Aminoglycoside Once Daily Dosing Guidelines for Adults

gentamicin, tobramycin and amikacin only

» For use in adults and adolescents 18 years and older.
» To maximise efficacy and safety, once daily (or less frequent) dosing is now the recommended method for dosing aminoglycosides in most clinical settings.
» Use with caution in patients with pre-existing hearing, vestibular or renal impairment.

**Flowchart**

For use in adults and adolescents 18 years and older.
To maximise efficacy and safety, once daily (or less frequent) dosing is now the recommended method for dosing aminoglycosides in most clinical settings.
Use with caution in patients with pre-existing hearing, vestibular or renal impairment.

**Contraindications present?**
- Previous vestibular or auditory disease
- Serious hypersensitivity reaction to an aminoglycoside (rare)
- Calculated creatinine clearance less than 20mL/min

**Considering once daily aminoglycoside therapy**

Follow the initial dose section of these guidelines

Microbiology culture results available?

Follow the subsequent dose section of these guidelines per **empirical therapy**

Is aminoglycoside therapy beyond 48 hours thought clinically necessary?

No further doses should be given beyond 48 hours

Seek Infectious Diseases advice

Follow the subsequent dose section of these guidelines per **directed therapy**

Strongly recommend using another class of antibiotic; consult Infectious Diseases physician for advice

**Aminoglycosides** are indicated for directed therapy in only a few circumstances. These include, but are not restricted to:
- Infections when resistance to other safer antimicrobials has been shown;
- Combination therapy for serious *Pseudomonas aeruginosa* infections and brucellosis;
- Low doses as synergistic treatment for streptococcal and enterococcal endocarditis;
- Mycobacterial infections (amikacin).

Monitoring plasma concentrations of aminoglycosides is recommended in these patients and should commence after the first dose of directed therapy.
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Initial dose

1 Determine patient weight and height

Use Ideal Body Weight (IBW) or actual body weight, whichever is less.

To calculate IBW:
- See Figure 1 OR

IBW for male

= 50kg + 0.9kg/each cm over 152cm

IBW for female

= 45.5kg + 0.9kg/each cm over 152cm

In cases of extremes of actual body weight, body mass index (BMI) should be calculated.

2 Calculate patient’s creatinine clearance (CrCl) using the Cockcroft-Gault equation

A minimum serum creatinine level (SeCr) of 60 micromol/L should be used to calculate creatinine clearance with the Cockcroft-Gault equation for aminoglycoside dosing. That is, when the SeCr is less than 60micromol/L, a value of 60micromol/L should be used in the calculation.

Figure 2: Cockcroft-Gault equation

CrCl (mL/minute) (males) = \( \frac{(140 – age) \times \text{weight (kg)}}{0.815 \times \text{SeCr (micromol/L)}} \) (Multiply by 0.85 if female)

CrCl = creatinine clearance; SeCr = serum creatinine

3 Calculate the first dose of aminoglycoside according to patient’s age

Table 1: Aminoglycoside starting doses

<table>
<thead>
<tr>
<th>Age</th>
<th>Gentamicin and Tobramycin</th>
<th>Amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 to 29 years</td>
<td>6mg/kg up to 560mg</td>
<td>24mg/kg up to 2.25g</td>
</tr>
<tr>
<td>30 to 60 years</td>
<td>5mg/kg up to 480mg</td>
<td>20mg/kg up to 2g</td>
</tr>
<tr>
<td>More than 60 years</td>
<td>4mg/kg up to 400mg</td>
<td>16mg/kg up to 1.5g</td>
</tr>
<tr>
<td>Severe sepsis (sepsis syndrome)†</td>
<td>7mg/kg up to 640mg</td>
<td>28mg/kg up to 2.5g</td>
</tr>
</tbody>
</table>

† Patients with severe sepsis have higher volumes of distribution and therefore require a higher mg/kg dose.

NB: Consider vial concentration e.g. Gentamicin/Tobramycin: 80mg/2mL round to nearest 40mg; Amikacin: 500mg/2mL round to nearest 250mg

NB: Cystic fibrosis/major burns may require higher doses. Not applicable for the long-term treatment of Mycobacterial disease.

NB: Streptococcal/enterococcal endocarditis: gentamicin 1 mg/kg IV, 8-hourly, trough level prior to the next dose should be less than 1mg/L.

NB: Once-daily dosing is now well accepted in patients with creatinine clearance (CrCl) above 20 mL/min. However, with CrCl below 20 mL/min, whether the dose should be reduced or the interval increased has not been evaluated, and dialysis markedly alters the kinetics. Using a single dose of an aminoglycoside as initial therapy for presumptive Gram-negative infection is entirely appropriate in patients with renal failure. Treatment in this group may be best continued with non-aminoglycoside antimicrobials. If an aminoglycoside is strongly indicated, careful monitoring and care not to underdose need to be the principles guiding dose and frequency determination.

4 Prescribe aminoglycoside in variable dose section of the medication chart

• All patients requiring aminoglycosides should receive the initial dose as soon as possible after microbiology samples are taken.

• Refer to subsequent dose section of these guidelines for timing of subsequent dose(s).

• When used in combination with other IV antibiotics, aminoglycosides should be administered first.

• Give aminoglycoside dose in 100mL normal saline by intravenous infusion over 30 minutes.

• Ensure the exact time the infusion is started and finished is recorded on the medication chart.


#BMI (kg/m²) = \( \frac{\text{Actual weight (kg)}}{\text{[Height (m)]}^2} \)

If BMI is less than 18.5kg/m² (underweight) or greater than 40kg/m² (obese grade III), use Lean Body Weight (LBW) in place of IBW:

Males: \( \text{LBW (kg)} = \frac{9270 \times \text{total body weight (kg)}}{6680 + \left[ \frac{216 \times \text{BMI (kg/m²)}}{244} \right]} \)

Females: \( \text{LBW (kg)} = \frac{9270 \times \text{total body weight (kg)}}{8780} \)

*All dosing and renal function calculations should be is based on ideal body weight (IBW) or actual body weight, whichever is less.
1 a) Next dose for empirical therapy

- The primary indication for aminoglycosides is as short-term empirical therapy pending the outcome of microbiological investigations.
- When used empirically, no further doses should be given beyond 48 hours. If further dosing is thought clinically necessary, seek Infectious Diseases advice.
- Monitoring of aminoglycoside plasma concentrations is not required if the clinical plan is to cease therapy within 72 hours of commencement.
- The dosing interval for subsequent empirical dosing is based on the patient’s renal function (calculated using the Cockcroft-Gault equation).

Table 2: Aminoglycoside dosing interval for subsequent empirical doses in adults

<table>
<thead>
<tr>
<th>CrCl (mL/minute)</th>
<th>Dosing interval (use the doses recommended in Table 1)</th>
<th>Maximum number of empirical doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than 60</td>
<td>24 hours</td>
<td>3 (at 0, 24 and 48 hours)</td>
</tr>
<tr>
<td>40 to 60</td>
<td>36 hours</td>
<td>2 (at 0 and 36 hours)</td>
</tr>
<tr>
<td>30 to 40</td>
<td>48 hours</td>
<td>2 (at 0 and 48 hours)</td>
</tr>
<tr>
<td>Less than 30</td>
<td>Give initial dose once, then seek expert advice</td>
<td></td>
</tr>
</tbody>
</table>

NB: Creatinine clearance estimate should be based on a creatinine measurement obtained as recently as possible (e.g. within the last 12 to 24 hours); however, this might still overestimate renal function in acute renal failure.

b) Next dose for directed therapy

- Aminoglycosides are indicated for directed therapy in only a few circumstances. These include, but are not restricted to:
  - infections when resistance to other safer antimicrobials is known or expected;
  - combination therapy for serious Pseudomonas aeruginosa infections and brucellosis;
  - low doses as synergistic treatment for streptococcal and enterococcal endocarditis;
  - mycobacterial infections (amikacin).8
- Order aminoglycoside plasma concentrations after the first dose and after any change in dose. Re-check aminoglycoside plasma concentrations every 48 hours if clinically unstable or every 72 hours if clinically stable.
- Current guidelines recommend using computerised methods of estimating Area Under the Curve (AUC) to determine dosage adjustment as they automatically adjust for significant individual variation in volume of distribution and elimination rate. Individual facilities will have varying levels of resources available to optimally utilise more sophisticated methods.
- Facilities should have a method of calculating subsequent doses of aminoglycosides and develop an associated workflow practice.
- Regional and smaller hospitals should liaise with their tertiary referral centre to develop a system to manage patients requiring directed therapy with aminoglycosides. Options include remote clinical supervision, or training and supervision of local staff.
- If any dose recommended by a calculator exceeds 640mg for gentamicin or tobramycin, review data entry and if dose still exceeds 640mg, seek expert advice.
- Seek expert advice for amikacin therapy.
- Infectious Diseases and/or specialist pharmacist review is essential for patients on an aminoglycoside for more than three days.

2 Monitor renal, hearing and vestibular function

- Serum creatinine should be checked and creatinine clearance calculated before commencing an aminoglycoside and then, if therapy is ongoing, 2 to 3 times each week or more frequently if renal function is unstable.
- Patients should be reviewed daily regarding the following, where possible:
  - Ataxia;
  - Disequilibrium and loss of balance;
  - Oscillopsia (reduced visual acuity with oscillating head movement).
- Where prolonged aminoglycoside courses (greater than 5 days) is anticipated, ideally, baseline audiometry (formal vestibular function testing and high-frequency audiometric testing) should be considered and recorded close to the time of initiation of therapy and repeated periodically, if available.
- Patients and/or guardians and carers should be informed of the potential toxicities of aminoglycoside therapy (e.g. balance or hearing problems) and documentation of this discussion should be recorded in the patient’s clinical notes.

References:

All dosing and renal function calculations should be based on ideal body weight (IBW) or actual body weight, whichever is less.