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Saudi Commission for Health Specialties

Aminoglycoside Clinical Pathway (for Adults)

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Saudi Society of Clinical Pharmacy
الجمعية السعودية للصيدلة الإكلينيكية

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Disclaimer:

The information included in this document has been adapted and compiled from various international sources and guidelines.

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Aminoglycoside Clinical Pathway (for Adults)

October 2020 Edition

LIST OF TABLES AND FIGURES

ABBREVIATIONS

Sl. no.	Abbreviation	Full form
01	AG	Aminoglycosides
02	IBW	Ideal body weight
03	AdBW	Adjusted body weight
04	ABW	Actual body weight
05	SrCr	Serum creatinine
06	CrCl	Creatinine clearance
07	PB	Protein binding
08	PK	Pharmacokinetic
09	IM	Intramuscular
10	HD	Hemodialysis
11	CRRT	Continuous renal replacement therapy
12	LD	Loading dose
13	MD	Maintenance dose
14	TDM	Therapeutic drug monitoring
15	MIC	Minimum inhibitory concentration
16	ESRD	End-stage renal disease
17	Ke	Elimination rate constant
18	$T_{1/2}$	Half-life
19	SS	Steady state
20	PAE	Post-antibiotic effect
21	IV	Intravenous

PURPOSE

This document provides guidance for the safe and effective use of aminoglycoside antibiotics in hospital settings. This clinical pathway is intended for use by all health care providers to ensure efficacy and prevent toxicity of commonly used intravenous aminoglycosides.

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INTRODUCTION TO THERAPEUTIC DRUG MONITORING

Pharmacologic category:
Aminoglycoside (AG)

Mechanism of action:
Interferes with bacterial protein synthesis by binding to 30S and 50S ribosomal subunits resulting in a defective bacterial cell membrane

Targeted audience:
Physicians in secondary and tertiary hospitals, clinical pharmacists, nurses

Impact of vancomycin therapeutic drug monitoring (TDM):
In the absence of a pharmacokinetic monitoring service, 40% of peak AG concentrations are subtherapeutic being below 4.0 µg/mL (mg/L) and about 15% of trough concentrations are potentially toxic, exceeding 2.0 µg/mL. Over approximately a 10-year period, the incidence of nephrotoxicity decreased from about 30% to 8% due to proper AG TDM

Side effects:
- Nephrotoxicity: (could be reversible) decreased creatinine clearance, decreased urine specific gravity, increased blood urea nitrogen, increased serum creatinine, polyuria, renal failure (high trough serum concentrations), renal tubular necrosis
- Ototoxicity: (usually irreversible) auditory impairment, hearing loss (associated with persistently increased serum concentrations; early toxicity usually affects high-pitched sound), tinnitus
- Others: neuromuscular blockade, edema, hypertension, hypotension, phlebitis, thrombophlebitis, hepatomegaly, increased liver enzymes, agranulocytosis, anemia, eosinophilia, granulocytopenia, leukopenia, purpura, thrombocytopenia

Spectrum of activity:
- Used to treat wide range of aerobic gram-negative bacilli including *Pseudomonas aeruginosa.*
- Used in combination for gram-positive synergy *(Staphylococcus aureus* and *Enterococcus spp.)*
- Some have coverage against mycobacteria (amikacin, streptomycin)

Monitoring:
Urinalysis, urine output, BUN, serum creatinine, plasma AG levels (as appropriate to dosing method)

Drug/drug interaction:
- Avoid concomitant use with agalsidase alfa, ataluren, BCG (intravesical) and cholera. Antibiotics may diminish the therapeutic effect of BCG, cholera vaccine, and foscarnet
- Certain medications may increase the risk of renal toxicity with AG, such as diuretics, colistin, radiographic contrast agent, ACE-Is, NSAIDs, amphotericin, and cisplatin

INTRODUCTION TO THERAPEUTIC DRUG MONITORING

Administration: amikacin and tobramycin

IV infuse over 30–60 minutes
IM in large muscle mass

Mechanism of action:

IV infuse over 30–120 minutes
IM deep IM if possible

- AG can be administered intrathecally, in patients with severe infection – not FDA approved
- Cost of amikacin: 100 mg vial: 20–28 SAR 500 mg vial: 33–125 SAR
- Cost of gentamicin: 20 mg vial: 26 SAR 80 mg vial: 67 SAR
- Cost of tobramycin: 20 mg vial: 38.9 SAR

Definitions:

- **Peak level:**
  The highest serum drug concentration that occurs following a single dose or at SS within a dosing interval
- **Trough level:**
  - The lowest drug concentration during a dosing interval when drug is given intermittently
  - The trough concentration generally occurs immediately before administration of the next dose
- **Random level:**
  A sample that may be collected at any time, irrelevant to the dose can be used in some situation to do pharmacokinetic calculations or when trough level cannot be predicted (in situation like acute kidney injury or fluctuating renal function)
- **Total drug level:**
  The sum of unbound and bound drug in serum or plasma
- **Free drug level:**
  - The amount of unbound drug in serum or plasma
  - Only fraction is available to act on the target tissues

Indications for TDM:

- Using AG for more than 3 days
- Drug monitoring is costly; it should be considered only when the following criteria are met:
  - Drug has narrow therapeutic range
  - There is a direct relationship between the drug levels and its pharmacological or toxic effects
  - The drug effects cannot be assessed only by clinical monitoring
  - Large individual variability in plasma concentration exits at a given dose
  - Availability of appropriate analytic techniques

INTRODUCTION TO THERAPEUTIC DRUG MONITORING

Pharmacokinetic parameters

Half-life ($T_{1/2}$)

- Definition: The time required for the concentration of the drug in the plasma to be reduced to one half of its initial value
- Depends on the drug volume of distribution and clearance
- Determines the time to reach a steady state level

Protein binding (PB)

- For any drug, pharmacologic activity depends only on the free drug concentration
- Changes in PB may significantly affect interpretation of reported levels for drug that are highly protein-bound

Metabolism

- Most drugs are metabolized via hepatic enzymes; however, in some cases metabolism takes place in other sites (GI tract, skin, plasma, kidney, lungs) to either active or inactive metabolites
- Drug metabolites are eliminated by the kidneys or biliary tract

Steady state (SS)

- The point at which drug intake and elimination reach an equilibrium
- At SS, height of the peak and the depth of the trough are predictable
- SS must be reached before meaningful TDM is possible EXCEPT when a LD or continuous infusion is used
- Generally, drug level will reach SS concentration after 4–5 $T_{1/2}$
- Drugs with longer $T_{1/2}$ need a longer time to reach SS

Drug level interpretation

For accurate level interpretation, the following information should be available:

- Age and gender
- Time of the last dose before sampling
- Duration of treatment with the current dose
- Current dosing frequency
- Concurrent drug therapy

- Relevant disease states
- Reason for TDM (e.g. lack of effect, routine monitoring, suspected toxicity)

NOTE: *In some cases, the clinical pharmacist need to be consulted for accurate drug level interpretation*

✚ Pharmacokinetic parameters

- Have the information in the above section ready for accurate interpretation
- Samples should be sent immediately to lab, otherwise should be stored as per laboratory specific regulations
- Follow the individual drug sampling time requirement
- Notify the medical team, physician on-call or the clinical pharmacist once the drug level become available
- Document time of last dose and time of sampling in the patient chart

NOTE: *Do not hold the drug administration waiting for the new concentration unless ordered by the physician; the new dose adjustment will be applied for subsequent doses*

The ADAPTE process was used, modified to Five Steps as developed by Kristiansen et al, which include:

1. Planning

2. Initial assessment of the recommendations

3. Modification

4. Publication

5. Evaluation

Multiple workshops were conducted over a one-year duration (2019-2020). The Five Steps adaptation process was selected because of its simple and practical approach. The final document was peer-reviewed and edited accordingly.

GENERAL FACTS ABOUT AG

- AG demonstrate bactericidal activity against gram-negative bacteria.
- AG show concentration-dependent killing: higher serum concentrations result in higher rate and extent of bactericidal activity
- AG exhibit a post-antibiotic effect: bacterial growth suppression is continued even after serum concentrations have decreased below the minimum inhibitory concentration (MIC)
- Gentamicin combined with a cell wall active agent (i.e., beta-lactam or vancomycin) shows a synergistic effect on certain gram-positive bacteria such as enterococci in the treatment of endocarditis
- AG are nephrotoxic, ototoxic, and can cause neuromuscular blockade (in patients with myasthenia gravis, the use of AG is contraindicated)
- AG is typically not used as monotherapy, except in cases of urinary tract infection treatment

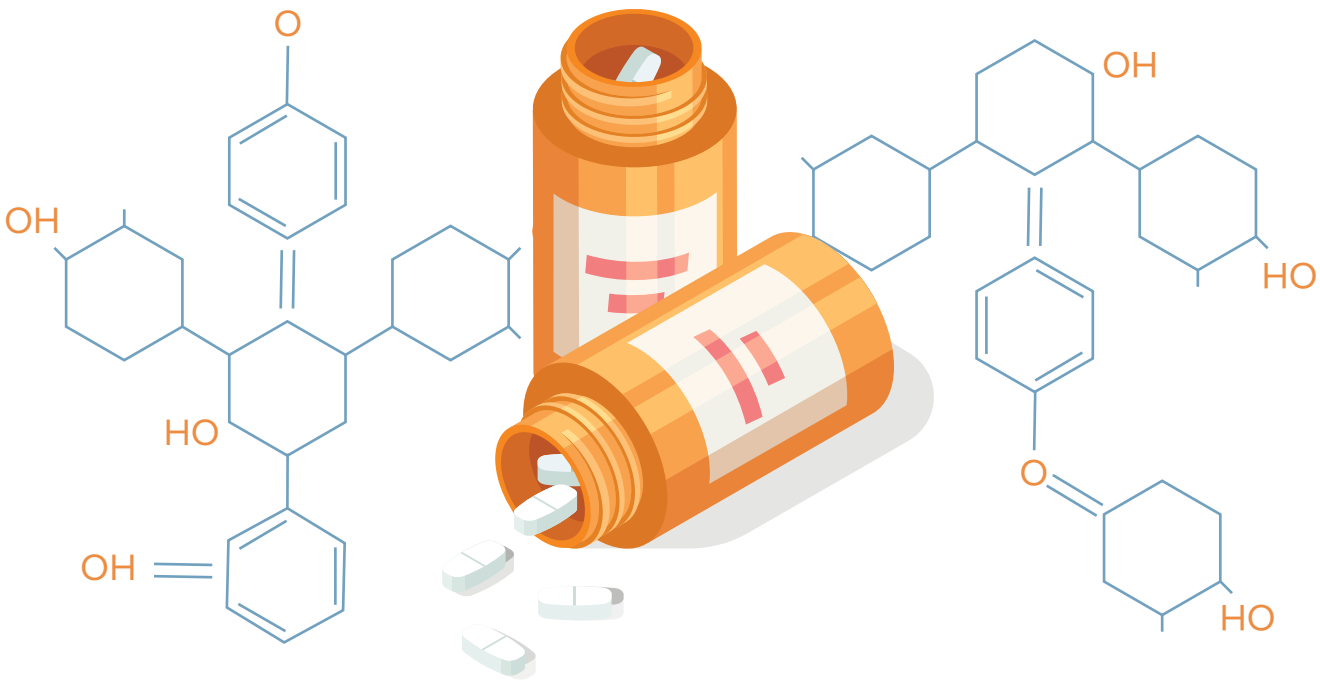
- **AG toxicity:**

  Nephrotoxicity:

  - An increase in serum creatinine (SrCr) of 0.5 mg/dL in 24 hours or a double of SrCr in 24 hours
  - Non-oliguric renal failure, with slow rise in serum creatinine and hypoosmolar urinary output
  - Develops after several days of therapy
  - Average incidence is 6% to 10%
  - Usually is reversible
  - All AG are nephrotoxic with the following reported percentages: gentamicin has the highest potential to cause nephrotoxicity (14%) followed by tobramycin (13%) then amikacin (10%) and streptomycin has the lowest because does not accumulate in renal cortex (8%)
  - Factors include: long duration of therapy, increased age, compromised renal function, volume depletion, elevated peak and trough levels, concurrent nephrotoxic drugs (i.e., vancomycin) and previous exposure to AG

Ototoxicity

- Usually permanent vestibular and/or auditory toxicity
- Incidence is 2% to 10%
- Generally associated with prolonged use (>1–2 weeks).
- Factors include: same as nephrotoxicity
- Patients need to be advised to be aware of and report signs and symptoms of cochlear toxicity (e.g. tinnitus, sense of fullness in ears, loss of hearing) and vestibular toxicity (e.g. disequilibrium, oscillopsia, cognitive dysfunction, visual sensitivity, nausea/vomiting, vertigo, headache, nystagmus)
- AG should be discontinued immediately if any signs/symptoms of ototoxicity.
- Audiometry and vestibular testing is recommended for patients receiving AG for 7 days or more, or at any time if ototoxicity is suspected
- If prolonged therapy is anticipated (greater than 7 days) baseline audiometry may be considered



Step-1: Determine the appropriate patients' weight to use

IBW

- Should be always used for AG dosing & CrCl calculations unless patient meets criteria for utilization of ABW or AdBW (see below)

Table I: IBW equations

Male	Female
50 kg + (2.3 × inches above 60 inches) OR 50 kg + (0.92 × cm above 150 cm)	45.5 kg + (2.3 × inches above 60 inches) OR 45.5 kg + (0.92 × cm above 150 cm)

AdBW

- AdBW = IBW + 0.4 (ABW – IBW)

- IBW should always be used unless ABW is lower. AdBW should be used if ABW is >30% above IBW

Step-2: Determine the patient's CrCl

- All AG are exclusively excreted by the kidneys
- Use Cockcroft-Gault equation to calculate the patient CrCl

Table II: CrCL equations

Male	Female
$\text{CrCl (mL/min) for male} = \frac{(140 - \text{Age}) \times \text{IBW (kg)}}{72 \times \text{SrCr}}$	$\text{CrCl (mL/min) for female} = 0.85 \times \frac{(140 - \text{Age}) \times \text{IBW (kg)}}{72 \times \text{SrCr}}$

Step-3: Determine which dosing model to use based on the indications

- There are three dosing models for AG:

High-dose extended-interval therapy (see Tables I & IV in the Appendix)

(also called “once daily dosing”)

Use this model whenever possible

Rationale:

- Bactericidal activity of AG is concentration dependent (the higher the peak/MIC ratio, the more bacteria are killed)
- AG exhibit a post-antibiotic effect (PAE) up to 8 hours
- Lower renal tissue concentration compared to divided doses, lower risk of nephrotoxicity
- Less down-regulation of AG uptake into bacterial cell, preserved antibacterial activity
- Decreased antibiotic resistance
- Convenience with less frequent administration
- Decreased frequency of drug level monitoring

Exclusion:

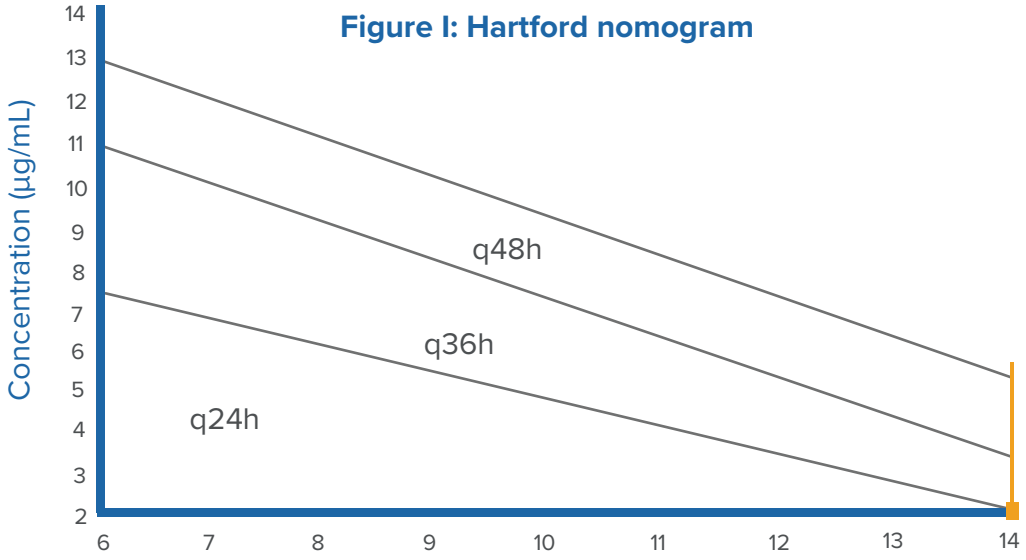
- Renal insufficiency (CrCl <20 mL/min or rapidly declining renal function)
- Patients requiring dialysis
- Synergy for gram-positive infections
- Pregnant women
- Patient with altered Vd: Ascites or severe liver disease
- Patients exhibit rapid clearance of AG: Burns (>20%)
- Patients with known auditory or vestibular disease or pre-existing impairment
- Meningitis

Use Hartford nomogram to adjust AG interval

- For amikacin: Use nomogram when a 15 mg/kg dose is used (divide serum amikacin level by 2, then plot it on graph)
- The nomogram assumes a Vd of 0.3 L/kg

- If interval falls in areas marked as q24h, q36h, q48h, dosing interval should be every 24, 36, or 48 hours respectively
- If the interval level is on one of the sloping lines, choose the longer interval
- If the interval level is above the q48h dosing interval area, stop extended interval dosing and switch to traditional dosing model
- Reassess AG dosing if the interval level is below the nomogram (i.e., <2 mg/L)

Figure I: Hartford nomogram



Conventional/traditional dosing (Tables II & V in the Appendix)

- Reduced more frequent dose administration using pharmacokinetic parameters to determine dose and frequency to achieve target peak and trough values
- Indications:
  Used when the patient is not a candidate for high-dose extended interval dosing therapy (see exclusion criteria above)

Gram-positive-synergy dosing (Table III in the Appendix)

- Only gentamicin is used in this model
- Used for the treatment of gram-positive infections at low doses in conjunction with an antibiotic that exhibits activity against cell wall of gram-positive bacteria (i.e. beta-lactams, vancomycin)

- Only gentamicin is used in this model
- Used for the treatment of gram-positive infections at low doses in conjunction with an antibiotic that exhibits activity against cell wall of gram-positive bacteria (i.e. beta-lactams, vancomycin)
- **Indications:**
  Used in combination therapy for endocarditis caused by *Enterococcus* species, viridans & bovis group *Streptococcus*

Algorithm for choosing initial AG dosing model based on indication (Algorithms 1-2 & 2-2 in the Appendix)

- A trough level should be obtained immediately before administration of third dose (see next page)
- A peak level should be obtained 30 min after the end of a 30-min infusion of the third dose

.

Monitoring

- Limiting the duration of AG to 7 days or less, when possible, is highly recommended
- TDM as indicated
- Renal function
  - SrCr at baseline and q2–3 days
- Audiometry and vestibular testing:
  - Baselines IF planned for prolonged therapy >7 days is planned
  - After >7 days of therapy
- Once patient is stabilized on target levels with stable renal function, levels should be repeated at least every 3–4 days
- More frequent monitoring should be considered in the following circumstances:
  - The patient is at increased risk of nephrotoxicity
  - Fluctuating/unstable renal function

PATIENT CASE EXAMPLES

Case 1:

JM is a 50-year-old, 70 kg (1.77 m) man with gram-negative pneumonia. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. The team plans to start a combination of cefepime gentamicin.

STEP 01

- Determine the appropriate patients' weight to use
- Calculate IBW: 50 kg + (0.92 × cm above 150 cm) = 73 kg
- IBW is more than ABW, so we will use the ABW (70 kg)

STEP 02

Determine the patient's CrCL using Cockroft-Gault equation

$$\text{For males: CrCl (mL/min) for male} = \frac{(140 - 50) \times 70\ (\text{kg})}{72 \times 0.9} = 97\ \text{mL/min}$$

STEP 03

- Determine which dosing model to use based on the indications
- Indication is for gram-negative bacterial treatment
- Patient is eligible for extended once daily dosing gentamicin:
  - Start with 7 mg/kg/day = 490 mg (round it to 500 mg)
  - Set the frequency to be q24h since CrCl is >0 or use Hartford monogram (see next step)

STEP 04

Level around the second dose:

- Order trough level 15–30 min before the second dose
- Order peak level 1–1.5 hours after the end of second dose infusion

Or use Hartford nomogram:

- Order random level any time between 8–12 hours after the 1st dose
- Determine the frequency as per the nomogram:
  - For example: If the level 9 hours after the dose was 8 µg/mL, then the new frequency will be q36h

STEP 05

Continue monitoring serum creatinine and levels as per Table I in the Appendix

Case 2:

Same patient profile as in Case 1 but serum creatinine is 3.5 mg/dL

STEP 01	Use ABW = 70 kg as IBW > ABW
STEP 02	Calculate CrCl: CrCl (mL/min) for male = $\frac{(140 - 50) \times 70\ (kg)}{72 \times 3.5}$ = 25 mL/min
STEP 03	Dosing model • Use traditional model because CrCl is between 20–49 as per Table II in the Appendix. ◦ Use dosing interval of 24 hours • However, high-dose extended interval dosing is not contraindicated

STEP 04	Monitoring
	• Sampling: around the second dose since the dosing interval is q24h
	  ◦ Target peak level is 8–10 µg/mL for pneumonia
	  ◦ Target trough is <1–2 µg/mL

STEP 05	Continue monitoring serum creatinine and levels as per Table I in the Appendix

Case 3:

The patient is a 20-year-old, 61 kg (165 cm) woman with intra-abdominal infection. Her current serum creatinine is 1.1 mg/dL and is stable. Compute amikacin dose for this patient

STEP 01

- Determine the appropriate patients' weight to use
- Calculate IBW: 45.5 kg + (0.92 × 15) = 59 kg
- IBW is <20% less than ABW, so we will use the IBW (59 kg)

STEP 02

Determine the patient's CrCl using Cockroft-Gault equation

$$\text{For females: CrCl (mL/min) for male} = 0.85 \times \left[\frac{(140 - 20) \times 59\ (\text{kg})}{72 \times 1.1}\right] = 62\ \text{mL/min}$$

STEP 03

- Determine which dosing model to use based on the indications
- Indication is for gram-negative bacterial treatment
- Patient is eligible for extended once daily dosing amikacin:
  - Start with 15 mg/kg/day = 885 mg (round it to 880 mg)
  - Set the frequency to be q24h since CrCl is >60 or use Hartford nomogram (see next step)

STEP 04

Monitoring

Level around the second dose:

- Order trough level 15–30 min before the second dose
- Order peak level 1–1.5 hours after the end of second dose infusion

Or use Hartford nomogram:

- Order random level any time between 8–12 hours after the 1st dose
- Divide the level by 2
- Determine the frequency as per the nomogram:
  - For example, if the level 12 hours after the dose was 7 µg/mL, then the new frequency will be q48h

STEP 05

Continue monitoring serum creatinine and levels as per Table I in the Appendix

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APPENDIX

Table I: Gentamicin & Tobramycin

High-dose extended-interval therapy model "Once Daily Dosing"

Pharmacokinetics parameters

$T_{1/2}$
- Normal: ~2 hours
- Renal failure: 6–127 hours

Absorption:
- IM: Rapid and complete
- Oral: Poor (<1%)

Distribution:
- Highly hydrophilic; Primarily into extracellular fluid
- Concentrated in the renal cortex
- CSF & Eye: minimal (CSF: blood level ratio: normal meninges: <10%; Inflamed meninges: ≤25%)
- Crosses placenta

Time to peak
- IM: 30–90 min
- IV: 30 min after 30 min infusion

Vd.:
- 0.2–0.3 L/kg
- Increased by edema, ascites, fluid overload;
- Decreased with dehydration

PB.: <30%

Excretion:
In urine ≥70% (as unchanged drug)

Clearance:
0.09 ± 0.03 L/hour/kg
(directly related to renal function)

Dialyzable:
(HD & PD) 50–100%

Initial dose

- **Start with** 5–7 mg/kg IV
- *Round dose to 20 mg*

Initial interval

Based on the patient's CrCl, use the following table:

CrCl (mL/min)	Dose interval
≥60	q24h
40–59	q36h
20–39	q48h, OR use traditional dosing (see below)
<20	Administer first dose, then draw serial serum drug levels to determine when to give next dose, OR use traditional dosing
HD	Use traditional dosing
CRRT	Use traditional dosing

Levels

CONVERSION:
- mcg/mL (mg/L) × 2.09 = mmol/L

NOTE:
TDM is done by measuring trough level alone in most cases. Peak level is measured in cases where individualized PK monitoring is required

THERAPEUTIC LEVELS:
- Trough: <1–2 mcg/mL (2.1–4.2 mmol/L)
- Peak: [only if indicated]: 15–25 mcg/mL (31–52 mmol/L)
- Toxic level: >38 mcg/mL (80 mmol/L)

Sampling

Sampling around the 2nd dose
- Trough: 15–30 min before the dose
- Peak: 1–1.5 hours after the end of drug infusion

FREQUENCY OF SAMPLING:
- Repeat weekly after having one therapeutic level
- Consider more frequent sampling in the following situation:
  - ➡ Fluctuation renal function
  - ➡ Concomitant nephrotoxic drugs
  - ➡ Using greater than the recommended dose
  - ➡ No improvement
  - ➡ Suspicion of toxicity
  - ➡ Dose change

NOTE:
Always verify sampling time

Interpretation & adjustment

- Ensure that samples were collected at appropriate time.

Trough level adjustment:
- Level >2.1–4.2 mmol/L suggests drug accumulation; extend dosing interval

Hartford nomogram may be used to adjust interval based on a random level (See Section)

Peak level adjustment:
Decreasing or increasing the dose by specific percentages will result in an equal decrease or increase in the percentages of peak levels since AG exhibit linear kinetics

FOR ADVANCED CASES, CONSULT THE CLINICAL PHARMACIST AT YOUR INSTITUTION TO ASSESS IN INTERPRETATION AND ADJUSTMENT

TABLE II: Gentamicin & Tobramycin

Conventional/Traditional dosing model

Initial dose

- **Start with**
  1.5–2 mg/kg IV
- **For HD patient:**
  1.5–2 mg/kg IV administered after each dialysis
  Round dose to 20 mg

Initial interval

Based on the patient's CrCl, use the following table:

CrCl (mL/min)	Dose interval
≥80	q8h
50–79	q12h
20–49	q24h, OR use traditional dosing (see below)
<20	q48–72h; give first dose and draw serial serum drug levels to determine when to give next dose; close monitoring is required
HD	After each dialysis
CRRT	After each dialysis

Levels

CONVERSION:

- mcg/mL (mg/L) × 2.09 = mmol/L

NOTE:
TDM is done by measuring both peak and trough levels

THERAPEUTIC LEVELS:

- Trough:
  <1-2 mcg/mL
  (2.1-4.2 mmol/L)
- In HD:
  1.5-3 mcg/mL
  (3.1-6.3 mmol/L)
- Peak:
  see the following table:

Suggested peak level as per Indication

Infection	Peak mcg/mL (mmol/L)
• Sepsis • Neutropenia • Burns • Pneumonia • Infections due to Pseudomonas (non-urinary) • Bone and joint infections	8–10 (16.7–20.9)
• Pelvic inflammatory disease (e.g., endometritis, salpingitis, tubo-ovarian abscess, pelvic peritonitis) • Chorioamnionitis • Pyelonephritis • Peritonitis • Soft tissue infections	6–8 (12.5–16.7)
• Cystic fibrosis	10–15 (20.9–31.3)
• UTI	14–6 (8.4–12.5)

- Toxic level: >38 mcg/mL (80 mmol/L)

Sampling

- **Usually after 4-5× $T_{1/2}$**

Interval (h)	Levels around
q8h, q12	3rd dose
q24, q48	2nd dose

OR use the following equation:

$T_{½}$ = 0.693/Ke*

* Ke = 0.00293(CrCL) + 0.014

- Trough:
  15–30 min before the dose
  → In HD:
  30 min before session
- Peak:
  1–1.5 hours after the end of drug infusion

FREQUENCY OF SAMPLING:

- Repeat weekly after having one therapeutic level
- Consider more frequent sampling in the following situation:
  - Fluctuation renal function
  - Concomitant nephrotoxic drugs
  - Using greater than the recommended dose
  - No improvement
  - Suspicion of toxicity
  - Dose change

NOTE:
Always verify sampling time

Interpretation & adjustment

- Ensure that samples were collected at appropriate time.
- Adjust dose as follows:

Level	Action
High trough	Extend interval
High peak	Decrease dose*
Low peak	Increase dose*

** Decreasing or increasing the dose by specific percentages will result in an equal decrease or increase in the percentages of peak levels since AG exhibit linear kinetics*

FOR ADVANCED CASES, CONSULT THE CLINICAL PHARMACIST AT YOUR INSTITUTION TO ASSESS IN INTERPRETATION AND ADJUSTMENT

TABLE III: Gentamicin

Synergetic dosing model

Initial dose

- **Start with**
  1 mg/kg q8h
  OR
  3 mg/kg q24h,
  depending on
  the organism
  identified
- **In HD**
  1 mg/kg
  After each
  session
- *Round dose to 20 mg*

Initial interval

Based on the patient's CrCl, use the following table:

CrCl (mL/min)	Dose interval
≥80	q8h
50–79	q12h
20–49	q24h
<20	q48–72h; give first dose and draw serial serum drug levels to determine when to give next dose; close monitoring is required
HD	After each dialysis
CRRT	After each dialysis

Levels

CONVERSION:

- mcg/mL (mg/L) × 2.09 = mmol/L

NOTE:

TDM is done by measuring trough level alone in most cases. Peak level is measured in cases where individualized PK monitoring is required

THERAPEUTIC LEVELS:

- Trough:
  <1 mcg/mL
  (2.1 mmol/L)
- Peak:
  (if done): 3–5 mcg/L
  (6.3–10.5 mmol/L)
- Toxic level:
  >38 mcg/mL
  (80 mmol/L)

Sampling

- **Usually after 4-5× $T_{1/2}$**

Interval (h)	Levels around
q8h, q12	3rd dose
q24, q48	2nd dose

OR use the following equation:

$T_{½}$ = 0.693/Ke*

* Ke = 0.00293(CrCL) + 0.014

- Trough:
  15–30 min
  before the dose
- Peak:
  30–60 min after the
  end of drug infusion

FREQUENCY OF SAMPLING:

- Repeat weekly after having one therapeutic level
- Consider more frequent sampling in the following situation:
  - ➡ Fluctuation renal function
  - ➡ Concomitant nephrotoxic drugs
  - ➡ Using greater than the recommended dose
  - ➡ No improvement
  - ➡ Suspicion of toxicity
  - ➡ Dose change

NOTE:

Always verify sampling time

Interpretation & adjustment

- Ensure that samples were collected at appropriate time.
- Adjust dose as follows:

Level	Action
High trough	Extend interval
High peak	Decrease dose*
Low peak	Increase dose*

** Decreasing or increasing the dose by specific percentages will result in an equal decrease or increase in the percentages of peak levels since AG exhibit linear kinetics*

FOR ADVANCED CASES, CONSULT THE CLINICAL PHARMACIST AT YOUR INSTITUTION TO ASSESS IN INTERPRETATION AND ADJUSTMENT

Table IV: Amikacin

High-dose extended-interval therapy model "Once Daily Dosing"

Pharmacokinetics parameters

$T_{1/2}$
- Normal: ~2 hours
- Anuric & ESRD: 17–150 hours

Absorption:
- IM: Rapid and complete
- Oral: Poor (<1%)

Distribution:
- Highly hydrophilic; Primarily into extracellular fluid
- Concentrated in the renal cortex
- CSF: minimal, (CSF: blood level ratio: normal meninges: 10-20%; Inflamed meninges: up to 50%)
- Crosses placenta

Time to peak
- IM: 60 min
- IV: 30 min after 30-min infusion

Vd.:
- 0.25 L/kg
- Increased by edema, ascites, fluid overload;
- Decreased with dehydration

PB.: ≤11% to albumin

Excretion:
In urine ≥95% (as unchanged drug)

Clearance:
Directly related to renal function

Dialyzable:
(HD & PD) 50–100%

Initial dose	Initial interval	Levels	Sampling	Interpretation & adjustment

Initial dose

- **Start with** 15–20 mg/kg IV
- *Rounded to nearest 25 mg*

Initial interval

Based on the patient's CrCl, use the following table:

CrCl (mL/min)	Dose interval
≥60	q24h
40–59	q36h
20–39	q48h, OR use traditional dosing (see below)
<20	Administer first dose, then draw serial serum drug levels to determine when to give next dose, OR use traditional dosing
HD	Use traditional dosing
CRRT	Use traditional dosing

Levels

CONVERSION:
- mcg/mL (mg/L) × 2.09 = mmol/L

NOTE:
TDM is done by measuring trough level alone in most cases. Peak level is measured in cases where individualized PK monitoring is required

THERAPEUTIC LEVELS:
- Trough: <1–2 mcg/mL (2.1–4.2 mmol/L)
- Peak: [only if indicated]: 15–25 mcg/mL (31–52 mmol/L)
- Toxic level: >38 mcg/mL (80 mmol/L)

Sampling

Sampling around the 2nd dose
- Trough: 15–30 min before the dose
- Peak: 1–1.5 hours after the end of drug infusion

FREQUENCY OF SAMPLING:
- Repeat weekly after having one therapeutic level
- Consider more frequent sampling in the following situation:
  - ➡ Fluctuation renal function
  - ➡ Concomitant nephrotoxic drugs
  - ➡ Using greater than the recommended dose
  - ➡ No improvement
  - ➡ Suspicion of toxicity
  - ➡ Dose change

NOTE:
Always verify sampling time

Interpretation & adjustment
- Ensure that samples were collected at appropriate time.

Trough level adjustment:
- Level >2.1–4.2 mmol/L suggests drug accumulation; extend dosing interval

Hartford nomogram may be used to adjust interval based on a random level (See Section)

Peak level adjustment:
Decreasing or increasing the dose by specific percentages will result in an equal decrease or increase in the percentages of peak levels since AG exhibit linear kinetics

FOR ADVANCED CASES, CONSULT THE CLINICAL PHARMACIST AT YOUR INSTITUTION TO ASSESS IN INTERPRETATION AND ADJUSTMENT

Table V: Amikacin

Conventional/Traditional dosing model

Initial dose

- **Start with** 5–7.5 mg/kg IV
- *Rounded to nearest 25 mg*

Initial interval

Based on the patient's CrCl, use the following table:

CrCl (mL/min)	Dose interval
≥80	q8h
50–79	q12h
10–50	7.5 mg/kg q48h
<10	q48-72h; give first dose then draw serial serum drug levels to determine when to give next dose; close monitoring is recommended usually ~7.5 mg/kg q48h
HD	After each dialysis
CRRT	After each dialysis

Levels

CONVERSION:

- mcg/mL (mg/L) × 2.09 = mmol/L

THERAPEUTIC LEVELS:

- Trough: <1-2 mcg/mL (2.1-4.2 mmol/L)
- In HD: 1.5-3 mcg/mL (3.1-6.3 mmol/L)
- Peak: see the following table:

Suggested peak level as per Indication

Infection	Peak mcg/mL (mmol/L)
Life-threatening	25–40 (42.7–68.4)
Serious infection	20–25 (34–42.7)
UTI	15–20 (25.7–34)

- Toxic level: >40 mcg/mL (68 mmol/L)

Sampling

- **Usually after 4-5× $T_{1/2}$**

Interval (h)	Levels around
q8h, q12	3rd dose
q24, q48	2nd dose

OR use the following equation:

$T_{½}$ = 0.693/Ke*

* Ke = 0.00293(CrCL) + 0.014

- Trough: 15–30 min before the dose
- Peak: 1–1.5 hours after the end of drug infusion

FREQUENCY OF SAMPLING:

Repeat weekly after having one therapeutic level

- Consider more frequent sampling in the following situation:
  - ➡ Fluctuation renal function
  - ➡ Concomitant nephrotoxic drugs
  - ➡ Using greater than the recommended dose
  - ➡ No improvement
  - ➡ Suspicion of toxicity
  - ➡ Dose change

NOTE:

Always verify sampling time

Interpretation & adjustment

- Ensure that samples were collected at appropriate time.
- Adjust dose as follows:

Level	Action
High trough	Extend interval
High peak	Decrease dose*
Low peak	Increase dose*

** Decreasing or increasing the dose by specific percentages will result in an equal decrease or increase in the percentages of peak levels since AG exhibit linear kinetics*

FOR ADVANCED CASES, CONSULT THE CLINICAL PHARMACIST AT YOUR INSTITUTION TO ASSESS IN INTERPRETATION AND ADJUSTMENT

ALGORITHM FOR CHOOSING INITIAL AMINOGLYCOSIDE DOSING MODEL BASED ON INDICATION (1-2)

Aminoglycoside for gram negative bacteria

Do any of the following criteria apply to the patient?

- CrCl <20 mL/min
- Patient on HD
- Synergy for gram-positive infection
- Pregnant
- Ascites or severe liver disease
- Burns (>20%)
- Known auditory or vestibular disease or pre-existing impairment

No

Use extended interval AG
Gentamicin & Tobramycin:
5–7 mg/kg
Amikacin 15 mg/kg

Calculate CrCl

≥60	40–59	20–39	<20	HD & CRRT
q24h dose	q36h dose	q48h dose	Use traditional dosing	

Check levels around the 2nd dose

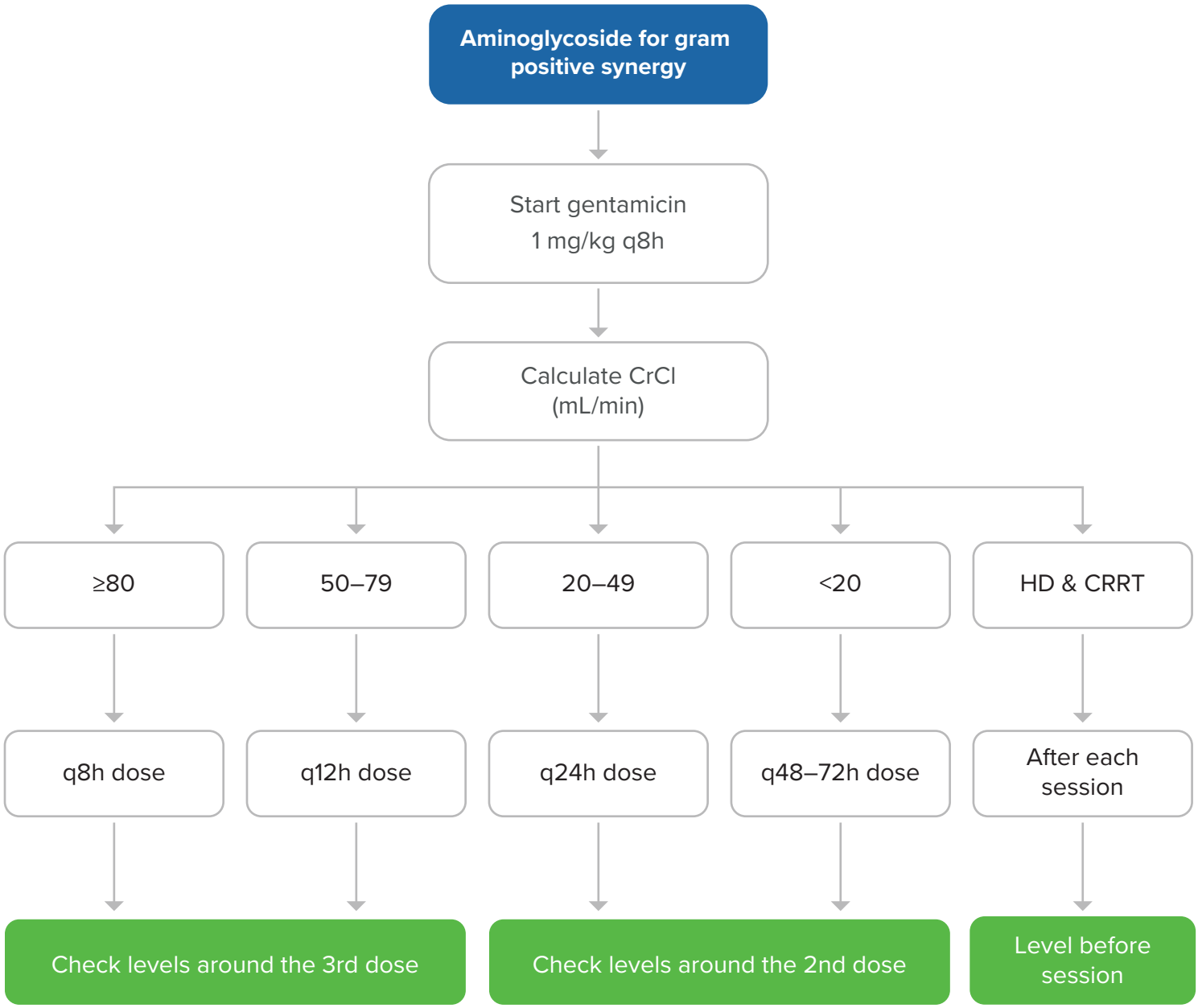
Yes

Use traditional dosing of AG
Gentamicin & Tobramycin:
1.5–2 mg/kg
Amikacin 5–7.5 mg/kg

Calculate CrCl

≥80	50–79	20–49	<20	HD & CRRT
q8h	q12h	q24h	q48–72h	After each session
Check levels around the 3rd dose		Check levels around the 3rd dose		Level before session

ALGORITHM FOR CHOOSING INITIAL AMINOGLYCOSIDE DOSING MODEL BASED ON INDICATION (2-2)



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