Pharmacology of Antibiotics: Aminoglycosides

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I am available to groups and individuals for pharmacology help and discussions by appointment.

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After completing the preparation materials, students will be able to:

1. Correlate the aminoglycosides' structure and pharmacokinetic properties with therapeutic monitoring of serum aminoglycoside concentrations and renal dosing.
2. Apply the aminoglycosides' pharmacokinetic / pharmacodynamic profile to dosing strategies.
3. Explain the aminoglycosides' mechanisms of antimicrobial action, antimicrobial spectrum, and mechanisms of resistance when selecting an aminoglycoside for the individual patient.
4. Predict the potential adverse effects, drug interactions, and contraindications of aminoglycoside therapy in relation to a patient's comorbidities and concomitant drug therapy when given a case vignette.

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Preparation Materials (links are in the CPG and on the next slide)

Required

- ScholarRx Bricks | Practice Questions

Highly relevant optional materials:

- Dr. Goldstein's Notes Handout | Video Lecture | Guided reading questions (GRQs)
- Textbooks and Examination Review Books (please see next slide)

SUGGESTIONS:

- ***Use the resources that work best for you.***
- ***You do not need to study all of them. (ScholarRx Bricks & Practice Questions are required.)***
- ***Work through the GUIDED READING QUESTIONS with pen/pencil and paper.***

Try answering them in your OWN WORDS first without looking at the readings, and then again after reviewing.

- ***Practice questions (not graded): Simple Recall and Case Vignettes***

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Resources listed in the class preparation guide (CPG):

Scholar Rx Brick: (required)

General Microbiology > Antimicrobial Agents > Antibacterial Drugs > Protein Synthesis Inhibitors
Link: https://exchange.scholarrx.com/brick/protein-synthesis-inhibitors

Suggested optional resources:

Katzung's Basic & Clinical Pharmacology, 16e, 2024; Chapter 45: Aminoglycosides & Spectinomycin

https://accessmedicine.mhmedical.com.nyit.idm.oclc.org/content.aspx?bookid=3382&sectionid=281754807

Katzung's Pharmacology: Examination & Board Review, 14e, 2024; Chapter 45: Aminoglycosides & Spectinomycin

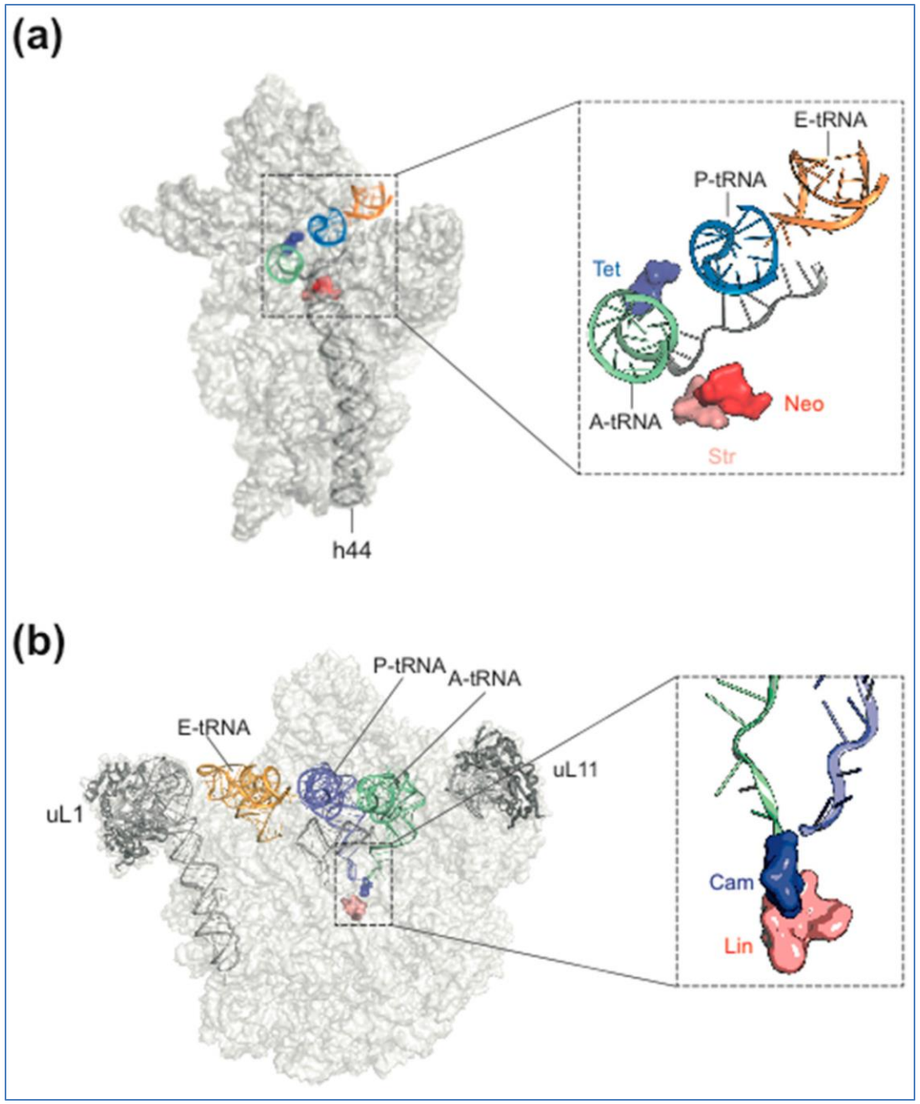
https://accessmedicine.mhmedical.com.nyit.idm.oclc.org/content.aspx?bookid=3461&sectionid=285598120

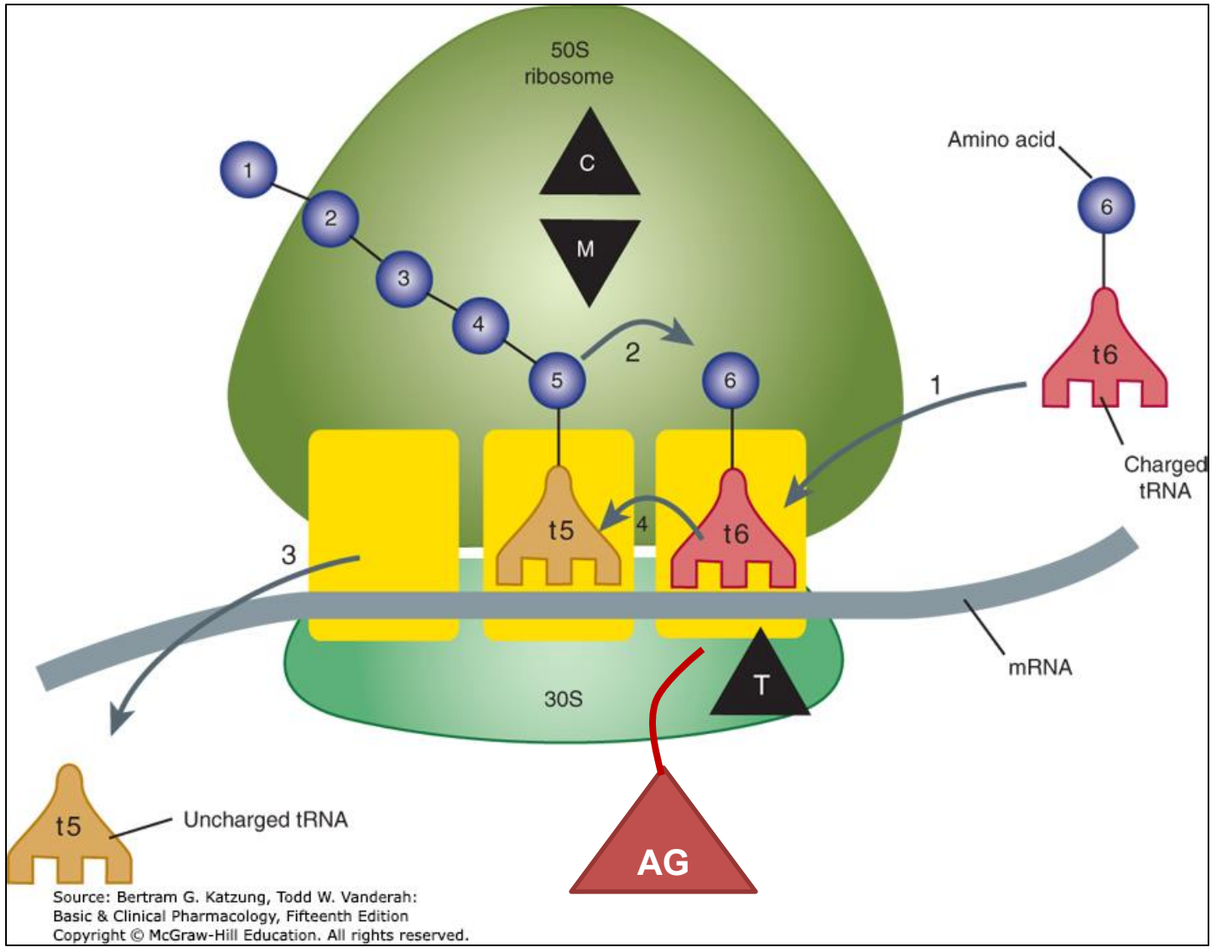
LWW Health Library, Medical Education: Lippincott's Illustrated Reviews: Pharmacology, 8e, 2023; Chapter 30: Protein Synthesis Inhibitors > Aminoglycosides

https://premiumbasicsciences.lwwhealthlibrary.com.nyit.idm.oclc.org/content.aspx?sectionid=253328689&bookid=3222

Medical Microbiology textbooks are available on NYITCOM Library website

Bacterial Ribosome





https://www.mdpi.com/2079-6382/5/2/18
MDPI Open Access
Ribosome Assembly as an Antimicrobial Target, 27 May 2016

McGraw-Hill Katzung Figure 44-1

Protein synthesis

- Several antibiotics produce antimicrobial effects by targeting bacterial ribosomes and inhibiting bacterial protein synthesis.
- Bacterial ribosomes are composed of 30S and 50S ribosomal subunits. They differ structurally from mammalian cytoplasmic ribosomes, which are composed of 40S and 60S subunits. However, mitochondrial ribosomes are similar to bacterial ribosomes in structure and size.
- In general, the antibacterial protein synthesis inhibitors are selective for the bacterial ribosome, minimizing potential adverse effects that would occur with inhibition of host protein synthesis.
- Protein synthesis inhibitors are bacteriostatic for the most part. Some have bactericidal activity against some bacteria. Aminoglycosides are bactericidal.
- Some protein synthesis inhibitors, notably chloramphenicol and linezolid and possibly others, can cause dose-dependent toxic effects due to inhibition of mitochondrial protein synthesis in host cells.

Definitions:

- The 30S and 50S ribosomes form the nucleosome complex that translates mRNA into protein.
- The 16S rRNA of the 30S ribosome is required for the initiation of protein synthesis and stabilization of correct codon-anticodon pairing in the A site of the ribosome during mRNA translation.
- The 23S rRNA of the 50S ribosome makes up the peptidyl transferase center, which catalyzes the polymerization of amino acids through peptide bonds.

Key points: What you need to know and understand about aminoglycosides

- Aminoglycosides (AGs) are amino sugars linked by glycosidic bonds → polar, hydrophilic compounds.
  PK properties:
  - Parenteral administration; they are not absorbed from the GI tract.
  - Distribute in body water; tissue penetration is limited with poor levels achieved in the cerebral spinal fluid unless meninges are inflamed. AGs cross the placenta.
  - Excretion as active drug is via glomerular filtration; clearance is directly proportional to creatinine clearance.
  - Half-life 2-3 h (adults with normal renal function) but once daily dosing for many infections

Plasma drug levels and serum creatinine monitoring are necessary for safe and effective use of aminoglycosides.

- AGs are bactericidal and are more active in alkaline pH than in acid pH.
- PK-PD profile: C_{max}/MIC
  - Concentration-dependent killing: The rate and extent of bacterial killing increase progressively with higher drug concentrations.
  - Prolonged persistent effects (post-antibiotic effect): Antibacterial activity persists beyond the time during which measurable drug is present. The post-antibiotic effect of aminoglycosides can last several hours.
- Dosing is also guided by AUC_{24}/MIC.

Key points

- AGs are protein synthesis inhibitors. They enter gram-negative bacteria across porins and are actively transported across the bacterial cytoplasmic membrane by an oxygen-dependent mechanism. AGs poorly penetrate the thick cell wall of gram-positive bacteria.
- AGs bind irreversibly to the 16S rRNA of the 30S ribosome and are believed to have a 3-way (at least) action:

  1) Interfere with the initiation complex of protein synthesis, which inhibits assembly of the functional ribosomal apparatus,

  2) Misreading and incorporation of incorrect amino acids resulting in production of abnormal nonfunctional proteins,

  3) Blocking translocation on the mRNA.
- Spectrum of activity: aerobic gram-negative bacteria, including Enterobacterales and *Pseudomonas* spp., and aerobic gram-positive bacteria, streptococci, enterococci, and staphylococci (but AGs poorly penetrate thick cell wall). Administration with a cell wall inhibitor enhances penetration and provides enhanced activity (synergy) for infectious endocarditis and certain other invasive gram-positive infections.
- Anaerobes and facultative anaerobes in anaerobic conditions are intrinsically resistant.

Key points

- Mechanisms of acquired resistance are:

  1) Expression of **drug-inactivating transferases** that acetylate, phosphorylate, or adenylate the aminoglycosides (the principal mechanism of resistance),

  2) Impaired drug entry by alteration or deletion of porin proteins or nonfunctional oxygen transport system, and

  3) Alteration or deletion of ribosomal receptor protein (uncommon – primary mechanism of *M. tuberculosis* resistance to streptomycin).
- Therapeutic uses: Empiric therapy for serious infections caused by drug-resistant bacteria in combination with other antibiotics to broaden the spectrum or for synergy
- When the susceptibility of the infective organism is established, the antibiotic therapy should be changed to a less toxic antibiotic, if appropriate.

Prolonged use of aminoglycosides is limited to life-threatening infections unresponsive to less toxic agents.

Key points

- Therapeutic uses:

Serious infections by 1) aerobic gram-negative bacilli, 2) infective endocarditis by aerobic gram-positive bacteria, 3) zoonoses: tularemia and plague, 4) drug-resistant tuberculosis

- Gentamicin and tobramycin are the most frequently used aminoglycosides.
- Amikacin and plazomicin are active against many gentamicin- and tobramycin-resistant strains and for multidrug resistant tuberculosis.
- Plazomicin: Treatment of complicated urinary tract infections not responsive to other antibiotics.
- Streptomycin: Treatment of tularemia and plague (zoonotic infections) and drug-resistant tuberculosis. Gram-negative resistance to streptomycin limits its use.
- Neomycin is too toxic for parenteral use. Formulated in combination with other antibacterial agents for topical skin, ophthalmic, and otic antibacterial products. Oral neomycin, which is not absorbed from the GI tract, is approved bowel sterilization prior to elective bowel surgery or to eliminate ammonia-producing bacteria in the management of hepatic encephalopathy.
- Paromomycin: Orally for luminal amoebias (not absorbed; remains in the GI tract). Intravenous paromomycin is a World Health Organization recommended topical treatment for cutaneous leishmaniasis and an intravenous alternative for visceral leishmaniasis (kala-azar).

Key points

- The aminoglycosides class adverse effects are:
  - nephrotoxicity,
  - ototoxicity, and
  - neuromuscular blockade (high doses).
- AGs accumulate in the proximal renal tubular cells leading to renal tubular dysfunction and glomerular dysfunction.
- Drug accumulation in the perilymph of the inner ear can cause vestibular toxicity with vertigo, ataxia, and loss of balance, and cochlear toxicity with high-frequency hearing loss. Ototoxicity may be irreversible.
- Neuromuscular blockade results from aminoglycoside inhibition of neurotransmitter release and decreased sensitivity of neuromuscular nicotinic receptors for acetylcholine with nondepolarizing neuromuscular block (curare-like effect).
- Aminoglycosides should be avoided in pregnant people unless the benefit to the mother outweighs the risk to the fetus due to the potential for irreversible bilateral congenital deafness. Of note, aminoglycosides' volume of distribution is increased in the pregnant patient, which reduces peak plasma concentrations, and the half-life is shortened due to increased clearance.

Key points

- Streptomycin, in addition to class toxicities, can cause neurotoxicities characterized by scotomas (blind spots) due to optic nerve toxicity and paresthesia commonly in the face and hands due to peripheral neuritis.
- Streptomycin can also cause hypersensitivity reactions and injection site reaction with pain and a hot tender mass developing.

Spectinomycin – Not an aminoglycoside – Rarely used but may be board relevant

Spectinomycin pharmacology is not included in this lecture. Here is a summary:

- Spectinomycin is an aminocyclitol antibiotic, not an aminoglycoside, given by I.M. injection and excreted by glomerular filtration.
- It binds the 30S ribosomal subunit and blocks protein synthesis as for the aminoglycosides except it does not cause misreading of mRNA. There is no cross-resistance.
- Spectinomycin is used almost exclusively for the treatment of drug-resistant gonorrhea. It is not used for treatment of pharyngeal gonococcal infections because of high failures rates.
- Pain at the injection site is common. Fever and nausea may occur.
- Spectinomycin is not available in the U.S. and availability elsewhere is limited.

Steps in bacterial protein synthesis and targets of several antibiotics. Amino acids are shown as numbered circles. The 70S ribosomal-mRNA complex is shown with its 50S and 30S subunits.

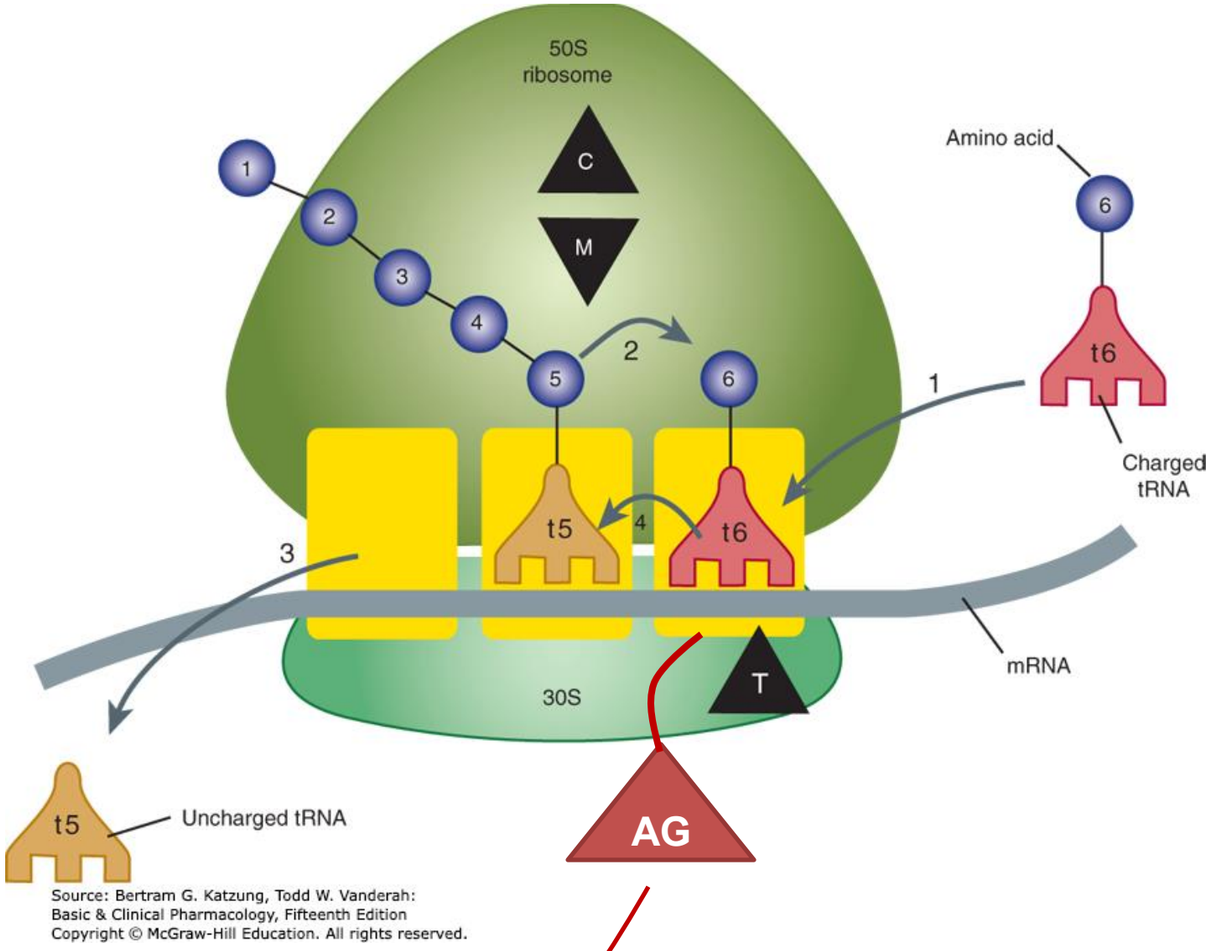
Step 1. The charged tRNA unit carrying amino acid 6 binds to the acceptor site on the 70S ribosome.

Step 2. The peptidyl tRNA at the donor site, with amino acids 1 through 5, then binds the growing amino acid chain to amino acid 6 (peptide bond formation).

The chain moves inside the polypeptide exit tunnel of the ribosome from the peptidyl transferase center towards the exit port where it emerges into the cytoplasm.

Step 3. The uncharged tRNA left at the donor site is released.

Step 4. The new 6-amino acid chain with its tRNA shifts to the peptidyl site (translocation).



The antibiotic binding sites are shown schematically as triangles.

Aminoglycosides (AG) irreversibly bind to the 16S rRNA on the 30S ribosome.

The tetracyclines (T) bind reversibly to the 30S subunit and prevent binding of the incoming charged tRNA unit (step 1).

Chloramphenicol (C) and macrolides (M) bind reversibly to the 50S subunit and block peptide bond formation (step 2).

Citation: Chapter 44 Tetracyclines, Macrolides, Clindamycin, Chloramphenicol, Streptogramins, Oxazolidinones, & Pleuromutilins, Katzung BG, Vanderah TW. *Basic & Clinical Pharmacology, 15e;* 2021, Figure 44-1. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=2988&sectionid=250601804 Accessed: October 27, 2021

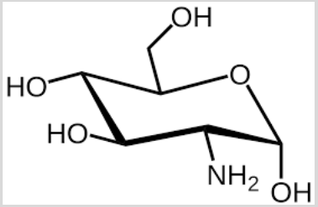
Figure adapted by LG

Aminoglycosides

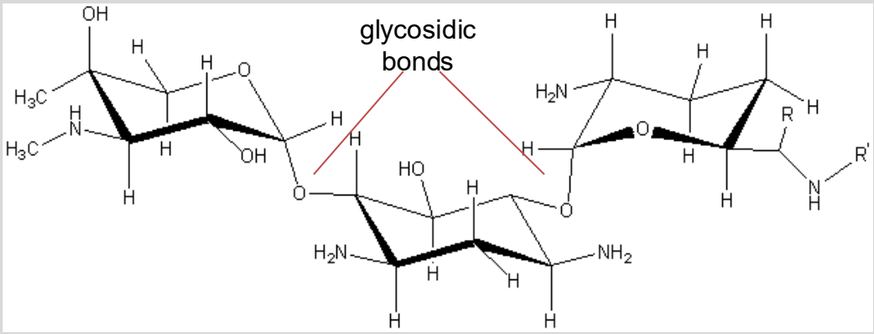
- Gentamicin
- Tobramycin
- Amikacin
- Streptomycin
- Plazomicin

Topical

- Paromomycin
- Neomycin



amino sugar



Gentamicin
Amino sugars are attached by glycosidic linkages.

Aminoglycosides (AGs) are…

- Amino sugars: Water soluble, highly polar, more active in alkaline pH than at acid pH
- Protein synthesis inhibitors, irreversible
- Bactericidal
- Active against aerobic gram-negative organisms
- Active against aerobic gram-positive streptococci, enterococci, staphylococci. Administered with a cell wall inhibitor for enhanced uptake of the AG and synergistic effect for treatment of certain gram-positive infections.

PK Properties of Aminoglycosides

THINK: NOT ORAL

- I.V. / I.M. / I.T., topical derm and ophthalmics

THINK: ↑ Vd in edema, fluid overload

- Distributed in extracellular fluid

- Poor penetration into tissues that are inflamed, low O_2 tension, low pH

Intrathecal →CNS (not neonates)

⇒ Poor penetration into CSF

THINK: TOXICITIES

- High concentrations accumulate in renal tubular cells and endolymph and perilymph of inner ear

THINK: potential FETOTOXICITY

- Cross placenta

THINK: DOSE ADJUSTMENT

- Rapid renal elimination (glomerular filtration)

⇒ $t_{1/2}$ normally: 2-3 hours

⇒ $t_{1/2}$ significant renal impairment: 24-48 hrs

Clearance

Aminoglycosides are cleared by the kidney.
Clearance is directly proportional to serum creatinine.

Caution ~

- ***Rapid changes in renal function can occur in critically ill patients and patients with acute kidney injury, septic shock, or major surgery.***
- Plasma drug levels and serum creatinine monitoring are necessary for safe and effective use of aminoglycosides.

Applying aminoglycosides PK-PD profile to dosing and efficacy

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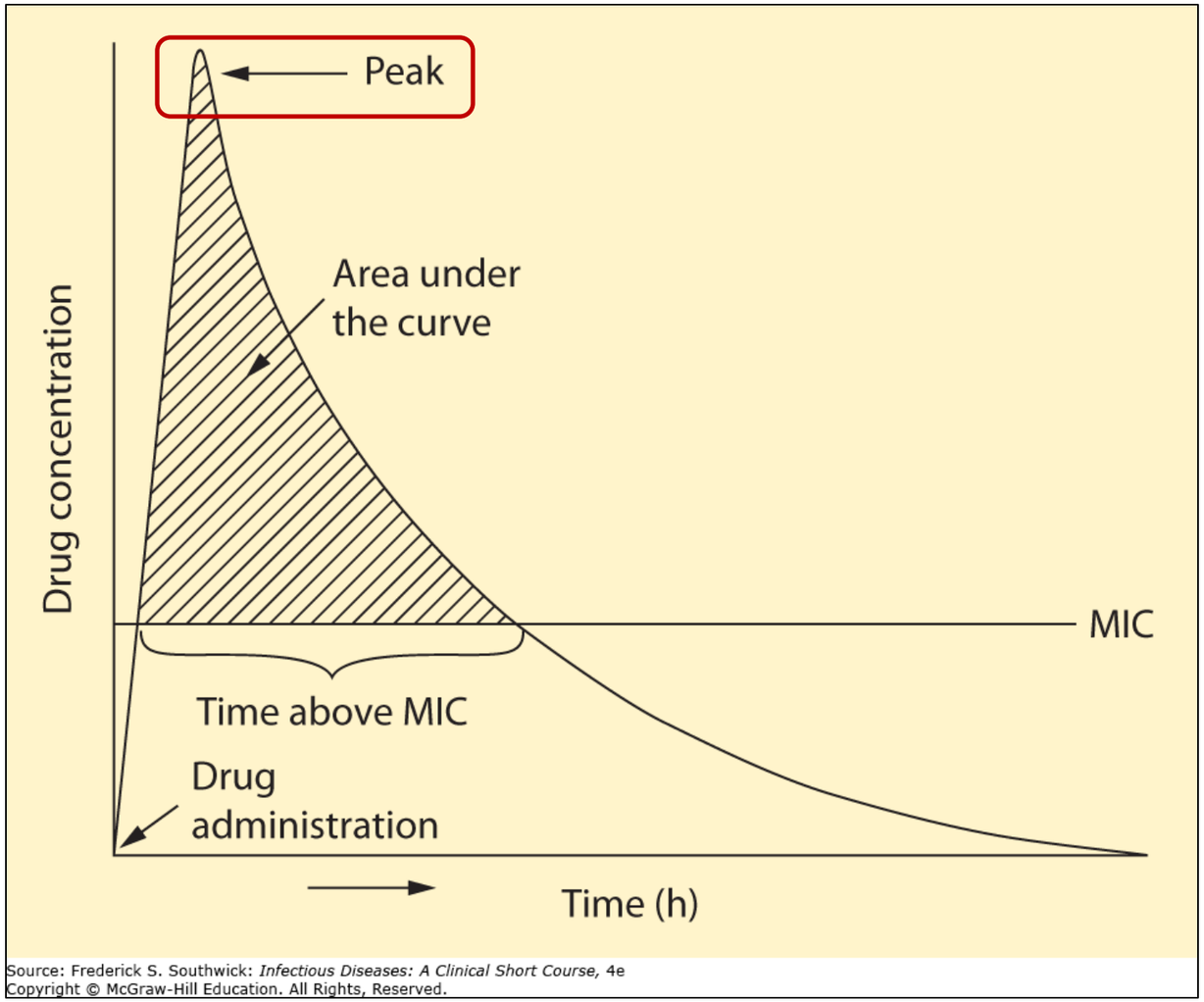
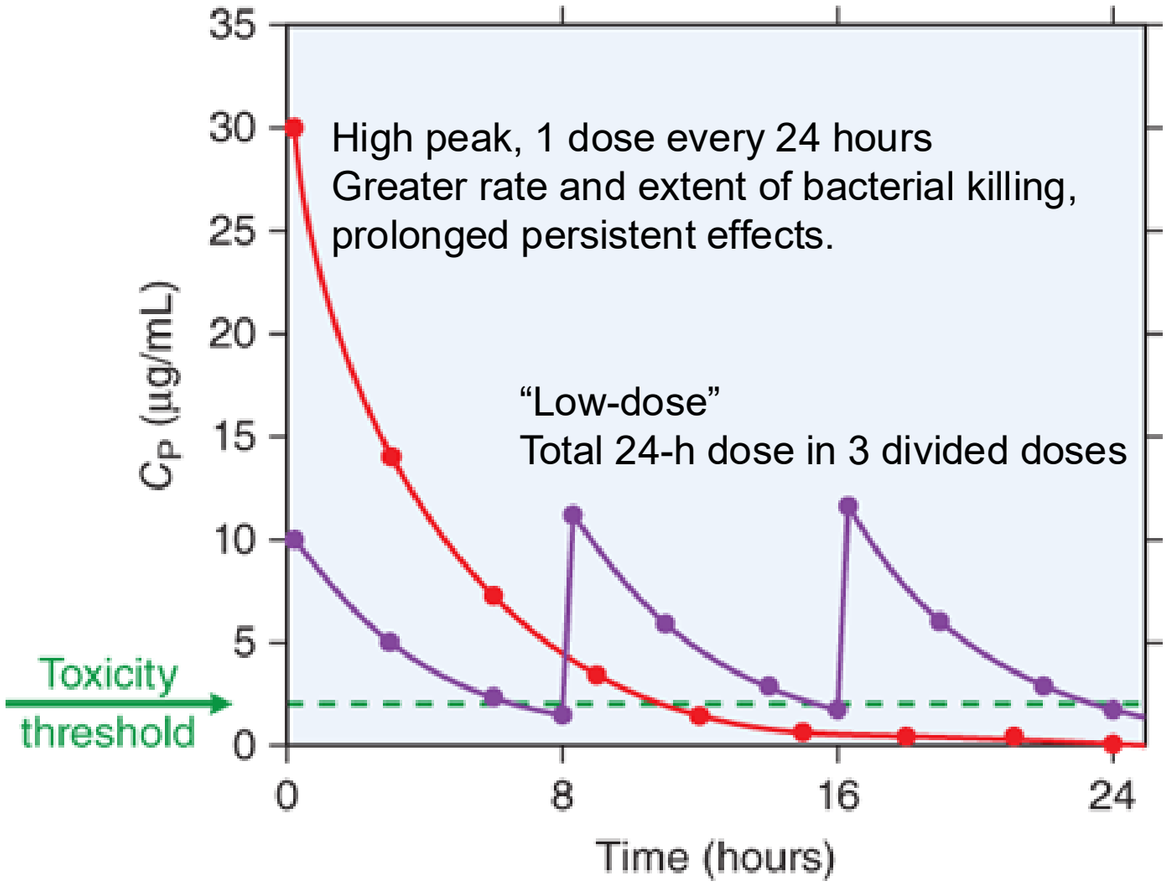
Peak / MIC (Cmax/MIC): **Concentration-dependent killing** ↑ $[Drug]_p$ → ↑ rate and ↑ extent of bacterial killing	**High-dose, extended interval dosing** Enhanced efficacy compared to lower dose regimens Associated with less nephrotoxicity
Post-antibiotic effect Suppression of bacterial growth persists beyond the time during which measurable drug is present. The duration of PAE is also concentration-dependent.	High-dose, extended interval dosing is the **preferred** means of administering aminoglycosides for most indications and patient populations, but not for pregnant patients, neonates, or for treatment of infective endocarditis.

AUC_{24}/MIC dosing strategies are consistent with efficacy.

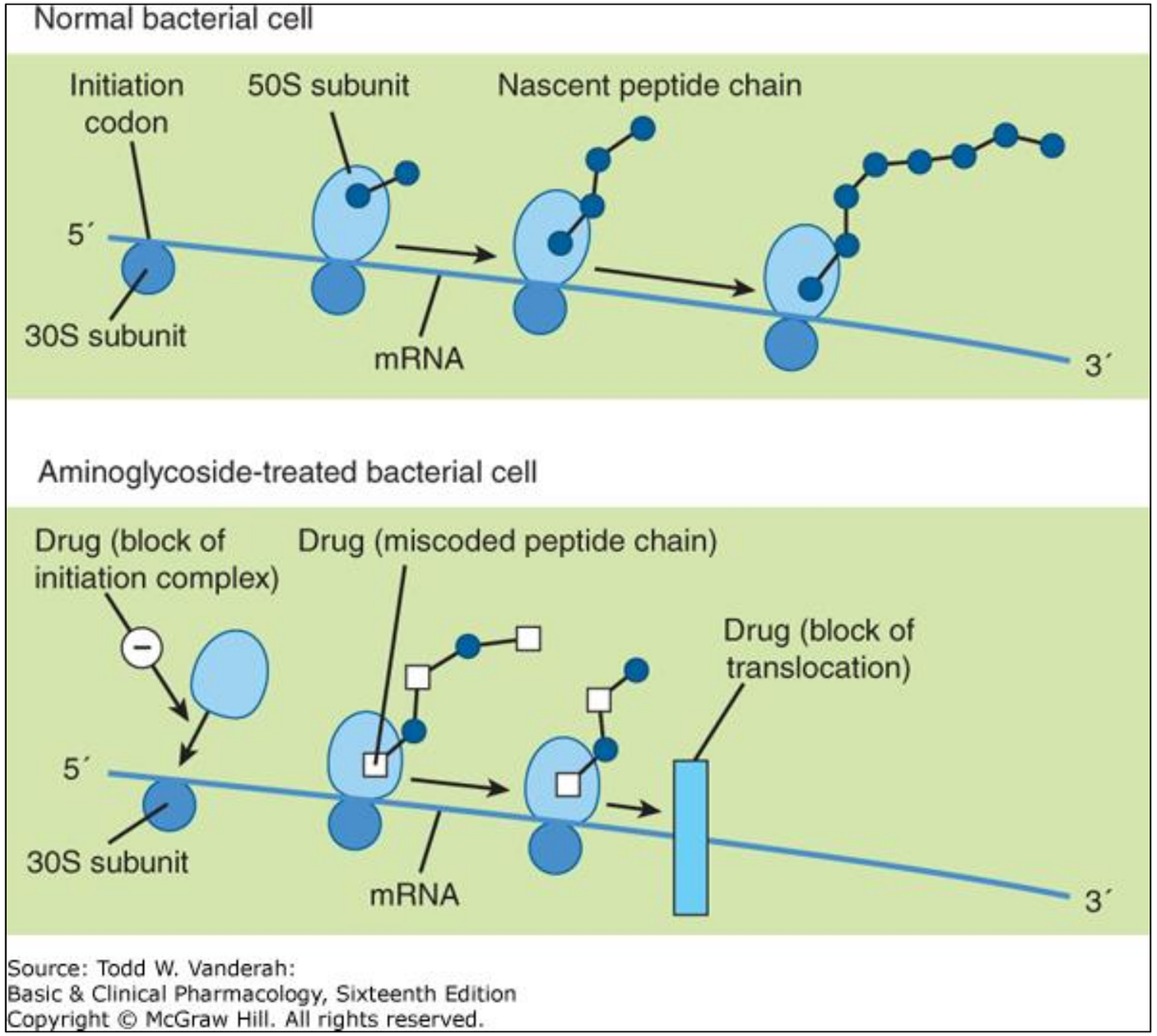
Goals have been defined for gram-negative bacilli.

Aminoglycosides PK-PD Profile: C_{max}/MIC and dosing strategies





AGs passively diffuse across porin channels in the outer membrane, then are actively transported across the cell membrane to the cytoplasm by an oxygen-dependent mechanism.



Source: Todd W. Vanderah:
Basic & Clinical Pharmacology, Sixteenth Edition

AGs bind the bacterial polysomes at the 16S rRNA on the 30S ribosome,

1. Blocking formation of the initiation complex;
2. Miscoding of amino acids in the emerging peptide chain due to misreading of the mRNA and incorporation of incorrect amino acid; and
3. Blocking translocation on mRNA.

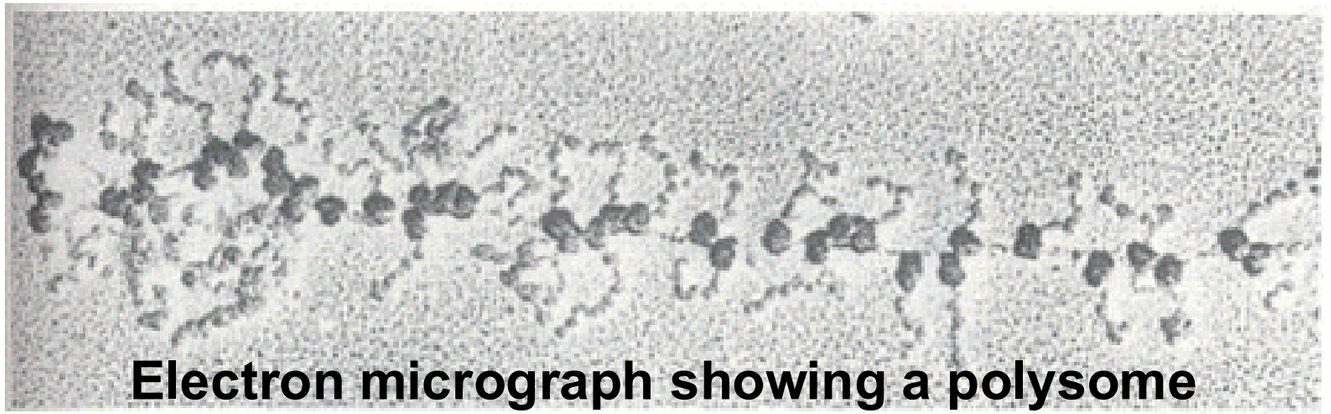
Other suggested mechanisms:

Aberrant proteins may be inserted into the cytoplasmic membrane causing leakage of small ions, then larger molecules, leading to cell death.

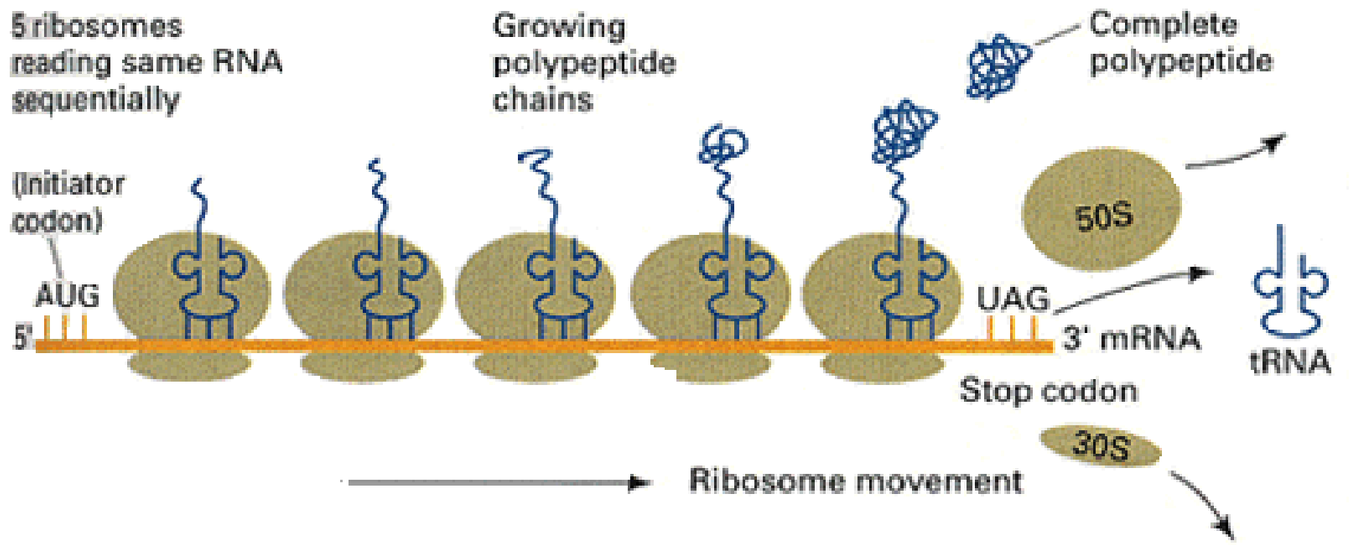
Blocking movement of the ribosome may occur after the formation of a single initiation complex, resulting in an mRNA chain with only a single ribosome on it, which is called a monosome.

Citation: Chapter 45 Aminoglycosides & Spectinomycin, Vanderah TW. *Katzung's Basic & Clinical Pharmacology, 16th Edition;* 2024, Figure 45-3. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3382&sectionid=281754807 Accessed: August 13, 2024

Bacterial polysome: Several ribosomes strung out along the mRNA strand



Electron micrograph showing a polysome



Schematic diagram of generalized polysome representing the process in the above panel.

http://www.slideshare.net/diverzippy/bioknowledgy-presentation-on-73-translation-ahl
http://urei.bio.uci.edu/~hudel/bs99a/lecture21/index.html (Harmut Hudel Lueke UC Irvine

Aminoglycosides Spectrum of Activity and Bacterial Resistance

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Spectrum of activity	Aerobic gram-negative bacilli (Enterobacterales) and *P. aeruginosa* Aerobic gram-positive bacteria (strepto-, staphylo-, enterococci) but poorly penetrate intact thick peptidoglycan cell wall and are not reliably effective when used alone.
Intrinsic resistance:	Anaerobic bacteria / Facultative anaerobes in anaerobic environment
Acquired resistance:	1. Inactivation: Production of transferase enzymes that inactivate the drugs by phosphorylation, adenylation, or acetylation The main type of resistance.
	2. Impaired entry: – Alteration or deletion of porin proteins involved in AG transport – Nonfunctional oxygen-dependent transport process, as in anaerobic conditions.
	3. Target alteration: Mutation of binding site on 30S ribosome, so that drug binding to the target does not occur (M. tuberculosis resistance to streptomycin)

Cross-resistance can occur but is unpredictable. Susceptibility tests should be done.

Aminoglycosides General Therapeutic Uses

Serious infections by 1) aerobic gram-negative bacilli, 2) infective endocarditis by aerobic gram-positive bacteria, 3) zoonoses: tularemia and plague, 4) drug-resistant tuberculosis

Empiric therapy: **aerobic gram-negative bacilli** Gentamicin, Tobramycin Amikacin: genta-, tobramycin resistance Always used in combination with antibiotics from another class to broaden spectrum	**Infective endocarditis for enhanced uptake of AG and synergy** Enterococcus, viridans Streptococcus, Staphylococcus Combination with penicillin, ampicillin, or ceftriaxone (vancomycin in penicillin-allergic patients)
Directed therapy: When the susceptibility of the infective organism is established, the antibiotic therapy should be changed to a less toxic antibiotic, if appropriate.	***Prolonged use of aminoglycosides is limited to life-threatening infections unresponsive to less toxic agents.***

Comparing the activity and uses of the aminoglycosides

<table>
<tr><td colspan="2">Gentamicin and Tobramycin: Comparable activity for treatment of serious infections</td></tr>
<tr><td>Gentamicin
• More active against Enterobacterales
• Synergy in combination with cell wall inhibitor against E. faecalis and E. faecium
(every 8 hours rather than once daily)
• Zoonoses: tularemia and plague</td><td>Tobramycin
• Slightly more active than gentamicin against P. aeruginosa.
• Not active against enterococci
• Oral inhalation: Pseudomonas lung infection in cystic fibrosis patients</td></tr>
<tr><td colspan="2">Amikacin and Plazomicin: Active against many gentamicin- and tobramycin-resistant strains</td></tr>
<tr><td>Amikacin
• Tx of gentamicin-resistant GNB infections
• Tx of MDR tuberculosis</td><td>Plazomicin
• Tx of complicated UTIs MDR GNBs – last line
• Plague</td></tr>
<tr><td>Streptomycin
Zoonoses: tularemia and plague
MDR tuberculosis</td><td>Neomycin: Topical only in combination with other antibiotics to broaden spectrum of activity
• GI: reduce bowel flora prior to bowel surgery
• Skin, Ophthalmic drops, Otic drops
• Hypersensitivity: frequent contact allergen → allergic dermatitis</td></tr>
</table>

GNB: gram-negative bacteria; MDR: multidrug resistant; UTI: urinary tract infection

Aminoglycoside Toxicities

Nephrotoxicity

Ototoxicity

Neuromuscular blockade (high AG doses)

Risk factors for nephrotoxicity and ototoxicity

- Advanced age
- Renal insufficiency
- Persistently elevated concentrations of drug in plasma
- Aminoglycoside therapy > 5 days
- Previous exposure to aminoglycosides
- Other nephrotoxic and/or ototoxic drugs

Nephrotoxicity

Aminoglycoside accumulation in the proximal tubular cells

⇓

progressive

tubular cell damage

and

glomerular dysfunction

- More likely with longer courses of therapy
- High-dose, extended-interval dosing

less nephrotoxicity than divided-dose approaches

- Renal impairment often reversible

(proximal tubular cells can regenerate)

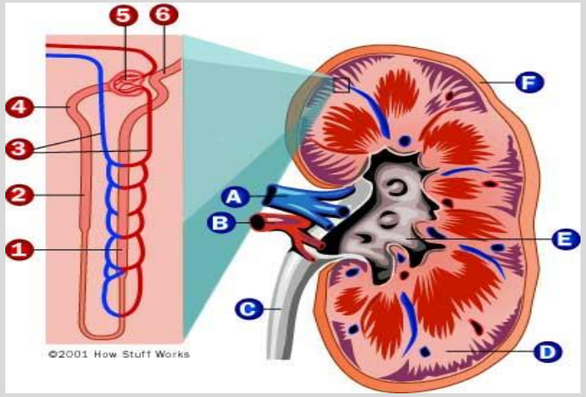

Figure Discovery Health health.howstuffworks.com/.../kidney2.htm

Ototoxicity: Aminoglycoside accumulation in perilymph of inner ear

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- **Progressive** destruction of vestibular or cochlear sensory cells
- **Irreversible** once sensory cells are lost

Associated with:

1. high peak plasma levels and
2. duration of aminoglycoside therapy

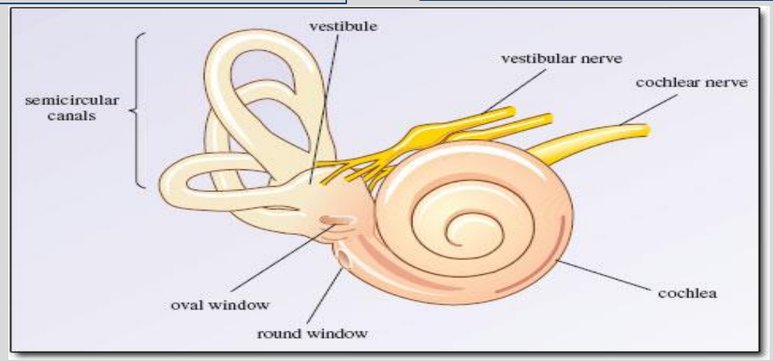
- **Risk factors:** preexisting auditory impairment; ototoxic drugs; genetic susceptibility?

Cochlear toxicity: degeneration of hair cells and neurons

- tinnitus, loss of hearing; regeneration does not occur

Vestibular toxicity: labyrinthine dysfunction

- acute Sx: headache, dizziness, loss of balance; nystagmus



openlearn.open.ac.uk/mod/oucontent/view.php?i

Neuromuscular Blockade

acute neuromuscular blockade can cause respiratory paralysis

1. May inhibit prejunctional release of the neurotransmitter, acetylcholine

Probable mechanism: competition with Ca^{2+} at prejunctional VG Ca^{2+} channels

2. May block NM nicotinic receptors $\rightarrow \downarrow$ sensitivity to acetylcholine
   - Anesthesia; neuromuscular blockers
   - Intrapleural or intraperitoneal installation of aminoglycoside
   - Reported with IV / IM injections

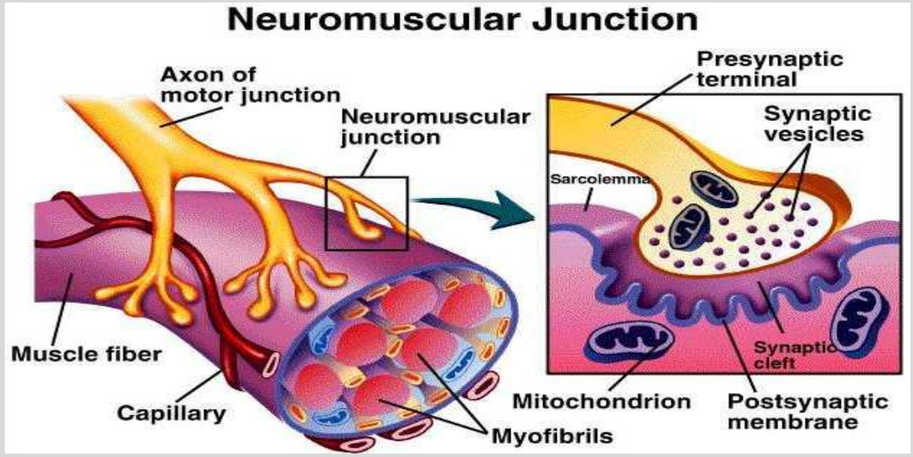


Figure: demo.classontheweb.com/CBSE/ClassX/Science/ge...

Streptomycin toxicities

In addition to class toxicities:

- Neurotoxicities
  - Optic nerve: Scotomas (blind spot) reported
  - Peripheral neuritis: Paresthesia, perioral, face, hands are common
    - occur within 30-60 minutes , may persist for several hours
- Hypersensitivity reactions
- Injection site reactions: hot tender mass

Figure: https://affinityeyecaregroup.com/why-do-i-have-a-blind-spot-in-my-vision-what-to-know-about-a-scotoma/

Aminoglycosides Cautions

Myathenia gravis	risk of respiratory depression due to neuromuscular acetylcholine receptor blocking effect (MG is an autoimmune disease that causes muscle weakness.)
Pregnancy	congenital bilateral deafness and renal toxicity reported
PK in pregnancy	$\uparrow V_d \rightarrow \downarrow C_{p\,max}$ (peak serum concentration) shorter t½ due to increased clearance
Lactation	not recommended; could cause modification of infant's intestinal flora
Drug interactions	Concomitant nephrotoxic and/or ototoxic drugs **vancomycin**; furosemide; cyclosporine; cisplatin; amphotericin B; **neuromuscular blockers** (succinylcholine, rocuronium, atracurium)

Summary of
Aminoglycosides Pharmacology

- Aminoglycosides in current use are streptomycin, gentamicin, tobramycin, amikacin, plazomicin, neomycin, and paromomycin. They are amino sugars used parenterally only for systemic infections, as they are not absorbed from the GI tract. They distribute in extracellular fluid and are renally excreted by glomerular filtration. Monitor renal function and serum drug levels.
- AGs bind the 16S rRNA on the 30S subunit. Their probable mechanisms are interference with the initiation complex, misreading the mRNA and incorporating incorrect amino acids, inhibiting translocation on mRNA.
- AGs are active against aerobic gram-negative bacteria. Combined with a cell wall inhibitor, AGs enhance efficacy (synergy) against aerobic gram-positive bacteria for certain infections (ie, infective endocarditis).
- The most frequent mechanism of resistance is drug-inactivating enzymes (acetyl-, phospho-, and adenyltransferases), which confer high-level resistance.
- Amikacin and plazomicin have activity against gentamicin- and tobramycin-resistant bacteria.

- AGs are used in combination with a cell wall inhibitor to treat serious gram-negative infections, including zoonoses tularemia and plague, and infective endocarditis, which is a gram-positive disease. Gentamicin, amikacin, and streptomycin are options for treatment of drug-resistant tuberculosis in combination with other antimycobacterial agents.
- Amikacin and plazomicin have activity against gentamicin- and tobramycin-resistant infections. Amikacin is used in the treatment of various AG-resistant GNB infections. Plazomicin is indicated for complicated MDR urinary tract infections not responsive to other antibiotics.
- Gentamicin, tobramycin, and neomycin are available in topical formulations for dermatological, ophthalmic, and otic products. Neomycin is for topical use only in combination with other antibiotics to broaden the spectrum of activity.
- All AGs are nephrotoxic and ototoxic. Risk factors are more than 5 days of use, renal insufficiency and older age. Other nephrotoxic and/or ototoxic drugs can potentiate the toxicities and should be avoided. At high doses, AGs can produce curare-like neuromuscular blockade that results in respiratory failure. Hypersensitivity occurs infrequently.
- Neomycin is a frequent cause of allergic dermatitis.

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