

Cefepime, Piperacillin/tazobactam, Meropenem Extended Infusion Dosing Guidelines for Critical Care Unit

Background

In an era of escalating resistance with limited antimicrobial options, dose optimization is an essential component for clinical success in the treatment of serious infections with multidrug-resistant Gram negative organisms as well as preventing further resistance. For β -lactam antibiotics, in vitro and animal studies indicate that the time that free drug remains above the MIC (fT>MIC) predicts bactericidal activity.^{1,2} Administering a β -lactam antibiotic as an infusion for longer than the conventional 30-60 minute duration can produce a lower peak with free drug concentrations above the MIC for a longer period. Multiple clinical studies support prolonged/extended infusion time of β -lactam antibiotics as a way to maximize their time-dependent bactericidal activity and improve the probability of target attainment.²⁻¹³

Cefepime, piperacillin/tazobactam, and meropenem are frequently used broad spectrum β -lactam antibiotics and are often given as intermittent infusions of 30-60 minutes. Studies have showed that prolonged infusions of cefepime, piperacillin/tazobactam, and meropenem over 3 to 4 hours improved the outcomes of critically ill patients with *P. aeruginosa* infection and ventilator associated pneumonia.³⁻¹³

Goal

To implement the extended infusion dosing strategy of cefepime, piperacillin/tazobactam, and meropenem in Intensive Care Unit (ICU) patients to optimize their pharmacodynamic profile and improve clinical outcomes.

Dosing Guideline for EXTENDED INFUSION

CrCl	Cefepime	
	Most Indications	Meningitis, Neutropenic Fever, <i>P. aeruginosa</i> ,
≥ 60 mL/min	1 gm q8h <i>or</i> 2 gm q12h over 4 hrs	2 gm q8h over 4 hrs
> 30 mL/min	1 gm q8h <i>or</i> 2 gm q12h over 4 hrs	2 gm q12h over 4 hrs
≤ 30 mL/min	1 gm q24h over 30 min	1 gm q12h <i>or</i> 2 gm q24h over 30 min
HD	1 gm q24h <i>or</i> 2gm after HD* over 30 min *For stable patients or upon discharge for mild to moderate infections. This dosing strategy should NOT be used for patients require >1g/day of cefepime (ie. morbidly obese, severe sepsis, CNS infection, etc.). References: UptoDate, Perez K, <i>etal.</i> Am J Kidney Dis. 2012; 59(5):738-742.	1-2 gm q24h over 30 min
CVVHD	2 gm q12h over 4 hrs	2 gm q12h over 4 hrs
CrCl	Piperacillin/tazobactam	
	Most Indications	<i>P. aeruginosa</i>
≥ 40 mL/min	4.5 gm q8h over 4 hrs	4.5 gm q6h over 4 hrs
20-39 mL/min	2.25 gm q8h over 30 min	2.25 gm q6h over 30 min

< 20 mL/min or HD	2.25 gm q12h over 30 min	2.25 gm q8h over 30 min
CVVHD	4.5 gm q12h over 4 hrs	4.5 gm q8h over 4 hrs
CrCl	Meropenem*	
	Most Indications	Intermediate Sensitivity, Meningitis
≥ 50 mL/min	1 gm q8h over 3 hrs	2 gm q8h over 3 hrs
26-49 mL/min	1 gm q12h over 3 hrs	2 gm q12h over 3 hrs
10-25 mL/min	500 mg q12h over 30 min	1 gm q12h over 30 min
< 10 mL/min or HD	500 mg q24h over 30 min	1 gm q24h over 30 min
CVVHD	1 gm q12h over 3 hrs	2 gm q12h over 3 hrs

*ID consult service can facilitate Meropenem extended infusion dosing strategy for **selected ICU patients** with severe infections associated with multidrug resistant gram-negative organisms. (Please note: Meropenem 500mg q6h will continue to be the regimen for regular 30-minute infusion for patient with normal renal function).

Nursing/Pharmacy

ICU and pharmacy staff will be educated by the Antibiotic Stewardship Program of ID/Pharmacy to ensure understanding of the new extended infusion dosing strategy. Alaris pumps are programmed to deliver 4-hr infusions for cefepime and piperacillin/tazobactam in all critical care units. Meropenem extended infusion (over 3-hr) will be recommended by ID consult service for selected patient cases, therefore, time of infusion 30-min and 3-hr infusion will be available for clinician to order.

See table for IV medications incompatible with cefepime, piperacillin/tazobactam, and meropenem via Y-site.

- Administration of the extended infusion should not be interrupted at anytime unless under special circumstances or specified by a physician
- If administration needs to be interrupted, it should not exceed 30 minutes at any given time

Incompatible IV Medications via a Y-site ^{14,15}		
(Do NOT administer chemotherapy with piperacillin/tazobactam, cefepime, meropenem via a Y-site)		
Cefepime		
Acetylcysteine	Filgrastim	Nicardipine (1mg/mL)
Acyclovir	Gallium nitrate	Ondansetron
Amphotericin B	Ganciclovir	Pantoprazole
Argatroban	Haloperidol	Phenytoin
Chlordiazepoxide	Hydroxyzine	Prochlorperazine
Chlorpromazine	Lansoprazole	Promethazine
Ciprofloxacin	Magnesium sulfate	Propofol (1mg/mL)
Diazepam	Mannitol	Quinupristin/Dalfopristin
Diltiazem	Meperidine	Tacrolimus
Diphenhydramine	Metoclopramide	Theophylline (aminophylline)
Dobutamine (250mg/mL undiluted)	Midazolam	Vancomycin (10mg/mL in D5W)
Dopamine (3.2mg/mL in D5W)	Morphine sulfate (1mg/mL in D5W)	Vecuronium
Enalaprilat	Mycophenolate (6mg/mL in D5W)	Voriconazole
Erythromycin lactobionate	Nalbuphine	
Famotidine	Nesiritide	
Piperacillin/tazobactam		
Acyclovir	Haloperidol	Nesiritide
Amiodarone	Hydralazine	Nicardipine
Amphotericin B	Hydroxyzine	Pentamidine

Azithromycin	Insulin	Pentazocine
Chlorpromazine	Labetalol	Phenytoin
Ciprofloxacin	Lactated Ringer's solution	Polymyxin B
Cisatracurium (5mg/mL)	Levofloxacin	Prochlorperazine
Codeine phosphate	Methadone	Promethazine
Diltiazem	Methyldopate	Propranolol
Dobutamine	Midazolam	Quinupristin/Dalfopristin
Doxycycline hyclate	Minocycline	Rocuronium
Famotidine	Mivacurium	Tobramycin
Ganciclovir	Mycophenolate	Vecuronium
Glycopyrrolate	Nalbuphine	Verapamil
Meropenem		
Amiodarone	Diazepam	Nicardipine
Acyclovir (50 mg/mL)	Doxycycline hyclate (50 mg/mL)	Ondansetron (50 mg/mL)
Amphotericin B	Ketamine hydrochloride	Pantoprazole
Calcium gluconate (50 mg/mL)	Multiple vitamin injection	Quinupristin-Dalfopristin
Ciprofloxacin	Mycophenolate	Zidovudine (50 mg/mL)

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