Antimicrobial Dosing Concepts and Recommendations for Critically Ill Adult Patients Receiving Continuous Renal Replacement Therapy or Intermittent Hemodialysis

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Infectious diseases and impaired renal function often occur in critically ill patients, and delaying the start of appropriate empiric antimicrobial therapy or starting inappropriate therapy has been associated with poor outcomes. Our primary objective was to critically review and discuss the influence of chronic kidney disease (CKD) and acute kidney injury (AKI) on the clinical pharmacokinetic and pharmacodynamic properties of antimicrobial agents. The effect of continuous renal replacement therapies (CRRTs) and intermittent hemodialysis (IHD) on drug disposition in these two populations was also evaluated. Finally, proposed dosing strategies for selected antimicrobials in critically ill adult patients as well as those receiving CRRT or IHD have been compiled. We conducted a PubMed search (January 1980–March 2008) to identify all English-language literature published in which dosing recommendations were proposed for antimicrobials commonly used in critically ill patients, including those receiving CRRT or IHD. All pertinent reviews, selected studies, and associated references were evaluated to ensure their relevance. Forty antimicrobial, antifungal, and antiviral agents commonly used in critically ill patients were included for review. Dosage recommendations were synthesized from the 42 reviewed articles and peer-reviewed, evidence-based clinical drug databases to generate initial guidance for the determination of antimicrobial dosing strategies for critically ill adults. Because of the evolving process of critical illness, whether in patients with AKI or in those with CKD, prospective adaptation of these initial dosing recommendations to meet the needs of each individual patient will often rely on prospectively collected clinical and laboratory data.

Key Words: antimicrobials, renal replacement therapy, dialysis, renal failure, critically ill, pharmacokinetics, pharmacodynamics.

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OUTLINE

Data Sources
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Critically ill patients often have multiple medical problems, including infectious diseases and impaired renal function requiring complex renal replacement and pharmacologic therapy. Infection-related mortality among critically ill patients with bacteremia, ventilator-associated pneumonia, and microbiologically confirmed severe sepsis or septic shock is a significant

concern. Delaying the start of appropriate empiric antimicrobial therapy or starting inappropriate therapy has been associated with poor outcomes. For instance, in numerous studies of a variety of serious bacterial infections, infection-related mortality rates were significantly higher in patients receiving inappropriate versus appropriate therapy (37.0–91.0% vs 12.2–38.0%, $p<0.05$).[1–7] The empiric selection of an antimicrobial regimen should consider, among other factors, the suspected site of infection, probable pathogens, immune status of the patient, previous antibiotic history, and clinical presentation of the patient. Since the pharmacokinetics of many antibiotics, especially those that are moderately to highly dependent on the kidney for elimination (e.g., fraction excreted unchanged > 25%), are altered in critically ill patients, modifications in dosage regimens have been proposed.[8]

Optimizing antimicrobial therapy in the dynamic critically ill patient can be challenging. Antimicrobial pharmacokinetic changes in critical illness (e.g., enhanced or reduced systemic clearance and increased volume of distribution) secondary to stress-induced renal and metabolic function alterations, aggressive fluid resuscitation, and other factors should be considered when initiating therapy. In addition, chronic kidney disease (CKD), acute kidney injury (AKI), and reduced cardiac or hepatic function may result in a marked reduction in antimicrobial clearance. Ultimately, pharmacokinetic alterations are dependent on the phase of critical illness. Together, these factors, among others, must be considered when optimizing a dosing regimen. Finally, the provision of renal replacement therapy (RRT), be it continuous (CRRT) or intermittent hemodialysis (IHD), may necessitate further dosing regimen adjustments to determine the optimal regimen for the individual critically ill patient.

Renal replacement therapies have dramatically evolved during the past 20 years and are now individualized according to each patient's clinical status and hemodynamic tolerance. Intermittent hemodialysis is still the most commonly used RRT for the management of patients with CKD and/or AKI. However, CRRTs are now commonly used for many critically ill patients because of improved hemodynamic tolerance associated with this form of RRT. Continuous renal replacement therapy includes three primary variants: continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodialfiltration (CVVHDF). Slow extended daily dialysis (SLEDD) has been developed more recently and combines the advantages of both IHD and CRRT. These approaches to RRT have been shown to improve patients' survival and recovery of renal function.[9–11] The benefits of CRRT and SLEDD include improved hemodynamic tolerability and metabolic control, and limited need to restrict fluids. This makes them attractive alternatives to IHD in the intensive care unit. However, several challenges have been identified including unplanned time off the circuit, consistency, and ability to predict the amount of substance removed when developing dosing regimens.

Despite the advances in critical care therapeutics and RRT, concurrent AKI is still associated with mortality rates ranging from 25–90%.[12] The 7–25% of all critically ill patients admitted to intensive care units who develop AKI have significantly higher mortality rates relative to patients not admitted to an intensive care unit.[13–19] Many of these patients need some form of RRT, which additionally complicates the design of the optimal dosage regimen. Drug-induced renal dysfunction is an important, and often overlooked, cause or further complicating factor of AKI in this patient population.[20] Further, renal failure exacerbates the risk for adverse drug events, resulting in increased morbidity, mortality, and health care costs. Adverse drug events occur in 10–12% of patients in the intensive care unit, which is twice the rate observed in patients admitted to general medicine wards.[21, 22] Approximately 50% of patients with an estimated creatinine clearance of less than 40 ml/minute receive drug doses that are 2.5 times higher than the recommended maximum dose.[23] Conversely, patients receiving CRRT can be underdosed due to variability in

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published dosing recommendations and approaches to CRRT currently used by institutions that in many cases may be more efficient than those reported observations. Combined, this can lead to lower than anticipated or desired systemic antimicrobial exposure, therapeutic failure, and the emergence of breakthrough resistance.[24–29]

Data on drug dialysis clearance to guide antimicrobial dosing in the critically ill patient in many cases have become outdated secondary to the introduction of the new RRTs and advances in RRT efficiency. Current dosing regimen approaches for dialysis-dependent patients are frequently based on data derived from patients with stable CKD who are receiving scheduled IHD and/or from studies that assessed a small number of patients and that used dialyzers no longer commercially available, limited sampling strategies, and in many cases nonrigorous analysis. Furthermore, most of these studies are confounded by the presence of multiple uncontrollable patient variables. These data often resulted in the proposal of a standardized, fixed antimicrobial dosage regimen in the dynamic critically ill patient. Thus, a reevaluation of existing data is warranted to generate new dosage recommendations with the goal of optimizing patient outcomes.

Optimized antimicrobial dosing regimens in critically ill patients with organ system failure are essential to maximize patient outcomes while limiting adverse drug events. In this review, we explore antimicrobial pharmacokinetic and pharmacodynamic concepts, RRT concepts including varying types and nomenclature, and antimicrobial dosing concepts. Finally, dosing recommendations for the optimal use of many antimicrobials commonly administered to critically ill adult patients receiving RRT are presented and critiqued.

Data Sources

A PubMed search was conducted to identify all English-language literature published between January 1980 and March 2008 in which dosing recommendations were proposed for antimicrobials commonly used in critically ill patients including those receiving CRRT or IHD. Search terms were antimicrobials, selected antimicrobial agents, dialysis, renal replacement therapy, hemodialysis, slow extended daily dialysis, continuous renal replacement therapy, continuous venovenous hemofiltration, continuous venovenous hemodialysis, continuous venovenous hemodialfiltration, renal failure, and critically ill. All pertinent reviews, selected studies, and associated references were evaluated to ensure their relevance. Forty antimicrobial, antifungal, and antiviral agents commonly used in critically ill patients were included for review.

Dosage recommendations were synthesized from the 42 reviewed articles (among 65 identified) and peer-reviewed, evidence-based clinical drug databases to generate initial guidance for the determination of antimicrobial dosing strategies for critically ill adults.

Pharmacokinetics and Pharmacodynamics in Acute and Chronic Renal Impairment

To optimize antimicrobial dosing regimens in the critically ill patient with renal failure, clinicians need to consider the pharmacokinetic properties of each drug: absorption, distribution and delivery to the site of action, metabolism, and renal elimination. These properties may be highly variable in critically ill patients because of stress-induced renal, metabolic, and cardiac function alterations; excess fluid; and drug interactions, among other factors.

Influence of Chronic Kidney Disease on Pharmacokinetics

Absorption of only a very few drugs has been reported to be reduced in the presence of CKD; however, there are only two drugs for which a reduction in bioavailability is clinically relevant—dihydrocodeine and propranolol.[8, 30] In theory, drug absorption after oral administration in patients with end-stage renal disease (ESRD) may be altered secondary to gastrointestinal edema, nausea and vomiting, gastroparesis, and delayed gastric emptying.[31] The volume of distribution of a drug is primarily affected by altered plasma protein binding and fluctuations in fluid status among patients with CKD and/or critically ill patients with AKI.[30] Decreased protein binding results in a decrease in the fraction of the drug that resides in the vascular space, and thus the volume of distribution may be increased. This shift from the vascular space to tissue may lead to increased pharmacologic effects. Drug-drug interactions may alter distribution when two highly plasma protein–bound drugs compete for binding to the same plasma protein. In addition, fluid status and total body water can be highly variable in critically ill

patients, especially those with impaired renal function, leading to changes in a drug's volume of distribution (Table 1).[30] These factors are accompanied by a decrease in serum drug concentrations of some antimicrobials (e.g., β-lactams), and for some patients, the dose of these antimicrobial agents may then require an upward adjustment. Although alterations in pharmacodynamics have been associated with a few classic agents (e.g., phenytoin, warfarin, and enoxaparin) largely due to reduced protein binding, no clinically significant effects have been noted with antimicrobials.

Alterations in drug metabolism have been associated with the presence of renal failure. Decreased intrarenal metabolism and hepatic metabolism have been noted in patients with CKD and may result in significant changes in systemic clearance of some agents.[30, 32] Examples of enzyme systems impaired in patients with CKD include cytochrome P450 (CYP) 2C6, 2C11, 3C11, 3A1, and 3A2.[32–34] This may be the result of the accumulation of endogenous inhibitors that can downregulate the activity of selected hepatic CYP enzymes.[35] The observed clinical reductions in nonrenal clearance in patients with CKD have been generally proportional to the reductions in glomerular filtration rate.[8] However, the effects of renal failure on nonrenal drug clearance also appear to depend on whether the renal failure is acute or chronic in nature. The degree of reduction in patients with AKI does not appear to be as great as that observed in patients with ESRD.[12, 36] In general, these studies should be interpreted with caution since concurrent drugs, age, smoking status, and alcohol consumption were often not controlled for. Furthermore, the possibility of pharmacogenetic variation in drug-metabolizing enzymes (e.g., CYP enzymes) must be considered. Prediction of the effect of renal insufficiency on the metabolism of a particular drug is thus difficult, and no quantitative strategy exists to factor these changes into an individualized treatment regimen.

Alterations in glomerular filtration and tubular secretion secondary to CKD may have a dramatic effect on drug disposition. For drugs that are primarily filtered, one can anticipate that a reduction in glomerular filtration rate will result in a proportional decrease in renal drug clearance. The impact of a reduction in renal function on drug elimination depends on two predominant factors: the fraction of drug normally eliminated unchanged by the kidney and the degree of renal insufficiency. Renal function (e.g., creatinine clearance for patients with CKD) is usually estimated based on the patient's stable serum creatinine concentration. Although several methods for estimating creatinine clearance in adults with AKI have been proposed, none of the methods have been rigorously validated, and their use in complex patient situations cannot be recommended.[8, 36]

Table 1. Effect of End-Stage Renal Disease on Volume of Distribution of Selected Antimicrobial Agents

	Volume of Distribution (L/kg)	
Antimicrobial	Normal Renal Function	End-Stage Renal Disease
Amikacin	0.2	0.3
Cefazolin	0.13	0.16
Cefoxitin	0.16	0.26
Cefuroxime	0.2	0.26
Erythromycin	0.57	1.09
Gentamicin	0.2	0.3
Trimethoprim	1.36	1.83
Vancomycin	0.64	0.85

From reference 30.

Influence of Critical Illness and Acute Kidney Injury on Pharmacokinetics

The pharmacokinetics of a drug in patients with CKD or healthy volunteers may not adequately describe its properties in critically ill patients with or without AKI.[37–44] Alterations have been noted predominantly in distribution volume and renal elimination, with only a few reports of marked changes in drug metabolism. Since sepsis is one of the most common causes of AKI and delayed initiation of antimicrobial treatment has been associated with higher mortality, many studies and reviews have focused on antimicrobial dosing needs of the critically ill patient.[45] The most common pharmacokinetic changes include increased volume of distribution of water-soluble drugs due to extracellular volume expansion, altered protein binding, and a decreased systemic clearance due to kidney and/or liver failure.[30] The inflammatory response associated with early sepsis results in a rapid decrease in serum albumin concentrations, large fluid shifts, and third-space losses.[43] This results in initial increased cardiac output, creatinine clearance, and drug clearance during early stages of sepsis.

During later stages, uncontrolled sepsis may result in renal and/or hepatic failure secondary to marked blood shunting.[43] Compromised tissue

Table 2. Factors Affecting Antimicrobial Dosing in Critically Ill Patients with Renal Failure

Factor	Comment
Type of dialysis	Drug removal for most antimicrobials is largely affected by the type of dialysis (see text)
Intrinsic renal function	Patients with residual renal function may clear more drug than predicted by dialysis alone
Site of infection (indication)	Deep-seated infections require larger doses to optimize pharmacodynamic target attainment, including drug penetration at the site(s) of infection
Severity of infection	Empiric aggressive dosing should be used for severe infections until culture and susceptibilities are available to guide therapy
Patient size	Larger patients may require larger loading and maintenance doses to optimize pharmacodynamic target attainment, especially with lipid-soluble antimicrobials
Immune function	Empiric aggressive dosing should be used for patients with impaired immune function
Antimicrobial factors	Pharmacokinetic and pharmacodynamic data should be considered when developing a dosing regimen: absorption, distribution, metabolism, and elimination; concentration-dependent vs time-dependent killing; postantibiotic effect (see text)
Susceptibility patterns (MIC data)	Local and unit-specific antibiograms, if available, should also be used when selecting an initial empiric antimicrobial regimen; the MIC of infecting pathogen(s), if available, should be used to optimize definitive antimicrobial therapy, pharmacodynamic target attainment, and patient outcomes
Drug-drug interactions	These may alter antimicrobial absorption, distribution, metabolism, and elimination (e.g., inhibition or induction of drug metabolism) and/or result in additive toxicity

MIC = minimum inhibitory concentration.

perfusion may affect drug distribution, resulting in a reduced volume of distribution of some antimicrobials, whereas increasing capillary permeability, interstitial edema, and large-volume fluid resuscitation during sepsis and septic shock tend to increase the volume of distribution of most water-soluble antimicrobials.[39] Presence of AKI and/or CKD can notably impair elimination of renally cleared antimicrobials, resulting in accumulation of the antimicrobial and/or its metabolites. The net elimination of antimicrobials in patients requiring RRT may be significantly faster in those with AKI compared with those with CKD, due in part to the multiplicity of the simultaneous physiologic responses to illness.[24–29, 46, 47] Finally, critically ill patients with renal failure often also have nonrenal conditions that may affect drug metabolism and systemic clearance, including decreased blood flow to the liver (e.g., shock-liver, use of vasopressors, and/or overwhelming sepsis), cirrhosis, or an underlying pharmacogenetic variability, or the condition may be secondary to drug-drug interactions (CYP inhibition or induction).[40]

Antimicrobial Pharmacodynamics

Antimicrobial dosing regimens must take into account the drug's pharmacodynamic properties, such as the relationship between the antimicrobial concentration at the site of infection relative to the in vitro microbiologic activity of the agent. Common antimicrobial pharmacodynamic parameters include the antimicrobial killing profile (e.g., concentration-dependent vs time-dependent killing), bacteriostatic versus bactericidal activity, and the postantibiotic effect (inhibitory effects that persist after the antimicrobial serum concentration decreases below the minimum inhibitory concentration [MIC]).[48] In addition to the level of renal function and type of dialysis, antimicrobial dosing is dependent on the site and severity of infection, patient size, status of the immune system, antimicrobial pharmacokinetic and pharmacodynamic parameters, and MIC of the infecting pathogen, among other factors, to optimize target attainment (Table 2).

The probability of attaining critical pharmacodynamic targets that are associated with optimal patient outcomes are based on two primary considerations: concentration-dependent killing and time-dependent killing.[48] Some antimicrobials also display activity related to the area under the plasma concentration–time curve (AUC), or the ratio of total drug exposure, relative to the MIC of the infecting pathogen (AUC:MIC).[48] Concentration-dependent killing occurs when higher drug concentrations are associated with greater rates and extent of bacterial killing.[48] Target attainment of concentration-dependent antimicrobials is maximized when peak antimicrobial concentrations at the site of infection are increased relative to the MIC of the infecting pathogen.[48] Aminoglycosides, fluoro-quinolones, metronidazole, ketolides, and daptomycin are

commonly used antimicrobials that exhibit concentration-dependent killing properties.[48] The AUC:MIC (area under the inhibitory curve [AUIC]) is also used to describe fluoroquinolone and ketolide pharmaco-dynamics.[49] Changes in the volume of distribution in critically ill patients with AKI and/or CKD may lead to lower target peak concentrations than expected. Dosing regimens, including the intervals between administrations, should consider the post-antibiotic effect exhibited by the antimicrobial agent. However, the postantibiotic effect associated with high-dose once-daily dosing of aminoglycosides and other select antimicrobials in patients with normal renal function may not apply to dosing regimens designed for patients with CKD or AKI. Overall, target peak concentrations, volume of distribution, and knowledge of the MIC of the infecting pathogen should guide the antimicrobial dose, whereas an understanding of total systemic clearance, including RRT clearance, and the postantibiotic effect of the antimicrobial agent should guide dosing frequency.

Time-dependent killing or concentration-independent killing activity is characterized by a minimal increase in the rate or extent of bacterial killing with an increased antimicrobial dose.[48] Time-dependent killing target attainment is maximized when these antimicrobials are dosed to maintain concentrations at the site of infection above the MIC of the infecting pathogen for an optimal proportion of the dosing interval (e.g., ≥ 40–70%).[48] Penicillins, cephalosporins, carbapenems, and aztreonam are commonly used antimicrobials that exhibit time-dependent killing properties.[48] Appropriate dosing regimens of time-dependent killing antimicrobials are dependent on achievable concentrations at the site of infection, the half-life and total systemic clearance of the drug, and the MIC of the infecting pathogen, among other factors. Generally, shorter dosing intervals, extended infusions, and continuous infusions optimize target attainment of time-dependent killing antimicrobials.[50] Linezolid, macrolides, clindamycin, tetracyclines, and vancomycin generally are considered to be time-dependent killing antimicrobials; however, their activity is also characterized by or associated with better outcomes when the achieved AUC:MIC (AUIC) is optimized.[48]

The pharmacokinetic and pharmacodynamic properties of each antimicrobial agent including molecular weight, fraction protein bound, volume of distribution, fraction of drug eliminated unchanged in urine, half-lives for normal renal function and ESRD, primary route of elimination, potential removal by dialysis, pharmacodynamic properties (time-dependent or concentration-dependent killing), and proposed optimal pharmacodynamic targets are summarized in Appendix 1.[8, 42, 43, 51–54]

Characteristics of Renal Replacement Therapies Used in Critically Ill Patients

Multiple RRTs are available in the intensive care units of many institutions and include IHD, SLEDD, and the several CRRT variants, all of which have variable contributions to systemic drug clearance. Some CRRT data are derived from arterial to venous access variants, which were initially used in the 1990s; however, this approach is no longer used in practice.[55–57] The primary differences in RRT include filter and dialyzer material composition and surface area, duration of the procedure, blood flow rate, dialysate flow rate, ultrafiltration rate, and pre- versus postreplacement fluid administration.[55–57] As the patient's clinical condition changes, including residual renal function, the RRT prescription should frequently be altered to ensure that the goals of therapy are attained and maintained. This may be evidenced by a reduction of ultrafiltration rates and/or shorter dialysis durations for patients who are hemodynamically unstable or with resolving renal dysfunction requiring less solute clearance. Adjustments in the RRT prescription may alter the amount of drug removed and the replacement doses needed to maintain target serum concentrations.

The two mechanisms of fluid and waste product or drug elimination used in RRT are diffusion and convection, with many variations or combinations of these modalities (Table 3).[55–58] Diffusion consists of the passive movement of substances down concentration gradients across the semipermeable hemofilter or dialyzer membrane.[42, 55] This results in removal of the drug from the blood, which is influenced by the dialyzer filter composition and surface area as well as the ultrafiltration rate. With convection, solutes and drugs are actively removed from blood by means of a pump-driven pressure gradient ("solvent drag") independent of concentration gradients or molecular size.[42, 55] Conventional IHD and CVVHD are primarily diffusion methods, whereas CVVH involves primarily convection drug and solute removal.[42, 55]

Table 3. Summary of Renal Replacement Therapy Techniques

Technique[a]	Clearance Mechanism		Vascular Access	Fluid Replacement	Typical Duration (hrs)
	Convection	Diffusion			
Hemodialysis					
IHD or VV	+	++++	Fistula	+	3–4
SLEDD or VV	+	++++	Fistula	+	6–12
CAVHD	+	++++	AV	+/0	24
CVVHD	+	++++	VV	+/0	24
CVVHFD	++	++++	VV	+/0	24
Hemofiltration					
CAVH	++++	–	AV	+++	24
CVVH	++++	–	VV	+++	24
Hemodialfiltration					
CAVHDF	+++	+++	AV	++	24
CVVHDF	+++	+++	VV	++	24
IHDF or VV	++	++++	Fistula	+	3–4
Ultrafiltration					
SCUF	+	–	Large vein	0	24

– = not occurring; 0 = not required; + = negligible; ++ = moderate; +++ = marked; ++++ = major; IHD = intermittent hemodialysis; VV = vein and vein; SLEDD = slow extended daily hemodialysis; CAVHD = continuous arteriovenous hemodialysis; AV = artery and vein; CVVHD = continuous venovenous hemodialysis; CVVHFD = continuous venovenous high-flux hemodialysis; CAVH = continuous arteriovenous hemofiltration; CVVH = continuous venovenous hemofiltration; CAVHDF = continuous arteriovenous hemodialfiltration; CVVHDF = continuous venovenous hemodialfiltration; IHDF = intermittent hemodialfiltration; SCUF = slow continuous ultrafiltration.

[a]When combining the mechanism of drug clearance by dialysis with the dialysis duration, as a general rule, the efficiency of drug removal is as follows: CVVHDF > CVVHD > CVVH > SLEDD > IHD.

From reference 55.

The CVVHDF variant of CRRT uses both convection and diffusion methods of drug and solute removal, resulting in greater drug removal than by the convection or diffusion method alone.[55]

The extent to which a drug is removed by IHD can be influenced by several physicochemical characteristics of the agent, including molecular size, protein binding, volume of distribution, water solubility, and plasma clearance.[8, 30, 36] In addition to these drug properties, technical aspects of the dialysis procedure (e.g., filter pore size, blood or ultrafiltration rates, duration of dialysis) may also affect the extent to which a drug is removed by dialysis.[30] The terms high-efficiency and high-flux describe dialysis membranes with large surface areas and high ultrafiltration rates, respectively. Drugs with a large volume of distribution (> 1.5–2 L/kg) tend to have greater drug concentrations in tissues, and thus they are not readily available for removal from the blood as are drugs with a volume of distribution that approximates total body water (≤ 0.7 L/kg). A useful tool to predict the likelihood of drug removal by convection dialysis is the sieving coefficient, which is defined as the ratio of the drug concentration in the ultrafiltrate to the drug concentration in the patient's plasma entering the dialyzer or hemofilter. It is important to note that the impact of each variable will be dependent on the type of dialysis. Finally, a rebound in plasma drug concentrations after IHD may occur as the drug redistributes out of the tissues to equilibrate with the lower postdialysis plasma concentrations.

Antimicrobial Dosing Considerations

Specific antimicrobial dosing recommendations for patients receiving various forms of dialysis (standard IHD, CVVH, CVVHD, and CVVHDF) are provided in Table 4.[8, 25–29, 37, 46, 47, 42, 51–54, 59–78] These recommendations serve as a guide or initial reference point, but clearly the choice for each individual patient should also include clinical judgment. Dosing ranges are provided for many antimicrobial agents to accommodate for differences in ultrafiltration and/or dialysis flow rates, patient size, severity and site of infection, MIC of infecting pathogen, level of intrinsic renal function and immune status, among other factors. Loading doses are provided for agents when supported by pharmacokinetic and pharmacodynamic properties of the drug and published observations. All CRRT doses, including dosing ranges, assume ultrafiltration and dialysis flow rates of at least 1–2 L/hour, intravenous drug administration, and minimal residual renal function. Patients undergoing CVVH at ultrafiltration rates of 3–4 L/hour and

Table 4. Recommended Adult Antimicrobial Dosages by Type of Renal Replacement Therapy

Antimicrobial[a]	Loading Dose for CRRT	Maintenance Dosage for CRRT[b]			
		CVVH[c]	CVVHD	CVVHDF	IHD[d]
Acyclovir[8, 51, 53, 54]	None	5–10 mg/kg q24h[e]	5–10 mg/kg q12–24h[e]	5–10 mg/kg q12–24h[e]	2.5–5 mg/kg q24h[e]
Amikacin[8, 51, 53, 54]	10 mg/kg	7.5 mg/kg q24–48h[f]	Same	Same	5–7.5 mg/kg q48–72h[g]
Amphotericin B deoxycholate[42, 51, 53, 54]	None	0.5–1 mg/kg q24h	Same	Same	Same
Amphotericin B liposomal[42, 51, 53, 54]	None	3–5 mg/kg q24h	Same	Same	Same
Ampicillin[8, 51]	2 g	1–2 g q8–12h	1–2 g q8h	1–2 g q6–8h	1–2 g q12–24h
Ampicillin-sulbactam[8, 51, 53]	3 g	1.5–3 g q8–12h	1.5–3 g q8h	1.5–3 g q6–8h	1.5–3 g q12–24h
Azithromycin[8, 51, 54]	None	250–500 mg q24h	Same	Same	Same
Aztreonam[51, 53, 54, 59]	2 g	1–2 g q12h	1 g q8h or 2 g q12h[h]	1 g q8h or 2 g q12h[h]	500 mg q12h
Caspofungin[51, 54]	70 mg	50 mg q24h	Same	Same	Same
Cefazolin[8, 51, 53, 54, 59]	2 g	1–2 g q12h	1 g q8h or 2 g q12h[h]	1 g q8h or 2 g q12h[h]	500–1000 mg q24h[i]
Cefepime[8, 42, 51, 53, 54, 60, 61]	2 g	1–2 g q12h	1 g q8h or 2 g q12h[h, j]	1 g q8h or 2 g q12h[h, j]	500–1000 mg q24h[i]
Cefotaxime[8, 42, 51–53, 59]	None	1–2 g q8–12h	1–2 g q8h	1–2 g q6–8h	1–2 g q24h
Ceftazidime[8, 42, 51–54, 62]	2 g	1–2 g q12h	1 g q8h or 2 g q12h[h, j]	1 g q8h or 2 g q12h[h, j, k]	500–1000 mg q24h[i]
Ceftriaxone[8, 42, 51, 53, 54]	2 g	1–2 g q12–24h	Same	Same	1–2 g q24h
Ciprofloxacin[8, 42, 51, 53, 54]	None	200–400 mg q12–24h	400 mg q12–24h	400 mg q12h	200–400 mg q24h
Clindamycin[8, 51, 53, 54]	None	600–900 mg q8h	Same	Same	Same
Colistin[42, 51, 53, 63]	None	2.5 mg/kg q48h[l]	Same[l]	Same[l, m]	1.5 mg/kg q24–48h
Daptomycin[51, 53, 54, 64, 65]	None	4–6 mg/kg q48h	Same	Same	4–6 mg/kg q48–72h[n]
Doxycycline[51, 52, 54]	None	100 mg q12h	Same	Same	Same
Fluconazole[8, 51–54, 66, 67]	400–800 mg	200–400 mg q24h	400–800 mg q24h[o]	800 mg q24h[p]	200–400 mg q48–72h or 100–200 mg q24h
Ganciclovir[8, 42, 51] (CMV infection)	None	I: 2.5 mg/kg q24h	I: 2.5 mg/kg q12h	I: 2.5 mg/kg q12h	I: 1.25 mg/kg q48–72h
		M: 1.25 mg/kg q24h	M: 2.5 mg/kg q24h	M: 2.5 mg/kg q24h	M: 0.625 mg/kg q48–72h
Gentamicin[47, 51, 54, 68]	2–3 mg/kg				2–3 mg/kg load x 1, then 1 mg/kg q48–72h[q]
Mild UTI or synergy		1 mg/kg q24–36h (redose when Cp < 1 mg/L)			
Moderate–severe UTI		1–1.5 mg/kg q24–36h (redose when Cp < 1.5–2 mg/L)			1–1.5 mg/kg q48–72h
Systemic GNR infection		1.5–2.5 mg/kg q24–48h (redose when Cp < 3–5 mg/L)			1.5–2 mg/kg q48–72h[q]
Imipenem[8, 27, 37, 42, 51, 53, 54, 69]	1 g	500 mg q8h[r]	500 mg q6–8h[r]	500 mg q6h[r]	250–500 mg q12h
Itraconazole[42, 51, 52, 54]	None	200 mg q12h x 4, then 200 mg q24h	Same	Same	Same
Levofloxacin[42, 51–54]	500–750 mg	250 mg q24h	250–500 mg q24h	250–750 mg q24h	250–500 mg q48h
Linezolid[42, 51–54]	None	600 mg q12h	Same	Same	Same
Meropenem[28, 29, 42, 51–54, 70–73]	1 g	0.5–1g q12h[s]	0.5–1 g q8–12h[s]	0.5–1 g q8–12h[s, t]	500 mg q24h
Metronidazole[51, 54]	None	500 mg q6–12h[u]	Same	Same	500 mg q8–12h[u]
Micafungin[51, 54]	None	100–150 mg q24h (treatment); 50 mg q24h (prophylaxis)			Same
Moxifloxacin[42, 51, 53, 54]	None	400 mg q24h	Same	Same	Same
Nafcillin[51, 53, 54]	None	2 g q4–6h	Same	Same	Same
Penicillin G[8, 51, 54]	4 MU	2 MU q4–6h	2–3 MU q4–6h	2–4 MU q4–6h	Normal dose load x 1, then 25–50% normal dose q4–6h or 50–100% normal dose q8–12h[v]
Piperacillin-tazobactam[25, 51, 54]	None	2.25–3.375 g q6–8h	2.25–3.375 g q6h	3.375 g q6h	2.25 g q8–12h
Rifampin[51, 54]	None	300–600 mg q12–24h[u]	Same	Same	Same
Ticarcillin-clavulanate[51, 53, 54]	3.1 g	2 g q6–8h	3.1 g q6–8h	3.1 g q6h	2 g q12h[w]
Tigecycline[51, 54]	100 mg	50 mg q12h	Same	Same	Same
Tobramycin[47, 51, 54, 68]	2–3 mg/kg	GNR infection: 1.5–2.5 mg/kg q24–48h (see gentamicin for redosing)			Same as gentamicin
TMP–SMX[51]	None	2.5–7.5 mg/kg (TMP) q12h[u]	Same	Same[x]	2.5–10 mg/kg (TMP) q24h or 5–20 mg/kg 3 times/wk after HD[u]

Table 4. Recommended Adult Antimicrobial Dosages by Type of Renal Replacement Therapy (continued)

Antimicrobial[a]	Loading Dose for CRRT	Maintenance Dosage for CRRT[b]			IHD[d]
		CVVH[c]	CVVHD	CVVHDF	
Vancomycin[42, 46, 51–54, 70, 74–78]	15–25 mg/kg	10–15 mg/kg q24–48h[x, z, aa]	10–15 mg/kg q24h[x, z, bb]	7.5–10 mg/kg q12h[x, z]	Load 15–25 mg/kg on day 1, then 5–10 mg/kg after HD[x, cc]
Voriconazole[42, 51–54]	400 mg p.o. q12h x 2	200.mg p.o. q12h[dd]	Same	Same	Same

CRRT = continuous renal replacement therapy; CVVH = continuous venovenous hemofiltration; CVVHD = continuous venovenous hemodialysis; CVVHDF = continuous venovenous hemodialfiltration; IHD = intermittent hemodialysis; I = induction dosing; M = maintenance dosing; CMV = cytomegalovirus; UTI = urinary tract infection; Cp = plasma drug concentration; MU = million units; GNR = gram-negative rods; TMP-SMX = trimethoprim-sulfamethoxazole; HD = hemodialysis; MIC = minimum inhibitory concentration; SLEDD = slow extended daily dialysis.

[a]Dosages are based on the provided references and/or the authors' opinion, especially when available references are limited or outdated; however, these recommendations should not replace clinical judgment.

[b]All CRRT dosages assume ultrafiltration and dialysis flow rates of 1–2 L/hr, intravenous administration, and minimal residual renal function. Dosing ranges are provided to accommodate for differences in ultrafiltration and dialysis flow rates, patient size, severity and site of infection, MIC of infecting pathogen(s), level of intrinsic renal function, and immune status, among other factors.

[c]Authors of one study[59] note that clearance of antimicrobials by CVVH depends on the CVVH filtration rate, primarily for antimicrobials with low protein binding and volume of distribution (see Appendix 1), and provide dosing recommendations for aztreonam, cefazolin, cefotaxime, ceftazidime, imipenem, and piperacillin for CVVH filtration rates of 1–4 L/hr.

[d]Hemodialysis assumes a thrice-weekly regimen and that the patient received the full dialysis session (use clinical judgment); administer after dialysis for q24–72h dosing; dosages assume critically ill patients with serious infections receiving standard IHD; extended daily dialysis may require larger doses than standard IHD.

[e]Use higher end of dosing range for viral meningoencephalitis and varicella-zoster virus infections (e.g., 10 mg/kg q12h for patients receiving CVVHDF).

[f]For severe GNR infections, target peak concentration = 15–30 mg/L; redose when Cp < 10 mg/L.

[g]Redose when pre-HD Cp < 10 mg/L; redose when post-HD Cp < 6–8 mg/L.

[h]Dosage of 1 g i.v. q8h results in similar steady-state Cp as 2 g i.v. q12h, but is more cost-effective.

[i]Administer after dialysis on dialysis days; as an alternative, use 1–2 g i.v. q48–72h after dialysis.

[j]Dosage of 2 g i.v. q8h may be needed for GNR pathogens with an MIC ≥ 4 mg/L.

[k]Authors of one study[62] recommend dosing ceftazidime 3 g i.v. as a continuous infusion over 24 hrs after 2-g loading dose to maintain Cp ≥ 4 x MIC for all susceptible pathogens in patients receiving CVVHDF.

[l]Drug clearance is highly dependent on the method of renal replacement, filter type, flow rate, site of infection, MIC of infecting pathogen(s), and other factors. For example, 2.5 mg/kg i.v. q24h may be required in patients receiving CVVHD with deep-seated infections and/or highly resistant GNR pathogens. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation, as well as drug concentrations in relation to target trough (if appropriate).

[m]Authors of one study[63] recommend dosing colistin up to 2.5 mg/kg i.v. q12h in patients receiving CVVHDF to achieve adequate Cp for highly resistant GNR pathogens.

[n]Authors of two studies[64, 65] note that dosing daptomycin 4–6 mg/kg i.v. q48h in patients receiving CRRT and SLEDD, respectively, may result in significant underdosing. Consider dosing 4–6 mg/kg i.v. q24h (or 8 mg/kg i.v. q48h) for critically ill patients receiving CRRT with deep-seated infections or those not responding to standard dosing. Therapeutic drug monitoring and/or more frequent serum creatine kinase levels may be warranted if dosing is increased.

[o]Authors of one study[66] recommend dosing fluconazole 800 mg q24h in patients receiving CVVHD if the dialysate flow rate is ≥ 2 L/hr and/or treating fungi with relative triazole resistance (e.g., *Candida glabrata*).

[p]Authors of one study[67] recommend dosing fluconazole 500–600 mg i.v. q12h in patients receiving CVVHDF.

[q]Need for gentamicin redosing is primarily dependent on the clinical indication and availability of gentamicin Cp, including reported values and timing (e.g., before vs after HD). Consider redosing gentamicin for pre-HD Cp < 1 mg/L (mild UTI and synergy), < 1.5–2 mg/L (moderate-to-severe UTI), and < 3–5 mg/L (severe GNR infection). Consider redosing gentamicin for post-HD Cp < 1 mg/L (UTI and synergy) and < 2 mg/L (severe GNR infection).

[r]Authors of one study[69] note imipenem dosage of 500 mg i.v. q8–12h appears to achieve adequate Cp needed to treat most GNR pathogens with MIC ≤ 2 mg/L in patients receiving CRRT; however, they recommend dosing imipenem 500 mg i.v. q6h to achieve adequate target attainment for pathogens with MIC = 4–8 mg/L or for deep-seated infections in patients receiving CRRT.

[s]Consider dosing meropenem 500 mg q8h or 1 g q12h in patients receiving CVVH, and 500 mg q6–8h or 1 g q8–12h in patients receiving CVVHD(F).

[t]Authors of one study[73] recommend dosing meropenem 750 mg i.v. q8h or 1500 mg i.v. q12h in patients receiving CVVHDF to optimize pharmacodynamic target attainment.

[u]Dosing regimen is highly dependent on clinical indication (e.g., trichomoniasis vs *Clostridium difficile* colitis for metronidazole, tuberculosis vs infective endocarditis for rifampin, and cystitis vs *Pneumocystis jiroveci* pneumonia for TMP-SMX).

[v]Mild-to-moderate infections: 0.5–1 MU i.v. q4–6h or 1–2 MU i.v. q8–12h; neurosyphilis, endocarditis, or serious infections: doses up to 2 MU i.v. q4–6h; administer after HD on days of dialysis, or supplement with 500,000 U after dialysis.

[w]A supplemental dose of 3.1 g is recommended after dialysis. As an alternative, consider dosing 2 g i.v. q8h without a supplemental dose for deep-seated infections.

[x]Dosages up to 10 mg/kg i.v. q12h may be required for critically ill patients with *P. jiroveci* pneumonia receiving CVVHDF.

[y]Recommended vancomycin doses and need for redosing should be individualized as they are dependent on a number of variables, including reported and targeted vancomycin concentrations (see text).

[z]Consider redosing vancomycin for Cp < 10–15 mg/L for CRRT.

[aa]Dosages of vancomycin typically range from 500–1500 mg i.v. q24–48h in patients receiving CVVH to achieve desired Cp; however, doses may need to be increased to achieve target vancomycin Cp of 15–20 mg/L (e.g., *Staphylococcus aureus* deep-seated infections).

[bb]Dosage of 7.5 mg/kg i.v. q12h may be required in patients receiving CVVHD to achieve desired Cp.

[cc]Consider redosing vancomycin for pre-HD Cp as follows: < 10 mg/L, give 1000 mg after HD; 10–25 mg/L, give 500–750 mg after HD; > 25 mg/L, hold vancomycin. Consider redosing vancomycin 500–1000 mg for post-HD Cp < 10–15mg/L; however, recommended dosages and need for redosing are dependent on reported and targeted vancomycin concentrations, use of high- vs low-flux filters, among other factors (see text).

[dd]Oral therapy preferred to prevent accumulation of cyclodextran vehicle; bioavailability > 95%.

receiving antimicrobials with volumes of distribution less than 0.7 L/kg and/or protein binding less than 80%, may require more aggressive dosing.[59] The IHD dosing guidelines assume intravenous administration and a thrice-weekly regimen over a 3–4-hour period, as typically used in the setting of CKD. The presence of distinctly different IHD approaches may require additional modifications to the doses suggested in Table 4. In general, dosage adjustments of antimicrobials are frequently necessary in patients receiving RRT.

Among patients receiving CVVHD, CVVHDF, and SLEDD, current dosing recommendations found in the literature run the risk of suboptimal antimicrobial target attainment (underdosing) due to accelerated drug removal, which may have detrimental effects in critically ill patients with life-threatening infections.[8, 24–26, 28, 29, 45, 59, 62–65, 69, 70, 73–82] In the setting of AKI managed with CVVHD, CVVHDF, or SLEDD, especially if the patient has considerable residual renal function (creatinine clearance > 20 ml/min), larger and/or more frequent dosing (depending on the pharmacodynamic properties of the antimicrobial agent and the clinical needs of the patient) may be necessary, relative to dosing regimens in the literature. In these situations, clinicians should consider using the higher end of a given dosing range in Table 4 for critically ill patients with serious infections. Although the body of clinical data available regarding antimicrobial dosing in patients receiving high-flux dialysis is considerable,[8, 30, 74–79] only limited data are available from patients receiving SLEDD.[65, 70] These data suggest that larger doses will often be needed for optimal target attainment and clinical outcomes, relative to standard IHD using conventional dialyzers.

Alterations in the antimicrobial regimen may be necessary over the course of therapy as the clinical status of the patient changes. The clinician needs to monitor changes in renal function, the patient's fluid status as an index of the drug's volume of distribution, the RRT prescription (e.g., ultrafiltration and dialysis flow rates) and the delivered dose, clinical response, and the presence of adverse events. Recovery of renal function as noted by increased urine output and falling serum creatinine and blood urea nitrogen levels, or reduction on the dependency of RRT, may suggest the need to increase the dose to maintain desired antimicrobial effects. More aggressive regimens may be necessary if the confirmed site of infection is deep seated, if the patient is immunocompromised, or if the infection has not responded to therapy as indicated by continued leukocytosis, temperatures spikes, hypotension, radiologic findings, and so forth. In contrast, a good clinical response, resolution of signs and symptoms of infection, and recovering immune function suggest that a change to oral therapy and/or a dose reduction may be feasible to minimize potential drug accumulation or adverse drug events. Current therapy may need to be narrowed or broadened based on culture and susceptibility results, or the dosages of individual agents can be adjusted to optimize target attainment based on the MIC of the pathogen. For select antimicrobial agents, periodic serum concentration monitoring may be warranted, especially for patients with deep-seated infections and/or those who are not responding to current therapy, are at high risk for drug toxicity, or have developed signs and symptoms consistent with drug toxicity. The pharmacometric methodologies to individualize therapy are discussed in detail in focused chapters and reference books.[8, 30, 79]

The rationale of therapeutic drug monitoring is to optimize efficacy while limiting toxicity. If possible, therapeutic drug monitoring should be considered to help guide antimicrobial dosing when there is a known, close relationship between serum drug concentration and efficacy and/or toxicity (e.g., vancomycin and aminoglycosides). Loading doses should be considered for vancomycin and aminoglycosides. Preferably, drug concentrations should be obtained before standard IHD or SLEDD if the type of dialyzer and approximate degree of drug removal can be estimated. For example, 30–50% of vancomycin is removed with most high-flux dialyzers.[8, 30] The respective antimicrobial maintenance dosage should be administered as soon as possible after dialysis to minimize the presence of low serum concentrations. Postdialysis concentrations of vancomycin (at 4–6 hrs) and gentamicin or tobramycin (at 1–2 hrs) can be used to avoid the confounding effect of drug redistribution after dialysis. Earlier serum concentrations that take into account some redistribution may limit potential periods of reduced pharmacodynamic activity.

Compared with IHD, SLEDD uses lower blood flow rates for a prolonged treatment period (8–12 hrs vs 3–4 hrs). Thus, rebound in serum concentrations are usually more pronounced after IHD than after SLEDD.[47] Serum concentrations obtained within the first 24 hours of the

initial dose may not accurately reflect the patient's subsequent pharmacokinetic parameters since, in the post–fluid resuscitation period, the volume of distribution will be lower and elimination rate faster as the drug may continue to distribute into tissue. If Gram's stain or culture results suggest that the antibiotic will be continued for more than 24–48 hours or if the patient's clinical status deteriorates, an assessment of serum drug concentrations is warranted. Peak concentrations of aminoglycosides should be delayed for 2 hours after the dose is administered in patients receiving RRT because distribution is apparently delayed in this setting.[47] Finally, random levels may be taken after 24 hours of therapy and as serum drug concentrations approach steady state (e.g., after the third dose) in patients receiving CRRT.

Since vancomycin and aminoglycosides are so commonly used in critically ill patients, a focused discussion on the initiation and monitoring of therapy for each is given here. Patients receiving IHD who begin to receive vancomycin should receive a loading dose of 15–25 mg/kg on the first day of therapy, preferably after dialysis (unless delays in dialysis are anticipated). The second dose of vancomycin 5–10 mg/kg should be given after the next dialysis session and a predialysis concentration should be measured before the third dialysis session. The dose to be given after the third dialysis treatment should be based on the predialysis vancomycin concentration (Table 4). Once target concentrations have been achieved consistently, a standard postdialysis regimen may be started. Patients receiving CRRT who begin taking vancomycin should receive a 15–25-mg/kg loading dose followed by a maintenance dose of 10–15 mg/kg intravenously every 24–48 hours as needed to maintain vancomycin concentrations of 10–15 mg/L or greater. Target vancomycin concentrations, need for redosing, and scheduled dosing regimens should consider factors such as the site and severity of infection (e.g., indication), type of dialysis and efficiency of drug removal, level of residual renal function and immune status, patient size and fluid status, and MIC of the infecting pathogen. For example, patients with deep-seated *Staphylococcus* infections receiving CVVHDF may initially require vancomycin 7.5–15 mg/kg intravenously every 12 hours to maintain vancomycin target concentrations of 15–20 mg/L.

Typically, patients receiving IHD who begin gentamicin or tobramycin for nonsynergy treatment should receive a loading dose of 2–3 mg/kg. Recent data suggest for systemic gram-negative rod infections, gentamicin or tobramycin should be redosed with 1–2 mg/kg after dialysis if the predialysis concentration is around 3–5 mg/L, to optimize target attainment and clinical outcomes.[33] If IHD is started shortly after the initial loading dose, where serum drug concentrations most closely represent peak concentrations, the lower end of the range for the second dose may be considered after dialysis. If IHD is delayed for more than a day after the initial loading dose, the predialysis serum concentration may have declined to a greater extent and the higher end of the range for the second dose may be considered after dialysis. Although gentamicin or tobramycin dosing recommendations in CRRT vary widely in the literature, the prevailing consensus is that a loading dose of 2–3 mg/kg should be given to all patients. Maintenance doses of 1–2.5 mg/kg (depending on the indication, estimated drug removal, and other factors) should be administered every 24–48 hours when serum concentrations have declined to 3 mg/L or less (systemic gram-negative rod infections) or less than 1–2 mg/L (gram-negative rod cystitis) or less than 1 mg/L (synergy against gram-positive cocci with β-lactams or vancomycin; Table 4). Once target concentrations have been achieved and a consistent dialysis regimen has been established, a standard dosing regimen may be started. Because accumulation can occur over the duration of the therapy, periodic serum concentrations (e.g., every 3–5 days) should be considered.

The time of dose administration may vary depending on patient availability and whether they are receiving a continuous or intermittent form of RRT. During CRRT, the clinician should consider if there has been any interruption in dialysis secondary to hemodynamic instability, or loss of the circuit, and make dosing modifications as appropriate. With intermittent procedures, dosing typically will occur at the end of dialysis; however, administering antimicrobial agents during the last hour of IHD has been proposed to allow removal of fluids associated with the infusion, ease of intravenous access, and elimination of unnecessary delays in therapy. Drug administration during IHD sessions may require the administration of higher doses to account for additional drug loss, given that plasma concentrations will be higher since the agent has not had time to distribute into the

tissues. It is also important to avoid excessive delays in therapy after IHD while waiting for a serum drug concentration to be reported, thus predialysis concentrations and serum creatinine concentration should be obtained if clinically appropriate to guide therapeutic decisions. Overall, due to the evolving process of critical illness, whether in patients with AKI or in those with CKD, prospective adaptation of these initial dosing recommendations to meet the needs of an individual patient will often rely on prospectively collected clinical and laboratory data.

Conclusion

Appropriate antimicrobial therapy selection and individualized dosing will contribute to optimal clinical outcomes, while decreasing the risk for toxicity, in the critically ill patient. Unfortunately, many dosing regimens found in the literature for critically ill patients receiving RRT suggest fixed doses and do not account for the multiple variables that may influence the antimicrobial dosing regimen. Dosing recommendations in the literature tend to be too low, especially for patients receiving CVVHD, CVVHDF, and SLEDD and/or those who have deep-seated infections with more drug-resistant pathogens. Finally, technologic advances in RRT continue to outpace the rate at which the new devices' effects on drug clearance can be assessed, and thus published data describing alterations in drug elimination are usually very conservative estimates. Optimal dosing recommendations are needed, but clinicians should always consider the source of the information and type of dialysis used, including technical aspects of the dialysis procedure. This review provides guiding principles along with specific insights and considerations for developing individualized antimicrobial dosing regimens in critically ill patients receiving CRRT, SLEDD, or standard IHD. Only when the multiple patient and RRT variables that can influence dosage requirements are assessed prospectively and are used along with the guiding principles to optimize antimicrobial therapy in critically ill patients will survival improve and the occurrence of adverse events be minimized.

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Appendix 1. Pharmacokinetic and Pharmacodynamic Parameters of Intravenous Antimicrobial Agents[8, 42, 43, 51–54]

Antimicrobial	Molecular Weight (daltons)	Fraction Protein Bound (%)[a]	Volume of Distribution (L/kg)[a]	Fraction Excreted Unchanged in Urine (%)	Half-Life, Normal Renal Function (hrs)	Half-Life, ESRD (hrs)	Primary Route of Elimination
Acyclovir	225	15–30	0.6–0.7	60–80	2–4	20	Renal
Amikacin	586	4–11	2.5–4	90–98	2	30–80	Renal
Amphotericin B deoxycholate	924	90	4–5	2–10	180–360 (terminal)		Tissue
Amphotericin B liposomal	924	90	131	2–10	180–360 (terminal)		Tissue
Ampicillin-sulbactam	349 233	17–28 38	0.17–0.29 0.36	70–90 —	1.2 —	10–20 —	Renal —
Azithromycin	749	7–51	33	11–14	68	NA	Hepatic
Aztreonam	435	56–60	0.2–0.35	60–75	1.7–2.9	6–8	Renal
Caspofungin	1213	97	0.11	1.4	9–11	NA	Hepatic
Cefazolin	455	85	0.13–0.22	74–86	1.5–2.5	40–70	Renal
Cefepime	480	16–20	0.25–0.3	85	1.7–2.3	13–19	Renal
Cefotaxime	455	27–38	0.15–0.55	30–60	0.8–1.4	2.6–8.2	Mixed
Ceftazidime	547	17–21	0.23–0.3	70–90	1.6–1.9	11–24	Renal
Ceftriaxone	555	85–95	0.12–0.18	33–44	5.8–8.8	12–20	Hepatic
Ciprofloxacin	331	20–40	1.8–2.7	40–60	4.1	8.6	Mixed
Clindamycin	425	60–95	0.6–1.2	5–28	1.5–4	1.9–6.1	Hepatic
Colistin	1155	55	0.2–0.5	60–75	2.1–4.2	7.5–20	Renal
Daptomycin	1620	92	0.10–0.13	78	8–9	30	Renal
Doxycycline	444	80–93	0.75	35–45	15–20	18–25	Nonrenal
Fluconazole	306	11–12	0.65	60–80	20–40	100	Renal
Ganciclovir	256	1–2	0.47–0.74	80–95	1.7–5.8	9–30	Renal
Gentamicin	478	0–30	0.25–0.4	70–100	1.5–4	20–60	Renal
Imipenem-cilastatin	317 380	13–21 —	0.17–0.3 —	50–70 70–75	1 —	3–4 —	Renal —
Itraconazole	706	> 99	10	< 1	16–25	25	Hepatic
Levofloxacin	361	24–38	1.1–1.5	67–87	6–8	> 20	Renal
Linezolid	338	31	0.5–0.8	30	4.8–5.4	7–8	Hepatic
Meropenem	384	2–9	0.25–0.35	62–83	1	7–8	Renal
Metronidazole	171	20	0.3–0.8	20	6–14	7–21	Hepatic
Micafungin	1292	> 99	0.28–0.5	< 15	11–21	NA	Hepatic
Moxifloxacin	401	30–50	1.7–3.5	15–21	12–15	12–15	Hepatic
Nafcillin	414	70–90	0.4	20–38	0.5–1	2	Hepatic
Penicillin G	334	50–65	0.3–0.5	60–85	0.5–1	6–10	Renal
Piperacillin-tazobactam	518 300	16–30 20–30	0.18–0.33 —	55–80 65–80	1 —	3.5–5 —	Mixed —
Rifampin	823	60–90	0.9	6–15	2–5	5–11	Hepatic
Ticarcillin-clavulanate	384 199	45–65 20–30	0.14–0.22 —	60–77 35–45	1.2–2 —	9–17 —	Mixed —
Tigecycline	586	71–89	7–9	22	27–43	NA	Hepatic
Tobramycin	467	< 30	0.25–0.4	60–85	1.5–3	30–60	Renal
Trimethoprim-sulfamethoxazole	290 253	44 70	1–2.1 0.36	50–80 10–30	8–14 9–15	> 20 —	Renal Hepatic
Vancomycin	1485	20–55	0.7	75–90	4–11	120–200	Renal
Voriconazole	349	58	4.6	< 2	12	13.7	Hepatic

ESRD = end-stage renal disease (creatinine clearance < 10 ml/min); CdK = concentration-dependent killing; TdK = time-dependent killing; C_{max} = maximum (peak) plasma concentration; C_{min} = minimum (trough) plasma concentration; NA = not available; AUC = area under the plasma concentration–time curve; MIC = minimum inhibitory concentration.

[a]Fraction protein bound and volume of distribution values are for healthy subjects; often fraction protein bound and volume of distribution values will be lower and higher, respectively, for patients with renal disease.

[b]For CdK antimicrobials, it is preferred to maximize concentrations (peak:MIC), whereas for TdK antimicrobials it is preferred to maximize the duration of exposure (time > MIC).

[c]Denotes the highest MIC in the susceptible range (MIC breakpoint) for applicable pathogens; target trough levels may vary based on the targeted pathogen (e.g., MIC breakpoints for piperacillin and tazobactam, respectively, are 64 and 4 mg/L for *Pseudomonas aeruginosa*, 16 and 4 mg/L for Enterobacteriaceae, and 8 and 4 mg/L for *Staphylococcus aureus*).

[d]C_{max}:MIC and AUC:MIC represent target ratios (e.g., C_{max} and AUC relative to the MIC of the infecting pathogen).

[e]Linezolid, macrolides, clindamycin, tetracyclines, and vancomycin also show activity related to the achieved AUC:MIC (area under the inhibitory curve [AUIC]).

[f]Voriconzole has been shown to be fungicidal against highly susceptible *Candida* species, and echinocandins are generally considered to be fungistatic against Aspergillus species.

[g]Approximately 30% of the drug is removed by dialysis during a standard 3–4-hour hemodialysis session.

[h]Range provided to accommodate for *Candida* species with an MIC in the dose-dependent, susceptible range (e.g., *Candida glabrata*).

Appendix 1. (continued)

Potential Removal by Dialysis	Pharmacodynamic Properties (CdK or TdK)[b]	Proposed Optimal Pharmacodynamic Target (mg/L)[c]
Yes	TdK	NA
Yes	CdK	C_{max}:MIC ≥ 10[d]
No	CdK	C_{max}:MIC ≥ 10[d]
No	CdK	C_{max}:MIC ≥ 10[d]
Yes	TdK	C_{min} ≥ 8
—	—	—
No	TdK[e]	C_{min} ≥ 2
Yes	TdK	C_{min} ≥ 8
No	CdK[f]	NA
Yes	TdK	C_{min} ≥ 8
Yes	TdK	C_{min} ≥ 8
Yes	TdK	C_{min} ≥ 8
Yes	TdK	C_{min} ≥ 8
Yes[g]	TdK	C_{min} ≥ 8
Yes	CdK	AUC:MIC > 100[d]
No	TdK[e]	C_{min} ≥ 0.5
Minimal	CdK	C_{min} ≥ 4
Yes	CdK	C_{min} ≥ 4
No	TdK[e]	C_{min} ≥ 4
Yes	TdK	C_{min} ≥ 8–16[h]
Yes	TdK	NA
Yes	CdK	C_{max}:MIC ≥ 10[d]
Yes	TdK	C_{min} ≥ 4
No	TdK	C_{min} ≥ 0.25–0.5[h]
Yes	CdK	AUC:MIC > 100[d]
Yes[g]	TdK[e]	C_{min} ≥ 4
Yes	TdK	C_{min} ≥ 4
Yes[g]	CdK	C_{min} ≥ 4
No	CdK[f]	NA
Minimal	CdK	AUC:MIC > 100[d]
No	TdK	C_{min} ≥ 1
Yes	TdK	C_{min} ≥ 1–8
Yes	TdK	C_{min} ≥ 16
—	—	C_{min} ≥ 4
No	CdK	C_{min} ≥ 1
Yes	TdK	C_{min} ≥ 16
—	—	—
No	TdK	C_{min} ≥ 2
Yes	CdK	C_{max}:MIC ≥ 10[d]
Yes	TdK	C_{min} ≥ 2
—	—	C_{min} ≥ 38
Yes	TdK[e]	C_{min} ≥ 10–20
No	TdK[f]	C_{min} ≥ 0.5–2