

Macrolides

Introduction

- Macrolides are a class of bacteriostatic antibiotics characterized by a macrocyclic lactone ring attached to one or more deoxy sugars.
- They are primarily used to treat:
 - **Respiratory tract infections**
 - **Skin and soft tissue infections**
 - **Atypical organisms** like *Mycoplasma*, *Chlamydia*, and *Legionella*
- They are particularly valuable as alternatives to penicillin in allergic patients and are active against Gram-positive cocci and intracellular pathogens.
- The name "macrolide" comes from the large (macro) lactone ring in their chemical structure.

Classification

Based on Generation and Structure:

1. First-generation (14-membered ring):

- **Erythromycin**
- **Roxithromycin**

2. Second-generation:

- **Clarithromycin** (14-membered)
- **Azithromycin** (15-membered ring, technically an azalide but grouped under macrolides)

3. Ketolides (semisynthetic macrolide derivatives):

- **Telithromycin** (developed to overcome resistance; limited use due to hepatotoxicity)

Mechanism of Action

- Macrolides bind to the 50S ribosomal subunit of bacterial ribosomes.
- They inhibit translocation of the growing peptide chain, preventing continuation of protein synthesis.
- This causes bacteriostatic action (inhibits growth), though at higher concentrations or against certain organisms, they can be bactericidal.

Pharmacokinetics (ADME)

Absorption:

- **Erythromycin:** Acid-labile → enteric-coated formulations or esters used
- **Clarithromycin and Azithromycin:** Well absorbed orally, acid-stable

Distribution:

- Wide tissue distribution; azithromycin concentrates intracellularly
- Poor CSF penetration, but adequate tissue levels for most infections
- Crosses placenta and enters breast milk

Metabolism:

- **Erythromycin and clarithromycin:** Metabolized in **liver** by CYP3A4
- **Azithromycin:** Minor liver metabolism, excreted unchanged in bile

Excretion:

- **Erythromycin and clarithromycin:** Primarily hepatic
- **Azithromycin:** Biliary excretion; long tissue half-life

Half-life:

- Erythromycin: ~1.5 hours
- Clarithromycin: ~3–7 hours
- Azithromycin: ~68 hours (allows once-daily dosing)

Pharmacodynamics

- Time-dependent or concentration-enhanced bacteriostatic activity
- Effective against:
 - **Gram-positive cocci** (*Streptococcus*, *Staphylococcus*)
 - **Atypical bacteria** (*Mycoplasma*, *Chlamydia*, *Legionella*)
 - **Some gram-negative organisms** (*H. influenzae*, *Moraxella*)

Antimicrobial Spectrum

Effective Against:

- **Gram-positive cocci:** *Streptococcus pyogenes*, *S. pneumoniae*, *Staphylococcus aureus* (excluding MRSA)
- **Gram-negative bacteria:** *H. influenzae*, *Bordetella pertussis*, *Neisseria spp.*
- **Atypical pathogens:** *Mycoplasma pneumoniae*, *Chlamydia trachomatis*, *Legionella pneumophila*
- **Spirochetes:** *Treponema pallidum*
- **Others:** *Toxoplasma*, *Helicobacter pylori* (with other drugs)

Therapeutic Uses

1. Respiratory tract infections

- Community-acquired pneumonia (CAP)

- Atypical pneumonia (*Mycoplasma*, *Legionella*)
- Pharyngitis, sinusitis, otitis media

2. Skin and soft tissue infections

- Especially in penicillin-allergic patients

3. Sexually transmitted infections (STIs)

- *Chlamydia trachomatis* (azithromycin single dose)
- Nongonococcal urethritis, cervicitis

4. Helicobacter pylori eradication

- Clarithromycin-based triple therapy (with amoxicillin and proton pump inhibitor)

5. Pertussis (whooping cough)

- Macrolides are first-line treatment and prophylaxis

6. Prophylaxis and treatment of Mycobacterium avium complex (MAC) in HIV patients

- Azithromycin is used for both prophylaxis (in CD4 count <50 cells/mm³) and treatment in combination with other antimicrobials

7. Alternative to penicillins in:

- Syphilis
- Rheumatic fever prophylaxis

Adverse Effects

1. Gastrointestinal disturbances

- Nausea, vomiting, abdominal cramps, diarrhea
- Erythromycin is most commonly associated due to motilin receptor stimulation

2. Cholestatic hepatitis

- Especially with erythromycin estolate

3. QT interval prolongation

- Risk of arrhythmias (e.g., Torsades de Pointes)

4. Ototoxicity

- Reversible hearing loss at high doses (especially erythromycin)

5. Allergic reactions

- Rash, fever, eosinophilia (rare)

Contraindications

- Known hypersensitivity to macrolides
- History of cholestatic jaundice or hepatic dysfunction with prior macrolide use
- **Caution in patients with:**
 - Pre-existing QT prolongation
 - Electrolyte imbalances (e.g., hypokalemia, hypomagnesemia)
 - Severe hepatic impairment

Drug Interactions

- Erythromycin and Clarithromycin inhibit CYP3A4 → increase levels of:
 - **Theophylline**
 - **Warfarin**
 - **Carbamazepine**
 - **Digoxin**
 - **Statins** → risk of myopathy/rhabdomyolysis
- Azithromycin has minimal CYP interaction → fewer drug interactions
- Combined with other QT-prolonging drugs (e.g., fluoroquinolones, antiarrhythmics) → increased arrhythmia risk

Dose and Route of Administration

Erythromycin

- 250–500 mg orally every 6 hours
- IV available for severe infections
- Often poorly tolerated due to GI effects

Clarithromycin

- 250–500 mg orally every 12 hours
- Extended-release: once daily
- Used in H. pylori therapy (usually 500 mg bid)

Azithromycin

- 500 mg on day 1, followed by 250 mg daily for 4 days (Z-pack)
- For STIs: 1 g orally single dose (Chlamydia)
- IV form used in severe infections

Roxithromycin

- 150 mg orally twice daily
- Used for respiratory and soft tissue infections (mainly outside the U.S.)

Note: Macrolides are usually given **orally**, but IV forms are available for severe infections.

Aminoglycosides

Introduction

- Aminoglycosides are a class of bactericidal antibiotics that are especially effective against aerobic Gram-negative bacilli and some Gram-positive cocci (in combination therapy).
- They were first derived from *Streptomyces* and *Micromonospora* species.
- **Key features:**
 - Contain amino sugars linked by glycosidic bonds
 - Act by irreversibly inhibiting protein synthesis
 - Exhibit concentration-dependent killing
 - Exhibit post-antibiotic effect (PAE)
- Due to poor oral absorption, they are mainly administered parenterally, except for intestinal infections (oral neomycin).

Classification

Commonly Used Aminoglycosides:

1. Streptomycin
2. Gentamicin
3. Tobramycin
4. Amikacin
5. Neomycin
6. Netilmicin

Topical Aminoglycosides:

- Neomycin (oral/topical)
- Framycetin

Mechanism of Action

- Aminoglycosides bind irreversibly to the 30S subunit of the bacterial ribosome.
- **They:**
 - Inhibit the initiation complex of protein synthesis
 - Cause misreading of mRNA → production of abnormal or nonfunctional proteins
 - Disrupt bacterial cell membrane integrity (at high concentrations)



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