AMINOGLYCOSIDE DOSING IN ADULT PATIENTS

EXTENDED INTERVAL DOSING OF AMINOGLYCOSIDES (EIDA)

EIDA is the preferred method for dosing aminoglycosides for gram-negative infections as it offers the potential of reducing nephrotoxicity while maximizing concentration-dependent killing. EIDA does NOT necessarily imply q24h dosing; rather, it denotes the use of empiric 5 mg/kg doses (gentamicin and tobramycin) or 15 mg/kg doses (amikacin) in an attempt to maximize peak concentration while also approximating undetectable troughs.

Standard EIDA should NOT be utilized in patients with Infective Endocarditis due to gram-positive organisms (synergy dosing). In addition, select patients may not be able to safely achieve an appropriate peak and trough concentration using the extended-interval approach. In these scenarios, consider changing to TRADITIONAL DOSING OF AMINOGLYCOSIDES (SEE TDA RECOMMENDATIONS BELOW).

We provide more specific guidance for the patient populations listed below because they may require more frequent monitoring and are expected to have unpredictable pharmacokinetics:

A. Renal dysfunction (CrCl <40 mL/min). Most patients with renal dysfunction should receive traditional dosing; extended-interval dosing may be considered in very specific patient scenarios (ICU patients with severe sepsis/shock possibly infected with multi-drug resistant gram-negative organisms). These patients should be given a single dose, with subsequent doses based on levels.
   1. Critically ill patients: Aminoglycosides are typically utilized as part of empiric combination therapy in ICU patients pending cultures. Most ICU patients either have renal dysfunction or are at high risk of developing nephrotoxicity. As such, as referenced above regarding patients with renal dysfunction, ICU patients should generally receive a single dose, with subsequent doses based on levels.
   2. End Stage Liver Disease: Many patients with ESLD have some degree of renal dysfunction and qualify for the above (renal dysfunction) recommendations. In patients without obvious renal dysfunction, these patients have unpredictable pharmacokinetics (due to increased volume from ascites) and are acutely susceptible to nephrotoxicity. Stable patients on the floor should generally receive traditional dosing. Critically ill patients receiving empiric aminoglycoside therapy should be managed according to the above (renal dysfunction) recommendations.

B. Cystic fibrosis, >20% BSA burns: May require doses in excess of 5 mg/kg (gentamicin/tobramycin or 15 mg/kg (amikacin) q24h. See below table for empiric dosing in CF patients.

C. Pregnancy and Morbid obesity (≥200% IBW): These patients may follow the EIDA dosing rubric described below, but very unpredictable pharmacokinetics mandates monitoring of levels after first dose, and likely more frequently during the course of therapy.

DOSE CALCULATIONS:

A. Determine patient’s dosing weight: (SEE FORMULAS BELOW)
   1. Dose is based on ideal body weight (IBW) unless either of the following apply:
      a. IF less than their IBW; use total body weight (TBW).
      b. IF total body weight (TBW) exceeding ideal body weight (IBW) by > 30%, then use adjusted body weight (ABW).

B. Dose based on dosing weight:

<table>
<thead>
<tr>
<th></th>
<th>Adult Patients (non-CF)</th>
<th>Adult CF Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin / Tobramycin*a</td>
<td>5 mg/kg x1(^a)</td>
<td>10 mg/kg x1(^a)</td>
</tr>
<tr>
<td>Amikacin**</td>
<td>15 mg/kg x1(^a)</td>
<td>20 mg/kg x1(^a)</td>
</tr>
</tbody>
</table>

+ Round doses to the nearest ~ 20 mg  ++ Round doses to the nearest ~ 50 mg
\(^a\) Patients with CrCl > 60 mL/min can likely be scheduled for q24h dosing, with monitoring as below. However, individual
judgement should be utilized to make this determination, and this does not apply to critically ill patients, patients with end-stage liver disease or morbid obesity.

* You should also or review the patient’s past medical records/history to assess previous aminoglycoside dosing, in order to determine most appropriate dose

FORMULAS:

**Ideal Body Weight (IBW) in kg:**
- Male = 50 + (2.3 * Height in inches > 5 feet)
- Female = 45 + (2.3 * Height in inches > 5 feet)

**Percent over IBW:**
\[ \% \text{ over } IBW = \frac{TBW - IBW}{IBW} \times 100 \]

**Creatinine Clearance (Cockcroft-Gault):**
\[ CrCl \left( \frac{mL}{min} \right) = \frac{(140 - \text{Age}) \times \text{Dosing Weight}}{(72 \times \text{Scr})} \times 0.85 \text{ for female} \]

† If age >70 years and SCr <1, assume SCr =1 for calculation

**Adjusted Body Weight (ABW) in kg:**
\[ ABW = 0.4(TBW - IBW) + IBW \]

Serum concentration monitoring with Extended Interval Dosing of Aminoglycosides: Reference ranges for levels are noted below in Appendix I.

A. Serum concentrations should be monitored in all patients receiving aminoglycosides for a duration of therapy projected to exceed 48 hours

B. After the 1st dose: Obtain 2 random levels at least one half-life apart (e.g., 3 hours after start of infusion and 8-12 hours after start of infusion). These levels can be utilized to determine peak and 18-hour and/or trough concentrations, and determine whether adjustments are needed.

1. Select patients with CrCl > 60 mL/min and with none of the above criteria associated with unpredictable pharmacokinetics may be monitored solely with an initial 18-hour level

C. Subsequent monitoring of levels depends on the indication for aminoglycoside therapy, patient clinical status, renal function, and initial serum concentrations; serum concentrations should be monitored every 3-7 days.

1. Recommend obtaining levels every 2-3 days in patients with changing fluid status or renal function.

2. Recommend obtaining levels every 5-7 days in patients with stable fluid status and renal function requiring long-term therapy, after initial level(s) are therapeutic

D. In ALL cases, dosing and frequency of monitoring requires assessment of the patient, indication for therapy, assessment of potential risk factors for treatment failure and/or toxicity, and clinical judgment

E. In stable patients, may consider monitoring 18-hour levels, with goals as in Appendix I.

F. Monitor BUN/SCr 2-3 times weekly.
TRADITIONAL DOSING OF AMINOGLYCOSIDES (TDA)

Recommended only for patients where the aminoglycoside is being used for gram-positive synergy, patients with contraindication to EXTENDED INTERVAL DOSING OF AMINOGLYCOSIDES, or in those patients who cannot safely achieve appropriate peak/trough concentrations with EIDA.

DOSE CALCULATIONS:

A. Determine patient’s dosing weight: (SEE FORMULAS BELOW)
   1. Dose is based on ideal body weight (IBW) unless either of the following apply:
      a. IF less than their IBW; use total body weight (TBW).
      b. IF total body weight (TBW) exceeding ideal body weight (IBW) by >30%, then use adjusted body weight (ABW).

B. Dose based on dosing weight:
   1. For gentamicin and tobramycin 1.5-2 mg/kg (per dosing weight) - round dose to the nearest 20 mg.
   2. For synergistic treatment for gram-positive infections, such as endocarditis – Please refer to UMHS endocarditis treatment guidelines to determine which below strategy is preferred:
      a. Gentamicin 1 mg/kg (per dosing weight) – round to nearest 20 mg or streptomycin 2.5 mg/kg – round to nearest 50 mg. Dosing interval recommendations in section C.
      b. Gentamicin 3 mg/kg (per dosing weight) q24h – round to nearest 20 mg. NOTE: this strategy should only be utilized in patients with adequate renal function (>40 mL/min) as to enable q24h dosing. Do NOT follow the dosing interval suggestions in C below for this strategy.
      c. For amikacin 5 mg/kg (per dosing weight) – round dose to the nearest 50 mg. Dosing interval recommendations in section C.

FORMULAS:

Ideal Body Weight (IBW) in kg:

Male = 50 + (2.3 * Height in inches > 5 feet)
Female = 45 + (2.3 * Height in inches > 5 feet)

Percent over IBW:

% over IBW = \frac{TBW - IBW}{IBW} * 100

Creatinine Clearance (Cockcroft-Gault):

\begin{align*}
CrCl (\text{mL/min}) &= \frac{(140 - \text{Age}) \times \text{Dosing Weight}}{(72 \times SCr)} \times 0.85 \text{ for female} \\
&\text{If age >70 years and SCr <1, assume SCr =1 for calculation}
\end{align*}

Adjusted Body Weight (ABW) in kg:

\begin{align*}
ABW &= 0.4(TBW - IBW) + IBW
\end{align*}

C. Dosing Interval Determination:

The suggested dosage of aminoglycosides depends on target serum concentrations, renal status and volume status. In a patient with normal volume status, the dose may be adjusted for renal function according to the following guidelines:

<table>
<thead>
<tr>
<th>CrCl</th>
<th>Dosing Interval (hr)</th>
<th>Dosing per Therapeutic Drug Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>50-30</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>29-10</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>48*</td>
<td></td>
</tr>
<tr>
<td>HD</td>
<td>Three-times weekly post-HD</td>
<td></td>
</tr>
<tr>
<td>CRRT</td>
<td>24</td>
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</tr>
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</table>
Serum concentration monitoring with Traditional Dosing of Aminoglycosides:

- Reference ranges for levels are noted below in Appendix I.
- Monitor kidney function (BUN/SCr at least 2 – 3 times/week, UOP daily)
- Serum concentrations should be monitored in all patients receiving aminoglycosides for a duration of therapy projected to exceed 48 hours
- Peak and trough concentrations should be monitored in patients receiving Traditional Dosing of Aminoglycosides. Order peak and trough around the 4th dose. If levels are not appropriate, dose adjustments should be based on a pharmacokinetic analysis based on the two levels.
- Subsequent monitoring of levels depends on the indication for aminoglycoside therapy, patient clinical status, renal function, and initial serum concentrations; serum concentrations should be monitored every 3 – 7 days.
  - In ALL cases, dosing and frequency of monitoring requires assessment of the patient, indication for therapy, assessment of potential risk factors for treatment failure and/or toxicity, and clinical judgment
  - Recommend obtaining levels every 2-3 days in patients with changing fluid status or renal function.
  - Recommend obtaining levels every 5-7 days in patients with stable fluid status and renal function requiring long-term therapy, after initial level(s) are therapeutic
- Monitoring and subsequent dosing in hemodialysis (non-ICU) (NOTE: these recommendations only apply to patients receiving a full HD session):
  - Pre-HD levels (preferred)
    - Gentamicin, tobramycin: If pre-HD level is ≤ 3 mcg/mL, give a dose of ~ 1.5 – 2 mg/kg x1 dose after HD. If pre-HD level is >3 mcg/mL, hold dose.
    - Amikacin: If pre-HD level is ≤10 mcg/mL, give dose ~ 5 – 7 mg/kg x1 dose after HD. If pre-HD level is >10, hold dose
  - Post-HD levels (Preferred in ICU and hemodynamically unstable patients, as post-HD levels are preferred as patients may not always receive their entire prescribed duration of hemodialysis). Levels should be drawn ≥2 hours after HD to allow for re-distribution.
    - Gentamicin, tobramycin: Re-dose if level ≤2 mcg/mL
    - Amikacin: Re-dose if level ≤8 mcg/mL
APPENDIX I: Reference ranges for gentamicin, tobramycin and amikacin:

<table>
<thead>
<tr>
<th></th>
<th>Traditional Dosing</th>
<th>Extended-Interval Dosing (≥5mg/kg every 24 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gentamicin/Tobramycin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram positive synergy</td>
<td>Goal peak 3-5 (1 mg/kg)</td>
<td>Goal Peak 18-20</td>
</tr>
<tr>
<td></td>
<td>N/A (3 mg/kg) &lt;1 Do not use EIDA</td>
<td></td>
</tr>
<tr>
<td>UTI</td>
<td>4-6 &lt;2 15-20 &lt;0.25 &lt;1</td>
<td></td>
</tr>
<tr>
<td>Intra-abd infection</td>
<td>6-8 &lt;2 15-20 &lt;0.25 &lt;1</td>
<td></td>
</tr>
<tr>
<td>Pneumonia, bacteremia, sepsis</td>
<td>8-10 &lt;2 15-20 &lt;0.25 &lt;1</td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>8-10 &lt;2 20-30 &lt;0.25 &lt;1</td>
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| **Amikacin**            |                    |                                               |
| UTI                    | Goal peak 15-25 | Goal Peak 35-50 | Goal Trough <4 | Goal Trough <6 |
| Intra-abd infection    | 20-30 <8 15-20 <4 <6 |
| Pneumonia, bacteremia, sepsis | 25-35 <8 35-50 <4 <6 |
| Cystic fibrosis        | 25-35 <8 40-60 <4 <6 |

| **Streptomycin**        |                    |                                               |
| Gram positive synergy  | Goal peak 15-25 | Goal Peak 18-20 | Goal Trough <5 | Goal Trough  Do not use EIDA |

The recommendations in this guide are meant to serve as treatment guidelines for use at Michigan Medicine facilities. If you are an individual experiencing a medical emergency, call 911 immediately. These guidelines should not replace a provider's professional medical advice based on clinical judgment, or be used in lieu of an Infectious Diseases consultation when necessary. As a result of ongoing research, practice guidelines may from time to time change. The authors of these guidelines have made all attempts to ensure the accuracy based on current information, however, due to ongoing research, users of these guidelines are strongly encouraged to confirm the information contained within them through an independent source.

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