Stanford Health Care Aminoglycoside Dosing Guideline

I. DETERMINING DOSE AND CREATININE CLEARANCE:

1. Use of total body weight (TBW) in underweight and non-obese patients is widely accepted. Use of ideal body weight (IBW) for determining the mg/kg/dose may also be considered. For obese patients dosage requirement may best be estimated using an adjusted body weight (ABW) of: IBW + 0.4 (TBW - IBW).\(^1\)
   - IBW (male) = 50 kg + (2.3 x height in inches > 60 inches)
   - IBW (female) = 45 kg + (2.3 x height inches > 60 inches)

2. Calculate creatinine clearance with the Cockcroft-Gault equation using an ideal body weight (IBW) or an adjusted body weight (ABW) if the patient is obese
   \[
   \text{CrCL (mL/min)} = \frac{(140 - \text{age}) \times \text{IBW} \times (0.85 \text{ for females})}{\text{SCr} \times 72}
   \]

II. AMINOGLYCOSIDE DOSING STRATEGIES

A. Gram negative infections

1. **High-dose Extended-Interval Therapy**

   **Rationale:**
   - Aminoglycoside bactericidal activity is generally regarded as concentration dependent.\(^2,3\)  The higher the peak/MIC ratio, the greater the rate and extent of bacterial kill. The pharmacodynamic goal is to maximize drug concentration at the site of infection. Optimal bactericidal activity for the aminoglycosides is achieved when the exposure concentration is approximately 8 to 10 times the MIC. Existing data also supports area under the plasma concentration-time curve (AUC) / MIC ratio as an indicator of bacterial killing and efficacy. The AUC:MIC targets are for efficacy range from AUC:MIC ratios of 30-50 in non-critically ill immunocompetent patients and upwards of 80-100 for critically ill patients with infections of high-bacterial burden.\(^4\)
   - Aminoglycosides exhibit a post-antibiotic effect (PAE).\(^2,5-7\) PAE ranges of 0.5 to 8-hours have been reported. Factors influencing the PAE include: height of the preceding AMG peak, in-vivo > in-vitro, shortened by neutropenia, and extended in the presents of beta-lactams.
   - Saturable aminoglycosides uptake in renal tubule cell and inner ear.\(^8\) This suggests that higher peaks do not result in greater risk of toxicity. A single dose of aminoglycoside results in significantly lower renal cortical tissue concentration compared to the same total dose administered through a continuous infusion or in divided doses.\(^9,10\) Modeling data suggests that thrice-daily administration is associated with nephrotoxicity that occurs more rapidly, with greater intensity, and for longer duration, as compared to once-daily aminoglycoside.\(^11\) Clinical data and experience suggests that high-dose extended interval may be less nephrotoxicity compared to traditional regimens.\(^12,13\)

   The **Hartford Nomogram** method utilizes high-dose, once daily dosing to optimize the peak/MIC ratio in most clinical situations by administering a dose of 7mg/kg of either gentamicin or tobramycin. The **Urban & Craig Nomogram** is another method of extended-interval therapy utilizing 5 mg/kg of gentamicin or tobramycin in patients without renal dysfunction. For patients with cystic fibrosis exacerbation the Cystic Fibrosis consensus guidelines recommend extended interval dosing with 10 mg/kg once daily.

   **Exclusion Criteria:**
   - Renal insufficiency (CrCl <30 mL/min or rapidly declining renal function)
   - Pregnancy
   - Synergy for gram-positive infections
   - Ascites
   - Burns (>20%)

2. **Conventional / Traditional Dosing**

   Tradition dosing of aminoglycosides includes lower doses with more frequent administration of aminoglycosides using pharmacokinetic parameters to determine dose and frequency to achieve target peak and trough values.

   **Indication:**
   - Treatment of gram-negative infections and NOT a candidate for high-dose extended interval dosing therapy (see exclusion criteria above)

B. **Gram positive-synergy**

Synergy dosing is a low dose of aminoglycoside in conjunction with an antimicrobial agent that exhibits activity against the cell wall of Gram-positive bacteria (i.e. beta-lactams, glycopeptides) for the treatment of Gram-positive infections

C. **Non-tuberculosis mycobacterium (NTM)**

Treatment of NTM infections include combination therapy of either macrolides, clarithromycin, azithromycin, ethambutol, rifamycin and possibly an aminoglycoside. The decision to add an aminoglycoside depends on multiple factors including the extensiveness of disease, drug-refractory/resistant profile, and drug tolerance.
Dosing Methods by Indication

Indication for Aminoglycoside

Gram-Negative Infection

Are there any contraindications for High-Dose Extended-Interval Dosing?
- Dialysis
- Burn > 20% BSA
- Significant Ascites
- Pregnancy

NO

High-Dose Extended-Interval (Appendix A)

Gentamicin/Tobramycin
1.7mg/kg q8h

Gentamicin 3 mg/kg q24h OR 1 mg/kg q8h
Gentamicin 1 mg/kg q8h OR 1.5 mg/kg q12h
Gentamicin 1 mg/kg q8h OR 1.5 mg/kg q12h

Gentamicin 1 mg/kg q8h

Hartford Nomogram
Gentamicin/Tobramycin 7 mg/kg q24h
Consider in the following scenarios (e.g.):
- Multi-drug resistant pseudomonal infections w/elevated MICs (MIC >2)
- Severe sepsis/septic shock
(Appendix A1)

Urban-Craig Nomogram
Gentamicin/Tobramycin 5 mg/kg q24h
Consider in the following scenarios (e.g.):
- Complicated urinary tract infections/pyelonephritis
- Surgical prophylaxis
- Gynecologic, GYN/ONC infections
- Orthopedic open-fracture (Appendix A2)

CF exacerbation
Tobramycin 7 – 10 mg/kg q24h

Gentamicin 1 mg/kg q8h

Consult ID Pharmacists for other indications not listed above (e.g. Nocardiosis, Listeriosis)

Gram-Positive Endocarditis (Appendix C)

Streptococcus virdans/bovis

Staphylococcus spp

Enterococcus spp

Nontuberculous Mycobacterial (NTM) Infection (Appendix D)

Amikacin 10-15 mg/kg q24h OR Amikacin 10-25 mg/kg 3 times weekly

Conventional/Traditional Dosing (Appendix B)

Gentamicin 3 mg/kg q24h OR 1 mg/kg q8h
Gentamicin 1 mg/kg q8h OR 1.5 mg/kg q12h
Gentamicin 1 mg/kg q8h OR 1.5 mg/kg q12h

• Dialysis
• Burn > 20% BSA
• Significant Ascites
• Pregnancy

YES

NO

• Dialysis
• Burn > 20% BSA
• Significant Ascites
• Pregnancy

YES

NO

Consult ID Pharmacists for other indications not listed above (e.g. Nocardiosis, Listeriosis)
Appendix A: High-Dose Extended-Interval Nomograms (Gram-negative infections)

Appendix A1: Hartford Nomogram

**Initial Dose:**

- 7 mg/kg using actual body weight (Nomogram was developed and validated with actual body weight)
- If obese, use adjusted body weight. Adjusted body weight = IBW + ( 0.4 [TBW – IBW] )
- The dose of 7 mg/kg is expected to achieve a \( C_{\text{max}} \) level of ~20 mcg/mL

<table>
<thead>
<tr>
<th>CrCL (mL/min)</th>
<th>Gentamicin / Tobramycin</th>
<th>Amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60 mL/min</td>
<td>7 mg/kg Q24H</td>
<td>15 mg/kg Q24H</td>
</tr>
<tr>
<td>40 – 59 mL/min</td>
<td>7 mg/kg Q36H</td>
<td>15 mg/kg Q36H</td>
</tr>
<tr>
<td>30 – 39 mL/min</td>
<td>7 mg/kg Q48H</td>
<td>15 mg/kg Q48H</td>
</tr>
<tr>
<td>20 – 29 mL/min</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>&lt; 20 mL/min</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>CRRT</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

**Monitoring:**

**Initial Monitoring**

- Random level drawn 8 – 12 hours after the first dose
- Use nomogram to confirm/modify dosage interval
- Hartford nomogram is only applicable for 7 mg/kg – plotting doses lower or higher than 7 mg/kg may under or overestimate clearance
  - Gentamicin/tobramycin (7 mg/kg/dose): Plot level on graph
  - Amikacin (15 mg/kg/dose): Divide level in half, then plot on graph

**Follow up trough level testing**

- An early trough (6-hours prior to dose) should be considered in patients demonstrating acute changes in renal function or suspicion of extended interval failure. Aiming for a level < 1 mcg/mL approximately 6-hours prior to the next dose ensures there is a drug-free window in order to minimize drug accumulation within the proximal tubules.
- Maintenance random levels should be monitored at least once weekly.
- If duration of therapy is anticipated to be > 2 weeks, audiometry should be considered.
Appendix A2: Urban & Craig Nomogram

**Initial Dosing:**

- Gentamicin/Tobramycin 5 mg/kg IV Q24H based on actual body weight
  - If obese, use adjusted body weight. Adjusted body weight = IBW + (0.4 [TBW – IBW])

<table>
<thead>
<tr>
<th>CrCL (mL/min)</th>
<th>Gentamicin / Tobramycin</th>
<th>Amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60 mL/min</td>
<td>5 mg/kg Q24H</td>
<td>15 mg/kg Q24H</td>
</tr>
<tr>
<td>40 – 59 mL/min</td>
<td>5 mg/kg Q36H</td>
<td>15 mg/kg Q36H</td>
</tr>
<tr>
<td>20 – 39 mL/min</td>
<td>5 mg/kg Q48H</td>
<td>15 mg/kg Q48H</td>
</tr>
<tr>
<td>&lt; 20 mL/min</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>CRRT</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

**Monitoring:**

**Initial Monitoring**

- Single level drawn 8 – 12 hours after the first dose.
- Use nomogram to confirm/modify dosage interval.
- Only applicable for 5 mg/kg – plotting doses lower or higher than 7 mg/kg may under or overestimate clearance
  - Gentamicin/Tobramycin (5 mg/kg/dose): Plot on graph
  - Amikacin (15 mg/kg/dose): Divide level by 3, then plot on graph

**Follow up monitoring**

- An early trough (6-hours prior to dose) should be considered in patients demonstrating acute changes in renal function or suspicion of extended interval failure. Aiming for a level < 1 mcg/mL approximately 6-hours prior to the next dose ensures there is a drug-free window in order to minimize drug accumulation within the proximal tubules.
- Maintenance random levels should be monitored at least once weekly.
- If duration of therapy is anticipated to be > 2 weeks, audiometry should be considered.
Appendix A3: Cystic Fibrosis Dosing

**Initial Dosing:**

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Tobramycin</th>
<th>Amikacin</th>
<th>Timing of Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60 mL/min</td>
<td>10 mg/kg Q24H</td>
<td>20 mg/kg Q24H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alt: *7 mg/kg Q24H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 – 59 mL/min</td>
<td>7 – 10 mg/kg Q36H</td>
<td>20 mg/kg Q36H</td>
<td></td>
</tr>
<tr>
<td>30 – 39 mL/min</td>
<td>7 – 10 mg/kg Q48H</td>
<td>20 mg/kg Q48H</td>
<td></td>
</tr>
<tr>
<td>20 – 29 mL/min</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td></td>
</tr>
<tr>
<td>&lt; 20 mL/min</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td></td>
</tr>
<tr>
<td>CRRT</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td></td>
</tr>
</tbody>
</table>

**7 mg/kg Q24H Dosing:**

Random Level approximately 8 – 10 hours after the first dose. Plot on Hartford Nomogram.

**Maintenance Levels:**

- Weekly peaks/troughs (6-hours before the next dose. Alternatively, 60-minutes before the next dose is also acceptable for outpatient monitoring).
- Acute renal changes
- Changes in dosing regimen

*Consider 7 mg/kg dosing if the patient has a history of AKI or SCr increase due to 10 mg/kg dosing

**Check medical record for a history of previously tolerated doses.**

**Monitoring:**

<table>
<thead>
<tr>
<th>Goal Levels</th>
<th>Target Peak</th>
<th>Target Trough</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin/Tobramycin</td>
<td>20 – 30 mcg/mL</td>
<td>&lt; 1 mcg/mL</td>
</tr>
<tr>
<td>Amikacin</td>
<td>40 – 60 mcg/mL</td>
<td>&lt; 4 mcg/mL</td>
</tr>
</tbody>
</table>
Appendix B: Conventional / Traditional Dosing (Gram-negative infections)

### Initial Dosing:

<table>
<thead>
<tr>
<th>CrCL (mL/min)</th>
<th>Gentamicin / Tobramycin</th>
<th>Amikacin</th>
<th>Timing of Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Peaks</td>
</tr>
<tr>
<td>&gt; 60 mL/min</td>
<td>1.7 mg/kg Q8H</td>
<td>7.5 mg/kg Q12H or 5 mg/kg Q8H</td>
<td>30-min after 3rd dose</td>
</tr>
<tr>
<td>40 – 59 mL/min</td>
<td>1.7 mg/kg Q12H</td>
<td>5 – 7.5 mg/kg Q12H</td>
<td>30-min after 2nd dose</td>
</tr>
<tr>
<td>30 – 39 mL/min</td>
<td>1.7 mg/kg Q24H</td>
<td>5 – 7.5 mg/kg Q24H</td>
<td>30-min after 2nd dose</td>
</tr>
<tr>
<td>20 – 29 mL/min</td>
<td>1.7 mg/kg Q24H</td>
<td>5 – 7.5 mg/kg Q24H</td>
<td></td>
</tr>
<tr>
<td>&lt; 20 mL/min; AKI</td>
<td>2 mg/kg load, then dose by level</td>
<td>5 mg/kg load, then dose by level</td>
<td>30-min after 1st dose</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>2 mg/kg load, then 1.5 mg/kg post-HD; Redose for 4-hr post-HD level Cp&lt;1 mg/L or pre-HD</td>
<td>5 – 7.5 mg/kg post-HD</td>
<td>30-min after 1st dose</td>
</tr>
<tr>
<td>CRRT</td>
<td>3 mg/kg loading dose, then 1.5 – 2.5 mg/kg Q24-48H.</td>
<td>10 mg/kg load, then 7.5 mg/kg Q24-48H</td>
<td>30-min after 2nd dose</td>
</tr>
</tbody>
</table>

**Monitoring:**

<table>
<thead>
<tr>
<th>Goal Levels</th>
<th>Indication</th>
<th>Target Peak</th>
<th>Target Trough</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin/Tobramycin</td>
<td>Life-threatening infection</td>
<td>8 – 10 mcg/mL</td>
<td>&lt; 1 – 2 mcg/mL</td>
</tr>
<tr>
<td></td>
<td>Serious Infections</td>
<td>6 – 8 mcg/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary tract infections</td>
<td>4 – 6 mcg/mL</td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>Life-threatening infection</td>
<td>25 – 30 mcg/mL</td>
<td>&lt; 4 – 8 mcg/mL</td>
</tr>
<tr>
<td></td>
<td>Serious Infections</td>
<td>20 – 25 mcg/mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary tract infections</td>
<td>15 – 20 mcg/mL</td>
<td></td>
</tr>
</tbody>
</table>
## Appendix C: Gram-Positive Synergy Dosing

### Initial Dosing:

<table>
<thead>
<tr>
<th>CrCL (mL/min)</th>
<th>Gentamicin Synergy Dosing</th>
<th>Timing of Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>1 mg/kg Q8H*</td>
<td></td>
</tr>
<tr>
<td>40-59</td>
<td>1 mg/kg Q12H</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>1 mg/kg Q24H</td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>1 mg/kg Q24H</td>
<td></td>
</tr>
<tr>
<td>&lt;20; AKI</td>
<td>1 mg/kg x 1 dose; redose when Cp &lt; 1 mcg/mL</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>1 mg/kg q48-72H; Redose for pre-HD or post-HD Cp &lt;1mcg/mL</td>
<td></td>
</tr>
<tr>
<td>CRRT</td>
<td>1 mg/kg Q24H, then by level</td>
<td></td>
</tr>
</tbody>
</table>

*Alternative dosing only for CrCl > 60 mL/min:
- Gentamicin 3 mg/kg q24h for treatment of endocarditis with Streptococci, *Streptococcus gollolyticus* (bovis), *Streptococcus viridans*
- Gentamicin 1.5 mg/kg q12h for treatment of endocarditis with Staphylococci; Enterococcus spp (strains susceptible to penicillin and gentamicin) endocarditis
- Refer to the IDSA Infective Endocarditis Guidelines for dosing strategies in specific scenarios

### Monitoring:

<table>
<thead>
<tr>
<th>Goal Levels</th>
<th>Target Peak</th>
<th>Target Trough</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin/Tobramycin</td>
<td>3 – 4 mcg/mL**</td>
<td>&lt; 1 mcg/mL</td>
</tr>
</tbody>
</table>

**Target Peak levels not applicable for alternative regimens of Gentamicin 3mg/kg q24h or 1.5 mg/kg q12h.

## Appendix D: Nontuberculous Mycobacterial Infections

### Initial Dosing:

Tobramycin is preferred in *M. chelonae* infection. Consult ID and/or ASP Pharmacists.

<table>
<thead>
<tr>
<th>CrCL (mL/min)</th>
<th>Amikacin Daily Regimen</th>
<th>Amikacin Thrice Weekly Regimen</th>
<th>Timing of Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60 mL/min</td>
<td>10 – 15 mg/kg Q24H</td>
<td>10 – 25 mg/kg TIW</td>
<td></td>
</tr>
<tr>
<td>Age &gt; 50 years old*</td>
<td>10 mg/kg Q24H (max single dose of 500 mg)</td>
<td>Age &gt; 50 years old: 10 mg/kg TIW (max single dose of 500 mg)</td>
<td></td>
</tr>
<tr>
<td>40 – 59 mL/min</td>
<td>10 – 15 mg/kg Q24 – 48H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age*</td>
<td>10 – 15 mg/kg M-F</td>
<td>10 – 25 mg/kg TIW</td>
<td></td>
</tr>
<tr>
<td>30 – 39 mL/min</td>
<td>10 – 15 mg/kg Q48 – 72H</td>
<td>10 – 25 mg/kg TIW</td>
<td></td>
</tr>
<tr>
<td>20 – 29 mL/min</td>
<td>Dose by level</td>
<td>Dose by level</td>
<td></td>
</tr>
<tr>
<td>&lt; 20 mL/min</td>
<td>Dose by level</td>
<td>Dose by level</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>Dose by level</td>
<td>Dose by level</td>
<td></td>
</tr>
<tr>
<td>CRRT</td>
<td>Dose by level</td>
<td>Dose by level</td>
<td></td>
</tr>
</tbody>
</table>

*Monday-Friday regimen (5 times per week) may be recommended by the ID or pulmonary service for patients that are elderly or have poor renal function

### Monitoring:

<table>
<thead>
<tr>
<th>Goal Levels</th>
<th>Peaks***</th>
<th>Target Trough</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 – 15 mg/kg Q24H</td>
<td>In clinical practice, a lower target peak of 20 – 30 mcg/mL is oftentimes targeted for patient tolerability</td>
<td>&lt; 4 mcg/mL</td>
</tr>
<tr>
<td>10 – 25 mg/kg three times weekly</td>
<td>May consider goal peaks of 35 – 45 mcg/mL as tolerability permits</td>
<td>&lt; 4 mcg/mL</td>
</tr>
</tbody>
</table>

***Note: There is no established PK/PD target for optimal microbiologic and clinical outcome. The above peak values are typically expected and therefore have been suggested TDM targets by national guidelines. The goal trough is to ensure drug clearance and minimize accumulation/toxicity.
Appendix E: PK Calculations

### Aminoglycoside Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability (F)</td>
<td>- Water soluble</td>
</tr>
<tr>
<td></td>
<td>- Poorly lipid soluble</td>
</tr>
<tr>
<td></td>
<td>- Poor oral absorption</td>
</tr>
<tr>
<td>Volume of Distribution</td>
<td>0.25 L/kg (0.1 – 0.5 L/kg)</td>
</tr>
<tr>
<td>Fraction unbound in plasma</td>
<td>&gt; 0.95</td>
</tr>
<tr>
<td>Clearance</td>
<td></td>
</tr>
<tr>
<td>Normal renal function</td>
<td>Same as CrCl</td>
</tr>
<tr>
<td>Functionally anephric</td>
<td>0.0043 L/kg/hr</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>1.8 L/hr</td>
</tr>
<tr>
<td>t ½</td>
<td></td>
</tr>
<tr>
<td>Normal renal function</td>
<td>2 – 3 hours</td>
</tr>
<tr>
<td>Functionally anephric</td>
<td>30 – 60 hours</td>
</tr>
</tbody>
</table>

### Abbreviations

- IBW = ideal body weight
- ABW = actual body weight
- DBW = dosing body weight
- kel = elimination rate constant
- Vd = volume of distribution
- t = time of infusion
- t_{before} = time between blood draw and start of infusion
- t_{end} = time from end of infusion to blood draw
- t½ = half-life
- C\_max = peak serum level at steady-state
- C\_min = trough serum level at steady-state
- SCr = serum creatinine

### Initial Dosing

1. **Determine CrCL using Cockcroft-Gault**
   
   \[
   CrCL \text{ (mL/min)} = \frac{(140 - \text{age}) \times \text{IBW} \times 0.85 \text{ for females}}{\text{SCr} \times 72}
   \]

2. **Estimate elimination rate constant (Ke) based on PK kinetics**
   
   \[
   Ke = (0.003 \times \text{CrCl}) + 0.01
   \]

3. **Estimate half-life (t ½)**
   
   \[
   t\frac{1}{2} = \frac{0.693}{\text{ke}}
   \]

4. **Calculate Volume of distribution (Vd) using ABW or AdjBW**
   
   - Gentamicin/Tobramycin = 0.25 L/kg
   - Amikacin = 0.3 L/kg

5. **Infusion time**
   
   - Gentamicin/Tobramycin = 30 minutes
   - Amikacin = 30 minutes; 60 minutes if doses > 15 mg/kg

6. **Estimated dosing interval based on goal levels**
   
   \[
   T = \left( \frac{\text{Ln (C\_max/C\_min)}}{\text{Ke}} \right) + t_i
   \]

   OR

   \[
   \text{Estimated (T)} = 3 \times t\frac{1}{2}
   \]

7. **Maintenance dose (MD):**

   \[
   \text{MD} = \frac{[(K_e) \times (V_D) \times (t_i) \times (C_{\text{peak \ desired}}) \times (1 - e^{-K_e \cdot T})]}{\left[ (1 - e^{-K_e \cdot t_i}) \right]}
   \]

   OR

   \[
   \text{MD} = (C_{\text{peak \ desired}} \times V_D)
   \]
**Individualized Dose Revisions**

1. **Determine elimination rate constant**
   - Use levels within the same dosing interval
   
   \[ K \, (hr^{-1}) = \frac{(\text{Ln peak}/\text{trough})}{\Delta \text{time between levels}} \]
   \[ OR \]
   \[ k = \frac{\ln (\text{Cmax}/\text{Cmin})}{\tau - (t + t_{\text{end}} + t_{\text{before}})} \]

2. **Determine actual Cmax**
   - (if level not drawn at correct time; 1 hour after the start or 30 minutes after completion of infusion)
   
   \[ C_{\text{max,actual}} = \frac{C_{\text{max}}}{e^{k(t_{\text{end}})}} \]

3. **Determine half-life**
   
   \[ t_{\frac{1}{2}} = 0.693 \frac{k}{k} \]
   
   Dosing interval for traditional dosing method = ~ 3-4 times the half-life

4. **Time to achieve goal trough level**
   
   Time to clearance = \[ \frac{\text{Ln (actual trough/ desired trough)}}{K_{e}} \]

5. **Estimate dosing interval**
   
   \[ \tau = \left[ \frac{\ln (\text{Cmax}/\text{Cmin})}{K} \right] + t_i \]
   \[ OR \]
   \[ \text{Estimated } \tau = 3 \times t_{\frac{1}{2}} \]

6. **Determine Vd**
   
   \[ t_i = \text{time from beginning infusion to Cpeak} \]

   \[ V_d \, (L) = \frac{\text{Dose}}{C_{\text{max,actual}} \times (1 - e^{-K(t_{\text{end}})})} \]
   \[ OR \]
   \[ V_d \, (L) = \frac{((\text{Dose} / C_{\text{peak}}) \times e^{-K_{i}})}{(1 - e^{-K_{i}})} \]

7. **New maintenance dose**
   
   \[ t_i = \text{infusion time} \]
   \[ \tau = \text{interval} \]

   \[ MD = \frac{((k_e) \times (V_d) \times (t_i) \times (C_{\text{peak desired}} \times (1 - e^{-K_{i}})))}{(1 - e^{-K_{i}})} \]
   \[ OR \]
   \[ MD = (\text{goal peak Cmax}) \times V_d \]
References


Document Information

A. **Original Author/Date**
   Emily Mui, PharmD: 05/2012

B. **Gatekeeper**
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C. **Review and Renewal Requirement**
   This document will be reviewed every three years and as required by change of law or practice

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   Lina Meng, PharmD: 05/2018
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   Jamie Kuo, PharmD: 05/2021, 06/2021
   Denise Kwong, PharmD: 05/2021, 06/2021
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E. **Approvals**
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