

Approved: September 2017

## AMINOGLYCOSIDES DOSING AND MONITORING GUIDELINES

NB Provincial Health Authorities Anti-Infective Stewardship Committee

### GENERAL COMMENTS

- Aminoglycosides (AG) include gentamicin, tobramycin, amikacin and streptomycin
- AG exert bactericidal activity against gram-negative bacteria
- Combination of gentamicin with a cell-wall active agent (i.e. beta-lactam) results in a synergistic effect on certain gram-positive bacteria such as Enterococci and Streptococci in the treatment of endocarditis
- Amikacin is generally reserved for infections due to organisms with documented resistance to gentamicin and tobramycin; refer to amikacin section for dosing and monitoring information
- Streptomycin is used infrequently to treat drug resistant tuberculosis and nontuberculous mycobacterial infections; its dosage and monitoring are *not* included in these guidelines
- There are three dosing strategies for AG:
  - Conventional dosing of AG: weight-based dose administered three times a day, or less frequently in decreased renal function
  - Extended-interval dosing of AG (also called “once daily dosing”): a larger weight-based dose (approximately triple conventional dosing) administered once a day, or less frequently in decreased renal function
  - Synergistic dosing for gram-positive infections
- AG exhibit concentration-dependent killing: higher serum concentrations result in higher rates and extent of bacterial killing
- AG demonstrate a post-antibiotic effect: suppression of bacterial growth is continued even after serum concentrations have decreased below the minimum inhibitory concentration (MIC)
- AG are nephrotoxic, ototoxic and can produce neuromuscular blockade



## GENTAMICIN AND TOBRAMYCIN IN ADULT PATIENTS

<b>ADULT EXTENDED INTERVAL DOSING</b>										
<ul style="list-style-type: none"> <li>• <b>Use extended interval dosing whenever possible</b></li> <li>• Takes advantage of concentration-dependent killing and post-antibiotic effect properties of AG with the goals of enhancing efficacy with higher peaks and potentially decreasing toxicity with greater drug-free intervals</li> <li>• Extended interval AG dosing should NOT be used in:                             <ul style="list-style-type: none"> <li>○ Patients requiring dialysis</li> <li>○ Patients with rapid clearance of AG, including burns exceeding 20% of body surface area</li> <li>○ Patients with gram-positive infections where AG is used for synergy (i.e. endocarditis)</li> </ul> </li> <li>• Extended interval AG dosing should be used with CAUTION in:                             <ul style="list-style-type: none"> <li>○ Patients with creatinine clearance (CrCl) less than 20 mL/min</li> <li>○ Patients with chronic ascites or serious liver disease (altered volume of distribution)</li> <li>○ Patients with known auditory or vestibular disease or pre-existing impairment</li> <li>○ Pregnant women</li> </ul> </li> </ul>										
<b>Initial Dose</b>										
<ul style="list-style-type: none"> <li>• <b>5-7 mg/kg IV</b> <ul style="list-style-type: none"> <li>○ based on ideal body weight or dosing weight (see appendix B)</li> <li>○ use 7 mg/kg for serious infections or infections due to <i>Pseudomonas aeruginosa</i> or multidrug resistant organisms</li> <li>○ round dose to nearest 20 mg</li> </ul> </li> </ul>										
<ul style="list-style-type: none"> <li>• An initial dosing interval is chosen based on renal function as per the following table</li> </ul>										
<table border="1" style="margin: auto; border-collapse: collapse;"> <thead> <tr style="background-color: #f2f2f2;"> <th style="padding: 5px;">Creatinine Clearance</th> <th style="padding: 5px;">Dosing Interval</th> </tr> </thead> <tbody> <tr> <td style="padding: 5px;">greater than or equal to 60 mL/min</td> <td style="padding: 5px;">q24h</td> </tr> <tr> <td style="padding: 5px;">40 to 59 mL/min</td> <td style="padding: 5px;">q36h</td> </tr> <tr> <td style="padding: 5px;">20 to 39 mL/min</td> <td style="padding: 5px;">q48h; consider conventional dosing</td> </tr> <tr> <td style="padding: 5px;">less than 20 mL/min</td> <td style="padding: 5px;">Give first dose then draw serial serum drug levels to determine when to give next dose. Consider conventional dosing.</td> </tr> </tbody> </table>	Creatinine Clearance	Dosing Interval	greater than or equal to 60 mL/min	q24h	40 to 59 mL/min	q36h	20 to 39 mL/min	q48h; consider conventional dosing	less than 20 mL/min	Give first dose then draw serial serum drug levels to determine when to give next dose. Consider conventional dosing.
Creatinine Clearance	Dosing Interval									
greater than or equal to 60 mL/min	q24h									
40 to 59 mL/min	q36h									
20 to 39 mL/min	q48h; consider conventional dosing									
less than 20 mL/min	Give first dose then draw serial serum drug levels to determine when to give next dose. Consider conventional dosing.									
<b>Levels</b>										
<ul style="list-style-type: none"> <li>• Monitoring of <u>trough levels</u> alone is generally sufficient with extended interval dosing</li> <li>• Trough levels verify that AG is being adequately eliminated and is not accumulating</li> <li>• Peak levels are typically NOT required, as the larger doses used are expected to produce concentrations well above those required for clinical efficacy</li> <li>• Peak levels are done in the rare cases where individualized pharmacokinetic monitoring is required</li> </ul>										
<p><b>Target serum concentrations:</b></p> <ul style="list-style-type: none"> <li>• Trough levels: less than 1 mg/L</li> <li>• Peak levels [<i>only if indicated</i>]: 15-25 mg/L                             <ul style="list-style-type: none"> <li>○ Optimal bactericidal activity for AG is achieved when maximum serum concentrations are approximately 8 to 10 times the MIC</li> </ul> </li> </ul>										
<p><b>Levels recommended are in:</b></p> <ul style="list-style-type: none"> <li>• Treatment anticipated to be longer than 3-5 days</li> <li>• Patients more than 65 years of age</li> <li>• Patients with renal dysfunction (CrCl less than 60 mL/min ) or significant changes in renal function from baseline</li> <li>• Patients receiving other nephrotoxic drugs (i.e. vancomycin, NSAIDs, diuretics, ACE-I, ARBs, etc.)</li> <li>• Patients with a large volume of distribution (e.g., ascites, third spacing)</li> <li>• Pregnant women</li> </ul>										

<p><b>Serum sampling:</b></p> <ul style="list-style-type: none"> <li>• Trough levels are taken immediately before a dose (within 30 minutes)</li> <li>• Peak levels are taken 90 minutes after the END of drug infusion, to allow for distribution</li> <li>• The timing and duration of drug administration and sample collection must be carefully documented</li> </ul>
<p><b>Timing of serum levels:</b></p> <ul style="list-style-type: none"> <li>• The notion of steady state does not apply with extended-interval dosing; therefore levels may be taken <u>prior to the 2<sup>nd</sup> dose</u></li> </ul>
<p><b>Interpreting serum levels and adjusting dose:</b></p> <ul style="list-style-type: none"> <li>• Ensure serum samples were collected at the appropriate time</li> <li>• Trough level result of 1 mg/L or more suggests accumulation; extend dosing interval</li> </ul>
<p><b>Hartford Hospital Nomogram (see appendix D):</b></p> <ul style="list-style-type: none"> <li>• A random level taken between 8 to 12 hours after the START of drug infusion may be used to determine appropriate dosing interval using the Hartford Hospital nomogram</li> <li>• Only to be used with a 7 mg/kg dose; has not been validated with other doses</li> </ul>
<p><b>Monitoring and patient counselling</b></p>
<p><b>Subsequent serum levels:</b></p> <ul style="list-style-type: none"> <li>• After a change in dose</li> <li>• At least once a week for most patients</li> </ul>
<p><b>Monitor:</b></p> <ul style="list-style-type: none"> <li>• Clinical response</li> <li>• Renal function <ul style="list-style-type: none"> <li>○ Serum creatinine (SCr) at baseline and every 2 to 3 days during therapy</li> <li>○ AG can cause renal dysfunction; typically reversible if discontinued in a timely manner; close monitoring is warranted</li> </ul> </li> <li>• Ototoxicity <ul style="list-style-type: none"> <li>○ Patients should be advised to watch for and report signs &amp; symptoms of cochlear toxicity (e.g., tinnitus, sense of fullness in ears, loss of hearing) and of vestibular toxicity (e.g., disequilibrium, oscillopsia, cognitive dysfunction, visual sensitivity, nausea/vomiting, vertigo, headache, nystagmus).</li> <li>○ AG should be discontinued immediately if any signs/symptoms of toxicity develop; ototoxicity caused by AG <i>may be irreversible</i>.</li> <li>○ Audiometry and vestibular testing recommended for patients receiving AG for 7 days or more, or at any time if ototoxicity suspected. Consult Audiology.</li> <li>○ If prolonged therapy expected (greater than 7 days) baseline audiometry may be considered</li> <li>○ Assess need for continued AG therapy based on microbial susceptibilities, clinical response, side effects, duration of therapy, etc.</li> </ul> </li> </ul>

<b>ADULT CONVENTIONAL DOSING</b>																	
<ul style="list-style-type: none"> <li>Use conventional dosing when extended-interval dosing is not indicated</li> </ul>																	
<b>Initial Dose</b>																	
<b>Loading dose:</b>																	
<ul style="list-style-type: none"> <li><b>2 mg/kg IV</b> <ul style="list-style-type: none"> <li>based on ideal body weight or dosing weight (see appendix B)</li> <li>round dose to nearest 20 mg</li> <li>loading doses DO NOT need to be adjusted in patients with renal dysfunction; only maintenance dosing interval requires adjustment</li> </ul> </li> </ul>																	
<b>Maintenance dose:</b>																	
<ul style="list-style-type: none"> <li><b>1.5 to 2 mg/kg IV</b> <ul style="list-style-type: none"> <li>based on ideal body weight or dosing weight (see appendix B)</li> <li>round dose to nearest 20 mg</li> </ul> </li> </ul>																	
<b>Dosing interval:</b>																	
<ul style="list-style-type: none"> <li>Interval depends on patient's renal function</li> </ul>																	
<table border="1"> <thead> <tr> <th>Creatinine Clearance</th> <th>Dosing Interval</th> </tr> </thead> <tbody> <tr> <td>greater than or equal to 80 mL/min</td> <td>q8h</td> </tr> <tr> <td>50 to 79 mL/min</td> <td>q12h</td> </tr> <tr> <td>20 to 49 mL/min</td> <td>q24h</td> </tr> <tr> <td>less than 20 mL/min</td> <td>q48-72h; give first dose and draw serial serum drug levels to determine when to give next dose; close monitoring is recommended</td> </tr> </tbody> </table>			Creatinine Clearance	Dosing Interval	greater than or equal to 80 mL/min	q8h	50 to 79 mL/min	q12h	20 to 49 mL/min	q24h	less than 20 mL/min	q48-72h; give first dose and draw serial serum drug levels to determine when to give next dose; close monitoring is recommended					
Creatinine Clearance	Dosing Interval																
greater than or equal to 80 mL/min	q8h																
50 to 79 mL/min	q12h																
20 to 49 mL/min	q24h																
less than 20 mL/min	q48-72h; give first dose and draw serial serum drug levels to determine when to give next dose; close monitoring is recommended																
<b>Levels</b>																	
<ul style="list-style-type: none"> <li>Therapeutic drug monitoring of AG dosed conventionally is typically done by measuring <u>both peak and trough levels at steady state</u> to confirm that therapeutic concentrations have been achieved and that drug accumulation has not taken place</li> </ul>																	
<b>Target serum concentrations:</b>																	
<table border="1"> <thead> <tr> <th>Infection</th> <th>Desired minimal (trough) plasma concentration (mg/L)</th> <th>Desired maximum (peak) plasma concentration (mg/L)</th> </tr> </thead> <tbody> <tr> <td>Lower urinary tract infection</td> <td>less than 1</td> <td>4-6</td> </tr> <tr> <td>Pelvic inflammatory disease (e.g., endometritis, salpingitis, tubo-ovarian abscess, pelvic peritonitis) Chorioamnionitis Pyelonephritis Peritonitis Soft tissue infections</td> <td>less than 2</td> <td>6-8</td> </tr> <tr> <td>Sepsis Neutropenia Burns Pneumonia Infections due to Pseudomonas (non-urinary) Bone and joint infections</td> <td>less than 2</td> <td>8-10</td> </tr> <tr> <td>Cystic fibrosis</td> <td>less than 2</td> <td>10-15</td> </tr> </tbody> </table>			Infection	Desired minimal (trough) plasma concentration (mg/L)	Desired maximum (peak) plasma concentration (mg/L)	Lower urinary tract infection	less than 1	4-6	Pelvic inflammatory disease (e.g., endometritis, salpingitis, tubo-ovarian abscess, pelvic peritonitis) Chorioamnionitis Pyelonephritis Peritonitis Soft tissue infections	less than 2	6-8	Sepsis Neutropenia Burns Pneumonia Infections due to Pseudomonas (non-urinary) Bone and joint infections	less than 2	8-10	Cystic fibrosis	less than 2	10-15
Infection	Desired minimal (trough) plasma concentration (mg/L)	Desired maximum (peak) plasma concentration (mg/L)															
Lower urinary tract infection	less than 1	4-6															
Pelvic inflammatory disease (e.g., endometritis, salpingitis, tubo-ovarian abscess, pelvic peritonitis) Chorioamnionitis Pyelonephritis Peritonitis Soft tissue infections	less than 2	6-8															
Sepsis Neutropenia Burns Pneumonia Infections due to Pseudomonas (non-urinary) Bone and joint infections	less than 2	8-10															
Cystic fibrosis	less than 2	10-15															
<b>Levels are recommended in:</b>																	
<ul style="list-style-type: none"> <li>Treatment anticipated to be longer than 3-5 days</li> <li>Patients more than 65 years of age</li> </ul>																	

<ul style="list-style-type: none"> <li>• Patients with renal dysfunction (CrCl less than 60 mL/min) or significant changes in renal function from baseline</li> <li>• Patients receiving other nephrotoxic drugs (e.g., vancomycin, NSAIDs, diuretics, ACE-I, ARBs, etc.)</li> <li>• Patients with a large volume of distribution (e.g., ascites, third spacing)</li> <li>• Pregnant women</li> </ul>						
<p><b>Serum sampling:</b></p> <ul style="list-style-type: none"> <li>• Trough levels are taken immediately before a dose (within 30 minutes)</li> <li>• Peak levels are taken 30 to 60 minutes after the END of the IV infusion</li> <li>• The timing and duration of drug administration and sample collection must be carefully documented</li> </ul>						
<p><b>Timing of serum levels:</b></p> <ul style="list-style-type: none"> <li>• Levels should be taken at <u>steady state</u>, typically before and after the <u>3<sup>rd</sup> dose</u> in patients with normal renal function</li> <li>• Steady state (SS) occurs in 4 to 5 half-lives and can be estimated by the following equations: <ul style="list-style-type: none"> <li>○ <math>K_e</math> (gentamicin) = <math>CrCl \times 0.00285 + 0.015</math></li> <li>○ <math>K_e</math> (tobramycin) = <math>CrCl \times 0.0031 + 0.01</math></li> <li>○ <math>T_{1/2} = 0.693/K_e</math></li> <li>○ <math>SS = 4 \text{ to } 5 T_{1/2}</math></li> </ul> </li> </ul>						
<p><b>Interpreting serum levels and adjusting dose:</b></p> <ul style="list-style-type: none"> <li>• Ensure serum samples were collected at the appropriate time and at steady state</li> <li>• Adjust AG dose if serum concentrations are not within the desired range as follows: <table border="1" data-bbox="240 856 792 961"> <tr> <td>high trough</td> <td>extend dosing interval</td> </tr> <tr> <td>high peak</td> <td>decrease dose</td> </tr> <tr> <td>low peak</td> <td>increase dose</td> </tr> </table> </li> <li>• AG exhibit linear kinetics; decreasing or increasing the dose by a specific percentage will result in an equal decrease/increase in percentage of peak levels</li> <li>• Pharmacokinetic calculations may be used determine the dose most likely to produce the desired levels, based on the pre and post levels obtained from the patient. Contact Pharmacy.</li> </ul>	high trough	extend dosing interval	high peak	decrease dose	low peak	increase dose
high trough	extend dosing interval					
high peak	decrease dose					
low peak	increase dose					
<p><b>Monitoring and patient counselling</b></p>						
<p><b>Subsequent serum levels:</b></p> <ul style="list-style-type: none"> <li>• After a change in dose, levels should be repeated at new steady state</li> <li>• At least once a week for most patients</li> </ul>						
<p><b>Monitor:</b></p> <ul style="list-style-type: none"> <li>• Clinical response</li> <li>• Renal function <ul style="list-style-type: none"> <li>○ Serum creatinine (SCr) at baseline and every 2 to 3 days during therapy</li> <li>○ AG can cause renal dysfunction; typically reversible if discontinued in a timely manner; close monitoring is warranted</li> </ul> </li> <li>• Ototoxicity <ul style="list-style-type: none"> <li>○ Patients should be advised to watch for and report signs &amp; symptoms of cochlear toxicity (e.g., tinnitus, sense of fullness in ears, loss of hearing) and of vestibular toxicity (e.g., disequilibrium, oscillopsia, cognitive dysfunction, visual sensitivity, nausea/vomiting, vertigo, headache, nystagmus).</li> <li>○ AG should be discontinued immediately if any signs/symptoms of toxicity develop; ototoxicity caused by AG <i>may be irreversible</i>.</li> <li>○ Audiometry and vestibular testing recommended for patients receiving AG for 7 days or more, or at any time if ototoxicity suspected. Consult Audiology.</li> <li>○ If prolonged therapy expected (greater than 7 days) baseline audiometry may be considered</li> </ul> </li> <li>• Assess need for continued AG therapy based on microbial susceptibilities, clinical response, side effects, duration of therapy, etc.</li> </ul>						

## ADULT GENTAMICIN SYNERGISTIC DOSING

- Used in combination therapy for endocarditis due to Viridans Group Streptococcus, Streptococcus gallolyticus (formerly Streptococcus bovis) or Enterococcus (refer to most recent IDSA/AHA Endocarditis Clinical Practice Guidelines for details)
- Only gentamicin is routinely used in this setting
- Dose: gentamicin 1 mg/kg q8h or 3 mg/kg q24h, depending on the organism identified
  - dosing based on IBW (see appendix B)
  - no initial loading dose
  - round dose to nearest 20 mg
  - in patients with renal impairment, consider using 1 mg/kg dosing strategy and lengthening the interval based on the table below

Creatinine Clearance	Dosing Interval
greater than or equal to 80 mL/min	q8h
50 to 79 mL/min	q12h
20 to 49 mL/min	q24h
less than 20 mL/min	q48-72h; give first dose then draw serial serum drug levels to determine when to give next dose; close monitoring is recommended

- Draw gentamicin trough level before the 3<sup>rd</sup> dose and at least once a week thereafter if patient is stable
  - Goal of monitoring is to avoid toxicity
  - Target trough level : less than 1 mg/L
  - If trough more than 1 mg/L, increase interval
- Peaks are NOT routinely recommended
  - If done, target peak level: 3 to 5 mg/L

## GENTAMICIN AND TOBRAMYCIN IN PEDIATRIC PATIENTS

### DEFINITIONS

- **Neonate:** 0-4 weeks of age
  - Gestational age: number of weeks from first day of the mother's last menstrual period until the birth of the baby
  - Postnatal age: chronological age since birth
  - Corrected Gestational Age: gestational age plus postnatal age  
Ex.: baby born at 28 weeks, presently 21 days old  
corrected gestational age = 31 weeks (28 weeks + 3 weeks)
- **Infant:** 1 month to 1 year of age
- **Child:** 1-12 years of age

### PEDIATRIC EXTENDED INTERVAL DOSING

- Extended interval AG dosing should NOT be used in pediatric patients who
  - have renal insufficiency at baseline (CrCl less than 50 mL/min)
  - require dialysis
  - have gram-positive infections where AG is used for synergy (use conventional dosing)
  - have endocarditis (use conventional dosing)
  - have rapid clearance of drug (e.g., burns exceeding 20% of body surface area)
  - have altered volume of distribution (e.g., ascites)
  - have meningitis
  - are receiving AG for surgical prophylaxis
- Use conventional dosing if any of the above exclusion criteria for extended interval dosing are met

### Neonates

#### Initial dose in neonates (less than 1 month of age):

Corrected Gestational Age (weeks)	Postnatal Age (days)	mg/kg/dose IV	Interval (hours)
29* or less	0-7	5	48
	8-28	4	36
	29 or more	4	24
30-34	0-7	4.5	36
	8 or more	4	24
35 or more	all	4	24

\*or significant asphyxia, Patent Ductus Arteriosus (PDA) or treatment with indomethacin or ibuprofen

- round dose to nearest 5 mg

#### Levels

#### Target serum concentrations at 22 hours:

- 1.2 mg/L or less

#### Levels recommended in:

- Treatment anticipated to be longer than 48h

#### Serum sampling:

- A random level (or interval level) should be drawn 22 hours after the first dose regardless of the dosing interval
- The timing and duration of drug administration and sample collection must be carefully documented

<b>Interpreting serum levels and adjusting dose:</b>	
<b>Level at 22 hours (mg/L)</b>	<b>Suggested dosing interval</b>
1.2 or less	q24h
1.3 to 2.6	q36h
2.7 to 3.5	q48h
3.6 or more	hold dose and repeat level in 24 hours; base dosing interval on time to achieve a level less than 2 mg/L

<b>Infants and children</b>
<p><b>Initial dose of gentamicin/tobramycin</b></p> <ul style="list-style-type: none"> <li>• Infants and children 1 month – up to 9 years: <ul style="list-style-type: none"> <li>○ 7-9 mg/kg IV q24h</li> </ul> </li> <li>• Children 9 years and older: <ul style="list-style-type: none"> <li>○ 7 mg/kg IV q24h</li> </ul> </li> </ul>
<p><b>Initial dose of tobramycin for Febrile Neutropenia</b></p> <ul style="list-style-type: none"> <li>• Infants and children 1 month – up to 6 years: <ul style="list-style-type: none"> <li>○ 10 mg/kg IV q24h</li> </ul> </li> <li>• Children 6 years and older: <ul style="list-style-type: none"> <li>○ 8 mg/kg IV q24h</li> </ul> </li> </ul>
<p><b>Dose:</b></p> <ul style="list-style-type: none"> <li>• based on actual body weight, unless 20% above IBW, in which case use dosing weight (appendix C)</li> <li>• maximum of 400 mg/24h prior to levels</li> <li>• round dose to nearest 5 mg</li> </ul>
<p><b>Levels</b></p> <ul style="list-style-type: none"> <li>• Monitoring of <u>trough levels</u> alone are generally sufficient with extended interval dosing of AG <ul style="list-style-type: none"> <li>○ verifies that AG is being adequately eliminated</li> </ul> </li> <li>• Peak levels are typically NOT required, as the larger doses used are expected to produce concentrations well above those required for clinical efficacy <ul style="list-style-type: none"> <li>○ may be done in the rare cases where individualized pharmacokinetic monitoring is required</li> </ul> </li> </ul>
<p><b>Target serum concentrations:</b></p> <ul style="list-style-type: none"> <li>• Trough level : less than 1 mg/L</li> <li>• Peak level [<i>only if indicated</i>]: 15-25 mg/L</li> </ul>
<p><b>Levels recommended in:</b></p> <ul style="list-style-type: none"> <li>• Treatment anticipated to be longer than 48h</li> </ul>
<p><b>Serum sampling:</b></p> <ul style="list-style-type: none"> <li>• Trough levels are taken immediately before a dose (within 30 minutes)</li> <li>• Peak levels are taken 90 minutes after the END of drug infusion</li> <li>• The timing and duration of drug administration and sample collection must be carefully documented</li> </ul>
<p><b>Timing of serum levels:</b></p> <ul style="list-style-type: none"> <li>• The notion of steady state does not apply with extended-interval dosing; therefore trough levels may be taken <u>prior to the 2<sup>nd</sup> dose</u></li> </ul>
<p><b>Interpreting serum levels and adjusting dose:</b></p> <ul style="list-style-type: none"> <li>• Trough level of 1 mg/L or more suggests accumulation; extend dosing interval</li> </ul>
<b>Monitoring</b>
<ul style="list-style-type: none"> <li>• Serum creatinine every 2 to 3 days while on therapy; daily if unstable renal function</li> <li>• Coordinate blood work when possible to minimize the number of times the child has blood drawn</li> </ul>



## PEDIATRIC CONVENTIONAL DOSING

### Initial dose

#### Neonates (less than 1 month of age):

Weight (kg)	Postnatal Age (days)	mg/kg/dose IV	Interval (hours)
Less than 1.2	0-28	2.5	18-24
1.2 to 2	less than 7	2.5	12
	7 or more	2.5	8 to 12
more than 2	less than 7	2.5	12
	7 or more	2.5	8

- round dose to nearest 5 mg

#### Infants and children:

- 1 month to less than 5 years of age: 2.5 mg/kg IV q8h
- children 5 years of age and older: 2 to 2.5 mg/kg IV q8h
- for treatment of cystic fibrosis: 2.5 to 3.3 mg/kg IV q6-8h
- for synergy: 1 mg/kg IV q8h
- dose based on actual body weight, unless 20% above IBW, in which case use dosing weight (appendix C)
- round dose to nearest 5 mg

### Levels

- Therapeutic drug monitoring of AG dosed conventionally is typically done by measuring both peak and trough levels at steady state to confirm that therapeutic concentrations have been achieved and that drug accumulation has not taken place

#### Target serum concentrations:

Infection	Desired minimal (trough) plasma concentration (mg/L)	Desired maximum (peak) plasma concentration (mg/L)
Synergy for gram-positive infections	less than 1	3-5
Lower urinary tract infection and mild-moderate infections	less than 2	4-8
Severe infections (Pneumonia, Sepsis, etc.)	less than 2	8-10
Cystic Fibrosis	less than 2	10-15

#### Levels are recommended in:

- Treatment anticipated to be longer than 48h

#### Serum sampling:

- Trough levels are taken immediately before a dose (within 30 minutes)
- Peak levels are taken 30 to 60 minutes after the END of drug infusion.
- The timing and duration of drug administration and sample collection must be carefully documented

#### Timing of serum levels:

- Level should be taken at steady state, typically before and after 3<sup>rd</sup> dose in patients with normal renal function

#### Interpreting serum levels and adjusting dose:

- Ensure serum samples were collected at the appropriate time and at steady state
- Adjust AG dose if serum concentrations are not within the desired range as follows:

high trough	extend dosing interval
high peak	decrease dose
low peak	increase dose

- AG exhibit linear kinetics; decreasing or increasing the dose by a specific percentage will result in an equal decrease/increase in percentage of peak levels.

- Pharmacokinetic calculations may be used determine the dose most likely to produce desired levels, based on the pre and post levels obtained from the patient. Contact Pharmacy.

**Monitoring**

- Serum creatinine every 2 to 3 days while on therapy; daily if unstable renal function
- Coordinate blood work when possible to minimize the number of times the child has blood drawn

## EXTENDED-INTERVAL TOBRAMYCIN IN CYSTIC FIBROSIS (PEDIATRIC and ADULT)

<b>GENERAL COMMENTS</b>													
<ul style="list-style-type: none"> <li>• Patients with Cystic Fibrosis (CF) will have increased AG requirements secondary to increased clearance</li> <li>• Extended interval dosing is as efficacious as conventional dosing of tobramycin in the treatment of CF pulmonary exacerbations in adults and children</li> <li>• Amikacin may also be used to treat CF; data is limited with gentamicin. There are insufficient data in CF patients for guiding extended interval dosing of AG apart from tobramycin. If other AG is needed, use conventional dosing.</li> <li>• For conventional dosing, refer to previous adult and pediatric sections. Target peak levels are 10 to 15 mg/L, while target trough levels are less than 2 mg/L.</li> </ul>													
<b>DOSE AND LEVELS</b>													
<b>Dose (pediatric and adults; from 1 months of age)</b>													
<ul style="list-style-type: none"> <li>• <b>Treatment naïve:</b> <table border="1" style="margin-left: 20px; border-collapse: collapse; width: 80%;"> <thead> <tr style="background-color: #f2f2f2;"> <th style="padding: 2px;">Creatinine Clearance</th> <th style="padding: 2px;">Initial tobramycin dose</th> </tr> </thead> <tbody> <tr> <td style="padding: 2px;">greater than or equal to 50 mL/min</td> <td style="padding: 2px;">10 mg/kg IV q24h</td> </tr> <tr> <td style="padding: 2px;">30-49 mL/min</td> <td style="padding: 2px;">10 mg/kg IV q36h</td> </tr> <tr> <td style="padding: 2px;">20-29 mL/min</td> <td style="padding: 2px;">10 mg/kg IV q48h</td> </tr> <tr> <td style="padding: 2px;">less than 20 mL/min</td> <td style="padding: 2px;">avoid</td> </tr> <tr> <td colspan="2" style="padding: 2px;">maximum tobramycin dose of 600 mg/day prior to levels</td> </tr> </tbody> </table> </li> <li>• <b>Previously treated with tobramycin:</b> dose based on previous therapeutic drug monitoring</li> <li>• Dose based on ideal body weight (see appendix B)</li> </ul>		Creatinine Clearance	Initial tobramycin dose	greater than or equal to 50 mL/min	10 mg/kg IV q24h	30-49 mL/min	10 mg/kg IV q36h	20-29 mL/min	10 mg/kg IV q48h	less than 20 mL/min	avoid	maximum tobramycin dose of 600 mg/day prior to levels	
Creatinine Clearance	Initial tobramycin dose												
greater than or equal to 50 mL/min	10 mg/kg IV q24h												
30-49 mL/min	10 mg/kg IV q36h												
20-29 mL/min	10 mg/kg IV q48h												
less than 20 mL/min	avoid												
maximum tobramycin dose of 600 mg/day prior to levels													
<b>Levels:</b>													
<ul style="list-style-type: none"> <li>• Monitoring of <u>trough levels</u> alone are generally sufficient with extended interval dosing of AG; trough levels verify that AG is being adequately eliminated</li> <li>• Peak levels are NOT routinely measured, but may be ordered to allow for individualized pharmacokinetic monitoring if concern about clinical progress                             <ul style="list-style-type: none"> <li>○ Because CF patients have more rapid clearance of AG, extrapolated peaks can be substantially higher than reported values.</li> </ul> </li> </ul>													
<b>Target serum concentrations:</b>													
<ul style="list-style-type: none"> <li>• Trough levels: less than 1 mg/L</li> <li>• Peak levels [<i>only if indicated</i>]: 20-30 mg/L, peaks NOT to exceed 50 mg/L</li> </ul>													
<b>Serum sampling:</b>													
<ul style="list-style-type: none"> <li>• Trough levels are taken immediately before a dose (within 30 minutes)</li> <li>• Peak levels are taken 90 minutes after the END of drug infusion</li> <li>• The timing and duration of drug administration and sample collection must be carefully documented</li> </ul>													
<b>Timing of serum levels:</b>													
<ul style="list-style-type: none"> <li>• notion of steady state does not apply in extended-interval dosing; trough levels may be taken before <u>2<sup>nd</sup></u> dose</li> </ul>													
<b>Interpreting serum levels and adjusting dose:</b>													
<ul style="list-style-type: none"> <li>• Ensure serum samples were collected at the appropriate time</li> <li>• If tobramycin is being administered via inhalation in addition to IV, absorption of inhaled tobramycin may contribute to tobramycin serum concentrations</li> <li>• If trough is less than 1 mg/L, continue current dose</li> <li>• Adjust AG dose if serum concentrations are not within the desired range as follows:                             <table border="1" style="margin-left: 20px; border-collapse: collapse; width: 60%;"> <tbody> <tr> <td style="padding: 2px;">high trough</td> <td style="padding: 2px;">extend dosing interval</td> </tr> <tr> <td style="padding: 2px;">high peak</td> <td style="padding: 2px;">decrease dose</td> </tr> <tr> <td style="padding: 2px;">low peak</td> <td style="padding: 2px;">increase dose</td> </tr> </tbody> </table> </li> </ul>		high trough	extend dosing interval	high peak	decrease dose	low peak	increase dose						
high trough	extend dosing interval												
high peak	decrease dose												
low peak	increase dose												
<b>Subsequent serum levels:</b>													
<ul style="list-style-type: none"> <li>• Trough levels should be monitored every 7 days or sooner if clinically necessary</li> </ul>													

## GENTAMICIN AND TOBRAMYCIN IN INTERMITTENT HEMODIALYSIS

GENERAL COMMENTS									
<ul style="list-style-type: none"> <li>• <b>Extended interval dosing not indicated for patients on hemodialysis; use conventional dosing</b></li> <li>• In patients on intermittent hemodialysis, AG is given on dialysis days, typically 3 times a week</li> <li>• AG doses are administered <i>after</i> dialysis</li> <li>• Give the first dose of AG the day it is ordered and subsequent doses on dialysis days</li> <li>• AG are removed by hemodialysis (to a greater extent than vancomycin)                             <ul style="list-style-type: none"> <li>○ High-flux dialyzers reduce AG serum concentrations by approximately 50%</li> <li>Example: pre-dialysis gentamicin serum concentration is 5 mg/L; following a 4h hemodialysis session, post-dialysis gentamicin serum concentration is approximately 2.5 mg/L</li> </ul> </li> </ul>									
DOSE									
<b>Loading dose:</b> <ul style="list-style-type: none"> <li>• <b>1.5-2 mg/kg IV</b> <ul style="list-style-type: none"> <li>○ based on dry weight/dosing weight (see appendix B)</li> <li>○ round dose to nearest 20 mg</li> </ul> </li> </ul>									
<b>Initial maintenance dose:</b> <ul style="list-style-type: none"> <li>• <b>1 mg/kg IV</b> <ul style="list-style-type: none"> <li>○ based on dry weight/dosing weight (see appendix B)</li> <li>○ round dose to nearest 20 mg</li> <li>○ administered at the end of dialysis session</li> </ul> </li> </ul>									
<b>Dosing weight:</b> <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 5px;"> <thead> <tr style="background-color: #d9ead3;"> <th style="width: 50%; padding: 5px;">Patient's dry weight....</th> <th style="width: 50%; padding: 5px;">Use as dosing weight</th> </tr> </thead> <tbody> <tr> <td style="padding: 5px;">is less than ideal body weight</td> <td style="padding: 5px;">dry weight</td> </tr> <tr> <td style="padding: 5px;">is less than 20% above ideal body weight</td> <td style="padding: 5px;">dry weight</td> </tr> <tr> <td style="padding: 5px;">is more than 20% above ideal body weight</td> <td style="padding: 5px;">adjusted weight Adjusted weight = <math>0.4 \times (\text{actual body weight} - \text{IBW}) + \text{IBW}</math></td> </tr> </tbody> </table>		Patient's dry weight....	Use as dosing weight	is less than ideal body weight	dry weight	is less than 20% above ideal body weight	dry weight	is more than 20% above ideal body weight	adjusted weight Adjusted weight = $0.4 \times (\text{actual body weight} - \text{IBW}) + \text{IBW}$
Patient's dry weight....	Use as dosing weight								
is less than ideal body weight	dry weight								
is less than 20% above ideal body weight	dry weight								
is more than 20% above ideal body weight	adjusted weight Adjusted weight = $0.4 \times (\text{actual body weight} - \text{IBW}) + \text{IBW}$								
LEVELS									
<b>Trough levels:</b> <ul style="list-style-type: none"> <li>• Draw trough level within 30 minutes before the start of the hemodialysis session</li> <li>• Target pre-hemodialysis level: 1.5 to 3 mg/L</li> </ul>									
<b>Peak levels:</b> <ul style="list-style-type: none"> <li>• NOT commonly done</li> <li>• Measure peak level 60 minutes after END of drug infusion, if required</li> <li>• Target peak: 6-10 mg/L, depending on the indication (refer to section "Adults-Conventional Dosing of Gentamicin and Tobramycin": target serum concentrations)</li> </ul>									

## GENTAMICIN AND TOBRAMYCIN IN PREGNANCY

### CONSIDERATIONS ON THE USE OF AMINOGLYCOSIDES IN PREGNANCY

- Glomerular filtration rate can be increased by up to 50% in pregnant and post-partum patients, resulting in a shorter half-life compared to nonpregnant women
- Volume of distribution is increased in pregnancy, while the post-partum period is associated with increased mobilization of fluid followed by diuresis as the body eliminates the increased fluid volume of pregnancy
- Extended interval dosing
  - Data limited on extended interval dosing of AG in pregnancy; use with caution
  - More data on extended-interval dosing of AG is available in post-partum
  - For pregnant and post-partum patients, the actual body weight should be used. For obese pregnant and post-partum patients, use maximum 500 mg dose prior to levels.
  - Initial dose and interval
    - 5 mg/kg IV q24h (if CrCl greater than or equal to 60 mL/min)
    - dose based on actual body weight
    - maximum 500 mg/24h prior to levels
    - dosing interval adjusted based on renal function
  - Monitoring
    - Trough levels, taken within 30 minutes before 2<sup>nd</sup> dose
      - target less than 1 mg/L
- Conventional dosing
  - Initial dose and interval
    - 2 mg/kg IV x 1 loading dose, then
    - 1.5-2 mg/kg IV q8h (if CrCl greater than or equal to 80 mL/min)
    - dose based on actual body weight
    - dosing interval adjusted based on renal function
  - Monitoring
    - target levels – refer to “Adults-Conventional Dosing of Gentamicin/Tobramycin” section

## AMIKACIN

### GENERAL COMMENTS, DOSING AND MONITORING

- Amikacin is a less commonly used AG with similar spectrum of activity and toxicity profile as gentamicin and tobramycin
- Dosing and serum concentrations are different compared to gentamicin and tobramycin
- Determination of serum concentration is sent to a laboratory outside the province; expect delays in obtaining results

- Extended interval dosing

- Initial dose
  - 15 mg/kg IV; dose based on IBW or dosing weight (see appendix B); rounded to nearest 25 mg

- Initial interval

Creatinine Clearance	Dosing Interval
greater than or equal to 60 mL/min	q24h
40 to 59 mL/min	q36h
20 to 39 mL/min	q48h; consider conventional dosing
less than 20 mL/min	Give first dose then draw serial serum drug levels to determine when to give next dose. Consider conventional dosing.

- Conventional dosing

- Initial dose
  - 7.5 mg/kg IV x 1 loading dose may be considered, then
  - 5 to 7.5 mg/kg IV; dose based on IBW or dosing weight; rounded to nearest 25 mg

- Initial interval

Creatinine Clearance	Dosing Interval
greater than or equal to 80 mL/min	q8h
50 to 79 mL/min	q12h
20 to 49 mL/min	q24h
less than 20 mL/min	q48-72h; give first dose then draw serial serum drug levels to determine when to give next dose; close monitoring is recommended

- For extended interval dosing of amikacin,

- Target trough level: less than 4 mg/L
- Target peak level [*only if indicated*]: 35-50 mg/L
- Hartford Hospital nomogram may be used to determine appropriate dosing interval based on a random level taken 8-12h after the first dose, provided a 15 mg/kg dose was used
  - Divide serum amikacin level obtained in half, then plot on graph (see Appendix D)

- For conventional dosing of amikacin, target serum concentrations:

	Desired minimal (trough) concentration (mg/L)	Desired maximum (peak) concentration (mg/L)
Moderate infections	less than 4	20-25
Severe infections	less than 2	25-30

## REFERENCES

### General references and nomograms

Drew RH. Dosing and administration of parenteral aminoglycosides (revised June 4, 2015). UpToDate. Accessed July 2016.

Avent ML et al. Current use of aminoglycosides: indications, pharmacokinetics and monitoring for toxicity. *Intern Med J* 2011;41:441-449

Stankowicz MS et al. Once-daily aminoglycoside dosing: an update on current literature. *Am J Health-Syst Pharm* 2015;72:1357-64

Nicolau DP et al. Experience with a once-daily aminoglycoside program administered to 2184 adult patients. *Antimicrob Agents Chemother* 1995;39:650-5 [Hartford Hospital nomogram]

Bailey TC et al. A meta-analysis of extended-interval dosing versus multiple daily dosing of aminoglycosides. *CID* 1997;24:786-95 [Barnes-Jewish Hospital Guidelines]

Anaizi N. Once-daily dosing of aminoglycosides: a consensus document. *Int J Clin Pharmacol Ther* 1997;35:223-6

Sarubbi FA et al. Amikacin serum concentrations: prediction of level and dosing guidelines. *Ann Int Med* 1978;89:612-8

Aminoglycosides high dose extended interval dosing/monitoring guidelines. In: *Bugs & Drugs, an antimicrobial/infectious diseases reference*. p. 59-63, 2012

Aminoglycosides conventional dosing/monitoring guidelines. In: *Bugs & Drugs, an antimicrobial/infectious diseases reference*. p.64-67, 2012

Aminoglycoside antibiotics – dosing and monitoring guidelines. In: *Capital Health Antimicrobial Handbook*. p. 22-27, 2012

### Pediatric reference

IWK Health Centre Aminoglycosides dosing & monitoring guidelines. April 2014.

### Cystic fibrosis references

Flume PA et al. Cystic Fibrosis Pulmonary Guidelines. Treatment of Pulmonary Exacerbations. *Am J Resp Crit Care Med* 2009;180:802-808

Prescott WA et al. Extended-interval once-daily dosing of aminoglycosides in adult and pediatric patients with cystic fibrosis. *Pharmacotherapy* 2010;30(1):95-108

Smyth AR, Bhatt J. Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2014, Issue 2, Art. No.:CD002009.

Smyth A et al. Once versus three-times daily regimens of tobramycin treatment for pulmonary exacerbations of cystic fibrosis – the TOPIC study: a randomized controlled trial. *Lancet* 2005;365:573-78

Stenbit AE et al. Timing of inhaled tobramycin affects assessment of intravenous tobramycin pharmacokinetic monitoring. *Journal of Cystic Fibrosis* 2013;12:403-406

### **Dialysis references**

Dager WE et al. Aminoglycosides in intermittent hemodialysis: pharmacokinetics with individual dosing. *Ann Pharmacother* 2006;40:9-14

Teigen MMG et al. Dosing of gentamicin in patients with end-stage renal disease receiving hemodialysis. *J Clin Pharmacol* 2006;46:1259-1267

Heintz BH et al. Clinical experience with aminoglycosides in dialysis-dependent patients: risk factors for mortality and reassessment of current dosing practices. *Ann Pharmacother* 2011;45:1338-45

Agarwal R and Weir MR. Dry Weight: A Concept Revisited in an Effort to Avoid Medication-Directed Approaches for Blood Pressure Control in Hemodialysis Patients. *Clin J Am Soc Nephrol*. 2010 Jul;5(7):1255-1260

### **Peripartum references**

Ward K et al. Once-daily dosing of gentamicin in obstetrics and gynecology. *Clin Obstet Gynecol* 2008;51(3):498-506



## APPENDIX A: Calculation of Creatinine Clearance (CrCl)

Women	Men
$\text{CrCl} = \frac{(140 - \text{age}) \times \text{weight (in kg)}^\dagger}{\text{SCr (in mcmol/L)}}$	$\text{CrCl} = \frac{(140 - \text{age}) \times \text{weight (in kg)}^\dagger \times 1.2}{\text{SCr (in mcmol/L)}}$
IBW = 45.5 Kg + (0.92 x cm above 150 cm) <i>or</i> 45.5 kg + (2.3 x inches above 60 inches)	IBW = 50 kg + (0.92 x cm above 150 cm) <i>or</i> 50 kg + (2.3 x inches above 60 inches)
†use actual body weight unless it is 20% above ideal body weight (IBW), in such case use adjusted weight: Adjusted weight = 0.4 x (actual body weight – IBW) + IBW	

## APPENDIX B: Adult Ideal Body Weight, Dosing Weight and Dry Weight

Patient's weight....	Use
is less than ideal body weight	actual body weight
is less than 20% above ideal body weight	ideal body weight
is more than 20% above ideal body weight	dosing weight = 0.4 x (actual body weight – IBW) + IBW

### Ideal body weight (IBW)

Women	Men
IBW = 45.5 kg + (0.92 x cm above 150 cm) <i>or</i> 45.5 kg + (2.3 x inches above 60 inches)	IBW = 50 kg + (0.92 x cm above 150 cm) <i>or</i> 50 kg + (2.3 x inches above 60 inches)

**Dry body weight in hemodialysis:** defined as the lowest tolerated post-dialysis weight at which there are minimal signs or symptoms of hypovolemia or hypervolemia

## APPENDIX C: Pediatric Ideal Body Weight and Dosing Weight

Child's weight....	Use
is less than 20% above ideal body weight	actual body weight
is more than 20% above ideal body weight	dosing weight = 0.4 x (actual body weight – IBW) + IBW

### Ideal body weight (1 to 18 years of age):

- Children less than 5 feet tall:  $\frac{\text{height (cm)}^2 \times 1.65}{1000}$
- Boys 5 feet and taller: 39 kg + (2.3 x inches above 60 inches)
- Girls 5 feet and taller: 42.2 kg + (2.3 x inches above 60 inches)

## APPENDIX D: Hartford Hospital nomogram

- This nomogram is only to be used for a 7 mg/kg dose of gentamicin or tobramycin
- This nomogram assumes a  $V_d$  of 0.3 L/kg
- If interval falls in areas marked as q24h, q36h, q48h, dosing interval should be every 24, 36, or 48 hours respectively.
- If the interval level is on one of the sloping lines, choose the longer interval.
- If the interval level is above the q48h dosing interval area, stop extended interval dosing and switch to conventional dosing.
- If the interval level is below the nomogram (i.e., less than 2 mg/L), AG dosing/therapy should be reassessed if patient not improved.
- For **amikacin** the Hartford Hospital nomogram may be used to determine appropriate amikacin dosing interval based on a random level taken 8-12h after the first dose, provided a 15 mg/kg dose was used
  - Divide serum amikacin level obtained in half, then plot on graph

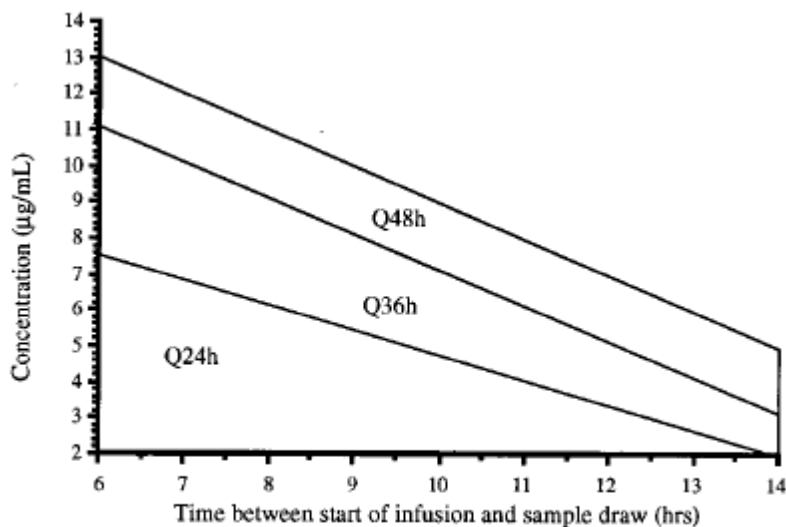


FIG. 1. ODA nomogram for gentamicin and tobramycin at 7 mg/kg.