Aminoglycosides

(Amikacin/Gentamicin/Tobramycin)

A. Kinetic Parameters[1-4]

Bioavailability (F):	NA
Protein Binding:	minimal
Volume of Distribution (V_d):	**Adults** 0.25-0.35 L/Kg **Preterm Neonates** 0.6-0.7 L/kg **Neonates** 0.5-0.6 L/kg **Infants** 0.4-0.5 L/kg **Children** 0.3-0.4 L/kg **Adolescents** 0.2-0.3 L/kg
Half-Life (t½):	dependant on renal function. **Adults**: Normal renal function 2-4 h Anuric patients ~50-70 h **Neonates** 7-12 h **Infants** 3-5 h **Children and adolescents** 1-3 h
Elimination:	renal (70-100%)
Time to Steady State:	1-2 days (longer with renal impairment)

B. Dosing

ADULT Empiric Dosing Guidelines

There is no known method to eliminate the risk of aminoglycoside nephrotoxicity or ototoxicity. Proper dosing and shorter duration of therapy attempts to reduce the risk.[1]

Ideal body weight (IBW) calculation
IBW (females) = 45.5 kg + (2.3 x inches > 5 feet)**
IBW (males) = 50 kg + (2.3 x inches > 5 feet)**
**or (0.92 x cm > 150 cm)

In underweight individuals if actual body weight (ABW) < IBW use ABW.

If obese (body mass index > 30 kg/m^2 or ABW > 20% over IBW) use dosing weight (DW) [DW = (ABW-IBW) x 0.4 + IBW]

Aminoglycosides are not recommended in renally impaired patients. Only use if possible benefits outweigh the risks of toxicity. Some clinicians suggest avoiding the use of aminoglycosides in patients with a Cr_{Cl} < 40 mL/min.[2]

a. Extended interval dosing (Once Daily Dosing)[5,6]

ROUTE	DOSE	Calculated Cr_{Cl}	Frequency
IV	gentamicin/tobramycin 5-7 mg/kg amikacin 15 mg/kg	≥ 60 mL/min > 40-60 mL/min 20-40 mL/min < 20 mL/min	Q24h Q36h Q48h Patient specific parameters may be estimated using pharmacokinetic calculations (see appendix)

- Hartford nomogram is based on 7 mg/kg dosing of gentamicin and tobramycin.[3]

b. Conventional dosing[3,7,8]

ROUTE	DOSE	Calculated Cr_{Cl}	Frequency
IV/IM	gentamicin or tobramycin 1.5-2 mg/kg	≥ 80 mL/min > 50-80 mL/min 20-50 mL/min < 20 mL/min	Q8h Q12h Q24h Patient specific parameters may be estimated using pharmacokinetic calculations (see appendix)
IV/IM	amikacin 5-7.5 mg/kg	> 60 mL/min 20-60 mL/min < 20 mL/min	Q12h** Q24h Patient specific parameters may be estimated using pharmacokinetic calculations (see appendix)

** Rarely amikacin may be ordered Q8h in patients with **Cr_{Cl}** > 60 mL/min

c. Gram positive synergy conventional dosing[3,7,8]

ROUTE	DOSE	Calculated Cr_{Cl}	Frequency
IV/IM	1.0-1.5 mg/kg IBW**	≥ 80 mL/min > 50-80 mL/min 20-50 mL/min < 20 mL/min	Q8h Q12h Q24h Patient specific parameters may be estimated using pharmacokinetic calculations (see appendix)

PEDIATRIC CONVENTIONAL DOSING

Empiric dosing for neonates[14] (adjust interval based on monitoring of serum levels):

Neonates less than 7 days of age:

Any Gestation: If on indomethacin, with RDS*, or asphyxia or renal impairment	5 mg/kg	q48h
< 30 weeks: No renal impairment	5 mg/kg	q48h
30-35 weeks: No renal Impairment	4 - 5 mg/kg	q36h
≥ 36 weeks: No renal impairment	4 - 5 mg/kg	q24h

Neonates over 7 days of age:

Dosing strategies differ between Calgary and Edmonton; both are listed here.

1. **Edmonton method:**
   - If < 30 weeks PCA: Dose as for neonates less than 7 days of age
   - If ≥ 30 weeks PCA: Dose at 4 mg/kg/dose q24h
2. **Calgary method:**

Corrected Gestational Age and Clinical Considerations		
All gestations, on indomethacin or renal impairment	5 mg/kg	q36h
< 36 weeks: No renal impairment	5 mg/kg	q24h
≥ 36 weeks: No renal impairment	6 mg/kg	q24h

*** RDS is respiratory distress syndrome**

Infants and children:

Dose: 2.5 mg/kg/dose every 8 hours; doses are based on ideal body weight.

Cystic Fibrosis patients: usually require higher doses at 2.5 to 3.3 mg/kg/dose every 6 to 8 hours

Synergistic dosing of aminoglycosides with beta-lactams:

- Use low doses (1 mg/kg/dose q8h)
- Treatment of *Enterococcus spp.* may require synergistic therapy with full dose (2.5 mg/kg/dose q8h)
- Levels for synergistic dosing are generally not required; if done only trough levels are recommended to rule out toxicity. Target trough is < 2 mg/L

PEDIATRIC EXTENDED-INTERVAL DOSING

*****Local practice of extended interval dosing in pediatrics may vary: REFER to LOCAL GUIDELINES*****

There is no extended interval dosing (EID) in neonates. Due to the immaturity of their kidneys, doses are administered every 24-48 hours but this is not due to EID principles. Because of this, the peak levels expected in neonates are 7-12 mg/L, and not the higher levels predicted for other patients.

Please note exceptions to use of extended interval dosing in infants and children:

- Renal dysfunction at baseline (serum creatinine higher than normal limits for age) or ≥ 30% increase in serum creatinine while on aminoglycoside therapy (consider alternate antibiotic)
- Synergistic dosing of aminoglycosides with beta-lactams, use conventional dosing

Empiric dosing in infants & children[16]:

Dose is based on actual body weight unless exceeds ideal body weight by > 25%, then use:

weight = IBW + 0.4(ABW - IBW)

1 month to < 9 years of age:	7 - 9 mg/kg/dose q24h
9 years of age and older:	7 mg/kg/dose q24h
Cystic Fibrosis (all ages)	10 mg/kg/dose q24h

C. MONITORING

*****Accurate documentation of previous dose administration time and serum level collection time are equally important to evaluate serum drug concentration*****

Levels may be drawn in specific clinical scenarios:

1. Receiving > 3-5 days of aminoglycoside therapy
2. Renal dysfunction and/or significant changes in renal function
3. Altered volume of distribution (ie. ascites)
4. Age > 65 years
5. Concurrent nephrotoxic drugs (e.g. amphotericin B, cyclosporine)
6. Synergy dosing for gram positive infections - recommend trough serum concentration monitoring to rule out toxicity in the following patients
   - poor renal function
   - concurrent nephrotoxic drugs
   - receiving prolonged therapy (> 5 days)

Frequency of Serum Levels

- once weekly (more frequent monitoring may be necessary in patients with unstable renal function or concurrent use of nephrotoxic drugs)
  - If creatinine changes (increase of > 40 mcmol/L or 50% of baseline), suggest drawing a trough aminoglycoside level to assess need for dosing change

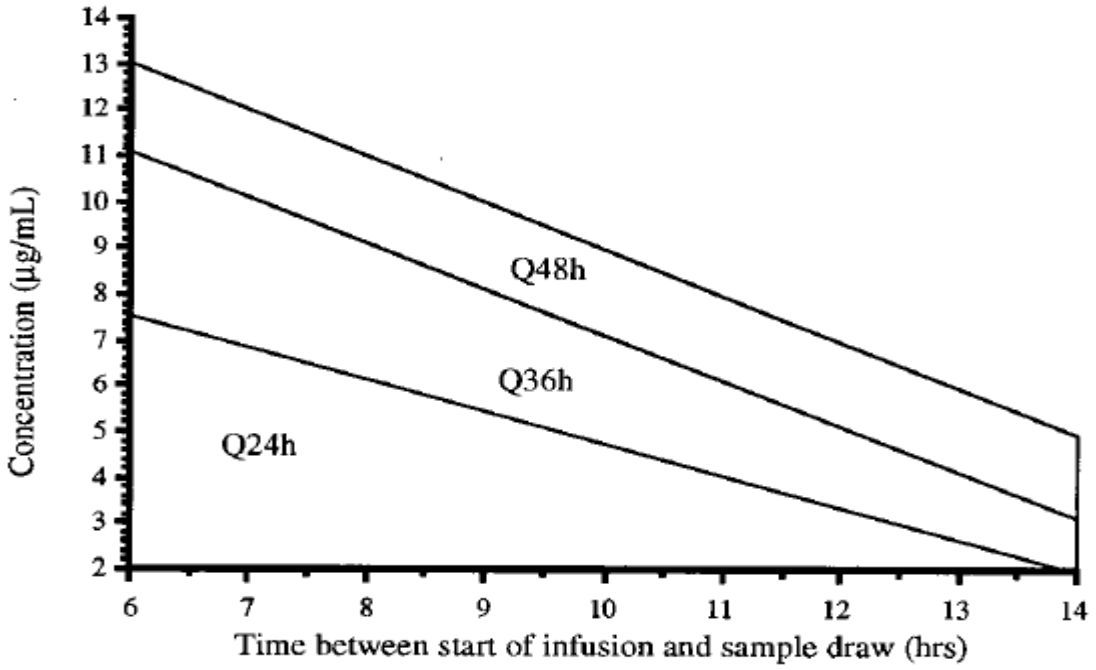
*****Baseline serum creatinine and then 2 to 3 times weekly during therapy*****

Serum Concentration Sampling Times for Conventional and Extended-Interval Dosing of Aminoglycosides[1,2,7] in Adult and Pediatric Populations

	Peak Sample Time	Trough Sample Time	Comments
Conventional Dosing	at least 1 hour post IM injection 30-60 minutes post IV infusion	≤ 60 minutes before dose (IM and IVPB)	First level should be drawn at steady state (usually occurs after 3-4 doses in patient with normal renal function)
For Extended Interval Dosing	Not indicated. If measured can expect peaks of ≈ 15 to 25 mg/L	≤ 60 min before dose	The **Hartford Nomogram** suggests a random level 6-14 hours after the dose. Level typically ordered 8 hours post infusion.

*****every attempt should be made to draw serum levels during normal working hours to avoid disturbing the patient between 0000 h to 0800 h *****

HARTFORD NOMOGRAM
FOR EXTENDED INTERVAL AMINOGLYCOSIDE MONITORING IN ADULT PATIENTS*



*** There is limited data to support the use of this nomogram in pediatrics.[18,19]**

1. Hartford nomogram applies only with doses of 7 mg/kg of gentamicin and tobramycin[3]
   Example: 65 year old male weighing 72 kg receiving gentamicin 300 mg IVPB daily for an *Escherichia coli* urinary tract infection. Cr_{Cl} 65 mL/min. An 8 hour post gentamicin level is 4.1 mg/L after the first dose. Must extrapolate level to a 7 mg/kg dose

   $\frac{4.2 \text{ mg/kg}}{4.1 \text{ mg/L}} = \frac{7 \text{ mg/kg}}{X}$

   X= 6.8 mg/L therefore the patient should receive gentamicin 300 mg IVPB Q36h
2. The nomogram assumes volume of distribution 0.3 L/kg

3. For amikacin divide measured serum level by 2 and plot on the nomogram
4. If the interval falls in the areas marked Q24h, Q36h, Q48h the dosing interval should be every 24, 36, 48 hours.
5. If the interval falls on one of the sloping lines, choose the longer interval.
6. If above the Q48h dosing interval, DISCONTINUE extended interval dosing and switch to conventional dosing of aminoglycosides.
7. If below 2 mg/L aminoglycoside dosing/interval should be reassessed if the patient is not improving.

Serum Level Monitoring

Serum level monitoring may be of value in patients on prolonged therapy or for those who are at increased risk of toxicity. Correlation of efficacy to peak or trough levels has not been well established in studies even though commonly used.[9]

Therapeutic Target Concentrations for Conventional Dosing[7] in Adult and Pediatric Populations

Medical Condition	Desired Peak (mg/L)	Desired Trough (mg/L)
Gentamicin/ Tobramycin		
synergy, lower UTI	3-4	<1
endometriosis, pyelonephritis, peritonitis, soft tissue	6-7	<2
neutropenia, burns pneumonia, sepsis, pseudomonas (nonurinary tract infections)	8-11	<2
cystic fibrosis	12-15	<2
Amikacin		
Moderate Infections	20-25	<4
Severe Infections	25-30	<8

Dose adjustment based on Serum Concentrations

1. **Extended interval** aminoglycoside dosing regimens are designed to have no measurable drug at the end of the dosing interval. Aminoglycosides have a long post-antibiotic effect allowing ongoing bactericidal activity even after the drug has been cleared from the serum. A trough level may be taken at the end of the dosing interval. If the aminoglycoside level is greater than 0.5-1 mg/L this suggests accumulation of the drug and indicates the need to lengthen the dosing interval or reconsider the use of the aminoglycoside. [2]
2. **Conventional dosing**– There are multiple methods used to the adjust dose based on the serum level of aminoglycosides. Since aminoglycosides display concentration dependant killing and time dependant nephrotoxicity, one should usually lengthen the dosing **interval** if the **trough** level is too high and adjust the **dose** if the **peak** level is outside of the desired range.

Aminoglycoside pharmacokinetic calculations can be done using

Lexi-CALC Lexicomp's Medical Calculation Database can found on the pharmacy home page on Insite

link → http://online.lexi.com/crlsql/servlet/crlonline?siteid=1

MONITORING OF PEDIATRIC PATIENTS:

Generally monitoring of pediatric patients is similar to adult patients (see tables in monitoring section above for details). Monitoring of these patients differs between zones in Alberta. The Calgary monitoring information is noted here as it differs from the information in the monitoring section above.

Calgary Protocol for Monitoring Levels in Neonates[15]

- Draw a 22 hour level on all neonates regardless of ordered dosing interval:
- On obtaining the 22 hour level, refer to the CHART below and in consultation with the medical resident/NNP adjust dosing interval if appropriate

Suggested Dosing Interval

Level at 22 hours *(mg/L)*	Suggested Dosing Interval *(hours)*
≤1.2	24
1.3 - 2.6	36
2.7 - 3.5	48
≥ 3.6	Hold next dose, repeat level in 24 hours. Base dosing interval on time to achieve a level < 2 mg/L

Calgary Protocol for Monitoring Levels in Infants & Children:

- Draw TWO levels, one at 2 to 3 hours and one at 6 to 8 hours after the dose[16]
- Refer to "Once Daily Aminoglycoside Calculator" on Pharmacy Website to calculate target parameters:
  1. C_{max} target: 20-25 mg/L, 25-35 mg/L for Cystic Fibrosis patients[12].
  2. AUC target: 70-110 mg/h/L[17]
  3. Drug free interval target ≥ 4 hours to reduce toxicity, if ≥ 18-20 hours and concern re: clinical deterioration, consider q18h interval or switch back to Conventional dosing[16]

D. TOXICITY

Duration Related

Aminoglycosides are recognized for nephrotoxicity, which has been associated with increased duration of therapy, older age and/or baseline renal impairment, concurrent exposure to other nephrotoxins (including radiographic contrast), shock etc. Most commonly aminoglycosides cause acute tubular necrosis (ATN) leading to increased serum creatinine, increased hyaline and granular casts in urine, hypomagnesemia, hypokalemia, hypocalcemia and hypophosphatemia, usually without urine output reduction. In most cases, recovery of renal function is complete after drug discontinuation.[10,11]

Cochlear or vestibular toxicity may be manifest after single doses or short exposures to aminoglycosides in vulnerable patients however it more commonly occurs after 9 days of therapy. Symptoms may manifest as decreased hearing acuity, tinnitus, a sense of fullness in the ears or other (new) hearing problems. Vestibular toxicity may present as vertigo, ataxia, and falls.[12]

Non Dose Related

Aminoglycosides have activity on neuromuscular end plates so can have paralytic or muscular weakening activity in patients with myasthenia gravis and/or receiving skeletal muscle relaxants.[13]
Sensitivity and anaphylaxis have been reported secondary to aminoglycoside use, but these events are rare.[13]

Appendix

EXTENDED INTERVAL AMINOGLYCOSIDE DOSING: BEDSIDE APPROACH

GENTAMICIN, TOBRAMYCIN , AMIKACIN

PATIENT INFORMATION:
age, wt, ht, infection, other medical conditions

Contraindications:
endocarditis, hemodialysis, hemoperfusion, peritoneal dialysis, synergy, surgical prophylaxis

Precautions:
liver disease/ascites, auditory/vestibular disease, pregnancy/postpartum, neonates

IS THIS A NEW ORDER ?

YES

IS SERUM CREATININE AVAILABLE?

NO

nomogram:
Get creatinine and level with 1st dose

Empiric dosing until creatinine and level available:

Dose = 7 mg/kg (based on IBW*)
Interval q24h

YES

Consider using Scr of 88.4 µmol/L in frail elderly

Calculate CrCl (ADULTS):

$$\text{CrCl (females)} = \frac{(140-\text{age}) \times \text{wt (IBW*)}}{\text{Scr (µmol/L)}}$$

males = CrCl(female) x 1.2

Calculate dose and interval:

1. Dose = 7 mg/kg (based on IBW* & rounded to nearest 20mg)

2. Interval - Use nomogram as follows:

Creatinine Clearance	Dosing interval
≥ 60	q24h
40-59	q36h
20-39	q48h**
<20	use conventional dosing

Level if meets criteria: > 5 days therapy, > 65 y.o., renal dysfunction, large Vd:

- 8-hour interval level with the 1st dose

Footnotes:

* If ABW < IBW, use ABW.
If obese (ABW>30% above IBW), use DW.

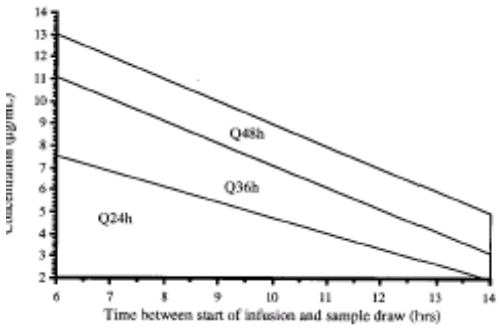
** Consider conventional dosing for this level of renal function.

NO

ARE LEVELS AVAILABLE AND DRAWN APPROPRIATELY?

YES

If the dose is 7 mg/kg: Plot level on Hartford



If the dose is 5-6 mg/kg:

1. Use ratio to find level which would represent the concentration if 7 mg/kg had been given:

$$\frac{\text{x}}{\text{7 mg/kg dose}} = \frac{\text{level with 5 mg/kg}}{\text{5 mg/kg dose}}$$

2. Plot expected level (x) with 7 mg/kg on Hartford nomogram

Choose the interval in the area the level falls.

If the level is on the line: choose the longer interval

If the level is < 2 mg/L: leave at same interval unless patient is seriously ill or not improving (use clinical judgement; pt is usually on another antibiotic)

If the level is above the q48h dosing interval area:
Switch to conventional dosing

1. Discontinue extended interval dosing (hold next dose!)
2. Recommend level in 24 hours from previous level
3. Calculate patient specific parameters (see back)
4. Calculate conventional dosage based on patient specific parameters (see back)

KEY

ke - elimination rate constant
c1 - first level
c2 - second level
Cmax - peak level
Cmin - trough level
t - time difference between two levels (time first level - time second level)
t1- time difference from end of infusion to c1
τ - interval

Calculate patient specific parameters:

1. Calculate ke:

$$ke = \frac{\ln (c1/c2)}{t}$$

2. Calculate half-life:

$$t1/2 = \frac{0.693}{ke}$$

3. Calculate true peak:

$$Cmax = peak \div e^{(-ke)(t1)}$$

4. Calculate volume of distribution:

$$Vd\ (L) = \frac{Dose}{Cmax}$$

(*Note: only if c1 is first dose*)

Calculate conventional dose and interval:

1. Identify desired Cmax and Cmin
   Use peak = 4 - 10 mg/L
   trough = 1 mg/L

2. Calculate dose:
   Dose = Vd x (Cmax -Cmin)

3. Calculate interval:
   Interval = 2.5 x t1/2 (round to appropriate interval)

4. Check Cmax

$$Cmax = \frac{Dose}{(Vd \times (1 - e^{(-ke)(\tau)})}$$

5. Check Cmin

$$Cmin = Cmax \times e^{(-ke)(\tau)}$$

AMINOGLYCOSIDE MONITORING CONVENTIONAL DOSING: BEDSIDE APPROACH

GENTAMICIN, TOBRAMYCIN

PATIENT INFORMATION:
age, wt, ht, infection, other medical conditions

Ideal body weight (IBW):
male = 50 + (2.3 x inch over 5ft)*
female = 45 + (2.3 x inch over 5ft)*
* or (0.92 x cm > 150cm)

Dosing weight (DW) in obesity:
DW = IBW + 0.4(ABW-IBW)

IS THIS A NEW ORDER ?

YES

IS SERUM CREATININE AVAILABLE?

NO

Get creatinine

Empiric dosing until creatinine available:
Maintenance dose = 1.5-2 mg/kg (IBW*)
Interval q8h unless:

1. patient ≥ 65 years - Use q12h interval

2. patient has medical condition that may indicate renal impairment - Get creatinine, use longer intervals (≥ q24h)

Footnote:

* If ABW < IBW, use ABW.
If obese (ABW>30% above IBW), use DW.

YES

Consider using Scr of 88.4 µmol/L in frail elderly

Calculate CrCl:
CrCl (females) = (140-age) x wt (IBW*) / Scr (µmol/L)

males = CrCl(female) x 1.2

Calculate dose and interval:
1. Loading dose = 2 mg/kg

2. Maintenance dose = 1.5-2 mg/kg (based on IBW* & rounded to nearest 10mg)

3. Interval - Use nomogram as follows:

Creatinine Clearance	Dosing interval
≥ 80	q8h
50-79	q12h
20-49	q24h
<20	use levels to assess or population parameters **

Levels:
peak and trough with third dose for initial assessment (can individualize to patient based on renal function, age, etc)

NO

ARE LEVELS AVAILABLE AND DRAWN APPROPRIATELY?

YES

Calculate patient specific parameters:

1. Calculate ke:
$ke = \frac{\ln(peak/trough)}{t}$

2. Calculate half-life:
$t1/2 = \frac{0.693}{ke}$

3. Calculate true peak:
$Cmax = peak \div e^{(-ke)(t1)}$

4. Calculate true trough:
$Cmin = trough \times e^{(-ke)(t2)}$

5. Calculate volume of distribution:
$Vd\ (L) = \frac{Dose}{Cmax - Cmin}$

Calculate dose and interval:
1. Identify desired Cmax and Cmin
Use peak = 4 - 10 mg/L
trough = 1 mg/L

2. Calculate dose:
Dose = Vd x (Cmax -Cmin)

3. Calculate interval:
Interval = 2.5 x t1/2 (round to appropriate interval)

4. Check Cmax
$Cmax = \frac{Dose}{(Vd \times (1 - e^{(-ke)(\tau)}))}$

5. Check Cmin
$Cmin = Cmax \times e^{(-ke)(\tau)}$

KEY
ABW - actual body weight
ke - elimination rate constant
Cmax - actual peak level
Cmin - actual trough level
t - time difference from measured peak and trough (τ - ($time_{peak}$ - $time_{trough}$)
t1- time difference from end of infusion to measured peak level.
t2 - time difference from measured trough level to start of infusion.
τ - interval

**** Population parameters:**
ke = 0.003(CrCl) + 0.01
t1/2 = 0.693/ke
Vd = 0.25-0.35 L/kg (ABW in nonobese/ DW in obese)

Regional Pharmacy Services, CH
Conventional AG Dosing
Last updated May08 S Fryters

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