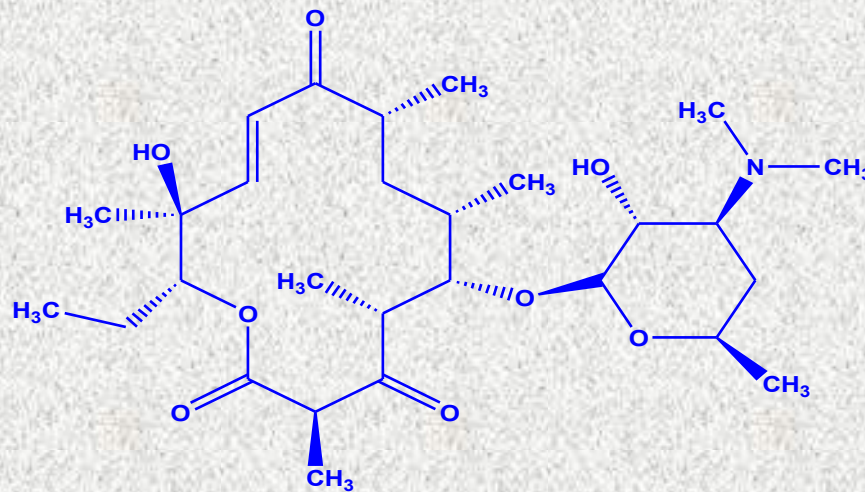


Introduction

- ✓ The term *Macrolide* was originally given to antibiotics produced by species of *Streptomyces*.
- ✓ In 1950 the first drug of this class was isolated: **Picromycin**
- ✓ In 1952 **Erythromycin** and **Carbomycin** were introduced into clinic.

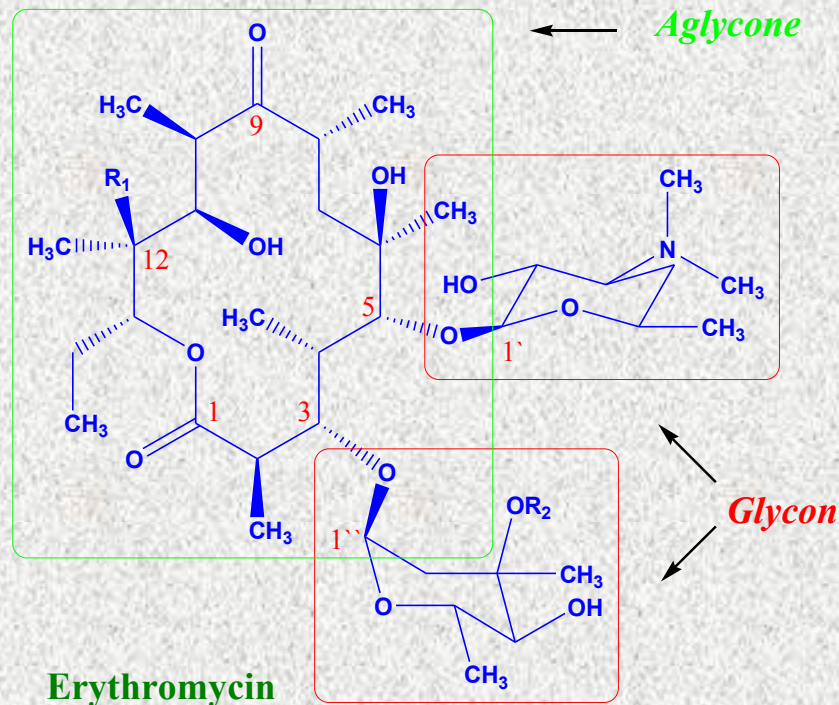


Picromycin

General Structure

They all contain three characteristic parts in the molecule:

- ✓ A highly substituted **macrocyclic lactone**: **aglycone**.
- ✓ A **ketone** group.
- ✓ An amino **desoxysugar**: **glycon**, and in some of the macrolides, a neutral desoxysugar which are glycosidically attached to the aglycone ring.



-
- ✓ The lactone ring usually has **12, 14, or 16 atoms** and is often unsaturated & conjugated with the **ketone group**.
 - ✓ Having a dimethyl amino group on the glycon part, macrolide antibiotics are weak bases and different salts with **pKa range of 6.0-9.0** can be formed on the amino group.
 - ✓ Macrolides are **water-insoluble** molecules.
 - ✓ Macrolides are stable in aqueous solutions at or below room temperature. They are unstable in acidic or basic conditions or at high temperatures.

Mechanism of Antimicrobial Activity

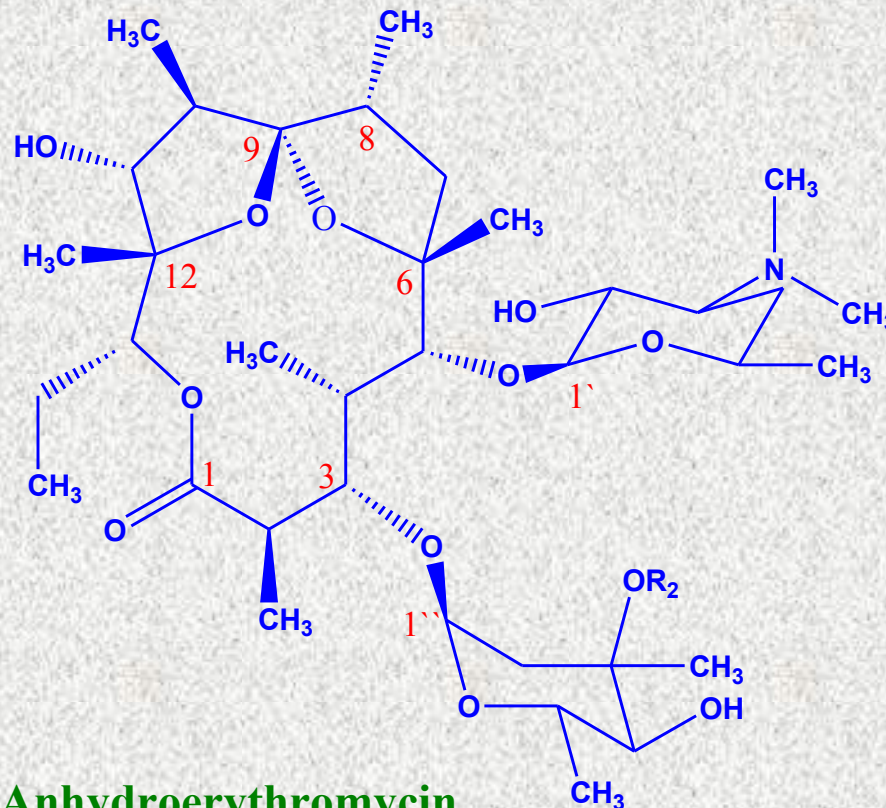
- ✓ Macrolides attach to the **50s** portion of **bacterial ribosomes** and **inhibit the protein synthesis (interferes with Translocation)**.
 - Suppression of RNA-dependent protein synthesis
- ✓ They block the enzymes that catalyse the transfer of the new amino acid residue to the peptide chain, that is, prevent elongation in prokaryotic cells.
- ✓ Macrolides typically display bacteriostatic activity, but may be bactericidal when present at high concentrations against very susceptible organisms

Macrolides – Adverse Effects

- ✓ Gastrointestinal – up to 33 %
 - Nausea, vomiting, diarrhea, dyspepsia
 - Most common with erythro; less with new agents
- ✓ On oral therapy – mild to severe epigastric pain.
- ✓ High doses may cause reversible hearing impairment.
- ✓ Hypersensitivity.
- ✓ Thrombophlebitis – IV Erythro and Azithro
(Dilution of dose; slow administration)

Chemical Instability of Macrolide Antibiotics

- Macrolides are unstable under acidic conditions and undergo an intramolecular reaction to form an inactive cyclic ketal.



Anhydroerythromycin
6,9;9,12-spiroketal

Chemical Instability....

- ✓ The cyclic ketal is the cause of intestinal cramp which is reported after the use of erythromycin.
- ✓ **Water-insoluble salts** and **enteric coated dosage** forms of macrolides have less such a side effect.
- ✓ Water insoluble forms cannot take part in the reactions which occur in aqueous solutions.
- ✓ **Stearate salt** is an example of insoluble salts of erythromycin.

Therapeutic Agents

Erythromycin

- ✓ **Erythromycin** is a naturally-occurring macrolide derived from *Streptomyces erythreus* – problems with acid lability, narrow spectrum, poor GI intolerance, short elimination half-life.
- ✓ Structural derivatives include **clarithromycin** and **azithromycin, roxithromycin (Newer macrolides)**-
 - Broader spectrum of activity
 - Improved PK properties – better bioavailability, better tissue penetration, prolonged half-lives
 - Improved tolerability

Clinical Application of Erythromycin

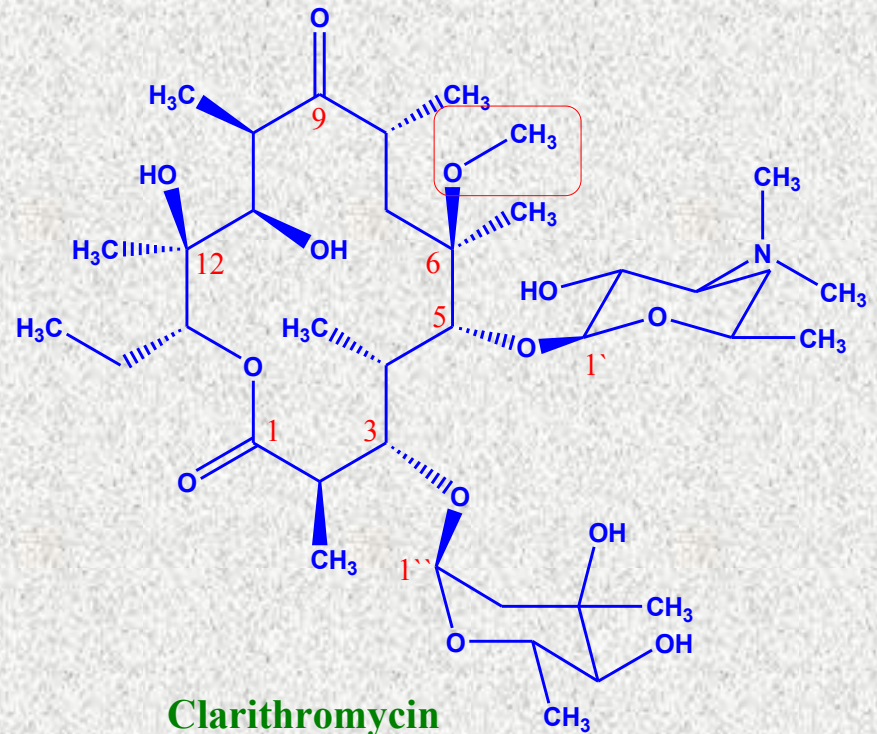
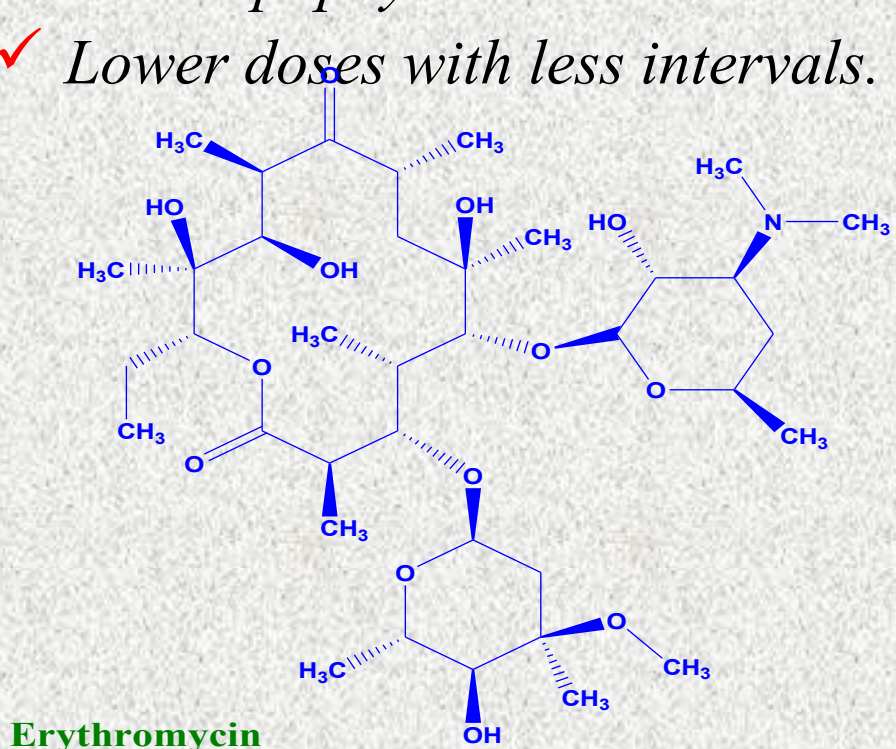
It is used to treat -

- ✓ The upper part of the respiratory tract infections,
- ✓ Soft tissue G(+) infections,
- ✓ *Mycoplasma pneumonia*
- ✓ Diphtheria
- ✓ Tetanus
- ✓ Chlamidia infections.
- ✓ Gonorrhoea & syphilis.

It is a good choice for penicillin-sensitive cases.


Clarithromycin

- ✓ *6-Methyl ether of erythromycin.*
- ✓ *Cannot undergo cyclic ketal formation, so doesn't cause cramp in GI.*
- ✓ *Higher blood concentrations.*
- ✓ *More lipophylic.*
- ✓ *Lower doses with less intervals.*



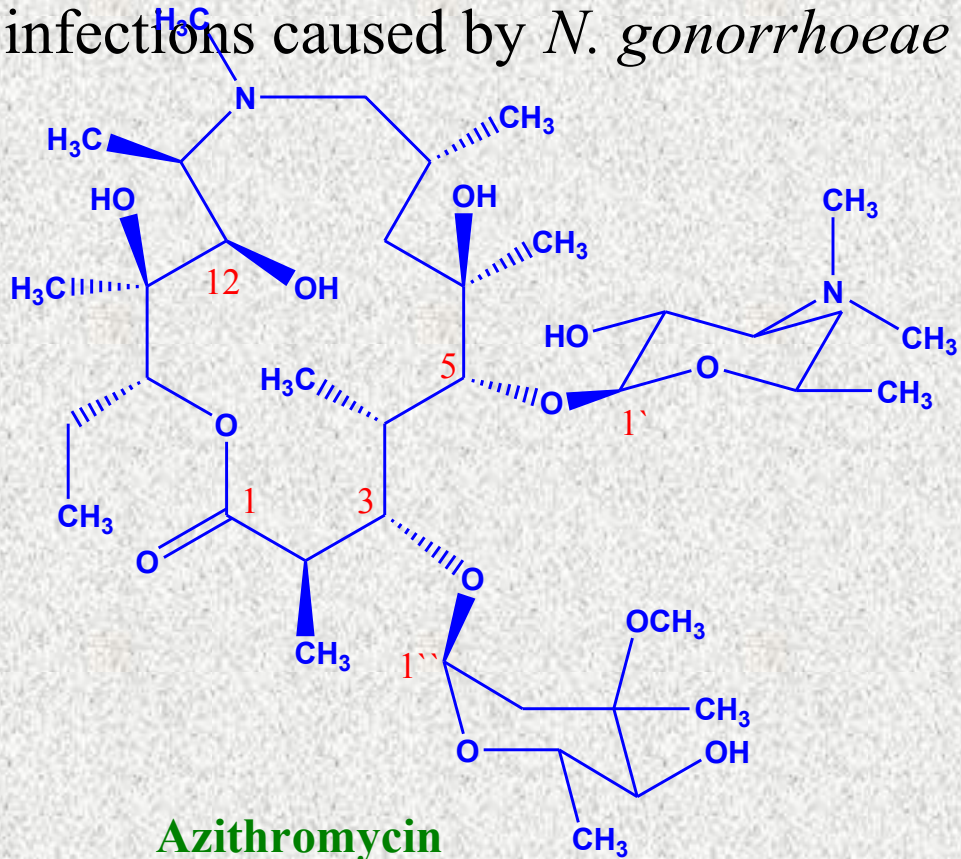
Clarithromycin

Pharmacokinetics

- ✓ Acid stable
- ✓ Food delays absorption.  **Take on an empty stomach**
- ✓ Metabolized by the liver to 14- hydroxy clarithro. (active)
- ✓ Widely distributed, except brain and CSF
- ✓ Protein binding 40 – 70 %
- ✓ Half- life clarithromycin 4 – 6 hr.
- ✓ **Dose: 250mg/BD/oral** **500mg/BD/in severe cases**
 7.5mg/kg/BD/oral **childrens**
- ✓ **Advantage over erythromycin**
- ✓ Lower frequency of GI intolerance
- ✓ Half life is about 3 times to erythromycin.

Azithromycin

- ✓ Azalide, a semisynthetic macrolide with a 15 membered ring.
- ✓ Stable under acidic conditions, because it doesn't form cyclic ketal.
- ✓ In the treatment of urogenital infections caused by *N. gonorrhoeae* and *Chlamidia trachomatis*.
- ✓ Longer half-life.



Azithromycin

Pharmacokinetics

- ✓ Rapidly absorbed from GIT
 - ✓ Food delays absorption
 - ✓ Widely distributed (extensive tissue distribution), except CSF
 - ✓ Protein binding 51%
 - ✓ Undergo some hepatic metabolism (inactive)
 - ✓ Biliary route is the major route of elimination
 - ✓ Only 6% is excreted unchanged in the urine
 - ✓ Half- life approx. 2-4 days.
- ✓ **Dose:** 500mg/OD/oral
 10mg/kg/BD Childrens
- ✓ **Advantage over erythromycin & clarithromycin**
 - ✓ Once daily dosing
 - ✓ No inhibition of cytochrome P- 450



Macrolide Spectrum of Activity

Gram-Positive Aerobes – erythromycin and clarithromycin display the best activity.

(Clarithro>Erythro>Azithro)

Gram-Negative Aerobes – newer macrolides with enhanced activity.

(Azithro>Clarithro>Erythro)

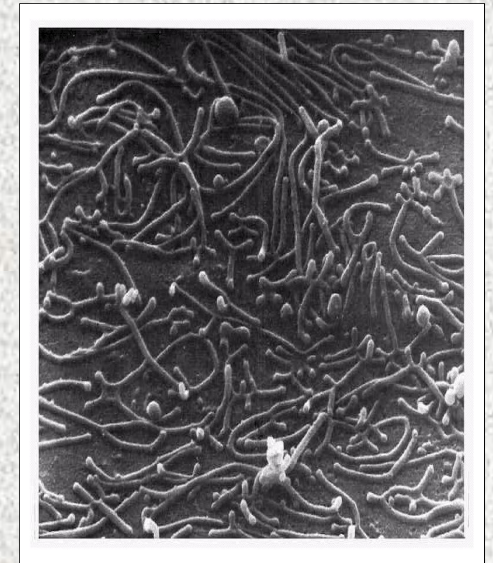
Spectrum of Antibacterial Activity

- ✓ Macrolides are similar to penicillins regarding their spectrum of activity.
- ✓ They are effective against penicillin-resistant strains.
- ✓ Macrolides are effective against most of the G(+) bacteria, cocci or bacillus, they have antibiotic activity against G(-) cocci, especially *Neisseria Spp* too.
- ✓ Macrolide antibiotics are effective against *Mycoplasma*, *Chlamidia*, *Campylobacter* and *Legionella* in contrast to penicillins.
- ✓ They are less effective against G(-) bacteria, though some strains of *H. influenza* and *Brucella* are sensitive to the antibacterial activity of this class of antibiotics.

Atypical Bacterias



*Legionella
pneumophila*



*Mycoplasma
pneumoniae*

*Chlamydia (Chlamydophila)
pneumoniae*

Spectrum of Antibacterial Activity

Erythromycin

A. Gram (+) bacteria

Staph. Aureus

S. pneumoniae

S. pyogens

C. diphtheria

B. Gram (-) bacteria

T. pallidum

C. Intracellular org.

L. pneumophila

M. pneumoniae

C. trachomatis

Indications

Mycoplasma pneumonia

Diphtheria, Tetanus

Clamidia infections.

Gonorrhoea & syphilis.

Clarithromycin

A. Gram (+) bacteria

Staph. Aureus

S. Pneumoniae

S. Pyogens

B. Gram (-) bacteria

H. influenzae

H. Pylori

M. catarrhalis

C. Intracellular org.

M. pneumoniae

L. Pneumophila

Indications

Pharyngitis / tonsilitis

Otitis, sinusitis

Adjunct in treatment of

duodenal ulcer (H. pylori)

Azithromycin

A. Gram (+) bacteria

Staph. Aureus

S. Pneumoniae

S. Pyogens

B. Gram (-) bacteria

M. catarrhalis

H. influenzae

C. Intracellular org.

L. Pneumophila

M. pneumoniae

Chlamydia species

Indications

Pharyngitis/ tonsilitis,

otitis, sinusitis, Uncomplicated

genital chlamydial infections

Macrolides

Drug Interactions

Erythromycin and Clarithromycin ONLY– are *inhibitors* of **cytochrome P 450** system in the liver; may increase concentrations of:

Theophylline

Carbamazepine

Cyclosporine

Phenytoin

Warfarin

Digoxin, Disopyramide

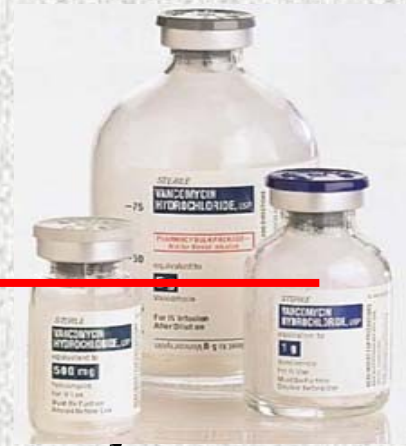
Valproic acid

Terfenadine, Astemizole

Cisapride

Ergot alkaloids

Vancomycin



- ✓ Tricyclic glycopeptide - *Streptomyces orientalis*.
- ✓ **Inhibits synthesis of cell wall** phospholipids and prevents cross-linking of peptidoglycans at an earlier step than B-lactams.
- ✓ Active against gram positive bacteria, highly resistant *Strep. pneumo*, *Clostridia*, *Enterococcus*, *Staph. epi* and **MRSA**.
- ✓ Synergy with aminoglycosides.
- ✓ Used in treatment of MRSA and highly resistant *Strep.* species.

Bacteria by Site of Infection

Mouth

Peptococcus
Peptostreptococcus
Actinomyces

Skin/Soft Tissue

S. aureus
S. pyogenes
S. epidermidis
Pasteurella

Bone and Joint

S. aureus
S. epidermidis
Streptococci
N. gonorrhoeae
Gram-negative rods

Abdomen

E. coli, Proteus
Klebsiella
Enterococcus
Bacteroides sp.

Urinary Tract

E. coli, Proteus
Klebsiella
Enterococcus
Staph saprophyticus

Upper Respiratory

S. pneumoniae
H. influenzae
M. catarrhalis
S. pyogenes

Lower Respiratory

Community

S. pneumoniae
H. influenzae
K. pneumoniae
Legionella pneumophila
Mycoplasma, Chlamydia

Lower Respiratory

Hospital

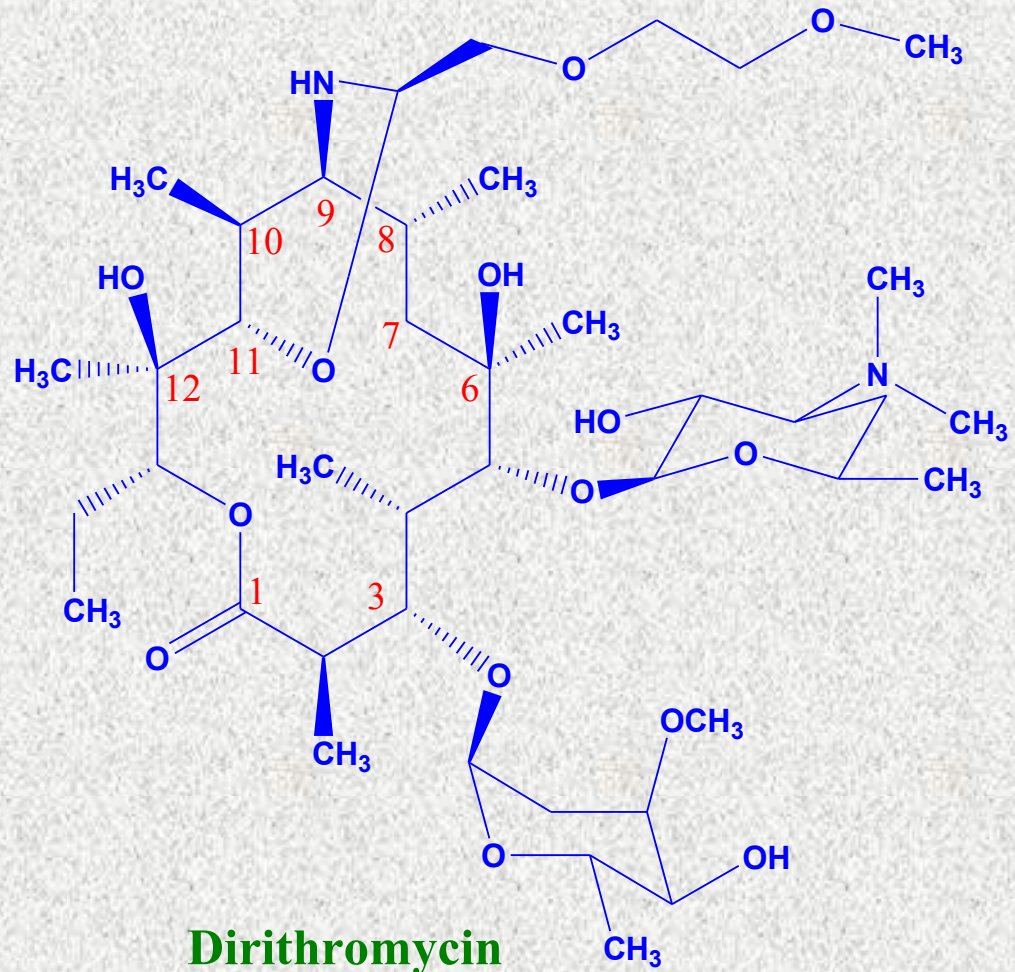
K. pneumoniae
P. aeruginosa
Enterobacter sp.
Serratia sp.
S. aureus

Meningitis

S. pneumoniae
N. meningitidis
H. influenza
Group B Strep
E. coli
Listeria

Dirithromycin

- A more lipophilic prodrug with high oral absorption.
- Unstable 9N,11O oxazine ring which easily hydrolyzes to erythromyclamine.

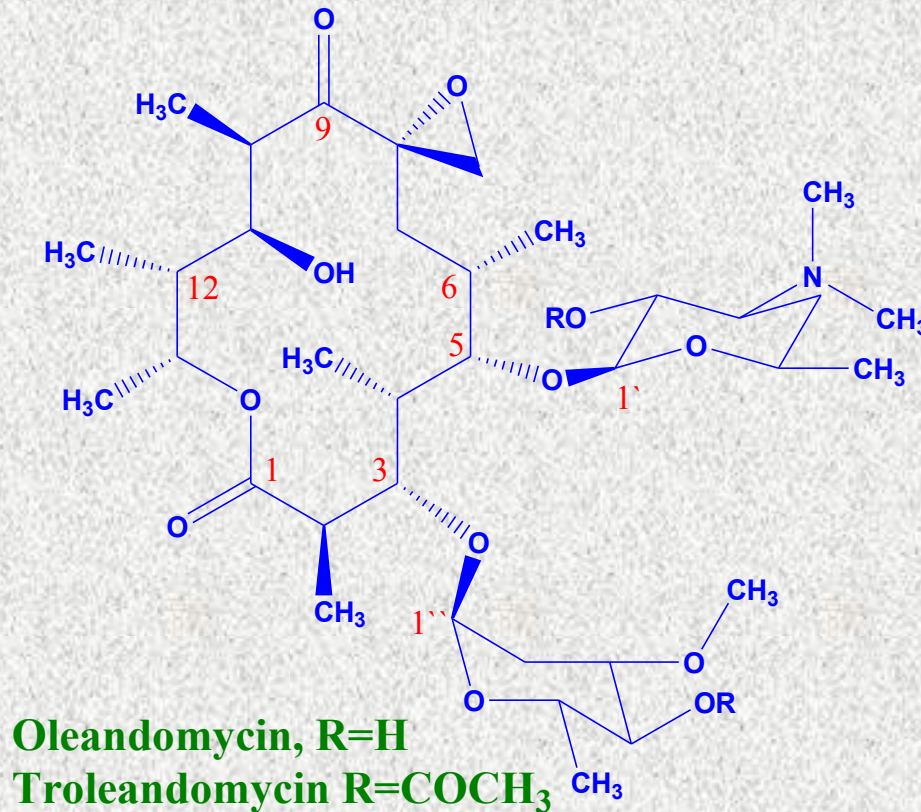


- ✓ Erythromyclamin is another semisynthetic derivative of erythromycin with 9-amino instead of 9-keto group.
-
- ✓ It has the same antibacterial effects as erythromycin.
 - ✓ Less oral absorption than erythromycin has lead chemists to prepare more lipophyl prodrug, dirithromycin.
 - ✓ Dirithromycin is protected against gastric acid with the enteric coated form.
 - ✓ It is readily absorbed orally, but has low plasma concentration because of high volume of distribution.
 - ✓ Infections of the upper and lower parts of respiratory system with only one oral dose.

Troleandomycin

Oleandomycin

- Oleandomycin is isolated from *Streptomyces antibioticus*. Troleandomycin is a prodrug of the former.
- Bacteriostatic effects the same as erythromycin.



Macrolide Spectrum of Activity

Gram-Positive Aerobes – erythromycin and clarithromycin display the best activity

(Clarithro>Erythro>Azithro)

- Methicillin-susceptible *Staphylococcus aureus*
- *Streptococcus pneumoniae* (only PSSP) – resistance is developing
- Group and viridans streptococci
- *Bacillus sp.*, *Corynebacterium sp.*

Macrolide Spectrum of Activity

Gram-Negative Aerobes – newer macrolides
with enhanced activity
(Azithro>Clarithro>Erythro)

- *H. influenzae* (not erythro), *M. catarrhalis*,
Neisseria sp.
- Do NOT have activity against any
Enterobacteriaceae

Macrolide Spectrum of Activity

Anaerobes – activity against upper airway anaerobes

Atypical Bacteria – all macrolides have excellent activity against atypical bacteria including:

- *Legionella pneumophila*
- *Chlamydia sp.*
- *Mycoplasma sp.*
- *Ureaplasma urealyticum*

Other Bacteria – *Mycobacterium avium complex* (MAC – only A and C), *Treponema pallidum*, *Campylobacter*, *Borrelia*, *Bordetella*, *Brucella*.
Pasteurella

Macrolides

Pharmacology

Absorption

- **Erythromycin** – variable absorption (F = 15-45%); food may decrease the absorption
 - Base: destroyed by gastric acid; enteric coated
 - Esters and ester salts: more acid stable
- **Clarithromycin** – acid stable and well-absorbed (F = 55%) regardless of presence of food
- **Azithromycin** – acid stable; F = 38%; food decreases absorption of capsules

Macrolides

Pharmacology

Distribution

- Extensive tissue and cellular distribution – clarithromycin and azithromycin with extensive penetration
- Minimal CSF penetration

Elimination

- Clarithromycin is the only macrolide partially eliminated by the kidney (18% of parent and all metabolites); requires dose adjustment when $\text{CrCl} < 30 \text{ ml/min}$
- Hepatically eliminated: ALL
- NONE of the macrolides are removed during hemodialysis!
- Variable elimination half-lives (1.4 hours for erythro; 3 to 7 hours for clarithro; 68 hours for azithro)

Macrolides

Adverse Effects

- Gastrointestinal – up to 33 %
 - Nausea, vomiting, diarrhea, dyspepsia
 - Most common with erythro; less with new agents
- Cholestatic hepatitis - rare
 - > 1 to 2 weeks of erythromycin estolate
- Thrombophlebitis – IV Erythro and Azithro
 - Dilution of dose; slow administration
- Other: ototoxicity (high dose erythro in patients with RI); QTc prolongation; allergy