# Antibiotic Dosing in Critically Ill Adult Patients Receiving Continuous Renal Replacement Therapy

**Robin L. Trotman,**[1] **John C. Williamson,**[1] **D. Matthew Shoemaker,**[2] **and William L. Salzer**[2]

[1]Department of Internal Medicine, Section of Infectious Diseases, Wake Forest University Health Sciences, Winston-Salem, North Carolina; and [2]Department of Internal Medicine, Division of Infectious Diseases, University of Missouri Health Science Center, Columbia, Missouri

**Continuous renal replacement therapy (CRRT) is now commonly used as a means of support for critically ill patients with renal failure. No recent comprehensive guidelines exist that provide antibiotic dosing recommendations for adult patients receiving CRRT. Doses used in intermittent hemodialysis cannot be directly applied to these patients, and antibiotic pharmacokinetics are different than those in patients with normal renal function. We reviewed the literature for studies involving the following antibiotics frequently used to treat critically ill adult patients receiving CRRT: vancomycin, linezolid, daptomycin, meropenem, imipenem-cilastatin, nafcillin, ampicillin-sulbactam, piperacillin-tazobactam, ticarcillin–clavulanic acid, cefazolin, cefotaxime, ceftriaxone, ceftazidime, cefepime, aztreonam, ciprofloxacin, levofloxacin, moxifloxacin, clindamycin, colistin, amikacin, gentamicin, tobramycin, fluconazole, itraconazole, voriconazole, amphotericin B (deoxycholate and lipid formulations), and acyclovir. We used these data, as well as clinical experience, to make recommendations for antibiotic dosing in critically ill patients receiving CRRT.**

Continuous renal replacement therapy (CRRT) is frequently used to treat critically ill patients with acute renal failure or chronic renal failure. CRRT is better tolerated by hemodynamically unstable patients and is as effective at removing solutes during a 24–48-h period as a single session of conventional hemodialysis [1]. Solute removal is particularly relevant to antimicrobial therapy, because many critically ill patients with acute renal failure have serious infections and require treatment with ≥1 antimicrobial. However, compared with data about antibiotic dosing in patients undergoing intermittent hemodialysis, there is a relative paucity of published data about antibiotic dosing during CRRT in critically ill patients. In addition, the rate of drug clearance during CRRT can be highly variable in critically ill patients.

We conducted a comprehensive review of Medline-referenced literature to formulate dosing recommendations for the following antibiotics frequently used to treat critically ill adult patients undergoing CRRT: vancomycin, linezolid, dapto-

mycin, meropenem, imipenem-cilastatin, nafcillin, ampicillin-sulbactam, piperacillin-tazobactam, ticarcillin–clavulanic acid, cefazolin, cefotaxime, ceftriaxone, ceftazidime, cefepime, aztreonam, ciprofloxacin, levofloxacin, moxifloxacin, clindamycin, colistin, amikacin, gentamicin, tobramycin, fluconazole, itraconazole, voriconazole, amphotericin B (deoxycholate and lipid formulations), and acyclovir. For drugs with no specific published data on dosing in patients receiving CRRT, we used known chemical properties and other clinical data (e.g., molecular weight, protein binding capacity, and removal by intermittent hemodialysis) to make dosing recommendations. The pharmacokinetic and pharmacodynamic properties of each antimicrobial and the typical susceptibilities of relevant pathogens were considered (table 1). In most cases, the recommended "target" drug concentration corresponds to the upper limit of the MIC range for susceptibility. The goal of our dosing recommendations is to keep the concentration above the target MIC for an optimal proportion of the dosing interval, reflecting known pharmacodynamic properties (time-dependent vs. concentration-dependent killing), while minimizing toxicity due to unnecessarily high concentrations. However, these recommendations are meant to serve only as a guide until more data are available, and they should not replace sound clinical judgment. Recommended dosages are listed in table 2.

**Table 1.** Pharmacokinetic and pharmacodynamic parameters of drugs used for treatment of critically ill adult patients receiving continuous renal replacement therapy.

| Drug | PBC, % | Primary route of elimination[a] | Volume of distribution, L/kg | Half-life for normal renal function, h | Time-dependent or concentration-dependent killing | Target trough level, mg/L[b] |
|---|---|---|---|---|---|---|
| Acyclovir | 15 | Renal | 0.6 | 2–4 | Time | NA[c] |
| Ampicillin | 28 | Renal | 0.29 | 1.2 | Time | 8 |
| Aztreonam | 56 | Renal | 0.2 | 1.7–2.9 | Time | 8 |
| Cefepime | 16 | Renal | 0.25 | 2.1 | Time | 8 |
| Cefotaxime | 27–38 | Renal | 0.15–0.55 | 1 | Time | 8 |
| Ceftazidime | 21 | Renal | 0.23 | 1.6 | Time | 8 |
| Ceftriaxone | 90 | Hepatic | 0.15 | 8 | Time | 8 |
| Cilastatin | 40 | Renal | 0.20 | 1 | NA | NA |
| Ciprofloxacin | 40 | Renal | 1.8 | 4.1 | Concentration | 1 |
| Clavulanate | 30 | Hepatic | 0.3 | 1 | NA | NA |
| Clindamycin | 60–95 | Hepatic | 0.6–1.2 | 3 | Time | 2 |
| Colistin | 55 | Renal | 0.34 | 2 | Concentration | 4 |
| Daptomycin | 92 | Renal | 0.13 | 8 | Concentration | 4 |
| Fluconazole | 12 | Renal | 0.65 | 30 | Time | 8–16[d] |
| Imipenem | 20 | Renal | 0.23 | 1 | Time | 4 |
| Itraconazole | 99 | Hepatic | 10 | 21 | Time | 0.125–0.25[d] |
| Levofloxacin | 24–38 | Renal | 1.09 | 7–8 | Concentration | 2 |
| Linezolid | 31 | Hepatic | 0.6 | 4.8–5.4 | Time | 4 |
| Meropenem | 2 | Renal | 0.25 | 1 | Time | 4 |
| Moxifloxacin | 50 | Hepatic | 1.7–2.7 | 12 | Concentration | 2 |
| Piperacillin | 16 | Renal | 0.18 | 1 | Time | 16 |
| Tazobactam | 20–23 | Renal | 0.18–0.33 | 1 | NA | 4 |
| Ticarcillin | 45–65 | Renal | 0.17 | 1.2 | Time | 16 |
| Sulbactam | 38 | Renal | 0.25–0.5 | 1 | Time | 1–4 |
| Vancomycin | 55 | Renal | 0.7 | 6 | Time | 10 |
| Voriconazole[e] | 58 | Hepatic | 4.6 | 12 | Time | 0.5 |

**NOTE.** NA, not applicable; PBC, protein-binding capacity.

[a] Data are for the parent compound.

[b] Denotes the highest MIC in the susceptible range for applicable pathogens, such as the β-lactam MIC for *Pseudomonas aeruginosa*.

[c] Trough concentrations of acyclovir are not routinely measured because this agent is phosphorylated into the active form acyclovir triphosphate.

[d] The higher level is the recommended target trough concentration for *Candida* species with an MIC in the dose-dependent, susceptible range (fluconazole MIC, 16–32 μg/mL; itraconazole MIC, 0.25–0.5 μg/mL).

[e] The oral bioavailability of voriconazole is estimated to be 96%.

## DESCRIPTION AND NOMENCLATURE OF CRRT

Several methods of CRRT exist, and there is inconsistency in the literature regarding nomenclature. For this review, we will use the following terms: continuous arteriovenous hemofiltration (CAVH), continuous venovenous hemofiltration (CVVH), continuous arteriovenous hemodialysis (CAVHD), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodialfiltration (CVVHDF). These are consistent with the definitions established by an international conference on CRRT [2]. The most common modalities currently used in intensive care units are CVVH, CVVHD, and CVVHDF [3]. During CVVH, solute elimination is through convection, whereas CVVHD utilizes diffusion gradients through counter-current dialysate flow, and drug removal depends on dialysate and blood flow rates. CVVHDF utilizes both diffusive and convective solute transports and can require a large amount of fluid to replace losses during ultrafiltration [1–6].

The pharmacokinetics of drug removal in critically ill patients receiving CRRT is very complex, with multiple variables affecting clearance. These variables make generalized dosing recommendations difficult. Drug-protein complexes have a larger molecular weight; therefore, antibiotics with low protein binding capacity in serum are removed by CRRT more readily. Similarly, antibiotics that penetrate and bind to tissues have a larger volume of distribution, reducing the quantity removed during CRRT. Sepsis itself increases the volume of distribution,

**Table 2. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy.**

| Drug | Dosage, by type of renal replacement therapy | |
|---|---|---|
| | CVVH | CVVHD or CVVHDF |
| Amphotericin B formulation | | |
|   Deoxycholate | 0.4–1.0 mg/kg q24h | 0.4–1 mg/kg q24h |
|   Lipid complex | 3–5 mg/kg q24h | 3–5 mg/kg q24h |
|   Liposomal | 3–5 mg/kg q24h | 3–5 mg/kg q24h |
| Acyclovir | 5–7.5 mg/kg q24h | 5–7.5 mg/kg q24h |
| Ampicillin-sulbactam[a] | 3 g q12h | 3 g q8h |
| Aztreonam | 1–2 g q12h | 2 g q12h |
| Cefazolin | 1–2 g q12h | 2 g q12h |
| Cefepime | 1–2 g q12h | 2 g q12h |
| Cefotaxime | 1–2 g q12h | 2 g q12h |
| Ceftazidime | 1–2 g q12h | 2 g q12h |
| Ceftriaxone | 2 g q12–24h | 2 g q12–24h |
| Clindamycin | 600–900 mg q8h | 600–900 mg q8h |
| Ciprofloxacin[b] | 200 mg q12h | 200–400 mg q12h |
| Colistin | 2.5 mg/kg q48h | 2.5 mg/kg q48h |
| Daptomycin | 4 or 6 mg/kg q48h | 4 or 6 mg/kg q48h |
| Fluconazole[b] | 200–400 mg q24h | 400–800 mg q24h[c] |
| Imipenem-cilastatin[d] | 250 mg q6h or 500 mg q8h | 250 mg q6h, 500 mg q8h, or 500 mg q6h |
| Levofloxacin[b] | 250 mg q24h[e] | 250 mg q24h[e] |
| Linezolid[b] | 600 mg q12h | 600 mg q12h |
| Meropenem | 1 g q12h | 1 g q12h |
| Moxifloxacin | 400 mg q24h | 400 mg q24h |
| Nafcillin or oxacillin | 2 g q4–6h | 2 g q4–6h |
| Piperacillin-tazobactam[f] | 2.25 g q6h | 2.25–3.375 g q6h |
| Ticarcillin-clavulanate[g] | 2 g q6–8h | 3.1 g q6h |
| Vancomycin | 1 g q48h[e] | 1 g q24h[e] |
| Voriconazole[h] | 4 mg/kg po q12h | 4 mg/kg po q12h |

**NOTE.** All dosages are administered intravenously, unless otherwise indicated. The recommendations assume an ultrafiltration rate of 1 L/h, a dialysate flow rate of 1 L/h, and no residual renal function. CAVHD, continuous arteriovenous hemodialysis; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodialfiltration.

[a] Available commercially in a fixed ratio of 2 mg of ampicillin to 1 mg of sulbactam.

[b] The switch from the intravenous to the oral formulation is possible when appropriate.

[c] A dose of 800 mg is appropriate if the dialysate flow rate is 2 L/h and/or if treating fungal species with relative azole resistance, such as *Candida glabrata*.

[d] Available commercially in a fixed ratio of 1 mg to 1 mg.

[e] Recommended loading dose is 15–20 mg/kg of vancomycin and 500 mg of levofloxacin.

[f] Available commercially in a fixed ratio of 8 mg to 1 mg.

[g] Available commercially in a fixed ratio of 30 mg to 1 mg.

[h] The oral bioavailability of voriconazole is estimated to be 96%. Consider 2 loading doses of 6 mg/kg po q12h. See Antifungals for details on contraindications associated with the intravenous formulation in patients with renal failure.

extends drug half-life, and alters the protein binding capacity of many antimicrobials. CRRT mechanical factors may also affect drug clearance. Increasing the blood or dialysate flow rate can change the transmembrane pressure and increase drug clearance. The dialysate concentration may also affect drug re-

moval in hemofiltration. Lastly, the membrane pore size is directly proportional to the degree of drug removal by CRRT, often expressed as a sieving coefficient. Generally, biosynthetic membranes have larger pores, which allow removal of drugs with a larger molecular weight, unlike conventional filters. These patient, drug, and mechanical variables significantly diminish the utility of routine pharmacokinetic calculations for determining antimicrobial dosing during CRRT [1, 4].

## ANTIBIOTICS FOR DRUG-RESISTANT GRAM-POSITIVE BACTERIA

*Vancomycin.* The half-life of vancomycin increases significantly in patients with renal insufficiency [7, 8]. It is a middle–molecular weight antibiotic, and although compounds of this size are poorly removed by intermittent hemodialysis, they are removed by CRRT [7, 9]. CVVH, CVVHD, and CVVHDF all effectively remove vancomycin [7, 9–11]. Because of the prolonged half-life, the time to reach steady state will also be prolonged. Therefore, a vancomycin loading dose of 15–20 mg/kg is warranted. Vancomycin maintenance dosing for patients receiving CVVH varies from 500 mg q24h to 1500 mg q48h [7, 10]. For patients receiving CVVHD or CVVHDF, we recommend a vancomycin maintenance dosage of 1–1.5 g q24h. Monitoring of plasma vancomycin concentrations and subsequent dose adjustments are recommended to achieve desired trough concentrations. A trough concentration of 5–10 mg/L is adequate for infections in which drug penetration is optimal, such as skin and soft-tissue infections or uncomplicated bacteremia. However, higher troughs (10–15 mg/L) are indicated for infections in which penetration is dependent on passive diffusion of drug into an avascular part of the body, such as osteomyelitis, endocarditis, or meningitis. Recent guidelines also recommend higher troughs (15–20 mg/L) in the treatment of health care–associated pneumonia, because of suboptimal penetration of vancomycin into lung tissue [12].

*Linezolid.* Fifty percent of a linezolid dose is metabolized in the liver to 2 inactive metabolites, and 30% of the dose is excreted in the urine as unchanged drug. There is no adjustment recommended for patients with renal failure; however, linezolid clearance is increased by 80% during intermittent hemodialysis. There are very few data on linezolid clearance during CRRT. On the basis of 4 studies [13–16], a linezolid dosage of 600 mg q12h provides a serum trough concentration of >4 mg/L, which is the upper limit of the MIC range for drug-susceptible *Staphylococcus* species [17]. The upper limit of the MIC range for drug-susceptible *Enterococcus* and *Streptococcus* species is 2 mg/L [17]. Thus, no linezolid dosage adjustment is recommended for patients receiving any form of CRRT; however, in such patients, neither the disposition nor the clinical relevance of inactive linezolid metabolites are known. Therefore, the reader is cautioned to pay attention to hematopoietic

and neuropathic adverse effects when administering linezolid for extended periods to patients receiving CRRT [14].

**Daptomycin.** Daptomycin is a relatively large molecule that is excreted primarily through the kidneys and requires dose adjustment in patients with renal failure. There are no published pharmacokinetic studies of daptomycin in patients receiving CRRT. However, a study of daptomycin clearance in an in vitro model suggests that CVVHD does not remove a significant amount of drug [18]. On the basis of these data and known chemical properties of daptomycin, the dose for patients receiving CRRT should be the manufacturer-recommended dose for patients with a creatinine clearance rate of <30 mL/min [19]. Care should be taken to monitor serum creatine phosphokinase levels at initiation of therapy and then weekly during receipt of daptomycin.

## β-LACTAMS

**Carbapenems.** Imipenem is metabolized at the renal brush-border membrane by the enzyme dehydropeptidase-I, which is inhibited by cilastatin. Seventy percent of the imipenem dose is excreted unchanged in the urine when it is administered as a fixed dose combination with cilastatin. Imipenem and cilastatin have similar pharmacokinetic properties in patients with normal renal function; however, both drugs accumulate in patients with renal insufficiency. Cilastatin may accumulate to a greater extent, because nonrenal clearance of cilastatin accounts for a lower percentage of its total clearance, compared with imipenem [20]. To maintain an imipenem trough concentration of ~2 mg/L during CRRT, a dosage of 250 mg q6h or 500 mg q8h is recommended [20–23]. A higher dosage (500 mg q6h) may be warranted in cases of relative resistance to imipenem (MIC, ≥4 mg/L) [23]. Cilastatin also accumulates in patients with hepatic dysfunction, and increasing the dosing interval may be needed to avoid potential unknown adverse effects of cilastatin accumulation.

In contrast to imipenem, meropenem does not require a dehydropeptidase inhibitor. The meropenem MIC for most susceptible bacteria is ≤4 mg/L. This represents an appropriate trough concentration for critically ill patients, especially when the pathogen and MIC are not yet known [24, 25]. Many studies have analyzed the pharmacokinetics of meropenem in patients receiving CRRT [24–30]. There is significant variability in the data, owing to different equipment, flow rates, and treatment goals. However, a meropenem dosage of 1 g q12h will produce a trough concentration of ~4 mg/L in most patients, regardless of CRRT modality. If the organism is found to be highly susceptible to meropenem, a lower dosage (500 mg q12h) may be appropriate.

**β-Lactamase–inhibitor combinations.** Of the 3 β-lactamase–inhibitor combinations available commercially, only piperacillin-tazobactam has been extensively studied in patients receiving CRRT. On the basis of published data, piperacillin is cleared by all modalities of CRRT [31–34]. The tazobactam concentration has been shown to accumulate relative to the piperacillin concentration during CVVH [32, 33]. Thus, piperacillin is the limiting factor to consider when choosing an optimal dose. On the basis of results of 4 studies evaluating piperacillin or the fixed combination of piperacillin-tazobactam in patients receiving CRRT [31–34], a dosage of 2 g/0.25 g q6h piperacillin-tazobactam is expected to produce trough concentrations of these agents in excess of the MIC for most drug-susceptible bacteria during the majority of the dosing interval. For patients receiving CVVHD or CVVHDF, one should consider increasing the dose to 3 g/0.375 g piperacillin-tazobactam if treating a relatively drug-resistant pathogen, such as *Pseudomonas aeruginosa* (in which case piperacillin alone should be considered). Again, for patients with no residual renal function who are undergoing CVVH and receiving prolonged therapy with piperacillin-tazobactam, it is not known whether tazobactam accumulates. Moreover, the toxicities of tazobactam are not known, and it has been recommended that alternating doses of piperacillin alone in these patients may avoid the potential toxicity associated with tazobactam accumulation [32, 33].

Although few data exist with ampicillin-sulbactam and ticarcillin-clavulanate [35], extrapolations are possible between piperacillin-tazobactam and ampicillin-sulbactam. Piperacillin, tazobactam, ampicillin, and sulbactam primarily are excreted by the kidneys, and all 4 drugs accumulate in persons with renal dysfunction. However, the ratio of β-lactam to β-lactamase inhibitor is preserved in persons with varying degrees of renal insufficiency, because each pair has similar pharmacokinetics. This is not true for ticarcillin-clavulanate. Although ticarcillin will also accumulate with renal dysfunction, clavulanate is not affected; it is metabolized by the liver. If the dosing interval is extended, only ticarcillin will remain in plasma at the end of the interval [36]. For this reason, an interval >8 h is not recommended with ticarcillin-clavulanate during CRRT. Because CVVHD and CVVHDF are more efficient at removing β-lactams such as ticarcillin, the dosing interval with these CRRT modalities should not exceed 6 h for ticarcillin-clavulanate.

**Cephalosporins and aztreonam.** Cefazolin, cefotaxime, ceftriaxone, ceftazidime, cefepime, and aztreonam were investigated. With the exception of ceftriaxone, these β-lactams are renally excreted and accumulate in persons with renal dysfunction. Because the rate of elimination is directly proportional to renal function, patients requiring intermittent hemodialysis may receive doses much less often. In some instances, 3 times weekly dosing after hemodialysis is adequate. However, clearance by CRRT is greater for most of these agents, necessitating more-frequent dosing to maintain therapeutic concentrations greater than the MIC for an optimal proportion of the dosing interval. Ceftriaxone is the

exception in this group of β-lactams, primarily because of its extensive protein-binding capacity, which prevents it from being filtered, and its hepatic metabolism and biliary excretion. Ceftriaxone clearance in patients receiving CVVH has been shown to be equivalent to clearance in subjects with normal renal function, and therefore, no dose adjustment is necessary for patients receiving CRRT [37, 38].

The other cephalosporins and aztreonam are cleared at a rate equivalent to a creatinine clearance rate of 30–50 mL/min during CVVHD or CVVHDF, whereas the rate of clearance by CVVH is lower. If the goal in critically ill patients is to maintain a therapeutic concentration for the entire dosing interval, a normal, unadjusted dose may be required. This is the case with cefepime. On the basis of 2 well-done studies involving critically ill patients, a cefepime dosage of 1 g q12h is appropriate for most patients receiving CVVH, and up to 2 g q12h is appropriate for patients receiving CVVHD or CVVHDF [39, 40].

Cefepime and ceftazidime pharmacokinetics are almost identical, and similar doses are advocated. Older recommendations for CVVH dosing (1–2 g q24–48 h) are based on CAVH data [41]. However, the current use of pump-driven systems provides more consistent blood flow and increases drug clearance. It is not clear whether CAVH data can be extrapolated to CVVH, CVVHD, and CVVHDF. Three studies determined ceftazidime doses using newer CRRT modalities [5, 6, 42]. As with cefepime and many other β-lactams, CVVHD removes ceftazidime more efficiently than does CVVH [6]. A ceftazidime dosage of 2 g q12h is needed to maintain concentrations above the MIC for most nosocomial gram-negative bacteria in critically ill patients receiving CVVHD and CVVHDF. Ceftazidime 1 g q12h is appropriate during CVVH. Studies have not been performed with cefazolin, cefotaxime, or aztreonam during CRRT. However, their pharmacokinetic and molecular properties are similar enough such that extrapolations are appropriate. Dosing recommendations for these β-lactams are listed in table 2.

## FLUOROQUINOLONES

Few antibiotic classes have more data supporting the influence of pharmacodynamics on clinical outcomes than fluoroquinolones. The ratio of the area under the curve (AUC) to the MIC is a particularly predictive pharmacodynamic parameter [43], and most authorities recommend maximizing this ratio. This is best accomplished by optimizing the dose, which may be difficult in the critical care setting where fluoroquinolone disposition may be altered and fluoroquinolone elimination may be reduced. The additional influence of CRRT makes dosing even more complex. Many studies have documented minimal effects of CRRT on fluoroquinolone elimination [44–50]. However, evidence exists that manufacturer-recommended dosing for ciprofloxacin will not always achieve a target AUC/

MIC ratio in critically ill patients, including those who are receiving CAVHD [43, 51]. A ciprofloxacin dosage of 400 mg q.d. is recommended by the manufacturer for patients with a creatinine clearance rate of ≤30 mL/min. In critically ill patients receiving CRRT, a dosage of 600–800 mg per day may be more likely to achieve an optimal AUC/MIC ratio, and for organisms with a ciprofloxacin MIC of ≥1 μg/mL, standard doses are less likely to achieve a target ratio. In addition, dose escalation may be warranted if ciprofloxacin is the only anti–gram-negative bacteria antibiotic prescribed, especially if the pathogen is *P. aeruginosa*.

Levofloxacin is excreted largely unchanged in the urine, and significant dosage adjustments are necessary for patients with renal failure. Intermittent hemodialysis does not effectively remove levofloxacin, and therefore, supplemental doses are not required after hemodialysis [40]. Levofloxacin is eliminated by CVVH and CVVHDF [48]. Malone et al. [44] found that a levofloxacin dosage of 250 mg q24h provided $C_{max}$/MIC and $AUC_{24}$/MIC values that were comparable to the values found in patients with normal renal function after a dosage of 500 mg q24h. Levofloxacin dosages of 250 mg q24h, after a 500-mg loading dose, are appropriate for patients receiving CVVH, CVVHD, or CVVHDF [44, 48, 49].

The pharmacokinetics of moxifloxacin have been recently studied in critically ill patients receiving CVVHDF [50]. These data, as well as known pharmacokinetics data, indicate no need to adjust the moxifloxacin dosage for patients receiving CRRT.

## COLISTIN

Polymyxins have recently reemerged as therapeutic options for multidrug-resistant gram-negative organisms, such as *P. aeruginosa* and *Acinetobacter* species. Colistimethate sodium is the parenteral formulation of colistin and is the product for which dosing recommendations are made. Colistin is a large cationic molecule with a molecular weight of 1750 D, and it is tightly bound to membrane lipids of cells in tissues throughout the body [52]. These 2 properties suggest that the impact of CRRT on colistin elimination is minimal. Colistin dosing should be based on the following 2 patient-specific factors: underlying renal function and ideal body weight. No clinical data exist on colistin dosing for patients receiving CRRT. On the basis of clinical experience and the pharmacokinetic properties of colistin, we recommend using colistin at a dosage of 2.5 mg/kg q48h in patients undergoing CRRT.

## AMINOGLYCOSIDES

Two pharmacokinetic parameters are essential predictors of aminoglycoside dosing. The volume of distribution can be used to predict the drug dose, and the elimination rate can be used to predict the required dosing interval. The volume of distribution may be significantly larger in critically ill patients and

**Table 3. Aminoglycoside dosing recommendations for critically ill adults receiving continuous renal replacement therapy.**

| Aminoglycoside | Gram-positive synergy, dosage | Infection with gram-negative bacteria | |
| --- | --- | --- | --- |
| | | Loading dose | Maintenance dosage |
| Gentamicin | 1 mg/kg q24–36h | 3 mg/kg | 2 mg/kg q24–48h |
| Tobramycin | Not applicable | 3 mg/kg | 2 mg/kg q24–48h |
| Amikacin | Not applicable | 10 mg/kg | 7.5 mg/kg q24–48h |

**NOTE.** See Aminoglycosides for recommendations on monitoring drug levels. Target peak and trough levels vary depending on the type of infection. Use calculated dosing body weight for obese patients.

may result in subtherapeutic concentrations after an initial loading dose. CRRT itself may contribute to a larger volume of distribution. However, CRRT offers some "control" in such a dynamic state, and if the variables of CRRT are held constant, aminoglycoside elimination is likely to be similarly constant.

Today's filters are capable of removing aminoglycosides at a rate equivalent to a creatinine clearance rate of 10–40 mL/min. This equates to an aminoglycoside half-life of 6–20 h. The typical dosing interval with aminoglycosides will be ~3 half-lives; therefore, the typical dosing interval during CRRT will be 18–60 h. Indeed, most patients undergoing CRRT will require an interval of 24, 36, or 48 h. The target peak concentration can also predict the dosing interval. If gentamicin is prescribed for synergy in the treatment of infection with gram-positive organisms, the target peak is 3–4 $\mu$g/mL. Only 2 half-lives are required to reach a concentration of ≤1 $\mu$g/mL, a typical trough level. If the target peak concentration is 8 $\mu$g/mL, it will take an additional half-life to get to 1 $\mu$g/mL. Therefore, the higher the target peak concentration, the longer the required dosing interval. These principles are reflected in the dosing recommendations in table 3. However, monitoring aminoglycoside concentrations is essential to determine the most appropriate dose. Performing first-dose pharmacokinetics may be the quickest way to ensure adequate and safe dosing. To determine the most appropriate dose, the volume of distribution and the elimination rate can be estimated by measuring the peak concentration and a 24-h concentration. Even if first-dose pharmacokinetics analysis is not performed, determination of the 24-h concentration is warranted to provide a measure of elimination and the ultimate dosing interval.

## ANTIFUNGALS

*Triazoles.* Unlike itraconazole and voriconazole, which are metabolized, 80% of the fluconazole dose is eliminated unchanged via the kidneys. Accumulation occurs in patients with renal insufficiency, for whom a dose reduction is recommended. However, clearance of fluconazole by CVVHD and CVVHDF in patients with renal insufficiency is significant and may be equal to or greater than that for patients with normal renal function [53–55]. With the emergence of azole-resistant *Can-*

*dida* species, routine antifungal susceptibilities are recommended to direct antifungal choice and dosing [56]. Empirical fluconazole should be administered at a daily dose of 800 mg for critically ill patients receiving CVVHD or CVVHDF with a combined ultrafiltration and dialysate flow rate of 2 L/h and at a daily dose of 400 mg for patients receiving CVVH. The dose may be decreased to 400 mg (CVVHD and CVVHDF) or to 200 mg (CVVH) if the species is not *Candida krusei* or *Candida glabrata* and the fluconazole MIC is ≤8 mg/L.

Itraconazole and voriconazole are available in oral and parenteral formulations. The parenteral formulations are solubilized in a cyclodextrin diluent, which is eliminated by the kidneys and will accumulate in patients with renal insufficiency. The clinical significance of cyclodextrin accumulation in humans is not fully understood. Use of intravenous itraconazole and voriconazole is not recommended for patients with creatinine clearance rates of <30 and 50 mL/min, respectively, or for patients receiving any form of renal replacement therapy. Although oral formulations are not contraindicated, there are few data about triazole dosing for patients receiving CRRT [57]. On the basis of pharmacokinetics data, no dose reduction is recommended for patients receiving CRRT.

*Amphotericin B.* Amphotericin B and its lipid preparations have not been thoroughly investigated in critically ill patients receiving CRRT. However, case reports and small series have been performed [58–60]. Amphotericin B is a large molecule, and when bound within a lipid structure, the product is even larger. In addition, amphotericin B is extensively and rapidly distributed in tissues. On the basis of limited clinical data and the pharmacokinetics of amphotericin B, dose adjustments for CRRT are not recommended.

## ACYCLOVIR

Acyclovir is eliminated by renal excretion and has a narrow therapeutic index in patients with renal impairment. Its small molecular size, low protein-binding capacity, and water solubility make it readily removed by all types of dialysis. Generally, acyclovir clearance during a 24-h period of CRRT is equivalent to a single session of intermittent hemodialysis [61–63]. Limited pharmacokinetic data suggest that an acyclovir dosage of 5 mg/

kg iv q24h (based on ideal body weight) is adequate for most infections, regardless of CRRT modality [61–63]. A dosage of 7.5 mg/kg iv q24h is appropriate for treatment of infections involving the CNS, such as herpes simplex virus encephalitis. Subsequent acyclovir concentration monitoring should be performed when available.

## CONCLUSIONS

These recommendations are based on very limited clinical data, and in many cases, our dosing recommendations are extrapolations from clinical experiences and known pharmacokinetic and pharmacodynamic properties. More clinical data are needed to support such extrapolations, and these recommendations should not supercede sound clinical judgment.

### Acknowledgments

### References

1. Joy M, Matzke G, Armstrong D, Marx M, Zarowitz B. A primer on continuous renal replacement therapy for critically ill patients. Ann Pharmacother **1998**; 32:362–75.
2. Bellomo R, Ronco C, Mehta RL. Nomenclature for continuous renal replacement therapies. Am J Kidney Dis **1996**; 28(Suppl 3):S2–7.
3. Cotterill S. Antimicrobial prescribing in patients on haemofiltration. J Antimicrob Chemother **1995**; 36:773–80.
4. Joos B, Schmidli M, Keusch G. Pharmacokinetics of antimicrobial agents in anuric patients during continuous venovenous haemifiltration. Nephrol Dial Transplant **1996**; 11:1582–5.
5. Traunmuller F, Schenk P, Mittermeyer C, Thalhammer-Scherrer R, Ratheiser K, Thalhammer F. Clearance of ceftazidime during continuous venovenous haemofiltration in critically ill patients. J Antimicrob Chemother **2002**; 49:129–34.
6. Matzke GR, Frye RF, Joy MS, Palevsky PM. Determinants of ceftazidime clearance by continuous venovenous hemofiltration and continuous venovenous hemodialysis. Antimicrob Agents Chemother **2000**; 44:1639–44.
7. Joy MS, Matzke GR, Frye RF, Palevsky PM. Determinants of vancomycin clearance by continuous venovenous hemofiltration and continuous venovenous hemodialysis. Am J Kidney Dis **1998**; 31:1019–27.
8. Matzke GR, Zhanel GG, Guay DR. Clinical pharmacokinetics of vancomycin. Clin Pharmacokinet **1986**; 11:257–82.
9. DelDot ME, Lipman J, Tett SE. Vancomycin pharmacokinetics in critically ill patients receiving continuous hemodialfiltration. Br J Clin Pharmacol **2004**; 58:259–68.
10. Boereboom FT, Ververs FF, Blankestijn PJ, Savelkoul TJ, van Dijk A. Vancomycin clearance during continuous venovenous haemofiltration in critically ill patients. Intensive Care Med **1999**; 25:1100–4.
11. Santre C, Leroy O, Simon M, et al. Pharmacokinetics of vancomycin during continuous hemodialfiltration. Intensive Care Med **1993**; 19: 347–50.
12. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med **2005**; 171:388–416.
13. Fiaccadori E, Maggiore U, Rotelli C, et al. Removal of linezolid by conventional intermittent hemodialysis, sustained low-efficiency dialysis, or continuous venovenous hemofiltration in patients with acute renal failure. Crit Care Med **2004**; 32:2437–52.
14. Brier ME, Stalker DJ, Aronoff GR, et al. Pharmacokinetics of linezolid in subjects with renal dysfunction. Antimicrob Agents Chemother **2003**; 47:2775–80.
15. Pea F, Viale P, Lugano M, et al. Linezolid disposition after standard dosages in critically ill patients undergoing continuous venovenous hemofiltration: a report of 2 cases. Am J Kidney Dis **2004**; 44:1097–102.
16. Kraft MD, Pasko DA, DePestel DD, Ellis JJ, Peloquin CA, Mueller BA. Linezolid clearance during continuous venovenous hemodialfiltration: a case report. Pharmacotherapy **2003**; 23:1071–5.
17. Zyvox (linezolid) [package insert]. New York, NY: Pfizer, **2005**.
18. Churchwell MD, Pasko DA, Mueller BA. CVVHD transmembrane clearance of daptomycin with two different hemodiafilters [abstract A-22]. In: Program and abstracts of the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, **2004**:5.
19. Cubicin (daptomycin) [package insert]. Lexington, MA: Cubist Pharmaceuticals, **2003**.
20. Mueller BA, Scarim SK, Macias WL. Comparison of imipenem pharmacokinetics in patients with acute or chronic renal failure treated with continuous hemofiltration. Am J Kidney Dis **1993**; 21:172–9.
21. Tegeder I, Bremer F, Oelkers R, et al. Pharmacokinetics of imipenem-cilastatin in critically ill patients undergoing continuous venovenous hemofiltration. Antimicrob Agents Chemother **1997**; 41:2640–5.
22. Hashimoto S, Honda M, Yamaguchi M, Sekimoto M, Tanaka Y. Pharmacokinetics of imipenem and cilastatin during continuous hemodialysis in patients who are critically ill. ASAIO J **1997**; 43:84–8.
23. Fish DN, Teitelbaum I, Abraham E. Pharmacokinetics and pharmacodynamics of imipenem during continuous renal replacement therapy in critically ill patients. Antimicrob Agents Chemother **2005**; 49:2421–8.
24. Giles LJ, Jennings AC, Thomson AH, Creed G, Beale RJ, McLuckie A. Pharmacokinetics of meropenem in intensive care units receiving continuous veno-venous hemofiltration or hemidialfiltration. Crit Care Med **2000**; 28:632–7.
25. Valtonen M, Tiula E, Backman JT, Neuvonen PJ. Elimination of meropenem during continuous veno-venous haemofiltration in patients with acute renal failure. J Antimicrob Chemother **2000**; 45:701–4.
26. Tegeder I, Neumann F, Bremer F, Brune K, Lotsch J, Geisslinger G. Pharmacokinetics of meropenem in critically ill patients with acute renal failure undergoing continuous venovenous hemofiltration. Clin Pharmacol Ther **1999**; 65:50–7.
27. Thalhammer F, Schenk P, Burgmann H, et al. Single-dose pharmacokinetics of meropenem during continuous venovenous hemofiltration. Antimicrob Agents Chemother **1998**; 42:2417–20.
28. Ververs T, van Dijk A, Vinks SA, et al. Pharmacokinetics and dosing regimen of meropenem in critically ill patients receiving continuous venovenous hemofiltration. Crit Care Med **2000**; 28:3412–6.
29. Kruger WA, Schroeder TH, Hutchison M, et al. Pharmacokinetics of meropenem in critically ill patients with acute renal failure treated by continuous hemodialfiltration. Antimicrob Agents Chemother **1998**; 42:2421–4.
30. Robatel C, Decosterd A, Biollaz J, Schaller MD, Buclin T. Pharmacokinetics and dosage adaption of meropenem during continuous venovenous hemodialfiltration in critically ill patients. J Clin Pharmacol **2003**; 43:1329–40.
31. Mueller SC, Majcher-Peszynska J, Hickstein H, et al. Pharmacokinetics of piperacillin-tazobactam in anuric intensive care patients during continuous venovenous hemodialysis. Antimicrob Agents Chemother **2002**; 46:1557–60.
32. Valtonen M, Tiula E, Takkunem O, Backman JT, Neuvonen PJ. Elimination of piperacillin/tazobactam combination during continuous venovenous haemofiltration and haemodialfiltration in patients with acute renal failure. J Antimicrob Chemother **2001**; 48:881–5.
33. van der Werf TS, Mulder PO, Zijlstra JG, Uges DR, Stegman CA. Pharmacokinetics of piperacillin and tazobactam in critically ill patients

with renal failure, treated with continuous veno-venous hemofiltration (CVVH). Intensive Care Med **1997**;23:873–7.

34. Cappellier G, Cornette C, Boillot A, et al. Removal of piperacillin in critically ill patients undergoing continuous venovenous hemofiltration. Crit Care Med **1998**;26:88–91.

35. Rhode B, Werner U, Hickstein H, Ehmcke H, Drewelow B. Pharmacokinetics of mezlocillin and sulbactam under continuous veno-venous hemodialysis (CVVHD) in intensive care patients with acute renal failure. Eur J Clin Pharmacol **1997**;53:111–5.

36. Hardin TC, Butler SC, Ross S, Wakeford JH, Jorgensen JH. Comparison of ampicillin-sulbactam and ticarcillin-clavulanic acid in patients with chronic renal failure: effects of differential pharmacokinetics on serum bactericidal activity. Pharmacotherapy **1994**;14:147–52.

37. Kroh UF, Lennartz H, Edwards D, Stoeckel K. Pharmacokinetics of ceftriaxone in patients undergoing continuous veno-venous hemofiltration. J Clin Pharmacol **1996**;36:1114–9.

38. Matzke GR, Frye RF, Joy MS, Palevsky PM. Determinants of ceftriaxone clearance by continuous venovenous hemofiltration and hemodialysis. Pharmacotherapy **2000**;20:635–43.

39. Malone RS, Fish DN, Abraham E, Teitelbaum I. Pharmacokinetics of cefepime during continuous renal replacement therapy in critically ill patients. Antimicrob Agents Chemother **2001**;45:3148–55.

40. Allaouchiche B, Breilh D, Jaumain H, Gaillard B, Renard S, Saux M-C. Pharmacokinetics of cefepime during continuous venovenous hemodialfiltration. Antimicrob Agents Chemother **1997**;41:2424–7.

41. Davies SP, Lacey LF, Kox WJ, Brown EA. Pharmacokinetics of cefuroxime and ceftazidime in patients with acute renal failure treated by continuous arteriovenous haemodialysis. Nephrol Dial Transplant **1991**;6:971–6.

42. Sato T, Okamoto K, Kitaura M, Kukita I, Kikuta K, Hamaguchi M. The pharmacokinetics of ceftazidime during hemodialfiltration in critically ill patients. Artif Organs **1999**;23:143–5.

43. Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother **1993**;37:1073–81.

44. Malone RS, Fish DN, Abraham E, Teitelbaum I. Pharmacokinetics of levofloxacin and ciprofloxacin during continuous renal replacement therapy in critically ill patients. Antimicrob Agents Chemother **2001**;45:2949–54.

45. Davies SP, Azadian BS, Kox WJ, Brown EA. Pharmacokinetics of ciprofloxacin and vancomycin in patients with acute renal failure treated by continuous haemodialysis. Nephrol Dial Transplant **1992**;7:848–54.

46. Wallis SC, Mullany DV, Lipman J, Rickard CM, Daley PJ. Pharmacokinetics of ciprofloxacin in ICU patients on continuous veno-venous haemodialfiltration. Intensive Care Med **2001**;27:665–72.

47. Fish DN, Chow AT. The clinical pharmacokinetics of levofloxacin. Clin Pharmacokinet **1997**;32:101–19.

48. Traunmuller F, Thalhammer-Scherrer R, Locker GJ, et al. Single-dose pharmacokinetics of levofloxacin during continuous veno-venous haemofiltration in critically ill patients. J Antimicrob Chemother **2001**;47:229–31.

49. Hansen E, Bucher M, Jakob W, Lemberger P, Kees F. Pharmacokinetics of levofloxacin during continuous veno-venous hemofiltration. Intensive Care Med **2001**;27:371–5.

50. Fuhrmann V, Schenk P, Jaeger W, Ahmed S, Thalhammer F. Pharmacokinetics of moxifloxacin in patients undergoing continuous venovenous haemodialfiltration. J Antimicrob Chemother **2004**;54:780–4.

51. Fish DN, Bainbridge JL, Peloquin CA. Variable disposition of ciprofloxacin in critically ill patients undergoing continuous arteriovenous hemodialfiltration. Pharmacotherapy **1995**;15:236–45.

52. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. Clin Infect Dis **2005**;40:1333–41.

53. Pittrow L, Penk A. Dosage adjustment of fluconazole during continuous renal replacement therapy (CAVH, CVVH, CAVHD, CVVHD). Mycoses **1999**;42:17–9.

54. Valtonen M, Tiula E, Neuvonen PJ. Effects of continuous venovenous haemofiltration and haemodialfiltration on the elimination of fluconazole in patients with acute renal failure. J Antimicrob Chemother **1997**;40:695–700.

55. Muhl E, Martens T, Iven H, Rob P, Bruch HP. Influence of continuous veno-venous haemodialfiltration and continuous veno-venous haemofiltration on the pharmacokinetics of fluconazole. Eur J Clin Pharmacol **2000**;56:671–8.

56. Pappas PG, Rex JH, Sobel JD, et al. Guidelines for treatment of candidiasis. Clin Infect Dis **2004**;38:161–89.

57. Robatel C, Rusca M, Padoin C, Marchetti O, Liaudet L, Buclin T. Disposition of voriconazole during continuous veno-venous haemodialfiltration (CVVHDF) in a single patient. J Antimicrob Chemother **2004**;54:269–70.

58. Bellmann R, Egger P, Djanani A, Wiedermann CJ. Pharmacokinetics of amphotericin B lipid complex in critically ill patients on continuous veno-venous haemofiltration. Int J Antimicrob Agents **2004**;23:80–3.

59. Bellmann R, Egger P, Gritsch W, et al. Amphotericin B lipid formulations in critically ill patients on continuous veno-venous haemofiltration. J Antimicrob Chemother **2003**;51:671–81.

60. Tomlin M, Priestly GS. Elimination of liposomal amphotericin B by hemodialfiltration. Intensive Care Med **1995**;21:699–700.

61. Boulieu R, Bastien O, Gaillard S, Flamens C. Pharmacokinetics of acyclovir in patients undergoing continuous venovenous hemodialysis. Ther Drug Monit **1997**;19:701–4.

62. Bleyzac N, Barou P, Massenavette B, et al. Assessment of acyclovir intraindividual pharmacokinetic variability during continuous hemofiltration, continuous hemodialfiltration, and continuous hemodialysis. Ther Drug Monit **1999**;21:520–5.

63. Khajehdehi P, Jamal JA, Bastani B. Removal of acyclovir during continuous veno-venous hemodialysis and hemodialfiltration with high-efficiency membranes. Clin Nephrol **2000**;54:351–5.