ADSP
Antimicrobial and Diagnostic Stewardship Program

NMH Beta-lactam Therapeutic Drug Monitoring Protocol

CLINICAL PROTOCOL:

A. 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.

B. 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)

C. Orderable Beta-Lactam serum concentrations can be ordered after at least 24 hr of continuous dosing (see Appendix A).

D. 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:
      a. Under 'Name of test requested,' manually enter the drug to be assayed.
      b. Under 'Comments,' enter the sample collection/transport instructions for the nurse.
      c. For dedicated collection, use a **plain red top vacuum tube**, and collect at the appropriate times.
         i. 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).
      d. 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:
         i. Place Misc lab order in EPIC (LAB3004 Miscellaneous order) by 1PM (1300)
         ii. Then call Referred Testing (61200) to alert them to the need to pull sample
         iii. Referred Testing will update the partially completed requisition form to reflect the collection time and date of the scavenged samples before shipping
         iv. Enter the sample time as the time of the BMP (eg, 04:00)
         v. Sample comments can be entered via .BETALACTAMTDMLABCOMMENT
   2. Use of a two-point pharmacokinetic assessment is the recommended approach for individualization and TDM:
      a. Pre-dose trough (either via AM BMP or drawn 30 mins prior to next dose)
      b. Post-dose peak drawn after end of infusion (refer to Appendix A).

E. The UFHealth IDPL requisition form 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:
   a. Cephalosporins: T36.1X6A
   b. 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

F. 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

G. 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:
   a. Levels can be interpreted using standard first order equations, the attached dosing calculator (see Appendix E), or Bayesian software (for cefepime only).
   b. General recommendations for PK/PD targets for TDM (Table 1):

Table 1. 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 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

2. Interpretation of TDM results
   a. Note: See Appendix E for Excel dosing calculator for first order PK and for $T_{>MIC}$
   b. Once PK analysis is complete, $T_{>MIC}$ can be assessed
   c. If floor patient and $T_{>MIC}$ is < 100%, increase dose or prolong infusion time to target 100% $T_{>MIC}$
   d. If ICU patient and $T_{>1\text{-}4x\ MIC}$ is < 100%, increase dose or prolong infusion time to target 100% $T_{>1\text{-}4x\ MIC}$
      i. If trough > 8x MIC, consider reducing dose or frequency by 50%
      ii. 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)
      iii. May consider changing agent or optimizing depending on clinical scenario
3. ID pharmacist to document as a note in Epic using the dotphrase (.BLMONITORING)

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APPENDICES:

A. APPENDIX A – ORDERABLE BETA-LACTAM ANTIBIOTICS
B. APPENDIX B – UFHEALTH IDPL REQUISITION FORM
C. APPENDIX C – PHARMACOKINETIC EQUATIONS
D. APPENDIX D – EPIC NOTE TEMPLATE FORMAT
E. APPENDIX E – DOSING CALCULATOR FOR FIRST ORDER PK AND FOR T>MIC

APPENDIX A – ORDERABLE BETA-LACTAM 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)

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APPENDIX B – UFHEALTH IDPL REQUISITION FORM

INFECTIOUS DISEASE PHARMACOKINETICS LABORATORY

1600 SW Archer Rd., P4-30
Gainesville, FL 32610
Phone: 352-273-6710 Fax: 352-273-6804
E-mail: peloquinlab@cop.ufl.edu
Website: http://idpl.pharmacy.ufl.edu

UFHealth
UNIVERSITY OF FLORIDA HEALTH

Patient Last, First Name, M.I. (Required)		☐ Male ☐ Female	**Mail results to: (Required)**
Date of Birth:	**Patient ID:**		
Referring Physician (Required):	**Physician NPI #**	**Physician Phone #**	
Fax #	**Facility Phone #**		

COMPLETE SECTION BELOW ONLY IF BILLING INFORMATION DIFFERS FROM "MAIL RESULTS TO" INFORMATION
Please note: We do not bill 3rd party payers. The laboratory or office shipping the samples accepts responsibility for payment.

Bill to / Contact Name:

Billing Address:

City **State** **Zip**

Telephone #

Drug(s) to be assayed *(provide 2 ml serum per test)*

						β-Lactams (intravenous doses) (30-60 min. post infusion & **trough**)	
AZL	Azithromycin (2-3 H & 6-7 H)	ETAH	Ethionamide (2 H & 6 H)	PZAH	Pyrazinamide (2 H & 6 H)		
BDQ	Bedaquiline (5 H & 24 H)	INH	Isoniazid (1-2 H & 6 H)	RBN	Rifabutin (3 H & 7 H)		
BIC	Bictegravir (**trough** & 2 H)	ITRL	Itraconazole (**trough** & 3-4 H)	RIFH	Rifampin (2 H & 6 H)	PIPE	Piperacillin
CIPH	Ciprofloxacin (2 H & 6 H)	LDV	Ledipasvir (**trough**& 4 H)	RPNT	Rifapentine (**trough** & 5-6H)	AMOX	Amoxacillin
CLART	Clarithromycin (2-3H&6-7 H)	LFLHL	Levofloxacin (2 H & 6 H)	RILP	Rilpivirine (**trough** & 4-5H)	AMPI	Ampicillin
CFH	Clofazimine (2-3 H & 6-7 H)	LNZL	Linezolid (**trough,** 2 & 5-6 H)	SOF	Sofosbuvir (**trough**& 1 H)	AZTRE	Aztreonam
CSH	Cycloserine (2-3 H & 6-7 H)	LOPV	Lopinavir (**trough** & 4-6H)	VORL	Voriconazole (**trough**& 2 H)	CEFAZ	Cefazolin
DARU	Darunavir (**trough** & 2-4 H)	MXFL	Moxifloxacin (2 H & 6 H)			CEFE	Cefepime
DTG	Dolutegravir (**trough** & 2 H)	PASH	*p*-Aminosalicylic acid (6 H)			CEFT	Ceftriaxone
EFVL	Efavirenz (**trough** & 5 H)	PMD	Pretomanid (5 H & 24 H)	NAFC	Nafcillin	IMIP	Imipenem
EMBH	Ethambutol (2-3 H & 6-7 H)	POSA	Posaconazole (**trough**& 3H)	MERO	Meropenem	OXA	Oxacillin

Sample preparation and shipment: Collect in a plain red top, 5 ml tube. Allow the sample to clot and separate serum from cells by centrifugation and aliquot into a labeled polypropylene or similar plastic tube. Use a separate tube for each test ordered. Allow room for expansion of sample inside tube. Freeze at -70°C if possible (otherwise -20°C.) Ship for overnight delivery on ≥ 5 lbs. dry ice. SHIP SAMPLES TO BE RECEIVED MONDAY THROUGH FRIDAY. DO NOT SHIP ON FRIDAY OR SATURDAY.

List other medications patient is currently taking: _____

For UFL Use Only
Date Received: _____
Time Received: _____
Condition: (circle one)
Frozen Partially Frozen Thawed

APPENDIX C – PHARMACOKINETIC EQUATIONS

Derived PK Equations:

$ke = \frac{\ln(C_1/C_2)}{T_2-T_1}$

$t½ = 0.693/ke$

$C_{max} = C_1 / e^{-ke \times time\ (obs. - prior\ dose)}$

$C_{min} = C_1 \times e^{-ke \times time\ (next\ dose - obs.)}$

fu= 1 – protein binding

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

$$Vd = [(Dose/time\_infused) / ke] \times (1 - e^{-ke \times time\_infused}) / (C_{max} - C_{min}) \quad \text{(Equation 1)}$$

For beta-lactams given as rapid infusions, $fT_{>MIC}$ can be approximated as:

$$fT_{>MIC} = \ln[(Dose / Vd) / MIC \times fu)] \times (1 / ke) \times 100 / Dosing\ interval \quad \text{(Equation 2)}$$

APPENDIX D – EPIC NOTE TEMPLATE 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 CALCULATOR FOR FIRST ORDER PK AND FOR $T_{>MIC}$

PK Data	Input	Label	Notes
Dose	1000	mg	Dose in mg
Interval	8	hr	Dosing interval
t	3	hr infused	Duration of infusion (this is a short-term infusion model)
MIC	8	mg/L	Actual or targeted pathogen MIC
Conc1	30	mg/L	First or highest observed concentration on curve
Conc2	15	mg/L	Second or lowest observed concentration on curve
delta_t	6	hr	Difference in time Conc1 to Conc2 (use superposition if needed)
t_min	0.25	hr	Time to true trough observation from Conc2
t_mid	1	hr	Time from Conc1 to halfway through infusion
PK Model	**Parameters**	**Label**	
Ke	0.116	h-1	
V	44.2	L	
CL	5.13	L/hr	
fu	0.9	fraction	Use known or literature values for fu = 1 - protein binding
Cmin	14.6	mg/L	
Cmid	33.7	mg/L	