

Aminoglycosides

Concentration-dependent bactericidal 30S inhibitors for aerobic gram-negative infection, defined clinically by nephrotoxicity, ototoxicity and mandatory monitoring.

Online guide: <https://www.medguideglobal.com/pharmacology/antibiotics/aminoglycosides>

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Quick revision

One Liner: Aminoglycosides bind the 30S A-site on 16S rRNA and cause genetic code misreading - bactericidal, concentration-dependent, aerobic gram-negative cover, and toxic enough that monitoring is part of the prescription.

1. Mechanism: bind the bacterial 30S ribosomal subunit at the A-site on 16S rRNA, causing misreading of the genetic code. [1]
2. Bactericidal and concentration-dependent - higher peak concentrations kill more effectively. [1]
3. Spectrum is broad against aerobic organisms, including gram-negative bacteria and mycobacteria. [1]
4. Ototoxicity affects 2 to 45% of patients; nephrotoxicity 10 to 25%. [1]
5. Gentamicin, streptomycin and tobramycin cause vestibular loss that may reverse; amikacin and kanamycin cause irreversible cochlear hearing loss. [1]
6. Nephrotoxicity is generally reversible, unlike cochlear damage. [1]
7. Avoid in myasthenia gravis because of prolonged neuromuscular blockade. [1]
8. There is no antidote for aminoglycoside toxicity, which is why therapeutic drug monitoring matters so much. [1]

Overview

1. Aminoglycosides are an older class of medication that remain clinically valuable, with broad-spectrum activity covering aerobic organisms including gram-negative bacteria and mycobacteria. The class includes gentamicin, tobramycin, amikacin, neomycin, plazomicin, paromomycin and streptomycin, and FDA-approved indications vary between individual members rather than applying to the class as a whole. [1]
2. They are unusual among protein synthesis inhibitors in being bactericidal rather than bacteriostatic. Binding the 30S subunit at the A-site of 16S rRNA causes the ribosome to misread the genetic code, so the organism produces defective proteins rather than simply stopping - an error catastrophe rather than a pause. [1]
3. What limits the class is toxicity rather than spectrum. Ototoxicity is reported in 2 to 45% of patients and nephrotoxicity in 10 to 25%, there is no antidote once toxicity occurs, and therapeutic drug monitoring is documented to reduce hospital stays, toxicities and mortality. Prescribing an aminoglycoside therefore means committing to monitoring it. [1]

Classification and drug examples

Intro: Best learned by the toxicity each agent is associated with and by role, since indications vary between individual aminoglycosides rather than applying across the class.

1. Name: Systemic agents associated with vestibular toxicity

1. Note: These cause vestibular and/or cochlear damage, with vestibular loss the characteristic pattern; that loss is potentially reversible.

1. Name: Gentamicin

1. Route: IV/IM

1. Note: Used in bacterial septicaemia, meningitis, urinary, gastrointestinal and soft-tissue infection, guided by local resistance patterns. [2]

2. Name: Tobramycin

2. Route: IV/inhaled

2. Note: Associated with the vestibular toxicity pattern. [1]

3. Name: Streptomycin

3. Route: IM

3. Note: The oldest member; associated with vestibular loss and used against resistant mycobacteria. [1] [1]

2. Name: Systemic agents associated with cochlear toxicity

2. Note: These cause cochlear damage, and the resulting hearing loss is irreversible.

1. Name: Amikacin

1. Route: IV/IM

1. Note: Cochlear damage with irreversible hearing loss is the characteristic risk. [1]

2. Name: Kanamycin

2. Route: IM

2. Note: Shares amikacin's cochlear toxicity pattern. [1]

3. Name: Plazomicin

3. Route: IV

3. Note: A newer member of the class. [1] [1]

3. Name: Poorly absorbed agents used locally

3. Note: Used where a local rather than systemic effect is wanted.

1. Name: Neomycin

1. Route: Oral/topical

1. Note: Used for local effect rather than systemic therapy. [1]

2. Name: Paromomycin

2. Route: Oral

2. Note: A member of the class used for luminal effect. [1] [1]

Mechanism of action

Summary: Aminoglycosides bind the bacterial 30S ribosomal subunit at the A-site on 16S rRNA, causing misreading of the genetic code, disrupting protein synthesis and killing the organism.

Target: A-site on 16S rRNA of the bacterial 30S ribosomal subunit

Cidal Static: bactericidal

Kill Kinetics: concentration-dependent

1. Step: 1

1. Title: The drug enters an aerobic organism

1. Detail: Activity is against aerobic organisms, which is why the class has no useful role against strict anaerobes. [1]

2. Step: 2

2. Title: It binds the 30S A-site

2. Detail: The drug binds the bacterial 30S ribosomal subunit, specifically the A-site on 16S rRNA. [1]

3. Step: 3

3. Title: The genetic code is misread

3. Detail: Binding causes the ribosome to misread the code, so the proteins produced are wrong rather than merely absent. [1]

4. Step: 4

4. Title: Protein synthesis is disrupted and the organism dies

4. Detail: The accumulation of defective protein eliminates the bacterium - the effect is bactericidal, not bacteriostatic. [1]

5. Step: 5

5. Title: Higher concentrations kill harder

5. Detail: The mechanism is concentration-dependent, so higher doses are more effective against aerobic organisms. [1]

Spectrum of activity

Intro: One aerobic, largely gram-negative spectrum across the class, with mycobacterial activity that matters for resistant tuberculosis.

Subclass Id: class-wide

Limited as monotherapy

1. Aerobic gram-negative bacteria

2. *Pseudomonas aeruginosa*

Mycobacteria, including resistant strains

Strict anaerobes [1]

Major clinical uses

1. Drug: Gentamicin

1. Organism: Aerobic gram-negative organisms

1. Indication: Bacterial septicaemia, meningitis, urinary tract, gastrointestinal and soft-tissue infection

1. Line: targeted

1. Note: Choice should follow patient age, presentation and local antimicrobial resistance patterns. [2]

2. Drug: Aminoglycosides as a class

2. Organism: Suspected severe infection before an organism is known

2. Indication: Empiric therapy in infective endocarditis, sepsis, complicated intra-abdominal and complicated genitourinary infection

2. Line: empiric

2. Note: Framed as 48 hours or less pending identification. [1]

3. Drug: Aminoglycosides as a class

3. Organism: *Pseudomonas aeruginosa*

3. Indication: Directed therapy against a confirmed organism

3. Line: targeted

3. Note: Directed therapy beyond 48 hours is acceptable once the organism is known. [1]

4. Drug: Streptomycin

4. Organism: Resistant mycobacteria

4. Indication: Mycobacterial infection resistant to first-line therapy

4. Line: targeted

4. Note: Also used in brucellosis and tularemia within the class's directed indications. [1]

5. Drug: Amikacin

5. Organism: Aerobic gram-negative organisms resistant to other aminoglycosides

5. Indication: Serious gram-negative infection

5. Line: reserve

5. Note: Weigh against irreversible cochlear toxicity. [1]

6. Drug: Neomycin

6. Organism: Gut flora

6. Indication: Local rather than systemic effect

6. Line: adjunct

6. Note: Poor absorption is what makes the local role possible. [1]

Pharmacokinetics

1. Drug: Gentamicin
1. Route: IV/IM
1. Absorption: Not orally absorbed for systemic effect
1. Csf Penetration: Used in meningitis under specialist direction
1. Metabolism: Minimal
1. Elimination: Renal
1. Half Life: See prescribing reference
1. Dose Adjust: Renal impairment; therapeutic drug monitoring required [2][1]
2. Drug: Amikacin
2. Route: IV/IM
2. Absorption: Not orally absorbed for systemic effect
2. Csf Penetration: See prescribing reference
2. Metabolism: Minimal
2. Elimination: Renal
2. Half Life: See prescribing reference
2. Dose Adjust: Renal impairment; therapeutic drug monitoring required [1]
3. Drug: Neomycin
3. Route: Oral/topical
3. Absorption: Poorly absorbed orally, which is what allows it to reduce intestinal bacteria
3. Csf Penetration: Not applicable
3. Metabolism: Minimal
3. Elimination: Faecal for the oral route
3. Half Life: Not clinically relevant by this route
3. Dose Adjust: See prescribing reference [1][3]
1. Most aminoglycosides are poorly absorbed orally and are given parenterally, by intravenous or intramuscular injection. Neomycin and paromomycin are the members given by mouth, precisely because they are not absorbed systemically, so their activity stays inside the bowel. [3][1]
2. Therapeutic drug monitoring is not optional housekeeping here: it is documented to reduce hospital stays, toxicities and mortality, and there is no antidote once toxicity has occurred. [1]
3. Critically ill, burn and obese patients have abnormal volumes of distribution and need specific dosing consideration. [1]
4. This page gives no dose regimens by design. Doses depend on indication, organism, renal function, age and weight, and belong in a prescribing reference used by the treating clinician.

Adverse effects

Effect: Nephrotoxicity

Detail: Reported in 10 to 25% of patients, through renal tubular toxicity, decreased renal blood flow and reduced glomerular filtration rate. Generally reversible. [1]

1. Effect: Ototoxicity

1. Detail: Reported in 2 to 45% of patients, affecting the vestibular apparatus, the cochlea, or both.

1. Action: Serial audiometry is used to detect it before irreversible cochlear loss develops. [1]

2. Effect: Irreversible hearing loss

2. Detail: Cochlear damage, characteristically from amikacin and kanamycin, does not recover.

2. Action: Monitor cochlear function and reassess the agent if hearing changes. [1]

3. Effect: Neuromuscular blockade

- 3. Detail: Less common than the other toxicities but serious; calcium channel blockers increase the risk.
- 3. Action: Avoid in myasthenia gravis and review concurrent drugs. [1]
- 1. Drug: Gentamicin, streptomycin, tobramycin
- 1. Effect: Vestibular loss, which is potentially reversible. [1]
- 2. Drug: Amikacin and kanamycin
- 2. Effect: Cochlear damage causing irreversible hearing loss. [1]
- 3. Drug: Aminoglycosides as a class
- 3. Effect: Liver injury is rare. Isolated reports of idiosyncratic hepatotoxicity exist for most agents but are not consistently convincing, partly because ototoxicity, neuropathy and nephrotoxicity limit the dose and duration patients tolerate. [3]

Contraindications, precautions and interactions

- Myasthenia gravis, because of the risk of prolonged neuromuscular blockade. [1]
- 1. Dehydration, pregnancy and hepatic dysfunction, all documented nephrotoxicity risk factors. [1]
- 2. Critical illness, burns and obesity, where volume of distribution is abnormal and standard dosing assumptions fail. [1]
- 1. With: Other nephrotoxic drugs - NSAIDs, ciclosporin, diuretics
- 1. Effect: Concurrent use raises nephrotoxicity risk. [1]
- 2. With: Calcium channel blockers
- 2. Effect: Increase the risk of neuromuscular blockade. [1]

Resistance mechanisms

- 1. Mechanism: Anaerobic conditions defeat the class outright
- 1. Detail: Aminoglycoside activity is confined to aerobic organisms, so a strictly anaerobic environment removes their usefulness regardless of any acquired resistance gene.
- Strict anaerobes
- 1. Countermeasure: Cover anaerobes with a different mechanistic class. [1]
- 2. Mechanism: Resistant mycobacteria
- 2. Detail: Resistance among mycobacteria is clinically recognised, which is why aminoglycosides feature in directed therapy for resistant mycobacterial disease rather than as a routine first choice.
- Resistant mycobacteria
- 2. Countermeasure: Susceptibility-directed regimens under specialist care. [1]
- Stewardship Note: The practical constraint on this class is toxicity rather than resistance: with no antidote available, the decision to start an aminoglycoside is inseparable from the commitment to monitor renal and cochlear function.

Comparison tables

- Title: Which aminoglycoside damages what
- Caption: The distinction that decides monitoring and counselling. Local susceptibility data and a prescribing reference govern actual therapy.
- 1. Key: drug
- 1. Label: Drug
- 1. Is Row Header: true
- 2. Key: toxicity
- 2. Label: Characteristic ototoxicity
- 3. Key: reversible
- 3. Label: Reversible?
- 4. Key: role

4. Label: Typical role

1. Drug: Gentamicin

1. Toxicity: Vestibular

1. Reversible: Potentially

1. Role: Septicaemia, urinary, soft tissue [1][2]

2. Drug: Tobramycin

2. Toxicity: Vestibular

2. Reversible: Potentially

2. Role: Gram-negative infection [1]

3. Drug: Streptomycin

3. Toxicity: Vestibular

3. Reversible: Potentially

3. Role: Resistant mycobacteria, brucellosis, tularemia [1]

4. Drug: Amikacin

4. Toxicity: Cochlear

4. Reversible: No - irreversible hearing loss

4. Role: Reserve gram-negative agent [1]

5. Drug: Kanamycin

5. Toxicity: Cochlear

5. Reversible: No - irreversible hearing loss

5. Role: Largely superseded [1]

High-yield exam pearls

1. Pearl: Aminoglycosides need oxygen to get in - they only work on aerobes.

1. Why: Their activity is against aerobic organisms, which is why they are useless against strict anaerobes and why anaerobic cover must come from another agent. [1]

2. Pearl: Vestibular versus cochlear damage splits by drug.

2. Why: Gentamicin, streptomycin and tobramycin damage the vestibular apparatus and that loss is potentially reversible; amikacin and kanamycin damage the cochlea and that hearing loss is irreversible. [1]

3. Pearl: Concentration-dependent killing drives the dosing strategy.

3. Why: Higher concentrations are more effective, which is the pharmacological basis for once-daily high-dose regimens rather than frequent small ones. [1]

4. Pearl: Myasthenia gravis is the classic contraindication.

4. Why: Aminoglycosides cause neuromuscular blockade, which is prolonged and dangerous in myasthenia gravis. [1]

5. Pearl: Empiric use is time-limited; directed use is not.

5. Why: Empiric aminoglycoside therapy is framed as 48 hours or less in severe infection, whereas directed therapy against a confirmed organism may continue beyond 48 hours. [1]

6. Pearl: Calcium channel blockers raise the neuromuscular blockade risk.

6. Why: A specific documented interaction, and an easy exam target. [1]

Common exam traps

1. Trap: "Nephrotoxicity and ototoxicity are equally permanent."

1. Correction: Nephrotoxicity is generally reversible. Cochlear damage from amikacin or kanamycin is irreversible hearing loss. [1]

2. Trap: "Aminoglycosides are broad-spectrum, so they cover anaerobes too."

2. Correction: Their broad activity is against aerobic organisms. Anaerobic cover has to come from a different agent. [1]

3. Trap: "Monitoring aminoglycosides is optional if the course is short."

3. Correction: Therapeutic drug monitoring reduces hospital stays, toxicities and mortality, and there is no antidote once toxicity occurs. [1]
4. Trap: "Standard dosing works for everyone."
4. Correction: Critically ill, burn and obese patients have abnormal volumes of distribution and need specific consideration. [1]

Self-test questions

1. Question: Why are aminoglycosides ineffective against strictly anaerobic organisms?
 1. Anaerobes lack a 30S ribosomal subunit for the drug to bind
 2. Aminoglycoside activity is confined to aerobic organisms, so an anaerobic environment removes their usefulness
 3. Anaerobes inactivate the drug by producing extended-spectrum beta-lactamases
 4. The drug is bound by anaerobic cell-wall teichoic acid before it reaches the ribosome
1. Explanation: These agents work only where oxygen is present. Their broad reputation describes breadth against aerobes, not universal cover, so an infection needing anaerobic treatment requires a different drug alongside them. [1]
2. Question: Which pairing of aminoglycoside toxicity is correct?
 1. Gentamicin - irreversible cochlear hearing loss; amikacin - reversible vestibular loss
 2. Both gentamicin and amikacin cause identical, permanent vestibular damage
 3. Gentamicin, streptomycin and tobramycin - vestibular loss that may reverse; amikacin and kanamycin - irreversible cochlear hearing loss
 4. Neither drug group causes ototoxicity; the class is limited by nephrotoxicity alone
2. Explanation: The split runs by drug. Gentamicin, streptomycin and tobramycin damage the vestibular apparatus and that loss is potentially reversible, whereas amikacin and kanamycin cause irreversible cochlear hearing loss. [1]
3. Question: At the molecular level, how do aminoglycosides kill bacteria?
 1. They bind the 50S subunit and block peptide bond formation
 2. They inhibit DNA gyrase, preventing supercoiling
 3. They bind the 30S subunit at the A-site on 16S rRNA, causing the genetic code to be misread
 4. They bind penicillin-binding proteins and halt cell-wall cross-linking
3. Explanation: Aminoglycosides bind the bacterial 30S ribosomal subunit at the A-site on 16S rRNA. The resulting misreading of the genetic code produces defective proteins, which is why the class is bactericidal rather than merely bacteriostatic. [1]
4. Question: What is the pharmacological basis for once-daily high-dose aminoglycoside regimens?
 1. Killing is time-dependent, so a single long exposure maximises the interval above MIC
 2. Killing is concentration-dependent, so higher peak concentrations kill more effectively
 3. The drug has a very long half-life, so more frequent dosing would accumulate
 4. Once-daily dosing removes the need for therapeutic drug monitoring
4. Explanation: Aminoglycoside killing is concentration-dependent - higher peak concentrations kill more effectively - which is the pharmacological rationale for once-daily high-dose regimens. It does not remove the need for monitoring. [1]
5. Question: Which condition is the classic contraindication to aminoglycoside use?
 1. Myasthenia gravis
 2. Type 2 diabetes mellitus
 3. Iron-deficiency anaemia
 4. Essential hypertension
5. Explanation: The class blocks neuromuscular transmission, and in myasthenia gravis that block is both unusually prolonged and dangerous. A documented interaction with calcium channel blockers pushes the same risk higher. [1]
6. Question: A student states that aminoglycoside nephrotoxicity and ototoxicity are equally permanent. Why is this wrong?

1. Both are in fact fully reversible once the drug is stopped
2. Nephrotoxicity is generally reversible, whereas cochlear damage from amikacin or kanamycin is irreversible
3. Ototoxicity is reversible, whereas renal damage is always permanent
4. Neither toxicity occurs at therapeutic concentrations
6. Explanation: Renal injury from this class generally recovers once the drug is stopped. Hearing loss of the cochlear pattern - the amikacin and kanamycin problem - does not recover. Reported frequencies run about 10 to 25% for renal toxicity and 2 to 45% for ototoxicity, and no antidote exists once either has occurred. [1]
7. Question: Why is neomycin given by mouth when most aminoglycosides must be given parenterally?
 1. Neomycin is the only member that resists gastric acid degradation
 2. Neomycin is actively absorbed from the gut, giving reliable systemic levels
 3. Neomycin is used orally precisely because it is not absorbed
 4. Oral neomycin is converted by gut flora into an absorbable active metabolite
7. Explanation: Most aminoglycosides are poorly absorbed from the gut and are given intravenously or intramuscularly. Two members are given by mouth for exactly that reason: neomycin and paromomycin are not absorbed systemically, so their effect is confined to the bowel lumen. [3][1]

Frequently asked questions

1. Question: Why are aminoglycosides bactericidal when other protein synthesis inhibitors are not?
 1. Answer: Because they cause the ribosome to misread the genetic code rather than simply stalling it. The organism produces defective proteins, and that error catastrophe kills it rather than pausing its growth. [1]
2. Question: Why do aminoglycosides not work against anaerobes?
 2. Answer: Their activity is directed at aerobic organisms. Anaerobic cover must come from a different class entirely. [1]
3. Question: Is aminoglycoside kidney damage permanent?
 3. Answer: Nephrotoxicity is generally reversible. The damage that does not recover is cochlear hearing loss, characteristically from amikacin and kanamycin. [1]
4. Question: Why is monitoring so heavily emphasised with this class?
 4. Answer: Because there is no antidote for aminoglycoside toxicity, and therapeutic drug monitoring is documented to reduce hospital stays, toxicities and mortality. Serial creatinine and serial audiometry are the two standard checks. [1]
5. Question: Which patients need special dosing consideration?
 5. Answer: Critically ill, burn and obese patients, because their volumes of distribution are abnormal and standard assumptions about concentration do not hold. [1]

References

- [1] Aminoglycosides (StatPearls). StatPearls Publishing / NCBI Bookshelf 2023. <https://www.ncbi.nlm.nih.gov/books/NBK541105/>
- [2] Gentamicin (StatPearls). StatPearls Publishing / NCBI Bookshelf 2023. <https://www.ncbi.nlm.nih.gov/books/NBK557550/>
- [3] Aminoglycosides (LiverTox). LiverTox, NIDDK / NCBI Bookshelf 2020. <https://www.ncbi.nlm.nih.gov/books/NBK548232/>

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