Chapter-8

Antibiotic

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ABSTRACT

Antibiotics are powerful medications used to treat infections caused by bacteria. They work by either killing the bacteria or inhibiting their growth, thus helping the body's immune system to combat the infection. Different antibiotics target specific bacterial processes, such as cell wall synthesis, protein production, or DNA replication. Common classes of antibiotics include penicillins, cephalosporins, tetracyclines, macrolides, and aminoglycosides, each with distinct mechanisms of action and spectra of activity. Antibiotics are typically prescribed based on the type of bacteria causing the infection and the location of the infection in the body. However, the overuse and misuse of antibiotics have led to the growing problem of antibiotic resistance, where bacteria evolve to withstand the effects of these drugs. This makes it increasingly challenging to treat common infections and underscores the importance of using antibiotics judiciously. Side effects of antibiotics can range from mild, such as gastrointestinal discomfort, to severe, including allergic reactions and antibiotic-associated colitis. Healthcare providers must carefully consider the appropriate antibiotic choice, dosage, and duration of therapy to ensure effectiveness and minimize the risk of resistance and side effects. Research continues to develop new antibiotics and strategies to combat resistant bacterial strains, but the prudent use of existing antibiotics remains crucial in safeguarding their efficacy for future generations.

Introduction

Antibiotics are a class of drugs or substances that are used to treat bacterial infections. They work by either killing bacteria or inhibiting their growth and reproduction, ultimately helping the body's immune system to overcome the infection. Antibiotics are specific to bacteria and do not work against viral infections. They have been a crucial tool in modern medicine for treating various bacterial diseases and have significantly contributed to improving human health and increasing life expectancy. Antibiotics can be prescribed by healthcare professionals, and their use should be strictly monitored to prevent the development of antibiotic-resistant bacteria.

Penicillins

Penicillins are a group of antibiotics that are derived from the mold Penicillium. They were the first antibiotics to be discovered and have played a crucial role in the treatment of bacterial infections. The discovery of penicillin by Sir Alexander Fleming in 1928 marked a

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significant milestone in the field of medicine, as it introduced an effective treatment for a wide range of bacterial diseases.

Classification of Penicillins

Penicillins are classified based on their spectrum of activity, resistance to beta-lactamase, and their pharmacokinetic properties. Here is a detailed classification:

1. **Natural penicillins** are the original penicillins derived from the Penicillium mold. They are primarily effective against Gram-positive organisms.
   - **Penicillin G (Benzylpenicillin):** Usually administered parenterally due to poor oral absorption.
   - **Penicillin V (Phenoxymethylpenicillin):** Acid-stable and can be taken orally.

2. **Penicillinase-Resistant Penicillins (Antistaphylococcal Penicillins)**

   These penicillins are resistant to degradation by beta-lactamase enzymes produced by Staphylococcus aureus.
   - **Methicillin:** No longer used clinically due to nephrotoxicity.
   - **Nafcillin:** Used for serious staphylococcal infections.
   - **Oxacillin:** Similar to nafcillin, used in treating staphylococcal infections.
   - **Dicloxacillin:** Oral formulation, used for staphylococcal infections.
   - **Cloxacillin:** Similar to dicloxacillin, available in oral and parenteral forms.

3. **Aminopenicillins**

   Aminopenicillins have a broader spectrum of activity, including some Gram-negative organisms. They are susceptible to beta-lactamase.
   - **Ampicillin:** Can be administered orally or parenterally; used for various infections including respiratory and urinary tract infections.
   - **Amoxicillin:** Better oral absorption compared to ampicillin; commonly used for respiratory infections, otitis media, and as part of the regimen for H. pylori eradication.

4. **Extended-Spectrum Penicillins (Antipseudomonal Penicillins)**

   These penicillins have an extended spectrum of activity, including activity against Pseudomonas aeruginosa and other Gram-negative bacteria.
   - **Carboxypenicillins**
     - **Carbenicillin:** Effective against Pseudomonas and other Gram-negative organisms; rarely used today.
     - **Ticarcillin:** Often used in combination with clavulanate to broaden the spectrum.
   - **Ureidopenicillins**
     - **Piperacillin:** Effective against a wide range of Gram-negative organisms, including Pseudomonas; often used in combination with tazobactam.

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- **Mezlocillin:** Similar to piperacillin but less commonly used.

5. **Beta-Lactamase Inhibitor Combinations**

   These combinations include a penicillin antibiotic and a beta-lactamase inhibitor, which extends the spectrum of activity by protecting the penicillin from degradation by beta-lactamase enzymes.

   - **Amoxicillin/Clavulanate (Augmentin):** Broad-spectrum antibiotic used for respiratory infections, UTIs, skin infections, etc.
   - **Ampicillin/Sulbactam (Unasyn):** Used for intra-abdominal infections, gynecological infections, and skin infections.
   - **Piperacillin/Tazobactam (Zosyn):** Used for severe infections, including intra-abdominal, skin, and respiratory infections.
   - **Ticarcillin/Clavulanate (Timentin):** Used for severe infections, particularly those caused by resistant Gram-negative organisms.

Pharmacology of Penicillins

1. **Mechanism of Action:** Penicillins are beta-lactam antibiotics that inhibit bacterial cell wall synthesis. They bind to and inactivate penicillin-binding proteins (PBPs), which are essential for the cross-linking of the bacterial cell wall peptidoglycan. This leads to a weakened cell wall and ultimately causes bacterial cell lysis and death, particularly during cell division.

2. **Spectrum of Activity:** Penicillins are effective against a variety of Gram-positive bacteria and some Gram-negative bacteria. They are particularly potent against Streptococcus species, Neisseria meningitidis, and some anaerobes.

3. **Pharmacokinetics:** Penicillins are absorbed from the gastrointestinal tract, though some are destroyed by gastric acid. They distribute widely in body tissues and fluids but have limited penetration into the cerebrospinal fluid except when the meninges are inflamed. They are primarily excreted by the kidneys, with a short half-life requiring frequent dosing.

4. **Clinical Uses:** Penicillins are used to treat infections such as streptococcal pharyngitis, syphilis, meningitis, and infections caused by susceptible staphylococci and pneumococci.

5. **Adverse Effects:** Common side effects include allergic reactions (rash, anaphylaxis), gastrointestinal disturbances, and rarely, interstitial nephritis and hematologic toxicity.

6. **Resistance Mechanisms:** Bacterial resistance to penicillins can occur via the production of beta-lactamase enzymes that hydrolyze the beta-lactam ring, altering PBPs, and reducing drug uptake.

Pharmacology of Cephalosporins

1. **Mechanism of Action:** Cephalosporins, like penicillins, are beta-lactam antibiotics that inhibit bacterial cell wall synthesis by binding to PBPs, leading to cell lysis and death.

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2. **Spectrum of Activity:** Cephalosporins have a broader spectrum of activity compared to penicillins, and their spectrum varies by generation:
   - **First-Generation:** Effective mainly against Gram-positive cocci and some Gram-negative rods.
   - **Second-Generation:** Increased activity against Gram-negative bacteria, including Haemophilus influenzae and Enterobacter species.
   - **Third-Generation:** Broad-spectrum activity, including Pseudomonas aeruginosa and better CNS penetration.
   - **Fourth-Generation:** Broad-spectrum activity with improved stability against beta-lactamases.
   - **Fifth-Generation:** Effective against MRSA and resistant Gram-negative bacteria.

3. **Pharmacokinetics:** Cephalosporins are well absorbed orally and parenterally, widely distributed in body tissues and fluids, and some can penetrate the CNS. They are primarily excreted by the kidneys.

4. **Clinical Uses:** Cephalosporins treat a variety of infections, including pneumonia, skin infections, urinary tract infections, septicemia, and meningitis.

5. **Adverse Effects:** Similar to penicillins, cephalosporins can cause allergic reactions, gastrointestinal disturbances, and in rare cases, nephrotoxicity and hematologic abnormalities.

6. **Resistance Mechanisms:** Resistance mechanisms include beta-lactamase production, altered PBPs, and reduced permeability to the drug.

Pharmacology of Chloramphenicol

1. **Mechanism of Action:** Chloramphenicol inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit, preventing peptide bond formation. This action is bacteriostatic, meaning it inhibits bacterial growth without killing the cells.

2. **Spectrum of Activity:** Chloramphenicol has a broad spectrum of activity, effective against many Gram-positive and Gram-negative bacteria, rickettsiae, and anaerobes. It is particularly useful for treating infections where other antibiotics are ineffective.

3. **Pharmacokinetics:** Chloramphenicol is well absorbed orally, widely distributed in body tissues and fluids, including the CNS, and metabolized in the liver. It is excreted in the urine primarily as inactive metabolites.

4. **Clinical Uses:** Chloramphenicol is used to treat serious infections like typhoid fever, meningitis, and rickettsial infections when other antibiotics are contraindicated or ineffective.

5. **Adverse Effects:** Chloramphenicol can cause serious side effects, including bone marrow suppression leading to aplastic anemia, dose-related anemia, and gray baby syndrome in neonates. Other side effects include gastrointestinal disturbances and hypersensitivity reactions.

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6. **Resistance Mechanisms:** Resistance to chloramphenicol can occur through the production of chloramphenicol acetyltransferase, which inactivates the drug, as well as through efflux pumps and ribosomal mutations.

Cephalosporins

Cephalosporins are a class of antibiotics that are structurally related to penicillins and are used to treat a wide range of bacterial infections. They are classified into different generations based on their spectrum of activity and characteristics. Here's a definition of cephalosporins with their classification:

Definition

Cephalosporins are a group of beta-lactam antibiotics that inhibit the synthesis of bacterial cell walls by binding to penicillin-binding proteins (PBPs), ultimately leading to bacterial cell death. They are used to treat various bacterial infections, including respiratory tract infections, urinary tract infections, skin and soft tissue infections, and more.

Classification of Cephalosporins by Generation

1. **First-Generation Cephalosporins:** These antibiotics are effective against Gram-positive bacteria, including some Streptococcus and Staphylococcus species. They also have some activity against a limited number of Gram-negative bacteria. Examples include cephalexin and cefazolin.

2. **Second-Generation Cephalosporins:** This generation offers a broader spectrum of activity, with improved coverage of Gram-negative bacteria. They are often used to treat respiratory and urinary tract infections. Examples include cefuroxime and cefoxitin.

3. **Third-Generation Cephalosporins:** These antibiotics have an even wider spectrum of activity against both Gram-positive and Gram-negative bacteria, including some that are resistant to earlier-generation cephalosporins. They are commonly used to treat serious infections. Examples include ceftriaxone and cefotaxime.

4. **Fourth-Generation Cephalosporins:** This generation retains a broad spectrum of activity and exhibits increased resistance to certain beta-lactamases. They are often used to treat infections caused by multidrug-resistant bacteria. An example of a fourth-generation cephalosporin is cefepime.

5. **Fifth-Generation Cephalosporins:** Fifth-generation cephalosporins have an even broader spectrum of activity, including enhanced activity against multidrug-resistant Gram-negative bacteria. They are often used in complex hospital-acquired infections. An example of a fifth-generation cephalosporin is ceftolozane/tazobactam.

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Classification of Macrolides

1. **Based on Structure and Spectrum of Activity**
   - **14-membered Ring Macrolides**
     - **Erythromycin:** The prototype macrolide, used for respiratory and skin infections.
     - **Clarithromycin:** Similar to erythromycin but with better absorption and a broader spectrum.
     - **Roxithromycin:** Improved gastrointestinal tolerance compared to erythromycin.
   - **15-membered Ring Macrolides (Azalides)**
     - **Azithromycin:** Enhanced tissue penetration and prolonged half-life, effective for respiratory and sexually transmitted infections.
   - **16-membered Ring Macrolides**
     - **Spiramycin:** Used in toxoplasmosis and some respiratory infections.
     - **Josamycin:** Effective for respiratory and skin infections, with a broader spectrum against Gram-positive bacteria.

2. **Based on Generations**
   - **First Generation**
     - Erythromycin
   - **Second Generation**
     - Clarithromycin
     - Azithromycin
     - Roxithromycin

Classification of Quinolones

1. **Based on Generations**
   - **First Generation (Non-fluorinated Quinolones)**
     - **Nalidixic Acid:** Primarily used for urinary tract infections.
   - **Second Generation (Early Fluoroquinolones)**
     - **Ciprofloxacin:** Broad spectrum, effective against Gram-negative bacteria and some Gram-positive bacteria, used for UTIs, respiratory, and gastrointestinal infections.
     - **Norfloxacin:** Primarily used for UTIs and prostatitis.
   - **Third Generation (Extended Spectrum Fluoroquinolones)**
     - **Levofloxacin:** Improved activity against Gram-positive bacteria, used for respiratory and urinary tract infections.
     - **Sparfloxacin:** Enhanced activity against Gram-positive bacteria and atypical pathogens.

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- **Fourth Generation (Advanced Spectrum Fluoroquinolones)**
  - **Moxifloxacin:** Broad spectrum, effective against Gram-positive, Gram-negative, and anaerobic bacteria, used for respiratory and skin infections.
  - **Trovafloxacin:** Broad spectrum, effective against Gram-positive, Gram-negative, and anaerobic bacteria, used for respiratory and skin infections.

Pharmacology of Macrolides

1. **Mechanism of Action:** Macrolides inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit. This binding prevents the translocation step of protein synthesis, effectively stopping the growth of bacteria. Macrolides are typically bacteriostatic but can be bactericidal at higher concentrations or against certain bacteria.

2. **Spectrum of Activity:** Macrolides have a broad spectrum of activity, particularly effective against Gram-positive cocci (e.g., Streptococcus and Staphylococcus species), some Gram-negative bacteria (e.g., Haemophilus influenzae, Bordetella pertussis), and atypical pathogens (e.g., Mycoplasma, Chlamydia, and Legionella).

3. **Pharmacokinetics:** Macrolides are well absorbed from the gastrointestinal tract, though food can affect absorption. They are widely distributed in body tissues and fluids but have limited penetration into the cerebrospinal fluid. They are metabolized in the liver and excreted in bile and urine.

4. **Clinical Uses:** Macrolides are used to treat respiratory tract infections, skin infections, sexually transmitted infections (e.g., chlamydia), and Helicobacter pylori infections in combination therapy. They are also an alternative for patients allergic to penicillins.

5. **Adverse Effects:** Common side effects include gastrointestinal disturbances (nausea, vomiting, diarrhea), hepatotoxicity, and ototoxicity. Macrolides can also prolong the QT interval, increasing the risk of cardiac arrhythmias.

6. **Resistance Mechanisms:** Resistance can develop through modification of the ribosomal target site (methylation), efflux pumps, and enzymatic inactivation of the drug.

Classification of Quinolones

1. **Based on Generations**
   - **First Generation (Non-fluorinated Quinolones)**
     - **Nalidixic Acid:** Primarily used for urinary tract infections.
   - **Second Generation (Early Fluoroquinolones)**
     - **Ciprofloxacin:** Broad spectrum, effective against Gram-negative bacteria and some Gram-positive bacteria, used for UTIs, respiratory, and gastrointestinal infections.
     - **Norfloxacin:** Primarily used for UTIs and prostatitis.

- **Third Generation (Extended Spectrum Fluoroquinolones)**
  - **Levofloxacin:** Improved activity against Gram-positive bacteria, used for respiratory and urinary tract infections.
  - **Sparfloxacin:** Enhanced activity against Gram-positive bacteria and atypical pathogens.
- **Fourth Generation (Advanced Spectrum Fluoroquinolones)**
  - **Moxifloxacin:** Broad spectrum, effective against Gram-positive, Gram-negative, and anaerobic bacteria, used for respiratory and skin infections.
  - **Trovafloxacin:** Broad spectrum, effective against Gram-positive, Gram-negative, and anaerobic bacteria, used for respiratory and skin infections.

Classification of Fluoroquinolones

1. **Based on Generations**

- **Second Generation (Early Fluoroquinolones)**
  - Ciprofloxacin
  - Norfloxacin
  - Ofloxacin
- **Third Generation (Respiratory Fluoroquinolones)**
  - Levofloxacin
  - Sparfloxacin
- **Fourth Generation (Enhanced Activity Against Gram-positive and Anaerobes):**
  - Moxifloxacin
  - Trovafloxacin
  - Gemifloxacin

2. **Based on Spectrum of Activity**

- **Gram-negative Activity**
  - Ciprofloxacin
  - Norfloxacin
- **Respiratory Pathogens**
  - Levofloxacin
  - Moxifloxacin
- **Anaerobic Activity**
  - Moxifloxacin
  - Trovafloxacin

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Pharmacology of Quinolones

1. **Mechanism of Action:** Quinolones inhibit bacterial DNA synthesis by targeting the bacterial enzymes DNA gyrase (topoisomerase II) and topoisomerase IV. This inhibition prevents the supercoiling of DNA, leading to breaks in the DNA strands and ultimately bacterial cell death. Quinolones are bactericidal.

2. **Spectrum of Activity:** Quinolones have a broad spectrum of activity against Gram-negative bacteria (e.g., Enterobacteriaceae, Pseudomonas aeruginosa) and limited activity against Gram-positive bacteria. They are also effective against some atypical bacteria and mycobacteria.

3. **Pharmacokinetics:** Quinolones are well absorbed orally, with excellent bioavailability. They are widely distributed in body tissues and fluids, including the prostate and bone. Quinolones are primarily excreted by the kidneys, with some liver metabolism.

4. **Clinical Uses:** Quinolones are used to treat urinary tract infections, gastrointestinal infections, respiratory tract infections, skin infections, and sexually transmitted infections. They are also used in the treatment of anthrax.

5. **Adverse Effects:** Side effects include gastrointestinal disturbances, CNS effects (headache, dizziness, seizures), tendonitis and tendon rupture, and photosensitivity. Quinolones can also prolong the QT interval.

6. **Resistance Mechanisms:** Resistance can occur through mutations in DNA gyrase or topoisomerase IV, efflux pumps, and decreased drug permeability.

Classification of Fluoroquinolones

1. **Based on Generations**
   - **Second Generation (Early Fluoroquinolones)**
     - Ciprofloxacin
     - Norfloxacin
     - Ofloxacin
   - **Third Generation (Respiratory Fluoroquinolones)**
     - Levofloxacin
     - Sparfloxacin
   - **Fourth Generation (Enhanced Activity Against Gram-positive and Anaerobes)**
     - Moxifloxacin
     - Trovafloxacin
     - Gemifloxacin

2. **Based on Spectrum of Activity**
   - **Gram-negative Activity**
     - Ciprofloxacin

- ➢ Norfloxacin
- **Respiratory Pathogens**
  - ➢ Levofloxacin
  - ➢ Moxifloxacin
- **Anaerobic Activity**
  - ➢ Moxifloxacin
  - ➢ Trovafloxacin

Pharmacology of Fluoroquinolones

1. **Mechanism of Action:** Fluoroquinolones, a subclass of quinolones, also inhibit bacterial DNA synthesis by targeting DNA gyrase and topoisomerase IV. They are more potent and have a broader spectrum of activity compared to the earlier quinolones. Fluoroquinolones are bactericidal.

2. **Spectrum of Activity:** Fluoroquinolones have an expanded spectrum of activity that includes both Gram-negative and Gram-positive bacteria, as well as atypical pathogens. They are particularly effective against Gram-negative bacteria, including Pseudomonas aeruginosa, and some Gram-positive bacteria like Streptococcus pneumoniae.

3. **Pharmacokinetics:** Fluoroquinolones are well absorbed orally, with high bioavailability. They distribute widely in body tissues and fluids, including the lungs, kidneys, and prostate. Most fluoroquinolones are excreted renally, although some are metabolized in the liver.

4. **Clinical Uses:** Fluoroquinolones are used to treat a wide range of infections, including urinary tract infections, respiratory tract infections, gastrointestinal infections, bone and joint infections, and certain sexually transmitted infections. They are also used in the treatment of anthrax and multi-drug-resistant tuberculosis.

5. **Adverse Effects:** Adverse effects are similar to those of other quinolones, including gastrointestinal disturbances, CNS effects, tendonitis and tendon rupture, photosensitivity, and QT interval prolongation. They may also cause dysglycemia (both hyperglycemia and hypoglycemia).

6. **Resistance Mechanisms:** Resistance mechanisms include mutations in the genes encoding DNA gyrase and topoisomerase IV, efflux pumps, and reduced drug permeability. Cross-resistance between fluoroquinolones and other quinolones is common.

Tetracyclines

Introduction

Tetracyclines are a class of broad-spectrum antibiotics that inhibit bacterial protein synthesis. They are derived from Streptomyces bacteria and were first discovered in the 1940s. Tetracyclines are widely used to treat a variety of infections caused by susceptible organisms.

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Classification

1. **Natural Tetracyclines**
   - Tetracycline
   - Chlortetracycline
   - Oxytetracycline

2. **Semisynthetic Tetracyclines**
   - **Doxycycline:** More lipid-soluble, better absorption and longer half-life.
   - **Minocycline:** Enhanced tissue penetration and longer half-life.
   - **Methacycline**

3. **Glycylcyclines**
   - **Tigecycline:** A newer derivative with a broader spectrum of activity, including some tetracycline-resistant bacteria.

Pharmacology

1. **Mechanism of Action:** Tetracyclines bind to the 30S ribosomal subunit, preventing the attachment of aminoacyl-tRNA to the ribosome, thereby inhibiting protein synthesis. This action is bacteriostatic, meaning it stops the growth of bacteria rather than killing them directly.

2. **Spectrum of Activity:** Tetracyclines are effective against a wide range of Gram-positive and Gram-negative bacteria, as well as atypical organisms such as Rickettsia, Chlamydia, Mycoplasma, and certain protozoa.

3. **Pharmacokinetics**
   - **Absorption:** Oral absorption is variable; doxycycline and minocycline have better absorption compared to tetracycline.
   - **Distribution:** Widely distributed in the body, including bones and teeth. They can cross the placenta and are excreted in breast milk.
   - **Metabolism and Excretion:** Primarily excreted in the urine and feces, with doxycycline and minocycline being primarily excreted in the feces.

4. **Clinical Uses**
   - Respiratory tract infections
   - Acne vulgaris
   - Sexually transmitted infections (e.g., Chlamydia)
   - Rickettsial infections (e.g., Rocky Mountain spotted fever)
   - Lyme disease
   - Malaria prophylaxis

5. **Adverse Effects**
   - Gastrointestinal disturbances (nausea, vomiting, diarrhea)
   - Photosensitivity
   - Discoloration of teeth and inhibition of bone growth in children
   - Hepatotoxicity
   - Vestibular toxicity (with minocycline)

6. **Resistance Mechanisms:** Resistance can occur via efflux pumps, ribosomal protection proteins, and enzymatic inactivation.

Aminoglycosides

Introduction

Aminoglycosides are a class of antibiotics derived from Streptomyces and Micromonospora species. They are primarily used to treat serious infections caused by Gram-negative bacteria. Aminoglycosides are bactericidal and work by inhibiting bacterial protein synthesis.

Classification

1. **Natural Aminoglycosides**
   - **Streptomycin:** Used for tuberculosis and certain other infections.
   - **Neomycin:** Used topically and orally for bowel decontamination.

2. **Semisynthetic Aminoglycosides**
   - **Gentamicin:** Widely used for severe Gram-negative infections.
   - **Tobramycin:** Similar to gentamicin, with enhanced activity against Pseudomonas aeruginosa.
   - **Amikacin:** Resistant to many aminoglycoside-inactivating enzymes, broader spectrum.

Pharmacology

1. **Mechanism of Action:** Aminoglycosides bind to the 30S ribosomal subunit, causing misreading of mRNA and inhibiting protein synthesis. This results in the production of defective proteins and leads to bacterial cell death.

2. **Spectrum of Activity:** Aminoglycosides are primarily active against aerobic Gram-negative bacteria, including Pseudomonas aeruginosa, Escherichia coli, and Klebsiella species. They also have some activity against Gram-positive bacteria when used in combination with other antibiotics.

3. **Pharmacokinetics**
   - **Absorption:** Poorly absorbed from the gastrointestinal tract; administered parenterally (intravenous or intramuscular).

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- **Distribution:** Distributes mainly in extracellular fluid, limited penetration into the cerebrospinal fluid. Concentrates in renal cortical and inner ear tissues.
- **Excretion:** Excreted unchanged in the urine, necessitating dose adjustment in renal impairment.

4. **Clinical Uses**
   - Severe Gram-negative infections (e.g., septicemia, respiratory tract infections, intra-abdominal infections)
   - Endocarditis (in combination with beta-lactams or glycopeptides)
   - Tuberculosis (streptomycin)
   - Pseudomonas infections (tobramycin)
5. **Adverse Effects**
   - Nephrotoxicity (renal toxicity)
   - Ototoxicity (hearing loss and balance issues)
   - Neuromuscular blockade (rare)
   - Allergic reactions (rare)
6. **Resistance Mechanisms:** Resistance can develop through enzymatic inactivation by aminoglycoside-modifying enzymes, alteration of the ribosomal binding site, and decreased uptake or increased efflux of the drug.