Stanford Children's Health | Lucile Packard Children's Hospital Stanford

Guidelines for Aminoglycoside Use

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Authors: L. Bio, A. Frymoyer

INDICATIONS

- Treatment of certain infections caused by aminoglycoside susceptible gram-negative bacteria.
  - *Pseudomonas sp. (*not gentamicin), *E. coli*, *Klebsiella spp.*, *Enterobacter spp.*, *Serratia spp.*, etc[1,2]
- Empiric therapy for cystic fibrosis (CF) patients with a history of *P. aeruginosa* admitted for acute pulmonary exacerbation (Guidelines for Tobramycin in Children with Cystic Fibrosis)
- Gentamicin only: Synergy with a beta-lactam for the treatment of infections caused by *Enterococcus spp.*, *Staphylococcus spp.*, and viridans group streptococci (VGS)
- Off label use of amikacin for the treatment of specific nontuberculous mycobacteria (NTM)
- Surgical prophylaxis (see Surgical Prophylaxis Choices for appropriate dose regimens)

PHARMACOKINETIC (PK)/PHARMACODYNAMIC (PD) PRINCIPLES

- Aminoglycosides have limited protein binding and are hydrophilic resulting in higher volume of distribution (Vd), especially in patients with edema; decreased Vd observed in dehydration.
- Aminoglycosides exhibit concentration-dependent bactericidal activity; higher **max** serum concentrations to minimum inhibitory concentrations (MIC) ratios result in higher bactericidal activity (target C_{max}:MIC ratio of 8-10:1) while troughs correspond to toxicity.
- High-dose extended interval optimizes PK/PD and post-antibiotic effect (drug-free interval)[3]

DEFINITIONS/CALCULATIONS

- TBW: Total body weight, i.e., actual body weight
- IBW: Ideal BW, male = 50 + (2.3 ∗ $Ht\ in\ in.$ > 5 ft); female = 45 + (2.3 ∗ $Ht\ in\ in.$ > 5 ft)
- ABW: Adjusted BW = IBW + 0.4 (TBW - IBW)

THERAPEUTIC DRUG MONITORING (TDM) DEFINITIONS (see 'Target' & 'Timing' below)

- Only perform TDM if anticipated duration >48 hours; perform TDM sooner (i.e., after first dose of HDEI) for critically ill patients (e.g., vasopressor required) or if worsening renal function.
- **Peak:** Level one hour after the end of infusion **≠ Cmax** which occurs at the end of the infusion and is extrapolated based on measured peak and random or trough based on calculations and/or InsightRX
- **Trough:** Level at end of dosing interval prior to the next conventional or q8h synergy dose.
- **Random (HDEI):** Level obtained 6-14 hours after the infusion start time

DOSE ADJUSTMENT BASED ON TDM

- **Perform calculations based on PK equations, use InsightRX predictions and estimates to guide dose adjustments, or hybrid depending on the situation and reliability of InsightRX models.**
- Review 'Model Fit' indicator in InsightRX (see InsightRX tip sheets in S-drive "vanc per pharm").

MONITORING

- Recheck aminoglycoside TDM and/or serum creatinine (SCr) within 24 hours of: change in dose, 'poor' model fit within InsightRX, change in renal function/ urine output or dialysis mode, addition of nephrotoxic medication (refer to NINJA), surgical procedure or major event (e.g., ischemic event)
- Monitor renal function (e.g., SCr, urine output) at baseline and every 24 hr while inpatient, per NINJA.
- Frequency of monitoring should be based on clinical judgment; however, monitoring of aminoglycoside serum concentrations in stable patients should be twice weekly.
- Consider audiometry for exposures >7 days (see Newborn Hearing Screening for neonates); consider mitochondrial variant testing when the indication necessitates a prolonged course.

Indication-specific dosing strategies and targets (assuming normal renal function): GENTAMICIN and TOBRAMYCIN

Dosing strategy	Indication	Empiric dose*	Target (mcg/mL)	TDM Timing and Considerations
High-dose extended interval (HDEI) [3]	Optimizes PK/PD and is preferred for the treatment of gram-negative infections, unless ***exclusion criteria present:*** **neonates, dialysis, renally impaired, extensive burn**	See HSM dosing for renal adjustment All ages > 28 days: 5 – 7 mg/kg IV q24h	C_{max}: 15 – 30 Trough: < 0.3	Obtain **peak** and **random** level to perform PK calculations or random level alone with InsightRX to determine C_{max} and trough. CF patients target higher peaks with emphasis on area under the curve (AUC) see Guidelines for Tobramycin in Cystic Fibrosis
Conventional	Treatment of gram-negative bacterial infections when HDEI exclusions are present	See HSM dosing for neonatal and renal adjustment All ages > 28 days: 2.5 mg/kg/dose IV q8h	C_{max}: 6 - 12 Trough: < 0.5 to 1	Obtain **peak** and **trough at steady state after 3rd dose**; lower C_{max} target for UTI: 4 – 6 mcg/mL
Synergy [4]	Gentamicin only: see "Indications" section	All ages: 1 mg/kg IV q8h or 3 mg/kg IV q24h (VGS)	C_{max}: 3 - 4 Trough: < 1	Obtain **peak** and **trough at steady state after 3rd dose** for q8h dosing, but no target for daily dosing (e.g., 3 mg/kg IV q24h)

Indication-specific dosing strategies and targets (assuming normal renal function): AMIKACIN

Dosing strategy	Indication	Empiric dose*	Target (mcg/mL)	TDM Timing and Considerations
HDEI	Same as above for gentamicin and tobramycin	Non-CF All ages > 28 days: 15-30 mg/kg/dose IV q24h, max 1.5 gm/day	C_{max}: 20 – 80 Trough: < 2.5 or undetectable	Obtain **peak** and **random** level; however, amikacin model in InsightRX is for burn patients and should be used with caution. Higher doses of up to 40 mg/kg IV q24h may be necessary for CF.
Conventional	Same as above for gentamicin and tobramycin	Neonates: 15 mg/kg/dose every 24 to 36 hours All ages > 28 days: 7.5 mg/kg/dose IV q8h	C_{max}: 20 - 40 Trough: < 5	Obtain **peak** and **trough at steady state after 3rd dose**; trough < 10 mcg/mL may be acceptable for severe infections
NTM [5]	Treatment of *Mycobacterium avium* complex (MAC) or *M. abscessus*, in combination	All ages > 28 days: 10 - 15 mg/kg/dose IV q24h or 15 – 25 mg/kg IV thrice weekly	C_{max}: 35 - 45 (daily) or 65 - 80 (weekly) Trough: < 5	Obtain **peak** and **random** level; HDEI dosing strategy may be preferred for CF children with NTM (higher dose and peak targets above)

*** Weight-based dosing: TBW** is preferred unless underweight (i.e., TBW < IBW) then **IBW** or TBW is acceptable, or if obese (i.e., TBW > 125% of IBW), then **ABW** is preferred.

REFERENCES **1.** Krause KM, et al. Aminoglycosides: An Overview. Cold Spring Harb Perspect Med. 2016;6(6): a027029. **2.** Humphries R. AST News Update June 2023: New! CLSI M100-Ed33: Updated Aminoglycoside Breakpoints for Enterobacterales and Pseudomonas aeruginosa. **3.** Hollander EM, et al. Evaluation of Dosing Guidelines for Gentamicin in Neonates and Children. Antibiotics (Basel). 2023 Apr 25;12(5):810. **4.** Infective Endocarditis in Childhood: 2015 Update: A Scientific Statement From the American Heart Association. Circulation. 2015 Oct 13;132(15):1487-515. **5.** Daley CL, et al. Treatment of Nontuberculous Mycobacterial Pulmonary Disease. Clin Infect Dis. 2020 Aug 14;71(4):e1-e36.