

Guidelines for monitoring aminoglycoside concentrations in adults

I. Why obtain concentrations of aminoglycosides?

Given the well-established inter- and intra- patient variability in pharmacokinetic processing, as well as the known association between toxicity and exposure, serum concentration is performed:

- A. To optimize dosing based on the indication
- B. To monitor for drug accumulation if renal function declines
- C. To ensure the aminoglycoside is still therapeutic if renal function improves

Note that the standard of care for aminoglycosides warrants monitoring of both renal function parameters (eg, serum creatinine, blood urea nitrogen, urine output) and serum concentrations; monitoring only one or the other is unacceptable.

II. What is the most appropriate timing to obtain an aminoglycoside concentration?

- A. Both peaks and troughs should be obtained for most infections requiring aminoglycoside therapy, except with extended interval dosing (see below)
 - a) Achieving a target peak optimizes microbiologic activity
 - b) Achieving a target trough minimizes risk of toxicity
- B. Optimal peaks are obtained 30-60 minutes after the end of the infusion
- C. Optimal troughs are obtained within 30 minutes before the next dose
- D. Acceptable peaks are obtained 60-120 minutes after the end of the infusion
- E. Acceptable troughs are obtained 30-60 minutes before the next dose
- F. If measuring concentrations with an initial or new dosing regimen, the clinician should evaluate the regimen with regard to steady state pharmacokinetics. Steady state is usually achieved by the 4th dose of a regimen if renal function and fluid status have not changed markedly during that period. A peak-trough pair should be obtained around or after this 4th dose.

III. What is the target trough for gentamicin and tobramycin (traditional dosing)?

- A. Pneumonia, bacteremia, abdominal infection: 0.5-2mg/L (around 1mg/L is preferred)
- B. All other infections: 0.5-1mg/L

IV. What is the target trough for amikacin (traditional dosing)?

- A. All infections: 2-4mg/L

V. What is the target peak for gentamicin and tobramycin (traditional dosing)?

Note that while peak concentrations should be obtained in the time frames shown in II above, it is common practice to adjust regimens to target end-of-infusion (C_{max}) concentrations in the ranges described below.

- A. UTI: 3-5mg/L
- B. Pneumonia: 8-10mg/L
- C. Bacteremia and abdominal infection: 6-8mg/L
- D. Sepsis from urinary source, cellulitis: 5-7mg/L
- E. Gram positive synergy, e.g. combining gentamicin with ampicillin or vancomycin for enterococcal endocarditis: 3-4mg/L

VI. What is the target peak for amikacin (traditional dosing)?

Note that while peak concentrations should be obtained in the time frames shown in II above, it is common practice to adjust regimens to target end-of-infusion (C_{max}) concentrations in the ranges described below.

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- A. UTI: 15-20mg/L
- B. Pneumonia: 27-30mg/L
- C. Bacteremia, abdominal infection, and cellulitis: 25-30mg/L
- E. Sepsis from urinary source: 20-25mg/L

VII. How should aminoglycoside peak-trough pairs be evaluated to determine an individualized dose?

- A. Serum concentrations, their timing, and patient parameters should be evaluated to determine elimination rate constant (k_e) and volume of distribution (V_d) using equations describing intermittent infusion pharmacokinetics (ie, Sawchuck-Zaske method). Using those parameters, a new individualized regimen should be designed that is predicted to achieve the infection-specific concentrations desired.
- B. When using pharmacokinetic equations, it is unacceptable to “plug-in” population V_d and k_e parameters without first evaluating patient-specific values using the serum concentrations obtained.
- C. It is unacceptable to evaluate the peak-trough pair and adjust regimens by superficial comparison with the target ranges.

VIII. How often should aminoglycoside concentrations be obtained?

- A. If an aminoglycoside will be part of ongoing therapy, a steady-state peak and trough should be documented to support definitive dosing. Monitoring troughs alone is unacceptable.
- B. Concentrations should be obtained if renal function changes (better or worse) or if there is suspicion of aminoglycoside toxicity
- C. Concentrations should be obtained at steady state after a dose change to document appropriateness of the new dose
- D. If a long duration of therapy is expected (eg, 3-6 weeks) and all clinical parameters are stable, a peak and trough should be obtained at least once weekly

IX. Extended Interval Dosing of Aminoglycosides, a.k.a. “Once Daily Aminoglycoside Dosing”

- A. Peaks and troughs should not be obtained
- B. A random concentration should be obtained within 6 – 14 hours after the start of the extended interval dose. It is acceptable to obtain this concentration after the first dose.
- C. The random concentration should be plotted on the appropriate nomogram specific for the drug and dose prescribed (see WFBH Antimicrobial Dosing Guide)
- D. If the plotted concentration falls below the nomogram line, the dose is validated and the patient should continue to receive the drug as prescribed
- E. If the plotted concentration falls above the line, the patient’s aminoglycoside should be converted to traditional dosing
- F. If a long duration of therapy is expected (eg, 3-6 weeks) and all clinical parameters are stable, a random concentration at 6 – 14 hours after the start of the infusion should be

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- obtained at least once weekly. This concentration should be plotted on the appropriate nomogram to determine ongoing use of extended interval dosing
- G. Extended interval dosing using gentamicin 3mg/kg Q24h is an option only for gram positive synergy in streptococcal endocarditis. A nomogram for this dose does not exist. Monitoring concentrations pre-dose to document absence of accumulation is reasonable in this setting, with verification of the administration of the previous dose. Alternatively, two post-dose concentrations may be drawn. Of note, gram positive synergy for enterococcal and staphylococcal endocarditis are not eligible for the 3mg/kg Q24h dosing strategy and should be dosed 3mg/kg divided into equal doses for patients with normal renal function and administered 2-3 times daily
 - H. When using extended interval dosing, if a Q24h dose is not validated by the nomogram, changing the interval to Q36h or Q48h is not preferred due to a relative paucity of data supporting these intervals compared with Q24h.

X. Measuring concentrations among patients receiving renal replacement therapy

- A. Intermittent hemodialysis (HD)
 - a) A “standard” HD session will remove approximately 50% of the pre-dialysis aminoglycoside concentration. However, removal is variable.
 - b) Alternate gram-negative therapy should be considered because doses sufficient to achieve higher peak targets (V, VI above) may not be adequately cleared by a single HD session.
 - c) For patients receiving a standard HD session, obtaining a pre-HD concentration is preferred in order to avoid distributional effects of HD
 - d) In order to avoid accumulation, a post-HD trough of approximately 2mcg/mL (gentamicin or tobramycin) or 6-8mcg/mL (amikacin) is acceptable
- B. Continuous renal replacement therapy (CRRT)
 - a) CRRT results in aminoglycoside elimination that is equivalent to a creatinine clearance of 30-40mL/min
 - b) Obtaining a random concentration 24 hours after a dose is reasonable until a dosing pattern is established; often times, the required dosing interval will be every 24-48 hours
 - c) Frequent interruptions in CRRT of more than 2 hours may produce an inconsistent pattern of concentrations, resulting in the need for variable intervals

XI. Monitoring for toxicity

- A. If the anticipated duration of aminoglycoside therapy is >2 weeks, audiometry should be performed at baseline and every 1-2 weeks during therapy
- B. A basic metabolic panel or comprehensive metabolic panel should be obtained at least 2-3 times per week to assess renal function

XII. Caveats about monitoring aminoglycoside concentrations

- A. Concentrations may be falsely elevated if the sample is drawn inappropriately:
 - a) When the sample is drawn through the same line used to infuse the aminoglycoside
 - b) When the sample is drawn “downstream” from the infusion site
 - c) When the sample is drawn too soon after the end of the infusion, (i.e, before the drug has had time to distribute)

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- B. Concentrations must be interpreted carefully in patients with extreme fluid shifts or rapidly changing renal function, eg, severe sepsis
 - a) Initial concentrations may be low due to a large volume of distribution (not due to rapid clearance)
 - b) After therapeutic concentrations are achieved, elimination may be slower than expected due to impaired renal function
- C. Concentration monitoring of conventional regimens prior to steady state
Pharmacokinetic evaluation of aminoglycoside regimens before steady state is possible following a first dose, but should be reserved for situations in which the benefits of the clinical information gained outweigh the known limited precision of such studies.
 - a) Determine an appropriate loading dose based on the patient's expected volume of distribution
 - b) Obtain a peak concentration 1-2 hours after the end of the loading dose infusion
 - c) Obtain a random concentration 8-12 hours after the peak
 - d) Use these two concentrations to determine k_e . Use the back-extrapolated C_{max} and the pre-dose concentration (presumably 0mg/L) to calculate V_d . Use these to determine an appropriate patient-specific dosing strategy.