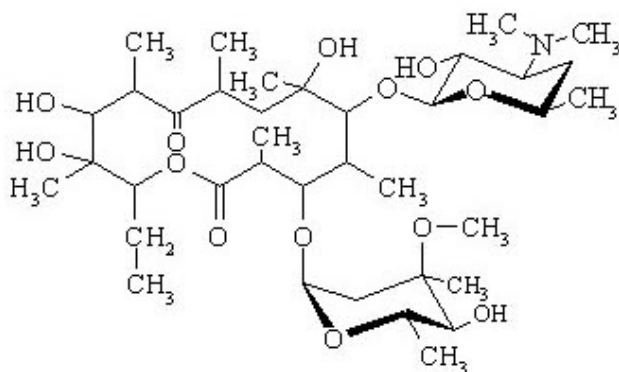




Macrolides...

- Belong to the polyketide class of natural products.
- are a group of antibiotics consisting of a *macrolide ring*
 - a large lactone ring to which one or more deoxy sugars, are attached.
 - The lactone ring can be either 14, 15 or 16-membered.

- Erythromycin - 1952 from *Streptomyces erythreus*.
- Clarithromycin
- Azithromycin
- Roxithromycin



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Other macrolides

- Spiramycin (used for treating toxoplasmosis),
- Ansamycin, oleandomycin, carbomycin and tylocine.
- A new class of antibiotics called ketolides that is structurally related to the macrolides.
- **Ketolides** such as telithromycin are used in respiratory tract infections caused by macrolide-resistant bacteria.

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Mechanism of Action

- Inhibit bacterial protein synthesis by binding reversibly to the subunit 50S of the bacterial ribosome, thereby inhibiting translocation of peptidyl-tRNA.
- Interferes with chloramphenicol binding
- Action is mainly bacteriostatic, but can also be bactericidal in high concentrations.
- Macrolides tend to accumulate within leukocytes, and are therefore actually transported **into** the site of infection.

- Gram positive bacteria accumulate macrolides 100 times more than gram negative
- Resistance occurs by:
 - active efflux mechanism in some bacteria
 - methylase enzyme which modifies ribosomal target
 - hydrolysis of macrolides by esterases
 - chromosomal mutation of ribosomal binding site

- Macrolides are administered orally.
- i.v. preparations can cause phlebitis
- Erythromycin is inactivated by gastric acid and thus given as an enteric coated formulation.
 - Esters of erythromycin -sterate/ estolate/ ethylsuccinate are resistant to inactivation.

- Clarithromycin is less susceptible to acid.
 - Undergoes extensive first pass hepatic metabolism.
- Roxithromycin and Azithromycin are well absorbed.
- All macrolides are widely distributed to tissues and fluids **except** CSF
- Azithromycin accumulates in tissue fibroblasts – act as a reservoir
 - Tissue concentrations > plasma levels

- Metabolised by CYP in liver
- Elimination is mainly through bile-erythromycin.
- Also through kidneys and urine for others

- Macrolides are used to treat **respiratory tract infections and soft tissue infections**.
- Antimicrobial spectrum is slightly wider than that of penicillin.
- **Beta-hemolytic streptococci, pneumococci, staphylococci and enterococci** are usually susceptible to macrolides.
- Unlike penicillin, macrolides are effective against mycoplasma, mycobacteria, some rickettsia and chlamydia.

- Alternative to penicillin in hypersensitive patients;
 - Strep and staph infections
 - ENT infections Tonsillitis ASOM
 - campylobacter enteritis,
 - pneumonia,
 - legionnaires' disease,
 - syphilis,
 - non-gonococcal urethritis,
 - respiratory-tract infections,
 - skin infections
 - chronic prostatitis:

- Diphtheria and whooping cough prophylaxis
- Acne vulgaris and rosacea
- Helicobacter pylori infection-Clarithromycin
- Tetanus
- Mycobacterial infection
 - Tuberculosis
 - M. avium complex
 - leprosy
- Toxoplasmosis
- Chlamydial infections

- Mild or moderate typhoid due to multiple-antibacterial-resistant organisms
- Prophylactic use in rheumatic fever as an alternative to penicillin.
- For prevention of bacterial endocarditis.

Doses

- Erythromycin
 - 1-2 g/ day divided into 4 doses
- Clarithromycin 250-500 mg twice a day.
- Azithromycin 250 mg/ day
 - Single 2 g dose for gonorrhoea

Adverse effects

- Nausea, vomiting, abdominal discomfort, diarrhoea (antibiotic-associated colitis reported)
- Urticaria, rashes and other allergic reactions
- Reversible hearing loss after large doses
- Cholestatic jaundice
- Cardiac effects (including chest pain and arrhythmias)
- Myasthenia-like syndrome,
- Stevens-Johnson syndrome, and toxic epidermal necrolysis.

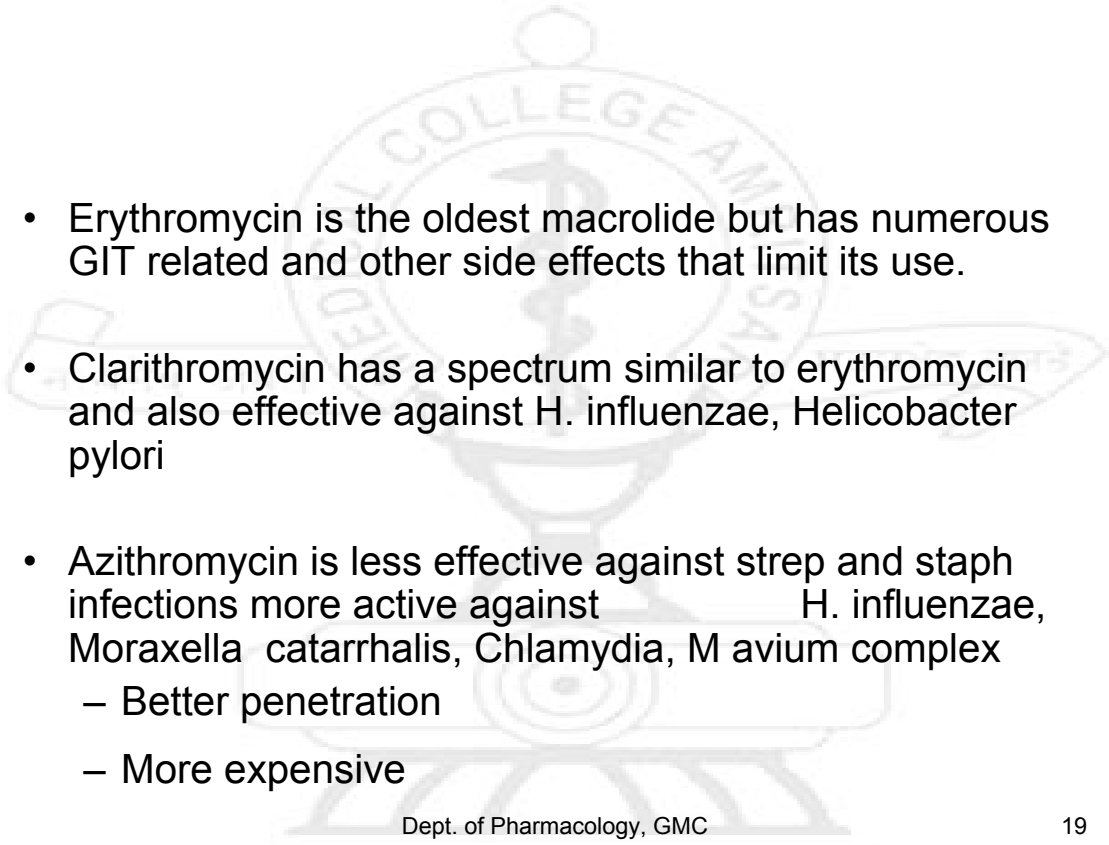
- Action on motilin receptors
- Arrhythmogenic potential
- Drug interactions with cisapride, terfenadine, digoxin, warfarin, corticosteroids by interfering with CYP mediated metabolism of these drugs.
- Azithromycin is relatively safe.

Non-antimicrobial Effects

- Anti-inflammatory effect
 - Decreased production of mediators IL, Cytokines and chemokines
- Immunomodulation
- Decrease production of mucus
- Helpful in cystic fibrosis, asthma, COPD, Chronic sinusitis and SOM.

Therapeutic Status

- Macrolides are effective antimicrobials
- Antibacterial spectrum is slightly wider than that of penicillin
- Most useful in patients sensitive to penicillin.
- Antiinflammatory effect and the ability to reduce mucoid secretions is helpful.
- Post-antibiotic effect is an advantage

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- Erythromycin is the oldest macrolide but has numerous GIT related and other side effects that limit its use.
 - Clarithromycin has a spectrum similar to erythromycin and also effective against H. influenzae, Helicobacter pylori
 - Azithromycin is less effective against strep and staph infections more active against H. influenzae, Moraxella catarrhalis, Chlamydia, M avium complex
 - Better penetration
 - More expensive