Aminoglycoside Dosing and Monitoring Clinical Practice Guideline

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Introduction

This document covers the intravenous (IV) use of gentamicin, tobramycin, and amikacin, and is intended to assist the clinical pharmacist in the safe and effective dosing of these antibiotics.

Aminoglycosides exhibit concentration-dependent bactericidal activity by irreversibly binding bacterial 16s ribosomal RNA, thus inhibiting bacterial protein synthesis and leading to cell death. They also have a marked post-antibiotic effect: Bacteria are killed by initial high concentrations of the medication, but bacterial growth remains suppressed for a time after the drug concentration falls below the bacteria's minimum inhibitory concentration (MIC). Aminoglycosides are broad-spectrum antibiotics primarily effective against Gram-negative organisms, however, they can also be utilized with another agent (typically a penicillin or cephalosporin) for a synergistic effect when treating serious Gram-positive infections such as endocarditis.

Aminoglycoside antibiotics are excreted almost exclusively in the urine, and are not metabolized in the liver. Given their hydrophilic nature, they do not distribute well into bile, adipose tissue, sputum, abscesses, or cerebrospinal fluid.

Side effects of aminoglycoside antibiotics include nephrotoxicity and ototoxicity. Nephrotoxicity may be reversible, but hearing loss, vertigo, and/or balance issues (ototoxicity) are not. In order to promote the safe and effective use of aminoglycoside antibiotics, pharmacokinetic monitoring is necessary.

A note on terminology used in this document: "Peak" will refer to the maximum *measured* value of a medication, while "C_{max}" will refer to the *calculated/extrapolated* value after pharmacokinetic analysis. Similarly, "trough" will refer to the measured value, while "C_{min}" will refer to the calculated/ extrapolated value. The two terms are sometimes be used interchangeably, but the distinction can be important for the purposes of analysis and documentation.

Using This Document and Scope of Practice

Sections below are designed to guide the pharmacist through the aminoglycoside monitoring process from initial order verification and empiric dosing recommendations, through documentation and order modification following serum level monitoring.

Empiric dosing recommendations are provided in this guideline. Deviations from this guideline on initial verification should be discussed with the ordering provider prior to verification and documented in an iVent with sound justification. Reasons a pharmacist may suggest a deviation from empiric dosing recommendations in this guideline include (but are not limited to): Severity of illness, expected trajectory of renal function, prior use of the medication in question, additional nephrotoxic medications, or provider preference.

Once the initial order is processed, the pharmacist may order laboratory tests as outlined in the Pharmacy Department Policy and Procedure document to aid in clinical monitoring and decision making.

When performing therapeutic drug monitoring, the pharmacist has the authority to make dosing modifications per protocol following the assessment of serum drug levels and publication of a progress note. Any adjustments should be justified in said note, and should take into account patient clinical status, indication, goal levels, culture results, and other relevant clinical factors that aided in the pharmacist's decision-making process. Discussion with the primary team may also occur as necessary to assist in clinical decision making.

When levels are unexpectedly high or low, the pharmacist must investigate potential reasons for the level and act as necessary to minimize risk to the patient. Reasons for unexpectedly high or low levels can include (but are not limited to) true toxicity, missed or delayed doses, procedures, blood loss, collection timing error, or medication present in the line/sampling error. The pharmacist has the authority to repeat a level as necessary to determine the cause for the aberrant level and to aid in determination of next steps.

Any orders placed by the pharmacist following pharmacokinetic assessment of levels should be done "**Per Protocol**." Initial recommendations made to the provider to direct empiric therapy must be entered on behalf of the provider, or the provider may elect to adjust the initial order based on the pharmacist's recommendations.

Gentamicin/Tobramycin

Gentamicin and tobramycin are dosed and monitored the same, and are thus listed together below.

Extended-interval dosing is preferred for patients over 90 days and 2kg unless the medication is specifically used for synergy, in Cystic Fibrosis patients, or otherwise contraindicated (CrCl <50mL/min/1.73m2, ECMO, Burns >20% BSA, ascites or liver failure, evidence or concern for decreased end-organ perfusion, or pregnancy). Refer to the Renal Dosing Chart for empiric dosing adjustments when CrCl falls below 50mL/min/1.73m2.

A note on CNS infections: While aminoglycosides do not penetrate the blood-brain barrier well due to their hydrophilic nature, they will be ordered at times in addition to a penicillin/cephalosporin for a patient with a CNS infection. This is not synergy, but **double coverage**, and should therefore be dosed as a standard or extended-interval aminoglycoside. *Synergy dosing will not yield sufficient CNS levels*.

Extended Interval Dosing (Unless Contraindicated)

	Gentamicin/Tobramycin		
CrCl	**Regimen**	**C_{max}**	**C_{min}**
≥50	7.5mg/kg q24hr	18-30	See below
<50	Contraindicated	X	X

Traditional Dosing: See the Renal Dosing Chart for Empiric Adjustments in Renal Impairment

Gentamicin/Tobramycin				
Age	**Weight**	**Regimen**	**Target C_{max}**	**Target C_{min}**
<28 days	<1.2 kg	4.5mg/kg q36hr	6-10 mcg/mL	< 1 mcg/mL
	≥1.2 kg	4mg/kg q24hr*		
>28 days	< 2 kg	4mg/kg q24hr*		
28-90 days	≥2 kg	3.75mg/kg q12hr		
>90 days	>2kg	2.5mg/kg q8hr		

*If therapeutic cooling for hypoxic-ischemic encephalopathy (HIE), increase frequency to q36hr

Synergy: See the Renal Dosing Chart for Empric Adjustments in Renal Impairment

	Gentamicin/Tobramycin	**Desired Target**	
Age	**Empiric Dosing Regimen**	**C_{max}**	**C_{min}**
Neonate or <2kg	Refer to traditional dosing	Refer to traditional targets	
30-90 days	1.5mg/kg IV q12hr	3-4 mcg/mL	< 1 mcg/mL
>90 days	1mg/kg IV q8hr		

Cystic Fibrosis: See the Renal Dosing Chart for Empiric Adjustments in Renal Impairment

	Gentamicin/Tobramycin		
CrCl	**Regimen**	**C_{max}**	**C_{min}**
>50	10mg/kg q24hr	20-40 mcg/mL	See below

Therapeutic Drug Monitoring for Gentamicin and Tobramycin:

- Routine turnaround time: 1-3 hours for a serum level
- When to check first levels^:
    - **Extended interval or Cystic Fibrosis**: Following 2nd dose (Peak and Midpoint)
    - **Standard interval**: Following 4th dose (Peak and Trough^^)
    - **Neonatal patient**: Following 3rd dose (Peak and Trough^^)
    - **Synergy**: Following 4th dose (Peak and Trough^^)
    - Peak 30-90min following dose, Midpoint 4-8 hours after peaks, trough 0-30min before dose
    - See Kinetics Level Ordering Guide in Q:/Pharmacy/Clinical Drug Information/Kinetics

^Levels may be checked sooner if clinically indicated per pharmacist judgement
^^<u>If judged to be at steady state</u>, a pharmacist may elect to order a trough before and peak after a single dose OR a peak and trough following the same dose administration.

Therapeutic Drug Targets – Gentamicin or Tobramycin		
	Peak (mcg/mL)	**Trough (mcg/mL)**
Extended Interval	18-30	< 1 at 6 hours prior to next dose administration
Standard Interval or Neonatal Patient	6-10	< 1
Cystic Fibrosis	20-40	< 1 at least 6 hours prior to next administration
Synergy (not CNS)	3-4	< 1

- When to repeat levels:
    - Following dose adjustments when new steady state is achieved
    - With clinical status changes (indication, renal function, cardiac support, etc.)
    - No more than one week has passed since previous level assessment
    - What levels to repeat:
        - Peak only if significant change to volume of distribution or target concentrations
        - Trough to assess clearance for **standard interval, synergy, or neonatal use**
        - Clearance level 6 hours before next dose for **cystic fibrosis** or **extended interval**
            - Target level less than 1mcg/mL – undetectable OK

- How to adjust gentamicin/tobramycin regimen for levels:
    - **<u>Peak and trough in range:</u>** No changes are typically needed
    - **<u>Peak in range, trough out of range:</u>** Typically adjust interval; keep same dose. The maximum interval/frequency = 8 hours.
        - Adjustments to frequency will have a small effect on the peak, but not as much as changes to dose.
    - **<u>Peak out of range, trough in range:</u>** Typically adjust dose; keep same interval.
        - Dose adjustments are usually proportional to the percentage of desired change to the measured peak (e.g. a 10% increase in dose results in roughly 10% change to peak). Adjustments to dose will also have a small effect on trough.
    - **<u>Peak AND trough out of range:</u>** Changes to dose and/or interval may both be required

Amikacin

Amikacin dosing and target levels are roughly 3x that of gentamicin/tobramycin dosing and target levels. There is no data on the use of amikacin for synergy at this time.

Extended-interval dosing is preferred for patients over 90 days and 2kg unless specifically used for Cystic Fibrosis patients or otherwise contraindicated (CrCl <50mL/min/1.73m2, ECMO, Burns >20% BSA, ascites or liver failure, evidence or concern for decreased end-organ perfusion, or pregnancy). Refer to the Renal Dosing Chart when CrCl falls below 50mL/min/1.73m2.

Extended Interval Dosing (Unless Contraindicated)

	Amikacin		
CrCl	**Regimen**	**C_{max}**	**C_{min}**
≥50	22.5mg/kg q24 hr	20-80 mcg/mL	See below
<50	Contraindicated	X	X

Traditional Dosing: See the Renal Dosing Chart for Empric Adjustments in Renal Impairment

Amikacin				
Age	**Weight**	**Regimen**	**Target C_{max}**	**Target C_{min}**
<28 days	<1.2 kg	13.5mg/kg q36hr	20-40mcg/mL	<5mcg/mL
	≥1.2 kg	12mg/kg q24hr*		
>28 days	< 2 kg	12mg/kg q24hr*		
28-90 days	≥2 kg	11.25mg/kg q12hr		
>90 days	>2kg	7.5mg/kg q8hr		

*If therapeutic cooling for hypoxic-ischemic encephalopathy (HIE), increase frequency to q36hr

Cystic Fibrosis: See the Renal Dosing Chart for Empric Adjustments in Renal Impairment

	Amikacin		
CrCl	**Regimen**	**C_{max}**	**C_{min}**
>50	30mg/kg q24 hr	40-80 mcg/mL	See below

Therapeutic Drug Monitoring (TDM) for Amikacin:

- Routine turnaround time: 4 hours for a serum level (local send-out)
- When to check first levels^:
    - **Extended interval or Cystic Fibrosis**: Following 2nd dose (Peak and Midpoint)
    - **Standard interval**: Following 4th dose (Peak and Trough^^)
    - **Neonatal patient**: Following 3rd dose (Peak and Trough^^)
- Peak 30-90min following dose, Midpoint 4-8 hours after peaks, trough 0-30min before dose
    - See Kinetics Level Ordering Guide in Q:/Pharmacy/Clinical Drug Information/Kinetics

^Levels may be checked sooner if clinically indicated per pharmacist judgement
^^<u>If judged to be at steady state</u>, a pharmacist may elect to order a trough before and peak after a single dose OR a peak and trough following the same dose administration.

Therapeutic Drug Targets – Amikacin		
	Target Peak (mcg/mL)	**Target Trough (mcg/mL)**
Extended Interval	20-80	Undetectable at 6 hours prior to next dose administration
Standard Interval or Neonatal Patient	20-40	< 5
Cystic Fibrosis	40-80	< 5 at least 6 hours prior to next administration

- When to repeat levels:
    - Following dose adjustments when new steady state is achieved
    - With clinical status changes (indication, renal function, cardiac support, etc.)
    - No more than one week has passed since previous level assessment
    - What levels to repeat:
        - Peak only if significant change to volume of distribution or target concentrations
        - Trough to assess clearance for **standard interval or neonatal use**
        - Clearance level 6 hours before next dose for **cystic fibrosis** or **extended interval**
            - Target level less than 5mcg/mL – undetectable OK
- How to adjust amikacin regimen for levels:
    - **<u>Peak and trough in range:</u>** No changes are typically needed
    - **<u>Peak in range, trough out of range:</u>** Typically adjust interval; keep same dose. The maximum interval/frequency = 8 hours.
        - Adjustments to frequency will have a small effect on the peak, but not as much as changes to dose.
    - **<u>Peak out of range, trough in range:</u>** Typically adjust dose; keep same interval.
        - Dose adjustments are usually proportional to the percentage of desired change to the measured peak (e.g. a 10% increase in dose results in roughly 10% change to peak). Adjustments to dose will also have a small effect on trough.
    - **<u>Peak AND trough out of range:</u>** Changes to dose and/or interval may both be required

Dialysis

Systemic aminoglycoside use in dialysis patients is rare due to the pharmacokinetics of these medications. The Renal Dosing Chart will guide the pharmacist to dose an aminoglycoside at 100% of a given dose (at standard interval dosing), with therapeutic drug monitoring dictating the frequency of administration. The frequency may meet or exceed the frequency of extended interval dosing, but the higher doses of true extended interval dosing can lead to toxicity in dialysis patients.

When aminoglycoside orders are placed for a patient on any form of dialysis, the pharmacist should:

- Modify the order frequency to "once"
- Enter an aminoglycoside placeholder order
- Order a peak level for 2-4 hours following the dose, or immediately before the next intermittent hemodialysis session, if applicable
- Order a trough level for one of the following:
    - 2 hours following the next intermittent hemodialysis session
    - 12-24 hours into continuous renal replacement therapy
    - 2-4 hours following peritoneal dialysate fluid change
- Gentamicin and Tobramycin are safe to re-administer when a level is below 2mcg/mL
- Amikacin is safe to re-administer when a level is below 5mcg/mL

Obesity

- Due to their hydrophilic chemical composition, aminoglycoside antibiotics are not well distributed into adipose tissue. For this reason, when a patient's Body Mass Index (BMI) exceeds the 95th percentile for age, an adjusted body weight should be used to determine initial, empiric dosing of aminoglycosides.
- Please see the Obesity Medication Dosing Guide on Children's Connect for specific formulas to calculate a patient's Adjusted Body Weight.

References

- Gentamicin. Lexi-drugs. Lexicomp Online. Lexicomp; 2023. Accessed 8/13/2023. http://online.lexi.com
- Tobramycin. Lexi-drugs. Lexicomp Online. Lexicomp; 2023. Accessed 8/13/2023. http://online.lexi.com
- Amikacin. Lexi-drugs. Lexicomp Online. Lexicomp; 2023. Accessed 8/13/2023. http://online.lexi.com
- Stankowicz MS, Ibrahim J, Brown DL. Once-daily aminoglycoside dosing: An update on current literature. Am J Health-Syst Pharm 2015;72:1357-1364.
- Jenh AM, Tamma PD, Milstone AM. Extended-interval aminoglycoside dosing in pediatrics. Pediatr Infect Dis J 2011;30(4)338-339.
- Lopez SA et al. Extended-interval gentamicin: Population pharmacokinetics in pediatric critical illness. Pediatr Crit Care Med 2010;11(2)267-274.
- Baddour LM et al. Infective endocarditis in adults: Diagnosis, antimicrobial therapy, and management of complications. A scientific statement for healthcare professionals from the American Heart Association. Circulation 2015;132:1435-1486.
- Contopoulos-Ioannidis DG et al. Extended-interval aminoglycoside administration for children: A meta-analysis. Pediatrics 114(1)111-118.
- Kendrick JG, Carr RR, Ensom MHH. Pediatric Obesity: Pharmacokinetics and implications for drug dosing. Clin Ther 37(9)1897-1923.
- Kimberlin DW et al. "Tables of antibacterial drug dosages", Red Book: 2021-2024 Report of the Committee of Infectious diseases, Committee on Infectious Disease, American Academy of Pediatrics. 2021
- Moffett et al. The "ideal" body weight for pediatric gentamicin dosing in the era of obesity: A population pharmacokinetic analysis. Ther Drug Monit 40(3)322-329.
- Natale et al. Pediatric obesity: Pharmacokinetic alterations and effects on antimicrobial dosing. Pharmacotherapy 37(3)361-378.

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