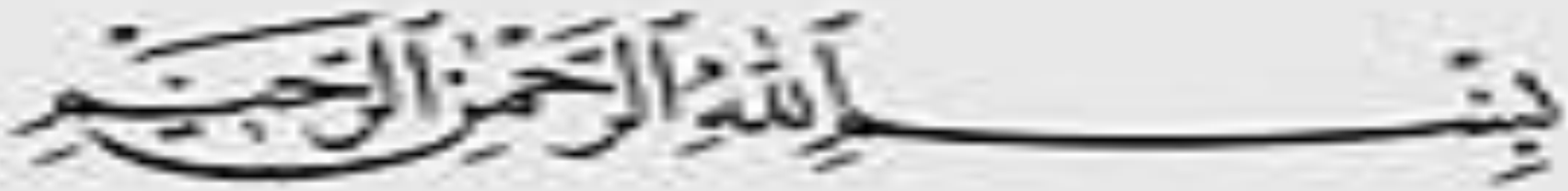

بسم الله الرحمن الرحيم

MACROLIDES

- Sources:
- Bertram G. katzung Basic & Clinical Pharmacology 14th Edition
- Goodman and Gilman's The Pharmacological Basis of Therapeutics 13th edition.

LEARNING OBJECTIVES

At the end of the lecture, students should:

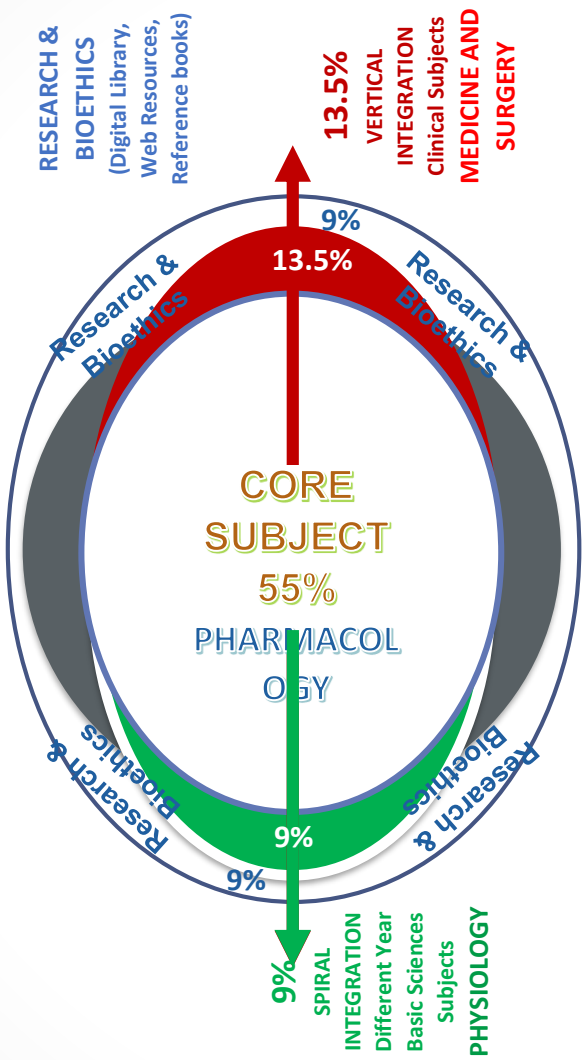
- Describe Mechanism of action, clinical uses and adverse effect of macrolides

- Explain Antibacterial spectrum and mechanism of resistance of macrolides

MOTTO AND VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

Prof. Umar's Clinically Oriented Integration Model
For Basic Sciences Interactive Lectures



Model 3rd Year Pharmacology CBL	
Core Subject – 70%	
Horizontal Integration – 10%	
Vertical integration (Clinical Subjects)	• Medicine (10 %)
Spiral Integration – 15%	
Different Year Basic Sciences Subjects	
Research & Bioethics 5%	

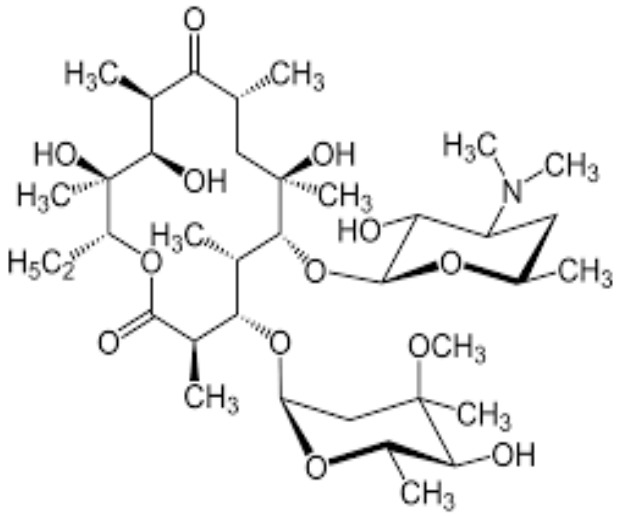
Core subject – Pharmacology

MACROLIDES

- Erythromycin
- Clarithromycin
- Azithromycin
- Roxithromycin
- KETOLIDES include telithromycin

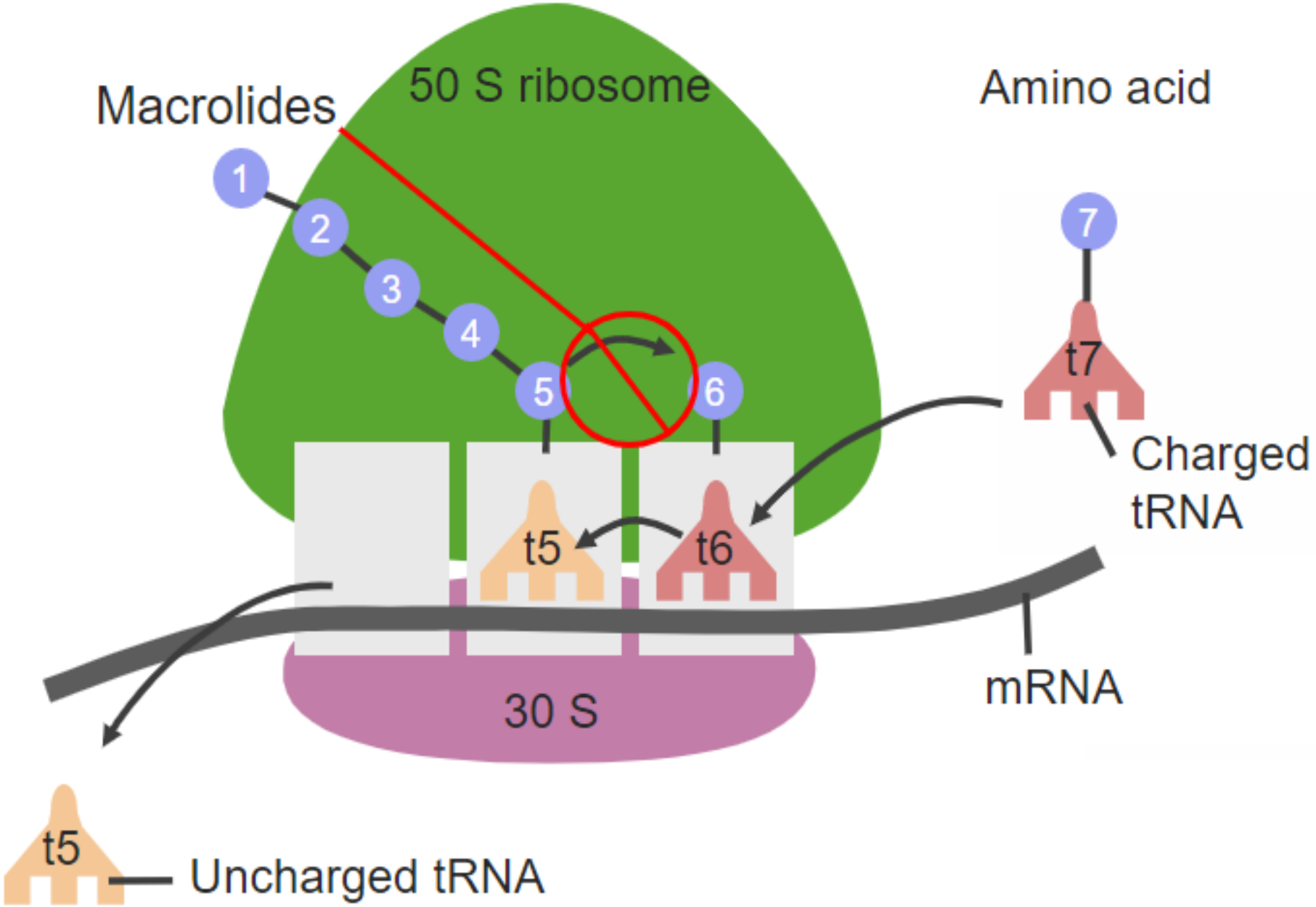
STRUCTURE

- Macrocyclic lactone ring to which deoxy sugars are attached



ERYTHROMYCIN

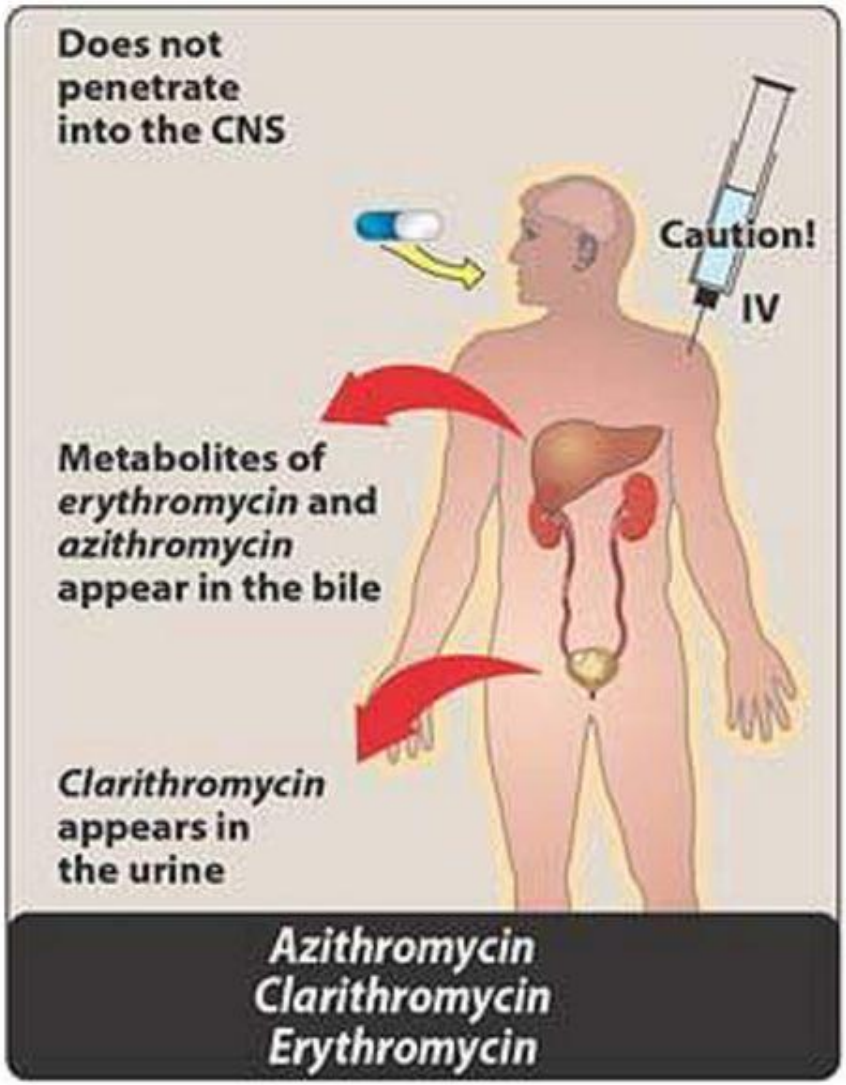
- Activity is enhanced at alkaline pH
- Binds to 50S subunit and blocks transpeptidation
- Also inhibit formation of 50S ribosomal subunit
- Bacteriostatic (bactericidal in high doses)


Macrolides
50 S ribosome
Amino acid
1
2
3
4
5
6
7
t7
Charged
tRNA
t5
t6
mRNA
30 S
t5
Uncharged tRNA

PHARMACOKINETICS

- Erythromycin administered with enteric coating
- Can also be given I/V
- Food interferes absorption of erythromycin
- Widely distributed except CNS , taken by polymorphonuclear leukocytes and macrophages
- Crosses the placenta
- No dose adjustment required in renal failure
- Excreted mainly in bile, some in feaces and urine

Excretion


Does not penetrate into the CNS
Caution!
IV
Metabolites of *erythromycin* and *azithromycin* appear in the bile
Clarithromycin appears in the urine
Azithromycin
Clarithromycin
Erythromycin

Horizontal integration – Microbiology

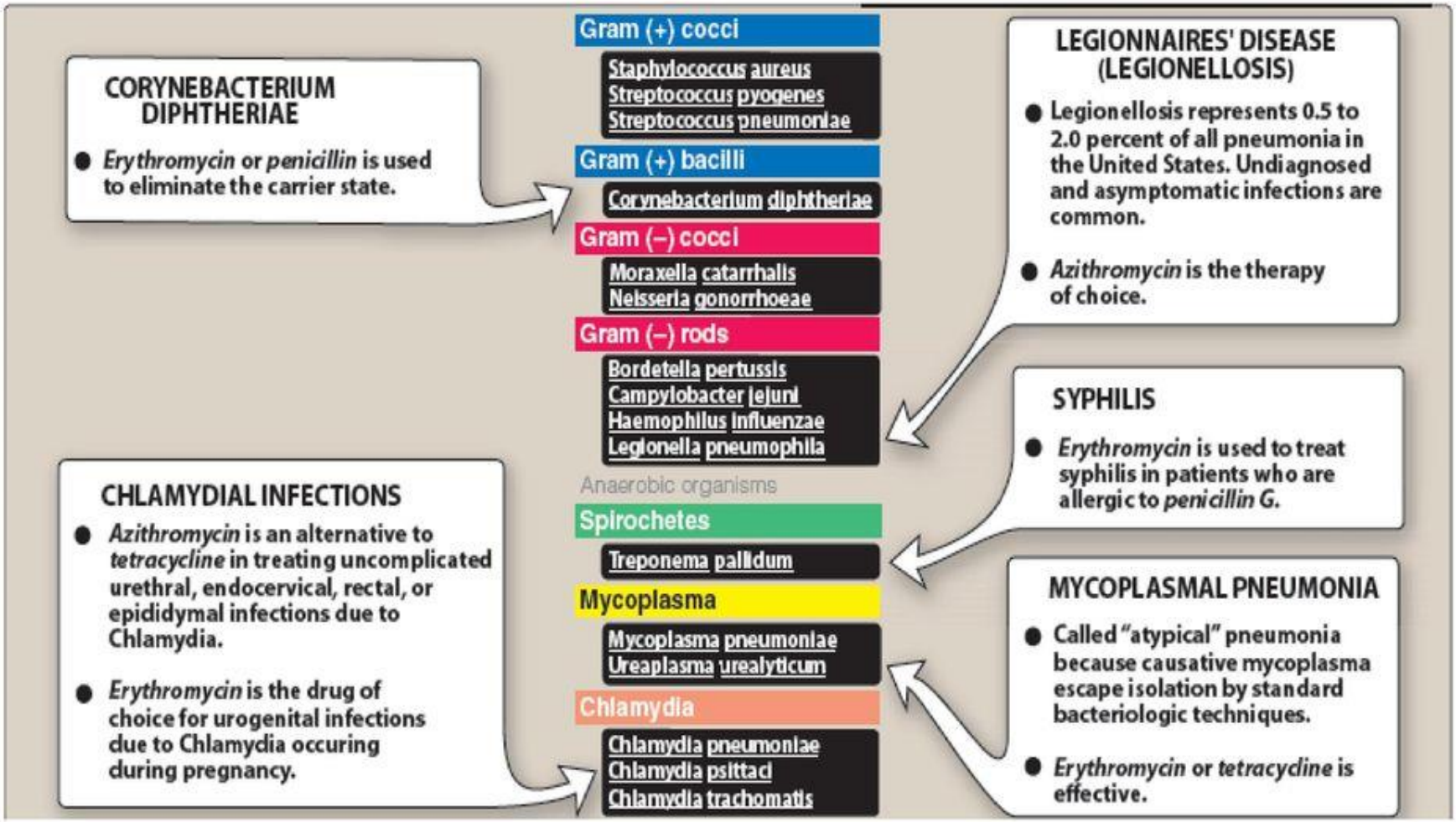
SPECTRUM OF ACTION

- Gram positive bacteria
- Gram negative bacteria
- Spirochetes
- Rickettsia
- Mycobacteria
- Treponema pallidium
- Campylobacter

RESISTANCE

- Reduced permeability of the cell membrane and active efflux (G+ve bacteria)
- Production of esterases that hydrolyze macrolides
- Modification of ribosomal binding sites by chromosomal mutation or by macrolide inducible or constitutive methylase (G+ve bacteria)
- MLS type B

- **VERTICLE INTEGRATION MEDICINE/ SURGERY**


CORYNEBACTERIUM DIPHTHERIAE
● Erythromycin or penicillin is used to eliminate the carrier state.
CHLAMYDIAL INFECTIONS
● Azithromycin is an alternative to tetracycline in treating uncomplicated urethral, endocervical, rectal, or epididymal infections due to Chlamydia.
● Erythromycin is the drug of choice for urogenital infections due to Chlamydia occuring during pregnancy.
Gram (+) cocci
Staphylococcus aureus
Streptococcus pyogenes
Streptococcus pneumoniae
Gram (+) bacilli
Corynebacterium diphtheriae
Gram (–) cocci
Moraxella catarrhalis
Neisseria gonorrhoeae
Gram (–) rods
Bordetella pertussis
Campylobacter jejuni
Haemophilus influenzae
Legionella pneumophila
Anaerobic organisms
Spirochetes
Treponema pallidum
Mycoplasma
Mycoplasma pneumoniae
Ureaplasma urealyticum
Chlamydia
Chlamydia pneumoniae
Chlamydia psittaci
Chlamydia trachomatis
LEGIONNAIRES' DISEASE (LEGIONELLOSIS)
● Legionellosis represents 0.5 to 2.0 percent of all pneumonia in the United States. Undiagnosed and asymptomatic infections are common.
● Azithromycin is the therapy of choice.
SYPHILIS
● Erythromycin is used to treat syphilis in patients who are allergic to penicillin G.
MYCOPLASMAL PNEUMONIA
● Called "atypical" pneumonia because causative mycoplasma escape isolation by standard bacteriologic techniques.
● Erythromycin or tetracycline is effective.

CLINICAL USES

- Corynebacterial infections (diphtheria, corynebacterial sepsis, erythema)
- Respiratory, neonatal, ocular or genital chlamydial infections
- Community-acquired pneumonia
- Penicillin-allergic individuals with infections caused by staphylococci
- As prophylaxis against endocarditis during dental procedures

- Preoperative bowel preparation with neomycin
- Chronic bronchitis, acute otitis media, sinusitis, pharyngitis, pertussis
- As prokinetic agent
- Cellulitis
- STDs
- Campylobacter gastroenteritis in children

PROPHYLACTIC USES OF MACROLIDES

- Rheumatic fever---erythromycin

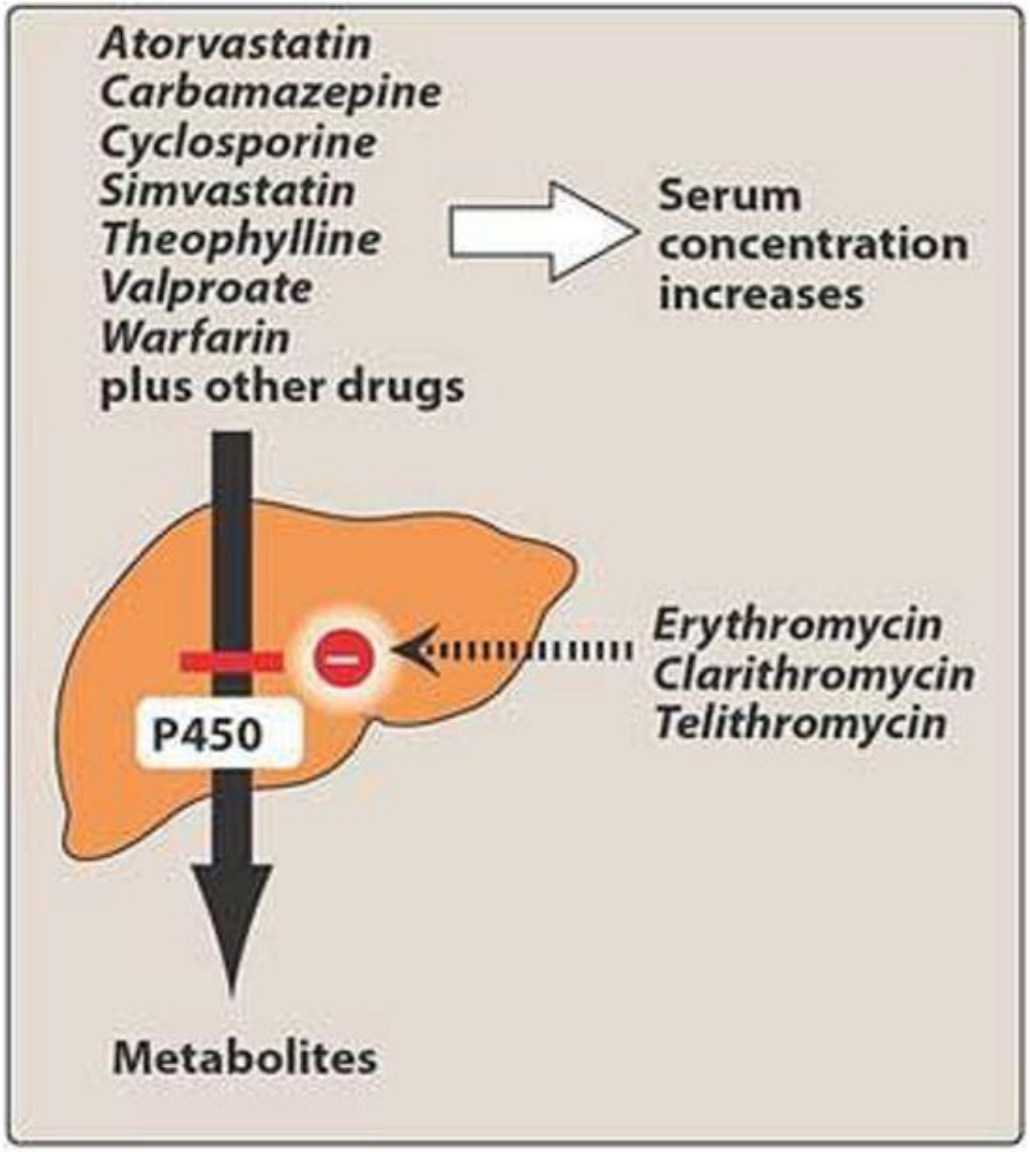
- As prophylaxis against endocarditis during dental procedures----- azithromycin and clarithromycin along with clindamycin

ADVERSE EFFECTS

- GIT- severe epigastric distress even with iv
- Hepatotoxicity– estolate formulation
- Ototoxicity- transient auditory impairment
- Allergic reactions

DRUG INTERACTIONS

- Inhibitor of CYP3A4
- Increases concentration of theophylline, oral anticoagulants, cyclosporin , methylprednisolone
- Erythromycin increases concentration of digoxin by increasing enterohepatic circulation


Atorvastatin
Carbamazepine
Cyclosporine
Simvastatin
Theophylline
Valproate
Warfarin
plus other drugs
Serum concentration increases
Erythromycin
Clarithromycin
Telithromycin
P450
Metabolites

CLARITHROMYCIN

- Improved oral bioavailability, IV formulations also available
- More active against Mycobacterium avium
- Longer half life
- Metabolized in liver
- Elimination through kidney
- H. pylori eradication

AZITHROMYCIN

- Well tolerated orally, IV formulation
- Highly active against chlamydia and H influenza, T. gondii
- Long half life
- Biliary excretion
- Prophylaxis and treatment of disseminated infection caused by M.avium intracellulare in AIDS patient
- QT interval prolongation

KETOLIDES

Telithromycin

-Is a ketolide structurally related to macrolides.
-same mechanism of action as erythromycin & a similar spectrum of antimicrobial activity.
-some macrolide–resistant strains are susceptible to telithromycin.

Clinical use:

Community acquired pneumonia,
other upper respiratory tract infections.
Telithromycin is given orally once daily.

ADVERSE EFFECTS

- Prolong QT interval
- Not used as it causes hepatitis and liver failure
- Not used in MG

Fidaxomicin

- Is a macrocyclic antibiotic with a structure similar to the macrolides;

Mechansim of action

- it has a unique mechanism of action.

-acts on the sigma subunit of RNA polymerase,

-thereby disrupting bacterial transcription,

- terminating protein synthesis,

-and resulting in cell death in susceptible organisms.

- Fidaxomicin has a **very narrow spectrum** of activity limited to gram-positive aerobes and anaerobes.
- it possesses activity against staphylococci and enterococci
- It is used primarily against Clostridium difficile.
- Following oral administration, has minimal systemic absorption and primarily remains within GIT .
- This is ideal for the treatment of C. difficile infection, which occurs in the gut.

- This characteristic also likely contributes to the low rate of adverse effects.

- Hypersensitivity reactions may occur.

- **Fidaxomicin** should be used with caution in patients with a macrolide allergy, as they may be at increased risk for hypersensitivity.

Macrolide Uses

Routes:

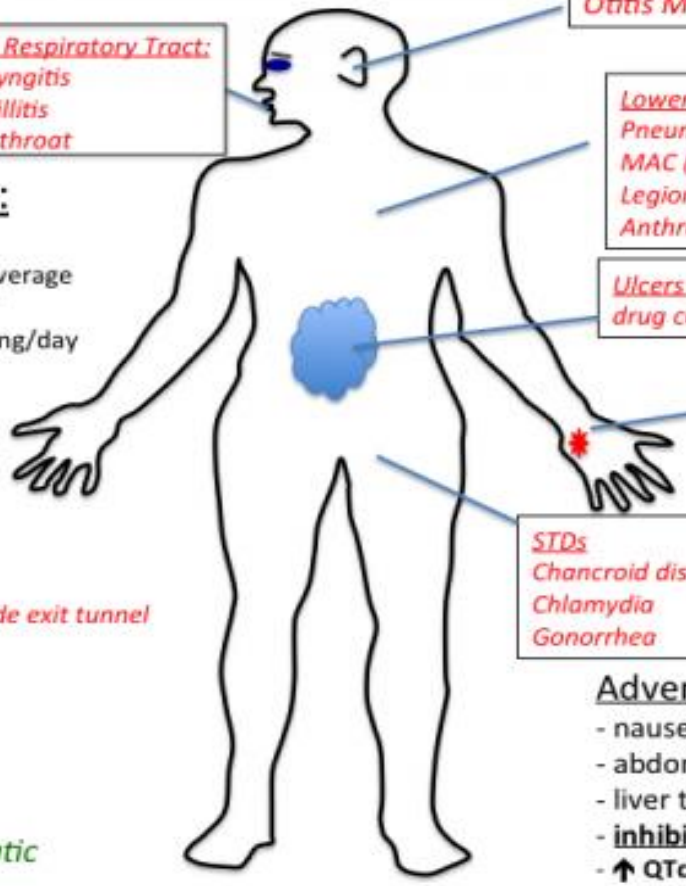
Pharmacokinetics:

- Azithromycin $t_{1/2}$ =3 days
- a 1 g dose provides 7 day coverage
- common therapy consists of 500 mg loading dose & 250 mg/day for 4 more days.

Mechanism:

Bind to 50S & block polypeptide exit tunnel to prevent chain elongation

bacteriostatic



Otitis Media

Upper Respiratory Tract:
- *Pharyngitis*
- *Tonsillitis*
- *Sore throat*

Lower respiratory tract infections:
Pneumonia
MAC (Mycobacterium avis complex)
Legionnaire's
Anthrax

Ulcers (H. pylori)
drug combo including Clarithromycin

Uncompliated skin infections (staph)

STDs
Chancroid disease in men
Chlamydia
Gonorrhea

Adverse Effects:

- nausea, vomiting, diarrhea
- abdominal pain
- liver toxicity (estolate related)
- **inhibit P-450** (drug interactions)
- ↑ QTc

RESEARCH

- https://www.ingentaconnect.com/content/ben/cpd/2004/00000010/00000025/art00003

- https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011825.pub2/abstract

ARTIFICIAL INTELLIGENCE

- Lv Z, Yin S, Jiang K, Wang W, Luan Y, Wu S, Shi J, Li Z, Ma X, Wang Z, Yan H. The whole-cell proteome shows the characteristics of macrolides-resistant Bordetella pertussis in China linked to the biofilm formation. Archives of Microbiology. 2023 Jun;205(6):219.

- Ferreira PM, Sousa RW, Dittz D, Torres-Leal FL, Bezerra DP. Antimalarials and macrolides: a review of off-label pharmacotherapies during the first wave of the SARS-CoV-2 pandemic. Brazilian Journal of Pharmaceutical Sciences. 2023 Apr 14;59:e21067.

MCQs

Major advantage of clarithromycin over erythromycin is that it

- Does not inhibit hepatic drug metabolizing enzymes
- Eradicates mycoplasmal infections in single dose
- Has greater activity against H. Pylori
- Is active against MRSA
- Is active against strains of streptococci that are resistant to erythromycin

A 26 years old female is pregnant and has gonorrhea. Medical history includes anaphylaxis with ampicillin. The most appropriate drug to use is

- Cefixime
- Doxycycline
- Azithromycin
- Ceftriaxone
- ciprofloxacin