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Antibiotic Dosing for Critically Ill Adult Patients Receiving Intermittent Hemodialysis, Prolonged Intermittent Renal Replacement Therapy, and Continuous Renal Replacement Therapy: An Update

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Abstract

Objective: To summarize current antibiotic dosing recommendations in critically ill patients receiving intermittent hemodialysis (IHD), prolonged intermittent renal replacement therapy (PIRRT), and continuous renal replacement therapy (CRRT), including considerations for individualizing therapy. **Data Sources:** A literature search of PubMed from January 2008 to May 2019 was performed to identify English-language literature in which dosing recommendations were proposed for antibiotics commonly used in critically ill patients receiving IHD, PIRRT, or CRRT. **Study Selection and Data Extraction:** All pertinent reviews, selected studies, and references were evaluated to ensure appropriateness for inclusion. **Data Synthesis:** Updated empirical dosing considerations are proposed for antibiotics in critically ill patients receiving IHD, PIRRT, and CRRT with recommendations for individualizing therapy. **Relevance to Patient Care and Clinical Practice:** This review defines principles for assessing renal function, identifies RRT system properties affecting drug clearance and drug properties affecting clearance during RRT, outlines pharmacokinetic and pharmacodynamic dosing considerations, reviews pertinent updates in the literature, develops updated empirical dosing recommendations, and highlights important factors for individualizing therapy in critically ill patients. **Conclusions:** Appropriate antimicrobial selection and dosing are vital to improve clinical outcomes. Dosing recommendations should be applied cautiously with efforts to consider local epidemiology and resistance patterns, antibiotic dosing and infusion strategies, renal replacement modalities, patient-specific considerations, severity of illness, residual renal function, comorbidities, and patient response to therapy. Recommendations provided herein are intended to serve as a guide in developing and revising therapy plans individualized to meet a patient's needs.

Keywords

antibiotic, renal replacement therapy, hemodialysis, hemodiafiltration, hemofiltration, pharmacokinetics, critical illness

Introduction

Severe infections combined with acute and/or chronic kidney disease (CKD) are common medical problems associated with high mortality among critically ill patients.[1,2] Optimizing antimicrobial therapy in the dynamic critically ill patient can be challenging because of unpredictable pathophysiological changes that can alter the immune system as well as the pharmacokinetics (PK) and pharmacodynamics (PD) of antimicrobials. Concomitant renal replacement therapy (RRT) adds to the complexity of care for these patients, and additional dosing considerations are needed to ensure adequate patient outcomes.

Data on drug clearance to guide antimicrobial dosing in the critically ill patient and in severe renal impairment are limited and becoming outdated with the advancing technology for RRT modalities and efficiency. Traditionally, the dosing of antimicrobial therapy in dialysis-dependent patients has

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not been based on any formal analysis in this population and, where a pharmacokinetic analysis is done, was extrapolated from single-dose observations in non–critically ill patients with stable CKD receiving scheduled intermittent hemodialysis (IHD).[3] However, this approach is likely to result in suboptimal regimens in critically ill patients with altered PK characteristics, presence of acute and chronic renal failure, residual renal function, and use of RRT approaches that can vary daily.[4] To optimize antibiotic exposure and maximize effectiveness, it is important to individualize the antimicrobial regimen to the patient and the method of RRT utilized. This is challenging for clinicians because it requires a good understanding of the different RRT modalities and their effects on drug clearance as well as the effects of critical illness on the antimicrobial PK/PD.[5-8] Furthermore, lack of standardization in continuous renal replacement therapy (CRRT), including fluid removal, the hemofilter characteristics, and effluent rates, have led to variabilities in published recommendations, which make it challenging to determine the optimal management approach.[9-12]

In 2009, Heintz et al[13] published a review of antimicrobial dosing in RRT with suggested dosing ranges as a starting point, but to be revised accordingly to meet the needs of the patient. However, expanding literature along with advancements in RRT and our understanding of antimicrobial PK/PD necessitates a reevaluation of this essential topic. This review will provide an updated summary of basic principles of RRT, antimicrobial PK/PD concepts, and augments for the 2009 review with dosing recommendations for commonly utilized antimicrobials in critically ill adult patients receiving IHD, CRRT, or prolonged intermittent renal replacement therapy (PIRRT), also referred to in the literature as sustained low-efficiency daily dialysis and extended daily dialysis.

Data Sources

A PubMed search was conducted to identify English-language literature in which dosing recommendations were proposed for antibiotics commonly used in critically ill patients receiving IHD, PIRRT, or CRRT between January 2008 and May 2019. The initial data retrieval occurred in October 2017, with incremental updates in September 2018 and May 2019. Search terms included *antibiotic, dialysis, hemofiltration, hemodiafiltration, continuous renal replacement therapy, low-efficiency dialysis, extended daily dialysis, prolonged intermittent renal replacement therapy, renal failure*, and *critically ill*. All pertinent reviews, selected studies, and references were evaluated to ensure appropriateness for inclusion. For hemodialysis, publications with cefazolin, vancomycin, and daptomycin PK/PD data and dosing recommendations were included. For PIRRT, limited data exist, and all evaluable antibiotics were included that published PK/PD data to support a dosing recommendation. Available studies were evaluated, and the following were deemed pertinent for inclusion: ampicillin/sulbactam, colistin and polymyxin B, daptomycin, ertapenem, gentamicin, levofloxacin, linezolid, meropenem, moxifloxacin, piperacillin-tazobactam, sulfamethoxazole-trimethoprim, and vancomycin. For CRRT, studies were included that published PK/PD data and dosing recommendations for cefepime, daptomycin, meropenem, piperacillin-tazobactam, and vancomycin in continuous venovenous hemodialysis (CVVHD), continuous venovenous hemofiltration (CVVH), or continuous venovenous hemodiafiltration (CVVHDF). The literature evaluation was performed by a single study team member for IHD, PIRRT, and CRRT, respectively. All study members interpreted the studies during the synthesis of this article. Drugs without sufficient literature to support a consensus dosing recommendation were excluded from the review.

Assessing Renal Function

Assessment of drug elimination and potential alterations in the volume of distribution (V_d) are critical steps in ensuring that the prescribed antibiotic therapies are both safe and effective. Critical illness is uniquely challenging because hemodynamic changes such as decreased renal perfusion can significantly alter the patient's renal function and antibiotic clearance. Glomerular filtration rate (GFR) and creatinine clearance estimation formulas such as the Modified Diet in Renal Disease, CKD Epidemiology Collaboration, and the Cockcroft-Gault equations inherently assume a stable serum creatinine and should not be used in patients with unstable renal function or on RRT.

Acute kidney injury (AKI) is identified either by an abrupt rise in serum creatinine or a decrease in urine output and is further classified into stages 1, 2, or 3.[14] Stage 3 is the most severe and defined as a serum creatinine increase by 3 times baseline, an absolute increase to $\geq$4.0 mg/dL, initiation of RRT, patients $<$18 years old with a GFR $<$35 mL/min/1.73 m^2, urine output $<$0.3 mL/kg/h for $\geq$24 hours, or anuria for $\geq$12 hours. In AKI, antibiotic elimination has been shown to be more rapid compared with CKD and may contribute to underdosed regimens if data derived from CKD populations is directly applied.[15,16] Although several formulas have been proposed to estimate renal function in patients with AKI, they have not been widely adopted in clinical practice because they lack validation and extrapolation for drug dosing adjustments.[17,18] In the early stages of AKI, slow accumulation of serum creatinine leads to an overestimation of actual GFR; thus, renal function can be expected to be significantly lower than estimated.[19] Measured creatinine clearance using 4-hour urine collection can be utilized to detect acute changes in renal function but requires a known serum creatinine at

baseline and urine production.[20] Furthermore, this process is cumbersome, error prone, and typically not performed in routine clinical practice. Patients with stage 3 AKI may require RRT either in the form of CRRT, IHD, or PIRRT. Specific RRT selection, dialysis system in use, and delivery vary substantially between institutions. Literature with a focus on AKI and antibiotic management is also very limited, and the dynamic nature of critical illness creates additional challenges in accurately describing evidence-based optimal management approaches.[4] Because varying RRT methods profoundly affect clearance of antibiotics, the lack of a standardized approach has led to inconsistencies among clinicians on how to appropriately dose antibiotics in this patient population.[11,21]

Management of patients with AKI and dosing adjustments should include consideration of 3 phases of AKI. Phase 1 involves declining renal function and, thus, lowering the dose according to the magnitude of failure. Urine output may help in trending renal function patterns. Second is the plateau phase where there may be minimal changes in renal function, but dosing adjustments should be considered based on the level of renal impairment, any approach of RRT, and presence of any residual renal function. Phase 3 involves recovery of renal function, observed with backing off on RRT and need to reasses antimicrobial dosing once again. We caution that post-AKI diuresis may lead to continued confusion and improper assessment of renal function during the recovery phase because there may be an initial overestimation of renal function return.

RRT System Properties Affecting Drug Clearance

Multiple RRTs are available in the intensive care setting, including IHD, PIRRT, and several variants of CRRT, all of which have varied impacts on systemic drug clearance.[22] The 2 main mechanisms of drug and solute removal are diffusion and convection, whereas ultrafiltration is utilized for fluid removal. Diffusion is the movement of solutes across the hemofilter membrane down the concentration gradient and is the main mechanism of removal for small molecules. Convection is the movement of solutes across the hemofilter membrane along with water as pressure is applied (known as "solvent drag") and allows for removal of larger solutes. Conventional IHD, CVVHD, and PIRRT primarily utilize diffusion, whereas CVVH primarily utilizes convection. The CVVHDF variant utilizes both mechanisms of removal, often resulting in greater drug removal than by convection or diffusion alone.

Other differences among RRT modalities include the hemofilter and dialyzer material composition and surface area, blood flow rate, dialysate flow rate, ultrafiltration rate (UFR), and duration of the procedure.[13,22,23] In general, higher dialysate and ultrafiltrate rates, longer durations of dialysis, and higher permeability hemofilters may drive greater drug removal. Combining the mechanism of drug clearance by dialysis with the dialysis duration, as a categorical rule, the efficiency of drug removal is as follows: CVVHDF $>$ CVVHD $>$ CVVH $>$ PIRRT $\geq$ IHD. However, other variables such as blood flow, high effluent rates, or newer generation filters influencing drug removal may drive a different order. The terms *high efficiency* and *high flux* describe dialysis membranes with large surface areas and high UFRs, respectively, and may result in greater drug removal of larger-molecular-weight drugs (eg, vancomycin).[24-26] As a patient's clinical condition changes, adjustments in the RRT prescription may require reevaluation of the antibiotic dosing strategy.[27] The potential for extended RRT interruption resulting from vascular access complications, surgery, hypotension, circuit failure (eg, thrombosed), or transport to procedures can exist. Hence, it is important to continuously assess the patient and make dosing modifications when appropriate.

Drug Properties Affecting Clearance During RRT

As with the variable technical aspects of the dialysis procedure described above, the extent to which a drug is removed by dialysis is influenced by several physicochemical characteristics of the agent. These properties include molecular size, protein binding, V_d, and organ clearance.[22,28,29] In general, drugs with a larger molecular weight, high protein binding ($>$80%), large V_d ($>$1 L/kg), or nonrenal clearance are least likely to be affected by RRT.[27] The sieving coefficient, 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, may be useful in predicting the likelihood of drug removal by dialysis. However, collection of the effluent may be difficult because many circuits are set up for direct discard. Finally, a rebound in plasma drug concentrations may occur after cessation of dialysis as the drug redistributes from the peripheral compartment (tissues) to the central compartment (vascular spaces), which is most pronounced in traditional IHD.[15] This can be several hours in some cases, limiting the accuracy of postdialysis levels. In addition, waiting for postdialysis results to be reported and acted on, and subsequent administration can create prolong periods where low concentrations may exist and reduce antimicrobial effects.

In addition to drug-specific factors, physiological changes and interventions commonly occurring in critical illness can affect PK characteristics of an antimicrobial agent. For example, decreased gastric motility and an increased gastric pH can affect absorption of orally administered drugs. Administration of large volumes of fluids through resuscitation, medications, blood products, and/or nutrition may increase the V_d of hydrophilic drugs. The

presence of hypoalbuminemia results in a higher fraction of unbound drug, which leads to greater distribution into the interstitial space and ultimately increased clearance by the liver, kidneys, and/or RRT. Residual renal function, concomitant hepatic failure, and accumulation of fluid in the interstitial space (third-spacing) should also be taken into consideration. Overall, many of the aforementioned changes lead to decreased therapeutic concentrations of antimicrobials, with rising concerns that many critically ill patients are being underdosed,[10,12,30] especially those undergoing CRRT. Table 1 contains considerations for individualizing antimicrobial therapy in patients requiring RRT.

Pharmacokinetic and Pharmacodynamic Dosing Considerations

Published PK/PD analyses involving antibiotics in highly variable critically ill populations increasingly support an emphasis on individualized patient therapy plans for the treatment of infectious diseases. Available data may have been derived in single centers, specific populations, and in small numbers. The diversity of the critically ill, including drug, RRT circuit, infection, and patient factors, creates notable challenges when extrapolating published literature that precludes implementation of a one-dose-fits-all approach commonly found in tertiary references. Clinician fluency in advanced PK/PD concepts and understanding management of comorbid conditions, including RRT is paramount to individualize therapy. Several publications thoroughly review and highlight the PK alterations commonly affecting antibiotic dosing in critically ill patients.[5-8] One consideration coming into greater focus in recent years is the impact of PD optimization by targeting pathogen-specific exposure thresholds necessary for organism eradication. Separately, expanding approaches to RRT include new-generation filters creating a time lag in understanding how novel filters affect the PK of antimicrobials.

Pharmacodynamic indices for antimicrobials include the time the free drug concentration remains above the minimum inhibitory concentration (MIC) during the dosing interval ($fT > MIC$), the ratio of the maximum free drug concentration to the MIC of the pathogen (fC_{max}:MIC), and the area under the concentration-time curve relative to the pathogen MIC ($fAUC_{0-24}$:MIC).[8,13] Published PD targets[11] are derived from antibiotic exposure models under conditions of normal renal function because validated models are lacking in the setting of renal failure and should be used cautiously. Many studies included in this review evaluate antibiotic PK/PD by performing a probability of target attainment (PTA) analysis. A PTA is a useful tool to predict how likely an antimicrobial dosing regimen would achieve pharmacodynamic targets based on several assumptions. Until sufficient clinical outcomes data are available to support optimal dosing recommendations in this population, analytical methods such as this will continue to be utilized. Although there is an increasing number of studies on antimicrobial dosing in critically ill patients receiving RRT, most utilize Monte Carlo simulation to determine the PTA and have not been validated in human subjects.[10,31-34] Additionally, Monte Carlo simulations require large study numbers to be valid. Some experts suggest that no initial adjustments for renal dysfunction occur for at least 24 hours, followed by a clinical assessment of the patient for dose reductions to avoid underdosing antibiotics in severe infections (exceptions include vancomycin and aminoglycosides).[4] Recovery of AKI or changes in the dialysis approach can occur on a daily or even hourly basis and should be incorporated into the patient's management plan.

Drug Dosing Updates for IHD, PIRRT, and CRRT

Intermittent Hemodialysis

Important considerations for antibiotic dosing in IHD include use of intradialytic dosing and/or the need for more aggressive dosing during the 72-hour postdialysis interval to account for nonrenal and residual renal clearance.[35-37] Updates in antimicrobial dosing in IHD have focused on agents targeting *Staphylococcus aureus* and other Gram-positive pathogens, including cefazolin, vancomycin, and daptomycin.

Dosing recommendations often assume a stable, thrice-weekly dialysis schedule; however, supplemental doses may be necessary for hospitalized patients who receive additional dialysis because of critical illness. Cefazolin dosed at 2 to 3 g postdialysis on days of IHD is associated with favorable clinical outcomes in methicillin-susceptible *S aureus* infections.[37-40] Earlier data suggest that a regimen of 2-g postdialysis would achieve adequate concentrations in high-flux IHD and is logistically simpler than a regimen including 3-g doses.[41] Daptomycin dosing ranges from 6 to 9 mg/kg, with considerations based on the interval between dialysis sessions and whether doses are given intradialytically. The dose should be increased by 50% during the 72-hour postdialysis interval even if the dose was given intradialytically (eg, increase from 6 to 9 mg/kg).[36,42-45] The dose should increase an additional 15% to 20% if dosed intradialytically for the 48-hour postdialysis intervals (eg, increase from 420 to 500 mg for a 70-kg patient targeting a 6-mg/kg dose).[36,42-45] Vancomycin loading doses of 15 to 25 mg/kg (actual dry body weight) are suggested to establish sufficient levels above the MIC to maximize exposure.[46,47] One previously published algorithm[48] utilizes a postdialysis dosing approach guided by predialysis vancomycin serum concentrations.[49] If the loading dose is given prior to or early during the IHD session, a

Table 1. Considerations for Individualizing Therapy.

Factor	Consideration	Comments
Changes in the RRT prescription	Method of RRT, residual renal function	• Method of renal replacement therapy and changes between methods affect drug clearance • Clinicians should be aware of daily or even hourly changes. Consider adding into the management plan provisions on modifying the regimen if CRRT is stopped • Patients with residual renal function or preserved diuresis require higher antimicrobial doses than anuric patients on RRT
Comorbid conditions	PK alterations, risk of toxicity	• Conditions such as ascites, large surface area burns, cystic fibrosis, pregnancy, and vascular disease may lead to inadequately low concentrations at the site of infection • Conditions such as hepatic and renal failure may lead to decreased clearance of antimicrobials resulting in toxic levels of antimicrobials in the body • Consider drug-specific toxicities in combination with comorbid conditions (eg, ototoxicity) • Consider drug-specific formulations with comorbid conditions (eg, salt content in heart failure) • Consider drug-drug interactions and additive effects (eg, lowering seizure threshold)
Filter used	High-flux, low-flux, surface area	• Antimicrobial clearance increases in high-flux filters, especially for primarily diffusion-dependent modalities (CVVHD, IHD, PIRRT) • Dosing recommendations should be thoughtful of the type of filters used in patients at your institution
Immune status	Neutropenia, immunocompromising medications	• Consider use of agents that are bactericidal, in particular β-lactam antibiotics • Administer higher doses for neutropenic patients • Evaluate the type (eg, cell line depletion) and degree of immunosuppression by medications
Infection site	Drug penetration to site of infection	• Consider higher doses for bone-joint, heart, lower-respiratory tract, and central nervous system infections • Consider if urine output is adequate based on antimicrobial renal elimination for urinary tract infections • Source control, including debridement and drainage, is often vital for severe infections (eg, empyema, large abscesses, necrotizing infections) • Blood flow to the region
Initial dosing	Timing of dose reductions	• Use full dose for initial 24 hours (except vancomycin or aminoglycosides) in critically ill, high-risk populations or those with severe infections • Caution in patients with low seizure thresholds and history of seizure activity for selected agents • Consider de-escalating the dosing regimen if infection has improved but renal function has not improved
Maintenance dosing timing	Predialytic vs intradialytic vs postdialytic dosing, circuit downtime	• Most antimicrobials should be administered after dialysis on days of dialysis • Aminoglycosides may be dosed before dialysis to optimize concentration-dependent activity and reduce toxicity as long as dialysis occurs frequently (ie, daily) • More aggressive dosing and/or supplemental dosing may be necessary for predialytic and intradialytic dosing strategies • Predialysis levels for vancomycin are preferred to facilitate timely maintenance dose administration after dialysis is completed • Prolonged circuit downtime may require holding therapy or lowering doses

(continued)

Table 1. (continued)

Factor	Consideration	Comments
Presence of multisystem organ failure	Antimicrobial elimination	• Assess the rate and change in degree of hepatic, renal (including evidence of intrinsic/residual renal function), biliary, and other elimination for the antimicrobial and estimate the degree of organ failure. In AKI, consider if the insult, maintenance, or recovery period is present • Antimicrobials with mixed renal clearance will shunt elimination toward nonrenal methods in the setting of renal failure • Evaluate the direction of change to allow a more prospective or real-time management approach
Role of pharmacist		• Clinical pharmacists can assist in selection of antibiotics based on patient dialysis schedule, appropriate drug dosing, and monitoring to conserve dialysis access and facilitate early hospital discharge[101]
RRT duration	Duration of circuit use	• Drug removal efficiency decreases over time (days) for RRT circuits unless circuit components are replaced
RRT flow	Blood flow rate, dialysate flow rate	• Higher blood flow rates lead to increased antimicrobial removal by RRT • One-size-fits-all dosing is inadequate to optimally dose antimicrobials in patients with high flow rates • IV access may limit the ability to reach goals
Severity of the infection	Loading doses, PK alterations in sepsis and septic shock	• Strongly consider loading doses, especially for β-lactam antibiotics and vancomycin • Aggressive fluid resuscitation in sepsis and hyperdynamic states (eg, augmented renal clearance) associated with early phases of sepsis may warrant more aggressive antimicrobial dosing • Consider delaying dose adjustments for 24 hours in RRT
Susceptibility of other antibiotics	Drug of choice, role of combination therapy	• Determine the drug of choice based on identification and culture/susceptibility reports • Consider susceptible agents with robust data to support dosing recommendations in RRT • Dosing in RRT should incorporate PK/PD goals specific to combination and synergy therapy
Type of renal failure: acute vs CKD	Drug elimination	• Drug elimination may be substantially faster in AKI than CKD
Weight	Obesity, fluid overload	• Consider higher doses and/or more frequent dosing intervals for morbidly obese patients, in particular for highly lipophilic antimicrobials

Abbreviations: AKI, acute kidney disease; CKD, chronic kidney disease; CRRT, continuous renal replacement therapy; CVVHD, continuous venovenous hemodialysis; IHD, intermittent hemodialysis; IV, intravenous; PIRRT, prolonged intermittent renal replacement therapy; PK, pharmacokinetic; PK/PD, pharmacokinetic and pharmacodynamic; RRT, renal replacement therapy.

supplemental dose may be necessary to ensure adequate target attainment. General IHD dosing principles and recommendations for other selected agents in the setting of IHD can be found elsewhere.[13]

Prolonged Intermittent Renal Replacement Therapy

PIRRT is an RRT modality that utilizes conventional dialysis machines but lower dialysate and blood flow rates running over longer time periods when compared with IHD. Advantages of PIRRT include use of conventional dialysis machines and standard dialysate concentrate, leading to lower operating costs compared with CRRT. PIRRT also allows for increased mobility and greater patient participation in physical and occupational therapy as compared with CRRT. Slower dialysate and blood flow rates allow for use in hemodynamically unstable patients who would not be able to tolerate IHD.[50,51] This approach is also common in AKI where renal drug elimination may be higher.[15]

There are significant differences in the prescriptions used in PIRRT, including frequency, duration, and blood and dialysate flow rates that can be altered on a daily basis.[50] This contributes to wide variabilities in antimicrobial doses prescribed among health care providers. A recent survey showed that pharmacist-recommended dosing regimens for commonly used antibiotics varied as much as by 12-fold,[21] likely because of knowledge limits, lack of available PK data, and inconsistencies in PIRRT operations. Inadequate dosing occurs frequently because of subtherapeutic doses.[52,53] Table 2 summarizes recent PK studies and considerations for a starting point for dosing commonly used antimicrobials in patients receiving PIRRT.[54-78] The supplemental materials discuss the literature in detail for each individual drug.

Continuous Renal Replacement Therapy

The following sections highlight significant publications since 2009 with antimicrobial PK/PD data and dosing recommendations for commonly used antibiotics in patients treated for sepsis or septic shock and receiving CVVHD, CVVH, or CVVHDF. Updated antibiotic dosing recommendations for CRRT are included in Table 3.

Cefepime. A study of cefepime elimination in CVVHD evaluated patients receiving cefepime with high dialysate (3 L/h) and high blood flow (300 mL/min).[79] The authors identified a strong inverse relationship between dialysate flow rate and cefepime half-life. They concluded that cefepime doses of 2 g every 12 hours or 1 g every 8 hours should increase time at therapeutic concentrations in high-flow CVVHD. The importance of UFRs on dosing requirements for cefepime to treat patients with septic shock was also highlighted in a recent study.[80] The investigators evaluated cefepime PK/PD in patients receiving CVVHDF or CVVH with UFRs of 1 to 2 L/h. They concluded that cefepime 2 g every 8 hours or 1 g every 6 hours is needed if the UFR is $\geq$1.5 L/h and 1 g every 8 hours if the UFR is $\leq$1 L/h. High doses such as 2 g every 8 hours should be used cautiously and with frequent monitoring because of patient and circuit factors described earlier (eg, circuit downtime) and the risk for neurotoxicity.

Daptomycin. Daptomycin dosing requirements are influenced by the infecting pathogen and the site of infection. FDA-approved doses of 4 and 6 mg/kg (actual body weight) are often exceeded for severe and deep-seated bloodstream infections caused by *S aureus* and *Enterococcus faecium.* Daptomycin dosing in critically ill patients on CVVHD at 2 L/h found that 4 mg/kg every 48 hours or below 500 mg/d may be inadequate to achieve desired AUC/MIC values.[81,82] Subsequent studies suggest dosing daptomycin at 8 mg/kg every 48 hours in critically ill patients with CVVHD or CVVHDF at 2 L/h with minimal residual renal function[83,84]; however, a more recent study evaluated 6 mg/kg every 24 hours and determined that no significant accumulation occurred.[85] The most robust study to date concluded that daptomycin doses of up to 12 mg/kg/d in CVVHD provided comparable exposure to patients with creatinine clearance $>$30 mL/min, but doses exceeding 8 mg/kg/d in CVVHDF may increase the risk for toxicity.[86] Close monitoring for elevations in creatinine kinase is strongly recommended.

Meropenem. Effluent flow rate appears to be a reliable predictor of meropenem clearance in critically ill patients, and a recent study suggests that higher dosing may be required for patients with high effluent flow rates and poorly susceptible pathogens.[23] The role of extended and continuous infusions has also been studied in patients receiving meropenem and CRRT[34,87]; however, continuous infusion may be limited by short stability. Meropenem 500 mg every 8 hours infused over 3 hours is recommended in critically ill patients receiving CRRT with intrinsic renal function, although these data are based on a PK model and have not been validated in a clinical trial.[34] More aggressive dosing at 1 g every 8 hours infused over 3 hours should be considered for pathogens with higher MICs (2-4 mg/L).[34]

Piperacillin-Tazobactam. Piperacillin-tazobactam clearance in critically ill patients receiving CRRT is reliably predicted by effluent flow rate.[23] Population pharmacokinetic models indicate that continuous infusions of piperacillin-tazobactam reach high plasma concentrations above the desired PK/PD target in the majority of critically ill patients receiving CVVH and CVVHDF.[31,88,89] However, continuous infusion piperacillin-tazobactam is challenging because of drug incompatibilities and line access considerations.

Table 2. Antimicrobial Dosing Recommendations for PIRRT

Drug	PIRRT Dose Recommendation[a]	Mean Blood/Dialysate Rates (mL/min)	Mean PIRRT Duration (hours)	Reference
Ampicillin/Sulbactam	2 g IV q12h	162/162	7.4	71
Daptomycin	6 mg/kg IV q24h[b]	166/166	7.6	54, 69
Ertapenem	1 g IV q24h	160/160	8	54, 56
Gentamicin/ Tobramycin	2-2.5 mg/kg Loading dose (or higher if the organism MIC is 2 mg/L), then adjusted using TDM[b,c,d]	200/300	8	54, 59, 65, 72, 73, 78
Levofloxacin	250 mg IV q24h	161/161	8	54, 58
Linezolid	600 mg IV q12h[e]	200/100	8	54, 62
Meropenem	1 g IV q12h[f]	100-250/100-200	8	54, 60, 68
	0.5-1 g IV q8h	160/160	8	
Moxifloxacin	400 mg IV q24h	161/161	8	54, 58
Piperacillin/ tazobactam	4.5 g IV q8h, or 4.5 g IV q12h + 2.25 g Replacement dose post-PIRRT[g]	200/200	6	66, 67, 75
	3.375 g IV q8h (Consider in severe infections)	200/300	8	
SMX/TMP	15 mg/kg/d In 4 divided doses[b]	140-170/170	7.4	55, 57
Vancomycin	If pre-PIRRT level >30 mg/L, hold If pre-PIRRT level 20-30 mg/L, give 500 mg at 6-8 hours If pre-PIRRT level <20 mg/L, give 1000 mg[h]	160/175	8	54, 61, 64, 68, 70
	20-25 mg/kg Starting dose, then use TDM to guide dosing	160/160, 300/300, 300/66.7 or 88.3[i]	8, 8-10, 8-10	

Abbreviations: IV, intravenous; MIC, minimum inhibitory concentration; PIRRT, prolonged intermittent renal replacement therapy; SMX/TMP, sulfamethoxazole/trimethoprim; TDM, therapeutic drug monitoring.

[a]Recommendations are derived from studies using a high-flux polysulfone filter type with 1.3 m^2 surface area unless otherwise specified. All milligram per kilogram doses are based on actual body weight unless otherwise specified. Some regimens not stated on a milligram per kilogram basis may vary based on the patient's weight.

[b]Adjusted body weight is recommended in obesity.

[c]Therapeutic drug monitoring is recommended to guide dosing. Dosing recommendation based on target peak levels depending on the MIC (eg, 7-10 mg/L if MIC is 1 or less) and a predialysis level between 3 and 5 mg/L. A higher peak of approximately 10 mg/L may be considered if the MIC is 2, but this has not been studied. The optimal dosing regimen must take into consideration the frequency of dialysis.

[d]Filter type and surface area: high-flux polysulfone 0.5 m^2.

[e]Filter type and surface area: low-flux polysulfone 1.6 m^2.

[f]Filter type and surface area: low-flux polysulfone 0.7 m^2.

[g]Filter type and surface area: high-flux polysulfone 1.4 m^2.

[h]Filter type and surface area: high-flux polysulfone 0.7 m^2.

[i]Filter types and surface area: high-flux polysulfone 1.4 and 1.3 m^2.

Extended-infusion strategies of piperacillin-tazobactam 4.5 over 4 hours are associated with favorable PD target attainment in patients undergoing CVVHDF.[90,91] The role of TDM has also been recommended to allow for individualized adjustment of dosing regimens according to pathogen-specific MICs; however, TDM may not be readily available in most institutions at this time.[90,92] Piperacillin-tazobactam 4.5 g every 8 hours in critically ill patients receiving CVVHDF has been shown to provide target attainment for organisms with an MIC ≤32 mg/L.[93]

Vancomycin. Vancomycin clearance in critically ill patients receiving CRRT is reliably predicted by effluent flow rate.[23,94] Variability in the published literature for vancomycin exists regarding dosing recommendations needed to achieve target trough or AUC goals. Increasingly, AUC-targeted regimens are utilized, although precise dosing targets have not been studied and validated in a population requiring RRT. A prospective study of intensive care unit patients receiving CVVH and vancomycin therapy concluded that 500 to 750 mg every 12 hours would be adequate to achieve the target trough goals, and serum vancomycin concentrations should be closely monitored.[95] High UFR CVVH (flow rate > 35-40 mL/kg/h) resulted in high variability in vancomycin clearance in a small case series.[96] The investigators recommended an initial dose of 20 to 25 mg/kg followed by TDM with dose adjustments. Another strategy could include continuous infusion with dose adjustments for CRRT intensity and TDM.[97] If the CRRT is stopped, the dosing regimen should be adjusted accordingly.

Table 3. Antibiotic Dosing Recommendations for CRRT.[a]

	CVVH and CVVHD		CVVHDF		
Drug	1-2 L/h	3+ L/h	1-2 L/h	3+ L/h	Reference
Cefepime (0.5-hour inf)	1 g q8h (1 L/h) 1 g q6h (2 L/h)[b]	1 g q6h[b,c]	1 g q8h (1 L/h) 1 g q6h (2 L/h)[b]	1 g q6h[b,c]	13, 79, 80
Daptomycin	6-8 mg/kg q24h	8 mg/kg q24h[d]	6-8 mg/kg q24h	8 mg/kg q24h[d]	13, 81, 84-86
Meropenem (3-hour inf)	500 mg q8h[e]	500 mg q8h[e]	500 mg q6-8h[e]	500 mg q6-8h[e]	13, 23, 33, 34, 87
Piperacillin/Tazobactam (4-hour inf)[f]	3.375 g q8h	3.375 g q8h[g]	3.375 g q8h	4.5 g q8h	13, 23, 31, 88, 90-93
Vancomycin	Load 20-25 mg/kg + 500-750 mg q12h with TDM adjustments	Load 20-25 mg/kg with TDM adjustments[h]	Load 20-25 mg/kg + 500-750 mg q12h with TDM adjustments	Load 20-25 mg/kg with TDM adjustments[h]	13, 23, 95, 96

Abbreviations: CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; *f*AUC:MIC, area under the concentration-time curve relative to the pathogen MIC; inf, infusion; MIC, minimum inhibitory concentration; TDM, therapeutic drug monitoring.

[a]The authors recommend individualizing dosing recommendations presented in the CRRT text portion of this publication to match local infusion strategies (extended vs continuous vs intermittent), pathogen susceptibility patterns, and individual patient needs.

[b]Cefepime 1 g q6h or 2 g q8h can be used interchangeably for efficacy; however, determination of the appropriate dose should be made by assessing risk of toxicity, site of infection, and pathogen susceptibility. Alternatively, clinicians may consider a 2-g bolus followed by a 4-g continuous infusion over 24 hours.

[c]Consider extended infusion (3-4 hours) or continuous infusion cefepime for flow rates ≥3 L/h.

[d]Doses > 8 mg/kg every 24 hours increase the risk of creatine phosphokinase (CPK) elevations and myopathy. Caution, clinical judgment, and frequent CPK monitoring, including a baseline value, should be used if pursuing as high as 10 to 12 mg/kg every 24 hours.

[e]Consider meropenem 500 mg q6h for organisms with an MIC of 2 mg/L. Consider higher doses for severe central nervous system infections or severely immunosuppressed patients.

[f]If extended infusions are not feasible, a dosing interval of 6 hours, instead of 8 hours, is recommended for intermittent infusions.

[g]Consider a loading dose + continuous infusion (11.25 g/d on day 1 followed by 9 g/d thereafter) or 4.5 g q8h for high flow rates or pathogens with reduced susceptibility.

[h]Because of large variability in vancomycin clearance in high-flow CRRT, frequent monitoring is recommended to target an *f*AUC:MIC of 400-600 mg h/L (consider 2 postdose levels or target troughs ≥15 mg/L if AUC-based dosing is not feasible). Evaluate feasibility of continuous infusion vancomycin for your patient.[102]

Relevance to Patient Care and Clinical Practice

Optimizing PK/PD in critically ill patients receiving RRT is essential to eradicate infections and improve patient outcomes. Several barriers still exist. PTA analyses alone cannot control for all variables necessary to determine optimal antimicrobial dosing. Published literature, although limited, continues to expand, highlighting potential dosing strategies for a variety of RRT methodologies and intensities. However, clinicians still face many challenges when applying the recommendations to individual patients. In the setting of AKI and the critically ill, underdosing of antibiotics is a common and notable concern. Variances in renal support and decline and recovery of renal function in AKI along with a plethora of additional considerations (Table 1) should be considered in the management plan.

The role of TDM is critical to tailor therapies in these situations and should consider an overall assessment of all the variables present.[98-100] Availability of β-lactam serum concentration assays for widespread clinical use will be instrumental to improving outcomes in patients with variable PK or infections by multidrug-resistant organisms with MICs at or above the breakpoint. Institution-specific RRT dosing guidelines should incorporate local epidemiology and antibiogram data, severity of the infection, current clinical PK/PD targets, adjustment for institution-specific RRT methodology (circuit type, membrane pore size, common CRRT intensity), patient demographics (obesity), availability of routine TDM, and considerations for other patient factors (heart or hepatic failure, residual renal function, immune system). Additionally, training for clinical pharmacists and medical intensivists on the advanced principles and importance of antimicrobial dosing in RRT might be an appropriate target for an institution's antimicrobial stewardship program.

Conclusion

Appropriate antimicrobial selection and dosing are vital to improve clinical outcomes in critically ill patients. Critical illness and RRT significantly alter the usual PK of patients treated with antimicrobials and increase the risk for underdosing antimicrobial agents. Dosing recommendations

from the literature should be interpreted cautiously with efforts to consider local epidemiology and resistance patterns; antibiotic dosing and infusion strategies; renal replacement modalities, including filter types; and patient-specific considerations such as site of infection, severity of illness, residual renal function, comorbidities, and patient response to therapy. In many cases, dosing revisions for most antibiotics, with exceptions to aminoglycosides or vancomycin, should wait for at least 24 hours in severe infections before being applied to reduce underdosing or adverse events. As the clinical situation stabilizes, adjustment to the dosing regimen should be considered. In AKI, the phase of the process may need to be tracked closely and the regimen modified accordingly as elimination declines or improves. The dosing suggestions in the tables provide a starting point to consider when developing an antibiotic regimen but should be individualized to the patient's situation, including changing approaches to RRT.

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