Pharmacodynamic Evaluation: Infectious Diseases

Smita Bhuyan, Sebastian Felgner, Dino Kocijancic, and Vinay Pawar

Contents

S. Bhuyan
Department of Microbial drugs, Helmholtz Center for Infection Research, Braunschweig, Germany
e-mail: Smita.Bhuyan@helmholtz-hzi.de

S. Felgner • D. Kocijancic
Department of Molecular Immunology, Helmholtz Center for Infection Research, Braunschweig, Germany
e-mail: Sebastian.Felgner@helmholtz-hzi.de; Dino.Kocijancic@helmholtz-hzi.de

V. Pawar (✉)
Department of Molecular Immunology, Helmholtz Center for Infection Research, Braunschweig, Germany

Institute of Immunology, Medical School Hannover, Hanover, Germany
e-mail: vinay.pawar@helmholtz-hzi.de

F.J. Hock, M.R. Gralinski (eds.), *Drug Discovery and Evaluation: Methods in Clinical Pharmacology*,
https://doi.org/10.1007/978-3-319-56637-5_53-1

Abstract

The past decades have witnessed an rise in the number of multidrug resistant bacteria, concurrent drug failures, and declining cure rates of several fatal bacterial infectious diseases. This has culminated in evaluation of existing drug regimens. An extensive evaluation of pharmacodynamics and pharmacokinetics of drugs and its application for drug regimen selection has become the cornerstone for successful antibiotic therapy against fatal bacterial infections. Recent years have witnessed an upsurge in the development of diverse models for preclinical and clinical pharmacokinetic-pharmacodynamic (PK-PD) analysis and robust simulation methods. Integration of infection microbiology knowledge and PK-PD analysis in an appropriate model can lead to optimal drug regimens against several acute/chronic bacterial infections. The present chapter provides a comprehensive overview of different models citing their advantages and limitations, along with simulations for optimizing treatment regimens. Furthermore, it describes the applications of pharmacodynamic models for treatment of bacterial infections and, finally, the pathophysiological conditions leading to treatment failures and strategies to overcome them.

Introduction

Rise of multidrug resistant (MDR) bacterial strains and long-term persistence of bacteria in chronic infections pose a critical challenge for public health. Immediate treatment regimen using currently available antibiotics or new formulations is of urgent need. Appropriate choice of antibiotics, doses, and treatment is absolutely essential for optimal therapy. Therefore, large numbers of antibiotics or antibiotic combinations are presently under investigation in clinical trials to treat a variety of acute and chronic fatal infectious diseases. For appropriate selection of antibiotics, it is imperative to gather the pharmacokinetic/pharmacodynamic (PK/PD) information using the different models (Schuck et al. 2005). An excellent background information on the dose-exposure relationship – pharmacokinetics (PK) – and the exposure-response relationship – pharmacodynamics (PD) – can lead to decreased antimicrobial resistance (AMR) and focused clinical trials with improved efficacy and cost-effectiveness. A quantitative representation of the dose–concentration–response relationship provides information that can be utilized to predict the level of response corresponding to a particular drug dose. Models based on different mathematical approaches can be used to describe such relationships. The mathematical relationship is determined by whether single dose or the steady-state measurements are carried out (Pérez-Urizar et al. 2000). Profound knowledge on PK/PD is bifaceted and would help to establish a computable relationship between dose and dosing regimen as well as potency and undesirable drug effects. Additionally, simulating the drug clearance profiles obtained from animal/human studies in different in vitro PK/PD model could lead to a detailed characterization of efficacy of antimicrobials (Vaddady et al. 2010). Meibohm and Derendorf (2002) provide a comprehensive overview on pharmacokinetic/pharmacodynamic studies in drug development. Various studies have been initiated involving extensive PK/PD modeling for a variety of infectious diseases and can be beneficial to implement strategies for successful disease elimination. Recent research in the development of powerful models, statistically robust software tools, and the integration of

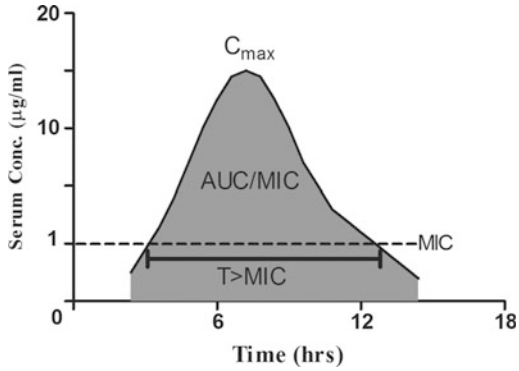

Fig. 1 Pharmacodynamic indices of antibiotics (MIC: Minimum inhibitory concentration; C_{max}: Maximum/peak antibiotic concentration achieved by a single dose of antibiotic; T > MIC: time for which the drug concentration remains above the MIC value of the infectious agent during a given dosing period; AUC/MIC: ratio of the area under the plasma concentration time curve to the MIC of the infectious agent)

pharmacokinetic-pharmacodynamic knowledge has led to excellent decision-making and development of effective dosage regimens for various infectious diseases. In the present chapter, we describe in brief terminologies, methods, models, and issues associated with pharmacodynamics of bacterial infectious diseases.

Pharmacokinetics and Pharmacodynamics

The term pharmacokinetics refers to the relationship between drug dosing and changes in the drug concentration over time in the body (Udy et al. 2008; Nielsen and Friberg 2013; Mouton 2014). The important PK properties include: (i) Drug clearance: Volume of plasma effectively cleared of the drug from each eliminating organ/tissue per unit time (CL); (ii) Volume of distribution: Apparent volume of fluid containing the total amount of administered drug, at the same concentration as that in plasma (Vd); (iii) Peak concentration achieved by a single dose (C_{max}); (iv) Lowest concentration during the dosing period (C_{min}); (v) Area under the plasm concentration-time curve (AUC); and (vi) Plasma half-life ($T_{1/2}$). These PK parameters have a profound influence on the PD parameters of a drug.

The term pharmacodynamics refers to the biochemical and physiological effect of the drug. In case of an infection, it refers to the ability of the drug to either inhibit or abolish the growth of a causative organism. In other words, antibiotic pharmacodynamics integrates the complex relationship between the susceptibility of an organism and the patient pharmacokinetics. The PD indices most correlated to bacteriological eradication are: (i) Time for which the drug concentration remains above the MIC value of the infectious agent during a given dosing period (T > MIC); (ii) Ratio of maximum/peak antibiotic concentration (C_{max}) achieved by a single dose of antibiotic to the MIC of the infectious agent (C_{max}/MIC); and (iii) Ratio of the area under the plasma concentration time curve to the MIC of the infectious agent (AUC_{24}/MIC) (see Fig. 1). The prefix, f, is sometimes introduced to indicate that the free, unbound fraction of the drug was used in the calculations. When no subscripts are included, it is assumed that the calculations of AUC and T > MIC were based on a 24-h interval at pharmacokinetic steady-state conditions (Mouton et al. 2005; Nielsen and Friberg 2013; Mouton 2014).

MIC values are usually determined using either the agar dilution or broth microdilution methods as specified by the CLSI guidelines. Typically, broth dilution methods use liquid medium in which a specified bacterial inoculum [5×10^5 colony-forming units (CFU)/ml] is exposed to a constant antibiotic concentration generally over an incubation period of 16–20 h. The MIC is defined as the lowest drug concentration that completely inhibits visible growth of the microorganism. The antibiotic concentrations chosen for MIC determinations are typically twofold dilutions of the antibiotic (e.g., 0.5, 1, 2, and 4 concentration units). Depending on the total volume used, the method is either termed macrodilution (1–2 ml) or microdilution ($\leq$ 500 μl). For agar diffusion methods, an agar plate is inoculated with the target organism and the antibiotic diffuses from a disk or a strip into the agar. The results are generally read off after 24 h. An E-test is a semiautomated agar diffusion test, which contains

a strip preimpregnated with an exponential gradient of the antibiotic (Nielsen and Friberg 2013; Wayne 2014). Cumulative fraction of response (CFR) can be calculated using the discrete distribution of MIC values. The AUC_{24} can be obtained directly from previously published literature. In other cases, it can be calculated as follows: $AUC_{24} = Dose/CL$.

A particular efficacy index better corelates to a given antibiotic/group of antibiotics (Zhanel 2001). Though MIC values are the most studied pharamcodynamic parameter, it gives incomplete information regarding activity of the antibiotic over time. Hence, the parameters mentioned above are most widely used as a measure of the PD index. The PK/PD index for a certain drug-bacteria combination is determined by plotting the value of an efficacy endpoint versus the magnitude of each of the three PK/PD indices.

It is evident that the pharmacodynamic properties directly depend on the infectious agent, severity of infection, phase of infection, and the MIC value or resistance pattern of the pathogen. This clearly indicates that the local MIC distribution must be taken into consideration in order to achieve the maximum likelihood of a successful antibiotic treatment regimen for an infectious disease (Canut et al. 2012). Extensive and accurate analysis of PD properties is of foremost importance in determining sustained in vivo efficacy of antimicrobial agents.

Optimization of Drug Dosage Regimen

Determination of PK/PD parameters is the first step in optimization of dose regimen for treatment of infectious diseases. They increase the likelihood of disease eradication and minimize the probability of exposure-related toxicity (Scaglione and Paraboni 2006). Once the population PK model has been developed and the PD parameters determined, they can be transferred to models to design dosing regimens that aim to achieve the recommended PD values affecting antimicrobial response. Monte Carlo simulations have been widely used to reliably predict the probability of achieving the PD parameters in case of antimicrobials. Monte Carlo simulation is a technique that integrates an agent's in vitro potency distribution with the pharmacokinetic profile to achieve a specifically targeted antimicrobial exposure (Nicolau 2003). Laboratory based in vitro or animal data, preclinical, or clinical PK/PD data are used in Monte Carlo simulations to obtain initial PK/PD breakpoints. The MIC distributions of the target populations based on this values are then determined. The robustness of the Monte Carlo simulation, target population, and dose adjustments are then made to determine the final PK/PD breakpoints for disease eradication (Mouton et al. 2012).

Pharmacokinetic and Pharmacodynamic (PK/PD) Models

The determination of PK/PD indices can be carried out using in vitro pharmacodynamic models (IVPM) or animal models. Ethical issues restrict the use of clinical subjects to evaluate PK/PD relationships in the field of anti-infectives. Hence, IVPM are increasingly used to determine PD indices to be utilized as an aid to dose selection and optimization for treatment of infectious diseases. Both preclinical and clinical PK/PD studies are then incorporated into simulations to determine the PK/PD breakpoints for antimicrobials (Mouton et al. 2012).

The in vivo or in vitro kill curves (described below) are generally used to build models to estimate PD parameters. It is imperative that different dosage schemes or concentrations of the anti-infective agent are applied in a PK/PD study. Placebo doses are mandatory and it is essential that varying dose intervals, multiple doses, and information on kinetics of absorption, dissimilation, and excretion are incorporated to guarantee the success of a model. PD parameters could be estimated by using nonlinear regression analysis, and it is absolutely crucial that the model takes all possible survival curves of the organisms under study into account (Czock and Keller 2007).

In Vitro *Models*

The PD in vitro models are broadly divided into static and dynamic models based on whether the concentration of the tested drug is constant or varying over a period of time. The static models usually consist of determination of MIC or continuous monitoring in shake flasks (Vaddady et al. 2010). Static in vitro time-kill studies provide information on killing capacity of a drug and the probability of emergence of antimicrobial resistance, although determination of MIC would be sufficient in clinical practice to determine the efficacy of antibiotics. However, it is of minimal use, as it represents an end-point detection method, therefore, giving no information on pharmacodynamic changes taking place over a period of time. Hence, static models based on MIC determination are of little relevance in development of dosing recommendations. It is therefore imperative that data should be collected using dynamic situations (Czock and Keller 2007; Gloede et al. 2010; Tängdén et al. 2017). Dynamic in vitro models permit continuous adjustment of drug concentrations to mimic the required in vivo PK profile. Target microbes are exposed to the antimicrobials in vessels that are perfused continuously with media to simulate actual conditions during an infection. Sampling to determine PK/PD properties can be done repetitively. This enables the study of various parameters like kill kinetics, drug concentrations, and emergence of resistance. A large number of dynamic models are in vogue, which includes dilution models (i.e., direct contact between infectious agent and the drug) or diffusion/dialysis models (i.e., indirect drug bacteria contact). A detailed description of all models is beyond the scope of this chapter. However, for a comprehensive reading the reader can refer to the published review by Michael et al. 2014, Vaddady et al. 2010, and Czock and Keller 2007. Different models can be used to mimic drug efficacy in humans. These include biofilm models, models for human immune system, multicompartment models, or models to study disease conditions such as otitis media, chronic pneumonia, cystic fibrosis, or tuberculosis (Gloede et al. 2010; Parra-Ruiz et al. 2010; Pawar et al. 2014; Lorenz et al. 2016). In vitro models have some advantages over in vivo animal models as they provide more flexibility and adaptability to the researcher and are comparatively less expensive and resource-intensive. However, they face certain disadvantages like the need of controlled environments and the risk of contamination of the culture vessel. Neither can these models completely mimic all in vivo conditions like the immunological response to and the virulence nor the metabolic behavior of a pathogen. Furthermore, the bacterial growth limits the analysis as it is much faster in vitro than in vivo (Gloede et al. 2010).

In Vivo *Models*

Evaluation of antibiotic therapy using animal models is essential for the evaluation of the therapeutic efficacies of antimicrobial agents. The advantages of animal models over in vitro models are enormous. Animal infection models allow to study drug efficacy with regard to virulence or antimicrobial resistance of an organism. Furthermore, they also relate to the role of the host immune system in response to the infection itself. Thus, it enables to study the antimicrobial effects at the exact site of infection and can mimic/simulate the conditions in humans and thereby human PK/PD profiles in contrast to in vitro models. However, the results from animal models must be interpreted with caution since the antimicrobial PK profile may turn to be extremely different from human subjects. Rodent, rabbit, or more recently porcine hosts are most predominantly used in PK/PD studies. Mice and rats are preferred due to low cost and handling ease in comparison to other animals (Tängdén et al. 2017). Establishment of infection may require the animals to be rendered neutropenic by prior administration of an immunosuppressant like cyclophosphamide in order to appropriately compare these results to those that might be expected in humans. Murine tumor models have been used to study the efficacy of antimicrobials in patients inflicted by cystic fibrosis and burn wound infections caused by *Salmonella* and *Pseudomonas aeruginosa* (Crull and Weiss 2011; Pawar et al. 2015). Other common

models are the murine thigh infection models, pneumonia model, peritonitis/bacteremia models, skin and soft tissue infection model, meningitis models, and endocarditis models (Andes and Craig 1998; Nielsen and Friberg 2013; Rybtke et al. 2015).

Mathematical Approach to Modeling

PK-PD modeling is the mathematical description of the relationships between PK and PD. The choice of the model and the underlying mathematical equation can depend on whether the system under study is in a steady state or an unsteady time-dependant phase. Steady state refers to a condition in that, the concentrations of the active form of the drug at the site of action are constant and the PD parameters are independent of time as in case of long-term intravenous infusions. These models assess how a bacterial culture responds to a constant environment and fixed antibiotic exposure. The growth of the infectious agent is limited by nutrition, space, aeration, and toxic metabolites. When the concentration and response data are in phase or steady state, basic models such as fixed-effect, linear, log-linear, E_{MAX}, and sigmoidal E_{MAX} models are used. When the kinetics and response are out of phase time-variant, pharmacodynamic models which are more complex are applied. These dynamic models utilize time kill curves, where microbial killing is dependent on both time and varying antibiotic concentration. Models can also be referred to as mechanistic, semimechanistic, or nonmechanistic (Pérez-Urizar et al. 2000; Vaddady et al. 2010). A mechanistic model is a model which takes into account the known or hypothesized mechanisms of behavior of an infectious agent. The parameters are in accordance with PK, physicochemical, biophysical, physiological, and pathophysiological principles of the system under consideration and relate drug concentrations to their observed effect. Nonmechanistic models do not take the underlying biological mechanisms into consideration (Vaddady et al. 2010; Felmlee et al. 2012). Semimechanistic models are those in which although mechanistic knowledge is utilized, but are far less complex compared to the mechanistic models. These are also referred to as mechanism-based models. In general, mechanism based PK-PD models contain equations describing microbial growth, effect of antimicrobial drug, and variable drug concentrations (the microorganism submodel, the antimicrobial submodel, and the pharmacokinetic submodel, respectively) (Czock and Keller 2007; Nielson et al. 2011). The final choice of PK/PD model is made based on the pharmacology of the drug and system. Once a model is defined, unknown parameter values are typically estimated using nonlinear regression techniques contained within computer programs such as WinNonlin (Pharsight, Mountain View, CA), Kinetica (Innaphase, Philadelphia, PA), and ADAPT II (Biomedical Simulations Resource, Los Angeles, CA) (Mager et al. 2003). Below we describe some of the commonly applied in vitro models used to rationalize the selection of antibiotics based on the PK/PD chratersitics.

Linear Model

This model is based on the assumption that a direct proportionality between drug concentration and its effect exists (1).

$$E = S * C + E_0 \tag{1}$$

Where S is the slope, E_0 the intercept. Pharmacodynamically, S represents the effect induced by one unit of C and E_0 represents the value in the absence of the drug. The parameter estimations are carried out by linear regression, and this model applies to measured effects with physiological baselines such as blood glucose or blood pressure levels.

Log-Linear Model

Log linear model takes into consideration that if the effect of concentration is hyperbolic, the log-concentration-effect relationship would roughly be linear in the range of 20–80% of maximal effect. This can be considered as a derivation of

Eq. 1 where S represents the change elicited by one unit of log C.

$$E = S * \log C + E_0 \tag{2}$$

E_{MAX} Model (Hill Equation)

This PK-PD model is extensively used to characterize a wide range of pharmacological effects. The model describes the relationship between concentration of a drug and its elicited effect relationship over a wide range of concentrations. Equation 3 assumes that the plasma drug concentration is in rapid equilibrium with the effect site.

$$E = \frac{E_{max} * C}{EC_{50} + C} + E_0 \tag{3}$$

E_{MAX} describes the maximum effect possible, EC_{50} the concentration required to produce 50% of E_{MAX}, and E_0 is the basal value E. This equation is also referred to as the Hill equation.

Sigmoidal E_{MAX} Model

This model is a derivate of the E_{max} model and allows convenient fitting of different types of PK/PD data. This is the most frequently used model due to the fact that the function asymptotes to an upper limit of stimulation or inhibition by a particular drug on the target infectious agent. Here, γ represents the steepness of the curve also referred to as sigmoidicity factor. $\gamma > 1$ for steep curve, $\gamma < 1$ for a smooth curve, and $\gamma = 1$ for a hyperbolic curve, while other parameters are same as in the E_{max} model.

$$E(t) = E_0 + \frac{E_{max} * C(t)^{\gamma}}{EC^{\gamma}{}_{50} + C(t)^{\gamma}} \tag{4}$$

The Bacterial Submodel

The simplest mechanism-based is the bacterial submodel and involves a single bacterial compartment. It is adapted from a model developed initially for anticancer agents. The model has a first-order rate constant for bacterial multiplication (K_{growth}) and a first-order rate for the death of the bacteria (K_{death}) as shown in Eq. 5.

$$\frac{dB}{dt} = k_{growth} * B - k_{death} * B \tag{5}$$

The equation accounts for observed exponential growth of bacteria as seen in the time-kill curve experiments in absence of drug (control experiments) as the net result of the growth rate and cell death.

The Logistic Growth Model

Most of the modern day antimicrobial models are based on the logistic growth model, which can be used to describe in vitro bacterial population dynamics. It is a very simple yet useful model and is based on the growth rate (r) and the carrying capacity of the environment (K). N is the bacterial population and N_0 the initial bacterial count. It is given by the Eq. 6

$$\frac{dN}{dt} = r\left(1 - \frac{N}{K}\right)N \tag{6}$$

The logistic growth model is sometimes modified to include the effect of the drug with a new equation as follows

$$\frac{dN}{dt} = k_{growth}N\left(1 - \frac{N}{N_{max}}\right) - f_{death}\,(drug) \tag{7}$$

Where f_{death} (drug) is a function that accounting for death of the bacteria due to the antibiotic and N_{max} is the maximum number of bacteria.

Pharmacokinetic-Pharmacodynamic Model

Pharmacokinetic-pharmacodynamic model is a combination of the bacterial submodel and the

PK model. The combined equations characterize the effect that the antibacterial drug has on the bacteria. The effect could be hypothesized to either inhibit the bacterial growth rate or enhance the bacterial killing rate.

$$\frac{dB}{dt} = k_{growth} * \left(1 - \frac{E_{max} * C^{\gamma}{}_{(t)}}{E\, C^{\gamma}{}_{50} + C^{\gamma}{}_{(t)}}\right) * B - k_{death} * B \quad (8)$$

Apart from these models, several other models and variants of the basic model or combinations of model are in use for PK/PD analysis. Detailed descriptions of various models have been described by different researchers. For further reading the reader can refer to the publications from Dayneka et al. (1993), Sharma and Jusko (1998), Czock and Keller (2007), Vaddady et al. (2010), Felmlee et al. (2012), and Mouton (2014).

Simulation Aided PK/PD for Infectious Diseases

Computer simulations have been widely used in diverse fields. In the field of pharmaceuticals, it is used in the discovery of new drugs, optimizing chemical processes, and, most recently, in designing clinical studies for the treatment of several acute and chronic diseases. Molecular modeling is the best-known example of simulation in drug discovery. In recent years, Monte Carlo simulation of clinical trials is the method of choice for appropriate dosing selection (Mouton et al. 2012). Monte Carlo is a different kind of simulation than the traditional ones by the fact that its model parameters are treated as stochastic or random variables, rather than as fixed values. In other words, the variability of the parameters is included in the model and the long-term impact of that variability is examined. Furthermore, by definition, Monte Carlo simulation is a random number generator that incorporates distributions of variability around PK parameters in a population to simulate drug concentration-time profiles for a large number of conjured individuals. Thus, instead of practically studying different concentrations over different periods of time, Monte Carlo simulation allows intensive analysis of outcome of different trails, even when data from single doses are coupled to the simulation (Crandon and Nicolau 2011).

How is a Monte Carlo simulation performed? First, the underlying structural pharmacokinetic model for the given antimicrobial agent against a particular infection is defined. This can be a done in a single compartment, 2-compartment, or multiple compartment models. One-compartment model assumes that elimination is first order and that PK parameters are independent of the dose and that there is immediate distribution and equilibrium of the drug throughout the body. However, 2-compartment model does not follow linear PK and comprise of absorption, along with the distribution and covariance between the pharmacokinetic parameters in the model. Next, a dose administration model and a compliance model are defined. This includes the number of patients being administered with a particular dose, number of patients who skipped the dose, and other such criteria related to the intake of the drug. Once the conceptual model is defined, it is translated into a computer code using different software programs like MATLAB, GAUSS, or the Pharsight Trial Designer. Once this is done, it is verified for accuracy and the simulation run. The number of replications of the simulation must be defined at the start. The number of replicates depends on the nature of analysis. Larger replicates are used when the variability of an outcome is to be studied. This is followed by the generation of a sequence of independent random numbers having a given distribution with finite mean and variance. Depending on the pharmacokinetic profile, the pharmacodynamic end point is simulated. The end point is assessed again after few days of treatment. Once the inputs are defined and the simulation is performed, the outputs are examined in the form of graphical results or summary statistics of a variable or the relationship between variables. This general protocol is used for simulating any drug to be used in clinical practices. Some of the important components among others to be defined in a clinical trial simulation include structural pharmacokinetic model, dose administration

model, distribution and covariance of pharmacokinetic parameters, link between PK and PD, pharmacodynamic model, disease progression model, relationship between pharmacodynamic effect, and outcome and survival model (Bonate 2001).

Pharmacodynamics of Antibiotics for Infectious Diseases

Gram-Positive Bacterial Infections

Large numbers of fatal infections are caused by various Gram-positive bacteria. For instance, *Staphylococcus aureus* is responsible for a wide range of infections including hospital acquired bacterial pneumonia, ventilator associated bacterial pneumonia, complicated skin and skin structure infections, and severe bacteremia. The most common drug of choice for such concurrent *S. aureus* bacteremia is Telavancin. Telavancin is a bactericidal lipoglycopeptide, which is also effective against methicillin susceptible and resistant *Staphylococcus aureus* (MSSA & MRSA) (Wilson et al. 2017). Additionally, Vancomycin and Linezoid have been widely used for the treatment of infections caused by MRSA. Over the years, most bacteria have evolved resistance mechanisms and hence it is imperative that timely preclinical and clinical studies are undertaken to evaluate the efficacy of such antibiotics. The underlying PK data and MIC can either be retrieved from data sets or databases or calculated for the infection under study. In an interesting study, Canut et al. (2012) have evaluated the usefulness of Daptomycin, Tigecycline, and Linezolid for the treatment of MRSA infection and compared it with vancomycin in four western European countries. They have estimated the probability of achieving the recommended value of AUC_{24}/MIC ratio using Monte Carlo simulation technique with 10,000 subjects. They calculated the fC_{min} using Eq. 9.

$$fC_{min} = \frac{f_u D}{V_d} \frac{e^{\frac{0.693}{t_{1/2}} * \tau}}{1 - e^{\frac{0.693}{t_{1/2}} * \tau}} \tag{9}$$

where f_u is the free fraction of drug in plasma, D the administered drug dose, V_d the volume of distribution,and $t_{1/2}$ the half-life elimination. For the analysis, steady-state exposure was evaluated for different intravenous drug dosing regimens, MIC values fixed at a particular concentration and then the probability of target attainment (PTA) calculated from these parameters. A regimen that achieved >90% CFR against bacterial population is considered as optimal. Their studies indicate that 2 g, 3 g, and 4 g daily of vancomycin seem be adequate in Belgium, Spain, and United Kingdom/Ireland, respectively. CFR obtained with 50 mg Tigecycline every 12 h was higher in Spain than in Belgium and the United Kingdom/Ireland. Additionally, a minimum of 8 mg/kg Daptomycin is necessary in United Kingdom/Ireland, while 4 mg/kg may be sufficient in Spain. The authors concluded that differences in the susceptibility of MRSA strains among countries may be responsible for differences in the antibiotic dose selection and suggest use of local MIC values to achieve success of a PK/PD model to achieve eradication of disease condition. As part of preclinical study, the effect of antimicrobials against infections caused by *Staphylococcus aureus* and *S. epidermidis* was evaluated in a novel in vitro PK/PD model of bacterial biofilm by Hall Snyder et al. 2015. Some persistent bacteria that can cause chronic infections are resistant to antibiotics due to their inherent property to form biofilms. Biofilms shield the bacteria against antibiotics and thereby posing an imminent threat especially in chronically infected or immunocompromised patients. Biofilm forming bacteria are difficult to eradicate from severe infection sites such as lungs of cystic fibrosis patients. They are equally notorious and resistant to eradication when associated with medical implants (Taraszkiewicz et al. 2013; Sanchez et al. 2013). Hence, this model by Hall Synder and coworkers could be further extended to study antimicrobials targeting other Gram-positive biofilm forming bacteria. The in vitro model consists of a CDC biofilm reactor (CBR) modified to run PK/PD and simulating human PK in order to evaluate the in vitro activity of antimicrobials. Biofilm conditioning is performed prior to initiation of drug therapy

initiation followed by continuous flow with peristaltic pumps in specific media. Upon completion of conditioning and continuous flow phases, boluses of antibiotics are injected into the reactor. Free drug concentrations were used, and simulated regimens were included. The model was used to study effect of high doses of Daptomycin versus Vancomycin either alone or in combination with Clarithromycin or Rifampin to treat infections caused by *Staphylococcus* species. Biofilm-embedded cell concentrations (mean and standard deviation in CFU/cm^2) were then computed. Time kill curves were plotted to determine total reduction in CFU counts and the therapeutic enhancement of combination regimens was calculated statistically. Pharmacokinetic samples were obtained through the injection port of each model. PK and PD parameters to verify target antibiotic concentrations were obtained at the same time points. PK parameters were estimated using routine procedures. The half-life ($t_{1/2}$), area under the curve (AUC), and fC_{max} were determined by the trapezoidal method utilizing software tools like the PK Analyst software (Hall Snyder et al. 2015). It is essential to maintain appropriate growth controls and replicates for any set of antibiotics to be tested in such model systems. Their study highlights that combinations of Daptomycin + Rifampin and Vancomycin + Rifampin were the most effective against biofilm-associated staphylococcal infections. Daptomycin + rifampin with the best activity emerged as a promising drug combination that could be used as a future regimen to treat resistant biofilm-associated staphylococcal infections. A similar but novel in vitro biofilm model has also been developed by Parra-Ruiz et al. in 2010. The authors used their model to assess the in vitro activities of several antimicrobials alone or in combination against *Staphylococcus aureus* isolates. Daptomycin, Vancomycin, and Moxifloxacin were evaluated either alone or in combination with Clarithromycin or Rifampin. This study was also performed using an in vitro model, which consisted of a CDC biofilm reactor wherein the concentrations of biofilm-embedded bacteria were computed and plotted to graph time-kill curves. The results clearly indicate that combinations of Daptomycin, Moxifloxacin with Clarithromycin were the most effective ($P < 0.01$) regimens. This may represent future regimen to treat persistent infections of biofilm forming Gram-positive bacteria such as *S. aureus* and *Streptococcus pneumoniae*.

Gram-Negative Bacterial Infections

Antimicrobial resistance in Gram-negative bacteria is increasing at an alarming rate. Additionally, the lack of new antibiotics limited treatment option to reappraise of currently available antibiotics. Cefepime, Ceftriaxone, Imipenem, and Piperacillin-Tazobactam antibiotics have been extensively used worldwide during the last three decades to treat acute/chronic hospital acquired infections. These antibiotics are resourceful in treatment of infections caused by Gram-negative bacteria like *Pseudomonas, Acinetobacter, Klebsiella, Enterobacter, Serratia, Stenothermophilus, Proteus,* and *Citrobacter* (Zervos and Nelson 1998; Drago and De Vecchi 2008; Saltoglu et al. 2010). In the past decades, antibiotic resistance is on the surge, and PK/PD modeling based on Monte Carlo simulations can be used reliably to predict the efficacy of antimicrobial regimes against an array of Gram-negative bacteria. This can foster microbial eradication and speed up the recovery rates of infectious diseases (Bonate 2001; Eagye et al. 2007). A two compartment multiple dose model was used by Eagye et al. in 2007 to determine 24-h concentration-time profile at steady-state conditions for different drugs against Gram-negative bacteria causing fatal infections. Patient-derived pharmacokinetic values combined with 5000 trial Monte Carlo simulation was used to determine the predicted cumulative fraction of response (CFR) values. The probability that the selected antibiotic regime will either meet or exceed a predefined

pharmacodynamic target at a given MIC dilution (PTA) was calculated for different antibiotics. The target index $fT > MIC$ was selected as the PD property of the drugs. The results of the study indicate that for Carbapenems, 40% $fT > MIC$ was considered bactericidal; 50% $fT > MIC$ for Piperacillin-Tazobactam and Cephalosporins. A CFR of 90% was the set threshold for reliable empirical therapy. A p-value of ≤ 0.05 indicated a statistically significant outcome. The confidence intervals were calculated at $\alpha = 0.05$ using Newcomb Wilson method without correction for continuity.

A novel standardized time kill-curve assay has been developed by Foerster et al. 2016. This assay and the subsequent pharmacodynamic modeling can be used to evaluate existing and novel antimicrobials against different strains of *Neisseria,* which have developed resistance to first-line empirical monotherapy. GraverWade (GW) medium, which supports the growth of a wide range of *N. gonorrhoeae* auxotypes and clinical isolates, was used. The time kill assay is a useful assay as described earlier and can be used for any antibiotic-pathogen combination. For time-kill curve analyses, *N. gonorrhoeae* was grown in GW medium in the presence of the desired antibiotics, covering a range of dilutions. A 0.5 McFarland inoculum of the test strains has to be prepared. Following this, 30 µl of the inoculum was diluted in 15 ml prewarmed (37 °C) antimicrobial-free GW medium and 90 µl per well was dispensed in round bottom 96-well microtiter plates. Plates were preincubated and 10 µl of the antimicrobial concentrations (or PBS in case of drug free control) was added to each well containing the reincubated bacteria. The growth rate was estimated as the coefficient of a linear regression from the logarithm of the colony counts. Pharmacodynamic model with Eq. 10 as described by Regoes et al. 2004 was used in the study.

$$\psi(a) = \psi_{max} - \frac{\left[(\psi_{max} - \psi_{min})(a/zMIC)^k\right]}{\left[(a/zMIC)^k - (\psi_{max}/\psi_{min})\right]} \quad (10)$$

ψ_{max} describes the maximal growth rate of the bacteria in the absence of antimicrobial agent, while ψ_{min} represents the minimal bacterial growth rate at high antimicrobial concentrations. zMIC is the pharmacodynamic MIC value where the bacterial growth rate is zero (ψ (zMIC) = 0). k is the Hill coefficient, describing the steepness of the sigmoidal relationship between bacterial growth and antimicrobial concentration. All parameters were estimated using the R software package and bacterial growth rates are estimated from the time-kill curves by linear regression. The pharmacodynamic model was finally fitted to the estimated growth rates at different antimicrobial concentrations. The authors suggest that PD parameters based on a wide range of concentrations below and above the MIC can provide valuable information that could be useful for improving future dosing strategies.

PD parameters obtained using time kill analysis coupled to evaluate the potential of Ciprofloxacin as an anti-infective agent (Schuck et al. 2005). Ciprofloxacin has been widely used for the treatment of a variety of nosocomial infections, especially in intensive care units (ICUs). Ciprofloxacin is a second-generation fluoroquinolone, which exhibits rapid concentration-dependent bactericidal activity against most Gram-negative aerobic species like *Pseudomonas aeruginosa* and *Acinetobacter baumannii.* A recent investigation by Khachman et al. (2011) provides an extensive and simplified methodology for optimizing ciprofloxacin dosing in ICU patients mediated by the use of population pharmacokinetic–pharmacodynamic analysis and Monte Carlo simulations. This model can be used as a guideline for studying various other antibiotics active against Gram-negative pathogens. The population PK model was based on a clinical study employing 102 ICU patients. Two sets of PK/PD simulations were carried out with each 10,000 patients simulated per dosage regimen

investigated. The first set included complete distribution of MIC values including susceptible and resistant strains, while the second set was carried out across each MIC value according to a geometric progression from 0.002 mg/L to 2 mg/L. This model was also a predictor to determine possible continued usage of ciprofloxacin for the treatment of Gram-negative infections in ICU patients due to their potential to develop resistances. Such population PK/PD modeling could be of great value for studying efficacy of existing and novel antimicrobials against infectious diseases. Colistin or its inactive prodrug Colistin methanesulfonate (CMS) is increasingly used as a last-line therapy to treat infections caused by multidrug-resistant (MDR) Gram-negative pathogens (Dudhani et al. 2010a). With significant improvements in the understanding of the chemistry, PK/PD characteristics and their interrelationship, substantial progress has been made in optimizing use of CMS in clinics. This includes the first scientifically based dosing algorithm for critically ill patients receiving CMS to generate a desired target steady-state plasma concentration of formed Colistin. Most PD data on Colistin has been generated using in vitro models. Colisitin exhibits a strong concentration-dependent killing against *P. aeruginosa, A. baumannii, and K. pneumoniae* and their MDR strains as indicated time-kill studies in static and dynamic systems. A consistent finding of both in vitro and in vivo studies is regrowth with Colistin monotherapy, even with concentrations above those which can be safely achieved clinically (Nation et al. 2014). Although owing to increased resistance as indicated by regrowth with Colistin monotherapy in in vitro and in vivo studies, combination therapy may be beneficial. It still appears that Colistin is the most promising antimicrobial for severe infections caused by Gram-negative bacteria. Studies have been performed employing dose-fractionation design to investigate the PK/PD index, which best correlates with Colistin efficacy. The overall killing effect was best correlated with fAUC/MIC followed by $f\mathrm{T} > \mathrm{MIC}$ (Nation et al. 2014). Studies in neutropenic thigh and lung mouse infection models again indicated that the PK/PD index that best correlated with Colistin efficacy was fAUC/MIC. Dose-fractionation studies with Colistin were conducted against *P. aeruginosa* strains, its MDR clinical strain, and a strain from cystic fibrosis patient to determine this index. The relationships between antibacterial effects and PD parameters were examined using an inhibitory sigmoid maximum-effect model (Dudhani et al. 2010a). Similar studies for other antimicrobials can be conducted to define optimum dosage regimens in humans. The models of antimicrobial therapy designed for planktonic infections are often of little importance in treating infections by biofilm forming bacteria. Additionally, models derived from two compartment analysis simulating the blood and various tissues as two compartments may also not be completely mimicking the exact conditions in biofilms. In 2015, Cao et al. have designed a new in vitro model which could mimic the conditions during the biofilm formation by bacteria. This seaweed alginate-embedded biofilm model allows the simultaneous measurement of antibiotics within the matrix and parallel bacterial killing. The authors hypothesized that biofilms may be considered as independent compartments with particular pharmacokinetics. The biofilm model was used to study the antibiotic penetration and concomitant killing of *Pseudomonas aeruginosa* by Tobramycin. Tobramycin is the drug of choice for treating biofilm-associated infections of *P. aeruginosa* like cystic fibrosis (Herrmann et al. 2010). Additionally, Pawar et al. 2015 showed the biofilm associated tolerance toward clinical antibiotics in murine tumor model. Such in vivo biofilm models will be able to simulate the clinical pharmacokinetics of antibiotics and could be an ideal model for testing new treatment strategies.

Pharmacodynamic Indices for Optimal Therapy

As described earlier, for any antimicrobial agent a particular PD parameter correlates best with the successful eradication of an infectious agent. Time above MIC ($\mathrm{T} > \mathrm{MIC}$) correlates best with the activity of β lactams. On the hand, AUC_{24}/MIC is adjudged the best for aminoglycosides and

Table 1 Pharmacodynamics of clinically available antibiotics

Antibiotic	Effective against/ Treatment of	Relevant pharmacodynamic parameter	Setting	Reference
Colistin	*Acinetobacter baumannii*	*f*AUC/MIC	Murine thigh and lung infection model	Dudhani et al. 2010b
Colistin	*Pseudomonas aeruginosa*	*f*AUC/MIC	In vitro model	Bergen et al. 2010
Tobramycin	*Pseudomonas aeruginosa*	*f*AUC/MIC, T > MIC	In patient studies	Mouton et al. 2005
Levofloxacin	*Pseudomonas aeruginosa*	AUC_{24}/MIC, Cp_{max}/MIC	Phase IV clinical trial	Lee et al. 2007
Amikacin	Gram-negative bacteria	T > MIC & log AUC	Thigh infection and pneumonia in mice models	Craig et al. 1991
Cefepime, Ceftriaxone, Imipene, Piperacillin-Tazobactam	Gram-negative bacteria like *Pseudomonas, Acinetobacter, Klebsiella, Enterobacter, Serratia, Stenothermophilus, Proteus, Citrobacter*	T > MIC	In vitro two compartment model	Eagye et al. 2007
Trovafloxacin, Ciprofloxacin	*Staphylococcus aureus*	AUC/MIC	In vitro dynamic model	Firsov et al. 1999
Daptomycin, Vancomycin, Tigecycline, Linezolid	Invasive MRSA infections including *S. aureus* bacteremia	AUC_{24}/MIC	In vitro PK/PD model of bacterial biofilm	Hall Snyder et al. 2015
Ciprofloxacin	Broad spectrum, treatment of acute uncomplicated and complicated urinary tract infections and uncomplicated pyelonephritis	AUC_{24}/MIC	Healthy human volunteers	Schuck et al. 2005
Telavancin, vancomycin plus Aztreonam or Piperacillin-Tazobactam	Mixed infection by *Pseudomonas aeruginosa*, *Escherichia coli,* and methicillin-resistant *Staphylococcus aureus*	Reduction in $\log_{10}$ CFU/ml	Clinical trials	Yim et al. 2016
Ceftriaxone-Sublactam	Bacteria causing complicated urinary tract infections	T > MIC	Clinical trials	Sharma et al. 2016

AUC_{24} – area under the curve at 24 h; Cpmax – maximum serum concentration; MIC – minimal inhibitory concentration; T – time; T > MIC – time over MIC; CFU – colony forming units; ml – milliliter

fluoroquinolones. However, sometimes in case of these two classes of antibiotic Cp_{max}/MIC is used (Zhanel 2001). A detailed account of PK/PD indices for all antibiotics is beyond the scope of this chapter, so here we describe representatives of the most widely studied values. Additionally, Table 1 briefly describes few antibiotics and their pharmacodynamic parameters.

For β lactams, a minimum T > MIC of 40–50% of the dosing interval is required to exercise bactericidal effects and a corresponding bacteriological cure of greater than 85%. Maximal bactericidal effects are achieved when T > MIC

ranges between 60 and 70% of the dosing interval as suggested by animal studies and clinical trials in otitis media (Craig and Andes 1996; Andes and Craig 1998). Additionally, animal studies indicate that for stasis, a *f*T/MIC of 20% is required for Carbapenams, 30% for Penicillins, and 40% for Cephalosporins. Maximal efficiency also described as 2 log reduction in CFU requires *f*T/MIC 40% for Carbapenams, 50% for Penicillins, and 50–70% for Cephalosporins (Crandon and Nicolau 2011). In a murine thigh infection model to evaluate the effect of Amoxicillin and Amoxicillin-Clavulanate against *Streptococcus pneumoniae,* highest mortality rates (80–100%) were seen when serum levels exceeded the MIC for less than 20% of the dosing interval. Maximal survival was approached when serum levels exceeded the MIC for 40% of the 8-h dosing interval (Andes and Craig 1998). Their studies demonstrate that a reduction of 1 $\log_{10}$ or greater in CFU/thigh at 24 h is consistently observed when amoxicillin levels exceed the MIC for 25–30% of the dosing interval.

The Aminoglycosides and Fluoroquinolones exhibit a concentration dependent killing. For Fluoroquinolones, an AUC_{24}/MIC ratio of at least 125 is required to successfully treat respiratory tract infections caused by Gram-negative bacteria in terminally ill, elderly patients (Schuck et al. 2005). Based on in vitro, in vivo, and clinical data, it has been suggested that the PK/PD parameter AUC_{24}/MIC describes the activity of Vancomycin the best, therefore giving an exact idea about time related bacteriological outcome in patients with respiratory tract infections caused by *S. aureus*. An AUC_{24}/MIC value $\geq$ 400 is required to improve the outcome of patients with severe staphylococcal infections (Moise-Broder et al. 2004). However, this value is relatively high when compared with other antibiotics.

Pathophysiological Conditions Leading to Treatment Failures

In spite of the in depth analysis of PK/PD parameters for comprehensive assessment of drug efficacy and undue toxic effects, most of the treatment regimen do not result in the optimal outcome often and thus lead to treatment failures. This is a major concern especially in critically ill patients and must be carefully assessed and addressed to realize successful treatment of acute and chronic infectious diseases. There are often different reasons contributing to reduced or incomplete cure in critically ill patients (Bamberger 1997). The major reason is attributed to the fact that PK/PD parameters are mostly studied in infection models/animals. Laboratory based in vitro and animal data are further used to determine antimicrobial PD, which determines the initial dosing regimens to be used in clinical practice. However, it is observed that the PK/PD of antimicrobials in critically ill patients/patients with severe infections differ significantly from the patient groups from whose data the prospective dosing regimens had been developed. This often leads to entirely different/inadequate antimicrobial concentrations at the site of infection in terminally ill patients and thus to poor outcomes. Such data give a general regimen to be used in clinical scenario, but often fail in individual patients due to differences in immunity and other health parameters.

The vast array of pathophysiological changes occurring in patients suffering from infectious disease with varying degree of severity can complicate antibiotic dosing. Pharmacokinetics may be vastly altered in case of critical illness, hepatic dysfunction, sepsis, burns, pregnancy, cystic fibrosis, or other primary and secondary bacterial infections. In such case, dosing may fail and individualized therapy may be necessary. For example, in case of sepsis low plasma concentration of drugs can be a result of either an increase in CL or Vd. This may be a result of increased cardiac output or increased capillary permeability (McKinnon and Davis 2004; Udy et al. 2008). Myocardial depression leading to decrease in organ perfusion and ultimately microvascular circulation failure adds to inefficiency of antibiotic regimen. In other cases, sepsis can induce multiple organ dysfunction, including renal and/or hepatic dysfunction, leading to drastic decrease in antibacterial clearance (Roberts and Lipman 2009). In case of severe burns, serum

concentrations of antibiotics may fall below the MICs of infecting pathogens, implicating an increased requirement of the drug or in some cases frequent dosing of the antibiotic (Dryden et al. 2011). Therefore, there is a potential for patients who are critically ill with sepsis or burns to have subinhibitory serum concentrations of Linezolid with standard dosing regimens. These altered PK factors in critically ill patients can have a significant effect attainment of adequate antibiotic doses. Moreover, considerable interpatient variability in drug absorption, distribution, metabolism, and elimination; protein binding; and tissue absorption can have a profound effect on the ability to achieve pharmacodynamic targets at conventional doses (McKinnon and Davis 2004; Vincent et al. 2016). Additionally, it is seen that the antimicrobial PK profile of small animal models can be extremely different to that in humans. The drug retention and/or clearance may be substantially different. Therefore, careful dosing strategies must be designed with care.

Most importantly, bacteria embedded in biofilms pose a serious challenge for antimicrobial action and is the major reason for failure of dosage regimens in fatal infections. Similarly, most of the chronic infections are due to mixed bacterial species or super-infections which possess an even greater threat. Such diseases are often critical and have extremely low survival rates. Hospital/ventilator-associated pneumonia, sepsis, diabetes foot infection are few such cases which warrant attention. Under such situations, often optimal PD targets cannot be achieved using single antibiotic and combination therapy may be required (McKinnon and Davis 2004; Tamma et al. 2012; Yim et al. 2016).

Overcoming Treatment Failures

To overcome the issue of treatment failures, several factors affecting PK/PD characteristics should be evaluated to achieve the desired pharmacodynamic targets in antimicrobial selection. A mere consideration of MIC values may not be sufficient. Additional consideration of patient-specific pharmacokinetic variation must be made. Concentration–time data of antimicrobials must be studied in terminally ill patients when developing population PK models. These will give a realistic dosing regimen that will account for drastically altered drug concentrations in patients (McKinnon and Davis 2004; Tängdén et al. 2017). Success can be achieved by employing therapeutic drug monitoring (TDM). TDM involves measurement of drug concentrations and dose adjustment based on the observed concentration in relation to a target drug exposure. Antimicrobial TDM can not only minimize drug toxicity, but also maximize drug efficacy leading to an overall therapeutic effect. TDM thus can be used for infected critically ill patients where early dose adaptation to the needs of the individual patient can give better outcome. Furthermore, TDM can be of great importance for such patients where prompt appropriate antibiotic therapy is crucial. Additionally, nomograms can be designed where PK characteristics derived from more than one patient can be used in models to determine dosing regimens (Tängdén et al. 2017). In case of tuberculosis patients with a greater risk of treatment failure, TDM ensures appropriate serum drug concentrations and may assist in the clinical decision-making process (Nuermberger and Grosset 2004). A good outcome of an infection episode may be achieved by early institution of appropriate antimicrobial therapy. Depending on the nature of the etiological agent, either a specific antimicrobial agent or combination of agents can be effective in achieving targeted infection clearance especially in critically ill patients (Bush and Levison 1988). Depending on the type of infection, severity of illness, or possible immunosuppression optimized dosing regimens can be designed for different combination of antibiotics. When studying the combination of drugs and their time–kill curves in vitro PK/PD models, differences in their PK properties can be taken into account. Prediction of PD target attainment can be made based on this study and specifically designed dosing regimens can be effective over normal regimens. However, these should be should be validated in clinical studies before they can be used in general practice.

Combination therapy involving two or more antibiotics can be used to treat complicated fatal/chronic diseases by mixed infections of Gram-positive and Gram-negative bacteria. However, a forehand analysis of the additive, synergistic, or antagonistic effect of the drugs is essential before such regimens can be introduced. In case of TB treatment, combination therapy is in vogue. It benefits from the additive and/or synergistic effects of antimycobacterial agents. This is practiced as there is a high potential for the development of drug resistance using monotherapy. Models similar to the in vitro PK/PD models for simultaneous simulation of serum kinetics of two or more drugs with different half-lives developed against *Streptococcus pneumonia* and *Staphylococcus aureus* could be used for development of anti-TB agents (Nuermberger and Grosset 2004; Vaddady et al. 2010). Combination therapy using Piperacillin/Tazobactam or Imipenem/Cilastatin can be used to treat mixed bacterial foot infections in diabetic patients (Saltoglu et al. 2010). It has also been found useful in the treatment of chronic biofilm infection by *Pseudomonas aeruginosa* in murine tumor model (Herrmann et al. 2010; Pawar et al. 2015). Clinical trials have been made to compare the efficacy of combination therapy for treatment of hospital-acquired pneumonia. Pharmacodynamic interactions between Telavancin and Aztreonam or Piperacillin/Tazobactam were evaluated against *P. aeruginosa, E. coli,* and *S. aureus* using an in vitro one compartment PK/PD model (Yim et al. 2016).

Conclusion

To counter the antimicrobial resistance and the persistence of bacteria in chronic infections, PK/PD properties should be considered from the point of selection of antibiotics. Additionally, it is of high importance to understand the nature of bacterial infection, the antibiotic resistance profile, and biofilm formation ability of the bacteria. An in depth analysis of PK/PD of antibiotics and use of right models and simulation data is essential for revamping existing treatment regimens. The same procedure should be considered while developing/evaluating new strategies against fatal infectious diseases. Incorporation of region or patient specific PK/PD values would be key factor determining successful outcome. Additionally, choice of particular model or antibiotic/s against infectious diseases should be governed by an extensive investigation of the causative agent/s, resistance mechanisms, underlying patho-physiological stage, and PK/PD parameters.

References and Further Reading

Andes D, Craig WA (1998) In vivo activities of amoxicillin and amoxicillin-clavulanate against Streptococcus pneumoniae: application to breakpoint determinations. Antimicrob Agents Chemother 42:2375–2379

Bamberger D (1997) Antibiotics: why they fail in patients who are critically ill. Crit Care Nurs Q 20:60–68

Bergen PJ, Bulitta JB, Forrest A, Tsuji BT, Li J, Nation RL (2010) Pharmacokinetic/pharmacodynamic investigation of colistin against pseudomonas aeruginosa using an in vitro model. Antimicrob Agents Chemother 54:3783–3789

Bonate PL (2001) A brief introduction to Monte Carlo simulation. Clin Pharmacokinetic 40:15–22

Bush LM, Levison ME (1988) Antibiotic selection and pharmacokinetics in the critically ill. Crit Care Clin 4:299–324

Canut A, Isla A, Betriu C, Gascón AR (2012) Pharmacokinetic – pharmacodynamic evaluation of daptomycin, tigecycline, and linezolid versus vancomycin for the treatment of MRSA infections in four western European countries. Eur J Clin Microbiol Infect Dis 31 (9):2227–2235

Cao B, Christophersen L, Thomsen K, Sønderholm M, Bjarnsholt T, Jensen PØ, Høiby N, Moser C (2015) Antibiotic penetration and bacterial killing in a Pseudomonas aeruginosa biofilm model. J Antimicrob Chemother 70:2057–2063

Carlton KK Lee, Michael P Boyle, Marie Diener-West, Lois Brass-Ernst, Michelle Noschese, Pamela L Zeitlin (2007) Levofloxacin Pharmacokinetics in Adult Cystic Fibrosis. Chest 131 (3):796-802

Craig WA, Andes D (1996) Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. Pediatr Infect Dis J 15:944–948

Craig, WA, Redington, J, Ebert, SC Pharmacodynamics of amikacin in vitro and in mouse thigh and lung infections. J. Antimicrob. Chemother. 27 (Suppl.) S29–S40 (1991).

Crandon JL, Nicolau DP (2011) Pharmacodynamic approaches to optimizing beta-lactam therapy. Crit Care Clin 27:77–93

Crull K, Weiss S (2011) Antibiotic control of tumor-colonizing Salmonella enterica serovar Typhimurium. Exp Biol Med 236:1282–1290

Czock D, Keller F (2007) Mechanism-based pharmacokinetic–pharmacodynamic modeling of antimicrobial drug effects. J Pharmacokinet Pharmacodyn 34:727–751

Dayneka NL, Garg V, Jusko WJ (1993) Comparison of four basic models of indirect pharmacodynamic responses. J Pharmacokinet Biopharm 21:457–478

Drago L, De Vecchi E (2008) The safety of cefepime in the treatment of infection. Expert Opin Drug Saf 7:377–387

Dryden M, Johnson AP, Ashiru-Oredope D, Sharland M (2011) Using antibiotics responsibly: right drug, right time, right dose, right duration. J Antimicrob Chemother 66:2441–2443

Dudhani RV, Turnidge JD, Coulthard K, Milne RW, Rayner CR, Li J, Nation RL (2010a) Elucidation of the pharmacokinetic/pharmacodynamic determinant of colistin activity against Pseudomonas aeruginosa in murine thigh and lung infection models. Antimicrob Agents Chemother 54:1117–1124

Dudhani RV, Turnidge JD, Nation RL, Li J (2010b) fAUC/MIC is the most predictive pharmacokinetic/pharmacodynamic index of colistin against Acinetobacter baumannii in murine thigh and lung infection models. J Antimicrob Chemother 65:1984–1990

Eagye KJ, Nicolau DP, Lockhart SR, Quinn JP, Doern GV, Gallagher G, Abramson MA (2007) A pharmacodynamic analysis of resistance trends in pathogens from patients with infection in intensive care units in the United States between 1993 and 2004. Ann Clin Microbiol Antimicrob 6:11

Felmlee MA, Morris ME, Mager DE (2012) Mechanism-based pharmacodynamic modeling BT. In: Reisfeld B, Mayeno AN (eds) Computational toxicology, vol I. Humana Press, Totowa, pp 583–600

Firsov AA, RG Vasilov, SN Vostrov, OV Kononenko, I Yu Lubenko, S H Zinner, (1999) Prediction of the antimicrobial effects of trovafloxacin and ciprofloxacin on staphylococci using an in-vitro dynamic model. Journal of Antimicrobial Chemotherapy 43 (4):483-490

Foerster S, Unemo M, Hathaway LJ, Low N, Althaus CL (2016) Time-kill curve analysis and pharmacodynamic modelling for in vitro evaluation of antimicrobials against Neisseria gonorrhoeae. BMC Microbiol 16 (1):1–11

Gloede J, Scheerans C, Derendorf H, Kloft C (2010) In vitro pharmacodynamic models to determine the effect of antibacterial drugs. J Antimicrob Chemother 65:186–201

Hall Snyder AD, Vidaillac C, Rose W, McRoberts JP, Rybak MJ (2015) Evaluation of high-dose daptomycin versus vancomycin alone or combined with clarithromycin or rifampin against Staphylococcus aureus and S. epidermidis in a novel in vitro PK/PD model of bacterial biofilm. Infect Dis Ther 4:51–65

Herrmann G, Yang L, Wu H, Song Z, Wang H, Høiby N, Ulrich M, Molin S, Riethmüller J, Döring G (2010) Colistin-tobramycin combinations are superior to monotherapy concerning the killing of biofilm Pseudomonas aeruginosa. J Infect Dis 202:1585–1592

José Pérez-Urizar, Vinicio Granados-Soto, Francisco J Flores-Murrieta, Gilberto Castañeda-Hernández, (2000) Pharmacokinetic-Pharmacodynamic Modeling. Archives of Medical Research 31 (6):539-545

Lorenz A, Pawar V, Häussler S, Weiss S (2016) Insights into host–pathogen interactions from state-of-the-art animal models of respiratory Pseudomonas aeruginosa infections. FEBS Lett 590:3941–3959

Mager DE, Diversity of Mechanism-Based Pharmacodynamic Models. Drug Metabolism and Disposition 31 (5):510-518

McKinnon PS, Davis SL (2004) Pharmacokinetic and pharmacodynamic issues in the treatment of bacterial infectious diseases. Eur J Clin Microbiol Infect Dis 23:271–288

Meibohm B, Derendorf H (2002) Pharmacokinetic/pharmacodynamic studies in drug product development. J Pharm Sci 91:18–31

Michael J, Barth A, Kloft C, Derendorf H (2014) Pharmacodynamic in vitro models to determine the effect of antibiotics. In: Vinks AA, Derendorf H, Mouton JW (eds) Fundamentals of antimicrobial pharmacokinetics and pharmacodynamics. Springer New York, New York, pp 81–112

Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ (2004) Pharmacodynamics of vancomycin and other antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections. Clin Pharmacokinet 43:925–942

Mouton JW (2014) Setting clinical MIC breakpoints from a PK/PD point of view: it is the dose that matters. In: Vinks AA, Derendorf H, Mouton JW (eds) Fundamentals of antimicrobial pharmacokinetics and pharmacodynamics. Springer New York, New York, pp 45–61

Mouton J, Dudley M, Cars O, Derendorf H, Drusano G (2005) Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update. J Antimicrob Chemother 55:601–607

Mouton JW, Brown DFJ, Apfalter P, Cantón R, Giske CG, Ivanova M, MacGowan AP, Rodloff A, Soussy C-J, Steinbakk M, Kahlmeter G (2012) The role of pharmacokinetics/pharmacodynamics in setting clinical MIC breakpoints: the EUCAST approach. Clin Microbiol Infect 18:E37–E45

Nation RL, Bergen PJ, Li J (2014) Pharmacokinetics and pharmacodynamics of colistin BT. In: Vinks AA, Derendorf H, Mouton JW (eds) Fundamentals of antimicrobial pharmacokinetics and pharmacodynamics. Springer New York, New York, pp 351–380

Nicolau DP (2003) Optimizing outcomes with antimicrobial therapy through pharmacodynamic profiling. J Infect Chemother 9:292–296

Nielsen EI, Friberg LE (2013) Pharmacokinetic-pharmacodynamic modeling of antibacterial drugs. Pharmacol Rev 65:1053–1090

Nuermberger E, Grosset J (2004) Pharmacokinetic and pharmacodynamic issues in the treatment of mycobacterial infections. Eur J Clin Microbiol Infect Dis 23:243–255

Parra-Ruiz J, Vidaillac C, Rose WE, Rybak MJ (2010) Activities of high-dose daptomycin, vancomycin, and moxifloxacin alone or in combination with clarithromycin or rifampin in a novel in vitro model of Staphylococcus aureus biofilm. Antimicrob Agents Chemother 54:4329–4334

Pawar V, Crull K, Komor U, Kasnitz N, Frahm M, Kocijancic D, Westphal K, Leschner S, Wolf K, Loessner H, Rohde M, Häussler S, Weiss S (2014) Murine solid tumours as a novel model to study bacterial biofilm formation in vivo. J Intern Med 276:130–139

Pawar V, Komor U, Kasnitz N, Bielecki P, Pils MC, Gocht B, Moter A, Rohde M, Weiss S, Häussler S (2015) In vivo efficacy of antimicrobials against biofilm producing Pseudomonas aeruginosa. Antimicrob Agents Chemother 59:AAC.00194-15

Regoes RR, Wiuff C, Zappala RM, Garner KN, Baquero F, Levin BR (2004) Pharmacodynamic functions: a multiparameter approach to the design of antibiotic treatment regimens. Antimicrob Agents Chemothe 48:3670–3676

Roberts J, Lipman J (2009) Pharmacokinetic issues for antibiotics in the critically ill patient pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 37:840–851

Rybtke M, Hultqvist LD, Givskov M, Tolker-Nielsen T (2015) Pseudomonas aeruginosa biofilm infections: community structure, antimicrobial tolerance and immune response. J Mol Biol 427:3628–3645

Saltoglu N, Dalkiran A, Tetiker T, Bayram H, Tasova Y, Dalay C, Sert M (2010) Piperacillin/tazobactam versus imipenem/cilastatin for severe diabetic foot infections: a prospective, randomized clinical trial in a university hospital. Eur Soc Clin Infect Dis 16:1252–1257

Sanchez CJ, Mende K, Beckius ML, Akers KS, Romano DR, Wenke JC, Murray CK (2013) Biofilm formation by clinical isolates and the implications in chronic infections. BMC Infect Dis 13:47

Scaglione F, Paraboni L (2006) Influence of pharmacokinetics/pharmacodynamics of antibacterials in their dosing regimen selection. Expert Rev Anti-Infect Ther 4:479–490

Schuck EL, Dalhoff A, Stass H, Derendorf H (2005) Pharmacokinetic/pharmacodynamic (PK/PD) evaluation of a once-daily treatment using ciprofloxacin in an extended-release dosage form. Infection 33:22–28

Sharma A, Jusko WJ (1998) Characteristics of indirect pharmacodynamic models and applications to clinical drug responses. Br J Clin Pharmacol 45:229–239

Tamma PD, Cosgrove SE, Maragakis LL (2012) Combination therapy for treatment of infections with gram-negative bacteria. Clin Microbiol Rev 25:450–470

Tängdén T, Martín VR, Felton TW, Nielsen EI, Marchand S, Brüggemann RJ, Bulitta JB (2017) The role of infection models and PK/PD modelling for optimising care of critically ill patients with severe infections. Intensive Care Med 43:1021–1032

Taraszkiewicz A, Fila G, Grinholc M, Nakonieczna J (2013) Innovative strategies to overcome biofilm resistance. Biomed Res Int 2013:1–13

Udy A, Roberts J, Boots R, Lipman J (2008) Dose adjustment and pharmacodynamic considerations for antibiotics in severe sepsis and septic shock BT. In: Rello J, Restrepo MI (eds) Sepsis: new strategies for management. Springer Berlin Heidelberg, Berlin/Heidelberg, pp 97–136

Vaddady PK, Lee RE, Meibohm B (2010) In vitro pharmacokinetic/pharmacodynamic models in anti-infective drug development: focus on TB. Future Med Chem 2:1355–1369

Vincent J, Bassetti M, François B, Karam G, Chastre J, Torres A, Roberts JA, Taccone FS, Rello J, Calandra T, De Backer D, Welte T (2016) Advances in antibiotic therapy in the critically ill. Crit Care 20:1–13

Vishnu Dutt Sharma, Aman Singla, Manu Chaudhary, Manish Taneja, (2016) Population Pharmacokinetics of Fixed Dose Combination of Ceftriaxone and Sulbactam in Healthy and Infected Subjects. AAPS PharmSciTech 17 (5):1192-1203

Wayne (2014) Performance standards for antimicrobial susceptibility testing; Twenty-fourth informational supplement, CLSI document M100–S24. In: Clinical and laboratory standards institute report. Clinical and Laboratory Standards Institute, Wayne (PA), pp 1–230

Wilson SE, Graham DR, Wang W (2017) Telavancin in the treatment of concurrent Staphylococcus aureus bacteremia: a retrospective analysis of ATLAS and ATTAIN studies. Infect Dis Ther 6(3):413–422

Yim J, Smith JR, Barber KE, Hallesy JA, Rybak MJ (2016) Evaluation of pharmacodynamic interactions between telavancin and aztreonam or piperacillin/tazobactam against Pseudomonas aeruginosa, Escherichia coli and methicillin-resistant Staphylococcus aureus. Infect Dis Ther 5:367–377

Zervos M, Nelson M (1998) Cefepime versus ceftriaxone for empiric treatment of hospitalized patients with community-acquired pneumonia. The Cefepime study group. Antimicrob Agents Chemother 42:729–733

Zhanel GG (2001) Influence of pharmacokinetic and pharmacodynamic principles on antibiotic selection. Curr Infect Dis Rep 3:29–34