AMINOGLYCOSIDES

Clinical PK  5th stage
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Msc in clinical pharmacy and Therapeutics
The aminoglycoside antibiotics are widely used for the treatment of severe gram-negative infections such as pneumonia or bacteremia, often in combination with a β-lactam antibiotic.
Aminoglycosides are also used for gram-positive infections such as infective endocarditis in combination with penicillins when antibiotic synergy is required for optimal killing.

Aminoglycoside antibiotics available in the United States that are in common use include gentamicin, tobramycin, netilmicin, and amikacin.
Aminoglycoside antibiotics are bactericidal, and the drugs exhibit concentration-dependent bacterial killing. Antibiotics with concentration-dependent killing characteristically kill bacteria at a faster rate when drug concentrations are higher. Also, aminoglycosides have a concentration-dependent postantibiotic effect.
Definition

- The post-antibiotic effect is the phenomenon of continued bacterial killing even though serum concentrations have fallen below the minimum inhibitory concentration (MIC).

- Because the postantibiotic effect is concentration-dependent for the aminoglycosides, higher drug concentrations lead to a longer postantibiotic effect.
The mechanisms of action for aminoglycosides are binding to the 30S ribosomal subunit inhibiting protein synthesis and misreading of mRNA causing dysfunctional protein production.
The MIC for susceptible bacteria is higher for amikacin than it is for the other aminoglycosides.

Because the pharmacokinetics is similar for all these drugs, higher doses of amikacin are needed to treat infections.

The conventional method of dosing aminoglycoside antibiotics is to administer multiple daily doses (usually every 8 hours).
In order to take advantage of concentration-dependent bacterial killing and the postantibiotic effect, extended-interval (usually the total daily dose given once per day) aminoglycoside administration is also an dosing option. Because of these two different methods of dosage administration, it is important to identify which is being used when discussing serum concentration monitoring.
The aminoglycosides are eliminated almost completely (≥90%) unchanged in the urine primarily by glomerular filtration (Table 4–1).

These antibiotics are usually given by short-term (1/2–1 hour) intermittent intravenous infusions, although they can be given intramuscularly.

When aminoglycosides are given intramuscularly they exhibit very good bioavailability of ~100% and are rapidly absorbed with maximal concentrations occurring
Exceptions to this situation are patients who are hypotensive or obese.

Hypotensive patients shunt blood flow away from peripheral tissues, such as muscle, to provide maximal blood flow to internal organs. As a result, intramuscularly administered drugs may be malabsorbed in hypotensive patients, such as those with gram-negative sepsis.
Care must be taken with obese individuals to use a long enough needle to penetrate subcutaneous fat and enter muscle tissue when administering aminoglycoside antibiotics.

Drug injected into poorly perfused fatty tissue will likely be malabsorbed.

Oral bioavailability is poor (<10%) so systemic infections cannot be treated by this route of administration.
Manufacture recommended doses for conventional dosing in patients with normal renal function are 3–5 mg/kg/d for gentamicin and tobramycin, 4–6 mg/kg/d for netilmicin, and 15 mg/kg/d for amikacin.
These amounts are divided into three equal daily doses for gentamicin, tobramycin, or netilmicin, or two or three equal daily doses for amikacin. Extended-interval doses obtained from the literature for patients with normal renal function are 4–7 mg/kg/d for gentamicin, tobramycin, or netilmicin and 11–20 mg/kg/d for amikacin.
Effects of disease states and conditions on aminoglycoside pharmacokinetics and dosing

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>HALF-LIFE</th>
<th>DISTRIBUTION</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult, normal renal function</td>
<td>2 hours (range: 1.5–3 hours)</td>
<td>0.26 L/kg (range: 0.2–0.3 L/kg)</td>
<td>Usual doses 3–5 mg/kg/d for gentamicin, tobramycin, netilmicin, or 15 mg/kg/d for amikacin when using conventional dosing. Usual doses are 5–7 mg/kg/d for gentamicin or tobramycin using extended-interval dosing.</td>
</tr>
<tr>
<td>Adult, renal failure</td>
<td>50 hours (range: 36–72 hours)</td>
<td>0.26 L/kg</td>
<td>Renal failure patients commonly have fluid imbalances that may decrease (underhydration) or increase (overhydration) the volume of distribution and secondarily change half-life.</td>
</tr>
<tr>
<td>Burns</td>
<td>1.5 hours</td>
<td>0.26 L/kg</td>
<td>Burn patients commonly have fluid imbalances that may decrease (underhydration) or increase (overhydration) the volume of distribution and secondarily change half-life.</td>
</tr>
</tbody>
</table>
## Effects of disease states and conditions on aminoglycoside pharmacokinetics and dosing

<table>
<thead>
<tr>
<th>Condition</th>
<th>Variable</th>
<th>Volume (L/kg)</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin therapy (patients with creatinine clearance &lt;30 mL/min)</td>
<td>0.26</td>
<td>Some penicillins (penicillin G, ampicillin, nafcillin, carbenicillin, ticarcillin) can bind and inactivate aminoglycosides in vivo or in vitro (e.g., lab test tubes).</td>
<td></td>
</tr>
<tr>
<td>Obesity (&gt;30% over IBW) with normal renal function</td>
<td>2–3 hours</td>
<td>( V \text{ (in L)} = 0.26 [\text{IBW} + 0.4 (\text{TBW} - \text{IBW})] )</td>
<td>Aminoglycosides enter the extracellular fluid contained in adipose tissue requiring a correction factor to estimate volume of distribution.</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1.5 hours</td>
<td>0.35</td>
<td>Larger volume of distribution and shorter half-life usually results in larger daily doses.</td>
</tr>
<tr>
<td>Acites/overhydration</td>
<td>Variable</td>
<td>( V \text{ (in L)} = (0.26 \cdot \text{DBW}) + (\text{TBW} - \text{DBW}) )</td>
<td>Aminoglycosides distribute to excess extracellular fluid; correction equation assumes that weight gain is due to fluid accumulation. Alterations in volume of distribution can cause secondary changes in half-life.</td>
</tr>
</tbody>
</table>
### Effects of disease states and conditions on aminoglycoside pharmacokinetics and dosing

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>HALF-LIFE</th>
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<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodialysis</td>
<td>3–4 hours</td>
<td>0.26 L/kg</td>
<td>While receiving hemodialysis, aminoglycoside half-life will decreases from ~50 hours to ~4 hours. Renal failure patients commonly have fluid imbalances that may decrease (underhydration) or increase (overhydration) the volume of distribution and secondarily change half-life.</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>36 hours</td>
<td>0.26 L/kg</td>
<td>While receiving peritoneal dialysis, aminoglycoside half-life will decrease from ~50 hours to ~36 hours. Renal failure patients commonly have fluid imbalances that may decrease (underhydration) or increase (overhydration) the volume of distribution and secondarily change half-life.</td>
</tr>
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</table>

Symbol key: IBW is ideal body weight, TBW is total body weight, DBW is dry body weight.
Pharmacokinetic Dosing Method

- The goal of initial dosing of aminoglycosides is to compute the best dose possible for the patient given their set of disease states and conditions that influence aminoglycoside pharmacokinetics and the site and severity of the infection.

- In order to do this, pharmacokinetic parameters for the patient will be estimated using average parameters measured in other patients with similar disease state and condition profiles.
1. ELIMINATION RATE CONSTANT

\[ k_e = 0.00293 \times \text{CrCl} + 0.014 \]

2. VOLUME OF DISTRIBUTION ESTIMATE
2. VOLUME OF DISTRIBUTION ESTIMATE

- The average volume of distribution for patients without disease states and conditions that change this parameter is 0.26 L/kg.

- If a patient weighs less than their ideal body weight, actual body weight is used to estimate volume of distribution.
In patients who are more than 30% above their ideal body weight, volume of distribution (V) estimates should include both ideal and actual total body weight using the following equation:

\[ V = 0.26[IBW + 0.4(TBW - IBW)] \]

where V is in L, IBW is ideal body weight in kilograms, and TBW is total body weight in kilograms.
In patients who are overhydrated or have ascites, their dry body weight (weight without the extra fluid) can be used to provide an improved volume of distribution estimate ($V$ in L) using the following formula:

$$V = (0.26 \cdot DBW) + (TBW - DBW),$$

Where $DBW$ is the patient’s dry body weight and $TBW$ is the patient’s actual total body weight.
2. VD

- For example, a patient with a significant amount of ascitic fluid currently weighs 80 kg.

- It is known from previous clinic visits and history that the patient usually weighs 70 kg without the additional fluid.

- The estimated volume of distribution for this patient would be 28.2 L: 
  \[ V = (0.26 \cdot DBW) + (TBW - DBW) = (0.26 \cdot 70 \text{ kg}) + (80 \text{ kg} - 70 \text{ kg}) = 28.2 \text{ L}. \]
2. VD

- For example, a patient with a significant amount of ascitic fluid currently weighs 80 kg.
- It is known from previous clinic visits and history that the patient usually weighs 70 kg without the additional fluid.
- The estimated volume of distribution for this patient would be 28.2 L: 
  \[ V = (0.26 \cdot DBW) + (TBW - DBW) \]
  \[ = (0.26 \cdot 70 \text{ kg}) + (80 \text{ kg} - 70 \text{ kg}) = 28.2 \text{ L} \]
Selection of appropriate pharmacokinetic model and equations
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<table>
<thead>
<tr>
<th>ROUTE OF ADMINISTRATION</th>
<th>DOSAGE INTERVAL ($\tau$), MAINTENANCE DOSE ($D$ OR $K_0$), AND LOADING DOSE ($LD$) EQUATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous bolus</td>
<td>$\tau = (\ln C_{ss_{\text{max}}} - \ln C_{ss_{\text{min}}}) / k_e$</td>
</tr>
<tr>
<td></td>
<td>$D = C_{ss_{\text{max}}} V(1 - e^{-k_e\tau})$</td>
</tr>
<tr>
<td></td>
<td>$LD = C_{ss_{\text{max}}} V$</td>
</tr>
<tr>
<td>Intermittent intravenous infusion</td>
<td>$\tau = [(\ln C_{ss_{\text{max}}} - \ln C_{ss_{\text{min}}}) / k_e] + t'$</td>
</tr>
<tr>
<td></td>
<td>$k_0 = C_{ss_{\text{max}}} k_e V[(1 - e^{-k_e\tau}) / (1 - e^{-k_e t'})]$</td>
</tr>
<tr>
<td></td>
<td>$LD = k_0 / (1 - e^{-k_e \tau})$</td>
</tr>
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Symbol key: $C_{ss_{\text{max}}}$ and $C_{ss_{\text{min}}}$ are the maximum and minimum steady-state concentrations, $k_e$ is the elimination rate constant, $V$ is the volume of distribution, $k_0$ is the continuous infusion rate, $t'$ is the infusion time.
Steady-state concentration selection

- Severe infections, such as gram-negative pneumonia or septicemia, or infections with organisms that have a high minimum inhibitory concentration (MIC) such as Pseudomonas aeruginosa (typical MIC $\approx 2 \mu g/mL$ for gentamicin, tobramycin, or netilmicin) generally require peak steady-state serum concentrations of 8-10 $\mu g/mL$ for gentamicin, tobramycin, or netilmicin or 25-30 $\mu g/mL$ for amikacin when using conventional dosing.
Steady-state concentration selection

- Moderate infections at sites that are easier to penetrate or with organisms that display lower MIC values, such as intraabdominal infections, are usually treated with peak gentamicin, tobramycin, or netilmicin steady-state serum concentrations equal to 5–7 μg/mL or with amikacin peak steady-state serum concentrations equal to 15–25 μg/mL.
When treating urinary tract infections due to susceptible organisms or using aminoglycosides for synergy in combination with penicillins or other antibiotics for the treatment of gram-positive infections such as infective endocarditis, steady-state peak concentrations of 3–5 μg/mL are usually adequate for gentamicin, tobramycin, or netilmicin; or 12–15 μg/mL for amikacin.
Pyelonephritis is considered a soft-tissue infection, not a urinary tract infection, and requires higher peak steady-state concentrations to achieve a cure.

Similar target peak steady-state concentrations for extended-interval aminoglycoside dosing are less established, although concentrations 20–30 μg/mL have been suggested for Pseudomonas aeruginosa and other serious infections including pulmonary exacerbations in cystic fibrosis patients.
Steady-state concentration selection

Desirable concentrations for steady-state trough concentrations are chosen based on avoidance of potential toxicity.

For conventional dosing, steady-state trough concentrations should be maintained <2 μg/mL for tobramycin, gentamicin, and netilmicin or <5–7 μg/mL for amikacin.

Using extended-interval dosing, steady-state trough concentrations should be <1 μg/mL for gentamicin,
JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission.

Q: Compute a gentamicin dose for this patient using conventional dosing.
Selection of appropriate pharmacokinetic model and equations

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<td>Intravenous bolus</td>
<td>(\tau = (\ln C_{SS_{max}} - \ln C_{SS_{min}}) / k_e)</td>
</tr>
<tr>
<td></td>
<td>(D = C_{SS_{max}} V(1 - e^{-k_e \tau}))</td>
</tr>
<tr>
<td></td>
<td>(LD = C_{SS_{max}} V)</td>
</tr>
<tr>
<td>Intermittent intravenous</td>
<td>(\tau = \left[\left(\ln C_{SS_{max}} - \ln C_{SS_{min}}\right) / k_e\right] + t')</td>
</tr>
<tr>
<td>infusion</td>
<td>(k_0 = C_{SS_{max}} k_e V\left[\frac{(1 - e^{-k_e \tau})}{(1 - e^{-k_e t'})}\right])</td>
</tr>
<tr>
<td></td>
<td>(LD = k_0 / (1 - e^{-k_e \tau}))</td>
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Symbol key: \(C_{SS_{max}}\) and \(C_{SS_{min}}\) are the maximum and minimum steady-state concentrations, \(k_e\) is the elimination rate constant, \(V\) is the volume of distribution, \(k_0\) is the continuous infusion rate, \(t'\) is the infusion time.
3. Estimate volume of distribution (V).

\[ V = 0.26 \text{ L/kg} \times 70 \text{ kg} = 18.2 \text{ L} \]

4. Choose desired steady-state serum concentrations.

- Set \( C_{ss\text{max}} = 9 \mu g/mL \) and
- \( C_{ss\text{min}} = 1 \mu g/mL \).
5. Use intermittent intravenous infusion equations to compute dose.

Calculate required dosage interval ($\tau$) using a 1-hour infusion:

$$\tau = \left[\frac{\ln C_{ssmax} - \ln C_{ssmin}}{ke}\right] + t'$$

$$\tau = \left[\frac{\ln 9 \mu g/mL - \ln 1 \mu g/mL}{0.298 \text{ h}^{-1}}\right] + 1 \text{ h} = 8.4 \text{ h}$$
5. Use intermittent intravenous infusion equations to compute dose.

Calculate required dosage interval ($\tau$) using a 1-hour infusion:

$$\tau = \left[ \frac{\ln C_{ss,max} - \ln C_{ss,min}}{k_e} \right] + t'$$

$$= \left[ \frac{\ln 9 \, \mu g/mL - \ln 1 \, \mu g/mL}{0.298 \, h^{-1}} \right] + 1 \, h = 8.4 \, h$$

$$k_0 = C_{ss,max} k_e V \left[ \frac{(1 - e^{-k_e \tau})}{(1 - e^{-k_e t'})} \right]$$

$$k_0 = (9 \, mg/L \cdot 0.298 \, h^{-1} \cdot 18.2 \, L) \left\{ \frac{[1 - e^{-(0.298 \, h^{-1})(8 \, h)}}{[1 - e^{-(0.298 \, h^{-1})(1 \, h)}] \right\} = 172 \, mg$$
Ex.2

Same patient profile as in example 1, but serum creatinine is 3.5 mg/Dl indicating renal impairment.
ZW is a 35-year-old, 150-kg (5 ft 5 in) female with an intraabdominal infection.

Her current serum creatinine is 1.1 mg/dL and is stable. Compute a tobramycin dose for this patient using conventional dosing.
1. Estimate creatinine clearance.

This patient has a stable serum creatinine and is obese \[ \text{IBW}_{\text{females}} \text{ (in kg)} = 45 + 2.3(\text{Ht} - 60 \text{ in}) = 45 + 2.3(65 - 60) = 57 \text{ kg} \]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

\[
\text{CrCl}_{\text{est(females)}} = \frac{(146 - \text{age})[(0.287 \cdot \text{Wt}) + (9.74 \cdot \text{Ht}^2)]}{(60 \cdot \text{S}_{\text{Cr}})}
\]

\[
\text{CrCl}_{\text{est(females)}} = \frac{(146 - 35 \text{ y})[(0.287 \cdot 150 \text{ kg}) + (9.74 \cdot (1.65 \text{ m})^2)]}{(60 \cdot 1.1 \text{ mg/dL})} = 117 \text{ mL/min}
\]

Note: Height is converted from inches to meters: \[ \text{Ht} = (65 \text{ in} \cdot 2.54 \text{ cm/in}) / (100 \text{ cm/m}) = 1.65 \text{ m} \].
2. Estimate elimination rate constant \( (k_e) \) and half-life \( (t_{1/2}) \).

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

\[
k_e = 0.00293(\text{CrCl}) + 0.014 = 0.00293(117 \text{ mL/min}) + 0.014 = 0.357 \text{ h}^{-1}
\]

\[t_{1/2} = \frac{0.693}{k_e} = \frac{0.693}{0.357 \text{ h}^{-1}} = 1.9 \text{ h}\]

3. Estimate volume of distribution \( (V) \).

The patient is obese, so the volume of distribution would be estimated using the following formula:

\[V = 0.26[\text{IBW} + 0.4(\text{TBW} - \text{IBW})] = 0.26[57 \text{ kg} + 0.4(150 \text{ kg} - 57 \text{ kg})] = 24.5 \text{ L}\]

4. Choose desired steady-state serum concentrations.

Intraabdominal infection patients treated with aminoglycoside antibiotics require steady-state peak concentrations \( (C_{ss_{\text{max}}}) \) equal to 5–7 \( \mu \text{g/mL} \); steady-state trough \( (C_{ss_{\text{min}}}) \) concentrations should be <2 \( \mu \text{g/mL} \) to avoid toxicity. Set \( C_{ss_{\text{max}}} = 6 \mu \text{g/mL} \) and \( C_{ss_{\text{min}}} = 0.5 \mu \text{g/mL} \).
5. Use intermittent intravenous infusion equations to compute dose (Table 4-2).

Calculate required dosage interval ($\tau$) using a 1-hour infusion:

$$\tau = [(\ln \text{Css}_{\text{max}} - \ln \text{Css}_{\text{min}}) / k_e] + t' = [(\ln 6 \, \mu\text{g/mL} - \ln 0.5 \, \mu\text{g/mL}) / 0.357 \, \text{h}^{-1}] + 1 \, \text{h} = 8 \, \text{h}$$

Dosage intervals should be rounded to clinically acceptable intervals of 8 hours, 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible. In this case, the dosage interval is 8 hours. Also, steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or $\frac{1}{2}$ hour after a $\frac{1}{2}$-hour infusion, so the dose could be administered either way.

$$k_0 = \text{Css}_{\text{max}} k_e V [(1 - e^{-k_e \tau}) / (1 - e^{-k_e t'})]$$

$$k_0 = (6 \, \text{mg/L} \cdot 0.357 \, \text{h}^{-1} \cdot 24.5 \, \text{L}) \left\{ [1 - e^{-(0.357 \, \text{h}^{-1})(8 \, \text{h})}] / [1 - e^{-(0.357 \, \text{h}^{-1})(1 \, \text{h})}] \right\} = 165 \, \text{mg}$$

Aminoglycoside doses should be rounded to the nearest 5–10 mg. This dose does not need to be rounded. (Note: $\mu\text{g/mL} = \text{mg/L}$ and this concentration unit was substituted for $\text{Css}_{\text{max}}$ so that unnecessary unit conversion was not required.)

The prescribed maintenance dose would be 165 mg every 8 hours.
6. Compute loading dose (LD), if needed.

Loading doses should be considered for patients with creatinine clearance values below 60 mL/min. The administration of a loading dose in these patients will allow achievement of therapeutic peak concentrations quicker than if maintenance doses alone are given. However, since the pharmacokinetic parameters used to compute these initial doses are only estimated values and not actual values, the patient’s own parameters may be much different than the estimated constants and steady state will not be achieved until 3–5 half-lives have passed.

\[ LD = \frac{k_0}{(1 - e^{-k e^t})} = 165 \, \text{mg} / [1 - e^{- (0.357 \, \text{h}^{-1}) (8 \, \text{h})}] = 175 \, \text{mg} \]
For patients who do not have disease states or conditions that alter volume of distribution, the only two patient-specific factors that change when using the pharmacokinetic dosing method is patient weight and creatinine clearance.

Because of this, it is possible to make a simple nomogram to handle uncomplicated patients with a standard volume of distribution.
The Hull and Sarubbi aminoglycoside dosing nomogram is a quick and efficient way to apply pharmacokinetic dosing concepts without using complicated pharmacokinetic equations.
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<table>
<thead>
<tr>
<th>Aminoglycoside</th>
<th>Usual Loading Doses</th>
<th>Expected Peak Serum Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobramycin</td>
<td>1.5–2.0 mg/kg</td>
<td>4–10 μg/mL</td>
</tr>
<tr>
<td>Gentamicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Netilmicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>5.0–7.5 mg/kg</td>
<td>15–30 μg/mL</td>
</tr>
<tr>
<td>Kanamycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl (mL/min)</td>
<td>EST. HALF-LIFE (HOURS)</td>
<td>8 HOURS (%)</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>&gt;90</td>
<td>2–3</td>
<td>90</td>
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<td>90</td>
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<td>25</td>
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<td>20</td>
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<td>15</td>
<td>15.1</td>
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<tr>
<td>12</td>
<td>17.9</td>
<td>27</td>
</tr>
<tr>
<td>10*</td>
<td>20.4</td>
<td>24</td>
</tr>
<tr>
<td>7*</td>
<td>25.9</td>
<td>19</td>
</tr>
<tr>
<td>5*</td>
<td>31.5</td>
<td>16</td>
</tr>
</tbody>
</table>
Example 1  JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a gentamicin dose for this patient using conventional dosing.

1. Estimate creatinine clearance.

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

\[
CrCl_{\text{est}} = \frac{(140 - \text{age})\text{BW}}{72 \cdot S_{\text{Cr}}} = \frac{(140 - 50 \text{ y})70 \text{ kg}}{72 \cdot 0.9 \text{ mg/dL}}
\]

\[
CrCl_{\text{est}} = 97 \text{ mL/min}
\]

2. Choose desired steady-state serum concentrations.

Gram-negative pneumonia patients treated with aminoglycoside antibiotics require steady-state peak concentrations (\(C_{\text{ss, max}}\)) equal to 8–10 \(\mu\text{g/mL}\).

3. Select loading dose (Table 4-3).

A loading dose (LD) of 2 mg/kg will provide a peak concentration of 8–10 \(\mu\text{g/mL}\).

\[
LD = 2 \text{ mg/kg}(70 \text{ kg}) = 140 \text{ mg}
\]

4. Determine estimated half-life, maintenance dose, and dosage interval.

From the nomogram the estimated half-life is 2–3 hours, the maintenance dose (MD) is 90% of the loading dose [\(\text{MD} = 0.90(140 \text{ mg}) = 126 \text{ mg}\)], and the dosage interval is 8 hours.
Example 2  Same patient profile as in example 1, but serum creatinine is 3.5 mg/dL indicating renal impairment.

1. Estimate creatinine clearance.

   This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

   \[ \text{CrCl}_{\text{est}} = \frac{[(140 - \text{age}) \cdot \text{BW}]}{72 \cdot \text{S}_{\text{Cr}}} = \frac{[(140 - 50 \text{ y}) \cdot 70 \text{ kg}]}{72 \cdot 3.5 \text{ mg/dL}} \]
   \[ \text{CrCl}_{\text{est}} = 25 \text{ mL/min} \]

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   \[ \text{LD} = 2 \text{ mg/kg(70 kg)} = 140 \text{ mg} \]

4. Determine estimated half-life, maintenance dose, and dosage interval.

   From the nomogram the estimated half-life is 9.9 hours, the maintenance dose (MD) is 81\% of the loading dose [MD = 0.81(140 mg) = 113 mg], and the dosage interval is 24 hours. Note: Because of the \(C_{\text{max ss}}\) and \(C_{\text{min ss}}\) chosen for this patient, the 24-hour dosage interval was used.
Hartford Nomogram Method for Extended-Interval Dosing

- Extended-interval dosing is now a mainstream method used to administer aminoglycoside antibiotics.

- Conventional dosing is still preferred for endocarditis patients because the aminoglycoside is usually used for antibiotic synergy.

- Extended-interval doses obtained from the literature for patients with normal renal function are 4–7 mg/kg/d for gentamicin, tobramycin, or netilmicin and 11–20 mg/kg/d for amikacin.
Hartford Nomogram Method for Extended-Interval Dosing

**ODA nomogram for gentamicin and tobramycin at 7 mg/kg.**

1. Administer 7-mg/kg gentamicin with initial dosage interval:

<table>
<thead>
<tr>
<th>ESTIMATED CrCl</th>
<th>INITIAL DOSAGE INTERVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60 mL/min</td>
<td>q24 h</td>
</tr>
<tr>
<td>40–59 mL/min</td>
<td>q36 h</td>
</tr>
<tr>
<td>20–39 mL/min</td>
<td>q48 h</td>
</tr>
<tr>
<td>&lt;20 mL/min</td>
<td>monitor serial concentrations and administer next dose when &lt;1 µg/mL</td>
</tr>
</tbody>
</table>
Example 1  JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a gentamicin dose for this patient using extended-interval dosing.

1. Estimate creatinine clearance.

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

\[
CrCl_{est} = \frac{(140 - \text{age}) \times \text{BW}}{72 \times S_{Cr}} = \frac{(140 - 50 \text{ y}) \times 70 \text{ kg}}{72 \times 0.9 \text{ mg/dL}}
\]

\[
CrCl_{est} = 97 \text{ mL/min}
\]

2. Compute initial dose and dosage interval (Table 4-4).

A dose (D) of 7 mg/kg will provide a peak concentration >20 µg/mL.

\[
D = 7 \text{ mg/kg}(70 \text{ kg}) = 490 \text{ mg}
\]