



PK/PD in Critical Illness

By Mohd Hafiz Abdul-Aziz, Ph.D., M.Clin Pharm, B.Pharm (Hons); and
Jason A. Roberts, Ph.D., B.Pharm (Hons), B.App.Sc, FSHP, FISAC

Reviewed by: Christopher M. Bland, Pharm.D., FCCP, FIDSA, BCPS; Conan MacDougall, Pharm.D., MAS, BCPS, BCIDP; and Lynn Wardlow, Pharm.D., MBA, MS, BCPS, BCIDP

LEARNING OBJECTIVES

1. Evaluate the impact of critical illness-related pharmacokinetic and pharmacodynamic differences on antimicrobial exposures and dosing requirements in critically ill patients.
2. Design and justify various alternative dosing strategies for commonly used antimicrobials that can be applied in critically ill patients on the basis of current pharmacokinetic and pharmacodynamic data.
3. Design and justify various antimicrobial dosing strategies for subgroups of patients in the ICU, such as patients with augmented renal clearance, renal replacement therapy and extracorporeal membrane oxygenation.
4. Evaluate and assess the latest pharmacokinetic and pharmacodynamic data presented to be applied in clinical decision-making.

ABBREVIATIONS IN THIS CHAPTER

AUC_{0-24}	Area under the concentration-time curve over a 24-hour period
ARC	Augmented renal clearance
CL	Clearance
C_{max}	Peak drug concentration over a dosing interval
C_{min}	Minimum drug concentration during a dosing interval
$fT_{>MIC}$	Duration of time that the free drug concentration remains above the MIC during a dosing interval
PD	Pharmacodynamic
PK	Pharmacokinetic
TDM	Therapeutic drug monitoring
V_d	Volume of distribution

Table of other common abbreviations.

INTRODUCTION

The management of critically ill patients in the ICU is highly challenging because it usually involves use of many drugs and requires rapidly changing dosing on the basis of patients' organ function and response. Patients in the ICU receive twice as many drugs and have a higher mortality compared with patients in general hospital wards, particularly as a result of sepsis and septic shock (Kane-Gill 2017). Source control of the infection, together with early and appropriate antimicrobial therapy, are the most effective strategies available to clinicians for the management of critically ill patients with sepsis or septic shock (Rhodes 2017). It is therefore not surprising that although critically ill patients in the ICU are fewer than 10% of all hospital admissions, per-patient antimicrobial consumption in ICUs is 10 times higher than those in other hospital wards (Dulhunty 2011). However, conventional antimicrobial dosing regimens and most antimicrobial dosing guidelines may not be appropriate for these ICU patients because they rarely address the altered physiology and illness severity associated with this patient population. Product information regarding dosing regimens, which are mostly derived from data in healthy volunteers and/or ambulatory patients, do not address the physiologic and PK differences associated with this special patient population. Therefore, applying a standard dosing or a "one-dose-fits-all" dosing strategy for all critically ill patients in the ICU may likely be a flawed approach that leads to insufficient antimicrobial exposure and therapeutic failure in these patients (Abdul-Aziz 2018). Optimizing antimicrobial dosing using PK and PD principles

can address these critical illness-related changes and promote therapeutic success. An in-depth knowledge of PK and PD is essential to comprehend the complex effect of pathophysiologic changes in critically ill patients with sepsis or septic shock, and how these phenomena can significantly alter antimicrobial exposures and dosing requirements in this patient population. This chapter focuses on antibacterial and antifungal drugs because data are insufficient to inform altered anti-viral dosing at this time.

INCIDENCE OF SEPSIS AND SEPTIC SHOCK IN CRITICALLY ILL PATIENTS

Despite recent therapeutic advances, sepsis and septic shock are still significant burdens in the ICU, with persistently high morbidity and mortality rates. The World Health Organization has highlighted sepsis as a serious health care burden and on May 24, 2017, WHO recommended necessary measures that can be adopted into clinical practice to improve the prevention, diagnosis, and management of sepsis. The measures and actions that WHO recently

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Basic pharmacokinetic and pharmacodynamic concepts
- Basic pharmacokinetic and pharmacodynamic characteristics in relation to antimicrobial activity and killing efficacy
- Common antimicrobial dosing regimens and their typical indications
- Basic knowledge of critical care medicine and management of critically ill patients in the ICU

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- IDStewardship. [Pharmacokinetics and Pharmacodynamics For Antibiotics: Back To Basics](#) [homepage on the Internet].
- RxKinetics. [A PK/PD Approach to Antibiotic Therapy](#) [homepage on the Internet].
- U.S. Pharmacist. [Prolonged Infusion Dosing of Beta-Lactam Antibiotics](#) [homepage on the Internet].
- Chinese University of Hong Kong. [PK Data](#) [homepage on the Internet].

proposed include current estimates suggesting 32 million sepsis cases annually, potentially leading to 5 million deaths per year worldwide (Fleischmann 2016). However, these estimates are likely to be conservative because data are mostly unavailable from the low- and middle-income countries, where about 90% of the world's population currently resides. Although the actual burden of sepsis remains controversial, the incidence of sepsis and septic shock have steadily increased over the past 10 years, gradually exhausting limited health care resources.

Global Burden of Sepsis-Related Mortality

The incidence of sepsis has been estimated at three cases per 1000 population in the United States, and about 50% of these patients are managed in the ICU (Angus 2001). In a multicenter point-prevalence study of 1265 ICUs across 75 countries (the EPIC II Study), 51% of the ICU patients were classified as infected on the day of study with an ICU mortality rate of 25.3% (Vincent 2009). Data from a large European study involving 198 ICUs across 24 countries have reported that sepsis accounted for 26.7% of ICU admissions with corresponding mortality rates of 32.2% for patients with sepsis and 54.1% for patients with septic shock (Vincent 2006). Despite an emerging trend for improved survival in ICU patients with sepsis or septic shock, the mortality rate in this patient population remains unacceptably high worldwide, ranging from 30%–50% in sepsis and may even reach 90% in patients with septic shock.

Economic Burden of Sepsis in the ICU

Significant health care resources are spent worldwide on critically ill patients with sepsis. Australian ICUs have 15,700 cases of sepsis per year, costing the health care system the equivalent of about USD \$400 million (Finfer 2004b). Hospitals in the United States spent more than USD \$24 billion in 2013 for the management of sepsis, representing 13% of total hospital expenses. The USD \$24 billion (about USD \$18,244 per admission) spent for sepsis management far exceeded other “costly” conditions and admissions, including osteoarthritis at USD \$17 billion (about USD \$16,148 per admission) and childbirth at USD \$13 billion (about US \$3529 per admission). Costs of managing sepsis in hospitals vary greatly by severity of disease; costs associated with the treatment of septic shock were reported to be at least 4-fold higher than patients with sepsis without shock (Paoli 2018). It is estimated that the United States health care system is currently spending between USD \$121–263 billion annually on critically ill patients with sepsis or septic shock (these estimates included the total hospital costs during an ICU stay and post-discharge care attributable to critical illness), representing more than 8% of the country's total health care expenditure, and more importantly, this amount continues to grow each year (Coopersmith 2012).

APPLYING CLINICAL PHARMACOLOGY TO OPTIMIZE ANTIMICROBIAL USE IN CRITICALLY ILL PATIENTS WITH SEPSIS

Significant research and time has been devoted to improve the provision of care for critically ill patients in the ICU. In contrast to novel treatment strategies, such as the use of activated protein C, antithrombin II and intensive insulin therapy, the current evidence strongly suggests that optimal antimicrobial therapy may have a greater influence on the survival of critically ill patients with sepsis or septic shock. Therefore, optimizing antimicrobial therapy should be the core focus in the treatment of infection-driven pathologies in this patient cohort. However, the process of optimizing antimicrobial therapy can be highly challenging in the ICU. Extreme physiologic changes and treatment differences associated with critical illness may alter antimicrobial concentrations and reduce antimicrobial exposures in critically ill patients. Of importance, dosing that does not account for these alterations may lead to therapeutic failure and the emergence of antimicrobial resistance.

An in-depth knowledge on PK and PD is essential to comprehend the complex effect of pathophysiologic changes in critically ill patients with sepsis and how these phenomena can significantly alter plasma and tissue antimicrobial concentrations and consequently the dosing requirements in this patient population. In addition, a personalized antimicrobial dosing regimen, which maximizes patient benefits while minimizing the emergence of resistance, can be established for critically ill patients with sepsis by applying PK/PD principles.

PK Considerations

The term *pharmacokinetic* refers to the study of concentration changes of a drug over a given time period. Some of the more important PK variables in relation to antimicrobials and their dosing requirements are the following:

- Volume of distribution (V_d)
- Clearance (CL)
- Peak drug concentration over a dosing interval (C_{max})
- Minimum drug concentration during a dosing interval (C_{min})
- Area under the concentration-time curve over a dosing interval or over a 24-hour period (AUC_{0-24})

PD Considerations

For antimicrobials, the term *pharmacodynamics* describes the relation of drug concentrations to the ability of an antibiotic or antifungal to kill or inhibit the growth of a pathogen. This goal can be achieved by integrating the PK data (i.e., exposure) with information on pathogen susceptibility (i.e., minimum inhibitory concentration, MIC). The free or unbound drug concentration is responsible for the antimicrobial activity.

Different PD properties that can be associated with antimicrobial efficacy can be categorized (Craig 1998) as follows:

- Duration of time that the free (unbound) drug concentration remains above the MIC during a dosing interval ($fT_{>MIC}$)
- Ratio of peak drug concentration (C_{max}) to MIC (C_{max}/MIC)
- Ratio of the area under the concentration-time curve during a 24-hour period (AUC_{0-24}) to MIC (AUC_{0-24}/MIC).

PK/PD Indices for Optimal Antimicrobial Activity

Killing or inhibition characteristics may differ between different classes of antimicrobials. These characteristics have been determined mostly from in vitro and in vivo animal models and describe the PK exposures that represent optimal bactericidal or fungicidal activity. On the basis of their kill or inhibition characteristics, antimicrobials are broadly described as either *concentration-* or *time-dependent*, or a combination (*concentration- and time-dependent antimicrobial*). More specifically, antimicrobials can be classified into three major categories on the basis of PK/PD indices that reflect their modes of bacterial/fungal killing (Craig 1998) as follows:

- Concentration-dependent antimicrobials, for which increasing concentrations progressively enhance antimicrobial killing and the ratio of C_{max}/MIC best describes their activity (e.g., aminoglycosides)
- Time-dependent antimicrobials, for which prolonging the duration of effective drug exposure leads to greater antimicrobial killing and $fT_{>MIC}$ best describes their activity (e.g., β -lactam antibiotics)
- Both concentration- and time-dependent kill characteristics, for which the ratio of AUC_{0-24}/MIC best describes their antimicrobial activity (e.g., fluoroquinolones and glycopeptides).

Each class of antimicrobials has its own PK/PD index for which optimal numerical values for selected pathogens and disease conditions can be established to predict microbiological and clinical response. Ideally this index should be met to have a higher likelihood of therapeutic success.

IMPACT OF CRITICAL ILLNESS ON ANTIMICROBIAL PK

Critical illness is characterized by marked physiologic derangements, which are driven by both the natural underlying disease process (e.g., sepsis) and the interventions provided (e.g., aggressive intravenous fluid and vasoactive drug infusions). Chronic comorbidity and the use of extracorporeal therapies can further exacerbate the existing pathophysiologic changes commonly encountered during critical illness. The interplay of these factors may significantly alter antimicrobial PK, affecting drug exposure and dosing requirements in critically ill patients with sepsis or septic shock. Standard or conventional antimicrobial dosing may likely lead to either under- or overexposure in this patient population.

Table 1. Antimicrobial Properties by Physicochemical Characteristics

Antimicrobial	Pharmacokinetic Properties	Drug/Class Examples
Hydrophilic	<ul style="list-style-type: none"> • Small volume of distribution • Primarily eliminated by kidneys • Poor intracellular and tissue penetration 	<ul style="list-style-type: none"> • Aminoglycosides • β-Lactams • Colistin • Daptomycin • Fluconazole • Fosfomycin • Glycopeptides • Lipoglycopeptides
Lipophilic	<ul style="list-style-type: none"> • Large volume of distribution • Primarily eliminated by liver • Good intracellular and tissue penetration 	<ul style="list-style-type: none"> • Fluoroquinolones • Lincosamides • Macrolides • Metronidazole • Oxazolidinones • Posaconazole • Tetracyclines • Voriconazole

Altered V_d

Volume of distribution is a proportionality constant that relates the dose administered to the systemic drug concentration. The V_d is therefore the hypothetical or the apparent volume of fluid (usually expressed in liters or liters/kilogram) into which a drug distributes in the body to equal its concentration in the blood, plasma, or serum. Hydrophilic antimicrobials are primarily distributed in the systemic circulation and these drugs demonstrate a low V_d . In contrast, lipophilic antimicrobials demonstrate a large V_d and are widely distributed throughout the body (Table 1).

Changes in the V_d of antimicrobials have been commonly observed in critically ill patients with sepsis or septic shock. A review of 57 clinical studies that investigated the PK of β -lactam antibiotics in critically ill patients found that large V_d differences were commonly observed in most studies, and more importantly, most studies reported a 2-fold variation in this PK variable compared with the noncritically population (Goncalves-Pereira 2011). For example, the mean V_d for meropenem in patients with sepsis or septic shock in these studies was 0.3–0.5 L/kg, whereas the values reported in other studies recruiting healthy volunteers or noncritically patients were 0.1–0.2 L/kg (Goncalves-Pereira 2011). This phenomenon is likely to decrease the concentrations of hydrophilic antimicrobials, particularly in the earlier phase of disease. Therefore, higher initial loading doses should be applied in critically ill patients with sepsis or septic shock to compensate for the enlarged V_d , particularly for hydrophilic and

concentration-dependent antimicrobials such as aminoglycoside antibiotics. Higher initial loading doses of amikacin (De Winter 2018, Roger 2016), β -lactam antibiotics (Taccone 2010a), colistin (Nation 2017), gentamicin (Allou 2016b, Roger 2016), teicoplanin (Nakano 2016), and vancomycin (Cristalini 2016) are needed to rapidly achieve effective concentrations in this patient population. The contributing factors of altered V_d in critical illness are discussed in more detail in the following.

Fluid Shifts and the Third Spacing Phenomenon

Sepsis involves the release of various inflammatory mediators that eventually increase capillary permeability. This “capillary leak” syndrome causes fluid shifts from the intravascular compartment to the interstitial space, which is commonly described as *third spacing*. This phenomenon substantially expands the V_d of hydrophilic antimicrobials, consequently decreasing their plasma and tissue concentrations in critically ill patients with sepsis or septic shock. The increase in V_d for aminoglycosides (Taccone 2010b), β -lactams (Goncalves-Pereira 2011), and glycopeptides (Bakke 2017) has been commonly reported in critically ill patients. Consequently, a higher initial dose of such an antimicrobial is needed to rapidly achieve adequate drug exposure in this patient population. In contrast, fluid shifts have a minimal effect on lipophilic antimicrobials (e.g., fluoroquinolones) because they inherently possess a larger V_d as a result of their greater partitioning intracellularly and sequestration into adipose tissue compartments (Gous 1995).

Medical Interventions in the ICU

Several medical interventions in the ICU, such as aggressive fluid resuscitation (Ocampos-Martinez 2012), mechanical ventilation (Conil 2007a), extracorporeal circuits (Hites 2014), the presence of post-surgical drains (Adnan 2013), and total parenteral nutrition (Ronchera-Oms 1995), have also been reported to be associated with enlarged V_d and consequently decreased concentrations of hydrophilic antimicrobials. The influence of ICU interventions on antimicrobials V_d was highlighted by an earlier study that demonstrated the impact of controlled mechanical ventilation on the PK of gentamicin in open-heart surgery patients (Triginer 1989). In this study, the authors reported that the V_d of gentamicin was significantly larger in patients during mechanical ventilation compared with when these patients were breathing spontaneously (0.36 L/kg vs. 0.25 L/kg). This study further highlighted that this phenomenon may likely lead to subtherapeutic C_{max} concentrations, particularly when standard gentamicin dosing regimens are used in this patient population.

Tissue Perfusion and Target Site Distribution of Antimicrobials

Effective antimicrobial concentrations are required in the interstitial fluid of tissues because most infections are thought to

occur here. However, critically ill patients with sepsis or septic shock may have diminished microvascular perfusion leading to impaired distribution of drugs, particularly to sites of infections such as alveolar compartments, cerebrospinal fluid, and soft tissues. Tissue penetration of several hydrophilic antibiotics such as imipenem (Tegeger 2002), meropenem (Varghese 2015), and piperacillin (Roberts 2009b) has been reported to be significantly impaired and delayed in critically ill patients with sepsis or septic shock. It was further observed that tissue antibiotic concentrations may be subtherapeutic even when optimal concentrations are achieved in the plasma of critically ill patients, particularly in patients with septic shock (Roberts 2009a, 2009b). Essentially, plasma concentrations may not accurately predict and may overestimate the corresponding tissue concentrations in this patient cohort.

In patients with septic shock, antimicrobial concentrations in interstitial fluid may be 5–10 times lower than the corresponding plasma concentrations, as well as those concentrations observed in healthy volunteers (Joukhadar 2001). However, in patients with sepsis but without shock, there seems to be a less significant effect on tissue distribution and penetration of antibiotics (Roberts 2009a, 2009b). In an earlier study showed that the interstitial piperacillin concentrations of patients with septic shock can be up to 10 times lower than the corresponding plasma concentrations (Joukhadar 2001). A later study found that the degree of antibiotic penetration may not be significantly affected in patients with sepsis but only in critically ill patients with septic shock (Roberts 2009b). These contrasting findings may be attributed to the level of sickness severity (i.e., sepsis vs. septic shock) whereby septic shock causes greater impairment in cardiovascular function and microvascular perfusion than in patients with sepsis. Thus ongoing evaluations of sickness severity are crucial to allow for timely adjustments of antimicrobial dosing and higher doses are probably needed to enhance tissue concentrations particularly in patients with septic shock.

Protein Binding and Hypoalbuminemia

Hypoalbuminemia is a common but often neglected condition in the ICU with reported incidences as high as 40%–50% (Finfer 2004a). In critically ill patients, hypoalbuminemia is usually caused by either extreme fluid extravasation or down-regulation of its hepatic synthesis. What follows hypoalbuminemia is an increase in the free fraction of drugs that are usually bound to this acute-phase protein. The unbound fraction of such antibiotics is not only available for elimination, but also for distribution. The V_d for highly protein-bound antibiotics, such as ceftriaxone (Schleibinger 2015), daptomycin (Falcone 2013b), ertapenem (Brink 2009, Burkhardt 2007), flucloxacillin (Ulldemolins 2010), teicoplanin (Enokiya 2015), and vancomycin (del Mar Fernandez de Gatta Garcia 2007), are found to be increased in critically ill patients with hypoalbuminemia; of importance,

this phenomenon has been associated with a 90% increase in their V_d . However, tissue concentrations remain low despite increased drug distribution because of significant fluid shifts during the acute phase response and the large requirements for intravenous fluids in critically ill patients (Roberts 2013).

It is also important to note that for those highly bound antimicrobials that are also cleared renally, the increase in the free fraction of drugs will also result in rapid CL. The CL of ceftriaxone (Schleibinger 2015), daptomycin (Falcone 2013b), ertapenem (Brink 2009, Burkhardt 2007), and flucloxacillin (Ulldemolins 2010) were reported to be higher in this patient population. Altered V_d and CL for these antibiotics may lead to low antibiotic concentrations particularly at the end of the dosing interval; therefore, maintenance doses for these antibiotics should be increased to compensate for these changes. This increase is especially relevant for time-dependent agents, such as β -lactams.

Changes in Drug Clearance

Drug clearance can be defined as the volume of blood, plasma or serum (usually expressed in liters/hour or liters/hour/kilogram) cleared of drug per unit time. Several different organs or elimination pathways are responsible for drug CL, including renal and biliary elimination, as well as hepatic metabolism. Changes in drug CL have been observed in critically ill patients and the contributing factors are discussed in following text.

Increase in Cardiac Output and Augmented Renal Clearance

Critically ill patients with severe infection commonly develop the systemic inflammatory response syndrome. A major component of this inflammatory response is a hyperdynamic cardiovascular state, which is characterized by an increase in cardiac output that enhances blood flow to major organs. The kidneys are one of the major organs affected, where the increase in renal blood flow leads to an increase in glomerular filtration rate and/or tubular secretion. After grouping a cohort of 77 critically ill patients according to their cardiac indices, researchers observed a higher gentamicin CL in hyperdynamic septic patients (4.1 L/min/m²) compared with hypodynamic septic patients (2.7 L/min/m²) or the controls (2.4 L/min/m²) (Tang 1999). Furthermore, pharmacologic interventions that are used to reverse hypotension in critically ill patients usually include large boluses of intravenous fluid and administration of vasopressor infusions, which are also associated with an early increase in cardiac output and glomerular filtration rate. In a prospective study involving 56 patients with intra-abdominal sepsis, the creatinine clearance in the study cohort was significantly increased from baseline values (75 mL/min vs. 102 mL/min), 48 hours after norepinephrine administration (Redl-Wenzl 1993). Consequently, all these factors lead to increased renal CL of some

drugs, a phenomenon referred to as *augmented renal clearance*, defined as CL_{CR} greater than 130 mL/min).

Identifying patients with ARC is not easy because critically ill patients may have elevated renal function despite normal serum creatinine concentrations (Udy 2013). Thus, antimicrobial dosing in this specific patient population is usually flawed if clinicians do not to address and consider this phenomenon. Most studies have attempted to compare the use of measured CL_{CR} versus estimated CL_{CR} equations to identify ARC. The clinical utility of such equations to estimate CL_{CR} in this setting is fairly limited, for which commonly used equations such as Cockcroft-Gault, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and Modification of Diet in Renal Disease (MDRD) are found to be poorly correlated and tend to underestimate CL_{CR} . Measured CL_{CR} should be considered to be the best bedside variable to estimate CL_{CR} in critically ill patients, as well as to screen and identify patients with ARC. This assessment can be accomplished in the ICU by performing continuous urine collections over a 2-, 6-, 8-, 12-, or 24-hour interval. Several scoring systems have also been developed to identify those ICU patients who are likely to manifest ARC. The Augmented Renal Clearance in Trauma Intensive Care (ARCTIC) scoring tool uses three variables in its scoring system (age, gender and serum creatinine) and a score of 6 or more best predicts the likelihood of ARC in trauma patients (Barletta

2017). Existing data indicate that the patients who are at risk of or are most likely to manifest ARC are the following:

- Critically ill patients with sepsis or septic shock (Carrie 2018)
- Young patients (<60 years old) (Fuster-Lluch 2008)
- Trauma patients (Cherry 2002)
- Neurosurgical patients (Udy 2017)
- Burn patients (Conil 2007b)
- Cystic fibrosis patients (Wang 1993)
- Febrile neutropenia patients (Hirai 2016)

Augmented renal clearance has been strongly associated with suboptimal β -lactam (Carrie 2018, Huttner 2015) and vancomycin (Bakke 2017, Hirai 2016, Baptista 2012) exposures, which may partly explain the poor clinical outcomes associated with critically ill patients. Therefore, for these antimicrobials—which display time-dependent properties and predominantly cleared by the kidneys—applying altered dosing strategies, such as extended or continuous infusion, may likely maintain effective drug concentrations for a longer duration in critically ill patients with ARC.

End-Organ Dysfunction

As disease progresses in a critically ill patient, myocardial depression may occur and lead to decreased organ perfusion and microcirculatory failure, eventually leading to

Patient Care Scenario

A 30-year-old man (height 65 inches, weight 90 kg) is admitted to the ICU with 28% total body surface area burns and inhalational injury. During his first week of ICU stay, he develops nosocomial pneumonia with *Pseudomonas aeruginosa*, susceptible to piperacillin/tazobactam. At this time, he is persistently tachycardic with vasopressor support. His serum creatinine is 0.7 mg/dL, urine output is greater than 1 mL/kg/hour, and a measured 8-hour CrCl is 151 mL/min. His estimated glomerular filtration

ANSWER

The likelihood for this patient to show ARC is high. He is age 30 years with significant physiologic reserve and is receiving medical treatment for burn injury, which may likely include aggressive fluid resuscitation and vasopressor/inotrope support, all of which can increase the glomerular filtration rate and clearance of renally cleared antimicrobials, including piperacillin/tazobactam. In addition, V_d enlargement in such a patient is also likely because of the aggressive fluid resuscitation being administered. Because piperacillin/tazobactam is a time-dependent antibiotic, which requires extended duration of effective exposure over a dosing interval, this phenomenon may likely reduce piperacillin/tazobactam concentrations, leading to suboptimal PK/PD target attainment and therapeutic failure. In such a situation, conventional β -lactam dosing regimens (e.g., 4.5 g every 6 hours as a 0.5-hour infusion) are likely to be suboptimal, particularly when pathogens with high MICs are involved. Being a time-dependent antimicrobial, superior

rate using the Modification of Diet in Renal Disease equation is greater than 90 mL/min; his Cockcroft-Gault estimated creatinine clearance (using ideal body weight) is 134 mL/min. A piperacillin/tazobactam dose of 4.5 g every 6 hours as a 0.5-hour infusion is started. What are the likely pathophysiologic changes that could have influenced piperacillin/tazobactam exposures in this patient? What are some approaches to optimize piperacillin/tazobactam dosing for this patient?

antimicrobial activity can be achieved by prolonging the duration that the drug concentrations remain above the MIC of the pathogen. In this case, the minimum PK/PD target should be 50% $fT_{>MIC}$; however, considering the patient's extreme PK changes (e.g., ARC), 100% $fT_{>MIC}$ might be a better target. Therefore, altered dosing strategies should be strongly considered in this patient. An initial loading dose can circumvent the enlarged V_d and ensure that therapeutic exposure is rapidly achieved, and the use of prolonged infusion is likely to maximize $fT_{>MIC}$. Potential dosing regimens are piperacillin/tazobactam loading dose 4.5 g as a 0.5-hour infusion followed by 4.5 g every 6 hours as a continuous infusion (infused over 6 hours) or loading dose 4.5 g as a 0.5-hour infusion followed by 4.5 g every 6 hours as an extended infusion (infused over 3 hours). This approach would ideally be guided by TDM performed often to ensure effective concentrations are achieved in patients such as described in this scenario.

end-organ damage or in extreme cases, multi-organ dysfunction syndrome (Hites 2014). This syndrome often includes renal and/or hepatic dysfunction that consequently results in decreased antimicrobial CL. In addition, the resulting accumulation of drugs and their metabolites in plasma increases the likelihood of toxicity. Similarly, the retention of waste products may displace antimicrobials from their plasma proteins leading to an increase in their unbound concentrations, which may also enhance the likelihood of toxicity.

Renal dysfunction significantly reduces the CL of antimicrobials that are predominantly cleared by renal elimination. However, elevated serum creatinine concentrations are usually interpreted as renal dysfunction and, unlike the ARC phenomenon, renal dysfunction in critically ill patients is routinely considered and promptly managed by appropriate dose reduction. Because creatinine clearance often correlates linearly with the CL of hydrophilic antimicrobials, dose reduction can be performed proportional to the decrease in creatinine clearance. Some antimicrobials can be cleared by other organs when the primary eliminating organ (usually the kidneys) is impaired. For example, some antibiotics such as ticarcillin and piperacillin demonstrate increased biliary CL that causes little change in their plasma concentrations despite mild to moderate renal dysfunction (Brogard 1989, 1990). It is also important to note that renal function in critically ill patients may greatly vary during an ICU stay; therefore, dosing requirements in this patient population may be highly dynamic. Regular dosing reviews and modifications are needed throughout antimicrobial treatment not only to prevent underdosing but also to minimize the risk of developing adverse events.

A decrease in hepatic blood flow during severe infections may decrease hepatic metabolism and CL for antimicrobials that have a high hepatic extraction ratio (McKindley 2002). In addition, hepatic blood flow reduction may also reduce the activity of CYP 3A4, which is an important enzyme in oxidative biotransformation of numerous drugs (Wilkinson 2005). The impact of hepatic dysfunction or altered hepatic physiology on the PK of most antimicrobials is likely to be minimal and the need to modify dosing in patients with hepatic dysfunction is uncommon (Scaglione 2008). However, several antimicrobials, including rifampin, metronidazole, and tigecycline, can demonstrate reduced CL and drug accumulation; consequently, dosing adjustments are required particularly in critically ill patients with severe liver disease. If suspected, assessment of hepatic function using the Child-Pugh classification of liver disease may be useful to guide dosing of some antimicrobials in critically ill patients with sepsis or septic shock, although loading doses should not change.

Acute Kidney Injury and Renal Replacement Therapy

As renal dysfunction progresses and if acute kidney injury occurs, critically ill patients with sepsis or septic shock may need various forms of renal replacement therapy (RRT) for

metabolic waste products and fluid removal. Patients with acute kidney injury may receive various forms of RRT that include continuous renal replacement therapy (CRRT), intermittent hemodialysis, or a hybrid of both RRT forms, such as sustained low-efficiency dialysis. The favored and common mode of RRT for critically ill patients in the ICU worldwide remains CRRT (Hoste 2015). However, CRRT has been shown to further exacerbate the existing PK alterations of many antimicrobials in critically ill patients, leading to variable antimicrobial CL and dosing requirements (Jamal 2014). The impact of CRRT on drug CL is difficult to predict and is associated with various factors, including filter type and surface area, blood and effluent flow rate, replacement fluid settings, CRRT configurations/modalities, and sequestration of drug molecules within the RRT circuit (Jamal 2014, 2015). In addition, CRRT is commonly not applied in a uniform way, and—in contrast to its “continuous” name—CRRT can be interrupted for several technical reasons. Therefore, CL may greatly vary and can be significantly lower than what has been initially prescribed. Antimicrobial dosing in this patient population should take all of these variables into account. Antimicrobials with a high V_d (1 L/kg or greater) and/or that are highly protein bound (80% or greater) are generally poorly eliminated by CRRT; therefore, supplemental dosing for these antimicrobials can be reduced (Jamal 2014, de Pont 2007). Nevertheless, no conclusive dosing recommendations can be made at this moment for critically ill patients receiving CRRT, and it is likely that a significant proportion of CRRT patients are at an increased risk for either antimicrobial underexposure or overexposure. One approach that can be used to individualize antimicrobial dosing in CRRT patients is to consider the estimated drug clearance on the basis of the CRRT modality and to then use this variable to calculate the dosing required using first principles (Figure 1). Antimicrobial dosing during intermittent hemodialysis and sustained low-efficiency dialysis are likely to be even more complex and difficult compared with CRRT because of the large variation in CL during and after therapy (Ronco 2015, Roberts 2011). Antibiotic dosing in this patient population should be individualized and tailored according to the RRT variables mentioned previously, and dosing should be guided by TDM when available. Table 2 shows the calculated clearance by use of the CRRT modality.

Extracorporeal Membrane Oxygenation

Optimal antimicrobial therapy is challenging in extracorporeal membrane oxygenation (ECMO) patients because the device is hypothesized to further exacerbate the PK alterations that occur during critical illness (Cheng 2017). Significant alterations in the primary PK variables (i.e., V_d and CL) of some antimicrobials have been described, but these have been mostly reported in neonatal and pediatric studies (Sherwin 2016). Emerging clinical PK data have highlighted several important considerations on dosing antimicrobials

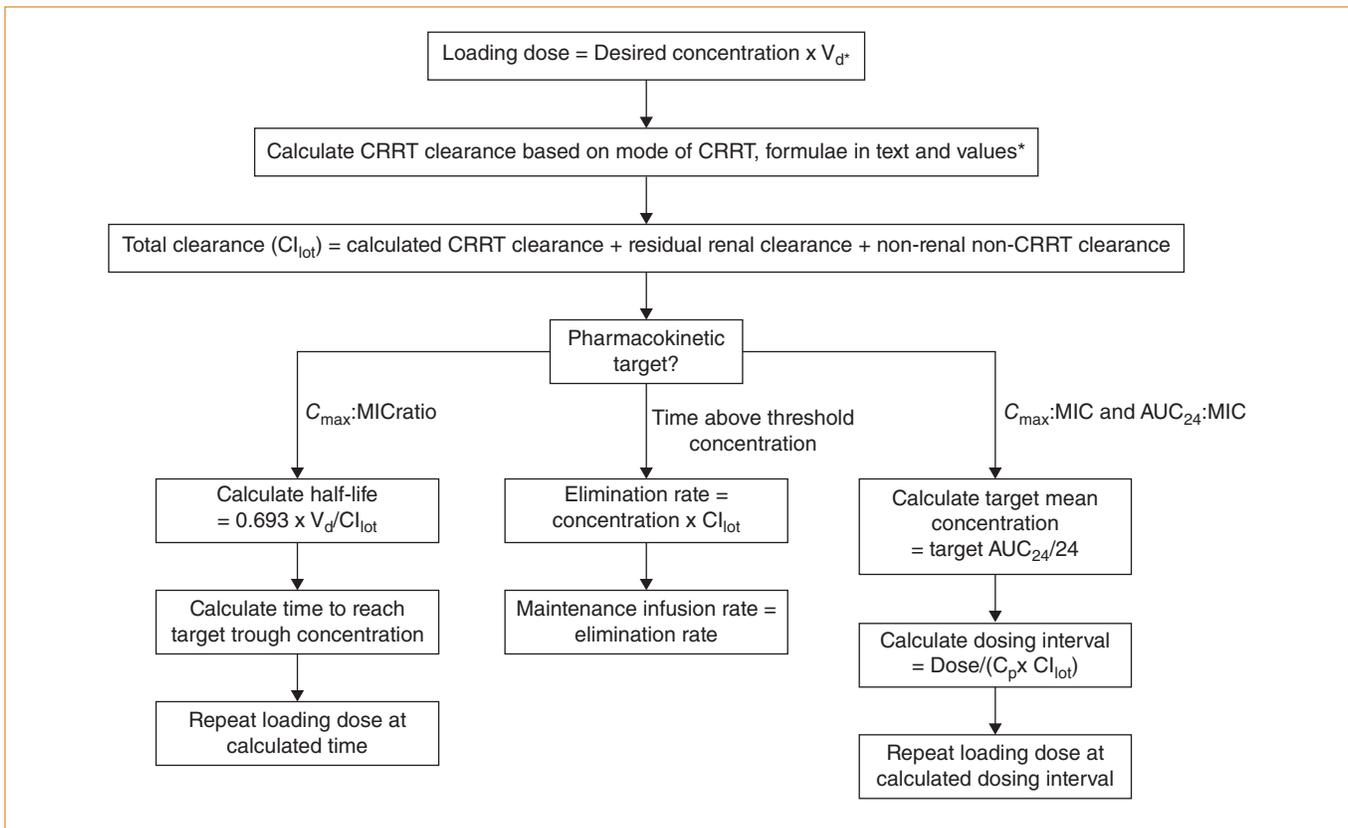


Figure 1. Estimation of antimicrobial doses using first principles.

AUC = area under the curve; CRRT = continuous renal replacement therapy; MIC = minimum inhibitory concentration.

in critically ill patients receiving ECMO, which include the following:

- Physicochemical properties of antimicrobials can influence the degree of drug loss/sequestration in the ECMO circuit.
- Modern ECMO circuits have minimal impact on the PK of most antimicrobials.

- Changes in PK in ECMO patients are more reflective of critical illness rather than ECMO therapy itself.

Apart from lipophilic and highly protein-bound antimicrobials (Shekar 2015a, 2015b), the impact of ECMO on the PK and dosing requirements of most antimicrobials is likely to be minimal. Therefore, antibiotic dosing in this patient population should generally align with the recommended dosing strategies for critically ill patients who are not receiving ECMO support.

Table 2. Calculated Clearance by Continuous Renal Replacement Therapy Modality

Modality	Clearance
Continuous venovenous hemofiltration, CVVH (pre)	$Q_f \times S_c \times (Q_b/Q_b + Q_{rep})$
Continuous venovenous hemofiltration, CVVH (post)	$Q_f \times S_c$
Continuous venovenous hemodialysis, CVVHD	$Q_d \times S_d$
Continuous venovenous hemodiafiltration, CVVHDF	$(Q_f \times Q_d) \times S_d$

Q_b = blood flow rate, Q_d = dialysate flow rate, Q_f = ultrafiltrate rate, Q_{rep} = predilution replacement rate, S_d = saturation coefficient, S_c = sieving coefficient

ALTERED PATHOGEN SUSCEPTIBILITY IN THE ICU

The MIC is a crucial component of the PK/PD index for antimicrobial activity. As the MIC (i.e., the denominator of the PK/PD index) increases, the PK exposure (i.e., the numerator of the PK/PD index) must also be increased to ensure that optimal PK/PD target for maximal efficacy is achieved. This relationship is highly relevant in the context of dosing antibiotics in critically ill patients with sepsis or septic shock because most infections in the ICU are usually caused by pathogens with reduced antimicrobial susceptibility, which demonstrate relatively higher MICs than any other clinical environment. Although the MICs of these pathogens are reported to be 2–4 times higher than those from the other wards (Sievert 2013, Valenza 2012, Zhanel 2008), critically ill patients in the

ICU typically receive standard antimicrobial dosing regimens, which are likely to be suboptimal for these patients and lead to therapeutic failures and the emergence of resistance. For example, a piperacillin/tazobactam dose of 3.375 g every 6 hours as a 30-minute infusion may only be effective against pathogens with a MIC of 2 mg/L or less, and in critically ill patients who are commonly infected with pathogens with higher MICs (4 mg/L or greater) this standard dosing regimen is likely to fail (Lodise 2007). Local microbiology and antimicrobial resistance patterns may greatly vary across different geographic regions (Kiratisin 2013), and these differences need to be considered when optimizing or individualizing antimicrobial therapy in critically ill patients. Any potential dosing adjustments must consider MIC variation and should be interpreted in the context of assay variation, species identification, and wild-type distributions. Using an individual MIC to modify an antimicrobial dosing regimen is currently not justified, and this approach may likely lead to potential underdosing of patients, particularly a critically ill population (Mouton 2018).

PK/PD OF VARIOUS ANTIBIOTIC CLASSES IN CRITICALLY ILL PATIENTS

Antibiotics

Aminoglycosides

Pharmacokinetics

Aminoglycosides are hydrophilic in nature with a low V_d and CL that is proportional to glomerular filtration rate. Significant V_d (Duszynska 2013, Conil 2011) and CL (Conil 2011, Barletta 2000) alterations have been widely described in critically ill patients with sepsis or septic shock.

PK/PD Targets in Critically Ill Patients

Aminoglycosides demonstrate concentration-dependent bactericidal activity, which is optimal when the C_{max} is 8–10 or greater times the MIC of the pathogen (Ruiz 2018, Duszynska 2013). However, recent data have suggested that the AUC_{0-24}/MIC ratio (60–180) might be a better predictor of activity (Mouton 2005), whereas earlier clinical studies had only included sparse PK sampling times and therefore AUC_{0-24}/MIC ratio was not considered in these studies. On importance, high collinearity exists between C_{max} and AUC and thus it follows that an increase in C_{max} will also lead to an increase in AUC. High C_{min} and AUC exposures over days have been associated with toxicity, most commonly oto- and nephrotoxicity.

Generic Dosing Recommendations for Critically Ill Patients

Critical illness-related changes can significantly expand the V_d of aminoglycoside antibiotics, consequently reducing effective C_{max} exposures and C_{max}/MIC ratios. To

exploit the maximum PK/PD potential of aminoglycosides, a once-daily or a high-dose, extended-interval dosing should be used in patients with gram-negative infections. Most antibiotic dosing guidelines still recommend a conservative approach to dosing aminoglycosides (e.g., 15–20 mg/kg for amikacin and 5–7 mg/kg for gentamicin or tobramycin). Of importance, although these dosing regimens may be appropriate for the general patient population, suboptimal PK/PD target attainment and clinical outcomes have been increasingly reported in critically ill patients receiving conventional dosing regimens such as these. Given that significant pathophysiologic changes are expected in this patient population, recent data suggest that higher-than-recommended aminoglycoside dosing regimen (e.g., 30 mg/kg for amikacin and 7–10 mg/kg for gentamicin or tobramycin with dosing intervals determined by renal function and TDM) may be required for critically ill patients with sepsis or septic shock (De Winter 2018, Allou 2016a, Roger 2016). For cases in which high concentrations are persisting, the dosing frequency should be reduced from once-daily to either 36- or 48-hourly dosing, rather than lowering the drug dose.

β -Lactam Antibiotics

Pharmacokinetics

β -Lactam antibiotics are generally hydrophilic in nature, demonstrating low V_d and are predominantly cleared by renal elimination. Most β -lactams have a moderate (30%–70%) to low (less than 30%) degree of protein binding, but variability exists within this group. Heterogeneity in β -lactam PK is significant in critically ill patients, which may affect treatment outcomes. Large V_d (Goncalves-Pereira 2011), and CL (Carrie 2018, Huttner 2015, Udy 2012) differences are common and these PK alterations may lead to inadequate β -lactam concentrations, particularly in the earlier phase of critical illness. Hypoalbuminemia has been associated with an increase in the free fraction (nonprotein bound) of highly protein-bound β -lactams (e.g., ceftriaxone, ertapenem, and flucloxacillin). Altered protein binding may potentially lead to low drug concentrations toward the end of a dosing interval for these highly protein-bound agents (Roberts 2013).

PK/PD Targets in Critically Ill Patients

The PK/PD index associated with optimal β -lactam activity is the % $fT_{>MIC}$ (40%–70%) (Craig 1998). These time-dependent antibiotics demonstrate superior bacterial killing the longer that the drug concentrations remain above the MIC of a pathogen. However, clinical data from critically ill patients suggest that these patients may benefit from longer (e.g., 100% $fT_{>MIC}$) (McKinnon 2008), and higher (e.g., 2–5 times MIC) (Aitken 2015, MacVane 2014) β -lactam exposures than those previously described in preclinical studies. Although the β -lactams generally have a wide therapeutic index, high exposures have been associated with neurotoxicity. Toxicity C_{min} thresholds have been described for cefepime (Huwylar

2017), flucloxacillin (Imani 2017), meropenem (Imani 2017), and piperacillin (Imani 2017, Quinton 2017).

Generic Dosing Recommendations for Critically Ill Patients

Because these antibiotics are eliminated renally and demonstrate slow continuous bacterial kill, V_d enlargements and high glomerular filtration rates, both of which are common in critically ill patients with sepsis or septic shock, they may significantly reduce the effective $\% fT_{>MIC}$ for optimal β -lactam activity. An aggressive β -lactam dosing strategy has been advocated and widely practiced in the ICU to compensate for these extreme PK alterations. An initial loading dose followed by prolonged β -lactam infusion (continuous or extended 2–4 hour infusion) is likely to maximize PK/PD (i.e., $\% fT_{>MIC}$) and clinical outcomes in this patient population (Vardakas 2018).

Daptomycin

Pharmacokinetics

Daptomycin is generally hydrophilic in nature, demonstrates a low V_d , and is predominantly cleared by renal elimination. Critical illness is associated with an increase in the V_d (Soraluce 2018, Di Paolo 2013, Falcone 2013a, 2013b), and CL (Goutelle 2016, Kielstein 2010) of daptomycin, leading to variable and low drug exposure. It is a highly protein-bound drug (92.0%–94.4%), and the unbound fraction increases in critically ill patients.

PK/PD Targets in Critically Ill Patients

Daptomycin demonstrates concentration-dependent bactericidal kill characteristics and *in vivo* data have suggested that the ratio of C_{max}/MIC in concert with AUC_{0-24}/MIC best predict its activity (Dandekar 2004). Similar AUC_{0-24}/MIC ratios have been described for daptomycin efficacy in critically ill patients (Di Paolo 2013, Falcone 2013a), and ratios of less than 666 mg/L have been associated with increased mortality (Falcone 2013a). More recently, a C_{min} of less than 3.18 mg/L has been linked to poor clinical outcomes in hospitalized patients with various gram-positive infections (Galar 2019). Higher C_{min} values have been associated with daptomycin-induced muscle toxicity, which is characterized by creatine phosphokinase elevation (Bhavnani 2010, Oleson 2000). A C_{min} of 24.3 mg/L or greater increases the likelihood of creatine phosphokinase elevation by more than 30-fold (Bhavnani 2010).

Generic Dosing Recommendations for Critically Ill Patients

Because daptomycin is highly protein bound and presents highly variable and unpredictable PK, altered dosing strategies with TDM may be required in critically ill patients. Current data suggest that optimal AUC_{0-24}/MIC ratios can easily be achieved with a product information dose of 6 mg/kg but only for pathogens with an MIC of 0.1 mg/L. With increasing MICs, a phenomenon that is likely in the ICU, higher doses

(10–12 mg/kg/day) are probably required to achieve these targets (Soraluce 2018, Cojutti 2017a, Di Paolo 2013, Falcone 2013a). Because daptomycin is primarily eliminated by the kidneys, prolongation of dosing interval from 24- to 48-hourly dosing is indicated in patients with CL_{CR} less than 30 mL/minute.

Fluoroquinolones

Pharmacokinetics

Fluoroquinolones are generally more lipophilic than aminoglycosides and β -lactams and demonstrate a larger V_d , meaning that this variable is expected to be minimally affected during critical illness, with the exception of levofloxacin (Roberts 2015, Conil 2008). Most fluoroquinolones have a moderate (30%–70%) to low (less than 30%) degree of protein and are cleared, at least to some degree, by renal elimination.

PK/PD Targets in Critically Ill Patients

Fluoroquinolones exhibit concentration-dependent bactericidal activity, and the most relevant PK/PD index predicting their clinical efficacy is the AUC_{0-24}/MIC ratio. However, previous studies have shown that the achievement of higher C_{max}/MIC ratios (more than 8–20) may also be required for optimal bactericidal activity. A range of AUC_{0-24}/MIC ratios from 25–30 may suffice against gram-positive organisms (Bhavnani 2008, Ambrose 2001), but higher values of 125 or more are needed against gram-negative organisms (Cojutti 2017b, Zelenitsky 2010, Forrest 1993). Although increasing reports of fluoroquinolone-associated seizures have emerged (Cone 2015, Mazzei 2012), no toxicity thresholds have been established.

Generic Dosing Recommendations for Critically Ill Patients

A quinolone dosing regimen that maximizes the AUC_{0-24}/MIC (e.g., using loading and higher doses) should be considered in critically ill patients to maximize clinical outcomes while limiting the emergence of resistance. Against susceptible gram-negative pathogens, these aims can likely be achieved with dosing regimens such as ciprofloxacin 400 mg every 8 hours or levofloxacin 500 mg every 12 hours (Haeseker 2013, Zelenitsky 2010). When treating pathogens with high MICs, dose escalation should be considered, but it is important to note that even higher doses may be unable to achieve optimal PK/PD targets in certain patients and could lead to significant toxicity (Szalek 2012, Zelenitsky 2010).

Glycopeptides

Pharmacokinetics

Vancomycin is hydrophilic in nature, demonstrates a low V_d , and is predominantly cleared by renal elimination. Critical illness has been observed to alter the V_d (Bakke 2017, del Mar Fernandez de Gatta Garcia 2007), and CL (Hirai 2016, Baptista 2012) of vancomycin, potentially leading to variable and low drug exposure.

PK/PD Targets in Critically Ill Patients

Previous in vitro and in vivo data have suggested that the bactericidal activity of vancomycin is time-dependent whereas some data have demonstrated that the C_{max}/MIC ratio to be equally important. It is generally accepted now that the AUC_{0-24}/MIC ratio is more closely linked to bacterial killing and clinical success (Jumah 2018; Martirosov 2017, Casapao 2015). Ratios for AUC_{0-24}/MIC of 400 or greater are recommended as a target against *Staphylococcus aureus* infection (Men 2016, Casapao 2015, Prybylski 2015, Zelenitsky 2013), whereas higher exposures are probably needed when treating critically ill patients with septic shock (Martirosov 2017, Casapao 2015, Ghosh 2014, Zelenitsky 2013). Prolonged (7 days or more) and high vancomycin exposures, such as C_{min} of more than 15 mg/L (Imai 2018, Tongsai 2016, van Hal 2013) or AUC_{0-24} of more than 600 (Zasowski 2018, Chavada 2017) are commonly associated with nephrotoxicity.

Generic Dosing Recommendations for Critically Ill Patients

Safely attaining optimal AUC_{0-24}/MIC ratios when treating pathogens with MICs of more than 1 mg/L is highly challenging with vancomycin (Choi 2011). A loading dose of 25–30 mg/kg followed by 15–20 mg/kg every 8–12 hours should be considered in critically ill patients without renal impairment to ensure rapid and optimal PK/PD target attainment. Current data have suggested that C_{min} may likely be an inconsistent and a poor surrogate for AUC_{0-24} (Neely 2014). Monitoring on the basis of AUC with Bayesian dose adaptation is a better tool to guide vancomycin therapy, and this recommendation will likely supersede that of C_{min} monitoring in future clinical practice guidelines (Rybak 2020). Although only a single C_{min} sample is needed for Bayesian AUC estimation, two samples (one taken at the end of infusion and the other one taken just before the next dose, meaning C_{min}) are preferable to provide a more accurate estimation. A ratio for AUC_{0-24}/MIC of 400–600 (assuming MIC of 1 mg/L) seems a reasonable range to target for maximal patient outcomes. Although continuous vancomycin infusion has been associated with a lower nephrotoxicity risk (Hao 2016), preferred use is not currently supported because clinical superiority has yet to be demonstrated over intermittent dosing. However, continuous infusion is particularly useful for patients requiring higher or vancomycin doses or doses administered more often, as well as patients with ARC. Vancomycin is excreted unchanged by the kidneys; therefore, CL diminishes in relation to renal function with the need for dosing adjustment. Patients with reduced renal CL thus require closer monitoring to both achieve sufficient plasma concentrations and avoid potentially toxic concentrations.

Oxazolidinones

Pharmacokinetics

Linezolid is hydrophilic in nature, demonstrates a low V_d , and is predominantly cleared by nonrenal elimination. Although

critical illness is not expected to influence the PK of linezolid, significant intra- and interpatient PK variability leading to variable linezolid exposure (less data are available for tedizolid) is commonly reported, supporting the use of TDM when this antibiotic is used in critically ill patients (Galar 2017, Pea 2017, Dong 2016, Zoller 2014).

PK/PD Targets in Critically Ill Patients

Oxazolidinones (linezolid and tedizolid) primarily show time-dependent activity with a modest concentration-dependent killing characteristic. Maximum efficacy is demonstrated at $\% fT_{>MIC}$ and AUC_{0-24}/MIC ratio of 85% or greater (Rayner 2003) and 80–120 (Dong 2016, Andes 2002, Rayner 2003), respectively. Linezolid-induced thrombocytopenia has been reported at C_{min} and AUC_{0-24} of greater than 7–10 and greater than 300–350, respectively (Morata 2016, Boak 2014, Cattaneo 2013).

Generic Dosing Recommendations for Critically Ill Patients

A standard dosing regimen of 600 mg every 12 hours is currently recommended in most antibiotic dosing guidelines. However, recent data suggest that this dosing regimen may likely be suboptimal for critically ill patients particularly when treating pathogens with MICs of 2 mg/L or greater, as well as those with ARC and acute respiratory distress syndrome. These subgroup of patients may benefit from higher linezolid doses (600 mg every 8 hours) (Ide 2018, Taubert 2017, Dong 2016) and/or altered dosing approaches including front-loaded dosing regimen and continuous infusion, but these approaches should be supported with TDM, if available (Minichmayr 2017, Adembri 2008).

Tigecycline

Pharmacokinetics

Tigecycline is lipophilic in nature, demonstrates a large V_d (7–10 L/kg), and is predominantly cleared by biliary elimination. Plasma protein binding is high (80%) and this property seems to determine clinical outcomes in critically ill patients, although the mechanism for this phenomenon is still unclear. In a large cohort of patients with hospital-acquired pneumonia, the rate of clinical success was reported to be significantly higher—13 times for every 1 g/dL increase in albumin. In the same analysis, the investigators also showed that the probability of clinical success with an albumin concentration of 2 g/dL was only 35% whereas it was close to 100% with an albumin concentration of 4 g/dL.

PK/PD Targets in Critically Ill Patients

The AUC_{0-24}/MIC ratio best predicts tigecycline antimicrobial activity. Significant correlation has been described between this index with clinical efficacy in patients with complicated skin and skin-structure infections (AUC_{0-24}/MIC ratio of 17.9), complicated intra-abdominal infections (AUC_{0-24}/MIC ratio

of 6.96), community-acquired pneumonia (fAUC₀₋₂₄/MIC ratio of 12.8 or greater) and hospital-acquired pneumonia (fAUC₀₋₂₄/MIC ratio of 0.9 or greater).

Generic Dosing Recommendations for Critically Ill Patients

Standard tigecycline dosing regimen may likely be marginally effective, at best, in critically ill patients, particularly those with lower respiratory tract infections. Critically ill patients with ventilator-acquired pneumonia have demonstrated low tigecycline exposures at the site of infection (i.e., epithelial lining fluid), and it is debatable whether maximal exposures can be obtained at all for pathogen eradication in such an infection. Lower AUC/MIC exposures have also been reported in patients with pneumonias versus other infections. The boxed warning associating tigecycline use with increased mortality could be a result of previous suboptimal dosing that led to disease progression in such patients. Higher-than-recommended dosing regimens (e.g., an initial loading dose of 200 mg intravenously followed by a maintenance dose of 100 mg intravenously every 12 hours) should be considered in critically ill patients, although this approach may be limited by nausea and vomiting. Of importance, such dosing regimens have been studied and used successfully in patients with hospital-acquired pneumonia, ventilator-acquired pneumonia, and complicated urinary tract infections with multi-drug resistant pathogens.

Antifungals

Azoles

Fluconazole

Pharmacokinetics

Fluconazole is available for parenteral and oral administration, is well absorbed from the gastrointestinal tract, and displays linear PK. It is hydrophilic in nature, demonstrates a low V_d (0.6 L/kg), and is predominantly cleared by renal elimination. Plasma protein binding is low (11%–12%). Significant interindividual PK variability has been observed in critically ill patients (Sinnollareddy 2015, Buijk 2001).

PK/PD Targets in Critically Ill Patients

Maximal clinical efficacy in patients with candidemia has been described with an AUC₀₋₂₄/MIC ratio of 55.2–100 or greater (Pai 2007, Rodriguez-Tudela 2007). Although the exposure–toxicity relationship has not been established and quantified, higher dosing (corresponding to concentration of 75 mg/L) may likely lead to hepatotoxicity and seizures (Anaissie 1995).

Generic Dosing Recommendations for Critically Ill Patients

A loading dose of 12 mg/kg intravenously followed by a maintenance dose of 6 or 12 mg/kg/day intravenously is advocated to achieve either the low (AUC₀₋₂₄/MIC ratio of 25) or high

(AUC₀₋₂₄/MIC ratio of 100) PK/PD target, respectively, in critically ill patients with CL_{CR} greater than 50 mL/min (Alobaid 2016).

Isavuconazole

Pharmacokinetics

Isavuconazole is available in oral (capsule) and intravenous formulations and switching between these formulations is acceptable. It has a large V_d and its CL is highly dependent on hepatic metabolism. Plasma protein binding is high (greater than 99%). It displays linear and favorable PK compared with the other triazoles.

PK/PD Targets in Critically Ill Patients

Current data do not identify any significant relationship between isavuconazole exposure with clinical efficacy and safety end points. However, an AUC to half-maximal effective concentration (AUC/EC₅₀) ratio of 108.6 results in a negative galactomannan index, a surrogate for therapeutic response in invasive aspergillosis infection (Kovanda 2017).

Generic Dosing Recommendations for Critically Ill Patients

A loading dose of 200 mg intravenously every 8 hours for six doses (or 48 hours) followed by a maintenance dose of 200 mg intravenous once daily is recommended to achieve an effective steady-state concentration by day 3 of treatment.

Polyenes

Pharmacokinetics

Although previously considered as the “gold standard” in the management of invasive fungal infections, conventional amphotericin B deoxycholate (AmB) has largely been abandoned in clinical practice due to dose- and infusion-related toxicities, including hypotension and nephrotoxicity. In order to limit these toxicities and optimise effectiveness, three lipid-based formulations have been developed, including amphotericin B lipid complex (ABLC), amphotericin B colloidal dispersion (ABCD) and liposomal amphotericin B (LAmB). These lipid formulations are generally less potent on a mg/kg basis when compared with AmB and differences in their structure result in several unique PK characteristics (Hamill 2013). LAmB exhibits high plasma and central nervous system concentrations as opposed to other lipid formulations and this feature has been associated with treatment efficacy, favouring LAmB over the other formulations, in a central nervous system invasive candidiasis model (Groll 2000). ABLC and ABCD achieve higher exposures in the intracellular space and organs of the reticuloendothelial system, demonstrating rapid and extensive tissue distribution to the liver, spleen and lungs (Andes 2006).

PK/PD Targets in Critically Ill Patients

The PK/PD of amphotericin B is currently poorly understood. Pre-clinical data suggest that amphotericin B demonstrates

concentration-dependent antifungal activity and most invasive candidiasis and aspergillosis models have found that C_{max}/MIC ratios (ranging from 2–4) to be the PK/PD index most predictive of efficacy (Lepak 2014). Although no clear clinical exposure–response relationship has been established for amphotericin B, higher C_{max}/MIC ratios have been associated with improved therapeutic response (Hong 2006). However, it is also important to note that MIC does not have a strong predictive value for all amphotericin B formulations and therefore, rarely provides useful information to personalize amphotericin B therapy in clinical practice.

Generic Dosing Recommendations in Critically Ill Patients

The recommended therapeutic dosing regimens for AmB, ABLC, ABCD and LAmB are unchanged in critical illness with 1 mg/kg/day, 5 mg/kg/day, 3–4 mg/kg/day and 3–5 mg/kg/day, respectively. Higher doses demonstrated no additional clinical benefit and may increase the likelihood of nephrotoxicity (Cornely 2007).

Posaconazole

Pharmacokinetics

Posaconazole is available in oral suspension, tablet, and intravenous formulations. It is lipophilic in nature, demonstrates a large V_d (5–25 L/kg), and is predominantly cleared by hepatic glucuronidation. Plasma protein binding is high (greater than 98%). Extreme inter- and intraindividual PK variability—and, consequently, suboptimal exposures—are typically seen with the oral suspension (Yi 2017, van der Elst 2015).

PK/PD Targets in Critically Ill Patients

Higher C_{min} values (i.e., greater than 0.5–0.7 mg/L) have been associated with reduced breakthrough infections in patients receiving posaconazole prophylaxis (Chen 2018, Cattaneo 2015, Eiden 2012). Patients with invasive aspergillosis demonstrated improved clinical response with an average posaconazole concentration of greater than 1 mg/L (Jang 2010, Walsh 2007). Exposure-related toxicity has not been described for posaconazole, although the European Medicines Agency (EMA) and most clinical studies have suggested a C_{min} threshold of greater than 3.75–4 mg/L (Boglione-Kerrien 2018), which has yet to be validated clinically.

Generic Dosing Recommendations in Critically Ill Patients

Although extensive PK variability has been previously described, it is likely that the newer oral tablets and intravenous formulations have improved these issues, meaning that a reduced proportion of patients will manifest subtherapeutic C_{min} values. An initial dose of 300 mg intravenously every 12 hours on day 1 followed by a maintenance dose of 300 mg intravenously once-daily is recommended for invasive fungal

infections. However, the intravenous vehicle or solubilizer in the intravenous formulation, sulfobutylether- β -cyclodextrin, may accumulate in patients with moderate to severe renal impairment. In patients with CL_{CR} less than 50 mL/minute, the use of intravenous posaconazole should be avoided to prevent cyclodextrin accumulation, which can adversely impair renal function further or potentially neurotoxicity, although the clinical relevance remains unclear.

Voriconazole

Pharmacokinetics

Voriconazole is lipophilic in nature, demonstrates a large V_d (2–4.6 L/kg) and is predominantly cleared by hepatic metabolism. Plasma protein binding is 58%. Voriconazole displays nonlinear PK in adults and exhibits extensive interindividual PK variability in all patient populations.

PK/PD Targets in Critically Ill Patients

A C_{min} of 1 mg/L or greater (Hashemizadeh 2017, Hoenigl 2013) or 2 mg/L or less (Miyakis 2010, Ueda 2009, Smith 2006), as well as a C_{min} to MIC (C_{min}/MIC) ratio of 2–5 (Trope 2011) all have been associated with improved clinical outcomes in the treatment of invasive fungal infections. Although no clear exposure–response relationship has been established for voriconazole prophylaxis, breakthrough fungal infections are reported to be more likely with a C_{min} of 1.5–2 mg/L or less (Mitsani 2012, Trifilio 2007). A C_{min} of 4.5–6 mg/L or greater has been linked with voriconazole-associated hepatotoxicity and neurotoxicity (Suzuki 2013, Dolton 2012, Kim 2011).

Generic Dosing Recommendations in Critically Ill Patients

An initial dose of 6 mg/kg intravenously every 12 hours for two doses followed by 3–4 mg/kg intravenously every 12 hours is recommended for invasive fungal infections. However, the intravenous vehicle or solubilizer in the intravenous formulation, sulfobutylether- β -cyclodextrin, may accumulate in patients with moderate to severe renal impairment. In patients with CL_{CR} less than 50 mL/minute, the use of intravenous voriconazole should be avoided to prevent cyclodextrin accumulation, which can adversely impair renal function further or potentially neurotoxicity, although the clinical relevance remains unclear.

Echinocandins

Pharmacokinetics

The echinocandin class of antifungals includes anidulafungin, caspofungin, and micafungin, which are only available for parenteral use. The echinocandins have high plasma protein binding (97%–99% or greater). Several small PK studies have been performed in critically ill patients with mixed findings (Boonstra 2017, Jullien 2017, Martial 2017, Bruggemann 2017, van der Elst 2017). Exposure in these patients is

generally lower and more variable compared with healthy volunteers but the clinical implication of this finding is unclear because of the heterogeneous case-mix and small sample sizes in these studies.

PK/PD Targets in Critically Ill Patients

Echinocandins demonstrate concentration-dependent killing characteristics and maximal in vivo efficacy is correlated with the AUC_{0-24}/MIC ratio (Andes 2008a, 2008b, 2010). Echinocandin exposures relating to optimal clinical outcomes and toxicity occurrence have not been identified thus far. However, optimal mycologic response for micafungin against *Candida* spp. has been observed in patients with AUC_{0-24}/MIC ratios of greater than 3000 (Andes 2011).

Generic Dosing Recommendations in Critically Ill Patients

Although echinocandins are presumed to be clinically comparable with each other, subtle dosing differences exist, such as the need for a loading dose for some agents (anidulafungin and caspofungin), their metabolic routes, and drug–drug interactions. Higher body weight may require a higher dose (Maseda 2018, van der Elst 2017, Lempers 2016). The CL of echinocandins is not influenced by renal function

and therefore dose adjustments are not required in patients with renal impairment. Echinocandin exposure can be influenced in patients with severe hepatic impairment, particularly for caspofungin. Lower exposure as well as higher exposure have been observed in these patients (Martial 2016, Undre 2015, Mistry 2007).

CONCLUSION

Conventional antimicrobial dosing regimens may not be appropriate for critically ill patients with sepsis or septic shock because they rarely consider the altered physiology and illness severity associated with this patient population. Dosing regimens detailed within the product information are mostly derived from data for noncritically ill patients and may lead to inadequate antimicrobial exposures and therapeutic failures in these patients. Therefore, an in-depth knowledge of PK and PD is essential for ICU pharmacists to comprehend the complex effect of pathophysiologic changes in critically ill patients and how these alterations can significantly influence dosing requirements in this patient population. Pending robust dosing guidelines in this complex patient population, routine antimicrobial TDM in the ICU is necessary to guide optimal dosing (Table 3, Table 4).

Table 3. PK/PD Indices and the Magnitudes Associated With Antibacterial and Antifungal Clinical Efficacy and Toxicity

Antibacterial Class	PK/PD Index	Pre-Clinical PK/PD Target for Efficacy	Clinical PK/PD Target for Efficacy	Clinical PK/PD Threshold for Toxicity
Aminoglycosides				
Amikacin	AUC_{0-24}/MIC	• AUC_{0-24}/MIC : 80–100	• $C_{max}/MIC \geq 8-10$	• $C_{min} > 5$ mg/L
Gentamicin/ Tobramycin	AUC_{0-24}/MIC	• AUC_{0-24}/MIC : 80–100	• $AUC_{0-24}/MIC \geq 110$ • $C_{max}/MIC \geq 8-10$	• $C_{min} > 1$ mg/L
β-Lactams				
Carbapenems	% $fT_{>MIC}$	• 40% $fT_{>MIC}$	• 50–100% $fT_{>MIC}$	• $C_{min} > 44.5$ mg/L
Cephalosporins	% $fT_{>MIC}$	• 60–70% $fT_{>MIC}$	• 45–100% $fT_{>MIC}$	• $C_{min} > 20$ mg/L
Penicillins	% $fT_{>MIC}$	• 50% $fT_{>MIC}$	• 50–100% $fT_{>MIC}$	• $C_{min} > 361$ mg/L
Co-Trimoxazole	Unclear	Unclear	• Unclear	• Unclear
Daptomycin	AUC_{0-24}/MIC	• $AUC_{0-24}/MIC \geq 517$	• $AUC_{0-24}/MIC \geq 666$ mg/L	• $C_{min} > 24$ mg/L
Fluoroquinolones	AUC_{0-24}/MIC	• $AUC_{0-24}/MIC \geq 100$ • $C_{max}/MIC \geq 8$	• $AUC_{0-24}/MIC \geq 125-250$ • $C_{max}/MIC \geq 12$	Unclear
Glycopeptides				
Teicoplanin	AUC_{0-24}/MIC	• $AUC_{0-24}/MIC \geq 610$	• $C_{min} \geq 10$ mg/L	Unclear
Vancomycin	AUC_{0-24}/MIC	• AUC_{0-24}/MIC : 86–460	• $AUC_{0-24}/MIC \geq 400$ • $C_{min} > 10-20$ mg/L	• $AUC_{0-24} > 600$ mg*hr/L • $C_{min} > 20$ mg/L
Linezolid	AUC_{0-24}/MIC	• $AUC_{0-24}/MIC \geq 100$	• AUC_{0-24}/MIC : 80–120 • $\geq 85\% fT_{>MIC}$	• $AUC_{0-24} > 300$ • $C_{min} > 7$

Table 3. PK/PD Indices and the Magnitudes Associated With Antibacterial and Antifungal Clinical Efficacy and Toxicity (*continued*)

Antibacterial Class	PK/PD Index	Pre-Clinical PK/PD Target for Efficacy	Clinical PK/PD Target for Efficacy	Clinical PK/PD Threshold for Toxicity
Antifungal class	PK/PD Index	Pre-clinical PK/PD Target for Efficacy	Clinical PK/PD Target for Efficacy	Clinical PK/PD Threshold for Toxicity
Echinocandins	AUC_{0-24}/MIC	• $fAUC_{0-24}/MIC$: 10–20	• $AUC_{0-24}/MIC >3000$	No data
Fluconazole	AUC_{0-24}/MIC	• AUC_{0-24}/MIC : 25–44	• $AUC_{0-24}/MIC \geq 55-100$	Unclear
Posaconazole	AUC_{0-24}/MIC	• $fAUC_{0-24}/MIC$: 25–50	• $C_{min} >0.5-1$ mg/L	No data
Voriconazole	AUC_{0-24}/MIC	• $fAUC_{0-24}/MIC$: 25–50	• $C_{min} \geq 1-2$ mg/L	• $C_{min} \geq 4.5-6$ mg/L

AUC_{0-24} = ratio of the area under the concentration-time curve during a 24-hour period; C_{max} = ratio of maximum drug concentration; C_{min} = trough drug concentration; $fAUC_{0-24}$ = free (unbound drug concentration) ratio of the AUC_{0-24} ; $fT_{>MIC}$ = duration of time that the free drug concentration remains above the MIC during a dosing interval; MIC = minimum inhibitory concentration; PK/PD = pharmacokinetic/pharmacodynamic.

Table 4. Suggested Empirical Dosing of Common Antibiotics and Antifungals in Critically Ill Patients

Patient Setting	General	Typical ICU	CRRT ^a	ECMO	ARC
Antibacterials					
Aminoglycosides	• High-dose and extended interval dosing regimen	• Amikacin 30 mg/kg IV • Dosing interval determined by renal function and TDM ^b • Gentamicin/tobramycin 7–10 mg/kg IV • Dosing interval determined by renal function and TDM ^b	• Amikacin 12–15 mg/kg IV; then TDM ^b • Gentamicin/tobramycin 3–4 mg/kg IV; then TDM ^b	• ICU dosing • ICU dosing	• ICU dosing • ICU dosing
β -lactams	• High initial loading doses followed by prolonged infusion ^{c,d}	• Cefepime 2 g IV LD (over 0.5 hr); then 2 g IV every 8 hr (as EI or CI) • Meropenem 1 g IV LD (over 0.5 hr); then 1 g IV every 8 hr (as EI or CI) • Piperacillin/tazobactam 4.5 g IV LD (over 0.5 hr); then 4.5 g IV every 6 hr (as EI or CI)	• Cefepime 2 g IV LD (over 0.5 hr); then 1–2 g every 12 hr • Meropenem 1 g IV LD (over 0.5 hr); then 0.5–1 g every 8–12 hr • Piperacillin/tazobactam 4.5 g IV LD (over 0.5 hr); then 4.5 g IV every 8 hr	• ICU dosing • ICU dosing • ICU dosing	• Cefepime 2 g IV LD (over 0.5 hr); then 2 g IV every 6–8 hr (as EI or CI) • Meropenem 1 g IV LD (over 0.5 hr); then 1 g IV every 6–8 hr (as EI or CI) • Piperacillin/tazobactam 4.5 g IV LD (over 0.5 hr); then 4.5 g IV every 4–6 hr (as EI or CI)

(*continued*)

Table 4. Suggested Empirical Dosing of Common Antibiotics and Antifungals in Critically Ill Patients (*continued*)

Patient Setting	General	Typical ICU	CRRT ^a	ECMO	ARC
Daptomycin	<ul style="list-style-type: none"> Higher-than-recommended dosing regimens needed 	<ul style="list-style-type: none"> Daptomycin 10–12 mg/kg IV with dosing interval determined by renal function^e 	<ul style="list-style-type: none"> Daptomycin 8 mg/kg IV every 24–48 hr^e 	<ul style="list-style-type: none"> ICU dosing 	<ul style="list-style-type: none"> Daptomycin 12 mg/kg IV with dosing interval determined by renal function^e
Fluoroquinolones	<ul style="list-style-type: none"> Dosing regimens that maximize the AUC₀₋₂₄/MIC Loading dose and higher daily doses 	<ul style="list-style-type: none"> Ciprofloxacin 400 mg IV every 8 hr Levofloxacin 750 mg IV every 24 hr Moxifloxacin 400 (or 600–800 for less susceptible pathogens) mg IV every 24 hr 	<ul style="list-style-type: none"> Ciprofloxacin 400 mg IV every 12 hr 	<ul style="list-style-type: none"> ICU dosing 	<ul style="list-style-type: none"> ICU dosing
Glycopeptides					
Teicoplanin	<ul style="list-style-type: none"> Use loading and higher daily doses 	<ul style="list-style-type: none"> Teicoplanin 12 mg/kg IV LD every 12 hr (for 3–5 doses); then 12 mg/kg every 24 hr 	<ul style="list-style-type: none"> Load then 6 mg/kg every 24 hr 	<ul style="list-style-type: none"> ICU dosing 	<ul style="list-style-type: none"> ICU dosing
Vancomycin	<ul style="list-style-type: none"> Loading dose and higher daily doses 	<ul style="list-style-type: none"> Vancomycin 25–30 mg/kg IV LD^f; then 15–20 mg/kg every 8–12 hr 	<ul style="list-style-type: none"> Vancomycin 20 mg/kg LD^f; then 10–15 mg/kg every 24–48 hr 	<ul style="list-style-type: none"> ICU dosing 	<ul style="list-style-type: none"> ICU dosing
Linezolid	<ul style="list-style-type: none"> Higher daily doses and altered dosing approaches Consider front-loaded dosing regimen and CI 	<ul style="list-style-type: none"> Linezolid 600 mg IV every 8–12 hr 	<ul style="list-style-type: none"> ICU dosing 	<ul style="list-style-type: none"> ICU dosing 	<ul style="list-style-type: none"> ICU dosing
Antifungals					
Echinocandins	<ul style="list-style-type: none"> Dosing depends on the indication 	<ul style="list-style-type: none"> Anidulafungin 200 mg IV LD on Day 1; then 100 mg IV daily Caspofungin 70 mg IV LD on Day 1; then 50 mg IV daily^g Micafungin 100 mg IV daily 	<ul style="list-style-type: none"> ICU dosing ICU dosing ICU dosing 	<ul style="list-style-type: none"> ICU dosing ICU dosing ICU dosing 	<ul style="list-style-type: none"> ICU dosing ICU dosing ICU dosing
Fluconazole	<ul style="list-style-type: none"> Dosing depends on the indication 	<ul style="list-style-type: none"> Fluconazole 12 mg/kg (800 mg) IV LD on Day 1; then 6 mg/kg (400 mg) daily 	<ul style="list-style-type: none"> Fluconazole 12 mg/kg IV LD on Day 1; then 3–6 mg/kg daily 	<ul style="list-style-type: none"> ICU dosing 	<ul style="list-style-type: none"> ICU dosing

Table 4. Suggested Empirical Dosing of Common Antibiotics and Antifungals in Critically Ill Patients (*continued*)

Patient Setting	General	Typical ICU	CRRT ^a	ECMO	ARC
Isavuconazole	—	• Isavuconazole LD 200 mg IV every 8 hr on Days 1 and 2; then 200 mg IV every 24 hr	• ICU dosing	• ICU dosing	• ICU dosing
Posaconazole	• Larger-than-approved LD possible in critically ill with increased BMI	• Posaconazole LD 300 mg IV every 12 hr on Day 1; then 300 mg IV every 24 hr	• ICU dosing	• ICU dosing	• ICU dosing
Voriconazole	—	• Voriconazole LD 6 mg/kg every 12 hr on Day 1; then 3–4 mg/kg every 12 hr	• ICU dosing	• ICU dosing	• ICU dosing

ARC = augmented renal clearance; CI = continuous infusion; CRRT = continuous renal replacement therapy; ECMO = extracorporeal membrane oxygenation; EI = extended infusion; IBW = ideal body weight; ICU = intensive care unit; IV = intravenous; LD = loading dose; TBW = total body weight; TDM = therapeutic drug monitoring.

^aConsider renal replacement therapy modality, filter type and flow rate. The following are general recommendations are made on the basis of dialysate flow/ultrafiltration rates of 1–2 L/hr with minimal residual function.

^bFor underweight patients, use TBW; for patients with $1-1.25 \times$ IBW, use IBW; for obese patients with $>1.25 \times$ IBW, use adjusted body weight ($IBW + [0.4 \times (TBW - IBW)]$).

^cPrinciples also apply to other members of the β -lactam class of antibiotic.

^dProlonged infusion refers to either continuous 24-hr infusion or extended 2–4 hr infusion.

^eFor obese patients, use IBW or adjusted body weight ($IBW + [0.4 \times (TBW - IBW)]$)

^fUse TBW. For obese patients, loading dose is capped at 3000 mg.

^gFor patients with weight >80 kg, continue with 70 mg daily

Practice Points

- Extreme pathophysiologic changes are common in critically ill patients in the ICU resulting from both the underlying pathologies and the aggressive pharmacologic interventions undertaken to reverse the conditions.
- Commonly prescribed antimicrobial dosing regimens may be sub-optimal for critically ill patients as most of these recommendations have been derived from pharmacokinetic/pharmacodynamic data involving mostly healthy and/or moderately ill participants.
- Higher-than-recommended dosing regimens may be needed in some sub-groups of patients to circumvent the extreme physiological changes associated with this patient population, particularly earlier in the course of antimicrobial therapy.
- Knowledge of antimicrobial physicochemical properties is vital to anticipate the likely pharmacokinetic changes and to guide antimicrobial dosing in critically ill patients.
- Altered dosing approaches, supplemented with therapeutic drug monitoring if available, can ensure optimal antibiotic exposure and better clinical outcomes in critically ill patients in the ICU.

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Self-Assessment Questions

Questions 1–5 pertain to the following case.

E.F. is a 23-year old man (height 1.88 m, weight 120 kg) admitted to the ICU after a severe traumatic brain injury; he requires intracranial pressure monitoring via an external ventricular drain. During the second week of his ICU stay, E.F. develops ventriculitis with *Pseudomonas aeruginosa* in his CSF, which is sensitive to meropenem. He is receiving mechanical ventilation and vasopressor/inotropic support. His heart rate and mean arterial pressure are 110 beats/minute and 90 mm Hg. His urine output has averaged 1 mL/kg/hr, with SCr 0.8 mg/dL and serum albumin 2.0 g/dL. His estimated Cockcroft-Gault CrCl (using ideal body weight) is 200 mL/min.

- Which one of the following patient factors is most likely to complicate E.F.'s meropenem dosing?
 - Serum albumin
 - Infection with *P. aeruginosa*
 - Intracranial pressure monitoring by external ventricular drain
 - Cockcroft-Gault-estimated CrCl
- You suspect E.F. is manifesting features of augmented renal clearance. Which one of the following patient factors best supports this clinical suspicion in E.F.?
 - Serum albumin
 - Young age and severe traumatic brain injury
 - External ventricular drain and mechanical ventilator
 - Vasopressor/inotropic support
- During daily ward rounds, you and your colleagues discuss alternative antimicrobial agents for E.F.'s ventriculitis. Which one of the following is best to recommend for E.F.?
 - Cefepime; it possesses a low V_d .
 - Ceftazidime; it demonstrates "time-dependent" bactericidal activity.
 - Ciprofloxacin; it demonstrates "concentration-dependent" bactericidal activity.
 - Piperacillin; it is cleared by both the renal and biliary routes.
- Which one of the following meropenem regimens is best to recommend to optimize pharmacokinetic/pharmacodynamic target attainment in E.F.?
 - 2 g every 8 hours as a 1-hour infusion
 - 2 g every 8 hours as a 4-hour infusion
 - Loading dose 2 g as a 0.5-hour infusion followed by 2 g every 8 hours as a 4-hour infusion.
 - 2 g every 8 hours as a continuous infusion (i.e., infused over 8 hours) without a loading dose

- A few days later, E.F.'s care team is informed that blood cultures grew methicillin-resistant *Staphylococcus aureus* with MIC of 1 mg/L. The team plans to start intravenous vancomycin. E.F. is still mechanically ventilated and receiving norepinephrine at a rate of 0.2 mcg/kg/min. His latest SCr has increased to 1.1 mg/dL. Which one of the following is best to recommend for E.F.?
 - If the MIC is determined by E-test, design a vancomycin dosing regimen that increases the probability of achieving AUC_{0-24}/MIC of 400–600.
 - If the MIC is determined by broth microdilution (BMD), design a vancomycin dosing regimen that increases the probability of achieving AUC_{0-24}/MIC of 400–600.
 - Start continuous vancomycin infusion to maximize clinical outcomes.
 - Starting an intermittent dosing of 15–20 mg/kg every 8 hours without a loading dose.

Questions 6 and 7 pertain to the following case.

P.E. is a 40-year old man (height 1.8 m, weight 80 kg) being treated for gram-negative septic shock. He receives 3 L of normal saline solution within 2 hours, is mechanically ventilated, and is receiving norepinephrine at a rate of 0.3 mcg/kg/min. P.E.'s urine output has averaged 1 mL/kg/hr, with SCr of 0.9 mg/dL and serum albumin of 2.5 g/dL. His estimated Cockcroft-Gault CrCl is 116 mL/min. P.E. is currently receiving piperacillin/tazobactam 4.5 g every 8 hours (as a 0.5-hour infusion) and gentamicin 7 mg/kg once daily.

- Which one of the following factors most likely affects the probability of achieving a C_{max}/MIC ratio of 10 for gentamicin in P.E.?
 - Increased clearance due to conserved renal function
 - Co-therapy with piperacillin/tazobactam
 - Hypoalbuminemia from fluid boluses and mechanical ventilation
 - Volume expansion from fluid boluses and vasopressor support
- Which one of the following is best to recommend to optimize piperacillin/tazobactam dosing and pharmacokinetic/pharmacodynamic target attainment in P.E.?
 - 4.5 g every 6 hours as a 1-hour infusion
 - 4.5 g loading dose as a 0.5-hour infusion followed by 4.5 g every 8 hours as a 4-hour infusion.
 - 4.5 g loading dose as a 0.5-hour infusion followed by 4.5 g every 6 hours as a 3-hour infusion
 - 4.5 g every 8 hours as a 4-hour infusion

Questions 8–10 pertain to the following case.

G.H. is a 38-year old man (height 1.70 m, weight 92 kg) admitted to the ICU requiring intubation and mechanical ventilation for respiratory failure. He recently underwent esophagectomy for adenocarcinoma, complicated by a trachea-esophageal fistula and mediastinitis. G.H. has a serum albumin of 1.9 g/dL and a measured urinary CrCl of 200 mL/min. *Enterobacter cloacae* is recovered from endotracheal specimens, and the isolate is only sensitive to carbapenems and fourth-generation cephalosporins.

8. Which one of the following is best to recommend for G.H.?
 - A. Piperacillin/tazobactam 4.5 g every 6 hours as a 3-hour infusion
 - B. Ertapenem 1 g every 24 hours as a 0.5-hour infusion
 - C. Cefepime 1 g every 8 hours as a 0.5 hour infusion
 - D. Meropenem loading dose 1 g as a 1-hour infusion followed by 1 g every 8 hours as an extended infusion (i.e., infused over 3 hours)
9. G.H.'s care team decides to start ertapenem 2 g every 24 hours as a 1-hour infusion. Based on emerging and current pharmacokinetic data, you think that this regimen would not be appropriate. Which one of the following best assesses how the suggested regimen will affect G.H.'s ertapenem serum concentration?
 - A. Increased at the end of dosing interval because of hypoalbuminemia
 - B. Decreased because of augmented renal clearance
 - C. Increased because of mechanical ventilation
 - D. Unchanged because of usage of a higher-than-standard ertapenem dosing regimen
10. Which one of the following interventions is most likely to improve the ertapenem pharmacokinetic/pharmacodynamic exposure for G.H.?
 - A. Increase infusion time from 1 hour to 3 hours per dose to increase $\%fT_{>MIC}$
 - B. Decrease infusion time from 1 hour to 30 minutes per dose to increase C_{max}
 - C. Shorten dosing interval from 24 hours to 12 hours to increase $\%fT_{>MIC}$
 - D. Administer 2 g every 24 hours by intravenous bolus push over 5 minutes to increase C_{max} and AUC.

Questions 11–13 pertain to the following case.

L.K. is a 40-year-old woman (height 1.65 m, weight 85 kg) admitted to the ICU for septic shock and respiratory failure, necessitating aggressive fluid resuscitation, vasopressor treatment, and mechanical ventilation. Given her progressive deterioration and ongoing clinical stability, veno-venous ECMO is started because of acute respiratory distress syndrome. L.K. is started on empirical antibiotic treatment with piperacillin/tazobactam. You have suggested to start with

piperacillin/tazobactam 4.5 g every 6 hours as a 3-hour infusion.

11. Which one of the following best justifies your dosing recommendation for L.K.?
 - A. Prolonged β -lactam infusion increases survival in critically ill patients receiving ECMO.
 - B. Prolonged β -lactam infusion ensures adequate drug exposure as ECMO alters the CL of piperacillin/tazobactam in critically ill patients.
 - C. Prolonged β -lactam infusion ensures adequate drug exposure as ECMO changes the V_d of piperacillin/tazobactam in critically ill patients.
 - D. ECMO does not change the PK of piperacillin/tazobactam and dosing should align with the recommended dosing strategies for critically ill patients not on ECMO support.
12. Which one of the following pharmacokinetic/pharmacodynamic targets for piperacillin/tazobactam is best to recommend for L.K.?
 - A. Concentration above the MIC for 40% of the dosing interval
 - B. Concentration above the MIC for 100% of the dosing interval
 - C. Peak concentration at least 16 mg/L
 - D. Concentration at least 5 times above the MIC for 100% of the dosing interval
13. You and a colleague discuss the potential impact of L.K.'s ECMO on the PK of piperacillin/tazobactam. If administered to L.K., which one of the following is most likely to be affected by the introduction of ECMO?
 - A. Caspofungin
 - B. Meropenem
 - C. Fluconazole
 - D. Amikacin

Questions 14 and 15 pertain to the following case.

B.D. is a 45-year old woman (height 1.75 m, weight 90 kg) who undergoes an aortic root replacement procedure, which is then complicated by a sigmoid diverticulitis with septic shock. Her urine output is <350 mL over the last 24 hours; therefore, continuous veno-venous hemofiltration (CVVH) is initiated.

14. As B.D.'s clinical team debates the best empirical antimicrobial therapy, you consider potential complications of antimicrobial dosing in this patient. Which one of the following agents is most likely to be affected by B.D.'s CVVH?
 - A. Ceftriaxone
 - B. Ciprofloxacin
 - C. Linezolid
 - D. Vancomycin

15. B.D.'s clinical team decides to start piperacillin/tazobactam. Which one of the following would be most important in determining the initial piperacillin/tazobactam dosing to recommend for B.D.?
- A. Piperacillin/tazobactam's published volume of distribution in critically ill patients
 - B. Determination of piperacillin/tazobactam's elimination half-life
 - C. Calculated CVVH clearance using saturation coefficient of piperacillin/tazobactam
 - D. Calculated total drug clearance using CVVH clearance only