Chapter 2
Antibiotic Pharmacodynamics

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2.1 Introduction

Pharmacodynamics is classically described as the effect of drugs on the body, which for most drugs relates to effects on pathophysiological processes so as to achieve the desired treatment outcomes. Unlike drugs which act on human cells/organs to elicit their pharmacological effect, antibiotics act on 'non-physiologic' bacterial cells to produce pharmacological effect. Because antibiotics are not meant to act on (affect) the human physiological system but rather directly bind or interact with bacterial cells, present both advantages and challenges in terms of our ability to characterize dose–effect relationships. One important advantage is that, unlike other drugs, we can easily describe concentration–effect relationships of antibiotics in vitro and

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describe concentrations that achieve inhibition of bacterial growth or maximal killing [1]. This is advantageous not only for designing dosing regimens, but also for optimizing treatment for individual patients relative to the susceptibility of the causative pathogen. Further, advanced in vitro infection models that can simulate human-like pharmacokinetic exposure of bacteria to changing antibiotics concentrations are now available to predict efficacy of novel dosing regimens in patients [2]. On the other hand, whilst for drugs which act by modifying human physiology (e.g. antihypertensive drugs) the actual clinical effect can be readily monitored by an objective clinical end point (e.g. blood pressure monitoring), such a direct objective end point is not possible for antibiotics which act directly on bacterial cells for therapeutic action, i.e. there is no direct human physiological change (signal) induced by the therapeutic action of antibiotics on bacteria. The clinical end point of antibiotic therapy, resolution of infection, remains largely subjective although a number of physiological markers of infection are considered useful surrogate indicators [3]. Unfortunately, the relationship between antibiotic exposure and biomarkers of infection that could signal optimal treatment outcome is not yet well established to guide the design and optimization of dosing regimens. It has not yet been possible to optimize antibiotic dosing based on a graded clinical response.

The best surrogate measures of antibiotic efficacy available to date have been consolidated from knowledge of antibiotic kill characteristics which is determined by the time course of changing antibiotic concentrations and in vitro susceptibility profile of bacteria. This chapter will summarize the pharmacodynamic properties of antibiotics most commonly used in intensive care settings and the various pharmacokinetic/pharmacodynamic predictors of efficacy utilized in the design and optimization of antibiotic dosing.

2.2 Minimum Inhibitory Concentration (MIC) and Susceptibility Break Points

To describe the potency of antibiotics, the minimum inhibitory concentration (MIC) has been used since the introduction of the early antibiotics [4]. The MIC refers to the lowest concentration of the antibiotic that prevents growth of standard bacterial inoculum of about 10^5 colony-forming units (CFU) per milliliter. Thus, the MIC is not necessarily a bactericidal concentration but rather bacteriostatic (inhibits growth) which means that exposure to such concentrations may not necessarily kill all of the bacteria [5]. In clinical practice, suppression of microbial growth by antibiotics will lead to clinical cure because in most cases, the immune system will eradicate the remaining pathogens [6]. This would mean that in the absence of active immunity, clinical exposure to the MIC does not guarantee prevention of regrowth up on discontinuation of therapy [5]. Another limitation is that it is not uncommon to see infections with high bacterial loads, greater than the 10^5 CFU/mL used in susceptibility testing. Higher bacterial load will certainly require a different degree of antibiotic exposure to achieve sufficient microbiological/clinical response.

Further, the MIC is usually quantified based on exposure to static concentrations over 18–24 h [7] and does not provide any information about possibilities of regrowth after an initial kill or the gradual proliferation of resistant sub-populations of microbes over time.

Given antibiotic concentrations in patients are dynamic, that is within a patient and also variable from patient to patient [8], a simple in vitro concentration–effect relationship described by MIC values cannot truly describe dose–effect relationships. However, as a measure of the potency of antibiotics, it may give a general indication as to whether clinically used dosing regimens will achieve adequate efficacy against a given pathogen. For such purposes, based on the pharmacokinetics of the drug, its pharmacodynamic properties and the likelihood of treatment success, clinical susceptibility breakpoints are defined to classify bacteria as either susceptible or resistant in reference to measured MICs [9]. In this sense, the major utility of MIC is to help select antibiotic agents that are highly likely to result in a positive outcome for the infected patient. However, it is imprecise and unlikely to predict treatment response in many scenarios. This is because it is not uncommon to see treatment failure in the presence of susceptible bacterial pathogens and also, treatment success is observed in cases where the pathogen is labelled resistant [10]. Clearly, the MIC values do not describe many other pharmacological effects of antibiotics that could affect the success of therapy, including the effect of sub-inhibitory concentrations, the extent and rate of bacterial killing, exposure to potentially bactericidal high concentrations during the early phase of therapy (i.e. first 24 h), and persistent inhibitory effects of antibiotics after the end of exposure [11].

2.3 Characteristic Relationships Between Antibiotic Concentrations and Antibacterial Activity

To some extent, the limitations of MIC in relating a static concentration to clinical efficacy can be addressed by characterizing the relationships between the dynamic antibiotic exposure (pharmacokinetics) and antibiotic effects (e.g. microbial killing). In describing these relationships, the MIC should be considered in combination with the exposure of the drug, that is, to relate observed concentrations profiles to the potency of the antibiotic, or MIC.

The pharmacodynamic index of antibiotic classes may differ from one another. These describe the optimal ‘shape’ of the concentration-time curve and can be influenced by the presence of a post-antibiotic effect. Pharmacodynamic bacterial kill characteristics can broadly be described as either concentration-dependent killing or time-dependent killing effect [11, 12]. More specifically, three major exposure–antibacterial activity relationships have been described for antibiotics based on the observation of correlations between antibacterial activity and either the duration of antibiotic exposure relative to the MIC or the magnitude of exposure relative to MIC or the time course of the magnitude of exposure relative the MIC. Accordingly, bacterial killing effects of antibiotics are often described as either time dependent or

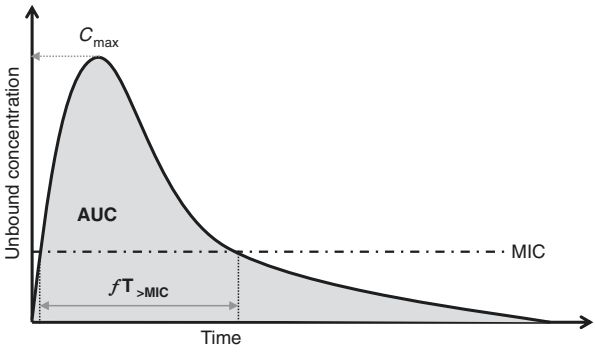

Fig. 2.1 Pharmacokinetic/pharmacodynamic predictors of antibiotic efficacy

concentration dependent [11, 12]. Different parameters that relate time and/or magnitude of exposure to efficacy have been described (Fig. 2.1). The index most predictive of microbiological/clinical response is specific to each class of antibiotics.

2.3.1 Time-Dependent Antibiotics

2.3.1.1 Beta-Lactam Antibiotics

Time-dependent antibacterial action was described for penicillin more than 75 years ago [13]. However, it was not until mid-late 1980s and early 1990s when a more elaborate description of the exposure–response relationships of beta-lactams became available [14, 15]. An example of the later studies is that of Fluckiger et al. [15] which used neutropenic mouse thigh infection model to illustrate that the bactericidal effect of imipenem was dependent on the duration of time concentrations were above the MIC, rather than the peak concentration during a dosing interval. Increasing the concentration of a beta-lactam antibiotic above the MIC will increase the bactericidal effect only up to a few multiples of the MIC, often up to four to five times [12, 15, 16]. Beyond this point, further increases in concentration do not appear to increase the rate or extent of bacterial killing [4]. However, bactericidal action is significantly and consistently correlated with the time the free antibiotic concentration remains above the MIC [12].

Thus, the proportion of dosing interval for which the free drug concentration remains above MIC (% $fT_{>MIC}$) is considered the best parameter that predicts antibacterial effect. The % $fT_{>MIC}$ required for optimal activity of beta-lactams is dependent on the specific drug class and bacteria [12, 17]. However, studies have shown that concentrations may not have to be above the MIC for the entire duration of treatment (dosing interval) [12, 15]. This result is more so when the immune system is functioning and the beta-lactam antibiotic being used has some persistent effects (i.e. post-antibiotic effect or post-antibiotic leucocyte enhancement) against the targeted bacteria [14, 16]. Short exposures of ~20–40% $fT_{>MIC}$ are generally bacteriostatic and prolonged exposures of 40–70% $fT_{>MIC}$ achieve near-maximal

bactericidal activity [12]. For the different classes of beta-lactams, namely carbapenems, penicillins, and cephalosporin, the optimal % $fT_{>MIC}$ associated with bacteriostatic or bactericidal effect are different [17], partly due to differences in their persistent antibiotic effect. Carbapenems exhibit a moderate post-antibiotic effect compared to penicillins and cephalosporins and thus may require lesser exposure (20% $fT_{>MIC}$ for bacteriostatic action and 40% $fT_{>MIC}$ bactericidal action). For penicillins about 30% and 50% $fT_{>MIC}$ achieve bacteriostatic and bactericidal effects, respectively. Cephalosporins have minimal post-antibiotic effects and thus relatively longer exposures of up to 40% and 70% $fT_{>MIC}$ are required for bacteriostatic and bactericidal effects, respectively [12, 17].

The status of host immune function may affect the optimal % $fT_{>MIC}$ of beta-lactams that is required for maximal activity as has been demonstrated by different animal studies [18–20]. In patients with poor immune function, such as neutropenic patients, exposures targeting 40–70% $fT_{>MIC}$ for beta-lactam antibiotics would mean that any residual bacterial sub-populations are exposed to sub-MIC concentrations for 30–60% of the dosing interval. In the absence of a post-antibiotic effect against the target bacteria and also adequate immune function, prolonged exposure of 100% $fT_{>MIC}$ is likely required to achieve maximal bacterial killing [14, 16]. Penicillins and cephalosporins have no significant post-antibiotic effect except their moderate effect against *Staphylococci* [17]. Also for carbapenems which demonstrate a moderate post-antibiotic effect against Gram-negative bacteria, prolonged exposure may be required in the setting of reduced immune function. For example, in febrile neutropenic patients, Ariano et al. [21] found that >75% $fT_{>MIC}$, rather than the traditional target of 40% $fT_{>MIC}$, was required for meropenem to achieve higher rates of clinical response. Another clinical study also has described significantly better bacteriological eradication and clinical cure rates when $fT_{>MIC}$ was 100% [22]. Consequently, 100% $fT_{>MIC}$ is proposed as a prudent target for beta-lactam antibiotics in the immunocompromised and critically ill patient populations [23, 24].

More aggressive exposures of four to five times above the MIC for the entire dosing interval (100% $fT_{>4–5\times MIC}$) have also been proposed in some clinical studies as a means to maximize microbiological/clinical outcomes [23–26]. These targets were based on previous in vitro and clinical observations of better antibacterial activity [27, 28]. For example, the in vitro study by Mouton et al. [27] simulated human-like pharmacokinetic exposures of ceftazidime against *Pseudomonas aeruginosa* and observed that a sustained exposure at or around the MIC is not associated with maximal antibacterial activity. The authors found that the rate and extent of bacterial killing was maximized when concentrations were maintained at or above five time the MIC. Another in vitro study simulating pharmacokinetic exposures for meropenem suggests, higher concentrations achieved by targeting 100% $fT_{>4–5\times MIC}$ may have additional advantage of suppressing selection of resistant subpopulations [29]. Acknowledging that these exposure–effect relationships were noted in the absence of immune activity (in vitro data), these results suggested that at least in neutropenic patients, 100% $fT_{>4–5\times MIC}$ may achieve better outcomes than conventional pharmacodynamic targets. In support of these findings, a retrospective analysis of clinical data from patients with lower respiratory tract infection identified trough concentrations

greater than five times the MIC as a predictor of clinical outcome [28]. Unfortunately, more clinical data comparing the effect of different exposures on clinical outcomes is still pending. However, the accumulating evidence suggest that the conventional targets (40–70 $fT_{>MIC}$) that were extrapolated from rodent models of infection should be carefully re-evaluated, at least in patients with severe infections. Genetic studies have elucidated poor correlation of responses in animal models with the human conditions [30] confirming experts' suggestions that any of these models are incapable of predicting clinical response in human [31]. Therefore, selection of the most appropriate dosing target should be supported by clinical studies.

2.3.1.2 Vancomycin

The glycopeptide vancomycin demonstrates time-dependent bactericidal activity [32]. Unlike the beta-lactams, vancomycin has a dose-dependent post-antibiotic effect that extends up to 2 h at concentrations beyond two to four times the MIC [33]. This could possibly influence the difference in exposure–response relationships relative to beta-lactams even though both exhibit time-dependent activity. Based on data from preclinical and clinical studies, the ratio of the area under the concentration time curve over 24 h (AUC/MIC) is considered as the best predictors of antibacterial activity for vancomycin [34]. A retrospective study by Moise-Broder et al. [35] evaluated 108 patients with lower respiratory tract infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and identified a strong association between AUC/MIC ratio ≥350 and therapeutic success [35]. Accordingly, the most widely accepted dosing guidelines for vancomycin consider AUC/MIC ≥400 as a preferred target to ensure positive infection outcome [36]. The guidelines use trough concentrations of 15–20 mg/L as surrogate for AUC/MIC ≥400 to simplify therapeutic drug monitoring (TDM) guided dose optimization [36]. Nevertheless recent studies, have illustrated that trough vancomycin concentrations are poor predictors of AUC/MIC ratio or clinical outcome, particularly in critically ill patients [37]. For other glycopeptides also, the AUC/MIC ratio has been identified to best correlate with antibacterial activity [34, 38]. For teicoplanin, Matsumoto et al. [39] retrospectively evaluated 46 patients with MRSA and observed a high probability (0.87) of microbiological outcome with AUC/MIC ≥900. Similarly, another study observed a relatively higher AUC/MIC ratio of 897.6 ± 71.7 in patients cured with teicoplanin therapy compared to ratio of 652.9 ± 83.4 in those with treatment failure [40].

2.3.1.3 Linezolid

Linezolid exhibits time-dependent antibacterial activity and a minimal to modest post-antibiotic effect [41]. Similar to beta-lactams, increasing linezolid concentrations above the MIC does not result in increased antibacterial activity. An in vivo study in mice by Andes et al. [41] identified AUC/MIC as best predictor of efficacy

against *Streptococcus pneumoniae* compared to both $fT_{>MIC}$ and C_{max}/MIC (R^2 = 82%, 57%, and 59%, respectively). However, both AUC/MIC and $fT_{>MIC}$ were comparable in predicting efficacy against *Staphylococcus aureus* (R^2 = 75% for both). The importance of $fT_{>MIC}$ to maximize efficacy of linezolid has also been described in a rabbit model of endocarditis although this study did not compare the different PK/PD ratios [42]. In seriously ill patients, a retrospective evaluation by Rayner et al. [43] found a high correlation of both AUC/MIC and $fT_{>MIC}$ with microbiological and clinical cure. The authors also noted a high degree of association between $\%fT_{>MIC}$ and AUC/MIC; AUC/MIC values in the range of 80–120 were associated with high success rates, as were a $fT_{>MIC}$ of 85–100% [43]. Thus, based on the available evidence, both AUC/MIC ratio of 80–100 and a $fT_{>MIC}$ greater than 85% are considered as dosing targets [44].

2.3.1.4 Tetracyclines

There is generally limited data on the pharmacodynamics of tetracyclines compared to other drugs such as beta-lactams [45]. Although often classified as time-dependent antibiotics, the time of exposure above MIC appears less predictive of antibacterial activity and the AUC/MIC ratio appears the best PK/PD index for most tetracyclines [45]; this may be attributable in part to the moderate to prolonged post-antibiotic effect of tetracyclines [46, 47]. In critically ill patients, tigecycline is a commonly used glycylcycline (tetracycline) in those patients with multi-drug-resistant infections. It exhibits time-dependent bactericidal activity against different organisms [48, 49] and can produce prolonged post-antibiotic effects (about 9 h against *Streptococcus pneumoniae* for example [47]). Analysis of data from patients with complicated skin and skin-structure infection identified an AUC/MIC ratio of 17.9 as a breakpoint above which the probability of microbiological and clinical cure was maximized [46]. On the other hand, analysis of data from patients with complicated intra-abdominal infection identified an AUC/MIC breakpoint of 6.96 [50].

2.3.2 Concentration-Dependent Antibiotics

2.3.2.1 Aminoglycosides

Aminoglycosides exhibit concentration-dependent killing that is largely independent of the duration of exposure, i.e. increases in concentration are associated with an increased rate of killing. Furthermore, with sufficiently high concentrations, prolonged exposure is not necessary because the bacteria die in a short period of time and/or stronger persistent antibiotic effects are achieved from the initial 'brief' exposure to high concentrations [51, 52]. The duration of post-antibiotic effect may be variable, usually from 2 to 4 h at concentrations observed clinically and may possibly extend up to 8 h after the drug concentrations become undetectable [53].

Generally, maximal killing is thought to occur at a concentration of at least about eight to ten times higher than the MIC [53, 54]. Furthermore, peak concentrations (C_{max}) greater than or equal to ten times the MIC correlate well with favorable outcomes and therefore C_{max}/MIC $\geq$ 10 is used as the conventional dosing target for aminoglycosides [44, 54]. However, when exposure is suboptimal (C_{max}/MIC < 10), the duration of exposure in addition to concentration is likely to influence antibacterial activity; thus, the product of concentration and time (which is area under the concentration-time curve, AUC) is important to relate exposure to antibacterial activity [51]. The AUC/MIC ratio correlates well with antibacterial effect. Indeed there is a co-variance between C_{max} and AUC when administered as intermittent infusions, and the association of both AUC/MIC and C_{max}/MIC with antibacterial activity has been described [14, 55]. In an animal infection model (murine thigh model), an AUC/MIC ratio in the range of 80–100 has been shown to produce maximal aminoglycoside effects [14].

2.3.2.2 Quinolones

Quinolones exhibit concentration-dependent antibacterial activity. Both C_{max}/MIC and AUC/MIC ratio correlate well with efficacy [12, 56]. For instance, a clinical study with levofloxacin by Preston et al. [57] suggested C_{max}/MIC ratio as the best predictor of efficacy with maximal clinical cure rate (99%) and microbiological cure rates (100%) achieved when the ratio is greater than 12. However, there was significant correlation of AUC/MIC with C_{max}/MIC, and for most quinolones, AUC/MIC is the recommended ratio. The minimum ratio required to ensure optimal outcomes may be variable depending on the specific agent, the etiologic bacteria, and patient's conditions. For the most studied ciprofloxacin, C_{max}/MIC ratio >10 is considered optimal [56, 58]. The study by Forrest et al. [59] showed that AUC/MIC >125 of ciprofloxacin is associated with optimal microbiological and clinical outcomes in the treatment of severe infections caused by Gram-negative bacteria. At AUC/MIC ratios <125, microbiological and clinical cure rates for ciprofloxacin were poor (26% and 42%, respectively) compared to when AUC/MIC > 125 (86% and 82%, respectively). Against bacteraemia caused by *Enterobacteriaceae*, Zelenitsky et al. [60], suggested higher magnitude of exposure (AUC/MIC > 250) may be necessary for maximize microbiological outcome. On the other hand, lower exposure may suffice for eradication of some Gram-positive bacteria. For example, an AUC/MIC ratio in the range of 32–44 was shown to achieve maximal killing for levofloxacin and ciprofloxacin in an in vitro infection model of *Streptococcus pneumoniae* [61]. Lower ratios have also been reported for other quinolones. For grepafloxacin for example, an AUC/MIC > 50 was associated with maximal clinical effect in the treatment of bronchitis [62]. In general, there is no well-defined universal dosing target although an AUC/MIC ratio of about 100 and C_{max}/MIC ratio of about 10 are considered prudent targets for most quinolones [63]. Most of the contemporary literature refers to AUC/MIC ratio >125 based on the Forrest et al. study [44, 59].

2.4 The Application of Antibiotic Pharmacodynamics into Clinical Practice

The knowledge of antibiotic pharmacodynamic properties that characterize the exposure–response relationships associated with maximal clinical outcomes is essential not only to design dosing regimens for new agents and indications, but also for optimization of therapy in individual patients [64]. Such knowledge can be combined with pharmacokinetic data of antibiotics to design and optimize dosing regimens for clinical use. A robust design of dosing regimens is possible through the application of population pharmacokinetic modelling and Monte Carlo dosing simulation. Population pharmacokinetic modelling describes the relationship between dosing regimens and observed drug exposure (concentration) to a greater degree of precision than traditional modelling, in part because it can consider clinical covariates specific to patients [65]. This information can then be analysed together with pharmacodynamic characteristics (index) and susceptibility profile (MIC distribution) of target pathogenic bacteria using Monte Carlo dosing simulations. In this way, the simulations will identify the dosing regimen that is highly likely to achieve target PK/PD exposure for different clinical conditions (e.g. renal function) and possible MIC values encountered in clinical practice [65]. The application of PK/PD modelling also extends to the development of novel dosing regimens that can suppress the emergence of resistance [66]. The traditional dosing regimens are mainly based on in vitro bactericidal activity or some subjective clinical end points and rarely account for suppression of emergence of resistance. Advanced PK/PD analysis can be used to model suppression of resistance as an end point to enable design dosing regimens that can prevent selective amplification of resistant sub-population during antibiotic therapy [1]. Another important application is to help guide individualization of antibiotic therapy in different patient populations. In the critically ill patients in particular, the interests in individualized therapy guided by TDM is increasing due to the accumulating evidence of variable pharmacokinetics that results in unique dosing requirements in each patients [64]. Given the lack of an objective end point for titration of antibiotic doses, PK/PD ratio are the best available surrogate targets for antibiotic efficacy that should be used to guide optimized dosing regimens [48, 67].

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