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AMINOGLYCOSIDE DOSING IN ADULT PATIENTS

DETERMINATION OF INITIAL AMINOGLYCOSIDE REGIMEN:

Empiric or definitive treatment of Gram-positive endocarditis with gentamicin?

Yes →

- **Penicillin-susceptible Streptococci:** typical dose of 3 mg/kg every 24 hours
- **Enterococcus, Staphylococcus, or Penicillin-intermediate or resistant Streptococci:** typical dose of 1 mg /kg every 8-24 hours

See Gram-positive dosing and monitoring section below for recommendations in calculating dose based on dosing weight, indication and renal function

Empiric or definitive treatment of Gram-negative infection?

ICU patients should NOT be started on traditional dosing.

Tobramycin is preferred.

Yes →

Gentamicin or Tobramycin Dosing

- **Cystic fibrosis patient:** 10 mg/kg every 24 hours or prior therapeutic regimen
- **Pneumonia, sepsis or intra-ab infection**:
  - 7 mg/kg x1 dose for all ICU patients, and subsequent doses based on renal function.
  - 7mg/kg x1 dose for floor patients with severe infections. Consider reducing the dose to 5 mg/kg or selecting an alternative agent for floor patients with AKI or dialysis. Adjust the regimen based on the pathogen, renal function and patient characteristics
- **Endometritis/Chorioamnionitis:** 5 mg/kg every 24 hours
- **Surgical prophylaxis:** 5 mg/kg x1 dose
- **Complicated UTI:** 5 mg/kg x1 dose

Amikacin Dosing

- **Cystic fibrosis patient:** 20 mg/kg every 24 hours or prior therapeutic regimen
- **Complicated UTI:** 10 mg/kg x1 dose
- **All other patients:**
  - 15 mg/kg x1 dose for all ICU patients, and subsequent doses based on renal function.
  - 15 mg/kg x1 for floor patients with severe infections. Consider reducing the dose or selecting an alternative agent for floor patients with AKI or dialysis. adjust the regimen based on the pathogen, renal function and patient characteristics

EIDA dosing is preferred for most patients. See below for dosing and monitoring instructions for EIDA and traditional dosing

Empiric or definitive treatment of Mycobacterial infection.

Streptomycin therapy for Enterococcal endocarditis

Yes →

Consult ID team or ID pharmacist for appropriate goal target levels and empiric dosing recommendations.

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EXTENDED INTERVAL DOSING OF AMINOGLYCOSIDES (EIDA)

EIDA is the preferred method for dosing aminoglycosides for gram-negative infections as it offers the potential of reducing nephrotoxicity while maximizing concentration-dependent killing. EIDA is an approach that utilizes higher doses (typically > 5 mg/kg for tobramycin or > 15 mg/kg for amikacin) to help achieve target peak concentrations.

Standard EIDA should NOT be utilized in patients with Infective Endocarditis due to gram-positive organisms. See Gram-Position Synergy Section Below.

Notes:

- You should also or review the patient's past medical records/history to assess previous aminoglycoside dosing to help determine the most appropriate dose
- Round gentamicin and tobramycin doses to nearest 20 mg and amikacin doses to nearest 50 mg

DOSE CALCULATIONS:

A. Determine patient's dosing weight: (SEE FORMULAS BELOW)-
   1. Dose is based on ideal body weight (IBW) unless either of the following apply:
      a. IF less than their IBW; use total body weight (TBW).
      b. IF total body weight (TBW) exceeding ideal body weight (IBW) by > 30%, then use adjusted body weight (ABW).
      c. If patient is pregnant use adjusted body weight (ABW)

FORMULAS:

Ideal Body Weight (IBW) in kg:

$Male = 50 + (2.3 * Height\ in\ inches > 5\ feet)$

$Female = 45 + (2.3 * Height\ in\ inches > 5\ feet)$

Adjusted Body Weight (ABW) in kg:

$ABW = 0.4(TBW - IBW) + IBW$

Percent over IBW:

$$\%\ over\ IBW = \frac{TBW - IBW}{IBW} * 100$$

Serum concentration monitoring with Extended Interval Dosing of Aminoglycosides:

A. Empiric therapy: Aminoglycosides are as almost never necessary as definitive therapy. Empiric therapy targeting gram-negative pathogens should almost always be limited to 24-48 hours. As a result, pharmacists should discuss the antibiotic treatment plan with the team before ordering levels. If the patient requires more than one empiric dose, then a level should be obtained approximately 24 hours later and re-dosing can occur when level is < 0.25 mcg/mL (tobramycin) or < 4 (amikacin). At all time points, however, the need for continued dosing should be ascertained first.

B. **Definitive Therapy: Given the availability of safer and more effective options, definitive therapy with an aminoglycoside is almost never appropriate. Please consult with an Antimicrobial Stewardship pharmacist if this scenario is encountered.**
   1. **In general, 2 levels are encouraged, with the goal of** targeting serum peaks of 8-10 times the MIC of the targeted organism and troughs < 0.25 mcg/mL (tobramycin) or < 4 mcg/mL (amikacin).
      a. In patients with renal insufficiency, this may not be possible unless dosing > 48 hours, which is discouraged.
      b. **ICU patients** have profound shifts in fluid status and renal function. The calculated volume of distribution (Vd) may be large, but doses > 7 mg/kg are generally discouraged. Doses > 7mg/kg should be used with caution, and clinical judgment should be applied when evaluating levels and determining subsequent dosing in ICU patients.

c. **Cystic fibrosis patients** on aminoglycoside definitive therapy should obtain 2 levels to ensure target levels are obtained. Subsequent monitoring can include 1 level at 18-24 hours to ensure clearance. Anytime significant changes in renal function or fluid status occur, 2 levels could be considered to ensure the regimen is safe and effective.

C. **Patients with acute renal insufficiency or dialysis.** Patients with severe sepsis with suspected GNR sepsis should be given a single 7 mg/kg dose. Providing a safe and effective dose to treat GNR infections is not possible in most dialysis patients or patients with AKI, and the pharmacist is encouraged to discuss alternative antimicrobial options with the primary team. If therapy is needed, pharmacists should try to achieve peaks of 8-10x MIC if possible (with 5-7 mg/kg), and trough < 0.25 within 72 hours of the dose. If clearance of aminoglycosides is expected to take longer than 72 hours to drop levels < 0.25, then the dose should be reduced below 5-7 mg/kg. Draw levels > 2 hours after HD to allow for re-distribution.

D. Subsequent monitoring of levels depends on the indication for aminoglycoside therapy, patient clinical status, renal function, and initial serum concentrations; serum concentrations should be monitored every 1-7 days.
1. Recommend obtaining levels every 1-3 days in patients with changing fluid status or renal function.
2. Recommend obtaining levels every 5-7 days in patients with stable fluid status and renal function requiring long-term therapy, after initial level(s) are therapeutic. Patients with stable renal function and fluid status can transition to trough monitoring after the establishment of therapeutic regimen based on 2-levels.

GRAM POSITIVE DOSING OF AMINOGLYCOSIDES (TDA)

Recommended only for patients where the aminoglycoside is being used for gram-positive synergy.

DOSE CALCULATIONS:

A. Determine patient's dosing weight: (**SEE FORMULAS BELOW**)
1. Dose is based on ideal body weight (IBW) unless either of the following apply:
   a. IF less than their IBW; use total body weight (TBW).
   b. IF total body weight (TBW) exceeding ideal body weight (IBW) by > 30%, then use adjusted body weight (ABW).

B. Dose based on dosing weight:
1. For **synergistic treatment for gram-positive infections:**

Gram-Positive Bacteria			
Bacteria	MIC	Gentamicin Dose	Goal
Viridans group streptococci OR Streptococcus gallolyticus (bovis)	PCN < 0.5	3 mg/kg q24h	1 mcg/mL (trough)
	PCN ≥ 0.5	1 mg/kg*	3-5 mcg/mL (peak) < 1 mcg/mL (trough)
Enterococcus Spp.	Resistant to PCN	1 mg/kg*	3-5 mcg/mL (peak) < 1 mcg/mL (trough)

**Dosing interval based on chart below

a. Gentamicin 1 mg/kg (per dosing weight) – round to nearest 20 mg or streptomycin 2.5 mg/kg – round to nearest 50 mg. Dosing interval recommendations in section C.

b. Gentamicin 3 mg/kg (per dosing weight) q24h – round to nearest 20 mg. NOTE: this strategy should only be utilized in patients with adequate renal function (> 40 mL/min) as to enable q24h dosing. Do NOT follow the dosing interval suggestions in C below for this strategy.
c. For amikacin 5 mg/kg (per dosing weight) – round dose to the nearest 50 mg.

C. Dosing Interval Determination:

The suggested dosage of aminoglycosides depends on target serum concentrations, renal status and volume status. In a patient with normal volume status, the dose may be adjusted for renal function according to the following guidelines:

Select interval based on CrCl from the table below.

CrCl	Dosing Interval (hr)
> 50	8
50-30	12
29-10	24
< 10	48* Dosing per Therapeutic Drug Monitoring
HD	Three-times weekly post-HD
CRRT	24

D. Dialysis patients can typically receive a dose following each HD sessions when treating gram-positive pathogens to achieve target levels described above.

Serum concentration monitoring with Traditional Dosing of Aminoglycosides:

- Reference ranges for levels are noted below
    - Monitor kidney function (BUN/SCr, UOP daily)
    - Peak and trough concentrations should be monitored in patients receiving Traditional Dosing of Aminoglycosides. Order peak and trough around the 4th dose. If levels are not appropriate, dose adjustments should be based on a pharmacokinetic analysis based on the two levels.
    - Subsequent monitoring of levels depends on the indication for aminoglycoside therapy, patient clinical status, renal function, and initial serum concentrations; serum concentrations should be monitored every 3-7 days.
        - In ALL cases, dosing and frequency of monitoring requires assessment of the patient, indication for therapy, assessment of potential risk factors for treatment failure and/or toxicity, and clinical judgment.
        - Recommend obtaining levels every 2-3 days in patients with changing fluid status or renal function.
        - Recommend obtaining levels every 5-7 days in patients with stable fluid status and renal function requiring long-term therapy, after established therapeutic levels on current regimen.

Reference ranges for gentamicin, tobramycin and amikacin for TRADITIONAL dosing:

	Therapeutic goal concentrations	
Gentamicin/Tobramycin	Goal peak (mcg/mL)	Goal peak (mcg/mL)
Gram positive synergy	3-5 (1 mg/kg) N/A (3 mg/kg)	< 1
Pneumonia, bacteremia, sepsis, cystic fibrosis	8-10	< 2

	Therapeutic goal concentrations	
Amikacin	Goal peak (mcg/mL)	Goal peak (mcg/mL)
Pneumonia, bacteremia, sepsis, cystic fibrosis	25-35	< 8

	Therapeutic goal concentrations	
Streptomycin	Goal peak (mcg/mL)	Goal peak (mcg/mL)
Gram positive synergy	15-25	< 5

Assessing and/or Adjusting a dose based on 2 serum concentrations (traditional dosing and extended-interval dosing):

Option 1: PK Calculator

https://www.med.umich.edu/asp/misc/UMich_PK_Calculator.xlsx

Option 2: Manual Calculation

τ = dosing interval (hours)

k_e = elimination rate constant (hr^{-1})

t_{inf} = time of infusion (hours)

Step 1: Calculate k_e and half-life using patient-specific data/levels

$$k_e(hr^{-1}) = \frac{\ln\left(\frac{C_1}{C_2}\right)}{\Delta t} \qquad t_{1/2} = \frac{0.693}{k_e}$$

Step 2: Back-calculate C_{pss} and C_{min} (remember, C_{pss} is concentration at 30-minutes after 30-minute infusion, or at the end of a 1-hour infusion). The below equation can be utilized to calculate any concentration (including peak, trough, 18-hour, etc.).

$$C_2 = C_1 e^{-k_e(\Delta t)}; \qquad \Delta t = time\ between\ C_1\ and\ C_2\ (hours)$$

IMPORTANT: C_1 MUST be a HIGHER concentration than C_2 for this equation to be accurate.

Step 3: If levels are within desired ranges, no changes needed. If not, calculate a new dose and/or interval using patient-specific data. In general, when utilizing EIDA regimens, dosing frequency should allow for a drug-free period (i.e., undetectable trough) of 6 – 8 hours. In rare cases, a frequency less than 24 hours may be calculated for a patient receiving extended interval dosing. If this is the case, contact the ID pharmacist on call for additional guidance.

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