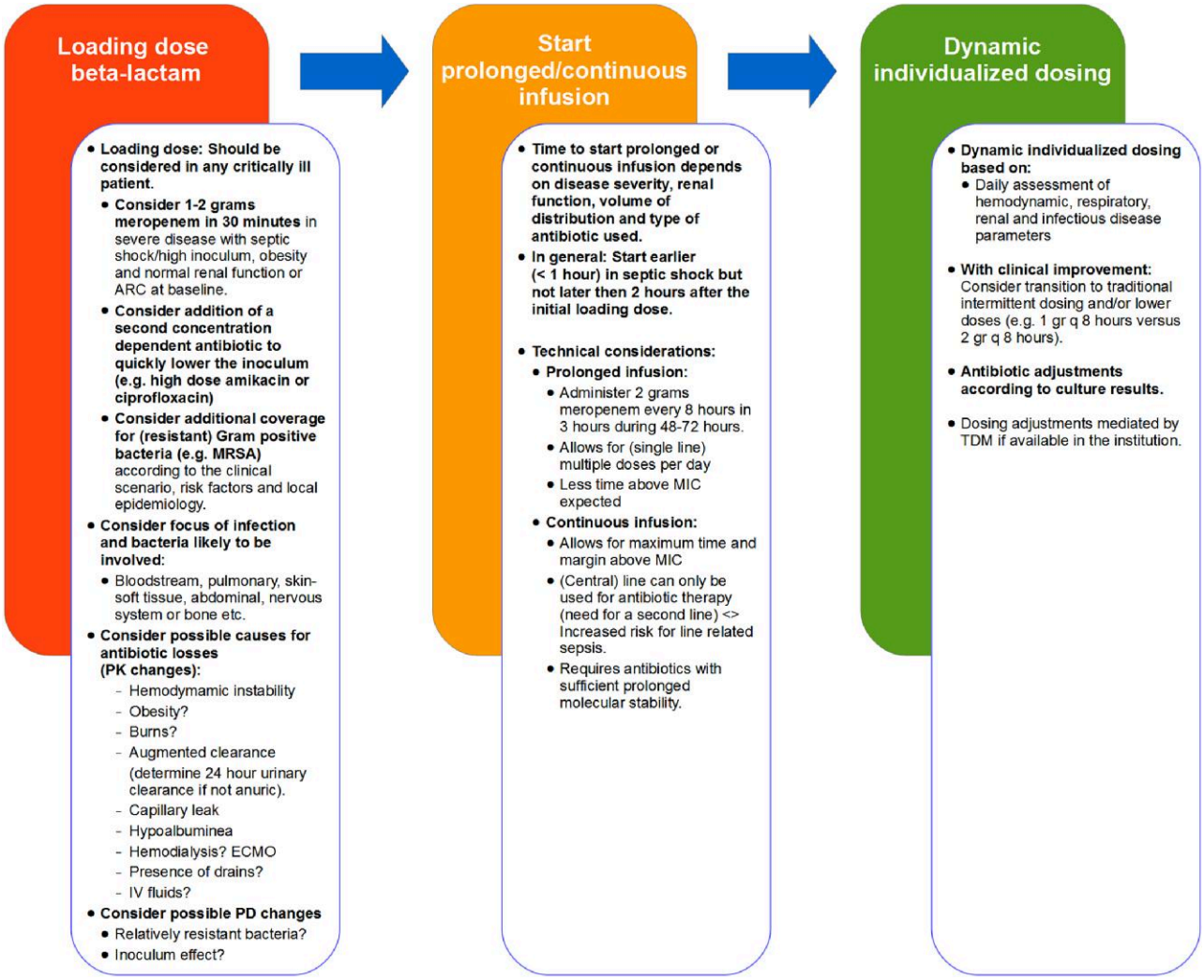

Figure 4. A simple 3-step model of "dynamic individualized dosing" in the early phase of critical illness, taking into account the compensation for losses of antibiotics associated with pharmacokinetics (PK) changes and/or more resistant bacteria (higher minimal inhibitory concentration [MIC] values). In high-inoculum infections, loading doses followed by high maintenance doses for the shortest duration possible will likely optimize clinical outcome and minimize the risk of resistance during treatment. In absence of therapeutic drug monitoring (TDM) and dosing software, dose adjustments should be based on daily assessment of PK-pharmacodynamics parameters to optimize dose and clinical/microbiological outcome. EMCO, extracorporeal membrane oxygenation; MRSA, methicillin-resistant *Staphylococcus aureus*.

the pulmonary PK status and clinical response in the case of severe pneumonia. Normalization of renal function and improved diuresis will directly affect the elimination of antibiotics, and, as such, provide information on the renal PK status. Finally, modulation of the leucocyte count, C-reactive protein, or procalcitonin provide important information with respect to clinical response to infection. Therefore, by combining these parameters, the clinician can obtain useful information about the actual PK-PD status of the patient and help to guide dosing decisions without TDM. With resolution of sepsis, the Vd will decrease, renal function is likely to improve, and/or when a bacterium with a low MIC is identified, de-escalation and administration of lower doses by intermittent infusion should be sufficient to further treat the infection and is likely to be safe [64].

Stepwise Individualized Dynamic Dosing and Dose Optimization

The "perfect" beta-lactam in the early phase of severe sepsis would be a molecule that covers a large spectrum of bacteria, shows a high affinity for the PBPs, is suitable for high-inoculum infections, is not highly protein bound, shows a PAE of at least a few hours, is not hydrolyzed by common beta-lactamases, and has adequate penetration in multiple tissues, a favorable toxicity profile, and prolonged molecular stability. Of the traditional beta-lactams, only meropenem most closely meets these requirements, although its molecular stability is a point of concern [65], especially when continuous infusion is being considered [43, 66]. A loading dose of 1–2 grams meropenem should be administrated in 30 minutes, with the higher dose reserved for patients with more severe disease (eg, APACHE II >

16, including immunocompromised patients). Obesity, high-inoculum infections [53], infection sites with suboptimal penetration of antibiotics [67], normal renal function or probable ARC at the moment of treatment initiation [68], and/or the risk for more resistant bacteria also justify the higher dose. When the loading dose is administrated, it is important to remember that the half-life of meropenem is approximately 1 hour in healthy volunteers [69] and is likely to be less in patients with ARC. Therefore, it is reasonable to start within 1–2 hours after the loading dose with prolonged infusion using a high maintenance dose, which should be administrated in no more than 3 hours. It is likely to be safe to start earlier (within 1 hour) in patients with septic shock but not later than 2 hours in patients without shock, as long as an increased Vd and/or ARC are present. When prolonged infusion is started later (eg, after 3 hours), the serum concentration of meropenem probably will drop at least 50%, and the pharmacological benefit of the loading dose to reach rapid target attainment will be minimal (Figure 3). With ongoing PK alterations and microbiology results pending, the prolonged infusion should be continued at least for 48–72 hours without dose adjustments, with the exception of patients with severe renal compromise at baseline [64, 70]. Subsequent dosing and de-escalation of therapy should be guided by TDM (if available) or daily assessment of clinical parameters and microbiology results (Figure 4).

With dynamic individualized dosing, continuous dose optimization can be achieved that likely results in improved clinical outcome, improvement of antimicrobial stewardship indicators/healthcare associated costs, minimal toxicity, and lowering the risk of resistance development.

CONCLUSIONS

Beta-lactam antibiotics act by acylation of the serine active site of PBPs in the bacterial cell wall, which requires a minimal concentration (higher than the MIC for the bacterium) and a minimal amount of time during the dosing interval. The time required above the MIC directly depends on the PBP affinity of the beta-lactam. Carbapenems show the highest PBP affinity and consequently require the least time above the MIC compared with other beta-lactams. With increasing saturation of the PBPs, bacteriostatic and bacterial killing can sequentially be observed as a function of time.

Because the acylation process of the PBPs is time dependent, increasing the dose is unnecessary in the noncritically ill patient and/or infection due to a bacterium with a low MIC. Multiple studies have consistently shown that serum concentrations of time-dependent antibiotics are too low in critically ill patients to achieve PK-PD targets and are the consequence of the dynamic PK-PD changes observed in this subgroup of patients. Increased Vd, alterations in renal function, and hypoalbuminemia together with additional sources of antibiotic losses should be the rational basis for loading doses, higher than conventional doses and/or prolonged infusion strategies, which are likely to be safe in the early critical phase of severe sepsis. High-dose meropenem seems to be superior in high-inoculum infections compared with cephalosporins and beta-lactam/beta-lactamase inhibitor combinations and serve to quickly lower the inoculum, which is associated with resistance suppression. However, to avoid unnecessary toxicity and antibiotic overconsumption, dose adjustments should be made with clinical improvement and associated reduction in Vd based on daily assessment of clinical parameters that indirectly assess the PK-PD status of the patient. Adequate dosing of antibiotics in a patient with ongoing PK-PD changes requires a paradigm shift towards a nonstatic individualized dynamic dosing approach and will likely optimize clinical and microbiological outcome.

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