NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

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

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.

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 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.

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

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

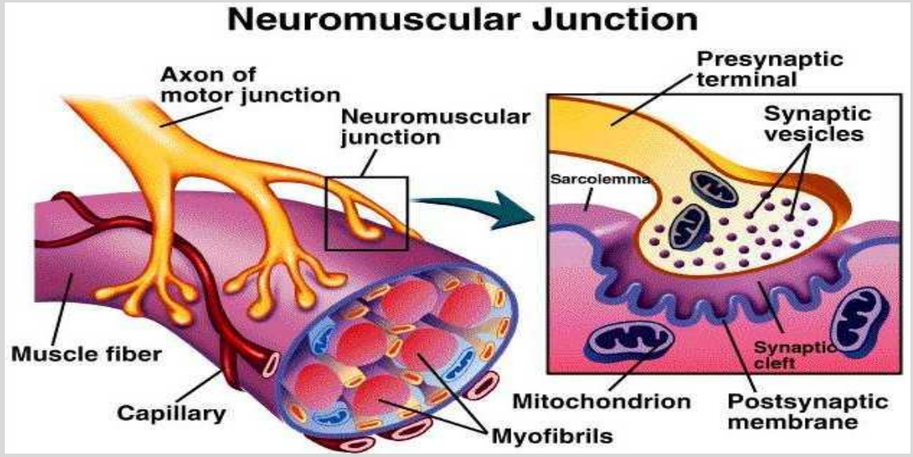

Figure: demo.classontheweb.com/CBSE/ClassX/Science/ge...