**NMH Beta-lactam Therapeutic Drug Monitoring Protocol**

**Clinical Protocol:**

* 1. Infectious Diseases (ID) pharmacist to identify patients who require antibiotic TDM.
		1. The patient’s primary team must also agree to monitoring.
		2. An ID consult is not required.
	2. Targeted 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 and/or life-threatening infections, consider the following:
		1. Likeliness of having altered PK/PD (eg, immunocompromised host, demonstrated risk for augmented clearance, or requires extracorporeal organ support).
		2. Likeliness of having a difficult-to-treat pathogen (eg, culture history shows pathogen with elevated MIC or multi-drug resistance).
		3. Clinical response to current treatment (eg, deep-seated infection without ability to obtain adequate source control, difficult-to-penetrate site of infection).
		4. Presence of known risk factors for antibiotic toxicity (eg, history of neurotoxicity, > 65 years of age with concurrent renal dysfunction, worsening mental status on antibiotic treatment)
	3. Orderable Beta-Lactam serum concentrations can be ordered after at least 24 hr of continuous dosing ([see Appendix A](#Aappendix)).
	4. ID pharmacist to order corresponding antibiotic levels in Epic
		1. The “Misc Lab Test, Referred” Lab order should be utilized for placing beta-lactam antibiotic blood samples:
			1. Under ‘Name of test requested,’ manually enter the drug to be assayed.
			2. Under ‘Comments,’ enter the sample collection/transport instructions for the nurse.
			3. For dedicated collection, use a **plain red top vacuum tube**, and collect at the appropriate times.
				1. Note: Red top tubes are preferred; green tops are also acceptable for most drugs per the University of Florida Health (UFHealth) Infectious Disease Pharmacokinetics Laboratory (IDPL).
			4. For use of scavenged blood samples from AM labs (eg, a complete metabolic panel or basic metabolic panel which are in green tops) as a time point for PK analysis:
				1. Place Misc lab order in EPIC (LAB3004 Miscellaneous order) by 1PM (1300)
				2. Then call Referred Testing (61200) to alert them to the need to pull sample
				3. Referred Testing will update the partially completed requisition form to reflect the collection time and date of the scavenged samples before shipping
				4. Enter the sample time as the time of the BMP (eg, 04:00)
				5. Sample comments can be entered via .BETALACTAMTDMLABCOMMENT
		2. Use of a two-point pharmacokinetic assessment is the recommended approach for individualization and TDM:
			1. Pre-dose trough (either via AM BMP or drawn 30 mins prior to next dose)
			2. Post-dose peak drawn after end of infusion (refer to [Appendix A](#Aappendix)).
	5. The [UFHealth IDPL requisition form](https://idpl.pharmacy.ufl.edu/forms-and-catalog/idpl-requisition/) should be completed and emailed to pathrt@nm.org
		1. Complete the following fields specific to the patient and treatment: patient information, ID attending information, drug name, ICD-10 code, current dosing regimen and doses per week, date/time of last doses prior to sampling, date/time of planned times (or leave blank if scavenged blood samples used).
		2. Referred testing phone: 312-926-1200
		3. Referred testing fax: 312-926-6010
		4. ICD-10 code:
			1. Cephalosporins: T36.1X6A
			2. All other systemic antibiotics: T36.8X6A
		5. Circle name of the drug to be assayed in lower right-hand corner of form of the PDF form
	6. Drug sample can be shipped Mon-Wed (must notify Referred Testing by 1PM on day of test). Samples are sent using standard overnight FedEx.
		1. For tests sent Monday-Wednesday, expect results within 24-48 hr
		2. Note: the sample may not arrive until after the morning assay run is completed
	7. ID pharmacist to interpret drug levels, communicate any required dose changes to team, and document in Beta-lactam monitoring note in Epic.
		1. PK/PD targets for measurable beta-lactams:
			1. Levels can be interpreted using standard first order equations, the attached dosing calculator (see [Appendix E](#Eappendix)), or Bayesian software (for cefepime only).
			2. General recommendations for PK/PD targets for TDM (Table 1):

|  |
| --- |
| Table 1. Population-Based Pharmacokinetic Targets  |
| PK/PD Index | Population | Target\* | Pathogens | Drug class |
| *f*T>MIC | ICU | 100% >1x to 4x MIC\*\* | All | All |
| *f*T>MIC | SOT/SCT | 100% >1x to 4x MIC | All | All |
| *f*T>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 nuanced to the clinical status of the patient\*\*For seriously ill patients and those with deep seated infections or immunocompromised status consider a more aggressive goal in the context of the patient’s status |

* + 1. Interpretation of TDM results
			1. Note: See [Appendix E](#Eappendix) for Excel dosing calculator for first order PK and for T>MIC
			2. Once PK analysis is complete, T>MIC can be assessed
			3. If floor patient and T > MIC is < 100%, increase dose or prolong infusion time to target 100% T > MIC
			4. If ICU patient and T > 1-4x MIC is < 100%, increase dose or prolong infusion time to target 100% T > 1-4x MIC
				1. If trough > 8x MIC, consider reducing dose or frequency by 50%
				2. If calculated/optimized beta-lactam dosing is great than that recommended in the NMH Optimizer or FDA label, consult with ID pharmacist on call (pager 55955)
				3. May consider changing agent or optimizing depending on clinical scenario
		2. ID pharmacist to document as a note in Epic using the dotphrase (.BLMONITORING)

**Appendices:**

* 1. [Appendix A – Orderable beta-lactam antibiotics](#Aappendix)
	2. [APPENDIX B – UFHEALTH IDPL REQUISITION FORM](#Bappendix)
	3. [APPENDIX C – PHARMACOKINETIC EQUATIONS](#Cappendix)
	4. [APPENDIX D – EPIC NOTE TEMPLATE FORMAT](#Dappendix)
	5. [APPENDIX E – DOSING CALCULATOR FOR FIRST ORDER PK AND FOR T>MIC](#Eappendix)

**Appendix A – Orderable beta-l****actam antibioticsUFHealth IDPL Requisition form**

|  |
| --- |
| Table 2. Orderable Beta-Lactam Antibiotics and Corresponding Desired Peak Sample Times |
| Antibiotic | **Infusion time** | **Desired peak sample time** |
| Ampicillin | 30 mins | 2 hrs post-dose |
| Aztreonam | 30 mins | 2 hrs post-dose |
| Oxacillin | 30 mins | 2 hrs post-dose |
| Cefazolin | 30 mins | 2 hrs post-dose |
| Cefepime | 30 mins | 2 hrs post-dose |
| Piperacillin-tazobactam | 4 hrs | 4 hrs post-dose (end of infusion) |
| Meropenem |  3 hrs |  3 hrs post-dose (end of infusion) |

**Appendix B – UFHe****alth IDPL Requisition form**





**Appendix C – Ph****armacokinetic Equations**

**Derived PK Equations:**

ke = ln(C1/C2)

 T2-T1

t½ = 0.693/ke

Cmax=C1 / e-ke x time (obs. – prior dose)

Cmin=C1 x e-ke x time (next dose – obs.)

 fu= 1 – protein binding

**For beta-lactams given as rapid infusions, Vd can be calculated as:**

 Vd = [(Dose/time\_infused) / ke] x (1 – e-ke x time\_infused) / (Cmax – Cmin) (Equation 1)

**For beta-lactams given as rapid infusions, *f*T>MIC can be approximated as:**

 *f*T>MIC = ln[(Dose / Vd) / MIC x fu)] x (1 / ke) x 100 / Dosing interval (Equation 2)

**Appendix D – Epic note te****mplate format**

**Adult** **Cefepime Therapeutic Monitoring**

**(Referred send-out test to University of Florida-IDPK Lab)**

Surely U ZZZTEST 26 y.o. female

|  |
| --- |
| **Wt Readings from Last 1 Encounters:** |
| 02/21/21 | 110 kg (242 lb 8.1 oz) |

|  |
| --- |
| **Ht Readings from Last 1 Encounters:** |
| 02/21/21 | 182 cm (71.65") |

**ID Consult:** {yes no:314532} **Date of consult:** 1/13/2022

|  |
| --- |
| **Creatinine** |
| Date | Value | Ref Range | Status |
| 07/02/2020 | 1.25 | 0.55 - 1.30 mg/dL | Final |

|  |
| --- |
| **WBC** |
| Date | Value | Ref Range | Status |
| 11/18/2019 | 7.0 | 3.5 - 10.5 K/UL | Final |

**Other Antimicrobials**:

|  |  |  |
| --- | --- | --- |
| Drug | Start Date | Stop date |
|  |  |  |

**Other Nephrotoxic meds:**

**Initial Order:**

**Estimated Kinetics Original Order:**

Bayesian PK Analysis? {yes no:314532}

|  |  |  |
| --- | --- | --- |
| Date: | 1/12/2022  | 1/13/2022  |
| Peak (mg/L) |  |  |
| Trough (mg/L) |  |  |
| Time Peak  |  |  |
| Time Trough  |  |  |
| Infusion Time (hr) |  |  |
| Ke (hr-1) |  |  |
| T 1/2 (hr) |  |  |
| Vd (L/kg) |  |  |
| Vd (L) |  |  |
| Extrapolated Peak (mg/L) |  |  |
| Extrapolated Trough (mg/L) |  |  |

**Relevant Microbiology:**

|  |  |  |
| --- | --- | --- |
| Date |  |  |
| Source |  |  |
| Organism |  |  |

**Recommendation:**

Assessment

Dose change necessary? {yes no:314532}

**Appendix E – Excel calcul****ator for first order PK and for T>MIC**

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