EXTENDED-INTERVAL AMINOGLYCOSIDE DOSING PROTOCOL FOR NON-TRANSPLANT ADULT CYSTIC FIBROSIS PATIENTS WITH ACUTE PULMONARY EXACERBATIONS

PURPOSE
This protocol was developed in order to provide consistent and optimal extended-interval tobramycin and amikacin dosing and monitoring in adult cystic fibrosis (CF) inpatients.

BACKGROUND
Aminoglycoside antibiotics are a critical component in the management of Gram-negative pathogens (most notably *Pseudomonas aeruginosa*) in CF exacerbations. CF patients are frequently exposed to aminoglycosides and other antibiotics at an early age and for extended periods of time, leading to concerns for ototoxicity and nephrotoxicity. Furthermore, the pharmacokinetics of aminoglycosides are altered in patients with CF. An increased volume of distribution (Vd) and more rapid elimination may be observed due to a larger percentage of lean body mass and decreased fat stores compared to non-cystic fibrosis patients. Generally, patients with CF also have a shorter half-life and lower Cmax, thus requiring higher doses. Extended-interval dosing maximizes concentration-dependent killing and reduces the overall time exposure to the drug. For example, a tobramycin dose of 10 mg/kg/day given every 24 hours in a CF patient with normal renal function results in a predicted peak of 25-35 mcg/mL with a 9-11 hour window of undetectable drug concentrations. Comparatively, 10 mg/kg/day given in 3 divided doses results in lower peaks (7-10 mcg/mL) and only a 1-2 hour window of undetectable drug, increasing the risk of toxicity. In response, the current Cystic Fibrosis Foundation (CFF) guidelines recommend treating patients using a once-daily dosing regimen compared to a three-times daily regimen. Goal peak and trough recommendations outlined in this protocol are based on recommendations in the CFF guideline and estimated internal MIC data.

Extended-interval dosing in this protocol is limited to q24h intervals. Calculations and dosing instructions for patients requiring >q24h interval dosing are not provided as this has not been extensively studied in the CF population.

The Department of Pharmacy Clinical and Patient Care Service (CPCS) division has worked in collaboration with the Antimicrobial Stewardship and Evaluation Team (ASET) and the Division of Pulmonary, Allergy and Critical Care Medicine to develop the following protocol.

INCLUSION CRITERIA
- Cystic fibrosis patients ≥ 18 years of age with an acute pulmonary exacerbation
- Patients with CrCl ≥ 70 mL/min

PROCEDURE

I. Choose the Appropriate Method of Dosing
   A. Prior Extended-Interval Therapy
      - Evaluate patient history for prior successful extended-interval dosing regimens at comparable renal function at the time of initiation of therapy.
   B. New Start Extended-Interval Therapy
      - Patients with an estimated CrCl ≥ 70 mL/min
      - Best Practice Advisory (BPA) alert for patients with estimated CrCl < 70 mL/min
   C. Traditional Dosing

http://Pharmacy.mc.duke.edu
II. Initial Extended-Interval Empiric Dosing
   A. Determine creatinine clearance using the normalized CrCl equation:
      \[
      \frac{140 \text{ age}}{\text{Scr}} \times 0.85 \quad \text{if female}
      \]
   B. Calculate the correct dosing weight (DW):

<table>
<thead>
<tr>
<th>Definition</th>
<th>Use this Dosing Weight (DW)</th>
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</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>TBW &lt; IBW</td>
</tr>
<tr>
<td>Normal Weight</td>
<td>TBW = 100-125% IBW</td>
</tr>
<tr>
<td>Obese</td>
<td>TBW &gt; 125% IBW</td>
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</tbody>
</table>

   C. Empiric Extended-Interval Dose Recommendations:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Peak &amp; Trough Goals (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobramycin</td>
<td>10 mg/kg q24h (max dose 700mg)</td>
<td>Peak: 20-40</td>
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<td></td>
<td></td>
<td>Trough: &lt;0.5</td>
</tr>
<tr>
<td>Amikacin</td>
<td>25 mg/kg q24h (max dose 1500mg)</td>
<td>Peak: 40-60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trough: &lt;0.5</td>
</tr>
</tbody>
</table>

   D. Tobramycin doses will be rounded to the nearest 20 mg for doses >40 mg. Amikacin doses will be rounded to the nearest 50 mg. Doses will be infused over 30 minutes.

III. Extended-Interval Therapeutic Monitoring and Dose Adjustments
   A. Timing of concentrations:
      - Two concentrations should be obtained: a peak concentration 30 min to 2 hours after the end of the infusion and a random concentration 8-12 hours later
   B. Estimate Ke from the two levels (2-point kinetics)
      \[
      Ke = \frac{\ln\left(\frac{C_1}{C_2}\right)}{T} \quad \text{where } T = \text{time between the two concentrations}
      \]
      If the peak concentration was drawn more than 2 hours after the end of the infusion, back-extrapolate the true Cmax:
      \[
      C_{\max, \text{true}} = \frac{C_{\max}}{e^{-Ke(t)}} \quad \text{where } t = \text{time peak drawn} - \text{time peak should be drawn}
      \]
   C. Calculate the predicted trough concentration:
      \[
      C_{\min} = C_{\max} \left( e^{-Ke(T-t')} \right) \quad \text{Where } T = \text{dosing interval} \text{ and } t' = \text{infusion time}
      \]
   D. If peak concentration is not within goal range, estimate a new dose:
E. Repeat steps A & B to determine if the new dose is within therapeutic range the following day.

F. Frequency of concentrations:
   - Maintenance trough concentrations should be monitored every 4-7 days or prior to discharge
   - If the patient’s SCr increases by 30% or more, draw a trough concentration. Hold the next dose until the concentration can be confirmed as within the target range.
   - If trough concentration is elevated above target but < 2.0 for tobramycin or < 8 for amikacin, empirically reduce dose by 20-30%. Recheck a trough level prior to the 3rd new dose or prior to discharge, whichever is first.
   - If the trough concentration is > 2.0 for tobramycin or > 8 for amikacin, hold dose and recheck concentration at next blood draw at least 12 hours afterwards. Consider traditional dosing.

G. Laboratory monitoring: SCr and BUN should be measured at baseline and at least 2x weekly

H. Procedures for patient monitoring and chart documentation are the same as those outlined in the Adult PK Policy.

References:
2. Flume et al. Am J Respir Crit Car Med 2009; 180:802-808