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REVIEW

Ensuring target concentrations of antibiotics in critically ill patients through dose adjustment

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ABSTRACT

Introduction: Antibiotics are commonly prescribed in critical care, and given the large variability of pharmacokinetic (PK) parameters in these patients, drug PK frequently varies during therapy with the risk of either treatment failure or toxicity. Therefore, adequate antibiotic dosing in critically ill patients is very important.

Areas covered: This review provides an overview of the basic principles of PK and pharmacodynamics of antibiotics and the main patient and pathogen characteristics that may affect the dosage of antibiotics and different approaches to adjust doses.

Expert opinion: Dose adjustment should be done for aminoglycosides and glycopeptides based on daily drug concentration monitoring. For glycopeptides, in particular vancomycin, the residual concentration (Cres) should be assessed daily. For beta-lactam antibiotics, a loading dose should be administered, followed by three different possible approaches, as TDM is rarely available in most centers: 1) antibiotic regimens should be adapted according to renal function and other risk factors; 2) nomograms or software can be used to calculate daily dosing; 3) TDM should be performed 24–48 h after the initiation of treatment; however, the results are required within 24 hours to appropriately adjust dosage regimens. Drug dosing should be reduced or increased according to the TDM results.

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KEYWORDS
Antibiotics; dosing adjustment; pharmacodynamics; pharmacokinetics; therapeutic drug monitoring; software

1. Introduction

Antibiotics are one of the most commonly prescribed drugs in critical care; up to 60% of patients receive antimicrobial drugs during their stay [1]. Given the large variability of pharmacokinetic (PK) parameters in these patients and rapid changes in their clinical conditions, drug PK frequently varies during therapy with the risk of either treatment failure or toxicity [2,3]. Infections in intensive care units are also frequently due to less susceptible or multi-drug-resistant pathogens; these infections are associated with poor outcome [4] and represent a significant challenge for antibiotic prescription. Therefore, adequate antibiotic dosing in critically ill patients is very important and it requires an individualized patient approach from initiation, until the end of treatment [5]. In this review, we will focus on antibacterial drugs that are commonly used in this setting.

2. Basic principles of pharmacokinetics and pharmacodynamics

The PK of a drug is governed by the four essential processes of absorption, distribution, metabolism, and excretion [6–11]. The maximum concentration (C_{max}) or peak corresponds to the highest plasma concentration of an active principle obtained after administration of the drug. The residual concentration (C_{res}) or trough corresponds to the plasma concentration of the active principle obtained at the end of a drug administration interval, i.e. just before the next dose. The volume of distribution (Vd) corresponds to the theoretical volume in which the quantity administered would be distributed in order to obtain the concentration observed in the plasma at the moment of C_{max} measurement; Vd takes into account the extravascular distribution, which itself depends on plasma and tissue protein binding (i.e. only the free fraction of the antibiotic is capable of diffusing into the tissues) but also its physicochemical properties, which influences its capacity to diffuse through biological membranes (i.e. Vd is higher for lipophilic drugs, which can more easily penetrate into the intracellular fluid, than hydrophilic drugs). The speed of distribution depends on the membrane permeability or the blood perfusion rate, which ensures the transport of the antibiotic to the tissues. A low Vd (i.e. 0.2 to 0.4 L/kg) corresponds to a molecule with exclusive extracellular distribution, while a high Vd (>1 L/kg) corresponds to a molecule with significant extravascular distribution reflecting either significant intracellular diffusion or significant tissue fixation. The elimination phase involves metabolism and excretion, which are mainly renal or biliary. Plasma clearance (CL) represents the number of molecules per unit of time to obtain purified plasma. It is defined by the following formula: CL = Dose/AUC, where AUC corresponds to the area under the curve describing the change in plasma concentrations as a function of time. The AUC gives an aggregate measure of the total amount of drugs to which the body is exposed. The half-life, directly related to

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Article highlights

- Organ dysfunctions, weight, patients' clinical presentation, therapeutics used (in particular continuous renal replacement therapy, mechanical ventilation, and/or extracorporeal membrane oxygenation), and the patient's inflammatory state are factors leading to pathophysiological changes influencing the pharmacokinetic (PK) and pharmacodynamic (PD) parameters of antibiotics in intensive care.
- The minimum inhibitory concentration value serves as the basis for assessing whether the pathogen is susceptible or resistant to a given antibiotic.
- Dosage adjustment is not only important to attain PK/PD targets but also to avoid overexposure in some patients and thus an increased risk of adverse effects.
- As most hydrophilic antimicrobials are cleared by the kidneys, renal function is one of the most important clinical factors that contributes to target non-attainment at the time of antibiotic initiation and therefore to individualized antibiotic dosing.
- Therapeutic drug monitoring (TDM), initially used to avoid drug toxicity, is now increasingly being used in critical care patients to attempt to improve PK/PD target attainment.
- TDM results can be integrated with other tools, such as dosing nomograms and/or software to help improve PK/PD target attainment by guiding dosage adjustment.

the CL of the antibiotic (T1/2 = (0.693 × Vd)/CL), contributes to the choice of its frequency of administration. The minimum inhibitory concentration (MIC) is the lowest concentration of the antibiotic which inhibits any visible growth of the given pathogen *in vitro* after 24 hours of incubation. The post-antibiotic effect corresponds to the maintenance of the absence of bacterial regrowth, while the concentration of the antibiotic remains below the threshold of effectiveness.

Antibiotics can be classified into two groups based on their bactericidal efficacy. 'Concentration-dependent' antibiotics are those whose bactericidal effect depends mainly on the maximal concentration achieved; these are most often antibiotics with a high bactericidal rate. High C_{max}/MIC, i.e. the ratio between the peak concentration achieved and the MIC, or fAUC/MIC, the ratio between the area under the free fraction concentration–time curve and the MIC of the pathogen, are important to predict clinical success [12,13]. The ratio fAUC/MIC has also been suggested as an interesting parameter in the prevention of bacterial resistance [14]. Animal models with fluoroquinolones have demonstrated that the 24-h AUC/MIC ratio of 385 prevented the emergence of resistance against *Pseudomonas aeruginosa* [15]. Studies in humans have also reported that a higher 24-h AUC/MIC ratio of 582 suppressed the emergence of resistance against E. coli, Enterobacter cloacae, Haemophilus influenzae, and Serratia marcescens in patients [16]. Aminoglycosides, fluoroquinolones, and daptomycin are typical examples of concentration-dependent antibiotics. 'Time-dependent' antibiotics are those for which the predictor of therapeutic outcome is the time interval between two administrations, during which the unbound antibiotic concentration remains above the MIC value (%fT > MIC). Ideally, this value should approach as close to 100%, as possible for optimal efficacy [5]. To obtain this target, the time between two administrations can be shortened or the antibiotic can be given as a continuous infusion. These antibiotics usually have slow bactericidal effects. Beta-lactam antibiotics serve as the archetypal class of time-dependent antibiotics, with the magnitude of the pharmacodynamic (PD) index, which varies according to beta-lactam subclass, with typical fT > MIC values of ≥60–70% for cephalosporins, ≥50% for penicillins, and ≥40% for carbapenems [7]. In a study assessing the adequacy of beta-lactam dosing regimens in 361 critically ill patients, the inability to attain a T > MIC > 50% was associated with a 32% decreased likelihood of a positive clinical outcome [17]. Glycopeptides are also time-dependent antibiotics.

PK/PD indexes offer a simplistic way for clinicians to approach antibiotic efficacy, however they have some limitations. First of all, in routine practice, total plasma concentrations are measured, whereas only molecules in the free form (not bound to plasma proteins) exert an antimicrobial effect. Second, since bacteria are most often present in the extravascular environment, tissue concentrations of antibiotics would be more useful than plasma concentrations for predicting the antimicrobial effect. Third, they do not differentiate between intra- and extracellular concentrations, so molecules with strong intracellular diffusion have higher tissue concentrations than those who do not diffuse into cells. Fourth, since the concentrations of antibiotics vary over time, a single measurement at a given time does not make it possible to correctly understand the profiles of changes in concentrations over time. Finally, the drug to MIC relationship could also be

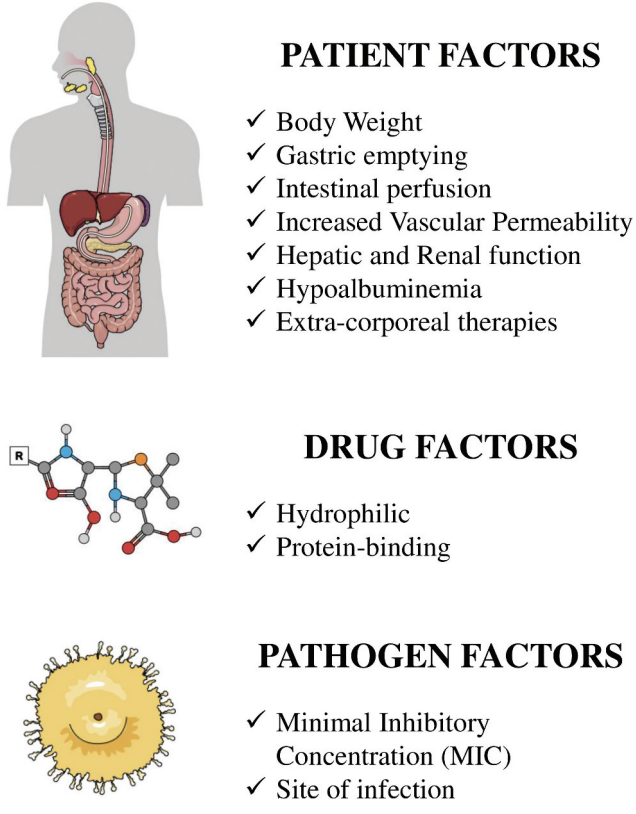

Figure 1. Factors that influence dose adjustements of antibiotics.

affected by the immune response of the patient (i.e. higher concentrations of the drug may be required in those patients with severe immunosuppression or neutropenia) or by the type of infection (i.e. an abdominal infection with uncontrolled source might be associated with poor clinical response, regardless of drug concentrations) [18,19].

3. Which are the main patient characteristics determining dose adjustment ?

Organ dysfunctions, weight, patients' disease (i.e. burns, hypoalbuminemia, polytrauma, etc.), concomitant therapeutics (i.e. continuous renal replacement therapy, mechanical ventilation, and/or extracorporeal membrane oxygenation, ECMO), or inflammatory states are important factors leading to pathophysiological changes influencing the PK and PD parameters of antibiotics in critically ill patients (figure 1) [20–22]. All PK parameters are potentially concerned by such factors.

Absorption: Gastric emptying disorders affect 30% to 40% of the most severely critically ill patients [23,24], with a higher risk in patients with severe burns, septic shock, peritonitis, and those with multiple trauma. In addition, transit disorders, either secondary to reduced splanchnic perfusion or some medications (i.e. opioids, neuromuscular blocking agents), are common in these patients. These factors result in reduced antibiotic absorption and bioavailability, with the risk of underdosing. As such, for life-threatening infections, antibiotics are almost always administered intravenously.

Distribution: Sepsis and, in particular, septic shock can lead to the development of endothelial damage and increased vascular permeability leading to capillary leak syndrome [25]. This capillary leak syndrome results in fluid shifts from the intravascular compartment to the interstitial space with the formation of edema [26]. This leads to an increased Vd of hydrophilic antibiotics and a decreased drug concentration in the plasma. The Vd of hydrophilic antimicrobials is also increased by administration of intravenous fluids [27], the use of mechanical ventilation [27], the use of extracorporeal circuits [27] and specific pathologies such as advanced liver disease [28,29], mediastinitis [30], and major burn injury [31]. Advanced liver cirrhosis may lead to an increase in extracellular compartment fluid through ascites formation [29]. Mediastinitis can increase Vd of antimicrobials through sequestration of plasma leading to a third compartment [30]. Extensive burn injury induces an inflammatory reaction and capillary leak resulting in massive edema formation [31]. Many studies have demonstrated the relationship between increased Vd of hydrophilic antibiotics and serum concentrations [32–34], in contrary to lipophilic antimicrobials where no significant increase in Vd was observed for ciprofloxacin in patients with intra-abdominal sepsis [35].

Metabolism: For drugs with a high hepatic extraction coefficient (>0.7), their hepatic clearance is dependent on hepatic blood flow [36]. Thus, all situations accompanied by a decrease in hepatic blood flow, such as a decrease in cardiac output, intra-abdominal hypertension, or severe hypotension, will be accompanied by an accumulation of these drugs. Antibiotics that are lipophilic and/or highly albumin-bound may undergo extensive liver metabolism, resulting in metabolites that are more easily eliminated. Hypoxemia can also alter the ability of enzyme systems, such as oxidative ones, to metabolize drugs [37].

Excretion: Renal clearance can also vary widely in critically ill patients. Renal failure, organic or functional, is accompanied by decreased renal clearance, leading to elevated plasma concentrations, with the risk of a prolonged effect or side effects. Augmented renal clearance is defined by a glomerular filtration rate greater than 130 mL/min [38]. This situation can be encountered when there is increased cardiac outputs, such as during the hypermetabolic phase of sepsis, in young subjects, those with multiple trauma, those receiving large volumes of fluids and vasoactive drugs, burn victims, or those with acute pancreatitis [39,40]. These phenomena, particularly important for antibacterial agents that are eliminated by the kidney and whose activity is time-dependent, such as beta-lactams, are accompanied by a decrease in plasma half-life and plasma concentrations, requiring an increase in dosage regimens, as demonstrated in several studies [41,42].

Additional factors that significantly impact antibiotic PK in critically ill patients are hypoalbuminemia, obesity, and the use of extracorporeal devices. Hypoalbuminemia is associated with an increase in Vd and drug clearance (CL). Given that albumin is the primary plasma-binding protein for the majority of antibiotics, the decrease in protein-binding sites due to hypoalbuminemia leads to an increase in the free fraction of the antibiotic in the plasma, accompanied by an increase in the elimination of renally cleared antibiotics. Therefore, hypoalbuminemia results in an increase of Vd and a decrease in the C_{max}, the C_{max}/MIC, and the AUC/MIC ratios, especially for time-dependent antibacterials [43–48].

The PK of antibiotics is also particularly impacted by obesity. Increased fat mass increases the Vd of lipophilic molecules, and similarly, an increase in lean mass is associated with an increase in the Vd of hydrophilic molecules [49,50]. Obesity can also modify protein binding [49], and because fatty tissue receives less blood flow from cardiac output than lean tissue, tissue fat antibiotic concentrations may be below the desired targets [51]. Regarding elimination, increased kidney size and blood flow in obese patients can lead to increased CL, which may contribute to the subtherapeutic concentrations observed. Conversely, some patients have glomerulopathies associated with their comorbidities, such as diabetic or hypertensive nephropathies, resulting in reduced renal CL and increased antibiotic concentrations [52]. These PK changes add to the particularities of intensive care patients, making it difficult to predict the PK of antibiotics in these patients. In a study by Hites et al., piperacillin plasma concentrations were equivalent between the obese group (BMI > 30 Kg/m^2) and the control group (BMI < 25 Kg/m^2) but decreased for meropenem in those patients not receiving continuous renal replacement (CRRT), while in the study by Alobaid et al., piperacillin concentrations were decreased in obese but similar

between the two groups for meropenem [53,54]. These conflicting data highlight the difficulty of predicting the PK/PD of antibiotics in these patients and the value of individualized dosage adjustment.

CRRT is commonly used in critically ill patients with acute kidney injury (AKI). There are different forms of CRRT: continuous venous–venous hemofiltration, hemodiafiltration, and hemodialysis, depending on whether the molecules cross the filter membrane by a mechanism of convection, diffusion, or both. Estimation of renal clearance is challenging due to the fact that we have to take into account non-CRRT CL (renal clearance due to residual renal function plus non-renal clearance such as hepatic clearance) and CRRT CL. There are several parameters that can influence the blood CL of an antibiotic during CRRT [55]. First, parameters related to the techniques such as the type of filter are considered. Secondly, parameters related to the molecule, such as protein binding and Vd, can be increased due to volume overload and molecular weight (MW). The larger the MW, the more difficult it is for the drug to cross the CRRT membrane. For example, blood proteins are too large to be cleared by the membrane. Thus, highly protein-bound drugs will remain on the blood side of the filter membrane. These changes lead to reduced antibiotic exposure. Thirdly, parameters related to the patient can influence the blood CL of an antibiotic during CRRT. Added to this, the delivered dose of CRRT may be less than the prescribed dose due to interruptions in treatment due to filter clotting and/or transport out of the intensive care unit for additional exams or surgery. Although antibiotic toxicity is sometimes observed, most studies, including the Multinational Sampling Antibiotics in Renal Replacement Therapy (SMARRT) study, find that these patients do not receive sufficient antibiotic dosage regimens to achieve desired PD targets [56–61].

Extracorporeal membrane oxygenation (ECMO) is an essential supportive therapy for severe cardiorespiratory failure in critically ill patients. Infections requiring antibiotic therapy occur frequently in these patients and have been associated with a higher probability of poor outcome than in patients without infections [62]. ECMO adds confounding factors to the already altered PK properties of antibiotics in these critically ill patients, such as an increase in the Vd, a decrease in the CL, or an altered drug extraction, which depends mainly on lipophilicity, protein binding, and the material components of the circuit [63–65]. Very few studies have been performed on patients receiving ECMO support, but globally they show a minimal effect of ECMO on PK/PD parameters, although this remains controversial and depends on studies. Indeed, a prospective study [64] showed that in the case of cefotaxime and piperacillin, PK targets were often achieved. However, Donadello et al. found other results concerning piperacillin. Less than 50% of patients attained the PK target of 4 to 8 times the MIC during 50% of the dosing interval [64]. In other studies, PD targets for imipenem were reached only in 10% of the cases and 62.5% of peak concentrations were subtherapeutic for aminoglycosides [66]. On the other hand, Gelisse et al. [67] showed that ECMO did not influence the PK of aminoglycosides. In all these studies, a wide interindividual PK variability was observed. More recently, the results of the Antibiotic, Sedative and Analgesic Pharmacokinetics during extracorporeal membrane oxygenation (ASAP ECMO) study confirmed that there were no substantial differences between the observed PK parameters of vancomycin, piperacillin, and tazobactam during ECMO and existing PK data from non-ECMO patients [68,69]. In conclusion, it seems that ECMO does not significantly influence the PK of most antimicrobials, and that most of the observed PK changes are probably due to the critical illness itself.

4. Which are the main pathogen characteristics determining antibiotic dose adjustments ?

The MIC represents the most elemental PD measure to determine *in vitro* efficacy of antibiotics; it is the antibiotic concentration that prevents visible bacterial growth with a standardized inoculum. The MIC value serves as the basis for assessing whether the pathogen is susceptible or resistant to a given antibiotic. According to the European Committee on antimicrobial susceptibility testing (EUCAST) recommendations, three categories are available since 2019: susceptible bacteria (S), standard dosing regimen: there is a high likelihood of therapeutic success using a standard dosing regimen of the agent; susceptible bacteria (I), increased exposure: there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection; resistant bacteria (R): there is a high likelihood of therapeutic failure even when there is increased exposure. Unfortunately, in real-life, the actual MIC of the infecting pathogen is often unknown. Furthermore, the MIC is unreliable to determine [70] because there are some biological and assay variations as a result of differences in inoculum preparation, media, incubation temperature and incubation time, and variation between laboratories as they have different facilities, technical skills, and degree of training. Also, the MIC value provides no information regarding the time course of the antimicrobial effect.

Infection usually occurs in extravascular sites (e.g. brain, eye, bone, lung, and prostate) and for these infections, serum antibiotic concentrations are used as surrogate values for tissue concentrations, due to the difficulty in obtaining local tissue concentrations. However, despite adequate antibiotic serum concentrations, some extravascular infections still result in poor infection outcome in critically ill patients [71] due to insufficient concentration of antibiotics in the tissues. Therefore, it seems important to better understand the transport and distribution of antibiotics within the tissue. Local antibiotic tissue concentrations depend on various factors, such as drug characteristics (i.e. molecular weight (MW), protein binding, and lipid solubility [72], tissue characteristics (i.e. membrane function and vascularization of the tissue), and the presence of inflammation (figure 1). Concerning drug characteristics, small lipophilic agents with low protein binding, such as fluoroquinolones, generally show a high degree of tissue penetration. Hydrophilic agents tend to remain in the interstitial fluid and have limited entry into tissue cells. Agents with

a high MW, such as glycopeptides, show a lower degree of tissue penetration. When these agents are also strongly protein bound, only a small fraction is available to enter the tissue. Regarding tissue characteristics, the blood–brain barrier (BBB) with its lack of capillary fenestrations and tight junctions restrict the passage of antibiotics into the central nervous system (CNS) [73,74]. To cross the BBB, antibiotics use diffusion or an active protein transporter [46]. Another specific barrier is the blood-alveolar barrier. Antibiotics need to pass through this barrier to reach the inner part of the lungs covered by a thin aqueous layer, the epithelial lining fluid (ELF), a natural barrier against pathogens. ELF concentrations are important determinants of efficacy in the treatment of bacterial pneumonia, and more particularly the pulmonary penetration ratio, which is the ratio between drug exposure in ELF and in plasma [75,76]. Indeed, *in-vitro* PD models have been used to examine the eradication rates of resistant and susceptible pathogens using this ratio; results have shown that selected antimicrobial agents (e.g. those with ELF to plasma concentration ratios of >1) are less likely to be associated with clinical treatment failures when compared to others. Bones, because they have a different composition and are less vascularized than other tissues such as the liver or skin, generally have lower antibiotic concentrations, at least in the initial phase of therapy [77]. Finally, inflammation plays a role in the penetration of the antibiotic into tissues. For example, inflammation increases BBB permeability, and as a result, drugs are capable of entering the CSF during bacterial meningitis, such as beta-lactam antibiotics [78–80]. Another example of inflammation influencing antibiotic penetration is seen in bone tissue, with higher antibiotic concentrations in infected bone samples compared to non-infected bone samples [81,82].

5. How can we adjust doses ?

Dosage adjustment is not only important to attempt PK/PD target attainment but also to avoid overexposure in some patients, and thus an increased risk of adverse effects [83–85]. Antibiotic-related toxicity mainly results from administration of high doses, lengthy administration, or low tolerability of antibiotics, such as observed in patients with renal dysfunction. All antibiotics, even beta-lactams, which are generally considered to have a wide safety range, can lead to dose-related toxicity [86]. Penicillins can cause side effects such as hepatotoxicity, neutropenia, and encephalopathy [87,88]; cephalosporins may cause neutropenia, nephrotoxicity, and neurotoxicity (in particular seizures) [89,90]; neurotoxicity has also been reported with carbapenems [91]. Aminoglycosides are associated with ototoxicity and nephrotoxicity [92]. As such, not only effectiveness but also drug-related toxicity is an important reason why we need specific guidance to adjust doses. Indeed, as more aggressive antibiotic dosage regimens than in the past are administered to patients, to better attain PK/PD targets, clinicians should be cautious on the occurrence of potential side effects, as it has recently been shown in a retrospective study that beta-lactam induced toxicity is underestimated [93].

Evidence suggests that renal function, as many antimicrobials are cleared by the kidneys, is one of the most important clinical factors that contribute to target non-attainment at the time of antibiotic initiation and drives the need to individualize antibiotic dosing [94]. In this context, Ehmann et al. developed a user-friendly tool to predict the risk of target non-attainment based on renal function [95]. Renal function should be continually assessed so that prompt dosage adjustments to antibiotics can be made to minimize toxicity without compromising efficacy (Figure 2). For time-dependent antibiotics, which are cleared via the kidneys, when there is renal failure, a dosage reduction rather than frequency reduction is likely to be the optimal choice to avoid drug accumulation but to ensure that the *f*T>MIC is maintained. Conversely, concentration-dependent antibiotics will require extending the dosing frequency rather than reducing the dose; to maximize bacterial killing by still attaining the C_{max}/MIC. In patients with increased renal clearance, higher dosing than the recommended dosing regimens of beta-lactam antibiotics may be safe and

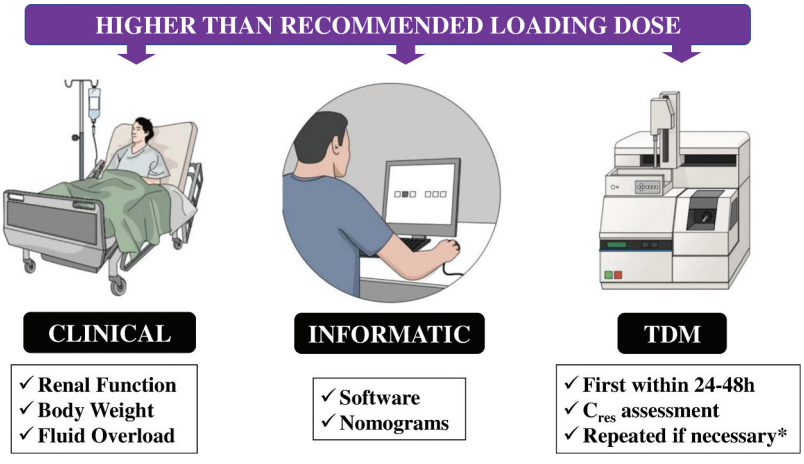

Figure 2. Modalities used for dose adjustments of antibiotics.

effective in reducing the rate of therapeutic failure [96]. Furthermore, the use of prolonged (extended or continuous) infusions is significantly associated with target attainment in these patients [97].

Therapeutic drug monitoring (TDM), one of the earliest forms of personalizing antimicrobial dosing, involves the measurement of drug concentrations followed by dose adjustment based on the observed concentration in relation to a target drug exposure (Figure 2). Drugs that are traditionally appropriate candidates for TDM have one or more of these criteria: narrow therapeutic range/index; drug toxicity that may lead to hospitalization, irreversible organ damage, and even death; no clearly defined clinical parameter that allows dose adjustments; correlation between serum concentration and efficacy as well as toxicity; unpredictable relationship between dose and clinical outcome; difficulties to predict PK. TDM, initially used to avoid drug toxicity in drugs with narrow therapeutic indices such as aminoglycosides [98], is now increasingly being used in critical care patients to attempt to improve PK/PD target attainment [99,100] Guidelines from the French society of pharmacology and therapeutics and the French society of anesthesia and intensive care medicine suggest to perform TDM in critical care patients with expected beta-lactam PK variability and/or in patients with clinical signs potentially related to beta-lactams toxicity, those undergoing renal replacement therapy, and in case of CNS infection (if possible on blood and cerebrospinal fluid samples collected concomitantly). They suggest performing beta-lactam TDM according to a validated chromatographic method 24–48 h after the onset of treatment, after any change in the dosage regimen, and in the event of a significant change in the patient's clinical condition [5]. The proposed optimal free plasma beta-lactam concentrations are the ones exceeding 4 to 8 times the MIC of the infecting bacteria for 100% of the dosing interval (i.e. $fT \geq 4–8\times$ MIC = 100%). The infection section of the European society of intensive care medicine (ESICM), the PKc/PD, and critical ill patients study groups of European society of clinical microbiology and Infectious Diseases (ESCMID), the International Association for Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT), and the International Society of Antimicrobial Chemotherapy (ISAC) also recommend routine TDM in critically ill patients for beta-lactam antibiotics, but also for aminoglycosides, linezolid, teicoplanin, and vancomycin [101]. Interestingly, the proposed optimal beta-lactam concentrations are different from those in the previous article (i.e. $fT \geq$ MIC 100%), underlying the need for a well-conducted study to identify the most effective PD target for these drugs. The need for well-conducted studies is also one of the conclusions of a recent in-depth review of the different PD targets for beta-lactam antibiotics in critically ill patients [102]. Furthermore, although different administration modalities may improve PK/PD attainment (i.e. extended or continuous infusions of beta-lactam antibiotics), it still remains unproven that this significantly improves clinical outcomes. Indeed, extended or continuous infusions may require different PK/PD targets than intermittent infusions to obtain similar bactericidal effects [103].

One of the current limitations with TDM is that currently, in many laboratories, the turnaround time to obtain results is several days, except for glycopeptides and aminoglycosides. Ideally, results should be available as soon as possible, to allow for rapid adjustment of the dosage regimen in case of under- or over-exposure. Another limitation is that data is lacking to connect TDM to patient outcomes, particularly in the case of beta-lactam antibiotics. Nevertheless, there are several ongoing clinical trials addressing this issue. The first is the TARGET study, evaluating 90-days all-cause mortality rates in adults with severe sepsis or septic shock randomized to either continuous infusion of piperacillin-tazobactam with TDM, compared to without TDM [104]. The second is the DOLPHIN study evaluating intensive care unit length of stay in 450 critically ill patients who receive beta-lactam antibiotics (cefotaxime, ceftazidime, ceftriaxone, cefuroxime, amoxicillin, amoxicillin-clavulanic acid, flucloxacillin, piperacillin-tazobactam, and meropenem) or ciprofloxacin, and are randomized to either TDM guided or not guided therapy [105]. Results from these studies will potentially add important insights on the relevance of TDM in this setting.

TDM results can be integrated with other tools, such as dosing nomograms [106,107] and/or software, to help improve PK/PD targets by guiding dosage adjustment (Figure 2). PK/PD models can combine available knowledge of PD, based on *in vitro*, animal, or clinical data, with clinical PK results. Due to PK variability in critically ill patients, dosing simulations for different clinical situations are required to propose dosing regimens suitable for individual patients, incorporating relevant patient characteristics known to affect PK, such as body weight, age, and renal function. With advances in the ability of computers to perform complex mathematical modeling and statistical analysis, there are a number of software packages able to perform population PK analyses [108]. Dosing software can be divided into systems that utilize linear regression models, population PK models, and/or models that incorporate Bayesian forecasting or artificial intelligence. The benefits of using dosing software when compared with dosing nomograms or standard TDM processes include simplification of the process of calculating complex PK/PD parameters (such as AUC/MIC ratios). Nevertheless, the accuracy of such tools to achieve adequate drug levels remains to be further defined.

6. Conclusions

The multiplicity of pathophysiological changes occurring in critically ill patients, together with drug interactions and the different organ replacement techniques used, leads to major PK changes. The significant inter-individual PK variations observed in these patients are in favor of using TDM-guided therapy to optimize treatment success while reducing the risk of toxicity.

Table 1. Suggested target concentrations for time-dependent and concentration-dependent antibiotics.

Antibiotics	PK/PD index	PD target
Concentration-dependent		
Aminoglycosides	Cmax/MIC	Efficacy: Cmax/MIC > 8–10, 1 hour after drug administration Toxicity: Cres < 5 mg/L for Amikacin, Cres < 1 mg/L for Gentamycin and Tobramycin
Time-dependent		
Beta-lactams	fT> MIC	fT ≥ MIC 100%(5), or fT ≥ 4–8× MIC = 100% (92)
Glycopeptides: intermittent infusion	fAUC /MIC	Cres < 15 mg/L
Glycopeptides: continuous infusion	fAUC /MIC	20–25 mg/L

7. Expert opinion

As dosing of aminoglycosides and glycopeptides is available in almost all laboratories, dose adjustment should be based on daily drug concentration monitoring in clinical practice, as shown in Table 1. For aminoglycosides, the first dose should be higher than the standard regimens: amikacin 25–30 mg/Kg; gentamycin and tobramycin 8–10 mg/Kg (on ideal body weight) [109]. As such, peak concentrations should be measured to evaluate the bactericidal effect (i.e. target = C_{max}/MIC 8–10) [110] in general 1 h after the onset of a 30-min dose, and C_{res} just before the following dose (i.e. at 23 hours after the onset of the previous administration) to assess potential toxicity [111]. For glycopeptides, in particular vancomycin, Cres should be assessed daily and kept at 15 mg/L to avoid potential nephrotoxicity [112], when the drug is given as intermittent infusion (i.e. q12h); if vancomycin is administered as continuous infusion, steady-state concentrations should be measured daily and kept at 25 mg/L, which corresponds to an adequate AUC/MIC to treat *Staphylococcus aureus* [113] and a reduced risk of nephrotoxicity [114]. Daily TDM would therefore help guide clinicians to adjust daily dosage regimens to increase effectiveness and/or reduce or suspend administrations in case of potential toxicity.

For beta-lactam antibiotics, TDM is rarely available in most centers. As such, clinicians should rely on alternative approaches for dose adjustment to ensure a high probability of achieving target concentrations of these drugs in critically ill patients. First of all, data coming from PK model simulations suggest that a higher than recommended loading dose is required in these patients to rapidly attain PD targets; for example, cefepime and ceftazidime 4 g over 3-h infusion; meropenem 2 g over 1-h infusion; piperacillin/tazobactam 8 g/1 g over a 3-h infusion [115]. For the following doses, three different approaches can be used:

(1) Antibiotic regimens should be adapted according to renal function. In case of renal failure, including oliguria, beta-lactam doses should be adjusted on the clearance of creatinine (CrCL). Measuring CrCL daily in critically ill patients, using urine collections over 8 to 12-h period, provide more accurate estimation of residual renal function than formulas applied to patients with chronic renal failure [39]. However, considering the increased Vd, the high occurrence of hypoalbuminemia, and the presence of less susceptible strains in critically ill patients, dose adjustment should be considered only after the first 48 hours of therapy, as underdosing can still occur in this setting [116,117]. Increased daily doses or the decision to give beta-lactam antibiotics as continuous/extended infusion [118] should be considered in patients with augmented renal clearance, obesity (i.e. BMI > 40 Kg/m^2) and overt fluid overload. This approach is the least precise in offering optimal individualized therapy and could still expose patients to underdosing or potentially toxic drug levels.

(2) The use of nomograms or software to calculate daily dosing based on patient's characteristics and biological variables (i.e. creatinine) can be used. This requires some skills and expertise in the use of such programs and has not been widely validated in critically ill patients.

(3) TDM should be performed 24–48 h after the initiation of treatment; however, the results are required within 24 hours to adjust the dosage regimens. At minimum, the C_{res} should be measured to calculate the T > MIC, targeting either the MIC in the worst clinical scenario (i.e. *Pseudomonas aeruginosa*) or the clinical breakpoint of the identified pathogen. The use of the clinical breakpoint rather than the measured MIC of the pathogen would take into account the presence of less susceptible microorganisms in the infectious inoculum [119] and would theoretically reduce the risk of selection for these strains. If the laboratory can provide a measurement of the free fraction of the antibiotic, this latter should be preferred (i.e. *f*T>MIC). Drug dosing should therefore be reduced or increased according to the TDM results as shown in Table 1, although some issues remain open (i.e. when to shift from intermittent to extended/continuous infusion; is it better to increase the dose or reduce the time between two administrations). Antibiotic TDM should be repeated every 72 hours or more frequently in case of significant changes of patients' condition, such as acute kidney injury, use of CRRT or ECMO, or suspected toxicity. If more PK parameters are required, a minimum of two drug samples (i.e. one 2 hours after the drug administration and C_{res}) is required to use simple PK models to calculate Vd and drug CL [120]. This third approach allows for the most precise attainment of PK/PD targets but is limited by the availability of devices and resources to perform TDM in daily practice.

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