Policy Title: Clinical Pharmacokinetics (PK) Service Policy

Policy Statement: It is the policy of UMHC that PK consult orders (for vancomycin or aminoglycosides) will establish a standardized monitoring approach. The following policy will outline the procedures that pharmacists will follow upon receipt of a “PK Consult”. Pharmacist responsibilities in accordance with this policy will include ordering and changing doses, as well as ordering serum concentration levels and relevant labs. Any order stating “consult pharmacy” or “pharmacy to dose” in regards to a PK consult will be interpreted as full dosing privileges as stated within this protocol.

Competency Standard: Pharmacist performing pharmacokinetic consults must be deemed competent in this function through department competency checklist.

Procedures:

I. Processing New Orders
   1. Upon initiation of a new “Vancomycin/Aminoglycoside PK Consult”:
      a. The verifying pharmacist will review and verify the consult order and ensure appropriate initial dosing regimen.
      b. All consults prior to 14:00 will be evaluated on the same day, if possible. All consults will be reviewed within 24 hours of receipt of consult.
      c. Follow-up interventions will be performed by the consulted pharmacist or a pharmacist within the department.

II. Data collection/ Patient assessment
   1. Upon receiving a new consult, the PK covering pharmacist will thoroughly review the appropriateness of the indication and dose of antibiotic.
   2. The PK covering pharmacist will systematically collect the information needed to make assessments and recommendations on a daily basis.
   3. The required data will be recorded in the progress notes section of the patient chart, which will serve as a means of communication with the primary provider/team. Information must be recorded clearly and completely as appropriate.
   4. The PK covering pharmacist is expected to follow PK consult patients daily until the antibiotic course is completed and/or the provider discontinues the “PK Consult” order.
III. Pharmacist Ordering

1. **Doses**
   a. Upon selecting a dosing and/or monitoring plan, the PK covering pharmacist will enter applicable orders. All orders by the PK covering pharmacist in response to a “PK Consult” order will be entered or discontinued under “per protocol” along with the pharmacist’s name.

2. **Serum Drug Levels**
   a. The PK covering pharmacist will order serum drug levels for the consult drug as warranted, under the PK protocol. The order will be signed “per pharmacokinetic protocol” along with the pharmacist’s name.
   b. Whenever a patient has a serum drug level resulted, the PK covering pharmacist will write a “PK Consult” note in the patient’s chart within 24 hours. In addition, if clinically warranted, the primary medical team will be notified of pertinent changes to the antibiotic regimen.

3. **Labs**
   a. In general, the PK covering pharmacist will ensure that each patient with a “PK Consult” will have medication levels, BUN, and SCr available as stated below in the protocol. In certain clinical circumstances BUN/Scr may not be required as frequently depending on the specific patient situation.
   b. Any lab orders by the PK covering pharmacist in response to a “PK Consult” order will be entered under “per pharmacokinetic protocol” along with the pharmacist’s name. Pertinent labs that may be ordered include the following: weights, heights, urine output, ins/outs, medications levels (peak, trough and random values), CBC, SCr, BUN.

4. **Consults**
   a. Pharmacy will recommend an audiology consult to primary provider for any patient receiving aminoglycosides for \( \geq 7 \) days.

IV. **Chart Documentation**

1. The PK covering pharmacist will provide a concise initial progress note in the chart and with each resulted serum drug level and/or subsequent dose change. This serves as the direct communication to the primary team. Further communication, such as phone calls, pages or face-to-face communication, will be dependent on the clinical situation and the pharmacist’s discretion.

2. The chart note, titled “Pharmacokinetic Consult- drug” (ex: “Pharmacokinetic Consult- Vancomycin” or “Pharmacokinetic Consult- Tobramycin”) must include:
   a. Date/time
   b. Day of therapy, indication
   c. Level and goal level
   d. Dose recommendation and/or recommendation of next level
   e. Signature/name of covering pharmacist and pager number

3. The PK covering pharmacist will be responsible for the follow-up monitoring and/or dose adjustments, as recommended in the progress note documentation.
### Table 1: Equations and Definitions for Pharmacokinetic Dosing

1. **Equation for Ideal Body Weight (IBW):**
   - Male kg = 50 + (2.3 X Each inch over 5 feet)
   - Female kg = 45.5 + (2.3 X Each inch over 5 feet)

2. **Equation for Adjusted Body Weight (ABW):**
   \[
   [\text{Actual Body Weight} - \text{Ideal Body Weight}] \times 0.4 = \text{ABW}
   \]

3. **Estimation of GFR using Cockcroft-Gault Equation (CGE):**
   \[
   \text{CrCl (ml/min)} = \frac{(140 - \text{Age})(\text{Wt in kg})}{(72)(\text{SCr})}; \text{ female, multiply by 0.85}
   \]
   Use Actual body weight unless obese (> 125% IBW), then use ABW

4. **Dosing Body Weight (DBW)**
   If > 125% IBW; ABW should be utilized for aminoglycosides and calculations of CrCl with CGE in obese patients. Patients < 125% IBW should use actual weight for aminoglycosides and calculations of CrCl with CGE. Vancomycin dosing should be based upon actual body weight.
Procedure for Vancomycin

1. The initial order will be 15 mg/kg based upon DBW, rounded to the nearest 250 mg increment. If a consulted patient is already receiving vancomycin, the dose may be adjusted depending upon patient weight, pertinent labs (SCr, Medication levels) and clinical indication per pharmacist discretion. A loading dose of 20 mg/kg may be clinically necessary in certain situations (see item 4 below) and should be discussed with primary provider prior to ordering. An appropriate interval will be selected based upon renal function which will be estimated with the CGE (See Table 2 below or Appendix A for alternative methods). Other established methods may be utilized at pharmacist discretion.

2. Vancomycin medication levels (peak/trough) and pertinent labs (BUN/SCr) will be ordered prior to the 4th dose or earlier, if clinically indicated. Vancomycin levels will be ordered every third day if the patient has fluctuating renal function. If renal function is stable, vancomycin levels will be ordered at least weekly. Renal function values (SCr/BUN) will be ordered at regular intervals (at a minimum of every 3 days) to monitor renal function.

3. Patients requiring hemodialysis will receive an initial dose of 15 mg/kg. Subsequent doses will be provided PRN or on scheduled hemodialysis days based upon the following guidelines:
   a. Random vancomycin levels should be ordered the morning prior to hemodialysis.
      - Once pt deemed clinically stable, weekly levels are appropriate for monitoring
   b. Random vancomycin level ≥ 25 mcg/ml = hold dose for that day and recheck random vancomycin level the following morning.
   c. Random vancomycin level < 25 mcg/ml = 7.5 mg/kg (max 750 mg) rounded to nearest 250 mg increment.
   d. Random vancomycin level ≤ 10 mcg/ml = 15 mg/kg (max 1500 mg) rounded to nearest 250 mg increment.
   e. Dose scheduling
      - Dialysis days: Schedule dose post dialysis at 2100
      - Non – dialysis days: Schedule as clinically indicated

4. Vancomycin trough level goals will be between 10 – 20 mcg/ml. Initial levels of 15 – 20 mcg/ml will be the goal for gram positive bacteremia, meningitis (confirmed and empiric), osteomyelitis, endocarditis, hardware infections and nosocomial pneumonia. Goal values may deviate based upon clinical circumstance and interaction with primary provider.

5. Potentially toxic trough values (> 30 mcg/ml) will be reported to primary team along with updated plan of action for correction.

6. Vancomycin dosing will be adjusted based upon medication levels at steady state, pharmacokinetic values (See Appendix B), clinical response, pharmacist clinical judgment and interaction with primary provider.

Table 2: Empirc Vancomycin Dosing Table

<table>
<thead>
<tr>
<th>CrCl A</th>
<th>Dosing Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50 ml/min</td>
<td>Q 12 Hours</td>
</tr>
<tr>
<td>25 ml/min – 50 ml/min</td>
<td>Q 24 Hours</td>
</tr>
<tr>
<td>&lt;25 ml/min</td>
<td>Q 48 hours OR based upon random levels</td>
</tr>
</tbody>
</table>

A Based upon CGE formula
**Procedure for Conventional Dosing of Aminoglycosides**

1. The initial order for tobramycin/gentamicin will be 1-2 mg/kg based upon DBW, rounded to the nearest 10 mg increment. The initial order for amikacin will be 5 mg/kg based upon DBW, rounded to the nearest “50 mg” increment. If a consulted patient is already receiving an aminoglycoside, the dose may be adjusted depending upon patient weight, pertinent labs (SCr, Medication levels) and clinical indication per pharmacist discretion. An appropriate interval will be selected based upon renal function which will be estimated with the CGE (See Table 3 or Appendix A for alternative methods). Alternate methods and sources for empiric dosing can be found in Appendix A. Other established methods may be utilized at pharmacist discretion.

2. Aminoglycoside medication levels (peak/trough) will be ordered around the 4th dose. Other pertinent labs (BUN/SCr) will be ordered earlier, if clinically indicated. Aminoglycoside levels will be ordered every third day if the patient has fluctuating renal function. If renal function is stable, aminoglycoside levels will be ordered at least weekly. Renal function values (SCr/BUN) will be ordered at regular intervals (at a minimum of every 3 days) to monitor renal function.

3. Patient requiring dialysis will be dosed PRN when random gentamicin/tobramycin and amikacin trough levels are less than the trough values for pertinent indication as indicated in table 5.

4. Initial therapeutic medication target level values will be based upon table 4 or table 5 below. Goal values may deviate based upon clinical circumstance and interaction with the primary provider.

5. Potentially toxic gentamicin/tobramycin peak (> 12 mcg/ml) and trough (> 2 mcg/ml) values will be reported to primary team along with updated plan of action for correction.

6. Potentially toxic amikacin peak (> 35 mcg/ml) and trough (> 10 mcg/ml) values will be reported to primary team along with updated plan of action for correction.

7. Aminoglycoside dosing will be adjusted based upon medication levels at steady state, pharmacokinetic values (See Appendix B), clinical response, pharmacist clinical judgment and interaction with primary provider.

**Table 3: Empiric Aminoglycoside Dosing Table**

<table>
<thead>
<tr>
<th>CrCl^A</th>
<th>Dosing Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;70 ml/min and Age &lt; 65</td>
<td>Q 8 Hours</td>
</tr>
<tr>
<td>30 ml/min – 70 ml/min or Age &gt; 65</td>
<td>Q 12 Hours</td>
</tr>
<tr>
<td>&lt;30 ml/min</td>
<td>Q 24 hours OR based upon random levels</td>
</tr>
</tbody>
</table>

^A Based upon CGE formula

Age > 65 may require less frequent interval dosing because of volume of distribution differences.
Table 4: Peak Concentration Goals for Conventional Tobramycin/Gentamicin Therapy

<table>
<thead>
<tr>
<th>Types of Infections</th>
<th>Suggested Peak Concentration (mcg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Infections</td>
<td>6 - 8</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>6 - 8</td>
</tr>
<tr>
<td>Empiric Therapy for Cystic Fibrosis</td>
<td>8 - 12</td>
</tr>
<tr>
<td>Endocarditis Gram Positive (Synergy)</td>
<td>3 - 5</td>
</tr>
<tr>
<td>Endocarditis Gram Negative</td>
<td>8 - 10</td>
</tr>
<tr>
<td>Eye Infections</td>
<td>6 - 8</td>
</tr>
<tr>
<td>Meningitis</td>
<td>8 - 10</td>
</tr>
<tr>
<td>Neutropenic Patients</td>
<td>6 - 10</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>6 - 8</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8 - 10</td>
</tr>
<tr>
<td>Skin and Soft Tissue Infections</td>
<td>6 - 8</td>
</tr>
<tr>
<td>Urinary Tract Infections</td>
<td>4 - 6</td>
</tr>
</tbody>
</table>

Table 5: Peak and Trough Concentration Goals for Conventional Aminoglycoside Therapy

<table>
<thead>
<tr>
<th>Indication</th>
<th>Gentamicin/Tobramycin</th>
<th>Amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peak (mcg/ml)</td>
<td>Trough (mcg/ml)</td>
</tr>
<tr>
<td>Uncomplicated UTI, Synergy in Gram positive infections</td>
<td>3 - 5</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Gram negative sepsis, other serious gram negative infections</td>
<td>5 - 10</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Gram negative pneumonia</td>
<td>7 - 9</td>
<td>&lt; 2</td>
</tr>
</tbody>
</table>
**Procedure of Once Daily Aminoglycoside Dosing**

1. Conventional dosing or once daily dosing will be utilized at pharmacist’s clinical discretion unless a dosing process is specifically requested in the pharmacokinetic consult.

2. Estimate dosing weight based upon DBW parameters as stated above.

3. Determine initial dosing interval based upon CrCl by utilizing the CGE.

4. Based upon CrCl, select dosing interval:
   a. CrCl > 60 ml/min = q 24 hour interval
   b. CrCl 40 – 59 ml/min = q 36 hour interval
   c. CrCl < 40 ml/min = Utilize convention dosing protocol

5. Calculate Initial dose of Gentamicin or Tobramycin:
   a. Monotherapy = 7 mg/kg DBW
   b. Synergy (endocarditis*)/UTI = 3 - 5 mg/kg DBW
   c. Cystic Fibrosis = 10 mg/kg DBW

6. Calculate initial dose of Amikacin:
   a. 15 – 20 mg/kg DBW
   b. Cystic Fibrosis = 20 mg/kg DBW

7. Exclusions to therapy:
   a. Patients with ascites
   b. Burn patients
   c. Pregnant patients
   d. Patients on dialysis
   e. CrCl < 40 ml/min
   f. Endocarditis*

* Conventional dosing is acceptable for all cases of endocarditis. Treatment guidelines for endocarditis suggest once daily or conventional dosing for viridans group streptococci and streptococcus bovis as an option. The Department of Pharmacy will utilize once daily dosing if requested by primary team. *Circulation.* 2005 Jun 14;111(23):e394-434.

8. Renal function monitoring will occur at the same frequency as “conventional dosing” protocol.

9. Dose can be adjusted with Hartford Hospital Nomogram ([appendix C](#)) or to an interval (24, 36, or 48 hours) to obtain a trough concentration at 24 hours less than 0.5 - 1 mcg/ml for gentamicin/tobramycin and less than 4 mcg/ml for amikacin. If greater, conventional dosing should be strongly considered.

10. Medication levels should be monitored twice weekly if patient is on therapy for greater than 5 days.
Appendix A

Empiric Vancomycin Dosing Methods and References

1. Modified Matzke Nomogram:
   Initial dose: 15 – 20 mg/kg DBW. Dosing intervals should produce concentrations of approximately 15 mcg/ml.

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Interval (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 120</td>
<td>q 8 - 12</td>
</tr>
<tr>
<td>100</td>
<td>q 12</td>
</tr>
<tr>
<td>80</td>
<td>q 12</td>
</tr>
<tr>
<td>60</td>
<td>q 18</td>
</tr>
<tr>
<td>40</td>
<td>q 24</td>
</tr>
<tr>
<td>30</td>
<td>q 36</td>
</tr>
<tr>
<td>20</td>
<td>q 48</td>
</tr>
<tr>
<td>≤ 10</td>
<td>Determined by random levels</td>
</tr>
</tbody>
</table>


Appendix A (cont.)

**Empiric Aminoglycoside Dosing Methods and References**

1. Sarubbi, Hull dosing nomogram

<table>
<thead>
<tr>
<th>Aminoglycoside</th>
<th>Loading Dose</th>
<th>Expected Peak (mcg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin/Tobramycin</td>
<td>1.5 – 2 mg/kg</td>
<td>4 -10 mcg/ml</td>
</tr>
<tr>
<td>Amikacin</td>
<td>5 – 7 mg/kg</td>
<td>15 – 30 mcg/ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>MD as % of Loading Dose</th>
<th>Dosing interval (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 90</td>
<td>90</td>
<td>8</td>
</tr>
<tr>
<td>80 – 90</td>
<td>80 – 84</td>
<td>8</td>
</tr>
<tr>
<td>70 – 80</td>
<td>76 – 80</td>
<td>8</td>
</tr>
<tr>
<td>60 – 70</td>
<td>71 – 76</td>
<td>8</td>
</tr>
<tr>
<td>50 – 60</td>
<td>79 – 84</td>
<td>12</td>
</tr>
<tr>
<td>40 – 50</td>
<td>72 - 79</td>
<td>12</td>
</tr>
<tr>
<td>30 – 40</td>
<td>86 – 92</td>
<td>24</td>
</tr>
<tr>
<td>25 – 30</td>
<td>81 – 86</td>
<td>24</td>
</tr>
<tr>
<td>20 – 25</td>
<td>75 – 81</td>
<td>24</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>Random Dosing</td>
<td>Random Dosing</td>
</tr>
</tbody>
</table>


Appendix B

Modification of Dose Based upon Medication Levels (Aminoglycosides and Vancomycin)


2. Sawchuk-Zaske Equations:

   A. Determine elimination rate (Kel)
      \[ Kel = \frac{\ln (Cpmax/Cpmin')}{\text{time between samples}} \]
      where \( Cpmax = \text{Peak level} \)
      \( Cpmin' = \text{Trough after dose} \)

   B. Determine Volume of distribution (Vd)
      \[ VD = \left[ \frac{(Dose/tinf)}{Kel} \right] \times \left( \frac{1 - e^{(-Kel \times tinf)} / Cpmax}{(Cpmin \times e^{-Kel \times t'})} \right) \]
      where \( Cpmax = \text{Peak level} \)
      \( Cpmin = \text{Trough level before the dose} \)
      \( t' = \text{hours between time Cpmin drawn and end of infusion} \)

   C. Determine ideal dosing interval (tau)
      \[ \tau = tinf + \left( \frac{-1}{Kel} \right) \times \ln \left( \frac{Cptmax}{Cptmin} \right) \]
      where \( Cptmin = \text{Target trough} \)
      \( Cptmax = \text{Target peak} \)

   D. Determine ideal maintenance dose (IMD)
      \[ \text{IMD} = Kel \times Vd \times Cptmax \times \left( \frac{1 - e^{-Kel \times \tau}}{1 - e^{-Kel \times tinf}} \right) \]

   E. User selects practical dosage and interval

   F. Calculate expected peak & trough levels
      \[ \text{CPssmax} = \left( \frac{MD \times tinf \times Vd \times Kel}{1 - e^{-Kel \times tinf}} \right) \]
      \[ \text{CPssmin} = \text{Peak} \times e^{-Kel \times (\tau - tinf)} \]
Appendix C

Once Daily Aminoglycoside Dosing

Hartford ODA Dose Adjustment Nomogram
(gent/tobra 7mg/kg)

Time between start of infusion and sample draw (hours)

Concentration mcg/ml

*For amikacin (15 mg/kg), the concentration should be multiplied by a factor of 2
*This nomogram is appropriate for use with gentamicin/tobramycin at a dose of 7 mg/kg only.

How to use the Hartford Nomogram
1. Obtain a single serum level 6-14 hours after the start of an infusion. It is very important that the exact time is documented. Evaluate on the nomogram.

2. If the level falls in the area designated 24, 36 or 48 hour dosing, the dosage interval should be 24, 36 or 48 hours respectively. If the level falls on one of the nomogram lines, use the longer dosing interval.

3. If the level is above the 48 hour line on the nomogram at the given time, stop the scheduled dosing and obtain further aminoglycoside levels to determine the appropriate time of the next dose (ie when the serum level is <2mcg/ml for gentamicin/tobramycin and < 4 mcg/ml for amikacin). Conventional dosing should be strongly considered at this point.