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REVIEW ARTICLE

Therapeutic Drug Monitoring of Beta-Lactams and Other Antibiotics in the Intensive Care Unit: Which Agents, Which Patients and Which Infections?

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Abstract Antibiotics are among the medications most frequently administered to the critically ill, a population with high levels of intra- and inter-individual pharmacokinetic variability. Our knowledge of the relationships among antibiotic dosing, exposure and clinical effect in this population has increased in recent decades. Therapeutic drug monitoring (TDM) of serum antibiotic concentrations is the most practical means of assessing adequate antibiotic exposure, though until recently, it has been underutilised for this end. Now TDM is becoming more widespread, particularly for the beta-lactam antibiotics, a class historically thought to have a wide therapeutic range. We review the basic requirements, indications, and targets for effective TDM of the glycopeptides, aminoglycosides, quinolones and beta-lactam antibiotics in the adult intensive-care setting, with a special focus on TDM of the beta-lactam antibiotics, the most widely used antibiotic class.

Key Points

Therapeutic drug monitoring (TDM) of beta-lactams and other antibiotics to ensure adequate drug exposure in critically ill patients is becoming increasingly important in light of this population's variable pharmacokinetics and rising antimicrobial resistance.

Beta-lactam TDM should be considered early on to ensure adequate antibiotic exposure in any critically ill patient with a severe infection. The recommended pharmacokinetic target for these time-dependent antibiotics is 100% $fT > MIC$; i.e. the drug's unbound (free, f) serum antibiotic concentration should remain at least above the drug's minimal inhibitory concentration (MIC) for the targeted pathogen through the entirety of the dosing interval (100%).

For aminoglycosides, the pharmacokinetic/pharmacodynamic index has shifted from maximal concentration over the MIC to the area under the unbound concentration–time curve over the MIC, and several studies suggest that currently used dosing regimens are inadequate. Optimising aminoglycoside administration through potentially higher doses while controlling for toxicity requires further exploration.

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1 Introduction

Antibiotics are among the therapeutic agents most commonly administered to the critically ill [1]. Our understanding of the relationships between these drugs' dosing, exposure and effect has increased in recent decades. Though intuitive, there is now clear evidence that optimising exposure directly increases the likelihood of clinical success [2–6]. Therapeutic drug monitoring (TDM) of serum concentrations is the most practical means of assessing exposure, but TDM has typically been employed only for antimicrobials known to have narrow therapeutic ranges; i.e. low toxicity and/or high efficacy thresholds, respectively (e.g. the aminoglycosides, early vancomycin formulations).

Beta-lactam antibiotics, the cornerstone of antibacterial therapy, never traditionally belonged to this group; with only a few exceptions [7], they are rarely toxic, and as a class have manifested strong clinical effectiveness even with fixed-dose, empiric regimens. [8]. Yet the global increases in antimicrobial resistance are slowly turning this paradigm. Minimal inhibitory concentrations (MIC)—the lowest levels of drug needed to hinder visible bacterial growth after 16–20 h of incubation—are increasing steadily, particularly for common intensive care unit (ICU) pathogens like *Pseudomonas aeruginosa* and *Acinetobacter* spp. [1].

Though a major focal point, less susceptible pathogens are not the only factor narrowing the beta-lactams' therapeutic range; the "average" human host has changed as well. The prevalence of both geriatric and "long-term immunosuppressed" patients is growing progressively; obesity rates have more than doubled in past decades [9, 10]; and the critically ill can now be maintained as a population in prolonged states of clinically important altered physiology. In all of these groups, who by no means resemble the younger, healthy volunteers typically participating in phase I pharmacokinetic trials, antibiotic exposure is both variable and understudied.

TDM of beta-lactam antibiotics, particularly in the ICU, is thus becoming more widespread, particularly in some European countries and Australia [11, 12], while TDM of aminoglycosides, quinolones and glycopeptides is being re-examined and modified. This narrative review will address the rationale and indications for TDM of antibiotics commonly used in adult ICUs, with a special focus on that of beta-lactam antibiotics. An in-depth discussion and review of the literature on continuous or prolonged versus intermittent antibiotic infusions, which are often guided by TDM, are beyond the article's scope.

2 The Chequered Origins of Antibiotic Therapeutic Drug Monitoring (TDM)

Any clinician would be forgiven for questioning the logic of our current patterns in antibiotic TDM. Why, for example, is vancomycin regularly monitored, while teicoplanin is not?

The logic becomes clearer when TDM is placed in its historical context. Some of the earliest antibiotics were poorly purified before being administered clinically. Vancomycin, which came to be known as "Mississippi mud" soon after its introduction in the 1950s [13], is the most blatant example: early preparations contained impurities responsible for not only its brownish appearance, but also high-grade fever and likely the nephrotoxicity observed in its first recipients [14]. With more modern formulations, nephrotoxicity due solely to vancomycin is relatively rare, especially in patients receiving ≤ 7 days of therapy [15, 16]. Yet it was not until the 1990s, when TDM of peak concentration (C_{max}) levels to guard against toxicity had become entrenched, that studies clearly indicated that supposed "vancomycin-related" nephrotoxicity occurred mainly when the drug was being given with an aminoglycoside [16]. Conversely, the newer glycopeptide teicoplanin was developed semi-synthetically, obviating concerns regarding impurities, in an era of more methodologically robust testing and less tolerance for clinical toxicity. Its phase III results allowed it to be released on the market with no specific recommendations for TDM [17, 18]. More recent studies indicate, however, that TDM is as important for teicoplanin's efficacy as it is for vancomycin [19, 20].

The example of vancomycin underlines the fact that TDM has historically been employed chiefly to guard against toxicity rather than to optimise clinical efficacy. The beta-lactam antibiotics were famously innocuous in comparison to early vancomycin and the aminoglycosides; in that earlier era of high antimicrobial susceptibility and more homogenous host pharmacodynamics, TDM of this antibiotic class would have been largely academic.

3 Goals of TDM Today

As always, the overall goal of antibiotic TDM remains the optimisation of antibiotic therapy. Yet in today's context, that optimisation is defined primarily by the attainment of adequate antibiotic exposure. Thus the immediate goal of TDM of common ICU antibiotics such as the beta-lactams and glycopeptides is to guard against clinically inadequate concentrations, though the avoidance of toxicity remains an important objective, particularly for antibiotics with low toxicity thresholds (e.g. aminoglycosides). Finally, an increasingly important goal is ecologic: to minimise the

development of resistance among the trillions of "bystander" microorganisms hosted by the patient [21–23]. While optimal exposure for clinical efficacy is crudely defined by that which is needed to achieve clinical cure in the patient at hand, there is mounting evidence that optimal exposure to prevent the development of resistance probably requires concentrations beyond that clinical minimum [21, 22, 24–26].

4 The Basic Requirements for Rational Antibiotic TDM

Whereas criteria have been developed for TDM in general, those for antimicrobials are even more specific [27], since measuring their concentrations without the ability to interpret their values has little purpose. Some knowledge of the following elements is required for the rational use of antibiotic TDM.

4.1 Pharmacokinetic/Pharmacodynamic (PK/PD) Indices

The pharmacokinetic/pharmacodynamic (PK/PD) index represents the quantitative relationship between a pharmacokinetic measure of exposure to the antibiotic, as illustrated in Fig. 1.

4.1.1 Historical Context and Evidence to Date for PK/PD Indices

An antibiotic's "best" PK/PD index is most often determined by animal models [28, 29] that are also referred to as dose fractionation studies. These reveal a somewhat complex picture, with differences in the kill kinetics of Gram-positive versus Gram-negative bacteria as well as differences in response to various antibiotic classes. For example, *P. aeruginosa* is known to require higher targets for maximum kill as compared to other Gram-negative bacteria [30, 31].

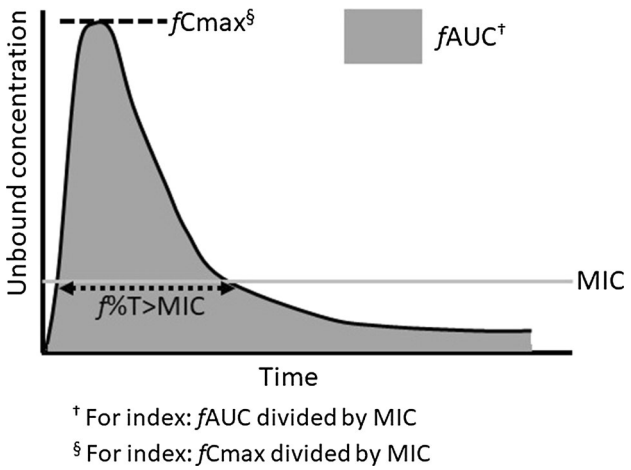

Fig. 1 Classic concentration–time curve with the different pharmacokinetic/pharmacodynamic indices. *fAUC* area under the unbound concentration–time curve, fC_{max} maximum unbound antibiotic concentration achieved in serum, *MIC* minimal inhibitory concentration

4.1.2 %fT > MIC

For the beta-lactam antibiotics, the PK/PD index associated with the most successful outcome (optimal bacterial killing and/or clinical outcome) is the $\%fT > MIC$, or the percentage of time (T) of the dosing interval during which the unbound (free, f) serum antibiotic concentration remains at least above the MIC for the targeted organism. In both animal and in vitro models, these so called "time-dependent" antibiotics achieve more bacterial killing the longer they remain at serum levels above the MIC. Increasing their concentration any more than three or four times that of the MIC does not ultimately make a difference in bacterial killing [32, 33].

4.1.3 fC_{max}/MIC

fC_{max} represents the maximum unbound antibiotic concentration achieved in serum. With this PK/PD index, "concentration-dependent" antibiotics would achieve optimal killing with higher immediate serum concentrations, and drawing out the time thereafter during which those concentrations remain above the MIC would have little effect on bacterial killing [34]. Historically, several antibiotics were believed to be primarily concentration dependent, chief among them the fluoroquinolones and the aminoglycosides. More recently, however, the optimal PK/PD index for both has proved to be the area under the unbound concentration–time curve (*f*AUC) over MIC (*f*AUC/MIC). Even the old antibiotic colistin has now been shown to correlate best with the *f*AUC/MIC rather than the C_{max}/MIC, as previously reported [35]. While there are non-antimicrobials that are classically concentration dependent in their effects, there are essentially no antibiotics left in this group.

4.1.4 fAUC/MIC

For the majority of antibiotics, the index most associated with optimal outcomes is the *f*AUC/MIC; the *f*AUC is a measure of the total exposure of the drug and is divided by the MIC. This ratio indicates the importance of both time and concentration for bacterial kill: the "area under the curve" (AUC) is the product of both the antibiotic's concentration (y axis) and the time during which those concentrations are elevated (x axis), i.e. the integral of drug concentrations over time (Fig. 1).

For antibiotics that have been used extensively in the clinic, some of these targets have been confirmed in human studies [3], but more clinical evidence is needed. We know from preclinical studies that for the cephalosporins, for example, the minimum value of $fT > MIC$ for bacteriostasis is 40% for Enterobacteriaceae, while 60–65% is needed for near-maximal bacterial kill [33, 36, 37]. Yet more recently, population pharmacokinetic modelling with clinical data from patients with nosocomial pneumonia has demonstrated that further increasing the percentage of the dosing interval during which concentrations are above the MIC provides an even higher probability of microbiologic eradication and clinical success [3].

4.2 The Minimal Inhibitory Concentration (MIC)

The antibiotic's MIC clearly plays a pivotal role in all of these indices, so obtaining its measurement would be essential for proper interpretation of TDM results. However, given the nature of MIC determination, there will always be variation among the values reported from all methods used [38, 39]. Guidance on how to use MIC laboratory results in TDM is described elsewhere [40].

4.3 Defining "Optimal Exposure"

4.3.1 Defining the Targets

Optimal antibiotic exposure is thus a moving target. It depends on the antibiotic class employed and the organism targeted—more specifically, on knowledge of the antibiotic's optimal PK/PD index and its wild-type MIC distribution for that organism. Knowing which PK/PD indices achieve the most killing for which antibiotics will help the clinician determine what minimum target should be attained. For beta-lactam antibiotics, the traditional minimal target range of 40–60% of the dosing interval was informed by animal studies and confirmed in some human studies [37, 41, 42]. As described above, there is increasing evidence that targeting 100% of the dosing interval for these time-dependent antibiotics further increases the probability for improved bacteriologic and clinical outcomes, especially in populations such as the critically ill, whose unpredictable pharmacokinetics increase their risk for inadequate dosing. Guidance for optimal sampling to assess attainment of the established target is provided below.

For some antibiotic classes it might appear that optimising doses is solely based on concentrations, rather than PK/PD indices. An example hereof is vancomycin. For TDM, trough levels between 15 and 20 mg/L are generally targeted. Though it might seem that this is based merely on a concentration, this specific value is derived from the PK/PD index, and correlates with a high likelihood of achieving the target AUC/MIC. This principle also applies to the aminoglycosides.

Finally, optimal exposure is of course the level of antibiotic to which microorganisms at the site of infection are exposed. Direct antibiotic TDM in fluids other than serum is understudied and not yet validated. Thus knowledge of an antibiotic's ability to penetrate the site of infection, whether it be lung parenchyma, osseous tissue, or cerebral meninges, is also essential. Serum TDM levels can then be used as a surrogate to approximate the percentage of antibiotic exposure achieved at the site.

4.4 Understanding the Altered and Variable Physiology of Intensive Care Unit (ICU) Patients

Critically ill patients are at increased risk for inadequate dosing [8, 43, 44] due to changes in physiology leading to significantly altered pharmacokinetics, as well as to external factors such as continuous renal replacement therapy or other supportive extracorporeal therapies. Patients with sepsis or burns often experience augmented renal clearance; this phenomenon is caused by increased renal blood flow and glomerular hyperfiltration and results in the accelerated elimination of renally cleared drugs, among them the beta-lactam antibiotics [45].

The critically ill may also manifest capillary leak syndrome, which in turn leads to elevated interstitial fluid volumes and thus an increased volume of distribution (V_d) of many drugs, in particular hydrophilic agents like the beta-lactams, aminoglycosides and glycopeptides [46]. Increased V_d, and thus lower than expected serum drug concentrations, should be anticipated in patients with oedema, pleural effusion, ascites, mediastinitis, fluid therapy, or hypoalbuminaemia [47]. In addition, critically ill patients may develop end-organ dysfunction and experience impaired drug distribution and elimination, with an increase in the serum concentration as a result [44]. Finally, there are subpopulations among ICU patients, an important one being the elderly: these individuals have additional physiologic differences, such as decreases in total body water distribution, that further cloud their pharmacokinetic behaviour [48].

These physiologic changes are the basis for the significant inter-patient pharmacokinetic variability observed among the critically ill. But intra-individual variability must also be anticipated, as these changes may co-exist and fluctuate within the same individual, rendering his or her pharmacokinetic profile unpredictable.

4.5 Practical Aspects

Effective TDM requires efficiency, reliability and appropriate measurements. Results should be available promptly; same-day results should be the goal, and turnaround times

>24 h should not be considered adequate for critically ill patients [27]. The TDM assay, whether high-performance liquid chromatography or, increasingly, mass spectrometry, should be cross-validated [49], and physicians and nurses should be given clear instructions regarding sample collection and transport methods (some antibiotics are unstable and require transport on ice to avoid spurious results). A note of the exact sample time is essential for drawing conclusions, but this is often not appreciated.

Ideally, the TDM assay should measure only the unbound fraction of antibiotic, as only this "free" concentration is antimicrobially active. But because of practical limitations, many centres—including the majority of those employing TDM for the beta-lactam antibiotics—measure and report total concentrations [11]. In this case, knowledge of the antibiotic's protein-binding fraction as well as the patient's albumin level will be necessary to estimate the true antibiotic exposure. It should be stressed, however, that the final value is a mere estimate whose reliability is inversely proportional to the antibiotic's level of protein binding (e.g. ceftriaxone, flucloxacillin) [50].

5 TDM of the Beta-Lactam Antibiotics

5.1 Evidence for Misdosing of Beta-Lactams in the Critically Ill

The purpose of TDM of most beta-lactam antibiotics in the critically ill is to correct for under-dosing. Under-dosing is significantly more common than overdosing given this population's physiologic alterations described above, the hydrophilic nature of these agents, and the fact that they are overwhelmingly renally cleared [51]. The increasing interest in beta-lactam TDM has enabled a fairly consistent demonstration of the miscalculation [8, 52, 53]. Indeed, measured serum concentrations in critically ill patients fall far short of those predicted by the pharmacokinetic data, usually derived from healthy volunteers, published for the respective antibiotic [8, 54, 55]. When continuous renal replacement therapy is employed, the risk increases further for subtherapeutic, or even undetectable, beta-lactam concentrations [56].

Increasing awareness of this discrepancy is driving the implementation of programmes for beta-lactam TDM in academic and non-academic centres alike, albeit slowly (see challenges below). Yet it should be noted that robust evidence definitively showing superior clinical outcomes using TDM guidance for optimised dosing is only beginning to be gathered. The DALI study, a multinational point-prevalence analysis of intermediate (50% $fT>MIC$) and trough (100% $fT>MIC$) beta-lactam serum concentrations in nearly 400 patients in ≥ 60 ICUs, is a strong early indicator [53]. It found an association between positive clinical outcome and an increasing 100% $fT>MIC$ ratio [odds ratio (OR) 1.56, 95% confidence interval (CI) 1.15–2.13]. The importance of optimised dosing was further supported by the finding that 16% of patients who did not achieve even 50% $fT>MIC$ were 32% less likely to have a positive clinical outcome. Yet it must be noted that the DALI study never actually measured MICs; it used susceptibility breakpoints as surrogates. Randomised controlled trials that define optimised TDM targets in line with actual MIC measurements are needed to demonstrate differences in clinical outcomes. Ultimately, such trials may be difficult to realise: the institutions that have beta-lactam TDM programmes are those that may not be in a state of clinical equipoise regarding their value, and thus may find it difficult to randomise patients to a control arm that is no longer their standard of care [57].

Cefepime is an exception to the rule that beta-lactam antibiotics are under-dosed [8]. Not surprisingly, it is also an exception to the widely held belief that these antibiotics are rarely toxic. Cefepime trough concentrations tend to be higher than those of other beta-lactam antibiotics, and the drug has a complicated record, with more than one meta-analysis showing slightly but consistently increased mortality in patients receiving it over other beta-lactam agents [58, 59]. A recent retrospective analysis of the clinical outcomes of 93 patients undergoing cefepime TDM shows a directly proportional relationship between cefepime trough concentrations and risk of clinical toxicity, as well as increased risk with durations exceeding 1 week [7]. We thus recommend cefepime TDM both for adequate exposure and to avoid toxicity, with readjustment of the dose when trough concentrations exceed 20 mg/L. Other beta-lactam agents may, like cefepime, trigger clinical toxicities such as liver enzyme elevations, renal insufficiency, and blood dyscrasias; more work is needed to characterise the correlations, if any, between their plasma concentrations and emergence of these toxicities.

5.2 Discrepancies in PK/PD Targets for Beta-Lactam Serum Levels

The sites that currently perform beta-lactam TDM vary in their pharmacokinetic targets, but almost all target serum concentrations with at least 100% $fT>MIC$, i.e. a trough concentration that is higher than the drug's MIC for the targeted organism [11]. Some aim for 100% $fT>4\times MIC$, a target whose higher concentration is derived from the seminal observation that, in Enterobacteriaceae kill kinetics, maximum kill is achieved at concentrations four times the MIC [30].

The results of the DALI study, which find an association between increasing antibiotic exposure from 50 to 100%

$fT > MIC$ and microbiologic or clinical cure, lend further support to the argument for ensuring concentrations above the MIC throughout the dosing interval (100% $fT > MIC$), especially in critically ill patients. Another argument, which requires further study and until then remains only theoretical, is that ensuring more comprehensive antibiotic exposure with coverage of 100% $fT > MIC$ or even 100% $fT > 4 \times MIC$ may guard against the development of resistance in bystander organisms (i.e. organisms not directly targeted by the antibiotic treatment, such as bacteria colonising the intestinal tract), as described above [26].

5.3 Practical Challenges to Beta-Lactam TDM

The single greatest impediment to standard clinical implementation of beta-lactam TDM is the lack of any commercial beta-lactam assay. Currently, laboratories must construct and cross-validate their own assays. Introducing and maintaining the service may add infrastructure, staffing and training costs. For these reasons, beta-lactam TDM remains inaccessible to many clinicians.

5.4 Some Broad Recommendations

Recommended indications for TDM of the beta-lactam antibiotics are summarised in Table 1. This type of TDM is early in its development; in cases of limited data, these recommendations are the authors' opinions only.

5.4.1 Recommended PK/PD Targets for Beta-Lactams

Given the enormous intra- and inter-patient variation among the critically ill, PK/PD targets should ideally be individualised. But until the availability of validated sampling and algorithms allowing the identification of individual targets, and given the increasing evidence described above indicating improved probabilities for bacteriologic and clinical outcomes with fuller coverage $>$MIC along the dosing interval, we recommend serum concentrations of at least 100% $fT > MIC$ as a reasonably reliable target to confirm appropriate exposure in critically ill patients.

5.4.2 Sampling at the Right Time

For dose adjustment during intermittent dosing, in contrast to continuous infusion, when and how often to sample are of major importance. The antibiotic's concentration over time is determined by at least two parameters, V_d and clearance. Thus, ideally, at least two samples should be drawn; one sample alone provides insufficient information to properly adjust the dose. (When only a trough level is available, the result might be below the limit of quantification [8]; such a result tells you that the concentration is too low and that the dose should be increased, but not by how much. When only a midpoint concentration is available, you will not know how rapidly that concentration will decline.) If only a single sample can be drawn, it is possible to improve dose adjustment using software programmes. These programmes are based on available population pharmacokinetic models and use several parameters of the individual patient, such as renal function and body weight [60, 61]. Unfortunately, pharmacokinetic models for all antibiotics in all clinical scenarios are not yet available and caution should be used; for example, a programme using a model based on the pharmacokinetics of pneumonia patients may not apply to critically ill patients with other infections.

Until these issues have been worked out, many centres simplify their timing of TDM sampling on the basis of practical concerns: requesting a simple trough level typically engenders the least confusion and risk for error among healthcare personnel. Thus trough levels can be drawn as a suboptimal but acceptable alternative.

5.4.3 Which Beta-Lactam Antibiotics

In broad terms, the beta-lactam antibiotics that (1) depend the most on renal elimination (and thus are at risk of accelerated elimination through augmented renal clearance) should be prioritised for TDM; this therefore includes the majority of the beta-lactams, with only ceftriaxone and flucloxacillin as less-pressing candidates. Clinicians should keep in mind, however, that even these can have variable exposure in the critically ill due to potential changes in protein binding, such that TDM of unbound concentrations may be indicated as well. The limited but growing literature on serum beta-lactam concentrations in critically ill patients indicates that carbapenems, particularly imipenem, often fail to achieve expected levels with, in a significant minority, trough concentrations that are undetectable [8], while the anti-pseudomonals piperacillin and cefepime can have wide-ranging trough concentrations with notable inter-patient variability [7, 8]. We therefore generally recommend TDM of most beta-lactam antibiotics for the following patients and/or infections.

5.4.4 Which Patients

The critically ill are probably the population most at risk for inadequate beta-lactam antibiotic exposure given their significant physiologic alterations. But other populations whose pharmacokinetics are understudied and poorly understood are also likely to benefit from beta-lactam TDM. The elderly have impaired homeostasis and wider

Table 1 Recommended indications for the use of therapeutic drug monitoring (TDM) of beta-lactam antibiotics. In cases of limited clinical data, these recommendations represent the authors' opinions

Indications for beta-lactam TDM	Comments, references
Patients	
Critically ill	[8, 43, 47]
Augmented renal clearance	Low serum creatinine predicts subtherapeutic plasma concentrations [8, 45]
Obesity	[63]
Renal insufficiency	Particularly haemodialysis or CRRT patients [56]
Elderly	[62]
Cystic fibrosis	[55]
Infections	
Any severe/life-threatening infection	[47, 104]
Infections in anatomic sites with variable drug penetration, e.g.:	*Some beta-lactams have strong penetration into lung epithelial lining fluid; for these and for a non-life-threatening pneumonia, TDM may not be necessary
Osteomyelitis	
Prostatitis	
Meningitis	
Pneumonia*	
Infections with poor source control, e.g.:	
Endocarditis or other endovascular infection without a removable focus	
Incompletely drained abscess	
Loculated empyema	
Antibiotics	
Imipenem, meropenem and other carbapenems	These drugs are typically eliminated rapidly; patients may have undetectable trough levels [8, 46]
Cephalosporins	All cephalosporins can be monitored for efficacy, and cefepime should be monitored for both efficacy and toxicity [7]
Penicillins	These antibiotics may achieve only low (e.g. oral amoxicillin) and/or variable (e.g. piperacillin) plasma levels [8]

inter-individual variability. Aging is associated with reduced protein binding and overall drug distribution and, for oral antibiotics, reduced absorption from the gastrointestinal tract [62]. In obese patients, beta-lactam and other antibiotics tend to have a higher V_d. In addition, commonly used creatinine clearance calculations may be inaccurate in this population, resulting in antibiotic exposure that is more difficult to predict [63]. Patients with specific diseases, such as cystic fibrosis, may also have altered pharmacokinetics [55, 64].

5.4.5 Which Infections

TDM of a beta-lactam antibiotic should be performed when that antibiotic is being used to treat any severe, life-threatening infection; sampling should occur early in the course and, if the patient remains critically ill, repeatedly in light of potential inter-patient swings in pharmacokinetic behaviour. For infections that are more moderate, subacute or chronic, TDM should be employed when the anatomic site of infection is difficult to penetrate (e.g. osteomyelitis, prostatitis, etc.) and/or when source control cannot be achieved (Table 1). If treatment is to be long term with an oral beta-lactam whose absorption may be variable (e.g. amoxicillin), serum levels should be obtained early on to ensure adequate exposure, and repeated in the event of a dose adjustment (e.g. due to side effects) or a change in renal function.

6 TDM of the Aminoglycosides

With the recent emergence and worldwide spread of multidrug-resistant Gram-negative bacteria, there has been a renaissance in the use of aminoglycosides, since they are one of the few classes of antibiotics to which these organisms may still be susceptible in vitro. TDM of aminoglycosides as a means to reduce toxicity while still assuring adequate levels for treatment of severe infections has been recommended since the 1970s [65, 66] and is the

standard of care in many hospitals. The 2016 guidelines by the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America on "Implementing an Antibiotic Stewardship Program" provide a strong recommendation (albeit based on "moderate-quality evidence") that "hospitals implement PK monitoring and adjustment programs for aminoglycosides" [67]. While there is a good theoretical basis to propose TDM for this drug class, it should be kept in mind that evidence for an actual impact on clinical outcomes also remains suboptimal [68].

Traditionally, aminoglycosides were administered several times per day, but originally it was thought that they should be administered by continuous infusion. Studies done in the 1980s suggested that the antibacterial activity of aminoglycosides was mainly concentration dependent [69], with a ratio of $\geq$ 8–10 of C_{max}/MIC thought to provide the best efficacy [70–72]. These findings, together with the risk for adaptive resistance (i.e. reduced antimicrobial killing in originally susceptible bacterial populations after initial incubation with the aminoglycoside) and animal studies suggesting the potential for decreased renal toxicity, have led to a shift from multiple daily dosing regimens to once-daily dosing, i.e. administering higher doses (to increase C_{max}), but at extended intervals [73–75].

Current dosing regimens are quite variable, with once-daily doses of 3–7.5 mg/kg the most frequently used. But higher doses have been described as well, for example, gentamicin at 8 mg/kg in ICU patients [76] and 10 mg/kg tobramycin in patients with cystic fibrosis [77]. A target attainment rate of approximately 50% was reported in a retrospective analysis of 102 ICU patients receiving a loading dose of 7 mg/kg tobramycin in the treatment of *P. aeruginosa* with a target C_{max}/MIC ratio of 10 [78], and another study using 8 mg/kg once-daily doses of gentamicin concluded that it seems impossible to obtain a C_{max}/MIC ratio of 8 in critically ill patients [76].

More recent data suggest, however, that the *f*AUC/MIC may actually be the better parameter to predict efficacy, with a target of 70–75 $fAUC_{24}$/MIC for Enterobacteriaceae and 82 $fAUC_{24}$/MIC for *P. aeruginosa* [31, 79, 80]. But since the PK/PD indices C_{max}/MIC and AUC/MIC correlate strongly for aminoglycosides, it is expected that higher doses will be recommended with the revised European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints when AUC/MIC is used as the index. Alternatively, it may be advised that aminoglycosides be used only in combination with a second active antimicrobial.

Until recently there has been some resistance to recommending extended interval (once-daily) dosing for aminoglycosides in the case of endocarditis caused by Gram-positive bacteria, since data from animal models suggested improved synergy with more frequent administrations [81]. The 2015 European guidelines for the management of infective endocarditis now, however, also recommend extended-interval dosing [82].

Some infectious disease societies have published guidelines on recommended dosing regimens and TDM of aminoglycosides [83, 84]. Simply stated, peak levels of aminoglycosides are associated with efficacy, and trough levels predict toxicity. Interestingly, the recent US endocarditis guidelines continue to recommend multiple daily administrations in the case of enterococcal endocarditis [85], illustrating that the issue of how best to administer aminoglycosides is far from being resolved.

6.1 Peak-Level Monitoring

If aminoglycosides are administered once daily, peak levels (obtained after the distribution phase usually 30 min after completion of the 30-min infusion) are typically assumed to be in the therapeutic range due to the high dose administered, and thus routine TDM of peak levels is often not recommended. It is important to keep in mind, however, that in critically ill patients, the V_d for these hydrophilic substances may be significantly increased. Thus in many situations in the ICU setting (septic shock, burns, ventilated patients, cystic fibrosis, febrile neutropenia), it may still be worthwhile to draw peak levels (roughly 1 h after the start of administration) to confirm that they are sufficiently elevated [84].

6.2 Trough-Level Monitoring

Given the risk of potentially irreversible renal and (potentially irreversible) ototoxicity, there is a general consensus to limit the duration of aminoglycoside administration to the strict minimum necessary (e.g. by limiting administration to the empiric phase of treatment until susceptibility data are available). Thus if the duration of administration does not exceed 3–5 days, TDM of trough levels is probably not useful. If the treatment plan includes longer durations (e.g. infections with extensively drug-resistant organisms or endocarditis), TDM of trough levels should be performed. There is no clear consensus on how often to repeat levels, but a frequent recommendation is to check levels at least weekly and more frequently if there is reason to believe that changes in pharmacokinetics have occurred (e.g. changes in renal function). Furthermore, recommended peak and trough target concentrations vary widely, reflecting the uncertainties in our knowledge of the PK/PD of these drugs despite their use for decades.

7 TDM of the Glycopeptides

Relative to beta-lactam TDM, vancomycin TDM is well researched and firmly established in clinical culture. As described above, regular serum levels to guard against toxicity were necessary with the earlier, non-purified formulations. As with most beta-lactams, the primary goal of vancomycin TDM today is to ensure adequate exposure, though toxicity can still be a concern, particularly when the drug is administered for durations of more than a few days.

Recommendations with specific PK/PD targets for vancomycin TDM were issued in 2009 by IDSA and continue to be highly relevant [86]. There is some clinical evidence that targeting higher trough levels increases the probability for improved clinical and microbiologic outcomes in infections due to methicillin-resistant *Staphylococcus aureus*. A value of AUC_{24}/MIC of ≥ 400 has been found to be associated with improved clinical outcome; trough levels of 15–20 mg/L correspond well to this ratio, making them appropriate for sampling [2]. A recent meta-analysis lends support; it assessed the impact of low (<15 mg/L) versus high (≥ 15 mg/L) vancomycin trough levels on clinical efficacy in these infections; this cutoff was chosen to match the 2009 recommendation for trough levels of 15–20 mg/L for serious infections. There was significantly higher mortality in pneumonia patients with lower trough concentrations (OR 1.78, 95% CI 1.11–2.84), and microbiologic failure rates were significantly higher in all patients with low vancomycin levels (OR 1.56, 95% CI 1.08–2.26) [87]. We thus recommend vancomycin TDM as described in the 2009 IDSA guidelines for *S. aureus* infections.

Few hospitals routinely perform TDM of teicoplanin, and thus it remains understudied. There are indications, however, that its use in optimising teicoplanin dosing is associated with improved bacteriologic [88] and clinical [89–91] outcomes. Yet most data are retrospective; here randomised trials are also needed. Harmonised recommendations for monitoring are also lacking; currently there are different targets for various clinical indications (see [92]).

8 TDM of Quinolones

Routine TDM of quinolones is practiced in few hospitals [93, 94], and there are very few reports in the literature. A positive outcome correlates with the AUC/MIC, and most studies on ciprofloxacin have used a target value of AUC_{24}/MIC >125 or $fAUC_{24}$/MIC >90 in the treatment of Gram-negative bacteria [94–98]. This target was reached in less than 50% of adults treated intravenously with ciprofloxacin 300mg every 12 hours (q12 h) for a respiratory tract infection [97]. In elderly patients with lower respiratory tract infections, wide inter-patient variability in exposure after treatment with ciprofloxacin was reported, indicating the need for TDM in this group [99]. TDM was also advised in a study of severely obese patients [body mass index (BMI) ≥ 40 kg/m^2], where doses were also guided by creatinine clearance [100]. But even among healthy volunteers, target attainment rates of the 400 mg every 8 hours (q8 h) regimen were low [101].

In critically ill patients, intravenous doses of ciprofloxacin 400 mg q12 h resulted in such wide inter-patient variability in exposure that study investigators generally recommended against reducing doses in critically ill patients with impaired renal function [94]; the same dosing scheme was shown to be inadequate in another pharmacokinetic study [102]. Khachman et al. also examined target attainment in critically ill patients, exploring different dosing regimens using Monte-Carlo simulations [98]. In line with other studies, they found attainments to be low, and even questioned the use of ciprofloxacin at all in the treatment of *P. aeruginosa* and *Acinetobacter baumannii*, since even with a daily dose of 2400 mg, target attainment rates for these microorganisms were 79 and 66%, respectively. These data are further supported by an interim analysis of an ongoing trial in critically ill patients suggesting that only a minority of patients receiving a high-dose regimen of ciprofloxacin (400 mg q8 h) reached pharmacokinetic targets [103]. Thus TDM for quinolones in this population is also likely warranted and requires further study.

9 Conclusions

The current practice of antibiotic TDM is heterogeneous, influenced by historical context, and often dependent upon local culture. TDM of the aminoglycosides and vancomycin is well known and generally practiced. But the use of this tool for other antibiotic classes is on the rise, particularly for the beta-lactam antibiotics, whose dosing optimisation is now critical in light of increasing global antimicrobial resistance. Beta-lactam TDM, with a recommended pharmacokinetic target of 100% $fT>$MIC, should be considered early on in order to ensure adequate antibiotic exposure in any critically ill patient with a severe infection, though well designed randomised trials directly showing the clinical benefit of beta-lactam TDM are lacking. For aminoglycosides, the PK/PD index has shifted from C_{max}/MIC to AUC/MIC, and several studies suggest that currently used dosing regimens are inadequate. Optimising aminoglycoside administration through potentially higher doses while controlling for toxicity requires further

exploration. Finally, while quinolone TDM is not regularly practiced, available evidence increasingly points to poor target attainment with currently used dosing schemes. For all TDM in individual patients, the antibiotic's MIC plays a crucial role in determining TDM targets, and should accordingly be measured whenever possible.

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Compliance with Ethical Standards

Conflict of Interest Anouk E. Muller, Benedikt Huttner, Angela Huttner declare no conflicts of interest.

References

1. Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis. 2009;48(1):1–12.
2. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. Clin Pharmacokinet. 2004;43(13):925–42.
3. Muller AE, Punt N, Mouton JW. Optimal exposures of ceftazidime predict the probability of microbiological and clinical outcome in the treatment of nosocomial pneumonia. J Antimicrob Chemother. 2013;68(4):900–6.
4. Muller AE, Punt N, Mouton JW. Exposure to ceftobiprole is associated with microbiological eradication and clinical cure in patients with nosocomial pneumonia. Antimicrob Agents Chemother. 2014;58(5):2512–9.
5. McKinnon PS, Paladino JA, Schentag JJ. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T > MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int J Antimicrob Agents. 2008;31(4):345–51.
6. MacVane SH, Kuti JL, Nicolau DP. Clinical pharmacodynamics of antipseudomonal cephalosporins in patients with ventilator-associated pneumonia. Antimicrob Agents Chemother. 2014;58(3):1359–64.
7. Huwyler T, Lenggenhager L, Abbas M, Ing Lorenzini K, Hughes S, Huttner B, et al. Cefepime plasma concentrations and clinical toxicity: a retrospective cohort study. Clin Microbiol Infect. 2017;23(7):454–9.
8. Huttner A, Von Dach E, Renzoni A, Huttner BD, Affaticati M, Pagani L, et al. Augmented renal clearance, low beta-lactam concentrations and clinical outcomes in the critically ill: an observational prospective cohort study. Int J Antimicrob Agents. 2015;45(4):385–92.
9. Menifield CE, Doty N, Fletcher A. Obesity in America. ABNF J. 2008;19(3):83–8.
10. Obesity statistics (internet). http://www.health.govt.nz/nz-health-statistics/health-statistics-and-data-sets/obesity-statistics. Accessed 1 Oct 2017.
11. Wong G, Brinkman A, Benefield RJ, Carlier M, De Waele JJ, El Helali N, et al. An international, multicentre survey of beta-lactam antibiotic therapeutic drug monitoring practice in intensive care units. J Antimicrob Chemother. 2014;69(5):1416–23.
12. Charmillon A, Novy E, Agrinier N, Leone M, Kimmoun A, Levy B, et al. The ANTIBIOPERF study: a nationwide cross-sectional survey about practices for beta-lactam administration and therapeutic drug monitoring among critically ill patients in France. Clin Microbiol Infect. 2016;22(7):625–31.
13. Griffith RS. Introduction to vancomycin. Rev Infect Dis. 1981;3(suppl):S200–4.
14. Elting LS, Rubenstein EB, Kurtin D, Rolston KV, Fangtang J, Martin CG, et al. Mississippi mud in the 1990s: risks and outcomes of vancomycin-associated toxicity in general oncology practice. Cancer. 1998;83(12):2597–607.
15. Wong-Beringer A, Joo J, Tse E, Beringer P. Vancomycin-associated nephrotoxicity: a critical appraisal of risk with high-dose therapy. Int J Antimicrob Agents. 2011;37(2):95–101.
16. Rybak MJ, Albrecht LM, Boike SC, Chandrasekar PH. Nephrotoxicity of vancomycin, alone and with an aminoglycoside. J Antimicrob Chemother. 1990;25(4):679–87.
17. Kureishi A, Jewesson PJ, Rubinger M, Cole CD, Reece DE, Phillips GL, et al. Double-blind comparison of teicoplanin versus vancomycin in febrile neutropenic patients receiving concomitant tobramycin and piperacillin: effect on cyclosporin A-associated nephrotoxicity. Antimicrob Agents Chemother. 1991;35(11):2246–52.
18. Menichetti F, Martino P, Bucaneve G, Gentile G, D'Antonio D, Liso V, et al. Effects of teicoplanin and those of vancomycin in initial empirical antibiotic regimen for febrile, neutropenic patients with hematologic malignancies. Gimema Infection Program. Antimicrob Agents Chemother. 1994;38(9):2041–6.
19. Byrne CJ, Roberts JA, McWhinney B, Fennell JP, O'Byrne P, Deasy E, et al. Variability in trough total and unbound teicoplanin concentrations and achievement of therapeutic drug monitoring targets in adult patients with hematological malignancy. Antimicrob Agents Chemother. 2017;61(6):e02466-16.
20. Wilson AP. Clinical pharmacokinetics of teicoplanin. Clin Pharmacokinet. 2000;39(3):167–83.
21. Lenggenhager L, Abbas M, Fankhauser C, Huttner B, Harbarth S, Huttner A. Emergence of Pseudomonas aeruginosa resistance in patients with imipenem therapeutic drug monitoring. In: 27th European congress on clinical microbiology and infection; 22–25 April 2017; Vienna, Austria.
22. Mouton JW, den Hollander JG. Killing of *Pseudomonas aeruginosa* during continuous and intermittent infusion of ceftazidime in an in vitro pharmacokinetic model. Antimicrob Agents Chemother. 1994;38(5):931–6.
23. Mouton RP, Glerum JH, van Loenen AC. Relationship between antibiotic consumption and frequency of antibiotic resistance of four pathogens–a seven-year survey. J Antimicrob Chemother. 1976;2(1):9–19.
24. Ambrose PG, Bhavnani SM, Owens RC Jr. Clinical pharmacodynamics of quinolones. Infect Dis Clin North Am. 2003;17(3):529–43.
25. Zinner SH, Lubenko IY, Gilbert D, Simmons K, Zhao X, Drlica K, et al. Emergence of resistant *Streptococcus pneumoniae* in an in vitro dynamic model that simulates moxifloxacin concentrations inside and outside the mutant selection window: related changes in susceptibility, resistance frequency and bacterial killing. J Antimicrob Chemother. 2003;52(4):616–22.
26. Goessens WH, Mouton JW, ten Kate MT, Bijl AJ, Ott A, Bakker-Woudenberg IA. Role of ceftazidime dose regimen on the selection of resistant *Enterobacter cloacae* in the intestinal flora of rats treated for an experimental pulmonary infection. J Antimicrob Chemother. 2007;59(3):507–16.

27. Ensom MH, Davis GA, Cropp CD, Ensom RJ. Clinical pharmacokinetics in the 21st century. Does the evidence support definitive outcomes? Clin Pharmacokinet. 1998;34(4):265–79.
28. Ambrose PG, Bhavnani SM, Rubino CM, Louie A, Gumbo T, Forrest A, et al. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. Clin Infect Dis. 2007;44(1):79–86.
29. Mouton JW, Ambrose PG, Canton R, Drusano GL, Harbarth S, MacGowan A, et al. Conserving antibiotics for the future: new ways to use old and new drugs from a pharmacokinetic and pharmacodynamic perspective. Drug Resist Updat. 2011;14(2):107–17.
30. Vogelman B, Gudmundsson S, Leggett J, Turnidge J, Ebert S, Craig WA. Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. J Infect Dis. 1988;158(4):831–47.
31. USCAST. Aminoglycoside in vitro susceptibility, test interpretive criteria evaluations. 2016 21 July 2016. Report No.: USCAST 0002.
32. Craig WA, Ebert SC. Killing and regrowth of bacteria in vitro: a review. Scand J Infect Dis Suppl. 1990;74:63–70.
33. Mouton JW, Punt N, Vinks AA. Concentration-effect relationship of ceftazidime explains why the time above the MIC is 40 percent for a static effect in vivo. Antimicrob Agents Chemother. 2007;51(9):3449–51.
34. Rybak MJ. Pharmacodynamics: relation to antimicrobial resistance. Am J Infect Control. 2006;34(5 Suppl 1):S38–45 **(discussion S64–73)**.
35. Cheah SE, Wang J, Nguyen VT, Turnidge JD, Li J, Nation RL. New pharmacokinetic/pharmacodynamic studies of systemically administered colistin against *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in mouse thigh and lung infection models: smaller response in lung infection. J Antimicrob Chemother. 2015;70(12):3291–7.
36. Drusano GL. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat Rev Microbiol. 2004;2(4):289–300.
37. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis. 1998;26(1):1–10 **(quiz 1–2)**.
38. Hombach M, Ochoa C, Maurer FP, Pfiffner T, Bottger EC, Furrer R. Relative contribution of biological variation and technical variables to zone diameter variations of disc diffusion susceptibility testing. J Antimicrob Chemother. 2016;71(1):141–51.
39. Voss A, Mouton JW, Elzakker EP, Hendrix MG, Howe RA, Goessens WH, et al. Linezolid susceptibility of MRSA and glycopeptide-intermediately susceptible *Staphylococcus aureus* (GISA)—the Dutch experience. ECCMID; 8 May 2003; Glasgow, Scotland.
40. Mouton JW, Muller AE, Canton R, Giske CG, Kahlmeter G, Turnidge J. MIC-based dose adjustment: facts and fables. J Antimicrob Chemother 2017. https://doi.org/10.1093/jac/dkx427.
41. Craig WA, Andes D. Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. Pediatr Infect Dis J. 1996;15(3):255–9.
42. Craig WA. Antimicrobial resistance issues of the future. Diagn Microbiol Infect Dis. 1996;25(4):213–7.
43. Udy AA, Roberts JA, De Waele JJ, Paterson DL, Lipman J. What's behind the failure of emerging antibiotics in the critically ill? Understanding the impact of altered pharmacokinetics and augmented renal clearance. Int J Antimicrob Agents. 2012;39(6):455–7.
44. Ulldemolins M, Roberts JA, Lipman J, Rello J. Antibiotic dosing in multiple organ dysfunction syndrome. Chest. 2011;139(5):1210–20.
45. Udy AA, Varghese JM, Altukroni M, Briscoe S, McWhinney BC, Ungerer JP, et al. Subtherapeutic initial beta-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. Chest. 2012;142(1):30–9.
46. Goncalves-Pereira J, Povoa P. Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of beta-lactams. Crit Care. 2011;15(5):R206.
47. Pea F, Viale P, Furlanut M. Antimicrobial therapy in critically ill patients: a review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability. Clin Pharmacokinet. 2005;44(10):1009–34.
48. Schlender JF, Meyer M, Thelen K, Krauss M, Willmann S, Eissing T, et al. Development of a whole-body physiologically based pharmacokinetic approach to assess the pharmacokinetics of drugs in elderly individuals. Clin Pharmacokinet. 2016;55(12):1573–89.
49. Guidance for industry: bioanalytical method validation. US Department of Health and Human Services; 2001.
50. Wong G, Briscoe S, Adnan S, McWhinney B, Ungerer J, Lipman J, et al. Protein binding of beta-lactam antibiotics in critically ill patients: can we successfully predict unbound concentrations? Antimicrob Agents Chemother. 2013;57(12):6165–70.
51. Vinks SA, Heijerman HG, de Jonge P, Bakker W. Photosensitivity due to ambulatory intravenous ceftazidime in cystic fibrosis patient. Lancet. 1993;341(8854):1221–2.
52. Sime FB, Roberts MS, Warner MS, Hahn U, Robertson TA, Yeend S, et al. Altered pharmacokinetics of piperacillin in febrile neutropenic patients with hematological malignancy. Antimicrob Agents Chemother. 2014;58(6):3533–7.
53. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, et al. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis. 2014;58(8):1072–83.
54. Jaruratanasirikul S, Raungsri N, Punyo J, Sriwiriyajan S. Pharmacokinetics of imipenem in healthy volunteers following administration by 2 h or 0.5 h infusion. J Antimicrob Chemother. 2005;56(6):1163–5.
55. Mouton JW, Punt N, Vinks AA. A retrospective analysis using Monte Carlo simulation to evaluate recommended ceftazidime dosing regimens in healthy volunteers, patients with cystic fibrosis, and patients in the intensive care unit. Clin Ther. 2005;27(6):762–72.
56. Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis. 2014;14(6):498–509.
57. Huttner A, Harbarth S, Hope WW, Lipman J, Roberts JA. Therapeutic drug monitoring of the beta-lactam antibiotics: what is the evidence and which patients should we be using it for? J Antimicrob Chemother. 2015;70(12):3178–83.
58. Paul M, Yahav D, Fraser A, Leibovici L. Empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2006;57(2):176–89.
59. Yahav D, Paul M, Fraser A, Sarid N, Leibovici L. Efficacy and safety of cefepime: a systematic review and meta-analysis. Lancet Infect Dis. 2007;7(5):338–48.
60. Fuchs A, Csajka C, Thoma Y, Buclin T, Widmer N. Benchmarking therapeutic drug monitoring software: a review of available computer tools. Clin Pharmacokinet. 2013;52(1):9–22.
61. Felton TW, Roberts JA, Lodise TP, Van Guilder M, Boselli E, Neely MN, et al. Individualization of piperacillin dosing for

critically ill patients: dosing software to optimize antimicrobial therapy. Antimicrob Agents Chemother. 2014;58(7):4094–102.
62. Hilmer SN, McLachlan AJ, Le Couteur DG. Clinical pharmacology in the geriatric patient. Fundam Clin Pharmacol. 2007;21(3):217–30.
63. Janson B, Thursky K. Dosing of antibiotics in obesity. Curr Opin Infect Dis. 2012;25(6):634–49.
64. Bulitta JB, Landersdorfer CB, Huttner SJ, Drusano GL, Kinzig M, Holzgrabe U, et al. Population pharmacokinetic comparison and pharmacodynamic breakpoints of ceftazidime in cystic fibrosis patients and healthy volunteers. Antimicrob Agents Chemother. 2010;54(3):1275–82.
65. Giamarellou H, Zimelis VM, Matulionis DO, Jackson GG. Assay of aminoglycoside antibiotics in clinical specimens. J Infect Dis. 1975;132(4):399–406.
66. Noone P, Parsons TM, Pattison JR, Slack RC, Garfield-Davies D, Hughes K. Experience in monitoring gentamicin therapy during treatment of serious gram-negative sepsis. Br Med J. 1974;1(5906):477–81.
67. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62(10):e51–77.
68. Jenkins A, Thomson AH, Brown NM, Semple Y, Sluman C, MacGowan A, et al. Amikacin use and therapeutic drug monitoring in adults: do dose regimens and drug exposures affect either outcome or adverse events? A systematic review. J Antimicrob Chemother. 2016;71(10):2754–9.
69. Lacy MK, Nicolau DP, Nightingale CH, Quintiliani R. The pharmacodynamics of aminoglycosides. Clin Infect Dis. 1998;27(1):23–7.
70. Kashuba AD, Nafziger AN, Drusano GL, Bertino JS Jr. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by Gram-negative bacteria. Antimicrob Agents Chemother. 1999;43(3):623–9.
71. Zelenitsky SA, Harding GK, Sun S, Ubhi K, Ariano RE. Treatment and outcome of *Pseudomonas aeruginosa* bacteraemia: an antibiotic pharmacodynamic analysis. J Antimicrob Chemother. 2003;52(4):668–74.
72. Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis. 1987;155(1):93–9.
73. Stankowicz MS, Ibrahim J, Brown DL. Once-daily aminoglycoside dosing: an update on current literature. Am J Health Syst Pharm. 2015;72(16):1357–64.
74. Hatala R, Dinh T, Cook DJ. Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis. Ann Intern Med. 1996;124(8):717–25.
75. Barclay ML, Begg EJ, Chambers ST. Adaptive resistance following single doses of gentamicin in a dynamic in vitro model. Antimicrob Agents Chemother. 1992;36(9):1951–7.
76. Allou N, Allyn J, Levy Y, Bouteau A, Caujolle M, Delmas B, et al. Assessment of the National French recommendations regarding the dosing regimen of 8 mg/kg of gentamicin in patients hospitalised in intensive care units. Anaesth Crit Care Pain Med. 2016;35(5):331–5.
77. Downes KJ, Dong M, Fukuda T, Clancy JP, Haffner C, Bennett MR, et al. Urinary kidney injury biomarkers and tobramycin clearance among children and young adults with cystic fibrosis: a population pharmacokinetic analysis. J Antimicrob Chemother. 2017;72(1):254–60.
78. Rea RS, Capitano B, Bies R, Bigos KL, Smith R, Lee H. Suboptimal aminoglycoside dosing in critically ill patients. Ther Drug Monit. 2008;30(6):674–81.
79. Smith PF, Ballow CH, Booker BM, Forrest A, Schentag JJ. Pharmacokinetics and pharmacodynamics of aztreonam and tobramycin in hospitalized patients. Clin Ther. 2001;23(8):1231–44.
80. Bowker KE, Noel AR, Nicholls D, Tomaselli SG, MacGowan AP. Pharmacodynamics of amikacin against aerobic Gram-negative rods studied in an in vitro model of infection. Washington: ICAAC; 2014. p. A-042.
81. Davis BD. Bactericidal synergism between beta-lactams and aminoglycosides: mechanism and possible therapeutic implications. Rev Infect Dis. 1982;4(2):237–45.
82. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis: the task force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;36(44):3075–128.
83. Agence francaise de securite sanitaire des produits de s. Update on good use of injectable aminoglycosides, gentamycin, tobramycin, netilmycin, amikacin. Pharmacological properties, indications, dosage, and mode of administration, treatment monitoring. Med Mal Infect. 2012;42(7):301–8.
84. Robert J, Pean Y, Alfandari S, Bru JP, Bedos JP, Rabaud C, et al. Application of guidelines for aminoglycosides use in French hospitals in 2013-2014. Eur J Clin Microbiol Infect Dis. 2017;36(7):1083–90.
85. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015;132(15):1435–86.
86. Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC, Craig WA, Billeter M, et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis. 2009;49(3):325–7.
87. Steinmetz T, Eliakim-Raz N, Goldberg E, Leibovici L, Yahav D. Association of vancomycin serum concentrations with efficacy in patients with MRSA infections: a systematic review and meta-analysis. Clin Microbiol Infect. 2015;21(7):665–73.
88. Matsumoto K, Watanabe E, Kanazawa N, Fukamizu T, Shigemi A, Yokoyama Y, et al. Pharmacokinetic/pharmacodynamic analysis of teicoplanin in patients with MRSA infections. Clin Pharmacol. 2016;8:15–8.
89. Greenberg RN. Treatment of bone, joint, and vascular-access-associated gram-positive bacterial infections with teicoplanin. Antimicrob Agents Chemother. 1990;34(12):2392–7.
90. Lee CH, Tsai CY, Li CC, Chien CC, Liu JW. Teicoplanin therapy for MRSA bacteraemia: a retrospective study emphasizing the importance of maintenance dosing in improving clinical outcomes. J Antimicrob Chemother. 2015;70(1):257–63.
91. Ueda T, Takesue Y, Nakajima K, Ichki K, Wada Y, Komatsu M, et al. High-dose regimen to achieve novel target trough concentration in teicoplanin. J Infect Chemother. 2014;20(1):43–7.
92. Summary of product characteristics for Targocid® (teicoplanin), electronic medicines companion (Internet). Electronic Medicines Companion. 2014. http://www.medicines.org.uk/emc/medicine/27321. Accessed 1 Oct 2017.
93. Sorgel F, Hohl R, Glaser R, Stelzer C, Munz M, Vormittag M, et al. Pharmacokinetics and pharmacodynamics of antibiotics in intensive care. Med Klin Intensivmed Notfmed. 2017;112(1):11–23.

94. Pea F, Poz D, Viale P, Pavan F, Furlanut M. Which reliable pharmacodynamic breakpoint should be advised for ciprofloxacin monotherapy in the hospital setting? A TDM-based retrospective perspective. J Antimicrob Chemother. 2006;58(2):380–6.
95. Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother. 1993;37(5):1073–81.
96. Schentag JJ. Antimicrobial action and pharmacokinetics/pharmacodynamics: the use of AUIC to improve efficacy and avoid resistance. J Chemother. 1999;11(6):426–39.
97. Matsuo K, Azuma M, Kasai M, Hanji I, Kimura I, Kosugi T, et al. Investigation of the clinical efficacy and dosage of intravenous ciprofloxacin in patients with respiratory infection. J Pharm Pharm Sci. 2009;11(2):111s–7s.
98. Khachman D, Conil JM, Georges B, Saivin S, Houin G, Toutain PL, et al. Optimizing ciprofloxacin dosing in intensive care unit patients through the use of population pharmacokinetic-pharmacodynamic analysis and Monte Carlo simulations. J Antimicrob Chemother. 2011;66(8):1798–809.
99. Pea F, Milaneschi R, Baraldo M, Lugatti E, Talmassons G, Furlanut M. Ciprofloxacin disposition in elderly patients with LRTI being treated with sequential therapy (200 mg intravenously twice daily followed by 500 mg per os twice daily): comparative pharmacokinetics and the role of therapeutic drug monitoring. Ther Drug Monit. 2000;22(4):386–91.
100. Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adult patients. Pharmacotherapy. 2007;27(8):1081–91.
101. Kuti JL, Nightingale CH, Nicolau DP. Optimizing pharmacodynamic target attainment using the MYSTIC antibiogram: data collected in North America in 2002. Antimicrob Agents Chemother. 2004;48(7):2464–70.
102. van Zanten AR, Polderman KH, van Geijlswijk IM, van der Meer GY, Schouten MA, Girbes AR. Ciprofloxacin pharmacokinetics in critically ill patients: a prospective cohort study. J Crit Care. 2008;23(3):422–30.
103. Abdulla A, Hunfeld N, Dijkstra A, Duran S, Mouton JW, Gommers D, et al. Beta-lactam and quinolone pharmacokinetic/pharmacodynamic target attainment in critically ill patients (EXPAT). ECCMID2017. p. EP0355.
104. Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med. 2009;37(3):840–51 **(quiz 59)**.