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# Preface

Sepsis continues to be a major cause of morbidity and mortality worldwide. In the United States alone, sepsis accounts for 210,000 deaths annually, at a cost of \$17 billion [1]. However this represents only a fraction of the global burden of this syndrome, with an estimated 15–19 million cases per year—the vast majority of which occur in low income countries [2]. Albeit there has been significant investment in developing clinical protocols and guidelines [3], and assessing novel pharmacological interventions [4], 28-day mortality from sepsis in high income countries remains around 20–25% [5, 6]. In addition to short-term mortality, septic patients suffer from numerous complications and are at an increased risk of death for up to 5 years following an acute event [7].

Fundamental principles in managing severe sepsis include early recognition, control of the source of infection, resuscitation with intravenous (IV) fluids, and infusion of vasoactive drugs [3]. Importantly, administration of appropriate broad-spectrum IV antibiotics as soon as possible is now considered a quality of care indicator in the management of this condition [8]. In this respect, the chosen antibiotic agent(s) should have suitable intrinsic bactericidal or bacteriostatic activity against the causative pathogen(s) and be administered in sufficient dose to ensure adequate drug concentrations at the site of infection. While generic critical care guidelines primarily focus on the former requirement, clinicians are generally less certain about adequate dose selection, despite the very real implications for patients.

This uncertainty is primarily a consequence of the marked clinical heterogeneity and multisystem physiological derangement encountered in critical illness, driven by both the underlying pathology and the interventions provided. Anthropometric irregularities, chronic disease, administration of large volumes of IV fluids, use of vasoactive medications, and application of extracorporeal support modalities, in addition to alterations in major native organ function, are common characteristics of this population. These perturbations will significantly impact drug handling, such that antibiotic doses extrapolated from studies in healthy volunteers or ambulatory patients are unlikely to achieve similar drug exposures in this setting.

Utilizing the knowledge and experience of numerous global experts in this field, this text aims to comprehensively review the pharmacokinetic/pharmacodynamic considerations concerning antibiotic prescription in the critically ill. Our principal aim is to provide the reader with a complete understanding of these issues, specifically the scientific and clinical imperatives underpinning dose optimization in this setting. In this respect, the subject material ranges from basic antibiotic pharmacokinetic/pharmacodynamic principles, through to dosing considerations in pediatric patients, and those receiving extracorporeal membrane oxygenation (ECMO).

Finally, while these data are critical in ensuring the right dose is selected for a specific patient, it is salient to remind the reader that inadequate antibiotic exposure also has significant ramifications for the wider community. Multidrug resistance is an increasing problem globally, particularly in critical care units [9], and the widespread use of antibiotics, in potentially subtherapeutic doses, may in part be to blame [10]. As such, the information provided in this text must be viewed in this context, in that the prescriber has a responsibility not only to their current patient, but also future ones.

We hope you find the information provided herein useful in your everyday practice, as well as stimulating future research and discussion. We are deeply indebted to all of the authors and collaborators involved with this project, as well as the medical, nursing, allied health staff, and patients who have generated much of the data highlighted throughout the text.

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# Chapter 1

## Basic Pharmacokinetic Principles

Kashyap Patel and Carl M. Kirkpatrick

### 1.1 Introduction

Pharmacokinetics (PK) describes the time course of drug concentration following dosing [1, 2]. It is broadly characterized by the transfer of drug into, within, and out of the body as:

1. *Input*—drug movement from the site of administration to the systemic circulation
2. *Disposition*—drug distribution and elimination from the systemic circulation

These kinetic processes are commonly referred to as the **A**bsorption, **D**istribution, **M**etabolism, and **E**limination (ADME) of a drug.

The ultimate goal of drug development is to identify the optimal dosing regimens that produce maximum treatment effect. Therapeutic benefit is achieved when drug exposures exceed a given threshold for efficacy, yet remain below the toxicity threshold [1]. An understanding of drug PK is therefore important as it provides the link between dose administered and the time course of pharmacodynamic (PD) or toxicokinetic (TK) response [3–5].

This chapter provides a brief overview of basic PK principles. The methods used for parameter estimation is then discussed, as applied to research and clinical settings. Finally, the implications of altered PK in critically ill patients are presented, with specific reference to antibiotic dosing.

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## 1.2 Linear Pharmacokinetics

For most drugs, a proportional relationship is observed between concentration at steady-state ( $C_{ss}$ ) or area under the concentration-time curve (AUC) and administered dose. The PK of these drugs is described as *linear* or dose independent and is characterized by first-order processes. For drugs exhibiting linear PK, semi-log concentration-versus-time plots will be parallel at different doses.

In contrast, *nonlinearity* occurs when the relationships between dose administered and  $C_{ss}$ , AUC or other PK parameters are not directly proportional. These drugs demonstrate dose-dependent PK that is described by mixed-order, saturable, Michaelis–Menten, or capacity-limited processes. Example antibiotics showing nonlinear PK include dicloxacillin, which is saturated by active renal secretion [6], and amoxicillin, for which absorption decreases with increasing dose [7].

## 1.3 Clearance

Clearance (CL) is the key PK parameter and is defined as the “volume of blood, plasma or serum from which drug is irreversibly removed per unit time.” It is therefore expressed in volume/time units. Drug clearance may occur via several different organs or pathways of elimination, including hepatic metabolism, renal, and biliary excretion. Total drug removal therefore comprises the sum of all clearance components (Eq. 1.1):

$$CL_{tot} = CL_{met} + CL_{ren} + CL_{bil} + CL_{oth} \quad (1.1)$$

where  $CL_{met}$ ,  $CL_{ren}$ ,  $CL_{bil}$ , and  $CL_{oth}$  represent the metabolic, renal, biliary, and other mechanisms that constitute total ( $CL_{tot}$ ) clearance.

Physiologically, the rate of drug elimination across an organ is equal to the product of blood flow rate ( $Q$ ) and the arterial-venous concentration difference ( $C_A - C_V$ ). The extraction ratio ( $E$ ) provides a measure of organ efficiency with respect to drug removal and is based on mass-balance considerations (Eq. 1.2):

$$E = \frac{\text{Rate of drug elimination}}{\text{Rate of drug presentation}} = \frac{Q \cdot (C_A - C_V)}{Q \cdot (C_A)} = \frac{C_A - C_V}{C_A} \quad (1.2)$$

Thus, organs that are highly efficient in eliminating drug will have venous concentrations ( $C_V$ ) that approximate zero and an extraction ratio approaching unity. In contrast, organs that are incapable of drug removal will have an extraction ratio approaching zero, as a consequence of equivalent arterial and venous drug concentrations (i.e.,  $C_A - C_V = 0$ ). The organ clearance of drug is defined as the product of the blood flow rate and extraction ratio (Eq. 1.3):

$$CL_{organ} = Q \times E \quad (1.3)$$

Practically, however, the estimation of organ drug clearance using the above formula is challenging. Firstly, the experimental determination of arterial and venous drug concentrations is difficult, particularly in humans. Secondly, blood flow rates may not remain constant over a given study interval, thereby constraining its accurate measurement.

The importance of drug clearance from a pharmacological perspective is demonstrated by its relationship to the rate of maintenance dosing. Clearance is “the proportionality constant that relates the rate of drug elimination to its corresponding concentration at a given time in a relevant biological fluid” (Eq. 1.4):

$$\text{Rate of drug elimination} = \text{CL} \times C \quad (1.4)$$

Steady-state average drug concentrations ( $C_{\text{ss ave.}}$ ) are achieved when the rate of drug input equals its rate of elimination and is the basis for maintenance dosing (Eq. 1.5):

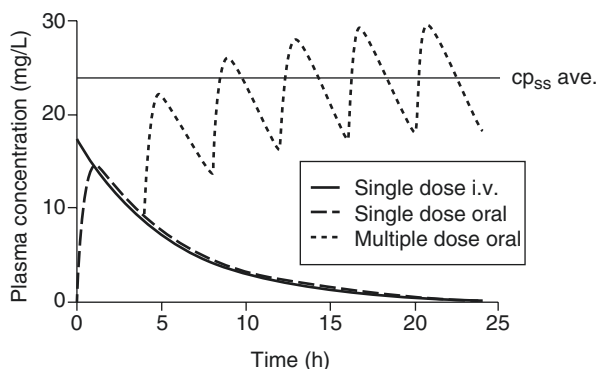
$$\text{Maintenance dosing rate} = \text{CL} \times C_{\text{ss ave.}} \quad (1.5)$$

The clinical impact of (Eq. 1.5) in achieving defined target steady-state concentrations is demonstrated in Fig. 1.1.

An alternative approach to estimating clearance is by using the AUC, which is a measure of the total systemic exposure of drug (Eq. 1.6):

$$\text{CL} = \frac{\text{Dose}}{\text{AUC}} \quad (1.6)$$

Thus, for drugs that are administered intravenously, clearance represents the reciprocal of dose-normalized AUC or systemic exposure.



**Fig. 1.1** Concentration-time profile of a hypothetical drug administered at 100 mg by single intravenous (*line*), single oral (*dashed line*), or multiple oral (*dotted line*) dosing. The latter illustrates use of maintenance dosing to achieve average steady-state plasma drug concentrations ( $C_{\text{pss ave.}}$ ), i.e., at five times the elimination half-life ( $T_{1/2}$ ). Drug disposition is described by a one-compartment model, with clearance 1 L/h, volume of distribution 5.77 L, and absorption rate constant  $3 \text{ h}^{-1}$ . Adapted from [8]

## 1.4 Volume of Distribution

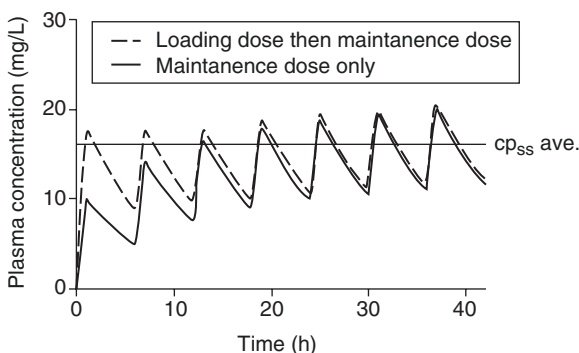
The volume of distribution ( $V_d$ ) is a “proportionality constant that relates dose administered to the achieved systemic drug concentration” (Eq. 1.7):

$$\text{Dose} = C \times V_d \quad (1.7)$$

This parameter is therefore the hypothetical or “apparent” volume into which a drug distributes to equal its concentration in blood, plasma, or serum. It is expressed in units of volume. Hydrophilic drugs are water soluble and are primarily distributed in the systemic circulation. As a result, these drugs have relatively small volumes of distribution, and thereby achieve high target concentrations. Example antibiotics that demonstrate low apparent volumes of distribution include the aminoglycosides such as gentamicin, tobramycin, and amikacin ( $V_d$  ranging from 14 L to 21 L) [9, 10]. In contrast, lipophilic drugs such as rifampicin or metronidazole ( $V_d \sim 70$  L) are distributed widely throughout the body and attain lower concentrations in the systemic circulation [11].

Pharmacologically, a “loading” dose is often administered to rapidly achieve defined target steady-state blood (plasma or serum) concentrations. Thus, Eq. 1.7 is useful for calculating this loading dose, provided that the drug volume of distribution is known (Fig. 1.2).

For doripenem and meropenem, typical loading doses of 1000–2000 mg ( $V_d$  15–20 L) provide exposures in the 65–135 mg/L desired total drug concentration range [12].



**Fig. 1.2** Demonstration of loading dose to quickly achieve average steady-state plasma drug concentrations ( $C_{pss}$  ave.). A loading dose of 1 g vancomycin was administered by intravenous infusion (1 h), followed by maintenance dosing of 500 mg every 6 h. Vancomycin pharmacokinetics is described for a 70 kg adult with creatinine clearance of 100 mL/min, using a model with clearance 2.99 L/h, central distribution volume 0.675 L/kg, peripheral distribution volume 0.732 L/kg and inter-compartmental clearance 2.28 L/h [8]

## 1.5 Half-Life

For drugs that demonstrate linear (dose-proportional) PK, the half-life ( $t_{1/2}$ ) is defined as the “time that it takes for its concentrations to halve.” The dimension of half-life is in units of time. Half-life is directly proportional to drug volume of distribution but inversely proportional to its clearance (Eq. 1.8). While clearance and volume of distribution are used to determine half-life, these two PK parameters are independent of each other.

$$t_{1/2} = \frac{\ln(2) \times V_d}{CL} \quad (1.8)$$

where  $\ln$  corresponds to the natural logarithm and is applicable to drugs displaying exponential kinetics. Alternatively, the half-life is calculated using elimination rate constant ( $k_{el}$ ) that has units of per unit time (Eq. 1.9). This parameter is obtained by determining the terminal slope of a log concentration-versus-time plot. Thus, if dosing is discontinued following intravenous infusion, the concentration will decline exponentially to <10% after four half-lives.

$$t_{1/2} = \frac{\ln(2)}{k_{el}} \quad (1.9)$$

The time course of drug accumulation is calculated using the elimination rate constant and dosing interval,  $\tau$  (Eq. 1.10):

$$\text{Accumulation factor} = \frac{1}{1 - \exp(-k_{el} \times \tau)} \quad (1.10)$$

For drugs administered via constant infusion, the concentration will approximate >90% of steady-state following four half-lives. Thus, a hypothetical drug with a 6 h half-life will achieve twice the steady-state concentration to monotherapy, if dosing occurs every  $t_{1/2}$  (i.e., 6 h). The dosing interval is determined by three factors that include administered dose, half-life, and drug potency (relating to efficacy, toxicity, or both) or  $EC_{50}$  [3].

## 1.6 Plasma Protein Binding

Only unbound (and not total) drug concentrations are available for metabolism, tissue distribution, or interaction with receptors to produce a pharmacological response. In general, most acidic drugs bind predominantly to albumin, while basic drugs bind to  $\alpha_1$ -acid glycoprotein or  $\beta$ -lipoproteins. In vitro, the concentration of

unbound drug changes with alterations in free fraction. However, in vivo the unbound concentration remains unchanged despite alterations in free fraction or total drug. This is because the steady-state unbound concentration is dependent only on the maintenance dose rate and free clearance (see Eq. 1.5). Dose modification is therefore not required with changes in protein binding since only unbound concentration produces a given pharmacological effect.

## 1.7 Absorption

Extravascular routes of drug administration include dosing via any method that is not intravenous, such as oral, subcutaneous, intramuscular, intranasal, intradermal, or topical. Absorption is defined by the “movement of drug from the site of administration to the systemic circulation.” Thus, any delay or loss of drug during absorption may contribute to variability in response or compromised therapeutic effect.

Bioavailability describes both the rate and extent of absorption from site of dosing to the systemic circulation. The extent of drug absorption ( $F$ ) is defined by the ratio of its AUC in blood, plasma, or serum after extravascular dosing, relative to that following intravenous administration (Eq. 1.11).

$$F = \frac{\text{AUC}_{\text{extravascular}}}{\text{AUC}_{\text{intravenous}}} \quad (1.11)$$

The rate of drug absorption is determined by the time at which maximal concentration is achieved ( $T_{\text{max}}$ ). Thus, oral formulations that are designed as slow, sustained, or controlled release, allow for a delayed  $T_{\text{max}}$  when prolonged drug action is required.

Several drug and physiological properties contribute to the rate and extent of absorption. Prior to reaching the general circulation, drugs must dissolve in solution and pass through various biological membranes. Drug physicochemical properties that may influence absorption include the degree of ionization, partition coefficient, and lipid solubility. Physiological factors comprise blood flow, vascularity, pH, membrane nature, and area of the absorptive surface. For orally administered drugs, additional contributors include gastric motility, food, and hepatic first-pass metabolism.

## 1.8 Pharmacokinetic Analysis

In general, there are three methods that are routinely used for the analysis of PK data, and comprise non-compartmental, standard two-stage and population modeling approaches. These models aim to quantify the dose–concentration relationship, which in turn, can assist with understanding the association between exposure and response [3, 4].

### 1.8.1 *Non-compartmental Analysis*

This approach is model independent and is often utilized to evaluate dose proportionality, drug disposition, and show bioequivalence [13]. Typically, the log trapezoidal rule is used to calculate AUC to infinity or last sampling time and area under the first moment curve (AUMC). Other PK parameters include maximal concentration ( $C_{\max}$ ), volume at steady-state ( $V_{ss}$ ), Mean residence time (MRT),  $T_{\max}$ , CL,  $t_{1/2}$ , and  $k_{el}$ .

Non-compartmental analysis is usually performed in a small number (10–30) of subjects that have similar disease, renal function, and other pathophysiological demographics. Patients are administered drug at a standard or test dose, followed intensive sampling of blood samples across the initial or steady-state dosing interval. The resulting data is then subject to non-compartmental calculations using statistical packages, or with specific software such as Phoenix WinNonlin®. Once computed, the estimated outputs are often compared to healthy volunteer studies or other patient subgroups using tests for demonstrating statistical significance.

A major disadvantage is that non-compartmental estimation is highly dependent on study design, including subject number, characteristics, and the timing of sample collection. Thus, while this approach may provide information on the statistical differences between studies, extrapolation to other patient groups is not recommended. Furthermore, no assumptions are made regarding drug distribution into other tissues, including the site of disease or infection [14]. Non-compartmental analysis is therefore not suitable for dose recommendation to patients with differing characteristics or pathophysiological status.

### 1.8.2 *Compartmental Modelling*

Unlike the model-independent approach, this analysis describes the kinetics of drug transfer into one or more hypothetical compartments [14]. In these models, the systemic circulation is referred to as the central compartment and is used to predict drug concentrations in blood, plasma, or serum. It should be noted that each compartment *does not* represent a specific organ of the body, unless observed data are directly obtained from that target site. Instead, each compartment characterizes differential rates of drug distribution that appear as biphasic profiles in concentration-versus-time curves. Thus, a rapid distribution of drug following intra- or extravascular dosing is adequately described using a one-compartment model. Here, the term rapid indicates that the rates of drug transfer from blood to all tissues or organs and back is equal and instantaneous. In contrast, slower distribution implies that the equilibrium between vasculature and a set of tissues or organs occurs over a finite period of time. As a consequence, drug disposition is represented by several rates of distribution comprising two or more compartments. Organs with high perfusion, such as the liver, blood, and kidney, may therefore be pooled together to signify a single central compartment. Other less perfused tissues, such as bones, cartilage, and fat, are indicative of a peripheral compartment, where drug distribution and equilibrium occurs at a slower rate.



### ***1.8.3 Standard Two-Stage Approach***

This method of data analysis is performed in two stages. The first step estimates PK parameters for each individual using their concentration-versus-time data after dosing. A suitable structural model is used to fit the data, using the method of ordinary least squares [15]. Specialized software packages such as Phoenix® WinNonlin are typically suitable for this purpose. The second stage involves tabulation of PK parameter estimates for all individuals and computation of summary statistics including arithmetic or geometric means, medians, and standard deviations.

In general, the number of subjects routinely used for the two-stage approach is comparable to that for non-compartmental analysis. However, some studies can recruit larger patient numbers with wider demographic ranges to investigate the influence of covariate effects on individual PK estimates. Statistical comparisons can therefore be made between two different pathophysiological groups, such as low and high renal function or healthy versus diseased subjects.

Several limitations exist when analyzing PK data using this method. Firstly, similar to non-compartmental analyses, parameter estimation relies on study design, subject-specific factors, and the frequency of obtaining blood or tissue samples. Secondly, the resulting summary statistics may be influenced by outliers and therefore result in biased estimates. While it is possible to reduce the total number of samples obtained per subject, a poor study design may produce inaccuracies in the estimation of PK parameters. Lastly, interindividual variability includes assay errors, thereby necessitating the development of sensitive and precise analytical methods. These limitations may preclude the applicability of two-stage analyses in designing future dosing recommendations.

### ***1.8.4 Population Modelling***

Nonlinear “mixed-effects” modelling is routinely used for PK estimation or simulation, as a means to supporting the clinical development of therapeutics [3, 4, 15–17]. The term nonlinear indicates that the relationship between drug concentration (dependent variable) is not proportional to time (independent variable) or PK model parameters. The term “mixed-effects” comprises fixed effects and random effects and are indicative of parameterization. The fixed effects component constitutes a structural model, where parameters do not differ between individuals. In contrast, random effects refer to the estimation of parameters that vary between subjects. Thus, this modelling approach analyses data at both population and individual levels, while simultaneously considering between-subject variability (BSV) and residual unexplained variability (RUV). The residual random error includes variability associated with assays, as well as dosing and sampling or measurement.

Unlike non-compartmental or standard two-stage approaches, population modelling has the ability to include small subject numbers with intensive sampling, or larger

patient groups that have very sparse datasets. As a consequence, this method is ideal for populations where frequent sampling is ethically or logistically constrained, such as children [18], neonates [19], or critically ill patient populations [20]. Furthermore, nonlinear mixed-effects modelling is less likely to be influenced by outlier subjects or concentration-time data. A useful feature of population analyses is the capacity to handle censored data that are reported as below the limit of quantitation [21].

A key benefit is the ability to explore the relationships between random interindividual variability and subject-specific covariate effects. The BSV is described by predictable and random components (Eq. 1.12):

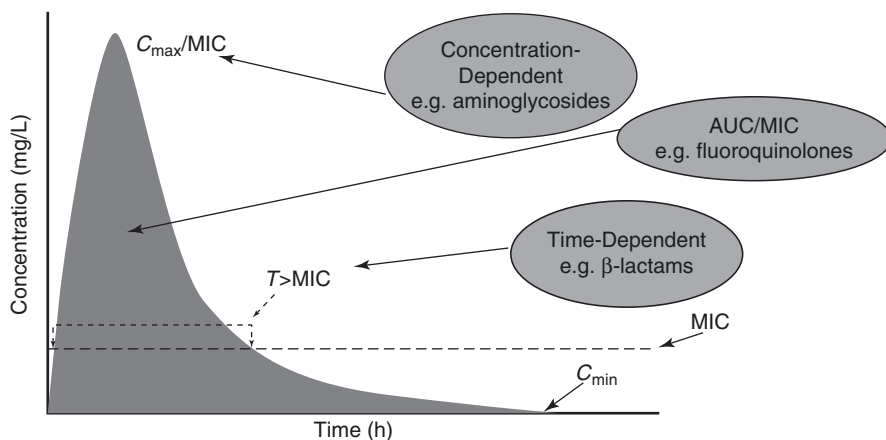
$$BSV_{\text{total}} = BSV_{\text{predictable}} + BSV_{\text{random}} \quad (1.12)$$

where  $BSV_{\text{predictable}}$  refers to that portion of the interindividual variability that is potentially explained by inclusion of a covariate effect. Thus,  $BSV_{\text{random}}$  indicates the remaining aspect that cannot be described by covariates or patient demographics. Thus, an informative covariate will lower the random variability associated with a given individual parameter estimate. Clinically, an understanding of the relationships between PK and covariate effects allows for the applicability of individualized dosing strategies.

Once fully developed, covariate PK models can be used to simulate hypothetical patient subgroups, including extrapolation to pediatric [22] or critically ill populations [20]. Examples of optimized antimicrobial dosing include tobramycin in children with cystic fibrosis [18], as well as cefepime [23] and ceftipime [24] in intensive care patients. In addition, population modelling has also provided valuable insights for dose recommendation of gentamicin [25], fluconazole, [26] and aminoglycosides [27] in renal dysfunction. Several software packages have the capability of conducting population analysis including NONMEM®, Monolix®, Phoenix® NLME, S-ADAPT, or WinBUGS®.

### 1.8.5 Therapeutic Monitoring

From a clinical perspective, the above methods for PK estimation and dose individualization are complex and relatively time consuming. Furthermore, therapeutic drug monitoring rarely provides intensive sampling, with only peak or trough concentrations. Dose adjustment is therefore often undertaken using first principles or educated guesses, rather than applying a formal PK modelling approach. A practical alternative is the use of Bayesian forecasting that incorporate established PK models with covariate-parameter relationships defined a priori. Individualized patient parameters can then be used to obtain a complete PK profile, with the ability to optimize dosing so that target concentrations are achieved [18, 27]. Bayesian methods can therefore allow for the development of improved outcomes and reduced toxicity following therapy in a practical clinical setting. Software packages that are suitable for Bayesian approaches and therapeutic monitoring include TCIWorks or USC-PAK.



**Fig. 1.3** Pharmacokinetic and pharmacodynamic parameters of antibiotics on a concentration-time curve. Key:  $T > \text{MIC}$  is the time for which a drug's plasma concentration remains above the minimum inhibitory concentration (MIC) for a dosing period;  $C_{\max}/\text{MIC}$ , the ratio of the maximum plasma antibiotic concentration ( $C_{\max}$ ) to MIC;  $\text{AUC}/\text{MIC}$ , the ratio of the area under the concentration-time curve during a 24 h time period ( $\text{AUC}_{0-24}$ ) to MIC. Adapted from [20]

## 1.9 Pharmacodynamic Indices

For antimicrobial agents, the ability to inhibit or kill the growth of an infective organism is related to the exposures achieved at a given dose [28]. The PD index is defined by determining the PK exposure relative to an *in vitro* measure known as the Minimum Inhibitory Concentration (MIC). Kill or inhibition characteristics of antibiotics are described as concentration- or time dependent or a combination of both. Thus, concentration-dependent killing is a measure of the ratio of  $C_{\max}$  to the defined MIC (i.e.,  $C_{\max}/\text{MIC}$ ). In contrast, time-dependence is characterized by the duration that an antimicrobial remains above the MIC in a given dosing interval (i.e.,  $T > \text{MIC}$ ). The ratio of AUC at 24 h to the MIC (i.e.,  $\text{AUC}_{0-24}/\text{MIC}$ ) describes drugs with both concentration- and time-dependent killing (Fig. 1.3). Examples of antibiotics classified using these PD indices include the aminoglycosides (concentration-dependent),  $\beta$ -lactams (time-dependent), and fluoroquinolones (concentration- with time-dependence) [20]. While the MIC is routinely used for PD assessment, a possible disadvantage is that it is routinely measured at a single time that ignore potential kinetic differences.

## 1.10 Critical Illness

In intensive care patients, pathophysiological changes are common and can influence changes in the time course of drug concentration. The extrapolation of loading or maintenance dose regimens using PK from healthy volunteer studies is therefore inappropriate for maximizing therapeutic benefit (Table 1.1).

**Table 1.1** Influence of altered physiology on pharmacokinetics and recommendations to improve dosing strategies

Physiology	PK effect	Possible drug effect	Dosing recommendation
↓ Intravascular volume	↑ Observed $C_{max}$	Toxicity	↑ Infusion time
↑ Capillary leakage	↓ $C_{max}$ ; ↑ $V_d$	Therapeutic failure	↑ Loading does; maintain daily dose
↑ Organ function	↑ CL	Therapeutic failure	↑ Daily dose
↓ Organ function	↓ CL	Toxicity	Maintain initial does; ↓ daily dose
Stress response	↑ AAG binding	Therapeutic failure	↑ Loading does; maintain daily does

Summarized from [8]

Several demographic factors may influence drug clearance in both healthy adult volunteers and critically ill patients. A theoretical basis exists for the allometric scaling of clearance to total bodyweight, based on evidence for metabolic rates in mammals [29, 30]. However, scaling to total bodyweight does not generally apply in the obese population, for which lean body weight is a more suitable size descriptor [31, 32]. Age or critical illness can also alter the clearance of some drugs, primarily due to renal dysfunction or metabolic insufficiency [20]. Furthermore, patients admitted to intensive care units usually receive several co-administered drugs, as a consequence of multiple changes in normal physiology or organ failure. Drug–drug interactions may therefore contribute to alterations drug clearance, when two or more therapies are used for treatment [20].

In critical illness and sepsis, bacterial or fungal endotoxins may stimulate the production of endogenous mediators, thereby increasing capillary permeability and endothelial damage [33]. This change in capillary structure causes a corresponding transfer of fluid from the vasculature to the interstitial space [34]. As a consequence of leaky capillary development, drug distribution can occur into regions that are usually restricted by the normal vasculature. Thus, critically ill patients could potentially have larger volumes of distribution than expected in a typical population, thereby lowering the concentrations achieved in the systemic circulation [20].

Hypoalbuminemia or elevated to  $\alpha_1$ -acid glycoprotein often occurs during critical illness, thus modifying overall concentrations of protein in plasma [35]. Higher unbound concentrations are observed for ceftriaxone in intensive care subjects due to hypoalbuminemia, increased volume of distribution and reduced clearance [36].

### 1.10.1 Antibiotic Dosing Considerations

*Aminoglycosides* demonstrate concentration-dependent killing, with a post-antibiotic effect that prevents bacterial regrowth even after drug concentrations fall below the MIC [37]. This class of antibiotics often show increased distribution volumes in critical care, with a consequent reduction in attained  $C_{max}$  exposures

[38–40]. Appropriate  $C_{\max}$ -to-MIC ratios are consistently achieved using maximal weight-based dosing regimens, such as 7 mg/kg for gentamicin or tobramycin [39]. An extended-interval dosing regimen is recommended to optimize aminoglycoside effectiveness, with simultaneous monitoring of trough concentrations to avoid toxicity [20].

*$\beta$ -lactams* are hydrophilic drugs that are renally eliminated and have a slow continuous kill characteristic that is time dependent [41]. Thus, treatment with this class of antibiotics must consider high glomerular filtration rates and/or increased distribution volume, which are common in the critically ill [20]. Favorable PK-PD outcomes are obtained with frequent dosing or extended continuous infusions [42, 43]. Altered  $\beta$ -lactam clearance due to renal or hepatic dysfunction, with corresponding increase in biliary elimination is also relevant to the intensive care setting [44, 45].

*Carbapenems* have comparable PK-PD to  $\beta$ -lactams and show time-dependent bactericidal effect when  $T > \text{MIC}$  is maintained for 40% of the dosing interval. In critical illness, increased distribution volume and higher clearance is reported for these antibiotics [46]. Optimal activity is suggested using continuous or extended carbapenem infusion, which is suitable for achieving the time-dependent PD index [47].

*Colistin* is a polymyxin antibiotic that is formed by hydrolysis following administration as the sodium colistin methanesulphate prodrug. These drugs demonstrate concentration-dependent bacterial killing [48, 49].

*Fluoroquinolones* are highly lipophilic antibiotics that are widely distributed to extra- and intracellular spaces, including neutrophil and lymphocyte penetration [50]. However, the volumes of distribution of most fluoroquinolones are generally less affected in intensive care subjects. The exception is levofloxacin, for which increased loading doses is required in the critically ill setting [51, 52]. These antibiotics display concentration- and some time-dependent killing of the infecting pathogen, with  $C_{\max}$ - or AUC-to-MIC ratios of 10 and 125 describing optimal microbial eradication, respectively [53, 54].

*Glycopeptides* are relatively hydrophilic for which the PD indices that produce maximum therapeutic benefit are relatively unknown. The elimination of these antibiotics is predominantly associated with creatinine clearance and significant variability in this PK parameter is observed for vancomycin in acute kidney failure [55–57]. As a result, therapeutic monitoring of achieved trough concentrations is suggested, with high minimum concentrations (>20 mg/L) of vancomycin potentially increasing the risk of nephrotoxicity [58].

*Linezolid*s are hydrophilic drugs that show extensive tissue distribution and are primarily cleared by hepatic metabolism with a minor component of renal elimination [59, 60]. The PD index is time dependent, with a 600 mg twice daily regimen maintaining target  $T > \text{MIC}$  at 40–80% throughout the dosing interval [59]. However, critical illness is not expected to influence the PD outcome of linezolid antibiotics, and dose adjustment is not recommended for hepatic or renal dysfunction [59, 60].

## 1.11 Conclusions

In conclusion, this chapter reviews the basic principles that define the pharmacokinetics of drugs following dose administration. An understanding of these theoretical concepts is essential to better consider appropriate dose adjustment with pathophysiological changes in intensive care patients. More specifically, antibiotic dosing considerations, with reference to PK-PD indices are presented. These examples demonstrate how an understanding of the time course of drug concentration can result in recommendations that individualize antibiotic dosing in the critical care setting.

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