Adult Aminoglycoside Policy and Dosing Guidelines

FMOLHS (Revised August 2023)

Purpose:

Pharmacists will assess, monitor, and treat all patients receiving systemic aminoglycoside agents. The purpose will be to ensure that patients receiving these drugs have serum concentrations maintained within the recognized therapeutic range to ensure efficacy and to help avoid toxicity.

Procedure:

The procedure serves to assist personnel in accomplishing the goals of the program. While following this procedure, personnel are expected to exercise clinical judgment within their scope of practice and job responsibilities.

Abbreviations: UTI = urinary tract infection, SSTI = skin soft tissue infection, PNA = pneumonia, FN = febrile neutropenia, TIW = three times weekly, SCr = serum creatinine, CrCl = creatinine clearance, HD = hemodialysis

***Pseudomonas aeruginosa* disclaimer:** Based off 2023 CLSI breakpoint updates, gentamicin should no longer be used for *P. aeruginosa* and amikacin can only be used if treating a *P. aeruginosa* UTI

Dosing Weight

Underweight	Normal Weight	Obese (TBW ≥ 120% of IBW)
Total body weight (TBW)	**Ideal body weight (IBW)** IBW (male) = 50 kg + (2.3 x height in inches > 60 inches) IBW (female) = 45.5 kg + (2.3 x height inches > 60 inches)	**Dosing weight (DW or adjusted body weight)** Dosing weight (DW) of: IBW + 0.4 x (TBW - IBW)

Dosing Strategies: **HIGH-DOSE EXTENTED INTERVAL IS THE PREFERRED DOSING STRATEGY!!** Please utilize traditional dosing if your patient meets exclusion criteria preventing them from receiving the high-dose extended interval therapy.

Synergy Dosing:

Refers to using gentamicin in combination with a cell-wall active agent for synergistic killing. Patients receiving aminoglycosides for Gram-negative infections (i.e. *Pseudomonas aeruginosa*) are excluded from this dosing. Peaks are not required to be obtained for synergy dosing.

Determine dose, desired trough, and interval:

Endocarditis Organism	Dose (mg/kg/dose)	Desired Trough (mcg/mL)	CrCl (mL/min) Interval
Viridans group Streptococci	3	<0.5	CrCl >55: q24h CrCl 36-55: q36h CrCl 26-35: q48h CrCl ≤25: traditional, pulse
Staphylococci or Enterococci	1	< 1	CrCl ≥ 50: q12h CrCl 20-49: q24h CrCl < 20: pulse

Obtain a trough 1 hour prior to the 3rd dose

Trough	Plan	Repeat
<1 mcg/mL (<0.5 if Strep)	No change	2-3 times weekly
1-2 mcg/mL (0.5-3 if Strep)	Extend interval by 12 hours	Prior to the 3rd dose
>2 mcg/mL (>3 if Strep)	Hold	Obtain random in 12-24 hours

High-Dose Extended Interval Dosing:

Refers to administering higher doses less frequently, which has comparable efficacy to traditional dosing while reducing risk of toxicity and frequency of administration/monitoring.

Exclusion Criteria for High-Dose Extended Interval:

- CrCl <25 mL/min or HD
- Pregnancy or post-partum breastfeeding
- Burns >20% of body surface area
- Ascites

Dosing*:

Indication	**Dose** (mg/kg/dose)	**CrCl** (mL/min) **Interval**
Tobramycin/Gentamicin		**CrCl >55:** q24h **CrCl 36-55:** q36h **CrCl 26-35:** q48h **CrCl ≤25:** Use traditional
Cystic Fibrosis†	10	
Gram-Negative Infections▲	5	
Uncomplicated UTI	See Traditional Dosing	
▲May consider up to 7 mg/kg tobramycin/gentamicin if patient is severely ill.		
Amikacin		
Cystic Fibrosis	30	
Gram-Negative Infections▲	15	
Uncomplicated UTI	See Traditional Dosing	
Mycobacterial	See Traditional Dosing	
▲May consider up to 20 mg/kg amikacin if patient is severely ill. Max amikacin dose 1400 mg.		

*Doses round automatically per FMOLHS System Dose Rounding protocol

†Tobramycin only

Therapeutic Monitoring and Dose Adjustment:

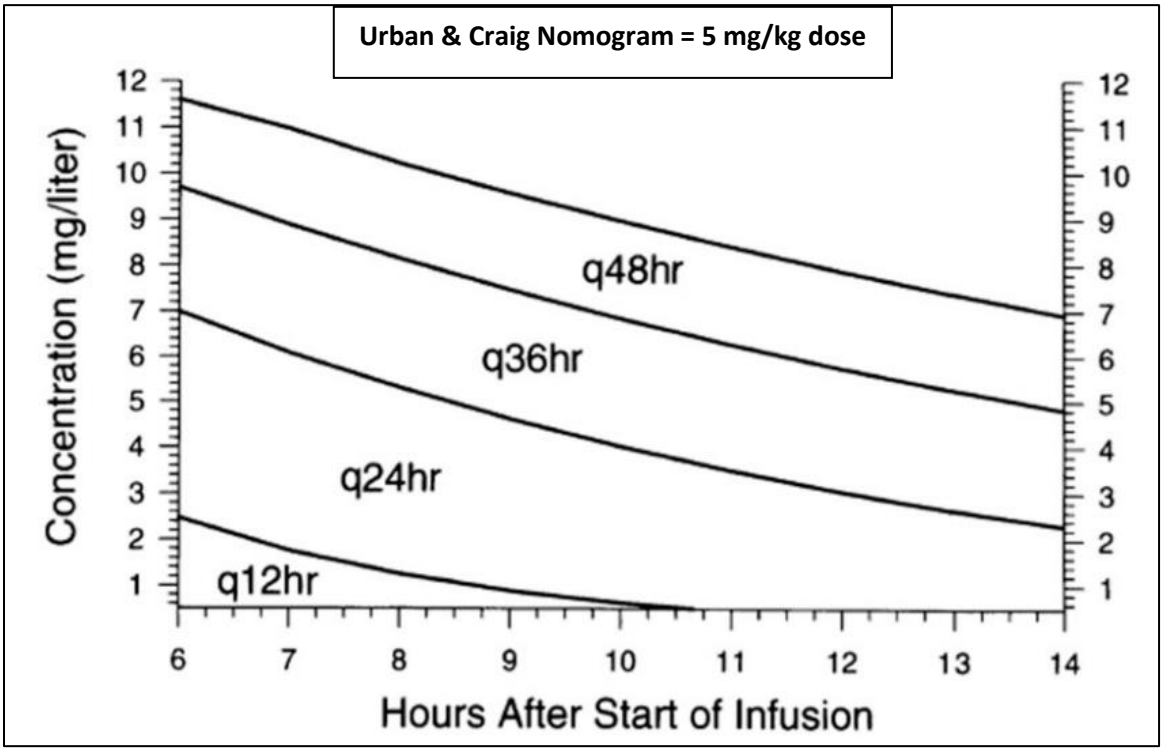
1. **Method 1** (preferred) – 2 random levels
   a. Obtain 2 random levels at 4-6 hours after the start of the first dose (C1) and at 12-14 hours after the start of the first dose (C2).
   b. Calculate Ke and half-life (t1/2) using the below equations:
      i. $$Ke = \frac{\ln(\frac{C1}{C2})}{time\ (hr) between\ C1\ and\ C2} \qquad t1/2 = \frac{0.693}{Ke}$$
   c. Use calculated t1/2 to determine appropriate dosing interval

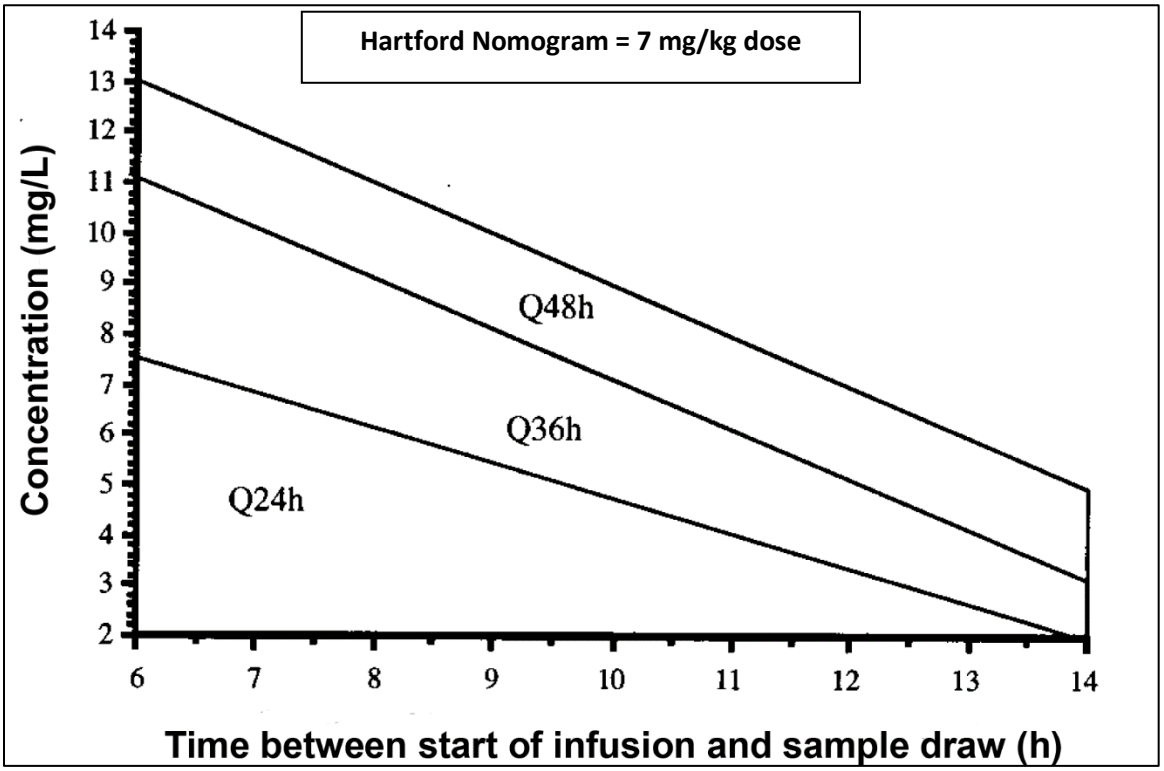
Half-life	Dosing Interval
<4 hours	q24h
4 to 6 hours	q36h
>6 to 8 hours	q48h
>8 hours	Convert to traditional dosing

   d. If only one level could be obtained, see Method 2
2. **Method 2** (if only 1 level obtained) – Dosing nomograms
   a. Plot level on either the Urban & Craig nomogram or the Hartford nomogram below and adjust interval as necessary.
      i. **Urban & Craig** – Use if dosed as tobramycin/gentamicin 5 mg/kg or amikacin 15 mg/kg
         1. For tobramycin/gentamicin (5 mg/kg), plot level on graph
         2. For amikacin (15 mg/kg), divide the level by 3 and then plot on graph

ii. **Hartford Nomogram** – Use if dosed as tobramycin/gentamicin 7 mg/kg or amikacin 15 mg/kg
    1. For tobramycin/gentamicin (7 mg/kg), plot level on graph
    2. For amikacin (15 mg/kg), divide the level by 2 and then plot on graph

b. If the level falls on a line, use the longer interval.
c. If the level falls on or above the q48h line, convert to traditional pulse dosing
d. If the level falls below the q12h line (Urban & Craig), proceed with q12h dosing as appropriate and monitor renal function and troughs closely to ensure no accumulation.





3. **Monitoring:** After interval is adjusted/confirmed with one of the 2 above methods, monitor renal function every 24-48 hours and obtain a trough **(4 hours prior to dose)** before the 3rd dose of the regimen. In patients with dynamic renal function or receiving q12h regimens, monitor subsequent troughs **(4 hours prior to dose)** every 3 days. In patients on prolonged courses with stable renal function, monitor subsequent troughs **(4 hours prior to dose)** every 5-7 days as deemed appropriate.

Trough (mcg/mL)	Plan	Repeat trough
Tobramycin/Gentamicin		
<1 (goal)	No change	1-2 times weekly
1-3	Extend interval by 12 hrs (if q48h, switch to traditional)	**4 hours prior** to new interval dose
>3	Consider switch to traditional	See Traditional Dosing
Amikacin		
<2 (goal)	No change	1-2 times weekly
2-4	Extend interval by 12 hrs (if q48h, switch to traditional)	**4 hours prior** to new interval dose
>4	Consider switch to traditional	See Traditional Dosing

   a. **Patients with AKI** (SCr increase by ≥0.3 mg/dL in 48 hours, SCr increase to ≥1.5 times baseline, or urine output decrease to <0.5mL/kg/hr):
      i. Hold next dose and check random level 24-48 after previous dose
      ii. Pulse dose for trough <1 mcg/mL (tobramycin/gentamicin) or <2 mcg/mL (amikacin)

Traditional Dosing:

Refers to dosing & adjusting based on desired blood levels determined by indication & renal function. Pharmacist will determine mg/kg doses by below or utilizing dosing calculations in the appendix based off population estimates.

Determine dose, peak, and trough:

Indication	**Dose** (mg/kg/dose)	**Desired Peak** (mcg/mL)	**Desired Trough** (mcg/mL)
Tobramycin/Gentamicin			
Uncomplicated UTI	5 mg/kg **x one dose**	-	<1 *
Gram-Negative Infections • Pyelonephritis, SSTI • PNA, Sepsis, FN	 1.5 2	 6-8 8-10	<1
Amikacin			
Uncomplicated UTI	15 mg/kg **x one dose**	-	<5 *
Gram-Negative Infections • Pyelonephritis, SSTI • PNA, Sepsis, FN	 6 7.5	 20-25 25-35	<5
Mycobacterium TIW • Avium (MAC) • Abscessus	15 mg/kg TIW ranges from 8-25 mg/kg (HD give 1x/week)	Peak ~5x MIC Guidelines: 65-80 Tolerability issues: ~30-40	<5

***** only monitor if scheduled regimen is ordered utilizing 1 mg/kg/dose for tobramycin/gentamicin or 5 mg/kg/dose for amikacin for UTI if providers do not elect to do the one time dose

Determine dosing interval:

CrCl (mL/min)	**>90**	**50-89**	**20-49**	**<20**	**HD**
Initial Interval	q8h	q12h	q24h	Pulse dose	q48-72h

Peaks and troughs:

1. Obtained with the 3rd or 4th dose after initiation or any dose change
    a. Peaks should be drawn 1.5 hours after the start of the infusion
    b. Troughs should be drawn 0.5-1 hour prior to the infusion is due
2. After obtaining levels, utilize kinetic calculations (preferred) or troughs only (if peaks are not indicated) to assess appropriateness of regimen

Peak Adjustment* Ratio
$\frac{\text{Actual Peak}}{\text{Goal Peak}} = \frac{\text{Current Dose}}{\text{New Dose}}$
*Can only use if renal function is stable If peak is at goal, do not need to repeat unless clinically indicated

Trough (mcg/mL)	Plan	Repeat
Tobramycin/Gentamicin		
<1	No change	2-3 times weekly
1-2	Extend interval by 12 hours	Prior to the 3rd dose
>2	Hold	Obtain random in 12-24 hours
Amikacin		
<5	No change	2-3 times weekly
5-8	Extend interval by 12 hours	Prior to the 3rd dose
>8	Hold	Obtain random in 12-24 hours

3. If current regimen is appropriate, consider obtaining repeat troughs every 72 hours if the duration is expected to be <14 days. If the patient is going to be on prolong therapy (synergy or mycobacterium) utilize clinical judgement and obtain levels 1-2x a week once stable.
4. **AKI/SLED/CRRT/Pulse dosing**: re-dose with the appropriate mg/kg based off indication once random level is below desired trough goal. Depending on SLED/CRRT patients may need random levels more often.
5. **HD dosing:** Re-dose when pre-HD level is < 2 mcg/mL (tobramycin/gentamicin) or < 6 mcg/mL (amikacin)
    - If pre-HD level is missed, obtain post-HD level ~6 hours after HD to allow for redistribution. Re-dose when post-HD < 1 mcg/mL (tobramycin/gentamicin) or < 5 mcg/mL (amikacin). HD removes 50% in 4 hours. The rate of removal of aminoglycosides is considerably less by peritoneal dialysis (PD) than by hemodialysis, use pulse dosing for PD with CrCl assumed <10mL/min.

Kinetic Calculations:

Determining Initial Dose
1. Estimate volume of distribution (Vd)* = 0.25 x weight (refer to which weight at top of guidance) *Factors that can dramatically increase Vd include: • Ascites: ○ Every kg of extra water increases the Vd by 10 times as much as a kg of extra fat. ○ Each L of extra fluid = 1 L in Vd calculation (e.g. Vd = 0.25 x kg + 1(estimated Liter(s) of extra fluid)) • Spinal cord injuries, pancreatitis, mechanical ventilation > 32 hours, severe sepsis ○ Consider using Vd of 0.3-0.4 L/kg
2. Dose = desired peak x Vd
3. Estimated ke = $\frac{CrCl\ x\ 0.06}{Vd}$
4. Dosing Interval (T) in hours = $\frac{\ln(\frac{Desired\ peak}{Desired\ trough})}{Ke} + t'$ **Desired tobramycin/gentamicin trough = < 1 mcg/mL** **Desired amikacin trough = <5 mcg/mL** **t' = infusion time (hours)**

5. Verify dosing regimen with C_{pk} & C_{tr}

$$C_{pk} = \frac{\text{new dose}(1-e^{-Ke})}{(Ke)(Vd)(1-e^{-KeT})} \qquad C_{tr} = C_{pk}(e^{-Ke(T-1)})$$

Modifying a Dose

1. New Ke = $\frac{\ln(\frac{C_1}{C_2})}{t}$ **C_1 = peak level**

C_2 = trough level

t = time between C_1 & C_2

2. True peak = $\frac{C_1}{e^{-Ke(t)}}$

True trough = $C_2 e^{(-Ke(t))}$ **t = time between when level was drawn & when it should have been drawn**

3. New Vd = $\frac{\text{dose}(1-e^{-Ke})}{(Ke)[C_{true\ pk}-(C_{true\ tr}\, e^{-KeT})]}$

4. Dosing interval (T) = $\frac{\ln(\frac{Desired\ peak}{Desired\ trough})}{Ke} + t'$ **t' = infusion time (hours)**

5. New Dose = $\frac{(\text{Desired } C_{pk})(\text{Ke})(\text{Vd})\ (1-e^{-KeT})}{(1-e^{-Ke})}$

6. Double verify Cpk and Ctr for a new calculated dose (see #5 in "Determining Initial Dose")

7. Does this new regimen make sense? Typical Vd is 0.25 L/kg and $T_{1/2}$ is 2-3 hours for a patient with normal renal function

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