Chapter 10
Generic and Optimized Antibacterial Dosing Strategies in the Critically Ill

Jan J. De Waele

10.1 Introduction

Although it is widely agreed that several factors significantly change antibiotic pharmacokinetics (PK) in critically ill patients, it is infrequent that this understanding is translated into dosing strategies for these patients [1]. Most of the focus of bedside physicians remains on the right choice of antibiotic agent and timely administration, as emphasized by prominent international guidelines, such as the Surviving Sepsis Campaign (SSC) [2].

Substantial research is underway to challenge the classical concept of antibiotic dosing, and many are investigating methods to improve antibiotic exposure. This includes the use of information technology (IT) to allow the application of complex PK models at the bedside, as well as therapeutic drug monitoring (TDM) of antibiotics [3]. Pharmaceutical companies and regulatory agencies are increasingly aware of the importance of antibiotic dosing, and often separate clinical trials are conducted in critically ill patients using increased dosing of an investigational agent to avoid underdosing and failure of antibiotic therapy. Similarly for new antibiotics coming to the market, loading doses are often employed in the packet insert as part of the recommended dosing. Optimized antibiotic dosing, aimed at improving patient outcomes and decreasing the opportunity for development of antibiotic resistance, is the next challenge.

J.J. De Waele, M.D., Ph.D.
Department of Critical Care Medicine, Ghent University Hospital,
De Pintelaan 185, Ghent 9000, Belgium
e-mail: Jan.DeWaele@UGent.be

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The potential role of optimized antibiotic dosing should not be underestimated [4]. Firstly, it will allow us to better use our currently available antibiotics, resulting in improved outcomes (clinical cure and mortality from severe infections), shorter duration of antibiotic therapy, and reduced exposure to multiple antibiotics after initial failure. Secondly it will—indirectly—slow down the spread of antibiotic resistance that is a reality in many countries and a global threat to healthcare.

In this chapter we will review current dosing strategies and their limitations, as well as the potential of optimized dosing in the treatment of severe infections.

10.2 Classical View of Antibiotic Dosing

Antibiotic dosing is only of secondary importance for many, and admittedly, when prescribing antibiotics, the first and most essential aspect is that the infecting microorganism is susceptible to the antibiotic administered (apart from the fact that the antibiotic should also penetrate into the infected tissue). Many clinicians consider this the most crucial step in antibiotic decision-making and antibiotic selection guidelines will generally focus on this process, rarely giving detailed, practical dosing advice other than general statements [5].

In the initial SSC guidelines [6], it was stated that "*All patients should receive a full loading dose of each antimicrobial. However, patients with sepsis or septic shock often have abnormal renal or hepatic function and may have abnormal volumes of distribution due to aggressive fluid resuscitation. The ICU pharmacist should be consulted to assure that serum concentrations are attained which maximize efficacy and minimize toxicity*," and little has changed in the subsequent iterations of the SSC guidelines. Although the 2012 guidelines include information for the first time that dose adjustment may be necessary, they acknowledge at the same time that "*significant expertise is required to ensure that serum concentrations maximize efficacy and minimize toxicity*" [2]. It is surprising to see that despite the currently available knowledge, we have as yet failed to translate this into clinical practice.

Compared to other drugs frequently used in critical care, the effect of antibiotics cannot be easily measured. When using vasoactive drugs, the effect is almost immediate and the therapy can easily be adjusted to the effect. For antibiotics, clinical response is usually delayed and identifying endpoints for measuring improvement of infection is difficult. Often we focus on organ dysfunction improvement, or indirect signs of tissue healing such as imaging (e.g., chest X-ray evolution), but fail to realize that many other processes may significantly impact these endpoints. The search for a biomarker that helps in antibiotic decision-making is intense, and although these may have value in limiting duration of antibiotic therapy, they have not yet been able to have a marked contribution in early antibiotic decision-making (within the first 48 h of infection management) [7].

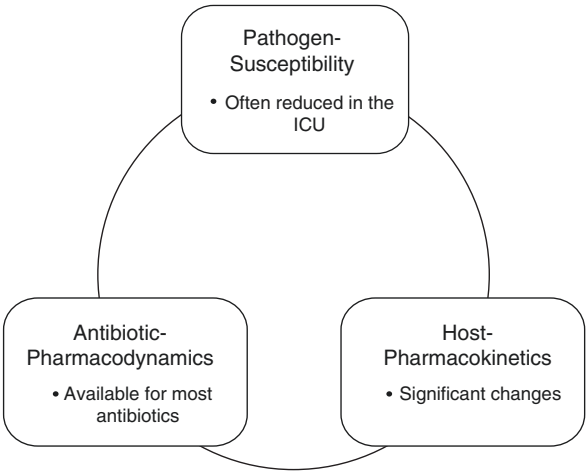

Fig. 10.1 Factors determining antibiotic efficacy

10.3 Determinants of Antibiotic Efficacy

Before moving to optimized antibiotic dosing, it is important to acknowledge the determinants of antibiotic efficacy, which are (1) the host/patient, (2) the causative pathogen, and (3) the antibiotic, which are summarized in Fig. 10.1. In critically ill patients, these differ considerably from outpatients or patients in the general ward, as discussed in previous chapters.

10.3.1 The Host

The altered physiology in the host will fundamentally change the pharmacokinetics of the antibiotic administered [8]. Changes in the volume of distribution (which can be up to four-fold larger) [9], in drug elimination, and in protein binding [10] (primarily due to decreased albumin concentrations) are the most distinct changes described and specifically pertinent for hydrophilic antibiotics. Drug elimination from the circulation, and especially increased clearance by the kidneys (augmented renal clearance (ARC)), defined as a glomerular filtration rate (GFR) of 130 mL/min or higher [11], is frequent and is associated with lower concentrations of renally cleared antibiotics such as beta-lactam antibiotics or glycopeptides.

10.3.2 The Pathogen

Because the microorganism causing the infection is unknown at the start of empirical therapy, this will only impact the later stages of antibiotic therapy. Often it will take up to 48 or 72 h before microbiology results may be final, although rapid diagnostic tools

including the use of polymerase chain reaction (PCR) may reduce the time to confirmation [12]. In the initial treatment, it is prudent to consider a worst-case scenario when it comes to identification and presumed susceptibility of the pathogen, which is often based on historical data in the unit or hospital; in practice, the epidemiological cutoffs of antibiotic susceptibility can be used, aiming at the least susceptible pathogens for which the antibiotic would be appropriate. Close collaboration with the microbiologist throughout the decision-making process is essential to improve outcome through early identification and susceptibility reporting [13]. It should be remembered that apart from the problem of multidrug resistance (MDR), minimal inhibitory concentrations (MIC) are higher in critically ill patients; although pathogens are reported as susceptible, they may already be less susceptible to the antibiotic.

10.3.3 The Antibiotic

Although the drug is the only consistent and well-known element in this decision-making process, there are significant differences between drugs when it comes to their PK and pharmacodynamics (PD) and these have been elaborated upon in previous chapters [14]. It is important to realize that the impact of these PK changes and the PD characteristics differ from antibiotic to antibiotic, and the resulting optimized dosing strategy may be very different from one antibiotic to another. Although often not considered in non-critically ill patients (where these changes have been accounted for in the recommended dose), the altered physiology of ICU patients, as well as the application of invasive interventions (such as renal replacement therapy), combined with the increase in multidrug resistance, requires a more sophisticated approach.

10.4 Generic Dosing: One Size Fits All

Generic dosing, defined as dosing according to the package insert, has systematically ignored the altered physiology of the critically ill patient, and may have contributed significantly to emergence of MDR bacteria. These dosing recommendations are generally based on Phase I and II PK data obtained in healthy volunteers and non-severely ill patients, and the extrapolation of these dosing recommendations has never been questioned. Also regulatory agencies did not—until recently—require data obtained from critically ill patient before a drug was licensed for a specific type of patient or infection. For reasons discussed above, there are many explanations why generic dosing may be inadequate in critically ill patients, with suboptimal antibiotic exposure being the most important risk associated with generic dosing.

For some generally more severe infection types, such as meningitis or endocarditis, higher doses have been advised. This was largely based on concerns with impaired tissue penetration, and not specifically due to other changes in the PK of the antibiotic in the critically ill.

Therefore, a one-size-fits-all approach is most widely used in ICUs globally, and a different attitude towards antibiotic dosing is urgently required.

It should be acknowledged that in generic dosing, dose adaptation is advised in some situations, although this generally involves dose reduction in cases of impaired function of the organ that is responsible for all (or a substantial part) of the elimination of the drug. Acute or chronic kidney injury is the most frequent reason to reduce antibiotic doses, but here, the same fallacy also applies, with data for dose adaptation obtained from patients with chronic renal insufficiency, that probably do not apply to patients with AKI in the ICU. Often the use of renal replacement therapy (RRT) will add another dimension of complexity [15]. Liver failure may be another trigger for dose modification of some drugs. Overall, the primary concern in generic antibiotic dosing is overdosing and potential toxicity. Although this may be relevant for drugs such as aminoglycosides, most of the antibiotics used daily in the treatment of severe infections have a broad therapeutic window, and can be safely used at higher doses, even if the patient physiology may not require this.

There are little data available on antibiotic prescription practices in the ICU, but it is clear that the current data are variably applied. The ADMIN-ICU survey demonstrated that there is wide variability in prescribing practices for many commonly used antibiotics (such as piperacillin/tazobactam, meropenem, vancomycin, aminoglycosides, and colistin), particularly in terms of dose administered, the use of a loading dose, the use of prolonged or continuous infusion, and the use of TDM [1]. From these data, it is clear that current information regarding appropriate dosing in critically ill patients is either not easily accessible or variably interpreted by practicing clinicians.

This uncertainty is often resolved by providing a range of dosing options in guidelines, where it is up to the team caring for the patient to administer an optimal dose for that patient. It is imperative that local guidelines do not only list antibiotics to be used but also the dose suitable for each situation, to assist the clinical team. Inevitably our current knowledge will change the use of our antibiotics and *generic antibiotic dosing* will soon be a relic of the past.

10.5 Optimized Antibiotic Therapy: Putting the Pieces of the Puzzle Together

Optimized dosing strategies refer to both improved dosing and different infusion strategies. These strategies are based on the chemical characteristics of the drug, the PK in the patient, and the PD characteristics of the antibiotic. This concept can be applied for most antibiotics in the majority of patients, but may be hampered by a lack of PK data in a specific patient population.

In a PK/PD-optimized strategy (see Fig. 10.2), all of the three factors determining antibiotic therapy discussed above are considered. A stepwise approach for this is advised. Step 1: selection of the PK/PD target for the antibiotic administered; step 2: front loading at the start of therapy; step 3: adjusted maintenance dosing.

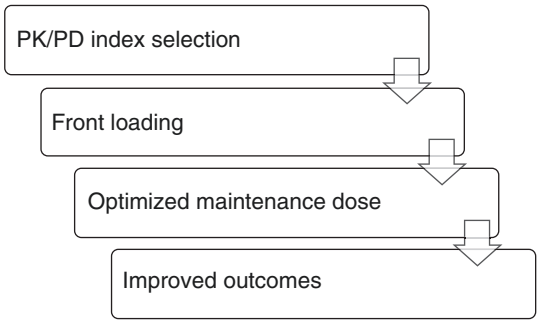

Fig. 10.2 PK/PD-optimized therapy

10.5.1 Step 1: Selecting the PK/PD Target

Depending on the antibiotic used, the PK/PD target will be different [8]. Some antibiotics such as the beta-lactam antibiotics are time-dependent antibiotics, which means that antibiotic efficacy is determined by the duration for which the antibiotic concentration is kept above the MIC. In vitro data found that this is between 40 and 60% of the dosing interval to achieve bacteriostasis, and in critically ill patients up to 100% of the time above 1–4 times the MIC has been advocated to maximize the antibacterial effect. Aminoglycosides are different and require high peak concentrations (C_{max}), with optimal efficacy at ratios of C_{max} to MIC of 8–10. Efficacy of other categories such as glycopeptides or fluoroquinolones will be determined by the area under the concentration (AUC) to MIC ratio ($AUC_{0–24}$/MIC). Determining this target will guide the clinician in selecting the dose, as well as the appropriate infusion strategy.

An important limitation during the first part of treatment is that we do not have the MIC available in most situations. The MIC determination takes time (up to 4 days) depending on the method used.

10.5.2 Step 2: Front Loading

Because of the changes in physiology in critically ill patients, a proper loading dose is needed to achieve sufficient concentrations from the first hours of therapy [16]. Although this concept is often used when administering antihypertensive and antiepileptic drugs or sedatives, this is rarely considered in antibiotic therapy. This loading dose is particularly important when prolonged infusion strategies are used (see step 3), but now has been applied in the standard dosing schemes of many newly developed antibiotics; its use should however not be limited to new antibiotics alone as the basic concept of why this is used applies to all infections.

Furthermore, in patients with acute or chronic renal insufficiency, the loading dose should not be reduced, as renal dysfunction primarily influences clearance from the circulation, and only the subsequent dose should be adapted to kidney function.

10.5.3 Step 3: Optimized Maintenance Therapy

Finally, the maintenance dose should also be optimized in terms of dose and method of administration. For beta-lactam antibiotics, given that $T >$ MIC is the PK/PD determinant, the use of prolonged infusion (either extended or continuous infusion) results in improved antibiotic exposure [17]. In some patients this change in administration may not yet be enough to reach the selected PK/PD target, and even higher doses are required to maintain sufficient concentrations.

A key element in the selection of the appropriate maintenance therapy for many antibiotics is kidney function. Many of our commonly employed antibiotics are renally excreted and in some patient's renal function appears normal but is actual "supra-normal." Augmented renal clearance occurs in situations where the kidney clears circulating solute at a higher rate than normal, including antibiotics. This phenomenon has the greatest implications in selecting a suitable maintenance dose. An important consideration, however, is the parameter used to estimate kidney function. Estimated glomerular filtration rate (GFR) formulas such as the modification of diet in renal disease (MDRD) or Cockcroft–Gault equation are unreliable in most critically ill patients and a measured creatinine clearance based on a urinary collection of at least 2 h is the most accurate, easily accessible method to estimate GFR in the ICU [18].

10.5.4 Choosing the Correct Dose

Apart from the above conceptual framework, the biggest challenge is selecting an appropriate dose when applying optimized antibiotic therapy. As discussed, one of the important differences is the altered pharmacokinetics in this patient group, such that dosing will have to compensate for these changes.

The information obtained from PK studies in critically ill patients can help us to guide dosing; these will offer us estimates of the volume of distribution and clearance that can be used to construct a model that describes how an antibiotic will behave in the target population [19]. Using this information, simulations of patient variability and pathogen susceptibility can be done that inform a prescriber of the expected probability of attaining a particular target in a patient using a certain dose, so-called "Monte-Carlo simulations." It should be acknowledged this is rarely an exact prediction, and some uncertainty is present at all times [20].

A similar approach, but less refined, is the use of dosing nomograms, in which—based on one or two variables—dosing recommendations can be read [21]. Dosing nomograms have been developed for a number of antibiotics such as vancomycin or meropenem but have not found their way to clinical practice, probably for many reasons that also apply to more advanced methods to individualize dosing.

Whereas these are a step in the right direction, more advanced methods are currently available in which PK models are integrated into software packages that calculate the optimal dose for a patient. These can easily be used at the bedside, but whereas they are popular among clinical pharmacists, their use in clinical practice appears to be limited.

A next step and further refinement of this approach involves integration of patient data management software in critical care units. This utilizes the full set of available patient parameters, and allows further improvement of the dosing recommendations as actual concentrations are measured and incorporated into the system. This will not only allow further fine-tuning of the dosing for individual patients but also further improve the original model that was used to calculate the initial doses, thereby improving future predictions.

Finally, the use of TDM of antibiotics has changed significantly over recent years [22]. Where TDM initially focused on avoiding or minimizing the risk of toxicity, the increased knowledge about the altered PK in critically ill patients has led to a paradigm shift. Antibiotic TDM is now advocated also as a tool to optimize dosing. As mentioned, TDM can be integrated into the above dosing optimization strategies to both increase and reduce dosing, always balancing PK/PD target attainment and potential toxicity or other side effects.

A loading dose is required to achieve rapid distribution of the antibiotic into tissues [16] and will usually be higher due to the increased volume of distribution, particularly for hydrophilic drugs such as beta-lactam antibiotics, but it is difficult to estimate how much higher this should be. As mentioned, this is absolutely relevant when administering antibiotics as prolonged and—even more so—as continuous infusions; this has been demonstrated for vancomycin and is equally relevant for beta-lactam antibiotics [23]. For these situations we recommend using a single dose as applied in intermittent dosing, immediately followed by the prolonged infusion dosing.

The maintenance dose on the other hand should be guided by the main route of elimination of the drug. In patients with normal renal function we advocate the use of the highest recommended dose for a particular infection, in situations where advanced methods are not available to guide dosing. Alternatively, if available, the methods discussed above such as nomograms or software package guided dosing is recommended, with or without the use of TDM.

10.6 Practical Considerations

Administering beta-lactam antibiotics as prolonged infusions poses a number of practical challenges and a number of caveats should be considered [16]. A practical consideration is the availability of a dedicated line for IV drug administration. Although central venous catheters may be preferred, prolonged infusions can be

safely administered via a peripheral venous catheter. When infusion pumps are used, care should be taken to avoid regular obstruction of the catheter due to patient movement as this may interrupt the therapy. Furthermore, the use of infusion pumps for extended infusion (e.g., over 3 h) poses a risk of incomplete infusion as the dead space in the infusion tubing may be an important part of the total dose. Therefore, we recommend the use of syringe pumps that have much smaller priming volumes.

The use of TDM in antibiotic therapy is increasing dramatically. When TDM is used to optimize therapy, the results should be available within a reasonable timeframe, optimally within 24 h. Anything beyond that may have limited impact, particularly considering that the initial 24–48 h of therapy is most important in determining outcome of infection. The use of TDM may be very valuable, but appropriate timing of the sampling is important as well. When peak concentrations are measured, this should be done within 30 min of completing the administration of the drug; trough levels should be sampled just prior to the next dose, and as such are only helpful in adjusting the subsequent dose. One advantage of continuous infusion of antibiotics is that timing is not important and any sample can be considered for adjusting the treatment.

10.7 Obstacles to Optimized Dosing

Although PK modelling can predict plasma concentrations in our patients with relative accuracy, many clinicians may be uncomfortable with giving doses that are twice or three times as high as the package insert recommendation. It is remarkable that where off-label use is very common for many drugs used in the ICU (referring to both indication and dose), the perceived risk of giving larger doses of antibiotics—even with the use of TDM—is too high, and many would rather rely on continuing to underdose or changing the antibiotic to another class (that obviously may have the same dosing issues). The use of antibiotic TDM could undoubtedly overcome these concerns.

TDM of antibiotics is often limited in its availability, and mostly limited to a number of relatively infrequently used drugs such as aminoglycosides or glycopeptides. Whereas the methodology for assaying beta-lactam antibiotics has been well described, it remains labor intensive and advanced analytical techniques are required such as high performance liquid chromatography (HPLC) coupled to mass spectrometry and is therefore limited to specialized centers [24]. There is no quality control program available for these assays; the development of immunoassays is underway and may radically improve TDM availability.

10.8 Unanswered Questions

Although this approach to optimized antibiotic dosing is a first step towards better treatment of severe infections, some things have not yet been completely understood and require more research to further refine this strategy. Many data on which this approach is based come from in vitro studies that have looked at the ability of

antibiotics to kill bacteria or suppress resistance in test tubes or more advanced models such as hollow fiber models. Although in recent years the data on PK of many antibiotics has increased substantially, for many other (often infrequently used) antibiotics, assays may be scarcely available, actual PK data coming from ICU patients may be limited or in some cases, MIC determination may not be standardized. All of these complications can prevent application of this concept at the bedside. An additional problem is that these complications often arise for antibiotics that are used for severe infections with MDR pathogens.

For many antibiotics the optimal PK/PD index may have been identified, but the preferred clinical PK/PD target to both optimally treat the infection and prevent antimicrobial resistance development has not been identified, or still is a matter of debate. For example, for beta-lactam antibiotics, the PK/PD index may also be different for intermittently administered antibiotics and antibiotics administered in continuous infusion.

Even if the plasma concentration of an antibiotic is within the PK/PD target range, we remain unsure about the tissue penetration of the drug. This can be caused by an impaired microcirculation or reduced tissue penetration, independently of possible disturbances in the microcirculation. The impact of protein binding in some drugs may further complicate the picture. All things considered there is ample evidence that plasma PK gives us an incomplete snapshot of the situation.

A blind reaction to our current understanding of the altered PK could be an indiscriminate dose increase in all patients. Although intuitively attractive, this will inevitably lead to increased toxicity in a patient population that is already prone to iatrogenic complications on the one hand, and still insufficient dosing for many patients at the other end of the spectrum. Increased costs will be another logical consequence of this approach.

10.9 Summary

There are many reasons why generic antibiotic dosing should be abandoned, but the increase in MDR infections is probably one of the most pressing arguments to redefine antibiotic administration in severe infections in the ICU. A better understanding of antibiotic PK and the link between antibiotic underdosing and inferior clinical outcomes requires an optimized and individualized approach to both improve cure rates and decrease selection of antibiotic resistant pathogens. Advanced technologies such as software that integrates PK models and the use of TDM will be indispensable in this approach, but also alternative dosing strategies will be required to achieve this goal.

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