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SUBJECT: Prolonged Infusion Antibiotics Protocol	**Effective: Nov 2017**
APPROVED BY: Antibiotic Committee	**Page 1 of 4**

Purpose: To provide guidelines for the use of prolonged infusion antimicrobial agents in the intensive care units and step down unit at University Health Shreveport.

Background:

Bactericidal activity with beta-lactam antibiotics is dependent on the duration of time that the free drug concentration is maintained above the minimum inhibitory concentration of the pathogen (T>MIC). Maximal bactericidal activity has been found to occur when the duration of time that the serum level is above the MIC is ≥50% of the dosing interval, and the serum level is two to four times the MIC.[1] Additionally, studies have shown that current dosing strategies of beta-lactam antibiotics are often inadequate to achieve these goals in critically ill patients.[2] One of the most efficient ways to maximize the duration of exposure, and increase the bacterial killing of beta-lactam antibiotics is to prolong the infusion. This is especially useful in patients who are critically ill, as they often have altered pharmacokinetic characteristics and are more likely to be infected with higher-MIC, hospital-acquired pathogens.

Scope: This policy applies to the intensive care units (ICUs) and step down unit (SDU) at University Health Shreveport. It applies to adult patients with confirmed or presumed sepsis, concern for multi-drug resistant bacteria, or per the recommendation of an infectious diseases specialist.

Responsibility: All staff and partners caring for patients in the ICUs and SDU.

Procedure:

A. Definitions:
    1. Intermittent infusion – infusion lasting <1 hour
    2. Extended infusion – infusion lasting 3 to 4 hours
    3. Continuous infusion – infusion given at a fixed rate over a 24 hour period
B. The provider shall be responsible for determining the eligibility of the patient for prolonged infusion antibiotics based on the patient's clinical status, their location in the ICU or SDU, and their IV access.
    1. The physician shall be responsible for ordering the prolonged infusion antibiotics. (See “Dosing Recommendations” chart)
    2. Prolonged infusion antibiotics shall only be ordered for adult patients in the ICUs and SDU.
    3. Prolonged infusion antibiotics shall only be ordered for the following indications: confirmed or presumed sepsis (defined as life-threatening organ dysfunction caused by a dysregulated host response to infection)[3], concern for multi-drug resistant bacteria as determined by the treating physician, or per the recommendation of an infectious diseases specialist.
C. The pharmacist shall be responsible for reviewing each order for appropriateness based on the following parameters (not exhaustive): correct dosage and rate (see “Dosing Recommendations” chart

below), indication, allergies, site of infection, suspected pathogen(s), drug interactions, and patient location (ICU/SDU).

D. The nurse shall be responsible for ensuring appropriate IV access, and for ensuring IV compatibility of the prolonged infusion antibiotics. (See attached IV compatibility chart)
    1. If IV access or IV compatibility issues arise, the provider or pharmacist should be notified to look for possible solutions.

E. The nurse shall notify the provider if the prolonged infusion antibiotics need to be held (examples include: loss of IV access, patient off the floor, patient transferred to another unit)

F. The nurse shall be responsible for assessing the patient for signs of adverse effects from the prolonged infusion antibiotics, and reporting to the provider when indicated.

Dosing recommendations:

Antibiotic	Dose/Frequency	Notes
Piperacillin-Tazobactam (Continuous Infusion)	CrCl ≥20 mL/min: Give 4.5g IV loading dose over 30 minutes, followed by 13.5g IV as continuous infusion every 24 hours (given as 4.5g over 8 hours every 8 hours) CrCl <20 or on renal replacement therapy: Continuous infusion use may be considered on a case-by-case basis	If continuous infusion must be held for >3hours: Give loading dose of 4.5g prior to resuming continuous infusion Transitioning from intermittent infusion If the patient has received a dose within the last 3 hours, start continuous infusion without loading dose. If the patient has not received a dose for >3 hours, give loading dose of 4.5g followed by the continuous infusion. Transitioning to intermittent infusion Discontinue the continuous infusion, and begin intermittent infusions after the standard dosing interval (in 6 or 8 hours).
Meropenem (Extended Infusion)	Give as standard dose and dosing interval (based upon indication and renal function), and infuse over 3 hours as opposed to 30 minutes.	Transitioning to/from intermittent infusion Start the new dosing regimen (intermittent or extended infusion) at the time the next dose is due.

References:

1. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis. 1998; 26:1; quiz 1-2.
2. Roberts JA, Paul SK, Akova M, et al. DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: Are Current β-Lactam Antibiotic Doses Sufficient for Critically Ill Patients? Clin Infect Dis, Volume 58, Issue 8, 15 April 2014, Pages 1072–1083.
3. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–810.

Common Y-site Compatibilities (NOT a comprehensive list)

Antibiotic	Known INCOMPATIBLE agents (Do NOT Infuse together via Y-site)	Known Compatible Agents
Piperacillin-Tazobactam	Acyclovir Amiodarone hydrochloride Amphotericin B (conventional) Azithromycin Chlorpromazine Ciprofloxacin Diltiazem Dobutamine Doxycycline Famotidine Ganciclovir Gentamicin Haloperidol Hydralazine Hydroxyzine Insulin Labetolol Levofloxacin Midazolam Nicardipine Prochlorperazine Promethazine Tobramycin	Acetaminophen Amikacin Amphotericin B, liposomal (AmBisome) Argatroban Calcium acetate/chloride/gluconate Clindamycin Daptomycin Dexamethasone Dexmedetomidine Diazepam Digoxin Diphenhydramine Dopamine Epinephrine Esmolol Fentanyl Fluconazole Furosemide Heparin Hydrocortisone Hydromorphone Ketamine Ketorolac Linezolid Lorazepam Magnesium Methylprednisolone Metoprolol Metronidazole Morphine Naloxone Nitroglycerin Nitroprusside Norepinephrine Octreotide Ondansetron Pentobarbital Phenobarbital Phenylephrine Potassium acetate/chloride/phosphate Sodium acetate/bicarbonate/phosphate

		Succinylcholine Sulfamethoxazole-trimethoprim Vasopressin Voriconazole Zidovudine
Meropenem	Amiodarone hydrochloride [ARS1] Amphotericin B (all formulations)[ARS2] Ciprofloxacin Diazepam Ketamine hydrochloride Mycophenolate mofetil hydrochloride Nicardipine hydrochloride Pantoprazole sodium Quinupristin-Dalfopristin	Argatroban Atropine Azithromycin Daptomycin Dexamethasone Dexmedetomidine Digoxin Diltiazem Diphenhydramine Fluconazole Furosemide Gentamicin Heparin Hydromorphone Insulin Linezolid Lorazepam Metronidazole Morphine Naloxone Norepinephrine Octreotide Phenobarbital Potassium acetate/chloride Vancomycin Vasopressin Voriconazole