Andrew A. Udy
Jason A. Roberts
Jeffrey Lipman *Editors*

Antibiotic Pharmacokinetic/ Pharmacodynamic Considerations in the Critically Ill

Adis

Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill

Andrew A. Udy • Jason A. Roberts • Jeffrey Lipman
Editors

Antibiotic Pharmacokinetic/ Pharmacodynamic Considerations in the Critically Ill

Adis

Editors
Andrew A. Udy
Australian and New Zealand Intensive Care Research Centre
School of Public Health and Preventive Medicine, Monash University
Melbourne
Victoria
Australia

Jason A. Roberts
Burns, Trauma and Critical Care Research Centre
The University of Queensland
UQ Centre for Clinical Research
Herston
Queensland
Australia

Jeffrey Lipman
Burns, Trauma and Critical Care Research Centre
The University of Queensland
Herston
Queensland
Australia

ISBN 978-981-10-5335-1 ISBN 978-981-10-5336-8 (eBook)
DOI 10.1007/978-981-10-5336-8

Library of Congress Control Number: 2017952539

Printed on acid-free paper

This Adis imprint is published by Springer Nature
The registered company is Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

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.

Melbourne, VIC, Australia — Andrew A. Udy
Herston, QLD, Australia — Jason A. Roberts
Herston, QLD, Australia — Jeffrey Lipman

References

1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 29(7):1303–1310. PubMed PMID: 11445675
2. Adhikari NK, Fowler RA, Bhagwanjee S, Rubenfeld GD (2010) Critical care and the global burden of critical illness in adults. Lancet 376(9749):1339–1346. PubMed PMID: 20934212
3. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al (2013) Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 39(2):165–228. PubMed PMID: 23361625
4. Artenstein AW, Higgins TL, Opal SM (2013) Sepsis and scientific revolutions. Crit Care Med 41(12):2770–2772. PubMed PMID: 23989175
5. Gaieski DF, Edwards JM, Kallan MJ, Carr BG (2013) Benchmarking the incidence and mortality of severe sepsis in the United States. Crit Care Med 41(5):1167–1174. PubMed PMID: 23442987
6. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R (2014) Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. JAMA 311(13):1308–1316. PubMed PMID: 24638143

7. Wang HE, Szychowski JM, Griffin R, Safford MM, Shapiro NI, Howard G (2014) Long-term mortality after community-acquired sepsis: a longitudinal population-based cohort study. BMJ Open 4(1):e004283. PubMed PMID: 24441058. Pubmed Central PMCID: 3902401
8. Levy MM, Rhodes A, Phillips GS, Townsend SR, Schorr CA, Beale R, et al. (2015) Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5-year study. Crit Care Med 43(1):3–12. PubMed PMID: 25275252
9. Eagye KJ, Banevicius MA, Nicolau DP (2012) Pseudomonas aeruginosa is not just in the intensive care unit any more: implications for empirical therapy. Crit Care Med 40(4):1329–1332. PubMed PMID: 22425824
10. Roberts JA, Kruger P, Paterson DL, Lipman J (2008) Antibiotic resistance—what's dosing got to do with it? Crit Care Med 36(8):2433–2440. PubMed PMID: 18596628

Contents

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.

K. Patel (✉)
Monash University, Melbourne, VIC, Australia

d3 Medicine, A Certara Company, Melbourne, VIC, Australia
e-mail: kashyap.patel@monash.edu

C.M. Kirkpatrick
Monash University, Melbourne, VIC, Australia
e-mail: carl.kirkpatrick@monash.edu

A.A. Udy et al. (eds.), *Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill*, DOI 10.1007/978-981-10-5336-8_1

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):

$$\mathrm{CL}_{\mathrm{tot}} = \mathrm{CL}_{\mathrm{met}} + \mathrm{CL}_{\mathrm{ren}} + \mathrm{CL}_{\mathrm{bil}} + \mathrm{CL}_{\mathrm{oth}} \tag{1.1}$$

where $\mathrm{CL}_{\mathrm{met}}$, $\mathrm{CL}_{\mathrm{ren}}$, $\mathrm{CL}_{\mathrm{bil}}$, and $\mathrm{CL}_{\mathrm{oth}}$ 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):

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

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):

$$\mathrm{CL}_{\mathrm{organ}} = Q \times E \tag{1.3}$$

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):

$$\text{Rate of drug elimination} = \text{CL} \times C \tag{1.4}$$

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):

$$\text{Maintenence dosing rate} = \text{CL} \times C_{\text{ss ave.}} \tag{1.5}$$

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):

$$\text{CL} = \frac{\text{Dose}}{\text{AUC}} \tag{1.6}$$

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

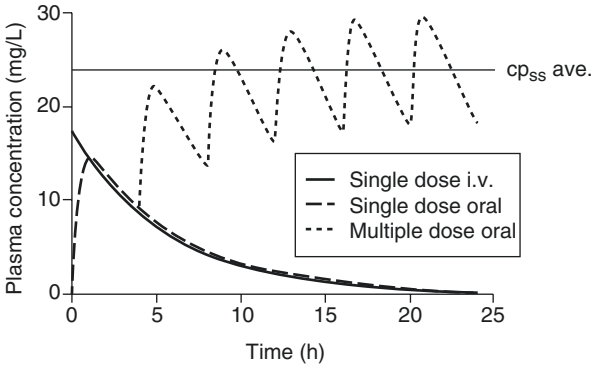

Fig. 1.1 Concentration-time profile of a hypothetical drug administered at 100 mg by single intravenous (*line*), single oral (*dashed line*), or multiple oral (*dotted line*) dosing. The latter illustrates use of maintenance dosing to achieve average steady-state plasma drug concentrations (Cpss ave.), 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 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):

$$\text{Dose} = C \times V_d \tag{1.7}$$

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 ~ 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].

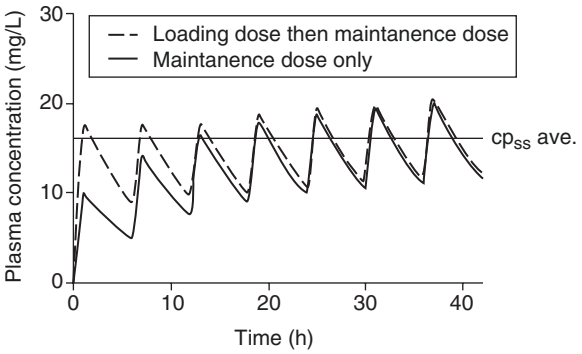

Fig. 1.2 Demonstration of loading dose to quickly achieve average steady-state plasma drug concentrations (Cpss ave.). A loading dose of 1 g vancomycin was administered by intravenous infusion (1 h), followed by maintenance dosing of 500 mg every 6 h. Vancomycin pharmacokinetics is described for a 70 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.

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

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.

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

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

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

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 α_1-acid glycoprotein or β-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).

$$F = \frac{\text{AUC}_{\text{extravascular}}}{\text{AUC}_{\text{intravenous}}} \tag{1.11}$$

The rate of drug absorption is determined by the time at which maximal concentration is achieved (T_{max}). Thus, oral formulations that are designed as slow, sustained, or controlled release, allow for a delayed T_{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 modelling 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 of explore the relationships between random interindividual variability and subject-specific covariate effects. The BSV is described by predictable and random components (Eq. 1.12):

$$\mathrm{BSV}_{\mathrm{total}} = \mathrm{BSV}_{\mathrm{predictable}} + \mathrm{BSV}_{\mathrm{random}} \tag{1.12}$$

where $\mathrm{BSV}_{\mathrm{predictable}}$ refers to that portion of the interindividual variability that is potentially explained by inclusion of a covariate effect. Thus, $\mathrm{BSV}_{\mathrm{random}}$ 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 cefpirome [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.

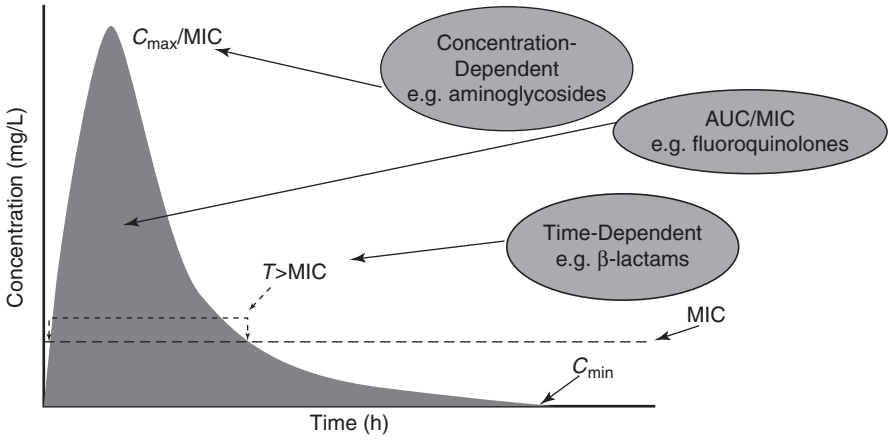

Fig. 1.3 Pharmacokinetic and pharmacodynamic parameters of antibiotics on a concentration-time curve. Key: $T >$ MIC is the time for which a drug's plasma concentration remains above the minimum inhibitory concentration (MIC) for a dosing period; C_{max}/MIC, the ratio of the maximum plasma antibiotic concentration (C_{max}) to MIC; AUC/MIC, the ratio of the area under the concentration-time curve during a 24 h time period ($AUC_{0–24}$) 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}/MIC). In contrast, time-dependence is characterized by the duration that an antimicrobial remains above the MIC in a given dosing interval (i.e., $T >$ MIC). The ratio of AUC at 24 h to the MIC (i.e., $AUC_{0–24}$/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), β-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 α_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].

β-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 β-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 β-lactams and show time-dependent bactericidal effect when $T > MIC$ 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 through concentrations is suggested, with high minimum concentrations (>20 mg/L) of vancomycin potentially increasing the risk of nephrotoxicity [58].

Linezolids 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 $T > MIC$ 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.

References

1. Begg EJ (2008) Instant clinical pharmacology, 2nd edn. Blackwell, Christchurch
2. Rowland M, Tozer TN (1995) Clinical pharmacokinetics: concepts and applications, 3rd edn. Williams & Wilkins, Philadelphia
3. Al-Sallami HS, Pavan Kumar VV, Landersdorfer CB, Bulitta JB, Duffull SB (2009) The time course of drug effects. Pharm Stat 8(3):176–185. doi:10.1002/pst.393
4. Holford N (1992) Clinical pharmacokinetics and pharmacodynamics: the quantitative basis for therapeutics. In: Melmon K, Morrelli H, Nierenberg D, Hoffman B (eds) Melmon and morrelli's clinical pharmacology: basic principles in therapeutics, 3rd edn. McGraw-Hill, New York, p 1141
5. Welling PG (1995) Differences between pharmacokinetics and toxicokinetics. Toxicol Pathol 23(2):143–147
6. Nauta EH, Mattie H (1976) Dicloxacillin and cloxacillin: pharmacokinetics in healthy and hemodialysis subjects. Clin Pharmacol Ther 20(1):98–108
7. Paintaud G, Alvan G, Dahl ML, Grahnen A, Sjovall J, Svensson JO (1992) Nonlinearity of amoxicillin absorption kinetics in human. Eur J Clin Pharmacol 43(3):283–288
8. Patel K, Kirkpatrick CM (2011) Pharmacokinetic concepts revisited—basic and applied. Curr Pharm Biotechnol 12(12):1983–1990
9. Bauer LA, Blouin RA (1983) Influence of age on amikacin pharmacokinetics in patients without renal disease. Comparison with gentamicin and tobramycin. Eur J Clin Pharmacol 24(5):639–642
10. Bauer LA, Blouin RA (1982) Gentamicin pharmacokinetics: effect of aging in patients with normal renal function. J Am Geriatr Soc 30(5):309–311
11. Ulldemolins M, Rello J (2011) The relevance of drug volume of distribution in antibiotic dosing. Curr Pharm Biotechnol 12(12):1996–2001
12. Petrosillo N, Giannella M, Lewis R, Viale P (2013) Treatment of carbapenem-resistant Klebsiella pneumoniae: the state of the art. Expert Rev Anti-Infect Ther 11(2):159–177
13. Bulitta JB, Holford NHG (2014) Non-compartmental analysis. In: Statistics reference online. Wiley. doi:10.1002/9781118445112.stat06889
14. DiStefano JJ III (1982) Noncompartmental vs. compartmental analysis: some bases for choice. Am J Phys 243(1):R1–R6
15. Sheiner LB (1984) The population approach to pharmacokinetic data analysis: rationale and standard data analysis methods. Drug Metab Rev 15(1–2):153–171. doi:10.3109/03602538409015063

16. Mould DR, Upton RN (2013) Basic concepts in population modeling, simulation, and model-based drug development-part 2: introduction to pharmacokinetic modeling methods. CPT Pharmacometrics Syst Pharmacol 2:e38. doi:10.1038/psp.2013.14
17. Mould DR, Upton RN (2012) Basic concepts in population modeling, simulation, and model-based drug development. CPT Pharmacometrics Syst Pharmacol 1:e6. doi:10.1038/psp.2012.4
18. Hennig S, Norris R, Kirkpatrick CM (2008) Target concentration intervention is needed for tobramycin dosing in paediatric patients with cystic fibrosis—a population pharmacokinetic study. Br J Clin Pharmacol 65(4):502–510. doi:10.1111/j.1365-2125.2007.03045.x
19. Stickland MD, Kirkpatrick CM, Begg EJ, Duffull SB, Oddie SJ, Darlow BA (2001) An extended interval dosing method for gentamicin in neonates. J Antimicrob Chemother 48(6):887–893
20. Roberts JA, Lipman J (2009) Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 37(3):840–851.; Quiz 859. doi:10.1097/CCM.0b013e3181961bff
21. Beal SL (2001) Ways to fit a PK model with some data below the quantification limit. J Pharmacokinet Pharmacodyn 28(5):481–504
22. Holford N, Heo YA, Anderson B (2013) A pharmacokinetic standard for babies and adults. J Pharm Sci 102(9):2941–2952. doi:10.1002/jps.23574
23. Roos JF, Bulitta J, Lipman J, Kirkpatrick CM (2006) Pharmacokinetic-pharmacodynamic rationale for cefepime dosing regimens in intensive care units. J Antimicrob Chemother 58(5):987–993. doi:10.1093/jac/dkl349
24. Roos JF, Lipman J, Kirkpatrick CM (2007) Population pharmacokinetics and pharmacodynamics of cefpirome in critically ill patients against Gram-negative bacteria. Intensive Care Med 33(5):781–788. doi:10.1007/s00134-007-0573-7
25. Roberts JA, Field J, Visser A, Whitbread R, Tallot M, Lipman J, Kirkpatrick CM (2010) Using population pharmacokinetics to determine gentamicin dosing during extended daily diafiltration in critically ill patients with acute kidney injury. Antimicrob Agents Chemother 54(9):3635–3640. doi:10.1128/aac.00222-10
26. Patel K, Roberts JA, Lipman J, Tett SE, Deldot ME, Kirkpatrick CM (2011) Population pharmacokinetics of fluconazole in critically ill patients receiving continuous venovenous hemodiafiltration: using Monte Carlo simulations to predict doses for specified pharmacodynamic targets. Antimicrob Agents Chemother 55(12):5868–5873. doi:10.1128/aac.00424-11
27. Matthews I, Kirkpatrick C, Holford N (2004) Quantitative justification for target concentration intervention—parameter variability and predictive performance using population pharmacokinetic models for aminoglycosides. Br J Clin Pharmacol 58(1):8–19. doi:10.1111/j.1365-2125.2004.02114.x
28. Craig WA (2003) Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. Infect Dis Clin N Am 17(3):479–501
29. West GB, Brown JH, Enquist BJ (1997) A general model for the origin of allometric scaling laws in biology. Science 276(5309):122–126
30. West GB, Brown JH, Enquist BJ (1999) The fourth dimension of life: fractal geometry and allometric scaling of organisms. Science 284(5420):1677–1679
31. Duffull SB, Dooley MJ, Green B, Poole SG, Kirkpatrick CM (2004) A standard weight descriptor for dose adjustment in the obese patient. Clin Pharmacokinet 43(15):1167–1178. doi:10.2165/00003088-200443150-00007
32. Han PY, Duffull SB, Kirkpatrick CM, Green B (2007) Dosing in obesity: a simple solution to a big problem. Clin Pharmacol Ther 82(5):505–508. doi:10.1038/sj.clpt.6100381
33. van der Poll T (2001) Immunotherapy of sepsis. Lancet Infect Dis 1(3):165–174. doi:10.1016/s1473-3099(01)00093-7
34. Gosling P, Sanghera K, Dickson G (1994) Generalized vascular permeability and pulmonary function in patients following serious trauma. J Trauma 36(4):477–481
35. Arredondo G, Martinez-Jorda R, Calvo R, Aguirre C, Suarez E (1994) Protein binding of itraconazole and fluconazole in patients with chronic renal failure. Int J Clin Pharmacol Ther 32(7):361–364

36. Joynt GM, Lipman J, Gomersall CD, Young RJ, Wong EL, Gin T (2001) The pharmacokinetics of once-daily dosing of ceftriaxone in critically ill patients. J Antimicrob Chemother 47(4):421–429
37. Vogelman B, Craig WA (1986) Kinetics of antimicrobial activity. J Pediatr 108(5 Pt 2):835–840
38. Beckhouse MJ, Whyte IM, Byth PL, Napier JC, Smith AJ (1988) Altered aminoglycoside pharmacokinetics in the critically ill. Anaesth Intensive Care 16(4):418–422
39. Buijk SE, Mouton JW, Gyssens IC, Verbrugh HA, Bruining HA (2002) Experience with a once-daily dosing program of aminoglycosides in critically ill patients. Intensive Care Med 28(7):936–942. doi:10.1007/s00134-002-1313-7
40. Triginer C, Izquierdo I, Fernandez R, Rello J, Torrent J, Benito S, Net A (1990) Gentamicin volume of distribution in critically ill septic patients. Intensive Care Med 16(5):303–306
41. McKinnon PS, Paladino JA, Schentag JJ (2008) Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int J Antimicrob Agents 31(4):345–351. doi:10.1016/j.ijantimicag.2007.12.009
42. Boselli E, Breilh D, Cannesson M, Xuereb F, Rimmele T, Chassard D, Saux MC, Allaouchiche B (2004) Steady-state plasma and intrapulmonary concentrations of piperacillin/tazobactam 4 g/0.5 g administered to critically ill patients with severe nosocomial pneumonia. Intensive Care Med 30(5):976–979. doi:10.1007/s00134-004-2222-8
43. Lipman J, Gomersall CD, Gin T, Joynt GM, Young RJ (1999) Continuous infusion ceftazidime in intensive care: a randomized controlled trial. J Antimicrob Chemother 43(2):309–311
44. Cooper BE, Nester TJ, Armstrong DK, Dasta JF (1986) High serum concentrations of mezlocillin in a critically ill patient with renal and hepatic dysfunction. Clin Pharm 5(9): 764–766
45. Green L, Dick JD, Goldberger SP, Angelopulos CM (1985) Prolonged elimination of piperacillin in a patient with renal and liver failure. Drug Intell Clin Pharm 19(6):427–429
46. Novelli A, Adembri C, Livi P, Fallani S, Mazzei T, De Gaudio AR (2005) Pharmacokinetic evaluation of meropenem and imipenem in critically ill patients with sepsis. Clin Pharmacokinet 44(5):539–549
47. Li C, Kuti JL, Nightingale CH, Nicolau DP (2006) Population pharmacokinetic analysis and dosing regimen optimization of meropenem in adult patients. J Clin Pharmacol 46(10):1171–1178. doi:10.1177/0091270006291035
48. Tam VH, Schilling AN, Vo G, Kabbara S, Kwa AL, Wiederhold NP, Lewis RE (2005) Pharmacodynamics of polymyxin B against Pseudomonas aeruginosa. Antimicrob Agents Chemother 49(9):3624–3630. doi:10.1128/aac.49.9.3624-3630.2005
49. Nation RL, Li J (2007) Optimizing use of colistin and polymyxin B in the critically ill. Semin Respir Crit Care Med 28(6):604–614. doi:10.1055/s-2007-996407
50. Smith RP, Baltch AL, Franke MA, Michelsen PB, Bopp LH (2000) Levofloxacin penetrates human monocytes and enhances intracellular killing of Staphylococcus aureus and Pseudomonas aeruginosa. J Antimicrob Chemother 45(4):483–488
51. Kiser TH, Hoody DW, Obritsch MD, Wegzyn CO, Bauling PC, Fish DN (2006) Levofloxacin pharmacokinetics and pharmacodynamics in patients with severe burn injury. Antimicrob Agents Chemother 50(6):1937–1945. doi:10.1128/aac.01466-05
52. Pea F, Di Qual E, Cusenza A, Brollo L, Baldassarre M, Furlanut M (2003) Pharmacokinetics and pharmacodynamics of intravenous levofloxacin in patients with early-onset ventilator-associated pneumonia. Clin Pharmacokinet 42(6):589–598
53. Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ (1993) Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 37(5):1073–1081
54. Preston SL, Drusano GL, Berman AL, Fowler CL, Chow AT, Dornseif B, Reichl V, Natarajan J, Corrado M (1998) Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. JAMA 279(2):125–129

55. Llopis-Salvia P, Jimenez-Torres NV (2006) Population pharmacokinetic parameters of vancomycin in critically ill patients. J Clin Pharm Ther 31(5):447–454. doi:10.1111/j.1365-2710.2006.00762.x
56. Macias WL, Mueller BA, Scarim SK (1991) Vancomycin pharmacokinetics in acute renal failure: preservation of nonrenal clearance. Clin Pharmacol Ther 50(6):688–694
57. Udy AA, Covajes C, Taccone FS, Jacobs F, Vincent JL, Lipman J, Roberts JA (2013) Can population pharmacokinetic modelling guide vancomycin dosing during continuous renal replacement therapy in critically ill patients? Int J Antimicrob Agents 41(6):564–568. doi:10.1016/j.ijantimicag.2013.01.018
58. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A (2006) High-dose vancomycin therapy for methicillin-resistant Staphylococcus aureus infections: efficacy and toxicity. Arch Intern Med 166(19):2138–2144. doi:10.1001/archinte.166.19.2138
59. MacGowan AP (2003) Pharmacokinetic and pharmacodynamic profile of linezolid in healthy volunteers and patients with Gram-positive infections. J Antimicrob Chemother 51(Suppl 2):ii17–ii25. doi:10.1093/jac/dkg248
60. Brier ME, Stalker DJ, Aronoff GR, Batts DH, Ryan KK, O'Grady M, Hopkins NK, Jungbluth GL (2003) Pharmacokinetics of linezolid in subjects with renal dysfunction. Antimicrob Agents Chemother 47(9):2775–2780

Chapter 2
Antibiotic Pharmacodynamics

Fekade B. Sime and Jason A. Roberts

2.1 Introduction

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

F.B. Sime
Centre for Translational Anti-infective Pharmacodynamics, School of Pharmacy, The University of Queensland, 20 Cornwall Street PACE Building, Woolloongabba 4102, QLD, Australia
e-mail: f.sime@uq.edu.au

J.A. Roberts (✉)
Centre for Translational Anti-infective Pharmacodynamics, School of Pharmacy, The University of Queensland, 20 Cornwall Street PACE Building, Woolloongabba 4102, QLD, Australia

Burns, Trauma and Critical Care Research Centre, The University of Queensland, UQ Centre for Clinical Research, Building 71/918, Herston Rd, Herston, QLD 4029, Australia

Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Butterfield St, Herston, Brisbane, QLD 4029, Australia

Pharmacy Department, Royal Brisbane and Women's Hospital, Butterfield St, Herston, Brisbane, QLD 4029, Australia
e-mail: j.roberts2@uq.edu.au

A.A. Udy et al. (eds.), *Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill*, DOI 10.1007/978-981-10-5336-8_2

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

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

2.2 Minimum Inhibitory Concentration (MIC) and Susceptibility Break Points

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

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

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

2.3 Characteristic Relationships Between Antibiotic Concentrations and Antibacterial Activity

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

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

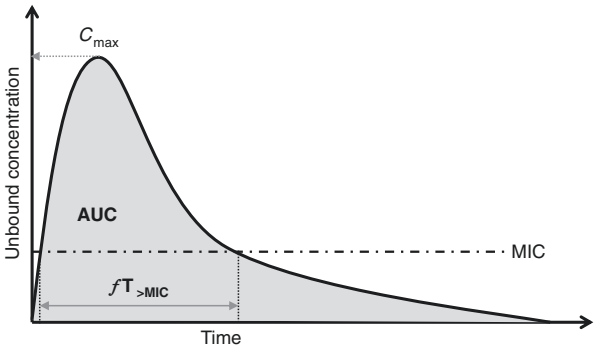

Fig. 2.1 Pharmacokinetic/pharmacodynamic predictors of antibiotic efficacy

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

2.3.1 Time-Dependent Antibiotics

2.3.1.1 Beta-Lactam Antibiotics

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

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

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

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

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

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

2.3.1.2 Vancomycin

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

2.3.1.3 Linezolid

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

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

2.3.1.4 Tetracyclines

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

2.3.2 Concentration-Dependent Antibiotics

2.3.2.1 Aminoglycosides

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

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

2.3.2.2 Quinolones

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

2.4 The Application of Antibiotic Pharmacodynamics into Clinical Practice

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

References

1. Drusano GL (2004) Antimicrobial pharmacodynamics: critical interactions of ‘bug and drug’. Nat Rev Microbiol 2(4):289–300
2. Cadwell JJS (2012) The hollow fiber infection model for antimicrobial pharmacodynamics and pharmacokinetics. Adv Pharmacoepidemiol Drug Saf S1. doi:10.4172/2167-1052.S1-007
3. Christ-Crain M, Muller B (2007) Biomarkers in respiratory tract infections: diagnostic guides to antibiotic prescription, prognostic markers and mediators. Eur Respir J 30(3):556–573
4. Wheat PF (2001) History and development of antimicrobial susceptibility testing methodology. J Antimicrob Chemother 48(Suppl 1):1–4

5. Levison ME (2004) Pharmacodynamics of antimicrobial drugs. Infect Dis Clin N Am 18(3):451–465, vii
6. Drusano GL, Fregeau C, Liu W, Brown DL, Louie A (2010) Impact of burden on granulocyte clearance of bacteria in a mouse thigh infection model. Antimicrob Agents Chemother 54(10):4368–4372
7. European Committee for Antimicrobial Susceptibility Testing of the European Society of Clinical M, Infectious D (2003) Determination of minimum inhibitory concentrations (MICs) of antibacterial agents by broth dilution. Clin Microbiol Infect 9(8):ix–xv
8. Roberts JA, Lipman J (2009) Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 37(3):840–851. Quiz 859
9. Dalhoff A, Ambrose PG, Mouton JW (2009) A long journey from minimum inhibitory concentration testing to clinically predictive breakpoints: deterministic and probabilistic approaches in deriving breakpoints. Infection 37(4):296–305
10. MacGowan AP, Wise R (2001) Establishing MIC breakpoints and the interpretation of in vitro susceptibility tests. J Antimicrob Chemother 48(Suppl 1):17–28
11. Craig W (1993) Pharmacodynamics of antimicrobial agents as a basis for determining dosage regimens. Eur J Clin Microbiol Infect Dis 12(Suppl 1):S6–S8
12. Craig WA (1998) Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 26(1):1–10. quiz 11-12
13. Eagle H, Fleischman R, Levy M (1953) "Continuous" vs. "discontinuous" therapy with penicillin; the effect of the interval between injections on therapeutic efficacy. N Engl J Med 248(12):481–488
14. Vogelman B, Gudmundsson S, Leggett J, Turnidge J, Ebert S, Craig WA (1988) Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. J Infect Dis 158(4):831–847
15. Fluckiger U, Segessenmann C, Gerber AU (1991) Integration of pharmacokinetics and pharmacodynamics of imipenem in a human-adapted mouse model. Antimicrob Agents Chemother 35(9):1905–1910
16. Craig WA, Ebert SC (1990) Killing and regrowth of bacteria in vitro: a review. Scand J Infect Dis Suppl 74:63–70
17. Turnidge JD (1998) The pharmacodynamics of beta-lactams. Clin Infect Dis 27(1):10–22
18. Roosendaal R, Bakker-Woudenberg IA, van den Berghe-van Raffe M, Michel MF (1986) Continuous versus intermittent administration of ceftazidime in experimental Klebsiella pneumoniae pneumonia in normal and leukopenic rats. Antimicrob Agents Chemother 30(3):403–408
19. Casal J, Gimenez MJ, Aguilar L, Yuste J, Jado I, Tarrago D, Fenoll A (2002) Beta-lactam activity against resistant pneumococcal strains is enhanced by the immune system. J Antimicrob Chemother 50(Suppl S2):83–86
20. Gerber AU, Brugger HP, Feller C, Stritzko T, Stalder B (1986) Antibiotic therapy of infections due to Pseudomonas aeruginosa in normal and granulocytopenic mice: comparison of murine and human pharmacokinetics. J Infect Dis 153(1):90–97
21. Ariano RE, Nyhlen A, Donnelly JP, Sitar DS, Harding GK, Zelenitsky SA (2005) Pharmacokinetics and pharmacodynamics of meropenem in febrile neutropenic patients with bacteremia. Ann Pharmacother 39(1):32–38
22. McKinnon PS, Paladino JA, Schentag JJ (2008) Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int J Antimicrob Agents 31(4):345–351
23. Sime FB, Roberts MS, Peake SL, Lipman J, Roberts JA (2012) Does beta-lactam pharmacokinetic variability in critically ill patients justify therapeutic drug monitoring? A systematic review. Ann Intensive Care 2(1):35
24. Wong G, Brinkman A, Benefield RJ, Carlier M, De Waele JJ, El Helali N, Frey O, Harbarth S, Huttner A, McWhinney B et al (2014) An international, multicentre survey of beta-lactam antibiotic therapeutic drug monitoring practice in intensive care units. J Antimicrob Chemother 69(5):1416–1423

25. De Waele JJ, Carrette S, Carlier M, Stove V, Boelens J, Claeys G, Leroux-Roels I, Hoste E, Depuydt P, Decruyenaere J et al (2014) Therapeutic drug monitoring-based dose optimisation of piperacillin and meropenem: a randomised controlled trial. Intensive Care Med 40(3):380–387
26. Roberts JA, Ulldemolins M, Roberts MS, McWhinney B, Ungerer J, Paterson DL, Lipman J (2010) Therapeutic drug monitoring of beta-lactams in critically ill patients: proof of concept. Int J Antimicrob Agents 36(4):332–339
27. Mouton JW, den Hollander JG (1994) Killing of Pseudomonas aeruginosa during continuous and intermittent infusion of ceftazidime in an in vitro pharmacokinetic model. Antimicrob Agents Chemother 38(5):931–936
28. Li C, Du X, Kuti JL, Nicolau DP (2007) Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. Antimicrob Agents Chemother 51(5):1725–1730
29. Tam VH, Schilling AN, Neshat S, Poole K, Melnick DA, Coyle EA (2005) Optimization of meropenem minimum concentration/MIC ratio to suppress in vitro resistance of Pseudomonas aeruginosa. Antimicrob Agents Chemother 49(12):4920–4927
30. Seok J, Warren HS, Cuenca AG, Mindrinos MN, Baker HV, Xu W, Richards DR, McDonald-Smith GP, Gao H, Hennessy L et al (2013) Genomic responses in mouse models poorly mimic human inflammatory diseases. Proc Natl Acad Sci U S A 110(9):3507–3512
31. Raven K (2012) Rodent models of sepsis found shockingly lacking. Nat Med 18(7):998
32. Larsson AJ, Walker KJ, Raddatz JK, Rotschafer JC (1996) The concentration-independent effect of monoexponential and biexponential decay in vancomycin concentrations on the killing of Staphylococcus aureus under aerobic and anaerobic conditions. J Antimicrob Chemother 38(4):589–597
33. Lowdin E, Odenholt I, Cars O (1998) In vitro studies of pharmacodynamic properties of vancomycin against Staphylococcus aureus and Staphylococcus epidermidis. Antimicrob Agents Chemother 42(10):2739–2744
34. Henson KE, Levine MT, Wong EA, Levine DP (2015) Glycopeptide antibiotics: evolving resistance, pharmacology and adverse event profile. Expert Rev Anti-Infect Ther 13(10):1265–1278
35. 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(13):925–942
36. Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC, Craig WA, Billeter M, Dalovisio JR, Levine DP (2009) Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis 49(3):325–327
37. Neely MN, Youn G, Jones B, Jelliffe RW, Drusano GL, Rodvold KA, Lodise TP (2014) Are vancomycin trough concentrations adequate for optimal dosing? Antimicrob Agents Chemother 58(1):309–316
38. Craig WA (2003) Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. Infect Dis Clin N Am 17(3):479–501
39. Matsumoto K, Watanabe E, Kanazawa N, Fukamizu T, Shigemi A, Yokoyama Y, Ikawa K, Morikawa N, Takeda Y (2016) Pharmacokinetic/pharmacodynamic analysis of teicoplanin in patients with MRSA infections. Clin Pharm 8:15–18
40. Hagihara M, Umemura T, Kimura M, Mori T, Hasegawa T, Mikamo H (2012) Exploration of optimal teicoplanin dosage based on pharmacokinetic parameters for the treatment of intensive care unit patients infected with methicillin-resistant Staphylococcus aureus. J Infect Chemother 18(1):10–16
41. Andes D, van Ogtrop ML, Peng J, Craig WA (2002) In vivo pharmacodynamics of a new oxazolidinone (linezolid). Antimicrob Agents Chemother 46(11):3484–3489
42. Jacqueline C, Batard E, Perez L, Boutoille D, Hamel A, Caillon J, Kergueris MF, Potel G, Bugnon D (2002) In vivo efficacy of continuous infusion versus intermittent dosing of linezolid compared to vancomycin in a methicillin-resistant Staphylococcus aureus rabbit endocarditis model. Antimicrob Agents Chemother 46(12):3706–3711

43. Rayner CR, Forrest A, Meagher AK, Birmingham MC, Schentag JJ (2003) Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. Clin Pharmacokinet 42(15):1411–1423
44. Wong G, Sime FB, Lipman J, Roberts JA (2014) How do we use therapeutic drug monitoring to improve outcomes from severe infections in critically ill patients? BMC Infect Dis 14:288
45. Agwuh KN, MacGowan A (2006) Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. J Antimicrob Chemother 58(2):256–265
46. Meagher AK, Passarell JA, Cirincione BB, Van Wart SA, Liolios K, Babinchak T, Ellis-Grosse EJ, Ambrose PG (2007) Exposure-response analyses of tigecycline efficacy in patients with complicated skin and skin-structure infections. Antimicrob Agents Chemother 51(6):1939–1945
47. van Ogtrop ML, Andes D, Stamstad TJ, Conklin B, Weiss WJ, Craig WA, Vesga O (2000) In vivo pharmacodynamic activities of two glycylcyclines (GAR-936 and WAY 152,288) against various gram-positive and gram-negative bacteria. Antimicrob Agents Chemother 44(4):943–949
48. Jones RN, Ferraro MJ, Reller LB, Schreckenberger PC, Swenson JM, Sader HS (2007) Multicenter studies of tigecycline disk diffusion susceptibility results for Acinetobacter spp. J Clin Microbiol 45(1):227–230
49. Petersen PJ, Jacobus NV, Weiss WJ, Sum PE, Testa RT (1999) In vitro and in vivo antibacterial activities of a novel glycylcycline, the 9-t-butylglycylamido derivative of minocycline (GAR-936). Antimicrob Agents Chemother 43(4):738–744
50. Passarell JA, Meagher AK, Liolios K, Cirincione BB, Van Wart SA, Babinchak T, Ellis-Grosse EJ, Ambrose PG (2008) Exposure-response analyses of tigecycline efficacy in patients with complicated intra-abdominal infections. Antimicrob Agents Chemother 52(1):204–210
51. Lacy MK, Nicolau DP, Nightingale CH, Quintiliani R (1998) The pharmacodynamics of aminoglycosides. Clin Infect Dis 27(1):23–27
52. Ambrose PG Jr, Owens RC, Grasela D (2000) Antimicrobial pharmacodynamics. Med Clin North Am 84(6):1431–1446
53. Turnidge J (2003) Pharmacodynamics and dosing of aminoglycosides. Infect Dis Clin N Am 17(3):503–528, v
54. Moore RD, Lietman PS, Smith CR (1987) Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis 155(1):93–99
55. Craig WA, Redington J, Ebert SC (1991) Pharmacodynamics of amikacin in vitro and in mouse thigh and lung infections. J Antimicrob Chemother 27(Suppl C):29–40
56. Pea F, Poz D, Viale P, Pavan F, Furlanut M (2006) Which reliable pharmacodynamic breakpoint should be advised for ciprofloxacin monotherapy in the hospital setting? A TDM-based retrospective perspective. J Antimicrob Chemother 58(2):380–386
57. Preston SL, Drusano GL, Berman AL, Fowler CL, Chow AT, Dornseif B, Reichl V, Natarajan J, Corrado M (1998) Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. JAMA 279(2):125–129
58. Rodvold KA, Neuhauser M (2001) Pharmacokinetics and pharmacodynamics of fluoroquinolones. Pharmacotherapy 21(10 Pt 2):233S–252S
59. Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ (1993) Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 37(5):1073–1081
60. Zelenitsky SA, Ariano RE (2010) Support for higher ciprofloxacin AUC 24/MIC targets in treating Enterobacteriaceae bloodstream infection. J Antimicrob Chemother 65(8):1725–1732
61. Lister PD, Sanders CC (1999) Pharmacodynamics of levofloxacin and ciprofloxacin against Streptococcus pneumoniae. J Antimicrob Chemother 43(1):79–86

62. Forrest A, Chodosh S, Amantea MA, Collins DA, Schentag JJ (1997) Pharmacokinetics and pharmacodynamics of oral grepafloxacin in patients with acute bacterial exacerbations of chronic bronchitis. J Antimicrob Chemother 40(Suppl A):45–57
63. Turnidge J (1999) Pharmacokinetics and pharmacodynamics of fluoroquinolones. Drugs 58(Suppl 2):29–36
64. Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, Hope WW, Farkas A, Neely MN, Schentag JJ et al (2014) Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis 14(6):498–509
65. Lodise TP, Butterfield J (2011) Use of pharmacodynamic principles to inform beta-lactam dosing: "S" does not always mean success. J Hosp Med 6(Suppl 1):S16–S23
66. Velkov T, Bergen PJ, Lora-Tamayo J, Landersdorfer CB, Li J (2013) PK/PD models in antibacterial development. Curr Opin Microbiol 16(5):573–579
67. Sime FB, Roberts MS, Roberts JA (2015) Optimization of dosing regimens and dosing in special populations. Clin Microbiol Infect 21(10):886–893

Chapter 3
Physiological Manifestations of Critical Illness

Federico Pea

3.1 Introduction

Critical illness is a condition that may greatly affect the pharmacokinetic behavior of antibiotics. It is characterized by several manifestations that may occur because of different underlying diseases. These manifestations, by altering mainly the volume of distribution (Vd) and the clearance (CL) of a given antibiotic, are expected to cause drug overexposure or underexposure when standard doses of antibiotics are administered to critically ill patients.

From a clinical standpoint, critically ill patients are very different from stable patients with normal renal function or even from healthy volunteers. This means that the dose of many antibiotics and the mode of administering them should be different in order to ensure adequate treatment.

3.2 Physicochemical Properties of Antibiotics and Critical Illness

As a rule, the influence that critical illness may exert on antibiotic pharmacokinetics may significantly differ according to the physicochemical properties of the antibiotics (Table 3.1). In this regard, it's very useful to split antibiotics into two major categories, namely hydrophilic and lipophilic agents [1].

F. Pea
Institute of Clinical Pharmacology, Santa Maria della Misericordia University Hospital of Udine, ASUIUD, Udine, Italy

Department of Medicine, University of Udine, Udine, Italy
e-mail: federico.pea@asuiud.sanita.fvg.it

A.A. Udy et al. (eds.), *Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill*, DOI 10.1007/978-981-10-5336-8_3

Table 3.1 Physicochemical properties of the antibiotics

Hydrophilic antibiotics	Lipophilic antibiotics
• Aminoglycosides – Amikacin, gentamicin • Beta-lactams – Penicillins – Cephalosporins – Carbapenems – Monobactams • Colistimethate sodium • Fosfomycin • Glycopeptides – Teicoplanin, vancomycin • Lipoglycopeptides – Dalbavancin, oritavancin, telavancin • Lipopeptides – Daptomycin	• Fluoroquinolones – Ciprofloxacin, levofloxacin, moxifloxacin • Glycylcyclines – Tigecycline • Lincosamides – Clindamycin, lincomycin • Macrolides and azalides – Azithromycin, clarithromycin • Metronidazole • Oxazolidinones – Linezolid, tedizolid • Rifampin

Hydrophilic antibiotics include beta-lactams, aminoglycosides, lipopeptides, lipoglycopeptides, fosfomycin, and colistimethate sodium. All of these agents have two major issues, which require particular attention when clinicians use them for treatment of critically ill patients. Firstly, the Vd of these agents is limited to the extracellular milieu, due to their inability to penetrate cells. This means that whenever the extracellular compartment expands in critical illness, the concentration of these agents decrease, as no drug reservoir within cells is available for retrograde diffusion into the interstitium. This clearly affects the required loading dose (LD) that is the very first dose needed to ensure effective therapeutic concentrations at the infection site. Considering that the LD is directly proportional to the Vd (LD = Vd × target concentration), this means that the LD needed to achieve the target concentration in critically ill patients should be higher than the one needed in clinically stable patients [2]. Secondly, all the hydrophilic antibiotics are almost completely eliminated via the kidneys. As such, drug CL often correlates linearly with creatinine clearance (CrCL) and the maintenance dose (MD) of these agents should be adjusted in relation to the estimated or measured CrCL [2]. CrCL should be measured daily during critical illness, considering the frequent occurrence of fluctuations in renal function, which may significantly modify the elimination rate of these drugs.

Lipophilic antibiotics include fluoroquinolones, macrolides, linezolid, tigecycline, rifampin, clindamycin, and metronidazole. These agents often do not require any particular dosage adjustment in the presence of critical illness (as compared with hydrophilic drugs), neither for the LD, nor the MD [2, 3]. The Vd is large, due to diffusion across the plasmatic membrane. Accordingly, the intracellular compartment represents a reservoir for lipophilic antibiotics, which allows for rapid correction of any interstitial dilution [2] (as the extracellular milieu expands), due to retrograde diffusion out of cells. Additionally, most of these agents (with the notable

exception of levofloxacin) are not renally cleared. They are eliminated mainly by the liver (by the cytochrome P450 pathway, by conjugation, or by biliary secretion) or by ubiquitous enzymatic or nonenzymatic pathways. Although nonlinear, these metabolic pathways are often preserved during critical illness, with significant dysfunction only noted with very severe end-stage diseases [4]. Consistently, no dosage adjustments for the MD of lipophilic antibiotics are usually needed in the critically ill, except that for some agents when in the presence of very severe end-stage liver diseases (i.e., tigecycline) [5].

From this analysis, it appears that clinicians should bear in mind that whenever they use antibiotics for treating critically ill patients, dosing is an issue and requires particular attention for hydrophilic antibiotics, whereas this is not the case for most lipophilic agents.

3.3 Physiological Manifestations of Critical Illness Affecting the Pharmacokinetic Behavior of Hydrophilic Antibiotics

Several physiological manifestations of critical illness may change the pharmacokinetic behavior of hydrophilic antibiotics. The major pharmacokinetic consequences of these manifestations may be summarized in three different scenarios: increased Vd, increased renal CL, or decreased renal CL (Fig. 3.1).

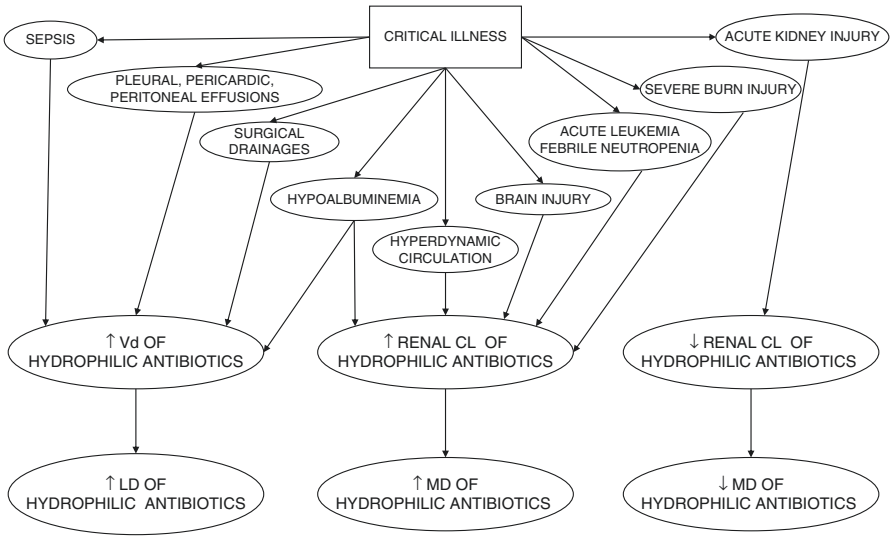

Fig. 3.1 Physiological manifestations of critical illness that may change the pharmacokinetic behavior of hydrophilic antibiotics, and the major pharmacokinetic consequences (Abbreviations: *CL* clearance, *LD* loading dose, *MD* maintenance dose, *Vd* volume of distribution)

3.3.1 Physiological Manifestations Leading to Increased Vd of Hydrophilic Antibiotics

Physiological manifestations that cause increases in the Vd of hydrophilic antibiotics are those responsible for an expansion of the extracellular fluid (ECF) compartment. Considering that the normal ECF volume in healthy subjects is typically <15–20 L, this means that a moderate increase (i.e., 5–10 L) will substantially alter the Vd for agents that are principally confined to this space [2]. Several situations may greatly have an impact on the Vd of hydrophilic antibiotics.

3.3.1.1 Sepsis and Septic Shock

Sepsis is a life-threatening disease, defined as organ dysfunction caused by a dysregulated host response to infection [6]. The sudden capillary leak that occurs leads to increased movement of albumin into tissues, with associated substantial fluid shifts. The expansion of the extracellular milieu causes a significant increase in the Vd of hydrophilic antibiotics. Consistently, the LDs of hydrophilic antibiotics in septic patients should be higher than the standard ones administered to clinically stable patients [2].

Several clinical studies have demonstrated the necessity of administering higher LDs of hydrophilic antibiotics in order to rapidly achieve effective concentrations in septic patients. This is especially relevant for concentration-dependent agents, like aminoglycosides, whose antibacterial activity is related to the peak concentration (C_{max}) to MIC ratio.

In a prospective, randomized study involving 120 patients with severe sepsis or septic shock, researchers assessed the ability to achieve a target C_{max} of >60 mg/L with different loading doses of amikacin. Two enhanced LD regimens (25 and 30 mg/kg/day) were compared with the standard 15 mg/kg/day dose [7]. Peak plasma concentrations at 1 h were significantly higher with these regimens (57.4 ± 9.8 and 72.1 ± 18.4 mg/L, respectively) than after standard dosing (35.2 ± 9.4 μg/mL; $P < 0.001$). Interestingly, whereas the recommended C_{max} (>60 mg/L) was reached by 39 and 76% of patients receiving the 25 and 30 mg/kg/daily dose, none of the patients receiving the standard 15 mg/kg/daily dose achieved the target concentration. These findings are in agreement with the almost 50–60% increase in the Vd of amikacin which was observed in these septic patients (0.44 ± 0.08 L/kg) in comparison with healthy volunteers (0.27 ± 0.06 L/kg). The need for higher amikacin loading in septic patients has also been confirmed by others [8, 9].

Likewise, similar findings in septic patients were recently documented for gentamicin [10]. Accordingly, a higher gentamicin LD of 8 mg/kg has been advocated for achieving the target C_{max} of >30 mg/L in septic patients [11]. A prospective observational cohort study showed that this approach resulted in some patients still having suboptimal concentrations [12].

The need for higher than standard LDs in septic patients was documented also for vancomycin and teicoplanin. A population pharmacokinetic study carried out in 206 critically ill patients with a median acute physiology and chronic health evaluation (APACHE) II score of 21 and mean sequential (sepsis-related) organ failure assessment (SOFA) score of 7.6 showed that the Vd of vancomycin was increased (mean 1.53 L/kg) [13]. Accordingly, Monte Carlo simulations demonstrated that a more than double LD compared to the standard (35 mg/kg vs. 15 mg/kg) may be necessary to rapidly achieve the recommended target vancomycin concentrations of 20 mg/L in septic patients [13]. Likewise, a recent Japanese retrospective study showed that the teicoplanin LD requirement necessary for rapid achievement of the target trough concentration of 15–30 mg/L changed from 12–18 mg/kg/daily up to 24–30 mg/kg/daily in relation to the severity of illness during sepsis (defined as increases of the systemic inflammatory response syndrome score) [14].

3.3.1.2 Hypoalbuminemia

Although hypoalbuminemia is frequent during sepsis due to capillary leak, changes in albumin levels may also occur because of several other underlying diseases. Hypoalbuminemia may be due to a decreased albumin production (i.e., due to aging, hepatic disease, malignancies, malnutrition) or due to increased albumin elimination (i.e., through extensive burns, nephrotic syndrome) [15]. Regardless of which is the underlying cause, it is expected that the Vd of those hydrophilic antibiotics with high plasma protein binding (for more than 80–85%) may significantly be enlarged in all of these situations, due to an increase in the free fraction. Increases in Vd in the presence of hypoalbuminemia were documented for several agents in critically ill patients, including ceftriaxone, daptomycin, ertapenem, flucloxacillin, fusidic acid, and teicoplanin [16]. Increases of Vd ranged from 10% up to 624%, as summarized in the review of Roberts and coworkers [16]. A comparative study also assessed the combined effect that "albumin status" and glycemic status had on the Vd of teicoplanin [17]. Patients were divided into four groups according to their serum albumin and blood glucose concentrations [hyperglycemic hypoalbuminemia (albumin <3.0 g/dL) (n = 16); non-hyperglycemic hypoalbuminemia (n = 29); hyperglycemic normoalbuminemia (albumin ≥3.0 g/dL) (n = 9); and non-hyperglycemic normoalbuminemia (n = 40)]. The authors showed that at 12 h after administration of an LD, patients with hyperglycemic hypoalbuminemia had significantly lower teicoplanin serum concentrations ($P < 0.05$) and higher teicoplanin Vd ($P < 0.05$) than those in the other three groups. Interestingly, it was found that in patients with hyperglycemic hypoalbuminemia, teicoplanin Vd increased in a proportional manner to the percentage of glycosylated albumin [17].

In addition, it should not be overlooked that for those highly plasma protein bound antibiotics that are renally cleared, the increase in the free fraction will result in a more rapid renal CL. This means that also the MD of these antibiotics should be increased in these instances.

3.3.1.3 Pleural, Pericardial, and Peritoneal Effusions

Effusions in serous cavities may generate the so-called third spacing phenomenon, namely an additional compartment into which antibiotics may distribute. This phenomenon is responsible for a consistent increase in the Vd of hydrophilic antibiotics.

Altered pharmacokinetics in the presence of pleural effusions has been documented for aminoglycosides [18], and for meropenem [19]. Likewise, significant increases in Vd were documented in patients with ascites related to end-stage liver diseases, with aminoglycosides [20–22] and with several beta-lactams [23–27]. Additionally, it should not be overlooked that significant alterations in the pharmacokinetics of antibiotics may also occur in patients with indwelling surgical drains, as recently documented for meropenem and piperacillin. In a recent prospective pharmacokinetic study carried out among ten surgical patients with indwelling drains, it was documented that the Vd of both meropenem (median 0.41 L/kg; IQ range 0.35–0.56 L/kg) and piperacillin (median 0.63 L/kg; IQ range 0.38–1.28 L/kg) were increased [28]. Additionally, it was demonstrated that a significant amount of the antibiotic may be lost via surgical drains (median 3.8%; IQ range 2.8–5.4% for meropenem; 8.2%, IQ range 3.3–14.0% for piperacillin), and the amount was linearly correlated with the volume of surgical drain fluid output. These findings led the authors to conclude that when very high drain fluid output is present (>1000 mL/day) an additional dose of antibiotic would be necessary.

3.3.2 Physiological Manifestations Leading to Increased Renal CL of Hydrophilic Antibiotics

Some physiological manifestations may cause an increase in the renal CL of hydrophilic and moderately lipophilic antibiotics. It has been hypothesized that the common mechanism involves augmentation of renal blood flow, which in turn leads to an increase of glomerular filtration rate and/or tubular secretion. Accordingly, it has been recently proposed to define the condition of augmented renal CL (ARC) whenever supra-physiological glomerular filtration rates occur (CrCL >130 mL/min/1.73 m^2) [29].

Recent studies suggest that ARC may occur more frequently with specific underlying diseases [30]. In these conditions, higher than standard MDs of hydrophilic antibiotics have been advocated for achieving therapeutically effective concentrations in these circumstances [3, 31–33].

3.3.2.1 Hyperdynamic Circulation

A hyperdynamic circulation is frequently present in the early phase of sepsis due to an increased cardiac output [34], and this may lead to increased renal blood flow and to glomerular hyperfiltration with ARC. As a consequence, in patients with hyperdynamic sepsis, the renal elimination of antibiotics may occur much faster than in clinically stable patients. In a population pharmacokinetic study carried out

in a cohort of 50 critically ill patients treated with daptomycin 6–8 mg/kg/day for primarily *Staphylococcus* species-related infections, significantly higher daptomycin CLs were observed, despite comparable doses, in a subset of patients ($n = 13$) with ARC [35]. Interestingly, this subset was significantly more likely to have severe sepsis or septic shock [35]. In a retrospective study assessing vancomycin exposure among septic patients receiving mean daily doses of around 3 g, it was noted that during the first 3 days of vancomycin treatment trough levels were much lower in patients with ARC than in those without ARC [36]. Likewise, decreased meropenem levels after standard dosing of 1 g q8h were documented in two Intensive Care Unit (ICU) septic patients with ARC [37]. Indeed, the inverse relationship between ARC and low plasma trough levels of beta-lactams has been documented by several authors [38, 39]. Of note, ARC was also found to be a more common finding in critically ill patients with worse clinical outcomes receiving antibiotic therapy and was independently associated with younger age [40].

3.3.2.2 Traumatic and Non-traumatic Brain Injury

Several studies indicate that ARC is a frequent occurrence in the presence of traumatic brain injury, with an incidence up to 85–100% during the first week in ICU [41–45]. It has been recently hypothesized that ARC in severe trauma brain injury may be driven by associated cardiovascular changes and/or elevated plasma atrial natriuretic peptide concentrations [42]. However, further studies are needed to better characterize these findings. The occurrence of ARC also seems common in the setting of non-traumatic neurological injury. A recent prospective pilot study carried out in 20 patients with subarachnoid hemorrhage (mean age 52 years) showed that ARC occurred in 100% of cases (measured CrCL 325.9 ± 135.2 mL/min/1.73 m^2) [46].

Overall, these findings are in agreement with those of a recent retrospective study carried out among 73 neurosurgical ICU patients, in which the CL of vancomycin was higher ($P < 0.05$) in both traumatic and non-traumatic brain injury, in comparison to non-ICU patients [47]. Accordingly, larger doses of vancomycin were advocated. The need for larger doses of vancomycin in this setting was recently confirmed in a population pharmacokinetic study demonstrating that doses up to 1500 mg q12h may be necessary for optimal treatment in trauma patients with ARC [48].

3.3.2.3 Acute Leukemia and Febrile Neutropenia

Another setting that has been associated with ARC and therefore the need for higher than standard dosages of hydrophilic antibiotics is that of patients with hematological malignancies. The mechanism of ARC in hematological malignancies is poorly understood. It has been hypothesized that in acute leukemia patients, ARC may occur in the early post-chemotherapy period due to glomerular hyperfiltration promoted by the high protein load, derived from massive cellular lysis of circulating cells [1]. Additionally, it has been suggested that febrile neutropenia may act to

promote increased cardiac output and glomerular hyperfiltration due to a widespread systemic inflammatory response [49]. Irrespective of the underlying mechanisms, several studies have documented that the renal CL of hydrophilic antibiotics is often augmented in these circumstances [1, 50–54]. In a recent retrospective observational study carried out in 292 patients who were treated with vancomycin and who had normal serum creatinine concentrations, febrile neutropenia was found to be an independent risk factor for the occurrence of ARC (OR: 2.76; 95% CI: 1.11–6.67; $P = 0.0254$) [52]. In a study assessing the pharmacokinetics of piperacillin among 12 febrile neutropenic patients, most of whom were affected with acute leukemia (8/12), it was shown that drug CL was significantly increased (20.2 ± 7.5 L/h) [53].

It should not be overlooked also that hypoalbuminemia is a frequent occurrence among hematological patients, and this may represent a further factor altering drug pharmacokinetics. For these reasons, several authors advocate the need for therapeutic drug monitoring (TDM) in order to optimize treatment in this setting [51, 55, 56]. A recent prospective randomized controlled study showed that TDM may represent a very useful tool for optimizing drug exposure with beta-lactams among febrile neutropenic patients [55]. It's worth noting that among the patients enrolled in that study ($n = 32$), acute myeloid leukemia was the most frequent malignancy (38%), ARC was present in 31% of cases and hypoalbuminemia was a very common finding (median albumin concentration −2.7 g/dL, IQ range 2.4–2.9 g/dL) [55]. Overall, the frequent occurrence of multiple factors altering the pharmacokinetics of hydrophilic antibiotics in patients with hematological malignancies suggests that TDM may be very valuable in this setting, as it may provide rapid feedback of dosing adequacy to guide dose optimization.

3.3.2.4 Severe Burn Injury

Severe and extensive burn injury involving more than 30% total body surface area (TBSA) may substantially alter the pharmacokinetics of hydrophilic antibiotics. The physiological changes in patients with severe burns are related to both the consequences of direct thermal injury and to the systemic response leading to significant hemodynamic changes [57, 58]. Generally speaking, the physiological changes may be divided into two subsequent phases in relation to the time elapsed from the burn injury. In the first 48 h following injury, corresponding to the acute or the resuscitation phase, altered capillary permeability may lead to huge loss of protein-rich fluid. The fluid shift from the vascular bed to tissues and the weeping from the burns may cause hypovolemia, and a drop in renal blood flow and in glomerular filtration rate. From a pharmacokinetic point of view, it may be expected that no major dosing adjustments are needed during this phase, as the decreased drug elimination depending on renal impairment is essentially compensated by the non-renal CL of the drug via the burn wound [1]. Beyond 48 h after injury and after appropriate fluid resuscitation, there is the hypermetabolic phase, which is characterized by

the systemic response to burn injury. The patient often manifests a hyperdynamic state with increased cardiac output, low peripheral vascular resistance and increased glomerular filtration, similar to that observed in the hyperdynamic sepsis. This phase may last days or weeks depending on the severity of illness and on the amount of the systemic inflammatory response. During this phase, ARC is a common occurrence and may cause a significant increase in the elimination rate of most hydrophilic and moderately lipophilic agents [1, 58], as observed in several pharmacokinetic studies.

A population pharmacokinetic study of meropenem was carried out in 59 burn patients during the hypermetabolic phase (mean time of 9.2 days from burn injury) [59]. Burns ranged from 3 to 97% TBSA, and the administered meropenem dosage regimens ranged from 500 mg every 12 h up to 1000 mg every 8 h in patients with mean measured CrCL of 31.2 and 155.1 mL/min, respectively. Meropenem CL was proportional to CrCL and the mean meropenem population CL was much higher than that observed in other patient populations (14.5 L/h vs. 9.7 L/h), in agreement with the physiologic changes leading to ARC in the hypermetabolic phase. Simulations of 1000 virtual patients' plasma meropenem concentrations treated with 1000 mg every 8 h infused over 30 min predicted a probability of target attainment (in terms of $t >$ MIC 40% of the dosing interval) against *P. aeruginosa* of 58.9%. A higher probability of target attainment was noted with 1000 mg every 8 h, administered as a 3-h extended infusion.

Another study assessed the population pharmacokinetics of meropenem following doses of 1000–2000 mg every 4–8 h administered to 12 adult patients with median burns of 41% TBSA [60]. The mean population CL of meropenem was around 20–40% higher than that reported in other patient groups. Monte Carlo simulations investigated dosage regimens needed to achieve optimal probability of target attainment in terms of $t >$ MIC of ≥40%, ≥60% and ≥80% of the dosing interval. The standard dose of 1000 mg every 8 h infused over 5 min was effective only against very susceptible pathogens, like *E. coli* or methicillin susceptible coagulase negative staphylococci. Conversely, higher doses, preferably with longer infusion times, were deemed necessary for empirical therapy or when dealing with bacteria with MIC values ≥4 mg/L.

A population pharmacokinetic analysis of piperacillin was carried out in 50 patients with mean burns of 34.56% TBSA and a mean CrCL estimate of 132.1 mL/min [61]. Patients were in the hypermetabolic phase (mean time of 12.8 days from burn injury) and were receiving piperacillin/tazobactam at a dose of 4 g/0.5 g every 8 h infused over 30 min. CrCL and time elapsed after burn injury were the two covariates that were associated with piperacillin CL and subsequently included in the final population pharmacokinetic model. Piperacillin CL was much higher than observed in cystic fibrosis patients or in healthy volunteers (16.6 L/h vs. 11.3 L/h). Piperacillin half-lives were estimated to be shorter in patients with CrCL estimates ≥160 mL/min (mean 0.89 h), in comparison to those with lower CrCL estimates (mean 1.27 h, if 100 ≤CrCL <160 mL/min; mean 2.78 h if CrCL <100 mL/min). Likewise, shorter half-lives were calculated when burn injury occurred <10 days

before (mean 1.38 h) compared with longer elapsed times from the event (mean 2.16 h if ≥10 days). Monte Carlo simulations suggested that dosing strategies should be more aggressive in order to optimize treatment in these cases. The most effective strategies were those of shortening the dosing interval (4 g/0.5 g every 6 h) or of increasing the dose amount (6 g/0.75 g every 8 h). In addition, an extension of the duration of infusion could be suitable.

Conil and coworkers assessed the pharmacokinetic behavior of ceftazidime in burn patients in two population pharmacokinetic studies [62, 63]. The first study was carried out in 50 burn patients with mean burns of 23% TBSA and with a mean CrCL of 105.3 mL/min [62]. CrCL was the only covariate that was associated with ceftazidime CL in burn patients. In the second study, a prospective pharmacokinetic/pharmacodynamic analysis was conducted in 70 adult patients with mean burns of 32% TBSA and with a mean CrCL estimate of 118 mL/min/1.73 m^2 [63]. Serum creatinine and age were the two covariates associated with ceftazidime CL. Monte Carlo simulations were performed to identify the ceftazidime continuous dosage regimen most likely to achieve a steady-state concentration of 20–100 mg/L, as a function of these two covariates. Dosages ranged from 3 g every 24 h in patients aged 90 years and with serum creatinine of 160 μmol/L up to 12 g every 24 h in those aged 20 years and with serum creatinine of 30 μmol/L.

A population pharmacokinetic analysis of colistin was recently carried out in 50 patients with mean burns of 50.5% TBSA and with a mean CrCL estimate of 128 mL/min [64]. Patients were treated with colistimethate sodium at a dose of 150 mg as colistin base activity every 12 h and the mean time after burn injury was 15.5 days. CrCL was the only covariate included in the final population pharmacokinetic model that accounted for the relative fraction of colistimethate sodium converted into colistin. This is in agreement with the fact that colistimethate sodium is mainly eliminated via the kidney. However, CrCL was not a significant covariate of colistin CL, which is consistent with colistin being eliminated predominantly by the non-renal route. It was concluded that higher dosages of colistimethate sodium might be necessary in patients with elevated CrCL estimates.

Overall, all of these studies suggest that CL of hydrophilic antimicrobials is significantly increased during the hypermetabolic phase of burn injury, mainly as a consequence of ARC. Accordingly, dosing strategies should be more aggressive for these agents during the first 7–10 days after burn injury in order to prevent subtherapeutic drug concentrations. However, it is worth mentioning that estimation of renal function by means of various formulas may be inaccurate in burn patients. In a prospective study including 36 adult burn patients with a serum creatinine <120 μmol/L during the second or the third week following the burn injury, it was demonstrated that neither the Cockcroft and Gault, Robert, Kirkpatrick nor simplified MDRD equations were specific enough for the assessment of renal function [65]. Accordingly, it was recommended that direct measurement of CrCL through 24 h urine collection is performed to accurately assess renal function in burn patients with normal serum creatinine during the hypermetabolic phase.

3.3.3 *Physiologic Manifestations Leading to Decreased Renal CL of Hydrophilic Antibiotics*

3.3.3.1 Acute Kidney Injury

Acute kidney injury (AKI) may frequently complicate sepsis. Recent clinical and experimental evidence seems to suggest that the development of sepsis-related AKI may be related more to inflammatory mechanisms and to microcirculatory dysfunction than to systemic alterations in renal perfusion [34].

AKI will greatly affect the CL and the elimination rates of those antibiotics that are normally eliminated via the kidney [1]. Dosage adjustments are necessary for most hydrophilic antibiotics and for those moderately lipophilic agents that are predominantly eliminated by the kidney, such as levofloxacin. As far as dosage adjustment is concerned, it has been demonstrated that CrCL often correlates linearly with drug CL of hydrophilic agents, and this means that dosage may be decreased proportionally to the decrease in CrCL. However, it should not be overlooked that renal function may greatly vary day by day or even hour by hour in the critically ill patients with AKI. It may happen that patients who are admitted to the ICU with AKI may quite rapidly recover from renal impairment after appropriate interventions. As such, it is recommended that renal function is assessed daily in these patients in order to provide more accurate dosage adjustments. Dosage decreases are generally recommended when CrCL is ≤50 mL/min, especially when dealing with hydrophilic or moderately lipophilic drugs with a low therapeutic index (i.e., vancomycin, the aminoglycosides, levofloxacin, colistimethate sodium).

As a rule, for concentration-dependent agents any decrease in dose should be applied mainly by extending the dosing interval while maintaining the amount. This approach will ideally maximize the peak concentration-to-MIC ratio. Extension of dosing intervals up to 36–48 h have been recommended for gentamicin [66], amikacin [67], and for daptomycin [68]. Conversely, no dosage reduction was shown to be necessary for ciprofloxacin, as no drug accumulation occurred in most critically ill patients with impaired renal function who were receiving the standard dose of 400 mg every 12 h [69]. This is probably due to a compensatory transintestinal elimination that may occur in such cases [70]. For time-dependent agents, it is most effective to reduce the dose amount and to maintain the dosing interval in order to maximize the $t >$ MIC [2]. This has been suggested for most beta-lactams when using intermittent dosing, even if this approach may sometimes cause unexpected underexposure [71]. Useful nomograms for dosage adjustments in relation to CrCL estimates have been recently provided for vancomycin [72] and for meropenem [73] when used by continuous infusion. However, in this regard it must be remembered that several studies showed that the different equations used to estimate glomerular filtration in critically ill patients may be inaccurate [74, 75]. Recently, Carlier and coworkers assessed the accuracies of four commonly used creatinine base equations (Cockcroft-Gault, simplified and standard MDRD, CKD-EPI), of five cystatin-based equations (Hoek, Larsson, Filler, Le Bricon, CKD-EPIcys), and of one

equation combining serum creatinine and cystatin C (CKD-EPIcr-cys) in assessing renal function among 68 critically ill patients [75]. Compared to measured inulin CL, all of the estimates of glomerular filtration had low accuracy and precision. It was concluded that measured urinary CrCL may represent the most valid alternative to measured inulin CL in assessing renal function, even if resulting in some overestimation of glomerular filtration rate [75]. Clearly, the availability of TDM may represent an invaluable tool to optimize treatment in this setting, even when dealing with relatively safe antibiotic agents, like the beta-lactams [71].

3.4 Conclusion

Critical illness is characterized by a range of physiological manifestations. These include hemodynamic perturbations (such as an increased cardiac output, and reduction in peripheral vascular resistance), fluid shifts, hypoalbuminemia, and alterations in major organ function (such as ARC or AKI). These are largely driven by the underlying biological insult (infection, burns, etc.) and the systemic inflammatory host response. Of note, these manifestations can significantly impact the pharmacokinetics of many antibiotics, principally those that are hydrophilic, because of changes in distribution and clearance. This chapter has outlined these issues in detail and reminds the clinician that doses routinely used in non-critically ill patients are likely to be inadequate in critically ill patients for these reasons.

References

1. Pea F, Viale P, Furlanut M (2005) Antimicrobial therapy in critically ill patients: a review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability. Clin Pharmacokinet 44(10):1009–1034. doi:10.2165/00003088-200544100-00002
2. Pea F (2013) Plasma pharmacokinetics of antimicrobial agents in critically ill patients. Curr Clin Pharmacol 8(1):5–12
3. Blot SI, Pea F, Lipman J (2014) The effect of pathophysiology on pharmacokinetics in the critically ill patient—concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev 77:3–11. doi:10.1016/j.addr.2014.07.006
4. Verbeeck RK (2008) Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol 64(12):1147–1161. doi:10.1007/s00228-008-0553-z
5. Korth-Bradley JM, Baird-Bellaire SJ, Patat AA, Troy SM, Bohmer GM, Gleiter CH, Buecheler R, Morgan MY (2011) Pharmacokinetics and safety of a single intravenous dose of the antibiotic tigecycline in patients with cirrhosis. J Clin Pharmacol 51(1):93–101. doi:10.1177/0091270010363477
6. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC (2016) The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 315(8):801–810. doi:10.1001/jama.2016.0287
7. Galvez R, Luengo C, Cornejo R, Kosche J, Romero C, Tobar E, Illanes V, Llanos O, Castro J (2011) Higher than recommended amikacin loading doses achieve pharmacokinetic targets without associated toxicity. Int J Antimicrob Agents 38(2):146–151. doi:10.1016/j.ijantimicag.2011.03.022

8. Taccone FS, Laterre PF, Spapen H, Dugernier T, Delattre I, Layeux B, De Backer D, Wittebole X, Wallemacq P, Vincent JL, Jacobs F (2010) Revisiting the loading dose of amikacin for patients with severe sepsis and septic shock. Crit Care 14(2):R53. doi:10.1186/cc8945
9. Allou N, Bouteau A, Allyn J, Snauwaert A, Valance D, Jabot J, Bouchet B, Galliot R, Corradi L, Montravers P, Augustin P (2016) Impact of a high loading dose of amikacin in patients with severe sepsis or septic shock. Ann Intensive Care 6(1):106. doi:10.1186/s13613-016-0211-z
10. Roger C, Nucci B, Molinari N, Bastide S, Saissi G, Pradel G, Barbar S, Aubert C, Lloret S, Elotmani L, Polge A, Lefrant JY, Roberts JA, Muller L (2015) Standard dosing of amikacin and gentamicin in critically ill patients results in variable and subtherapeutic concentrations. Int J Antimicrob Agents 46(1):21–27. doi:10.1016/j.ijantimicag.2015.02.009
11. Roger C, Nucci B, Louart B, Friggeri A, Knani H, Evrard A, Lavigne JP, Allaouchiche B, Lefrant JY, Roberts JA, Muller L (2016) Impact of 30 mg/kg amikacin and 8 mg/kg gentamicin on serum concentrations in critically ill patients with severe sepsis. J Antimicrob Chemother 71(1):208–212. doi:10.1093/jac/dkv291
12. Allou N, Allyn J, Levy Y, Bouteau A, Caujolle M, Delmas B, Valance D, Brulliard C, Martinet O, Vandroux D, Montravers P, Augustin P (2016) Assessment of the national French recommendations regarding the dosing regimen of 8 mg/kg of gentamicin in patients hospitalised in intensive care units. Anaesth Crit Care Pain Med 35(5):331–335. doi:10.1016/j.accpm.2015.12.012
13. Roberts JA, Taccone FS, Udy AA, Vincent JL, Jacobs F, Lipman J (2011) Vancomycin dosing in critically ill patients: robust methods for improved continuous-infusion regimens. Antimicrob Agents Chemother 55(6):2704–2709. doi:10.1128/AAC.01708-10
14. Nakano T, Nakamura Y, Takata T, Irie K, Sano K, Imakyure O, Mishima K, Futagami K (2016) Change of teicoplanin loading dose requirement for incremental increases of systemic inflammatory response syndrome score in the setting of sepsis. Int J Clin Pharmacol 38(4):908–914. doi:10.1007/s11096-016-0308-3
15. Gatta A, Verardo A, Bolognesi M (2012) Hypoalbuminemia. Intern Emerg Med 7(Suppl 3):S193–S199. doi:10.1007/s11739-012-0802-0
16. Roberts JA, Pea F, Lipman J (2013) The clinical relevance of plasma protein binding changes. Clin Pharmacokinet 52(1):1–8. doi:10.1007/s40262-012-0018-5
17. Enokiya T, Muraki Y, Iwamoto T, Okuda M (2015) Changes in the pharmacokinetics of teicoplanin in patients with hyperglycaemic hypoalbuminaemia: impact of albumin glycosylation on the binding of teicoplanin to albumin. Int J Antimicrob Agents 46(2):164–168. doi:10.1016/j.ijantimicag.2015.03.010
18. Etzel JV, Nafziger AN, Bertino JS Jr (1992) Variation in the pharmacokinetics of gentamicin and tobramycin in patients with pleural effusions and hypoalbuminemia. Antimicrob Agents Chemother 36(3):679–681
19. Makino J, Yoshiyama Y, Kanke M, Kamata M, Ozawa S, Maruyama H, Shibasaki T, Masuhara K, Kobayashi T, Nakashima E (2002) [Pharmacokinetic study of penetration of meropenem into pleural effusion in patients with pleurisy]. Jpn J Antibiot 55(1): 77–88
20. Gill MA, Kern JW (1979) Altered gentamicin distribution in ascitic patients. Am J Hosp Pharm 36(12):1704–1706
21. Lanao JM, Dominguez-Gil A, Macias JG, Diez JL, Nieto MJ (1980) The influence of ascites on the pharmacokinetics of amikacin. Int J Clin Pharmacol Ther Toxicol 18(2):57–61
22. Sampliner R, Perrier D, Powell R, Finley P (1984) Influence of ascites on tobramycin pharmacokinetics. J Clin Pharmacol 24(1):43–46
23. Buijk SL, Gyssens IC, Mouton JW, Van Vliet A, Verbrugh HA, Bruining HA (2002) Pharmacokinetics of ceftazidime in serum and peritoneal exudate during continuous versus intermittent administration to patients with severe intra-abdominal infections. J Antimicrob Chemother 49(1):121–128
24. el Touny M, el Guinaidy MA, Abd el Barry M, Osman L, Sabbour MS (1991) Pharmacokinetics of ceftazidime in patients with liver cirrhosis and ascites. J Antimicrob Chemother 28(1):95–100
25. Hary L, Andrejak M, Leleu S, Orfila J, Capron JP (1989) The pharmacokinetics of ceftriaxone and cefotaxime in cirrhotic patients with ascites. Eur J Clin Pharmacol 36(6):613–616
26. Hary L, Smail A, Ducroix JP, Baillet J, Andrejak M (1991) Pharmacokinetics and ascitic fluid penetration of piperacillin in cirrhosis. Fundam Clin Pharmacol 5(9):789–795

27. el Touny M, el Guinaidy M, Abdel Barry M, Osman L, Sabbour MS (1992) Pharmacokinetics of aztreonam in patients with liver cirrhosis and ascites. J Antimicrob Chemother 30(3):387–395
28. Adnan S, Li JX, Wallis SC, Rudd M, Jarrett P, Paterson DL, Lipman J, Udy AA, Roberts JA (2013) Pharmacokinetics of meropenem and piperacillin in critically ill patients with indwelling surgical drains. Int J Antimicrob Agents 42(1):90–93. doi:10.1016/j.ijantimicag.2013.02.023
29. Udy AA, Putt MT, Boots RJ, Lipman J (2011) ARC—augmented renal clearance. Curr Pharm Biotechnol 12(12):2020–2029
30. De Waele JJ, Dumoulin A, Janssen A, Hoste EA (2015) Epidemiology of augmented renal clearance in mixed ICU patients. Minerva Anestesiol 81(10):1079–1085
31. Udy AA, Roberts JA, Boots RJ, Paterson DL, Lipman J (2010) Augmented renal clearance: implications for antibacterial dosing in the critically ill. Clin Pharmacokinet 49(1):1–16. doi:10.2165/11318140-000000000-00000
32. Hobbs AL, Shea KM, Roberts KM, Daley MJ (2015) Implications of augmented renal clearance on drug dosing in critically ill patients: a focus on antibiotics. Pharmacotherapy 35(11):1063–1075. doi:10.1002/phar.1653
33. Sime FB, Udy AA, Roberts JA (2015) Augmented renal clearance in critically ill patients: etiology, definition and implications for beta-lactam dose optimization. Curr Opin Pharmacol 24:1–6. doi:10.1016/j.coph.2015.06.002
34. Prowle JR, Bellomo R (2015) Sepsis-associated acute kidney injury: macrohemodynamic and microhemodynamic alterations in the renal circulation. Semin Nephrol 35(1):64–74. doi:10.1016/j.semnephrol.2015.01.007
35. Falcone M, Russo A, Venditti M, Novelli A, Pai MP (2013) Considerations for higher doses of daptomycin in critically ill patients with methicillin-resistant Staphylococcus aureus bacteremia. Clin Infect Dis 57(11):1568–1576. doi:10.1093/cid/cit582
36. Baptista JP, Sousa E, Martins PJ, Pimentel JM (2012) Augmented renal clearance in septic patients and implications for vancomycin optimisation. Int J Antimicrob Agents 39(5):420–423. doi:10.1016/j.ijantimicag.2011.12.011
37. Troger U, Drust A, Martens-Lobenhoffer J, Tanev I, Braun-Dullaeus RC, Bode-Boger SM (2012) Decreased meropenem levels in intensive care unit patients with augmented renal clearance: benefit of therapeutic drug monitoring. Int J Antimicrob Agents 40(4):370–372. doi:10.1016/j.ijantimicag.2012.05.010
38. Udy AA, Varghese JM, Altukroni M, Briscoe S, McWhinney BC, Ungerer JP, Lipman J, Roberts JA (2012) Subtherapeutic initial beta-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. Chest 142(1):30–39. doi:10.1378/chest.11-1671
39. Carlier M, Carrette S, Roberts JA, Stove V, Verstraete A, Hoste E, Depuydt P, Decruyenaere J, Lipman J, Wallis SC, De Waele JJ (2013) Meropenem and piperacillin/tazobactam prescribing in critically ill patients: does augmented renal clearance affect pharmacokinetic/pharmacodynamic target attainment when extended infusions are used? Crit Care 17(3):R84. doi:10.1186/cc12705
40. Claus BO, Hoste EA, Colpaert K, Robays H, Decruyenaere J, De Waele JJ (2013) Augmented renal clearance is a common finding with worse clinical outcome in critically ill patients receiving antimicrobial therapy. J Crit Care 28(5):695–700. doi:10.1016/j.jcrc.2013.03.003
41. Udy AA, Boots R, Senthuran S, Stuart J, Deans R, Lassig-Smith M, Lipman J (2010) Augmented creatinine clearance in traumatic brain injury. Anesth Analg 111(6):1505–1510. doi:10.1213/ANE.0b013e3181f7107d
42. Udy AA, Jarrett P, Lassig-Smith M, Stuart J, Starr T, Dunlop R, Deans R, Roberts JA, Senthuran S, Boots R, Bisht K, Bulmer AC, Lipman J (2017) Augmented renal clearance in traumatic brain injury: a single-center observational study of atrial natriuretic peptide, cardiac output, and creatinine clearance. J Neurotrauma 34(1):137–144. doi:10.1089/neu.2015.4328
43. Cook AM, Arora S, Davis J, Pittman T (2013) Augmented renal clearance of vancomycin and levetiracetam in a traumatic brain injury patient. Neurocrit Care 19(2):210–214. doi:10.1007/s12028-013-9837-y
44. Dias C, Gaio AR, Monteiro E, Barbosa S, Cerejo A, Donnelly J, Felgueiras O, Smielewski P, Paiva JA, Czosnyka M (2015) Kidney-brain link in traumatic brain injury patients? A preliminary report. Neurocrit Care 22(2):192–201. doi:10.1007/s12028-014-0045-1

45. Minville V, Asehnoune K, Ruiz S, Breden A, Georges B, Seguin T, Tack I, Jaafar A, Saivin S, Fourcade O, Samii K, Conil JM (2011) Increased creatinine clearance in polytrauma patients with normal serum creatinine: a retrospective observational study. Crit Care 15(1):R49. doi:10.1186/cc10013
46. May CC, Arora S, Parli SE, Fraser JF, Bastin MT, Cook AM (2015) Augmented renal clearance in patients with subarachnoid hemorrhage. Neurocrit Care 23(3):374–379. doi:10.1007/s12028-015-0127-8
47. Lin Wu FL, Liu SS, Yang TY, Win MF, Lin SW, Huang CF, Wang KC, Shen LJ (2015) A larger dose of vancomycin is required in adult neurosurgical intensive care unit patients due to augmented clearance. Ther Drug Monit 37(5):609–618. doi:10.1097/FTD.0000000000000187
48. Medellin-Garibay SE, Ortiz-Martin B, Rueda-Naharro A, Garcia B, Romano-Moreno S, Barcia E (2016) Pharmacokinetics of vancomycin and dosing recommendations for trauma patients. J Antimicrob Chemother 71(2):471–479. doi:10.1093/jac/dkv372
49. Udy AA, Putt MT, Shanmugathasan S, Roberts JA, Lipman J (2010) Augmented renal clearance in the intensive care unit: an illustrative case series. Int J Antimicrob Agents 35(6):606–608. doi:10.1016/j.ijantimicag.2010.02.013
50. Tod M, Lortholary O, Seytre D, Semaoun R, Uzzan B, Guillevin L, Casassus P, Petitjean O (1998) Population pharmacokinetic study of amikacin administered once or twice daily to febrile, severely neutropenic adults. Antimicrob Agents Chemother 42(4):849–856
51. Pea F, Viale P, Candoni A, Pavan F, Pagani L, Damiani D, Casini M, Furlanut M (2004) Teicoplanin in patients with acute leukaemia and febrile neutropenia: a special population benefiting from higher dosages. Clin Pharmacokinet 43(6):405–415. doi:10.2165/00003088-200443060-00004
52. Hirai K, Ishii H, Shimoshikiryo T, Shimomura T, Tsuji D, Inoue K, Kadoiri T, Itoh K (2016) Augmented renal clearance in patients with febrile neutropenia is associated with increased risk for subtherapeutic concentrations of vancomycin. Ther Drug Monit 38(6):706–710. doi:10.1097/FTD.0000000000000346
53. Sime FB, Roberts MS, Warner MS, Hahn U, Robertson TA, Yeend S, Phay A, Lehman S, Lipman J, Peake SL, Roberts JA (2014) Altered pharmacokinetics of piperacillin in febrile neutropenic patients with hematological malignancy. Antimicrob Agents Chemother 58(6):3533–3537. doi:10.1128/AAC.02340-14
54. Binder L, Schworer H, Hoppe S, Streit F, Neumann S, Beckmann A, Wachter R, Oellerich M, Walson PD (2013) Pharmacokinetics of meropenem in critically ill patients with severe infections. Ther Drug Monit 35(1):63–70. doi:10.1097/FTD.0b013e31827d496c
55. Sime FB, Roberts MS, Tiong IS, Gardner JH, Lehman S, Peake SL, Hahn U, Warner MS, Roberts JA (2015) Can therapeutic drug monitoring optimize exposure to piperacillin in febrile neutropenic patients with haematological malignancies? A randomized controlled trial. J Antimicrob Chemother 70(8):2369–2375. doi:10.1093/jac/dkv123
56. Mareville J, Gay J, Cliquennois E, Herbaux C, Pasquier F, Allorge D, Blondiaux N, Berthon C, Alfandari S (2012) Therapeutic drug monitoring of aminoglycosides in acute myeloid leukaemia patients. Scand J Infect Dis 44(5):398–401. doi:10.3109/00365548.2011.645868
57. Latenser BA (2009) Critical care of the burn patient: the first 48 hours. Crit Care Med 37(10):2819–2826. doi:10.1097/CCM.0b013e3181b3a08f
58. Blanchet B, Jullien V, Vinsonneau C, Tod M (2008) Influence of burns on pharmacokinetics and pharmacodynamics of drugs used in the care of burn patients. Clin Pharmacokinet 47(10):635–654. doi:10.2165/00003088-200847100-00002
59. Doh K, Woo H, Hur J, Yim H, Kim J, Chae H, Han S, Yim DS (2010) Population pharmacokinetics of meropenem in burn patients. J Antimicrob Chemother 65(11):2428–2435. doi:10.1093/jac/dkq317
60. Ramon-Lopez A, Allen JM, Thomson AH, Dheansa BS, James SE, Hanlon GW, Stewart B, Davies JG (2015) Dosing regimen of meropenem for adults with severe burns: a population pharmacokinetic study with Monte Carlo simulations. J Antimicrob Chemother 70(3):882–890. doi:10.1093/jac/dku429
61. Jeon S, Han S, Lee J, Hong T, Paek J, Woo H, Yim DS (2014) Population pharmacokinetic analysis of piperacillin in burn patients. Antimicrob Agents Chemother 58(7):3744–3751. doi:10.1128/AAC.02089-13

62. Conil JM, Georges B, Lavit M, Laguerre J, Samii K, Houin G, Saivin S (2007) A population pharmacokinetic approach to ceftazidime use in burn patients: influence of glomerular filtration, gender and mechanical ventilation. Br J Clin Pharmacol 64(1):27–35. doi:10.1111/j.1365-2125.2007.02857.x
63. Conil JM, Georges B, Ravat F, Ruiz S, Seguin T, Metsu D, Fourcade O, Saivin S (2013) Ceftazidime dosage recommendations in burn patients: from a population pharmacokinetic approach to clinical practice via Monte Carlo simulations. Clin Ther 35(10):1603–1612. doi:10.1016/j.clinthera.2013.08.014
64. Lee J, Han S, Jeon S, Hong T, Song W, Woo H, Yim DS (2013) Population pharmacokinetic analysis of colistin in burn patients. Antimicrob Agents Chemother 57(5):2141–2146. doi:10.1128/AAC.00271-13
65. Conil JM, Georges B, Fourcade O, Seguin T, Lavit M, Samii K, Houin G, Tack I, Saivin S (2007) Assessment of renal function in clinical practice at the bedside of burn patients. Br J Clin Pharmacol 63(5):583–594. doi:10.1111/j.1365-2125.2006.02807.x
66. Xuan D, Nicolau DP, Nightingale CH (2004) Population pharmacokinetics of gentamicin in hospitalized patients receiving once-daily dosing. Int J Antimicrob Agents 23(3):291–295. doi:10.1016/j.ijantimicag.2003.07.010
67. Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R (1995) Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother 39(3):650–655
68. Chaves RL, Chakraborty A, Benziger D, Tannenbaum S (2014) Clinical and pharmacokinetic considerations for the use of daptomycin in patients with Staphylococcus aureus bacteraemia and severe renal impairment. J Antimicrob Chemother 69(1):200–210. doi:10.1093/jac/dkt342
69. Pea F, Poz D, Viale P, Pavan F, Furlanut M (2006) Which reliable pharmacodynamic breakpoint should be advised for ciprofloxacin monotherapy in the hospital setting? A TDM-based retrospective perspective. J Antimicrob Chemother 58(2):380–386. doi:10.1093/jac/dkl226
70. Rohwedder RW, Bergan T, Thorsteinsson SB, Scholl H (1990) Transintestinal elimination of ciprofloxacin. Diagn Microbiol Infect Dis 13(2):127–133
71. Casu GS, Hites M, Jacobs F, Cotton F, Wolff F, Beumier M, De Backer D, Vincent JL, Taccone FS (2013) Can changes in renal function predict variations in beta-lactam concentrations in septic patients? Int J Antimicrob Agents 42(5):422–428. doi:10.1016/j.ijantimicag.2013.06.021
72. Pea F, Furlanut M, Negri C, Pavan F, Crapis M, Cristini F, Viale P (2009) Prospectively validated dosing nomograms for maximizing the pharmacodynamics of vancomycin administered by continuous infusion in critically ill patients. Antimicrob Agents Chemother 53(5):1863–1867. doi:10.1128/aac.01149-08
73. Pea F, Viale P, Cojutti P, Furlanut M (2012) Dosing nomograms for attaining optimum concentrations of meropenem by continuous infusion in critically ill patients with severe gram-negative infections: a pharmacokinetics/pharmacodynamics-based approach. Antimicrob Agents Chemother 56(12):6343–6348. doi:10.1128/aac.01291-12
74. Eppenga WL, Kramers C, Derijks HJ, Wensing M, Wetzels JF, De Smet PA (2016) Drug therapy management in patients with renal impairment: how to use creatinine-based formulas in clinical practice. Eur J Clin Pharmacol 72(12):1433–1439. doi:10.1007/s00228-016-2113-2
75. Carlier M, Dumoulin A, Janssen A, Picavet S, Vanthuyne S, Van Eynde R, Vanholder R, Delanghe J, De Schoenmakere G, De Waele JJ, Hoste EA (2015) Comparison of different equations to assess glomerular filtration in critically ill patients. Intensive Care Med 41(3):427–435. doi:10.1007/s00134-014-3641-9

Chapter 4
Dosing in Obese Critically Ill Patients

Maya Hites and Fabio Silvio Taccone

4.1 Introduction

The worldwide prevalence of obesity, defined as a body mass index (BMI) ≥30 kg/m^2, continues to rise dramatically [1]. Despite efforts to curb this problem, over 300 million people were obese in 2005, and over 500 million people are projected to be obese in 2030 [2].

As compared to their non-obese counterparts, obese individuals have a greater risk of morbidity from both acute and chronic health conditions. Moreover, the number of obese surgical patients is growing: the number of bariatric surgeries performed worldwide has increased from 146,301 in 2002 [3] to 468,609 procedures in 2013 [4]. Also, in a large prospective study performed in Spain following 105,189 patients with knee osteoarthritis, obese patients had over a 100% increased risk of total knee replacement compared to normal weight patients [5]. Furthermore, obesity is a risk factor for both hospital and intensive care unit (ICU) admission, in addition to longer hospital and ICU lengths of stay [6–9]. Finally, obese patients also have a greater risk of developing community acquired and hospital-related infections than non-obese individuals [10, 11].

To optimally treat severe infections in critically ill patients, careful antibiotic dose adjustment based on pharmacokinetic/pharmacodynamic (PK/PD) considerations is necessary. This is because hospital-related infections are often caused by pathogens with decreased susceptibility (as compared to community isolates) and

M. Hites
Department of Infectious Diseases, CUB-Erasme, Université Libre de Bruxelles, Brussels, Belgium
e-mail: Maya.Hites@erasme.ulb.ac.be

F.S. Taccone (✉)
Department of Intensive Care, CUB-Erasme, Université Libre de Bruxelles, Brussels, Belgium
e-mail: ftaccone@ulb.ac.be

A.A. Udy et al. (eds.), *Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill*, DOI 10.1007/978-981-10-5336-8_4

drug handling is altered in this patient population, due to changes in the volume of distribution (VD) and the total body clearance (CL) (see Sect. 4.6.4). Obesity is associated with physiological changes that may further alter antibiotic PK parameters, making optimization of doses in this population especially challenging. Contrary to most beliefs, the excess weight in obese patients is not only due to an increase in adipose tissue (into which hydrophilic antibiotics distribute poorly) but also due to an increase in their lean mass (into which hydrophilic antibiotics distribute well). However, the ratio of lean body mass to total body mass in obese patients is not similar to individuals of normal weight. The majority of currently available standard dosage regimens (SDR) include recommendations based on normal weight patients, and dose adjustments using calculated lean body mass (as established from data obtained from normal weight patients). As such, this may lead to underdosing in obese patients, increasing the risk of antibiotic treatment failure, and/or emergence of bacterial resistance (by subjecting bacteria to sublethal antibiotic concentrations). On the other hand, dosing regimens based on total body weight (TBW) may lead to overdosing, with risk of drug toxicity [12].

4.2 Causes for the Increased Risk of Infections in Obese Patients

As stated above, obesity is a risk factor for acquiring infections in general, including skin, urinary tract, respiratory, surgical site, and hospital-related infections [13]. The causes are both mechanical and immunological. To begin with, the obese patient represents a heavy burden for care-givers. Delivering effective respiratory physical therapy and ensuring general mobilization of the patient may be challenging. The urinary catheter may therefore be left longer than required, diapers may be changed less frequently, and patients may remain in bed longer than otherwise recommended, thus increasing the risk of catheter-related urinary tract infections, skin maceration, bed sores, and even respiratory infections. Furthermore, obesity is an independent risk factor for obstructive sleep apnea [14], gastric-esophageal reflux [15], increased volume and acidity of gastric liquid, and increased intra-abdominal pressure [16, 17]. These are all themselves risk factors for aspiration pneumonia.

Obesity is also associated with lymphedema (due to elevated intra-abdominal pressure) and may lead to recurrent skin infections. Fungal foot infections are also more common in obese subjects [18]; which may predispose individuals to acute skin and soft-tissue infections of the lower extremities [19].

In the surgical setting, obesity is associated with risk factors for surgical site infections, such as increased duration of surgery, greater local trauma to the incised tissues [20], diminished oxygenation of subcutaneous tissue [21], increased local production of tumor necrosis factor-alpha (TNF-α) and nitric oxide due to changes in the lipid metabolism (less arginine and glutamine available) [6], and increased

Staphylococcus aureus nasal carriage [22]. Furthermore, SDR of antibiotics for prophylaxis may not result in adequate serum and tissue concentrations of the antibiotic in all obese patients [23, 24].

Obese patients may respond poorly to vaccines due to insufficient doses, poor absorption (injection of the vaccine into adipose tissue instead of muscle tissue) and/or inadequate overall immunological response. Indeed, obesity is associated with a decreased antibody response to hepatitis B vaccine in adults [25, 26], a greater decline in influenza vaccine antibody titres, and a defective influenza-specific CD8+ T cell response [27]. Influenza-specific CD8+ T cells limit progression of disease, allow for more rapid viral clearance, and lessen the severity of the disease [28].

Finally, adipose tissue stores excess calories in the form of triacylglycerol (TAG). As the tissue expands, its ability to store more TAG declines, resulting in elevated blood TAG and free fatty acids (FFA). The accumulation of lipids in the peripheral circulation and other sites (liver, islets of the pancreas, skeletal muscle) leads to insulin resistance and hyperglycemia [29]. However, adipose tissue is not only an energy store, but also an active metabolic and endocrine organ that produces and releases pro-inflammatory and anti-inflammatory factors such as adipokines (leptin and adiponectin), cytokines (TNF-α, IL-6), and chemokines. Adiponectin levels are negatively correlated [30] and leptin levels are positively correlated with BMI [31]. Adiponectin has immunosuppressive properties while leptin can stimulate an inflammatory response, by activating neutrophils and T-lymphocytes, increasing cytokine production and regulating the activation of monocytes/macrophages, as well as contributing to healing [32].

The consequences of hyperglycemia and production of pro-inflammatory cytokines and adipokines is systemic inflammation which may impair innate and adaptive immune function by causing endoplasmic reticulum stress, lipotoxicity, oxidative stress, and leptin resistance [33, 34]. The connection between the pro-inflammatory state of obesity and risk of infection has not yet been clearly demonstrated, but leptin seems to play an important role in the immune response [6, 35, 36].

4.3 Need for Antibiotic Therapy

Because of their increased risk of infection, many critically ill obese patients may need either prophylactic or therapeutic antibiotic therapy during their ICU stay. Antibiotic prophylaxis is recommended for most surgical interventions [37]. A systematic review of published studies and online surveillance reports on antibiotic consumption in acute care hospitals from 1997 to 2013 showed that the ICU antibiotic consumption rate was 1563 defined daily dose/1000 hospital days (95% confidence interval: 1472–1653) [38]. Furthermore, in a multicenter point prevalence study (EPIC II) carried out in 2007, 71% of the 13,796 ICU patients included in the cohort were receiving antibiotic therapy [39].

4.4 Possible PK Changes Due to Obesity

Obesity may per se alter antibiotic PK. The PK changes due to obesity could affect drug absorption, distribution, or elimination (Fig. 4.1).

4.4.1 Absorption

Drug absorption of intravenously administered antibiotics will not be altered in the obese patient; however, this is not true for those administered intramuscularly or enterally. Attempted intramuscular injection of antibiotics may result in delivery into deep subcutaneous tissue instead of muscle, possibly resulting in lower absorption of the drug [40]. Reduced enteral absorption of antibiotics may also occur due to slower gastric emptying in obese patients due to gastric distension or higher fat diet [41, 42]. On the other hand, absorption may be increased in obese patients who have high fat consumption if the absorption of the antibiotic is increased with a fatty meal. Furthermore, enteral absorption of antibiotics may be affected in patients who have undergone bariatric surgery.

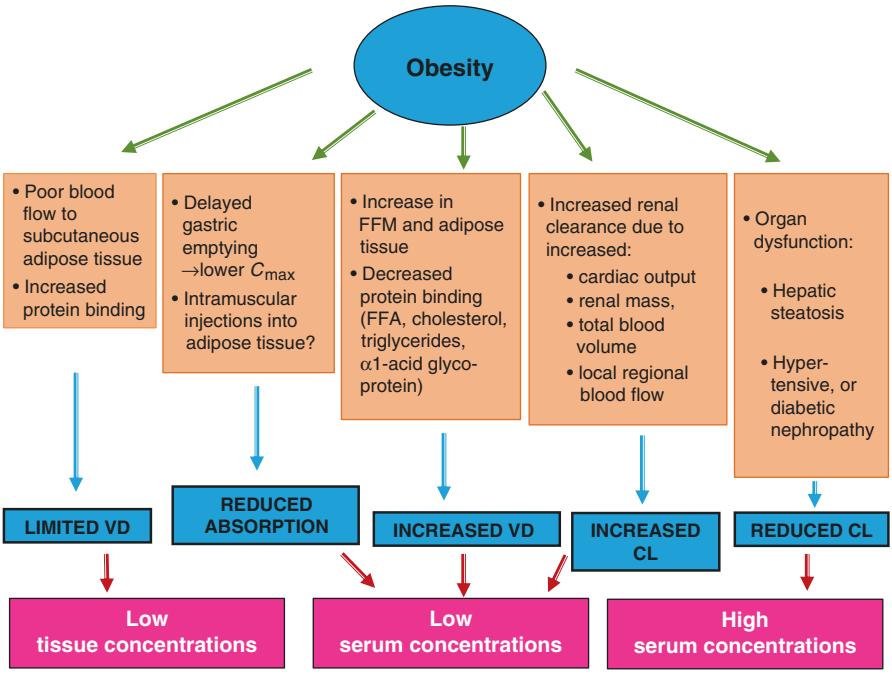

Fig. 4.1 Mechanisms by which obesity alters antibiotic pharmacokinetics. Abbreviations: C_{max} peak concentration, *FFM* fat free mass, *FFA* free fatty acids, *VD* volume of distribution, *CL* total body clearance

4.4.2 *Drug Distribution*

Most antibiotics will demonstrate an increased VD in obese patients due to increased adipose tissue (composed of 30% water) [43], and increased lean mass, which may account for 20–40% of the patients excess TBW [44]. Nevertheless, the VD of hydrophilic drugs is theoretically less likely to be influenced by obesity than lipophilic drugs. Table 4.1 provides a classification of antibiotics of the basis of their physical properties. Adding complexity is the observation that the VD of a drug does not only depend on its lipophilic or hydrophilic characteristics, but also its molecular weight and the extent of protein binding. As an example, the VD of diazepam, a very lipophilic drug, has a more than threefold increase in the obese population [45, 46], while the VD of digoxin, another very lipophilic drug, is not affected by obesity [47]. Furthermore, the VD of vancomycin, a hydrophilic drug, has been shown to increase significantly in a linear fashion with an increase in TBW [48].

Altered protein binding may also affect the VD of drugs in obese individuals. The proteins principally responsible for drug binding are albumin, α_1-acid glycoprotein, and lipoproteins. Albumin is the major protein to which acidic drugs bind; levels of serum albumin appear to be unaltered in healthy moderate and morbidly obese patients [49]. Hypoalbuminemia is frequent in the critically ill although little is known about serum albumin levels in obese critically ill patients specifically. Alpha$_1$-acid glycoprotein is an "acute phase" protein, increasing in arthritis, cancer, myocardial infarction, and is an important binding site for basic drugs [50–52]. Lipoproteins are a biochemical structure of both proteins and lipids; their role is to transport triglycerides and cholesterol in the blood from one tissue to another. Free fatty acids are circulating fatty acids that are released from adipocytes. Serum levels of α_1-acid glycoprotein [49], cholesterol [53], triglycerides [54], and FFA [55] may be increased in the obese individual.

These serum components (α_1-acid glycoprotein, cholesterol, triglycerides, FFA) may increase or decrease protein binding by directly binding to the antibiotic, or by displacing or preventing the antibiotic from binding to serum proteins. A significant positive correlation between α_1-acid glycoprotein levels and protein binding of vancomycin has been observed [56], and high levels of FFA significantly decreased in vitro protein binding of cefamandole, dicloxacillin, and sulfamethoxazole, but increased protein binding of benzylpenicillin, cephalothin, and cefoxitin [57].

Table 4.1 Classification of antibiotics in function of their physical properties

	Hydrophilic	Lipophilic
Pharmacokinetic characteristics	Small volume of distribution Poor intracellular and tissue penetration Essentially eliminated by the kidneys	Large volume of distribution Good intracellular and tissue penetration Essentially eliminated by the liver
Classes of antibiotics	Beta-lactams Aminoglycosides Glycopeptides Polymyxines	Fluoroquinolones Linezolid Tigecycline

Finally, the VD may also be altered by blood flow to tissues. Obese patients may have poor peripheral perfusion, resulting in lower blood flow to adipose tissue [58, 59] and thus poorer distribution of antibiotics (e.g., ciprofloxacin and cefazolin) to subcutaneous tissues [23, 60]. On the contrary, higher subcutaneous ciprofloxacin concentrations have been observed in healthy, non-obese volunteers, due to enhanced subcutaneous blood flow [61].

4.4.3 Drug Clearance

4.4.3.1 Liver

The liver plays an important role in the CL of drugs and chemicals from the body. In obese individuals, liver abnormalities are frequent, ranging from steatosis to non-alcoholic liver disease, the most common liver disease worldwide [62], or even liver cirrhosis [63]. In a systematic review on nonalcoholic liver disease, it was estimated that 66% of patients older than 50 years old with diabetes or obesity are thought to have nonalcoholic steato-hepatitis with advanced fibrosis [64].

Many drugs metabolized by the liver undergo hepatic first-pass metabolism: the drug is absorbed by the digestive system, and immediately brought to the liver via the portal vein where the drug is then metabolized. Clearance of drugs via first-pass metabolism is influenced mostly by hepatic blood flow. Lidocaine, a highly extracted drug for first-pass metabolism whose systemic clearance parallels hepatic blood flow, was evaluated in obese and lean individuals: no differences were observed, suggesting that hepatic blood flow is not greatly altered in obese individuals [65].

Drugs are then metabolized in the liver by phase I reactions responsible for oxidation (e.g., cytochrome P450), reduction, or hydrolysis, and by phase II reactions responsible for conjugation by glucuronidation, sulfation, or acetylation. Obesity can increase or decrease the activity of certain enzymes, responsible for phase I oxidative metabolism [66, 67], and enhance some conjugation pathways [68]. Indeed, the CL of oxazepam and lorazepam, eliminated in the form of a glucuronide, were much higher in obese compared to lean subjects [69]. On the other hand, the CL of paracetamol, eliminated by both glucuronide and sulfate conjugation, was only moderately increased [70], and the CL of procainamide, eliminated by acetylation, was unchanged in obese compared to non-obese patients [71].

Despite some research efforts, little is known concerning the global effect of obesity on hepatic metabolism. Even less is known on the effect that obesity and critical illness has on the hepatic metabolism of antibiotics.

4.4.3.2 Kidneys

The kidneys are responsible for renal clearance of drugs, metabolic waste products, and excess water. Renal clearance depends on glomerular filtration, tubular secretion, and/or tubular reabsorption. Morphological changes have been observed in the

kidneys of obese individuals compared to lean individuals: kidneys increase in size as TBW and body surface area (BSA) increase [72, 73].

On a functional level, obesity is associated with glomerular hyperfiltration in animal models [74, 75], and with increased glomerular filtration rates (GFR), increased renal blood flow (RBF), or both, in humans [76–78]. Clinically, these functional changes may translate into augmented renal clearance (ARC), defined as a creatinine clearance (CrCl) greater than or equal to 130 mL/min/1.73 m^2. These patients manifest enhanced renal elimination of hydrophilic solutes [79], resulting in subtherapeutic serum levels of antibiotics in patients receiving SDR of antimicrobial therapy [80]. ARC has been described in the obese, non-critically ill patient [81], and is a common finding in critically ill patients with normal plasma creatinine concentrations [82].

Chronic renal disease is also frequently observed in the obese population [83]. Many obese patients have comorbidities such as hypertension and diabetes, which are also well-defined risk factors for chronic renal disease.

4.5 Theoretical Antibiotic Dosage Adjustments

Standard dosage regimens of antibiotics could theoretically be adjusted based on body size descriptors, renal function, or hepatic function.

4.5.1 On Body Size Descriptors

BMI is the most commonly used size descriptor for obesity. BMI increases with TBW, but it does not take into account sex, race [84], or extreme muscle mass, as it cannot differentiate adipose tissue from muscle mass [85]. Adapting doses of antibiotics using BMI is therefore probably not optimal because a patient with a large muscle mass would receive the same dose as another patient with a high fat mass. Therefore, other size descriptors that take into account varying proportions of muscle to fat may prove more helpful in adapting dosage regimens in the obese patient, as shown in Table 4.2 [86–88].

Antibiotic dosage selection should account for changes in VD and CL. Theoretically, lipophilic drugs require TBW dosing because they distribute extensively into tissues. On the other hand, hydrophilic drugs require adjusted body weight (ABW) or ideal body weight (IBW) dosing because hydrophilic drugs do not distribute to all tissues [89, 90]. However, supporting clinical evidence is lacking or contradictory: vancomycin is a hydrophilic antibiotic, yet PK studies support TBW dosing [48, 91–93].

Up until now, no single size descriptor best correlates with the VD and CL of antibiotics in the obese individual [6, 86]. The size descriptor that best describes the

Table 4.2 Body size descriptors [86, 87]

Body size descriptor	Equation
Total body weight (TBW) (kg): total weight of the individual	Measured on a scale (kg)
Body mass index (BMI) (kg/m²): the most frequently used size descriptor	=TBW (kg)/HT $(m)^2$
Body surface area (BSA) (m^2): often used to calculate doses for chemotherapy	$=TBW^{0.425} \times HT^{0.725} \times 0.007184$ or $=\sqrt{[(HT(cm) \times TBW)/3600]}$
Ideal body weight for males (IBW) (kg): developed to relate body size to mortality	=45.4 + (0.89 × HT (cm) − 152.4) + 4.5
Ideal body weight for females (IBW) (kg): developed to relate body size to mortality	=45.4 + (0.89 × HT (cm) − 152.4)
Adjusted body weight (ABW) (kg): adds a proportion or a correction factor of excess TBW above IBW added on to IBW. The correction factor takes into account the distribution of the given antibiotic into adipose tissue	=IBW + correction factor × (TBW − IBW)
Free fat mass for males (FFM) (kg): body weight without any adipose tissue	=(0.285 × TBW) + (12.1 × HT $(m)^2$)
Free fat mass for females (FFM) (kg): body weight without any adipose tissue	=(0.287 × TBW) + (9.74 × HT $(m)^2$)
Lean body weight for females (LBW) (kg): developed to relate patient's size to epidemiological trends in morbidity and mortality	=1.1 × TBW − 0.0128 × BMI × TBW or =(9270 × TBW)/(8780 + 244 × BMI) [88]
Lean body weight for males (LBW) (kg): developed to relate patient's size to epidemiological trends in morbidity and mortality	=1.07 × TBW − 0.0148 × BMI × TBW or =(9270 × TBW)/(6680 + 216 × BMI) [88]
Percent ideal body weight (%)	=(TBW − IBW)/IBW × 100
Predicted normal weight for females (kg): new size descriptor, developed to better describe the PK of drugs	=1.75 × TBW − 0.0242 × BMI × TBW − 12.6
Predicted normal weight for males (kg): new size descriptor, developed to better describe the PK of drugs	=1.57 × TBW − 0.0183 × BMI × TBW − 10.5

VD in the obese patient seems to depend mainly on the drug being studied. However, Green et al. found that TBW was the best size descriptor for VD in 40% of the studies they evaluated, and LBW was the best descriptor for CL in 35% [86]. Another systematic review and meta-analysis examining the relationship between drug CL and body size in studies published between 2000 and 2007 showed that although many studies showed a linear relationship between CL and TBW, the average relationship was nonlinear, suggesting that another size descriptor such as LBW or IBW may be more appropriate [94].

4.5.2 On Liver Function

Hepatic clearance of drugs is currently not measured in a routine fashion, and no dosage adjustments for altered hepatic clearance of antibiotics have been proposed.

4.5.3 On Renal Function

It is current clinical practice to adjust antibiotic dosage regimens according to the patient's renal function. Although different GFR estimating equations are available, they estimate most accurately the GFR when renal function is stable. This is rarely the case in the critically ill patient. As such, 8–24 h urine collections are probably the most precise and practical way to evaluate GFR in this setting [95, 96].

The situation is not much different in obese patients. Only one study has evaluated GFR estimation equations in 22 extremely obese patients in the ICU setting. Despite stable renal function, none of the equations provided acceptable GFR estimations when compared with measured values. Twenty-four hour urine collections were also recommended to assess CrCl in critically ill, obese patients [95].

Even in obese, non-critically ill patients, the accuracy of different GFR estimation equations depends greatly on the stability of renal function, the level function, and the body size of the individual (obese, morbidly obese, or extremely morbidly obese). Table 4.3 provides results from different clinical studies evaluating the different estimation equations available for obese patients [97–106].

4.6 Dosing of Antibiotics in Obese Critically Ill Patients

Only a handful of PK studies on antibiotics have been carried out in the obese, critically ill patient. There are a number of limitations in the studies already performed: sample sizes are often small, most of the studies compare PK data obtained from obese individuals with historical controls, and unbound antibiotic concentrations are most often calculated, instead of measured. Thus, the dosage recommendations must be considered with caution (Table 4.4).

4.6.1 Beta-Lactams

Beta-lactams are time-dependent antibiotics and the PK/PD index that best describes their efficacy is the time that the concentration of the antibiotic remains above the MIC of the infecting pathogen (fT > MIC). Beta-lactams can be used for surgical

Table 4.3 Available equations to estimate GFR in obese patients

Name of the equation	Estimating equation	Clinical evaluation of the equation in obese patients
Cockcroft-Gault equation	=[(140 − age (years) × TBW)/(72 × Screat (mg/dL))] × 0.85 in females	• Shown to be slightly more accurate than the Cockcroft-Gault equation, but only at low GFR in 380 obese and lean patients with and without kidney disease [97] • No reliable estimations were obtained by using the Cockcroft-Gault equation in obese patients in a prospective study on 850 obese and lean patients with creatinine levels less than 1.5 mg/dL. The Cockcroft-Gault equation underestimated GFR in lean patients, and overestimated clearance in obese individuals [98]
Cockcroft-Gault equation with ABW (using a correction factor of 0.4)	=[(140 − age (years) × ABW)/(72 × Screat (mg/dL))] × 0.85 in females	• Yielded accurate estimates of GFR in 366 obese patients with mild renal insufficiency [100]
Cockcroft-Gault equation with LBW	=[(140 − age (years) × LBW)/(72 × Screat (mg/dL))] × 0.85 in females	• Yielded accurate GFR estimates in morbidly obese patients, but small cohort of only 56 patients [103] • Accuracy of GFR estimates similar in ABW- and LBW-based equations in a study on 73 patients with BMI >40 kg/m^2 [99]
MDRD4	=175 × Scr (mg/dL)$^{-1.154}$ × age (years)$^{-0.203}$ × (0.742 in females) × (1.21 in black individuals)	• No reliable estimations were obtained by using MDRD in obese patients in a prospective study on 850 obese and lean patients with creatinine levels less than 1.5 mg/dL. MDRD underestimated GFR in patients, irrespective of BMI [98] • Shown to be slightly more accurate than the Cockcroft-Gault equation, but only at low GFR in 380 obese and lean patients with and without kidney disease [97] • Yielded inaccurate estimates of GFR in 81 obese potential kidney donors [101] • Overestimated GFR in 29 obese otherwise healthy individuals without overt kidney disease [104]

MDRD4 de-indexed	=[(Estimated GFR by MDRD4) × BSA]/1.73 m^2	• Yielded accurate estimates of GFR in 366 obese patients with mild renal insufficiency [100]
2009 CKD-EPI creatinine	=k1 × (Screat/k2)$^{-\alpha}$ × 0.993^{age} where: k1 = 141 (white men); 143 (white women); 163 (black men); 166 (black women) k2 = 0.7 (men); 0.9 (women) α = 1.209 (men with Screat >0.9 mg/dL); 1.209 (women with Screat >0.7 mg/dL); 0.411 (men with Screat ≤0.9 mg/dL); 0.329 (women with Screat ≤0.7 mg/dL)	• Yielded inaccurate estimates of GFR in 81 obese potential kidney donors [101]
2012 CKD-EPI cystatin C	ScystC ≤0.8 mg/L: =133 × (ScystC/0.8)$^{-0.499}$ × (0.996)^{age} (× 0.932 if female)	• Cystatine-based equations were more accurate in estimating GFR than creatinine-based equations in 101 overweight and obese Malaysian patients [106]
	ScystC >0.8 mg/L: =133 × (ScystC/0.8)$^{-1.328}$ × (0.996)^{age} (× .932 if female)	
2012 CKD-EPI creatinine-cystatin C for females	Screat ≤0.7 mg/dL and ScystC ≤0.8 mg/L: =130 × (Screat/0.7)$^{-0.248}$ × (ScystatC/0.8)$^{-0.375}$ × (0.995)^{age}	• This equation best predicted measured GFR compared to 2009 CKD-EPI creatinine C and 2012 CKD-EPI cystatin C in 36 severely obese caucasian individuals with normal kidney function before and after bariatric surgery [105]
	Screat ≤0.7 mg/dL and ScystC >0.8 mg/L: =130 × (Screat/0.7)$^{-0.248}$ × (ScystatC/0.8)$^{-0.711}$ × (0.995)^{age}	
	Screat >0.7 mg/dL and ScystC ≤0.8 mg/L: =130 × (Screat/0.7)$^{-0.601}$ × (ScystatC/0.8)$^{-0.375}$ × (0.995)^{age}	
	Screat >0.7 mg/dL and ScystC >0.8 mg/L: =130 × (Screat/0.7)$^{-0.601}$ × (ScystatC/0.8)$^{-0.711}$ × (0.995)^{age}	
2012 CKD-EPI creatinine-cystatin C for males	Screat ≤0.9 mg/dL and ScystC ≤0.8 mg/L: =135 × (Screat/0.7)$^{-0.207}$ × (ScystatC/0.8)$^{-0.375}$ × (0.995)^{age}	
	Screat ≤0.9 mg/dL and ScystC >0.8 mg/L: =135 × (Screat/0.7)$^{-0.207}$ × (ScystatC/0.8)$^{-0.711}$ × (0.995)^{age}	
	Screat >0.9 mg/dL and ScystC ≤0.8 mg/L: =130 × (Screat/0.7)$^{-0.601}$ × (ScystatC/0.8)$^{-0.375}$ × (0.995)^{age}	
	Screat >0.9 mg/dL and ScystC >0.8 mg/L: =130 × (Screat/0.7)$^{-0.601}$ × (ScystatC/0.8)$^{-0.711}$ × (0.995)^{age}	

(continued)

Table 4.3 (continued)

2009 CKD-EPI creatinine de-indexed	=[(Estimated GFR by CKD-EPI creatinine) × BSA]/1.73 m^2	• Yielded accurate estimates of GFR in 366 obese patients with mild renal insufficiency [100]
Salazar-Corocan for males	=((137 − age) × (0.285 × TBW)) + (12.1 × HT$(m)^2$)/(51 × Screat (mg/dL))	• Overestimated GFR estimates in morbidly obese patients, but small cohort of only 56 patients [100]
Salazar-Corocan for females	=((146-age) × (0.287 × TBW)) + (9.74 × HT$(m)^2$)/(60 × Screat (mg/dL))	

Abbreviations: *TBW* total body weight, *ABW* adjusted body weight, *LBW* lean body weight, *MDRD4* modification of diet in renal disease, *CKD-EPI* chronic kidney disease epidemiology collaboration, *Screat* serum creatinine, *ScystatC* serum cystatin C, *BSA* body surface area

Table 4.4 Clinical PK studies on antibiotics in obese critically ill patients

Author, year [reference]	Study design	Size of cohort	Antibiotic	Conclusions
Beta-Lactams				
Hites et al. 2013 [111]	Retrospective case-control study	68 TDMs (49 obese patients)	MEM, CEF, and TZP	No PK differences between obese and non-obese patients
Cheatham et al. 2014 [112]	PK Prospective study	9 morbidly obese patients	MEM	PK parameters were no different in morbidly obese patients compared to non-obese historical controls
Alobaid et al. 2016 [113]	Population PK study	19 obese and non-obese patients	MEM	Obesity was associated with an increase in the VD of MEM in the central compartment, but only increased CrCL and not BMI affected PD target attainment
Sturm et al. 2014 [114]	PK prospective study	9 morbidly obese patients	TZP	All patients achieved PD target attainment for pathogens with an MIC ≤16 mg/L
Alobaid et al. 2016 [116]	Multicentric, retrospective study	1400 patients (trough concentrations)	MEM and TZP	Obesity was not identified in multivariate analysis as a risk factor for not attaining the PD target
Roberts and Lipman 2013 [117]	Multicentric, prospective PK study	31 obese and non-obese patients	Doripenem	Probability of target attainment decreased as TBW increased for infections due to less susceptible pathogens
Aminoglycosides				
Taccone et al. 2010 [120]	Prospective PK study	74 obese and non-obese patients, (exclusion criteria: BMI ≥40 kg/m^2)	Amikacin	Probability of PD target attainment was better when dosage was based on TBW compared to ABW
Glycopeptides				
Lin et al. 2016 [124]	Retrospective cohort study	26 obese patients	Vancomycin	Majority of obese patients attained rapidly the PD target with reduced total-weight-based daily exposure compared to lean patients

(continued)

Table 4.4 (continued)

Author, year [reference]	Study design	Size of cohort	Antibiotic	Conclusions
Fluoroquinolones				
Malone et al. 2001 [133]	Prospective PK study	10 patients	Ciprofloxacin	No correlation between body size and CL or VD of ciprofloxacin was observed
Utrup et al. 2010 [134]	Case report	1 patient	Ciprofloxacin	PK was similar to PK described in study by Malone et al. [133], and clinical and microbiological cure was obtained with dose of 800 mg BID of ciprofloxacin
Oxazolidinones				
Muzevich and Lee 2013 [139]	Case report	1 patient	Linezolid	Subtherapeutic concentrations correlated with decreased efficacy

prophylaxis or to treat a suspected or confirmed infection. Cefazolin (CFZ), a first-generation cephalosporin, is the antibiotic most frequently used for prophylaxis [37]. Despite the EPIC II study showing that about one-third of patients in the ICU receive antibiotic prophylaxis [39], data on this practice in the critically ill are extremely scarce. Indeed, only one study on CFZ prophylaxis in 30 post-trauma critically ill patients is available for consideration. Population PK analysis showed that TBW was a significant covariate in determining the VD of the central compartment [107]. Other studies (in non-critically ill patients) have also identified a positive correlation between TBW and the VD of CFZ [23, 24, 108]. Studies in obese, non-critically ill patients suggest that SDR of CFZ may not provide adequate prophylaxis in all obese patients because serum and/or tissue concentrations are lower in heavier patients after administering the same dose [23, 108–110].

Broad-spectrum beta-lactams such as piperacillin-tazobactam (TZP) and meropenem (MEM) are used to treat nosocomial infections. Some studies suggest that dosage regimens of TZP and MEM should not differ between obese and non-obese critically ill patients. A retrospective, case-control study utilizing 68 episodes of TZP and MEM therapeutic drug monitoring (TDM), obtained from 49 obese critically ill patients (median BMI of 40 kg/m^2) were matched for age, SOFA score, gender and renal function, with 68 TDM episodes from 59 non-obese critically ill patients. The study showed no significant PK differences between obese and non-obese patients [111]. Another PK study on MEM was carried out in nine obese, critically ill patients, without non-obese controls. Results showed that PK parameters were similar to those observed in non-obese individuals reported in the literature, except for a larger absolute VD, but smaller VD when normalized for weight [112]. A population PK analysis of MEM collected in 19

critically ill obese and non-obese patients found that obesity was associated with an increase in the VD of the central compartment. However, BMI had little effect on PD target attainment; only higher CrCL was associated with a lower probability of PD target attainment [113]. A PK study on TZP was carried out in nine morbidly obese, critically ill patients without non-obese controls. All patients attained the PD target of fT > MIC for 100% of the dosing interval for infections due to pathogens with an MIC of ≤16 mg/L [114]. Finally, a large, retrospective multicenter study analyzed trough concentrations of MEM and TZP from 1400 critically ill patients. No differences in MEM trough concentrations were observed between obese and lean patients. On the other hand, in univariate analysis, obese patients had significantly lower trough concentrations of TZP and lower PD target attainment (PD target of fT >4 × MIC for 100% of the time) than non-obese patients. However, obese patients in the study were more often younger, male, with a higher estimated CrCl than the non-obese group, representing factors associated with lower antibiotic concentrations [115]. Furthermore, more non-obese patients received prolonged infusions of TZP than in the obese group. Finally, in multivariable logistic regression, obesity was not identified as a significant factor affecting TZP PD target attainment. Even in this large study, obesity was not identified as a clear risk factor for insufficient MEM or TZP serum concentrations in critically ill patients [116].

On the other hand, in a PK study of doripenem in 31 critically ill patients with nosocomial pneumonia (seven of whom were obese), the probability of PD target attainment was significantly lower in patients with greater TBW. Higher dosage regimens or extended infusions of doripenem were recommended in obese patients [117].

Therefore, in obese, critically ill patients, doses of MEM and TZP should not differ with doses given to lean patients. However, an increased dosage regimen with or without prolonged infusion is probably necessary for doripenem, particularly if the infecting pathogen is less susceptible.

4.6.2 Aminoglycosides

Aminoglycosides are concentration-dependent antibiotics used to treat confirmed or suspected severe Gram-negative infections. Their accepted PD target is a peak concentration to MIC ratio (C_{max}/MIC) >8–10. A retrospective analysis of data on the PK of gentamycin and tobramycin obtained from 40 morbidly obese patients with serum creatinine levels of ≤1.5 mg/dL, who had received a once-daily aminoglycoside regimen based on adjusted body weight (ABW), has been reported. Severity of disease was not available. The authors recommended to continue using ABW-based dosage regimens in obese patients, despite the observation that 16% of the patients did not attain PD targets to treat less susceptible pathogens [118]. In a PK analysis of prospective data on gentamycin and tobramycin collected from 2073 adults (of unknown clinical severity) from 1982 to 2003, LBW-based dosage

regimens (using the Janmahasatian method [88]), performed better than ABW-based regimens to attain PD targets [119].

PK data on obese, critically ill patients is very sparse. In one study evaluating the loading dose of amikacin in patients with sepsis or septic shock, patients with a BMI >40 kg/m^2 were excluded. Out of 74 patients who participated in the study, nine were obese. The probability of PD target attainment was significantly better when doses of 30 mg/kg were administered based on TBW compared to a dose of 25 mg/kg based on ABW [120]. No other studies have been carried out in obese critically ill patients. These data suggest that initial aminoglycoside dosing should be based on TBW for patients with a BMI up to 40 kg/m^2, and on ABW or LBW for patients with a BMI ≥40 kg/m^2. Dosage regimens should then be adapted based on TDM.

4.6.3 Glycopeptides

Glycopeptides are used to treat infections due to Gram-positive pathogens. The accepted PK/PD target for vancomycin, the most commonly used glycopeptide, is an area under the concentration time curve to MIC ratio (AUC_{0-24}/MIC) >400. In the critically ill patient, continuous infusion of vancomycin (CIV) is preferred to intermittent infusion of vancomycin (IIV) because despite no differences in terms of PK properties, clinical efficacy, or mortality [121–123], studies have shown that CIV allows for faster acquisition of target concentrations, requires fewer serum samples per treatment to monitor vancomycin concentrations, presents less variability in the daily given dose, is less expensive, and the risk of drug-related nephrotoxicity is significantly lower than with IIV, when the same daily dosage regimens are administered [122, 123].

In obese, non-critically ill patients, both the VD and the CL of vancomycin have been shown to correlate in a linear fashion with TBW [48]. However, in a recent retrospective case-control study using CIV in obese and non-obese critically ill patients, researchers failed to show any difference in the CL of vancomycin between obese (BMI ≥35 kg/m^2) and non-obese patients (BMI < 35 kg/m^2), and there was no clear relationship with TBW. The majority of obese patients (15/17) achieved rapid (24 h) PD target achievement after having received a loading dose of 25.3 mg/kg, followed by a maintenance dose of 13.3 mg/kg. Utilization of CIV in obese patients reduced the total-weight based daily exposure of vancomycin compared to lean patients [124].

In a previous retrospective study of 332 randomly selected patients receiving IIV, TBW ≥101.4 kg, and large vancomycin doses (≥4 g/jour) were independently associated with nephrotoxicity [125]. No other study has confirmed the association between nephrotoxicity and weight, but other studies have confirmed that elevated trough concentrations, duration of therapy, and IIV are associated with nephrotoxicity [126–128]. Continuous infusion of vancomycin in the obese critically ill patient may indeed allow for good PD target attainment, at lower daily doses, and a lower risk of nephrotoxicity in these patients. These results need to be confirmed in a prospective study.

Current vancomycin dosage recommendations are to administer it as a continuous infusion, with a loading dose based on TBW, followed by a maintenance dose based on the patient's CrCL and TDM.

4.6.4 Fluoroquinolones

Fluoroquinolones are antimicrobials with both concentration and time-dependent PK/PD, used to treat Gram-positive and Gram-negative infections. The PK/PD index that best describes their efficacy is the AUC_{0-24}/MIC ratio.

One PK study on moxifloxacin was performed in 12 morbidly obese non-critically ill patients. No significant plasma PK differences were observed between obese patients and non-obese historical controls. The authors suggested that no dose adjustment was necessary [129].

Studies on levofloxacin have provided conflicting results. In one PK study in 15 obese individuals and one case report involving an obese individual weighing 179 kg, no dosage adjustment was needed [130, 131]. However, after reviewing data from TDM episodes collected in 68 severely morbidly obese patients, dosage adjustment was recommended. The new recommended regimens were stratified by CrCl, calculated using the Cockcroft-Gault equation based on IBW [132].

The only PK studies of fluoroquinolones in obese, critically ill patients involve ciprofloxacin. A PK study on ciprofloxacin was carried out in ten critically ill patients receiving continuous renal replacement therapy (CRRT); six of the patients were obese. No correlation was found between body size and VD or CL [133]. Microbiological and clinical success was reported in a case report of a critically ill patient with a BMI of 53.7 kg/m^2 and on CRRT, receiving 800 mg twice daily of ciprofloxacin. Because the PK of ciprofloxacin was similar to that described in the previous study, the authors recommended giving higher doses to obese patients infected with pathogens with higher MICs [134].

No other relevant PK studies have been performed in the obese, critically ill patient. Therefore, no recommendations for dosage adjustments can be made. Obese, critically ill patients should receive similar fluoroquinolone dosage regimens as lean critically ill patients.

4.6.5 Oxazolidinone

Linezolid is an antimicrobial with both concentration and time-dependent PK/PD, used to treat Gram-positive infections. The PK/PD index that best describes efficacy for Linezolid is the AUC_{0-24}/MIC ratio. A PK study in 20 obese, but otherwise healthy volunteers, showed that despite a significant positive correlation between TBW and total VD, linezolid exposure in patients up to about 150 kg was similar to historical non-obese controls. The authors suggested that no dose adjustment was

needed in obese patients up to approximately 150 kg [135]. Several other case reports [136, 137] and case series [138] have shown that drug exposure is decreased in obese non-critically ill patients, but that clinical cure and microbiological success remains high.

There are currently no PK studies on linezolid in obese, critically ill patients. Only one case report of a critically ill patient weighing 256 kg (BMI of 82 kg/m^2) with a methicillin-resistant *S. aureus* pneumonia demonstrated that subtherapeutic linezolid concentrations correlated with decreased clinical efficacy [139]. Current recommendations on dosage regimens should not differ from non-obese critically ill patients.

4.6.6 Polymyxines

Colistin is an antimicrobial with both concentration and time-dependent PK/PD, used to treat multidrug-resistant Gram-negative infections. The PK/PD index that best describes its efficacy is the AUC_{0-24}/MIC ratio. Four PK studies have been carried out in critically ill patients. Three of the studies did not find any correlation between body size and VD of colistin, but these studies were small with only 10 [140], 14 [141], and 18 [142] participants. Furthermore, few heavy patients were included in these studies as the median TBW was 80 kg in two of the studies [140, 141], and the mean TBW was 72.5 kg in the last study [142]. In a larger study with 105 participants, IBW was identified as a covariate for the VD of the central compartment, representing the principle reason for which IBW-based loading doses have been proposed. However, the heaviest patient that participated in the study was 106 kg [143]. Nevertheless, in a retrospective study of colistin associated nephrotoxicity in 42 obese and overweight critically ill and non-critically ill patients, a BMI $\geq$31.5 kg/m^2 was identified as an independent risk factor for nephrotoxicity, possibly due to excessive dosing in the majority of the patients because this was based on TBW instead of IBW. Thirty-day all-cause in-hospital mortality was 40% in patients who developed nephrotoxicity compared to 15% in those who did not develop nephrotoxicity ($p = 0.14$) [144].

Other dosage regimens of colistin have been suggested, such as a loading dose of 6–9 MIU followed by 4.5 MIU of colistin twice daily, regardless of the body size. However, these regimens still need clinical validation, particularly in the case of critically ill obese patients [142, 143].

There are currently no available PK data on the obese, critically ill patient; therefore, no recommendations for dosage adjustment can be made. Obese, critically ill patients should receive similar dosage regimens as lean critically ill patients.

4.6.7 Glycylines

Tigecycline has a broad-spectrum activity against Gram positive and negative bacteria. However, in the ICU, the antibiotic is used essentially to treat infections due to multidrug-resistant Gram-negative pathogens. The PK/PD index that best predicts efficacy is the AUC_{0-24}/MIC ratio. The probability of PD target attainment to

treat infections due to Gram-negative pathogens was very low with the SDR of 100 mg followed by 50 mg twice daily. PD target attainment was significantly improved (67%) when a higher dosage regimen of 200 mg followed by 100 mg twice daily for Gram-negative pathogens with an MIC of 0.5 mg/L was administered [145]. The high-dose regimens may be more effective than low-dose regimens, without major safety issues [146].

There are currently no available PK data on the obese, critically ill patient; therefore, no recommendations for dosage adjustment can be made. Obese, critically ill patients should receive similar dosage regimens as lean critically ill patients.

4.6.8 Lipopeptides

Daptomycin is an antibiotic used to treat Gram-positive infections. The PK/PD index that best describes efficacy is the C_{max}/MIC or $AUC_{0–24}$/MIC ratio. The SDR for patients with a normal renal function is 6 mg/kg; however, higher dosage regimens (e.g., ≥8 mg/kg) may be necessary in critically ill patients [147].

Total body weight was identified to be the appropriate body size descriptor to adapt doses in a population PK study using data from phase 1–3 clinical trials (n = 282) on daptomycin [148]. TBW was confirmed to be the appropriate dosing weight in two other PK studies. The first PK study evaluated a single dose of daptomycin in seven lean and seven morbidly obese healthy volunteers: CL of the drug was similar in both groups, and no differences were observed between the two groups when $AUC_{0–24}$ and C_{max} were normalized to TBW [149]. The second PK study evaluated daptomycin in moderately and morbidly obese volunteers matched to non-obese volunteers for age, gender, and renal function. In this study, obese patients had lower CL of daptomycin than normal weight individuals with matched renal function [150].

There are currently no available PK data on the obese, critically ill patient; therefore, no recommendations for dosage adjustment can be made. Obese, critically ill patients should receive similar dosage regimens as lean critically ill patients.

4.7 Conclusions

Despite the growing numbers of obese critically ill patients, PK studies on antibiotics in these patients are greatly lacking, and yet, these patients are particularly vulnerable for developing infections. Adequate prophylactic and therapeutic antibiotic therapy is therefore essential. Optimizing treatment in this patient population is important to avoid insufficient serum concentrations potentially responsible for therapeutic failure and/or emergence of resistance and to avoid excessive serum concentrations potentially responsible for toxicity. Much research still needs to be carried out in this domain because currently we are lacking data to make sound recommendations concerning dosage regimens. In the meantime, because the PK of antibiotics is extremely variable in the critically ill patient, we recommended to use TDM to guide antibiotic treatment whenever possible.

References

1. WHO (2016) Obesity. http://www.who.int/topics/obesity/en/
2. Kelly T et al (2008) Global burden of obesity in 2005 and projections to 2030. Int J Obes (Lond) 32(9):1431–1437
3. Buchwald H, Williams SE (2004) Bariatric surgery worldwide 2003. Obes Surg 14(9):1157–1164
4. Angrisani L et al (2015) Bariatric surgery worldwide 2013. Obes Surg 25(10):1822–1832
5. Leyland KM et al (2016) Obesity and the relative risk of knee replacement surgery in patients with knee osteoarthritis: a prospective cohort study. Arthritis Rheumatol 68(4):817–825
6. Falagas ME, Kompoti M (2006) Obesity and infection. Lancet Infect Dis 6(7):438–446
7. Falagas ME et al (2009) Effect of body mass index on the outcome of infections: a systematic review. Obes Rev 10(3):280–289
8. Choban PS et al (1995) Increased incidence of nosocomial infections in obese surgical patients. Am Surg 61(11):1001–1005
9. Bertakis KD, Azari R (2005) Obesity and the use of health care services. Obes Res 13(2):372–379
10. Serrano PE, Khuder SA, Fath JJ (2010) Obesity as a risk factor for nosocomial infections in trauma patients. J Am Coll Surg 211(1):61–67
11. Dodds Ashley ES et al (2004) Risk factors for postoperative mediastinitis due to methicillin-resistant Staphylococcus aureus. Clin Infect Dis 38(11):1555–1560
12. Pai MP (2015) Treatment of bacterial infections in obese adult patients: how to appropriately manage antimicrobial dosage. Curr Opin Pharmacol 24:12–17
13. Thelwall S et al (2015) Impact of obesity on the risk of wound infection following surgery: results from a nationwide prospective multicentre cohort study in England. Clin Microbiol Infect 21(11):1008.e1–1008.e8
14. Koenig SM (2001) Pulmonary complications of obesity. Am J Med Sci 321(4):249–279
15. Beal M et al (2004) A pilot study of quantitative aspiration in patients with symptoms of obstructive sleep apnea: comparison to a historic control group. Laryngoscope 114(6):965–968
16. Vaughan RW, Conahan TJ III (1980) Part I: cardiopulmonary consequences of morbid obesity. Life Sci 26(25):2119–2127
17. Marik P, Varon J (1998) The obese patient in the ICU. Chest 113(2):492–498
18. Chan MK, Chong LY, Achilles K, Project Working Group in Hong Kong (2002) A prospective epidemiologic survey on the prevalence of foot disease in Hong Kong. J Am Podiatr Med Assoc 92(8):450–456
19. Roujeau JC et al (2004) Chronic dermatomycoses of the foot as risk factors for acute bacterial cellulitis of the leg: a case-control study. Dermatology 209(4):301–307
20. Canturk Z et al (2003) Nosocomial infections and obesity in surgical patients. Obes Res 11(6):769–775
21. Fleischmann E et al (2005) Nitrous oxide and risk of surgical wound infection: a randomised trial. Lancet 366(9491):1101–1107
22. Polgreen PM, Herwaldt LA (2004) Staphylococcus aureus colonization and nosocomial infections: implications for prevention. Curr Infect Dis Rep 6(6):435–441
23. Brill MJ et al (2014) Reduced subcutaneous tissue distribution of cefazolin in morbidly obese versus non-obese patients determined using clinical microdialysis. J Antimicrob Chemother 69(3):715–723
24. Hites M, Deprez G, Wolff F, Ickx B, Verleije A, Closset J, Loi P, Prevost J, Taccone FS, Racapé J, Cotton F, Jacobs F (2016) Evaluation of total body weight and body mass index cut-offs for increased cefazolin dose for surgical prophylaxis. Int J Antimicrob Agents 48(6):633–640
25. Weber DJ et al (1985) Obesity as a predictor of poor antibody response to hepatitis B plasma vaccine. JAMA 254(22):3187–3189

26. Weber DJ et al (1986) Response to deltoid muscle injection of hepatitis B vaccine after failure to respond to gluteal injections. JAMA 255(16):2157
27. Sheridan PA et al (2012) Obesity is associated with impaired immune response to influenza vaccination in humans. Int J Obes (Lond) 36(8):1072–1077
28. Piet B et al (2011) CD8(+) T cells with an intraepithelial phenotype upregulate cytotoxic function upon influenza infection in human lung. J Clin Invest 121(6):2254–2263
29. Goossens GH (2008) The role of adipose tissue dysfunction in the pathogenesis of obesity-related insulin resistance. Physiol Behav 94(2):206–218
30. Ouchi N et al (1999) Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. Circulation 100(25):2473–2476
31. Considine RV et al (1996) Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 334(5):292–295
32. Faggioni R, Feingold KR, Grunfeld C (2001) Leptin regulation of the immune response and the immunodeficiency of malnutrition. FASEB J 15(14):2565–2571
33. Karlsson EA, Sheridan PA, Beck MA (2010) Diet-induced obesity in mice reduces the maintenance of influenza-specific CD8+ memory T cells. J Nutr 140(9):1691–1697
34. Donath MY, Shoelson SE (2011) Type 2 diabetes as an inflammatory disease. Nat Rev Immunol 11(2):98–107
35. Marti A, Marcos A, Martinez JA (2001) Obesity and immune function relationships. Obes Rev 2(2):131–140
36. Mancuso P (2013) Obesity and respiratory infections: does excess adiposity weigh down host defense? Pulm Pharmacol Ther 26(4):412–419
37. Bratzler DW et al (2013) Clinical practice guidelines for antimicrobial prophylaxis in surgery. Surg Infect (Larchmt) 14(1):73–156
38. Bitterman R et al (2016) Systematic review of antibiotic consumption in acute care hospitals. Clin Microbiol Infect 22(6):561.e7–561.e19
39. Vincent JL et al (2009) International study of the prevalence and outcomes of infection in intensive care units. JAMA 302(21):2323–2329
40. Cockshott WP et al (1982) Intramuscular or intralipomatous injections? N Engl J Med 307(6):356–358
41. Jackson SJ et al (2004) Delayed gastric emptying in the obese: an assessment using the non-invasive (13)C-octanoic acid breath test. Diabetes Obes Metab 6(4):264–270
42. Maddox A et al (1989) Gastric and oesophageal emptying in obesity. Scand J Gastroenterol 24(5):593–598
43. Gundersen K, Shen G (1966) Total body water in obesity. Am J Clin Nutr 19(2):77–83
44. Forbes GB, Welle SL (1983) Lean body mass in obesity. Int J Obes 7(2):99–107
45. Abernethy DR et al (1982) Prolongation of drug half-life due to obesity: studies of desmethyldiazepam (clorazepate). J Pharm Sci 71(8):942–944
46. Abernethy DR et al (1983) Prolonged accumulation of diazepam in obesity. J Clin Pharmacol 23(8–9):369–376
47. Abernethy DR, Greenblatt DJ, Smith TW (1981) Digoxin disposition in obesity: clinical pharmacokinetic investigation. Am Heart J 102(4):740–744
48. Blouin RA et al (1982) Vancomycin pharmacokinetics in normal and morbidly obese subjects. Antimicrob Agents Chemother 21(4):575–580
49. Benedek IH, Blouin RA, McNamara PJ (1984) Serum protein binding and the role of increased alpha 1-acid glycoprotein in moderately obese male subjects. Br J Clin Pharmacol 18(6):941–946
50. Routledge PA et al (1981) Relationship between alpha 1-acid glycoprotein and lidocaine disposition in myocardial infarction. Clin Pharmacol Ther 30(2):154–157
51. Jackson PR, Tucker GT, Woods HF (1982) Altered plasma drug binding in cancer: role of alpha 1-acid glycoprotein and albumin. Clin Pharmacol Ther 32(3):295–302
52. Piafsky KM et al (1978) Increased plasma protein binding of propranolol and chlorpromazine mediated by disease-induced elevations of plasma alpha1 acid glycoprotein. N Engl J Med 299(26):1435–1439

53. Chapman JM, Massey FJ Jr (1964) The interrelationship of serum cholesterol, hypertension, body weight, and risk of coronary disease. Results of the first ten years' follow-up in the Los Angeles Heart Study. J Chronic Dis 17:933–949
54. Rifkind BM, Gale M, Jackson ID (1967) Serum lipid levels and body fat distribution in obese females. J Clin Pathol 20(3):249–251
55. Nestel PJ, Ishikawa T, Goldrick RB (1978) Diminished plasma free fatty acid clearance in obese subjects. Metabolism 27(5):589–597
56. Morita K, Yamaji A (1995) Changes in the serum protein binding of vancomycin in patients with methicillin-resistant Staphylococcus aureus infection: the role of serum alpha 1-acid glycoprotein levels. Ther Drug Monit 17(2):107–112
57. Suh B et al (1981) Effect of free fatty acids on protein binding of antimicrobial agents. J Infect Dis 143(4):609–616
58. Summers LK et al (1996) Subcutaneous abdominal adipose tissue blood flow: variation within and between subjects and relationship to obesity. Clin Sci (Lond) 91(6):679–683
59. Rossi M et al (2012) Subcutaneous adipose tissue blood flow and vasomotion in morbidly obese patients: long term effect of gastric bypass surgery. Clin Hemorheol Microcirc 51(3):159–167
60. Hollenstein UM et al (2001) Soft tissue concentrations of ciprofloxacin in obese and lean subjects following weight-adjusted dosing. Int J Obes Relat Metab Disord 25(3):354–358
61. Joukhadar C et al (2005) Increase of microcirculatory blood flow enhances penetration of ciprofloxacin into soft tissue. Antimicrob Agents Chemother 49(10):4149–4153
62. Katsiki N, Mikhailidis DP, Mantzoros CS (2016) Non-alcoholic fatty liver disease and dyslipidemia: an update. Metabolism 65(8):1109–1123
63. Nascimbeni F et al (2013) From NAFLD in clinical practice to answers from guidelines. J Hepatol 59(4):859–871
64. Rinella ME (2015) Nonalcoholic fatty liver disease: a systematic review. JAMA 313(22):2263–2273
65. Abernethy DR, Greenblatt DJ (1984) Lidocaine disposition in obesity. Am J Cardiol 53(8):1183–1186
66. Brill MJ et al (2012) Impact of obesity on drug metabolism and elimination in adults and children. Clin Pharmacokinet 51(5):277–304
67. Kotlyar M, Carson SW (1999) Effects of obesity on the cytochrome P450 enzyme system. Int J Clin Pharmacol Ther 37(1):8–19
68. Abernethy DR et al (1983) Enhanced glucuronide conjugation of drugs in obesity: studies of lorazepam, oxazepam, and acetaminophen. J Lab Clin Med 101(6):873–880
69. Abernethy DR et al (1984) The influence of obesity on the pharmacokinetics of oral alprazolam and triazolam. Clin Pharmacokinet 9(2):177–183
70. Abernethy DR et al (1982) Obesity, sex, and acetaminophen disposition. Clin Pharmacol Ther 31(6):783–790
71. Christoff PB et al (1983) Procainamide disposition in obesity. Drug Intell Clin Pharm 17(7–8):516–522
72. Naeye RL, Roode P (1970) The sizes and numbers of cells in visceral organs in human obesity. Am J Clin Pathol 54(2):251–253
73. McIntosh JF, Moller E, Van Slyke DD (1928) Studies of urea excretion. III: the influence of body size on urea output. J Clin Invest 6(3):467–483
74. Henegar JR et al (2001) Functional and structural changes in the kidney in the early stages of obesity. J Am Soc Nephrol 12(6):1211–1217
75. Schmitz PG et al (1992) Renal injury in obese Zucker rats: glomerular hemodynamic alterations and effects of enalapril. Am J Physiol 263(3 Pt 2):F496–F502
76. Pecly IM, Genelhu V, Francischetti EA (2006) Renal functional reserve in obesity hypertension. Int J Clin Pract 60(10):1198–1203
77. Ribstein J, du Cailar G, Mimran A (1995) Combined renal effects of overweight and hypertension. Hypertension 26(4):610–615

78. Chagnac A et al (2000) Glomerular hemodynamics in severe obesity. Am J Physiol Renal Physiol 278(5):F817–F822
79. Claus BO et al (2013) Augmented renal clearance is a common finding with worse clinical outcome in critically ill patients receiving antimicrobial therapy. J Crit Care 28(5):695–700
80. Udy AA et al (2010) Augmented renal clearance: implications for antibacterial dosing in the critically ill. Clin Pharmacokinet 49(1):1–16
81. Hites M et al (2014) Broad-spectrum beta-lactams in obese non-critically ill patients. Nutr Diabetes 4:e119
82. Udy AA et al (2014) Augmented renal clearance in the ICU: results of a multicenter observational study of renal function in critically ill patients with normal plasma creatinine concentrations*. Crit Care Med 42(3):520–527
83. Grundy SM (2004) Obesity, metabolic syndrome, and cardiovascular disease. J Clin Endocrinol Metab 89(6):2595–2600
84. WHO Expert Consultation (2004) Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 363(9403):157–163
85. Cresci B et al (2014) False and true pre-treatment predictors of weight loss in obese patients starting a program for lifestyle change. Eat Weight Disord 19(4):489–494
86. Green B, Duffull SB (2004) What is the best size descriptor to use for pharmacokinetic studies in the obese? Br J Clin Pharmacol 58(2):119–133
87. Duffull SB et al (2004) A standard weight descriptor for dose adjustment in the obese patient. Clin Pharmacokinet 43(15):1167–1178
88. Janmahasatian S et al (2005) Quantification of lean bodyweight. Clin Pharmacokinet 44(10):1051–1065
89. Wurtz R, Itokazu G, Rodvold K (1997) Antimicrobial dosing in obese patients. Clin Infect Dis 25(1):112–118
90. Janson B, Thursky K (2012) Dosing of antibiotics in obesity. Curr Opin Infect Dis 25(6):634–649
91. Penzak SR et al (1998) Therapeutic drug monitoring of vancomycin in a morbidly obese patient. Ther Drug Monit 20(3):261–265
92. Vance-Bryan K et al (1993) Effect of obesity on vancomycin pharmacokinetic parameters as determined by using a Bayesian forecasting technique. Antimicrob Agents Chemother 37(3):436–440
93. Bauer LA, Black DJ, Lill JS (1998) Vancomycin dosing in morbidly obese patients. Eur J Clin Pharmacol 54(8):621–625
94. McLeay SC et al (2012) The relationship between drug clearance and body size: systematic review and meta-analysis of the literature published from 2000 to 2007. Clin Pharmacokinet 51(5):319–330
95. Snider RD et al (1995) Accuracy of estimated creatinine clearance in obese patients with stable renal function in the intensive care unit. Pharmacotherapy 15(6):747–753
96. Baptista JP et al (2011) A comparison of estimates of glomerular filtration in critically ill patients with augmented renal clearance. Crit Care 15(3):R139
97. Cirillo M, Anastasio P, De Santo NG (2005) Relationship of gender, age, and body mass index to errors in predicted kidney function. Nephrol Dial Transplant 20(9):1791–1798
98. Verhave JC et al (2005) Estimation of renal function in subjects with normal serum creatinine levels: influence of age and body mass index. Am J Kidney Dis 46(2):233–241
99. Bouquegneau A et al (2016) Creatinine-based equations for the adjustment of drug dosage in an obese population. Br J Clin Pharmacol 81(2):349–361
100. Bouquegneau A et al (2013) Modification of diet in renal disease versus chronic kidney disease epidemiology collaboration equation to estimate glomerular filtration rate in obese patients. Nephrol Dial Transplant 28(Suppl 4):iv122–iv130
101. Aggarwal N et al (2012) Creatinine-based estimations of kidney function are unreliable in obese kidney donors. J Transplant 2012:872894

102. Salazar DE, Corcoran GB (1988) Predicting creatinine clearance and renal drug clearance in obese patients from estimated fat-free body mass. Am J Med 84(6):1053–1060
103. Demirovic JA, Pai AB, Pai MP (2009) Estimation of creatinine clearance in morbidly obese patients. Am J Health Syst Pharm 66(7):642–648
104. Friedman AN et al (2010) Measuring the glomerular filtration rate in obese individuals without overt kidney disease. Nephron Clin Pract 116(3):c224–c234
105. Friedman AN et al (2014) Predicting the glomerular filtration rate in bariatric surgery patients. Am J Nephrol 39(1):8–15
106. Marwyne MN et al (2011) Estimation of glomerular filtration rate using serum cystatin C in overweight and obese subjects. Med J Malaysia 66(4):313–317
107. Roberts JA et al (2015) Plasma and target-site subcutaneous tissue population pharmacokinetics and dosing simulations of cefazolin in post-trauma critically ill patients. J Antimicrob Chemother 70(5):1495–1502
108. van Kralingen S et al (2011) Pharmacokinetics and protein binding of cefazolin in morbidly obese patients. Eur J Clin Pharmacol 67(10):985–992
109. Edmiston CE et al (2004) Perioperative antibiotic prophylaxis in the gastric bypass patient: do we achieve therapeutic levels? Surgery 136(4):738–747
110. Ho VP et al (2012) Cefazolin dosing for surgical prophylaxis in morbidly obese patients. Surg Infect (Larchmt) 13(1):33–37
111. Hites M et al (2013) Case-control study of drug monitoring of beta-lactams in obese critically ill patients. Antimicrob Agents Chemother 57(2):708–715
112. Cheatham SC et al (2014) Steady-state pharmacokinetics and pharmacodynamics of meropenem in morbidly obese patients hospitalized in an intensive care unit. J Clin Pharmacol 54(3):324–330
113. Alobaid AS et al (2016) Effect of obesity on the population pharmacokinetics of meropenem in critically ill patients. Antimicrob Agents Chemother 60(8):4577–4584
114. Sturm AW et al (2014) Pharmacokinetic analysis of piperacillin administered with tazobactam in critically ill, morbidly obese surgical patients. Pharmacotherapy 34(1):28–35
115. Udy AA et al (2012) Subtherapeutic initial beta-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. Chest 142(1):30–39
116. Alobaid AS et al (2016) What is the effect of obesity on piperacillin and meropenem trough concentrations in critically ill patients? J Antimicrob Chemother 71(3):696–702
117. Roberts JA, Lipman J (2013) Optimal doripenem dosing simulations in critically ill nosocomial pneumonia patients with obesity, augmented renal clearance, and decreased bacterial susceptibility. Crit Care Med 41(2):489–495
118. Ross AL et al (2013) Evaluation of extended interval dosing aminoglycosides in the morbidly obese population. Adv Pharmacol Sci 2013:194389
119. Pai MP, Nafziger AN, Bertino JS Jr (2011) Simplified estimation of aminoglycoside pharmacokinetics in underweight and obese adult patients. Antimicrob Agents Chemother 55(9):4006–4011
120. Taccone FS et al (2010) Revisiting the loading dose of amikacin for patients with severe sepsis and septic shock. Crit Care 14(2):R53
121. James JK et al (1996) Comparison of conventional dosing versus continuous-infusion vancomycin therapy for patients with suspected or documented gram-positive infections. Antimicrob Agents Chemother 40(3):696–700
122. Wysocki M et al (2001) Continuous versus intermittent infusion of vancomycin in severe Staphylococcal infections: prospective multicenter randomized study. Antimicrob Agents Chemother 45(9):2460–2467
123. Cataldo MA et al (2012) Continuous versus intermittent infusion of vancomycin for the treatment of Gram-positive infections: systematic review and meta-analysis. J Antimicrob Chemother 67(1):17–24

124. Lin H, Yeh DD, Levine AR (2016) Daily vancomycin dose requirements as a continuous infusion in obese versus non-obese SICU patients. Crit Care 20(1):205
125. Lodise TP et al (2008) Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. Antimicrob Agents Chemother 52(4):1330–1336
126. Lodise TP et al (2009) Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. Clin Infect Dis 49(4):507–514
127. van Hal SJ, Paterson DL, Lodise TP (2013) Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. Antimicrob Agents Chemother 57(2):734–744
128. Hanrahan TP et al (2014) Vancomycin-associated nephrotoxicity in the critically ill: a retrospective multivariate regression analysis*. Crit Care Med 42(12):2527–2536
129. Kees MG et al (2011) Pharmacokinetics of moxifloxacin in plasma and tissue of morbidly obese patients. J Antimicrob Chemother 66(10):2330–2335
130. Cook AM et al (2011) Pharmacokinetics of intravenous levofloxacin administered at 750 milligrams in obese adults. Antimicrob Agents Chemother 55(7):3240–3243
131. Luque S et al (2011) Levofloxacin weight-adjusted dosing and pharmacokinetic disposition in a morbidly obese patient. J Antimicrob Chemother 66(7):1653–1654
132. Pai MP, Cojutti P, Pea F (2014) Levofloxacin dosing regimen in severely morbidly obese patients (BMI >/=40 kg/m(2)) should be guided by creatinine clearance estimates based on ideal body weight and optimized by therapeutic drug monitoring. Clin Pharmacokinet 53(8):753–762
133. Malone RS et al (2001) Pharmacokinetics of levofloxacin and ciprofloxacin during continuous renal replacement therapy in critically ill patients. Antimicrob Agents Chemother 45(10):2949–2954
134. Utrup TR et al (2010) High-dose ciprofloxacin for serious gram-negative infection in an obese, critically ill patient receiving continuous venovenous hemodiafiltration. Ann Pharmacother 44(10):1660–1664
135. Bhalodi AA et al (2013) Pharmacokinetics of intravenous linezolid in moderately to morbidly obese adults. Antimicrob Agents Chemother 57(3):1144–1149
136. Mersfelder TL, Smith CL (2005) Linezolid pharmacokinetics in an obese patient. Am J Health Syst Pharm 62(5):464–467
137. Tsuji Y et al (2012) Evaluation of the pharmacokinetics of linezolid in an obese Japanese patient. Scand J Infect Dis 44(8):626–629
138. Stein GE et al (2005) Pharmacokinetics and pharmacodynamics of linezolid in obese patients with cellulitis. Ann Pharmacother 39(3):427–432
139. Muzevich KM, Lee KB (2013) Subtherapeutic linezolid concentrations in a patient with morbid obesity and methicillin-resistant Staphylococcus aureus pneumonia: case report and review of the literature. Ann Pharmacother 47(6):e25
140. Mohamed AF et al (2012) Application of a loading dose of colistin methanesulfonate in critically ill patients: population pharmacokinetics, protein binding, and prediction of bacterial kill. Antimicrob Agents Chemother 56(8):4241–4249
141. Markou N et al (2008) Colistin serum concentrations after intravenous administration in critically ill patients with serious multidrug-resistant, gram-negative bacilli infections: a prospective, open-label, uncontrolled study. Clin Ther 30(1):143–151
142. Plachouras D et al (2009) Population pharmacokinetic analysis of colistin methanesulfonate and colistin after intravenous administration in critically ill patients with infections caused by gram-negative bacteria. Antimicrob Agents Chemother 53(8):3430–3436
143. Garonzik SM et al (2011) Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. Antimicrob Agents Chemother 55(7):3284–3294

144. Gauthier TP et al (2012) Incidence and predictors of nephrotoxicity associated with intravenous colistin in overweight and obese patients. Antimicrob Agents Chemother 56(5):2392–2396
145. Xie J et al (2014) Optimal tigecycline dosage regimen is urgently needed: results from a pharmacokinetic/pharmacodynamic analysis of tigecycline by Monte Carlo simulation. Int J Infect Dis 18:62–67
146. Falagas ME et al (2014) Effectiveness and safety of high-dose tigecycline-containing regimens for the treatment of severe bacterial infections. Int J Antimicrob Agents 44(1):1–7
147. Falcone M et al (2013) Considerations for higher doses of daptomycin in critically ill patients with methicillin-resistant Staphylococcus aureus bacteremia. Clin Infect Dis 57(11):1568–1576
148. Dvorchik B, Damphousse D (2004) Single-dose pharmacokinetics of daptomycin in young and geriatric volunteers. J Clin Pharmacol 44(6):612–620
149. Pai MP et al (2007) Influence of morbid obesity on the single-dose pharmacokinetics of daptomycin. Antimicrob Agents Chemother 51(8):2741–2747
150. Dvorchik BH, Damphousse D (2005) The pharmacokinetics of daptomycin in moderately obese, morbidly obese, and matched nonobese subjects. J Clin Pharmacol 45(1):48–56

Chapter 5
Hypoalbuminaemia and Altered Protein Binding

Adrian Brink

5.1 Introduction

Critical illness is associated with such substantial metabolic and physiological changes that antibiotic pharmacokinetics (PK) are altered, concentrations are unpredictable and dosing decisions are complicated and mostly unresolved. There is increasing evidence that dosing should be individualized according to many factors, such as weight, renal function and albumin levels. The Defining Antibiotic Levels in ICU patients (DALI) study recently showed a greater than 500-fold variation in plasma beta-lactam concentrations in the patients studied [1]. Alterations to PK have been identified not only for beta-lactams [2–5], but also to other antibiotic classes such as the oxazolidinones [6–8], the glycopeptides [8, 9] and the aminoglycosides [8, 9]. Failure to meet pharmacokinetic/pharmacodynamics (PK/PD) targets is associated with a reduction in bacterial kill, and may adversely impact patient outcomes [1, 8, 10–13].

The degree to which a drug is protein bound under normal circumstances and the extent to which this is altered in critical illness are seldom considered when deciding on a dosing regimen [14]. Both of these factors may have a significant impact on two independent determinants affecting PK, apparent volume of distribution (Vd) and clearance (CL) of the drug. Somewhat conflicting views exist though whether changes in plasma protein binding will influence the clinical exposure of a patient to a drug, and this may be as result of the lack of standardization for PD models [15–18]. Albumin as the serum protein responsible for most drug-protein binding, may have a profound effect on the Vd and CL, particularly of highly protein-bound drugs, as it is only the unbound fraction that is pharmacodynamically active [14, 19–21].

A. Brink
Ampath National Laboratory Services, Milpark Hospital,
Heritage house, 9 Guild Road, Parktown, 2193 Johannesburg, South Africa

Division of Infectious Diseases and HIV Medicine, Department of Medicine,
Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa
e-mail: brinka@ampath.co.za

A.A. Udy et al. (eds.), *Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill*, DOI 10.1007/978-981-10-5336-8_5

High inter- and intra-patient variability in V_d is exacerbated by aggressive fluid resuscitation, and CL may be significantly influenced by augmented renal clearance (ARC) [22, 23], acute kidney injury (AKI) [24], renal replacement therapy (RRT) and extracorporeal membrane oxygenation (ECMO) [8, 25]. In addition, multiple other pathophysiological processes are present in critically ill patients that can alter drug–albumin interactions. These processes include: decreased albumin synthesis and capillary leak [that occurs as a consequence of the systemic inflammatory response syndrome (SIRS)], or a loss of albumin in patients with an open abdomen or with burns. In fact, hypoalbuminaemia (≤25 g/dL) occurs in more than 40% of patients admitted to ICU [9, 26, 27]. Displacement by endogenous molecules with a high affinity for albumin (e.g. bilirubin and urea) or by concurrent administration of other highly protein bound drugs can also play an important role. Finally, conformational changes to the albumin molecule, such as occur with glycosylation induced by hyperglycaemia, have also been shown to decrease binding capacity, with the increased unbound fraction resulting in an increased V_d [28].

Given these pathophysiological changes it is not surprising that protein binding may be clinically relevant, particularly for antimicrobial agents with high intrinsic clearance (CL_{int}), that are also highly protein bound (>85–90%) and predominantly cleared by glomerular filtration [9]. This is of particular relevance to hydrophilic agents such as the beta-lactams (e.g. ceftriaxone, ertapenem, flucloxacillin), the glycopeptides (e.g. teicoplanin) and the lipopeptides (e.g. daptomycin) [8, 9]. Hypoalbuminaemia may lead to an increased proportion of the active, unbound fraction of an antimicrobial, although paradoxically, as a consequence of increased V_d and CL, antimicrobial concentrations may actually be reduced throughout the dosing interval. Higher doses or, preferably, shorter dosing intervals may be advisable for such antimicrobials when higher drug exposure is warranted.

5.2 Albumin-Antimicrobial Binding Dynamics

Human serum albumin is an extremely soluble, 66.5-kDa, negatively charged, elliptically shaped protein, which makes up 50% of total plasma protein [29–32]. It has been reported to have four reversible binding sites [33] which are important not only for binding to free ions (e.g. calcium), fatty acids and amino acids, but also for carriage of numerous endogenous (e.g. insulin, cortisol and glucagon) and exogenous molecules on domains I and II [30, 31]. Albumin only binds to acidic and neutral drugs. In addition, thiol groups on albumin have an important antioxidant function, donating electrons and neutralizing toxic oxygen radicals [30, 32]. This property is crucial in septic patients [31, 34].

In the healthy state, intravascular albumin mass is estimated as 120 g, in contrast to the approximate 160 g found in the extravascular space [29]. Following synthesis in the liver, it is secreted into the intravascular space and rapidly (at a rate of 6–7 g h^{-1}) achieves equilibrium with the interstitial space. This occurs through "trans-capillary filtration" via passive filtration in areas with large gaps in the endothelium and by active filtration via the receptor albondin [30–32]. Simultaneously, albumin is returned to the intravascular compartment via lymphatics at a rate of

120 ml h^{-1} [29, 31]. The binding of albumin to an antimicrobial occurs as a reversible equilibrium dependent on the concentrations of each and on an association (affinity) constant determined by several properties, such as the number of antimicrobial binding sites and the molecular weight of the antimicrobial [14]. The association (equilibrium) constant (K_a) of an antimicrobial for albumin can be defined by using Eq. 5.1, where *b, f* and *t* refer to the molar concentrations of bound, free and total antibiotic respectively, and *P* is the total molar concentration of albumin:

$$K_a = \frac{b}{f(P-b)} \tag{5.1}$$

$$b = t - f$$

At standard doses, most drugs display linear binding—where the unbound fraction remains unchanged as drug concentrations increase. When unbound concentrations of the antimicrobial exceed the number of available binding sites on albumin, protein binding becomes concentration-dependent [14]. Ertapenem, ceftriaxone and cefazolin are examples of antimicrobials for which non-linear protein binding has been reported [14, 35].

The representation of the reversible equilibrium between bound, unbound and distributed drug in critically ill patients is best described graphically as a two-compartment model initially proposed by Tilament et al. in 1978 [36] and subsequently substantially modified by Ulldemolins et al. [27] and Roberts et al. [9]. As depicted in Fig. 5.1, the bloodstream represents the central compartment and the extravascular tissue, into which

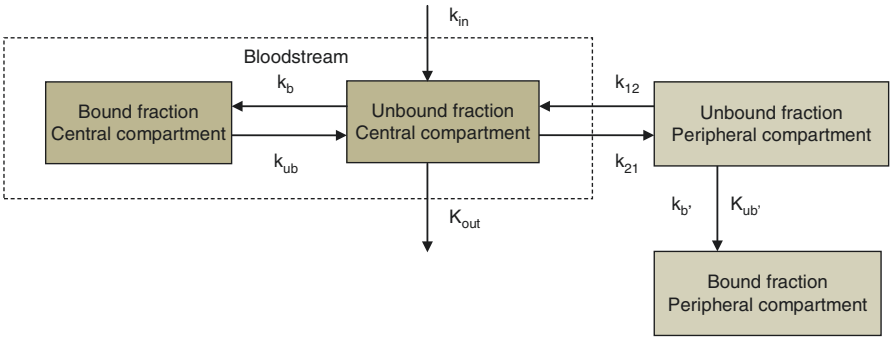

Fig. 5.1 A two-compartment model for albumin binding equilibrium. The central and peripheral compartments represent the intravascular blood volume and the extravascular tissues, respectively: k_{in} corresponds to the absorption constant (in oral administration) or the infusion rate (in intravenous infusion) while k_{out} corresponds to the elimination constant from the central compartment, k_b and k_{ub} represents the equilibrium between bound and unbound drug, respectively, and albumin in the central compartment that is dependent on binding affinity, k_{12} corresponds to the constant that describes the movement of drug from the central compartment (1) to the peripheral compartment (2) while k_{21} conversely, describes the movement from the peripheral compartment(s) back to the central compartment, k_b' and k_{ub}' describes the equilibrium between bound and unbound drug and albumin in the peripheral compartment where binding can occur to extravasated albumin or to cell membranes or include intracellular distribution. Adapted from Roberts et al. [9], with permission from Springer International Publishing AG (2013)

the unbound drug distributes from the central compartment, constitutes the peripheral compartment. The albumin-bound fractions in both compartments act as a "reservoir" or "depot" for unbound drug within the vascular compartment where dissociation of the albumin–drug complex provides constant unbound concentrations [19, 27, 37].

Roberts et al. [38] examined the unbound concentrations of cefazolin, a highly bound antibiotic [plasma protein binding (PPB) ~ 90%] to illustrate the binding dynamics during the dosing interval, following administration of 1,000 mg infused over five minutes in 30 critically ill patients with traumatic soft tissue injuries [9, 38]. The authors demonstrated how the unbound fraction changes in the same dosing interval (6h) in patients without hypoalbuminaemia. In fact, immediately after administration, the very high cefazolin plasma concentrations resulted in disproportionately high unbound concentrations until binding to plasma proteins took place. Once equilibrium between bound, unbound and distributed drug was achieved, both the unbound fraction and concentration declined and stabilized after two hours. Similar data have been shown for ceftriaxone [39].

It is of paramount importance to note that the unbound fraction and unbound concentration are different [9, 27].

The PK/PD effect is governed by changes in unbound drug concentration, which is not equivalent to changes in the unbound drug fraction. For many drugs, different unbound fractions have been described during a dosing interval which depends on the total drug concentration and several other factors such as saturation [40]. The unbound fraction is expressed as a function of both the unbound concentration and the two binding parameters—the maximal binding capacity (B_{max}), which is related to the molar concentration of the binding protein, and the equilibrium dissociation constant (K_d), which is equal to the inverse of the affinity constant K_a. Data describing both the unbound fraction and the corresponding unbound drug concentration should be considered together to interpret likely drug effects during drug discovery [9, 40]. However, the change in unbound plasma concentration (C_{free}) of the drug during the dosing interval should be the primary focus rather than the unbound fraction (f_u) when predicting the effects of changes in albumin concentration [9, 40–42].

5.3 Causes of Altered Albumin Binding

Altered albumin levels may result not only in an alteration of intra- and extravascular fluid flux, but also in decrease all of the secondary functions of albumin, including its function as an antioxidant, its role in maintenance of capillary integrity and of particular relevance to this review, drug transport [29, 32, 43]. Hypoalbuminaemia is a non-specific marker of severity of illness and levels rapidly decrease during the stress response [33, 44]. There is currently no consensus as to what level defines hypoalbuminaemia nor what should be considered a moderate or severe decrease. Hypoalbuminaemia may be defined as <35 g/L [31], based on the SAFE (Saline versus Albumin Fluid Evaluation) study. Most PK studies define hypoalbuminaemia as a serum albumin <25 g/L, with a reported incidence in critically ill patients of 40–50% [26, 27].

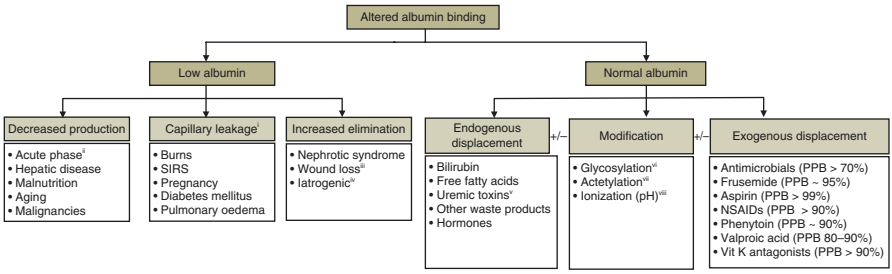

Fig. 5.2 Clinical factors responsible for alterations in drug–albumin binding. (*i*) Serum to tissues, (*ii*) Stress, injury, systemic inflammatory response syndrome, (*iii*) Burns, open abdomen, (*iv*) Binding to starch, (*v*) Includes indoxyl sulphate, indole acetate, hippuric acid and 3-Carboxy-4-Methyl-5-Propyl-2-Furanpropanoic Acid (CMPF), (*vi*) due to hyperglycaemia, (*vii*) due to low doses of aspirin or *p*-nitrophenyl acetate (intermediate in the synthesis of paracetamol), (*viii*) leads to N-B = Neutral-to-Base isomer transition. *SIRS* systemic inflammatory response syndrome, *PPB* plasma protein binding, *NSAIDs* non-steroidal anti-inflammatory drugs, *Vit* vitamin. Adapted from Ulldemolins et al. [27], with permission from Springer International Publishing AG (2011)

Alterations in binding may involve albumin, the drug itself or conditions required for binding. The causes of altered albumin binding are therefore multifactorial and these may occur concurrently as depicted in Fig. 5.2. Most result from disease-driven physiological changes as a consequence of decreased synthesis and increased transcapillary leak and elimination. The coexistence of these factors accounts for the frequency of hypoalbuminaemia documented in critically ill patients. Concomitant endogenous and exogenous displacement of the drug, due most probably to modification of albumin, may also occur.

SIRS in critically ill patients is associated with elevated levels of tumour necrosis factor (TNF)-alpha and interleukin (IL)-6 which results in increased synthesis of acute-phase proteins, such as C-reactive protein, complement-3 and fibrinogen, at the expense of visceral proteins [31, 33, 44]. This is compounded by the fact that critically ill patients are at high risk for malnutrition with an insufficient dietary amino acid intake [32, 45, 46]. The SIRS response is also associated with a disruption of the endothelial glycocalyx and of intercellular tight junctions with increased capillary permeability and transcapillary loss, particularly prominent in patients with shock [47, 48]. These mechanisms can be exaggerated by exogenous loss such as that observed with burns or with other surgical causes such as blood loss or an open abdomen [3, 9, 27]. Notably, up to 2 g of nitrogen (12.5 g of protein) per litre may be lost in patients with an open abdomen [49].

Diminished plasma drug binding by exogenous drugs (co-administered) is usually a result of competitive displacement from the same binding site or allosteric displacement following micro-environmental changes at the binding site [43]. Endogenous binding inhibitors found in plasma (such as bilirubin, urea and free fatty acids) were initially thought to lead to drug displacement but it appears that complex interactions with these molecules may actually involve conformational changes of the albumin molecule which may reduce or increase binding, depending on the substance, rather than direct competition [50]. Although conventional drug–drug interactions with displacement from competing plasma protein binding

sites may still occur, they usually do not result in changes in the unbound levels of most antimicrobials [16, 17].

As such, albumin has been called a "breathing" molecule—referring to the dynamic nature of its physiological interactions [50]. This is due to the fact that its tertiary and quaternary structures are not rigid and can be altered by multiple factors including pH, calcium ions, its redox state, chloride, the albumin concentration per se and hyperglycaemia [18, 36, 51]. One such effect, known as Neutral ⇌ Base (N-B) transition, is significantly influenced by pH. The transition leads to a differential affinity of drugs for the N- or B-isomers. For example, the unbound fraction of ciprofloxacin is approximately 80% higher with the B isoform compared to the N isoform [52]. The impact of the N-B transition on the binding of other antibiotics is unclear. Hyperglycaemia may also affect the structure of albumin through glycosylation via a non-enzymatic process involving Schiff base formation and Amadori rearrangement to a ketoamine derivative [28]. In summary, the physical and biological properties of albumin render the molecule easily modifiable by multiple processes which may compromise its ability to bind to albumin-binding drugs [28, 53].

A recent prospective study of teicoplanin (PPB ~90–95%) found that 12 h after administration of a loading dose in hyperglycaemic critically ill patients with hypoalbuminaemia ($n = 28$), serum teicoplanin concentrations were significantly lower and the V_d significantly higher compared to the control group [28]. The study also found that the percentage of glycosylated albumin was significantly correlated with the equilibrium constant of teicoplanin for albumin ($P = 0.004$) and the teicoplanin V_d ($P = 0.031$). The significant impact of conformational changes due to glycosylation of albumin on the PKs of a highly protein bound antimicrobial was thus confirmed for teicoplanin but the impact on other antimicrobials is unknown. The clinical consequences and implications of displacement from albumin or conformational changes depend ultimately on the extent of changes in distribution and clearance of each drug and the effect this has on the unbound antimicrobial concentration relative to the therapeutic PK/PD target.

In critically ill patients with acute or chronic renal or liver insufficiency, binding of drugs is reduced but this is only partially accounted for by hypoalbuminaemia and the accumulation of endogenous binding inhibitors such as urea or bilirubin [15, 36, 43]. Unknown factors appear to modify the albumin structure in such a way as to lead to decreased affinity for various drugs; for example, carbamylation (decomposition) of albumin has been suggested to be one mechanism. Recent protein binding studies of drugs such as vancomycin, ertapenem and ceftriaxone to albumin [15, 54, 55] have confirmed that there is more to altered binding in critically ill patients than hypoalbuminaemia alone. The results of a Michaelis–Menten kinetic analysis for ertapenem highlight the differences in binding characteristics between healthy volunteers and critically ill patients [55]. The study found the number of binding sites per albumin molecule was 1.22 (95% CI 1.07–1.38) in plasma from healthy volunteers versus only 0.404 (95% CI 0.158–0.650) in plasma from ICU patients [55]. This result supports the assertion that binding properties may be affected by other plasma components in critically ill patients. Some antibiotics may also bind to a range of other proteins, for example transferrin, lactoferrin and alpha-1-acid glycoprotein (AAG).

In vitro assays might have important effects on drug binding which may be extrapolated to measured effects in vivo and may be one of the reasons for contradictory

publications regarding relevance of protein binding for specific drugs [54, 56]. Consensus is required with regard to standardization of temperature, pH and other conditions such as centrifugal force ("pressure effect") during the process of ultrafiltration to determine the unbound concentration. Similarly, close attention should be given to antimicrobial stability to ensure robust, reproducible and comparable experimental measurements [18, 56] not only to enable informed dosing decisions during antimicrobial development, but also to facilitate patient-specific dosing regimens, such as Bayesian dose adaption.

5.4 Impact of Altered Protein Binding on Antibacterial Pharmacokinetics

The most important pathophysiological changes that occur in critically ill patients that may alter the PK of antibacterials are the expansion of the extracellular space [57], dysfunction of the eliminating organs including both ARC [22–24] and impaired renal clearance [24], and alterations in plasma protein binding.

If one accepts the paradigm that only the unbound drug is responsible for antibacterial activity, it is probable that alterations in protein binding are applicable only to a limited number of antimicrobials depending on certain properties of the drug such as whether they are hydrophilic or lipophilic and the extent to which they are protein bound. In this regard, Mimoz et al. [58] described a model which explored the PK effect of decreased protein binding capacity on a highly protein bound antibiotic. The study investigated ceftriaxone (PPB ~85–95%), during iatrogenic hydroxyethyl starch-induced hypoalbuminaemia in post-surgery, critically ill patients. In this study, in which no other concurrent confounding factors were present, the authors reported significant increases in the V_d and CL of ceftriaxone, when compared to healthy subjects. The study also established an inverse correlation between serum albumin concentration and ceftriaxone CL.

The effect of plasma protein binding on both V_d and CL can be predicted by the following PK equations [9, 59]:

5.4.1 Impact of Protein Binding on Drug Distribution

V_d can be calculated using Eq. 5.2:

$$V_d = \left(\frac{f_u}{f_{uT}} \right) V_T + V_P \tag{5.2}$$

where f_u is the unbound plasma fraction, f_{uT} the unbound tissue fraction, V_T the tissue volume and V_P the plasma volume. From this equation it can be seen that the larger the f_u, the larger the V_d and that acute or chronic alterations in albumin binding would lead to changes to the V_d [9]. Of particular relevance for critically ill patients, where

early and appropriate therapy is the cornerstone of effective treatment of life-threatening infection [60, 61], increases in the V_d could result in decreases of unbound drug resulting in subtherapeutic concentrations at any point following drug administration. The effects of changes in V_d are confined predominantly to hydrophilic drugs, where their distribution is limited to the extracellular space which is significantly influenced by factors that affect the extracellular volume and/or renal perfusion, such as hyperdynamic circulation and aggressive fluid resuscitation [57, 62–68]. In contrast, the V_d for lipophilic drugs, such as the fluoroquinolones, is usually unchanged in critically ill patients when compared with that of healthy volunteers [57]. For hydrophilic antibacterials, such as beta-lactams, glycopeptides, lipopeptides, linezolid, aminoglycosides and colistin, the impact of hypoalbuminaemia as a major determinant of V_d should not be underestimated, as it may be linearly correlated with the pharmacodynamically active unbound concentration [2–4, 9, 69–72]. The increase in V_d of hydrophilic drugs in critically ill patients, compared with other patient populations, provides the rationale for the administration of a loading dose and increased frequency of dosing.

5.4.2 Impact of Protein Binding on Drug Clearance

The CL can be calculated using Eq. 5.3:

$$\mathrm{CL} = \frac{Q\left(f_u.\mathrm{CL}_{int}\right)}{Q+\left(f_u.\mathrm{CL}_{int}\right)} \tag{5.3}$$

where Q is blood flow in the eliminating organ and CL_{int} is intrinsic clearance which, together with the f_u, affects drug removal from the intravascular compartment. This CL_{int} varies in the presence of hepatic enzyme or renal tubular excretory activity [9]. The kidneys and liver clear unbound drug and therefore the larger the f_u, the higher the renal and/or hepatic clearance would be. For antibacterials cleared predominantly by glomerular filtration and/or tubular excretion, augmented glomerular filtration, as a result of increased renal perfusion due to the high cardiac output and low systemic vascular resistance associated with sepsis, may lead to profound increases in CL [22]. As shown in Table 5.1, and particularly relevant to antibacterials with high renal excretion (CL_{int}), the impact on CL is even more substantial when hypoalbuminaemia is present [2–5, 15, 55, 70, 72–77].

Hypoalbuminaemia may lead to a greater proportion of unbound drug in plasma, which although temporarily increases concentrations [78] is rapidly distributed from the central to peripheral compartments translating into a larger V_d and increased CL, compared to patients with normal albumin levels. In time an equilibrium between bound and distributed drug is achieved such that the former functions as a reservoir for the latter until the bound fraction is sufficiently reduced later in the dosing interval when insufficient unbound concentrations occur [9, 78].

The impact of protein binding on the PK of antibacterials that are moderately (30–70%) or minimally bound (<30%) has yet to be clarified [79]. Wong et al. [80]

Table 5.1 Changes in total drug clearance and apparent volume of distribution of moderate-to-highly bound antibacterials in critically ill patients with hypoalbuminaemia compared with healthy subjects

	Subjects								
	Healthy volunteers		Critically ill patients					% Δ in ICU patients[a]	
Drug [reference]	*n*	% PPB	*n*	Study group	%PPB[b]	CL_{CR} (mL/min)[b]	Albumin (g/L)[b]	CL (ml/min)	V_d (L/kg)
Aztreonam:									
Swabb et al. [84]	48	60	–	–	–	N	–	–	–
Janicke et al. [73]	–	–	7	Gram-negative infections	30 ± 8	103 ± 21	24 ± 5	+15	Nil change
Friedrich et al. [5]	–	–	8	Burns	NA	90 ± 69	21 ± 2	–8	+94
Ceftriaxone:									
Stoeckel et al. [39]	6	85–95	–	–	–	N	–	–	–
Joynt et al. [2]	–	–	11	Severe sepsis	73 (41–99)	97.7 ± 49.6	22.2 ± 6.1	+99	+167
Van Dalen et al. [74]	–	–	18	NA	NA	112 ± 29	NA	+39	+42
Schleibinger et al. [15]	–	–	6	Miscellaneous	74.8 ± 13.4	119.83 ± 28.9	25.2 (13.6–27)	+60	+98
Daptomycin:									
Divorchick et al. [85]	24	90–93	–	–	–	N	–	–	–
Mohr et al. [72]	–	–	9	Burns	NA	132 ± 43	18 ± 4	+151	+80
Falcone et al. [119]	–	–		MRSA bacteraemia	NA	52.2 (±23.6)	NA	+33	+40
Ertapenem:									
Pletz et al. [86]	10	85–95	–	–	–	N	–	–	–
Boeckhart et al. [4]	–	–	17	VAP	NA	93.8 ± 52.4	15.9 ± 5.7	+114	+200
Brink et al. [3]	–	–	8	Severe sepsis	NA	89.9 ± 36.3	26.9 ± 9	+462	+624
Liebchen et al. [55]	–	–	6	VAP/HAP		91.83 ± 32.9	25.6 (24–30.6)	+111	+134
Flucloxacillin:									
Landersdorfer et al. [87]	10	95	–	–	–	N	–	–	–

(continued)

Table 5.1 (continued)

	Subjects								
	Healthy volunteers		Critically ill patients					% Δ in ICU patients[a]	
Drug [reference]	*n*	% PPB	*n*	Study group	%PPB[b]	CL_{CR} (mL/min)[b]	Albumin (g/L)[b]	CL (ml/min)	V_d (L/kg)
Uldemolins et al. [70]	–	–	10	Gram-positive infections	NA	134.3 ± 52.5	20.7 (19.3–22.8)	+10	+57
Fusidic Acid:									
Taboret et al. [88]	8	95–97	–	–		N	–	–	–
Peter et al. [75]	–	–	6	Post-operative pneumonia or septicaemia		N/A	29.2 ± 3.7	+ 94	NA
Teicoplanin:									
Outman et al. [89]	6	90–95	–	–	–	103 ± 22.9	–	–	–
Barbot et al. [76]	–	–	12	Nosocomial infections	NA	174.5 ± 59.7	19 (11–33)	+36	NA
Enokiya et al. [28]		–	28	NA	NA	102.0 (25.3–228.0)	29 (20–49)	−17	+16
Vancomycin:									
Healy et al. [90]	11		–	–	–	110 ± 19.3	–	–	–
Fernandez DG et al. [77]		30–60	46	Severe sepsis ($n = 25$)[c]	NA	65.5 ± 48.1	23 ± 7	−30	+ 185
Dalton et al. [102]	–	–	37	Severe burns	NA	124.4 ± 55.5	24.3 (7–35)	+14	+292

ICU intensive care unit (critically ill), *PPB* plasma protein binding, *N* normal/within reference values, *NA* not available, *CL* clearance, V_d apparent volume of distribution, *VAP* ventilator-associated pneumonia, *HAP* hospital-acquired pneumonia
Adapted from Uldemolins et al. [27] and Roberts et al. [9], with permission from Springer International Publishing AG (2013)

[a]Calculated as $= \dfrac{\text{Observed value} - \text{Reference value}}{\text{Reference value}} \times 100$

[b]Values are reported as median [range] or mean ± SD
[c]Septic shock in 16/25 patients

recently demonstrated marked variability in critically ill patients, both in unbound and total concentrations of seven beta-lactams, irrespective of whether they were highly protein bound or not [80]. Variability occurred with ampicillin, piperacillin and benzylpenicillin where PPB under normal circumstances is 20%, 30% and 65%, respectively. This was also recently confirmed for linezolid (PPB 31%), where the percentage bound in hypoalbuminaemic patients was significantly lower than that in non-hypoalbuminaemic patients ($P = 0.024$) [81]. Similarly, a multivariate analysis has revealed a relationship between plasma protein binding (PPB 50%) and plasma albumin concentrations for voriconazole ($P < 0.001$), with higher unbound concentrations with decreasing albumin concentrations. The correlation was more pronounced in the presence of an elevated bilirubin ($P = 0.05$) [82, 83].

5.5 Clinical Relevance of Altered Albumin Binding

The clinical implications of altered protein binding are dependent on the effect it has on the PK of the unbound antimicrobial, and whether the PK/PD target associated with optimal efficacy is achieved. For time-dependent antimicrobials (e.g. beta-lactams), increased CL may reduce the time that the concentration of unbound antimicrobial is maintained above the minimum inhibitory concentration (MIC) of the bacteria throughout the dosing interval (fT > MIC) [27]. Cephalosporins should exceed 60–70%, penicillins (including monobactams) 50–60% [91], and carbapenems 40% [92] fT > MIC for maximal bactericidal activity. For concentration-dependent antimicrobials (e.g. aminoglycosides), the PK/PD target is the ratio of the maximum concentration (C_{max}) to the MIC of the bacteria (C_{max}/MIC), which may not be achieved because of an increase in V_d [9, 27]. For concentration-dependent antimicrobials with time dependence (e.g. linezolid and daptomycin), the attainment of the PK/PD target of the area under the curve (AUC) to the MIC (fAUC/MIC) can also be compromised, as the AUC is a function of both CL and V_d [81]. Given the alterations in PK discussed in Sect. 5.4, in addition to the higher MICs associated with less susceptible bacteria which are increasingly encountered globally, these indices are of utmost importance to improve infection-related mortality in critically ill patients.

While both V_d and CL of highly protein bound antimicrobials (PPB >70%) may be significantly altered with hypoalbuminaemia, for other antibacterials that have moderate (PPB 30–70%) or low (PPB <30%) protein binding, the effect on V_d and CL is thought to be less substantial or even negligible [16–18]. Consideration of hypoalbuminaemia in the context of the extent and degree of concurrent pathophysiological alterations in critically ill patients might be necessary to optimize dosing regimens for such antimicrobials. Where data are available the impact of hypoalbuminaemia on PK parameters for specific antimicrobials will be briefly discussed below [9, 17]. Unfortunately, the majority of PK studies have not measured unbound concentrations or where they have been measured, the impact on V_d and CL has not been provided. Table 5.2 documents the studies ($n = 4$) where alterations in PK parameters of unbound concentrations of moderate-to-highly bound antibacterials in critically ill patients with hypoalbuminaemia are compared with those in

Table 5.2 Alterations in unbound total drug clearance and apparent volume of distribution of moderate-to-highly bound antibacterials in critically ill patients with hypoalbuminaemia compared with healthy subjects

Drug [reference]	Subjects							% Δ in ICU patients[a]				
	Healthy volunteers		Critically ill patients									
	n	% PPB	*n*	Study group	% PPB	CL_{CR}	Albumin (g/L)[b]	CL	V_d	$t_{1/2}$	C_{max} (mg/L)	$AUC_{0-\infty}$ (mg h/L)
Cephalothin:	–											
Dalley et al. [93]	5	71	–	–	–	–	–	–	–	–	–	–
Dalley et al. [93]	–	–	9	Severe burns	59 ± 8	148 ± 45	25 ± 5	−25	+5	+58	+82	+26
Ertapenem:												
Majumdar et al. [98]	16	85–95	–	–	–	–	–	–	–	–	–	–
Boseli et al. [97]	–		15	VAP	NA	74 (66–109)	32.6 (28.1–39.4)	−84	−59	+95	+135	+583
Brink et al. [3]	–		8	Severe sepsis	62.2 (46.4–69.1)	96.8 ± 43.3	26.9 ± 9	−38	−26	+144	+259	+444
Liebchen et al. [55]	–	–	6	VAP/HAP		91.8 ± 32.9	25.6 (24–30.6)	−82	−61	+6	+84	+439

ICU intensive care unit (critically ill), *PPB* plasma protein binding, CL_{CR} creatinine clearance, *CL* clearance, V_d apparent volume of distribution, $t_{½}$ half-life, C_{max} maximum (or peak) serum concentration, $AUC_{0-\infty}$ area under the concentration–time curve from 0 h to infinity, *VAP* ventilator-associated pneumonia, *HAP* hospital-acquired pneumonia, *NA* not available

Adapted from Uldemolins et al. [27] and Roberts et al. [9] with permission from Springer International Publishing AG (2013)

[a]Calculated as $= \dfrac{\text{Observed value} - \text{Reference value}}{\text{Reference value}} \times 100$

[b]Values are reported as median [range] or mean ± SD

[c]Septic shock in 16/25 patients

Table 5.3 Classification of antimicrobials according to percentage protein binding[a]

Highly bound (>70%)	Moderately bound (30–70%)	Minimally bound (<30%)
Amphotericin B (90%)	Azithromycin (7–51%)	Amikacin (0–11%)
Anidulafungin (>99%)	Aztreonam (60%)	Amoxicillin (17–20%)
Caspofungin (97%)	Cefotaxime (40%)	Ampicillin (15–25%)
Cefazolin (75–85%)	Cefuroxime (33–50%)	Cefepime (16–19%)
Cefonicid (98%)	Cephalothin (55–75%)	Ceftaroline (20%) [133]
Cefoperazone (90%)	Ciprofloxacin (20–40%)	Ceftazidime/Avibactam
Cefoxitin (80–50%)	Clarithromycin (42–50%)	(<10%/6–8%) [131]
Ceftriaxone (85–95%)	Chloramphenicol (60%)	Ceftazidime (17%)
Clindamycin (90%)[a]	Levofloxacin (50%)	Ceftobiprole (22%)
Cloxacillin (94%)	Linezolid (31%)	Ceftolozane/Tazobactam
Dalbavancin (93%)	Moxifloxacin (30–50%)	(16–21%/30%) [129]
Daptomycin (90–93%)[b]	Nitrofurantoin (40%)	Cefpirome (9%)
Dicloxacillin (97%)	Benzylpenicillin	Colistin (<10%)
Doxycycline (93%)	[Penicillin-G] (65%)	Doripenem (8%)
Ertapenem (85–95%)	Piperacillin (30%)	Ethambutol (20–30%)
Erythromycin (73–81%)	Piperacillin/tazobactam	Fluconazole (11–12%)
Faropenem (96–99%)	(30/30%) [130]	Fosfomycin (0%)
Flucloxacillin (95%)	Sulfamethoxazole (68%)	Gentamycin (<30%)
Fusidic acid (95–97%)	Ticarcillin (55%)	Imipenem (20%)
Iclaprim (93%)	Trimethoprim (45%)	Isoniazide (0–10%)
Itraconazole (99.8%)	Vancomycin (30–60%)	Meropenem (2%)
Lincomycin (80–90%)	Voriconazole (58%)	Metronidazole (<20%)
Minocycline (75%)		Norfloxacin (10–15%)
Nafcillin (90%)		Polymyxin B (<10%)
Oxacillin (93%)		Quinupristin/dalfopristin
Oritavancin (85%) [123][c]		(11–26%)
Posaconazole (>97%)		Tobramycin (<30%)
Rifampicin [rifampin] (80%)		
Sulfisoxazole (92%)		
Tedizolid (60–70%) [134]		
Teicoplanin (90–95%)		
Telavancin (92–94%)		
Tigecycline (71–89%)		

Adapted from Uldemolins et al. [27] with permission from Springer International Publishing AG (2011)
[a]Unless references specified in bracket after a drug, all protein binding data reproduced from Ulldemolins et al. [27]
[b]90% bound to α_1-acid glycoprotein
[c]30% bound to α_1-acid glycoprotein

healthy subjects; studies were included only if unbound concentrations were measured, as opposed to being estimated. Table 5.3 provides a classification of antimicrobials according to their published values of albumin binding.

5.5.1 Beta-Lactams

With a few exceptions, the beta-lactam family of time-dependent antimicrobials ($fT > MIC$) have low to moderate protein binding (Table 5.3). Based on the following studies, we recommend alternative dosing and administration strategies be considered to increase drug exposure in critically ill patients.

Penicillins, cephalosporins and monobactams: In a study of burns patients with a mean serum albumin concentration of 25 ± 5 g/L, the V_d and CL of the unbound fraction of the cephalosporin, cephalothin (PPB 55–75%), was shown not to be substantially affected, compared to that in healthy subjects (Table 5.3) [93]. The lack of PK alteration was evident despite a 10% decrease in binding even in those patients with serum albumin concentrations <25 g/L and substantial increases in creatinine clearance. This study was unique and perhaps not representative, as the unbound cephalothin PK was related to the elapsed time after injury where hypovolaemia and cardiac dysfunction were thought to affect drug distribution in the initial phase and may account for the lack of changes in V_d and CL [27, 94]. Compared to healthy adults, however, the half-life ($t_{½}$) and AUC were increased by 58% and 22%, respectively. This study highlights the fact that the clinical impact of antimicrobial PK alterations in critically ill patients depends on certain properties, such as extent of protein binding and renal excretion rate, and these do not necessarily apply to cephalothin, i.e. a moderately bound drug that is partially cleared by biliary excretion.

In contrast, an increased CL has been observed for ceftriaxone, a third-generation cephalosporin (PPB 83–96%), with dose-dependent saturation of binding sites resulting in higher unbound concentrations at higher doses [2, 39]. Joynt et al. [2] demonstrated that following a 2 g dose of ceftriaxone once-daily in patients with hypoalbuminaemia, increased V_d and CL led to failure of PD attainment of both total and unbound concentrations in four of eight patients with normal renal function for the entire dosing interval, and in another three for a substantial part thereof. This has also been supported by other PK studies [58, 74, 95] (refer to Table 5.1).

Schleibinger et al. [15] also published PK data for total and unbound ceftriaxone in a cohort of critically ill patients where, compared to healthy subjects, the total ceftriaxone V_d and CL increased by 98% and 60%, respectively, in 6 of 17 patients with normal renal function (Table 5.1). Despite this, all but one patient (with normal renal function) in the cohort ($n = 17$) showed unbound trough concentrations >2 mg/L [the European Committee on Antimicrobial Susceptibility Testing (EUCAST) resistance breakpoint for *Enterobacteriaceae* and *Streptococcus pneumoniae*], and >8 mg/L (4× the breakpoint) at the mid-dosing interval. The authors also showed that among patients with normal bilirubin, those with renal impairment (CL_{CR}<60 ml min^{-1}) had higher unbound fractions (median 35.9%; interquartile range (IQR) 31.1–44.1%; $n = 9$) than patients with normal renal function (19.5%; 14.7–25.1%; $n = 7$). Moreover, according to the binding characteristics of ceftriaxone to albumin that was elucidated by Michaelis–Menten kinetics, the binding curve for plasma from ICU patients without renal impairment was nearly identical to that of healthy volunteers. However, both maximal binding capacity and affinity were reduced in patients with renal impairment, and severely reduced in patients with hyperbilirubinaemia [15].

Alterations of the PK parameters of flucloxacillin, a highly protein bound antistaphylococcal agent, (PPB 95–97%) were investigated in hypoalbuminaemic, critically ill patients. Ulldemolins et al. [70] documented that administration of standard maintenance doses (2 g) of flucloxacillin (PPB 95–97%) by intermittent infusion would be likely to result in under-dosing. The authors reported that the total flucloxacillin V_d was increased compared with that of healthy adults (Table 5.1) and that 4 h

after the end of the infusion the unbound concentrations fell below 1 mg/L. In contrast for the treatment of methicillin-susceptible *Staphylococcus aureus* (MSSA), evidence was provided that a continuous infusion of 8 g/24 h would ensure 100% target attainment of 50% $fT > MIC$ of 2 mg/L. In contrast to most antibiotics depicted in Table 5.1, the authors did not observe any substantial changes in total flucloxacillin CL compared with previous clearance data obtained from healthy subjects [87]. This was attributed to the fact that flucloxacillin has multiple elimination pathways which include both glomerular filtration (40%) and non-renal excretion, of which hepatic metabolism accounts for 30–40% of total clearance [70]. No data are available for unbound clearance of flucloxacillin in healthy subjects to clarify this further.

Aztreonam PK is also altered as a result of pathophysiological changes in critically ill patients. In subjects with normal renal and hepatobiliary function, the drug is primarily excreted by renal mechanisms (60–68%); it displays linear kinetics over a wide dosage range (125–4000 mg) and has serum protein binding of approximately 60%. In two PK studies, one in patients with thermal injuries [5] and another in patients with Gram-negative urosepsis [73], aztreonam V_d and CL were higher compared to that of healthy volunteers (Table 5.1). In the burns cohort, the significant increase in aztreonam V_d was inversely correlated with serum albumin concentrations [5].

Carbapenems: Ertapenem, in contrast to other carbapenems, displays concentration-dependent protein binding of 85–95%, thus prolonging its half-life to 4.5 h compared with meropenem (half-life 1.2 h) and allowing for once-daily dosing [27, 86, 96]. In patients with ventilator-associated [4, 97] and hospital-acquired pneumonia [55] and severe sepsis [3], ertapenem demonstrates a strikingly different PK profile with much lower C_{max} and AUC, and substantial increases in the major PK determinants, total V_d and renal CL, than that observed by Pletz et al. [86] and Majumdar et al. [98] in young, healthy volunteers. Besides a range of different pathophysiological conditions presumed to be present in the four reports, mixed effect modelling indicated that renal function, expressed as creatinine clearance, may also be responsible for the observed inter-study variability of ertapenem PK [4, 55]. The profound increases in the AUC and half-life of unbound ertapenem in hypoalbuminaemic patients compared with data from healthy adults (Table 5.2) warrants close attention. While the unbound concentration was less than the PD target of 40% $fT>MIC$ in some critically ill patients [3, 4], it actually exceeded the target in other cohorts [55, 97]. The clinical relevance of these findings on dosing or administration strategies is still unknown.

5.5.2 Glycopeptides

Glycopeptides are still widely used for the treatment of serious Gram-positive infections and include vancomycin (PPB 30–60%) and teicoplanin (PPB 90–95%), both with binding mostly dependent on serum albumin levels. Vancomycin has a relatively short half-life of 5–6 h. Conversely, in patients without renal insufficiency, teicoplanin has a much longer half-life of 50 h, thus mandating several loading doses to expedite attainment of therapeutic steady-state concentrations [99].

Vancomycin: Vancomycin elimination is almost exclusively via glomerular filtration [100, 101]. Conflicting studies either report a strong correlation with estimated CL_{CR} or found a large increase in vancomycin elimination independent of CL_{CR}. Alternative pathways may be contributing to elimination, particularly in burns patients in whom vancomycin is known to exhibit significant inter-patient variability in total clearance [101–103]. This variability occurs as a consequence of a multitude of pathophysiological changes including enhanced renal CL (either due to increased tubular secretion, increased glomerular filtration, or a combination of both) during the hypermetabolic phase (>48 h post burn) [94, 104, 105]. Dalton et al. recently investigated the impact of severe burns on vancomycin in a large cohort of hypoalbuminaemic patients and demonstrated an increase in total CL and V_d, compared to healthy subjects (Table 5.1) [101]. Fernandez de Gata Garcia et al. [77] published vancomycin PK data for another large cohort of critically ill patients in a medical ICU and demonstrated a substantial increase in V_d and a 30% decrease in CL. Of the 46 patients in the study, 25 had severe sepsis and 16 had septic shock. A confounding factor was that neither study published alterations of in vivo protein binding nor did they measure unbound vancomycin concentrations.

Published data on the unbound fraction of vancomycin in critically ill patients has exhibited significant variability ranging from 45% to 73% [106–110]. In a PK study of 25 critically ill patients, Kees et al. [106] demonstrated that the unbound vancomycin level was independent of total concentration and/or albumin concentration. This unexpected result is contradictory to data that demonstrates that vancomycin is mostly bound to albumin. The dependency of binding on the plasma protein concentration and the lack of a relationship with total drug concentration is typical of relatively weakly bound drugs with dissociation constants much larger than the therapeutic drug concentrations [106, 111]. Conflicting results have also been published for the correlation between unbound vancomycin and the acute-phase protein, AAG and immunoglobulin M [107, 112–114].

Optimization of vancomycin dosing regimens in critically ill patients is complicated and highlights the need for individualized dosing to achieve the required PK/PD target of AUC/MIC ≥400 [102, 115]. Given the narrow therapeutic range of vancomycin and the variability of unbound vancomycin, the use of total drug concentration to guide dosing may be inappropriate.

Teicoplanin: Teicoplanin is highly bound to serum proteins (mainly albumin), and the free fraction accounts for 6–12% of its total serum concentration in normal subjects [116]. In a study of teicoplanin in critically ill surgical patients with a median albumin concentration of 19 g/L (range 11–33), an inverse correlation was found between serum albumin concentration and CL (Table 6.1) [76]. Thus low serum albumin induces low teicoplanin concentrations in plasma and high total apparent CL [76]. Such PK alterations related to increases in the unbound teicoplanin concentrations have been confirmed for other critically ill patients with hypoalbuminaemia (<30.0 g/L) [117]. In a population pharmacokinetic study by Ogawa et al., involving 65 patients with systemic MRSA infections and albumin concentrations ranging from 17 to 44 g/L [118], serum albumin concentration correlated with the V_d of teicoplanin. The impact of hypoalbuminaemia on teicoplanin

V_d was confirmed by Enokiya et al. [28] in a cohort of hyperglycaemic critically ill patients ($n = 28$). In this study, the percentage of glycosylated albumin was significantly correlated with the teicoplanin V_d ($P = 0.031$) (see Sect. 5.3). Therefore, teicoplanin regimens that include high loading doses might be warranted for patients with hyperglycaemic hypoalbuminaemia, if subtherapeutic serum concentrations are to be avoided.

5.5.3 Lipoglycopeptides

The lipoglycopeptides, including daptomycin, oritavancin, dalbavancin and telavancin, are of particular importance in the therapy of Gram-positive pathogens with reduced susceptibility to vancomycin. All lipoglycopeptides are highly protein bound (Table 5.3) and display both concentration-dependent protein binding and concentration-dependent bacterial killing.

Daptomycin: Daptomycin has a PPB of 90–93% (of which 60% is bound to albumin and 30% to AAG) and is primarily eliminated by the kidneys. A PK study in a cohort of patients with thermal burn injury found increases in both total CL and V_d [72], compared to data from healthy adults [85]. The authors noted that the C_{max} and AUC in the burns patients decreased by 44% and 47%, respectively, and concluded that in burns patients, daptomycin at 10–12 mg/kg of body weight/day would be required to achieve adequate drug exposures. This result was confirmed by Falcone et al. [119] in a cohort of critically ill patients with MRSA bacteraemia (Table 5.1). Higher total daptomycin CL and V_d was noted in the subset of patients with normal renal function ($n = 37$) which resulted in a lower probability of target attainment and cumulative fraction of response (CFR) if 6–8 mg/kg was prescribed. The CFR was >90% for all targets with a dose of 10 mg/kg/day or >750 mg/day [119]. In another PK study, the same authors established that hypoalbuminaemia, infection acquired in ICU and failure to achieve a PD target of >666 AUC/MIC were independent risk factors for a poor patient outcome [120].

These studies support recommendations that higher daptomycin doses (8–10 mg/kg/day) should be considered in critically ill patients with sepsis [121, 122]. For the other lipopeptides, dalbavancin (PPB 93%) [27], telavancin (PPB 92–94%) [27] and oritavancin (PPB 85%) [123], no comparative studies in critically ill patients are available, but based on PK data for daptomycin the new lipopeptides may also be affected by hypoalbuminaemia.

5.5.4 Oxazolidinones

Yagi et al. [81] evaluated the variability in plasma levels of unbound linezolid (PPB 31%), its relationship to susceptibility of MRSA, as well as to the variation of PK/PD parameters associated with efficacy (AUC/MIC and *f*AUC/MIC) in critically ill

patients. The percentage of bound linezolid in hypoalbuminaemic (median, 15.5%) patients was significantly lower than that in non-hypoalbuminaemic patients (28.0%) ($P = 0.024$). As a result of variable unbound concentrations, failure to achieve an AUC/MIC >80–120 and/or *f*AUC/MIC >51 (the levels associated with efficacy) was documented for 2 of 20 of the critically ill patients. Based on this study and others [6, 7], individualized dosing of linezolid might be of benefit to critically ill patients.

5.5.5 *Antifungals*

Van Straelen et al. [82] recently investigated the impact of hypoalbuminaemia (<35 g/L) on voriconazole PK in adult intensive care unit patients ($n = 13$). This study reported higher unbound voriconazole concentrations with decreasing albumin concentrations [82, 83]. The correlation was more pronounced in the presence of elevated bilirubin concentrations. Voriconazole has non-linear pharmacokinetics, with elevated unbound drug concentration in plasma not rapidly metabolized and eliminated. This is likely to occur as a consequence of a "saturated metabolism" and the fact that only 2% of voriconazole is excreted unchanged in urine [83, 124]. Therefore, equilibrium between protein binding and metabolism cannot take place or it occurs slowly. This may lead to an increased risk of toxicity without achieving adequate therapeutic targets, despite total voriconazole concentrations remaining within the reference range [82, 125]. Selecting an adequate dose of voriconazole using therapeutic drug monitoring (TDM), preferably by measurement of unbound drug, with consideration of the drugs variable pharmacokinetics, particularly in patients with hypoalbuminaemia, may be preferable. The use of TDM in optimizing exposure to voriconazole has recently been confirmed in a randomized, controlled trial which demonstrated improved outcomes for patients [126].

5.5.6 *New Antimicrobials*

Pharmacokinetic analysis of unbound concentrations in hypoalbuminaemic patients of the following antimicrobials have not been performed. These drugs are in development, are in Phase 2–4 trials, or have been only recently registered. Where PPB have been published, these have been incorporated in Table 5.3.

5.5.6.1 Second-Generation B-Lactam-B-Lactamase Inhibitors

Ceftolozane/tazobactam. Ceftolozane, which is structurally similar to ceftazidime, provides bacteriocidal activity to extended spectrum beta-lactamase producing *Enterobacteriaceae* and multidrug-resistant (MDR) *Pseudomonas aeruginosa,*

including carbapenem-resistant isolates [127, 128]. The binding of ceftolozane and tazobactam to human plasma proteins is 16–21% and 30%, respectively [129]. Piperacillin and tazobactam display similar binding (PPB 30% and 30%, respectively), and it was found that the protein binding is unaffected by the presence of the other compound [130]. This may be similar for this new beta-lactam/beta-lactamase combination.

Ceftazidime/avibactam. Avibactam is a novel semi-synthetic non-beta-lactam (diazabicyclooctane)/beta-lactamase inhibitor with in vitro activity against selected carbapenemase producing *Enterobacteriaceae* (CPE), e.g. *Klebsiella pneumoniae* carbapenemase (KPC) and oxacillinases-48 (OXA-48) [127, 128]. Less than 10% of ceftazidime is protein bound and the degree of protein binding is independent of the concentration. The binding of avibactam to human plasma proteins is also very low (5.7–8.2%) and is similar across the range of concentrations tested in vitro (0.5–50 mg/L) [131].

Aztreonam/avibactam. Combining avibactam to aztreonam (PPB 60%) extends the in vitro activity to include metallo-beta-lactamase producing *Enterobacteriaceae*, e.g. New Delhi metallo-beta-lactamase (NDM) and Verona integron-encoded metallo-beta-lactamase (VIM) [127, 128].

Imipenem/relebactam (*MK-7655*). Relebactam, another non-beta-lactam (diazabicyclooctane)/beta-lactamase inhibitor, has a structure similar to that of avibactam except for the addition of a piperidine ring. In combination with imipenem (PPB 20%), relebactam is highly active against KPC and imipenem-non-susceptible *P. aeruginosa* [127, 128].

Meropenem/RPX2009. RPX2009 is a novel boronic acid-based beta-lactamase inhibitor. RPX2009 can inhibit class A beta-lactamases, mainly KPC enzymes and most AmpC beta-lactamases. Carbavance®, the combination of RPX2009 and meropenem (PPB 2%), is thus active against selected CPE and cefepime-resistant *Enterobacter cloacae* that hyperproduce AmpC [132].

Cephalosporins. The average binding of ceftaroline fosamil to human plasma proteins is approximately 20% and decreases slightly with increasing concentrations over 1–50 mg/mL (14.5–28.0%) [133].

Oxazolidinones. Tedizolid (formerly torezolid) (TR-700) is the active moiety of the prodrug tedizolid phosphate ([TP] TR-701), a second-generation oxazolidinone. Tedizolid has a 4- to 16-fold greater potency than linezolid against Gram-positive species, including MRSA. Protein binding of tedizolid to human plasma proteins is 70–90% [134]. Radezolid (RX-1741) is the first biaryloxazolidinone in clinical development. It shows improved activity, including against linezolid-resistant strains, and is also highly protein bound (PPB 97%).

Aminoglycosides. PK properties of plazomicin were recently determined in two randomized clinical trials in healthy individuals. These studies found a linear and dose-proportional PK profile, good penetration into the epithelial-lining fluid, and, compared to older aminoglycosides, no evidence of side effects relating to renal or auditory function [127]. Plazomicin has a chemical structure similar to that of traditional aminoglycosides (amikacin, tobramycin and gentamicin), and the V_d is likely to be affected by the hydrophilicity of the compound. Plazomicin is structurally

distinguished from traditional aminoglycosides by an unsaturated hydroxyethyl tail and an amino group in the gentamicin ring [128].

Fluorocycline. Eravacycline is a novel fluorocycline, highly active against Gram-positive and Gram-negative pathogens in vitro, including those that are tetracycline resistant and MDR [135]. Eravacycline has wide extravascular tissue distribution (3.2–15 L/kg) and exhibits substantial tissue binding. The PPB rather similar to tigecycline ranges from 41 to 89% [135].

Fluoroquinolones. Delafloxacin is a promising 8-chloro-fluoroquinolone with activity against Gram-negative pathogens, similar to levofloxacin and ciprofloxacin, but more active against quinolone-resistant Gram-positive pathogens (including MRSA, streptococci and enterococci) [127, 128]. Finafloxacin is an 8-cyano-fluoroquinolone that is similar to delafloxacin, but characteristically is more active against anaerobic pathogens when compared to moxifloxacin [128].

5.6 Conclusions

Critically ill patients with hypoalbuminaemia have variable and different PK profiles to healthy volunteers or patients that are less severely ill. Dosing regimens based on studies performed in healthy volunteers or non-critically ill patients may result in drug accumulation (e.g. voriconazole), with risk for toxicity due to a prolonged half-life. Or conversely, may contribute to subtherapeutic unbound concentrations, due to increased V_d and/or CL associated with decreased protein binding, particularly with highly bound antimicrobials [2–4, 28, 70, 72, 76]. Frequently in critically ill patients, multiple conditions beyond hypoalbuminaemia are present and may influence PK concurrently. This may exacerbate the challenge of interpreting PK studies to predict whether concentrations achieved can ensure good clinical outcomes in critically ill patients.

The clinical consequences of PK alterations experienced by critically ill patients may not necessarily be significant. Optimal bacteriological and clinical outcomes depend mostly on three archetypical properties of each drug, namely, the magnitude of protein binding, CL_{int} and the rate of renal excretion [9]. The implications of subtherapeutic antimicrobial concentrations due to hypoalbuminaemia and the monitoring of unbound concentrations need to be clarified to ascertain well defined therapeutic regimens for critically ill patients during drug development. The fundamental tenet that should apply is that dosing regimens should be based on PK data derived from patients whose severity of disease is comparable to that of the patients to be treated. Based on the uncertainty of predicting protein binding and the impact on PK, direct measurement of unbound antibiotic concentrations should be preferred [79, 136]. As antimicrobial stewardship evolves, the use of antibiotic dose-optimization strategies is likely to become the standard of care, particularly for critically ill patients, in order to negate the consequences of hypoalbuminaemia for moderate and highly bound antimicrobials [137, 138].

References

1. Roberts JA, Paul SK, Akova M et al (2014) DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 58:1072–1083
2. Joynt GM, Lipman J, Gomersall CD et al (2001) The pharmacokinetics of once-daily dosing of ceftriaxone in critically ill patients. J Antimicrob Chemother 47:421–429
3. Brink AJ, Richards GA, Schillack V et al (2009) Pharmacokinetics of once-daily dosing of ertapenem in critically ill patients with severe sepsis. Int J Antimicrob Agents 33:432–436
4. Burkhardt O, Kumar V, Katterwe D et al (2007) Ertapenem in critically ill patients with early-onset ventilator-associated pneumonia: pharmacokinetics with special consideration of free-drug concentration. J Antimicrob Chemother 59:277–284
5. Friedrich LV, White RL, Kays MB et al (1991) Aztreonam pharmacokinetics in burn patients. Antimicrob Agents Chemother 35:57–61
6. Zoller M, Maier B, de Cyrill H et al (2014) Variability of linezolid concentrations after standard dosing in critically ill patients: a prospective observational study. Crit Care 18:R148
7. Richards GA, Brink AJ (2014) Therapeutic drug monitoring: linezolid too? Crit Care 18:525
8. Roberts JA, Taccone FS, Lipman J (2015) Understanding PK/PD. Intensive Care Med. doi:10.1007/s00134-015-4032-6
9. Roberts JA, Pea F, Lipman J (2013) The clinical relevance of plasma protein binding changes. Clin Pharmacokinet 52:1–8
10. Tam VH, McKinnon PS, Akins RL et al (2002) Pharmacodynamics of cefepime in patients with Gram-negative infections. J Antimicrob Chemother 50:425–428
11. Forrest A, Nix DE, Ballow CH et al (1993) Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 37:1073–1081
12. Rayner CR, Forrest A, Meagher AK et al (2003) Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. Clin Pharmacokinet 42:1411–1423
13. Li C, Du X, Kuti JL, Nicolau DP (2007) Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. Antimicrob Agents Chemother 51:1725–1730
14. Gonzalez D, Schmidt S, Derendorf H (2013) Importance of relating efficacy measures to unbound drug concentrations for anti-infective agents. Clin Microbiol Rev 26:274–288
15. Schleibinger M, Steinbach CL, Töpper C et al (2015) Protein binding characteristics and pharmacokinetics of ceftriaxone in intensive care unit patients. British J Clin Pharmacology 80:525–533
16. Benet LZ, Hoener B (2002) Changes in plasma protein binding have little clinical relevance. Clin Pharmacol Therap 71:115–121
17. Heuberger J, Schmidt S, Derendorf H (2013) When is protein binding important? J Pharma Sci. doi:10.1002/jps.23559
18. Zeitlinger MA, Derendorf H, Mouton JW et al (2011) Protein binding: do we ever learn? Antimicrob Agents Chemother 55:3067–3074
19. Liu P, Derendorf H (2003) Antimicrobial tissue concentrations. Infect Dis Clin North Am 17:599–613
20. Merrikin DJ, Briant J, Rolinson GN (1983) Effect of protein binding on antibiotic activity in vivo. J Antimicrob Chemother 11:233–238
21. Goldstein A (1949) The interactions of drugs and plasma proteins. J Pharmacol Exp Ther 95:102–165
22. Udy AA, Varghese JM, Altukroni M et al (2012) Subtherapeutic initial beta-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. Chest 142:30–39
23. Sime FB, Udy AA, Roberts JA (2015) Augmented renal clearance in critically ill patients: etiology, definition and implications for beta-lactam dose optimization. Curr Opin Pharmacol 24:1–6

24. Blot S, Lipman J, Roberts DM et al (2014) The influence of acute kidney injury on antimicrobial dosing in critically ill patients: are dose reductions always necessary? Diagn Microbiol Infect Dis 79:77–84
25. Jamal JA, Economou CJ, Lipman J et al (2012) Improving antibiotic dosing in special situations in the ICU: burns, renal replacement therapy and extracorporeal membrane oxygenation. Curr Opin Crit Care 18:460–471
26. Finfer S, Bellomo R, McEvoy S et al (2006) Effect of baseline serum albumin concentration on outcome of resuscitation with albumin or saline in patients in intensive care units: analysis of data from the saline versus albumin fluid evaluation (SAFE) study. BMJ 333:1044
27. Ulldemolins M, Roberts JA, Rello J et al (2011) The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet 50:99–110
28. Enokiya T, Muraki Y, Iwamoto T et al (2015) Changes in the pharmacokinetics of teicoplanin in patients with hyperglycaemic hypoalbuminaemia: impact of albumin glycosylation on the binding of teicoplanin to albumin. Int J Antimicrob Agents 46:164–168
29. Mendez CM, McClain CJ, Marsano LS (2005) Albumin therapy in clinical practice. Nutr Clin Pract 20:314–320
30. Farrugia A (2010) Albumin usage in clinical medicine: tradition or therapeutic? Transfus Med Rev 24:53–63
31. Caironi P, Gattinoni L (2009) The clinical use of albumin: the point of view of a specialist in intensive care. Blood Transfus 7:259–267
32. Margarson MP, Soni N (1998) Serum albumin: touchstone or totem? Anaesthesia 53:789–803
33. Pulimood TB, Park GR (2000) Debate: albumin administration should be avoided in the critically ill. Crit Care 4:151–155
34. Dubois MJ, Orellana-Jimenez C, Melot C et al (2006) Albumin administration improves organ function in critically ill hypoalbuminemic patients: a prospective, randomized, controlled, pilot study. Crit Care Med 34:2536–2540
35. Burkhardt O, Brunner M, Schmidt S et al (2006) Penetration of ertapenem into skeletal muscle and subcutaneous adipose tissue in healthy volunteers measured by in vivo microdialysis. J Antimicrob Chemother 58:632–636
36. Tillement JP, Lhoste F, Giudicelli JF (1978) Diseases and drug protein binding. Clin Pharmacokinet 3(2):144–154
37. Roberts JA, Roberts MS, Semark A et al (2011) Antibiotic dosing in the 'at risk' critically ill patient: linking pathophysiology with pharmacokinetics/pharmacodynamics in sepsis and trauma patients. BMC Anesthesiol 11:3
38. Roberts JA, Udy AA, Jarrett P et al (2015) Plasma and target-site subcutaneous tissue population pharmacokinetics and dosing simulations of cefazolin in post-trauma critically ill patients. J Antimicrob Chemother 70:1495–1502
39. Stoeckel K, McNamara PJ, Brandt R et al (1981) Effects of concentration-dependent plasma protein binding on ceftriaxone kinetics. Clin Pharmacol Ther 29(5):650–657
40. Smith DA, Di L, Kerns EH (2010) The effect of plasma protein binding on in vivo efficacy: misconceptions in drug discovery. Nat Rev Drug Discov 9:929–939
41. Ensom MH (2002) Comment: unbound drug concentration versus unbound drug fraction. Ann Pharmacother 36:731–732
42. Toutain PL, Bousquet-Melou A (2002) Free drug fraction vs. free drug concentration: a matter of frequent confusion. J Vet Pharmacol Ther 25:460–463
43. Yamasaki K, Chuang GVT, Maruyama T et al (2013) Albumin–drug interaction and its clinical implication. Biochim Biophys Acta 1830:5435–5443
44. Neel DR, McClave S, Martindale R (2011) Hypoalbuminaemia in the perioperative period: clinical significance and management options. Best Pract Res Clin Anaesthesiol 25:395–400
45. Kirsch R, Frith L, Black E et al (1968) Regulation of albumin synthesis and catabolism by alteration of dietary protein. Nature 217(5128):578–579
46. Heyland DK, TougasG KD et al (1996) Impaired gastric emptying in mechanically ventilated, critically ill patients. Intensive Care Med 22(12):1339–1344
47. Lee WL, Slutsky AS (2010) Sepsis and endothelial permeability. N Engl J Med 363:689–691

48. Fleck A, Raines G, Hawker F et al (1985) Increased vascular permeability: a major cause of hypoalbuminaemia in disease and injury. Lancet 1(8432):781–784
49. Cheatham ML, Safcsak K, Brzezinski SJ et al (2007) Nitrogen balance, protein loss, and the open abdomen. Crit Care Med 35:127–131
50. McNamara PJ, Trueb V, Stoeckel K (1990) Ceftriaxone binding to human serum albumin: indirect displacement by probenecid and diazepam. Biochem Pharmacol 40:1247–1253
51. Oettl K, Stauber RE (2007) Physiological and pathological changes in the redox state of human serum albumin critically influence its binding properties. Br J Pharmacol 151:580–590
52. Ahmad B, Parveen S, rh K (2006) Effect of albumin conformation on the binding of ciprofloxacin to human serum albumin: a novel approach directly assigning binding site. Biomacromolecules 7:1350–1356
53. Rondeau P, Bourdon E (2011) The glycation of albumin: structural and functional impacts. Biochimie 93:645–658
54. Kees MG, Wicha SG, Seefeld A et al (2013) Unbound fraction of vancomycin in intensive care unit patients. J Clin Pharm 54(3):318–323
55. Liebchen U, Kratzer A, Wicha SG et al (2014) Unbound fraction of ertapenem in intensive care unit patients. J Antimicrob Chemother 69:3108–3111
56. Kratzer A, Liebchen U, Schleibinger M et al (2014) Determination of free vancomycin, ceftriaxone, cefazolin and ertapenem in plasma by ultrafiltration: impact of experimental conditions. J Chromatogr B 961:97–102
57. Roberts JA, Lipman J (2009) Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 37(3):840–851
58. Mimoz O, Soreda S, Padoin C et al (2000) Ceftriaxone pharmacokinetics during iatrogenic hydroxyethyl starch-induced hypoalbuminemia: a model to explore the effects of decreased protein binding capacity on highly bound drugs. Anesthesiology 93(3):735–734
59. Burton ME, Shaw LM, Schentag JJ et al (2006) Applied pharmacokinetics and pharmacodynamics: principles of therapeutic drug monitoring, 4th edn. Lippincott Williams and Wilkins, Baltimore
60. Rello J, Gallego M, Mariscal D et al (1997) The value of routine microbial investigation in ventilator-associated pneumonia. Am J Respir Crit Care Med 156:196–200
61. Kumar A, Roberts D, Wood KE et al (2006) Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 34:1589–1596
62. del Mar Fernández de Gatta Garcia M, Revilla N, Calvo MV et al (2007) Pharmacokinetic/pharmacodynamic analysis of vancomycin in ICU patients. Intensive Care Med 33(2):279–285
63. Lipman J, Wallis SC, Rickard CM et al (2001) Low cefpirome levels during twice daily dosing in critically ill septic patients: pharmacokinetic modelling calls for more frequent dosing. Intensive Care Med 27(2):363–370
64. Felton TW, Hope WW, Roberts JA (2014) How severe is antibiotic pharmacokinetic variability in critically ill patients and what can be done about it? Diagn Microbiol Infect Dis 79:441–447
65. Boselli E, Breilh D, Rimmelé T et al (2005) Pharmacokinetics and intrapulmonary concentrations of linezolid administered to critically ill patients with ventilator-associated pneumonia. Crit Care Med 33(7):1529–1533
66. Roberts JA, Kirkpatrick CM, Roberts MS et al (2009) Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. J Antimicrob Chemother 64(1):142–150
67. Taccone FS, Laterre P-F, Dugernier T et al (2010) Insufficient beta-lactam concentrations in the early phase of severe sepsis and septic shock. Crit Care 14(4):R126
68. Sime FB, Roberts MS, Peake SL et al (2012) Does beta-lactam pharmacokinetic variability in critically ill patients justify therapeutic drug monitoring? A systematic review. Ann Intensive Care 2(1):35

69. Nix DE, Goodwin SD, Peloquin CA et al (1991) Antibiotic tissue penetration and its relevance: impact of tissue penetration on infection response. Antimicrob Agents Chemother 35:1953–1959
70. Ulldemolins M, Roberts JA, Wallis SC et al (2010) Flucloxacillin dosing in critically ill patients with hypoalbuminaemia: special emphasis on unbound pharmacokinetics. J Antimicrob Chemother 65(8):1771–1778
71. Lugo G, Castañeda-Hernández G (1997) Relationship between hemodynamic and vital support measures and pharmacokinetic variability of amikacin in critically ill patients with sepsis. Crit Care Med 25(5):806–811
72. Mohr JF III, Ostrosky-Zeichner L, Wainright DJ et al (2008) Pharmacokinetic evaluation of single-dose intravenous daptomycin in patients with thermal burn injury. Antimicrob Agents Chemother 52(5):1891–1893
73. Janicke DM, Cafarell RF, Parker SW et al (1985) Pharmacokinetics of aztreonam in patients with Gram-negative infections. Antimicrob Agents Chemother 27:16–20
74. Van Dalen R, Vree TB, Baars IM (1987) Influence of protein binding and severity of illness on renal elimination of four cephalosporin drugs in intensive-care patients. Pharm Weekbl Sci 9(2):98–103
75. Peter JD, Jehl F, Pottecher T et al (1993) Pharmacokinetics of intravenous fusidic acid in patients with cholestasis. Antimicrob Agents Chemother 37(3):501–506
76. Barbot A, Venisse N, Rayeh F et al (2003) Pharmacokinetics and pharmacodynamics of sequential intravenous and subcutaneous teicoplanin in critically ill patients without vasopressors. Intensive Care Med 29(9):1528–1534
77. Fernandez de Gatta Garcia M, Revilla N, Calvo MV et al (2007) Pharmacokinetic/pharmacodynamic analysis of vancomycin in ICU patients. Intensive Care Med 33(2):279–285
78. Blot SI, Pea F, Lipman J (2014) The effect of pathophysiology on pharmacokinetics in the critically ill patient — concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev 77:3–11
79. Brink AJ, Richards GA, Lautenbach EEG et al (2015) Albumin concentration significantly impacts on free teicoplanin plasma concentrations in non-critically ill patients with chronic bone sepsis. Int J Antimicrob Agents 45:647–651
80. Wong G, Briscoe S, Adnan S et al (2013) Protein binding of β-lactam antibiotics in critically ill patients: can we successfully predict unbound concentrations? Antimicrob Agents Chemother 57:6165–6170
81. Yagi T, Naito T, Doi M et al (2013) Plasma exposure of free linezolid and its ratio to minimum inhibitory concentration varies in critically ill patients. Int J Antimicrob Agents 42:329–334
82. Vanstraelen K, Wauters J, Vercammen I et al (2014) Impact of hypoalbuminemia on voriconazole pharmacokinetics in critically ill adult patients. Antimicrob Agents Chemother 58:6782–6789
83. Vanstraelen K, Wauters J, deLoor H et al (2014) Protein-binding characteristics of voriconazole determined by high-throughput equilibrium dialysis. J Pharm Sci 103:2565–2570
84. Swabb EA, Leitz MA, Pilkiewicz FG et al (1981) Pharmacokinetics of the monobactam SQ 26,776 after single intravenous doses in healthy subjects. J Antimicrob Chemother 8:131–140
85. Dvorchik B, Sica D, Gehr T (2002) Pharmacokinetics and safety of single-dose daptomycin in subjects with graded renal insufficiency and end-stage renal disease. Poster presented at the 42nd interscience conference on antimicrobial agents and chemotherapy, San Diego, 27–30 September
86. Pletz MW, Rau M, Bulitta J et al (2004) Ertapenem pharmacokinetics and impact on intestinal microflora, in comparison to those of ceftriaxone, after multiple dosing in male and female volunteers. Antimicrob Agents Chemother 48(10):3765–3772
87. Landersdorfer CB, Kirkpatrick CM, Kinzig-Schippers M et al (2007) Population pharmacokinetics at two dose levels and pharmacodynamic profiling of flucloxacillin. Antimicrob Agents Chemother 51(9):3290–3297

88. Taburet AM, Guibert J, Kitzis MD et al (1990) Pharmacokinetics of sodium fusidate after single and repeated infusions and oral administration of a new formulation. J Antimicrob Chemother 25(Suppl B):23–31
89. Outman WR, Nightingale CH, Sweeney KR et al (1990) Teicoplanin pharmacokinetics in healthy volunteers after administration of intravenous loading and maintenance doses. Antimicrob Agents Chemother 34(11):2114–2117
90. Healy DP, Polk RE, Garson ML et al (1987) Comparison of steady-state pharmacokinetics of two dosage regimens of vancomycin in normal volunteers. Antimicrob Agents Chemother 31(3):393–397
91. Craig WA (1998) Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 26(1):1–10
92. Drusano GL (2004) Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat Rev 2(4):289–300
93. Dalley AJ, Deans R, Lipman J et al (2009) Unbound cephalothin pharmacokinetics in adult burn patients are related to the elapsed time after injury. Antimicrob Agents Chemother 53:5303–5305
94. Bonate PL (1990) Pathophysiology and pharmacokinetics following burn injury. Clin Pharmacokinet 18(2):118–130
95. Jungbluth GL, Pasko MT, Beam TR et al (1989) Ceftriaxone disposition in openheart surgery patients. Antimicrob Agents Chemother 33(6):850–856
96. Leroy A, Fillastre JP, Borsa-Lebas F et al (1992) Pharmacokinetics of meropenem (ICI 194,660) and its metabolite (ICI 213,689) in healthy subjects and in patients with renal impairment. Antimicrob Agents Chemother 36(12):2794–2798
97. Boselli E, Breilh D, Saux M et al (2006) Pharmacokinetics and lung concentrations of ertapenem in patients with ventilator associated pneumonia. Intensive Care Med 32:2059–2062
98. Majumdar AK, Musson DG, Birk KL et al (2002) Pharmacokinetics of ertapenem in healthy young volunteers. Antimicrob Agents Chemother 46:3506–3511
99. Brink AJ, Richards GA, Cummins RR et al (2008) Recommendations to achieve rapid therapeutic teicoplanin plasma concentrations in adult hospitalised patients treated for sepsis. Int J Antimicrob Agents 32:455–458
100. Rice TL (1992) Simplified dosing and monitoring of vancomycin for the burn care clinician. Burns 18:355–361
101. Dalton M, Xu H, Cheong E et al (2010) Vancomycin pharmacokinetics in patients with severe burn injuries. Burns 36:469–476
102. Álvarez R, López Cortés LE, Molina J et al (2016) Vancomycin: optimizing its clinical use. Antimicrob Agents Chemother 60:2601–2609
103. Rybak MJ, Albrecht LM, Berman JR et al (1990) Vancomycin pharmacokinetics in burn patients and intravenous drug abusers. Antimicrob Agents Chemother 34:792–795
104. Jaehde U, Sorgel F (1995) Clinical pharmacokinetics in patients with burns. Clin Pharmacokinet 29:15–28
105. Boucher BA, Kuhl DA, Hickerson WL (1992) Pharmacokinetics of systemically administered antibiotics in patients with thermal injury. Clin Infect Dis 14:458–463
106. Kees MG, Wicha SG, Seefeld A et al (2013) Unbound fraction of vancomycin in intensive care unit patients. J Clin Pharm 54(3):318–323
107. Berthoin K, Ampe E, Tulkens PM et al (2009) Correlation between free and total vancomycin serum concentrations in patients treated for Gram-positive infections. Int J Antimicrob Agents 34:555–560
108. Ampe E, Delaere B, Hecq J-D et al (2013) Implementation of a protocol for administration of vancomycin by continuous infusion: pharmacokinetic, pharmacodynamic and toxicological aspects. Int J Antimicrob Agents 41:439–446
109. Butterfield JM, Patel N, Pai MP et al (2011) Refining vancomycin protein binding estimates: identification of clinical factors that influence protein binding. Antimicrob Agents Chemother 55:4277–4282

110. Crandon JL, MacVane SH, Nicolau DP (2013) Clinical laboratory-based assay methodologies may underestimate and increase variability of vancomycin protein binding in hospitalized patients. Pharmacotherapy. doi:10.1002/phar.1323
111. Schmidt S, Gonzalez D, Derendorf H (2010) Significance of protein binding in pharmacokinetics and pharmacodynamics. J Pharm Sci 99:1107–1122
112. Morita K, Yamaji A (1995) Changes in the serum protein binding of vancomycin in patients with methicillin-resistant Staphylococcus aureus infection: the role of serum alpha 1-acid glycoprotein levels. Ther Drug Monit 17:107–112
113. Shin WG, Lee MG, Lee MH et al (1991) Factors influencing the protein binding of vancomycin. Biopharm Drug Dispos 12:637–646
114. Sun H, Maderazo EG, Krusell AR (1993) Serum protein-binding characteristics of vancomycin. Antimicrob Agents Chemother 37:1132–1136
115. Lodise TP, Drusano GL, Zasowski E et al (2014) Vancomycin exposure in patients with methicillin-resistant Staphylococcus aureus bloodstream infections: how much is enough? Clin Infect Dis 59(5):666–675
116. Wilson AP (2000) Clinical pharmacokinetics of teicoplanin. Clin Pharmacokinet 39:167–183
117. Yano R, Nakamura T, Tsukamoto H et al (2007) Variability in teicoplanin protein binding and its prediction using serum albumin concentrations. Ther Drug Monit 29:399–403
118. Ogawa R, Kobayashi S, Sasaki Y et al (2013) Population pharmacokinetic and pharmacodynamic analyses of teicoplanin in Japanese patients with systemic MRSA infection. Int J Clin Pharmacol Ther 51:357–366
119. Falcone M, Russo A, Venditti M et al (2013) Considerations for higher doses of daptomycin in critically ill patients with methicillin-resistant *Staphylococcus aureus* bacteremia. Clin Infect Dis 57(11):1568–1576
120. Falcone M, Russo A, Cassetta MI et al (2013) Variability of pharmacokinetic parameters in patients receiving different dosages of daptomycin: is therapeutic drug monitoring necessary? J Infect Chemother 19:732–739
121. Liu C, Bayer A, Cosgrove SE et al (2011) Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children: executive summary. Clin Infect Dis 52:285–292
122. Brink AJ (2012) Does resistance in severe infections caused by methicillin-resistant Staphylococcus aureus give you the 'creeps'? Curr Opin Crit Care 18:451–459
123. Brade KD, Rybak JM, Rybak MJ (2016) Oritavancin: a new lipoglycopeptide antibiotic in the treatment of Gram-positive infections. Infect Dis Ther 5:1–15
124. Donnelly JP, De Pauw BE (2004) Voriconazole-a new therapeutic agent with an extended spectrum of antifungal activity. Clin Microbiol Infect 10:107–117
125. Dolton MJ, Mikus G, Weiss J et al (2014) Understanding variability with voriconazole using a population pharmacokinetic approach: implications for optimal dosing. J Antimicrob Chemother 69:1633–1641
126. Park WB, Kim N-H, Kim K-H et al (2012) The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. Clin Infect Dis 55:1080–1087
127. Bassetti M, Righi E (2015) New antibiotics and antimicrobial combination therapy for the treatment of Gram-negative bacterial infections. Curr Opin Crit Care 21:402–411
128. Syue L-S, Chen Y-H, Ko W-C et al (2016) New drugs for the treatment of complicated intra-abdominal infections in the era of increasing antimicrobial resistance. Int J Antimicrob Agents 47:250–258
129. Federal Drug Administration (FDA). Prescribing information ZERBAXA (ceftolozane and tazobactam) for injection, for intravenous use. Initial U.S. Approval. 2014. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206829s001lbl.pdf. Last Accessed 30 May 2016.

130. Federal Drug Administration (FDA). Prescribing information ZOZYN (piperacillin and tazobactam) for injection, for intravenous use. http://www.fda.gov/ohrms/dockets/dockets/06p0195/06P-0195-EC1-Attach-1.pdf. Last Accessed 30 May 2016.
131. Federal Drug Administration (FDA). Prescribing information AVYCAZ (ceftazidime and avibactam) for injection, for intravenous use. Initial U.S. Approval. 2015. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206494s002lbl.pdf. Last Accessed 30 May 2016.
132. Hecker SJ, Reddy KR, Totrov M et al (2015) Discovery of a cyclic boronic acid β-lactamase inhibitor (RPX7009) with utility vs class a serine carbapenemases. J med Chem 58:3682–3692
133. Federal Drug Administration (FDA). Prescribing information TEFLARO® (ceftaroline fosamil) for injection, for intravenous use. Initial U.S. Approval. 2010. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/200327s016s017lbl.pdf. Last Accessed 3 June 2016.
134. Federal Drug Administration (FDA). Prescribing information SIVEXTRO (tedizolid phosphate) for injection, for intravenous use. Initial U.S. Approval. 2014. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/0205435s001,0205436s001lbl.pdf. Last Accessed 3 June 2016.
135. Bassetti M, Righi E (2014) Eravacycline for the treatment of intra-abdominal infections. Expert Opin Investig Drugs 23(11):1–10
136. Roberts JA, Abdul-aziz MH, Lipman J et al (2014) Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis 14(6):498–509
137. Barlam TF, Cosgrove SE, Abbo LM et al (2016) Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. doi:10.1093/cid/ciw118
138. Monogue ML, Kuti JL, Nicolau DP (2016) Optimizing antibiotic dosing strategies for the treatment of Gram-negative infections in the era of resistance. Expert Rev Clin Pharmacol 9:459–476

Chapter 6
Acute Kidney Injury and Renal Replacement Therapy

Gordon Y.S. Choi and Gavin M. Joynt

6.1 Definition of Acute Kidney Injury (AKI)

For the purposes of risk stratification, renal failure has been defined functionally, and the term acute kidney injury (AKI) coined to describe progressive grades of functional abnormality. AKI of varying grades, in the presence of sepsis requiring antibacterial therapy is common in critically ill patients. AKI has been defined as a rapid decline in glomerular filtration rate (GFR) that occurs over hours and days. It corresponds with a rapid decrease in renal excretory function and the accumulation of products of nitrogen metabolism such as creatinine and urea, and other unmeasured waste products [1]. The term AKI is a consensus based, graded definition developed by the Acute Dialysis Quality Initiative (ADQI) group in 2004 [2], and the grading classification, under the acronym RIFLE were modified and improved by the Acute Kidney Injury Network (AKIN), which included the ADQI group, in 2007 [3–5]. The RIFLE classification is divided into three levels of renal dysfunction and two levels of clinical outcome: "Loss" and "End-stage kidney disease." The AKIN criteria proposed refinements to the RIFLE criteria by the introduction of a smaller change in serum creatinine (≥26.5 μmol/L) as a threshold to define the presence of AKI and identify patients with Stage 1 AKI (analogous to RIFLE-Risk). In addition, changes in serum creatinine are determined within a time window of 48 h instead of referring to a baseline value. Finally, any patients receiving renal replacement therapy (RRT) are to be classified as Stage 3 AKI (RIFLE-Failure).

G.Y.S. Choi (✉) • G.M. Joynt
Department of Anaesthesia and Intensive Care, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong
e-mail: gchoi@cuhk.edu.hk

A.A. Udy et al. (eds.), *Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill*, DOI 10.1007/978-981-10-5336-8_6

More recently, the Kidney Disease: Improving Global Outcomes (KDIGO) AKI Workgroup proposed a modified definition, harmonizing differences between the RIFLE and AKIN definitions [6]. No individual definition provides a consistently advantageous level of risk stratification. A summary of definitions is provided in Table 6.1.

The presence of renal failure contributes to altered antibacterial PK behavior by a number of mechanisms. Renal protein loss and competition for protein binding sites by unexcreted toxins may result in increased free fraction of antibacterial agents [7]. Reduced creatinine clearance is important for antibiotics substantially excreted via the renal route. Thus, accurate estimations of creatinine clearance and corresponding antibacterial clearance is necessary. Formulae that estimate creatinine clearance from serum creatinine are generally inadequate for this purpose [8]. We recommend direct measurement, for example, 8-h creatinine clearance, as the most viable and accurate method [9].

Table 6.1 Current definitions of renal failure based on function. Criteria are to be applied after an optimal state of hydration is achieved, and criterion that leads to the worst classification should be used

Classification	Definition for AKI	Stage	Serum creatinine	Urine output
RIFLE	An increase in SCr ≥50% within 7 days	Risk	To ≥1.5 times baseline	Less than 0.5 mL/kg/h for more than 6 h
		Injury	To ≥2 times baseline	Less than 0.5 mL/kg/h for more than 12 h
		Failure	To ≥3 times baseline or >0.5 mg/dL (>44 μmol/L) increase to at least 4.0 mg/dL (>354 μmol/L)	Less than 0.3 mL/kg/h for 24 h or anuria for 12 h
AKIN	An increase in SCr within 48 h	I	Increase of ≥0.3 mg/dL (≥26.5 μmol/L) or to 1.5–2 times baseline	Less than 0.5 mL/kg/h for more than 6 h
		II	To >2–3 times baseline	Less than 0.5 mL/kg/h for more than 12 h
		III	To >3 times baseline or ≥0.5 mg/dL (>44 μmol/L) increase to at least 4.0 mg/dL (>354 μmol/L) or initiation of RRT	Less than 0.3 mL/kg/h for 24 h or anuria for 12 h
KDIGO	An increase in SCr within 48 h or ≥50% within 7 days	1	Increase in SCr ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h, or to 1.5–1.9 times baseline	Less than 0.5 mL/kg/h for more than 6 h
		2	To 2.0–2.9 times baseline	Less than 0.5 mL/kg/h for more than 12 h
		3	To 3.0 times baseline or to at least 4.0 mg/dL (>354 μmol/L) or initiation of RRT	Less than 0.3 mL/kg/h for 24 h or anuria for 12 h

AKI acute kidney injury, *Scr* serum creatinine, *RRT* renal replacement therapy

6.2 Epidemiology, Outcome, and Management of Sepsis and AKI

AKI has a hospital prevalence of 1.9% [10] but is more common in critically ill patients, and the prevalence of AKI rises to 40% at the time of admission to the intensive care unit (ICU) if sepsis is present [11]. Of patients in the ICU who develop new AKI, sepsis, and septic shock has been reported to be the likely cause in 11–50% of cases [12–14]. The incidence of AKI increases with increasing severity of sepsis, from approximately 19% in patients with moderate sepsis to 23% and 51% in those with severe sepsis and septic shock, respectively [15]. Conversely, the prevalence of sepsis amongst patients with AKI has been reported by two independent international multicenter studies; sepsis or septic shock occurring in 40.7% and 47.5% of the AKI patients, respectively [16, 17].

Mortality in patients with sepsis-associated AKI appears high. The BEST Kidney investigators reported a 70% overall hospital mortality in patients with septic AKI [12] and prognosis of AKI worsened with increasing age and severity of illness, use of vasoactive drugs, and mechanical ventilation [17]. Moreover, septic AKI patients had a longer duration of stay in both ICU and hospital than non-septic AKI patients [12]. In the same retrospective analysis of 120,000 patients described above, septic AKI was associated with significantly higher covariate adjusted ICU (OR 1.60, 95% CI 1.5–1.7) and hospital mortality (OR 1.53, 95% CI 1.46–1.60), compared with non-septic AKI [11].

The management of established severe sepsis and the varying degrees of AKI has important implications for antibacterial dosing. Treatment is based on initial resuscitation, maintenance of hemodynamic parameters, timely administration of antibacterial agents and source control, while supporting the failing organs and restoring the patient's homeostasis. Accordingly, the administrations of an effective intravenous antibacterial agent within the first hour of recognition of severe sepsis with or without shock are Grade 1C and 1B recommendations, respectively [18].

The use of renal replacement therapy (RRT) remains the mainstay of supportive therapy in patients with severe AKI. Timing of initiation of RRT remains controversial [19–22]. Nevertheless, RRT is often commenced when preventive and medical strategies have clearly failed to correct the underlying laboratory abnormalities with the aim to correct metabolic derangements, fluid overload, and to optimize the administration of fluids including medications, blood products, and nutrition.

Three fundamental forms of RRT are available: continuous, intermittent (either as intermittent hemodialysis (IHD) or sustained low-efficiency dialysis (SLED)), and peritoneal dialysis. Except in developing countries, the use of peritoneal dialysis is limited in the intensive care setting. The use of continuous renal replacement therapy (CRRT) for hemodynamically unstable patients is a Grade 2B recommendation according to the KDIGO guideline and is most commonly used worldwide [23]. This approach is supported by a small number of studies suggesting that continuous therapy might provide a greater benefit in terms of renal recovery [24–27].

The use of a hybrid form of RRT—sustained low-efficiency dialysis (SLED), also known as slow low-efficiency dialysis and extended daily dialysis is moderate intensity dialysis, often with a component of filtration, applied over a period of 6–12 h daily. The method is gaining some popularity. It has advantanges over other forms of IHD in terms of achieving comparable hemodynamic stability with CRRT [28], low anticoagulant requirements, lower cost, and improved patient mobility [29, 30]. However, resultant clearance is inconsistent and highly variable over short periods.

Although the options for performing RRT remain numerous, based on the epidemiological data from BEST and AKI-EPI, CRRT still remains the predominant mode of RRT used worldwide [16, 17].

6.3 Sepsis and Inflammatory Response: Effects on Pharmacokinetic Parameters

The inflammatory response associated with sepsis involves a complex interaction that involves cytokine and mediator release, endothelial damage, and changes in capillary permeability. The acute phase response is also associated with a rapid decrease in serum albumin concentration. In addition, systemic pH, heparin, free fatty acids, and drugs such as salicylate and sulfonamide may act as competitive displacers for drug binding [31]. Fluid shifts result in large extravascular, interstitial fluid accumulation [32]. In addition, therapeutic intervention contributes to total body fluid accumulation as a consequence of the infusion of a large volume of resuscitation fluid. Consequently, in the critically ill, hydrophilic antibacterials (e.g., aminoglycosides, beta-lactams, and glycopeptides) demonstrate a large increase in volume of distribution (V_d) [33–38]. By contrast, lipophilic antibacterials (e.g., fluoroquinolones) have an inherently larger V_d that is often not greatly affected by the inflammatory response and therapeutic interventions [39]. Although the V_d is generally expected to increase in the critically ill, this change is consistent only for certain antibacterials in those with AKI. Specifically, the V_d of amikacin is considerably higher in critically patients with severe sepsis and burns who develop AKI requiring the need of CRRT [40, 41]. For the beta-lactam group, the V_d of pipercillin/tazobactam, ceftriaxone, and ceftazidime is increased in patients with AKI with CRRT when compared to the general group of critically ill patients [42–45]. However, the V_d for cefepime is similar in the critically and non-critically ill [44, 46]. For the glycopeptide—vancomycin, despite a V_d in the critically ill that is nearly twice that of the general population (1.68 vs. 0.4–1 L/kg) [47, 48], the V_d in patients with AKI and CRRT is similar if not somewhat lower than expected 0.32–0.74 L/kg [49, 50]. The V_d of ciprofloxacin is unpredictable and is generally high in non-critically ill patients [51], critically ill patients [52, 53], and those with AKI needing CRRT [54–56]. Therefore, when formulating an individualized dosing

regimen, it is important that actual pharmacokinetic data, relevant to the specific antibacterial agent, is used, rather than making assumptions that broad groups of antibacterials behave similarly. The most accurate possible knowledge of V_d is critical for determining the loading dose of the chosen antibacterial with accuracy.

The physiological response of patients with infection is markedly heterogeneous, and organ failure, with an associated increase in mortality, is a common accompaniment of severe sepsis [18]. Until terminal hemodynamic collapse, the cardiac out in sepsis is generally high [57]. Thus in early sepsis, the glomerular filtration rate (GFR) is frequently increased, both by sepsis and by therapeutic interventions. The combination of hemodynamic alterations, together with fluid resuscitation, and the use of vasopressors as part of the management of sepsis leads to an increase in cardiac output [58, 59]. Increased cardiac output leads to increased renal blood flow and has been shown to be associated with increased glomerular filtration pressure and consequently an increased GFR. This augmented renal clearance (ARC) has consequences for antibacterial dosing [60].

However, should the sepsis response persist, progression to septic shock and multiple organ dysfunction syndrome (MODS) will develop. The definitive mechanisms resulting in septic AKI are yet to be elucidated. It is clear that renal dysfunction does not result from systemic hypoperfusion and ischemia alone [61, 62], but is more likely the result of renal inflammation and tubular responses to sepsis mediators [63, 64]. Septic AKI is associated with reduced GFR and elimination of filtered substances, including many antibacterials. Thus, individualized dosing regimes are necessary to ensure adequate therapeutic, but nontoxic antimicrobial exposure in patients with septic AKI.

The changes in the excretory function of the native kidneys are further complicated by the use of RRT to maintain homeostasis. Thus, a thorough understanding of the principles of RRT is also essential to advise dosing during the maintenance phase of the dosing regimen.

6.4 Goal of Antibacterial Administration

The goal of antibacterial administration is to rapidly attain therapeutic blood concentrations, based on an in vitro minimum inhibitory concentration (MIC), sufficient to kill the offending pathogen(s) [65–68]. Underdosing may result in decreased bacterial killing, failure of clinical resolution and increased resistance, while overdosing may result in toxicity [69].

In addition, understanding the relationship between the pharmacokinetic and pharmacodynamic properties of a chosen antibacterial is important to determine the optimal dosing regimen. Important pharmacodynamic parameters to consider are time above MIC, peak concentration (C_{max}), and the area under the serum concentration-time curve (AUC).

6.5 Achieving an Optimal Pharmacokinetic (PK)–Pharmacodynamics (PD) Relationships

For antibacterial agents that exhibit time-dependent killing (e.g., beta-lactams), maximal bacterial eradication is related to the time for which the serum concentration is above a threshold concentration: MIC ($\%T >$ MIC). Recommended concentrations range from 1 to 5 times MIC [70] for 40–100% of the dosing interval [71]. Using extended or continuous infusions should be superior to maximize time above the threshold concentration without unnecessarily high peak concentrations [72–76].

For concentration-dependent antibacterials (e.g., aminoglycosides), maximizing the C_{max}, between 8 and 10 times higher than the minimum inhibitory concentration (MIC) of the causative pathogen (C_{max}/MIC 8–10) [70, 77], is likely to result in maximal bacterial killing. Clinically, maintaining a fixed dosage with a prolonged dosing interval not only increases the efficacy of the treatment but also minimizes toxicity [77–79].

For antibacterials with both time and concentration-dependent killing characteristics (e.g., vancomycin and fluoroquinolones), achieving a sufficient ratio of the area under the concentration-time curve during a 24 h period (AUC24) to MIC (AUC 24/MIC) is required to optimize killing activity [80–82].

6.6 Basic Principles of Continuous Renal Replacement Therapy (CRRT)

In the critically ill, CRRT is the most common modality of RRT [16, 17]. Rapid fluid and electrolyte shifts in hemodynamically unstable patients are avoided and control of patient fluid balance is more precise than with traditional intermittent hemodialysis (IHD). CRRT is usually performed through a double lumen venous catheter situated in a large (usually femoral or internal jugular) vein, either as continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), or a combination of the two, continuous venovenous hemodiafiltration (CVVHDF) [83–85].

CVVH uses a predominantly hydrostatic pressure gradient to drag solute along with water across a filter membrane to achieve clearance by the principle of convection. Replacement fluid can be added to the circuit either before blood reaches the membrane (predilution) or after passage over the filter membrane (postdilution). Similarly to traditional IHD, CVVHD uses the principle of diffusion across a membrane to provide clearance of solute. This is achieved by generating a continuous concentration gradient using counter-current flow of blood and dialysate fluid, between which equilibration occurs. A combination of the two above techniques at the same time is known as CVVHDF.

6.6.1 Hemofiltration

Most commonly used antibacterials, including larger molecules such as vancomycin (1448 Da) and teicoplanin (1878 Da), are small enough that convective transport across commonly used modern membranes (pore sized 10,000–30,000 Da) is unimpeded [86, 87]. The ability of a solute (including antibacterials) to pass through the membrane is expressed as the sieving coefficient (S_c): the ratio of drug concentration in the ultrafiltrate to plasma.

In general, the S_c ranges from 0 to 1. The relatively small size of antibacterial agents means that protein binding (PB) is the main determinant of S_c. It has been suggested that the S_c can be estimated from published values of PB, such that $S_c = 1 - \text{PB}$, and measured S_c and S_c estimated from published values of protein binding are correlated [88]. However, because protein binding in the critically ill is variable, the S_c can vary widely for the same antimicrobial agent [54, 89–91]. Furthermore, the S_c may also be affected by membrane material and flux properties [92].

Replacement fluid can be added to the circuit either before the filter (predilution) or after (postdilution). In postdilution mode, solute clearance simply depends on ultrafiltration rate and S_c such that:

$$\text{Cl}_{\text{CVVH}}\left(\text{post}\right) = Q_f \times S_c$$

In predilution mode, the plasma entering the hemofilter is diluted by replacement fluid and antimicrobial clearance will be lowered by a correction factor (CF) determined by blood flow rate (Q_b) and predilution replacement rate (Q_{rep}). Thus,

$$\text{Cl}_{\text{CVVH}}\left(\text{pre}\right) = Q_f \times S_c \times \text{CF}, \quad \text{where CF} = Q_b / Q_b + Q_{rep}$$

The point of dilution is only likely to be significant if the rate of fluid replacement is high. The proportion of predilution may influence the S_c. For example, the S_c for vancomycin steadily decreases as the proportion of predilution increases, with higher clearances observed at a predilution:postdilution ratio of 1:2 when compared to the predilution mode [93].

6.6.2 Hemodialysis

Equilibration across the filter membrane is dependent on the interaction between drug molecular weight, blood flow, and dialysate flow. As the dialysate flow rate in CVVHD and CVVHDF is relatively low compared with blood flow rate [94], neither blood flow nor molecular size (for the same reasons as above) are important factors in clearance of most commonly used antibacterial agents. The ability of a solute to diffuse through the filter membrane is expressed as the saturation coefficient (S_d):

$$S_d = \frac{\left[\text{Drug}\right]\text{dialysate}}{\left[\text{Drug}\right]\text{plasma}}$$

Similarly to S_c, protein binding is the main determinant of S_d. It is membrane specific and ranges in value from 0 to 1. In usual practice, as blood flow rate is so much greater than dialysate flow, complete saturation is likely to occur and antibacterial clearance is effectively dependent on dialysate flow rate (Q_d) and S_d:

$$\mathrm{Cl}_{\mathrm{CVVHD}} = Q_d \times S_d$$

6.6.3 Hemodiafiltration

Hemodiafiltration combines both convection and diffusion clearance to eliminate solutes. In general, drug clearance in CVVHDF may be estimated as:

$$\mathrm{Cl}_{\mathrm{CVVHDF}} = \left(Q_f + Q_d\right) \times S_d$$

Although the two processes interact and simple addition of each component potentially leads to an overestimation of total clearance, the clinical relevance is unclear [86]. Interestingly, CVVHDF has shown to provide greater clearance than predilution CVVH with equivalent effluent (ultrafiltrate plus dialysate) flow [95]. For both CVVHD and CVVHDF, the estimation of S_d may be affected by protein binding, membrane material, and flux properties.

From these equations it can be seen that the main determinants of elimination by CRRT are sieving or saturation coefficient and effluent flow rate (ultrafiltration rate, dialysate flow rate, or the two combined). Antimicrobial S_c and S_d are closely related to the unbound protein fraction and acute phase changes in plasma protein concentrations are common in critical illness, affecting both S_c and S_d. Therefore, it is essential that the S_c and S_d used for antibacterial dosing estimation should be based from actual studies with substantially similar categories of critically ill patients. In addition, operating parameters (i.e., filter membrane type) should be similar. A summary of the different modes of CRRT and clearance calculations are outlined in Table 6.2.

Table 6.2 Calculated clearance based on the different CRRT modalities

Mode of CRRT	Calculation of CRRT clearance
CVVH (post)	$\mathrm{Cl}_{\mathrm{CVVH}}$ (post) = $Q_f \times S_c$
CVVH (pre)	$\mathrm{Cl}_{\mathrm{CVVH}}$ (pre) = $Q_f \times S_c \times (Q_b/Q_b + Q_{rep})$
CVVHD	$\mathrm{Cl}_{\mathrm{CVVHD}} = Q_d \times S_d$
CVVHDF	$\mathrm{Cl}_{\mathrm{CVVHDF}} = (Q_f + Q_d) \times S_d$

$\mathrm{CL}_{\mathrm{CVVH}}$ (post), clearance from continuous venovenous hemofiltration using postfilter hemodilution; Q_f, ultrafiltrate rate; S_c, sieving coefficient; $\mathrm{CL}_{\mathrm{CVVH}}$ (pre), clearance from continuous venovenous hemofiltration using prefilter hemodilution; Q_b, blood flow rate; Q_{rep}, predilution replacement rate; $\mathrm{CL}_{\mathrm{CVVHD}}$, dialysate flow rate; S_d, saturation coefficient; $\mathrm{CL}_{\mathrm{CVVHDF}}$, clearance from continuous venovenous hemodiafiltration

Unfortunately, CRRT is not a single modality applied in a uniform way. Variations in type of filter material, blood flow rate, pre- or postdilution fluid replacement, and effluent flow rate settings could result in substantially different antibacterial pharmacokinetics [96–98]. Furthermore, CRRT is frequently not continuous but is interrupted for technical reasons and to transport patients for imaging or surgery and delivered clearance may be considerably lower than prescribed. Thus, dosing of antibacterials should take these variables into account.

6.7 Individualized Dosing Based on First Principles (in Patients Receiving CRRT)

A number of factors contribute to altered antibiotic efficacy in this patient population, such as changes in V_d, the killing characteristics of the antibiotic, the MIC of the target organism, changes in non-CRRT clearance, the effluent rate (depending on the different CRRT modality), and saturation or sieving coefficient, as well as the fact that these coefficients may change with acute phase changes in plasma protein concentrations [23]. As a result, it is not surprising that rigid, protocol-based dosing results in a large proportion of patients being either under or overdosed [99–101]. Even adjustments based only on estimated or measured renal clearance are likely to be inadequate and there have been several calls for the development of methods of individualized dosing [101–104].

We, therefore, recommend a method of individualized antibacterial dosing based on first principles.

Following administration of a drug, the initial fall in concentration is due to the distribution of the drug through the various body compartments. The extent of this distribution is reflected by the V_d. The antibacterial loading dose should therefore be based on the *appropriate* V_d for critically ill patients. Thereafter falls in concentration are predominantly dependent on *total* clearance—total clearance being the sum of CRRT clearance, residual renal clearance, and non-renal non-CRRT clearance in a critically ill patient.

Our recommendation is to base the initial dose on the published V_d of each specific antibiotic in critically ill patients, and the target concentration of that antibacterial (Fig. 6.1) as dosing that does not take into account changes in V_d will frequently lead to low initial serum concentrations [44]. The target blood concentration is based on the MIC of the suspected organism, indicative local MIC data, or published breakpoint data for the organism published by international bodies such as European Committee on Antimicrobial Susceptibility Testing—EUCAST (www.eucast.org).

While V_d determines the initial or loading dose, subsequent dosing is determined by total drug clearance. In patients with oliguric AKI, total drug clearance is the sum of CRRT clearance, residual renal clearance, and non-renal non-CRRT clearance (e.g., hepatic clearance). In general, drugs with a high V_d (>1 L/kg) and high

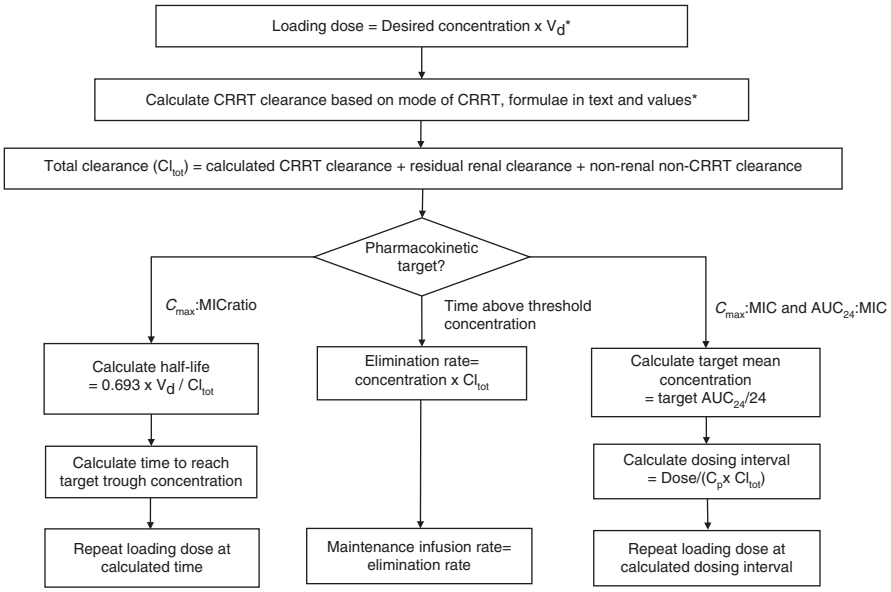

Fig. 6.1 Calculation of intravenous antibacterial doses based on first principles. CRRT, continuous renal replacement therapy; C_{max}, maximum postdistribution plasma concentration; MIC, minimum inhibitory concentration; AUC24, area under concentration-time curve over 24 h; V_d, volume of distribution; C_p, target plasma concentration. (*Asterisk*) Data obtained from website: http://www.aic.cuhk.edu.hk/web8/PK_data.htm

protein binding (>80%) are poorly eliminated by CRRT as the plasma concentration of drug available for filtration is low relative to the amount of antibacterial in the body [105]. This has led to the recommendation of reduced supplemental dosing of these drugs [106]. Nevertheless, this recommendation should be considered with caution. For example, for the lipophilic fluoroquinolones, such as ciprofloxacin and levofloxacin, V_ds are large (>1.5 L/kg), but renal clearance still accounts for ≥70% of total clearance [107, 108]. As V_d does not change, elimination half-life of both drugs will approach that of normal healthy volunteers when ultrafiltration and/or dialysate flow rates are high, obviating the need for reduced dosing [89]. For different reasons, some antibacterials with high protein binding will have an increased V_d as a result of reduced protein concentrations in the critically ill. This also leads to increased elimination by CRRT (and native kidneys) because of the increase in the free fraction of the drug. Appropriately adjusted CRRT clearance can be determined from the equations given above, assuming appropriate S_d and S_c are chosen.

For residual renal clearance, creatinine clearance should be measured. There is a risk of underdosing for agents with important tubular secretion or overdosing for drugs with tubular reabsorption although this is likely to be of limited clinical relevance [78].

Non-renal, non-CRRT clearance, for example, hepatic clearance may be variable depending on the degree of underlying organ failure and severity of illness [109, 110]. Dosing should also take into account the effect of hepatic failure. For example, the half-life of ciprofloxacin was increased in renal failure, but this was greatly exacerbated by additional hepatic failure [56]. Alternative elimination pathways such as transintestinal excretion (e.g., for ciprofloxacin) may represent compensatory mechanisms that also prevent accumulation in patients with renal failure [56]. Quantitative or at least qualitative evaluation of hepatic function should therefore be considered prior to formulating an antibacterial dosing regimen, in particular for agents with multiple routes of clearance (e.g., ciprofloxacin and meropenem).

Further examples of antibacterial dosing utilizing the principles outlined above are illustrated in Figs. 6.2 and 6.3.

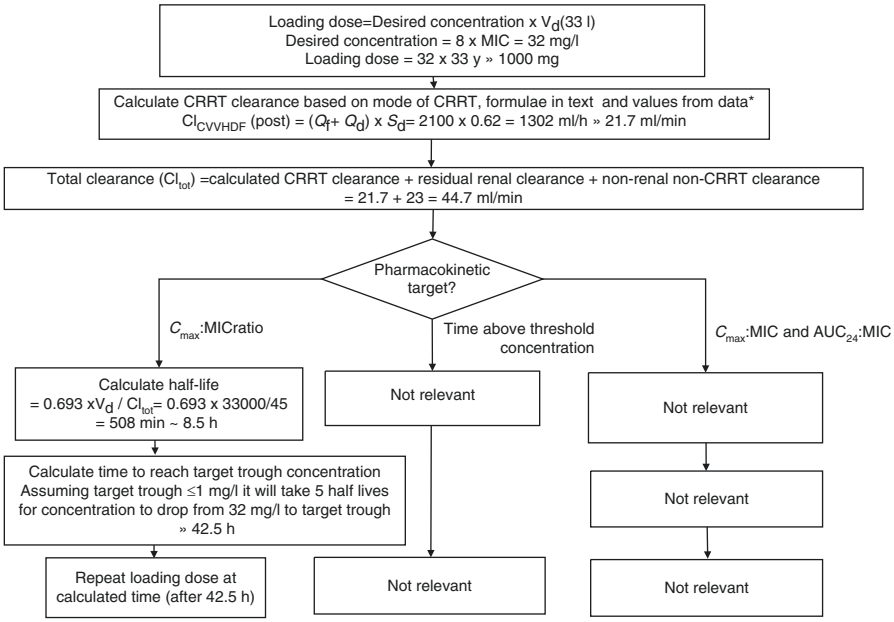

Fig. 6.2 Calculation of amikacin dose for empirical non-enterobacteriaceae (with MIC of 4 mg/L) nosocomial sepsis for a 70-kg patient with anuric acute renal failure on continuous venovenous hemodiafiltration using an AN69 filter and with targeted total effluent of 30 mL/kg/h. Note that figures are included for illustrative purposes. Dose prescribed should also take into account the risk of toxicity and may need to be reduced to comply with dose range approved by regulatory authorities. A formula for dose calculation for bolus dosing is given in the text. Cl_{tot}, total clearance; C_{max}, maximum postdistribution plasma concentration; MIC, minimum inhibitory concentration; AUC24, area under concentration-time curve over 24 h; CRRT, continuous renal replacement therapy; Q_f, ultrafiltrate flow rate; Q_d, dialysate flow rate; S_d, saturation coefficient; Cl_{CVVH}, clearance by continuous venovenous hemofiltration; V_d, volume of distribution; Cl_{CVVHDF}, clearance by continuous venovenous hemodiafiltration. (*Asterisk*) Data obtained from website: http://www.aic.cuhk.edu.hk/web8/PK_data.htm

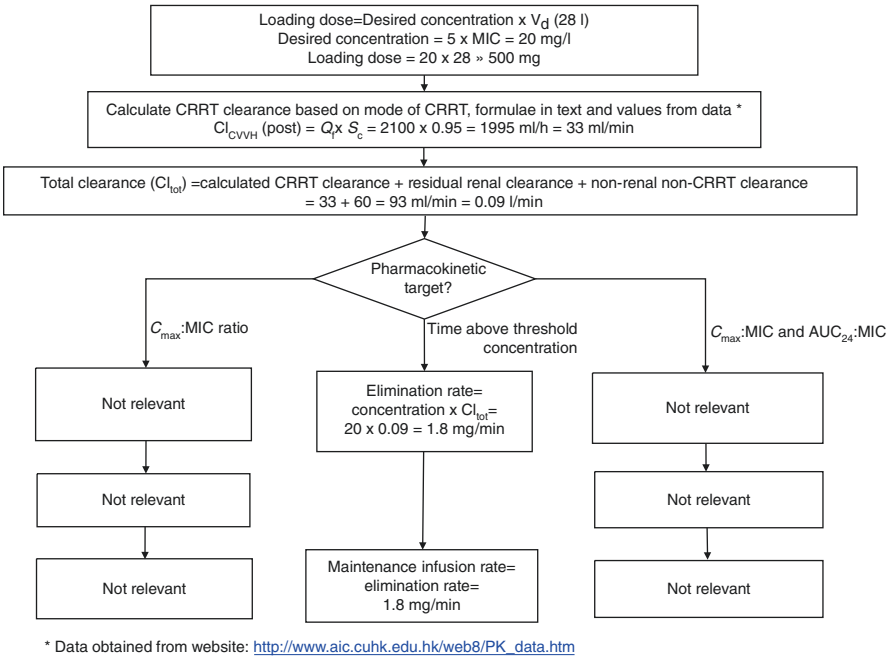

Fig. 6.3 Calculation of dose of meropenem for empirical non-enterobacteriaceae/enterobacteriaceae (with MIC of 4 mg/L) nosocomial sepsis for a 70-kg patient with anuric acute renal failure on continuous venovenous hemofiltration (postdilution) using AN69 0.9 m^2 filter with a targeted ultrafiltration rate of 30 mL kg h. Note that figures are included for illustrative purposes. Note that figures are included for illustrative purposes. Dose prescribed should also take into account the risk of toxicity and may need to be reduced to comply with dose range approved by regulatory authorities. A formula for dose calculation for bolus dosing is given in the text. Cl_{tot}, total clearance; C_{max}, maximum postdistribution plasma concentration; MIC, minimum inhibitory concentration; AUC24, area under concentration-time curve over 24 h; CRRT, continuous renal replacement therapy; Q_f, ultrafiltrate flow rate; Q_d, dialysate flow rate; S_d, saturation coefficient; Cl_{CVVH}, clearance by continuous venovenous hemofiltration; V_d, volume of distribution; Cl_{CVVHDF}, clearance by continuous venovenous hemodiafiltration. (*Asterisk*) Data obtained from website: http://www.aic.cuhk.edu.hk/web8/PK_data.htm

6.8 Critique of Currently Available Dosage Regimes in AKI

Details of published recommendations (Table 6.3) and their limitations for antibacterial dosing in critically ill patients have been previously summarized [112]. In brief, dosing regimes derived from either downward adjustment from healthy individuals or upward titration from chronic renal failure with adjustments based primarily on creatinine clearance are unlikely to result in consistently appropriate blood concentrations of antimicrobial agents in the critically ill [31, 111]. Doses recommended for anuric patients may also not achieve the appropriate PK-PD targets as a result of the changes in PK parameters expected in the critically ill. In addition, the optimal PK-PD target requires knowledge of the usual MIC of the

Table 6.3 Alternative equations to calculate dosing based on the modality of CRRT

Methods	Authors	Formula	Mode of CRRT
1	Schetz et al. [111]	$D = \dfrac{D_{\text{anuria}}}{1-\left(\dfrac{\text{Cl}_{\text{EC}}}{\text{Cl}_{\text{EC}}+\text{Cl}_{\text{NR}}+\text{Cl}_{\text{R}}}\right)}$	All modes
2	Bugge [31]	$D = D_{\text{N}} \times \left(P_{\text{x}} + \left(1-P_{\text{x}}\right)\right)\dfrac{\text{Cl}_{\text{CRtot}}}{\text{Cl}_{\text{CRn}}}$	CVVHDF
3	Schetz et al. [111]	$D = D_{\text{N}}\left(\dfrac{\text{Cl}_{\text{NR}}+\left(\text{UFR}\times S_{\text{c}}\right)}{\text{Cl}_{\text{N}}}\right)$	CVVH
4	Golper and Marx [88]	$D = C_{\text{SS}} \times \text{UBF} \times \text{UFR} \times I$	CVVH

C_{ss}, measured blood concentration at steady state; Cl_{ANUR}, drug clearance in anuric patient; Cl_{CRn}, normal creatinine clearance; Cl_{CRtot}, sum of renal and extracorporeal creatinine clearance; Cl_{EC}, extracorporeal clearance; Cl_N, normal total drug clearance; Cl_{NR}, non-renal clearance; Cl_R, renal clearance; D_{anuria}, recommended dose for anuric patients, D_N, dose recommended for patients with normal renal function; I, dosing interval; P_x, extrarenal clearance fraction (=Cl_{ANUR}/Cl_N); *UBF* unbound fraction, *UFR* ultrafiltration rate

suspected pathogen in the prescribing clinician's locality, and no previous dosing recommendation adjusts for this parameter. Furthermore, the assumption that S_d or S_c can be accurately estimated from data on protein binding [88] obtained from non-critically ill patients is likely to be inaccurate as these coefficients change with changes in plasma protein concentrations and binding capacity in the critically ill.

6.9 A Proposed Individualized Dosing Regime for Patients Receiving CRRT, Based on First Principles

We recommend individualized antibacterial dosing should be based on a dataset derived from published data in the critically ill receiving CRRT. The patient's dose should thus be derived from a dataset chosen by matching as far as possible the severity of illness, organ failure, and modes of support used. A selection of datasets from which to choose relevant PK data is available from our website (http://www.aic.cuhk.edu.hk/web8/PK_data.htm). This section is best understood if read with reference to the examples in Figs. 6.1, 6.2, and 6.3.

The loading dose is calculated using the published V_d of the specific antibacterial agent derived from a population of critically ill patients receiving CRRT. The desired blood concentration of the antibiotic is dependent on the MIC of the target organism(s). This information is sourced from the laboratory reported MIC, local MIC data accumulated within the ICU, or appropriate published clinical break-points, such as those published by EUCAST.

The maintenance dose is based on an estimate of total clearance, which is the sum of CRRT clearance, residual renal clearance, and non-renal non-CRRT clearance. Data selected (i.e., S_c and S_d) used to determine CRRT clearance should be from published data, where the operational characteristics such as blood flow rate, point of dilution of replacement fluid, and membrane material are as close to the individual patient's therapy as possible. Residual renal clearance should be determined by timed creatinine clearance, rather than formula-based estimation, and non-renal non-CRRT clearance should also be based on published data derived from critically ill patients receiving CRRT.

There are limitations to these recommendations. Firstly, for simplicity, the formula recommended for the calculation of the half-life is based on a single compartment and is therefore not strictly accurate. Second, continuous intravenous infusion of antibacterials with time-dependent killing characteristics is recommended because dose estimation is much simpler and evidence demonstrates better PK-PD target attainment in critically ill patients with [44, 45] and without RRT [113]. Thirdly, both residual renal clearance and non-renal non-CRRT clearance need to be accounted for. Thus, measurement of timed creatinine clearance is preferentially required, as estimations based on serum creatinine are inaccurate in critically ill patients [8]. This is of particular importance if CRRT is being employed early, before anuria, or during the recovery phase of oliguric/anuric AKI, for indications other than for AKI, such as maintenance of fluid control in massive blood transfusion, dysnatremia, temperature dysregulation, and toxin removal. Dosing should also take into account the effect of concomitant renal and hepatic failure. This is of particular importance for antibacterials with multiple routes of elimination, such as ciprofloxacin and meropenem. Actual values for non-renal non-CRRT clearance in critically ill patients are available [55, 56, 97, 114] and should be utilized as part of determination of total clearance. S_c and S_d may be derived for the individual patient from measured blood and effluent antimicrobial concentrations, but this capability is often not available for many commonly used agents or information is delayed. Reliance on published values from the critical care literature is a reasonable alternative.

Maintenance antibacterial doses are required to be amended whenever CRRT doses are altered (resulting in a change in effluent flow rate), or when the delivered dose of CRRT differs substantially from the prescribed dose. Lastly, the calculated dose may result in administration of very large doses, depending on the exact pharmacokinetic target chosen (e.g., C_{max}/MIC or %T >MIC) and the MIC. It is important that these doses are prescribed with due consideration of the risks of toxicity and may require consideration of the possibility that using another agent with a more favorable risk: benefit ratio as a preferable clinical choice. Where no suitable alternative exists it may be prudent to restrict doses to those approved by regulatory authorities. It is interesting to note that other authors have used a more aggressive regimen of dosing with antibacterials such as daptomycin in the healthy individual [115] and colistin in the critically ill [116], without apparently increasing the risk of toxicity.

The approach to individualized dosing described above, like all other dose adjustments for CRRT, has not been formally validated. Nevertheless, other authors

have advocated similar approaches, and recent data provide some supportive evidence [117–119] for this, by demonstrating a strong association between blood concentrations and effluent rate. In an in vitro model, Yamamoto et al. found that the ratio of predicted clearance (based on measurement of unbound fraction and effluent rate) to actual clearance ranged from 0.67 to 1.5 [119]. Beumier et al. found that serum concentrations of meropenem, ceftazidime, cefepime, and piperacillin-tazobactam were correlated with effluent rate when an unadjusted dosing regimen for patients were given to a group of septic patients requiring CRRT [99]. Similarly, effluent rate has been shown to be associated with doripenem clearance [120], piperacillin clearance [121] and vancomycin serum concentration [122]. Jamal et al. systematically reviewed the literature and demonstrated that CRRT clearance of meropenem, piperacillin-tazobactam, and vancomycin is associated with the effluent rate [123]. In some cases quoted above, CRRT clearance was derived from the equations given above and therefore CRRT clearance and effluent rate would have been mathematically coupled. However, not all current data supports the relationship between effluent rate and clearance. Roberts et al. found that trough concentrations of meropenem, piperacillin-tazobactam, vancomycin, and ciprofloxacin were not associated with effluent rate [100]. However, in this investigation, the dose of antibacterial given was at the discretion of the treating clinicians who may have taken the effluent rate into account, thus directly influencing the trough concentration despite the different effluent rates reported in the study. Udy et al. also found there was no relationship between vancomycin clearance and CRRT effluent rate, based on population pharmacokinetic analysis, suggesting the presence of multiple confounders influencing antibacterial prescription [124].

6.10 Intermittent Hemodialysis Techniques and Antibacterial Dosing

Several factors make antimicrobial dose optimization in patients requiring IHD difficult. These include the intermittent nature of dialysis, the high clearance rate for very short periods (2–5 h), rapid fluid removal, and the interaction of the timing of antibacterial dosing and the dialysis period [125]. While guidelines for the adjustment of antimicrobial dosage in patients requiring IHD are ubiquitous, the optimization of antimicrobial dosing *in critically ill patients* receiving IHD has received less attention than dosing associated with the use of continuous modes. Guidelines for IHD dose adjustments generally assume a thrice weekly HD exposure of 3–4 h duration as typically utilized in non-critically ill, chronic renal failure patients [126]. It is thus necessary to make intuitive adjustments to account for expected PK changes induced by critical illness. Recommendations also inconsistently stipulate that additional doses, or dose timing be adjusted to coincide with the end of dialysis sessions. The authors recommend that whenever possible, therapeutic drug monitoring (TDM) should be considered when IHD is utilized in critically ill patients.

In particular, there is an increased risk of antibacterial underdosage during SLED, especially during the second half of the extended dialysis session [127]. Dosing during SLED is likely to be more difficult than in continuous forms of RRT because of the large variation in clearance on and off SLED [125], with a period of high antimicrobial clearance (around 75 mL/min) alternating with no dialysis. It has therefore been recommended that institutions who utilize SLED should establish their own dosing guidelines to ensure delivery of antibacterials at adequate concentrations [128]. Antibacterials that are likely to require adjusted dosing are those that have a small molecular size, high water solubility, low protein binding, and are substantially dependent on renal clearance. The clinical use of SLED has, until now, been limited to only a relatively small number of centers, and consequently pharmacokinetic data to guide the establishment of guidelines in critically ill patients receiving SLED is limited. More data to guide dosing of antimicrobial agents is urgently needed to allow optimization of dosage when SLED is utilized, and once again, point of care TDM may offer the best solution for optimized dosage.

6.11 Therapeutic Drug Monitoring

The individualized antibacterial dosing regimes proposed in this chapter are based on first principles taking into account the optimal PK-PD goals. While it is possible to use published data in critically ill patients and calculations of CRRT clearance to improve dosing, considerable risk of inaccuracy remains. For example, the V_d of many antibacterials may vary considerably between individual patients, as may sieving and saturation coefficients. The magnitude of change is dependent on illness severity that fluctuates with time. Furthermore, changes in hepatic or gastrointestinal function, which are difficult to monitor clinically, may result in changes in non-renal non-CRRT clearance.

The use of therapeutic drug monitoring may be useful to adjust dosing regimes and adjust for individual patient variation. Currently, TDM is focused on a few antibacterials with emphasis on the prevention of toxicity (e.g., aminoglycoside trough concentration monitoring), with empirical adjustment by the clinician. To be successful from a therapeutic perspective, patient selection, sampling time, assay methods, and dose adjustment strategies need to be individualized for different classes of antibacterials [129]. To overcome the inherent inaccuracy in empirical clinician adjustments, future use should combine therapeutic drug monitoring with sophisticated population-based pharmacokinetic models, which take into account critical illness and the variability described above to generate more appropriate individualized antibacterial dosing regimes [130]. Studies to develop population PK models based on data from critically ill patients with AKI are currently underway [131]. Presently, only a limited number of ICUs utilize TDM routinely as a comprehensive therapeutic strategy [132].

6.12 Conclusion

Both AKI and sepsis are common in the critically ill, with the prevalence of AKI increasing in association with increasing severity of sepsis; the combination resulting in a high mortality rate. Recent agreed consensus definitions of AKI will facilitate the standardization of epidemiological and outcome studies to delineate optimal therapies in this special group of critically ill patients. While the pathophysiological mechanism of sepsis-induced AKI is yet to be completely elucidated, it is now thought that inflammation, microcirculatory dysfunction, and tubular cell adaptation to injury are the more common pathways involved. Recognition of AKI is important as it must be accompanied by measurement of creatinine clearance to facilitate appropriate antibacterial dosing. Similarly, awareness of the increased incidence of augmented renal clearance in subgroups of patients (e.g., resuscitated trauma, major surgical and burns patients) should lead to appropriate measurement of creatinine clearance and dose adjustment.

Timely administration of appropriately chosen antibacterial agents and optimal dosage combine to improve patient outcomes. In the critically ill, sepsis and/or AKI are associated with marked physiological alterations that are often associated with unrecognized pharmacokinetic changes. A thorough understanding of pharmacokinetic principles and organ function in the critically ill is required to guide appropriate dosing.

Although controversy exists regarding the optimal timing and mode of renal replacement therapy, continuous modes of renal replacement therapy are predominantly employed worldwide. However, CRRT is not a single modality and variability in practice leading to markedly different clearance may exist between and within the same institution and even the same patient.

The use of TDM informed by population-based PK data in critically ill patients offers further promise for the optimization of antibacterial dosing. Future directions should include the conduct of large-scale studies of AKI patients receiving CRRT with the development of pharmacokinetic models that can be used to generate optimized dosing applications.

References

1. Simsek A, Tugcu V, Tasci AI (2013) New biomarkers for the quick detection of acute kidney injury. ISRN Nephrol 2013:394582. doi:10.5402/2013/394582
2. Bellomo R, Ronco C, Kellum JA et al (2004) Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 8(4):R204–R212. doi:10.1186/cc2872
3. Levin A, Warnock DG, Mehta RL et al (2007) Improving outcomes from acute kidney injury: report of an initiative. Am J Kidney Dis 50(1):1–4. doi:10.1053/j.ajkd.2007.05.008
4. Mehta RL, Kellum JA, Shah SV et al (2007) Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 11(2):R31. doi:10.1186/cc5713

5. Molitoris BA, Levin A, Warnock DG et al (2007) Improving outcomes from acute kidney injury. J Am Soc Nephrol 18(7):1992–1994. doi:10.1681/ASN.2007050567
6. Kidney Disease: Improving Global Outcome (KDIGO) Acute Kidney Injury Work Group (2011) Section 2: AKI definition (2012) Kidney Int Suppl 2(1):19–36. doi:10.1038/kisup.2011.32
7. Keller F, Maiga M, Neumayer HH et al (1984) Pharmacokinetic effects of altered plasma protein binding of drugs in renal disease. Eur J Drug Metab Pharmacokinet 9(3):275–282
8. Hoste EA, Damen J, Vanholder RC et al (2005) Assessment of renal function in recently admitted critically ill patients with normal serum creatinine. Nephrol Dial Transplant 20(4):747–753. doi:10.1093/ndt/gfh707
9. Baumann TJ, Staddon JE, Horst HM et al (1987) Minimum urine collection periods for accurate determination of creatinine clearance in critically ill patients. Clin Pharm 6(5):393–398
10. Liangos O, Wald R, O'Bell JW et al (2006) Epidemiology and outcomes of acute renal failure in hospitalized patients: a national survey. Clin J Am Soc Nephrol 1(1):43–51. doi:10.2215/CJN.00220605
11. Bagshaw SM, George C, Bellomo R et al (2008) Early acute kidney injury and sepsis: a multicentre evaluation. Crit Care 12(2):R47. doi:10.1186/cc6863
12. Bagshaw SM, Uchino S, Bellomo R et al (2007) Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. Clin J Am Soc Nephrol 2(3):431–439. doi:10.2215/CJN.03681106
13. Douma CE, Redekop WK, van der Meulen JH et al (1997) Predicting mortality in intensive care patients with acute renal failure treated with dialysis. J Am Soc Nephrol 8(1):111–117
14. Metnitz PG, Krenn CG, Steltzer H et al (2002) Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med 30(9):2051–2058. doi:10.1097/01.CCM.0000026732.62103.DF
15. Riedemann NC, Guo RF, Ward PA (2003) The enigma of sepsis. J Clin Invest 112(4):460–467. doi:10.1172/JCI19523
16. Hoste EA, Bagshaw SM, Bellomo R et al (2015) Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 41(8):1411–1423. doi:10.1007/s00134-015-3934-7
17. Uchino S, Kellum JA, Bellomo R et al (2005) Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 294(7):813–818. doi:10.1001/jama.294.7.813
18. Dellinger RP, Levy MM, Rhodes A et al (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 41(2):580–637. doi:10.1097/CCM.0b013e31827e83af
19. Bagshaw SM, Cruz DN, Gibney RT et al (2009a) A proposed algorithm for initiation of renal replacement therapy in adult critically ill patients. Crit Care 13(6):317. doi:10.1186/cc8037
20. Bagshaw SM, Uchino S, Bellomo R et al (2009b) Timing of renal replacement therapy and clinical outcomes in critically ill patients with severe acute kidney injury. J Crit Care 24(1):129–140. doi:10.1016/j.jcrc.2007.12.017
21. Gaudry S, Hajage D, Schortgen F et al (2016) Initiation strategies for renal-replacement therapy in the intensive care unit. N Engl J Med. doi:10.1056/NEJMoa1603017
22. Liu KD, Himmelfarb J, Paganini E et al (2006) Timing of initiation of dialysis in critically ill patients with acute kidney injury. Clin J Am Soc Nephrol 1(5):915–919. doi:10.2215/CJN.01430406
23. Kidney Disease: Improving Global Outcome (KDIGO) Acute Kidney Injury Work Group (2011) Section 5: Dialysis interventions for treatment of (2012) Kidney Int Suppl 2(1):89–115. doi:10.1038/kisup.2011.35
24. Bell M, Swing GF et al (2007) Continuous renal replacement therapy is associated with less chronic renal failure than intermittent haemodialysis after acute renal failure. Intensive Care Med 33(5):773–780. doi:10.1007/s00134-007-0590-6
25. Prowle JR, Bellomo R (2010) Continuous renal replacement therapy: recent advances and future research. Nat Rev Nephrol 6(9):521–529. doi:10.1038/nrneph.2010.100

26. Schneider AG, Bellomo R, Bagshaw SM et al (2013) Choice of renal replacement therapy modality and dialysis dependence after acute kidney injury: a systematic review and meta-analysis. Intensive Care Med 39(6):987–997. doi:10.1007/s00134-013-2864-5
27. Uchino S, Bellomo R, Kellum JA et al (2007) Patient and kidney survival by dialysis modality in critically ill patients with acute kidney injury. Int J Artif Organs 30(4):281–292
28. Fieghen HE, Friedrich JO, Burns KE et al (2010) The hemodynamic tolerability and feasibility of sustained low efficiency dialysis in the management of critically ill patients with acute kidney injury. BMC Nephrol 11:32. doi:10.1186/1471-2369-11-32
29. Baldwin I, Naka T, Koch B et al (2007) A pilot randomised controlled comparison of continuous veno-venous haemofiltration and extended daily dialysis with filtration: effect on small solutes and acid-base balance. Intensive Care Med 33(5):830–835. doi:10.1007/s00134-007-0596-0
30. Ricci Z, Ronco C (2008) Dose and efficiency of renal replacement therapy: continuous renal replacement therapy versus intermittent hemodialysis versus slow extended daily dialysis. Crit Care Med 36(4 Suppl):S229–S237. doi:10.1097/CCM.0b013e318168e467
31. Bugge JF (2001) Pharmacokinetics and drug dosing adjustments during continuous veno-venous hemofiltration or hemodiafiltration in critically ill patients. Acta Anaesthesiol Scand 45(8):929–934
32. Pinder M, Bellomo R, Lipman J (2002) Pharmacological principles of antibiotic prescription in the critically ill. Anaesth Intensive Care 30(2):134–144
33. Buerger C, Plock N, Dehghanyar P et al (2006) Pharmacokinetics of unbound linezolid in plasma and tissue interstitium of critically ill patients after multiple dosing using microdialysis. Antimicrob Agents Chemother 50(7):2455–2463. doi:10.1128/AAC.01468-05
34. Conil JM, Georges B, Breden A et al (2006) Increased amikacin dosage requirements in burn patients receiving a once-daily regimen. Int J Antimicrob Agents 28(3):226–230. doi:10.1016/j.ijantimicag.2006.04.015
35. Goncalves-Pereira J, Povoa P (2011) Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of beta-lactams. Crit Care 15(5):R206. doi:10.1186/cc10441
36. Marik PE (1993) Aminoglycoside volume of distribution and illness severity in critically ill septic patients. Anaesth Intensive Care 21(2):172–173
37. Roberts JA, Taccone FS, Udy AA et al (2011b) Vancomycin dosing in critically ill patients: robust methods for improved continuous-infusion regimens. Antimicrob Agents Chemother 55(6):2704–2709. doi:10.1128/AAC.01708-10
38. Sime FB, Roberts MS, Peake SL et al (2012) Does beta-lactam pharmacokinetic variability in critically Ill patients justify therapeutic drug monitoring? A systematic review. Ann Intensive Care 2(1):35. doi:10.1186/2110-5820-2-35
39. Gous A, Lipman J, Scribante J et al (2005) Fluid shifts have no influence on ciprofloxacin pharmacokinetics in intensive care patients with intra-abdominal sepsis. Int J Antimicrob Agents 26(1):50–55. doi:10.1016/j.ijantimicag.2005.04.005
40. Akers KS, Cota JM, Frei CR et al (2011) Once-daily amikacin dosing in burn patients treated with continuous venovenous hemofiltration. Antimicrob Agents Chemother 55(10):4639–4642. doi:10.1128/AAC.00374-11
41. Taccone FS, de Backer D, Laterre PF et al (2011) Pharmacokinetics of a loading dose of amikacin in septic patients undergoing continuous renal replacement therapy. Int J Antimicrob Agents 37(6):531–535. doi:10.1016/j.ijantimicag.2011.01.026
42. Hayashi Y, Roberts JA, Paterson DL et al (2010) Pharmacokinetic evaluation of piperacillin-tazobactam. Expert Opin Drug Metab Toxicol 6(8):1017–1031. doi:10.1517/17425255.2010.506187
43. Joynt GM, Lipman J, Gomersall CD et al (2001) The pharmacokinetics of once-daily dosing of ceftriaxone in critically ill patients. J Antimicrob Chemother 47(4):421–429
44. Seyler L, Cotton F, Taccone FS et al (2011) Recommended beta-lactam regimens are inadequate in septic patients treated with continuous renal replacement therapy. Crit Care 15(3):R137. doi:10.1186/cc10257

45. Young RJ, Lipman J, Gin T et al (1997) Intermittent bolus dosing of ceftazidime in critically ill patients. J Antimicrob Chemother 40(2):269–273
46. Chapuis TM, Giannoni E, Majcherczyk PA et al (2010) Prospective monitoring of cefepime in intensive care unit adult patients. Crit Care 14(2):R51. doi:10.1186/cc8941
47. Giuliano C, Haase KK, Hall R (2010) Use of vancomycin pharmacokinetic-pharmacodynamic properties in the treatment of MRSA infections. Expert Rev Anti Infect Ther 8(1):95–106. doi:10.1586/eri.09.123
48. Rybak MJ (2006) The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin Infect Dis 42(Suppl 1):S35–S39. doi:10.1086/491712
49. DelDot ME, Lipman J, Tett SE (2004) Vancomycin pharmacokinetics in critically ill patients receiving continuous venovenous haemodiafiltration. Br J Clin Pharmacol 58(3):259–268. doi:10.1111/j.1365-2125.2004.02143.x
50. Roberts DM, Liu X, Roberts JA et al (2015) A multicenter study on the effect of continuous hemodiafiltration intensity on antibiotic pharmacokinetics. Crit Care 19:84. doi:10.1186/s13054-015-0818-8
51. Vance-Bryan K, Guay DR, Rotschafer JC (1990) Clinical pharmacokinetics of ciprofloxacin. Clin Pharmacokinet 19(6):434–461. doi:10.2165/00003088-199019060-00003
52. Lipman J, Scribante J, Gous AG et al (1998) Pharmacokinetic profiles of high-dose intravenous ciprofloxacin in severe sepsis. The Baragwanath Ciprofloxacin Study Group. Antimicrob Agents Chemother 42(9):2235–2239
53. Szalek E, Tomczak H, Kaminska A et al (2012) Pharmacokinetics and pharmacodynamics of ciprofloxacin in critically ill patients after the first intravenous administration of 400 mg. Adv Med Sci 57(2):217–223. doi:10.2478/v10039-012-0028-4
54. Malone RS, Fish DN, Abraham E et al (2001) Pharmacokinetics of levofloxacin and ciprofloxacin during continuous renal replacement therapy in critically ill patients. Antimicrob Agents Chemother 45(10):2949–2954. doi:10.1128/aac.45.10.2949-2954.2001
55. Spooner AM, Deegan C, D'Arcy DM et al (2011) An evaluation of ciprofloxacin pharmacokinetics in critically ill patients undergoing continuous veno-venous haemodiafiltration. BMC Clin Pharmacol 11:11. doi:10.1186/1472-6904-11-11
56. Wallis SC, Mullany DV, Lipman J et al (2001) Pharmacokinetics of ciprofloxacin in ICU patients on continuous veno-venous haemodiafiltration. Intensive Care Med 27(4):665–672
57. Parrillo JE (1993) Pathogenetic mechanisms of septic shock. N Engl J Med 328(20):1471–1477. doi:10.1056/NEJM199305203282008
58. Di Giantomasso D, May CN, Bellomo R (2003) Norepinephrine and vital organ blood flow during experimental hyperdynamic sepsis. Intensive Care Med 29(10):1774–1781. doi:10.1007/s00134-003-1736-9
59. Parrillo JE, Parker MM, Natanson C et al (1990) Septic shock in humans. Advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. Ann Intern Med 113(3):227–242
60. Udy AA, Roberts JA, Boots RJ et al (2010) Augmented renal clearance: implications for antibacterial dosing in the critically ill. Clin Pharmacokinet 49(1):1–16. doi:10.2165/11318140-000000000-00000
61. Chvojka J, Sykora R, Krouzecky A et al (2008) Renal haemodynamic, microcirculatory, metabolic and histopathological responses to peritonitis-induced septic shock in pigs. Crit Care 12(6):R164. doi:10.1186/cc7164
62. Langenberg C, Wan L, Egi M et al (2006) Renal blood flow in experimental septic acute renal failure. Kidney Int 69(11):1996–2002. doi:10.1038/sj.ki.5000440
63. Gomez H, Ince C, De Backer D et al (2014) A unified theory of sepsis-induced acute kidney injury: inflammation, microcirculatory dysfunction, bioenergetics, and the tubular cell adaptation to injury. Shock 41(1):3–11. doi:10.1097/SHK.0000000000000052
64. Honore PM, Jacobs R, Hendrickx I et al (2015) Prevention and treatment of sepsis-induced acute kidney injury: an update. Ann Intensive Care 5(1):51. doi:10.1186/s13613-015-0095-3

65. De Paepe P, Belpaire FM, Buylaert WA (2002) Pharmacokinetic and pharmacodynamic considerations when treating patients with sepsis and septic shock. Clin Pharmacokinet 41(14):1135–1151. doi:10.2165/00003088-200241140-00002
66. Rayner CR, Forrest A, Meagher AK et al (2003) Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. Clin Pharmacokinet 42(15):1411–1423. doi:10.2165/00003088-200342150-00007
67. Roberts DM, Roberts JA, Roberts MS et al (2012b) Variability of antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy: a multicentre pharmacokinetic study. Crit Care Med 40(5):1523–1528. doi:10.1097/CCM.0b013e318241e553
68. Roberts JA, Norris R, Paterson DL et al (2012a) Therapeutic drug monitoring of antimicrobials. Br J Clin Pharmacol 73(1):27–36. doi:10.1111/j.1365-2125.2011.04080.x
69. Roberts JA, Kruger P, Paterson DL et al (2008) Antibiotic resistance--what's dosing got to do with it? Crit Care Med 36(8):2433–2440. doi:10.1097/CCM.0b013e318180fe62
70. Craig WA (1998) Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 26(1):1–10. quiz 11–12
71. Burgess DS (1999) Pharmacodynamic principles of antimicrobial therapy in the prevention of resistance. Chest 115(3 Suppl):19S–23S
72. Lipman J, Gomersall CD, Gin T et al (1999) Continuous infusion ceftazidime in intensive care: a randomized controlled trial. J Antimicrob Chemother 43(2):309–311
73. Mouton JW, Vinks AA (2007) Continuous infusion of beta-lactams. Curr Opin Crit Care 13(5):598–606. doi:10.1097/MCC.0b013e3282e2a98f
74. Roberts JA, Boots R, Rickard CM et al (2007) Is continuous infusion ceftriaxone better than once-a-day dosing in intensive care? A randomized controlled pilot study. J Antimicrob Chemother 59(2):285–291. doi:10.1093/jac/dkl478
75. Roberts JA, Webb S, Paterson D et al (2009) A systematic review on clinical benefits of continuous administration of beta-lactam antibiotics. Crit Care Med 37(6):2071–2078. doi:10.1097/CCM.0b013e3181a0054d
76. Tessier PR, Nicolau DP, Onyeji CO et al (1999) Pharmacodynamics of intermittent- and continuous-infusion cefepime alone and in combination with once-daily tobramycin against Pseudomonas aeruginosa in an in vitro infection model. Chemotherapy 45(4):284–295. doi:10.1159/000007198
77. Moore RD, Lietman PS, Smith CR (1987) Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis 155(1):93–99
78. Roberts JA, Lipman J (2006) Antibacterial dosing in intensive care: pharmacokinetics, degree of disease and pharmacodynamics of sepsis. Clin Pharmacokinet 45(8):755–773. doi:10.2165/00003088-200645080-00001
79. Rybak MJ, Abate BJ, Kang SL et al (1999) Prospective evaluation of the effect of an aminoglycoside dosing regimen on rates of observed nephrotoxicity and ototoxicity. Antimicrob Agents Chemother 43(7):1549–1555
80. Drusano GL, Preston SL, Fowler C et al (2004) Relationship between fluoroquinolone area under the curve: minimum inhibitory concentration ratio and the probability of eradication of the infecting pathogen, in patients with nosocomial pneumonia. J Infect Dis 189(9):1590–1597. doi:10.1086/383320
81. Forrest A, Nix DE, Ballow CH et al (1993) Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 37(5):1073–1081
82. Rybak M, Lomaestro B, Rotschafer JC et al (2009) Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 66(1):82–98. doi:10.2146/ajhp080434
83. Oda S, Hirasawa H, Shiga H et al (2002) Continuous hemofiltration/hemodiafiltration in critical care. Ther Apher 6(3):193–198

84. Ronco C, Bellomo R, Ricci Z (2001) Continuous renal replacement therapy in critically ill patients. Nephrol Dial Transplant 16(Suppl 5):67–72
85. Uchino S, Bellomo R, Ronco C (2001) Intermittent versus continuous renal replacement therapy in the ICU: impact on electrolyte and acid-base balance. Intensive Care Med 27(6):1037–1043
86. Brunet S, Leblanc M, Geadah D et al (1999) Diffusive and convective solute clearances during continuous renal replacement therapy at various dialysate and ultrafiltration flow rates. Am J Kidney Dis 34(3):486–492. doi:10.1053/AJKD03400486
87. Clark WR, Ronco C (1999) CRRT efficiency and efficacy in relation to solute size. Kidney Int Suppl 72:S3–S7
88. Golper TA, Marx MA (1998) Drug dosing adjustments during continuous renal replacement therapies. Kidney Int Suppl 66:S165–S168
89. Guenter SG, Iven H, Boos C et al (2002) Pharmacokinetics of levofloxacin during continuous venovenous hemodiafiltration and continuous venovenous hemofiltration in critically ill patients. Pharmacotherapy 22(2):175–183
90. Hansen E, Bucher M, Jakob W et al (2001) Pharmacokinetics of levofloxacin during continuous veno-venous hemofiltration. Intensive Care Med 27(2):371–375
91. Traunmuller F, Thalhammer-Scherrer R, Locker GJ et al (2001) Single-dose pharmacokinetics of levofloxacin during continuous veno-venous haemofiltration in critically ill patients. J Antimicrob Chemother 47(2):229–231
92. Phillips GJ, Davies JG, Olliff CJ et al (1998) Use of in vitro models of haemofiltration and haemodiafiltration to estimate dosage regimens for critically ill patients prescribed cefpirome. J Clin Pharm Ther 23(5):353–359
93. Uchino S, Cole L, Morimatsu H et al (2002) Clearance of vancomycin during high-volume haemofiltration: impact of pre-dilution. Intensive Care Med 28(11):1664–1667
94. Bohler J, Donauer J, Keller F (1999) Pharmacokinetic principles during continuous renal replacement therapy: drugs and dosage. Kidney Int Suppl 72:S24–S28
95. Troyanov S, Cardinal J, Geadah D et al (2003) Solute clearances during continuous venovenous haemofiltration at various ultrafiltration flow rates using multiflow-100 and HF1000 filters. Nephrol Dial Transplant 18(5):961–966
96. Choi G, Gomersall CD, Lipman J et al (2004) The effect of adsorption, filter material and point of dilution on antibiotic elimination by haemofiltration an in vitro study of levofloxacin. Int J Antimicrob Agents 24(5):468–472. doi:10.1016/j.ijantimicag.2004.06.005
97. Tegeder I, Neumann F, Bremer F et al (1999) Pharmacokinetics of meropenem in critically ill patients with acute renal failure undergoing continuous venovenous hemofiltration. Clin Pharmacol Ther 65(1):50–57. doi:10.1016/s0009-9236(99)70121-9
98. Thalhammer F, Schenk P, Burgmann H et al (1998) Single-dose pharmacokinetics of meropenem during continuous venovenous hemofiltration. Antimicrob Agents Chemother 42(9):2417–2420
99. Beumier M, Casu GS, Hites M et al (2014) beta-lactam antibiotic concentrations during continuous renal replacement therapy. Crit Care 18(3):R105. doi:10.1186/cc13886
100. Roberts JA, De Waele JJ, Dimopoulos G et al (2012b) DALI: Defining Antibiotic Levels in Intensive care unit patients: a multi-centre point of prevalence study to determine whether contemporary antibiotic dosing for critically ill patients is therapeutic. BMC Infect Dis 12:152. doi:10.1186/1471-2334-12-152
101. Ulldemolins M, Vaquer S, Llaurado-Serra M et al (2014) Beta-lactam dosing in critically ill patients with septic shock and continuous renal replacement therapy. Crit Care 18(3):227. doi:10.1186/cc13938
102. Goldstein SL, Nolin TD (2014) Lack of drug dosing guidelines for critically ill patients receiving continuous renal replacement therapy. Clin Pharmacol Ther 96(2):159–161. doi:10.1038/clpt.2014.102
103. Jamal JA, Mueller BA, Choi GY et al (2015) How can we ensure effective antibiotic dosing in critically ill patients receiving different types of renal replacement therapy? Diagn Microbiol Infect Dis 82(1):92–103. doi:10.1016/j.diagmicrobio.2015.01.013

104. Roberts JA, Roberts DM (2014) Antibiotic dosing in critically ill patients with septic shock and on continuous renal replacement therapy: can we resolve this problem with pharmacokinetic studies and dosing guidelines? Crit Care 18(3):156. doi:10.1186/cc13939
105. de Pont AC (2007) Extracorporeal treatment of intoxications. Curr Opin Crit Care 13(6):668–673. doi:10.1097/MCC.0b013e3282f0febd
106. Kubin C (2005) The effects of continuous renal replacement on anti-infective therapy in the critically Ill. J Pharm Pract 18(2):109–117. doi:10.1177/0897190004273596
107. Chow AT, Fowler C, Williams RR et al (2001) Safety and pharmacokinetics of multiple 750-milligram doses of intravenous levofloxacin in healthy volunteers. Antimicrob Agents Chemother 45(7):2122–2125. doi:10.1128/AAC.45.7.2122-2125.2001
108. Gonzalez MA, Moranchel AH, Duran S et al (1985) Multiple-dose ciprofloxacin dose ranging and kinetics. Clin Pharmacol Ther 37(6):633–637
109. Hawker F (1991) Liver dysfunction in critical illness. Anaesth Intensive Care 19(2):165–181
110. Rolando N, Wade J, Davalos M et al (2000) The systemic inflammatory response syndrome in acute liver failure. Hepatology 32(4 Pt 1):734–739. doi:10.1053/jhep.2000.17687
111. Schetz M, Ferdinande P, Van den Berghe G et al (1995) Pharmacokinetics of continuous renal replacement therapy. Intensive Care Med 21(7):612–620
112. Choi G, Gomersall CD, Tian Q et al (2009) Principles of antibacterial dosing in continuous renal replacement therapy. Crit Care Med 37(7):2268–2282. doi:10.1097/CCM.0b013e3181aab3d0
113. Abdul-Aziz MH, Sulaiman H, Mat-Nor MB et al (2016) Beta-lactam infusion in severe sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis. Intensive Care Med. doi:10.1007/s00134-015-4188-0
114. Thalhammer F, Horl WH (2000) Pharmacokinetics of meropenem in patients with renal failure and patients receiving renal replacement therapy. Clin Pharmacokinet 39(4):271–279. doi:10.2165/00003088-200039040-00003
115. Benvenuto M, Benziger DP, Yankelev S et al (2006) Pharmacokinetics and tolerability of daptomycin at doses up to 12 milligrams per kilogram of body weight once daily in healthy volunteers. Antimicrob Agents Chemother 50(10):3245–3249. doi:10.1128/AAC.00247-06
116. Honore PM, Jacobs R, De Regt J et al (2014) Colistin dosing for treatment of multidrug-resistant Pseudomonas in critically ill patients - please, be adequate! Crit Care 18(2):412. doi:10.1186/cc13747
117. Awdishu L, Bouchard J (2011) How to optimize drug delivery in renal replacement therapy. Semin Dial 24(2):176–182. doi:10.1111/j.1525-139X.2011.00826.x
118. Moriyama B, Henning SA, Neuhauser MM et al (2009) Continuous-infusion beta-lactam antibiotics during continuous venovenous hemofiltration for the treatment of resistant gram-negative bacteria. Ann Pharmacother 43(7):1324–1337. doi:10.1345/aph.1L638
119. Yamamoto T, Yasuno N, Katada S et al (2011) Proposal of a pharmacokinetically optimized dosage regimen of antibiotics in patients receiving continuous hemodiafiltration. Antimicrob Agents Chemother 55(12):5804–5812. doi:10.1128/aac.01758-10
120. Ohchi Y, Hidaka S, Goto K et al (2011) Effect of hemopurification rate on doripenem pharmacokinetics in critically ill patients receiving high-flow continuous hemodiafiltration. Yakugaku Zasshi 131(9):1395–1399
121. Bauer SR, Salem C, Connor MJ Jr et al (2012) Pharmacokinetics and pharmacodynamics of piperacillin-tazobactam in 42 patients treated with concomitant CRRT. Clin J Am Soc Nephrol 7(3):452–457. doi:10.2215/CJN.10741011
122. Covajes C, Scolletta S, Penaccini L et al (2013) Continuous infusion of vancomycin in septic patients receiving continuous renal replacement therapy. Int J Antimicrob Agents 41(3):261–266. doi:10.1016/j.ijantimicag.2012.10.018
123. Jamal JA, Udy AA, Lipman J et al (2014) The impact of variation in renal replacement therapy settings on piperacillin, meropenem, and vancomycin drug clearance in the critically ill: an analysis of published literature and dosing regimens*. Crit Care Med 42(7):1640–1650. doi:10.1097/CCM.0000000000000317

124. Udy AA, Covajes C, Taccone FS et al (2013) Can population pharmacokinetic modelling guide vancomycin dosing during continuous renal replacement therapy in critically ill patients? Int J Antimicrob Agents 41(6):564–568. doi:10.1016/j.ijantimicag.2013.01.018
125. Roberts JA, Mehta RL, Lipman J (2011a) Sustained low efficiency dialysis allows rational renal replacement therapy, but does it allow rational drug dosing? Crit Care Med 39(3):602–603. doi:10.1097/CCM.0b013e31820e6a0d
126. Heintz BH, Matzke GR, Dager WE (2009) Antimicrobial dosing concepts and recommendations for critically III adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. Pharmacotherapy 29(5):562–577
127. Ronco C, Ricci Z, De Backer D et al (2015) Renal replacement therapy in acute kidney injury: controversy and consensus. Crit Care 19:146. doi:10.1186/s13054-015-0850-8
128. Bogard KN, Peterson NT, Plumb TJ et al (2011) Antibiotic dosing during sustained low-efficiency dialysis: special considerations in adult critically ill patients. Crit Care Med 39(3):560–570. doi:10.1097/CCM.0b013e318206c3b2
129. Wong G, Sime FB, Lipman J et al (2014b) How do we use therapeutic drug monitoring to improve outcomes from severe infections in critically ill patients? BMC Infect Dis 14:288. doi:10.1186/1471-2334-14-288
130. Roberts JA, Abdul-Aziz MH, Lipman J et al (2014) Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis 14(6):498–509. doi:10.1016/S1473-3099(14)70036-2
131. Roberts JA, Choi GY, Joynt GM et al (2016) SaMpling Antibiotics in Renal Replacement Therapy (SMARRT): an observational pharmacokinetic study in critically ill patients. BMC Infect Dis 16:103. doi:10.1186/s12879-016-1421-6
132. Wong G, Brinkman A, Benefield RJ et al (2014a) An international, multicentre survey of beta-lactam antibiotic therapeutic drug monitoring practice in intensive care units. J Antimicrob Chemother 69(5):1416–1423. doi:10.1093/jac/dkt523

Chapter 7
Augmented Renal Clearance

João Pedro Baptista

7.1 Introduction

Renal clearance is the process by which the kidneys eliminate circulating metabolites, toxins, waste products, and drugs. This involves filtration, secretion, and reabsorption. Along with the liver, the kidneys constitute a key organ in human body homeostasis. From a physiological point of view, renal clearance is the volume of plasma from which a substance is completely removed by the kidney in a given amount of time. This process affects predominantly hydrophilic substances, as is the case for most antibiotics.

These drugs are crucial to the successful treatment of sepsis and septic shock in the intensive care unit (ICU). However, critically ill patients are different from those encountered in a ward setting. Critical illness and its therapies often induce profound pathophysiological changes, contributing to inadequate antibiotic therapy. Hypoalbuminaemia, expansion of the volume of distribution (V_d), tissue hypoperfusion, organ dysfunction, use of vasoactive drugs, and the co-existence of renal replacement or extracorporeal membrane oxygenation therapies are among the most important factors. Renal dysfunction is common in critical care settings, and is often a focus for clinicians. Indeed, the converse—*supra-normal function of the kidneys* is infrequently considered.

J.P. Baptista
Intensive Care Unit, Centro Hospitalar e Universitário de Coimbra (CHUC), Coimbra, Portugal
e-mail: joaopedrobaptista@gmail.com

A.A. Udy et al. (eds.), *Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill*, DOI 10.1007/978-981-10-5336-8_7

This chapter will focus on the key aspects of the concept, diagnosis, pathophysiology, epidemiology, and clinical implications of augmented renal clearance (ARC) in the critically ill patient.

7.2 Definition of Augmented Renal Clearance

According to Udy et al. [1], ARC is defined as the enhanced renal elimination of circulating solutes as compared with an expected baseline. However, to date, there is no standard accepted definition of an accurate cut-off value to define ARC and there are several reasons for this. First, although the clinical recognition of ARC is by all means not recent [2], it was only in the last few years that a considerable amount of medical literature emerged reporting the features of ARC in the critically ill. Second, the "normal" values of glomerular filtration rate (GFR) physiologically decline with age, depend on sex, race, and body surface area, and show important variation within normal individuals. Third, different groups of investigators have used varying cut-offs to define ARC, between 120 and 160 mL/min/1.73 m^2. Finally, several methods have been used to measure or estimate the GFR, leading to significant heterogeneity in the results, and difficulties in interpretation and comparison.

The concept of ARC is likely more dynamic, representing the changeable physiology encountered when the body reacts to an acute severe disease or medical intervention (e.g., severe brain injury or intravenous fluid challenge, respectively), provided that renal reserve is preserved. The quantification of *renal function*, and its implications for antibiotic drug dosing is by far more important, that the restrictive qualitative classification based on the presence or absence of ARC (Fig. 7.1).

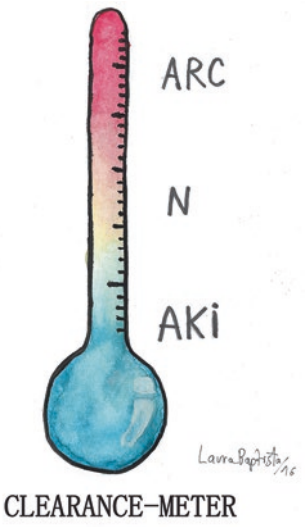

Fig. 7.1 The full spectrum of renal dysfunction—be aware of both under and *over*-function of kidneys

In this respect, GFR values at the upper limit of normal (120 mL/min/1.73 m^2) have also been associated to suboptimal levels of some antibiotics [3, 4], exposing patients to under-treatment, potentially poor outcomes and emergence of bacterial resistances.

From a practical point of view, the cut-off value of 130 mL/min/1.73 m^2 has several advantages, namely: (a) it represents, with reliability, the upper limit of normal renal physiology for the majority of healthy persons [5]; (b) renal clearance of creatinine greater than 130 mL/min/1.73 m^2 has been linked to sub-therapeutic serum concentrations of several antibiotics [6–11]; and (c) there is a growing amount of clinical studies which have used this cut-off, which provides good methodological consistency. This value should be adapted for the female gender, probably by the same factor used in several estimates—10% less, corresponding to 120 mL/min/1.73 m^2. However, some issues need clarification, such as the influence of race, the rate of decline with age, and the standardization of the method of measurement, as each may imply a different threshold value.

7.3 Identification of the Critically Ill Patient with ARC

The evaluation of renal function is essential in the critical setting, aiming to prevent and diagnose any deviation from "normality", and providing useful clinical information concerning specific treatments and drug dosing adjustments. GFR is the best overall measure of kidney function [12], and it is essential to identify patients with ARC.

The gold standard for determining GFR is the measurement of the renal clearance of inulin [13]. More convenient and simpler methods are available, such as the administration of iothalamate, iohexol, diethethylenetriaminopenta-acetic acid (DTPA), or ethylenediamine tetraacetic acid (EDTA); however, these tests are not suitable for use in daily clinical practice.

Serum creatinine concentrations are a commonly used surrogate of renal function; however, they are an insensitive marker of the GFR. Though some reliability lies in the stable patient, this is untrue within the context of the unstable patient, even outside the ICU. On the contrary, by definition the critically ill patient is not stable, and the information provided by isolated values of serum creatinine in these patients is poor and potentially dangerous: on the one hand, they are not always useful in the timely and accurate diagnosis of acute kidney injury, and on the other, are unable to identify ARC. Although elevated levels of serum creatinine identify patients with renal failure, the inverse is not true. The majority of patients with ARC show contemporaneous levels of serum creatinine within the normal range.

Some authors have described a "non-invasive" method for identifying ARC, through the biochemical analysis of urine, where the combination of creatininuria higher than 45 mg/L and patient's age below 65-years-old allows the identification of patients with ARC with significant accuracy (78%) and specificity (88%) [14]. Another group of researchers developed an ARC scoring system based on three risk

factors: age below 51 years, trauma as the ICU admission diagnosis, and a modified SOFA score below 5. The accuracy of this combined ARC score was 89% [15]. Both methods can be useful to screen patients with ARC in ICUs where the measurement of renal clearance is still not established. In addition, in theory they can be combined; however, a confirmatory diagnostic test is typically needed.

Several methods use mathematical equations based on the serum creatinine concentration to estimate GFR. These calculations are suitable and validated for the evaluation of renal function in patients with chronic but stable kidney diseases. Nonetheless, knowing that the serum creatinine level is not reliable in the critically ill patient, and that it does not accurately reflect renal function, estimation of GFR based on these equations e.g. Cockroft–Gault (CG), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and Modification of Diet in Renal Disease Study (MDRD) formulae—is flawed, and is not recommended in the critical care setting with fluctuating renal function [16–21].

Despite this, the use of mathematical estimates continues to be the standard tool for evaluation of renal function and drug adjustment calculations in many ICUs around the world, and in addition they are frequently used in clinical research. In a point prevalence, single-day, prospective study of 919 patients in 42 ICUs in Spain, Herrera-Gutierrez et al. reported that the method used for estimating GFR was serum creatinine in 36.6%, measured creatinine clearance in 41.5% and equations in 22% [22].

Taking into account simplicity, availability, costs, and feasibility, a measured urinary creatinine clearance (CL_{CR}) should be considered the single most accessible bedside parameter providing information on the potential pharmacokinetic (PK) implications of dynamic changes in renal function in the critically ill. In addition, it is the best method to screen patients for ARC [17]. This can be easily accomplished in the ICU, using continuous urine collections (via an indwelling catheter) of 2, 6, 8, 12, or 24 h.

Nevertheless, some limitations should be observed regarding CL_{CR}. Firstly, it is not a "gold-standard" for the assessment of GFR [12]. Secondly, the assessment of GFR is difficult in non-steady states and frequently changing volume status in critically ill patients [23]. Thirdly, overestimation of true GFR can occur with this measure (10–20% higher), related to tubular secretion of creatinine, albeit this difference will be more significant at lower GFR values [24]. Finally, the bias can be introduced if the urinary collection is not performed accurately.

7.4 Physiopathology of ARC

The specific pathophysiology of ARC is far from being fully understood and multiple factors contribute to the development of this condition (Fig. 7.2). Based on current knowledge, we can divide contributing factors into two categories: endogenous and exogenous.

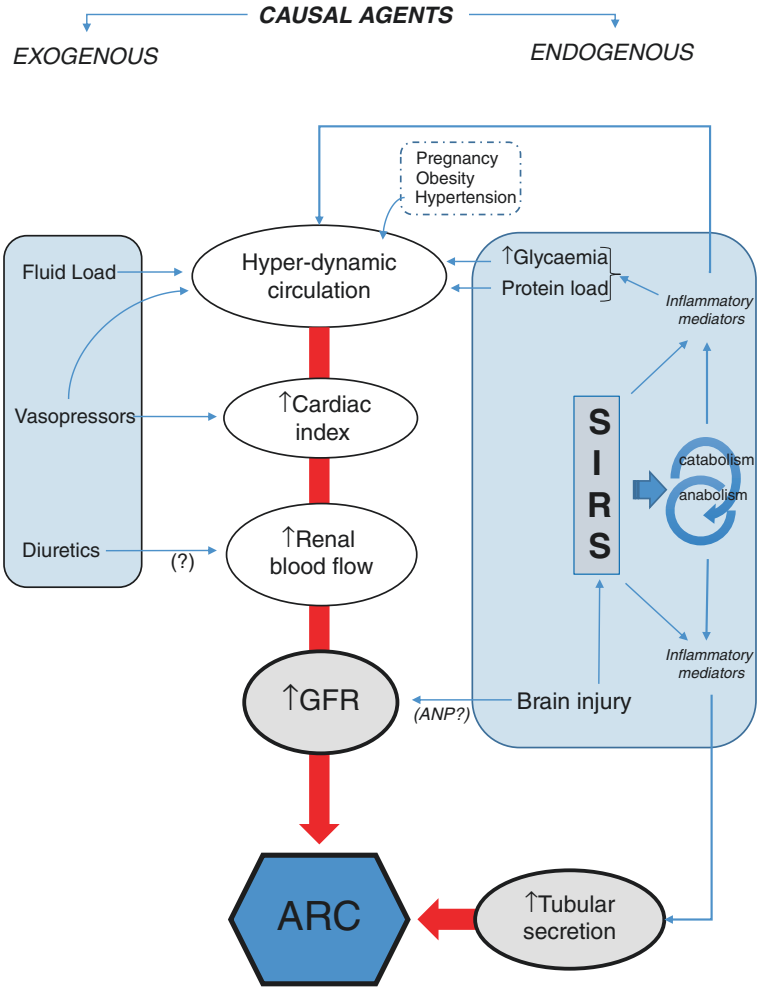

Fig. 7.2 A contextual framework for the pathogenesis of ARC, dividing causal agents of ARC in two categories: endogenous and exogenous. *ARC* augmented renal clearance, *SIRS* systemic inflammatory response syndrome, *GFR* glomerular filtration rate, *ANP* atrial natriuretic peptide

7.4.1 Endogenous Factors

In the critically ill, extreme physiological stress is applied, regardless of the underlying aetiology. Sepsis, trauma, burns, pancreatitis, autoimmune diseases, and major surgery, among others, are all prone to inciting an inflammatory and hypermetabolic state which, results in broad and profound changes in organ function, including the kidneys. This "storm of mediators" induces changes in the cardiovascular system,

namely a hyperdynamic state, characterized by increased cardiac output and diminished vascular resistance. Major organ blood flow is increased, including that of the kidneys, leading to a significant increase in GFR. These effects were demonstrated in an animal model of hyperdynamic sepsis [25] and are described in burns, post-surgical, and trauma critically ill patients [15, 26–28], although the correlation between cardiac index and CL_{CR} was greater in septic patients and absent in the trauma group [15]. Of note, Udy et al. demonstrated increased sinistrin clearance in a selected cohort of 20 critically ill patients considered at risk of ARC, with significant correlation with CL_{CR}, thus supporting the concept of hyperfiltration in these patients [27].

Additionally, they demonstrated elevated renal tubular anion secretion, which at least theoretically, could contribute to enhanced clearance of certain beta-lactams—known anionic antibiotics [27]. Moreover, it has been known for some time that hyperaminoacidemia, as a result of catabolism and/or inflammation, stimulates the secretion of several hormones that increase GFR and renal flow [29]. In addition, the high levels of CL_{CR} could be secondary to the renal response to a protein load. Finally, increased levels of GFR have been described in pregnant women, obesity, after nephrectomy, and among patients with essential hypertension and diabetes mellitus [30–34]. Taking all these factors into account, it seems plausible that the kidneys are able to recruit physiological reserve when exposed to systemic biological stress, such as hyperperfusion, a high protein load, or hyperglycaemia.

Recently, a significant correlation was described between cerebrovascular pressure reactivity index (as a measure of cerebrovascular reactivity) and estimated creatinine clearance, in a group of patients with severe traumatic brain injury. These results suggest there may be a physiological link between brain injury and kidney function, with the possible involvement of mediators, such as atrial natriuretic peptide (ANP) [35, 36].

7.4.2 Exogenous Factors

In the early stages of sepsis with hypotension, aggressive administration of crystalloid fluid (30 mL/kg) is recommended, and this strategy can be continued until haemodynamic improvement occurs [37]. Generalization of this practice in the critical care setting, including in the non-septic patient, conceivably contributes to producing a high cardiac index and increased renal blood flow, which in turn leads to an increase in GFR and urine output [38]. Similarly, the use of vasopressor support in sepsis is associated with an increase in cardiac output and CL_{CR} [39, 40]. Both therapeutic interventions induce these alterations in the absence of renal dysfunction.

Diuretics are still commonly used in the treatment critically ill patients; however, the influence of these drugs on renal function is controversial. Although mannitol does not seem to affect GFR in normal individuals [41], independent groups of researchers [42, 43] found that post-surgical patients and severely injured patients showed an increase in GFR, in the order of between 20 and 26%. Likewise, research

exploring the effects of frusemide on renal function in healthy volunteers are conflicting; data separately demonstrate no effect, a decrease in GFR, and an increase of GFR [44–46]. As such, the implications of diuretics in terms of ARC remain uncertain.

7.5 Epidemiology of ARC

Identification of patients at risk of ARC is likely to be helpful in optimizing treatment, particularly when renally eliminated drugs are being employed. However, data concerning the natural history, incidence, prevalence, risk factors, and implications of ARC are still scarce. Of note, over the past decade an increasing amount of epidemiological data has identified certain clinical characteristics associated with ARC. Currently, the absence of clear and well-defined criteria for ARC hampers the interpretation of these data.

7.5.1 Prevalence of ARC

Previous studies have shown that ARC is a frequent condition in the critical care setting; however, there are only few large-scale epidemiological data available (Table 7.1).

Table 7.1 Selected epidemiological data from recent studies investigating ARC (modified by author from "Baptista JP, Udy AA: Augmented renal clearance in critical illness: 'The Elephant in the ICU'? Minerva Anestesiol. 2015. 81(10):1050–2")

Year	First author	Country	ICU patients (*n*)	Measurements (*n*)	ARC criteria (mL/m)	Urine time collection (h)	ARC incidence (%)
2016	Baptista	Portugal	477	4271	≥130	8	33
2015	De Waele	Belgium	1081	4472	≥130	24	55.8
2015	Ruiz	France	360	360	≥130	24	33
2014	Campassi	Brazil	363	363	>120	24	28
2014	Baptista	Portugal	54	644	>130	8	55.6
2014	Udy	Australia, Portugal, Malaysia, Hong-Kong	281	1660	≥130	8	65.1
2013	Claus	Belgium	128	599	≥130	24	51.6
2013	Udy	Australia	71	213	≥130	2	57.7
2012	Lautrette	France	32	224	>140	24	47
2012	Grootaert	Belgium	1317	4019	≥120	24	41

ICU Intensive care unit, *ARC* augmented renal clearance; *h* hours

De Waele et al. performed a single-centre retrospective cohort study of 1081 ICU patients during a period of 15 months [47], generating 4472 ICU patient-days for evaluation. They found that more than 50% of the patients had at least one episode of ARC during their ICU stay, and the incidence per 100 patient-days was 36.6 episodes; in addition, 32.8% of these patients manifest ARC throughout their ICU stay [47]. Similarly, although primarily designed to evaluate the accuracy of mathematical estimates of renal function in critically ill patients, an observational, retrospective, single-centre study was performed by Grootaert et al. in a cohort of 1317 patients, providing 4019 measured 24 h–CL_{CR} [18], showing an ARC incidence of 41%. A prospective observational study by Ruiz et al. [48] described an incidence of 33% in a population of 360 consecutive critically ill patients, with normal serum creatinine concentrations. Recently, Baptista et al. conducted an observational retrospective single-centre study in a large population of critically ill patients with normal plasma creatinine concentrations—477 patients within the period of 1 year, corresponding to 4271 measurements [49]. This study concluded that ARC was a frequent condition, which was identified in 33% of the admission days. Udy et al. conducted a multicentre, multinational, prospective, observational study in 281 critically ill patients without evidence of renal impairment [50], and concluded that nearly 65% showed ARC on at least one occasion in the first week of ICU admission.

Smaller studies in different countries have reported a significant prevalence of ARC, with values of 17.9 and 25% on ICU admission [51, 52], 39, 51.6, 55.6, 57.7, and 85% over the ICU length of stay [15, 21, 53–55] and 30–47% during the first week in ICU [51, 52].

ARC is therefore common in the critically ill, with a not insignificant prevalence, and underlies why this phenomenon has been described as a "devil in disguise" [56] or the "elephant in the ICU" [57], particularly in that, despite its ubiquity, ARC is often overlooked by clinicians.

7.5.2 Gender and Age

Studies focusing on the influence of gender on ARC are scarce. Nevertheless, the current available data coherently shows that the incidence of this condition is higher in males [15, 49, 50, 53, 58]. Similarly, different groups of researchers conclude that younger patients exhibit more ARC more frequently [4, 15, 48–51, 53, 59–61].

Men have, physiologically, higher rates of GFR [5] and show higher renal vascular resistance; thus, this gender difference can persist even in hyperfiltration status. One possible explanation for this difference is the distinct production of and sensitivity to vasoactive substances that influence renal vascular resistance [62].

As mentioned earlier, the influence of age fits into the concept of "renal reserve", which is higher in younger people by virtue of better glomerular preservation and function. It was only very recently that studies addressing the issue of ARC in children have been published. In 2015, De Cock et al. reported the augmented renal clearance of amoxicillin-clavulanic acid in 50 paediatric critically ill patients [63]. The authors

concluded that renal function was a significant covariate on amoxicillin-clavulanic acid clearance and that ARC could be the cause of the sub-therapeutic concentrations observed. More recently, another group of researchers [64] performed an observational study on 109 children (>1 year) who received vancomycin therapy. These authors found globally elevated values of (estimated) glomerular filtration, which were even higher in the group of 21 patients with febrile neutropenia, compared to the remainder (182.0 vs. 156.2 mL/min/1.73 m^2, $p < 0.05$), in addition to the increased renal clearance of vancomycin (0.151 vs. 0.119 L/h/kg, $p < 0.05$). It should be noted that febrile neutropenia was the unique independent risk factor for ARC (defined here as an estimated GFR $\geq$ 160 mL/min/1.73 m^2).

7.5.3 Patient Populations

Previous studies recognized ARC as a frequent condition in selected populations of critically ill patients.

Victims of severe multi-trauma, namely when associated with trauma brain injury (TBI), seem to be at increased risk of developing ARC. In an observational small cohort study [54], in patients receiving active treatment for the optimization of cerebral perfusion, Udy et al. reported that ARC was a very frequent occurrence (85%). Similarly, in an observational study aimed at investigating renal and cardiac performance in patients with isolated TBI [36], the authors founded very significant augmented CL_{CR} measures, with median values of 201 mL/min on the first day of the study. Minville et al. [58] retrospectively studied 284 patients in a mixed ICU, evaluating 24 h–CL_{CR} within two distinct groups: non-trauma and multi-trauma patients. Notably, despite the fact that no significant differences were found between serum creatinine concentrations between the groups, a significant difference existed in regard to measured 24 h–CL_{CR}: 85 vs. 131 mL/min/1.73 m^2, respectively. Other groups [15, 28, 49–51, 65, 66] found similar results, reporting increased measured CL_{CR} in primarily multi-trauma, post-surgical or TBI patients. An important fact is that in two of these studies [15, 49], trauma was identified as a risk factor for ARC in a multivariate analysis model, strengthening the validity of these epidemiological data.

Patients with non-traumatic sub-arachnoid haemorrhage (SAH) are another subgroup of critically ill patients who are likely to demonstrate ARC. Recently, a prospective single-centre study performed by May et al. [67] evaluated 20 consecutive patients with new aneurysmal SAH. They demonstrated that ARC was present in all 20 patients, with a mean 24 h–CL_{CR} value of 325 ± 135 mL/min/1.73 m^2. The cohort was predominately made up of women and was relatively young, which may partially explain the remarkable prevalence (100%) in this population, in addition to the proposed link between ARC and cerebrovascular autoregulation [35, 67]. Significantly, the authors did not find a difference in 24 h–CL_{CR} between patients receiving, or not receiving, hyperdynamic therapy to treat cerebral vasospasm [67]. High values of CL_{CR} were also frequently observed in 32 consecutive ICU patients admitted with community-acquired meningitis [52].

Patients with major burns are also at risk of manifesting ARC. Interestingly, probably the first clinical description of very high values of CL_{CR} was performed in 1978 by Loirat et al. in a group of 20 patients with burn injury [2]; the average CL_{CR} was 172 ± 48 mL/min/1.73 m^2 and 13 patients showed values above 200 mL/min/1.73 m^2. Recently, Conil et al. prospectively studied 36 adult patients with burn injury (all with normal serum creatinine concentrations) and found 42% (15 patients) had a CL_{CR} above 120 mL/min/1.73 m^2 [68]. Increased catabolism, a hyperdynamic circulation, frequent episodes of sepsis, vasopressor support, and a generally young population, all contribute to the high prevalence of ARC in this subgroup of patients.

Studies involving patients with sepsis illustrate the high prevalence of ARC in the critically ill. Although the majority of these reports were not designed as epidemiological studies, each included a diverse case-mix of medical, neurologic, trauma, non-trauma, and post-surgical critically ill patients. In these studies [6, 7, 10, 52, 53, 59, 60, 69, 70], ARC was noted to have a prevalence of between 40 and 79%.

Patients with haematological malignancies and febrile neutropenia are also at risk of manifesting ARC, as suboptimal levels of meropenem and glycopeptides have been described [64, 71–74]. However, each study included patients with severe sepsis, who were mostly young men, generating uncertainty in regard to the role of the malignancy in the genesis of ARC.

7.5.4 Severity of Disease

Patients in critical care settings with lower illness severity, as reflected by lower Acute Physiology and Chronic Health Evaluation (APACHE) II scores and/or lower Sequential Organ Failure Assessment (SOFA) scores, seem to be at greater risk of developing ARC [4, 15, 60, 61], although this has not been confirmed in all reports [53]. This interaction may be confounded by age being included in the APACHE score although the observation that lower SOFA scores are associated with ARC implies the absence of organ dysfunction as a key factor. Recently, an ARC risk score based in three factors (age, trauma, and SOFA) and used to define three distinct categories (low, medium, high) has been described [15]. A subsequent simplification (reclassification into two categories) was tested [75] and demonstrated a sensitivity of 100% and specificity of 71%, in accurately identifying patients with ARC.

7.5.5 ARC Outside the ICU

Until recently, ARC was almost exclusively reported in the critical care setting. In 2016, a prospective observational single-centre point prevalence study was conducted in 232 adult non-critically ill surgical patients [76]. This revealed that ARC was present in 30% of abdominal and 35% of trauma surgery patients, when

evaluated by means of 8 h–CL_{CR}. In addition, these researchers identified younger age and male gender (specifically in the trauma subgroup) as risk factors for ARC. In accordance with these results, Hites et al. found, in a pharmacokinetic study of beta-lactams, that over 25% of 56 non-critically ill septic and obese patients had a 24 h–CL_{CR} above 150 mL/min [9]. Another study [59] previously showed that ARC was present in 61% (11/18) of a small sample of non-critically ill patients. However, this was a retrospective study and the CG formulae was used for estimating renal function; notably, estimated clearance was remarkably high—median of 150.5 mL/min/1.73 m^2.

These findings are in keeping with the more representative results observed in the critically ill. More importantly, these studies underline that ARC is an underestimated diagnosis, even in non-critical care settings. The severity of a disease is a continuum; thus, it seems logical that severely ill patients, before having absolute criteria to warrant ICU admission or even those who have never been admitted at an ICU, can show similar pathophysiology, including an inflammatory systemic response, hyperdynamic circulation, augmented renal flow, and supra-normal glomerular filtration.

7.5.6 ARC and Outcome

Few studies have investigated the link between ARC and outcome. In a prospective, single-centre, observational study, the relationship between ARC and 30-day mortality was explored in a cohort of 36 critically ill patients without brain lesions or neurologic disease [77]. This pilot research showed that patients demonstrating ARC ($n = 23$; 63%), independently of their diagnosis or the presence of sepsis, had a significantly lower mortality (8.7% vs. 38.5%, $p < 0.05$). On the contrary, in another prospective observational study performed in patients in a mixed ICU receiving antimicrobial therapy, Claus et al. [53] reported that therapeutic failure was more frequent in the subgroup of ARC patients. Similarly, Falcone et al. [78] found that critically ill patients with severe sepsis caused by Gram-positive microorganisms and exhibiting augmented renal clearance of daptomycin presented higher in-hospital mortality (30.7% vs. 10.8%). However, this subset of 13 patients had higher SOFA scores, a much higher rate of MRSA bacteraemia, severe sepsis, and septic shock, when compared to the remaining 37 patients. In a prospective, double-blind, randomized trial involving 272 patients with late-onset ventilator-associated pneumonia (comparing 7-day doripenem with 10-day imipenem-cilastatin), Kollef et al. [79] found that clinical cure rates in the subgroup of 46 patients with a $CL_{CR} \geq 150$ mL/min, favoured imipenem (28 patients). Finally, another group of researchers was unable to find an association between ARC and clinical outcome, in a cohort of 100 critically ill patients [6].

These data suggest an urgent need to conduct additional outcome studies concerning ARC.

7.6 Clinical Implications of ARC

7.6.1 Assessing Renal Function: More Than Just Kidney Injury

Clinicians generally assess renal function from a conservative perspective, such that "normal" renal function is typically inferred from plasma biomarkers (such as creatinine or cystatin C), which are often flawed and/or misleading in the critically ill [16, 21]; while, the possibility of "supra-normal" clearance is infrequently considered.

In daily practice, clinicians frequently adjust medication on the basis of impaired renal function. However, rarely does the same clinicians consider dose adjustment in patients with ARC. This is principally because most practitioners unfamiliar with this condition, and routine daily measured CL_{CR} is usually not performed in the ICU. Instead, clinicians tend to prefer mathematical estimates of renal function, which are insensitive in identifying critically ill patients with ARC [17]. Taking into consideration emerging data which suggests a not insignificant prevalence of ARC in the critically ill, the daily measure of urinary CL_{CR} should arguably be more common in the ICU. Moreover, it is inexpensive, easy to apply, reliable, reproducible, and both clinically and scientifically useful. Finally, considering existing prevalence data for ARC (Sect. 7.5.1), at least one in four patients in the ICU without renal impairment are likely to manifest this phenomenon; and will be exposed to undertreatment when prescribed standard doses of renally eliminated antibiotics. Importantly, the pharmaceutical industry and regulators should consider this when new agents enter clinical practice.

7.6.2 Antibiotics: Drugs with Specific Characteristics

In severe sepsis, control of the primary focus, haemodynamic resuscitation, organ support, and initial empiric antibiotic therapy are paramount, and any delay will result in increased morbidity and mortality [80]. Applied to antibiotic therapy, the proverb indicating *"there is only one opportunity to make a first good impression",* means that an adequate dose of antibiotic must be delivered very early, ideally at first administration. In addition, in critical care settings, clinicians rely on clinical feedback to validate the efficacy of therapy. For the majority of drugs used in such cases, it is possible to perform a rapid, obvious, and easy assessment of the clinical response of the patient. The use of vasopressors, antihypertensive, diuretics, sedatives, antipyretics, and analgesia are classic examples. However, this is not the case with antibiotics: a favourable clinical response is difficult to assess in the first days of therapy, even if the treatment is adequate in terms of dosing, spectrum of bacterial cover, and penetration.

In addition, the emergence of antibiotic resistance correlates with selective pressure as a consequence of using these drugs [81–83], even after brief exposure in the ICU environment [84]. Plus, the prevalence of less susceptible bacteria is higher in the ICU setting [85]. Moreover, inadequate antibiotic therapy affects not only the "target" patient but also subsequent patients to be treated, jeopardizing the success of future treatments and increasing the ecological risk to the hospital and to the community. While waiting for new agents, the strategy of maximal optimization of antibiotics must be incorporated into daily clinical practice, in addition to reviving old antibiotics, such as in the case of fosfomycin and colistin [86]. Indeed, on June 26th 1945, Sir Alexander Fleming (1881–1955) pronounced the following wise words: "*the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted*" [87].

7.6.3 ARC and Beta-Lactams Antibiotics

The beta-lactams (penicillins, cephalosporins, carbapenems, monobactams) are the most commonly prescribed and studied class of antibiotics, including in the ICU setting. Most beta-lactam antibiotics show time-dependent pharmacokinetic/pharmacodynamics (PK/PD), with the duration the free drug concentration exceeds the minimum inhibitory concentration ($f\ T_{>MIC}$) being the optimal index associated with clinical efficacy. In addition, this family of antibiotics exhibit short half-lives, low volumes of distribution, low to moderate binding to serum proteins, poor or absent post-antibiotic effect (except for carbapenems) and are predominantly cleared by the kidney. More specifically, the clearance of this class of antibiotics directly correlates with renal clearance [60, 88–91] and inversely correlates with trough drug serum concentration [7, 92]. Importantly, increased drug elimination will predominantly affect the half-life of beta-lactam antibiotics.

Huttner and colleagues [6] performed a single-centre, prospective, observational study in 100 critically ill septic patients, treated with imipenem, meropenem, piperacillin/tazobactam, or cefepime. They concluded that patients with ARC were three times more likely to have one or more undetectable trough concentrations (odds ratio of 3.3; confidence interval: 1.1–9.9). In a selected group of 48 critically ill patients treated with six different beta-lactams, researchers showed that a significant proportion received inadequate dosing even though standard regimens were used [7]; furthermore, using multivariate analysis, a robust relationship was demonstrated between low trough concentrations and 8 h–CL_{CR}. In a prospective, observational, PK study [8], Carlier et al. analysed data from 61 ICU patients receiving treatment with meropenem or piperacillin-tazobactam administered by extended infusion. They demonstrated that, in the subset of ARC patients, 76% (22/29) did not reach 100% $f\ T_{>MIC}$ and 37% (7/19 patients) did not reach 50% $f\ T_{>MIC}$. In a recent single-centre

observational study [60], Udy et al. examined the impact of ARC in a convenience sample of 48 septic critically ill patients receiving piperacillin-tazobactam, 4.5 g four times a day. They found that a significant proportion of patients (~2/3rds) manifest inferior drug exposure, when using the MIC at the upper limit of susceptibility (16 mg/L). Besides low concentrations, these authors demonstrated that the study cohort had an increased clearance of piperacillin-tazobactam (1.5 × values in healthy volunteers). Similarly, a post hoc analysis of the DALI study—a prospective, multicentre PK point prevalence study performed across 68 ICUs [93]—found that 19% and 41% of patients did not reach 100% $f\ T_{>MIC}$ and 50% $f\ T_{>MIC}$, respectively. Of note, increased CL_{CR} (using mathematical estimates) was a significant co-factor associated with PK/PD target failure [94]. These results are consistent with other analyses [61], where higher estimated CL_{CR} significantly reduces the probability of the target attainment. Significantly, the probability of reaching 100% $f\ T_{>MIC}$ decreased by 3% with every 1 mL/min increase in the estimated CL_{CR}. Another group [95] performed a prospective randomized controlled study in 32 critically ill patients treated with piperacillin/tazobactam, investigating the added value of using therapeutic drug monitoring in achieving PK/PD targets. The authors observed that plasma piperacillin concentrations were significantly lower in patients with ARC when compared to those without this condition. Finally, Hites et al. demonstrated, in a cohort of 56 non-critically ill obese patients, that ARC (defined by a 24 h–CL_{CR} > 150 mL/min) was the only risk factor identified for insufficient serum concentrations of standard doses of ceftazidime, cefepime, piperacillin/tazobactam, and meropenem [9].

Studies exploring higher than normal doses of beta-lactams are scarce and largely from single centres [96], or are small case series and case reports [97–99]. Further studies are urgently needed specifically addressing the optimization of antibiotic dosing in patients with ARC. This new information should be quickly incorporated into the summary of product characteristics (SPC) by regulatory authorities and drug developers. Of note, this is the case for ceftobiprole—a recent new-generation cephalosporin—for which a recommendation exist in the SPC [100] in order to prolong the infusion time to 4 h in patients with a supra-normal creatinine clearance (above 150 mL/min). Similarly, the SPC for doripenem was updated and currently recommends that 1 g every 8 h, as a 4-h infusion, should be considered in patients with ARC [101]. A new combination product (ceftazidime with avibactam) has obtained initial authorization from the European Medicines Agency (EMA); within the assessment report of the product several, PK considerations are made regarding ARC and sepsis [102].

7.6.4 ARC and Glycopeptides Antibiotics

Vancomycin is the most commonly prescribed glycopeptide in the intensive care setting and is the most common first-line option for treating resistant Gram-positive bacteria. Briefly, vancomycin is a hydrophilic antibiotic, with moderate binding to serum proteins, is mainly excreted by the kidneys, with a low volume of distribution, long half-life, and a moderate post-antibiotic effect. The best PK/PD index

associated with clinical efficacy is the ratio between the area under the curve of drug concentrations over 24 h ($AUC_{0–24}$) and the MIC of the bacteria ($AUC_{0–24}$/MIC), ideally exceeding 400 [103, 104]. Like beta-lactams, vancomycin's body clearance correlates very well with creatinine clearance, both in critically ill and non-critically ill patients [105–111].

In the recent past, a growing body of evidence has emerged demonstrating that standard doses of vancomycin result in suboptimal serum or tissue concentrations in critically ill patients [4, 10, 26, 59, 64, 106, 112–118]. Of note, the authors of a secondary analysis from the DALI study [119] concluded that an important proportion of critically ill patients (43%) did not achieve adequate vancomycin exposure, defined as a trough concentration at least 15 mg/L. Although the reasons for this is multifactorial, ARC is likely to be a key driver. However, published studies specifically dedicated to this issue are relatively scarce.

Two contemporaneous studies investigated the relationship between ARC and vancomycin concentrations in the initial few days of therapy in ICU patients receiving continuous infusion. Ocampos-Martinez et al. [3] prospectively studied 261 critically ill patients, of which 16% (43 patients) had a 24 h–CL_{CR} higher than 120 mL/min/1.73 m^2. ARC was associated with suboptimal serum levels in 84% during the early phase of treatment with vancomycin (the first 2 days of drug administration). Consistent with these results, Baptista et al. [10], in a prospective single-centre study involving 93 ICU patients, demonstrated that the serum concentration of vancomycin on the first day of treatment had a moderate inverse correlation with 24 h–CL_{CR} and that, in those with ARC, significantly lower levels on the first three consecutive days of the study were noted. Equally, in another prospective study, Campassi et al. [4] recruited 363 patients in a general ICU over a 1-year period. They observed that none of the 103 patients with 24 h–CL_{CR} > 120 mL/min/1.73 m^2 reached the targeted trough level on the first day; in addition, these patients showed persistently lower levels over the first three days when compared to the patients without ARC, despite being exposed to increased doses of vancomycin.

Another group [59] performed a retrospective study evaluating the influence of ARC (estimated by CG method) on the exposure to vancomycin in a heterogeneous population (critical and non-critical care setting). They concluded that ARC cases had double the risk of sub-therapeutic vancomycin serum concentration. Shimamoto et al. [26] found significantly lower trough vancomycin levels in septic ICU patients with a greater systemic inflammatory response; of note the estimated renal function was "supra-normal" in this group (>120 mL/min, CG estimated). Very recently, Chu et al. [11] reached similar conclusions in a study involving 148 infected patients receiving empirical vancomycin therapy. The authors demonstrated that patients with ARC (>130 mL/min, CG estimated) treated with conventional dosage of vancomycin exhibited significantly lower steady-state trough serum concentrations. Equally, Spadaro et al. identified ARC (here defined as measured 24 h–CL_{CR} > 130 mL/min/1.73 m^2) as the main determinant of sub-therapeutic vancomycin serum concentrations, in a group of 348 critically ill patients treated with continuous infusion of vancomycin [120]. Similar results were also published recently in a retrospective study involving neurosurgical patients [121].

Teicoplanin is another glycopeptide used in ICU. It is hydrophilic, highly protein bound, and predominantly renally eliminated [122]. Recently, Nakano et al. [123] reported that septic patients manifesting a systemic inflammatory response syndrome (SIRS) had significantly lower plasma trough concentrations during the first 3 days of treatment, when compared to non-SIRS patients administered an equivalent loading dose. Similarly, distinct groups have reported an augmented rate of teicoplanin clearance in febrile, severely neutropenic patients and in critically ill patients [71, 125].

7.6.5 ARC and Other Antibiotic Drugs

From a theoretical point of view, the PK of any agent that is renally cleared, will potentially be altered by ARC. However, depending on the bacterial kill PK/PD profile, the magnitude of this effect will vary.

For hydrophilic antibiotics exhibiting a time-dependent profile, particularly with low protein binding, an effect similar to that with beta-lactams is expected. This is the case of oxazolidinones (e.g. linezolid, the first to be approved for clinical use) and fosfomycin. Although the level of renal clearance of linezolid is modest (less than 30%) higher values of glomerular filtration are documented as a risk factor for suboptimal serum concentrations in patients with severe sepsis [125]. On the contrary, fosfomycin is eliminated almost entirely by the kidneys [126]. Consequently, higher dosing, shortening of intervals and alternative ways of administration of these drugs—such as extended or continuous infusion—should be considered [127–129].

For hydrophilic antibiotics exhibiting a concentration-dependent profile, such as with aminoglycosides, the peak plasma concentration is less affected by ARC and more affected by the increased volume of distribution [130]. However, ARC has been described as a covariate leading to the requirement of higher than standard dosage in critically ill patients [131–133]. In addition, the shortening of dosing intervals to less than 24 h can be considered.

For levofloxacin, a moderately lipophilic drug with a high volume of distribution and almost totally cleared by the kidneys, recent work by Pai et al. [134] showed that in a population of morbidly obese septic patients, a standard dosage was insufficient to achieve the defined PK/PD target, and that CL_{CR} constituted the best predictor of levofloxacin renal clearance. In line with others [135], the final recommendation by these authors is that the dosage of levofloxacin should be increased in patients with higher CL_{CR} [134].

Daptomycin, a novel cyclic lipopeptide, is a hydrophilic antibiotic characterized by a low volume of distribution, predominant renal excretion, prolonged post-antibiotic effect, and a concentration-dependent PK/PD profile. Falcone et al. studied 50 critically ill patients treated with standard doses of this antibiotic and reported augmented daptomycin clearance and significantly lower drug exposures in a subset of 13 patients [78]. Similar results were observed in cancer patients with febrile neutropenia and in patients with burn injuries treated with daptomycin, suggesting the need for higher doses at the onset of treatment [136, 137].

7.6.6 My Septic Patient Has ARC: So What?

Based on growing literature, it seems rational to conclude that augmented CL_{CR} is a significant predictor of sub-therapeutic beta-lactam and vancomycin concentrations in critically ill patients, when standard doses are employed. Moreover, as discussed above, current data regarding other antibiotics are in keeping with this, reinforcing the clinical importance of ARC as a determinant of antibiotic exposure in the early phase of severe sepsis. Importantly, these data are highly generalizable, and suggest intensive care physicians, pharmacists, researchers, and pharmaceutical regulators should be cognizant of the implications of ARC. A "one-size-fits-all" approach to dosing is likely to be grossly flawed in the critically ill. It is imperative that all those involved in the treatment of critically ill patients move towards an individualized dosing approach.

Adequacy of antibiotic therapy is of paramount importance in achieving optimal outcomes in septic patients [138, 139]. The prescription of an antibiotic should always consider the "bug-drug-host" triad, with efficacy of therapy intimately linked to optimizing each of these factors. Although ARC is only one piece of this intricate chain, ignoring this phenomenon will significantly impact the success of antibiotic therapy. In this respect, three recent position papers—one from "Antimicrobials: A Global Alliance for Optimizing their Rational Use in Intra-Abdominal Infections" (AGORA), another by the most recent "Surviving Sepsis Campaign Guidelines" Committee, and the third from the "Infectious Diseases Society of America/American Thoracic Society 2016 Clinical Practice Guidelines"—underline the need to optimize antimicrobial exposure to obtain better clinical outcomes and reduce resistance, and make special mention of the clinical relevance of ARC [140–142].

From a practical point of view at the bedside of a severely ill patient with ARC, clinicians should strongly consider: (a) the use of the maximal recommended doses of antibiotics that are renally cleared; (b) optimization of the mode of administration with extended or continuous infusions (vancomycin, beta-lactams); and (c) the shortening of dosing intervals with intermittent schedules (aminoglycosides, beta-lactams). Often, larger "off-label" doses may be required. In this respect, a number of nomograms based on CL_{CR} values have been developed to assist prescribers [96, 106, 111, 112, 143]. Traditionally, therapeutic drug monitoring (TDM) is used to largely prevent toxic effects, particularly in older patients, patients with rapid changes in renal function and in the critical care setting. However, TDM can and should be used for dose titration where available, and is especially useful in patients with ARC, although this practice is still infrequently applied [144].

Of note, *over-dosing* of adequate antibiotic drugs at the beginning of the treatment of the severely ill septic patient is probably more advantageous and life-saving than *under-dosing*. Logically, when more aggressive antibiotic doses using agents with a narrow therapeutic window are applied, such as vancomycin and aminoglycosides, complications can also occur (such as nephrotoxicity) [145, 146]. However, in our experience, with tight monitoring any elevation of serum creatinine is usually transient and mild, and the frequency of severe AKI is low [111, 147–150].

7.7 Conclusions

Septic patients in the ICU are severely ill, with frequent organ dysfunction, and are often infected with more resistant microorganisms. Because of numerous physiological changes, the PK characteristics of antibiotics are grossly altered, and an individualized approach to the critically ill patient, must be considered when prescribing these agents.

Augmented renal clearance has emerged recently as a common feature in some subsets of critically ill patients and has been increasingly described in this setting. This condition is often overlooked by clinicians, albeit can have profound and severe consequences on the efficacy of drugs that are predominantly eliminated by the kidneys. The use of traditional antibiotic dosing strategies in patients showing persistent ARC may lead to suboptimal antibiotic exposure, increasing the risk of treatment failure, when standard doses are used. Consequently, this may contribute to an increase in bacterial resistance and the prevalence of (even more) difficult-to-treat infections. As such clinicians should be cognizant of this phenomenon, using simple and reliable methods (such as a measured CL_{CR}) to identify patients where dose adjustment is needed.

References

1. Udy AA, Roberts JA, Boots RJ, Paterson DL, Lipman J (2010) Augmented renal clearance: implications for antibacterial dosing in the critically ill. Clin Pharmacokinet 49:1–16
2. Loirat P, Rohan J, Baillet A, Beaufils F, David R, Chapman A (1978) Increased glomerular filtration rate in patients with major burns and its effect on the pharmacokinetics of tobramycin. N Engl J Med 299(17):915–919
3. Ocampos-Martinez E, Penaccini L, Scolletta S, Abdelhadii A, Devigili A, Cianferoni S et al (2012) Determinants of early inadequate vancomycin concentrations during continuous infusion in septic patients. Int J Antimicrob Agents 39(4):332–337
4. Campassi ML, Gonzalez MC, Masevicius FD, Vazquez AR, Moseinco M, Navarro NC et al (2014) Augmented renal clearance in critically ill patients: incidence, associated factors and effects on vancomycin treatment. Rev Bras Ter Intensiva 26(1):13–20
5. Stevens LA, Coresh J, Greene T, Levey AS (2006) Assessing kidney function—measured and estimated glomerular filtration rate. N Engl J Med 354:2473–2483
6. Huttner A, Von Dach E, Renzoni A, Huttner BD, Affaticati M, Pagani L et al (2015) Augmented renal clearance, low beta-lactam concentrations and clinical outcomes in the critically ill: an observational prospective cohort study. Int J Antimicrob Agents 45(4): 385–392
7. Udy AA, Varghese JM, Altukroni M, Briscoe S, McWhinney BC, Ungerer JP et al (2012) Subtherapeutic initial beta-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. Chest 142(1):30–39
8. Carlier M, Carrette S, Roberts JA, Stove V, Verstraete A, Hoste E et al (2013) Meropenem and piperacillin/tazobactam prescribing in critically ill patients: does augmented renal clearance affect pharmacokinetic/pharmacodynamic target attainment when extended infusions are used? Crit Care 17(3):R84
9. Hites M, Taccone FS, Wolff F, Maillart E, Beumier M, Surin R et al (2014) Broad-spectrum beta-lactams in obese non-critically ill patients. Nutr Diabetes 4:e119

10. Baptista JP, Sousa E, Martins PJ, Pimentel JM (2012) Augmented renal clearance in septic patients and implications for vancomycin optimisation. Int J Antimicrob Agents 39(5):420–423
11. Chu Y, Luo Y, Qu L, Zhao C, Jiang M (2016) Application of vancomycin in patients with varying renal function, especially those with augmented renal clearance. Pharm Biol 54(12):2802–2806
12. Wesson L (1969) Physiology of the human kidney. Grune & Stratton, New York
13. Rahn KH, Heidenreich S, Bruckner D (1999) How to assess glomerular function and damage in humans. J Hypertens 17(3):309–317
14. Baptista JP, Silva N, Costa E, Fontes F, Marques M, Ribeiro G, Pimentel J (2014) Identification of the critically ill patient with augmented renal clearance: make do with what do you have! Intensive Care Med 40:S110
15. Udy AA, Roberts JA, Shorr AF, Boots RJ, Lipman J (2013) Augmented renal clearance in septic and traumatized patients with normal plasma creatinine concentrations: identifying at-risk patients. Crit Care 17(1):R35
16. Udy AA, Morton FJA, Nguyen-Pham S, Jarrett P, Lassig-Smith M, Stuart J et al (2013) A comparison of CKD-EPI estimated glomerular filtration rate and measured creatinine clearance in recently admitted critically ill patients with normal plasma creatinine concentrations. BMC Nephrol 14:250
17. Baptista JP, Udy AA, Sousa E, Pimentel J, Wang L, Roberts JA et al (2011) A comparison of estimates of glomerular filtration in critically ill patients with augmented renal clearance. Crit Care 15(3):R139
18. Grootaert V, Willems L, Debaveye Y, Meyfroidt G, Spriet I (2012) Augmented renal clearance in the critically ill: how to assess kidney function. Ann Pharmacother 46:952–959
19. McNeill GB, Martin JH (2011) How reliable is eGFR when calculating drug dosage in acute medical admissions? Intern Med J 41:327–331
20. Martin JH, Fay MF, Udy AA, Roberts JA, Kirkpatrick C, Ungerer J et al (2011) Pitfalls of using estimations of glomerular filtration rate in an intensive care population. Intern Med J 41(7):537–543
21. Baptista JP, Neves M, Rodrigues L, Teixeira L, Pinho J, Pimentel J (2014) Accuracy of the estimation of glomerular filtration rate within a population of critically ill patients. J Nephrol 27(4):403–410
22. Herrera-Gutierrez ME, Seller-Perez G, Maynar-Moliner J, Sanchez-Izquierdo Riera JA (2012) Variability in renal dysfunction defining criteria and detection methods in intensive care units: are the international consensus criteria used for diagnosing renal dysfunction? Med Intensiva 36:264–269
23. Prowle JR (2014) Does augmented creatinine clearance accurately reflect glomerular hyperfiltration in critical illness? Crit Care Med 42:e674–e675
24. Kim KE, Onesti G, Ramirez O, Brest AN, Swartz C (1969) Creatinine clearance in renal disease. A reappraisal. Br Med J 4(5674):11–14
25. Di Giantomasso D, May CN, Bellomo R (2003) Vital organ blood flow during hyperdynamic sepsis. Chest 124:1053–1059
26. Shimamoto Y, Fukuda T, Tanaka K, Komori K, Sadamitsu D (2013) Systemic inflammatory response syndrome criteria and vancomycin dose requirement in patients with sepsis. Intensive Care Med 39(7):1247–1252
27. Udy AA, Jarrett P, Stuart J, Lassig-Smith M, Starr T, Dunlop R et al (2014) Determining the mechanisms underlying augmented renal drug clearance in the critically ill: use of exogenous marker compounds. Crit Care 18(6):657
28. Brown R, Babcock R, Talbert J, Gruenberg J, Czurak C, Campbell M (1980) Renal function in critically ill postoperative patients: sequential assessment of creatinine osmolar and free water clearance. Crit Care Med 8(2):68–72
29. Castellino P, Giordano C, Perna A, DeFronzo RA (1988) Effects of plasma amino acid and hormone levels on renal hemodynamics in humans. Am J Phys 255(3 Pt 2):F444–F449

30. Moran P, Baylis PH, Lindheimer MD, Davison JM (2003) Glomerular ultrafiltration in normal and preeclamptic pregnancy. J Am Soc Nephrol 14(3):648–652
31. Chagnac A, Weinstein T, Herman M, Hirsh J, Gafter U, Ori Y (2003) The effects of weight loss on renal function in patients with severe obesity. J Am Soc Nephrol 14(6):1480–1486
32. Schmieder RE, Veelken R, Schobel H, Dominiak P, Mann JF, Luft FC (1997) Glomerular hyperfiltration during sympathetic nervous system activation in early essential hypertension. J Am Soc Nephrol 8(6):893–900
33. Vallon V, Blantz RC, Thomson S (2003) Glomerular hyperfiltration and the salt paradox in early [corrected] type 1 diabetes mellitus: a tubulo-centric view. J Am Soc Nephrol 14(2):530–537
34. Blantz RC, Steiner RW (2015) Benign hyperfiltration after living kidney donation. J Clin Invest 125(3):972–974
35. Dias C, Gaio AR, Monteiro E, Barbosa S, Cerejo A, Donnelly J et al (2015) Kidney-brain link in traumatic brain injury patients? A preliminary report. Neurocrit Care 22(2):192–201
36. Udy AA, Jarrett P, Lassig-Smith M, Stuart J, Starr T, Dunlop R et al (2017) Augmented renal clearance (ARC) in traumatic brain injury (TBI): a single-center observational study of atrial natriuretic peptide, cardiac output, and creatinine clearance. J Neurotrauma 34(1):137–144
37. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M et al (2016) The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 315(8):801–810
38. Wan L, Bellomo R, May CN (2007) The effects of normal and hypertonic saline on regional blood flow and oxygen delivery. Anesth Analg 105(1):141–147
39. Di Giantomasso D, May CN, Bellomo R (2003) Norepinephrine and vital organ blood flow during experimental hyperdynamic sepsis. Intensive Care Med 29(10):1774–1781
40. Redl-Wenzl EM, Armbruster C, Edelmann G, Fischl E, Kolacny M, Wechsler-Fordos A et al (1993) The effects of norepinephrine on hemodynamics and renal function in severe septic shock states. Intensive Care Med 19(3):151–154
41. Goldberg M, McCurdy DK, Ramirez MA (1965) Differences between saline and mannitol diuresis in hydropenic man. J Clin Invest 44:182–192
42. Redfors B, Sward K, Sellgren J, Ricksten SE (2009) Effects of mannitol alone and mannitol plus furosemide on renal oxygen consumption, blood flow and glomerular filtration after cardiac surgery. Intensive Care Med 35(1):115–122
43. Valdes ME, Landau SE, Shah DM, Newell JC, Scovill WA, Stratton H et al (1979) Increased glomerular filtration rate following mannitol administration in man. J Surg Res 26:473–477
44. Bradley VE, Shier MR, Lucas CE, Rosenberg IK (1976) Renal hemodynamic response to furosemide in septic and injured patients. Surgery 79:549–554
45. Sward K, Valsson F, Sellgren J, Ricksten SE (2005) Differential effects of human atrial natriuretic peptide and furosemide on glomerular filtration rate and renal oxygen consumption in humans. Intensive Care Med 31(1):79–85
46. Passmore AP, Copeland S, Johnston GD (1990) The effects of ibuprofen and indomethacin on renal function in the presence and absence of frusemide in healthy volunteers on a restricted sodium diet. Br J Clin Pharmacol 29(3):311–319
47. De Waele JJ, Dumoulin A, Janssen A, Hoste EA (2015) Epidemiology of augmented renal clearance in mixed ICU patients. Minerva Anestesiol 81:1079–1085
48. Ruiz S, Minville V, Asehnoune K, Virtos M, Georges B, Fourcade O et al (2015) Screening of patients with augmented renal clearance in ICU: taking into account the CKD-EPI equation, the age, and the cause of admission. Ann Intensive Care 5(1):49
49. Baptista JP, Martins P, Marques M, et al (2016) Trauma, male gender and young age are significant risk factors for the presence of augmented renal clearance (ARC) in critical care ill patients. Intensive Care medicine. Intensive Care Med Exp (Supplement)
50. Udy AA, Baptista JP, Lim NL, Joynt GM, Jarrett P, Wockner L et al (2014) Augmented renal clearance in the ICU: results of a multicenter observational study of renal function in critically ill patients with normal plasma creatinine concentrations. Crit Care Med 42(3):520–527

51. Fuster-Lluch O, Geronimo-Pardo M, Peyro-Garcia R, Lizan-Garcia M (2008) Glomerular hyperfiltration and albuminuria in critically ill patients. Anaesth Intensive Care 36(5):674–680
52. Lautrette A, Phan TN, Ouchchane L, Aithssain A, Tixier V, Heng AE et al (2012) High creatinine clearance in critically ill patients with community-acquired acute infectious meningitis. BMC Nephrol 13:124
53. Claus BO, Hoste EA, Colpaert K, Robays H, Decruyenaere J, De Waele JJ (2013) Augmented renal clearance is a common finding with worse clinical outcome in critically ill patients receiving antimicrobial therapy. J Crit Care 28(5):695–700
54. Udy AA, Boots R, Senthuran S, Stuart J, Deans R, Lassig-Smith M et al (2010) Augmented creatinine clearance in traumatic brain injury. Anesth Analg 111:1505–1510
55. Adnan S, Ratnam S, Kumar S, Paterson D, Lipman J, Roberts JA et al (2014) Select critically ill patients at risk of augmented renal clearance: experience in a Malaysian intensive care unit. Anaesth Intensive Care 42(6):715–722
56. de Lange DW (2013) Glomerular hyperfiltration of antibiotics. Netherlands J Crit Care 17(5):10–14
57. Baptista JP, Udy AA (2015) Augmented renal clearance in critical illness: "The Elephant in the ICU"? Minerva Anestesiol 81:1050–1052
58. Minville V, Asehnoune K, Ruiz S, Breden A, Georges B, Seguin T et al (2011) Increased creatinine clearance in polytrauma patients with normal serum creatinine: a retrospective observational study. Crit Care 15(1):R49
59. Minkute R, Briedis V, Steponaviciute R, Vitkauskiene A, Maciulaitis R (2013) Augmented renal clearance—an evolving risk factor to consider during the treatment with vancomycin. J Clin Pharm Ther 38(6):462–467
60. Udy AA, Lipman J, Jarrett P, Klein K, Wallis SC, Patel K et al (2015) Are standard doses of piperacillin sufficient for critically ill patients with augmented creatinine clearance? Crit Care 19:28
61. Abdul-Aziz MH, Lipman J, Akova M, Bassetti M, De Waele JJ, Dimopoulos G et al (2016) Is prolonged infusion of piperacillin/tazobactam and meropenem in critically ill patients associated with improved pharmacokinetic/pharmacodynamic and patient outcomes? An observation from the defining antibiotic levels in intensive care unit patients (DALI) cohort. J Antimicrob Chemother 71:196–207
62. Baylis C (1994) Age-dependent glomerular damage in the rat. Dissociation between glomerular injury and both glomerular hypertension and hypertrophy. Male gender as a primary risk factor. J Clin Invest 94(5):1823–1829
63. De Cock PA, Standing JF, Barker CI, de Jaeger A, Dhont E, Carlier M et al (2015) Augmented renal clearance implies a need for increased amoxicillin-clavulanic acid dosing in critically ill children. Antimicrob Agents Chemother 59(11):7027–7035
64. Hirai K, Ihara S, Kinae A, Ikegaya K, Suzuki M, Hirano K et al (2016) Augmented renal clearance in pediatric patients with febrile neutropenia associated with vancomycin clearance. Ther Drug Monit 38(3):393–397
65. Benmalek F, Behforouz N, Benoist JF, Lafay M, Mimoz O, Samii K et al (1999) Renal effects of low-dose dopamine during vasopressor therapy for posttraumatic intracranial hypertension. Intensive Care Med 25(4):399–405
66. Barletta JF, Mangram AJ, Byrne M, Hollingworth AK, Sucher JF, Ali-Osman FR et al (2016) The importance of empiric antibiotic dosing in critically ill trauma patients: Are we under-dosing based on augmented renal clearance and inaccurate renal clearance estimates? J Trauma Acute Care Surg 81(6):1115–1121
67. May CC, Arora S, Parli SE, Fraser JF, Bastin MT, Cook AM (2015) Augmented renal clearance in patients with subarachnoid hemorrhage. Neurocrit Care 23(3):374–379
68. Conil JM, Georges B, Lavit M, Laguerre J, Samii K, Houin G et al (2007) A population pharmacokinetic approach to ceftazidime use in burn patients: influence of glomerular filtration, gender and mechanical ventilation. Br J Clin Pharmacol 64:27–35
69. Lipman J, Wallis SC, Rickard C (1999) Low plasma cefepime levels in critically ill septic patients: pharmacokinetic modeling indicates improved troughs with revised dosing. Antimicrob Agents Chemother 43(10):2559–2561

70. Lipman J, Wallis SC, Rickard CM, Fraenkel D (2001) Low cefpirome levels during twice daily dosing in critically ill septic patients: pharmacokinetic modelling calls for more frequent dosing. Intensive Care Med 27(2):363–370
71. Lortholary O, Tod M, Rizzo N, Padoin C, Biard O, Casassus P et al (1996) Population pharmacokinetic study of teicoplanin in severely neutropenic patients. Antimicrob Agents Chemother 40(5):1242–1247
72. Zeitany RG, El Saghir NS, Santhosh-Kumar CR, Sigmon MA (1990) Increased aminoglycoside dosage requirements in hematologic malignancy. Antimicrob Agents Chemother 34(5):702–708
73. Fernandez de Gatta MM, Fruns I, Hernandez JM, Caballero D, San Miguel JF, Martinez Lanao J et al (1993) Vancomycin pharmacokinetics and dosage requirements in hematologic malignancies. Clin Pharm 12(7):515–520
74. Lamoth F, Buclin T, Csajka C, Pascual A, Calandra T, Marchetti O (2009) Reassessment of recommended imipenem doses in febrile neutropenic patients with hematological malignancies. Antimicrob Agents Chemother 53(2):785–787
75. Akers KS, Niece KL, Chung KK, Cannon JW, Cota JM, Murray CK (2014) Modified augmented renal clearance score predicts rapid piperacillin and tazobactam clearance in critically ill surgery and trauma patients. J Trauma Acute Care Surg 77(3 Suppl 2):S163–S170
76. Declercq P, Nijs S, D'Hoore A, Van Wijngaerden E, Wolthuis A, de Buck van Overstraeten A et al (2016) Augmented renal clearance in non-critically ill abdominal and trauma surgery patients is an underestimated phenomenon: a point prevalence study. J Trauma Acute Care Surg 81(3):468–477
77. Baptista JP, Teixeira L, Rodrigues L, Neves M, Pimentel J (2012) Augmented creatinine renal clearance in critically ill patients: is there a place for a new prognostic marker? Intensive Care Med 38:S298
78. Falcone M, Russo A, Venditti M, Novelli A, Pai MP (2013) Considerations for higher doses of daptomycin in critically ill patients with methicillin-resistant Staphylococcus aureus bacteremia. Clin Infect Dis 57:1568–1576
79. Kollef MH, Chastre J, Clavel M, Restrepo MI, Michiels B, Kaniga K et al (2012) A randomized trial of 7-day doripenem versus 10-day imipenem-cilastatin for ventilator-associated pneumonia. Crit Care 16(6):R218
80. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S et al (2006) Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 34(6):1589–1596
81. Paramythiotou E, Lucet JC, Timsit JF, Vanjak D, Paugam-Burtz C, Trouillet JL et al (2004) Acquisition of multidrug-resistant Pseudomonas aeruginosa in patients in intensive care units: role of antibiotics with antipseudomonal activity. Clin Infect Dis 38:670–677
82. Fantin B, Farinotti R, Thabaut A, Carbon C (1994) Conditions for the emergence of resistance to cefpirome and ceftazidime in experimental endocarditis due to Pseudomonas aeruginosa. J Antimicrob Chemother 33(3):563–569
83. Hyatt JM, Schentag JJ (2000) Pharmacodynamic modeling of risk factors for ciprofloxacin resistance in Pseudomonas aeruginosa. Infect Control Hosp Epidemiol 21:S9–11
84. Armand-Lefevre L, Angebault C, Barbier F, Hamelet E, Defrance G, Ruppe E et al (2013) Emergence of imipenem-resistant gram-negative bacilli in intestinal flora of intensive care patients. Antimicrob Agents Chemother 57(3):1488–1495
85. Valenza G, Seifert H, Decker-Burgard S, Laeuffer J, Morrissey I, Mutters R (2012) Comparative activity of carbapenem testing (COMPACT) study in Germany. Int J Antimicrob Agents 39(3):255–258
86. Muller AE, Theuretzbacher U, Mouton JW (2015) Use of old antibiotics now and in the future from a pharmacokinetic/pharmacodynamic perspective. Clin Microbiol Infect 21:881–885
87. Fleming A (1945) Penicillin's finder assays its future. New York Times, 26 June
88. Roos JF, Lipman J, Kirkpatrick CM (2007) Population pharmacokinetics and pharmacodynamics of cefpirome in critically ill patients against Gram-negative bacteria. Intensive Care Med 33(5):781–788

89. Li C, Kuti JL, Nightingale CH, Mansfield DL, Dana A, Nicolau DP (2005) Population pharmacokinetics and pharmacodynamics of piperacillin/tazobactam in patients with complicated intra-abdominal infection. J Antimicrob Chemother 56(2):388–395
90. Joynt GM, Lipman J, Gomersall CD, Young RJ, Wong EL, Gin T (2001) The pharmacokinetics of once-daily dosing of ceftriaxone in critically ill patients. J Antimicrob Chemother 47(4):421–429
91. Goncalves-Pereira J, Povoa P (2011) Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of beta-lactams. Crit Care 15(5):R206
92. Conil JM, Georges B, Mimoz O, Dieye E, Ruiz S, Cougot P et al (2006) Influence of renal function on trough serum concentrations of piperacillin in intensive care unit patients. Intensive Care Med 32(12):2063–2066
93. Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G et al (2014) DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 58(8):1072–1083
94. De Waele JJ, Lipman J, Akova M, Bassetti M, Dimopoulos G, Kaukonen M et al (2014) Risk factors for target non-attainment during empirical treatment with beta-lactam antibiotics in critically ill patients. Intensive Care Med 40(9):1340–1351
95. Sime FB, Roberts MS, Tiong IS, Gardner JH, Lehman S, Peake SL et al (2015) Can therapeutic drug monitoring optimize exposure to piperacillin in febrile neutropenic patients with haematological malignancies? A randomized controlled trial. J Antimicrob Chemother 70:2369–2375
96. Pea F, Viale P, Cojutti P, Furlanut M (2012) Dosing nomograms for attaining optimum concentrations of meropenem by continuous infusion in critically ill patients with severe gram-negative infections: a pharmacokinetics/pharmacodynamics-based approach. Antimicrob Agents Chemother 56:343–348
97. Troger U, Drust A, Martens-Lobenhoffer J, Tanev I, Braun-Dullaeus RC, Bode-Boger SM (2012) Decreased meropenem levels in intensive care unit patients with augmented renal clearance: benefit of therapeutic drug monitoring. Int J Antimicrob Agents 40:370–372
98. Udy AA, Putt MT, Shanmugathasan S, Roberts JA, Lipman J (2010) Augmented renal clearance in the intensive care unit: an illustrative case series. Int J Antimicrob Agents 35: 606–608
99. Taccone FS, Cotton F, Roisin S, Vincent JL, Jacobs F (2012) Optimal meropenem concentrations to treat multidrug-resistant Pseudomonas aeruginosa septic shock. Antimicrob Agents Chemother 56(4):2129–2131
100. Summary of product characteristics—Zevtera. 2013. https://www.medicines.org.uk/emc/medicine/29764
101. Direct Healthcare Professional Communication—new recommendations on dosing, duration and precautions for treatment of patients with Nosocomial Pneumonia with DORIBAX® (doripenem). 2012. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Product_Information/human/000891/WC500037148.pdf
102. Ceftazidime-Avibactam For Injection for Treatment of Complicated Intra-abdominal Infection (used in combination with metronidazole), Complicated Urinary Tract Infection including Acute Pyelonephritis, and Limited Use Indication: Aerobic Gram-negative Infections with Limited Treatment Options. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM425459.pdf
103. 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(13):925–942
104. Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC, Craig WA, Billeter M et al (2009) Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis 49(3):325–327

105. Pea F, Furlanut M, Negri C, Pavan F, Crapis M, Cristini F et al (2009) Prospectively validated dosing nomograms for maximizing the pharmacodynamics of vancomycin administered by continuous infusion in critically ill patients. Antimicrob Agents Chemother 53(5):1863–1867
106. Dailly E, Le Floch R, Deslandes G, Pannier M, Jolliet P (2008) Influence of glomerular filtration rate on the clearance of vancomycin administered by continuous infusion in burn patients. Int J Antimicrob Agents 31(6):537–539
107. Kees MG, Hilpert JW, Gnewuch C, Kees F, Voegeler S (2010) Clearance of vancomycin during continuous infusion in intensive care unit patients: correlation with measured and estimated creatinine clearance and serum cystatin C. Int J Antimicrob Agents 36(6):545–548
108. del Mar Fernandez de Gatta Garcia M, Revilla N, Calvo MV, Dominguez-Gil A, Sanchez Navarro A (2007) Pharmacokinetic/pharmacodynamic analysis of vancomycin in ICU patients. Intensive Care Med 33(2):279–85
109. Moellering RC Jr, Krogstad DJ, Greenblatt DJ (1981) Vancomycin therapy in patients with impaired renal function: a nomogram for dosage. Ann Intern Med 94(3):343–346
110. Ducharme MP, Slaughter RL, Edwards DJ (1994) Vancomycin pharmacokinetics in a patient population: effect of age, gender, and body weight. Ther Drug Monit 16(5):513–518
111. Baptista JP, Roberts JA, Sousa E, Freitas R, Deveza N, Pimentel J (2014) Decreasing the time to achieve therapeutic vancomycin concentrations in critically ill patients: developing and testing of a dosing nomogram. Crit Care 18(6):654
112. Jeurissen A, Sluyts I, Rutsaert R (2011) A higher dose of vancomycin in continuous infusion is needed in critically ill patients. Int J Antimicrob Agents 37(1):75–77
113. Conil JM, Georges B, Breden A, Ruiz S, Cougot P, Fourcade O et al (2014) Estimation of glomerular filtration rate to adjust vancomycin dosage in critically ill patients: superiority of the Chronic Kidney Disease Epidemiology Collaboration equation? Anaesth Intensive Care 42(2):178–184
114. De Waele JJ, Danneels I, Depuydt P, Decruyenaere J, Bourgeois M, Hoste E (2013) Factors associated with inadequate early vancomycin levels in critically ill patients treated with continuous infusion. Int J Antimicrob Agents 41(5):434–438
115. Roberts JA, Taccone FS, Udy AA, Vincent JL, Jacobs F, Lipman J (2011) Vancomycin dosing in critically ill patients: robust methods for improved continuous-infusion regimens. Antimicrob Agents Chemother 55(6):2704–2709
116. Pea F, Porreca L, Baraldo M, Furlanut M (2000) High vancomycin dosage regimens required by intensive care unit patients cotreated with drugs to improve haemodynamics following cardiac surgical procedures. J Antimicrob Chemother 45(3):329–335
117. Li J, Udy AA, Kirkpatrick CM, Lipman J, Roberts JA (2012) Improving vancomycin prescription in critical illness through a drug use evaluation process: a weight-based dosing intervention study. Int J Antimicrob Agents 39(1):69–72
118. Revilla N, Martin-Suarez A, Perez MP, Gonzalez FM, Fernandez de Gatta Mdel M (2010) Vancomycin dosing assessment in intensive care unit patients based on a population pharmacokinetic/pharmacodynamic simulation. Br J Clin Pharmacol 70(2):201–212
119. Blot S, Koulenti D, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, Kaukonen KM, Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Lipman J, Roberts JA (2014) Does contemporary vancomycin dosing achieve therapeutic targets in a heterogeneous clinical cohort of critically ill patients? Data from the multinational DALI study. Crit Care 18(3):R99
120. Spadaro S, Berselli A, Fogagnolo A, Capuzzo M, Ragazzi R, Marangoni E et al (2015) Evaluation of a protocol for vancomycin administration in critically patients with and without kidney dysfunction. BMC Anesthesiol 15:95
121. Kim AJ, Lee JY, Choi SA, Shin WG (2016) Comparison of the pharmacokinetics of vancomycin in neurosurgical and non-neurosurgical patients. Int J Antimicrob Agents 48(4):381–387
122. Domart Y, Pierre C, Clair B, Garaud JJ, Regnier B, Gibert C (1987) Pharmacokinetics of teicoplanin in critically ill patients with various degrees of renal impairment. Antimicrob Agents Chemother 31(10):1600–1604

123. Nakano T, Nakamura Y, Takata T, Irie K, Sano K, Imakyure O et al (2016) Change of teicoplanin loading dose requirement for incremental increases of systemic inflammatory response syndrome score in the setting of sepsis. Int J Clin Pharm 38:908–914
124. Barbot A, Venisse N, Rayeh F, Bouquet S, Debaene B, Mimoz O (2003) Pharmacokinetics and pharmacodynamics of sequential intravenous and subcutaneous teicoplanin in critically ill patients without vasopressors. Intensive Care Med 29(9):1528–1534
125. Morata L, Cuesta M, Rojas JF, Rodriguez S, Brunet M, Casals G et al (2013) Risk factors for a low linezolid trough plasma concentration in acute infections. Antimicrob Agents Chemother 57(4):1913–1917
126. Patel SS, Balfour JA, Bryson HM (1997) Fosfomycin tromethamine. A review of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy as a single-dose oral treatment for acute uncomplicated lower urinary tract infections. Drugs 53(4):637–656
127. Pea F, Viale P (2006) The antimicrobial therapy puzzle: could pharmacokinetic-pharmacodynamic relationships be helpful in addressing the issue of appropriate pneumonia treatment in critically ill patients? Clin Infect Dis 42(12):1764–1771
128. Parker S, Lipman J, Koulenti D, Dimopoulos G, Roberts JA (2013) What is the relevance of fosfomycin pharmacokinetics in the treatment of serious infections in critically ill patients? A systematic review. Int J Antimicrob Agents 42(4):289–293
129. Mimoz O, Montravers P, Paiva JA (2015) Continuous administration of linezolid in pneumonia: what is the level of proof? Intensive Care Med 41(1):157–159
130. Goncalves-Pereira J, Martins A, Povoa P (2010) Pharmacokinetics of gentamicin in critically ill patients: pilot study evaluating the first dose. Clin Microbiol Infect 16(8):1258–1263
131. Conil JM, Georges B, Breden A, Segonds C, Lavit M, Seguin T et al (2006) Increased amikacin dosage requirements in burn patients receiving a once-daily regimen. Int J Antimicrob Agents 28(3):226–230
132. Rea RS, Capitano B, Bies R, Bigos KL, Smith R, Lee H (2008) Suboptimal aminoglycoside dosing in critically ill patients. Ther Drug Monit 30(6):674–681
133. Marsot A, Guilhaumou R, Riff C, Blin O (2017) Amikacin in critically ill patients: a review of population pharmacokinetic studies. Clin Pharmacokinet 56(2):127–138
134. Pai MP, Cojutti P, Pea F (2014) Levofloxacin dosing regimen in severely morbidly obese patients (BMI >/=40 kg/m(2)) should be guided by creatinine clearance estimates based on ideal body weight and optimized by therapeutic drug monitoring. Clin Pharmacokinet 53(8):753–762
135. Graninger W, Zeitlinger M (2004) Clinical applications of levofloxacin for severe infections. Chemotherapy 50(Suppl 1):16–21
136. Bubalo JS, Munar MY, Cherala G, Hayes-Lattin B, Maziarz R (2009) Daptomycin pharmacokinetics in adult oncology patients with neutropenic fever. Antimicrob Agents Chemother 53(2):428–434
137. Mohr JF 3rd, Ostrosky-Zeichner L, Wainright DJ, Parks DH, Hollenbeck TC, Ericsson CD (2008) Pharmacokinetic evaluation of single-dose intravenous daptomycin in patients with thermal burn injury. Antimicrob Agents Chemother 52(5):1891–1893
138. MacArthur RD, Miller M, Albertson T, Panacek E, Johnson D, Teoh L et al (2004) Adequacy of early empiric antibiotic treatment and survival in severe sepsis: experience from the MONARCS trial. Clin Infect Dis 38:284–288
139. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C (2003) Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med 31(12):2742–2751
140. Sartelli M, Weber DG, Ruppe E, Bassetti M, Wright BJ, Ansaloni L et al (2016) Antimicrobials: a global alliance for optimizing their rational use in intra-abdominal infections (AGORA). World J Emerg Surg 11:33
141. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ,

Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP (2017) Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Medicine 43(3):304–377

142. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB et al (2016) Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 63(5):e61–e111
143. Cristallini S, Hites M, Kabtouri H, Roberts JA, Beumier M, Cotton F et al (2016) New regimen for continuous infusion of vancomycin in critically ill patients. Antimicrob Agents Chemother 60(8):4750–4756
144. Elyasi S, Khalili H (2016) Vancomycin dosing nomograms targeting high serum trough levels in different populations: pros and cons. Eur J Clin Pharmacol 72:777–788
145. Hanrahan TP, Kotapati C, Roberts MJ, Rowland J, Lipman J, Roberts JA et al (2015) Factors associated with vancomycin nephrotoxicity in the critically ill. Anaesth Intensive Care 43(5):594–599
146. Streetman DS, Nafziger AN, Destache CJ, Bertino AS Jr (2001) Individualized pharmacokinetic monitoring results in less aminoglycoside-associated nephrotoxicity and fewer associated costs. Pharmacotherapy 21(4):443–451
147. Bamgbola O (2016) Review of vancomycin-induced renal toxicity: an update. Ther Adv Endocrinol Metab 7(3):136–147
148. Golenia BS, Levine AR, Moawad IM, Yeh DD, Arpino PA (2013) Evaluation of a vancomycin dosing nomogram based on the modification of diet in renal disease equation in intensive care unit patients. J Crit Care 28:710–716
149. De Waele JJ, De Neve N (2014) Aminoglycosides for life-threatening infections: a plea for an individualized approach using intensive therapeutic drug monitoring. Minerva Anestesiol 80:1135–1142
150. Galvez R, Luengo C, Cornejo R, Kosche J, Romero C, Tobar E et al (2011) Higher than recommended amikacin loading doses achieve pharmacokinetic targets without associated toxicity. Int J Antimicrob Agents 38:146–151

Chapter 8
Antibiotic Dosing During Extracorporeal Membrane Oxygenation

Mohd. H. Abdul-Aziz, Kiran Shekar, and Jason A. Roberts

8.1 Introduction

Despite recent therapeutic advancements, conventional therapy for life-threatening forms of cardiac and/or respiratory failure remains predominantly reliant on high-dose vasopressor/inotrope support, mechanical ventilation, and renal replacement therapy. This is likely due to lack of other viable treatment strategies and less invasive medical devices to acutely support circulatory and respiratory function [1]. With modern refinements of technology however, extracorporeal membrane

M.H. Abdul-Aziz (✉)
Burns, Trauma and Critical Care Research Centre, The University of Queensland, Herston, Brisbane, QLD, Australia

School of Pharmacy, International Islamic University of Malaysia, Kuantan, Pahang, Malaysia
e-mail: mohd.abdulaziz1@uqconnect.edu.au

K. Shekar
Critical Care Research Group, The University of Queensland, Brisbane, QLD, Australia

Adult Intensive Care Unit, The Prince Charles Hospital, Brisbane, QLD, Australia

J.A. Roberts
Centre for Translational Anti-infective Pharmacodynamics, School of Pharmacy, The University of Queensland, 20 Cornwall Street PACE Building, Woolloongabba 4102, QLD, Australia

Burns, Trauma and Critical Care Research Centre, The University of Queensland, UQ Centre for Clinical Research, Building 71/918, Herston Rd, Herston, QLD 4029, Australia

Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Butterfield St, Herston, Brisbane, QLD 4029, Australia

Pharmacy Department, Royal Brisbane and Women's Hospital, Butterfield St, Herston, Brisbane, QLD 4029, Australia
e-mail: j.roberts2@uq.edu.au

A.A. Udy et al. (eds.), *Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill*, DOI 10.1007/978-981-10-5336-8_8

oxygenation (ECMO) is increasingly being advocated as a rescue therapy for patients with severe cardiorespiratory failure in the intensive care unit (ICU). ECMO is a form of extracorporeal life support, initially adapted from the cardiopulmonary bypass, that can be used temporarily to provide cardiac and/or respiratory support for critically ill patients who are refractory to maximal conventional medical management [2, 3]. Despite lacking any definitive evidence to guide its use, there has been a tremendous surge in the utilisation of ECMO worldwide, particularly after the H1N1 pandemic in 2009. The use of ECMO in the United States alone has dramatically increased (≥400%) within a 5-year period, and there are ≥130 active centres that are currently providing the service [4, 5].

8.2 The Patient on ECMO

The primary goal of ECMO is not to cure the underlying cause of cardiorespiratory failure, but rather to "buy time", through ensuring adequate oxygen delivery, whilst the underlying pathology is being assessed and treated [6]. This supportive technique provides an important bridge, either to organ recovery or to long-term support devices [2] and/or transplantation [7], and may even be used to facilitate therapeutic intervention (e.g. cardiopulmonary resuscitation) [8] and palliative care [2]. Whilst traditionally being used more frequently in neonates and paediatrics, the use of ECMO has markedly increased in adults since the publication of the CESAR trial [9]. Indications for ECMO can be divided into two groups; either cardiac or

Table 8.1 Common indications for extracorporeal membranous oxygenation (ECMO) support

Veno-venous ECMO	Veno-arterial ECMO
Common indications	Common indications
1. Acute respiratory distress syndrome	1. Cardiogenic shock
2. Aspiration syndrome	2. Chronic cardiomyopathy
3. Primary graft failure post-lung transplantation	3. Drug overdose/toxicity with profound cardiac depression
4. Severe bacterial or viral pneumonia	4. Myocarditis
	5. Primary graft failure post-heart or heart-lung transplantation
	6. Severe sepsis with profound cardiac depression
Other indications	Other indications
1. Airway obstruction	1. Acute anaphylaxis
2. Alveolar proteinosis	2. Cardiac arrhythmic storm refractory to other measures
3. Pulmonary contusion	3. Isolated cardiac trauma
4. Pulmonary haemorrhage with massive haemoptysis	4. Periprocedural support for high-risk percutaneous cardiac interventions
5. Smoke inhalation	5. Pulmonary embolism
6. Status asthmaticus	

respiratory aetiologies (Table 8.1). The main indications for ECMO in paediatric patients are: (a) cardiovascular failure secondary to congenital heart disease and; (b) respiratory failure due to persistent pulmonary hypertension, meconium aspiration syndrome, congenital diaphragmatic hernia, and severe acute respiratory distress syndrome (ARDS). In adults, ECMO is usually used in: (a) patients with cardiovascular failure after cardiac surgery and (b) patients with respiratory failure secondary to severe ARDS.

As ECMO is only a supportive therapy, effective drug treatment, which is directed at reversing the underlying disease, is critical to ensure therapeutic success. However, optimal drug therapy in critically ill patients is usually complicated by extreme physiological derangements that may consequently alter drug exposure and pharmacokinetics (PK) [10, 11]. The PK changes, which can occur from either pharmacological interventions or the natural course of critical illness, are suggested to be more pronounced in the presence of ECMO [12]. ECMO introduces additional variables, namely through the extracorporeal circuit itself and the effects of systemic inflammation due to prolonged use of such circuits, which may further alter drug exposure in severely ill patients who already have profound PK changes. For many important drugs (e.g. antibiotics and sedatives), it is being increasingly shown that ECMO markedly affects PK, and this phenomenon may likely impact treatment outcomes [13, 14].

8.3 Modes of ECMO

ECMO circuits are primarily made up of five fundamental components (Fig. 8.1): (a) large bore cannulae (access cannulae) for drainage of the venous system; (b) return cannulae to either the venous or arterial system; (c) an oxygenator that allows for addition of oxygen and removal of carbon dioxide; (d) a centrifugal blood pump for the propulsion of blood through the circuit and; (e) a thermoregulatory unit that allows for temperature control of the extracorporeal blood. This artificial circuit carries venous blood of the patient through an "artificial lung" (i.e. the oxygenator) where the blood becomes enriched with oxygen and has carbon dioxide removed. The blood then re-enters the patient circulation via either the venous or arterial system. The two most common forms of ECMO configuration are either veno-venous (VV) ECMO, where blood is drained from and returned to the venous system, or veno-arterial (VA) ECMO, where blood is drained from the venous system and returned to the arterial system.

8.3.1 VV ECMO

VV ECMO is used to provide adequate oxygenation and removal of carbon dioxide in critically ill patients with isolated respiratory failure. This approach is preferred in such a condition because there is relatively minimal risk of systemic embolism.

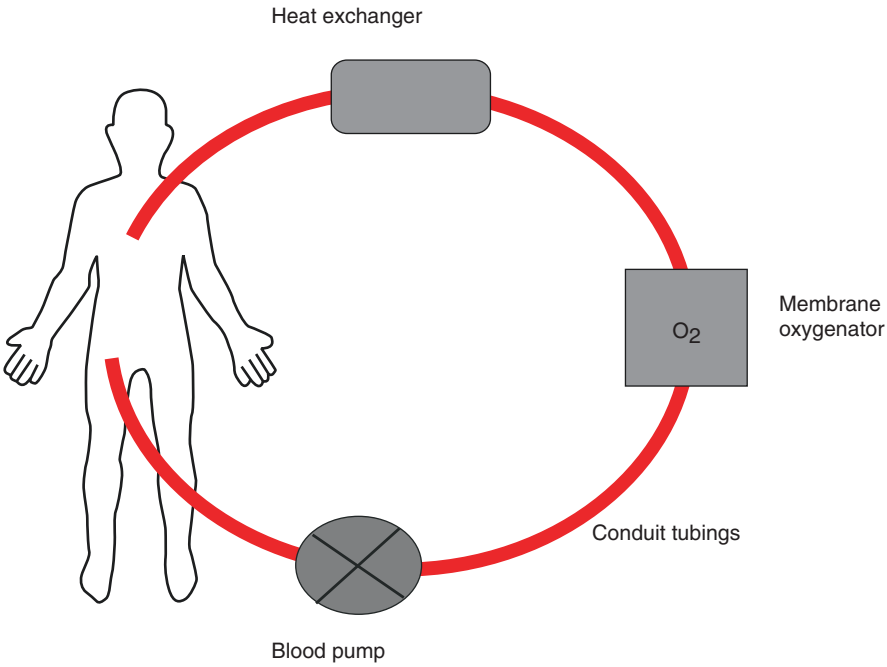

Fig. 8.1 Schematic representation of the main components of ECMO

The survival rate for VV ECMO in patients with severe respiratory failure is approximately 71% [15]. VV ECMO requires native cardiovascular function as the system provides no direct circulatory support. During VV ECMO, venous blood from the patient is drained from the inferior vena cava and/or superior vena cava via the femoral and/or the internal jugular veins. The blood then passes through an oxygenator, where gas exchange occurs, and it then returns to the venous system via a large bore cannula placed near the right atrium. The oxygenated blood is then pumped through the lungs to the left heart and systemic circulation. Therefore, this mode of extracorporeal support requires adequate native haemodynamics to ensure optimal delivery of oxygen to systemic circulation.

8.3.2 VA ECMO

VA ECMO provides support for both respiratory and cardiovascular function. However, in critically ill patients with preserved cardiovascular function and isolated respiratory failure, the VV configuration is commonly preferred to VA ECMO because it avoids the risks associated with large bore arterial access. The reported survival rate for VA ECMO in patients with severe cardiac failure is approximately 53% [4]. During VA ECMO, deoxygenated blood is drained from the right atrium

by either direct surgical cannulation or through a cannula positioned percutaneously in a major vein. Oxygenation and carbon dioxide removal occurs in the oxygenator before the blood is pumped back to the arterial system via a cannula placed either centrally in the ascending aorta or peripherally in a large artery.

8.4 Determinants of Pharmacokinetics on ECMO

Whilst ECMO is slowly finding its niche in adult intensive care, it is important that its "interactions" and influence on conventional medical management is fully understood. Patients on ECMO commonly receive numerous drugs, which include sedatives, analgesics, antibiotics, anticoagulants, and vasoactive agents, to reverse the underlying pathology. It follows that the success of ECMO and optimal patient outcomes rely substantially on successful use of these agents. Importantly, optimal use of some of these agents can be more challenging than others, e.g. although sedatives and vasoactive agents can be titrated to the desired clinical effect, there are no reliable clinical markers to guide antibiotic therapy in critically ill patients. Extreme alterations in PK of commonly used drugs, particularly increases in volume of distribution (V_d) and profound increases or decreases in renal drug clearance (CL), are common occurrences among critically ill patients who are not receiving ECMO and these phenomena may severely influence drug exposure [16–18]. Neonatal and paediatric ECMO studies have reported significant alteration in the PK of analgesics, antibiotics, antiepileptics, and sedatives [12, 19] but the extent of such changes remain poorly characterised, particularly in adult patients [20]. Emerging data however are suggesting that these PK changes may likely lead to altered dosing requirements and dosing that does not compensate for these changes are likely to fail [21, 22].

Although the relationship is highly complex and remains poorly described, ECMO has been generally shown to affect the PK of drugs in three ways: (a) drug sequestration by the circuit; (b) increased V_d; and (c) altered drug CL. These relationships are graphically described in Fig. 8.2.

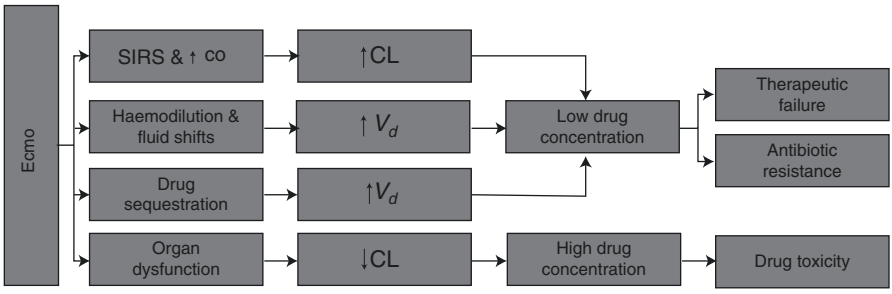

Fig. 8.2 Impact of ECMO on the pharmacokinetics of antibiotics. *CL* drug clearance, *CO* cardiac output, *ECMO* extracorporeal membranous oxygenation, V_d volume of distribution

8.4.1 ECMO and Drug Sequestration

Drug sequestration in ECMO circuits is a widely known but poorly characterised phenomenon. The intricate interaction between the circuit itself and the physicochemical properties of an individual drug may likely lead to significant perturbations in the PK of drugs, subsequently altering the dosing requirements for patients on ECMO [12, 20, 23].

8.4.1.1 Circuit Factors

ECMO circuits have relatively large surface area due to the attached conduit tubing and oxygenator membrane. It is therefore likely that significant amounts of drugs may be trapped on these surfaces over time, resulting in an increase in V_d and subsequent decreases in plasma drug concentrations [24–26]. It should be noted that saturation of binding is possible, meaning that increased dosing to overcome initial adsorption may later lead to high than desired concentrations. Conversely, the circuit may continue to release the sequestered drug even after drug administration stops, potentially prolonging the pharmacological effect in an undesirable manner. Sequestration of drugs can be influenced by several factors such as the design of the oxygenator, types of conduit tubing, and the composition of the priming solution [20].

Types of Oxygenator

The types of oxygenators available include the silicone rubber membrane oxygenator, polymethylpentene microporous hollow-fibre, and solid hollow-fibre oxygenator. In an in vitro experiment, Wildschut et al. demonstrated that >99% of fentanyl was lost within 180 min in an ECMO circuit with a silicone membrane oxygenator [27]. However, when the same experiment was performed using a microporous, hollow-fibre polypropylene oxygenator, fentanyl loss was only 66% at 180 min [27]. Nevertheless, current data suggest that oxygenators may only have a minor role in the context of drug loss [28–30]. In an ex vivo study, Preston et al. compared the losses of fentanyl and morphine in ECMO circuits with and without an oxygenator [30]. The average losses of fentanyl were 80% in circuits without oxygenators and 83–86% in circuits with different types of oxygenators. Similarly, morphine losses were approximately 40% in all circuits and were not determined by the presence of oxygenators.

Conduit Tubing

The conduit tubing however, which is mainly composed of polyvinyl chloride (PVC), may sequester drugs more than the oxygenators [12]. Despite the large surface area of the oxygenators, Preston et al. observed that most of fentanyl and morphine losses in their study occurred through the conduit tubing [30]. The PVC

tubing is available in unmodified and modified types but data comparing the two types are currently limited [20]. However, the newer modified (surface-coated) tubing has been shown to sequester a significant amount of fentanyl (30–40%) and morphine (35–58%) [31].

Age of the Circuit

Age of a circuit may also influence the level of drug sequestration [28, 32, 33]. In a single-dose in vitro study, Bhatt et al. observed that approximately 50% of morphine and 40% of lorazepam were extracted at 24 h by the circuit [34]. Additionally, the extent of sequestration also depends on the age of the circuit, with older circuits recording higher drug losses. This may partly explain the need to increase the dosing for sedatives over time for patients on ECMO [13, 14, 35].

Circuit Priming

Circuit priming has been theorised to alter the PK of drugs through increasing the circulating volume of the patient. The associated variables with circuit priming that may influence drug sequestration include the type of priming fluids, additional electrolytes, pH, and temperature. Collectively, these variables could affect protein binding of drugs, as well as adsorption onto the conduit tubing and oxygenator, although this phenomenon remains poorly characterised [36]. Haemodilution from priming solutions may increase V_d of drugs and demonstrates its greatest impact on hydrophilic drugs, which are mainly distributed in the plasma compartment. In an ex vivo ECMO model, Mehta et al. compared the effects of crystalloid-primed circuits vs. blood-primed circuits on the amount of various drugs sequestered overtime [37]. At 24 h, 71% of ampicillin, 17% of fosphenytoin, 33% of heparin, and 87% of fentanyl were lost in crystalloid-primed circuits. In blood-primed circuits, drug loss was 15% for ampicillin, 31% for fosphenytoin, 53% for heparin, and 100% for fentanyl. The implications of these findings are profound; statistically significant decreases in drug concentrations were observed regardless of the priming fluids used, and the reductions may potentially be clinically significant. It is most likely that priming related alterations in PK will be greatest in paediatrics rather than adults where the priming volume and surface area of tubing is much greater relative to patient size including the circulating blood (and extracellular fluid) volume.

8.4.1.2 Drug Factors

Various physicochemical properties of drugs, which include molecular size, degree of ionisation, lipophilicity, and plasma protein binding, may all influence the degree of drug sequestration in the ECMO circuits. Importantly, ex vivo data have demonstrated that the drugs with the highest degree of lipophilicity and protein binding are likely to be highly extracted by the circuits [24–26, 38].

Lipophilicity

Lipophilic drugs tend to be sequestered more in ECMO circuits because these agents are more soluble in organic components of the circuits. The measure of lipophilicity is usually designated by the *n*-octanol/water partition coefficient (log *P*); the degree of lipophilicity for a compound increases as the log *P* value increases [39]. The importance of this physicochemical property on drug sequestration is further highlighted by a recent ex vivo study by Shekar et al., which aimed to determine the degree of sequestration of commonly used drugs in ECMO circuits [26]. The majority of fentanyl (96%) and midazolam (87%) were lost in the circuit, whilst no significant loss of morphine was observed at 24 h. The findings may be explained by the higher value of log *P* for fentanyl (4.05) and midazolam (3.89) as opposed to morphine, which has a log *P* of 0.84. These observations corroborated the results of an earlier in vitro study by Wildschut et al., which demonstrated that log *P* values are associated with the degree of drug loss in ECMO circuits [27].

Protein Binding

For drugs with similar lipophilicity, the extent of protein binding may determine the degree of drug sequestration in ECMO circuits. In a recent ex vivo experiment, Shekar et al. demonstrated the influence of plasma protein binding on drug disposition in ECMO circuits [24]. Despite having a similar degree of lipophilicity (log *P* 2.3), the mean losses of thiopentone (88%) in the circuit was relatively higher when compared to that of ciprofloxacin (4%). The large difference in drug loss between the two drugs could be attributed to the degree of protein binding; whilst thiopentone is 80% bound, only 20–40% of ciprofloxacin is bound to plasma proteins.

8.4.2 ECMO and Increased Volume of Distribution

The use of ECMO may alter the V_d of drugs by several mechanisms: (a) drug sequestration by ECMO circuits; (b) haemodilution from priming solutions and; (c) critical illness and ECMO-related physiological changes. In many ways similar to critically ill patients who are not receiving ECMO, critical illness-related changes such as the systemic inflammatory response syndrome (SIRS) [40, 41] and fluid shifts [40–42] may likely increase the V_d of hydrophilic drugs. Additionally, patients on ECMO may have significant alterations in blood pH leading to further changes in drug distribution and protein binding. The activation of the renin-angiotensin system observed during VA ECMO may result in increased circulating blood volume and subsequently a larger V_d for several drugs [43].

Notably, most of the data concerning the impact of ECMO on V_d are mainly derived from ex vivo ECMO circuits and neonatal PK studies. Due to significant physiological and body composition differences, extrapolating these data to critically ill adult patients may potentially be misleading and should be performed with caution [12, 23].

8.4.3 ECMO and Drug Clearance

Drug CL is generally reduced in patients who are receiving ECMO [12]. However, the CL of some drugs may be increased initially due to increased cardiac output secondary to SIRS as well as aggressive fluid therapy and inotropic support [40]. As the disease progresses in a critically ill patient, myocardial depression occurs leading to decreased organ perfusion and microcirculatory failure eventually resulting in end-organ damage or in extreme cases, multiple organ dysfunction syndrome [44, 45]. This syndrome often includes renal and/or hepatic dysfunction that consequently results in a decrease in drug CL. The resulting accumulation of drugs and their metabolites in plasma increases the likelihood of toxicity [46].

8.4.3.1 Renal Dysfunction

The incidence of renal dysfunction in adults during VV ECMO and VA ECMO has been reported as 32% and 47%, respectively [4, 47]. Although the reasons for this phenomenon remain unclear, patients who receive ECMO are commonly critically ill and hence, often have a preceding hypoxia/hypoperfusion-related insult to their kidneys [44]. Non-pulsatile blood flow during VA ECMO is associated with a decrease in glomerular filtration rate [48]. However, in VV ECMO where the blood flow is pulsatile, the incidence of renal dysfunction is similarly high as compared to VA ECMO [4]. Decreased CL of drugs during ECMO as demonstrated in neonatal studies should be interpreted with caution and extrapolating these data to critically ill patients should be performed in the context of immature glomerular and tubular function in the newborn [49].

8.4.3.2 Hepatic Dysfunction

The impact of ECMO on drug metabolism is not well described. However, critically ill patients with severe sepsis and septic shock commonly demonstrate hepatic dysfunction, which reduces regional blood flow to the liver, therefore decreasing the metabolism and CL of some "high-clearance" hepatically cleared drugs. Additionally, the use of ECMO is associated with SIRS, and this phenomenon may likely decrease the expression and impair the functions of metabolising enzymes [50–53].

8.4.3.3 ECMO and Renal Replacement Therapy

Approximately 50% of patients on VV ECMO and 41% on VA ECMO may require some form of renal replacement therapy (RRT) [4]. Describing altered PK in this patient sub-population is highly challenging because different modes of RRT and ECMO are sometimes being used concomitantly and importantly, their interactions can be variable. This significantly limits the capability of population PK modelling

to characterise the resultant PK alterations. Given the scarcity of data, most clinical approaches to guide drug treatment could be considered arbitrary rather than being evidence-based. Available data however have highlighted the importance of therapeutic drug monitoring (TDM) due to the uncertain effect of significant PK alterations on drug dosing requirements associated with this sub-population [54, 55]. More research is urgently needed to guide effective dosing in critically ill patients receiving RRT whilst on ECMO support.

8.5 The Impact of ECMO on Specific Antibiotic Classes

ECMO on its own is not a disease-modifying intervention. Therefore, drug treatment that is directed to reverse the underlying pathology is essential to ensure overall therapeutic success. Notably, infections are one of the phenomena commonly associated with ECMO; between 1998 and 2008, 2418 infections were reported during 20,741 (11.7%) ECMO cases with an infection rate of 15.4 per 1000 ECMO days [56]. Importantly, the Extracorporeal Life Support Organization (ELSO) also reported that the treatment for those with an infection were likely to be complicated with a longer duration of ECMO, a longer duration of post-ECMO ventilator support as well as a higher prevalence of mortality than those without infection [56]. Therefore, the success of ECMO in critically ill patients with severe infections is heavily dependent on whether optimal antibiotic therapy is provided to these patients.

As described in earlier sections, important pathophysiological changes in critically ill patients receiving ECMO may alter antibiotic PK and consequently, impair pharmacokinetic/pharmacodynamic (PK/PD) target attainment [10]. Consequently, optimal dosing recommendations during ECMO may significantly different than that initially proposed for critically ill patients without ECMO support. It follows that sub-optimal antibiotic dosing in this patient population may not only promote adverse clinical consequences, but also increase the emergence of bacterial resistance [57]. Whilst sedatives and analgesics can be titrated to effect, there are currently no established guidelines to direct effective dosing of antibiotics for patients on ECMO. Furthermore, most of the available studies concerning ECMO were performed either in animals or paediatric patients, and it is therefore difficult to extrapolate the findings to critically ill adult patients.

8.5.1 Beta-Lactams

The beta-lactam antibiotics include penicillins, cephalosporins, monobactams, and carbapenems. The duration of time that the drug concentration remains above the minimum inhibitory concentration (MIC) of a pathogen during a dosing interval ($fT_{>MIC}$) is regarded as the optimal PK/PD index which best predicts their killing activity [58]. The % $fT_{>MIC}$ required for bactericidal effect is 60–70%, 50%, and

40% for cephalosporins, penicillins, and carbapenems, respectively [58]. However, recent clinical data suggest potential benefits from higher and longer antibiotic exposures than those described in pre-clinical studies [59–64]. It has been advocated that beta-lactam concentrations should be maintained at least four-to-five times MIC for extended periods during each dosing interval, particularly in patients with severe infections [65]. However, achieving such an exposure is a complex clinical challenge as the initiation of ECMO may introduce additional physiological insults to further impair beta-lactam exposures in critically ill patients who already have extreme PK changes.

Several ex vivo models [24, 25, 66] and small-scale clinical studies [55, 67–72] have evaluated the PK of various beta-lactam antibiotics with ECMO. In most studies, the PK of beta-lactam antibiotics were highly variable and largely unpredictable in the presence of ECMO support. This phenomenon may likely lead to subtherapeutic drug exposure and therapeutic failure, particularly in the treatment of pathogens with a high MIC [67, 69]. In a recent retrospective matched-cohort study, Donadello et al. investigated the impact of ECMO on the PK of meropenem and piperacillin/tazobactam in 26 critically ill patients [67]. In this study, ECMO support did not significantly alter the PK and PK/PD target attainment of the two beta-lactams (i.e. 40% $fT_{>4\times MIC}$ for meropenem and 50% $fT_{>4\times MIC}$ for piperacillin/tazobactam) against *Pseudomonas aeruginosa* when compared to non-ECMO controls. Nevertheless, the V_d was significantly larger and CL was significantly lower than those reported in healthy volunteers. Marked PK heterogeneity was also a prominent feature in the study and therefore, standard beta-lactam dosing is likely to fail in such patients. Of great concern, approximately one-third of the patient cohort did not achieve the optimal PK/PD target against *P. aeruginosa*. These findings are in-line with the observations of another case report [71] and a matched-cohort PK study by Shekar et al. [69]. Although conventional beta-lactam dosing may be sufficient for highly susceptible pathogens [67, 69], the available sparse data currently recommends that higher beta-lactam doses would need to be considered when treating less susceptible pathogens (e.g. *P. aeruginosa* and *Acinetobacter baumannii*), which are commonly isolated in the ICU [60].

As the presence of ECMO has not been found to significantly alter the PK of beta-lactam antibiotics, the recommended dosing strategies for critically ill patients without ECMO support can be applied in this patient population [10, 73]. Until robust PK data are available, regular dosing review aided by TDM is also warranted to maximise therapeutic outcomes [74].

8.5.2 Vancomycin

Vancomycin is a glycopeptide antibiotic and is a relatively hydrophilic drug. Some in vitro [75, 76] and in vivo animal studies [77] suggest that the bactericidal activity of the antibiotic is time-dependent whereas some have shown that the ratio of peak drug concentration (C_{max}) to MIC (C_{max}/MIC) to be equally important [78]. More recently, it has been generally accepted that achieving a high area under the

concentration-time curve during a 24-h period ($AUC_{0–24}$) to MIC ($AUC_{0–24}$/MIC) ratio is more predictive of clinical success. A $AUC_{0–24}$/MIC ratio of ≥400 is needed for optimal bacteriological and clinical outcome when treating patients with *Staphylococcus aureus* [79, 80]. Due to common clinical practice of measuring trough concentrations when this antibiotic is used, a trough concentration ranging between 15 and 20 mg/L is advocated for optimal outcome in hospital-acquired pneumonia and complicated infections [81, 82].

Most of the data available on the PK of antibiotics during ECMO support originated from neonatal studies, with vancomycin being the most frequently investigated [83–86]. The PK data of vancomycin during ECMO are somewhat conflicting; although an increase in V_d with a decrease in drug CL is largely anticipated [83–85], many of the newer studies have not corroborated this notion [87–90]. In a retrospective matched-cohort study, Donadello et al. compared the PK of vancomycin in critically ill patients with and without ECMO support [90]. In this study, ECMO initiation did not significantly alter the PK and PK/PD target attainment of vancomycin (i.e. $AUC_{0–24}$/MIC of ≥400 or plasma concentration of ≥20–30 mg/L) when compared to non-ECMO controls. Several plausible reasons may explain the dissociation between earlier neonatal data and current clinical studies. Neonates, as opposed to adults, may be more susceptible to V_d changes due to their smaller body composition and total body water. It is also reasonable to assume that the reduced vancomycin CL often seen in earlier studies stemmed from immature hepatic and renal function of the newborns rather than the ECMO circuitry itself [49]. Further, modern ECMO circuits utilise less priming fluids with less conduit tubing, and these may attenuate the impact of ECMO on vancomycin V_d.

Nevertheless, the PK of vancomycin in the Donadello et al. study is significantly different than those reported in healthy volunteers [90]. It is likely that these PK changes are more reflective of critical illness rather than ECMO itself. It is also worth noting that Donadello et al. employed continuous infusion (CI) with a higher-than-recommended vancomycin dosing regimen, which may potentially negate the ECMO-related PK changes. In a retrospective, observational PK study, Park et al. showed that conventional intermittent vancomycin dosing during ECMO may likely be a flawed dosing strategy [89]. In this study, 95% of ECMO patients achieved sub-optimal PK/PD target attainment with a vancomycin dosing regimen of 15–20 mg/kg every 8–12 h, and this phenomenon may have occurred for at least 3 days before dosing adjustment was made. A loading dose of 25–30 mg/kg followed by 30–40 mg/kg/day should be considered in critically ill patients receiving ECMO [91, 92].

8.5.3 Aminoglycosides

Although previous studies have suggested that achieving a C_{max}/MIC ratio of 10–12 predicts optimal outcome against Gram-negative pathogens [93], several investigators have since suggested that an $AUC_{0–24}$/MIC ratio of 80–160 better predicts aminoglycoside efficacy [94]. The PK of aminoglycosides are profoundly altered in severe infections [95–98], and this may be further exacerbated by ECMO leading to

sub-optimal plasma drug exposure. Aminoglycosides are also one of the best studied antibiotics in infants receiving ECMO. The PK disposition of gentamicin in infants receiving ECMO has been reported in several small clinical studies [19, 99–103]. These studies have reported relatively similar findings; the V_d of gentamicin is typically increased whilst CL is usually decreased with ECMO support. The implication of these findings has been the prolongation of dosing intervals when gentamicin is used in neonates on ECMO support. However, most of the studies were undertaken in the early 1990s and since then, major improvements have been made in ECMO technology as well as in the PK/PD knowledge of aminoglycosides. These have made the earlier PK data and dosing recommendations potentially irrelevant to current practice. More clinical studies are clearly needed in this area, particularly those which aim to describe the PK of aminoglycosides in adults during ECMO support. There are currently no clinical data available describing aminoglycoside PK in adult patients on ECMO support.

8.5.4 Quinolones

Quinolones display largely concentration-dependent kill characteristics with some time-dependent features [58]. It has been suggested that the $AUC_{0–24}$/MIC best predicts its bactericidal effect, even better than the C_{max}/MIC ratio, and at least 125 and 30 is required for optimal patient outcomes in the treatment of Gram-negative and Gram-positive infections, respectively [104–107].

There are limited clinical data available on the PK of fluoroquinolones in patients receiving ECMO [20]. In an ex vivo experiment, Shekar et al. employed closed-loop ECMO circuits to investigate the degree of sequestration of various drugs including ciprofloxacin [24]. No significant loss of the antibiotic was observed in the study and this suggests that the PK and PK/PD exposures of ciprofloxacin may not be impaired with ECMO support. Other members of the group such as levofloxacin and moxifloxacin are less lipophilic and demonstrate similar protein binding properties to ciprofloxacin [108]. Therefore, it is highly likely that these antibiotics have a similar degree of drug sequestration and consequently, require no dosing adjustment when ECMO support is initiated. However, more robust PK data are urgently required to corroborate this finding. Importantly, when this antibiotic class is used, dosing should seek to maximise the C_{max}/MIC ratio, as this ensures an optimal $AUC_{0–24}$/MIC ratio. These PK/PD goals may be achieved with a 400 mg 8-hourly or 600 mg 12-hourly for ciprofloxacin.

8.5.5 Linezolid

Linezolid belongs to an antibiotic class known as the oxazolidinones, which was developed for the treatment of Gram-positive infections. Rayner et al. reported that optimal linezolid activity correlates well with an $AUC_{0–24}$/MIC ratio of 80–120 [109]. Some in vivo animal studies also described linezolid as a time-dependent

antibiotic where a $fT_{>MIC}$ of 40% is required for optimal bactericidal effect [110, 111]. A standard dose of 600 mg 12-hourly commonly achieves these PK/PD targets in critically ill patients. The PK disposition of linezolid during ECMO was recently described in three critically ill patients by De Rosa et al. [112]. With standard linezolid dosing, the minimum conservative PK/PD targets (i.e. AUC_{0-24}/MIC ≥ 80 and $fT_{>MIC}$ ≥ 40%) were achieved against *methicillin-resistant S. aureus* (MRSA) with an MIC of ≤1 mg/L. However, the rate of target attainment decreases when the MRSA MIC is >1 mg/L. Although this study is the first and only report to date that describes the PK of linezolid during ECMO, the finding suggests that altered dosing strategies should be considered when the antibiotic is used to treat less susceptible pathogens [113, 114]. A "front-loading" regimen followed by continuous linezolid infusion has been suggested to improve PK/PD target attainment in critically ill patients; 1200 mg/24-h as continuous infusion following a 600 mg single dose (total 1800 mg for first 24 h) [114]. It is also imperative to emphasise that the PK of linezolid is highly variable in patients with severe infections and the phenomenon has been suggested to increase the likelihood of treatment failures and occurrence of adverse events in such patients [113, 115–119]. As such TDM of linezolid is beneficial in this respect and emerging data are suggesting that general TDM may optimise patient outcomes when the antibiotic is used in critically ill patients [113].

8.6 A Practical Approach to Antibiotic Dosing During ECMO

Despite a dramatic increase in global ECMO usage, there are currently no established guidelines to guide antibiotic dosing in critically ill patients on ECMO support. Most of the PK data concerning this area were derived from either in vitro or ex vivo experiments, as well as small-scale clinical studies that mainly investigated neonates [12]. It is therefore difficult to draw broad conclusions on how antibiotics should be dosed during ECMO, particularly in critically ill adult patients. In this respect, it would be prudent to use currently available data to optimise antibiotic dosing before more robust information becomes available. Importantly, dosing of antibiotics in this population should be in-line with the recommended dosing strategies for critically ill patients without ECMO support.

8.6.1 Choosing Antibiotics Based on Physicochemical Properties

Lipophilicity and protein binding are key determinants of drug loss in ECMO circuits. For lipophilic and highly protein-bound drugs, the effects of ECMO on PK may be more significant than those induced by critical illness depending on the extent of organ failure present in the patient [24–26]. By way of example, ceftriaxone,

which is ≥85% protein-bound, is likely to be highly adsorbed by the ECMO circuit [24], and therefore may not be an ideal antibiotic to be used for ECMO patients. In such a case, it would be prudent to choose another antibiotic with lower protein binding or if it is used, regular dosing review with TDM should be performed.

8.6.2 Altering Dosing Strategies for Antibiotics

To address the PK alterations associated with ECMO and critical illness, altered dosing approaches such as the use of higher doses or increased dosing frequency may be necessary to ensure effective antibiotic exposure [10]. Higher initial loading doses of hydrophilic antibiotics should be applied to compensate for the enlarged V_d. In a retrospective matched-cohort study, Donadello et al. showed that a loading dose of 35 mg/kg followed by CI administration of vancomycin provided optimal PK/PD exposures in ECMO patients, particularly in the earlier phase of therapy [90]. For time-dependent antibiotics (e.g. beta-lactams and vancomycin), the therapeutic potential of these agents may be maximised via CI or extended infusion dosing, which maintains higher concentrations throughout a dosing interval, as opposed to traditional intermittent bolus dosing [71, 90].

8.6.3 Therapeutic Drug Monitoring

Although altered dosing strategies can be employed to maximise antibiotic exposures, the inherent PK variability among critically ill patients means that some patients may still receive sub-optimal exposures with variable clinical responses. Therefore, TDM is highly warranted in this population and the approach would be advantageous, not only to prevent underdosing but also to minimise the risk of adverse effects during ECMO. Although minimal data currently exist in this patient population, TDM has been shown to be meritorious for aminoglycoside [120–122], beta-lactam [59, 123, 124], fluoroquinolone [124], glycopeptide [125], and linezolid [126] dosing in critically ill patients. In the presence of ECMO, TDM is strongly recommended to guide effective antibiotic treatment pending definitive clinical PK data.

8.7 Conclusion

ECMO may exacerbate significant antibiotic PK changes observed during critical illness leading to potential therapeutic failure or toxicity. Until robust dosing guidelines become available, physicochemical properties of antibiotics can be used to predict PK changes and consequently, guide effective antibiotic treatment in patients receiving ECMO. Antibiotic dosing in this patient population should also be in-line

with the recommended dosing strategies for critically ill patients without ECMO support. Regular review of dosing requirements with the aid of TDM would be appropriate, not only to prevent sub-optimal antibiotic dosing but also to minimise the likelihood of adverse effects during ECMO.

References

1. Shekar K (2014) Extracorporeal respiratory support: breaking conventions? Anaesth Intensive Care 42(2):175–177
2. Shekar K et al (2014) Extracorporeal life support devices and strategies for management of acute cardiorespiratory failure in adult patients: a comprehensive review. Crit Care 18(3):219
3. Brodie D, Bacchetta M (2011) Extracorporeal membrane oxygenation for ARDS in adults. N Engl J Med 365(20):1905–1914
4. Extracorporeal Life Support Organization (2017) ECLS registry report, international summary. Ann Arbor
5. Sauer CM, Yuh DD, Bonde P (2015) Extracorporeal membrane oxygenation use has increased by 433% in adults in the United States from 2006 to 2011. ASAIO J 61(1):31–36
6. Zapol WM, Kitz RJ (1972) Buying time with artificial lungs. N Engl J Med 286(12):657–658
7. Strueber M (2011) Bridges to lung transplantation. Curr Opin Organ Transplant 16(5):458–461
8. Thiagarajan RR et al (2009) Extracorporeal membrane oxygenation to support cardiopulmonary resuscitation in adults. Ann Thorac Surg 87(3):778–785
9. Peek GJ et al (2009) Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 374(9698):1351–1363
10. Tsai D, Lipman J, Roberts JA (2015) Pharmacokinetic/pharmacodynamic considerations for the optimization of antimicrobial delivery in the critically ill. Curr Opin Crit Care 21(5):412–420
11. Blot SI, Pea F, Lipman J (2014) The effect of pathophysiology on pharmacokinetics in the critically ill patient—concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev 77:3–11
12. Shekar K et al (2012) Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. J Crit Care 27(6):741.e9–741.18
13. Anton-Martin P et al (2017) A retrospective study of sedation and analgesic requirements of pediatric patients on extracorporeal membrane oxygenation (ECMO) from a single-center experience. Perfusion 32(3):183–191
14. Nigoghossian CD et al (2016) Effect of extracorporeal membrane oxygenation use on sedative requirements in patients with severe acute respiratory distress syndrome. Pharmacotherapy 36(6):607–616
15. Davies A et al (2009) Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. JAMA 302(17):1888–1895
16. Hirai K et al (2016) Augmented renal clearance in patients with febrile neutropenia is associated with increased risk for subtherapeutic concentrations of vancomycin. Ther Drug Monit 38(6):706–710
17. Udy AA et al (2014) Augmented renal clearance in the ICU: results of a multicenter observational study of renal function in critically ill patients with normal plasma creatinine concentrations*. Crit Care Med 42(3):520–527
18. Goncalves-Pereira J, Povoa P (2011) Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of beta-lactams. Crit Care 15(5):R206
19. Buck ML (2003) Pharmacokinetic changes during extracorporeal membrane oxygenation: implications for drug therapy of neonates. Clin Pharmacokinet 42(5):403–417

20. Ha MA, Sieg AC (2017) Evaluation of altered drug pharmacokinetics in critically ill adults receiving extracorporeal membrane oxygenation. Pharmacotherapy 37(2):221–235
21. Shekar K et al (2012) Increased sedation requirements in patients receiving extracorporeal membrane oxygenation for respiratory and cardiorespiratory failure. Anaesth Intensive Care 40(4):648–655
22. Shekar K et al (2012) Sedation during extracorporeal membrane oxygenation-why more is less. Anaesth Intensive Care 40(6):1067–1069
23. Sherwin J, Heath T, Watt K (2016) Pharmacokinetics and dosing of anti-infective drugs in patients on extracorporeal membrane oxygenation: a review of the current literature. Clin Ther 38(9):1976–1994
24. Shekar K et al (2015) Protein-bound drugs are prone to sequestration in the extracorporeal membrane oxygenation circuit: results from an ex vivo study. Crit Care 19:164
25. Shekar K et al (2015) Can physicochemical properties of antimicrobials be used to predict their pharmacokinetics during extracorporeal membrane oxygenation? Illustrative data from ovine models. Crit Care 19:437
26. Shekar K et al (2012) Sequestration of drugs in the circuit may lead to therapeutic failure during extracorporeal membrane oxygenation. Crit Care 16(5):R194
27. Wildschut ED et al (2010) Determinants of drug absorption in different ECMO circuits. Intensive Care Med 36(12):2109–2116
28. Wagner D et al (2013) In vitro clearance of dexmedetomidine in extracorporeal membrane oxygenation. Perfusion 28(1):40–46
29. Watt KM et al (2012) Pharmacokinetics and safety of fluconazole in young infants supported with extracorporeal membrane oxygenation. Pediatr Infect Dis J 31(10):1042–1047
30. Preston TJ et al (2007) In vitro drug adsorption and plasma free hemoglobin levels associated with hollow fiber oxygenators in the extracorporeal life support (ECLS) circuit. J Extra Corpor Technol 39(4):234–237
31. Preston TJ et al (2010) Modified surface coatings and their effect on drug adsorption within the extracorporeal life support circuit. J Extra Corpor Technol 42(3):199–202
32. Mulla H et al (2000) In vitro evaluation of sedative drug losses during extracorporeal membrane oxygenation. Perfusion 15(1):21–26
33. Dagan O et al (1993) Preliminary studies of the effects of extracorporeal membrane oxygenator on the disposition of common pediatric drugs. Ther Drug Monit 15(4):263–266
34. Bhatt-Meht V, Annich G (2005) Sedative clearance during extracorporeal membrane oxygenation. Perfusion 20(6):309–315
35. Caron E, Maguire DP (1990) Current management of pain, sedation, and narcotic physical dependency of the infant on ECMO. J Perinat Neonatal Nurs 4(1):63–74
36. Mulla HGL, Firmin RK, David RU (2001) Drug disposition during extracorporeal membrane oxygenation (ECMO). Paediatr Perinat Drug Ther 4(3):109–120
37. Mehta NM et al (2007) Potential drug sequestration during extracorporeal membrane oxygenation: results from an ex vivo experiment. Intensive Care Med 33(6):1018–1024
38. Harthan AA et al (2014) Medication adsorption into contemporary extracorporeal membrane oxygenator circuits. J Pediatr Pharmacol Ther 19(4):288–295
39. Rosenbaum S (2016) Basic pharmacokinetics and pharmacodynamics: an integrated textbook and computer simulation, 2nd edn. Wiley, Hoboken, p 576
40. Mc IRB et al (2010) Plasma concentrations of inflammatory cytokines rise rapidly during ECMO-related SIRS due to the release of preformed stores in the intestine. Lab Investig 90(1):128–139
41. Butler J et al (1996) Acute-phase responses to cardiopulmonary bypass in children weighing less than 10 kilograms. Ann Thorac Surg 62(2):538–542
42. Seghaye MC et al (1996) Inflammatory reaction and capillary leak syndrome related to cardiopulmonary bypass in neonates undergoing cardiac operations. J Thorac Cardiovasc Surg 112(3):687–697
43. Bartlett RH (1990) Extracorporeal life support for cardiopulmonary failure. Curr Probl Surg 27(10):621–705

44. Ulldemolins M et al (2011) Antibiotic dosing in multiple organ dysfunction syndrome. Chest 139(5):1210–1220
45. Parrillo JE et al (1990) Septic shock in humans. Advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. Ann Intern Med 113(3):227–242
46. Power BM et al (1998) Pharmacokinetics of drugs used in critically ill adults. Clin Pharmacokinet 34(1):25–56
47. Kielstein JT et al (2013) Renal function and survival in 200 patients undergoing ECMO therapy. Nephrol Dial Transplant 28(1):86–90
48. Many M et al (1967) The physiologic role of pulsatile and nonpulsatile blood flow. II. Effects on renal function. Arch Surg 95(5):762–767
49. Alcorn J, McNamara PJ (2003) Pharmacokinetics in the newborn. Adv Drug Deliv Rev 55(5):667–686
50. Richardson TA et al (2006) Expression of UDP-glucuronosyltransferase isoform mRNAs during inflammation and infection in mouse liver and kidney. Drug Metab Dispos 34(3):351–353
51. Rivory LP, Slaviero KA, Clarke SJ (2002) Hepatic cytochrome P450 3A drug metabolism is reduced in cancer patients who have an acute-phase response. Br J Cancer 87(3):277–280
52. Siewert E et al (2000) Hepatic cytochrome P450 down-regulation during aseptic inflammation in the mouse is interleukin 6 dependent. Hepatology 32(1):49–55
53. Abdel-Razzak Z et al (1993) Cytokines down-regulate expression of major cytochrome P-450 enzymes in adult human hepatocytes in primary culture. Mol Pharmacol 44(4):707–715
54. Aebi C et al (1997) Intravenous ribavirin therapy in a neonate with disseminated adenovirus infection undergoing extracorporeal membrane oxygenation: pharmacokinetics and clearance by hemofiltration. J Pediatr 130(4):612–615
55. Lindsay CA, Bawdon R, Quigley R (1996) Clearance of ticarcillin-clavulanic acid by continuous venovenous hemofiltration in three critically ill children, two with and one without concomitant extracorporeal membrane oxygenation. Pharmacotherapy 16(3):458–462
56. Bizzarro MJ et al (2011) Infections acquired during extracorporeal membrane oxygenation in neonates, children, and adults. Pediatr Crit Care Med 12(3):277–281
57. Abdul-Aziz MH et al (2015) Applying pharmacokinetic/pharmacodynamic principles in critically ill patients: optimizing efficacy and reducing resistance development. Semin Respir Crit Care Med 36(1):136–153
58. Craig WA (1998) Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 26(1):1–10; quiz 11-2
59. Pea F et al (2017) Might real-time pharmacokinetic/pharmacodynamic optimisation of high-dose continuous-infusion meropenem improve clinical cure in infections caused by KPC-producing Klebsiella pneumoniae? Int J Antimicrob Agents 49(2):255–258
60. Rhodes NJ et al (2015) Defining clinical exposures of cefepime for Gram-negative bloodstream infections that are associated with improved survival. Antimicrob Agents Chemother 60(3):1401–1410
61. Aitken SL et al (2015) Cefepime free minimum concentration to minimum inhibitory concentration (fCmin/MIC) ratio predicts clinical failure in patients with Gram-negative bacterial pneumonia. Int J Antimicrob Agents 45(5):541–544
62. Crandon JL et al (2010) Clinical pharmacodynamics of cefepime in patients infected with Pseudomonas aeruginosa. Antimicrob Agents Chemother 54(3):1111–1116
63. McKinnon PS, Paladino JA, Schentag JJ (2008) Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int J Antimicrob Agents 31(4):345–351
64. Tam VH et al (2002) Pharmacodynamics of cefepime in patients with Gram-negative infections. J Antimicrob Chemother 50(3):425–428
65. Osthoff M et al (2016) Prolonged administration of beta-lactam antibiotics—a comprehensive review and critical appraisal. Swiss Med Wkly 146:w14368
66. Leven C et al (2017) Ex vivo model to decipher the impact of extracorporeal membrane oxygenation on beta-lactam degradation kinetics. Ther Drug Monit 39(2):180–184

67. Donadello K et al (2015) beta-Lactam pharmacokinetics during extracorporeal membrane oxygenation therapy: a case-control study. Int J Antimicrob Agents 45(3):278–282
68. Welsch C et al (2015) Alveolar and serum concentrations of imipenem in two lung transplant recipients supported with extracorporeal membrane oxygenation. Transpl Infect Dis 17(1):103–105
69. Shekar K et al (2014) The combined effects of extracorporeal membrane oxygenation and renal replacement therapy on meropenem pharmacokinetics: a matched cohort study. Crit Care 18(6):565
70. Cies JJ et al (2014) Pharmacokinetics of continuous-infusion meropenem in a pediatric patient receiving extracorporeal life support. Pharmacotherapy 34(10):e175–e179
71. Shekar K et al (2013) Altered antibiotic pharmacokinetics during extracorporeal membrane oxygenation: cause for concern? J Antimicrob Chemother 68(3):726–727
72. Ahsman MJ et al (2010) Pharmacokinetics of cefotaxime and desacetylcefotaxime in infants during extracorporeal membrane oxygenation. Antimicrob Agents Chemother 54(5):1734–1741
73. Roberts JA, Kumar A, Lipman J (2017) Right dose, right now: customized drug dosing in the critically ill. Crit Care Med 45(2):331–336
74. Jager NG et al (2016) Therapeutic drug monitoring of anti-infective agents in critically ill patients. Expert Rev Clin Pharmacol 9(7):961–979
75. Lowdin E, Odenholt I, Cars O (1998) In vitro studies of pharmacodynamic properties of vancomycin against Staphylococcus aureus and Staphylococcus epidermidis. Antimicrob Agents Chemother 42(10):2739–2744
76. Larsson AJ et al (1996) The concentration-independent effect of monoexponential and biexponential decay in vancomycin concentrations on the killing of Staphylococcus aureus under aerobic and anaerobic conditions. J Antimicrob Chemother 38(4):589–597
77. Chambers HF, Kennedy S (1990) Effects of dosage, peak and trough concentrations in serum, protein binding, and bactericidal rate on efficacy of teicoplanin in a rabbit model of endocarditis. Antimicrob Agents Chemother 34(4):510–514
78. Knudsen JD et al (2000) Pharmacodynamics of glycopeptides in the mouse peritonitis model of Streptococcus pneumoniae or Staphylococcus aureus infection. Antimicrob Agents Chemother 44(5):1247–1254
79. Zelenitsky S et al (2013) Vancomycin pharmacodynamics and survival in patients with methicillin-resistant Staphylococcus aureus-associated septic shock. Int J Antimicrob Agents 41(3):255–260
80. Moise-Broder PA et al (2004) Pharmacodynamics of vancomycin and other antimicrobials in patients with Staphylococcus aureus lower respiratory tract infections. Clin Pharmacokinet 43(13):925–942
81. Kalil AC et al (2016) Management of adults with hospital-acquired and ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 63(5):e61–e111
82. Rybak MJ et al (2009) Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis 49(3):325–327
83. Mulla H, Pooboni S (2005) Population pharmacokinetics of vancomycin in patients receiving extracorporeal membrane oxygenation. Br J Clin Pharmacol 60(3):265–275
84. Buck ML (1998) Vancomycin pharmacokinetics in neonates receiving extracorporeal membrane oxygenation. Pharmacotherapy 18(5):1082–1086
85. Amaker RD, DiPiro JT, Bhatia J (1996) Pharmacokinetics of vancomycin in critically ill infants undergoing extracorporeal membrane oxygenation. Antimicrob Agents Chemother 40(5):1139–1142
86. Hoie EB et al (1990) Vancomycin pharmacokinetics in infants undergoing extracorporeal membrane oxygenation. Clin Pharm 9(9):711–715

87. Moore JN et al (2016) A population pharmacokinetic model for vancomycin in adult patients receiving extracorporeal membrane oxygenation therapy. CPT Pharmacometrics Syst Pharmacol 5(9):495–502
88. Wu CC et al (2016) Pharmacokinetics of vancomycin in adults receiving extracorporeal membrane oxygenation. J Formos Med Assoc 115(7):560–570
89. Park SJ et al (2015) Trough concentrations of vancomycin in patients undergoing extracorporeal membrane oxygenation. PLoS One 10(11):e0141016
90. Donadello K et al (2014) Vancomycin population pharmacokinetics during extracorporeal membrane oxygenation therapy: a matched cohort study. Crit Care 18(6):632
91. Cristallini S et al (2016) New regimen for continuous infusion of vancomycin in critically ill patients. Antimicrob Agents Chemother 60(8):4750–4756
92. Roberts JA et al (2011) Vancomycin dosing in critically ill patients: robust methods for improved continuous-infusion regimens. Antimicrob Agents Chemother 55(6):2704–2709
93. Kashuba AD et al (1999) Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. Antimicrob Agents Chemother 43(3):623–629
94. Drusano GL et al (2007) Back to the future: using aminoglycosides again and how to dose them optimally. Clin Infect Dis 45(6):753–760
95. Roger C et al (2016) Impact of 30 mg/kg amikacin and 8 mg/kg gentamicin on serum concentrations in critically ill patients with severe sepsis. J Antimicrob Chemother 71(1):208–212
96. Roger C et al (2015) Standard dosing of amikacin and gentamicin in critically ill patients results in variable and subtherapeutic concentrations. Int J Antimicrob Agents 46(1):21–27
97. de Montmollin E et al (2014) Predictors of insufficient amikacin peak concentration in critically ill patients receiving a 25 mg/kg total body weight regimen. Intensive Care Med 40(7):998–1005
98. Taccone FS et al (2010) Revisiting the loading dose of amikacin for patients with severe sepsis and septic shock. Crit Care 14(2):R53
99. Dodge WF et al (1994) Population pharmacokinetic models: effect of explicit versus assumed constant serum concentration assay error patterns upon parameter values of gentamicin in infants on and off extracorporeal membrane oxygenation. Ther Drug Monit 16(6):552–559
100. Bhatt-Mehta V, Johnson CE, Schumacher RE (1992) Gentamicin pharmacokinetics in term neonates receiving extracorporeal membrane oxygenation. Pharmacotherapy 12(1):28–32
101. Munzenberger PJ, Massoud N (1991) Pharmacokinetics of gentamicin in neonatal patients supported with extracorporeal membrane oxygenation. ASAIO Trans 37(1):16–18
102. Cohen P et al (1990) Gentamicin pharmacokinetics in neonates undergoing extracorporal membrane oxygenation. Pediatr Infect Dis J 9(8):562–566
103. Southgate WM, DiPiro JT, Robertson AF (1989) Pharmacokinetics of gentamicin in neonates on extracorporeal membrane oxygenation. Antimicrob Agents Chemother 33(6):817–819
104. Zelenitsky SA, Ariano RE (2010) Support for higher ciprofloxacin AUC 24/MIC targets in treating Enterobacteriaceae bloodstream infection. J Antimicrob Chemother 65(8):1725–1732
105. Drusano GL et al (2004) Relationship between fluoroquinolone area under the curve: minimum inhibitory concentration ratio and the probability of eradication of the infecting pathogen, in patients with nosocomial pneumonia. J Infect Dis 189(9):1590–1597
106. Forrest A et al (1993) Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 37(5):1073–1081
107. Peloquin CA et al (1989) Evaluation of intravenous ciprofloxacin in patients with nosocomial lower respiratory tract infections. Impact of plasma concentrations, organism, minimum inhibitory concentration, and clinical condition on bacterial eradication. Arch Intern Med 149(10):2269–2273
108. Wishart DS et al (2006) DrugBank: a comprehensive resource for in silico drug discovery and exploration. Nucleic Acids Res 34(Database issue):D668–D672
109. Rayner CR et al (2003) Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. Clin Pharmacokinet 42(15):1411–1423

110. Andes D et al (2002) In vivo pharmacodynamics of a new oxazolidinone (linezolid). Antimicrob Agents Chemother 46(11):3484–3489
111. Buchanan LV et al (2002) Time-dependent antibacterial effects of linezolid in experimental rabbit endocarditis. J Antimicrob Chemother 50(3):440–442
112. De Rosa FG et al (2013) Pharmacokinetics of linezolid during extracorporeal membrane oxygenation. Int J Antimicrob Agents 41(6):590–591
113. Sazdanovic P et al (2016) Pharmacokinetics of linezolid in critically ill patients. Expert Opin Drug Metab Toxicol 12(6):595–600
114. Minichmayr IK et al (2017) Clinical determinants of target non-attainment of linezolid in plasma and interstitial space fluid: a pooled population pharmacokinetic analysis with focus on critically ill patients. Clin Pharmacokinet 56(6):617–633
115. Taubert M et al (2016) Predictors of inadequate linezolid concentrations after standard dosing in critically ill patients. Antimicrob Agents Chemother 60(9):5254–5261
116. Zoller M et al (2014) Variability of linezolid concentrations after standard dosing in critically ill patients: a prospective observational study. Crit Care 18(4):R148
117. Yagi T et al (2013) Plasma exposure of free linezolid and its ratio to minimum inhibitory concentration varies in critically ill patients. Int J Antimicrob Agents 42(4):329–334
118. Dong H et al (2011) Clinical pharmacokinetic/pharmacodynamic profile of linezolid in severely ill intensive care unit patients. Int J Antimicrob Agents 38(4):296–300
119. Adembri C et al (2008) Linezolid pharmacokinetic/pharmacodynamic profile in critically ill septic patients: intermittent versus continuous infusion. Int J Antimicrob Agents 31(2):122–129
120. Bartal C et al (2003) Pharmacokinetic dosing of aminoglycosides: a controlled trial. Am J Med 114(3):194–198
121. Streetman DS et al (2001) Individualized pharmacokinetic monitoring results in less aminoglycoside-associated nephrotoxicity and fewer associated costs. Pharmacotherapy 21(4):443–451
122. van Lent-Evers NA et al (1999) Impact of goal-oriented and model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: a cost-effectiveness analysis. Ther Drug Monit 21(1):63–73
123. De Waele JJ et al (2014) Therapeutic drug monitoring-based dose optimisation of piperacillin and meropenem: a randomised controlled trial. Intensive Care Med 40(3):380–387
124. Scaglione F et al (2009) Feedback dose alteration significantly affects probability of pathogen eradication in nosocomial pneumonia. Eur Respir J 34(2):394–400
125. Ye ZK, Tang HL, Zhai SD (2013) Benefits of therapeutic drug monitoring of vancomycin: a systematic review and meta-analysis. PLoS One 8(10):e77169
126. Pea F et al (2010) Therapeutic drug monitoring of linezolid: a retrospective monocentric analysis. Antimicrob Agents Chemother 54(11):4605–4610

Chapter 9
Therapeutic Drug Monitoring: More Than Avoiding Toxicity

Jana Stojanova and Sonia Luque

9.1 Introduction

Therapeutic drug monitoring (TDM) is a clinical science centered around the quantification of drug concentrations in bodily fluids, most often serum or plasma derived from a venous blood sample. This may be for the purposes of determining lack of response (suspected poor compliance or dosing/administration errors, or of unknown cause), elevated levels following intentional or unintentional overdosing; however most often it is used for adjusting the course of therapy to achieve optimal concentrations in the systemic circulation where a "therapeutic range" or target has been defined. TDM is traditionally applied to a finite set of drugs including a limited number of antibiotics, early generation anti-epileptics, mood stabilizers and antipsychotics, immunosuppressants, specific anticancer agents and other, often older, drugs such as digoxin and theophylline. Commercially available immunoassays encompass the most widely used technique to determine drugs that are commonly monitored, principally because procedural aspects are simplified, costs are lower, and the turnaround time is faster.

J. Stojanova (✉)
University of Valparaiso, Valparaíso, Chile
e-mail: jana.stojanova@uv.cl

S. Luque
Pharmacy Service, Parc de Salut Mar, Barcelona, Spain
e-mail: sluque@parcdesalutmar.cat

A.A. Udy et al. (eds.), *Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill*, DOI 10.1007/978-981-10-5336-8_9

Professional societies and individual authors have put forward characteristics for drugs to be considered candidates for TDM [1]:

- There is a relationship between systemic concentrations and efficacy or toxicity, and this relationship has been evidenced and defined.
- Knowledge of the concentration would impact clinical decision making: adjustment of dose would be difficult or impossible to perform based on clinical observation alone.
- The relationship between the dose and circulating concentrations is poor, and large inter-patient variability exists.
- A narrow therapeutic range; that is, the concentration required for efficacy is close to concentrations where toxicity might be observed.

While this list aims to orient a rational application of the discipline, it has driven common use to a limited list of drugs that are considered classic TDM candidates, primarily selected due to their narrow therapeutic indices; in other words, to avoid toxicity at traditionally used doses. Large inter-patient variability is an important criterion; however prior to market this is often evaluated during trials in healthy subjects or relatively homogenous target populations. Additionally, in modern drug development, strategies are employed to limit the causes of inter-patient variation observed in earlier generations of drugs, namely absorption and hepatic transformation. Care is also taken to determine toxicity at standard dosing. Thus, as concerns drug development, regulation, and health policy, TDM based on the definition and scope above has had limited clinical application, and this has continued as newer drugs have emerged.

The relationship between dose and systemic concentration is particularly poor and unpredictable in special populations liable to different and/or dynamically changing pharmacokinetics [2]. In these patients, it might be difficult to gauge if doses and administration regimens used result in appropriate systemic concentrations. In general terms, they include patients at extremes of age, complex drug regimens with likely interactions between co-administered drugs, pregnant women, and obese patients. Disease processes where pharmacokinetics may differ from an "average" patient chronically, and alter further with acute disease, include cystic fibrosis, patients with renal and hepatic disease, and hematological malignancy, amongst others. Acute and severe pathophysiological processes that can influence pharmacokinetics include sepsis, septic shock, severe burns, traumatic brain injury, major surgery, organ transplantation, and pancreatitis.

Adequate antimicrobial concentrations for efficacy are especially pertinent in the critically ill patient, in whom unique pharmacokinetic changes may result in essentially diluted concentrations resulting from standard dosing regimens. Further, illness severity and disease processes may impact access to the site of infection, and infectious organisms are often less sensitive [3]. In this context, careful dosing based on drug concentrations may improve efficacy, help to avoid resistance, or detect and control for it if it emerges during the course of treatment [4–6]. This theoretical clinical need would augment the list of drugs that may require TDM beyond the traditional list for which immunoassays are available, provided suitable target concentrations can be established.

While immunoassays are used in health care systems worldwide, clinical chemistry laboratories providing a specialized service based on in-house methods and chromatographic techniques are relatively few. Instrumentation involved can include High Performance Liquid Chromatography (HPLC) or LC separation, with ultraviolet (UV), mass spectrometry (MS), and more recently with tandem MS detection, which provides additional sensitivity and specificity, improved throughput and turnaround, reduced sample volumes and analysis of multiple drugs simultaneously [7]. Specific drug assays, especially for older candidate TDM drugs, might be standardized and approved by regulatory bodies, while emerging assays pose challenges to standardize between centers, and participation in proficiency testing schemes is advocated. Development of new immunoassays and improvement of existing ones by the diagnostic industry has been limited in responding to clinical need. In deed, insufficient analytical quality associated with specific immunoassays may be part of the limited acceptance of TDM in clinical practice. The clinical chemistry laboratory can thus provide an invaluable service when it is positioned to articulate with clinical teams. A dedicated TDM program may contribute to ensuring a rational approach to requests, appropriate sampling and recording of complementary information, and foster quality control and ongoing education.

9.2 Beyond "Numbers Only" TDM: Additional Considerations for Antimicrobial Drugs

Across the traditional list of TDM candidate drugs, a drug level is taken at a single time point, and related to a range representing a margin of efficacy and absence of toxicity within a given population. This is typically a trough level, taken at the end of a dose interval, but could be at any point during the dosing interval that best relates to the area under the concentration–time curve (AUC). Taking a single sample is considered convenient and cost-effective; however, timing must be precise.

Antimicrobial activity for a given class of antimicrobial drugs is best described by one of three pharmacokinetic/pharmacodynamic (PK/PD) models: concentration-dependent, contingent on the drug's maximal concentration above the microorganism's minimum inhibitory concentration for the same drug (C_{max}/MIC); time-dependent, dependent on the duration that the concentration is above the MIC(%T > MIC); and concentration- and time-dependent, contingent on AUC/MIC [8]. For drugs where toxicity is observed at clinical dosing schedules, such as the aminoglycosides and vancomycin, this often relates to accumulated exposure and might be best represented by AUC.

The AUC for a given dose interval can be calculated by a variety of means; however, most involve multiple samples and require specialized knowledge. Dose adaptation based on Bayesian forecasting and control, also referred to as Bayesian feedback and Target Concentration Intervention, promises several advantages. Calculations require prior information, including patient characteristics, and pharmacokinetic parameters for the drug from a similar population to the patient being treated.

Advantages of using Bayesian dose adaptation software:

- Allows calculating an initial dose or loading dose
- It is not necessary to wait for steady state to be achieved, and TDM can proceed from the first dosing interval
- Allows calculating the AUC, and determining AUC-based outcome measures
- AUC can be calculated with a minimum number of samples, often a single sample
- Time of sampling is more flexible. An inadvertently taken sample can be useful so long as sampling time is accurately taken into account
- If a visual representation of the concentration–time curve is provided, this is useful for educating patients (when relevant) or staff involved in the TDM process
- For antimicrobial drugs, MIC can be included for an optimal PK/PD target

Beyond logistical challenges and the learning curve for implementation, one disadvantage of some of these software is an inability to include covariates that are not traditonal PK covariates. Biomarkers related to hepatic metabolism pose a particular challenge, as they are typically surrogates, and may vary between drugs. Examples include liver enzymes, C-reactive protein [9], and genotypes of genes of metabolic enzymes that exhibit polymorphism. Some experienced practitioners use the population modelling software NONMEM [10] for Bayesian dose adaptation in individuals, but we will foscus on specific tools here.

9.2.1 Available Dose Adaptation Tools for Clinical Use

There has been an interest in dose adaption since the 1970s; however, few centers worldwide apply the use of dedicated software to routine TDM. While there are many options, we will focus on tools that employ Bayesian methods, and have relatively large drug libraries or can accommodate additional models. Generally, these are academic initiatives, or commence as such. Most are Windows based, although some overcome system interoperability by providing web versions, also permitting use on personal smart devices. For an excellent historical review and evaluation, the reader is referred to Fuchs et al. [11].

USC*PACK was released in 1973 and represents an initiative from the Laboratory of Applied Pharmacokinetics of the University of Southern California [12]. Of the various software within the pack, MM-USC*PACK permits dose adaptation. The software has continually evolved, was briefly renamed RightDose but subsequently superseded by BestDose, which is currently being actively and commercially developed [13]. BestDose and predecessors are unique amongst the software described here in that they are based on nonparametric methods.

MWPharm was developed in 1982 at the Department of Pharmacology and Pharmacotherapy of the University of Groningen [14]. Mediware, a company originating from Charles University, Prague, continued development of the software from the late 1980s. The DOS version has been used since the 1990s in clinical

pharmacology departments, including the University Medical Centre of Groningen, and national training programs for clinical pharmacists and pharmacologists in the Netherlands. Windows versions of the software have been developed by Mediware, the latest being MWPharm++ released in 2014. It is one of the few software that permits interfacing with hospital inpatient systems through Mirth TM Connect Technology. MWPharm Online is a recently released browser version.

RxKinetics is a suite of software tools for pharmacists, including Bayesian dose adaptation tools, developed by Rick Tharp, pharmacist and certified developer [15]. Antibiotic Kinetics and APK offer one-compartment models, while Kinetics offers multi-compartment models. In addition to Windows versions, Antibiotic Kinetics and APK offer versions for smart devices, and Antibiotic Kinetics offers an inexpensive iPhone application. Analyses for non-steady-state conditions are a recent initiative [16]. The website fosters an online community of users.

Two commercial solutions from the United States were released in the 1990s. Abbott Laboratories released Abbottbase Pharmacokinetic Systems [17]; however, it is no longer distributed. The original software was used widely in the United States, and is widely cited. T.D.M.S. 2000 by Healthware Incorporated was released in the 1990s and continues to be distributed [18]. A trial version permits individual calculations without the ability to save data, and is widely used.

TCIWorks, Target Concentration Intervention software, was released in 2011 and is a joint initiative of collaborators from the University of Otago, Dunedin, and the University of Queensland, Brisbane [19]. It has been widely used in Australia, primarily for challenging scenarios involving traditional TDM candidate drugs and where estimation of AUC has been advocated. TCIworks can be used on systems supporting JAVA applications, including Windows, Linux, and Mac, and is free of charge. The website is currently inaccessible and it is unclear if the software will continue to be developed; however, available versions of the software continue to be used.

DoseMe is a comprehensive software released in 2013 by an Australian proprietary company of the same name [20]. It appears to offer an extremely easy to use interface, and is supported on all platforms (Windows, Mac, Linux, Android, and iOS devices). Pricing is not disclosed on the website but appears to be in the format of an annual fee to clinical institutions. Finally, InsightRx is a recent spin-off from the University of California, San Fransisco, currently undergoing pilot studies for Busulfan and Vancomycin.

A unique initiative is the web-based service provided by the Limoges University Hospital, France [21]. While immunosuppressant dosing is the specialty (ImmunoSuppressant Bayesian dose Adjustment, ISBA platform), the more recent PK-JUST platform covers other drugs, including aminoglycoside and glycopeptide antibiotics. Clinical area is taken into account, including ICU, hematology, pediatrics, and aged care. Users enter drug levels through a form, modelling is performed and reviewed by a pharmacologist, and a report generated including dosing suggestions, a modelled pharmacokinetic curve, and historical concentration plots when relevant. The average turnaround time is 2 h. To date, the portal is free to use for international users, and a small fee is applied for national requests.

9.3 Pathophysiological Changes in the Critically Ill Patient

While other chapters of this book elaborate pathophysiological changes in the critically ill patient in greater detail, we will briefly cover some aspects here to consider the impact on circulating drug concentrations (Table 9.1). Pathophysiological changes are dynamic in these patients, and are liable to change and influence plasma concentrations over the course of therapy.

Inflammatory processes in severe infection may cause third spacing, which, in addition to supportive measures, can greatly impact the volume of distribution of hydrophilic drugs, resulting in doubled volume of distribution compared to patients who are not critically ill, and circulating concentrations might be lower than expected. Severe inflammation can also influence the metabolism of hepatically cleared drugs [9].

Hypoalbuminemia is frequently observed in the critically ill, impacting drugs that are highly protein bound. While a greater free fraction of the drug is available for the clearance of hydrophilic drugs, augmented tissue distribution can also occur, coincident with third spacing. An augmented volume of distribution is thus observed, which can be double that of patients without hypoalbuminemia. Renal clearance in these instances might be normal or augmented, leading to increased clearance of the free fraction, or impaired causing accumulation of the free fraction. Plasma/serum concentrations measured in this scenario may reflect the total rather than unbound drug, a challenge when making dosing decisions based on concentration measurements.

Infection and supportive measures may result in augmented renal clearance (creatinine > 130 mg/min) in some patients, producing lower than expected concentrations for renally cleared drugs. Progressing infection may lead to an abrupt loss of kidney function (acute kidney injury), necessitating a dialysis modality. Pre-existing renal impairment may also impact drug handling, and nephrotoxic agents may impact function over the course of treatment. Extracorporeal interventions, including renal replacement therapy, for example continuous or intermittent dialysis, sustained low-efficiency dialysis/extended daily diafiltration, and extracorporeal membrane oxygenation, impact volume of distribution and clearance, particularly for hydrophilic drugs. The outcome on circulating concentrations is difficult to predict given different modalities and large differences in procedural aspects between institutions.

9.4 Classic TDM Candidate Drugs: Aminoglycosides and Vancomycin

TDM experience with aminoglycosides and vancomycin spans several decades. They conform to the requisites as traditional TDM candidates, namely possessing narrow therapeutic indices due to nephrotoxicity and ototoxicity. Immunoassays have been available for individual drugs since the late 1970s, exhibit excellent sensitivity and are used routinely to determine plasma concentration levels.

9.4.1 Aminoglycosides

Aminoglycosides have broad-spectrum activity against gram-negative bacteria. Drugs in this class are small hydrophilic molecules, with similar pharmacokinetic properties between agents. Due to their concentration-dependent bactericidal activity, once-daily administration is the traditional dosing form in most contexts [22]. For patients in whom pharmacokinetic alterations are not expected, empirical short-term therapy with once-daily dosing will likely not require monitoring as adequate peak concentrations are expected to be achieved. For empirical treatment that extends beyond 48h, directed therapy including prolonged treatment due to resistance to other agents, combination therapy, or synergistic low-dose use, plasma concentrations should be determined to guide dosing. Higher initial dosing is suggested in severe sepsis (7 mg/kg up to 640 mg) due to altered volume of distribution [22].

In individuals with normal or augmented renal function, trough concentrations are likely to fall below the limit of detection by immunoassay platforms. It is reasonable to measure trough concentrations in individuals with impaired renal function to avoid toxicity, especially since concentration–time profiles begin to approximate continuous infusions [23]. Peak concentrations are measured 30 min following the end of the infusion. A reasonable target is 6–10 mg/L for gentamycin and tobramycin, and 12–20 mg/L for amikacin [23]. If considering local biogram data or when microbiological data are available, a C_{max}/MIC ratio of 8–10 is a reasonable target, although >10 might be necessary in severely ill patients. For Bayesian calculations, some guidelines recommend that the second level after the peak be taken 6–14 h following the end of the infusion to avoid undetectable trough levels.

An excellent narrative review describes the history of nomograms and forecasting solutions for use in aminoglycoside dose adaptation [24]. Nomograms based on drug concentrations have been found to result in under-dosing in some patients [25, 26], including in the critical care setting [27]. While superior to nomograms, Sawchuk and Zaske's computationally simple, one-compartment model for individualizing dosing requires several samples [28]. Some authors report inferiority of this method compared to Bayesian forecasting [25]. Various software based on Bayesian methods are available and several have been used in the context of aminoglycoside treatment in critically ill patients [29–31]. Gauthier et al. highlight the importance of using population parameters from the appropriate population in critical care patients [29]. In addition to favorable sampling conditions (single sample, flexible timing, and not having to wait for a steady-state condition), Bayesian forecasting provides individual estimates for C_{max} and AUC, covering efficacy and toxicity. While minor differences in calculations between software have been observed, recommendations for the purposes of dose adaptation are similar [11, 25, 29, 32].

9.4.2 Dose Adaptation Tools for Aminoglycosides: Impact on Clinical Outcomes

Gillaizeau and colleagues performed a systematic review of clinical trials for the Cochrane collaboration evaluating computer-assisted dose adaptation in various clinical scenarios [33]. Most reports concerned anticoagulants and insulin (25/46), while five represented aminoglycosides [27, 34–37]. It is uncertain if TDM was performed in the context of once-daily dosing, although Begg, Hickling and colleagues targeted maximal concentrations in the range 6–10 mg/L [27, 34]. Interventions represented computer-supported advice from clinical pharmacists or pharmacologists, with the control arm representing dosing and adaptation based on blood levels by physicians from the treating team, either following a nomogram or a defined therapeutic range. Programs were based on the Sawchuk and Zaske linear regression model with modification [28], or Bayesian models [38, 39]. Interventions resulted in improved attainment of target concentrations, while the impact on treatment success and length of stay was significant but minor. For nephrotoxicity, despite a large cohort, reduced risk was not significant. Software-based dose adaptation was superior to targeting within a C_{max} range in the two reports evaluating this outcome [27, 34].

Eleven studies involving antimicrobials were identified as within scope, but were not included in the review, concerning gentamycin, amikacin, and vancomycin [33]. Reasons cited by the authors included not randomized controlled trial, dose calculations not performed by computer, or absence of primary outcome data sought by the authors. Despite a before and after design, the work by Van Lent-Evers and colleagues represents a large, well-powered cohort and evaluation of several clinically important outcomes [40]. The TDM intervention involved pharmacy input in dosing regimens through a 24 h service, with initial dosing and adjustment calculated by MWPharm, although the population model was developed using the nonparametric NPEM2 algorithm of the USC*PACK. The model included samples from ICU patients. Prior to the intervention physicians dosed according to nomograms, and when levels were requested, pharmacy performed dose calculations using the Sawchuk and Zaske method. The intervention resulted in reduced length of hospital stay, reduced days with signs of infection, fewer individuals with nephrotoxicity, and was more cost-effective. A trend toward improved survival was observed, but was likely underpowered.

9.4.3 Vancomycin

TDM for vancomycin has a controversial history with respect to both achieving efficacy and avoiding toxicity. The 2009 consensus review for TDM represents an effort to achieve an agreement between various organizations (American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the

Society of Infectious Diseases Pharmacists) based on the literature available to that date [41].

Trough levels obtained at steady state are recommended for practical reasons, and assume an acceptable relationship between trough and AUC. A trough of 15 mg/L is proposed for pathogens with an MIC 1 mg/L, to achieve an AUC/MIC ratio of 400 [41]. The minimum trough level of 10 mg/L required to avoid resistance is frequently cited, and based on observations from a case with recurrent MRSA bacteremia [42] and in vitro work supported by clinical relevance [43, 44]. To interpret trough levels, samples should be taken at steady state, for example, following the fourth dose for twice-daily dosing. In patients with altered renal function, the observed half-life will change, thus impacting time to steady state. For pathogens with reduced susceptibility, for example those with MIC ≥ 2 mg/L, achievement of the requisite AUC > 800 would not be possible with conventional dosing (15 mg/kg daily based on actual body weight, ABW). A loading dose (25–30 mg/kg ABW) is advocated for severely ill patients, permitting attainment of target concentrations more rapidly; sampling in this instance can be performed following the first conventional dose. These guidelines do not recommend continuous infusion, as superiority for patient outcomes to intermittent infusion had not been evidenced. Subsequent meta-analyses did not find a significant impact on clinical success [45, 46], although nephrotoxicity appeared reduced [45–47]. This is not significant in the work by Hanrahan et al., although the authors provide reasoning for this. Continuous infusion may be especially useful in critically ill patients for quicker attainment of pharmacokinetic targets, together with a loading dose 35 mg/kg to rapidly achieve plasma concentrations of 20 mg/L. Sampling can occur at any point during the infusion, with this concentration likely to achieve the target AUC/MIC ratio of 400 in appropriately sensitive microorganisms.

Following the 2009 guideline, and resulting change in practice, several research groups have performed meta-analyses evaluating proposed targets; trough levels above 15 mg/L, and, as it became more frequently reported, AUC/MIC. The body of work represented was essentially observational, principally prospective and retrospective cohort studies [48–52]. Nephrotoxicity, typically defined by a prespecified increase in creatinine, is elevated approximately twofold in individuals with trough levels above 15 mg/L [49, 51, 52]. Van Hal et al. highlight that a dose–effect can be observed in studies reporting multiple dose strata [53–56], and that a time–effect relationship can be observed in reports noting that most nephrotoxic events occurred after 7 days of therapy [57–60]. Steinmetz et al. highlight that no cases of irreversible damage were reported amongst the reports they included. Concerning treatment failure, some authors report a modest effect after accounting for heterogeneity (OR = 0.68 (0.52–0.89), n = 611/657, high arm/low arm, respectively) [51], while others only when restricting to bacteremia (RR = 0.72 (0.59–0.88), n = 374/420) [49], or persistent bacteremia (OR = 0.3 (0.14–0.62), n = 104/129) [50].

A body of work relating AUC/MIC to outcome measures has emerged and recent meta-analyses have attempted to summarize findings [48, 50]. Authors of included reports typically calculate breakpoints determined by CART (classifica-

tion and regression tree) analyses. Reports in which MICs are determined by the broth dilution method (BMD) the cutoff is around the AUC/MIC target 400 ± 15%. A twofold improvement in treatment failure is observed in patients with higher AUC/MIC breakpoints compared to lower AUC/MIC breakpoints (OR = 0.41 (0.31–0.53), *n* = 694/397, [50]; RR = 0.47 (0.30–0.73), *n* = 419/236, [48]). Of note is that the largest study included in both analyses, by the group that authored the 2009 guideline, detected a smaller effect size compared to other reports, influencing heterogeneity [54]. This group uniquely included MICs determined by both BMD and Etest methods, although Men et al. also noted relatively higher APACHE II scores relative to other reports included in their meta-analysis. In contrast to trough level based comparisons, those based on AUC/MIC thresholds demonstrate an improvement in mortality, when reported (RR = 0.47 (0.31–0.70), *n* = 188/132) [48].

The vast but essentially observational literature concerning monitoring and dose adjustment for vancomycin appears to favor an AUC-based approach for improving patient outcomes. The target AUC/MIC ratio of 400 seems reasonable, though the local method used to determine MICs must be taken into account. In this context, a clinical trial comparing trough- and AUC-based dose adjustment is warranted, including patients where vancomycin TDM would be rationally applied.

Table 9.1 Drug properties and scenarios where circulating concentrations might be altered in the critically ill patient

Drug properties	Clinically relevant scenarios
General: pharmacodynamics	– Pathogens with reduced susceptibility
	– Severe illness
	– More than 3 days of treatment, directed therapy
Impaired tissue penetration (*vancomycin, cefpirome, piperacillin, levofloxacin, fosfomycin*)	– Severe nosocomial pneumonia
	– Central nervous system infections
Hydrophilic drugs (*aminoglycosides, glycopeptides, beta-lactams, linezolid, colistin, daptomycin, flucytosine, antivirals, fluconazole*)	– Increased volume of distribution: burns, septic shock, mechanical ventilation
	– Augmented renal clearance
	– Unstable hemodynamic and/or renal function
Renally cleared drugs with toxicities observed at therapeutic concentrations (*aminoglycosides, glycopeptides, linezolid, colistin, daptomycin*)	– Concomitant nephrotoxic agents, or other drugs with similar toxicities
	– Chronic renal impairment, acute kidney injury
Challenging to dose in RRT (*aminoglycosides, glycopeptides, ciprofloxcin, beta-lactams*)	– Extracorporeal therapies
Significant protein binding (*ceftriaxone, flucloxacillin, ertapenem, daptomycin*)	– Hypoalbumineamia
	– Mechanical ventilation

9.5 TDM for Other Antimicrobial Agents

TDM presently requiring chromatographic methods for quantification is limited to clinical institutions with a specialized service. Despite technical advances, turnaround times are rate limiting for dose adaptation. In the critical care setting, there is concern to ensure adequate systemic concentrations, especially important for antimicrobials that are frequently used such as broad-spectrum beta-lactams and fluoroquinolones, though in principle may apply to any antimicrobial. A case for TDM has also been made for additionally avoiding toxicity with some drugs that are last-line agents or reserved for severe or resistant infections including linezolid, colistin, and daptomycin. TDM is becoming increasingly accepted for antifungal agents, and there is emerging evidence for antiviral agents; however, these are beyond the scope of the present work and the reader is referred to a recent review [61]. Selected additional antimicrobials with some evidence for a breakpoint related to clinical outcomes are included in Table 9.2.

Table 9.2 Pharmacokinetic/pharmacodynamics indices with evidence for clinical outcomes

Anti-infective	Efficacy	Toxicity
Concentration-dependent		
Aminoglycosides	C_{max}/MIC 8–10	
Severe infections	C_{max}/MIC > 10	
Gentamycin, tobramycin	C_{max} 6–10 mg/L	C_{min} < 1 mg/L
	AUC 70–120 mg h/L	
Amikacin	C_{max} 12–20 mg/L	C_{min} < 5 mg/L
Time-dependent		
Beta-lactams (broad spectrum)	(*f*)T > MIC	
Based on preclinical work		
Carbapenems *meropenem*	40%	
Cephalosporins *cefepime/ceftazidime*	70%	
Penicillins *piperacillin–tazobactam*	50%	
Based on clinical work	50–100%, 1 × MIC	
	50–100%, 4 × MIC	
Concentration- and time-dependent		
Glycopeptides	AUC/MIC ≥ 400 h	
Vancomycin		C_{min} < 20 mg/L
Traditional	C_{min} 10–15 mg/L	
Avoiding resistance	C_{min} > 10 mg/L	
Higher MIC (MRSA, when tissue penetration is a concern?)	C_{min} 15–20 mg/L	
Continuous infusion	C_{min} 20–25 mg/L	
Teicoplanin	C_{min} > 10 mg/L	
Higher MIC (MRSA, endocarditis, osteomyelitis)	C_{min} > 20 mg/L	

(continued)

Table 9.2 (continued)

Anti-infective	Efficacy	Toxicity
Fluoroquinolones		
Ciprofloxacin		
Gram-negative organisms	AUC/MIC > 125–250h	
	C_{max}/MIC 8–10	
Gram-positive organisms	AUC/MIC > 30–40 h	
Levofloxacin	C_{max}/MIC ≥ 12	
Others		
Linezolid	AUC/MIC 80–120	C_{min} < 6mg/L
	T > MIC > 85%	
	C_{min} > 2 mg/L	
Colistin		C_{min} < 2.4 mg/L
Daptomycin	AUC/MIC 666 h	C_{min} < 25 mg/L
	C_{max} > 100 mg/L	
	C_{max}/MIC 59–94	
Tigecycline	AUC/MIC 12.8–17.9 h	
Azole antifungals (treatment)		
Itraconazole	C_{min} > 1.0 mg/L	
Posaconazole	C_{min} > 1.0 mg/L	
Voriconazole	C_{min} > 2 mg/L	C_{min} < 6 mg/L

AUC is over 24 h

9.5.1 Beta-Lactams

The role of TDM for beta-lactams has gained interest for wider application, principally in the critical care setting. Various authors have reflected over the relevance, potential benefits, and challenges of beta-lactam TDM, specifically in the critically ill [3, 62–64]. Important distinctions between individual drugs within the class that might influence TDM-directed dosing include a significant post-antimicrobial effect for meropenem, significant protein binding with ceftriaxone and flucloxacillin, and long half-life for ceftriaxone.

Beta-lactams demonstrate a time above MIC dependent effect relationship, primarily evidenced through preclinical PK/PD models [8]. Several reports for clinically derived PK/PD indices in recent literature contrast with preclinical work and suggest a longer time above MIC may be necessary [65–69]. Most reports simulate plasma concentrations based on creatinine clearance, typically using population parameters from a model involving a similar population; in one report a microbiological assay was used to determine concentrations [69]. Ariano et al. report an 80% response rate for 60 individuals with *f*T > MIC: >75% for meropenem in bacteremia, excluding concurrent infections and renal impairment [65]. McKinnon et al. report an 82% clinical cure rate for individuals with T > MIC = 100% for ceftazidime or cefepime in 76 patients with sepsis [68]. Individual patient data for patients with AUIC < 500 are presented, thus it is possible to determine clinical cure at other

breakpoints: T > MIC: >75% results in 81%, and T > MIC: >60% results in 79.4% [68]. Crandon et al. arrive at a breakpoint of *f*T > MIC: >60% for cefepime using CART analysis and report a microbiological success rate of 63.8%, in 56 patients with an active *P. aeruginosa* infection (varied sites) [66]. The Etest method was used to determine MICs. Two reports are used to promote *f*T > MIC × 5 as a PK/PD index. Li et al. found fC_{min}/MIC > 5 as the only significant predictor of clinical success in 101 adults with lower respiratory infections, the authors noting that *f*T > MIC 100% was achieved in most patients [67]. Tam et al. report MIC × 4.3 as an indicator for clinical success for cefepime-treated individuals with diverse gram-negative infections; 1/23 individuals manifested clinical failure [69]. DALI (Defining Antibiotic Levels in ICU patients), an international point prevalence study, explored outcomes at the cutoffs *f*T > MIC 50% and 100%, and *f*T > MIC × 4 50% and 100% [70]. Free beta-lactam concentrations in plasma were measured in a central laboratory, and related to clinical outcomes. Two hundred forty-eight patients were treated for infection, representing eight beta-lactams. MIC results were available for 34.2%, EUCAST MIC90 was used for 38.7%, and the highest possible MIC for the given beta-lactam was assumed for 27.1% of participants; the authors highlight that many centers lacked services to determine MIC. While prudent, this strategy may have influenced risk estimates related to outcomes. Positive clinical outcome was observed in individuals achieving 50% *f*T > MIC (OR = 1.02) and 100% *f*T > MIC (OR = 1.56), $p < 0.03$ in the multivariable model including indices for sickness severity. These data empirically suggest that 100% *f*T > MIC is superior to 50%; however, the optimal index may vary between agents.

These data indicate that microbial sensitivity plays an important role in achievement of PK/PD indices. Further work is required to determine an optimal parameter that is both clinically useful and practical to apply. An emerging body of work demonstrates that PK/PD indices are difficult to achieve in the critically ill, especially in the early phases of sepsis [71] and with augmented renal clearance [72–76]. Non-critically ill obese patients likewise present augmented renal clearance that impact target attainment of beta-lactams [77]. However, different target indices are used across reports, and some authors report a lack of relationship between augmented renal clearance and clinical success [73]. Tools based on creatinine clearance developed in critically ill populations, such as nomograms [78] or the augmented renal clearance score [79], together with optimized administration strategies (loading dose, extended/continuous infusions) may be sufficient for the purposes of dose adaptation, but further validation and wider application is warranted.

A large investigative effort has compared clinical outcomes between continuous/extended infusions and intermittent bolus dosing. Multiple meta-analyses have attempted to synthesize data from observational work and clinical trials [80–87]. Randomized controlled trials in this setting have been critiqued for including patients with lower disease severity, use of inconsistent total antibiotic doses between comparator groups, and heterogeneity between studies, including differences in pathogens and their MICs, duration of follow-up, and definitions of outcomes [83, 84, 88, 89]. A recent meta-analysis employed strict inclusion criteria, limiting inclusion to clinical trials recruiting patients with severe sepsis or septic

shock [83]. Mortality at 30 days was 19.6% versus 26.3% (RR 0.74 (0.56–1.00)) and clinical cure 55.4% versus 46.3% (RR 1.20 (1.03–1.40)), for continuous infusion and intermittent bolus dosing, respectively. The authors further highlight that benefits of continuous infusions are especially pronounced in individuals treated for severe sepsis caused by non-fermenting gram-negative bacilli, and diminished in patients requiring renal replacement therapy where bolus dosing begins to approximate the kinetics of continuous infusions.

9.5.2 Fluoroquinolones

Fluoroquinolones have dose-dependent antimicrobial activity for the treatment of bacterial infections caused by gram-negative, gram-positive pathogens and mycobacteria. The best PK/PD index predicting efficacy is the AUC/MIC ratio, followed by the C_{max}/MIC ratio [90, 91], and quantitatively depends on the infective pathogen. While for gram-positive microorganisms, such as *Streptococcus pneumoniae*, AUC/MIC has been defined to be ≥30–35, for gram-negatives it should be greater than 100 [92, 93]. A C_{max}/MIC of 8–10 results in maximum antibacterial efficacy in in vivo animal models [92, 93].

Several studies have correlated an AUC/MIC of 30–60 for different fluoroquinolones (levofloxacin, ciprofloxacin, gatifloxacin, moxifloxacin, etc.) to in vitro antimicrobial activity [92–94] and improved clinical outcomes, such as bacterial eradication [95]. For levofloxacin, population pharmacokinetic studies have demonstrated that standard dosing of 500 mg/day results in inadequate achievement of target PK/PD indices, especially for certain patients and Gram-negative infections [96, 97]. Moxifloxacin exhibits a better PK profile, with AUC/MIC > 35 achieved in 100% of patients, where strains exhibited MICs of 1 mg/L [98]. Treatment failures with fluoroquinolones administered at standard doses (ciprofloxacin and levofloxacin) in patients with respiratory tract infections due to fluoroquinolone-resistant *S. pneumoniae* have been reported, especially in patients previously treated with these antimicrobials [99]. An increased dose of levofloxacin to 750 mg/day or 500 mg/12 h has been suggested. A multicenter, randomized, double-blind study demonstrated no differences in clinical success and microbiologic eradication when comparing levofloxacin dosages of 750 mg/day for 5 days with the dose of 500 mg/day for 10 days for the treatment of mild to severe community-acquired pneumonia [100]. This high-dose short course regimen maximizes its concentration-dependent bactericidal activity and may reduce resistance. A dose of 500 mg twice-daily of levofloxacin has been proposed for the treatment of early-onset ventilator-associated pneumonia in intensive care patients [101, 102]. TDM for fluoroquinolones with increased dosing might be a complementary tool to avoid toxicity.

The declining susceptibilities to fluoroquinolones of Gram-negative isolates pose an important challenge [103]. Some authors have attempted to define a PK/PD-based threshold to minimize the development of resistance. Homma et al. evaluated different clinical isolates of *S. pneumoniae* in vitro with various MIC and MPC

(Mutant Prevention Concentration) values for levofloxacin and moxifloxacin, and propose a target AUC/MPC ≥ 13.41 or C_{max}/MPC above 1.20 for complete eradication without decreased susceptibility [104].

While the PK/PD behavior of the fluoroquinolones has been widely described, few authors have evaluated the necessity or clinical benefit of TDM. Scaglione et al. report their local experience of a TDM program for ciprofloxacin, using C_{max}/MIC of 10 as a target, but do not report clinical outcomes [105]. Pea et al. evaluated ciprofloxacin TDM in 89 critically ill patients and report wide and unpredictable interindividual pharmacokinetic variability. They conclude that fixed dosing of 200 or 400 mg/12 h is only useful for fully susceptible microorganisms (MIC < 0.3 mg/L), further supporting use of higher doses and potential usefulness of TDM [106]. Other centers only monitor fluoroquinolones in certain patients such as obese patients or with significant burn injuries [107]. Restricting TDM to special populations may be a rational approach [108, 109].

TDM of fluoroquinolones has been more widely applied for the treatment of tuberculosis (TB) due to the observed high pharmacokinetic drug variability [110–112] and the high frequency of patients with low serum concentrations [113]. Fluoroquinolones are used for the treatment of TB, including the multidrug-resistant (MDR) TB, levofloxacin and moxifloxacin being preferred due to potency and relative safety. Manika et al. report wide variability of moxifloxacin concentrations amongst patients with multidrug-resistant TB receiving the same regimen (400 mg per day), concluding that this standard dose may not be sufficient for all patients [112]. A limited-sampling strategy has been proposed [114]; however, the pharmacodynamic target for *Mycobacterium tuberculosis* has not been defined. In addition, the presence of low serum concentrations of anti-MDR-TB drugs might not affect the 2-month sputum conversion rate [113].

9.5.3 Linezolid

Linezolid is a member of the oxazolidinones with bacteriostatic activity against enterococci and staphylococci, and is bactericidal for most streptococci strains. Recommended dosing is 600 mg twice-daily in a fixed dose formulation, irrespective of renal or hepatic function, and pharmacokinetic parameters are claimed to be insignificantly altered by age, gender, or renal/hepatic insufficiency. Recent reports, however, evidence wide inter- and intraindividual variability [115, 116], especially amongst the critically ill or those with renal impairment [117–120]. Pea at al. suggest that TDM of linezolid may be worthwhile in 30% of individuals to avoid treatment failure or dose-dependent toxicity [121]. Patients with renal impairment, the elderly, or those with low body weight risk overexposure and toxicity, while acute illness may exacerbate linezolid-related hematological toxicity [119, 122–124]. On the other hand, critically ill patients are at risk of subtherapeutic levels, especially those with augmented clearance and greater volume of distribution, thus TDM might optimize dosing and prevent clinical failure [120]. Data concerning the pharmacokinetics of

linezolid in patients with excessive body weight are limited and controversial [125, 126] and TDM may cover inconsistencies. Standard dose of linezolid results in suboptimal concentrations in more than 40% of pediatric patients [127]. Further, higher doses were required for pathogens with borderline susceptibility (MIC > 1 mg/L).

The main reason to perform TDM of linezolid is to avoid or prevent hematological toxicity. High linezolid trough concentrations are associated with thrombocytopenia in patients with Gram-positive bacterial infections [128]. The trough concentration limit to prevent toxicity remains to be defined. Different thresholds have been proposed including 6.5 mg/L [124], 7–10 mg/L [117, 123, 129, 130], and 22.1 mg/L [131]. It is surprising that this relationship between exposure and toxicity was not confirmed in patients receiving linezolid for the treatment of drug-resistant tuberculosis, in whom the AUC of linezolid did not associate with any drug-related adverse event [132].

Administration by continuous infusion has been proposed to optimize achievement of the PK/PD index for clinical efficacy; however, data are lacking [133]. Optimal linezolid plasma concentrations to achieve the highest clinical efficacy are unknown. Some authors have identified a trough concentration of ≥2 mg/L as a predictor of bacterial eradication [134] and a therapeutic range 2–7 mg/L has been proposed [124]. Furthermore, target concentrations should consider MIC to achieve an optimal PK/PD ratio: an AUC/MIC ratio between 80 and 120 is frequently cited. AUC calculations based on a minimal sampling strategy can be used to individualize dosing [128, 135].

9.5.4 Colistin

Colistin, or polymyxin E, is a cationic polypeptide antibiotic active against gram-negative bacteria, including multidrug-resistant strains. Its use has reemerged worldwide as rescue therapy for infections caused by multidrug-resistant bacilli, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and Enterobacteriaceae species. It is administered parenterally as a prodrug, colistin methanesulfonate sodium (CMS), which is converted in vivo to the active compound, colistin. It exhibits concentration-dependent antibacterial activity. This polymyxin was developed in Japan in the 1940s–1950s but its clinical and parenteral use were abandoned in most countries due to reports of serious adverse events, such as nephrotoxicity and neurotoxicity [136]. Initial dosing regimens of CMS relied on PK/PD data from older work that lacked appropriate methods and provided unreliable findings [137]. In addition, most PK/PD studies were performed in patients with cystic fibrosis which exhibit unique PK characteristics as a population. In recent years, specific chromatographic methods for the accurate analysis of CMS and colistin have been established [138]. This has led to novel PK/PD work in animals and humans, providing updated data to optimize colistin dosing and improve its clinical efficacy, while limiting toxicities and emergence of resistance [139, 140]. This is of extreme importance in difficult-to-treat multi-resistant pathogens with no therapeutic alternatives.

A steady-state colistin trough concentration of 2–2.5 mg/L has been proposed, corresponding to a target AUC 0–24 of 60 mg h/L [138, 139]. This AUC/MIC value is based on the results of a preclinical work testing three strains each of *A. baumannii* and *P. aeruginosa* in murine thigh and lung infection models that demonstrated that an AUC 0–24/MIC of 60 h associated with an effect between stasis and 1-log kill. This target concentration of 2.5 mg/L is optimal for an MIC of 1 mg/L, and requires adjustment for other MIC values.

To date, this target concentration has not correlated with positive clinical outcomes. A randomized clinical trial assessing TDM of colistin (using C_{max}/CMI) failed to demonstrate a benefit in terms of clinical cure or 30-day mortality in patients with different types of multidrug-resistant gram-negative bacterial infections [141]. Yamada et al. describe a case with bacteremia due to multidrug-resistant *Pseudomonas aeruginosa* who was successfully treated with colistin in conjunction with TDM [142–144].

One important conclusion of recent PK work is the need to administer an initial loading dose and a higher CMS maintenance dose to rapidly attain therapeutic concentrations as the manufacturer dosage recommendations are insufficient, especially in critically ill patients [139, 145, 146]. Updated dosing recommendations for intravenous colistin based on renal function vary between the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [147]. Currently, newer dosage regimens are being widely implemented, although TDM is not routinely performed in the majority of centers; this could have implications for toxicity observed with clinical use [137]. A prospective observational cohort study demonstrated that the trough plasma level of colistin is an independent risk factor for nephrotoxicity, and that acute kidney injury is best predicted at 2.42 mg/L [148]. This value has been validated in a prospective cohort of individuals treated for multidrug-resistant gram-negative infections [149]. It is clear that the therapeutic window for colistin is narrow, with concentrations required for efficacy being quite close to those in which toxicities are observed [150].

9.5.5 Daptomycin

Daptomycin is a lipoglycopeptide with a concentration-dependent antimicrobial activity best described by AUC/MIC [151, 152]. The mean AUC/MIC value associated with a static, 1-log killing, and 2-log killing effect against *S. aureus* has been defined as 438, 666, and 1061, respectively [153]. In addition, an AUC/MIC ratio of <666 was associated with increased mortality in patients with gram-positive severe infections [154]. Other authors have identified that an AUC/MIC > 200 is required to prevent *S. aureus* resistance [155].

The approved dose of daptomycin for soft-tissue infections is 4 mg/kg daily and for bacteremia 6 mg/kg daily. For infections with a high inoculum, such as endocarditis, microbiological data suggest that doses higher than 6 mg/kg/daily are required, especially against strains with reduced daptomycin susceptibility [156]. In an

in vitro PD model, a dose of 10 mg/kg was required to prevent resistance [152]; however, further clinical data are warranted [151].

Vast variability in the pharmacokinetics of daptomycin has been observed with clinical use, including high-dose regimens [154, 157]. Much of the variability could not be accounted for by clinical factors (creatinine clearance, albumin, or dose interval), suggesting the need for TDM, which may be especially useful in critical illness, severe sepsis, dynamically changing renal function, and acute kidney injury [153, 154, 158, 159]. Excessive exposure is related to musculoskeletal toxicity [154, 157, 158]. Bhavnani et al. report a C_{min} breakpoint of 24.3 mg/L associated with an elevation of creatine kinase in patients treated with standard dosing (6 mg/kg/day) [160]. The clinical application of TDM for daptomycin remains limited, and the literature is represented by only a few reports [5, 157, 161, 162].

9.6 Conclusions and Future Directions

Interest in TDM for optimizing therapy is becoming rekindled, particularly for special populations. Antimicrobial use in the intensive care setting has received special attention and there is a growing body of literature to support that pathophysiological changes in critically ill patients influence circulating concentrations. Data concerning optimal PK/PD targets for emerging TDM candidates, and the clinical impact of concentration guided dose adaptation, remains limited. Clinical trials exploring the impact of monitoring on clinical outcomes are only useful when breakpoints are well established; well-conducted prospective observational studies based on measured concentrations can help to determine optimal indices. Further, wider implementation and investigation is contingent on laboratories for measurement. Sensitive and specific immunoassays for emerging candidates would aid wider implementation but also research efforts in the clinical setting. Aptamer-based technology may help to overcome the challenges of antibody-based immunoassays [163], and has been used together with a microfluidic electrochemical detector for real-time tracking of circulating drug concentrations [164]. Therapeutic drug monitoring complements innovations in other areas including microbial diagnostics and response-related biomarkers and is an important tool in achieving personalized medicine [165, 166].

References

1. Dasgupta A (2012) Introduction to therapeutic drug monitoring. Frequently and less frequently monitored drugs. In: Therapeutic drug monitoring, 1st edn. Elsevier, New York, p 1–29
2. Walson PD (1998) Therapeutic drug monitoring in special populations. Clin Chem 44:415–419
3. Roberts JA, Abdul-Aziz MH, Lipman J et al (2014) Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis 14:498–509. doi:10.1016/S1473-3099(14)70036-2

4. Fish DN, Piscitelli SC, Danziger LH (1995) Development of resistance during antimicrobial therapy: a review of antibiotic classes and patient characteristics in 173 studies. Pharmacotherapy 15:279–291
5. Pea F, Cojutti P, Sbrojavacca R et al (2011) TDM-guided therapy with daptomycin and meropenem in a morbidly obese, critically ill patient. Ann Pharmacother 45:e37. doi:10.1345/aph.1P745
6. Taccone FS, Cotton F, Roisin S et al (2012) Optimal meropenem concentrations to treat multidrug-resistant Pseudomonas aeruginosa septic shock. Antimicrob Agents Chemother 56:2129–2131. doi:10.1128/AAC.06389-11
7. Shipkova M, Svinarov D (2016) LC-MS/MS as a tool for TDM services: where are we? Clin Biochem 49:1009–1023. doi:10.1016/j.clinbiochem.2016.05.001
8. Craig WA (1998) Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 26:1–10
9. Veringa A, Ter Avest M, Span LFR et al (2017) Voriconazole metabolism is influenced by severe inflammation: a prospective study. J Antimicrob Chemother 72:261–267. doi:10.1093/jac/dkw349
10. Beal S, Sheiner LB, Boeckmann A, Bauer A (2009) NONMEM user's guides (1989–2009). Icon Development Solutions, Ellicott City
11. Fuchs A, Csajka C, Thoma Y et al (2013) Benchmarking therapeutic drug monitoring software: a review of available computer tools. Clin Pharmacokinet 52:9–22. doi:10.1007/s40262-012-0020-y
12. Jelliffe RW (1991) The USC*PACK PC programs for population pharmacokinetic modeling, modeling of large kinetic/dynamic systems, and adaptive control of drug dosage regimens. Proc Symp Comput Appl Med Care: 922–924
13. LAPK (2016) BestDose Software. http://www.lapk.org/bestdose.php. Accessed 28 Dec 2016
14. Proost JH, Meijer DK (1992) MW/Pharm, an integrated software package for drug dosage regimen calculation and therapeutic drug monitoring. Comput Biol Med 22:155–163
15. RxKinetics (2016) RxKinetics pharmacokinetics and nutrition software for pharmacists. In: RxKinetics Pharmacokinet. Nutr. Softw. Pharm. http://www.rxkinetics.com/. Accessed 28 Dec 2016
16. Tharpe R (2016) Complex non-steady-state analysis | RxRick's Blog. http://rxkinetics.com/blog/?p=1495. Accessed 28 Dec 2016
17. Lacarelle B, Pisano P, Gauthier T et al (1994) Abbott PKS system: a new version for applied pharmacokinetics including Bayesian estimation. Int J Biomed Comput 36:127–130
18. T.D.M.S. 2000 (2016) T.D.M.S. 2000™. http://tdms2000.com/. Accessed 28 Dec 2016
19. Duffull SB, Kirkpatrick CJ, Van Den Berg L (2016) TCIWorks. In: TCIWorks. tciworks.info. Accessed 2016
20. DoseMe (2016) DoseMe—personalised medicine: making complex simple. In: DoseMe—Pers. Med. Mak. Complex simple. https://www.doseme.com.au/. Accessed 28 Dec 2016
21. Limoges University Hospital (2016) Limoges University Hospital Laboratory of Pharmacology. https://pharmaco.chu-limoges.fr/. Accessed 28 Dec 2016
22. Antibiotic Expert Group (2010) Therapeutic guidelines: antibiotic. Therapeutic Guidelines Limited, Melbourne
23. Begg EJ, Barclay ML, Kirkpatrick CJ (1999) The therapeutic monitoring of antimicrobial agents. Br J Clin Pharmacol 47:23–30
24. Begg EJ, Barclay ML (1995) Aminoglycosides—50 years on. Br J Clin Pharmacol 39:597–603
25. Avent ML, Teoh J, Lees J et al (2011) Comparing 3 methods of monitoring gentamicin concentrations in patients with febrile neutropenia. Ther Drug Monit 33:592–601. doi:10.1097/FTD.0b013e31822c78e9
26. Martin J, Barras M, Yui NA et al (2012) Gentamicin monitoring practices in teaching hospitals—time to undertake the necessary randomised controlled trial. Clin Toxicol 2:1000146. doi:10.4172/2161-0495.1000146
27. Hickling K, Begg E, Moore ML (1989) A prospective randomised trial comparing individualised pharmacokinetic dosage prediction for aminoglycosides with prediction based on estimated creatinine clearance in critically ill patients. Intensive Care Med 15:233–237

28. Sawchuk RJ, Zaske DE (1976) Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions: gentamicin in burn patients. J Pharmacokinet Biopharm 4:183–195
29. Gauthier T, Lacarelle B, Marre F et al (1994) Predictive performance of two software packages (USC*PACK PC and Abbott PKS system) for the individualization of amikacin dosage in intensive care unit patients. Int J Biomed Comput 36:131–134
30. Mar Fernández de Gatta MD, Victoria Calvo M, Ardanuy R et al (2009) Evaluation of population pharmacokinetic models for amikacin dosage individualization in critically ill patients. J Pharm Pharmacol 61:759–766. doi:10.1211/jpp/61.06.0008
31. Rodvold KA, Pryka RD, Kuehl PG et al (1990) Bayesian forecasting of serum gentamicin concentrations in intensive care patients. Clin Pharmacokinet 18:409–418
32. Duffull SB, Kirkpatrick CM, Begg EJ (1997) Comparison of two Bayesian approaches to dose-individualization for once-daily aminoglycoside regimens. Br J Clin Pharmacol 43:125–135
33. Gillaizeau F, Chan E, Trinquart L, et al (2013) Computerized advice on drug dosage to improve prescribing practice. Cochrane Database Syst Rev (11):CD002894. doi: 10.1002/14651858.CD002894.pub3
34. Begg EJ, Atkinson HC, Jeffery GM, Taylor NW (1989) Individualised aminoglycoside dosage based on pharmacokinetic analysis is superior to dosage based on physician intuition at achieving target plasma drug concentrations. Br J Clin Pharmacol 28:137–141
35. Burton ME, Ash CL, Hill DP et al (1991) A controlled trial of the cost benefit of computerized bayesian aminoglycoside administration. Clin Pharmacol Ther 49:685–694
36. Destache CJ, Meyer SK, Bittner MJ, Hermann KG (1990) Impact of a clinical pharmacokinetic service on patients treated with aminoglycosides: a cost-benefit analysis. Ther Drug Monit 12:419–426
37. Leehey DJ, Braun BI, Tholl DA et al (1993) Can pharmacokinetic dosing decrease nephrotoxicity associated with aminoglycoside therapy. J Am Soc Nephrol JASN 4:81–90
38. Burton ME, Brater DC, Chen PS et al (1985) A Bayesian feedback method of aminoglycoside dosing. Clin Pharmacol Ther 37:349–357
39. Sheiner LB, Rosenberg B, Melmon KL (1972) Modelling of individual pharmacokinetics for computer-aided drug dosage. Comput Biomed Res Int J 5:411–459
40. van Lent-Evers NA, Mathôt RA, Geus WP et al (1999) Impact of goal-oriented and model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: a cost-effectiveness analysis. Ther Drug Monit 21:63–73
41. Rybak M, Lomaestro B, Rotschafer JC et al (2009) Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health-Syst Pharm 66:82–98. doi:10.2146/ajhp080434
42. Sakoulas G, Gold HS, Cohen RA et al (2006) Effects of prolonged vancomycin administration on methicillin-resistant Staphylococcus aureus (MRSA) in a patient with recurrent bacteraemia. J Antimicrob Chemother 57:699–704. doi:10.1093/jac/dkl030
43. Tsuji BT, Rybak MJ, Cheung CM et al (2007) Community- and health care-associated methicillin-resistant Staphylococcus aureus: a comparison of molecular epidemiology and antimicrobial activities of various agents. Diagn Microbiol Infect Dis 58:41–47. doi:10.1016/j.diagmicrobio.2006.10.021
44. Tsuji BT, Rybak MJ, Lau KL, Sakoulas G (2007) Evaluation of accessory gene regulator (agr) group and function in the proclivity towards vancomycin intermediate resistance in Staphylococcus aureus. Antimicrob Agents Chemother 51:1089–1091. doi:10.1128/AAC.00671-06
45. Cataldo MA, Tacconelli E, Grilli E et al (2012) Continuous versus intermittent infusion of vancomycin for the treatment of Gram-positive infections: systematic review and meta-analysis. J Antimicrob Chemother 67:17–24. doi:10.1093/jac/dkr442
46. Hao J-J, Chen H, Zhou J-X (2016) Continuous versus intermittent infusion of vancomycin in adult patients: a systematic review and meta-analysis. Int J Antimicrob Agents 47:28–35. doi:10.1016/j.ijantimicag.2015.10.019

47. Hanrahan T, Whitehouse T, Lipman J, Roberts JA (2015) Vancomycin-associated nephrotoxicity: a meta-analysis of administration by continuous versus intermittent infusion. Int J Antimicrob Agents 46:249–253. doi:10.1016/j.ijantimicag.2015.04.013
48. Men P, Li H-B, Zhai S-D, Zhao R-S (2016) Association between the AUC0-24/MIC ratio of vancomycin and its clinical effectiveness: a systematic review and meta-analysis. PLoS One 11:e0146224. doi:10.1371/journal.pone.0146224
49. Meng L, Fang Y, Chen Y et al (2015) High versus low vancomycin serum trough regimen for Gram-positive infections: a meta-analysis. J Chemother Florence Italy 27:213–220. doi:10.1179/1973947814Y.0000000182
50. Prybylski JP (2015) Vancomycin trough concentration as a predictor of clinical outcomes in patients with Staphylococcus aureus bacteremia: a meta-analysis of observational studies. Pharmacotherapy 35:889–898. doi:10.1002/phar.1638
51. Steinmetz T, Eliakim-Raz N, Goldberg E et al (2015) Association of vancomycin serum concentrations with efficacy in patients with MRSA infections: a systematic review and meta-analysis. Clin Microbiol Infect 21:665–673. doi:10.1016/j.cmi.2015.04.003
52. van Hal SJ, Paterson DL, Lodise TP (2013) Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. Antimicrob Agents Chemother 57:734–744. doi:10.1128/AAC.01568-12
53. Cano EL, Haque NZ, Welch VL et al (2012) Incidence of nephrotoxicity and association with vancomycin use in intensive care unit patients with pneumonia: retrospective analysis of the IMPACT-HAP Database. Clin Ther 34:149–157. doi:10.1016/j.clinthera.2011.12.013
54. Kullar R, Davis SL, Levine DP, Rybak MJ (2011) Impact of vancomycin exposure on outcomes in patients with methicillin-resistant Staphylococcus aureus bacteremia: support for consensus guidelines suggested targets. Clin Infect Dis 52:975–981. doi:10.1093/cid/cir124
55. Lodise TP, Patel N, Lomaestro BM et al (2009) Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. Clin Infect Dis 49:507–514. doi:10.1086/600884
56. Wunderink RG, Niederman MS, Kollef MH et al (2012) Linezolid in methicillin-resistant Staphylococcus aureus nosocomial pneumonia: a randomized, controlled study. Clin Infect Dis 54:621–629. doi:10.1093/cid/cir895
57. Hidayat LK, Hsu DI, Quist R et al (2006) High-dose vancomycin therapy for methicillin-resistant Staphylococcus aureus infections: efficacy and toxicity. Arch Intern Med 166:2138–2144. doi:10.1001/archinte.166.19.2138
58. Jeffres MN, Isakow W, Doherty JA et al (2007) A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care-associated methicillin-resistant Staphylococcus aureus pneumonia. Clin Ther 29:1107–1115. doi:10.1016/j.clinthera.2007.06.014
59. Minejima E, Choi J, Beringer P et al (2011) Applying new diagnostic criteria for acute kidney injury to facilitate early identification of nephrotoxicity in vancomycin-treated patients. Antimicrob Agents Chemother 55:3278–3283. doi:10.1128/AAC.00173-11
60. Prabaker KK, Tran TP-H, Pratummas T et al (2012) Elevated vancomycin trough is not associated with nephrotoxicity among inpatient veterans. J Hosp Med 7:91–97. doi:10.1002/jhm.946
61. Jager NGL, van Hest RM, Lipman J et al (2016) Therapeutic drug monitoring of anti-infective agents in critically ill patients. Expert Rev Clin Pharmacol 9:961–979. doi:10.1586/17512433.2016.1172209
62. Huttner A, Harbarth S, Hope WW et al (2015) Therapeutic drug monitoring of the β-lactam antibiotics: what is the evidence and which patients should we be using it for? J Antimicrob Chemother 70:3178–3183. doi:10.1093/jac/dkv201
63. Sime FB, Roberts MS, Peake SL et al (2012) Does beta-lactam pharmacokinetic variability in critically ill patients justify therapeutic drug monitoring? A systematic review. Ann Intensive Care 2:35. doi:10.1186/2110-5820-2-35

64. Wong G, Sime FB, Lipman J, Roberts JA (2014) How do we use therapeutic drug monitoring to improve outcomes from severe infections in critically ill patients? BMC Infect Dis 14:288. doi:10.1186/1471-2334-14-288
65. Ariano RE, Nyhlén A, Donnelly JP et al (2005) Pharmacokinetics and pharmacodynamics of meropenem in febrile neutropenic patients with bacteremia. Ann Pharmacother 39:32–38. doi:10.1345/aph.1E271
66. Crandon JL, Bulik CC, Kuti JL, Nicolau DP (2010) Clinical pharmacodynamics of cefepime in patients infected with Pseudomonas aeruginosa. Antimicrob Agents Chemother 54:1111–1116. doi:10.1128/AAC.01183-09
67. Li C, Du X, Kuti JL, Nicolau DP (2007) Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. Antimicrob Agents Chemother 51:1725–1730. doi:10.1128/AAC.00294-06
68. McKinnon PS, Paladino JA, Schentag JJ (2008) Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int J Antimicrob Agents 31:345–351. doi:10.1016/j.ijantimicag.2007.12.009
69. Tam VH, McKinnon PS, Akins RL et al (2002) Pharmacodynamics of cefepime in patients with Gram-negative infections. J Antimicrob Chemother 50:425–428
70. Roberts JA, De Waele JJ, Dimopoulos G et al (2012) DALI: defining antibiotic levels in intensive care unit patients: a multi-centre point of prevalence study to determine whether contemporary antibiotic dosing for critically ill patients is therapeutic. BMC Infect Dis 12:152. doi:10.1186/1471-2334-12-152
71. Taccone FS, Laterre P-F, Dugernier T et al (2010) Insufficient β-lactam concentrations in the early phase of severe sepsis and septic shock. Crit Care 14:R126. doi:10.1186/cc9091
72. Carlier M, Carrette S, Roberts JA et al (2013) Meropenem and piperacillin/tazobactam prescribing in critically ill patients: does augmented renal clearance affect pharmacokinetic/pharmacodynamic target attainment when extended infusions are used? Crit Care 17:R84. doi:10.1186/cc12705
73. Huttner A, Von Dach E, Renzoni A et al (2015) Augmented renal clearance, low β-lactam concentrations and clinical outcomes in the critically ill: an observational prospective cohort study. Int J Antimicrob Agents 45:385–392. doi:10.1016/j.ijantimicag.2014.12.017
74. Udy AA, Lipman J, Jarrett P et al (2015) Are standard doses of piperacillin sufficient for critically ill patients with augmented creatinine clearance? Crit Care 19:28. doi:10.1186/s13054-015-0750-y
75. Udy AA, Putt MT, Shanmugathasan S et al (2010) Augmented renal clearance in the intensive care unit: an illustrative case series. Int J Antimicrob Agents 35:606–608. doi:10.1016/j.ijantimicag.2010.02.013
76. Udy AA, Varghese JM, Altukroni M et al (2012) Subtherapeutic initial β-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. Chest 142:30–39. doi:10.1378/chest.11-1671
77. Hites M, Taccone FS, Wolff F et al (2014) Broad-spectrum β-lactams in obese non-critically ill patients. Nutr Diabetes 4:e119. doi:10.1038/nutd.2014.15
78. Pea F, Viale P, Cojutti P, Furlanut M (2012) Dosing nomograms for attaining optimum concentrations of meropenem by continuous infusion in critically ill patients with severe gram-negative infections: a pharmacokinetics/pharmacodynamics-based approach. Antimicrob Agents Chemother 56:6343–6348. doi:10.1128/AAC.01291-12
79. Akers KS, Niece KL, Chung KK et al (2014) Modified augmented renal clearance score predicts rapid piperacillin and tazobactam clearance in critically ill surgery and trauma patients. J Trauma Acute Care Surg 77:S163–S170. doi:10.1097/TA.0000000000000191
80. Falagas ME, Tansarli GS, Ikawa K, Vardakas KZ (2013) Clinical outcomes with extended or continuous versus short-term intravenous infusion of carbapenems and piperacillin/tazobactam: a systematic review and meta-analysis. Clin Infect Dis 56:272–282. doi:10.1093/cid/cis857
81. Korbila IP, Tansarli GS, Karageorgopoulos DE et al (2013) Extended or continuous versus short-term intravenous infusion of cephalosporins: a meta-analysis. Expert Rev Anti Infect Ther 11:585–595. doi:10.1586/eri.13.44

82. Lal A, Jaoude P, El-Solh AA (2016) Prolonged versus intermittent infusion of β-lactams for the treatment of nosocomial pneumonia: a meta-analysis. Infect Chemother 48:81–90. doi:10.3947/ic.2016.48.2.81
83. Roberts JA, Abdul-Aziz M-H, Davis JS et al (2016) Continuous versus intermittent β-lactam infusion in severe sepsis. A meta-analysis of individual patient data from randomized trials. Am J Respir Crit Care Med 194:681–691. doi:10.1164/rccm.201601-0024OC
84. Roberts JA, Webb S, Paterson D et al (2009) A systematic review on clinical benefits of continuous administration of beta-lactam antibiotics. Crit Care Med 37:2071–2078. doi:10.1097/CCM.0b013e3181a0054d
85. Shiu J, Wang E, Tejani AM, Wasdell M (2013) Continuous versus intermittent infusions of antibiotics for the treatment of severe acute infections. Cochrane Database Syst Rev CD008481. doi: 10.1002/14651858.CD008481.pub2
86. Teo J, Liew Y, Lee W, Kwa AL-H (2014) Prolonged infusion versus intermittent boluses of β-lactam antibiotics for treatment of acute infections: a meta-analysis. Int J Antimicrob Agents 43:403–411. doi:10.1016/j.ijantimicag.2014.01.027
87. Yang H, Zhang C, Zhou Q et al (2015) Clinical outcomes with alternative dosing strategies for piperacillin/tazobactam: a systematic review and meta-analysis. PLoS One 10:e0116769. doi:10.1371/journal.pone.0116769
88. Abdul-Aziz MH, Dulhunty JM, Bellomo R et al (2012) Continuous beta-lactam infusion in critically ill patients: the clinical evidence. Ann Intensive Care 2:37. doi:10.1186/2110-5820-2-37
89. Yusuf E, Spapen H, Piérard D (2014) Prolonged vs intermittent infusion of piperacillin/tazobactam in critically ill patients: a narrative and systematic review. J Crit Care 29:1089–1095. doi:10.1016/j.jcrc.2014.07.033
90. Forrest A, Nix DE, Ballow CH et al (1993) Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 37:1073–1081
91. Shandil RK, Jayaram R, Kaur P et al (2007) Moxifloxacin, ofloxacin, sparfloxacin, and ciprofloxacin against Mycobacterium tuberculosis: evaluation of in vitro and pharmacodynamic indices that best predict in vivo efficacy. Antimicrob Agents Chemother 51:576–582. doi:10.1128/AAC.00414-06
92. Andes DR, Craig WA (1998) Pharmacodynamics of fluoroquinolones in experimental models of endocarditis. Clin Infect Dis 27:47–50
93. Turnidge J (1999) Pharmacokinetics and pharmacodynamics of fluoroquinolones. Drugs 58(Suppl 2):29–36
94. Lacy MK, Lu W, Xu X, et al (1999) Pharmacodynamic comparisons of levofloxacin, ciprofloxacin, and ampicillin against Streptococcus pneumoniae in an in vitro model of infection. Antimicrob Agents Chemother 43:672–677.
95. Ambrose PG, Grasela DM, Grasela TH et al (2001) Pharmacodynamics of fluoroquinolones against Streptococcus pneumoniae in patients with community-acquired respiratory tract infections. Antimicrob Agents Chemother 45:2793–2797. doi:10.1128/AAC.45.10.2793-2797.2001
96. Kiser TH, Hoody DW, Obritsch MD et al (2006) Levofloxacin pharmacokinetics and pharmacodynamics in patients with severe burn injury. Antimicrob Agents Chemother 50:1937–1945. doi:10.1128/AAC.01466-05
97. Burgess DS, Hall RG (2007) Simulated comparison of the pharmacodynamics of ciprofloxacin and levofloxacin against Pseudomonas aeruginosa using pharma-cokinetic data from healthy volunteers and 2002 minimum inhibitory concentra-tion data. Clin Ther 29:1421–1427. doi:10.1016/j.clinthera.2007.07.024
98. Kiffer CR, Pignatari AC (2011) Pharmacodynamic evaluation of commonly prescribed oral antibiotics against respiratory bacterial pathogens. BMC Infect Dis 11:286. doi:10.1186/1471-2334-11-286
99. Fuller JD, Low DE (2005) A review of Streptococcus pneumoniae infection treatment failures associated with fluoroquinolone resistance. Clin Infect Dis 41:118–121. doi:10.1086/430829
100. Dunbar LM, Wunderink RG, Habib MP et al (2003) High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. Clin Infect Dis 37:752–760. doi:10.1086/377539

101. Pea F, Di Qual E, Cusenza A et al (2003) Pharmacokinetics and pharmacodynamics of intravenous levofloxacin in patients with early-onset ventilator-associated pneumonia. Clin Pharmacokinet 42:589–598
102. Sánchez Navarro A, Colino Gandarillas C-I, Alvarez Lerma F et al (2005) Pharmacokinetics and pharmacodynamics of levofloxacin in intensive care patients. Clin Pharmacokinet 44:627–635
103. Labreche MJ, Frei CR (2012) Declining susceptibilities of gram-negative bacteria to the fluoroquinolones: effects on pharmacokinetics, pharmacodynamics, and clinical outcomes. Am J Health-Syst Pharm 69:1863–1870. doi:10.2146/ajhp110464
104. Homma T, Hori T, Sugimori G, Yamano Y (2007) Pharmacodynamic assessment based on mutant prevention concentrations of fluoroquinolones to prevent the emergence of resistant mutants of Streptococcus pneumoniae. Antimicrob Agents Chemother 51:3810–3815. doi:10.1128/AAC.01372-06
105. Scaglione F (2002) Can PK/PD be used in everyday clinical practice. Int J Antimicrob Agents 19:349–353
106. Pea F, Poz D, Viale P et al (2006) Which reliable pharmacodynamic breakpoint should be advised for ciprofloxacin monotherapy in the hospital setting? A TDM-based retrospective perspective. J Antimicrob Chemother 58:380–386. doi:10.1093/jac/dkl226
107. Roberts JA, Norris R, Paterson DL, Martin JH (2012) Therapeutic drug monitoring of antimicrobials. Br J Clin Pharmacol 73:27–36. doi:10.1111/j.1365-2125.2011.04080.x
108. Gao C-H, L-S Y, Zeng S et al (2014) Personalized therapeutics for levofloxacin: a focus on pharmacokinetic concerns. Ther Clin Risk Manag 10:217–227. doi:10.2147/TCRM.S59079
109. Montay G, Gaillot J (1990) Pharmacokinetics of fluoroquinolones in hepatic failure. J Antimicrob Chemother 26(Suppl B):61–67
110. Alsultan A, An G, Peloquin CA (2015) Limited sampling strategy and target attainment analysis for levofloxacin in patients with tuberculosis. Antimicrob Agents Chemother 59:3800–3807. doi:10.1128/AAC.00341-15
111. Long R, Barrie J, Peloquin CA (2015) Therapeutic drug monitoring and the conservative management of chronic tuberculous empyema: case report and review of the literature. BMC Infect Dis 15:327. doi:10.1186/s12879-015-1093-7
112. Manika K, Chatzika K, Zarogoulidis K, Kioumis I (2012) Moxifloxacin in multidrug-resistant tuberculosis: is there any indication for therapeutic drug monitoring? Eur Respir J 40:1051–1053. doi:10.1183/09031936.00202411
113. Lee SH, Seo K-A, Lee YM et al (2015) Low serum concentrations of moxifloxacin, prothionamide, and cycloserine on sputum conversion in multi-drug resistant TB. Yonsei Med J 56:961–967. doi:10.3349/ymj.2015.56.4.961
114. Pranger AD, Kosterink JGW, van Altena R et al (2011) Limited-sampling strategies for therapeutic drug monitoring of moxifloxacin in patients with tuberculosis. Ther Drug Monit 33:350–354. doi:10.1097/FTD.0b013e31821b793c
115. Di Paolo A, Malacarne P, Guidotti E et al (2010) Pharmacological issues of linezolid: an updated critical review. Clin Pharmacokinet 49:439–447. doi:10.2165/11319960-000000000-00000
116. Dryden MS (2011) Linezolid pharmacokinetics and pharmacodynamics in clinical treatment. J Antimicrob Chemother 66(Suppl 4):iv7–iv15. doi:10.1093/jac/dkr072
117. Matsumoto K, Takeshita A, Ikawa K et al (2010) Higher linezolid exposure and higher frequency of thrombocytopenia in patients with renal dysfunction. Int J Antimicrob Agents 36:179–181. doi:10.1016/j.ijantimicag.2010.02.019
118. Tsuji Y, Hiraki Y, Matsumoto K et al (2011) Thrombocytopenia and anemia caused by a persistent high linezolid concentration in patients with renal dysfunction. J Infect Chemother 17:70–75. doi:10.1007/s10156-010-0080-6
119. Tsuji Y, Yukawa E, Hiraki Y et al (2013) Population pharmacokinetic analysis of linezolid in low body weight patients with renal dysfunction. J Clin Pharmacol 53:967–973. doi:10.1002/jcph.133
120. Zoller M, Maier B, Hornuss C et al (2014) Variability of linezolid concentrations after standard dosing in critically ill patients: a prospective observational study. Crit Care 18:R148. doi:10.1186/cc13984

121. Pea F, Furlanut M, Cojutti P et al (2010) Therapeutic drug monitoring of linezolid: a retrospective monocentric analysis. Antimicrob Agents Chemother 54:4605–4610. doi:10.1128/AAC.00177-10
122. Abe S, Chiba K, Cirincione B et al (2009) Population pharmacokinetic analysis of linezolid in patients with infectious disease: application to lower body weight and elderly patients. J Clin Pharmacol 49:1071–1078. doi:10.1177/0091270009337947
123. Nukui Y, Hatakeyama S, Okamoto K et al (2013) High plasma linezolid concentration and impaired renal function affect development of linezolid-induced thrombocytopenia. J Antimicrob Chemother 68:2128–2133. doi:10.1093/jac/dkt133
124. Pea F, Viale P, Cojutti P et al (2012) Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients. J Antimicrob Chemother 67:2034–2042. doi:10.1093/jac/dks153
125. Bhalodi AA, Papasavas PK, Tishler DS et al (2013) Pharmacokinetics of intravenous linezolid in moderately to morbidly obese adults. Antimicrob Agents Chemother 57:1144–1149. doi:10.1128/AAC.01453-12
126. Hamilton R, Thai XC, Ameri D, Pai MP (2013) Oral bioavailability of linezolid before and after Roux-en-Y gastric bypass surgery: is dose modification necessary in obese subjects? J Antimicrob Chemother 68:666–673. doi:10.1093/jac/dks431
127. Cojutti P, Maximova N, Crichiutti G et al (2015) Pharmacokinetic/pharmacodynamic evaluation of linezolid in hospitalized paediatric patients: a step toward dose optimization by means of therapeutic drug monitoring and Monte Carlo simulation. J Antimicrob Chemother 70:198–206. doi:10.1093/jac/dku337
128. Matsumoto K, Shigemi A, Takeshita A et al (2014) Analysis of thrombocytopenic effects and population pharmacokinetics of linezolid: a dosage strategy according to the trough concentration target and renal function in adult patients. Int J Antimicrob Agents 44:242–247. doi:10.1016/j.ijantimicag.2014.05.010
129. Boak LM, Rayner CR, Grayson ML et al (2014) Clinical population pharmacokinetics and toxicodynamics of linezolid. Antimicrob Agents Chemother 58:2334–2343. doi:10.1128/AAC.01885-13
130. Cattaneo D, Orlando G, Cozzi V et al (2013) Linezolid plasma concentrations and occurrence of drug-related haematological toxicity in patients with gram-positive infections. Int J Antimicrob Agents 41:586–589. doi:10.1016/j.ijantimicag.2013.02.020
131. Hiraki Y, Tsuji Y, Hiraike M et al (2012) Correlation between serum linezolid concentration and the development of thrombocytopenia. Scand J Infect Dis 44:60–64. doi:10.3109/00365548.2011.608712
132. Cattaneo D, Gervasoni C, Clementi E (2016) Is there still room for therapeutic drug monitoring of linezolid in patients with tuberculosis? Eur Respir J 47:1287–1288. doi:10.1183/13993003.01913-2015
133. De Pascale G, Fortuna S, Tumbarello M et al (2015) Linezolid plasma and intrapulmonary concentrations in critically ill obese patients with ventilator-associated pneumonia: intermittent vs continuous administration. Intensive Care Med 41:103–110. doi:10.1007/s00134-014-3550-y
134. Dong H, Xie J, Chen L et al (2014) Developments in the pharmacokinetic/pharmacodynamic index of linezolid: a step toward dose optimization using Monte Carlo simulation in critically ill patients. Int J Infect Dis 22:35–40. doi:10.1016/j.ijid.2014.01.016
135. Alffenaar J-WC, Kosterink JGW, van Altena R et al (2010) Limited sampling strategies for therapeutic drug monitoring of linezolid in patients with multidrug-resistant tuberculosis. Ther Drug Monit 32:97–101. doi:10.1097/FTD.0b013e3181cc6d6f
136. Falagas ME, Kasiakou SK (2005) Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. Clin Infect Dis 40:1333–1341. doi:10.1086/429323
137. Zavascki AP (2014) Polymyxins for the treatment of extensively-drug-resistant Gram-negative bacteria: from pharmacokinetics to bedside. Expert Rev Anti Infect Ther 12:531–533. doi:10.1586/14787210.2014.902307

138. Nation RL, Li J, Cars O et al (2015) Framework for optimisation of the clinical use of colistin and polymyxin B: the Prato polymyxin consensus. Lancet Infect Dis 15:225–234. doi:10.1016/S1473-3099(14)70850-3
139. Garonzik SM, Li J, Thamlikitkul V et al (2011) Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. Antimicrob Agents Chemother 55:3284–3294. doi:10.1128/AAC.01733-10
140. Plachouras D, Karvanen M, Friberg LE et al (2009) Population pharmacokinetic analysis of colistin methanesulfonate and colistin after intravenous administration in critically ill patients with infections caused by gram-negative bacteria. Antimicrob Agents Chemother 53:3430–3436. doi:10.1128/AAC.01361-08
141. Sorlí L, Luque S, Campillo N, et al (2016) Impact of colistin therapeutic drug monitoring in a clinical setting. Amsterdam, Netherlands
142. Bode-Böger SM, Schopp B, Tröger U et al (2013) Intravenous colistin in a patient with serious burns and borderline syndrome: the benefits of therapeutic drug monitoring. Int J Antimicrob Agents 42:357–360. doi:10.1016/j.ijantimicag.2013.06.009
143. Yaita K, Sameshima I, Takeyama H et al (2013) Liver abscess caused by multidrug-resistant Pseudomonas aeruginosa treated with colistin; a case report and review of the literature. Intern Med Tokyo Jpn 52:1407–1412
144. Yamada T, Ishiguro N, Oku K et al (2015) Successful colistin treatment of multidrug-resistant Pseudomonas aeruginosa infection using a rapid method for determination of colistin in plasma: usefulness of therapeutic drug monitoring. Biol Pharm Bull 38:1430–1433. doi:10.1248/bpb.b15-00323
145. Karaiskos I, Friberg LE, Pontikis K et al (2015) Colistin population pharmacokinetics after application of a loading dose of 9 MU colistin methanesulfonate in critically ill patients. Antimicrob Agents Chemother 59:7240–7248. doi:10.1128/AAC.00554-15
146. Mohamed AF, Karaiskos I, Plachouras D et al (2012) Application of a loading dose of colistin methanesulfonate in critically ill patients: population pharmacokinetics, protein binding, and prediction of bacterial kill. Antimicrob Agents Chemother 56:4241–4249. doi:10.1128/AAC.06426-11
147. Nation RL, Garonzik SM, Li J et al (2016) Updated US and European dose recommendations for intravenous colistin: how do they perform? Clin Infect Dis 62:552–558. doi:10.1093/cid/civ964
148. Sorlí L, Luque S, Grau S et al (2013) Trough colistin plasma level is an independent risk factor for nephrotoxicity: a prospective observational cohort study. BMC Infect Dis 13:380. doi:10.1186/1471-2334-13-380
149. Horcajada JP, Sorlí L, Luque S et al (2016) Validation of a colistin plasma concentration breakpoint as a predictor of nephrotoxicity in patients treated with colistin methanesulfonate. Int J Antimicrob Agents 48:725–727. doi:10.1016/j.ijantimicag.2016.08.020
150. Landersdorfer CB, Nation RL (2015) Colistin: how should it be dosed for the critically ill? Semin Respir Crit Care Med 36:126–135. doi:10.1055/s-0034-1398390
151. Moise PA, North D, Steenbergen JN, Sakoulas G (2009) Susceptibility relationship between vancomycin and daptomycin in Staphylococcus aureus: facts and assumptions. Lancet Infect Dis 9:617–624. doi:10.1016/S1473-3099(09)70200-2
152. Rose WE, Leonard SN, Sakoulas G et al (2008) daptomycin activity against Staphylococcus aureus following vancomycin exposure in an in vitro pharmacodynamic model with simulated endocardial vegetations. Antimicrob Agents Chemother 52:831–836. doi:10.1128/AAC.00869-07
153. Safdar N, Andes D, Craig WA (2004) In vivo pharmacodynamic activity of daptomycin. Antimicrob Agents Chemother 48:63–68
154. Falcone M, Russo A, Cassetta MI et al (2013) Variability of pharmacokinetic parameters in patients receiving different dosages of daptomycin: is therapeutic drug monitoring necessary? J Infect Chemother 19:732–739. doi:10.1007/s10156-013-0559-z
155. Firsov AA, Smirnova MV, Lubenko IY et al (2006) Testing the mutant selection window hypothesis with Staphylococcus aureus exposed to daptomycin and vancomycin in an in vitro dynamic model. J Antimicrob Chemother 58:1185–1192. doi:10.1093/jac/dkl387

156. Chambers HF, Basuino L, Diep BA et al (2009) Relationship between susceptibility to daptomycin in vitro and activity in vivo in a rabbit model of aortic valve endocarditis. Antimicrob Agents Chemother 53:1463–1467. doi:10.1128/AAC.01307-08
157. Reiber C, Senn O, Müller D et al (2015) Therapeutic drug monitoring of daptomycin: a retrospective monocentric analysis. Ther Drug Monit 37:634–640. doi:10.1097/FTD.0000000000000196
158. D'Avolio A, Pensi D, Baietto L et al (2016) Daptomycin pharmacokinetics and pharmacodynamics in septic and critically ill patients. Drugs 76:1161–1174. doi:10.1007/s40265-016-0610-3
159. Falcone M, Russo A, Cassetta MI et al (2012) Daptomycin serum levels in critical patients undergoing continuous renal replacement. J Chemother 24:253–256. doi:10.1179/1973947812Y.0000000033
160. Bhavnani SM, Rubino CM, Ambrose PG, Drusano GL (2010) Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. Clin Infect Dis 50:1568–1574. doi:10.1086/652767
161. Barreau S, Benaboud S, Kernéis S et al (2016) Staphylococcus aureus osteo-articular infection: usefulness of the determination of daptomycin serum concentration to explain a treatment failure. Int J Clin Pharmacol Ther 54:923–927. doi:10.5414/CP202538
162. Cohen-Wolkowiez M, Smith PB, Benjamin DK et al (2008) Daptomycin use in infants: report of two cases with peak and trough drug concentrations. J Perinatol Off J Calif Perinat Assoc 28:233–234. doi:10.1038/sj.jp.7211898
163. Soto D, Silva C, Andresen VM et al (2015) Monitorización terapéutica de antibióticos: Nuevas metodologías: biosensores. Rev Médica Chile 143:1050–1057. doi:10.4067/S0034-98872015000800013
164. Ferguson BS, Hoggarth DA, Maliniak D et al (2013) Real-time, aptamer-based tracking of circulating therapeutic agents in living animals. Sci Transl Med 5:213ra165. doi:10.1126/scitranslmed.3007095
165. Tsalik EL, Henao R, Nichols M et al (2016) Host gene expression classifiers diagnose acute respiratory illness etiology. Sci Transl Med 8:322ra11. doi:10.1126/scitranslmed.aad6873
166. Webster M, Kumar VS (2016) A blood scan for sepsis? Clin Chem 62:538–540. doi:10.1373/clinchem.2015.253682

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

Jan J. De Waele

10.1 Introduction

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

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

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

A.A. Udy et al. (eds.), *Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill*, DOI 10.1007/978-981-10-5336-8_10

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

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

10.2 Classical View of Antibiotic Dosing

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

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

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

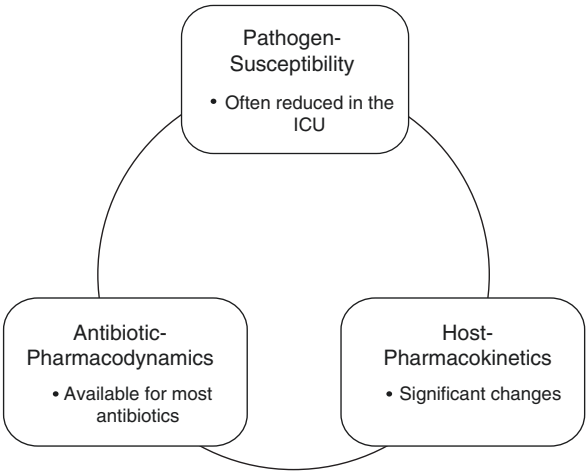

Fig. 10.1 Factors determining antibiotic efficacy

10.3 Determinants of Antibiotic Efficacy

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

10.3.1 The Host

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

10.3.2 The Pathogen

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

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

10.3.3 The Antibiotic

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

10.4 Generic Dosing: One Size Fits All

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

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

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

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

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

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

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

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

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

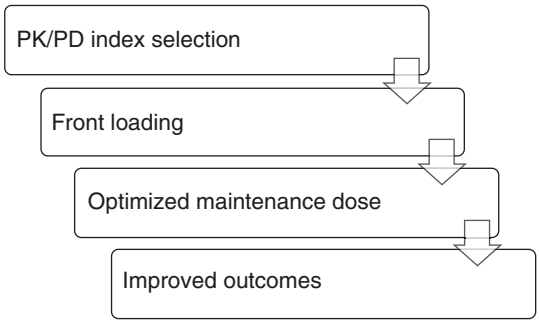

Fig. 10.2 PK/PD-optimized therapy

10.5.1 Step 1: Selecting the PK/PD Target

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

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

10.5.2 Step 2: Front Loading

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

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

10.5.3 Step 3: Optimized Maintenance Therapy

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

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

10.5.4 Choosing the Correct Dose

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

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

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

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

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

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

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

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

10.6 Practical Considerations

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

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

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

10.7 Obstacles to Optimized Dosing

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

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

10.8 Unanswered Questions

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

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

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

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

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

10.9 Summary

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

References

1. Tabah A, De Waele J, Lipman J, Zahar JR, Cotta MO, Barton G, Timsit JF, Roberts JA, Working Group for Antimicrobial Use in the ICU within the Infection Section of the European Society of Intensive Care Medicine ESICM (2015) The ADMIN-ICU survey: a survey on antimicrobial dosing and monitoring in ICUs. J Antimicrob Chemother 70:2671–2677

2. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 39:165–228
3. Felton TW, Hope WW, Roberts JA (2014) How severe is antibiotic pharmacokinetic variability in critically ill patients and what can be done about it. Diagn Microbiol Infect Dis 79:441–447
4. Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, Hope WW, Farkas A, Neely MN, Schentag JJ, Drusano G, Frey OR, Theuretzbacher U, Kuti JL (2014) Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis 14(6):498–509
5. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, Napolitano LM, O'Grady NP, Bartlett JG, Carratalà J, El Solh AA, Ewig S, Fey PD, File TM, Restrepo MI, Roberts JA, Waterer GW, Cruse P, Knight SL, Brozek JL (2016) Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 63:e61–e111
6. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM (2004) Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Intensive Care Med 30:536–555
7. Póvoa P, Salluh JI (2012) Biomarker-guided antibiotic therapy in adult critically ill patients: a critical review. Ann Intensive Care 2:32
8. Tsai D, Lipman J, Roberts JA (2015) Pharmacokinetic/pharmacodynamic considerations for the optimization of antimicrobial delivery in the critically ill. Curr Opin Crit Care 21:412–420
9. Goncalves-Pereira J, Povoa P (2011) Antibiotics in critically ill patients: a systematic review of the pharmacokinetics of beta-lactams. Crit Care 15:R206
10. Ulldemolins M, Roberts JA, Rello J, Paterson DL, Lipman J (2011) The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet 50:99–110
11. Udy AA, Roberts JA, Lipman J (2011) Implications of augmented renal clearance in critically ill patients. Nat Rev Nephrol 7:539–543
12. Douglas IS (2016) New diagnostic methods for pneumonia in the ICU. Curr Opin Infect Dis 29:197–204
13. De Waele JJ, Schouten J, Dimopoulos G (2015) Understanding antibiotic stewardship for the critically ill. Intensive Care Med 42(12):2063–2065
14. Roberts JA, Lipman J (2009) Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 37:840–851. Quiz 859
15. Jamal JA, Economou CJ, Lipman J, Roberts JA (2012) Improving antibiotic dosing in special situations in the ICU: burns, renal replacement therapy and extracorporeal membrane oxygenation. Curr Opin Crit Care 18:460–471
16. De Waele JJ, Lipman J, Carlier M, Roberts JA (2015) Subtleties in practical application of prolonged infusion of β-lactam antibiotics. Int J Antimicrob Agents 45:461–463
17. Abdul-Aziz MH, Lipman J, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, Dulhunty J, Kaukonen KM, Koulenti D, Martin C, Montravers P, Rello J, Rhodes A, Starr T, Wallis SC, Roberts JA, SG DALI (2016) Is prolonged infusion of piperacillin/tazobactam and meropenem in critically ill patients associated with improved pharmacokinetic/pharmacodynamic and patient outcomes? An observation from the Defining Antibiotic Levels in Intensive care unit patients (DALI) cohort. J Antimicrob Chemother 71:196–207
18. Carlier M, Dumoulin A, Janssen A, Picavet S, Vanthuyne S, Van Eynde R, Vanholder R, Delanghe J, De Schoenmakere G, De Waele JJ, Hoste EA (2015) Comparison of different equations to assess glomerular filtration in critically ill patients. Intensive Care Med 41:427–435
19. Roberts JA, Taccone FS, Lipman J (2015) Understanding PK/PD. Intensive Care Med 42(11):1797–1800

20. Colin P, Eleveld DJ, Jonckheere S, Van Bocxlaer J, De Waele J, Vermeulen A (2016) What about confidence intervals? A word of caution when interpreting PTA simulations. J Antimicrob Chemother 71:2502–2508
21. Sime FB, Roberts MS, Roberts JA (2015) Optimization of dosing regimens and dosing in special populations. Clin Microbiol Infect 21(10):886–893
22. Huttner A, Harbarth S, Hope WW, Lipman J, Roberts JA (2015) Therapeutic drug monitoring of the β-lactam antibiotics: what is the evidence and which patients should we be using it for. J Antimicrob Chemother 70:3178–3183
23. Roberts JA, Taccone FS, Udy AA, Vincent JL, Jacobs F, Lipman J (2011) Vancomycin dosing in critically ill patients: robust methods for improved continuous-infusion regimens. Antimicrob Agents Chemother 55:2704–2709
24. Carlier M, Stove V, Wallis SC, De Waele JJ, Verstraete AG, Lipman J, Roberts JA (2015) Assays for therapeutic drug monitoring of β-lactam antibiotics: a structured review. Int J Antimicrob Agents 46:367–375

Chapter 11
Antifungal PK/PD in the Critically Ill

Roger J.M. Brüggemann, Dylan W. de Lange, and Jan-Willem C. Alffenaar

11.1 Introduction

Invasive fungal disease (IFD) can be life-threatening. In the past two decades, the incidence of these infections has increased significantly, largely because of the increasing number of patients at risk [1]. Although IFD can affect people with an intact immune systems as well, the vast majority of these infections occur as opportunistic infections in the immunocompromised host. IFD can be caused by both yeasts and filamentous molds. Yeasts are a type of fungi that consist of solitary cells that reproduce by budding, whereas molds occur in the form of hyphae: long, tubular branches with multiple, genetically identical nuclei which grow by apical extension. The most common forms of IFD in the immunocompromised host include invasive candidiasis (yeast) and invasive aspergillosis (mold).

11.2 Invasive Candidiasis

Yeasts such as *Candida* spp. are part of our normal microbial flora on mucosal surfaces (primarily the gut, the oral cavity, and the upper respiratory tract, although the skin may also provide a habitat), from where they may translocate into the tissues or blood in patients with varying underlying diseases or host factors, causing

R.J. Brüggemann, Pharm.D., Ph.D. (✉)
Radboud University Medical Center, Nijmegen, The Netherlands
e-mail: Roger.Bruggemann@radboudumc.nl

D.W. de Lange, M.D., Ph.D.
University Medical Center Utrecht, Utrecht, The Netherlands

J.-W. C. Alffenaar, Pharm.D., Ph.D.
University Medical Center Groningen, Groningen, The Netherlands

A.A. Udy et al. (eds.), *Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill*, DOI 10.1007/978-981-10-5336-8_11

invasive disease (invasive candidiasis), most often presenting as candidemia [2]. At a later stage, candidemia can undergo secondary dissemination to organs (e.g., eyes, liver, spleen, bones, heart valves, central nervous system) or present as deep-seated candidiasis [2, 3].

The pathogenesis of invasive candidiasis involves three major components: (a) increased fungal burden or colonization, mostly resulting from the use of broad-spectrum antibiotics; (b) disruption .of normal mucosal barriers induced by disease, drugs, trauma, or intravascular catheters; and (c) immune impairment (e.g., neutropenia) [4]. Not surprisingly, invasive candidiasis occurs most frequently in immunocompromised hosts and critically ill patients, with mortality rates reported to be as high as 40%, despite the use of antifungal therapy [2].

11.3 Invasive Aspergillosis

Molds such as *Aspergillus* spp. are saprophytic filamentous fungi and found widely in the environment. They are commonly found in both the outdoor and the indoor environment, including hospitals [5, 6]. Invasive aspergillosis, i.e., *Aspergillus hyphae* penetrating the lung tissue and entering the bloodstream via the distal airways and alveolar spaces of the lung [7], is a serious opportunistic infection that mainly affects immunocompromised patients, particularly patients with hematological malignancies (e.g., leukemia), solid-organ and hematopoietic stem cell transplant patients, patients on prolonged corticosteroid therapy, and patients suffering from genetic immunodeficiencies (e.g., chronic granulomatous disease) [8, 9]. In addition, prolonged critical illness is now considered an additional risk factor for invasive aspergillosis [10]. In these high-risk populations, mortality rates for invasive aspergillosis range from 40 to 90% [8, 11].

Other pathogens besides *Candida* spp. and *Aspergillus* spp. that cause IFD in the immunocompromised host are *Mucorales* spp. (zygomycosis), *Fusarium, Scedosporium* spp. (hyalohyphomycosis), *Pneumocystis*, and *Cryptococcus* spp. Although these infections are less common, specifically in the intensive care unit, they are associated with a high mortality rate.

11.4 Antifungal Drugs in Clinical Use

Based on their mode of action (Fig. 11.1), antifungal drugs frequently administered for systemic use have been grouped into four classes, namely, triazoles (fluconazole, itraconazole, posaconazole, voriconazole, isavuconazole), echinocandins (anidulafungin, caspofungin, micafungin), polyenes (lipid complexes of amphotericin B), and fluoro-pyrimidines (flucytosine [5-FC]).

Triazoles act by targeted inhibition of the cytochrome (CYP) P450 dependent enzyme lanosterol demethylase, thereby interrupting the synthesis of ergosterol.

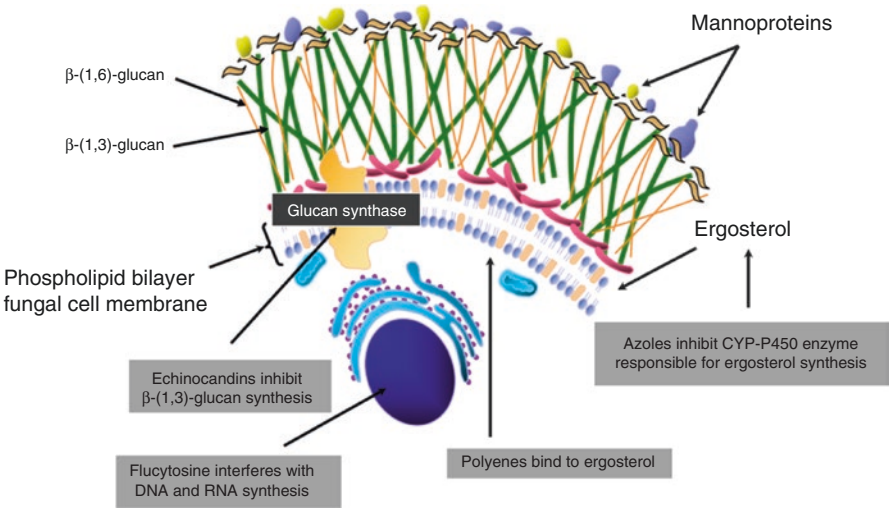

Fig. 11.1 Schematic overview of current antifungal agents and their mechanism of action. Adapted from Kartsonis et al. [159]

This inhibition leads to depletion of ergosterol and the accumulation of sterol precursors in the fungal cell membrane, causing increased membrane permeability and inhibition of fungal growth [12]. Echinocandins act by noncompetitive inhibition of β-(1,3)-D-glucan synthase, thereby blocking the synthesis of this major component of the fungal cell wall. This compromises cellular structural integrity and morphology, ultimately resulting in osmotic lysis of the fungal cell [13].

Amphotericin B acts by binding directly to membrane sterols (especially ergosterol) in the fungal cell membrane. Through self-assembly of amphotericin B molecules, ionic transmembrane channels are formed that cause the fungal cell to leak its intracellular contents (e.g., potassium), subsequently leading to cell death [14].

The pyrimidine analog 5-FC itself has no intrinsic antifungal activity, but once it has been taken up by fungal cells, it is converted to 5-fluorouracil (5-FU). Metabolites of 5-FU act by inhibiting the DNA and RNA synthesis in the nucleus of the fungal cell [15].

11.5 Pharmacokinetics of Echinocandins in Critically Ill Patients

The pharmacokinetics (PK) of antifungal drugs, much like antimicrobials, can be highly variable in critically ill patients due to several physiological factors such as a hyperdynamic state, third spacing, hypoalbuminemia, renal dysfunction, hepatic dysfunction, and organ support [16, 17]. Furthermore, extracorporeal membrane oxygenation (ECMO) can alter the PK of drugs due to the addition of blood

products to the circuit and potential binding of drugs to the surface of the ECMO circuit [18]. The consequence of these changes in PK is that the echinocandins might present lower exposure in critically ill patients.

Echinocandins have been extensively studied in critically ill patients with the consequence that many issues around their altered PK in critical illness are now more thoroughly understood. There are, however, noticeable differences in PK between the three echinocandins including the need for loading doses of anidulafungin and caspofungin, the metabolic pathways (hepatic versus non-hepatic or a combination of both), and the number and extent of clinically relevant drug–drug interactions (see http://www.fungalpharmacology.org for an extensive overview of drug–drug interactions with echinocandins). There are no head-to-head comparative efficacy trials in critically ill patients and, at present, the three available echinocandins are considered equivalent. With such comparable guideline recommendations, apart from those in neonates and children, the PK differences are the only aspects that may support a specific choice (Table 11.1).

Anidulafungin is given as a 200 mg loading dose on day 1 followed by a 100 mg daily maintenance dose. PK in critically ill patients have been fairly well described for anidulafungin. Both comparable exposure in critically ill patients and reduced exposure (decreases in the area under the concentration time curve [AUC0–24] of 25% and trough concentrations [C_{min}] of 40%) [19–21] have been reported in reference to healthy volunteers. There is a general tendency to lower exposure of anidulafungin in critically ill patients, but up until today no major dominant factors associated with altered PK have been identified. Disease severity scores and albumin concentrations appear not to influence anidulafungin PK [19–21]. The pharmacodynamic goals of anidulafungin are not yet well defined and underdosing looms in critically ill patients.

Caspofungin is given as a 70 mg loading dose followed by a 50 mg maintenance dose. It is recommended to increase the maintenance dose to 70 mg if body weight exceeds 80 kg. Like anidulafungin, PK data for caspofungin in critically ill patients are conflicting. In surgical ICU patients, caspofungin C_{min} plasma concentrations were slightly increased compared to healthy volunteers (2.16 mg/L vs. 1.41 mg/L) [22]. Another study in 20 ICU patients with (suspected) invasive candidiasis found lower exposure to caspofungin on day 3 compared to historical controls [23]. But in a marginally larger cohort of general ICU patients ($n = 27$), caspofungin AUC was comparable to healthy volunteers [24–26]. No factors that might influence the PK of caspofungin were identified, although the sample size might have been too low to detect significant covariates [24, 25].

Unlike anidulafungin and caspofungin, micafungin does not require a loading dose. From day 1 onwards, it is given as a single daily dose of 100 mg. Similar to caspofungin, the PK of micafungin has been extensively studied. Critical illness appears to impact the exposure to micafungin as ICU patients had lower exposure after standard dosages of micafungin compared to healthy controls. Unfortunately, this study did not identify any relevant covariates to explain the lower exposure, which was potentially caused by the limited number of patients ($n = 20$). In a second study in 100 patients, the micafungin clearance of 1.34 L/min was markedly higher than

Table 11.1 Comparative pharmacokinetics of triazole and echinocandin antifungal agents in healthy volunteers [12, 154–158]

PK parameter	Antifungal drug							
	FLZ	ITZ[a]	PSZ[b]	VCZ	ISA	ANF	CAS	MCF
Drug formulations	IV/C/S	IV[c]/C/S	IV/T/S	IV/T/S	IV/C	IV	IV	IV
F (%)	>90	50	54	96	98	<5	<5	<5
AUC_{0-24} (mg*h/L)	400–800	29.2	8.9	20.3	121.4	110	97.6	132.6
C_{max} (mg/L)	6–20	0.5–2.3	1.5–2.2	3–4.6	7.5	7.2	12.1	8.8
T_{max} (h)	1–2	2.2–2.5	4–5	1–2	3	N/A	N/A	N/A
V_D (L/kg)	0.56–0.82	~11	7–25	4.6	4.4–7.7	0.6	N/A	0.25–0.27
PPB (%)	11–12	99.8	99	58	>99	99	97	>99
CSF (%)	>60	<10	ND	60	Poor in CSF, good in brain[d]	<5	<5	<5
Vitreous (%)	28–75[d,e]	10[d]	26[d,e]	38[d]	Good	0[e]	0[d]	<1[e]
Urine (%)	90	1–10	<2	<2	<1	<2	<2	<2
Metabolism	Minor hepatic	Hepatic (CYP3A4)	Minor Hepatic (UGT)	Hepatic (CYP2C19, 2C9, 3A4)	Hepatic (CYP3A4, UGT)	N/A (nonenzymatic degradation)	Hepatic (hydrolysis, N-acetylation)	Hepatic (arylsulfatase and catechol-O-methyltransferase)
Elimination	Renal	Hepatic	Feces	Renal	Feces	Feces	Urine	Feces
CL (L/h)	0.27–0.63	22.9	32	20	2.6	0.96	0.63	0.63
$T_{1/2}$ (h)	30	24	25	6 (but nonlinear PK)	130	~24	10.6 (β-phase)	14.7

[a]Oral solution formulation
[b]Tablet formulation
[c]IV formulation not available in all countries
[d]Data from human studies
[e]Data from animal studies

reported in the literature, and higher than the study reported by Lempers et al. [27]. Body weight, albumin, and SOFA score were found to significantly influence the interindividual variability in clearance (CL), volume of the central compartment, and peripheral compartment. In general, the exposure of critically ill patients to micafungin is potentially lower than healthy controls and dosages should be adjusted upward.

11.6 Use of Echinocandins in Patients with Renal Impairment, Renal Replacement Therapy, and ECMO

Patients with varying stages of renal impairment showed no statistical differences in PK for anidulafungin and micafungin compared to matched healthy volunteers. Therefore, these echinocandins provide an excellent therapeutic option in patients with renal failure. The PK of anidulafungin 50 mg and micafungin 100 mg single dose was unaffected by renal impairment, as no significant differences in AUC, peak concentration (C_{max}), CL, volume of distribution (Vd), or half-life were observed compared to healthy volunteers [28, 29]. Contrary to anidulafungin and micafungin, there are no publications on PK of caspofungin in patients with renal failure. The scarce information that is available on caspofungin is derived from the medicines authorities [30]. Increases in exposure to caspofungin were seen in patients with different degrees of renal impairment (increases in AUC of 31%, 49%, and 30% in patients with moderate, severe, and end-stage renal disease, respectively). Whether these higher exposures lead to either toxicity or improved pharmacodynamics in critically ill patients needs to be investigated.

In the ICU, when native renal function deteriorates precipitously, continuous renal replacement therapy (CRRT) is typically provided. Continuous exposure to extracorporeal devices (e.g., tubing, catheters, filters) might profoundly alter the PK of echinocandins. In this fashion, the PK of anidulafungin in patients dependent on chronic intermittent hemodialysis were comparable to healthy volunteers and were not influenced by the time of drug administration in relation to the time of dialysis. Furthermore, no anidulafungin concentrations were found in dialysate [29]. Extended daily dialysis (8 h) did not change PK of anidulafungin, and no measurable anidulafungin concentrations were found in the dialysate [31].

Like in intermittent hemodialysis, anidulafungin PK in critically ill patients undergoing CRRT were comparable to PK in healthy volunteers, and patients with a fungal infection. No accumulation of anidulafungin was seen within 3 days of treatment [32, 33]. Similarly effluent samples did not contain measurable levels of anidulafungin [32, 33]. Therefore, at present, there is no adjustment of anidulafungin advised for patients on CRRT.

The PK parameters of caspofungin after a single dose and multiple doses during CRRT in critically ill patients were, like anidulafungin, unchanged [26, 34]. Small differences in pre-filter and post-filter concentrations suggest that there might be some adsorption of caspofungin to the hemofilter membranes, but caspofungin PK parameters were not significantly influenced [26].

In critically ill patients undergoing CRRT, the PK of micafungin was similarly unaffected [35, 36]. During CRRT, plasma samples from the inlet and outlet of the extracorporeal circuit were comparable and no micafungin was detected in effluent [35]. No adsorption to or saturation of the polysulfone and polyethersulfone filters was reported [36].

Data on caspofungin PK in patients on ECMO therapy is limited and provides varying results. Plasma concentrations of caspofungin in surgical ICU patients varied between undetectable or low (1.8 and 3.4 mg/L; single patient two occasions) and normal concentrations in comparison to healthy volunteers [18, 37]. Anidulafungin has been applied to critically ill patients while on ECMO. Anidulafungin concentrations were not influenced by the oxygenator or tubing [38]. Research in adult patients on ECMO receiving micafungin is lacking. Micafungin was evaluated in pediatric patients on ECMO and the Vd and CL were at the upper limits of normal in comparison to patients not on ECMO [39].

11.7 Use of Echinocandins in Patients with Hepatic Insufficiency

No significant changes in the PK of anidulafungin are observed in patients with mild and moderate hepatic impairment when compared to healthy volunteers [29]. However, patients with severe hepatic impairment show significantly decreased AUC and C_{max} values compared to healthy volunteers [29]. AUC and C_{max} are decreased by 33% and 36%, respectively. CL and Vd are increased by 57% and 78%, respectively, but were not considered clinically relevant by the authors. The most likely explanation for this lower exposure is an increase in Vd caused by ascites and edema [29]. However, in a single severely hepatic impaired patient requiring albumin dialysis, anidulafungin PK did not appear to be affected [40].

For caspofungin, the AUC0-∞ is increased by 55 and 76% in patients with mild and moderate hepatic impairment, respectively. In addition, the C_{min} and elimination half-life are increased as well in comparison to healthy volunteers [41]. After multiple dose administration of caspofungin (70 mg loading dose, followed by 35 mg OD), moderate PK changes were observed in mild hepatic impairment, but these changes were not considered clinically relevant [41]. More specifically, on days 1, 7, and 14 AUC0–24 increased by 17%, 26%, and 21%, respectively; whereas on days 1, 7, and 14 C_{min} increased with 50%, 70%, and 44%, respectively. Multiple dose administration of caspofungin (70 mg loading dose followed by 35 mg OD) to patients with moderate hepatic impairment showed no significant differences in AUC0–24 on days 7 and 14 as compared to healthy volunteers receiving the standard dose; C_{max} and C_{min} were decreased by 20% and 23% and by 71% and 50% on days 7 and 14, respectively [41]. A maintenance dose reduction to 35 mg OD in patients with moderate or severe hepatic impairment, as classified by Child Pugh score, is advised as caspofungin PK is affected by the degree of hepatic impairment [30, 41]. Even though the patient populations in these registration studies were

small (6–8 patients for each degree of hepatic impairment), these results were the rationale for dose adjustment in patients with moderate and severe hepatic impairment. The differences in caspofungin PK in hepatically impaired patients are possibly due to decreased clearance mediated by the uptake transporter OATP1B1 in hepatocytes [41]. In contrast, case reports and cohort studies with critically ill patients with mild to moderate hepatic impairment treated with caspofungin 70 mg OD or 50 mg OD showed that dose reductions to 35 mg would possibly have led to suboptimal exposure of caspofungin [24, 42–44].

Pediatric patients with hepatic impairment, similar to adult patients, demonstrate high variability of caspofungin exposure; PK parameters after a daily dose of 1 mg/kg range from being comparable to adult patients to less than half of those seen in adults (AUC0–24 40–50% C_{max} 50% and C_{min} 60% of adult values) in combination with significant increases in CL and Vd (155% and 218%, respectively) [45].

Micafungin exposure in patients with moderate and severe hepatic impairment is decreased in comparison to healthy volunteers (98 mg h/L in patients with moderate hepatic impairment versus 126 mg h/L in healthy volunteers and 100 mg h/L in patients with severe hepatic impairment versus that of 142 mg h/L in healthy volunteers, respectively) [28, 46]. There is no change in the unbound fraction of micafungin in patients with both moderate and severe hepatic impairment compared to healthy volunteers. Interestingly, patients with severe hepatic impairment have higher plasma concentrations of the M5 metabolite, compared to healthy volunteers, possibly due to reduced clearance of the M5 metabolite (the activity of the M5 metabolite is estimated to be only 1/125th of the parent compound) [46]. For patients with both moderate and severe hepatic impairment, the differences in exposure were not considered to be clinically relevant, as a consequence no dose adjustments are advised for patients with any grade of hepatic impairment [28, 46]. In accordance, in living donor liver transplant recipients, micafungin PK was comparable to healthy subjects [47–49].

11.8 Clinical Pharmacology of Echinocandin Drugs

Only very few studies have investigated the relationship between PK and efficacy or toxicity. For echinocandins, the AUC to minimum inhibitory concentration (fAUC:MIC) ratio (using free drug concentration) is the index linking PK to PD [50–53]. Much like other antimicrobial agents, target concentrations have only been defined in animal models or from a single analysis from phase II/III studies. These targets must be defined prior to installing a personalized treatment approach using therapeutic drug monitoring.

Once these target concentrations are established, they will allow Monte Carlo simulations to determine the probability of target attainment (PTA) with specific dosing regimes in critically ill patients [24, 27, 50–52, 54].

Echinocandins are generally administered as a fixed dose (with or without a loading dose) and partly adjusted for body weight. Mixed results have been noted in several smaller PK studies showing lower but also normal concentrations in critically

ill patients compared to non-critically ill patients. Clinical studies that correlate exposure with outcome are urgently needed to be able to make definitive recommendations on using TDM with echinocandins [20, 21, 23, 24, 55, 56].

For caspofungin, no clinical target concentrations have been identified. A limitation of the PTA analysis with caspofungin is thus the absence of a human PK/PD target. A preclinical target derived from a neutropenic mouse model has been used instead [50, 57]. Future studies are warranted to identify the human fAUC:MIC ratio of caspofungin associated with better treatment outcomes. This may be performed similar to a previous analysis on the micafungin PK/PD target as proposed by Andes et al., in which a large group of patients were evaluated on both PK, susceptibility pattern of the pathogen and clinical outcome [58]. Their statistical analysis yielded the most probable fAUC:MIC value associated with mycological response based on two phase 2/3 studies. Even this analysis had some limitations. For instance, "mycological response" was used for treatment outcome. Mycological cure was based on "periodic" or weekly mycology laboratory assessment. It is questionable whether weekly mycology assessment is frequent enough. Moreover, in cases of missing information on micafungin exposure, they used population values, despite high variability between individual predictions and population predictions (precision was about 20%). Such an approach is challenging, as demonstrated by Liu et al. [19], where they could not identify a solid fAUC/MIC target for anidulafungin, using "mycological cure endpoint" data from phase 2/3 studies. Alternative approaches must be found to derive these crucial targets to guide therapy.

An alternative to direct clinical outcome measures such as "mycological cure" or "survival" might be the use of surrogate parameters such as B-glucan. Currently, this biomarker is a promising early diagnostic screening tool for invasive fungal infections, but its role in PK/PD target identification and PD assessment remains to be explored. It may prove beneficial to link B-glucan as a PD endpoint to drug concentrations.

11.9 Pharmacokinetics of Azole Drugs in Critically Ill Patients

Currently, three azole antifungal drugs are frequently used in the intensive care unit, fluconazole, voriconazole, and posaconazole. The use of itraconazole is very limited due to the lack of an intravenous formulation in many countries. Isavuconazole has recently entered the market but data on PK in critically ill patients are lacking as well as PK/PD analyses of isavuconazole in this cohort.

Fluconazole, posaconazole, and voriconazole show markedly different PK behavior in both healthy volunteers but specifically in critically ill patients. These differences between the three azole drugs can be explained by extent of protein binding, the metabolic pathways involved in degradation (including variability due to genetic mutations), renal clearance, and drug–drug interactions [59–62]. Clearly, the variability in clinical condition of the critically ill patient will likely influence the PK of azole drugs [16].

The number of papers on voriconazole PK in critically ill patients is very limited and most of the evidence comes from hematological patients [63–66]. Despite the lack of intensive PK studies in this population, some similarities with other populations may be expected. Voriconazole PK is highly variable in all populations due to age, liver function, polymorphisms in drug metabolizing enzymes, and drug–drug interactions [59]. Recently, an association between clearance of voriconazole and inflammation was suggested. The authors demonstrated that higher voriconazole concentrations were associated with increased C-reactive protein concentrations [67]. Although voriconazole is not extensively bound to plasma proteins, a multivariate analysis revealed a significant relationship with plasma protein binding and plasma albumin concentrations ($P < 0.001$), demonstrating higher unbound voriconazole concentrations with decreasing albumin levels. Of note, the correlation is more pronounced in the presence of elevated bilirubin concentrations [68]. Measurement of the unbound voriconazole concentration may help to detect toxic unbound drug concentrations, even when the total drug concentration is within the therapeutic range [68, 69]. The nonlinear behavior of voriconazole makes it difficult to predict the plasma drug concentration and TDM has therefore been recommended [63] (Table 11.2).

The number of publications on posaconazole PK in critically ill patients is even less abundant than voriconazole [70]. Posaconazole is a highly protein bound, lipophilic drug with a very large Vd. This azole was only available as an oral suspension until 2015, but has since been manufactured as a solid oral formulation (tablet), as well as an intravenous solution. Posaconazole oral solution demonstrated a large interindividual and intraindividual variation in bioavailability as pH and food affected the absorption of the drug [71–73]. Moreover, administration by nasogastric tube of this formulation further reduced the bioavailability [74]. The use of posaconazole oral solution in critically ill patients had substantial drawbacks [70]. Data on the new solid oral formulation and the intravenous formulation in critically ill patients is completely lacking. Since posaconazole is highly protein bound (98%), changes in the unbound fraction in patients with hypoalbuminemia should be considered when interpreting measured total concentrations.

Several studies have been performed with fluconazole in critically ill patients. Buijk et al., Nicolau et al., and Rosemurgy et al. performed studies to determine the bioavailability of enteral fluconazole compared to intravenous fluconazole in relatively small

Table 11.2 Contemporary target drug concentrations for voriconazole and posaconazole when used in critically ill patients

Triazole	Efficacy target (mg/L)	Toxicity target (mg/L)	Timing of first trough sample
Voriconazole	>1–2	<5–6	After 2–5 days
Prophylaxis Therapy	>1–2	<5–6	(Repeat sampling recommended)
Posaconazole	>0.7	No recommend	Tablet/IV: after 3-5 days
Prophylaxis Therapy	>1.0	No recommend	3 days: Suspension: 5–7 days*

*means that the use of posaconazole suspension is discouraged and that the oral tablet is prefered due to the favourable absorption profile

patient populations (n = 5–14 patients). All showed an increase in Vd compared to healthy volunteers. In addition, bioavailability showed significant intrapatient variability [75–78]. However, results concerning CL and half-life were conflicting. Nicolau et al. and Rosemurgy et al. showed an increase in CL, but no effect on half-life compared to healthy volunteers, while others showed an increase in half-life without an increase in CL compared to healthy volunteers [75, 76]. Fluconazole was also studied in the multinational study on defining antibiotic levels in the intensive care (DALI) and again showed a large interindividual variability with about a third of the patients not reaching a therapeutic target concentration [56]. Aoyama and colleagues studied covariates that might influence the PK of fluconazole, and found creatinine clearance and body weight to key determinants of CL and Vd, respectively [79].

11.10 Use of Azole Drugs in Patients with Renal Impairment, Renal Replacement Therapy, and ECMO

It is well known that significant differences exist between the azole drugs with respect to protein binding and renal clearance. This determines whether dosages have to be adjusted in patients with deteriorating renal function or in patients already on supportive treatment like CRRT or ECMO.

Voriconazole at the licensed dose resulted in highly variable drug concentrations in critically ill patients [66]. Despite high interindividual variability in voriconazole concentrations, none of the patients experienced deterioration in renal function. Several studies have been performed investigating the effect of CRRT on voriconazole CL, which was not significant altered. Results were consistent between studies and standard dosages of voriconazole can be used without dose adjustment in patients undergoing CRRT. However, as described earlier, since the voriconazole concentration itself was highly variable, monitoring seems required.

In addition, the excipient sulfobutylether-β-cyclodextrin (SBECD) present in the parenteral formulation of voriconazole accumulates with renal impairment, and therefore intravenous administration of voriconazole to a patient with an estimated glomerular filtration rate below 50 mL/min is discouraged by the manufacturer [80]. However, critically ill patients often have impaired renal function and require IV administration because oral administration is complicated by gastroparesis or malabsorption. Therefore several studies have investigated the PK of SBECD and demonstrated it can be safely administered without a further decline in renal function [81–84]. In addition, CRRT effectively removed SBECD without a significant risk accumulation. Intermittent hemodialysis was able to effectively eliminate SBECD, but could not prevent a certain degree of accumulation [81, 85, 86]. Although the total number of studied subjects was low to make definite safety recommendations, toxicity due to SBECD was not observed.

Being a lipophilic drug, voriconazole showed significant sequestration in the ECMO circuit (Mehta et al. reported a 71% loss of voriconazole), necessitating higher doses of the drug to maintain adequate trough concentrations [87]. If this

initial loss is not compensated for, voriconazole levels will be subtherapeutic. However, later, when the circuit is saturated, voriconazole can accumulate and toxicity has been observed by several groups [18, 37, 88]. Confirmation of these findings are needed. In such a scenario, TDM may be helpful in optimizing voriconazole concentrations.

Posaconazole PK was studied in subjects with varying degrees of renal impairment including dialysis. No correlation was observed between posaconazole clearance and mild to moderate renal disease. In addition, posaconazole clearance was unaffected by dialysis which could be explained by the high protein binding (>98%). Dose adjustments were therefore not considered relevant.

Approximately 80% of fluconazole is eliminated unchanged via the kidneys. Renal function therefore impacts the PK of fluconazole; half-life is increased from 30 to 96 h in patients with a GFR <20 mL/min [89]. As such, the product information of fluconazole advises dose adjustments for patients with a GFR ≤50 mL/min [90]. Unfortunately, patients with impaired renal function (and impaired hepatic function) were excluded from studies on fluconazole PK by Buijk et al., Nicolau et al., and Rosemurgy et al. [75–77], such that the PK parameters in renally impaired ICU patients are lacking. As such, dose reductions are recommended in patients with renal insufficiency after the standard loading dose is administrated. However, cut-off values for renal function range from a GFR 10–50 mL/min. Once renal replacement therapy is indicated, the dose has to be increased again because clearance of fluconazole by CRRT is significant [91–94]. A daily dose of 800 mg may be required to reach therapeutic concentrations, and should be guided by monitoring of drug concentrations.

Fluconazole was not affected by ECMO as shown in an ex-vivo circuit [95]. However, in children, it was shown that it took much longer to reach comparable concentrations compared to children not on ECMO [96, 97]. Clearly, the additional volume had a more distinct effect in children than in adults. Watt et al. recommend a fluconazole loading dose of 25 mg/kg to overcome this problem [96, 97].

11.11 Use of Azole Drugs in Patients with Hepatic Insufficiency

Voriconazole is extensively metabolized by cytochrome P450 enzymes (2C19, 3A4, and 2C9). It is recommended to maintain the loading dose but to reduce the maintenance dose by 50% for Child-Pugh A and B cirrhosis [80]. In this context, the half-life of voriconazole is extended in patients with hepatic impairment [98]. Furthermore, higher voriconazole concentrations have been associated with a deterioration in liver function tests, but a clear cut-off concentration has not been established [99]. A concentration above 4 mg/L has been proposed as a risk factor for hepatotoxicity [100].

In a single dose study of posaconazole in patients with hepatic impairment, no clear difference was observed in drug exposure between different groups [101]. In a pooled analysis, a modest increase in exposure was observed in subjects with

impaired hepatic function compared to healthy volunteers. Although there is no clear need to adjust the dose in patients with hepatic impairment, TDM may be used to assure that toxic concentrations are not occurring.

In patients with mild to moderate hepatic impairment, no statistically significant effect on fluconazole PK parameters was observed [102]. This can be explained by predominant renal excretion of the unchanged compound.

11.12 Clinical Pharmacology of Azole Drugs

In general, drugs used for life-threatening diseases with a proven PK/PD relationship, narrow therapeutic range, large interindividual variation in PK, and severe adverse effects are particularly good candidates for TDM [103, 104]. In this fashion, PK/PD relationships need to be well defined. In the clinical setting, there are observational data suggesting that achieving plasma concentrations above a certain threshold may confer greater efficacy for voriconazole, posaconazole, and itraconazole [15, 105–111], although this has yet to be shown in prospective trials.

It should be noted that robust data on PK/PD relationships in critically ill patients are currently lacking. Most of the evidence collected is from hematology patients. Thus extrapolations from this population to the ICU population must be made. This should be done with caution as the course of disease, immune response, and drug behavior will be different in ICU patients compared to hematology patients.

The importance of TDM for these antifungals is acknowledged, although trials to evaluate this practice have not been performed, and data are not yet conclusive enough to support its routine use [108].

11.12.1 Voriconazole

It has been widely reported in the literature that the PK/PD index for triazole antifungal drugs is the AUC/MIC ratio [112–114]. Trough concentrations correlate well with AUC [109, 115] and are therefore used as surrogate markers for total exposure. Several retrospective studies have identified a relationship between voriconazole trough concentrations and clinical outcomes during prophylaxis or treatment [116–118]. Moreover, several prospective clinical trials have demonstrated an association between plasma trough concentrations and efficacy and toxicity during treatment of invasive fungal infections, whereas others had too few patients [105, 119–123]. New research points us towards a possible role for galactomannan as it appears to be a very elegant surrogate marker that can help guide therapy [124, 125].

Both retrospective and prospective clinical studies have shown that trough concentrations $\geq$1.0–2.0 mg/L were associated with optimal clinical response in treatment of invasive fungal infections [108, 121, 123]. A prospective clinical trial validated the breakpoint of voriconazole and demonstrated the added value of TDM

during voriconazole treatment, by demonstrating a more favorable response in the TDM group, compared to the non-TDM group [108]. Furthermore, a retrospective study suggested that patients receiving prophylactic therapy with voriconazole concentrations >2 mg/L had a lower risk of obtaining an invasive fungal infection [117].

There is lively discussion on the relationship between voriconazole trough concentrations and the risk of toxicity. Trough concentrations ≥4.5–6 mg/L have been associated with a higher risk of voriconazole-associated neurotoxicity (visual and auditory hallucinations, encephalopathy) but the relationship with liver dysfunction is not as clear [99, 119, 123]. No reliable upper "cut-off" concentration can be identified to minimize risk of hepatotoxic effects with the possible exception of Japanese patients where hepatotoxicity was more common if voriconazole trough concentrations ≥3.9 mg/L [126, 127].

In summary, TDM is advised during treatment and also prophylaxis in critically ill patients prescribed voriconazole. Trough samples should be taken after about 2 days, and a range of 2–6 mg/L should be used as a reference.

11.12.2 Posaconazole

For posaconazole, evidence is accumulating as to the benefits of TDM [107, 128–130]. The likelihood of encountering low exposure was typically seen with the older pharmaceutical formulation (suspension) [72]. With the development of the new solid oral tablet formulation, as well as the intravenous formulation, new debate has arisen on the benefits of TDM, as erratic absorption seems less of a problem and most patients will attain target concentrations [131–133]. One of the most important recommendations is therefore to use these new formulations to ascertain that high exposure is achieved specifically for the ICU patient. The downside of higher exposure is obviously the increased probability of encountering side effects. Concentration-dependent side effects of posaconazole include liver function test abnormalities, QT prolongation, and electrolyte disturbances.

Data on posaconazole TDM in critical illness are absent, and one must rely on that from hematology patients. Several clinical studies have reported a concentration–response relationship between posaconazole plasma trough concentrations and the risk of breakthrough infections, where $C_{min} > 0.7$ mg/L is suggested to result in optimal prophylactic efficacy [107, 130, 134–137]. For the treatment of invasive aspergillosis, a target trough concentration of >1 mg/L is suggested [128]. There is no upper limit for posaconazole exposure defined as yet, although the scientific discussion at the European Medicines Agency points towards an upper target of 3.75 mg/L [European Medicine Agency. Assessment report: Noxafil. 2014. Available at: http://www.ema.europa.eu/ema/]. There are unfortunately no clinical published data to substantiate this target.

The first assessment of trough concentrations is generally recommended on day 5. In the prophylactic setting, this is acceptable but in the setting of treatment this might be too late. Specific algorithms are proposed in literature to interpret earlier samples using nomograms [107, 138].

11.12.3 Fluconazole

In general, TDM of fluconazole is not required as long as current dose recommendations are followed and renal function is closely monitored. However, in critically ill patients, stable conditions are seldom and situations may arise in which the measurement of fluconazole concentration can be highly informative. Augmented renal clearance, administration of high volumes of fluids, or infections in sanctuary sites may prevent reaching therapeutic targets in situations with higher MIC values and may require TDM. Moreover, the place of fluconazole to treat *Candida* infections in children is still substantial and TDM may be of added value [139]. As fluconazole is often included in multi-analyte antifungal assays and the information can be critical in specific situations, one should always consider obtaining these levels [140].

Based on the variation in absorption, bioavailability, Vd, and drug–drug interactions, the predictability of fluconazole concentration in critically ill patients is questionable. TDM on a regular basis (e.g., twice weekly) is strongly advised. Trough levels of 25–50 mg/L are associated with an adequate AUC:MIC, although proper dose-outcome studies in critically ill patients still need to be performed.

Finally, reports have emerged on resistance of *Aspergillus* to azole drugs, particularly in the setting of critically ill patients [141–145]. One must keep in mind that the presented breakpoints are valid for susceptible *Aspergillus* spp. But higher concentrations may be needed when a patient is infected with a species with a higher MIC [115]. Specific guidance on the management of disease caused by azole-resistant species has recently been published and can be used a starting point for treatment [146].

11.13 Pharmacokinetics of Liposomal Amphotericin B in Critically Ill Patients

Conventional amphotericin B deoxycholate has historically been considered the "gold standard" in the treatment of invasive fungal infections, although it has largely been abandoned in modern practice. In order to attenuate its toxicity and increase the therapeutic potential, alternative formulations of amphotericin B have been developed. The molecular structure of amphotericin B deoxycholate makes the drug an ideal candidate for incorporation into lipid-based preparations. The use of lipid formulations is associated with good fungicidal activity, low emergence of resistance and specifically fewer adverse effects, in particular nephrotoxicity, with no difference in efficacy. Liposomal amphotericin B (AmBisome) is an intravenous liposomal formulation that differs from other lipid-associated amphotericin B products in its uniform, small, spherical size, and the fact that it is a stable, lyophilized product. These liposomes are small unilamellar vesicles composed of molecules of amphotericin B intercalated into a phospholipid bilayer. The diameter of these liposomes is less than 100 nm. Liposomes provide a unique delivery system, which enhances delivery to fungal cells while reducing drug-associated toxicities.

Liposomal amphotericin B has a broad spectrum of activity, including against *Candida* species (with the exception of *Candida lusitaniae* and *Candida guilliermondii)*, Mucor species, *Aspergillus* spp. (with reduced efficacy against *Aspergillus flavus* and *Aspergillus terreus*), and *Cryptococcus* spp. The development of resistance to amphotericin B is rare.

11.14 General Pharmacokinetics of Liposomal Amphotericin B in ICU Patients

Despite the fact that liposomal amphotericin B has been licensed and marketed for many years, the PK of this drug is poorly understood. Multiple PK analyses studying a wide variety of dosages have been conducted in immunocompromised (pediatric) patients [147], although ICU patients are underrepresented. A study in critically ill patients gave liposomal amphotericin B at doses ranging from 1.2 to 4.2 mg/kg [148]. There was considerable variability in exposure in the 10 patients that received the most commonly used dosages (2.8–3.0 mg/kg). The apparent Vd was comparatively small with a median value of 0.42 liters/kg, and the median terminal elimination half-life was 13.05 h (range 8.7–41.4 h). There was no correlation, also in the other dosage groups, between dose and exposure nor between dose and C_{max}. These data corroborate with the data from previous studies with regard to large intra- and intersubject variability. C_{max} concentrations in ICU patients were comparable to those reported in other groups of patients with similar dosages [149–152].

Yet, differences were also noted. For instance, in 17 hematology patients receiving dosages ranging from 2.67 to 3.46 mg/kg (average 3.0 mg/kg) [147], the terminal half-life of 54.3 h was substantially longer in this cohort than in the ICU population. The authors argued that the observed difference in half-life might be due to differences in the uptake of the liposomal carrier with bound drug into non-blood compartments or in the dissolution of the drug from the liposomal carriers with consequences for its disposition in the blood; additional potential factors include differences in disease status and inflammatory molecules, the composition of plasma proteins, and solutions used for concomitant parenteral nutrition.

11.15 Use of Liposomal Amphotericin B in Patients with Renal Impairment, Renal Replacement Therapy, and ECMO

As PK information on liposomal amphotericin B is scarce, robust data on drug handling in patients with deteriorating renal function or while receiving extracorporeal support is even more limited. According to the product information and the renal drug handbook [available via https://kdpnet.kdp.louisville.edu/drugbook/adult/], no dose adjustment is needed for patients with renal failure.

A previously reported study in critically ill patients had a subpopulation of patients also receiving hemodialysis. It appears that liposomal amphotericin B is not removed by this modality, but more data are needed to confirm this in a larger cohort of patients and other forms of dialysis [148]. At present, there are no publications on the PK of various formulations of amphotericin B and ECMO. Given the fact that all formulations of amphotericin B are lipophilic, adsorption to the ECMO tubing can be expected.

11.16 Use of Liposomal Amphotericin B in Patients with Hepatic Insufficiency

Hepatic side effects of liposomal amphotericin B have been reported in literature and these side effects are also listed in the product information. However, it is unknown whether changes in hepatic function have an impact on the clearance of liposomal amphotericin B. No formal recommendations are given for dose adaptations of liposomal amphotericin B in patients with varying degrees of hepatic impairment.

11.17 Clinical Pharmacology of Amphotericin B

A relationship between the PK profile of liposomal amphotericin B and its antifungal effect has been demonstrated in several in vitro studies but no study has been conducted to validate an optimal PK/PD index for liposomal amphotericin B in humans. In a population-PK analysis in nine patients with proven fungal infection, eight patients treated with liposomal amphotericin B manifest a clinical response (either complete or partial). In patients with a complete response, the steady-state C_{max}/MIC ratio was significantly higher than in patients with a partial response ($P = 0.021$), while no significant correlation was found between AUC/MIC and response [153]. Obviously, this study is not powered to derive a final breakpoint and only guides us towards the fact that based on these data it appears that exposure (especially C_{max}) to liposomal amphotericin B is the intermediate link between the doses administered and their clinical effects.

References

1. Oren I, Paul M (2014) Up to date epidemiology, diagnosis and management of invasive fungal infections. Clin Microbiol Infect 20(Suppl 6):1–4
2. Kullberg BJ, Arendrup MC (2016) Invasive Candidiasis. N Engl J Med 374(8):794–795
3. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L et al (2016) Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 62(4):e1–50

4. Andes DR, Safdar N, Baddley JW, Playford G, Reboli AC, Rex JH et al (2012) Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. Clin Infect Dis 54(8):1110–1122
5. Anaissie EJ, Stratton SL, Dignani MC, Lee CK, Summerbell RC, Rex JH et al (2003) Pathogenic molds (including Aspergillus species) in hospital water distribution systems: a 3-year prospective study and clinical implications for patients with hematologic malignancies. Blood 101(7):2542–2546
6. Verweij PE, Snelders E, Kema GH, Mellado E, Melchers WJ (2009) Azole resistance in Aspergillus fumigatus: a side-effect of environmental fungicide use? Lancet Infect Dis 9(12):789–795
7. Dagenais TR, Keller NP (2009) Pathogenesis of Aspergillus fumigatus in invasive Aspergillosis. Clin Microbiol Rev 22(3):447–465
8. Baddley JW, Stephens JM, Ji X, Gao X, Schlamm HT, Tarallo M (2013) Aspergillosis in Intensive Care Unit (ICU) patients: epidemiology and economic outcomes. BMC Infect Dis 13:29
9. Baddley JW (2011) Clinical risk factors for invasive aspergillosis. Med Mycol 49(Suppl 1):S7–S12
10. Taccone FS, Van den Abeele AM, Bulpa P, Misset B, Meersseman W, Cardoso T et al (2015) Epidemiology of invasive aspergillosis in critically ill patients: clinical presentation, underlying conditions, and outcomes. Crit Care 19:7
11. Meersseman W, Lagrou K, Maertens J, Van WE (2007) Invasive aspergillosis in the intensive care unit. Clin Infect Dis 45(2):205–216
12. Lewis RE (2011) Current concepts in antifungal pharmacology. Mayo Clin Proc 86(8):805–817
13. Sucher AJ, Chahine EB, Balcer HE (2009) Echinocandins: the newest class of antifungals. Ann Pharmacother 43(10):1647–1657
14. Gray KC, Palacios DS, Dailey I, Endo MM, Uno BE, Wilcock BC et al (2012) Amphotericin primarily kills yeast by simply binding ergosterol. Proc Natl Acad Sci U S A 109(7): 2234–2239
15. Vermes A, Guchelaar HJ, Dankert J (2000) Flucytosine: a review of its pharmacology, clinical indications, pharmacokinetics, toxicity and drug interactions. J Antimicrob Chemother 46(2):171–179
16. Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW et al (2014) Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis 14(6):498–509
17. Ulldemolins M, Roberts JA, Rello J, Paterson DL, Lipman J (2011) The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet 50(2):99–110
18. Spriet I, Annaert P, Meersseman P, Hermans G, Meersseman W, Verbesselt R et al (2009) Pharmacokinetics of caspofungin and voriconazole in critically ill patients during extracorporeal membrane oxygenation. J Antimicrob Chemother 63(4):767–770
19. Liu P (2013) Population pharmacokinetic-pharmacodynamic analysis of anidulafungin in adult patients with fungal infections. Antimicrob Agents Chemother 57(1):466–474
20. van Wanrooy MJ, Rodgers MG, Uges DR, Arends JP, Zijlstra JG, van der Werf TS et al (2014) Low but sufficient anidulafungin exposure in critically ill patients. Antimicrob Agents Chemother 58(1):304–308
21. Bruggemann RJ, Middel-Baars V, de Lange DW, Colbers A, Girbes AR, Pickkers P et al (2017) Pharmacokinetics of Anidulafungin in critically ill patients in the Intensive Care Unit with suspected or proven invasive fungal infections. Antimicrob Agents Chemother 61(2):e01894–e01816
22. Nguyen TH, Hoppe-Tichy T, Geiss HK, Rastall AC, Swoboda S, Schmidt J et al (2007) Factors influencing caspofungin plasma concentrations in patients of a surgical intensive care unit. J Antimicrob Chemother 60(1):100–106
23. van der Elst KC, Veringa A, Zijlstra JG, Beishuizen A, Klont R, Brummelhuis-Visser P et al (2017) Low caspofungin exposure in patients in the Intensive Care Unit. Antimicrob Agents Chemother 61(2):e01582–e01516

24. Martial LC, Bruggemann RJ, Schouten JA, van Leeuwen HJ, van Zanten AR, de Lange DW et al (2016) Dose reduction of caspofungin in intensive care unit patients with child Pugh B will result in suboptimal exposure. Clin Pharmacokinet 55(6):723–733
25. Muilwijk EW, Schouten JA, van Leeuwen HJ, van Zanten AR, de Lange DW, Colbers A et al (2014) Pharmacokinetics of caspofungin in ICU patients. J Antimicrob Chemother 69(12):3294–3299
26. Weiler S, Seger C, Pfisterer H, Stienecke E, Stippler F, Welte R et al (2013) Pharmacokinetics of caspofungin in critically ill patients on continuous renal replacement therapy. Antimicrob Agents Chemother 57(8):4053–4057
27. Jullien V, Azoulay E, Schwebel C, Le Saux T, Charles PE, Cornet M et al (2017) Population pharmacokinetics of micafungin in ICU patients with sepsis and mechanical ventilation. J Antimicrob Chemother 72(1):181–189
28. Hebert MF, Smith HE, Marbury TC, Swan SK, Smith WB, Townsend RW et al (2005) Pharmacokinetics of micafungin in healthy volunteers, volunteers with moderate liver disease, and volunteers with renal dysfunction. J Clin Pharmacol 45(10):1145–1152
29. Dowell JA, Stogniew M, Krause D, Damle B (2007) Anidulafungin does not require dosage adjustment in subjects with varying degrees of hepatic or renal impairment. J Clin Pharmacol 47(4):461–470
30. European Medicines Agency (2011) Cancidas; summary of product characteristics—28-09-2011. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/000610/WC500037784.pdf. Accessed Oct 2011
31. Burkhardt O, Kaever V, Burhenne H, Kielstein JT (2009) Extended daily dialysis does not affect the pharmacokinetics of anidulafungin. Int J Antimicrob Agents 34(3):282–283
32. Aguilar G, Azanza JR, Carbonell JA, Ferrando C, Badenes R, Parra MA et al (2014) Anidulafungin dosing in critically ill patients with continuous venovenous haemodiafiltration. J Antimicrob Chemother 69(6):1620–1623
33. Leitner JM, Meyer B, Fuhrmann V, Saria K, Zuba C, Jager W et al (2011) Multiple-dose pharmacokinetics of anidulafungin during continuous venovenous haemofiltration. J Antimicrob Chemother 66(4):880–884
34. Roger C, Wallis SC, Muller L, Saissi G, Lipman J, Bruggemann RJ et al (2016) Caspofungin population pharmacokinetics in critically ill patients undergoing continuous veno-venous haemofiltration or haemodiafiltration. Clin Pharmacokinet. doi:10.1007/s40262-016-0495-z
35. Hirata K, Aoyama T, Matsumoto Y, Ogawa F, Yamazaki H, Kikuti A et al (2007) Pharmacokinetics of antifungal agent micafungin in critically ill patients receiving continuous hemodialysis filtration. Yakugaku Zasshi 127(5):897–901
36. Maseda E, Grau S, Villagran MJ, Hernandez-Gancedo C, Lopez-Tofino A, Roberts JA et al (2014) Micafungin pharmacokinetic/pharmacodynamic adequacy for the treatment of invasive candidiasis in critically ill patients on continuous venovenous haemofiltration. J Antimicrob Chemother 69(6):1624–1632
37. Ruiz S, Papy E, Da Silva D, Nataf P, Massias L, Wolff M et al (2009) Potential voriconazole and caspofungin sequestration during extracorporeal membrane oxygenation. Intensive Care Med 35(1):183–184
38. Aguilar G, Ferriols R, Carbonell JA, Ezquer C, Alonso JM, Villena A et al (2016) Pharmacokinetics of anidulafungin during venovenous extracorporeal membrane oxygenation. Crit Care 20(1):325
39. Autmizguine J, Hornik CP, Benjamin DK Jr, Brouwer KL, Hupp SR, Cohen-Wolkowiez M et al (2016) Pharmacokinetics and safety of micafungin in infants supported with extracorporeal membrane oxygenation. Pediatr Infect Dis J 35(11):1204–1210
40. Aguilar G, Azanza JR, Sadaba B, Badenes R, Ferrando C, Delgado C et al (2014) Pharmacokinetics of anidulafungin during albumin dialysis. Crit Care 18(2):422
41. Mistry GC, Migoya E, Deutsch PJ, Winchell G, Hesney M, Li S et al (2007) Single- and multiple-dose administration of caspofungin in patients with hepatic insufficiency: implications for safety and dosing recommendations. J Clin Pharmacol 47(8):951–961
42. Spriet I, Meersseman W, Annaert P, de Hoon J, Willems L (2011) Pharmacokinetics of caspofungin in a critically ill patient with liver cirrhosis. Eur J Clin Pharmacol 67(7):753–755

43. van der Elst KC, Bruggemann RJ, Rodgers MG, Alffenaar JW (2012) Plasma concentrations of caspofungin at two different dosage regimens in a patient with hepatic dysfunction. Transpl Infect Dis 14(4):440–443
44. Spriet I, Meyfroidt G, Maleux G, Verslype C, Willems L (2012) The impact of a transjugular intrahepatic portosystemic shunt on the pharmacokinetics of caspofungin in a critically ill patient. Pharmacology 90(5–6):247–250
45. Neely M, Jafri HS, Seibel N, Knapp K, Adamson PC, Bradshaw SK et al (2009) Pharmacokinetics and safety of caspofungin in older infants and toddlers. Antimicrob Agents Chemother 53(4):1450–1456
46. Undre N, Pretorius B, Stevenson P (2015) Pharmacokinetics of micafungin in subjects with severe hepatic dysfunction. Eur J Drug Metab Pharmacokinet 40(3):285–293
47. Kishino S, Ohno K, Shimamura T, Furukawatodo H (2004) Optimal prophylactic dosage and disposition of micafungin in living donor liver recipients. Clin Transpl 18(6):676–680
48. Mochizuki N, Matsumoto K, Ohno K, Shimamura T, Furukawa H, Todo S et al (2006) Effects of hepatic CYP3A4 activity on disposition of micafungin in liver transplant recipients with markedly small-for-size grafts. Transplant Proc 38(10):3649–3650
49. Muraki Y, Iwamoto T, Kagawa Y, Sakurai H, Usui M, Isaji S et al (2009) The impact of total bilirubin on plasma micafungin levels in living-donor liver transplantation recipients with severe liver dysfunction. Biol Pharm Bull 32(4):750–754
50. Andes D, Diekema DJ, Pfaller MA, Bohrmuller J, Marchillo K, Lepak A (2010) In vivo comparison of the pharmacodynamic target among echinocandin drugs and Candida species. Antimicrob Agents Chemother 54(6):2497–2506
51. Andes D, Diekema DJ, Pfaller MA, Prince RA, Marchillo K, Ashbeck J et al (2008) In vivo pharmacodynamic characterization of anidulafungin in a neutropenic murine candidiasis model. Antimicrob Agents Chemother 52(2):539–550
52. Andes DR, Diekema DJ, Pfaller MA, Marchillo K, Bohrmueller J (2008) In vivo pharmacodynamic target investigation for micafungin against Candida albicans and C. glabrata in a neutropenic murine candidiasis model. Antimicrob Agents Chemother 52(10):3497–3503
53. Andes DR, Reynolds DK, Van Wart SA, Lepak AJ, Kovanda LL, Bhavnani SM (2013) Clinical pharmacodynamic index identification for micafungin in esophageal candidiasis: dosing strategy optimization. Antimicrob Agents Chemother 57(11):5714–5716
54. Yang Q, Wang T, Xie J, Wang Y, Zheng X, Chen L et al (2016) Pharmacokinetic/pharmacodynamic adequacy of echinocandins against Candida spp. in intensive care unit patients and general patient populations. Int J Antimicrob Agents 47(5):397–402
55. Martial LC, Ter Heine R, Schouten JA, Hunfeld NG, van Leeuwen HJ, Verweij PE et al (2017) Population pharmacokinetic model and pharmacokinetic target attainment of micafungin in intensive care unit patients. Clin Pharmacokinet. doi:10.1007/s40262-017-0509-5
56. Sinnollareddy MG, Roberts JA, Lipman J, Akova M, Bassetti M, De Waele JJ et al (2015) Pharmacokinetic variability and exposures of fluconazole, anidulafungin, and caspofungin in intensive care unit patients: data from multinational defining antibiotic levels in intensive care unit (DALI) patients study. Crit Care 19(1):33
57. Pfaller MA, Diekema DJ, Ostrosky-Zeichner L, Rex JH, Alexander BD, Andes D et al (2008) Correlation of MIC with outcome for Candida species tested against caspofungin, anidulafungin, and micafungin: analysis and proposal for interpretive MIC breakpoints. J Clin Microbiol 46(8):2620–2629
58. Andes D, Ambrose PG, Hammel JP, Van Wart SA, Iyer V, Reynolds DK et al (2011) Use of pharmacokinetic-pharmacodynamic analyses to optimize therapy with the systemic antifungal micafungin for invasive candidiasis or candidemia. Antimicrob Agents Chemother 55(5):2113–2121
59. Brüggemann RJ, Alffenaar JW, Blijlevens NM, Billaud EM, Kosterink JG, Verweij PE et al (2009) Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. Clin Infect Dis 48(10):1441–1458

60. Zonios D, Yamazaki H, Murayama N, Natarajan V, Palmore T, Childs R et al (2014) Voriconazole metabolism, toxicity, and the effect of cytochrome P450 2C19 genotype. J Infect Dis 209(12):1941–1948
61. Kim SH, Lee DG, Kwon JC, Lee HJ, Cho SY, Park C et al (2013) Clinical impact of cytochrome P450 2C19 genotype on the treatment of invasive aspergillosis under routine therapeutic drug monitoring of voriconazole in a korean population. Infect Chemother 45(4): 406–414
62. Wang G, Lei HP, Li Z, Tan ZR, Guo D, Fan L et al (2009) The CYP2C19 ultra-rapid metabolizer genotype influences the pharmacokinetics of voriconazole in healthy male volunteers. Eur J Clin Pharmacol 65(3):281–285
63. Friberg LE, Ravva P, Karlsson MO, Liu P (2012) Integrated population pharmacokinetic analysis of voriconazole in children, adolescents, and adults. Antimicrob Agents Chemother 56(6):3032–3042
64. Liu P, Mould DR (2014) Population pharmacokinetic analysis of voriconazole and anidulafungin in adult patients with invasive aspergillosis. Antimicrob Agents Chemother 58(8):4718–4726
65. Brüggemann RJM, Blijlevens NMA, Burger DM, Smiet TCM, Bijlsma T, Mouton JW, et al (2007) Pharmacokinetics of intravenous voriconazole in allogeneic haematopoietic stem cell transplant recipients ID-193
66. Myrianthefs P, Markantonis SL, Evaggelopoulou P, Despotelis S, Evodia E, Panidis D et al (2010) Monitoring plasma voriconazole levels following intravenous administration in critically ill patients: an observational study. Int J Antimicrob Agents 35(5):468–472
67. Veringa A, Ter Avest M, Span LF, van den Heuvel ER, Touw DJ, Zijlstra JG et al (2017) Voriconazole metabolism is influenced by severe inflammation: a prospective study. J Antimicrob Chemother 72(1):261–267
68. Vanstraelen K, Wauters J, Vercammen I, de Loor H, Maertens J, Lagrou K et al (2014) Impact of hypoalbuminemia on voriconazole pharmacokinetics in critically ill adult patients. Antimicrob Agents Chemother 58(11):6782–6789
69. Vanstraelen K, Wauters J, De Loor H, Vercammen I, Annaert P, Lagrou K et al (2014) Protein-binding characteristics of voriconazole determined by high-throughput equilibrium dialysis. J Pharm Sci 103(8):2565–2570
70. Ray J, Campbell L, Rudham S, Nguyen Q, Marriott D (2011) Posaconazole plasma concentrations in critically ill patients. Ther Drug Monit 33(4):387–392
71. Walravens J, Brouwers J, Spriet I, Tack J, Annaert P, Augustijns P (2011) Effect of pH and comedication on gastrointestinal absorption of posaconazole: monitoring of intraluminal and plasma drug concentrations. Clin Pharmacokinet 50(11):725–734
72. Dolton MJ, Bruggemann RJ, Burger DM, McLachlan AJ (2014) Understanding variability in posaconazole exposure using an integrated population pharmacokinetic analysis. Antimicrob Agents Chemother 58(11):6879–6885
73. van der Elst KC, Brouwers CH, van den Heuvel ER, van Wanrooy MJ, Uges DR, van der Werf TS et al (2015) Subtherapeutic posaconazole exposure and treatment outcome in patients with invasive fungal disease. Ther Drug Monit 37(6):766–771
74. Dodds Ashley ES, Varkey JB, Krishna G, Vickery D, Ma L, Yu X et al (2009) Pharmacokinetics of posaconazole administered orally or by nasogastric tube in healthy volunteers. Antimicrob Agents Chemother 53(7):2960–2964
75. Rosemurgy AS, Markowsky S, Goode SE, Plastino K, Kearney RE (1995) Bioavailability of fluconazole in surgical intensive care unit patients: a study comparing routes of administration. J Trauma 39(3):445–447
76. Buijk SL, Gyssens IC, Mouton JW, Verbrugh HA, Touw DJ, Bruining HA (2001) Pharmacokinetics of sequential intravenous and enteral fluconazole in critically ill surgical patients with invasive mycoses and compromised gastro-intestinal function. Intensive Care Med 27(1):115–121

77. Nicolau DP, Crowe H, Nightingale CH, Quintiliani R (1995) Bioavailability of fluconazole administered via a feeding tube in intensive care unit patients. J Antimicrob Chemother 36(2):395–401
78. Rajagopalan P, Pelz RK, Lipsett PA, Swoboda SM, Rinaldi MG, Hendrix CW (2003) Enteral fluconazole population pharmacokinetics in patients in the surgical intensive care unit. Pharmacotherapy 23(5):592–602
79. Aoyama T, Hirata K, Hirata R, Yamazaki H, Yamamoto Y, Hayashi H et al (2012) Population pharmacokinetics of fluconazole after administration of fosfluconazole and fluconazole in critically ill patients. J Clin Pharm Ther 37(3):356–363
80. EMA (2009) Vfend; summary of product characteristics 13-03-2009. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/000387/WC500049756.pdf. Accessed June 2009
81. Hafner V, Czock D, Burhenne J, Riedel KD, Bommer J, Mikus G et al (2010) Pharmacokinetics of sulfobutylether-beta-cyclodextrin and voriconazole in patients with end-stage renal failure during treatment with two hemodialysis systems and hemodiafiltration. Antimicrob Agents Chemother 54(6):2596–2602
82. Luke DR, Tomaszewski K, Damle B, Schlamm HT (2010) Review of the basic and clinical pharmacology of sulfobutylether-beta-cyclodextrin (SBECD). J Pharm Sci 99(8):3291–3301
83. Oude Lashof AM, Sobel JD, Ruhnke M, Pappas PG, Viscoli C, Schlamm HT et al (2012) Safety and tolerability of voriconazole in patients with baseline renal insufficiency and candidemia. Antimicrob Agents Chemother 56(6):3133–3137
84. Lilly CM, Welch VL, Mayer T, Ranauro P, Meisner J, Luke DR (2013) Evaluation of intravenous voriconazole in patients with compromised renal function. BMC Infect Dis 13:14
85. Kiser TH, Fish DN, Aquilante CL, Rower JE, Wempe MF, MacLaren R et al (2015) Evaluation of sulfobutylether-beta-cyclodextrin (SBECD) accumulation and voriconazole pharmacokinetics in critically ill patients undergoing continuous renal replacement therapy. Crit Care 19:32
86. Burkhardt O, Thon S, Burhenne J, Welte T, Kielstein JT (2010) Sulphobutylether-beta-cyclodextrin accumulation in critically ill patients with acute kidney injury treated with intravenous voriconazole under extended daily dialysis. Int J Antimicrob Agents 36(1):93–94
87. Mehta NM, Halwick DR, Dodson BL, Thompson JE, Arnold JH (2007) Potential drug sequestration during extracorporeal membrane oxygenation: results from an ex vivo experiment. Intensive Care Med 33(6):1018–1024
88. Bruggemann RJ, Antonius T, Heijst A, Hoogerbrugge PM, Burger DM, Warris A (2008) Therapeutic drug monitoring of voriconazole in a child with invasive aspergillosis requiring extracorporeal membrane oxygenation. Ther Drug Monit 30(6):643–646
89. Toon S, Ross CE, Gokal R, Rowland M (1990) An assessment of the effects of impaired renal function and haemodialysis on the pharmacokinetics of fluconazole. Br J Clin Pharmacol 29(2):221–226
90. Cbg MEB (2003) Diflucan; summary of product characteristics
91. Trotman RL, Williamson JC, Shoemaker DM, Salzer WL (2005) Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. Clin Infect Dis 41(8):1159–1166
92. Pittrow L, Penk A (1999) Dosage adjustment of fluconazole during continuous renal replacement therapy (CAVH, CVVH, CAVHD, CVVHD). Mycoses 42(1–2):17–19
93. Valtonen M, Tiula E, Neuvonen PJ (1997) Effect of continuous venovenous haemofiltration and haemodiafiltration on the elimination of fluconazole in patients with acute renal failure. J Antimicrob Chemother 40(5):695–700
94. Muhl E, Martens T, Iven H, Rob P, Bruch HP (2000) Influence of continuous veno-venous haemodiafiltration and continuous veno-venous haemofiltration on the pharmacokinetics of fluconazole. Eur J Clin Pharmacol 56(9–10):671–678
95. Shekar K, Roberts JA, McDonald CI, Ghassabian S, Anstey C, Wallis SC et al (2015) Protein-bound drugs are prone to sequestration in the extracorporeal membrane oxygenation circuit: results from an ex vivo study. Crit Care 19:164

96. Watt KM, Benjamin DK Jr, Cheifetz IM, Moorthy G, Wade KC, Smith PB et al (2012) Pharmacokinetics and safety of fluconazole in young infants supported with extracorporeal membrane oxygenation. Pediatr Infect Dis J 31(10):1042–1047
97. Watt KM, Gonzalez D, Benjamin DK Jr, Brouwer KL, Wade KC, Capparelli E et al (2015) Fluconazole population pharmacokinetics and dosing for prevention and treatment of invasive candidiasis in children supported with extracorporeal membrane oxygenation. Antimicrob Agents Chemother 59(7):3935–3943
98. Alffenaar JW, de Vos T, Uges DR, Daenen SM (2009) High voriconazole trough levels in relation to hepatic function: how to adjust the dosage? Br J Clin Pharmacol 67(2):262–263
99. Tan K, Brayshaw N, Tomaszewski K, Troke P, Wood N (2006) Investigation of the potential relationships between plasma voriconazole concentrations and visual adverse events or liver function test abnormalities. J Clin Pharmacol 46(2):235–243
100. Wang Y, Wang T, Xie J, Yang Q, Zheng X, Dong W et al (2016) Risk factors for voriconazole-associated hepatotoxicity in patients in the intensive care unit. Pharmacotherapy 36(7):757–765
101. Moton A, Krishna G, Ma L, O'Mara E, Prasad P, McLeod J et al (2010) Pharmacokinetics of a single dose of the antifungal posaconazole as oral suspension in subjects with hepatic impairment. Curr Med Res Opin 26(1):1–7
102. Sobue S, Tan K, Haug-Pihale G (2005) The effects of hepatic impairment on the pharmacokinetics of fosfluconazole and fluconazole following a single intravenous bolus injection of fosfluconazole. Br J Clin Pharmacol 59(2):160–166
103. Ensom MH, Davis GA, Cropp CD, Ensom RJ (1998) Clinical pharmacokinetics in the 21st century. Does the evidence support definitive outcomes? Clin Pharmacokinet 34(4):265–279
104. Brüggemann RJ, Aarnoutse RE (2015) Fundament and prerequisites for the application of an antifungal tdm service. Curr Fungal Infect Rep 9(2):122–129
105. Pascual A, Csajka C, Buclin T, Bolay S, Bille J, Calandra T et al (2012) Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: population pharmacokinetics-based analysis of adult patients with invasive fungal infections. Clin Infect Dis 55(3):381–390
106. Pascual A, Nieth V, Calandra T, Bille J, Bolay S, Decosterd LA et al (2007) Variability of voriconazole plasma levels measured by new high-performance liquid chromatography and bioassay methods. Antimicrob Agents Chemother 51(1):137–143
107. Jang SH, Colangelo PM, Gobburu JV (2010) Exposure-response of posaconazole used for prophylaxis against invasive fungal infections: evaluating the need to adjust doses based on drug concentrations in plasma. Clin Pharmacol Ther 88(1):115–119
108. Park WB, Kim NH, Kim KH, Lee SH, Nam WS, Yoon SH et al (2012) The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. Clin Infect Dis 55(8):1080–1087
109. Seyedmousavi S, Mouton JW, Verweij PE, Bruggemann RJ (2013) Therapeutic drug monitoring of voriconazole and posaconazole for invasive aspergillosis. Expert Rev Anti-Infect Ther 11(9):931–941
110. Hope WW, Billaud EM, Lestner J, Denning DW (2008) Therapeutic drug monitoring for triazoles. Curr Opin Infect Dis 21(6):580–586
111. Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW (2014) Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. J Antimicrob Chemother 69(5):1162–1176
112. Mavridou E, Bruggemann RJ, Melchers WJ, Mouton JW, Verweij PE (2010) Efficacy of posaconazole against three clinical Aspergillus fumigatus isolates with mutations in the cyp51A gene. Antimicrob Agents Chemother 54(2):860–865
113. Mavridou E, Bruggemann RJ, Melchers WJ, Verweij PE, Mouton JW (2010) Impact of cyp51A mutations on the pharmacokinetic and pharmacodynamic properties of voriconazole in a murine model of disseminated aspergillosis. Antimicrob Agents Chemother 54(11):4758–4764

114. Howard SJ, Lestner JM, Sharp A, Gregson L, Goodwin J, Slater J et al (2011) Pharmacokinetics and pharmacodynamics of posaconazole for invasive pulmonary aspergillosis: clinical implications for antifungal therapy. J Infect Dis 203(9):1324–1332
115. Seyedmousavi S, Mouton JW, Melchers WJ, Bruggemann RJ, Verweij PE (2014) The role of azoles in the management of azole-resistant aspergillosis: from the bench to the bedside. Drug Resist Updat 17(3):37–50
116. Trifilio S, Ortiz R, Pennick G, Verma A, Pi J, Stosor V et al (2005) Voriconazole therapeutic drug monitoring in allogeneic hematopoietic stem cell transplant recipients. Bone Marrow Transplant 35(5):509–513
117. Trifilio S, Singhal S, Williams S, Winter J, Tallman M, Gordon L, et al (2006) Breakthrough fungal infections after allogeneic hematopoietic stem cell transplantation in patients on prophylactic voriconazole ID-159
118. Smith J, Safdar N, Knasinski V, Simmons W, Bhavnani SM, Ambrose PG et al (2006) Voriconazole therapeutic drug monitoring. Antimicrob Agents Chemother 50(4):1570–1572
119. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O (2008) Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin Infect Dis 46(2):201–211
120. Hope WW, Walsh TJ, Goodwin J, Peloquin CA, Howard A, Kurtzberg J et al (2016) Voriconazole pharmacokinetics following HSCT: results from the BMT CTN 0101 trial. J Antimicrob Chemother 71(8):2234–2240
121. Neely M, Rushing T, Kovacs A, Jelliffe R, Hoffman J (2010) Voriconazole pharmacokinetics and pharmacodynamics in children. Clin Infect Dis 50(1):27–36
122. Troke PF, Hockey HP, Hope WW (2011) Observational study of the clinical efficacy of voriconazole and its relationship to plasma concentrations in patients. Antimicrob Agents Chemother 55(10):4782–4788
123. Dolton MJ, Ray JE, Chen SC, Ng K, Pont LG, McLachlan AJ (2012) Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. Antimicrob Agents Chemother 56(9):4793–4799
124. Huurneman LJ, Neely M, Veringa A, Docobo Perez F, Ramos-Martin V, Tissing WJ et al (2016) Pharmacodynamics of voriconazole in children: further steps along the path to true individualized therapy. Antimicrob Agents Chemother 60(4):2336–2342
125. Chai LY, Kullberg BJ, Johnson EM, Teerenstra S, Khin LW, Vonk AG et al (2012) Early serum galactomannan trend as a predictor of outcome of invasive aspergillosis. J Clin Microbiol 50(7):2330–2336
126. Suzuki Y, Tokimatsu I, Sato Y, Kawasaki K, Sato Y, Goto T et al (2013) Association of sustained high plasma trough concentration of voriconazole with the incidence of hepatotoxicity. Clin Chim Acta 424:119–122
127. Matsumoto K, Ikawa K, Abematsu K, Fukunaga N, Nishida K, Fukamizu T et al (2009) Correlation between voriconazole trough plasma concentration and hepatotoxicity in patients with different CYP2C19 genotypes. Int J Antimicrob Agents 34(1):91–94
128. Walsh TJ, Raad I, Patterson TF, Chandrasekar P, Donowitz GR, Graybill R et al (2007) Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. Clin Infect Dis 44(1):2–12
129. Dolton MJ, Ray JE, Chen SC, Ng K, Pont L, McLachlan AJ (2012) Multicenter study of posaconazole therapeutic drug monitoring: exposure-response relationship and factors affecting concentration. Antimicrob Agents Chemother 56(11):5503–5510
130. Dolton MJ, Ray JE, Marriott D, McLachlan AJ (2012) Posaconazole exposure-response relationship: evaluating the utility of therapeutic drug monitoring. Antimicrob Agents Chemother 56(6):2806–2813
131. Duarte RF, Lopez-Jimenez J, Cornely OA, Laverdiere M, Helfgott D, Haider S et al (2014) Phase 1b study of new posaconazole tablet for prevention of invasive fungal infections in high-risk patients with neutropenia. Antimicrob Agents Chemother 58(10):5758–5765

132. Maertens J, Cornely OA, Ullmann AJ, Heinz WJ, Krishna G, Patino H et al (2014) Phase 1B study of the pharmacokinetics and safety of posaconazole intravenous solution in patients at risk for invasive fungal disease. Antimicrob Agents Chemother 58(7):3610–3617
133. Cornely OA, Duarte RF, Haider S, Chandrasekar P, Helfgott D, Jimenez JL et al (2016) Phase 3 pharmacokinetics and safety study of a posaconazole tablet formulation in patients at risk for invasive fungal disease. J Antimicrob Chemother 71(3):718–726
134. Lebeaux D, Lanternier F, Elie C, Suarez F, Buzyn A, Viard JP et al (2009) Therapeutic drug monitoring of posaconazole: a monocentric study with 54 adults. Antimicrob Agents Chemother 53(12):5224–5229
135. Bryant AM, Slain D, Cumpston A, Craig M (2011) A post-marketing evaluation of posaconazole plasma concentrations in neutropenic patients with haematological malignancy receiving posaconazole prophylaxis. Int J Antimicrob Agents 37(3):266–269
136. Hoenigl M, Raggam RB, Salzer HJ, Valentin T, Valentin A, Zollner-Schwetz I et al (2012) Posaconazole plasma concentrations and invasive mould infections in patients with haematological malignancies. Int J Antimicrob Agents 39(6):510–513
137. Cattaneo C, Panzali A, Passi A, Borlenghi E, Lamorgese C, Petulla M et al (2015) Serum posaconazole levels during acute myeloid leukaemia induction therapy: correlations with breakthrough invasive fungal infections. Mycoses 58(6):362–367
138. Prattes J, Duettmann W, Hoenigl M (2016) Posaconazole plasma concentrations on days three to five predict steady-state levels. Antimicrob Agents Chemother 60(9):5595–5599
139. van der Elst KC, Pereboom M, van den Heuvel ER, Kosterink JG, Scholvinck EH, Alffenaar JW (2014) Insufficient fluconazole exposure in pediatric cancer patients and the need for therapeutic drug monitoring in critically ill children. Clin Infect Dis 59(11):1527–1533
140. Alffenaar JW, Wessels AM, van HK, Greijdanus B, Kosterink JG, Uges DR (2010) Method for therapeutic drug monitoring of azole antifungal drugs in human serum using LC/MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci 878(1):39–44
141. Snelders E, Melchers WJ, Verweij PE (2011) Azole resistance in Aspergillus fumigatus: a new challenge in the management of invasive aspergillosis? Future Microbiol 6(3): 335–347
142. van de Veerdonk FLKE, Lestrade PA, Rahamat-Langendoen JC, Hodiamont CJ, Freudenburg W, Roescher N, Wiersinga WJ, van den Berg CHSB, Kullberg BJ, Rijnders BJA, Vonk AG, van der Hoven B, van der Beek MT, van Paassen J, Haas PJ, Derde LPG, Brüggemann RJ, Oliveira dos Santos C, Kampinga GA, van Leer C, Aardema H, Oude Lashof A, Bergmans DCJJ, van Dijk K, Ang CW, Netea MG, de Haan AFJ, van Dissel JT, Hoedemaekers AW, Melchers WJG, van der Hoeven HG, Verweij PE (2016) Invasive pulmonary aspergillosis complicating influenza in critically ill patients: a nationwide retrospective observational cohort study. submitted
143. Verweij PE, Ananda-Rajah M, Andes D, Arendrup M, Brüggemann R, Chowdhary A et al (2013) International expert opinion on the management of infection caused by azole resistant Aspergillus fumigatus. AIDS
144. van der Linden JW, Arendrup MC, Melchers WJ, Verweij PE (2016) Azole resistance of aspergillus fumigatus in immunocompromised patients with invasive aspergillosis. Emerg Infect Dis 22(1):158–159
145. van der Linden JW, Arendrup MC, Warris A, Lagrou K, Pelloux H, Hauser PM et al (2015) Prospective multicenter international surveillance of azole resistance in Aspergillus fumigatus. Emerg Infect Dis 21(6):1041–1044
146. Verweij PE, Ananda-Rajah M, Andes D, Arendrup MC, Bruggemann RJ, Chowdhary A et al (2015) International expert opinion on the management of infection caused by azole-resistant Aspergillus fumigatus. Drug Resist Updat 21-22:30–40
147. Wurthwein G, Young C, Lanvers-Kaminsky C, Hempel G, Trame MN, Schwerdtfeger R et al (2012) Population pharmacokinetics of liposomal amphotericin B and caspofungin in allogeneic hematopoietic stem cell recipients. Antimicrob Agents Chemother 56(1):536–543

148. Heinemann V, Bosse D, Jehn U, Kahny B, Wachholz K, Debus A et al (1997) Pharmacokinetics of liposomal amphotericin B (Ambisome) in critically ill patients. Antimicrob Agents Chemother 41(6):1275–1280
149. Walsh TJ, Goodman JL, Pappas P, Bekersky I, Buell DN, Roden M et al (2001) Safety, tolerance, and pharmacokinetics of high-dose liposomal amphotericin B (AmBisome) in patients infected with Aspergillus species and other filamentous fungi: maximum tolerated dose study. Antimicrob Agents Chemother 45(12):3487–3496
150. Walsh TJ, Yeldandi V, McEvoy M, Gonzalez C, Chanock S, Freifeld A et al (1998) Safety, tolerance, and pharmacokinetics of a small unilamellar liposomal formulation of amphotericin B (AmBisome) in neutropenic patients. Antimicrob Agents Chemother 42(9):2391–2398
151. Seibel NL, Shad AT, Bekersky I, Groll AH, Gonzalez C, Wood LV et al (2017) Safety, tolerability, and pharmacokinetics of liposomal amphotericin B in immunocompromised pediatric patients. Antimicrob Agents Chemother 61(2):e01477–e01416
152. Stone NR, Bicanic T, Salim R, Hope W (2016) Liposomal amphotericin B (AmBisome): a review of the pharmacokinetics, pharmacodynamics, clinical experience and future directions. Drugs 76(4):485–500
153. Hong Y, Shaw PJ, Nath CE, Yadav SP, Stephen KR, Earl JW et al (2006) Population pharmacokinetics of liposomal amphotericin B in pediatric patients with malignant diseases. Antimicrob Agents Chemother 50(3):935–942
154. Muilwijk EW, Lempers VJ, Burger DM, Warris A, Pickkers P, Aarnoutse RE et al (2015) Impact of special patient populations on the pharmacokinetics of echinocandins. Expert Rev Anti-Infect Ther 13(6):799–815
155. Dodds Ashley ES, Lewis R, Lewis JS, Martin C, Andes D (2006) Pharmacology of systemic antifungal agents. Clin Infect Dis 43(S1):S28–S39
156. Fungal Pharmacology (2014) http://www.fungal.pharmacology.com
157. Felton T, Troke PF, Hope WW (2014) Tissue penetration of antifungal agents. Clin Microbiol Rev 27(1):68–88
158. Seyedmousavi S, Verweij PE, Mouton JW (2015) Isavuconazole, a broad-spectrum triazole for the treatment of systemic fungal diseases. Expert Rev Anti-Infect Ther 13(1):9–27
159. Kartsonis NA, Nielsen J, Douglas CM (2003) Caspofungin: the first in a new class of antifungal agents. Drug Resist Updat 6(4):197–218

Chapter 12
Antibiotic Dosing in Pediatric Critically Ill Patients

Pieter A.J.G. De Cock, Karel Allegaert, Matthew W. Linakis, and Catherine M.T. Sherwin

Abbreviations

ADME	Absorption, distribution, metabolism, elimination
AKI	Acute kidney injury
ARC	Augmented renal clearance
AUC	Area under the concentration time curve
Cmax	Maximal concentration, peak concentration
CPB	Cardiopulmonary bypass
CRRT	Continuous renal replacement therapy
ECMO	Extracorporeal membrane oxygenation

P.A.J.G. De Cock, Pharm.D, Ph.D.
Department of Pharmacy, Ghent University Hospital, Ghent, Belgium

Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium

Department of Paediatric Intensive Care, Ghent University Hospital, Ghent, Belgium

K. Allegaert, M.D, Ph.D.
Intensive Care and Department of Surgery, Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands

Department of Development and Regeneration, KU Leuven, Leuven, Belgium

M.W. Linakis, B.S.
Division of Clinical Pharmacology, Department of Pediatrics, University of Utah School of Medicine, SLC, Utah 295 Chipeta Way, Salt Lake City, UT 84108, USA

C.M.T. Sherwin, Ph.D. (✉)
Division of Clinical Pharmacology, Department of Pediatrics, University of Utah School of Medicine, SLC, Utah 295 Chipeta Way, Salt Lake City, UT 84108, USA

Department of Pharmacology and Toxicology, College of Pharmacy, University of Utah, Salt Lake City, UT, USA
e-mail: Catherine.sherwin@hsc.utah.edu

A.A. Udy et al. (eds.), *Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill*, DOI 10.1007/978-981-10-5336-8_12

eGFR	Estimated glomerular filtration rate
F	Bioavailability
GA	Gestational age
GFR	Glomerular filtration rate
ICU	Intensive care unit
MIC	Minimal inhibitory concentration
NICU	Neonatal intensive care unit
PD	Pharmacodynamics
PICU	Pediatric intensive care unit
PK	Pharmacokinetics
PNA	Postnatal age
TDM	Therapeutic drug monitoring
Vd	Distribution volume

12.1 Introduction

12.1.1 Off-Label Practices

Antimicrobial agents are among the most commonly administered drugs in neonates, infants, and children during intensive care unit (ICU) admission. For instance, three of the top five most commonly administered drugs in the neonatal intensive care unit (NICU) are antibiotics (ampicillin, gentamicin, and vancomycin) [1]. Infections and sepsis are major concerns in this population because of the related mortality, morbidity, and costs.

Despite their frequent prescriptions, off-label prescription of antimicrobial agents is still very common. Though there is evidence to support the use of some off-label practices, in cases where evidence is lacking, off-label use of antibiotics can result in unpredictable responses related to either toxicity or therapeutic failure. Chloramphenicol with the associated "gray baby" syndrome is a historical illustration of toxicity related to maturation. Off-label practices have the potential to result in inadequate or inaccurate dosing, illustrated by the extensive variability in dosing regimens of off-label antibiotics within European NICUs [2]. In fact, older drugs such as vancomycin and penicillins were dosed below or above recommendations with extensive variability in daily dosing (e.g., *vancomycin*: −100% up to +60%; *cefotaxime*: −50% up to +120% compared to the mg/kg reference dose guideline) [2]. In contrast, newer antibiotics, such as meropenem, tend to have dosing guidelines built into their label, resulting in a much smaller variability in dosing regimens [2].

In those cases where a dosing regimen is not well established, caregivers will commonly have to prescribe antibiotics in neonates and children based on dosing regimens linearly extrapolated from adults. This situation arises because appropriate dosing studies have not been performed or because clinicians are not using existing pediatric PK models to obtain dose information. This becomes not only an issue

of science, but also an implementation and labeling issue. Although this practice is not limited to antibiotics, specific concerns related to dosing inaccuracy for antibiotics are treatment failure, antimicrobial resistance, and maturational toxicity [3, 4].

12.1.2 Accurate Antibiotic Dosing in Critically Ill Children: A Complex Interplay Between Physiology and Pathophysiology

Clinical pharmacology aims to predict drug-specific (side) effects based on pharmacokinetics and pharmacodynamics. Pharmacokinetics (PK, ***a***bsorption, ***d***istribution and **e**limination, through ***m***etabolism or primarily renal *excretion*, ***ADME***) describes the drug concentration over time (“*what the body does to the drug”*) at a specific site (e.g., blood, cerebrospinal fluid). Pharmacodynamics (PD) estimates the relationship between a drug concentration and effect over time (“*what the drug does to the body”*) and covers both intended effects, as well as side effects.

The regulatory framework (Fig. 12.1) for pediatric drug development in Europe and the United States provides guidance on how this should be addressed [5]. Governmental oversight bodies such as the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) usually seek information regarding: (*1*) how similar disease progression is between adults and other patient populations, such as children; (*2*) how similar the response to intervention is between these populations; and (*3*) which valid and relevant pharmacodynamic measurements (biomarkers, outcome variables) are available, in order to decide on the type of product development program. When applying this decision tree to antibiotics, these regulatory bodies currently consider it to be reasonable to postulate similarities antimicro-

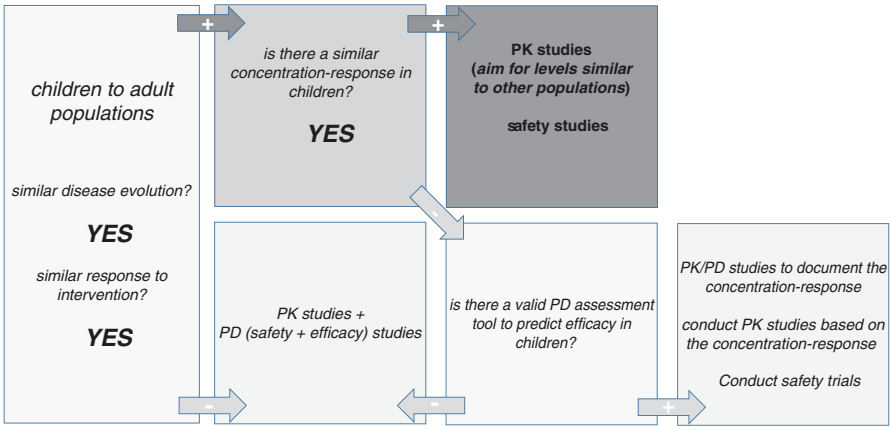

Fig. 12.1 The currently used pediatric decision tree to evaluate antibiotics in neonates. This is in general based on pharmacokinetics and safety data

bial pharmacodynamics between patient populations (concentration-response), because the treatment is aimed at the infectious organism (which is considered to behave the same between patient populations) and not the host per se. Consequently, differences in PK and safety aspects [6] are the primary focus for optimizing antibiotic utilization across populations. Three main PKPD targets, regardless the patient population, have been defined for maximum killing of the infecting pathogen depending on the properties of the antibiotic: peak plasma concentration > threshold, area under the concentration time curve > threshold, or time during which the concentration remains above a threshold.

Drug disposition in healthy children is driven by the physiological processes of growth and development (common descriptors: weight and age). Maturational PK changes are most dynamic in infancy and early childhood [4]. However, among children that are critically ill, pathophysiological changes can occur that can also have a significant influence on PK. Finally, the impact of treatment modalities [e.g., interacting co-medication, whole body cooling, extracorporeal membrane oxygenation (ECMO), and renal replacement therapy] should not be neglected. Consequently, drug dosing in critically ill children should be based on integrated knowledge concerning all (patho)-physiological and treatment characteristics of the child receiving the drug, the specific diseases to be treated, and the pharmacokinetic and dynamic parameters of the compound [7].

In this chapter, we first discuss the impact of maturation and critical illness on PK among pediatric patients (Sect. 12.2.1–12.2.3). These aspects will subsequently be considered in the context of children with burns (Sect. 12.2.4.1) and the impact of certain invasive treatments on PK (ECMO, cardiopulmonary bypass, renal replacement) (Sect. 12.2.4.2). The section on PD focuses on the developmental safety of antibiotics (Sect. 12.3). This is followed by some compound-specific PK/PD observations (aminoglycosides, vancomycin, meropenem) in neonates and children to further highlight the complex interaction between normal physiology and disease-state changes (Sect. 12.4). In the final part of the chapter, we discuss approaches to improve knowledge and practices including population PK models, physiology-based models, therapeutic drug monitoring, and individualized dosing (Sect. 12.5).

12.2 Pharmacokinetics in the Critically Ill Pediatric Patient

12.2.1 Absorption

Absorption is the process of drug transport from the site of administration to systemic circulation. The extent of absorption is described by bioavailability (F), the fraction of the dose reaching the systemic circulation. If a drug is administered intravenously, F is 100%, for other routes, this is between 0 and 100%. Drug- and patient-specific factors are responsible for the rate and magnitude of absorption. Drug-specific factors include particle size, solubility, lipophilicity, ionization, and

dissociation constant of the drug [8]. For enteral drug administration, the main patient determinants for the rate and extent for absorption are gastric emptying time, gastrointestinal pH, intestinal motility, drug metabolism at the intestinal epithelium, and absorption surface area.

Gastric emptying matures over a period of 6–8 months to adult levels [8]. Furthermore, antral contractions and intestinal motor activity improve during the first weeks of life with possible consequences on enteral absorption. Delayed gastric emptying is estimated to appear in 50% of critically ill children, especially in the youngest ones where a developmental pattern further strengthens this phenomenon as described above [9, 10]. Gastroparesis may occur as a side effect of opioids, while the use of naso-duodenal gavage feeding will bypass gastric effects. Similarly, chronic kidney disease can also affect gastric emptying time through visceral neuropathy [11]. However, no studies specifically evaluated the effect of developmental and disease-related changes in gastric emptying and intestinal motility on absorption of antibiotics in infants and children. Generally speaking, one could suppose that delayed gastric emptying leads to a delayed intestinal appearance of the antibiotic and results in a more blunted peak concentration that is reached later compared to a patient without delayed emptying. The clinical relevance of it depends on the concentration-effect profile of the compound. If a minimum effective concentration has to be reached. this effect could be delayed [8]. Besides this, diarrhea is also common on the pediatric ICU with a reported incidence between 10 and 20%. One could expect that the faster passage of substances through the digestive tract could have possible effects on the absorption profile and absolute bioavailability of the compound [12].

Although there are no significant differences between neonates (a few hours after delivery), infants and older children in baseline pH, one should consider that gastric pH will rise postprandially as milk and feedings in general have a buffering effect. As a consequence, during the day, younger children and children on enteral feeding tend to have more often a basic gastric environment [13]. These changes in gastric pH are important for acid-labile drugs like penicillin G which can be absorbed more efficiently in a higher gastric pH environment. Huang et al. showed that neonates (less acidic stomach environment) tend to have a higher bioavailability of penicillin G as compared to older children [14]. Similar effects may occur in the case of stress ulcer prophylaxis with pH modulating agents, which is commonly prescribed at the PICU. Little is known about the age-related changes in intestinal pH.

Lipophilic antibiotics given enterally need biliary salts to be absorbed. One could speculate that due to maturation of conjugation and transport of bile salts up to the age of 4, absorption of these antibiotics can be age dependent. Other age-dependent factors are villi formation and absorptive surface and age-dependent increase of splanchnic blood flow [4, 13, 15].

Circulatory dysfunction in pediatric sepsis and septic shock leads to shunting of blood flow towards the vital organs like brain and heart and to a decreased peripheral tissue perfusion like muscles, skin, and splanchnic organs. Vasopressors and inotropes are very often used in hemodynamically unstable children and are known to alter splanchnic perfusion. Although several studies have assessed the gut-specific

effects of these vasoactive drugs in critically ill adult patients, it's not really known whether these effects are beneficial or detrimental in terms of gut perfusion and at what specific dose they occur [16]. This could be explained that "critically ill" is a term describing a very heterogeneous population in adults and maybe even more in children. King et al. evaluated in a retrospective manner the tolerance of enteral feeding in patients admitted to the pediatric intensive care unit receiving cardiovascular medication. Dopamine was the most commonly used vasopressor. 29% of patients had feedings held for a perceived gastrointestinal intolerance [17]. In another study [9], epinephrine at a dose more than 0.3 μg/kg/min was identified to be a significant factor for gastrointestinal complications in critically ill children receiving transpyloric enteral nutrition. One of the explanations for gastrointestinal intolerance could be a body's failure to meet the higher splanchnic metabolic demands when the gut is hypoperfused [18]. To our knowledge, there are no studies available investigating the impact of impaired peripheral perfusion on drug absorption specifically in children although it's hypothesized that drug absorption from these sites can be erratic. Cardiovascular failure in general can result in a reduced enteral absorption of drugs, not only due to the decreased organ perfusion but also due to an increased backward pressure (venous congestion) in the gut circulation.

Reduced skeletal muscle blood flow and inefficient muscular contractions may prevent or alter absorption from the site of intramuscular injection in neonates but can be counterbalanced by the relatively higher density of capillaries in skeletal muscles. Despite the known factors of variability in absorption, the intramuscular administration of benzyl penicillin and gentamicin have been evaluated as part of neonatal sepsis treatment (AFRINEST studies) due to the ease of administration in resource poor settings [19].

12.2.2 Distribution

The apparent volume of distribution is a theoretical measure of the extent to which a drug will migrate into extravascular tissues. It can be affected by normal developmental and pathophysiologic changes that influence cardiac output, regional blood flow, and tissue permeability. The latter depends on several factors including, the degree of drug binding in blood and tissues, presence of transporters (influx/efflux), tissue mass, and physicochemical properties of the drug. Of special note, the blood–brain barrier is less mature and more permeable in infancy or in the presence of inflammation and will have potential impact on antibiotic disposition when treating central nervous system infections.

In neonates and infants, the *extracellular and total body water* is higher compared to adults. This results in higher volumes of distribution and lower (peak) concentrations of water-soluble antibiotics (e.g., aminoglycosides, vancomycin, beta-lactam antibiotics, linezolid) when administered on an mg/kg basis. Increased capillary permeability, increased hydrostatic pressure, or decreased tissue oncotic pressure due to hypoproteinemia is commonly encountered in critically ill children

and may augment the distribution volume. These increases in volume of distribution may necessitate the use of a higher dose (mg/kg) to reach a given concentration. To illustrate this, Lingvall et al. documented that the gentamicin volume of distribution was significantly higher in blood culture confirmed septic neonates compared to non-septic cases [20]. In contrast, redistribution of blood during shock results in a reduced volume of distribution with decreased delivery of hydrophilic drugs to the capillary system and poor peripheral tissue penetration. In a study by Joukhadar et al., this resulted in a five to tenfold decrease of piperacillin distribution into fat and muscle tissues in adults [21]. We speculate that these patients with impaired tissue penetration would probably benefit from alternative dosing regimens (higher antibiotic doses or shortening the dosing interval).

Similarly, maturational changes in the overall plasma binding protein pool will have an impact on the unbound fraction of drug and, therefore, the ability of drug to migrate into tissues. The most important plasma proteins for drug binding are albumin and the acute phase reactant α-1 acid glycoprotein. Albumin preferentially binds acidic molecules whereas α-1 acid glycoprotein tends to bind compounds with basic moieties. Plasma albumin concentrations and binding capacity will reach adult levels around the end of infancy (~2 years of age) [4]. In states of severe illness, hypoproteinemia (<61 g/L) and hypoalbuminemia (<33 g/L) are frequently observed in children and are the result of a number of mechanisms such as increased protein catabolism, capillary permeability, and decreased production. In contrast, α-1 acid glycoprotein levels often increase during periods of critical illness [22, 23]. Smits et al. very recently evaluated protein binding of the highly protein-bound antibiotic cefazolin in postoperative neonates. As expected, the median unbound CFZ fraction was higher than in adults [24]. Besides protein concentration, the binding affinity of antibiotic to plasma proteins also depends on conformational changes. These conformational changes can be induced by fluctuations in pH and urea concentration, phenomena likely to occur in critical illness.

Competitive binding of co-administered drugs or endogenous substances may also have an impact on the degree of drug-protein binding. In neonates, competitive binding of antibiotics (e.g., ceftriaxone, cefazolin) and bilirubin to albumin has been described [24, 25]. As a clinical consequence, the highly albumin-bound antibiotic ceftriaxone is currently contraindicated because of displacement of unconjugated bilirubin which could potentially result in kernicterus [25, 26].

12.2.3 Elimination

Clearance of a drug generally occurs through metabolism and/or renal excretion. Drug metabolism is the process by which a drug undergoes biotransformation to a moiety that is more readily eliminated from the body. Typically, drug metabolites are more polar, water-soluble molecules than the parent drug molecule, and often they are biologically inactive. Drug excretion is the process by which parent drug and/or its metabolite(s) are removed from the body. This is mainly accomplished by

the kidneys (glomerular filtration and proximal renal tubular secretion) and hepatobiliary route. Both processes undergo maturational changes and can also be affected by critical illness. Out of scope for this chapter are maturational or critical illness-related changes in drug metabolism, since this only rarely applies to antibiotics (e.g., cefotaxime and desacetylcefotaxime) and we refer interested readers to recent reviews on this topic [3, 27–29].

Many of the commonly used antibiotics in critically ill children are subject to clearance by renal elimination. Glomerular integrity, physicochemical properties of the drug, and extent of protein binding determine the total amount to be filtered. Since only unbound drug can be filtered, the unbound fraction drives elimination of antibiotics excreted by glomerular filtration. In addition to glomerular filtration, drugs can be eliminated by active secretion in the proximal renal tubules, where transporters of cationic and anionic drugs are highly expressed. Weak acids and bases (i.e., most drugs) can be reabsorbed in non-ionized forms in the distal tubule. This applies to endogenous as well as exogenous compounds.

The glomerular filtration rate (GFR) matures starting from fetal organogenesis into late infancy. At birth, newborns experience profound hemodynamic changes. Among these changes, increased renal blood flow and decreased renal vascular resistance cause a rapid rise in GFR over the first weeks of life, with adult GFR typically attained by 12 months of age. Among preterm neonates, GFR is very low (2–4 mL/min) and can only be maintained due to a delicate balance between vasodilatory effects (regulated by prostaglandins) on the afferent and vasoconstrictor effects on the efferent glomerular arterioli [8]. The maturation of the active tubular secretion process is less well known but is assumed to reach adult capacity in early childhood [4, 30]. Evidently, all these maturation processes likely have a major impact on the dosing of renally cleared antibiotics in children below 1–2 years of age.

Besides maturation, disease characteristics also affect renal elimination capacity. Acute kidney injury (AKI) is common in the neonatal and pediatric ICU unit and may directly lead to impaired renal drug clearance [31, 32]. In critically ill neonates, co-administration of nephrotoxic drugs (e.g., indomethacin, ibuprofen) or peripartal asphyxia were covariates of decreased renal drug clearance of aminoglycosides [31–33]. In a prospective observational study on a tertiary care pediatric intensive care unit (PICU), the incidence of AKI was 27.4%. Risk factors included young age, lower weight, fluid overload, received inotropic support, diuretics, or aminoglycosides [34]. Also here, depending on the severity of renal insufficiency, antibiotic dosing reductions may be necessary.

Augmented renal clearance (ARC) of antibiotics is frequently observed in critically ill adults. The exact pathophysiological mechanism remains unknown but an increased renal blood flow due to vasodilation and increased cardiac output during sepsis has been suggested [35]. Although the commonly used definition (estimated GFR > 130 ml/min) cannot be applied throughout the time span of renal maturation, the concept of supraphysiological, augmented renal clearance very likely also applies in children. However, the available observations are still very limited. De Cock et al. documented hyperfiltration in a cohort of 50 pediatric (range 4.1–65 kg)

cases exposed to amoxicillin-clavulanic acid during intensive care. Median clearance of amoxicillin and clavulanic acid were 17.9 and 12.2 L/70 kg, respectively, with the exposure to inotropics leading to a lower clearance (−18%). Due to the augmented renal clearance, the studied dosing regimen (25–35 mg/kg q6h, based on the amoxicillin compound) resulted in subtherapeutic concentrations in the early period of sepsis, and 25 mg/kg q4h was suggested [36]. Hirai et al. documented ARC (eGFR >160 mL/min 1.73 m^2) and increased vancomycin clearance in pediatric patients with febrile neutropenia, but not in pediatric patients after trauma with systemic inflammatory response syndrome or following surgery [37].

12.2.4 Specific Conditions in Pediatric Critically Ill Patients

12.2.4.1 Children with Burns

The mechanisms behind the alteration in PK remain poorly understood in burn wound patients. Physiological responses to severe burn wounds can be divided into two stages. The first is a resuscitative phase with increased capillary permeability leading to hypovolemia, hypoalbuminemia, tissue edema, and a decrease in cardiac output. The pharmacokinetic consequences of these physiological changes are typically a larger volume of distribution and lower drug clearance. The second phase consists of a hypermetabolic and hyper-inflammatory response with glomerular hyperfiltration, increased tissue perfusion and hypoalbuminemia. During this stage, changes in volume of distribution evolve over time and mainly relate to an increased unbound fraction of protein-bound antibiotics due to hypoalbuminemia. At this stage, patients also display augmented clearance.

Based on observations of vancomycin and amikacin PK in children, these phenomena have also been described in children with burn injuries. Both the distribution volume and clearance of vancomycin were increased in a dataset collected in 13 burned children with normal creatinine values [median age 6 (1–11) years, median weight 25 (12–45) kg], resulting in the recommendation to administer 90–100 mg/kg/day [38]. Amikacin PK were also altered in 70 burned children (median age 4.5 years, median weight 20 kg) with burn injury with an increased distribution volume [18.7–22.7 L, +21%] and clearance [5.36–7.22 L/h, +35%] compared to non-burned cases. The authors hereby suggested to use higher doses (25 mg/kg) to improve PD target attainment rates [39].

The burned skin, scars, and subcutaneous tissues are generally only poorly perfused and are a deep compartment. This matters since these tissues contain potential pathogens. Consequently, blood compartment PK do not necessarily reflect tissue kinetics. Following a distribution half-life, subeschar tissue fluid vancomycin and amikacin concentrations allowed confirmation that the elimination half-lives were significantly longer in the subeschar tissue fluid [40]. In a single dose study of teicoplanin PK in burn patients, including five children, the median teicoplanin concentrations in burn wound fluid were about 60% of the serum levels [41].

12.2.4.2 Use of Organ Support Equipment and the Consequences for Antibiotic Dosing in Children

In the absence of proper PK studies, basic PK principles guide dose selection in children with an extracorporeal circuit. In this circumstance, the initial dose is mainly driven by the distribution volume, while the maintenance dose is based on an estimated clearance. Even if data are available, we would like to suggest that PK observations also may depend on the specific equipment used and cannot simply be extrapolated to other equipment (e.g., priming volume, silicone membrane vs. hollow-fiber oxygenator, coating tubing, surface/flow rate, filter membrane).

Extracorporeal membrane oxygenation: Severe infection may be an indication to initiate ECMO, while the technique itself may also result in nosocomial infections. Consequently, optimal dosing of antibiotics is highly relevant for this specific subgroup of critically ill patients [42]. In an ECMO setting, PK of intravenous antibiotics may be affected by higher volumes of distribution through hemodilution with the additional volume of the extracorporeal circuit, and potential adsorption of antibiotics on ECMO component material, capillary leakage, and reduced drug clearance through secondary ECMO-related effects on elimination organs. The extent of extraction or sequestration, in part, depends on the lipophilicity of the drug (log P) and circuit material. This has been well illustrated using in vitro experiments [43].

Renal dysfunction is common in the ECMO setting, usually related to the underlying indication (e.g., shock, asphyxia, poor perfusion, and hypoxia). By initiating ECMO, there is a loss in the pulsatility of the blood flow and the intrusive equipment can induce an inflammatory state that may affect renal function [44]. Whenever renal function becomes erratic, ECMO is used in combination with renal replacement therapy (see below in renal replacement section).

Limited data are available on antibiotic disposition in children on ECMO [45]. For the aminoglycoside antibiotic gentamicin, it was described that distribution volume is higher and the clearance lower in comparison [45]. Using a contemporary extended dosing interval concept, it was appropriate to use 5 mg/kg of gentamicin in young infants and 9–10 mg/kg in 3–24 months, q24h with the option to prolong the dosing interval in neonates to 30–36 h, depending on therapeutic drug monitoring (TDM) results. Similar to the findings with gentamicin, a review of vancomycin PK in neonates and infants treated with ECMO, also documented that the distribution volume was consistently higher and clearance consistently lower relative to those not treated with ECMO [45]. Based on this pattern, the authors suggest using an initial 20 mg/kg dose of vancomcyin in neonates and children, with subsequent individualization using TDM (trough level target 15–20 μg/mL). Data on meropenem PK in children on ECMO are limited to two case reports from the same center. A first infant was treated with continuous meropenem administration (8-month-old infant, *Pseudomonas aeruginosa* pneumonia, estimated clearance 4.5 mL/kg/min) [46]. A second newborn was treated with both ECMO and renal replacement therapy (2.8 kg, term, 10 days). Following a positive blood culture with *Pseudomonas aeruginosa* (MIC 0.25 mg/L), meropenem (40 mg/kg bolus, 10 mg/kg/h continuous) was initiated and resulted in adequate concentrations (21 μg/mL) and clinical

recovery [47]. Sherwin et al. suggests a similar approach, with 40 mg/kg bolus dose, followed by 200 mg/kg/24 h continuous administration [45].

Cardiopulmonary bypass: While the cardiopulmonary bypass (CPB) equipment and its impact on PK are very similar to ECMO, the reasons for antibiotics mainly cover perioperative prophylaxis. In a cohort of 15 infants and children (3–34 months), cefuroxime (25 mg/kg) administration resulted in a median 8 h post dose simulated cefuroxime concentration of 16 mg/L [48]. A single dose of vancomycin (15 mg/kg) before CPB results in concentrations >5 mg/L throughout the CPB run, with subsequent dosing within 6 h after the initial vancomycin administration. A higher initial dose (20 mg/kg) can be considered if higher concentrations are necessary [49]. Amoxicillin and flucloxacillin (both 30 mg/kg) resulted in serum concentrations above the MIC throughout cardiac surgery, in part due to the reduced clearance [50]. A new dosing prophylactic regimen was proposed for cefazolin (40 mg/kg at induction, 20 mg/kg at start and end of CPB, and 40 mg/kg q8h after the third and fourth dose), based on a PK/PD model using the free fraction of cefazolin in serum from 56 neonates and infants [36]. A decreased tissue disposition into skeletal muscle during CPB with deep hypothermic circulatory arrest was observed in seven infants despite higher overall plasma exposure [51].

Renal replacement: The combination of sepsis and renal failure is common among critically ill patients, including children. While the PK of antibiotics in AKI are substantially different (commonly higher distribution volume and much lower clearance), renal clearance by artificial modes [intermittent hemodialysis or forms of continuous renal replacement therapy (CRRT), such as venovenous hemodialysis, venovenous hemodiafiltration, venovenous hemofiltration, or continuous peritoneal dialysis] necessitates additional considerations besides patient and drug characteristics that relate to the dialysis equipment itself. Dialysis membranes differ in pore size and may be subject to drug adsorption, which can have an effect on antibiotic clearance. Blood and dialysate/ultrafiltration flow rate also influence drug clearance since it affects renal clearance.

To date, guidance and knowledge in children on pediatric drug dosing during renal replacement therapy is scarce [52]. Moreover, polypharmacy in pediatric patients with acute renal failure managed with hemodialysis is common, potentially leading to cumulative drug exposure, complexity of drug interactions, and toxicity [53]. In a study of 2783 pediatric patients with acute renal failure treated with hemodialysis, longer courses of hemodialysis correlated with increasing drug exposure. Of the 50 most frequently prescribed drugs in this cohort, only 5 (10%) had accessible information on dosing adjustments. Overall, >75% received antibiotics (frequency of use: vancomycin > piperacillin/tazobactam > meropenem > trimethoprim/sulfamethoxazole > cefazolin > clindamycin > cefepime). Six out of seven of these drugs had dosing guidance for pediatric patients during pediatric renal dysfunction, but of these only three had guidance related to renal replacement therapy [52].

Compound-specific observations are available for cefazolin and vancomycin. Cefazolin PK data was collected in four children (1.9–17 years, 10.9–57.5 kg) during chronic hemodialysis (3–4 sessions/week) at a dose of 35 mg/kg post dialysis.

This regimen maintained adequate serum concentrations (>8 mg/L) until the next session [54]. Vancomycin is effectively removed by high-flux hemodialysis [55]. In a single case report of a child (6 years, anephric) on intermittent hemodialysis, the serum vancomycin half-life was found to decrease by more than 90% during each course [56]. There was no guidance on aminoglycosides, but its use in this clinical setting is not a first- or second-line treatment modality.

12.3 Pharmacodynamics: Developmental Safety of Antibiotics

As suggested in Fig. 12.1, evaluation of antibiotics in pediatric age categories should at least cover PK and safety since developmental aspects can also affect the safety profile of a given drug. To illustrate this, we use the example of meropenem which was recently labeled to treat abdominal infections in children less than 3 months of age. These labeling changes were based on PK as well as safety aspects collected in prospective studies [57, 58]. Adverse events included sepsis (6%), seizures (5%), elevated conjugated bilirubin (5%), or hypokalemia (5%) and none were judged to be probably or definitely related, while two serious adverse events (fungal sepsis, isolated ileal perforation) were judged to be possibly related. Seizures were of specific interest since this is explicitly mentioned as a warning in the label, independent of the age category. Clinical seizures were observed in 10 (pre)term neonates and 5/10 neonates were known to have an intracranial hemorrhage. Moreover, the predicted meropenem Cmax in subjects with seizures did not differ from those without seizures. In another retrospective analysis in 5566 infants treated with either meropenem or imipenem/cilastatin, the combined outcome of death or seizures was lower with meropenem (Odds Ratio = 0.77) [59].

Nephrotoxicity and ototoxicity related to aminoglycosides and/or vancomycin exposure is an example of the need to monitor safety in every subpopulation. Toxicity has limited the use of aminoglycosides but there is a consistently lower rate of oto- and nephrotoxicity in neonates when compared to adults. This suggests maturational toxicodynamics in favor of infancy [60]. The most recent Cochrane review on one dose per day compared to multiple doses per day for gentamicin in neonates suggests (pooled, all dosing regimens) that the incidence of ototoxicity was 1.4% (n = 3/214) with no cases (n = 0/348) of nephrotoxicity (increased creatinine or decreased creatinine clearance) [61]. Nestaas et al. also reported a pooled analysis (all aminoglycosides) in neonates, including nephrotoxicity (increased creatinine, urinary aminopeptidase, 50/589 events, 8.4%), and ototoxicity (1/210 events, 0.5%) [62]. Similarly, a recent review on the current evidence supports the favorable safety profile of vancomycin in neonates. However, observations on safety of high-dose intermittent dosing regimens are still very limited [63]. In an observational study on vancomycin-induced nephrotoxicity in children, admission

to the ICU and co-treatment with aminoglycosides were identified as predisposing factors [64].

Developmental aspects may alter relative risks (exposure/toxicity), but some aspects are specific to the pediatric age category. The duration of antibiotic exposure is associated with an increased risk to develop necrotizing enterocolitis, a disease very specific to (pre)term neonates. Similarly, there is an association between antibiotic exposure in early life and the risk to subsequently develop obesity. Both phenomena are claimed to be due to the impact on the intestinal microflora [65, 66]. Another risk factor specific to neonates and young infants relates to the use of calcium containing perfusions to avoid hypocalcemia. Combined with low flow rates of perfusions to avoid fluid overload, co-administration of ceftriaxone with calcium-containing solutions holds a risk for intravascular precipitation and cardiovascular collapse [67]. Finally, because of potential competitive binding to plasma proteins with highly bound antibiotics, hyperbilirubinemia is another population-specific risk, since unconjugated hyperbilirubinemia is common in early neonatal life [24].

12.4 Compound-Specific Observations

12.4.1 Aminoglycosides

Aminoglycosides are frequently used (in combination with a penicillin) to treat suspected neonatal sepsis. Consequently, gentamicin is the most commonly administered drug in neonates. Other aminoglycosides commonly used are amikacin, netilmicin, or tobramycin [68].

The concentration-dependent response supports the use of high doses to attain peak concentrations for aminoglycosides. Aminoglycosides are hydrophilic, distribute to the extracellular water compartment, and are eliminated by glomerular filtration. In neonates, this means that higher doses (mg/kg, higher distribution volume) combined with extended dosing intervals (lower renal clearance) are needed [8]. In a pediatric meta-analysis comparing extended interval dosing with multiple daily doses for aminoglycosides, there were no significant differences in clinical failure rate, microbiologic failure rate, and combined clinical or microbiologic failure rates, but trends favored extended interval dosing consistently [69]. In neonates, extended interval dosing of aminoglycosides was safe and effective, with a reduced risk of serum drug concentrations outside the therapeutic range [61, 62].

Since elimination of aminoglycosides is exclusively by glomerular filtration, covariates of GFR will affect clearance [70]. In neonates, this means that gestational age (GA), birth weight, postnatal age (PNA), ibuprofen co-administration (−20%), and peripartal asphyxia (−40%) affect aminoglycoside clearance. To further illustrate this, the impact of ibuprofen on the elimination half-life of amikacin (+ 32%) in preterm neonates (<30 weeks, at birth) is provided in Fig. 12.2 [71]. Similarly, the impact

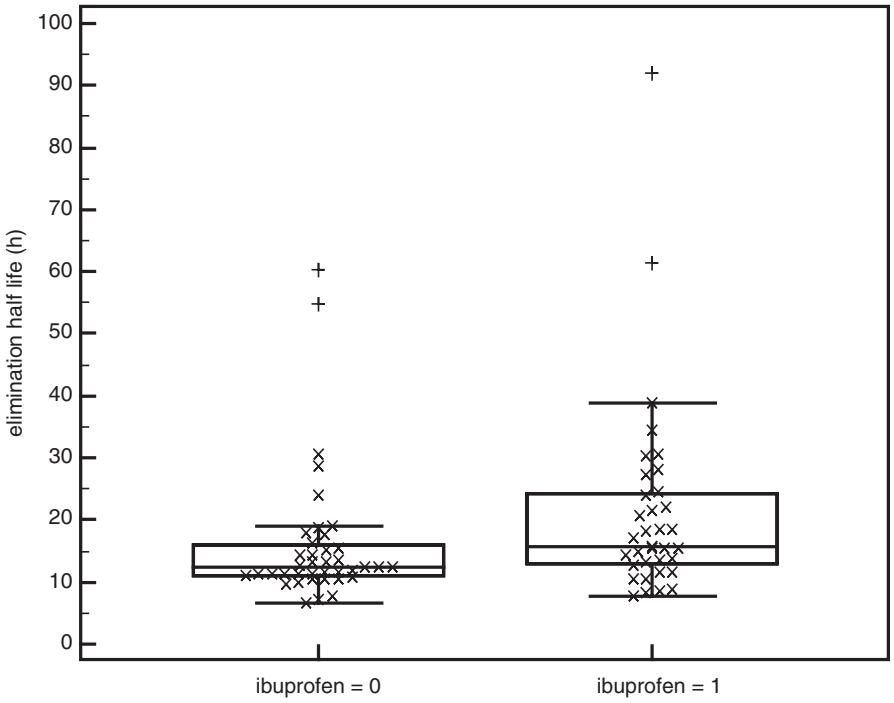

Fig. 12.2 The impact of ibuprofen exposure (yes/no) on the median amikacin elimination half-life in preterm neonates (<30 weeks, 16.4 instead of 12.4 h) in the first days of life [71]

of whole body cooling following perinatal asphyxia on amikacin clearance in early neonatal life (day 1, 2, 3, and 4) is compared to reference data in Fig. 12.3 [72, 73]. There is a 40% reduction in clearance on any of the consecutive days (day 1–4) [60].

12.4.2 Vancomycin

Vancomycin is commonly used in neonatal and pediatric intensive care units to treat Gram-positive infections. *Staphylococcus epidermidis and aureus*, including strains resistant to methicillin, are usually inhibited by concentrations of 1–4 μg/mL vancomycin (depending on the MIC). *Staphylococcus pyogenes*, *Streptococcus pneumoniae*, and *viridians* are susceptible to 2 μg/mL vancomycin. *Bacillus spp.* are inhibited by 2 μg/mL, *Corynebacterium spp*. by 0.04–3.1 and *Clostridium spp*. by 0.39–6 μg/mL vancomycin, respectively [3, 63]. Vancomycin is fairly water-soluble molecule with limited plasma protein binding (albumin, IgA) in adults and is mainly eliminated by the kidneys.

Studies in adults have shown that the advocated PK/PD index of favorable clinical outcome is an AUC over a 24 h period at steady-state divided by the minimum inhibitory concentration (MIC) of the suspected pathogen (AUC/MIC) of at least

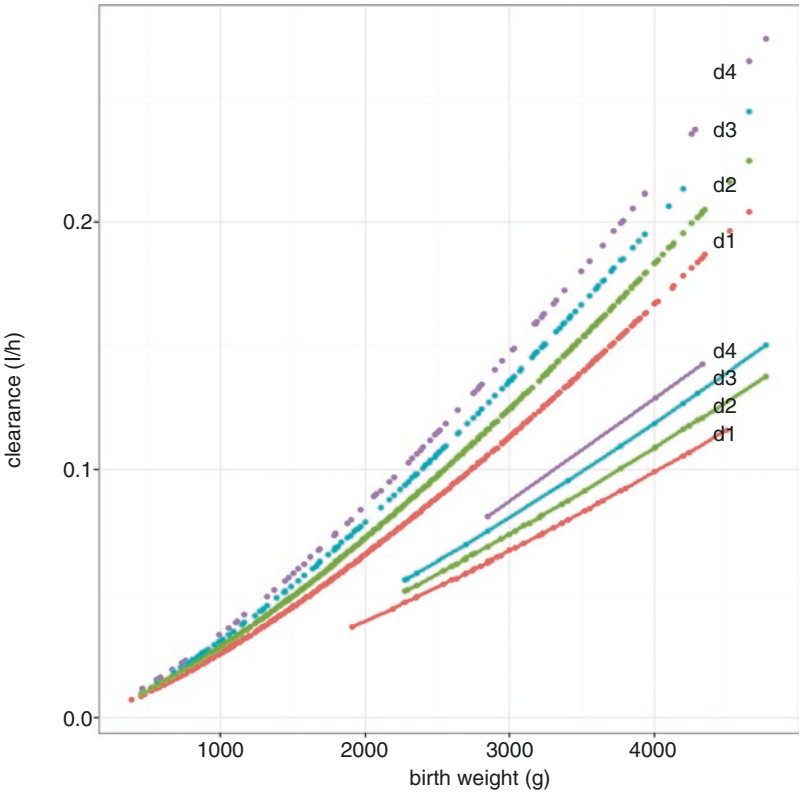

Fig. 12.3 Estimates of amikacin clearance trends in early neonatal life based on pooling of reported datasets. There is a maturational trend in clearance, related to birth weight and postnatal age (day 1, 2, 3, 4, as reflected by the colors) compared to a subgroup of term neonates undergoing whole body cooling as treatment for perinatal asphyxia. The lower group of lines are the "whole body cooled group" and the upper set of lines are those who were not "cooled" [72, 73]

400 [74]. In routine clinical practice, trough concentrations, which correlate well with AUC/MIC ratios, are used as a "surrogate" parameter to optimize vancomycin dosing regimens, because AUC/MIC calculations are labor- and cost-intensive.

Similar to the earlier mentioned findings on aminoglycosides, the maturational PK are mainly driven by changes in body water content and renal clearance. Based on an integrated analysis of gentamicin, tobramycin, and vancomycin, a semi-physiological function for GFR-mediated clearance from preterm neonates to adults was derived [75]. In critically ill children, altered PK was reported with around 50% of patients remaining below the AUC/MIC target of 400 [76]. However, lower protein binding (20–30%) has been suggested in two pediatric studies, when compared to non-critically ill adults (50%) [36, 77]. This lower protein binding had direct consequences on target attainment rates in critically ill children when using PK/PD indices based on unbound concentrations rather than those based on total concentrations [36]. Since unbound drug is pharmacologically active, these data support the need to assess protein binding in pediatric drug development of intermediate to highly bound antibiotics.

Table 12.1 Vancomycin dosing guidelines throughout pediatric life, depending on maturation and renal impairment [78]

Neonates, i.e., up to 28 days of postnatal life		
Initial dose	15 mg/kg	
Maintenance	10 mg/kg q12h, postnatal age < 8 days	
	10 mg/kg q8h, postnatal age 8–28 days	
Additional comment:		
In preterm neonates, vancomycin clearance decreases as postconceptional age decreases. Consequently, longer dosing intervals may be necessary and therapeutic drug monitoring is recommended		
Children		
10 mg/kg q6h		
Patients with impaired renal function		
(*Children not explicitly mentioned, nor excluded, but based on the reference creatinine clearance in adults*) Initial dose 15 mg/kg to achieve therapeutic drug concentrations In the anephric patient, the maintenance dose is 1.9 mg/kg/24 h		
Creatinine clearance mL/min	***Vancomycin dose mg/24 h***	***%, normal dose***
>100 mL/min	2000	100
100	1545	77
90	1390	70
80	1235	62
70	1090	55
60	925	46
50	770	38
40	620	31
30	465	23
20	310	16
10	155	8

These dosing regimen are different from the dosing regimens proposals based on PK study in specific NICU or PICU setting

All the above-mentioned dosing regimens differ substantially from the currently labeled dosing recommendations [78, 79], as summarized in Table 12.1, reflecting the paucity of evidence available to inform a uniform dosing regimen. Irrespective of the initial dose used, TDM is strongly recommended. Vancomycin is usually administered intermittently, with a target trough concentration of 10–15 μg/mL, but there is preliminary experience with continuous administration (after an initial loading dose) [80].

12.4.3 Carbapenems: Meropenem

Carbapenems are beta-lactam antimicrobial agents with an exceptionally broad spectrum, with activity against aerobic Gram-negative and Gram-positive and anaerobic pathogens. Older carbapenems like imipenem are susceptible to degradation and require co-administration of an inhibitor like cilastatin. More recently introduced carbapenems like meropenem, ertapenem, or doripenem demonstrated increased

stability. Meropenem is at present the most frequently administered carbapenem. It seems reasonable that other carbapenems will display similar patterns and impact of covariates since all are cleared by renal elimination (GFR + renal tubular).

Meropenem has recently been labeled for infants less than 3 months of age (30 mg/kg q8h for all neonates >32 weeks GA and >2 weeks PNA or 20 mg/kg, q12h when <32 weeks GA and <2 weeks PNA; q8h for <32 weeks GA and >2 weeks PNA or >32 weeks GA and <2 weeks) for abdominal infections (necrotizing enterocolitis). Complicated skin and skin structure infections, intra-abdominal infections and meningitis are dosed at 10 mg/kg (max 500 mg) q8h, 20 mg/kg (max 1000 mg) q8h, and 40 mg/kg (max 2000 mg) q8h, respectively, in children >3 months (weight based dosing), while 500 mg up to 1000 mg q8h is suggested in adults.

The SPC also provides guidance in the presence of renal impairment in adults [no adaptations >50 mL/min; 26–50 mL/min q12h instead of q8h; 10–26 mL/min q12h 50% recommended dose; <10 mL/min q24h 50% recommended dose]. These recommendations strongly support the fact that the main route of elimination is renal (GFR + renal tubular secretion).

The SPC states that there is no experience in pediatric patients with renal impairment. However, there is some guidance available in the literature in the setting of continuous renal replacement therapy in children. Goldstein et al. studied meropenem PK (single dose, 20 mg/kg, max 500 mg) in seven pediatric patients (age range 1.4–17 years) with end-stage renal disease and chronic renal replacement therapy [81]. Clinical trial simulations (in silico model predictions) demonstrated that children >5 years achieved target concentrations (>40 or 75% of time above MIC) with a dosing regimen of 20 mg/kg q12h, while in children <5 years, a dose of 20 mg/kg q8h was needed to optimize target attainment [82]. During hemodialysis (*intradialytic*), meropenem was cleared in a manner that correlated with the percent urea reduction. Median meropenem half-life was 1.3 (range 1.1–1.7) h while the meropenem half-life off dialysis (*interdialytic*) was 7.3 (range 4.9–11.7) h. Aiming for >70% of time a meropenem concentration > 4 μg/mL, dosing simulations revealed that either 25 mg/kg q24h or 40 mg/kg q48h between consecutive dialysis sessions is appropriate [82]. As mentioned earlier, there is—limited—experience with a loading dose (40 mg/kg), followed by a maintenance dose (200–240 mg/kg/24 h) in a newborn and an infant during CVVH. Finally, we want to mention a specific drug–drug interaction between meropenem and valproate of relevance in both adults and children since simultaneous administration results in a significant decrease in valproate levels with the potential of levels and seizures.

12.5 Approaches to Improve Knowledge and Clinical Practice

Traditionally, pharmacokinetic studies have involved intensive serial blood sampling performed in a limited number of healthy, male, adult volunteers [83–85]. These studies allow the investigator to estimate the variability in plasma drug concentrations between individuals following the administration of a certain dose. In

contrast, the population pharmacokinetic approach allows the investigator to characterize the pharmacokinetics of the drug of interest using fewer blood samples by treating all of the individuals in the study as a random sample from a larger population. From these data, it is then possible to estimate measures of central tendency for the pharmacokinetic parameters of the entire population, while simultaneously estimating within and between subject variability and quantifying the amount of residual, unexplained variability [86]. This improves the population mean and variance estimates and improves accuracy when selecting an initial dosing regimen or adjusting a dosing regimen in response to therapeutic drug monitoring data.

Population pharmacokinetic modeling is used to increase our understanding of the quantitative relationships between drug dosing regimens, patient characteristics, and drug pharmacokinetics. Today, the use of population pharmacokinetic modeling is actively encouraged by the FDA and the EMA [87, 88]. Despite the widespread acceptance of population pharmacokinetic methods in the drug approval process, relatively few population pharmacokinetics studies have been conducted among neonates [89].

Deriving the "optimal" individualized dose that is neither ineffective nor toxic is the ultimate goal of many physicians, pharmacologists, regulatory agencies, and pharmaceutical companies [90]. Achieving this goal is challenging for many drugs due to pharmacokinetic variability within and between patients. For drugs with narrow therapeutic windows (a small margin separates subtherapeutic from toxic concentrations), it is necessary to conduct population pharmacokinetic studies to determine whether predictable factors (covariates) can be identified that influence the extent and peak of drug exposure [91]. If substantial variability remains after such investigations and a target concentration range has been established, then it may be prudent to measure drug concentrations in each patient (a practice known as therapeutic drug monitoring) [92, 93]. Drug concentration measurements obtained from therapeutic drug monitoring can then be used to refine the model's pharmacokinetic parameter predictions for that patient in a Bayesian manner [23, 94].

The first step to improving the use of antibiotics in critically ill children is generating evidence of how a certain (critical) disease state affects a given drug. General trends have been discussed by Thakkar et al. and in this chapter, but additional clinical trials explicitly designed to monitor concentrations and compare pharmacokinetics of antibiotics in critically ill children to those who are not critically ill are needed [7]. One way by which this may be accomplished is through the collection and use of TDM and/or opportunistic sampling. For example, TDM is routinely performed as part of standard of care for certain antibiotics such as vancomycin to ensure that trough concentrations are in the desired range. Instead of simply discarding these sample concentrations, they could be used as part of a pharmacokinetic analysis. Alternately, if the antibiotic itself doesn't require TDM, collection of blood samples to monitor for endogenous markers and/or concomitant drugs (such as in burns patients) could also be salvaged and analyzed for the antibiotic. Interestingly, this process can also be useful in the opposite direction: Germosevek et al. presented a PK model that allows healthcare providers to take a gentamicin TDM sample at a time that is convenient (i.e., during a routine blood test) rather than needing to take a specific "trough" sample to determine whether drug levels are high enough [95].

Another potentially beneficial technique for facilitating PK studies in this protected population is microsampling. Microsampling, as the name implies, is the collection of smaller-than-normal plasma samples for bioanalysis. Use of microsampling in critically ill children would allow a significant reduction in the blood volume required, thereby reducing the risk of further upsetting fluid balance in patients whose fluid balance may already be compromised [95].

The next step is to then take the information available and utilize it to help improve predictions of antibiotic concentrations based on developmental status and disease state (in addition to other factors), which will in turn help inform dosing recommendations. A tool with great potential to help achieve this goal is pharmacokinetic analyses. Previous pharmacokinetic analyses of antibiotics have had a direct impact on care of critically ill pediatric patients. For example, current aminoglycoside dosing regimens have been driven by PK/PD analyses demonstrating improved efficacy and safety when dosing is once per day rather than multiple times a day [96, 97]. Two types of PK analyses in particular, population modeling (popPK) and physiologically based modeling (PBPK), could be at the forefront of antibiotic investigations in critically ill children moving forward. Population PK modeling leverages nonlinear curve fitting with fixed and random effects (error) to allow understanding of a drug's PK in both a population and an individual. One of the major benefits of popPK in this population is that it can effectively describe the PK of a drug even if patient plasma concentrations have only been sparsely sampled. As such, critically ill children, for whom taking more than two or three plasma samples is often impractical, could still provide valuable data to inform a popPK model. In fact, a number of PK models for antibiotics have been developed using only TDM samples [39, 43, 98], as described above. Conversely, a vetted and well-characterized PBPK model could help predict appropriate antibiotic doses and subsequent concentrations, thereby obviating the need for frequent TDM sampling [99]. Indeed, PBPK models, such as that developed by De Cock et al. could be used to establish evidence-based dosing regimens for renally excreted drugs (such as most antibiotics) in critically ill children [75].

Declaration of Interest The research activities of Pieter De Cock and Karel Allegaert were facilitated by the Agency for Innovation by Science and Technology in Flanders (IWT) through the SAFEPEDRUG project (IWT/SBO/130033). Pieter De Cock is also funded by the Clinical Research Fund of the Ghent University Hospital (KW/1294/APO/001).

References

1. Hsieh EM, Hornik CP, Clark RH, Laughon MM, Benjamin DK Jr, Smith PB (2014) Medication use in the neonatal intensive care unit. Am J Perinatol 31(9):811–821. doi:10.1055/s-0033-1361933
2. Metsvaht T, Nellis G, Varendi H, Nunn AJ, Graham S, Rieutord A, Storme T, McElnay J, Mulla H, Turner MA, Lutsar I (2015) High variability in the dosing of commonly used anti-

biotics revealed by a Europe-wide point prevalence study: implications for research and dissemination. BMC Pediatr 15:41. doi:10.1186/s12887-015-0359-y
3. Johnson JK, Laughon MM (2016) Antimicrobial agent dosing in infants. Clin Ther 38(9):1948–1960. doi:10.1016/j.clinthera.2016.06.017
4. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE (2003) Developmental pharmacology—drug disposition, action, and therapy in infants and children. N Engl J Med 349(12):1157–1167. doi:10.1056/NEJMra035092
5. Manolis E, Pons G (2009) Proposals for model-based paediatric medicinal development within the current European Union regulatory framework. Br J Clin Pharmacol 68(4):493–501. doi:10.1111/j.1365-2125.2009.03484.x
6. Coppini R, Simons SH, Mugelli A, Allegaert K (2016) Clinical research in neonates and infants: challenges and perspectives. Pharmacol Res 108:80–87. doi:10.1016/j.phrs.2016.04.025
7. Thakkar N, Salerno S, Hornik CP, Gonzalez D (2017) Clinical pharmacology studies in critically ill children. Pharm Res 34(1):7–24. doi:10.1007/s11095-016-2033-y
8. Smits A, Kulo A, de Hoon JN, Allegaert K (2012) Pharmacokinetics of drugs in neonates: pattern recognition beyond compound specific observations. Curr Pharm Des 18(21):3119–3146
9. Lopez-Herce J, Sanchez C, Carrillo A, Mencia S, Santiago MJ, Bustinza A, Vigil D (2006) Transpyloric enteral nutrition in the critically ill child with renal failure. Intensive Care Med 32(10):1599–1605. doi:10.1007/s00134-006-0271-x
10. Lopez-Herce J, Santiago MJ, Sanchez C, Mencia S, Carrillo A, Vigil D (2008) Risk factors for gastrointestinal complications in critically ill children with transpyloric enteral nutrition. Eur J Clin Nutr 62(3):395–400. doi:10.1038/sj.ejcn.1602710
11. Rowland Yeo K, Aarabi M, Jamei M, Rostami-Hodjegan A (2011) Modeling and predicting drug pharmacokinetics in patients with renal impairment. Expert Rev Clin Pharmacol 4(2):261–274. doi:10.1586/ecp.10.143
12. van Boekel GA, Aarnoutse RE, van der Heijden JJ, Hoogtanders KE, Hilbrands LB (2012) Effect of mild diarrhea on tacrolimus exposure. Transplantation 94(7):763–767. doi:10.1097/TP.0b013e3182629e13
13. Mooij MG, de Koning BA, Huijsman ML, de Wildt SN (2012) Ontogeny of oral drug absorption processes in children. Expert Opin Drug Metab Toxicol 8(10):1293–1303. doi:10.1517/17425255.2012.698261
14. Huang NN, High RH (1953) Comparison of serum levels following the administration of oral and parenteral preparations of penicillin to infants and children of various age groups. J Pediatr 42(6):657–658
15. van den Anker JN, Schwab M, Kearns GL (2011) Developmental pharmacokinetics. Handb Exp Pharmacol 205:51–75. doi:10.1007/978-3-642-20195-0_2
16. Woolsey CA, Coopersmith CM (2006) Vasoactive drugs and the gut: is there anything new? Curr Opin Crit Care 12(2):155–159. doi:10.1097/01.ccx.0000216584.72427.e4
17. King W, Petrillo T, Pettignano R (2004) Enteral nutrition and cardiovascular medications in the pediatric intensive care unit. JPEN J Parenter Enteral Nutr 28(5):334–338
18. Lopez-Herce J, Mencia S, Sanchez C, Santiago MJ, Bustinza A, Vigil D (2008) Postpyloric enteral nutrition in the critically ill child with shock: a prospective observational study. Nutr J 7:6. doi:10.1186/1475-2891-7-6
19. Dewez JE, Chellani HK, Halim A, van den Broek N (2015) Simplified antibiotic regimens for neonatal sepsis—AFRINEST. Lancet 386(10001):1337–1338. doi:10.1016/s0140-6736(15)00330-x
20. Lingvall M, Reith D, Broadbent R (2005) The effect of sepsis upon gentamicin pharmacokinetics in neonates. Br J Clin Pharmacol 59(1):54–61. doi:10.1111/j.1365-2125.2005.02260.x
21. Joukhadar C, Frossard M, Mayer BX, Brunner M, Klein N, Siostrzonek P, Eichler HG, Muller M (2001) Impaired target site penetration of beta-lactams may account for therapeutic failure in patients with septic shock. Crit Care Med 29(2):385–391

22. Durward A, Mayer A, Skellett S, Taylor D, Hanna S, Tibby SM, Murdoch IA (2003) Hypoalbuminaemia in critically ill children: incidence, prognosis, and influence on the anion gap. Arch Dis Child 88(5):419–422
23. Horowitz IN, Tai K (2007) Hypoalbuminemia in critically ill children. Arch Pediatr Adolesc Med 161(11):1048–1052. doi:10.1001/archpedi.161.11.1048
24. Smits A, Kulo A, Verbesselt R, Naulaers G, de Hoon J, Vermeersch P, Allegaert K (2012) Cefazolin plasma protein binding and its covariates in neonates. European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical. Microbiology 31(12):3359–3365. doi:10.1007/s10096-012-1703-x
25. Martin E, Fanconi S, Kalin P, Zwingelstein C, Crevoisier C, Ruch W, Brodersen R (1993) Ceftriaxone—bilirubin-albumin interactions in the neonate: an in vivo study. Eur J Pediatr 152(6):530–534
26. Brodersen R, Robertson A (1989) Ceftriaxone binding to human serum albumin: competition with bilirubin. Mol Pharmacol 36(3):478–483
27. de Wildt SN, Tibboel D, Leeder JS (2014) Drug metabolism for the paediatrician. Arch Dis Child 99(12):1137–1142. doi:10.1136/archdischild-2013-305212
28. Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW, Hope WW, Farkas A, Neely MN, Schentag JJ, Drusano G, Frey OR, Theuretzbacher U, Kuti JL (2014) Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis 14(6):498–509. doi:10.1016/s1473-3099(14)70036-2
29. Vet NJ, de Hoog M, Tibboel D, de Wildt SN (2011) The effect of inflammation on drug metabolism: a focus on pediatrics. Drug Discov Today 16(9–10):435–442. doi:10.1016/j.drudis.2011.02.014
30. Brouwer KL, Aleksunes LM, Brandys B, Giacoia GP, Knipp G, Lukacova V, Meibohm B, Nigam SK, Rieder M, de Wildt SN (2015) Human ontogeny of drug transporters: review and recommendations of the pediatric transporter working group. Clin Pharmacol Ther 98(3):266–287. doi:10.1002/cpt.176
31. Gupta S, Sengar GS, Meti PK, Lahoti A, Beniwal M, Kumawat M (2016) Acute kidney injury in Pediatric Intensive Care Unit: incidence, risk factors, and outcome. Indian J Crit Care Med 20(9):526–529. doi:10.4103/0972-5229.190368
32. Momtaz HE, Sabzehei MK, Rasuli B, Torabian S (2014) The main etiologies of acute kidney injury in the newborns hospitalized in the neonatal intensive care unit. J Clin Neonatol 3(2):99–102. doi:10.4103/2249-4847.134691
33. Vieux R, Fresson J, Guillemin F, Hascoet JM (2011) Perinatal drug exposure and renal function in very preterm infants. Arch Dis Child Fetal Neonatal Ed 96(4):F290–F295. doi:10.1136/adc.2009.197699
34. Soler YA, Nieves-Plaza M, Prieto M, Garcia-De Jesus R, Suarez-Rivera M (2013) Pediatric risk, injury, failure, loss, end-stage renal disease score identifies acute kidney injury and predicts mortality in critically ill children: a prospective study. Pediatr Crit Care Med 14(4):e189–e195. doi:10.1097/PCC.0b013e3182745675
35. Hobbs AL, Shea KM, Roberts KM, Daley MJ (2015) Implications of augmented renal clearance on drug dosing in critically ill patients: a focus on antibiotics. Pharmacotherapy 35(11):1063–1075. doi:10.1002/phar.1653
36. De Cock PA, Standing JF, Barker CI, de Jaeger A, Dhont E, Carlier M, Verstraete AG, Delanghe JR, Robays H, De Paepe P (2015) Augmented renal clearance implies a need for increased amoxicillin-clavulanic acid dosing in critically ill children. Antimicrob Agents Chemother 59(11):7027–7035. doi:10.1128/aac.01368-15
37. Hirai K, Ishii H, Shimoshikiryo T, Shimomura T, Tsuji D, Inoue K, Kadoiri T, Itoh K (2016) Augmented renal clearance in patients with febrile neutropenia is associated with increased risk for subtherapeutic concentrations of vancomycin. Ther Drug Monit 38(6):706–710. doi:10.1097/ftd.0000000000000346

38. Gomez DS, Campos EV, de Azevedo RP, Silva-Jr JM, Ferreira MC, Sanches-Giraud C, Silva-Jr CV, Santos SR (2013) Individualised vancomycin doses for paediatric burn patients to achieve PK/PD targets. Burns 39(3):445–450. doi:10.1016/j.burns.2012.07.005
39. Yu T, Stockmann C, Healy DP, Olson J, Wead S, Neely AN, Kagan RJ, Spigarelli MG, Sherwin CM (2015) Determination of optimal amikacin dosing regimens for pediatric patients with burn wound sepsis. J Burn Care Res 36(4):e244–e252. doi:10.1097/BCR.0000000000000159
40. Yang RH, Rong XZ, Hua R, Zhang T (2009) Pharmacokinectics of vancomycin and amikacin in the subeschar tissue fluid in patients with severe burn. Burns 35(1):75–79. doi:10.1016/j.burns.2008.05.016
41. Steer JA, Papini RP, Wilson AP, Dhillon S, Hichens MF, McGrouther DA, Frame JD, Parkhouse N (1996) Pharmacokinetics of a single dose of teicoplanin in burn patients. J Antimicrob Chemother 37(3):545–553
42. Wildschut ED, Ahsman MJ, Houmes RJ, Pokorna P, de Wildt SN, Mathot RA, Tibboel D (2012) Pharmacotherapy in neonatal and pediatric extracorporeal membrane oxygenation (ECMO). Curr Drug Metab 13(6):767–777
43. Sherwin CM, Zobell JT, Stockmann C, McCrory BE, Wisdom M, Young DC, Olson J, Ampofo K, Spigarelli MG (2014) Pharmacokinetic and pharmacodynamic optimisation of intravenous tobramycin dosing among children with cystic fibrosis. J Pharmacokinet Pharmacodyn 41(1):71–79. doi:10.1007/s10928-013-9348-7
44. Wildschut ED, Ahsman MJ, Allegaert K, Mathot RA, Tibboel D (2010) Determinants of drug absorption in different ECMO circuits. Intensive Care Med 36(12):2109–2116. doi:10.1007/s00134-010-2041-z
45. Sherwin J, Heath T, Watt K (2016) Pharmacokinetics and dosing of anti-infective drugs in patients on extracorporeal membrane oxygenation: a review of the current literature. Clin Ther 38(9):1976–1994. doi:10.1016/j.clinthera.2016.07.169
46. Cies JJ, Moore WS II, Dickerman MJ, Small C, Carella D, Chopra A, Parker J (2014) Pharmacokinetics of continuous-infusion meropenem in a pediatric patient receiving extracorporeal life support. Pharmacotherapy 34(10):e175–e179. doi:10.1002/phar.1476
47. Cies JJ, Moore WS II, Conley SB, Dickerman MJ, Small C, Carella D, Shea P, Parker J, Chopra A (2016) Pharmacokinetics of continuous infusion meropenem with concurrent extracorporeal life support and continuous renal replacement therapy: a case report. J Pediatr Pharmacol Ther 21(1):92–97. doi:10.5863/1551-6776-21.1.92
48. Knoderer CA, Saft SA, Walker SG, Rodefeld MD, Turrentine MW, Brown JW, Healy DP, Sowinski KM (2011) Cefuroxime pharmacokinetics in pediatric cardiovascular surgery patients undergoing cardiopulmonary bypass. J Cardiothorac Vasc Anesth 25(3):425–430. doi:10.1053/j.jvca.2010.07.022
49. Hatzopoulos FK, Stile-Calligaro IL, Rodvold KA, Sullivan-Bolyai J, Del Nido P, Levitsky S (1993) Pharmacokinetics of intravenous vancomycin in pediatric cardiopulmonary bypass surgery. Pediatr Infect Dis J 12(4):300–304
50. Adrianzen Vargas MR, Danton MH, Javaid SM, Gray J, Tobin C, Brawn WJ, Barron DJ (2004) Pharmacokinetics of intravenous flucloxacillin and amoxicillin in neonatal and infant cardiopulmonary bypass surgery. Eur J Cardiothorac Surg 25(2):256–260
51. Himebauch AS, Nicolson SC, Sisko M, Moorthy G, Fuller S, Gaynor JW, Zuppa AF, Fox E, Kilbaugh TJ (2014) Skeletal muscle and plasma concentrations of cefazolin during cardiac surgery in infants. J Thorac Cardiovasc Surg 148(6):2634–2641. doi:10.1016/j.jtcvs.2014.06.064
52. Sargel C, Karsies T, Lutmer J (2013) Pediatric drug dosing during renal replacement therapy: searching for help. Pediatr Crit Care Med 14(9):904–906. doi:10.1097/PCC.0b013e3182a1262a
53. Rizkalla NA, Feudtner C, Dai D, Zuppa AF (2013) Patterns of medication exposures in hospitalized pediatric patients with acute renal failure requiring intermittent or continuous hemodialysis. Pediatr Crit Care Med 14(9):e394–e403. doi:10.1097/PCC.0b013e31829f5bc8

54. Lee J, Geer J, Swartz S, Srivaths P (2016) Cefazolin in 4 children on chronic hemodialysis: a proposed dosing regimen. Ann Pharmacother. doi:10.1177/1060028016667381
55. Stidham T, Reiter PD, Ford DM, Lum GM, Albietz J (2011) Successful utilization of high-flux hemodialysis for treatment of vancomycin toxicity in a child. Case Rep Pediatr 2011:678724. doi:10.1155/2011/678724
56. Schoumacher R, Chevalier RL, Gomez RA, Rogol AD, Cummings R, Spyker DA (1989) Enhanced clearance of vancomycin by hemodialysis in a child. Pediatr Nephrol 3(1): 83–85
57. Cohen-Wolkowiez M, Poindexter B, Bidegain M, Weitkamp JH, Schelonka RL, Randolph DA, Ward RM, Wade K, Valencia G, Burchfield D, Arrieta A, Mehta V, Walsh M, Kantak A, Rasmussen M, Sullivan JE, Finer N, Rich W, Brozanski BS, van den Anker J, Blumer J, Laughon M, Watt KM, Kearns GL, Capparelli EV, Martz K, Berezny K, Benjamin DK Jr, Smith PB (2012) Safety and effectiveness of meropenem in infants with suspected or complicated intra-abdominal infections. Clin Infect Dis 55(11):1495–1502. doi:10.1093/cid/cis758
58. Smith PB, Cohen-Wolkowiez M, Castro LM, Poindexter B, Bidegain M, Weitkamp JH, Schelonka RL, Ward RM, Wade K, Valencia G, Burchfield D, Arrieta A, Bhatt-Mehta V, Walsh M, Kantak A, Rasmussen M, Sullivan JE, Finer N, Brozanski BS, Sanchez P, van den Anker J, Blumer J, Kearns GL, Capparelli EV, Anand R, Benjamin DK Jr (2011) Population pharmacokinetics of meropenem in plasma and cerebrospinal fluid of infants with suspected or complicated intra-abdominal infections. Pediatr Infect Dis J 30(10):844–849. doi:10.1097/INF.0b013e31822e8b0b
59. Hornik CP, Herring AH, Benjamin DK Jr, Capparelli EV, Kearns GL, van den Anker J, Cohen-Wolkowiez M, Clark RH, Smith PB (2013) Adverse events associated with meropenem versus imipenem/cilastatin therapy in a large retrospective cohort of hospitalized infants. Pediatr Infect Dis J 32(7):748–753. doi:10.1097/INF.0b013e31828be70b
60. Kent A, Turner MA, Sharland M, Heath PT (2014) Aminoglycoside toxicity in neonates: something to worry about? Expert Rev Anti-Infect Ther 12(3):319–331. doi:10.1586/14787210.2014.878648
61. Rao SC, Srinivasjois R, Hagan R, Ahmed M (2011) One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. Cochrane Database Syst Rev (11):Cd005091. doi:10.1002/14651858.CD005091.pub3
62. Nestaas E, Bangstad HJ, Sandvik L, Wathne KO (2005) Aminoglycoside extended interval dosing in neonates is safe and effective: a meta-analysis. Arch Dis Child Fetal Neonatal Ed 90(4):F294–F300. doi:10.1136/adc.2004.056317
63. Lestner JM, Hill LF, Heath PT, Sharland M (2016) Vancomycin toxicity in neonates: a review of the evidence. Curr Opin Infect Dis 29(3):237–247. doi:10.1097/qco.0000000000000263
64. Ragab AR, Al-Mazroua MK, Al-Harony MA (2013) Incidence and predisposing factors of vancomycin-induced nephrotoxicity in children. Infect Dis Ther 2(1):37–46. doi:10.1007/s40121-013-0004-8
65. Cotten CM (2016) Adverse consequences of neonatal antibiotic exposure. Curr Opin Pediatr 28(2):141–149. doi:10.1097/mop.0000000000000338
66. Turta O, Rautava S (2016) Antibiotics, obesity and the link to microbes—what are we doing to our children? BMC Med 14:57. doi:10.1186/s12916-016-0605-7
67. Monte SV, Prescott WA, Johnson KK, Kuhman L, Paladino JA (2008) Safety of ceftriaxone sodium at extremes of age. Expert Opin Drug Saf 7(5):515–523. doi:10.1517/14740338.7.5.515
68. Roberts JK, Stockmann C, Constance JE, Stiers J, Spigarelli MG, Ward RM, Sherwin CM (2014) Pharmacokinetics and pharmacodynamics of antibacterials, antifungals, and antivirals used most frequently in neonates and infants. Clin Pharmacokinet 53(7):581–610. doi:10.1007/s40262-014-0147-0
69. Contopoulos-Ioannidis DG, Giotis ND, Baliatsa DV, Ioannidis JP (2004) Extended-interval aminoglycoside administration for children: a meta-analysis. Pediatrics 114(1):e111–e118

70. Rhodin MM, Anderson BJ, Peters AM, Coulthard MG, Wilkins B, Cole M, Chatelut E, Grubb A, Veal GJ, Keir MJ, Holford NH (2009) Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol 24(1):67–76. doi:10.1007/s00467-008-0997-5
71. Allegaert K, Cossey V, Langhendries JP, Naulaers G, Vanhole C, Devlieger H, Van Overmeire B (2004) Effects of co-administration of ibuprofen-lysine on the pharmacokinetics of amikacin in preterm infants during the first days of life. Biol Neonate 86(3):207–211. doi:10.1159/000079618
72. De Cock RF, Allegaert K, Schreuder MF, Sherwin CM, de Hoog M, van den Anker JN, Danhof M, Knibbe CA (2012) Maturation of the glomerular filtration rate in neonates, as reflected by amikacin clearance. Clin Pharmacokinet 51(2):105–117. doi:10.2165/11595640-000000000-00000
73. Smits A, Kulo A, van den Anker J, Allegaert K (2016) The amikacin research program: a stepwise approach to validate dosing regimens in neonates. Expert Opin Drug Metab Toxicol 13(2):157–166. doi:10.1080/17425255.2017.1234606
74. 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(13):925–942
75. De Cock RF, Allegaert K, Brussee JM, Sherwin CM, Mulla H, de Hoog M, van den Anker JN, Danhof M, Knibbe CA (2014) Simultaneous pharmacokinetic modeling of gentamicin, tobramycin and vancomycin clearance from neonates to adults: towards a semi-physiological function for maturation in glomerular filtration. Pharm Res 31(10):2643–2654. doi:10.1007/s11095-014-1361-z
76. Giachetto GA, Telechea HM, Speranza N, Oyarzun M, Nanni L, Menchaca A (2011) Vancomycin pharmacokinetic-pharmacodynamic parameters to optimize dosage administration in critically ill children. Pediatr Crit Care Med 12(6):e250–e254. doi:10.1097/PCC.0b013e3181fe4047
77. Oyaert M, Spriet I, Allegaert K, Smits A, Vanstraelen K, Peersman N, Wauters J, Verhaegen J, Vermeersch P, Pauwels S (2015) Factors impacting unbound vancomycin concentrations in different patient populations. Antimicrob Agents Chemother 59(11):7073–7079. doi:10.1128/aac.01185-15
78. Hospira I (2016) Vancomycin hydrochloride for injection, USP. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/062911s035lbl.pdf. Accessed 26 Oct 2016
79. Pharmaceuticals A (2016) MERREM® I.V. (meropenem for injection). http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/050706s022lbl.pdf. Accessed 26 Oct 2016
80. Jacqz-Aigrain E, Leroux S, Zhao W, van den Anker JN, Sharland M (2015) How to use vancomycin optimally in neonates: remaining questions. Expert Rev Clin Pharmacol 8(5):635–648. doi:10.1586/17512433.2015.1060124
81. Goldstein SL, Murry DJ, May S, Aleksic A, Sowinski KM, Blaney S (2001) Meropenem pharmacokinetics in children and adolescents receiving hemodialysis. Pediatr Nephrol 16(12):1015–1018. doi:10.1007/s004670100015
82. Nehus EJ, Mizuno T, Cox S, Goldstein SL, Vinks AA (2016) Pharmacokinetics of meropenem in children receiving continuous renal replacement therapy: validation of clinical trial simulations. J Clin Pharmacol 56(3):291–297. doi:10.1002/jcph.601
83. Depre M, van Hecken A, Verbesselt R, Tjandra-Maga TB, Gerin M, de Schepper PJ (1992) Tolerance and pharmacokinetics of propacetamol, a paracetamol formulation for intravenous use. Fundam Clin Pharmacol 6(6):259–262
84. Jenner P, Konen-Bergmann M, Schepers C, Haertter S (2009) Pharmacokinetics of a once-daily extended-release formulation of pramipexole in healthy male volunteers: three studies. Clin Ther 31(11):2698–2711. doi:10.1016/j.clinthera.2009.10.018
85. Rashid A, Ahmad M, Minhas MU, Hassan IJ, Malik MZ (2014) Pharmacokinetic studies of metformin and glibenclamide in normal human volunteers. Pak J Pharm Sci 27(1):153–159

86. Mould DR, Upton RN (2013) Basic concepts in population modeling, simulation, and model-based drug development-part 2: introduction to pharmacokinetic modeling methods. CPT Pharmacometrics Syst Pharmacol 2:e38. doi:10.1038/psp.2013.14
87. Administration USFaD (1999) FDA guidance for industry-population pharmacokinetics. Tech. rep., Food and Drug Administration
88. European Medicines Agency (2007) Guideline on reporting the results of population pharmacokinetic analyses. EMA, London
89. Ward RM, Sherwin CM (2016) Newborns still lack drug data to guide therapy. Br J Clin Pharmacol 82(6):1410–1411. doi:10.1111/bcp.13074
90. Samara E, Granneman R (1997) Role of population pharmacokinetics in drug development. A pharmaceutical industry perspective. Clin Pharmacokinet 32(4):294–312. doi:10.2165/00003088-199732040-00003
91. Wahlby U, Jonsson EN, Karlsson MO (2002) Comparison of stepwise covariate model building strategies in population pharmacokinetic-pharmacodynamic analysis. AAPS PharmSci 4(4):E27. doi:10.1208/ps040427
92. MacDonald A, Scarola J, Burke JT, Zimmerman JJ (2000) Clinical pharmacokinetics and therapeutic drug monitoring of sirolimus. Clin Ther 22(Suppl B):B101–B121
93. Smith J, Andes D (2008) Therapeutic drug monitoring of antifungals: pharmacokinetic and pharmacodynamic considerations. Ther Drug Monit 30(2):167–172. doi:10.1097/FTD.0b013e318167d0e0
94. Dansirikul C, Morris RG, Tett SE, Duffull SB (2006) A Bayesian approach for population pharmacokinetic modelling of sirolimus. Br J Clin Pharmacol 62(4):420–434. doi:10.1111/j.1365-2125.2005.02533.x
94. Dorofaeff T, Bandini RM, Lipman J, Ballot DE, Roberts JA, Parker SL (2016) Uncertainty in antibiotic dosing in critically Ill neonate and pediatric patients: can microsampling provide the answers? Clin Ther 38(9):1961–1975. doi: 10.1016/j.clinthera.2016.07.093. Epub 2016 Aug 17
95. Germovsek E, Kent A, Metsvaht T, Lutsar I, Klein N, Turner MA, Sharland M, Nielsen EI, Heath PT, Standing JF (2016) Development and evaluation of a gentamicin pharmacokinetic model that facilitates opportunistic gentamicin therapeutic drug monitoring in neonates and infants. Antimicrob Agents Chemother 60(8):4869–4877. doi:10.1128/aac.00577-16
96. Marik PE, Lipman J, Kobilski S, Scribante J (1991) A prospective randomized study comparing once-versus twice-daily amikacin dosing in critically ill adult and paediatric patients. J Antimicrob Chemother 28(5):753–764
97. Munckhof WJ, Grayson ML, Turnidge JD (1996) A meta-analysis of studies on the safety and efficacy of aminoglycosides given either once daily or as divided doses. J Antimicrob Chemother 37(4):645–663
98. Sherwin CM, Wead S, Stockmann C, Healy D, Spigarelli MG, Neely A, Kagan R (2014) Amikacin population pharmacokinetics among paediatric burn patients. Burns 40(2):311–318. doi:10.1016/j.burns.2013.06.015
99. Kuepfer L, Niederalt C, Wendl T, Schlender JF, Willmann S, Lippert J, Block M, Eissing T, Teutonico D (2016) Applied concepts in PBPK modeling: how to build a PBPK/PD model. CPT Pharmacometrics Syst Pharmacol 5(10):516–531. doi:10.1002/psp4.12134

Chapter 13
Antibiotic Stewardship in the Intensive Care Unit

M. Gilchrist, E.T. Brannigan, G. Satta, and M. Laundy

13.1 Background

Antimicrobial resistance (AMR) is a global patient safety challenge. The development of AMR is inevitable, but the overuse and misuse of antimicrobials has accelerated this process. Of particular concern is the rise in multidrug-resistant Gram-negative organisms. One example of this is the global rise and dissemination of *Klebsiella pneumoniae* carrying the *kpc* gene encoding a carbapenemase enzyme, conferring resistance to almost all beta-lactam antibiotics including carbapenems [1, 2]. Treatment options for these organisms are somewhat limited due to the lack of new licensed antimicrobials, and poor efficacy and toxicity of existing antibiotics.

Poor control of the use of antibiotics within the healthcare and agricultural industries coupled with the lack of a financially supportive environment for new antimicrobial compound development has been recognized by international and national leaders as a global emergency [3]. The AMR agenda has been raised at the United Nations General Assembly high level meeting of Heads of State to discuss sustainable access to effective antimicrobials [4]. It was only the third time (after HIV and chronic diseases) that a health topic has being discussed at this forum and followed the economic report that suggested by 2050, the number of people dying from resistant pathogens could be ten million per year [5]. Within human medicine, the issue of AMR is further complicated by advances in medical management including transplantation, use of prosthetic materials, biological therapies, and vascular devices, which all rely on having effective antimicrobials.

M. Gilchrist (✉) • E.T. Brannigan • G. Satta
Imperial College Healthcare NHS Trust, London, UK
e-mail: Mark.Gilchrist@imperial.nhs.uk

M. Laundy
St George's University Hospitals NHS Foundation Trust, London, UK

A.A. Udy et al. (eds.), *Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill*, DOI 10.1007/978-981-10-5336-8_13

The challenge faced by many practitioners is to balance the immediate prudent use of antimicrobials at the individual sick patient level, against the wider but seemingly more distant threat of AMR.

This chapter will set out the goals and principles of an antimicrobial stewardship program (ASP). It will discuss key components of a typical program in specific relation to intensive care and look at applicability on the shop floor and what the future might hold in this area.

13.2 Goals and Steps to Consider When Implementing an Antimicrobial Stewardship Program

The goals of an antimicrobial stewardship program should be focused around four key domains. Improving patient outcomes, minimizing the unintended consequences of antimicrobials (improved patient safety), reducing the development of resistance and reducing associated healthcare costs [6].

To aid in achieving these goals, there are a number of tools which can be deployed depending on the maturity of the ASP. Critical to this, is understanding the environment in which the ASP will operate, defining the priorities of the ASP, and how the ASP will measure progress and success. Only after this, can ASPs identify effective interventions and key measurements for improvement. For example, for newly formed ASPs, focusing on recognized core tools which have a large quality of evidence to support the intervention may be advantageous, compared with more mature programs which may use a wide range of core and supplemental tools [6, 7]. Both however are determined by available resource (both financial and human).

The range of tools that can be deployed will be discussed later in this chapter but include policy development and prescribing guidelines, antimicrobial restriction, dose optimization through therapeutic drug monitoring, intravenous to oral switching, audit and feedback, antimicrobial consumption and resistance trends, prospective audit with intervention and feedback, and the development of structural (e.g., availability of guidelines), processes (e.g., compliance with guidelines), and outcome (e.g., healthcare-associated infection rates) measures which are driven through quality improvement initiatives.

Central to supporting these tools are four key threads. These include

- Organizational and local leadership
- Effective multidisciplinary working
- Accountability and governance
- Strong program plan

Having healthcare professionals with a diversity of experience and skills, not necessarily all infection specialists, within the ASP to work on stewardship activities is important. At a minimum, an ASP should have an appropriate clinician (infectious diseases physician or medical microbiologist) and a clinical pharmacist (with

infection training if possible). Additional members of the team could include senior nursing, hospital epidemiologists, infection control specialists, infection trainees with a link clinician to the area that is trying to affect a change within the ASP, e.g., an acute medicine physician, surgeon, or anesthetist [8–12]. The use of these link clinicians or champions is essential to establish local ownership of the process, local buy in and ultimately success of the ASP.

The ASP should function under the auspices of an established quality assurance/clinical governance and/or patient safety program to provide clear lines of accountability and collaborate closely with the hospital infection prevention and control and pharmacy/therapeutics committees. The program should have the support of senior management ideally the medical director of the organization. Collaboration, consensus, and engagement with hospital administrators, medical staff leaders, and local providers are also crucial to the success of antimicrobial stewardship (Fig. 13.1).

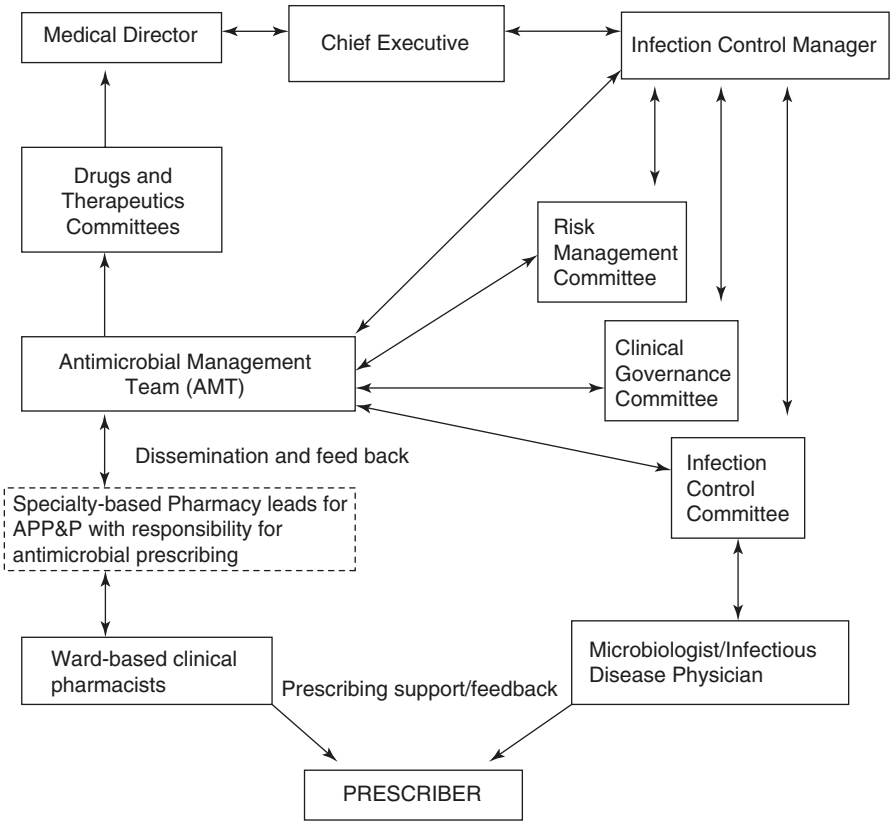

Fig. 13.1 Model antimicrobial prescribing practice pathway in acute hospitals [10]. *APP&P* antimicrobial prescribing policy and practice

13.3 The Intensive Care Setting

Intensive Care Units (ICUs) represent a peculiar environment within the hospital setting. They accommodate the sickest patients, with various degrees of organ failure, and invasive devices (in particular ventilators and blood/urinary catheters) are routinely required. Hence, it is not a surprise that ICUs account for more than 20% of all nosocomial infection in the hospital [13]. Data from the Extended Prevalence of Infection in Intensive Care (EPIC II) study [14] (a 1-day snapshot of ICUs from 75 countries) has shown that more than two thirds of patients were on antibiotics although only half of them were considered as infected. This highlights the role of infection and sepsis as major cause of mortality, but also the need of antimicrobial stewardship within the intensive care setting.

The most important infections in ICU are represented by catheter-related bloodstream infections (CRBSIs), ventilator-associated pneumonia (VAP), and catheter-associated urinary tract infections (CAUTIs) [15–17]. The high frequency of indwelling catheters is a continuous breach on the body's natural defense barriers and their maintenance requires frequent manipulation by healthcare staff, increasing the chance of pathogen transmission [18]. Pathogens are becoming increasingly more resistant, threatening to kill an estimated ten million people annually worldwide by 2050 and to cost the global economy US$100 trillion [19]. However, the epidemiology of multidrug resistance is constantly evolving in time and space and knowledge of local epidemiological data is essential to tailor appropriate treatment [20, 21]. Coagulase-negative staphylococci (CoNS), *Pseudomonas* species, *Enterobacter* species, *Serratia* species, and *Acinetobacter* species are more likely to cause infections in patients in ICUs. Also, the length of stay has an impact on the epidemiology, with *Escherichia coli* infections developing after an average of 13 days, 16 days for *Staphylococcus aureus* (including Meticillin-resistant, MRSA), 22 days for *Candida* species and *Klebsiella* species, 23 days for enterococci, and 26 days for *Acinetobacter* species [22].

However, the isolation of pathogen from a clinical sample (i.e., sputum, catheter urine or routine skin, and rectal screening tests) does not necessarily imply infection. For example, bacteriuria in patients with indwelling urinary catheters occurs at a rate of up to 10% per day of catheterization [23] but only a minority of patients will actually develop an infection [24]. It is important to distinguish colonization from infection and inflammation:

- Colonization is the presence of organism without any inflammatory response.
- Infection is the invasion by and multiplication of pathogenic microorganisms in a body part or tissue, which may produce subsequent tissue injury and progress to overt disease through a variety of cellular or toxic mechanism.
- Inflammation is a protective reaction of tissue to irritation, injury, or infection, characterized by pain, redness, swelling, and sometimes loss of function.

In the ICU setting, there is always a conflict between the need to promptly treat infections and antimicrobial stewardship programs trying to reduce the unnecessary usage of antibiotics [25]. The new definition of sepsis (as life-threatening organ dysfunction caused by a dysregulated host response to infection) should help to

identify those patients that certainly need antimicrobials [26]. Limitations of previous definitions included an excessive focus on inflammation, the misleading model that sepsis follows a continuum through severe sepsis to shock, and inadequate specificity and sensitivity of the systemic inflammatory response syndrome (SIRS) criteria. On the other hand, antimicrobial stewardship programs have demonstrated their efficacy in reducing multidrug resistance. In a study from ICUs in the United States that implemented a comprehensive stewardship program, the proportion of infection caused by multidrug-resistant Gram-negative bacilli, decreased from 37 to 8% [27].

13.4 Antimicrobial Stewardship and ICU: A Practical Approach

What can practically be done with respect to antibiotic stewardship in critical care settings where patients are among the sickest in the hospital and great weight is placed on administration of broad spectrum high dose antimicrobials in unstable patients in an empiric and often emergency fashion?

The context of the deteriorating unstable patient is important and the critical care clinicians need access to relevant local guidelines for their patient cohort ideally at the point at which a decision on choice, route, and dose of antibiotic agent is being made [28]. To support this, critical care and infection specialists' collaboration in development of such policy principles and local guidelines adds weight, credibility, and feasibility to such resources and ensures that agreed strategies include the relevant perspectives [29]. Building on this concept, participatory action research seeks to influence prescriber and other stakeholder behavior in stewardship by involvement in developing local solutions to the challenge of antibiotic use [30]. Finally, the importance of establishing good professional relationships cannot be understated. Reliable and frequent interaction between infection and critical care specialists during ward rounds can support education and decision-making on initial empiric choices, timing with respect to diagnostic sampling and results of these, and early and daily review to optimize antibiotic agent, dose, route of administration, and duration [31].

13.5 Managing Antimicrobials on the Shop Floor

There are several tools that can enable healthcare organizations in secondary care to achieve improved practice. These include systematic review at a predetermined time point from initiation of antibiotics, daily prompts to review current antibiotic prescriptions, often with IT support, input by pharmacists on daily rounds, input from infection specialists, and input from nurses on promoting review of antibiotics [32–36].

Determining which are most useful is difficult as across various studies, these have been implemented in a range of types of intensive care or critical care settings,

both adult and pediatric, for variable periods of time and usually as one of a number of contemporaneous interventions [37].

The context and culture [34, 38, 39], in which these interventions are applied contributes to their success or otherwise, and the engagement of critical care clinicians in development of antimicrobial policy for the unit is key, including strategies on rotation or cycling of antimicrobials [40], protocols for intravenous to oral switching, or de-escalation policy for certain conditions such as VAP. In addition, choice of agents from a restricted formulary [41] with some form of pre-use authorization by senior clinician or infection specialist can support best practice and limit inappropriate use. While usually such interventions are by a senior critical care clinician, infection specialist or pharmacist with or without specialist infection training, it is increasingly recognized that nurses have key roles in antibiotic stewardship and could prove a skilled resource with the correct support [36] (Table 13.1).

Technological developments and new diagnostics may help in supporting further programs. In a study from Australia, the ICU use of a computerized antibiotic decision support system was associated with a significant increase in susceptibility of *Pseudomonas* and *Enterobacter* [43]. The utility of procalcitonin in reducing duration of antimicrobial treatment has been demonstrated in critically ill patients with presumed bacterial infection. This reduction was associated with a significant decrease in mortality [44]. Other biomarkers may play an important role in the near future but further research is still needed due to the complex heterogeneity of sepsis [45]. Rapid microbiologic tests may also provide opportunities for antimicrobial stewardship programs to improve antimicrobial use and clinical outcomes. Standard techniques for identification of bacteria require at least 48–72 h for final results, compared with rapid diagnostic tests that provide final organism identification within hours of growth [46]. However, best algorithms and their clinical impacts still need to be demonstrated, but the ICU setting should be prioritized for their use.

13.6 Measuring Antibiotic Consumption and Outcomes

13.6.1 Antibiotic Consumption

Antibiotic stewardship interventions of many types have been found to reduce overall consumption of antibiotics [47] leading to reduced costs. How to measure consumption and make this digestible to clinicians is a challenge, but an important component of feedback regarding the impact of interventions. Standardization of consumption metrics makes for meaningful comparison within units over time and between units for benchmarking purposes. Commonly used metrics include defined daily doses, days of therapy, antibiotic costs, usually standardized per 1000 patient days. Patient level information is time-consuming to collect and validate without electronic prescribing systems and thus pharmacy IT systems are often used to

Table 13.1 Types of antimicrobial stewardship interventions and their role/impact

Intervention type	Description/role in antimicrobial stewardship	Comments
Formulary restriction	Antibiotics only for certain linked indications; or only able to be prescribed by certain physicians	Often implemented with pre-authorization system
Drug pre-authorization	Permission required to access certain antibiotics—aims to promote interaction of clinicians with the infection or pharmacist team to limit inappropriate use of usually very broad spectrum agents or those for multidrug-resistant organisms	Often with formulary restriction To limit inappropriate use of usually very broad spectrum agents or those for multidrug-resistant organisms
Prospective audit and feedback	Case review by ASP team and feedback of recommendation on appropriate antibiotic management; has education opportunities, evidence to support its benefits; labor intensive	
Prescriber education	Can have benefits beyond targeted area if prescribers move between clinical areas	Can be supported by systems prompting review at certain time points, or de-escalation protocols
Patient education	Focus groups or broad community campaigns	
Clinical guidelines	Treatment protocols—can include prescribing principles to support de-escalation in certain conditions; may be empiric or may be syndrome or organism specific; can be tailored to known epidemiology of unit	
Clinical decision support systems	IT support for prescribers either on initiation or during early management	Can include standard order sets for certain clinical presentations (e.g., septic patient) or draw on local epidemiological and patient level data to suggest antibiotic agents for use; daily prompt to review antibiotics
Point of care diagnostic tests	Some evidence of utility in community infection and for decisions on starting or early stopping of antibiotics	
Microbiology lab susceptibility reporting	Selective reporting of susceptibility on positive cultures which can be linked to local unit policy to support protocol; can promote avoidance of one agent or entire classes of antibiotics	
Antimicrobial cycling	Substitution of selected antibiotics or antibiotic classes over predefined periods	In theory, this offers heterogeneity of selection pressure on organisms; some evidence of benefit on susceptibility in a unit where this implemented

Adapted with permission from [42]

derive ward, specialty, critical care unit or organizational consumption metrics, the important feature being consistency of collection and review rather than perfection of accuracy [39].

13.6.2 Antibiotic Outcomes

Most studies measure impact of an intervention on antibiotic use, i.e., on consumption of overall antibiotics or on the targeted antibiotics or antibiotic class, and most indicate reduction in this measure. Where particular antibiotics are targeted, there are often compensatory increases in use of other agents with a similar spectrum of action. There has been variable reporting of impact of interventions on cost or cost-effectiveness, impact on appropriateness, duration, or adverse effects of antibiotics. There is a tendency towards a favorable impact on these outcomes where these are reported [48].

13.6.3 Clinical and Microbiological Outcomes

Of course a major concern for clinicians, when modifying usual practice by implementing an ASP, is patient outcome, in particular, whether harm arises from a shorter course of antibiotics, or from using narrower spectrum agents. It is useful then to learn from several studies that there is either no harm or some benefit with respect to length of stay in critical care or overall mortality from stewardship interventions. These include shorter than usual durations, narrowing spectrum, and stopping in response to biomarker results, suggesting that these can be considered safe to implement. Broader questions regarding whether the ASP has an impact on the ecology of the critical care unit have also been examined in studies of variable periods of follow-up. These report variously [47] no impact on some organisms, considerable increase in susceptibility in others and some unanticipated consequences on organisms other than those directly of interest, for example, reduction in MRSA with restrictive policy on ciprofloxacin. Understanding of the ecology and resistance rates of key pathogens in the critical care unit as well as the local patient community is also central to design of appropriate antibiotic guidelines or policies and potentially to reduce time to microbiologically appropriate treatment for individual patients with sepsis [49].

Linkage of prescribing and resistance data at individual patient level as well as at local and national level provides greater ability to evaluate clinical and microbiological outcomes for patients, critical care units, and organizations [48]. Locally useful data for reflection on by prescribers could include unit resistance rates, antibiotic consumption data, and clinical outcomes such as adverse effects of antibiotics as well as healthcare-associated infections particularly bacteremias with resistant organisms or *Clostridium difficile*-associated diarrhea.

13.7 Measuring and Feeding Back on Stewardship Practice

13.7.1 Benchmarking of Units/Individual Clinicians

Prospective audit and feedback have been shown to be one of the most effective ways of changing and influencing antibiotic prescribing practice and use. What is not established is the best way in which to feedback to prescribers and which component of feedback has the most impact [39]. Such audit and feedback methods are often used in the context of quality improvement projects or strategies, intended for sustained impact. While education alone has been found to be unlikely to deliver lasting impact on behavior, feedback on prescribing can be delivered in an educational context such that learning from real world clinical scenarios can be reflected upon and integrated into improved practice. Quality improvement methodologies have been employed in healthcare as a way of measuring performance. Building such methods into the ASP, antibiotic prescriptions are actively audited and any variance from good practice is fed back to the prescriber. Prescribing performance against a local agreed policy or against national policy principles can form part of prospective audit for feedback to units and indeed to individual clinicians for benchmarking.

Point prevalence surveys are well tried and tested methods of capturing data for feedback to prescribers and to organizations and can fit well amid other metrics familiar to senior healthcare management. These are not so much about day-to-day implementation of policy or support for best practice at the coal face, but instead should act as a prompt for an organization or unit to focus on areas for improvement on the indicators in question. Such surveys have become established internationally, and are considered cornerstones in ASPs, and have become incorporated into national guidance on best practice [12]. Monitoring antimicrobial use and patient outcomes are key components of stewardship and are crucial to understanding and communicating local priorities and demonstrating the effects of a stewardship program.

References

1. Schwaber M et al (2011) Containment of a country-wide outbreak of carbapenem-resistant *Klebsiella pneumoniae* in Israeli hospitals via a nationally implemented intervention. Clin Infect Dis 52(7):848–855
2. Gupta N et al (2011) Carbapenem-resistant enterobacteriaceae: epidemiology and prevention. Clin Infect Dis 53(1):60–67
3. World Health Organisation (2013) Antibiotic resistance—a threat to global health security. http://www.who.int/drugresistance/activities/wha66_side_event/en/. Accessed Aug 2016
4. World Health Organisation (2016) United Nations high-level meeting on antimicrobial resistance. http://www.who.int/drugresistance/events/UNGA-meeting-amr-sept2016/en/. Accessed Sept 2016
5. (2014) The review on antimicrobial resistance: tackling a crisis for the health and wealth of nations. http://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf. Accessed Aug 2016

6. Nathwani D, Sneddon J. Practical guide to antimicrobial stewardship in hospitals. http://bsac.org.uk/wp-content/uploads/2013/07/Stewardship-Booklet-Practical-Guide-to-Antimicrobial-Stewardship-in-Hospitals.pdf. Accessed Aug 2016
7. Duguid M., Cruickshank M. Antimicrobial stewardship in Australian hospitals 2011. Australian Commission on Safety and Quality in Health Care. https://www.safetyandquality.gov.au/wp-content/uploads/2011/01/Antimicrobial-stewardshipin-Australian-Hospitals-2011.pdf. Accessed June 2017
8. Dellit T, Owens R, McGowan J, Gerding D, Weinstein R, Burke J, Huskins W, Paterson D, Fishman N, Carpenter C, Brennan P, Billeter M, Hooten T (2007) Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 44(2):159–177
9. Gould IM (2001) Minimum antimicrobial stewardship measures. Clin Microbiol Infect 7(Suppl 6):22–26
10. Nathwani D (2006) Antimicrobial prescribing policy and practice in Scotland: recommendations for good antimicrobial practice in acute hospitals. J Antimicrob Chemother 57:1189–1196
11. Davey P, Brown E, Fenelon L, Finch R, Gould I, Hartman G, Holmes A, Ramsay C, Taylor E, Wilcox M, Wiffen P (2005) Interventions to improve antimicrobial prescribing practices for hospital inpatients. Cochrane Database Syst Rev 4:CD003543
12. Public Health England (2015) Start smart then focus. Antimicrobial stewardship toolkit for England hospitals. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/417032/Start_Smart_Then_Focus_FINAL.PDF. Accessed June 2017
13. Fridkin SK, Welbel SF, Weinstein RA (1997) Magnitude and prevention of nosocomial infections in the intensive care unit. Infect Dis Clin North Am 11:479
14. Vincent JL, Rello J, Marshall J et al (2009) International study of the prevalence and outcomes of infection in intensive care units. JAMA 302:2323
15. Marschall J, Mermel LA, Fakih M et al (2014) Strategies to prevent central line-associated bloodstream infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 35:753
16. Coffin SE, Klompas M, Classen D et al (2008) Strategies to prevent ventilator-associated pneumonia in acute care hospitals. Infect Control Hosp Epidemiol 29(Suppl 1):S31
17. Lo E, Nicolle L, Classen D et al (2008) Strategies to prevent catheter-associated urinary tract infections in acute care hospitals. Infect Control Hosp Epidemiol 29(Suppl 1):S41
18. Kaye KS, Marchaim D, Smialowicz C, Bentley L (2010) Suction regulators: a potential vector for hospital-acquired pathogens. Infect Control Hosp Epidemiol 31:772
19. Cole J (2016) Antimicrobial resistance—a 'rising tide' of national (and international) risk. J Hosp Infect 92(1):3–4
20. Rello J, Sa-Borges M, Correa H, Leal SR, Baraibar J (1999) Variations in etiology of ventilator-associated pneumonia across four treatment sites: implications for antimicrobial prescribing practices. Am J Respir Crit Care Med 160(2):608–613
21. Gaynes R, Edwards JR (2005) National Nosocomial Infections Surveillance System. Overview of nosocomial infections caused by gram-negative bacilli. Clin Infect Dis 41(6):848–854
22. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB (2004) Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis 39(3):309–317
23. Warren JW, Platt R, Thomas RJ et al (1978) Antibiotic irrigation and catheter-associated urinary-tract infections. N Engl J Med 299:570
24. Tambyah PA, Maki DG (2000) Catheter-associated urinary tract infection is rarely symptomatic: a prospective study of 1,497 catheterized patients. Arch Intern Med 160:678
25. Paul M, Shani V, Muchtar E et al (2010) Systematic review and meta-analysis of the efficacy of appropriate empiric antibiotic therapy for sepsis. Antimicrob Agents Chemother 54:4851
26. Singer M, Deutschman CS, Seymour CW et al (2016) The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 315(8):801–810
27. Dortch MJ, Fleming SB, Kauffmann RM et al (2011) Infection reduction strategies including antibiotic stewardship protocols in surgical and trauma intensive care units are associated with reduced resistant gram-negative healthcare-associated infections. Surg Infect (Larchmt) 12:15

28. Chiu CH, Michelow I, Cronin J et al (2011) Effectiveness of a guideline to reduce vancomycin use in the neonatal intensive care unit. Paediatr Infect Dis J 30(4):273–278
29. Gonçalves-Pereira J (2013) Cooperative approach: a further step in antimicrobial stewardship programs. Crit Care Med 41(9):2226–2227
30. van Buul LW, Sikkens JJ et al (2014) Participatory action research in antimicrobial stewardship: a novel approach to improving antimicrobial prescribing in hospitals and long-term care facilities. J Antimicrob Chemother 69(7):1734–1741
31. Pagani L, Falciani M, Aschbacher R (2009) Use of microbiologic findings to manage antimicrobials in the intensive care unit. Infect Control Hosp Epidemiol 30(3):309–311
32. Singh N, Rogers P, Atwood CW et al (2000) Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. Am J Respir Crit Care Med 162(2 Pt 1):505–511
33. Chastre J, Wolff M, Fagon MY et al (2003) Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 290(19):2588–2598
34. Allan PA, Newman MJ, Oehmen R, English WA (2016) The use of daily electronic prompts to help improve antimicrobial stewardship in a critical care unit. J Infect Prev. 1757177416645346
35. Rimawi RH, Mazer MA, Siraj DS, Gooch M, Cook PP (2013) Impact of regular collaboration between infectious diseases and critical care practitioners on antimicrobial utilization and patient outcome. Crit Care Med 41(9):2099–2107
36. Olans RN, Olans RD, DeMaria A Jr (2016) The critical role of the staff nurse in antimicrobial stewardship—unrecognized, but already there. Clin Infect Dis 62(1):84–89
37. Zhang YZ, Singh S (2015) Antibiotic stewardship programmes in intensive care units: why, how, and where are they leading us. World J Crit Care Med 4(1):13–28
38. Charani E, Edwards R, Sevdalis N et al (2011) Behavior change strategies to influence antimicrobial prescribing in acute care: a systematic review. Clin Infect Dis 53(7):651–662
39. Morris AM (2014) Antimicrobial stewardship programs: appropriate measures and metrics to study their impact. Curr Treat Options Infect Dis 6(2):101–112
40. van Duijn PJ, Bonten MJ (2014) Antibiotic rotation strategies to reduce antimicrobial resistance in gram-negative bacteria in European intensive care units: study protocol for a cluster-randomized crossover controlled trial. Trials 15:277
41. Meyer E, Lapatschek M, Bechtold A et al (2009) Impact of restriction of third generation cephalosporins on the burden of third generation cephalosporin resistant *K. pneumoniae* and *E. coli* in an ICU. Intensive Care Med 35(5):862–870
42. Chung G, Wu J, Leng Yeo C (2013) Antimicrobial stewardship—a review of prospective audit and feedback systems and an objective evaluation of outcomes. Virulence 4(2):151–157
43. Yong MK, Buising KL, Cheng AC, Thursky KA (2010) Improved susceptibility of gram-negative bacteria in an intensive care unit following implementation of a computerized antibiotic decision support system. J Antimicrob Chemother 65:1062
44. de Jong E, van Oers JA, Beishuizen A et al (2016) Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. Lancet Infect Dis 16(7):819–827
45. Biron BM, Ayala A, Lomas-Neira JL (2015) Biomarkers for sepsis: what is and what might be? Biomark Insights 10(Suppl 4):7–17
46. Bauer KA, Perez KK, Forrest GN, Goff DA (2014) Review of rapid diagnostic tests used by antimicrobial stewardship programs. Clin Infect Dis 59(Suppl 3):S134–S145
47. Kaki R, Elligsen M, Walker S et al (2011) Impact of antimicrobial stewardship in critical care: a systematic review. J Antimicrob Chemother 66(6):1223–1230
48. Mertz D, Brooks A, Irfan N et al (2015) Antimicrobial stewardship in the intensive care setting—a review and critical appraisal of the literature. Swiss Med Wkly 145:w14220
49. Randhawa V, Sarwar S, Walker S et al (2014) Weighted-incidence syndromic combination antibiograms to guide empiric treatment of critical care infections: a retrospective cohort study. Crit Care 18:R112