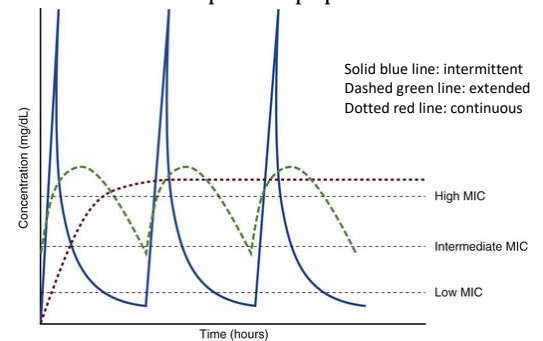


## UCDMC Extended Infusion Beta-Lactam Guideline

With the relative lack of novel antimicrobials available to address the increasing concern for multidrug resistance, there has been a shift to focus on optimizing use of currently available antimicrobials to overcome increasing minimum inhibitory concentrations (MICs) and avoid breeding resistance. This is particularly important to consider in patient populations that exhibit increased drug clearance (e.g. critically ill, young, obese, burn, trauma) and for patients who develop hospital-acquired infections with pathogens exhibiting higher MICs.

Beta-lactams exhibit time-dependent bactericidal activity when serum drug concentrations are maintained above the MIC, which can be augmented by increasing the frequency, dose, or infusion time of the antibiotic. Of these options, prolonging the infusion time of beta-lactams has shown to be the most efficacious and cost-effective while carrying the lowest risk for adverse drug reactions (i.e. nephrotoxicity, neurotoxicity), which are often peak-dependent.



Infusion type	Duration	Candidates
<b>Intermittent</b>	30-60 min	Multiple concurrent IV medications, end-stage renal disease
<b>Extended</b>	3-4 hours	<b>Preferred method of B-lactam administration</b> Critically ill, hyperdynamic

Drug	Standard daily dose	Loading dose	Maintenance dose and renal adjustment by CrCl*
<b>Cefazolin</b>	6 g/day	2 g	<u>Standard dose:</u> 2 g q8h infused over 4 hours <u>CrCl less than 30 mL/min:</u> Renally adjusted intermittent infusion
<b>Ceftazidime</b>	6 g/day	2 g	<u>Standard dose (greater than 60 mL/min):</u> 2 g q8h infused over 4 hours <u>CrCl 30-60 mL/min:</u> 2 g q12h infused over 4 hours <u>CrCl Less than 30 mL/min:</u> Renally adjusted intermittent infusion
<b>Cefepime</b>	6 g/day	2 g	<u>Standard dose (greater than 60 mL/min):</u> 2 g q8h infused over 4 hours <u>CrCl 30-60 mL/min:</u> 2 g q12h infused over 4 hours <u>CrCl Less than 30 mL/min:</u> Renally adjusted intermittent infusion or consider piperacillin/tazobactam for HD or CKD 5 patients
<b>Meropenem</b>	1.5 g/day – 3g/day	1 g	<u>UTI dose:</u> 500 mg q8h infused over 3 hours <u>Standard dose:</u> 1g q8h infused over 3 hours <u>Cystic Fibrosis/Meningitic dose:</u> 2g q8h over 3 hours <u>Less than 30 mL/min:</u> Renally adjusted intermittent infusion
<b>Nafcillin</b>	12g/day	2 g	<u>Standard dose:</u> 2g q4h infused over 4 hours No renal dosage adjustment required
<b>Piperacillin-tazobactam</b>	10.125 g/day – 13.5g/day	4.5 g	<u>Standard dose (greater than 60 mL/min):</u> 3.375 g q8h infused over 4 hours <u>High dose (Cystic Fibrosis, Obesity (&gt;120kg):</u> 4.5g q8h infused over 4 hours <u>CrCl Less than 20 mL/min:</u> 3.375g q12h infused over 4 hours

\*Please note all dosing recommendations are based on a 70 kg adult - further dosing adjustments may be required by clinical pharmacy

Y-Site Incompatibility: Refer to Trissel's IV Compatibility online through Lexicomp or discuss with pharmacist.

Consider monitoring trough levels for cefepime, especially in patients with altered renal function or enhanced drug clearance. Toxicity was associated with trough levels greater than 38 mg/L. Please collect a trough level and mid-point level to allow for PK calculations. Therapeutic range is based on MIC of targeted organism. When treating empirically target a cefepime trough range of less than or equal to 7.5 mg/L.<sup>6</sup>

Consider monitoring peak and trough levels for meropenem, especially in patients with altered renal function or enhanced drug clearance. Trough goal 8mg/L for meropenem. Toxicity observed at 45mg/L. Recommend obtaining a trough and midpoint level for PK calculations. Troughs for routing monitoring.

- Roberts JA, Paul SK, Akova M, et al. DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current  $\beta$ -Lactam Antibiotic Doses Sufficient for Critically Ill Patients? *Clinical Infectious Diseases* 2014;58(8):1072–83.
- Abdul-Aziz MH, Sulaiman H, Mat-Nor MB, et al. BLISS study Beta-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis. *Intensive Care Med* 2016;42:1535-1545.
- Bauer KA, Gentene AJ, West JE, Shidham G, Goff DA. An antimicrobial stewardship program's evaluation of the safety and efficacy of continuous infusion of nafcillin in the treatment of methicillin-sensitive staphylococcus aureus bacteremia. *Infect Dis Clin Pract.* 2013;21(2):111–113
- Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's clinical practice guidelines for healthcare-associated ventriculitis and meningitis [published online ahead of print February 14, 2017]. *Clin Infect Dis.* doi: 10.1093/cid/ciw861
- Zhu LL, Zhou, Q. Optimal infusion rate in antimicrobial therapy explosion of evidence in the last five years. *Infec Drug Resist.* 2018 Aug 8;11:1105-1117. doi: 10.2147/IDR.S167616

6. Boschung-Pasquier, L., et al. Cefepime neurotoxicity: thresholds and risk factors. A retrospective cohort study. *Clinical Microbiology and Infection*. 26 (2020) 333-339.
7. Scharf, C et. al. Therapeutic Drug Monitoring of meropenem and piperacillin in critical illness – experience and recommendations from one year in routine clinical practice. *Antibiotics*. 2020 Mar; 9(3): 131.

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