NMH Beta-lactam Therapeutic Drug Monitoring Protocol

CLINICAL PROTOCOL:

A. Clinical pharmacist to identify patients who require antibiotic TDM. Only pharmacists can order and interpret levels.
   1. The patient's primary team must also agree to monitoring.

B. Recommended patients include those with impaired organ function, altered beta-lactam PK/PD, and/or pathogens with minimum inhibitory concentration (MIC) near breakpoint.

For patients with serious infections, consider the following:

1. Concern for altered PK (e.g., immunocompromised, risk for augmented clearance, obesity, low or high rate CRRT, renal replacement with residual urine output, or requires ECMO).
2. Likelihood of having a difficult-to-treat pathogen (e.g., MIC near breakpoint).
3. Clinical response to current treatment or difficult-to-penetrate site of infection.
4. Risk factors for antibiotic toxicity (e.g., history of neurotoxicity, > 65 years of age with concurrent renal dysfunction, worsening mental status).
5. BAL or Blood Biofire with *Pseudomonas*, *Enterobacter cloacae*, *Klebsiella aerogenes*, Enterobacterales, *Acinetobacter baumanii*
6. Planned prolonged surgical prophylaxis post-procedure (e.g. lung transplant)

C. Clinical pharmacist to order corresponding antibiotic levels in EPIC for cefepime, meropenem, piperacillin, or tazobactam (typically will order piperacillin, tazobactam infrequently)
   1. A post-distribution peak level and trough level should be ordered:
      a. For dedicated collection instructions, refer to lab handbook
   2. A cefepime trough level alone may be considered in patients who have a predictable volume of distribution (two levels are still recommended for obesity, CRRT, ECMO whenever feasible)
   3. Beta-Lactam plasma concentrations can be ordered after a single dose with Bayesian analysis (Table 1.)
      a. Additional doses, creatinine trend, or levels will increase model accuracy of prediction for individual patients.
      b. For beta-lactams other than those listed below, there may be a send out option depending on the drug and timing, reach out to ADSP pharmacist on a case-by-case basis
   4. Use of a two-point PK assessment is recommended for TDM:
      a. Post-dose peak drawn after end of infusion (refer to **Table 1**).
      b. Pre-dose trough (drawn 30 mins prior to dose).
      c. For cefepime trough only patients: Pre-dose trough (drawn 30 mins prior to dose)

Table 1. Orderable Beta-Lactam Antibiotics and Corresponding Desired Peak Sample Times at NMH

Antibiotic	Infusion time	Desired peak sample time	Lab Range
Cefepime	30 mins	2 hrs post-dose	1-200 mcg/mL
Cefepime (if extended infusion)	3 hrs	End of infusion	1-200 mcg/mL
Piperacillin-tazobactam	4 hrs	End of infusion	1-200 mcg/mL pip 1-100 mcg/mL tazo
Meropenem	3 hrs	End of infusion	1-200 mcg/mL

D. Clinical pharmacist to interpret drug levels, communicate any required dose changes to team, and document in Beta-lactam monitoring note in EPIC using the dotphrase (.BLMONITORING)
   i. General recommendations for PK/PD targets for TDM (Table 2):

Table 2. Population-Based Pharmacokinetic Targets

PK/PD Index	Population	Target*	Pathogens	Drug class
$fT_{>MIC}$	ICU	100% >1x to 4x MIC**	All	All
$fT_{>MIC}$	SOT/SCT	100% >1x to 4x MIC	All	All
$fT_{>MIC}$	Floor/Ward	100% > 1x MIC	All	All

Abbreviations: ICU, intensive care unit; MIC, minimum inhibitory concentration; SCT, stem cell transplantation; SOT, solid organ transplant
* The choice of the PK/PD target should be selected based on the clinical status of the patient
**For seriously ill patients and those with deep seated infections or immunocompromised status consider selecting a more aggressive PK/PD target in the context of the patient's status and response to therapy

E. Interpretation of TDM results:

1. Once PK analysis is complete, $T_{>MIC}$ can be assessed
2. If **floor patient** and $T_{>MIC}$ is < 100%, increase dose or prolong infusion time to target 100% $T_{>MIC}$
3. If **ICU patient** and $T_{>1\text{-}4x\ MIC}$ is < 100%, increase dose or prolong infusion time to target 100% $T_{>1\text{-}4x\ MIC}$
4. If calculated/optimized beta-lactam dosing is greater than that recommended in the NM Renal Dose Adjustment Guidance or FDA label, if challenging interpretation, or if unexpected PK/PD, consult with ID pharmacist on call (pager 55955)
   a. ID pharmacy consult to assess model accuracy in the context of the patient
   b. May consider changing agent or optimizing dosing depending on clinical scenario
5. General considerations for toxicity:
   a. **Consider dose reduction in populations who are at increased risk for toxicity:**
      i. Increased risk for toxicity documented among older patients, those with renal dysfunction, and patients who have trough >5x breakpoint
   b. Examples of potentially elevated plasma trough concentrations:
      i. The following are suggested upper bounds for plasma. These may not account for target site concentrations. Consider risk vs. benefit for plasma trough-based dose adjustment for deep-seated infections.
         1. Piperacillin: trough >160 mg/L
         2. Meropenem: trough >20 mg/L
         3. Cefepime: trough >20-40 mg/L
   c. If a patient has signs of neurotoxicity and an elevated trough, consider holding dose for 2 half-lives and restarting a half-life adjusted dose or changing agents.
   d. Of note, these are suggested upper bounds and have not been well validated, use clinical judgement.
6. Clinical pharmacist to document as a note in Epic using the dotphrase **(.BLMONITORING)**