Stanford Health Care Aminoglycoside Dosing Guideline

I. DETERMINING DOSE AND CREATININE CLEARANCE:

1. Use of total body weight (TBW) in underweight and non-obese patients is widely accepted. Use of ideal body weight (IBW) for determining the mg/kg/dose may also be considered. For obese patients dosage requirement may best be estimated using an adjusted body weight (ABW) of: IBW + 0.4 (TBW - IBW).[1]

   IBW (male) = 50 kg + (2.3 x height in inches > 60 inches)
   IBW (female) = 45 kg + (2.3 x height inches > 60 inches)

2. Calculate creatinine clearance with the Cockcroft-Gault equation using an ideal body weight (IBW) or an adjusted body weight (ABW) if the patient is obese

$$\text{CrCL (mL/min)} = \frac{(140 - \text{age}) \times \text{IBW}}{\text{SCr} \times 72} \quad (\times 0.85 \text{ for females})$$

II. AMINOGLYCOSIDE DOSING STRATEGIES

A. Gram negative infections

1. High-dose Extended-Interval Therapy

Rationale:

- **Aminoglycoside bactericidal activity is generally regarded as concentration dependent.**[2,3] The higher the peak/MIC ratio, the greater the rate and extent of bacterial kill. The pharmacodynamic goal is to maximize drug concentration at the site of infection. Optimal bactericidal activity for the aminoglycosides is achieved when the exposure concentration is approximately 8 to 10 times the MIC. Existing data also supports area under the plasma concentration-time curve (AUC) / MIC ratio as an indicator of bacterial killing and efficacy. The AUC:MIC targets are for efficacy range from AUC/MIC ratios of 30-50 in non-critically ill immunocompetent patients and upwards of 80-100 for critically ill patients with infections of high-bacterial burden.[4]
- **Aminoglycosides exhibit a post-antibiotic effect (PAE).**[2,5–7] PAE ranges of 0.5 to 8-hours have been reported. Factors influencing the PAE include: height of the preceding AMG peak, in-vivo > in-vitro, shortened by neutropenia, and extended in the presents of beta-lactams.
- **Saturable aminoglycosides uptake in renal tubule cell and inner ear.**[8] This suggests that higher peaks do not result in greater risk of toxicity. A single dose of aminoglycoside results in significantly lower renal cortical tissue concentration compared to the same total dose administered through a continuous infusion or in divided doses.[9,10] . Modeling data suggests that thrice-daily administration is associated with nephrotoxicity that occurs more rapidly, with greater intensity, and for longer duration, as compared to once-daily aminoglycoside.[11] Clinical data and experience suggests that high-dose extended interval may be less nephrotoxicity compared to traditional regimens.[12,13]

The **Hartford Nomogram** method utilizes high-dose, once daily dosing to optimize the peak/MIC ratio in most clinical situations by administering a dose of **7mg/kg** of either gentamicin or tobramycin. The **Urban & Craig Nomogram** is another method of extended-interval therapy utilizing **5 mg/kg** of gentamicin or tobramycin in patients without renal dysfunction. For patients with **cystic fibrosis exacerbation** the Cystic Fibrosis consensus guidelines recommend extended interval dosing with **10 mg/kg** once daily.

Exclusion Criteria:

- Renal insufficiency (CrCl <30 mL/min or rapidly declining renal function)
- Pregnancy
- Synergy for gram-positive infections
- Ascites
- Burns (>20%)

2. Conventional / Traditional Dosing

Tradition dosing of aminoglycosides includes lower doses with more frequent administration of aminoglycosides using pharmacokinetic parameters to determine dose and frequency to achieve target peak and trough values.

Indication:

- Treatment of gram-negative infections and **NOT** a candidate for high-dose extended interval dosing therapy (see exclusion criteria above)

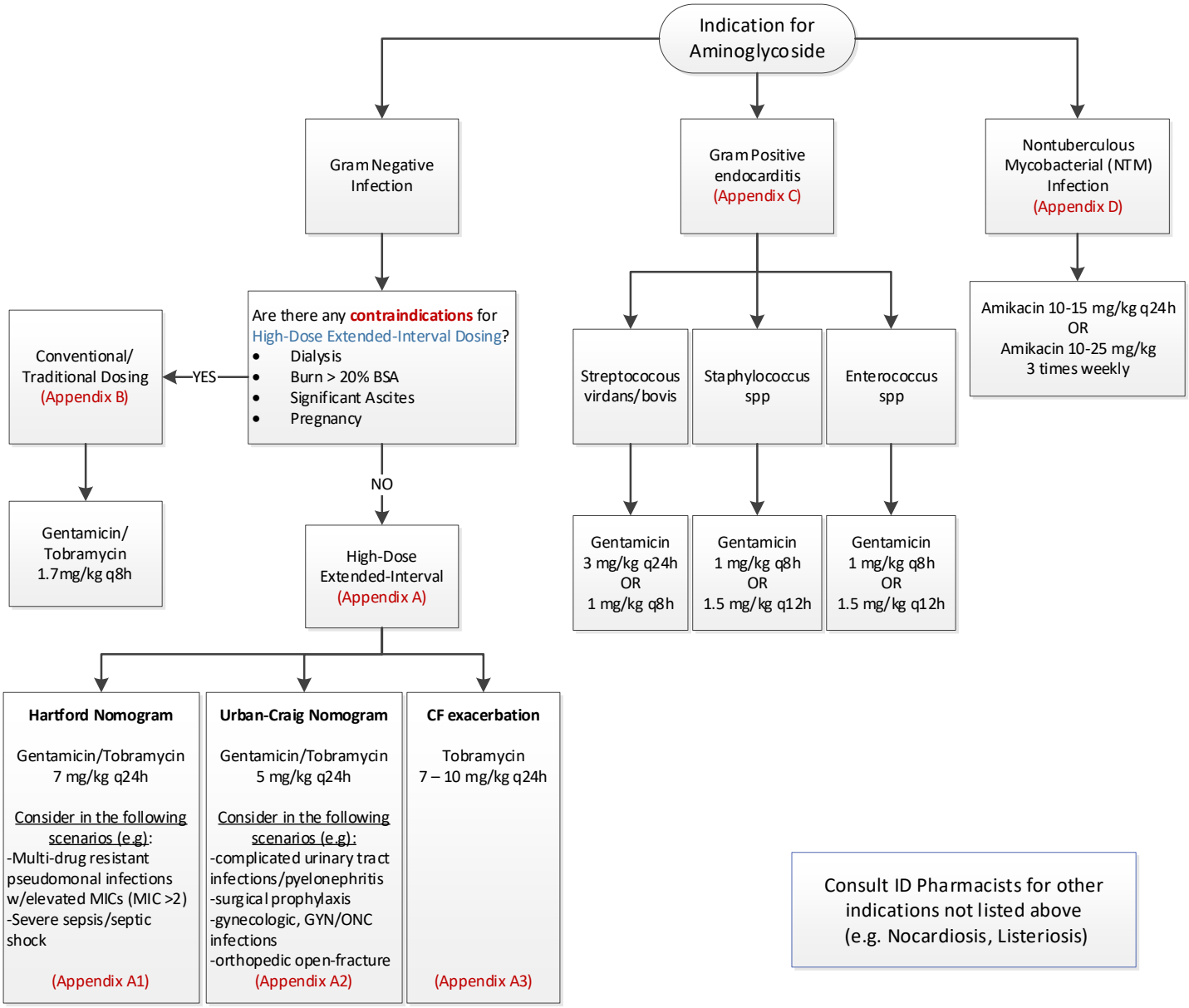
B. Gram positive-synergy

Synergy dosing is a low dose of aminoglycoside in conjunction with an antimicrobial agent that exhibits activity against the cell wall of Gram-positive bacteria (i.e. beta-lactams, glycopeptides) for the treatment of Gram-positive infections

C. Non-tuberculosis mycobacterium (NTM)

Treatment of NTM infections include combination therapy of either macrolides, clarithromycin, azithromycin, ethambutol, rifamycin and possibly an aminoglycoside. The decision to add an aminoglycoside depends on multiple factors including the extensiveness of disease, drug-refractory/resistant profile, and drug tolerance.

Dosing Methods by Indication



Appendix A: High-Dose Extended-Interval Nomograms (Gram-negative infections)

Appendix A1: Hartford Nomogram[17]

Initial Dose:

- **7 mg/kg using actual body weight** (Nomogram was developed and validated with actual body weight)
- If obese, use adjusted body weight. Adjusted body weight = IBW + (0.4 [TBW – IBW])
- The dose of 7 mg/kg is expected to achieve a C_{max} level of ~20 mcg/mL

CrCL (mL/min)	Gentamicin / Tobramycin	Amikacin
≥ 60 mL/min	7 mg/kg Q24H	15 mg/kg Q24H
40 – 59 mL/min	7 mg/kg Q36H	15 mg/kg Q36H
30 – 39 mL/min	7 mg/kg Q48H	15 mg/kg Q48H
20 – 29 mL/min	Not recommended	Not recommended
< 20 mL/min	Not recommended	Not recommended
Hemodialysis	Not recommended	Not recommended
CRRT	Not recommended	Not recommended

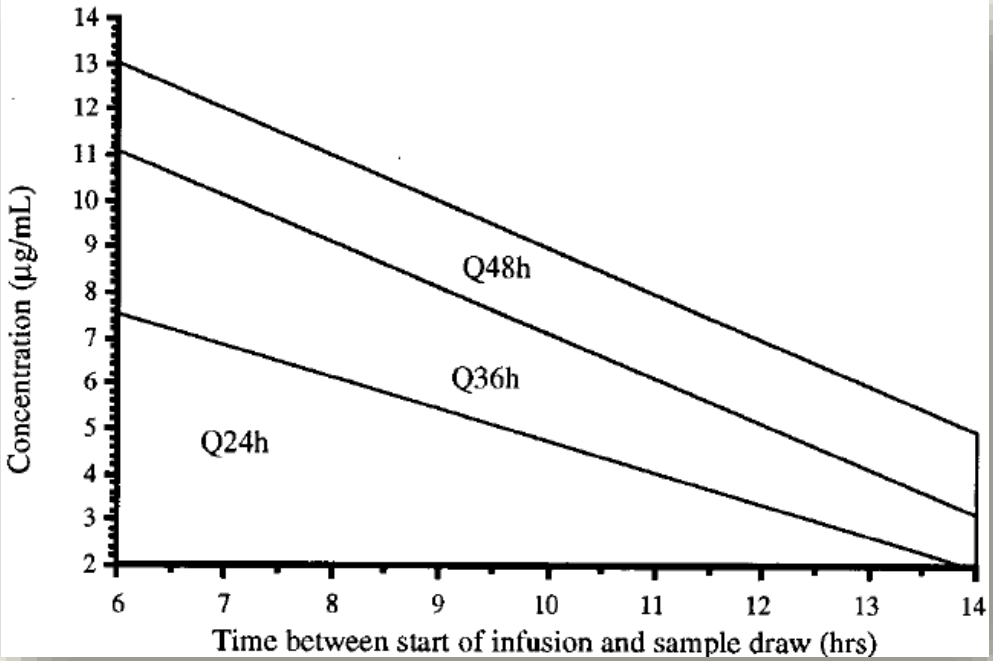
Monitoring:

Initial Monitoring

- Random level drawn 8 – 12 hours after the first dose
- Use nomogram to confirm/modify dosage interval
- Hartford nomogram is only applicable for 7 mg/kg – plotting doses lower or higher than 7 mg/kg may under or overestimate clearance
  - Gentamicin/tobramycin (7 mg/kg/dose): Plot level on graph
  - Amikacin (15 mg/kg/dose): Divide level in half, then plot on graph

Follow up trough level testing

- An early trough (6-hours prior to dose) should be considered in patients demonstrating acute changes in renal function or suspicion of extended interval failure. Aiming for a level < 1 mcg/mL approximately 6-hours prior to the next dose ensures there is a drug-free window in order to minimize drug accumulation within the proximal tubules.
- Maintenance random levels should be monitored at least once weekly.
- If duration of therapy is anticipated to be > 2 weeks, audiometry should be considered.



Appendix A2: Urban & Craig Nomogram

Initial Dosing:

- **Gentamicin/Tobramycin 5 mg/kg IV Q24H based on actual body weight**
  - If obese, use adjusted body weight. Adjusted body weight = IBW + (0.4 [TBW – IBW])

CrCL (mL/min)	Gentamicin / Tobramycin	Amikacin
≥ 60 mL/min	5 mg/kg Q24H	15 mg/kg Q24H
40 – 59 mL/min	5 mg/kg Q36H	15 mg/kg Q36H
20 – 39 mL/min	5 mg/kg Q48H	15 mg/kg Q48H
< 20 mL/min	Not recommended	Not recommended
Hemodialysis	Not recommended	Not recommended
CRRT	Not recommended	Not recommended

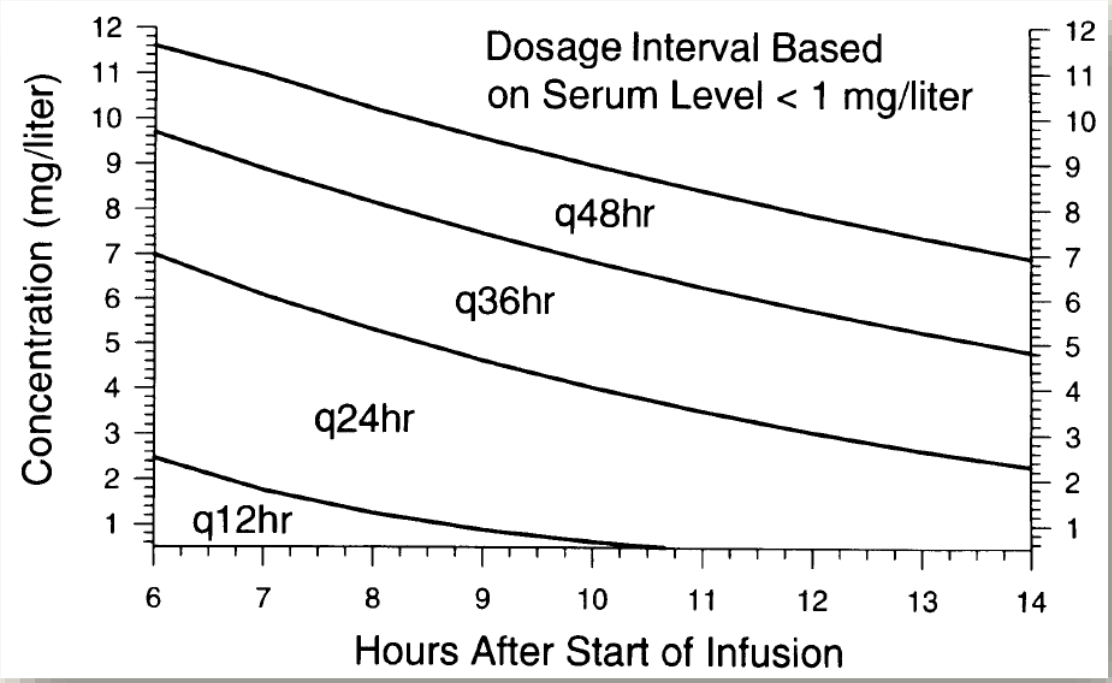
Monitoring:

Initial Monitoring

- Single level drawn 8 – 12 hours after the first dose.
- Use nomogram to confirm/modify dosage interval.
- Only applicable for 5 mg/kg – plotting doses lower or higher than 7 mg/kg may under or overestimate clearance)
  - Gentamicin/Tobramycin (5 mg/kg/dose): Plot on graph
  - Amikacin (15 mg/kg/dose): Divide level by 3, then plot on graph

Follow up monitoring:

- An early trough (6-hours prior to dose) should be considered in patients demonstrating acute changes in renal function or suspicion of extended interval failure. Aiming for a level < 1 mcg/mL approximately 6 -hours prior to the next dose ensures there is a drug-free window in order to minimize drug accumulation within the proximal tubules.
- Maintenance random levels should be monitored at least once weekly.
- If duration of therapy is anticipated to be > 2 weeks, audiometry should be considered.



Appendix A3: Cystic Fibrosis Dosing[18]

Initial Dosing:

CrCl (mL/min)	Tobramycin	Amikacin	Timing of Levels
≥ 60 mL/min	10 mg/kg Q24H Alt:* 7 mg/kg Q24H	20 mg/kg Q24H	**10 mg/kg Q24H Dosing:** **Peak**: 30-min after completion of 1st dose **Trough**: An early trough 6-hours before the 2nd dose (A paired peak/trough should be timed after the same dose. **7 mg/kg Q24H Dosing:** Random Level approximately 8 – 10 hours after the first dose. Plot on Hartford Nomogram **Maintenance Levels:** • Weekly peaks/troughs (6-hours before the next dose. Alternatively, 60-minutes before the next dose is also acceptable for outpatient monitoring). • Acute renal changes • Changes in dosing regimen
40 – 59 mL/min	7 – 10 mg/kg Q36H	20 mg/kg Q36H	
30 – 39 mL/min	7 – 10 mg/kg Q48H	20 mg/kg Q48H	
20 – 29 mL/min	Not recommended	Not recommended	
< 20 mL/min	Not recommended	Not recommended	
Hemodialysis	Not recommended	Not recommended	
CRRT	Not recommended	Not recommended	

Check medical record for a history of previously tolerated doses.
*Consider 7 mg/kg dosing if the patient has a history of AKI or SCr increase due to 10 mg/kg dosing

Monitoring:

Goal Levels		
	Target Peak	**Target Trough**
Gentamicin/Tobramycin	20 – 30 mcg/mL	< 1 mcg/mL
Amikacin	40 – 60 mcg/mL	< 4 mcg/mL

Appendix B: Conventional / Traditional Dosing (Gram-negative infections)

Initial Dosing:

CrCL (mL/min)	Gentamicin / Tobramycin	Amikacin	Timing of Levels	
			Peaks	Troughs
> 60 mL/min	1.7 mg/kg Q8H	7.5 mg/kg Q12H or 5 mg/kg Q8H	30-min after 3rd dose	Before 4th dose
40 – 59 mL/min	1.7 mg/kg Q12H	5 – 7.5 mg/kg Q12H	30-min after 2rd dose	Before 3rd dose
30 – 39 mL/min	1.7 mg/kg Q24H	5 – 7.5 mg/kg Q24H	30-min after 2nd dose	Before 3rd dose
20 – 29 mL/min	1.7 mg/kg Q24H	5 – 7.5 mg/kg Q24H		
< 20 mL/min; AKI	2 mg/kg load, then dose by level	5 mg/kg load, then dose by level	30-min after 1st dose	Before 2nd dose, redose when Cp < 1 mcg/mL
Hemodialysis	2 mg/kg load, then 1.5 mg/kg post-HD; Redose for 4-hr post-HD level Cp<1 mg/L or pre-HD ▪ Cp < 1 mg/L (mild UTI) ▪ Cp < 2–3 mg/L (moderate-severe UTI) ▪ Cp < 3–5 mg/L (severe GNR infection)	5 – 7.5 mg/kg post-HD	30-min after 1st dose	4-hr post-HD level Cp < 1 mcg/mL -- OR – pre-HD levels based on indication
CRRT	3 mg/kg loading dose, then 1.5 – 2.5 mg/kg Q24-48H. • Adjust dose based on the indication and the targeted peak & trough level.	10 mg/kg load, then 7.5 mg/kg Q24-48H	30-min after 2rd dose	Before 3rd dose

Monitoring:

Goal Levels			
Antibiotic	**Indication**	**Target Peak**	**Target Trough**
Gentamicin/Tobramycin	Life-threatening infection Serious Infections Urinary tract infections	8 – 10 mcg/mL 6 – 8 mcg/mL 4 – 6 mcg/mL	< 1 – 2 mcg/mL
Amikacin	Life-threatening infection Serious Infections Urinary tract infections	25 – 30 mcg/mL 20 – 25 mcg/mL 15 – 20 mcg/mL	< 4 – 8 mcg/mL

Appendix C: Gram-Positive Synergy Dosing

Initial Dosing:

CrCL (mL/min)	Gentamicin Synergy Dosing	Timing of Levels	
		Peaks	Troughs
> 60	1 mg/kg Q8H*	30 minutes after 3rd dose	Before 4th dose
40-59	1 mg/kg Q12H	30 minutes after 2nd dose	Before 3rd dose
30-39	1 mg/kg Q24H	30 minutes after 1st dose	Before 2nd dose
20-29	1 mg/kg Q24H		
<20; AKI	1 mg/kg x 1 dose; redose when Cp < 1 mcg/mL	30 minutes after 1st dose	Before 2nd dose, redoes when Cp < 1 mcg/mL
Hemodialysis	1 mg/kg q48-72H; Redose for pre-HD or post-HD Cp <1mcg/mL	30 minutes after 1st dose	Immediately *before* HD; Redose for pre-HD or 4-hr post-HD levels < 1 mcg/mL
CRRT	1 mg/kg Q24H, then by level	30 minutes after 2nd dose	Before 3rd dose

***Alternative dosing only **for CrCl > 60 mL/min:**

- **Gentamicin 3 mg/kg q24h** for treatment of endocarditis with Streptococci, *Streptococcus gallolyticus (bovis)*, *Streptococcus viridans*
- **Gentamicin 1.5 mg/kg q12h** for treatment of endocarditis with Staphylococci; Enterococcus spp (strains susceptible to penicillin and gentamicin) endocarditis
- Refer to the IDSA Infective Endocarditis Guidelines for dosing strategies in specific scenarios

Monitoring:

Goal Levels	Target Peak	Target Trough
Gentamicin/Tobramycin	3 – 4 mcg/mL**	< 1 mcg/mL

**Target Peak levels not applicable for alternative regimens of Gentamicin 3mg/kg q24h or 1.5 mg/kg q12h.

Appendix D: Nontuberculous Mycobacterial Infections

Initial Dosing:

Tobramycin is preferred in *M. chelonae* infection. Consult ID and/or ASP Pharmacists.

CrCL (mL/min)	Amikacin Daily Regimen	Amikacin Thrice Weekly Regimen	Timing of Levels
≥ 60 mL/min	10 – 15 mg/kg Q24H Age > 50 years old*: 10 mg/kg Q24H (max single dose of 500 mg)	10 – 25 mg/kg TIW Age > 50 years old: 10 mg/kg TIW (max single dose of 500 mg	**Peaks** • Dose is administered over 30-60 minutes. Draw peak level 30-minutes after the completion of the 1st dose . **Troughs** • 30 – 60 minutes before 2nd dose **Maintenance Monitoring** • Weekly peaks/troughs for prolonged duration of therapy • Repeat peak/trough levels for acute renal changes • Repeat peak/troughs for changes in dosing regimen
40 – 59 mL/min	10 – 15 mg/kg Q24 – 48H Alt*: 10 – 15 mg/kg M-F		
30 – 39 mL/min	10 – 15 mg/kg Q48 – 72H		
20 – 29 mL/min	Dose by level	Dose by level	
< 20 mL/min	Dose by level	Dose by level	
Hemodialysis	Dose by level	Dose by level	
CRRT	Dose by level	Dose by level	

*Monday-Friday regimen (5 times per week) may be recommended by the ID or pulmonary service for patients that are elderly or have poor renal function

Monitoring:

Goal Levels		
Regimen	**Peaks*** **	**Target Trough**
10 – 15 mg/kg Q24H	• In clinical practice, a lower target peak of 20 – 30 mcg/mL is oftentimes targeted for patient tolerability *Expected* levels: 25 – 40 mcg/mL	< 4 mcg/mL
10 – 25 mg/kg three times weekly	• May consider goal peaks of 35 – 45 mcg/mL as tolerability permits • In clinical practice, a lower target peak of 20 – 30 mcg/mL is oftentimes targeted for patient tolerability • Note: *Expected* levels with 25 mg/kg: 65 – 85 mcg/mL	< 4 mcg/mL

****Note**: There is no established PK/PD target for optimal microbiologic and clinical outcome. The above peak values are typically expected and therefore have been suggested TDM targets by national guidelines. The goal trough is to ensure drug clearance and minimize accumulation/toxicity.

Appendix E: PK Calculations

Aminoglycoside Pharmacokinetic Parameters

PK parameter	Value
Bioavailability (F)	-Water soluble -Poorly lipid soluble -Poor oral absorption
Volume of Distribution	0.25 L/kg (0.1 – 0.5 L/kg)
Fraction unbound in plasma	> 0.95
Clearance • Normal renal function • Functionally anephric • Hemodialysis	 Same as CrCL 0.0043 L/kg/hr 1.8 L/hr
t ½ • normal renal function • functionally anephric	 2 – 3 hours 30 – 60 hours

Abbreviations
IBW = ideal body weight
ABW = actual body weight
DBW = dosing body weight
kel = elimination rate constant
Vd = volume of distribution
τ = dosing interval
t = time of infusion
t_{before} = time between blood draw and start of infusion
t_{end} = time from end of infusion to blood draw
$t_{1/2}$ = half-life
C_{max} = peak serum level at steady-state
C_{min} = trough serum level at steady-state
SCr = serum creatinine

Initial Dosing

1. Determine CrCL using Cockcroft-Gault	CrCL (mL/min) = $\frac{(140 - age) \times IBW}{SCr \times 72}$ (x 0.85 for females)
2. Estimate elimination rate constant (Ke) based on PK kinetics	Ke = (0.003 x CrCl) + 0.01
3. Estimate half-life (t ½)	$t\,½ = \frac{0.693}{ke}$
4. Calculate Volume of distribution (Vd) using ABW or AdjBW	Gentamicin/Tobramycin = 0.25 L/kg Amikacin = 0.3 L/kg
5. Infusion time	Gentamicin/Tobramycin = 30 minutes Amikacin = 30 minutes; 60 minutes if doses > 15 mg/kg
6. Estimated dosing interval based on goal levels Ctr = Cmin = desired trough Cpeak = Cmax = desired peak Ti = infusion time	$T = \frac{Ln (C\,max / C\,min)}{Ke} + ti$ OR Estimated (T) = 3 x t ½
7. Maintenance dose (MD):	$MD = \frac{[(K_e) \times (VD) \times (ti) \times (C_{peak}\ desired) \times (1 - e^{-Ke\,T})]}{[(1 - e^{-Ke\,ti})]}$ OR MD = (Cpeak desired) x VD

Individualized Dose Revisions

1. Determine elimination rate constant Use levels within the same dosing interval	$K\ (hr^{-1}) = \frac{\text{(Ln peak/trough)}}{\Delta \text{ time between levels}}$ OR $k = \frac{\ln (Cmax/Cmin)}{\tau - (t + t_{end} + t_{before})}$
2. Determine actual Cmax (if level not drawn at correct time;1 hour after the start or 30 minutes after completion of infusion)	$Cmax_{actual} = \frac{Cmax}{e^{-k(tend)}}$
3. Determine half-life	$t\,½ = \frac{0.693}{k}$ Dosing interval for traditional dosing method = ~ 3-4 times the half-life
4. Time to achieve goal trough level	Time to clearance = $\frac{\text{Ln (actual trough/ desired trough)}}{Ke}$
5. Estimate dosing interval ti = infusion time τ = interval	$\tau = \left[\frac{\text{Ln (Cmax/Cmin)}}{K}\right] + ti$ OR Estimated $\tau = 3 \times t½$
6. Determine Vd t1 = time from beginning infusion to Cpeak	$Vd\ (L) = \frac{Dose}{Cmax_{actual}\ (1 - e^{-k(tau)})}$ OR $Vd\ (L) = \frac{[(Dose/C_{peak})}{(1 - e^{-K\tau})]} \times e^{-Kt_1}$
7. New maintenance dose ti = infusion time τ = interval	$MD = \frac{[(k_e) \times (Vd) \times (ti) \times (C_{peak}\ desired) \times (1 - e^{-K\tau})]}{[\ (1 - e^{-K\,ti})\ ]}$ OR MD = (goal peak Cmax) x Vd

References

1. Velissaris D, Karamouzos V, Marangos M, Pierrakos C, Karanikolas M. Pharmacokinetic changes and dosing modification of aminoglycosides in critically ill obese patients: a literature review. *J Clin Med Res*. 2014;6(4):227-233. doi:10.14740/jocmr1858w

2. Craig WA, Ebert SC. Killing and regrowth of bacteria in vitro: a review. *Scand J Infect Dis Suppl*. 1990;74:63-70.

3. Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. *J Infect Dis*. 1987;155(1):93-99.

4. Bland CM, Pai MP, Lodise TP. Reappraisal of Contemporary Pharmacokinetic and Pharmacodynamic Principles for Informing Aminoglycoside Dosing. *Pharmacother J Hum Pharmacol Drug Ther*. 2018;38(12):1229-1238. doi:10.1002/phar.2193

5. Zhanel GG, Hoban DJ, Harding GK. The postantibiotic effect: a review of in vitro and in vivo data. *DICP Ann Pharmacother*. 1991;25(2):153-163.

6. Spivey JM. The postantibiotic effect. *Clin Pharm*. 1992;11(10):865-875.

7. Fantin B, Ebert S, Leggett J, Vogelman B, Craig WA. Factors affecting duration of in-vivo postantibiotic effect for aminoglycosides against gram-negative bacilli. *J Antimicrob Chemother*. 1991;27(6):829-836.

8. Blaser J, Simmen HP, Thurnheer U, König C, Lüthy R. Nephrotoxicity, high frequency ototoxicity, efficacy and serum kinetics of once versus thrice daily dosing of netilmicin in patients with serious infections. *J Antimicrob Chemother*. 1995;36(5):803-814.

9. Verpooten GA, Giuliano RA, Verbist L, Eestermans G, De Broe ME. Once-daily dosing decreases renal accumulation of gentamicin and netilmicin. *Clin Pharmacol Ther*. 1989;45(1):22-27.

10. De Broe ME, Verbist L, Verpooten GA. Influence of dosage schedule on renal cortical accumulation of amikacin and tobramycin in man. *J Antimicrob Chemother*. 1991;27 Suppl C:41-47.

11. Rougier F, Claude D, Maurin M, et al. Aminoglycoside Nephrotoxicity: Modeling, Simulation, and Control. *Antimicrob Agents Chemother*. 2003;47(3):1010-1016. doi:10.1128/AAC.47.3.1010-1016.2003

12. Hatala R, Dinh T, Cook DJ. Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis. *Ann Intern Med*. 1996;124(8):717-725.

13. Smyth AR, Bhatt J, Nevitt SJ. Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis. *Cochrane Database Syst Rev*. 2017;3:CD002009. doi:10.1002/14651858.CD002009.pub6

14. Daikos GL, Jackson GG, Lolans VT, Livermore DM. Adaptive resistance to aminoglycoside antibiotics from first-exposure down-regulation. *J Infect Dis*. 1990;162(2):414-420.

15. Daikos GL, Lolans VT, Jackson GG. First-exposure adaptive resistance to aminoglycoside antibiotics in vivo with meaning for optimal clinical use. *Antimicrob Agents Chemother*. 1991;35(1):117-123.

16. Nightingale, Mur. *Antimicrobial Pharmacodynamics in Theory and Clinical Practice, Second Edition*. CRC Press; 2007.

17. Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrob Agents Chemother*. 1995;39(3):650-655.

18. Flume PA, Mogayzel PJ, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. *Am J Respir Crit Care Med*. 2009;180(9):802-808. doi:10.1164/rccm.200812-1845PP

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