# Renal Dose Adjustment Guidelines for Antimicrobials

## Continuous Renal Replacement Therapy (CRRT) Dosing Recommendations

**CRRT Background:**

- When a patient is initiated on CRRT, antimicrobial therapy dosing often requires adjustment to ensure adequate drug concentrations are achieved.
- **CVVHD** removes solutes (including drug) via diffusion. An electrolyte solution (dialysate) runs countercurrent to the patient's blood flow which creates a concentration gradient, driving the removal of solutes.
    - Drug removal is impacted by protein binding (e.g., highly protein bound drugs will be minimally removed), the rate of dialysate flow (increased removal with higher flow rates), and molecular weight (increased removal with lower molecular weight drugs).
    - Drugs that are renally cleared or removed by hemodialysis are likely to be impacted by CVVHD.
- **CVVH** removes solutes (including drugs) via convection. Convection is a transport mechanism that is accomplished by using a high-permeability membrane to generate a large ultrafiltrate volume. Along with the ultrafiltrate, plasma water and certain solutes are forced across the membrane.

**Important Considerations:**

- In patients with renal failure, the time to achievement of steady-state is increased for renally-eliminated agents. Additionally, patients on CRRT may have an increased volume of distribution (specifically for hydrophilic drugs). Therefore, **a loading dose should be utilized if not initiating therapy at the full dose.**
- Patients undergoing CRRT may be predisposed to changes in pharmaceutical agents' volume of distributions (Vd). When agents with relatively large therapeutic windows (e.g., beta-lactams) and low levels of toxicity are utilized in critically ill patients, it may be prudent to err on the side of more aggressive dosing to account for any increases in Vd.
- While on CRRT, patients' residual renal function may continue to change. Improvements or reductions in residual renal function may warrant a change in dosing strategy. Residual renal function should be evaluated on a daily basis when making CRRT dosing plans.
- Monitor patients for interruption of CRRT (e.g., clotting) or changing filtration rates. When CRRT is off, dose as hemodialysis patients or based on any residual renal function.
- **The recommendations below should be used as a guide** to aid in antibiotic dosing while on CRRT. Dosing regimens should be tailored based on presumed source of infection, MIC data (when available), and residual renal function. When a dosing range is indicated in the tables below (e.g., ampicillin/sulbactam 1.5-3g q6-8h), a more aggressive dose should be selected for severe infections.
- Pharmacists should document final dosing recommendations and any necessary rationale using the preformatted note available in One Chart.

## Prolonged Intermittent Renal Replacement Therapy (PIRRT) Dosing Recommendations

**PIRRT Background:**

- PIRRT is a hybrid renal replacement therapy similar to CRRT; however, it is run over a fraction of a 24-hour period (e.g., "nocturnal CRRT"). Advantages of PIRRT include earlier patient mobilization and greater flexibility for procedures during the day.
- Antimicrobials in patients undergoing PIRRT have two pharmacokinetic phases (intra-dialytic and inter-dialytic phases).
    - For dialyzable drugs, the half-life of the drug is typically shorter in the intra-dialytic phase compared to the inter-dialytic phase.
    - Extrapolating all CRRT antimicrobial dosing regimens to patients undergoing PIRRT may not be appropriate.

**Important Considerations:**

- PIRRT settings (flow rate and session duration) may vary among centers/institutions and caution should be used when extrapolating these recommendations to each patient.
    - Drug removal is related to plasma drug concentration and initiation of a new dose close to PIRRT (or iHD) session may result in more initial drug removal (during the intra-dialytic phase). Thus, **doses should be separated from PIRRT initiation to allow for adequate drug distribution**.
- There is limited clinical data to inform antimicrobial dosing in PIRRT and this resource was developed with the limited published data available. Thus, **the recommendations below should be used as a guide** to aid in antibiotic dosing while on PIRRT. Dosing regimens should be tailored based on presumed source of infection, MIC data (when available), and residual renal function.

## The following anti-infectives do NOT require dose adjustment during CRRT/PIRRT:

- Amphotericin
- Azithromycin
- Ceftriaxone
- Clindamycin
- Doxycycline
- Letermovir
- Linezolid
- Maribavir
- Metronidazole
- Micafungin
- Oxacillin
- Rifampin
- Tigecycline
- Voriconazole

**Table 1: CVVHD Dosing Recommendations**

| Drug \| Indication | | Loading Dose for CRRT | Standard Anephric Dose | Dose by CVVHD Dialysate Flow Rate | | | Ref. |
|---|---|---|---|---|---|---|---|
| | | | | 1 L/h | 2 L/h | 3-4 L/h | |
| Aminoglycosides | | | Provide loading dose then dose per TDM | Provide loading dose then dose per TDM: patients may require repeat dosing q24h at flow rate > 1 L/h | | | 1-5 |
| Amikacin | | 15-25 mg/kg | | | | | |
| Gentamicin | | Gram negative: 5-7 mg/kg<br>Gram positive synergy: 1 mg/kg | | | | | |
| Tobramycin | | 5-7 mg/kg | | | | | |
| Acyclovir[a] | Mucocutaneous HSV | N/A | 2.5 mg/kg q24h | 5 mg/kg q24h | | 5 mg/kg q12h[a] | 1, 4, 6, 7 |
| | VZV or HSV encephalitis | | 5 mg/kg q24h | 7.5 mg/kg q24h | 10 mg/kg q24h | 10 mg/kgq12h[a] | |
| Ampicillin | Cystitis | N/A | 1 g q24h | 1 g q12h | 1 g q8h | 1 g q6h | 1,6 |
| | Systemic infection | | 2 g q24h | 2 g q12h | 2 g q8h | 2 g q6h | |
| Ampicillin/sulbactam | Cystitis | 3 g | 1.5 g q24h | 1.5 g q8h | | 1.5 g q6h | 6 |
| | Systemic infection | | 3 g q24h | 3 g q8h | | 3 g q6h | |
| Aztreonam[b] | Cystitis | 2 g | 1 g q24h | 1 g q8h or 2 g q12h | | 2 g q8h | 6 |
| | Systemic infection | | 2 g q24h | 2 g q8h | | 2 g q6h | |
| Cefazolin[b] | Cystitis | 2 g | 1 g q24h | 1 g q8h | | | 1,7 |
| | Systemic infection | | | 2 g q12h | 2 g q12h | 2 g q8h | |
| Cefepime | Standard dose | 2 g | 1 g q24h | 1 g q8h | 1 g q6h | 1 g q6h or 2 g q8h | 31-33,49 |
| | Neutropenic fever | | | 2 g q12h | | 2 g q8h | |
| Cefiderocol (administer over 3 hours) | | N/A | 750 mg q12h | 1.5 g q12h | 2 g q12h | 1.5 g q8h<br>2 g q8h (if > 4 L/h) | 1 |
| Ceftazidime | | 2 g | 1 g q24h | 1 g q8h or 2 g q12h | | 2 g q8h | 1 |
| Ceftazidime/avibactam | Standard dosing | N/A | 0.94 g q48h | 1.25 g q8h | | | 4, 34-36 |
| | MIC > 4, deep-seeded infection | | | 2.5 g q8h | | | |
| Cefoxitin | | N/A | 1-2 g q24h | 1 g q12h | 2 g q12h | 2 g q8h | 34 |
| Ceftolazone/tazobactam | Urinary & intra-abdominal infections | 1.5 g | 150 mg q8h | 750 mg q8h | | | 4, 37-41 |
| | Systemic infection, MDR *Pseudomonas*, HAP/VAP | | 450 mg q8h | 1.5 g q8h | | | |
| Ceftaroline | Standard dosing | N/A | 200 mg q12h | 400 mg q12h | | | 1, 42 |
| | Endocarditis/SAB | | 200 mg q8h | 400 mg q8h | | | |
| Colistin (dosed on CBA)* | | 300 mg | 300 mg x 1, followed by 180 mg on HD days, 130 mg on non-HD days | 100 mg q8h | | | 1, 14, 15 |

| Drug \| Indication | | Loading Dose for CRRT | Standard Anephric Dose | Dose by CVVHD Dialysate Flow Rate | | | Ref. |
|---|---|---|---|---|---|---|---|
| | | | | 1 L/h | 2 L/h | 3-4 L/h | |
| Daptomycin[c,]* | | N/A | 6 mg/kg q48h | 6-8 mg/kg q24h | | | 12, 43-46 |
| Ertapenem | | N/A | 500 mg q24h | 1 g q24h | | | 1, 22 |
| Fluconazole* | Cystitis or oropharyngeal thrush | 800 mg (12 mg/kg) | 400 mg (6 mg/kg) after HD three times weekly | 200 mg q24h | | | 34, 47, 48 |
| | Systemic infection for non-*C. glabrata* | | | 400 mg q24h | | | |
| | *C. glabrata,* initial therapy for candidemia, or treatment of *Candida* endophthalmitis | | | 800 mg q24h | | | |
| Ganciclovir[d] | Induction | N/A | 1.25 mg/kg after HD three times weekly | 2.5 mg/kg q24h | 2.5 mg/kg q12h | | 1, 4, 6, 8 |
| | Maintenance/ Prophylaxis | | 0.625 mg/kg after HD three times weekly | 1.25 mg/kg q24h | 1.25 mg/kg q12h | | |
| Imipenem/cilastatin (empiric treatment, MIC ≤ 2)[e] | | 1 g (or none) | Not recommended | 500 mg q12h | 500 mg q8h | 500 mg q6h | 27, 28 |
| Imipenem/cilastatin/relebactam (MIC ≤ 2)[f] | | N/A | Not recommended | 500 mg q6h | | | 29 |
| Levofloxacin[g] | Cystitis | 750 mg | 250 mg q48h | 250-500 mg q24h | | | 1, 4, 16-18 |
| | Systemic infection, pyelonephritis | | 500 mg q48h | 500-750 mg q24h | | | |
| Meropenem | Standard dose | 1 g | 500 mg q24h | 500 mg q6h | | | 1, 23-25 |
| | Meningitis, cystic fibrosis, MIC = 4 | 2 g | 1 g q24h | 2 g q12h | 2 g q8h | | |
| Meropenem/vaborbactam | | N/A | 1 g q12h | 2 g q8h | | | 26 |
| Oseltamivir | Influenza treatment | N/A | 30 mg x 1, then after each HD session | 75 mg q12h | | | 19-21 |
| | Influenza prophylaxis | | 30 mg x 1, then weekly | No data available | | | |
| Piperacillin/tazobactam (EI)[h] | | N/A | 4.5 g EI q12h | 4.5 g EI q8h | | | 13 |
| Trimethoprim/sulfamethoxazole (TMP/SMX)* | Prophylaxis | N/A | Not recommended | 80-160 mg (TMP) q24h | | | 1, 9, 10 |
| | Systemic GNR | | Not recommended | 10 mg/kg/day (TMP) divided q12h | | | |
| | *Stenotrophomonas* | | Not recommended | 10-15 mg/kg/day (TMP) divided q8-12h | | | |
| | *Pneumocystis* Pneumonia | | 5-7.5 mg/kg/day (TMP) | 15 mg/kg/day (TMP) divided q8h | | | |
| Valganciclovir | | N/A | 100-200 mg after HD three times weekly | Not recommended, use ganciclovir instead | | | 30 |
| Vancomycin | | 20-25 mg/kg | Provide loading dose, then re-dose per TDM | After loading dose, either 7.5-10 mg/kg q12h OR 15-20 mg/kg q24h<br>Adjust accordingly to obtain serum concentrations within desired range for target AUC (400-600 mg/L*h) | | | 1, 6, 11, 12 |

**Abbreviations:** h = hours, TDM = therapeutic drug monitoring, EI = extended infusion (over 3 or 4 h), CBA = colistin base activity, HD = hemodialysis, N/A = not applicable, MDR = multi-drug resistant, HAP = hospital-acquired pneumonia, VAP = ventilator acquired pneumonia, SAB = *Staphylococcus aureus* bacteremia

[a] Limited evidence available for dosing with dialysate flow rate > 2 L/h

[b] Flow rates > 2 L/h are rarely addressed in literature; decreasing the interval is done empirically to maintain levels above MIC for time-dependent antibiotics, specifically those with limited protein binding

[c] Doses > 8 mg/kg q24h increase risk of CPK elevations and myopathy. Clinical judgment and frequent CPK monitoring should be used if pursuing doses of 10-12 mg/kg q24h

[d] Based on a usual induction dose of 5 mg/kg q12h and a maintenance dose of 5 mg/kg q24h. Note there is limited information with flow rates > 1-1.5 L/h.

[e] For organisms with MIC $\geq$ 4, higher doses (e.g., 1 g q6h) may be required to achieve PK/PD targets; however, risk of neurotoxicity is significantly higher, an alternative antimicrobial agent may be preferred

[f] For organisms with MIC of 4, 750 mg q6h may be required to achieve PK/PD targets

[g] Avoid for empiric monotherapy to treat gram negative infections

[h] Tazobactam can accumulate as it is not removed as readily; caution in decreasing interval beyond q8h (i.e., q6h) in patients with lack of residual renal function

* May have alternative dosing recommendations for CVVH, see Appendix A

**Table 2: PIRRT Dosing Recommendations**

| Drug \| Indication | | Recommended PIRRT Dose | Timing of Dose | Comments | Ref. |
|---|---|---|---|---|---|
| Aminoglycosides | | | | | 1, 2 |
| Amikacin | | 15-25 mg/kg | 30-60 min prior to PIRRT | Based on expert opinion, re-dose per TDM | |
| Gentamicin | | 6 mg/kg | 30-60 min prior to PIRRT | Based on flow rate of ~2 L/h, duration of 10 h session | |
| Tobramycin | | 6 mg/kg | 30-60 min prior to PIRRT | Extrapolated from gentamicin data | |
| Acyclovir | | No data available | | | - |
| Ampicillin | | 1-2 g q8h | No specific recommendation | Extrapolated from ampicillin/sulbactam data | 1, 6, 7 |
| Ampicillin/sulbactam | | 3 g q8h | No specific recommendation | Based on duration of 8 h session | 6 |
| Aztreonam | | 2 g loading dose, followed by 1-2 g q12h | Administer at least 1 dose after end of daily PIRRT | Based on duration of 7 h session | 1 |
| Cefazolin | | 1 g q8h or 2 g q12h | No specific recommendation | Based on expert opinion | 1 |
| Cefepime | Standard dose | 1 g q6h or 2 g q12h | Alternative dosing recommendation of 2 g before daily PIRRT and 3 g after end of daily PIRRT | Based on flow rate of 4-5 L/h, duration of 8-10 h session | 8, 13 |
| | Neutropenic fever | | | | |
| Cefiderocol (administer over 3 hours) | | No data available | | | - |
| Ceftazidime | | 2 g q12h | No specific recommendation | Based on flow rate of 4-5 L/h, duration of 8-10 h session | 8 |
| Ceftazidime/avibactam | | 1.25 g q12h | Administer 1 of the doses after end of daily PIRRT | Based on expert option<br>If PIRRT > 12 hour session, may need q8h dosing | 1 |
| Cefoxitin | | No data available | | | - |
| Ceftolazone/tazobactam | | 750 mg q8h | Administer 1 dose at the beginning of PIRRT and 1 dose after end of daily PIRRT | Based on flow rate of 200 mL/min, duration of 7.5 h session | 14 |
| Ceftaroline | Standard dosing | 400 mg q12h | No specific recommendation | Based on expert opinion | 1 |
| | Endocarditis/SAB | 400 mg q8h | | | |
| Colistin (dosed on CBA) | | 300 mg CBA loading dose | Administer after end of daily PIRRT | Add 10% per 1 hour of PIRRT replacement to the recommended baseline daily dose for kidney function (e.g., CrCl < 5 mL/min = 130 mg CBA/day, administer in 2 divided doses 12 hours apart starting 12 hours after the loading dose) | 1, 10 |
| Daptomycin | | 6 mg/kg q24h | Administer after end of daily PIRRT | Based on flow rate of 160 mL/min, duration of 8 h session | 15, 16 |
| Ertapenem | | 500 mg loading dose, followed by 500 mg post-PIRRT | Administer 1 dose after end of daily PIRRT | Based on flow rate of 4-5 L/h, duration of 8-10 h session | 1, 12 |
| Fluconazole | | 400 mg q24h | No specific recommendation | Based on flow rate of 4-5 L/h, duration of 8-10 h session | 17, 18 |
| Ganciclovir | Induction | 2.5 mg/kg q24h | Administer after end of daily PIRRT | Based on expert opinion | 1 |
| | Maintenance/Prophylaxis | 1.25 mg/kg q24h | | | |
| Imipenem/cilastatin (empiric treatment, MIC < 2)[a] | | 500 mg q6h or 1 g q8h | No specific recommendation | Based on flow rate of 4-5 L/h, duration of 8-10 h session | 12 |
| Imipenem/cilastatin/relebactam (MIC $\leq$ 2) | | 500 mg q6h | No specific recommendation | Specific data not available, use with caution<br>May extrapolate from imipenem/cilastatin | - |

| Drug \| Indication | | Recommended PIRRT Dose | Timing of Dose | Comments | Ref. |
|---|---|---|---|---|---|
| Levofloxacin[b] | Cystitis | 250-500 mg | Administer after end of daily PIRRT | Based on expert opinion<br>For regimens of 750 mg q24h, administer 48h<br>For regimens of 500 mg q24h, administer 250 mg q24h | 1 |
| | Systemic infection, pyelonephritis | 500-750 mg | | | |
| Meropenem | Standard dose | 1 g EI q12h | Administer 1 dose after end of daily PIRRT | Based on flow rate of 4-5 L/h, duration of 8-10 h session | 1, 12 |
| | Meningitis, cystic fibrosis, MIC = 4 | 2 g EI q12h | Administer 1 dose after end of daily PIRRT | Specific data not available, use with caution<br>May extrapolate from standard dose | |
| Meropenem/vaborbactam | | No data available | | | - |
| Oseltamivir | Influenza treatment | 75 mg q24h | Administer after end of daily PIRRT | Based on expert opinion | 1 |
| | Influenza prophylaxis | No data available | | | |
| Piperacillin/tazobactam (EI) | | 4.5 g EI q8h | Administer 1 dose after end of daily PIRRT | Based on flow rate of 6 L/h, duration of 6 h session | 1, 7, 8, 9 |
| Trimethoprim/ sulfamethoxazole (TMP/SMX) | Prophylaxis | No data available | | | - |
| | Systemic GNR | | | | |
| | *Stenotrophomonas* | 10-15 mg/kg/day (TMP) | Divided q8h | Based on blood and dialysate flow rates of 170 mL/min, duration of 6-8 h session | 1, 3, 4 |
| | *Pneumocystis* Pneumonia | | | | |
| Valganciclovir | | Not recommended, use ganciclovir instead | | | 11 |
| Vancomycin | | 20-25 mg/kg loading dose | 15 mg/kg after end of each PIRRT session | Based on blood and dialysate flow of 160 mL/min, duration of 8 h session | 1, 4, 5 |

**Abbreviations:** TDM = therapeutic drug monitoring, EI = extended infusion, CBA = colistin base activity, HD = hemodialysis, N/A = not applicable, MDR = multi-drug resistant, HAP = hospital-acquired pneumonia, VAP = ventilator acquired pneumonia, SAB = *Staphylococcus aureus* bacteremia

[a] Risk of neurotoxicity is significantly higher at doses recommended in PIRRT, use of an alternative antimicrobial agent may be preferred

[B] Avoid for empiric monotherapy to treat gram negative infections

## Appendix A: CVVH Dosing Recommendations

| Drug \| Indication | | Loading Dose for CRRT | Standard Anephric Dose | Dose by CVVH Dialysate Flow Rate | | | Ref. |
|---|---|---|---|---|---|---|---|
| | | | | 1 L/h | 2 L/h | 3-4 L/h | |
| Colistin (dosed on CBA) | | N/A | 300 mg x 1, followed by 180 mg on HD days, 130 mg on non-HD days | 2.5 mg/kg q24h | | 2-3 mg/kg q12h | 1 |
| Daptomycin | | N/A | 6 mg/kg q48h | No adjustment necessary; dose as anephric | | | 1 |
| Fluconazole | | 800 mg (12 mg/kg) | 400 mg (6 mg/kg) after HD three times weekly | 200 mg q24h | 400 mg q24h | 400 mg q12h | 1, 2 |
| Trimethoprim/sulfamethoxazole (TMP/SMX) | Severe infections/PJP | N/A | 5-7.5 mg/kg/day (TMP) | 2.5-7.5 mg/kg (TMP) q12h | | | 1 |

**Abbreviations:** CBA = colistin base activity, HD = hemodialysis, N/A = not applicable, MDR = multi-drug resistant, PJP = *Pneumocystis jiroveci* pneumonia

**Document prepared by:** Shawnalyn Sunagawa, PharmD; Rachel Ballard, PharmD; Brita Jensen, PharmD; Andrew Sabers, PharmD; Kelsey Whiston, PharmD; Greg Peitz, PharmD
**Reviewed by:** Scott Bergman, PharmD; Bryan Alexander, PharmD; Molly Miller, PharmD; Jeremy Tigh, PharmD; Trevor Van Schooneveld, MD
**Approved by:** Nebraska Medicine Antimicrobial Stewardship Program

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