



## **Aminoglycoside Dosing & Monitoring: Neonatal & Pediatric Guideline**

Aminoglycosides have bactericidal activity against most Gram-negative bacteria and can be utilized as synergistic agents against various Gram-positive bacteria. This guideline is designed to facilitate the dosing and monitoring of aminoglycosides in neonatal and pediatric patients. Pharmacokinetic calculations are available at the end of this document. For the purposes of this document, the term “neonate” refers to patients within their first month of life and the term “pediatric” refers to those who are at least one month of age or older.

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## AMINOGLYCOSIDE DOSING STRATEGIES OVERVIEW

### A. NEONATAL DOSING

Aminoglycoside dosing in neonates is unique due to the reduced clearance of these antibiotics, leading to extended interval dosing that is dependent on postmenstrual and postnatal age. Additionally, the majority of aminoglycoside use in this patient population is in empiric sepsis rule-out episodes.

### B . HIGH-DOSE EXTENDED INTERVAL DOSING

Aminoglycoside's bactericidal activity is concentration-dependent, which means the higher the peak (i.e.,  $C_{max}$ ) to minimum inhibitory concentration ratio ( $C_{max}:MIC$ ), the greater the rate and extent of bacterial kill. This also helps prevent subpopulation resistance. Optimum activity is achieved when the exposure concentration is approximately 8 to 10 times the MIC. The high-dose extended interval (HDEI) dosing strategy optimizes this pharmacodynamic property without increasing risk of toxicities. When using HDEI, target peaks are typically 2-3 times greater than traditional peaks; troughs remain unchanged. Not all patients are indicated for HDEI aminoglycosides; see text for additional inclusion/exclusion criteria.

### C. PULMONARY EXACERBATION IN CYSTIC FIBROSIS & PRIMARY CILIARY DYSKINESIA DOSING

Patients with cystic fibrosis (CF) and primary ciliary dyskinesia (PCD) are often colonized with *Pseudomonas aeruginosa* and other Gram-negative pathogens. Additionally, these patients may be admitted multiple times for exacerbations of their underlying pulmonary disease. These episodes are generally treated with an anti-pseudomonal beta-lactam in combination with an aminoglycoside. The preferred aminoglycoside for CF exacerbations is tobramycin due to demonstrated failures with gentamicin. Additionally, the preferred aminoglycoside dosing strategy for CF exacerbations is HDEI to limit toxicities while maintaining efficacy.

### D. CONVENTIONAL/TRADITIONAL DOSING FOR GRAM-NEGATIVE INFECTIONS

Conventional dosing utilizes reduced doses and frequent administration of aminoglycosides based on pharmacokinetic parameters. Dose and frequency is dependent on the desired target peak & trough values for the specific indication. For patients who are not able to receive high-dose extended interval aminoglycosides, conventional dosing is the preferred therapy strategy.

### E. GRAM-POSITIVE SYNERGY DOSING

Aminoglycosides exhibit synergy when used in conjunction with an antimicrobial agent (e.g., beta-lactams, glycopeptides) that has activity against the cell wall of Gram-positive bacteria (e.g., *Staphylococcus*, *Streptococcus*, & *Enterococcus*). Aminoglycoside synergy is NOT recommended in right-sided native valve staphylococcal endocarditis given increased risk of nephrotoxicity and no clinical benefit.

### F. AMIKACIN DOSING

Amikacin is more rarely used in pediatrics compared to gentamicin and tobramycin. Use of amikacin may be indicated in patients with infections caused by more resistant pathogens, including non-tuberculous mycobacteria (NTM). Mycobacteria replicate slowly which allows for amikacin dosing at extended intervals, such as daily or three times weekly. Dosing and goal concentration levels differ from those of gentamicin and tobramycin; thus, amikacin is discussed in a separate section in this guideline.

## INITIAL DOSING CONSIDERATIONS

In the majority of children and adolescents starting aminoglycosides, it is pertinent to investigate the patient’s aminoglycoside history. If the patient has tolerated a regimen that was used within the past year, it is reasonable to re-initiate this aminoglycoside regimen as long as the patient has not had significant changes in weight, renal, or auditory function, as clinically determined by the primary pharmacist. This is particularly true for patients who have multiple admissions requiring aminoglycosides (e.g., cystic fibrosis exacerbations).

Initial dosing is based on estimated ideal body weight (IBW), except for those whose total body weight is less than their IBW; in that case, the patient’s total body weight should be used. There are various methods of calculating IBW in pediatric patients, and there is not a consensus on which should be used in dosing of aminoglycosides. Adjusted body weight (AjBW) may be considered in obese and morbidly obese pediatric patients. See Table 1 below for a few examples of calculations that may be used to assist the pharmacist in determining which weight to use.

**TABLE 1. IDEAL & ADJUSTED BODY WEIGHT CALCULATIONS**

Method	Calculation
Traub & Johnson (Children 1-17yo & ≤ 5ft tall), kg	$IBW = (\text{height}[\text{cm}]^2 \times 1.65) / 1000$
Traub & Johnson (Children 1-17yo & > 5ft tall), kg	$IBW_{\text{male}} = 39 + [2.27 \times (\text{height} [\text{in}] - 60)]$ $IBW_{\text{female}} = 42.2 + [2.27 \times (\text{height} [\text{in}] - 60)]$
Devine (adult), kg	$IBW_{\text{male}} = 50 + [2.3 \times (\text{height} [\text{in}] - 60)]$ $IBW_{\text{female}} = 45.5 + [2.3 \times (\text{height} [\text{in}] - 60)]$
Adjusted Body Weight (AjBW), kg	$AjBW = IBW + [0.4 \times (\text{actual body weight} [\text{kg}] - IBW)]$

## CALCULATING CREATININE CLEARANCE

Use the following calculations in conjunction with urine output when estimating the patient’s renal function.

### NEONATES: Schwartz Equation (mL/min/1.73m<sup>2</sup>)

$$eGFR = \frac{\text{length} [\text{cm}] * k}{SCr}$$

k = 0.33 for preterm infants up to one year old

k = 0.45 for term infants up to one year old

### INFANTS, CHILDREN, & ADOLESCENTS: Bedside Schwartz Equation (mL/min/1.73m<sup>2</sup>)

$$eGFR = 0.413 * \frac{\text{height} [\text{cm}]}{SCr}$$

## TIMING OF LEVELS FOR THERAPEUTIC DRUG MONITORING

Serum concentrations (i.e., peak, trough) should be monitored to ensure safe and effective use of aminoglycosides. Timing of levels depends on the dosing strategy used; see Table 2. In general, peak levels are obtained one hour after the start of infusion, and trough levels are obtained 0-30 minutes prior to a dose. For patients receiving aminoglycoside therapy for  $\leq 48$  hours (e.g., neonatal sepsis rule-out) therapeutic drug monitoring is not necessary. In addition to aminoglycoside levels, renal function should be monitored closely, which may include daily urine output as well as BUN/SCr at least weekly.

*When ordering levels for a patient in the Neonatal Critical Care Center (NCCC), coordinate with the NCCC team caring for the patient to minimize the number of lab draws obtained.*

Once therapeutic levels have been achieved with a given regimen, repeat peak and/or trough levels may be obtained every 5-7 days or more frequently if necessary, based on clinical status (e.g., change in renal function). Dose adjustments and lab orders may be ordered by the pharmacist via “Per protocol: cosign required” under the Pharmacy to Dose protocol.

**TABLE 2. AMINOGLYCOSIDE LEVELS AND WHEN TO OBTAIN THEM**

Patient Population	Indication / Dosing Strategy	Levels to be Obtained	When to Obtain Levels
Neonates	Extremely low birth weight (<1kg)	Peak	Obtain peak and/or trough with next dose if therapy is continued beyond 48 hours. <i>Trough may be indicated sooner if low urine output or cooling</i>
		Trough	
	Critically ill, Gram-negative infection, meningitis	Peak	
		Trough	
All others	Trough		
Infants, Children, & Adolescents	Conventional / Gram-positive synergy strategies	Peak	1h after start of 4 <sup>th</sup> dose
		Trough	0-30min prior to 4 <sup>th</sup> dose
	High-dose extended interval dosing strategy	Peak	2h after start of 2 <sup>nd</sup> dose
		Trough	6-8h after start of 2 <sup>nd</sup> dose

## NEONATAL DOSING

See Table 3 below for dosing recommendations of gentamicin and tobramycin. Gentamicin is the preferred aminoglycoside in empiric neonatal sepsis management; however, tobramycin may be used if needed. Amikacin is not routinely used in the neonate population.

**TABLE 3. NEONATAL (NeoFax®) DOSING RECOMMENDATIONS (GENTAMICIN & TOBRAMICIN)**

PMA (weeks)	Postnatal Age (days)	Dose (mg/kg)	Interval (hours)
≤ 29	0 to 7	5	48
	8 to 28	4	36
	≥ 29	4	24
30 to 34	0 to 7	4.5	36
	≥ 8	4	24
≥ 35	ALL	4	24

PMA (postmenstrual age) = gestational age + weeks of life

**TABLE 4. DESIRED GENTAMICIN/TOBRAMYCIN PEAK & TROUGH LEVELS IN NEONATAL PATIENTS**

Scenario	Desired Peak (mcg/mL)	Desired Trough (mcg/mL)
Neonatal Sepsis	8-12	< 1.5
Neonatal Sepsis in setting of ELBW, concurrent vancomycin, or HIE/cooling protocol	8-12	< 1

ELBW: extremely low birth weight; HIE: hypoxic ischemic encephalopathy

## HIGH-DOSE EXTENDED INTERVAL DOSING (Gentamicin & Tobramycin)

High-dose extended interval (HDEI) aminoglycoside dosing has been evaluated in patients who are at least three months of age and with normal renal function. Only studies evaluating HDEI efficacy in urinary tract infections (e.g., cystitis) have included infants as young as 1 month old. When considering HDEI, there are age-directed (Table 5) and UTI-specific (Table 6) recommendations based on available literature. Final dosing used is dependent on the clinical judgement of the primary pharmacist.

Patients excluded from HDEI: unstable or impaired renal function (eGFR <50, peritoneal dialysis, and hemodialysis), ECMO, pregnant, ascites, burns with ≥ 20% body surface area involvement, and treatment of endocarditis or meningitis. The conventional/traditional dosing strategy is recommended for these patients.

**TABLE 5. HIGH-DOSE EXTENDED INTERVAL DOSING: AGE-DIRECTED (GENTAMICIN & TOBRAMICIN)**

Age	Dose (mg/kg)	Interval (hours)	Desired Peak* (mcg/mL)	Desired Trough (mcg/mL)
≥ 3 mo to < 2 yo	9.5	24	20-30	< 1
2 to < 8 yo	8.5	24	20-30	< 1
≥ 8 yo	7	24	20-30	< 1

\*If the MIC is known for the organism, desired peak concentration is 8-10x the MIC value.

**TABLE 6. HIGH-DOSE EXTENDED INTERVAL DOSING FOR UTI (GENTAMICIN & TOBRAMICIN)**

Age	Dose (mg/kg)	Interval (hours)	Desired Peak*† (mcg/mL)	Desired Trough (mcg/mL)
≥ 1 mo to < 5 yo	7.5	24	10-20	< 1
5 to < 11 yo	6	24	10-20	< 1
≥ 11 yo	5	24	10-20	< 1

\*If the MIC is known for the organism, desired peak concentration is 8-10x the MIC value.

†For uncomplicated cystitis, peak concentrations are not typically required; consider monitoring peak level in setting of pyelonephritis

### PULMONARY EXACERBATION IN CF & PCD DOSING

The preferred aminoglycoside regimen for pulmonary exacerbation in the setting of CF or PCD is HDEI tobramycin. This dosing strategy is not recommended for those with impaired renal function (eGFR <50); alternative therapies should be considered. Amikacin may also be used for more resistant bacterial pathogens; refer to the section titled “AMIKACIN DOSING” for more information, including dosing for infections caused by NTM.

Prior to initiating aminoglycoside therapy in a patient with CF or PCD, check the following:

- Prior dosing regimens and patient-specific information
- Review dosing regimen and pharmacist note(s) from most recent hospitalization. If it is within the last year and the patient has not had a significant change in weight or renal function, then it is reasonable to use this same regimen. If this is not the case, use a new regimen with doses recommended in Table 7.

**TABLE 7. PULMONARY EXACERBATION IN CF & PCD DOSING (TOBRAMYCIN & AMIKACIN)**

Aminoglycoside / Indication	Dose (mg/kg)	Interval (hours)	Desired Peak† (mcg/mL)	Desired Trough (mcg/mL)
Tobramycin, CF/PCD Exacerbation	10	24	20-30	< 1
Amikacin*, CF/PCD Exacerbation	30-35	24	80-120	< 5

\*This does not refer to dosing recommendations for NTM; refer to section AMIKACIN DOSING for more details

†If the MIC is known for the organism, desired peak concentration is 8-10x the MIC value.

### CONVENTIONAL DOSING FOR GRAM-NEGATIVE INFECTIONS (Gentamicin & Tobramycin)

For patients not meeting criteria for HDEI aminoglycosides, the conventional/traditional dosing strategy is preferred. Conventional strategy dosing is based on indication.

**TABLE 8. CONVENTIONAL AMINOGLYCOSIDE DOSING (GENTAMICIN & TOBRAMICIN)**

Indication	Dose (mg/kg/DAY)	Interval (hours)	Desired Peak* (mcg/mL)	Desired Trough (mcg/mL)
Bacteremia, Sepsis, Pneumonia (non-CF)	7.5	8	8-12	< 1
Gram-negative Endocarditis	7.5	8	8-12	< 1
Meningitis	7.5	8	8-12	< 1
UTI	5	8	4-6	< 1

\*For uncomplicated cystitis, peak concentrations are not typically required; consider monitoring peak level in setting of pyelonephritis

## SYNERGY DOSING FOR GRAM-POSITIVE INFECTIONS (Gentamicin & Tobramycin)

Aminoglycosides exhibit synergy when used in conjunction with an antimicrobial agent (e.g., beta-lactams, glycopeptides) that has activity against the cell wall of Gram-positive bacteria (e.g., *Staphylococcus*, *Streptococcus*, & *Enterococcus*). Examples of indications that may warrant synergistic aminoglycoside therapy include native valve endocarditis caused by enterococci or viridans group streptococci, as well as prosthetic valve endocarditis caused by *Staphylococcus aureus* or enterococci. While gentamicin is the preferred agent for synergy in Gram-positive infections, tobramycin may be used if necessary. It is recommended to confirm susceptibility of the organism to the aminoglycoside prior to starting therapy, if possible. When using aminoglycosides for Gram-positive synergy, obtaining trough levels is warranted to monitor for accumulation. Peak levels are not necessary; however, goal peak levels are included in Table 9 for completeness.

**TABLE 9. GRAM-POSITIVE AMINOGLYCOSIDE SYNERGY DOSING (GENTAMICIN & TOBRAMICIN)**

Aminoglycoside	Dose (mg/kg/DAY)	Interval (hours)	Desired Peak (mcg/mL)	Desired Trough (mcg/mL)
Gentamicin or Tobramycin	3	8	4-6	< 1

## AMIKACIN DOSING

Amikacin is more rarely used in pediatrics compared to gentamicin and tobramycin. Use of amikacin may be indicated for infections caused by more resistant pathogens, including non-tuberculous mycobacteria (NTM). Mycobacteria replicate slowly which allows for amikacin dosing at extended intervals, such as daily or three times weekly. Dosing and goal concentrations differ from those of gentamicin and tobramycin.

**TABLE 10. AMIKACIN DOSING PER DOSING STRATEGY & INDICATION**

Dosing Strategy / Indication	Dose (mg/kg/DAY)	Interval (hours)	Desired Peak (mcg/mL)	Desired Trough (mcg/mL)
Conventional, Gram-negative Infection	15-20	8	20-40	< 5
HDEI, Gram-negative Infection	15-30*	24	20-60†	< 5
HDEI, NTM Infection	15-30*	24	20-40	< 5

\*Infants and children may require doses greater than 15mg/kg/day

†Theoretically, peak >60 may be needed to achieve  $C_{max}:MIC >8$ ; however, must weigh risk of toxicity with potential benefit.

## CONSIDERATIONS IN RENAL IMPAIRMENT

This section encompasses patients with acute renal impairment as well as those receiving hemodialysis (HD), peritoneal dialysis (PD), and continuous renal replacement therapy (CRRT). Dosing recommendations in renal impairment are based off the conventional dosing strategy (e.g., q8h). The conventional dosing interval is empirically extended based on reduced renal function; see Table 11. Alternatively, individual one-time doses followed by spot-checking a level prior to re-dosing may be done (“dosing by levels”); this is routinely used in patients with fluctuating renal function as well as those receiving CRRT. Serial levels following a single dose may also be obtained to calculate a patient-specific elimination constant ( $k_e$ ) and unique interval. See the section Additional Pharmacokinetic Equations for Therapeutic Drug Monitoring for more detail.

The high-dose extended interval dosing strategy is not recommended in patients with renal impairment.

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**TABLE 11. EMPIRIC AMINOGLYCOSIDE DOSE ADJUSTMENTS BASED ON RENAL FUNCTION**

Aminoglycoside	Dose (mg/kg)	Renal Function (mL/min/1.73m <sup>2</sup> ) & Recommended Dosing Interval			
		> 50	30-50	10-29	<10
Gentamicin	2.5	No adjustment	Q 12-18 hours	Q 18-24 hours	Q 48-72 hours
Tobramycin	2.5	No adjustment	Q 12-18 hours	Q 18-24 hours	Q 48-72 hours
Amikacin	5-7.5	No adjustment	Q 12-18 hours	Q 18-24 hours	Q 48-72 hours

**DOSING IN RENAL IMPAIRMENT: GENTAMICIN & TOBRAMYCIN****1. ONE-TIME DOSE FOLLOWED BY SPOT-CHECKING LEVELS & PATIENTS ON CRRT**

- a. Administer 2-2.5 mg/kg IV x1 dose
- b. Obtain a random level 8-12 hours after the start of infusion
  - i. If level > 1.5, repeat random level at 8-24 hour interval until level ≤ 1.5 before repeating a dose
  - ii. If level ≤ 1.5, repeat dose of 2-2.5 mg/kg IV x1 dose and obtain a level 8-12 hours after the start of infusion
- c. Consider scheduling doses if the patient demonstrates stable renal function and consistent aminoglycoside goal levels.

**2. HEMODIALYSIS & PERITONEAL DIALYSIS**

- a. HD: doses are to be given after HD on dialysis days
- b. PD: systemic aminoglycoside is only necessary in cases of extra-peritoneal infections
  - i. Intraperitoneal aminoglycosides do not routinely require monitoring
- c. Administer 2 mg/kg IV x1 dose
- d. Levels may be obtained before or after HD on dialysis days. If the level is obtained after HD, it is recommended to obtain this level 3-4 hours after the end of HD/PD to allow for fluid redistribution.
  - i. Level obtained immediately prior to HD or intermittent PD:
    1. This is recommended for those receiving outpatient HD
    2. If level > 3, repeat another level in 12-24 hours
    3. If level > 1.5-3, repeat level 3-4h after HD and repeat dose 2 mg/kg if level is ≤ 1.5; otherwise, repeat level in 12-24 hours until ≤ 1.5
    4. If level ≤ 1.5, repeat dose 2 mg/kg x1 and obtain a level in 12-24 hours
  - ii. Level obtained after HD or intermittent PD:
    1. If level > 1.5, repeat another random level in 12-24 hours until level is ≤ 1.5 before repeating a dose
    2. If level ≤ 1.5, repeat dose 2 mg/kg x1 and obtain a level in 12-24 hours
  - iii. Consider scheduling doses if the patient demonstrates stable dialysis schedule and consistent aminoglycoside goal levels.
- e. Intraperitoneal administration of gentamicin and tobramycin:
  - i. Intermittent PD, anuric: 0.6 mg/kg/dose every 24h in the long dwell
  - ii. Intermittent PD, nonanuric: 0.75 mg/kg/dose every 24h in the long dwell
  - iii. Continuous PD: loading dose 8 mg/L of dialysate followed by 4 mg/L



## **DOSING IN RENAL IMPAIRMENT: AMIKACIN**

### **1. ONE-TIME DOSE FOLLOWED BY SPOT-CHECKING LEVELS & PATIENTS ON CRRT**

- a. Administer 5-7.5 mg/kg IV x1 dose
- b. Obtain a random level 8-12 hours after the start of infusion
  - i. If level > 5, repeat random level at 8-24 hour interval until level ≤ 5 before repeating a dose
  - ii. If level ≤ 5, repeat dose of 2-2.5 mg/kg IV x1 dose and obtain a level 8-12 hours after the start of infusion
- c. Consider scheduling doses if the patient demonstrates stable renal function.

### **2. HEMODIALYSIS & PERITONEAL DIALYSIS**

- f. HD: doses are to be given after HD on dialysis days
- g. PD: systemic aminoglycoside is only necessary in cases of extra-peritoneal infections
  - i. Intraperitoneal aminoglycosides do not routinely require monitoring
- h. Administer 5 mg/kg IV x1 dose
- i. Levels may be obtained before or after HD on dialysis days. If the level is obtained after HD, it is recommended to obtain this level 3-4 hours after the end of HD/PD to allow for fluid redistribution.
  - i. Level obtained immediately prior to HD or intermittent PD:
    1. This is recommended for those receiving outpatient HD
    2. If level > 10, repeat another level in 12-24 hours
    3. If level > 5-10, repeat level 3-4h after HD and repeat dose 2 mg/kg if level is ≤ 5; otherwise, repeat level in 12-24 hours until ≤ 5
    4. If level ≤ 5, repeat dose 5 mg/kg x1 and obtain a level in 12-24 hours
  - ii. Level obtained after HD or intermittent PD:
    1. If level > 5, repeat another random level in 12-24 hours until level is ≤ 5 before repeating a dose
    2. If level ≤ 5, repeat dose 5 mg/kg x1 and obtain a level in 12-24 hours
  - iii. Consider scheduling doses if the patient demonstrates stable dialysis schedule and consistent aminoglycoside goal levels.
- j. Intraperitoneal administration of gentamicin and tobramycin:
  - i. Intermittent PD: 2 mg/kg/dose every 24h in the long dwell
  - ii. Continuous PD: loading dose 25 mg/L of dialysate followed by 12 mg/L

## ADDITIONAL PHARMACOKINETIC EQUATIONS FOR THERAPEUTIC DRUG MONITORING

If levels are both obtained after same dose:

$$k_e = \frac{\ln\left(\frac{\text{level 1}}{\text{level 2}}\right)}{t}$$

If a trough is obtained before a dose, and the peak is obtained after the dose:

$$k_e = \frac{\ln\left(\frac{\text{level 1}}{\text{level 2}}\right)}{T - t}$$

**Half-life:**

$$t_{1/2} = \frac{0.693}{k_e}$$

**Extrapolated Peak:**

$$C_{max} = \frac{\text{Peak or Level 1}}{e^{-k_e(t_a)}}$$

$k_e$  = elimination constant

T = dosing frequency

t = time between the trough & peak OR time between level 1 & 2  
 $t_a$  = time between end of the infusion and when peak or level 1 is drawn

$t_b$  = time between trough or level 2 and the end of the next infusion

$t_1$  = infusion time

**Extrapolated Trough:**

$$C_{min} = (\text{Trough or Level 2})(e^{-k_e(t_b)})$$

**Volume of Distribution:**

$$V_d = \left(\frac{\text{Dose}}{k_e}\right) * \left(\frac{1 - e^{-k_e(t_1)}}{C_{max} - C_{min}}\right)$$

**Determining a New Regimen Based on Individual PK Parameters:**

$$\text{New Dose} = k_e * V_d * \text{Desired Peak} * t_1 * \frac{1 - e^{-k_e(T)}}{1 - e^{-k_e(t_1)}}$$

$$\text{Optimal Interval} = \frac{\ln\left(\frac{\text{peak}}{\text{trough}}\right)}{k_e} + t_1$$

$$\text{Estimated Peak} = \left(\frac{\text{Dose}}{k_e * V_d}\right) * \left(\frac{1 - e^{-k_e(t_1)}}{1 - e^{-k_e(T)}}\right)$$

$$\text{Estimated Trough} = \text{Estimated Peak} * e^{-k_e(T - t_1)}$$

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