

PROTEIN SYNTHESIS INHIBITORS

MACROLIDES



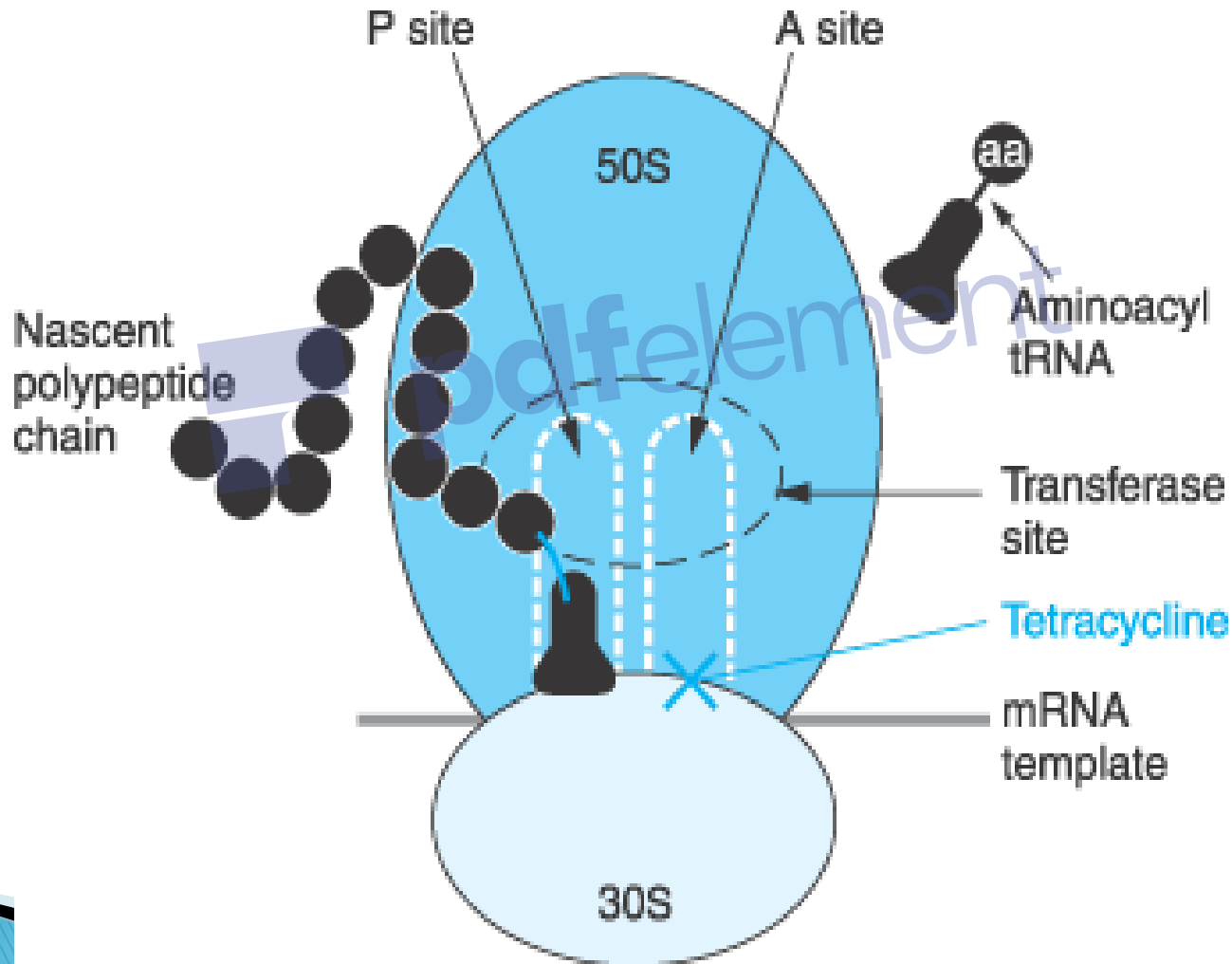
Dr. Asma inam

▶ Yesterday we have covered:

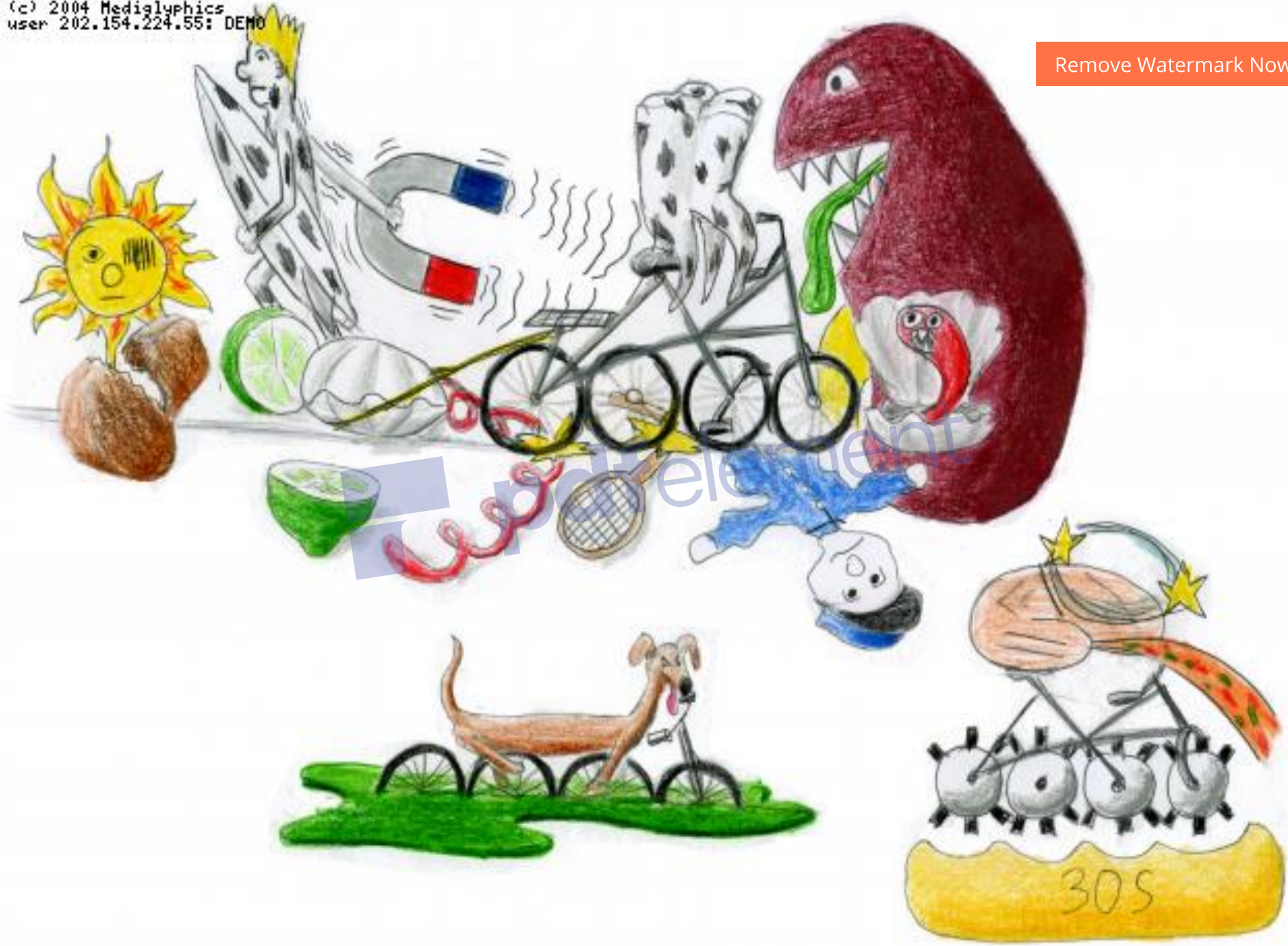
Tetracyclines & Tigecyclines

- ▶ Classification, MOA, resistance mechanism
- ▶ Pharmacokinetics
- ▶ Spectrum
- ▶ Clinical uses and adverse effects

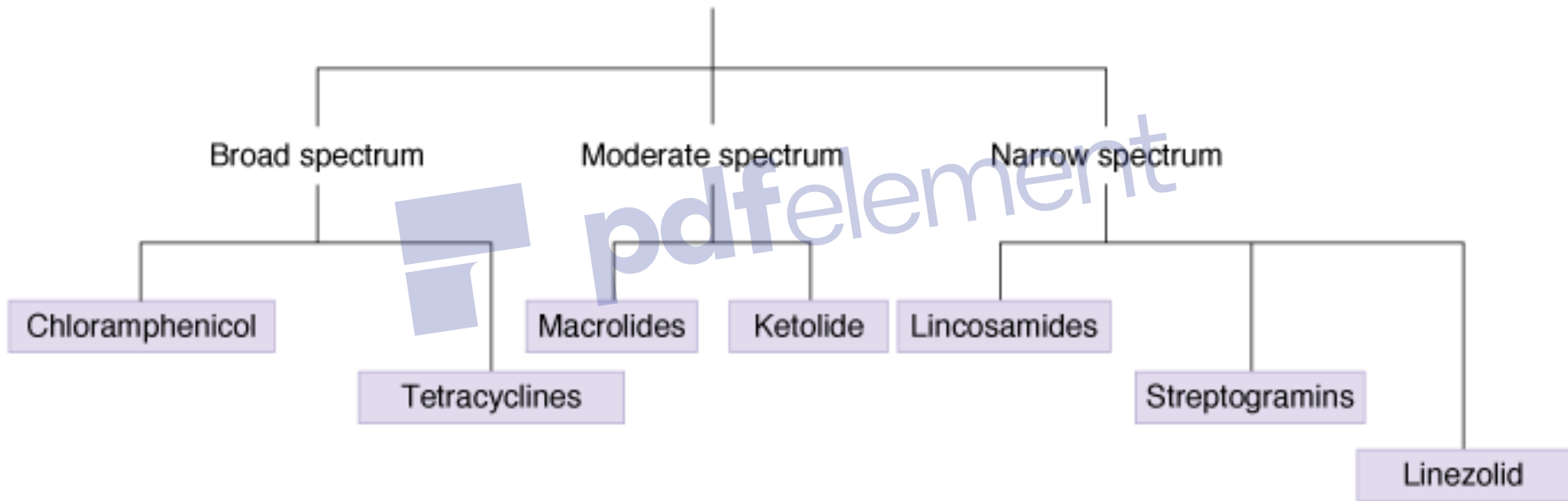
MECHANISM OF ACTION(TETRACYCLINE)



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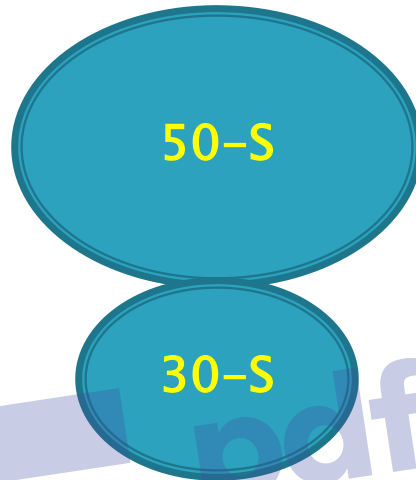
Bacterial protein synthesis inhibitors



SUMMARY OF BACTERIAL PROTEIN SYNTHESIS INHIBITORS

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▶ CLEAN TAG



CHLORAMPHENICOL, **C**LINDAMYCIN

ERTHROMYCIN, **A**ZITHROMYCIN. (50-S)

TETRACYCLINE, **A**MINOGLYCOSIDE (30-S)

PROTEIN SYNTHESIS INHIBITORS

TETRACYCLINES

- Demeclocycline*
- Doxycycline*
- Minocycline*
- Tetracycline*

GLYCYLCYCLINES

- Tigecycline*

AMINOGLYCOSIDES

- Amikacin*
- Gentamicin*
- Neomycin*
- Streptomycin*
- Tobramycin*

MACROLIDES/ KETOLIDES

- Azithromycin*
- Clarithromycin*
- Erythromycin*
- Telithromycin*

CHLORAMPHENICOL

CLINDAMYCIN

QUINUPRISTIN/
DALFOPRISTIN

LINEZOLID

MACROLIDES

× Macrolide antibiotics are *bacteriostatic (sometimes bactericidal)* agents.

+ Erythromycin

+ Clarithromycin

+ Azithromycin

+ Ketolides

× Telithromycin

×

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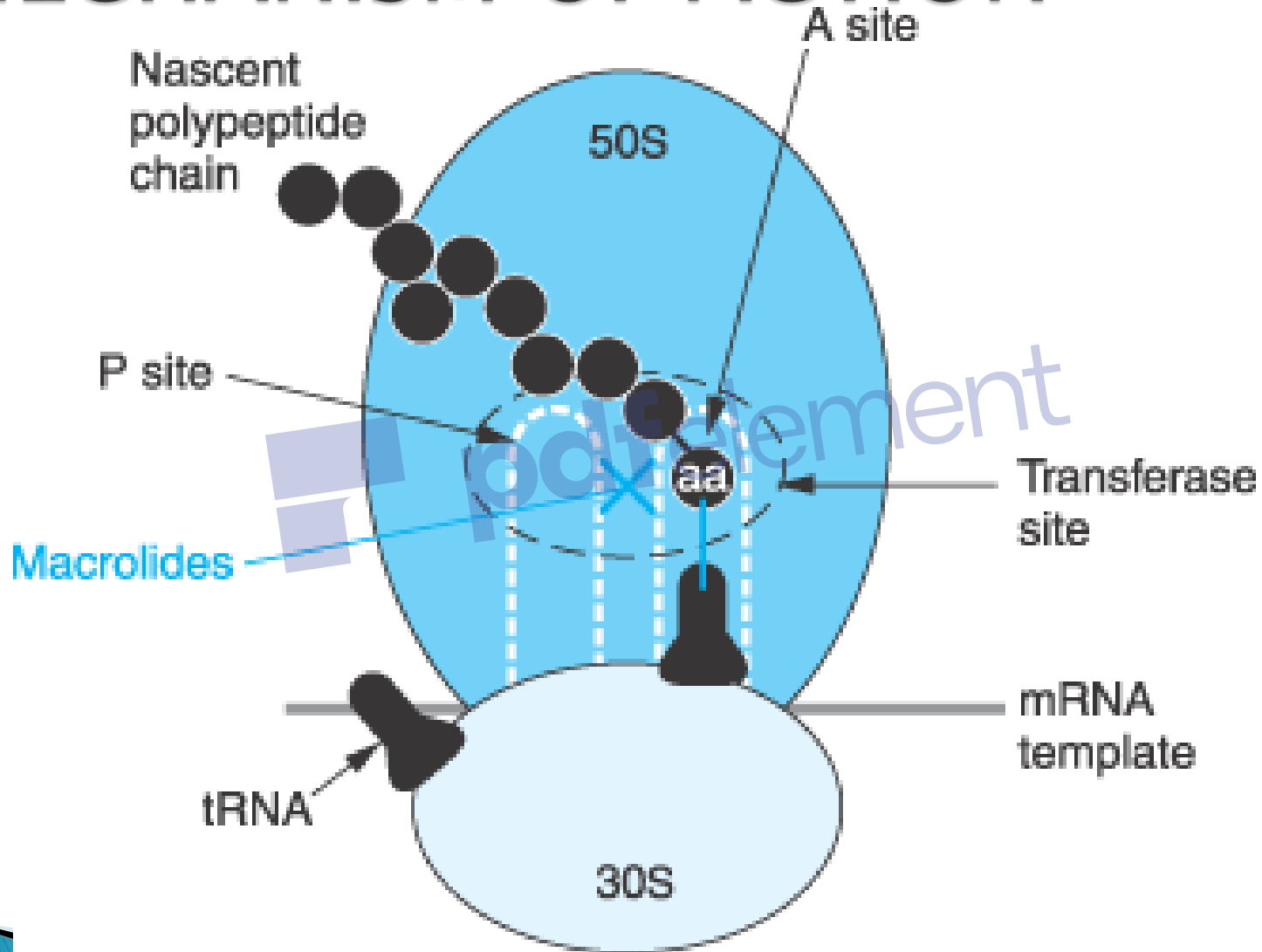
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MECHANISM OF ACTION

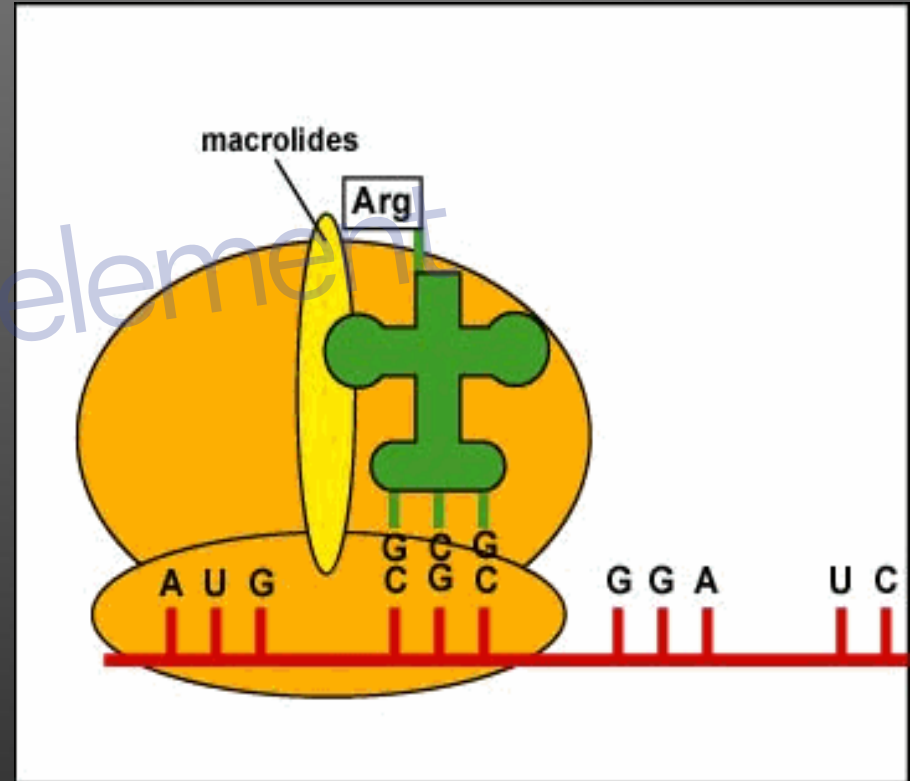
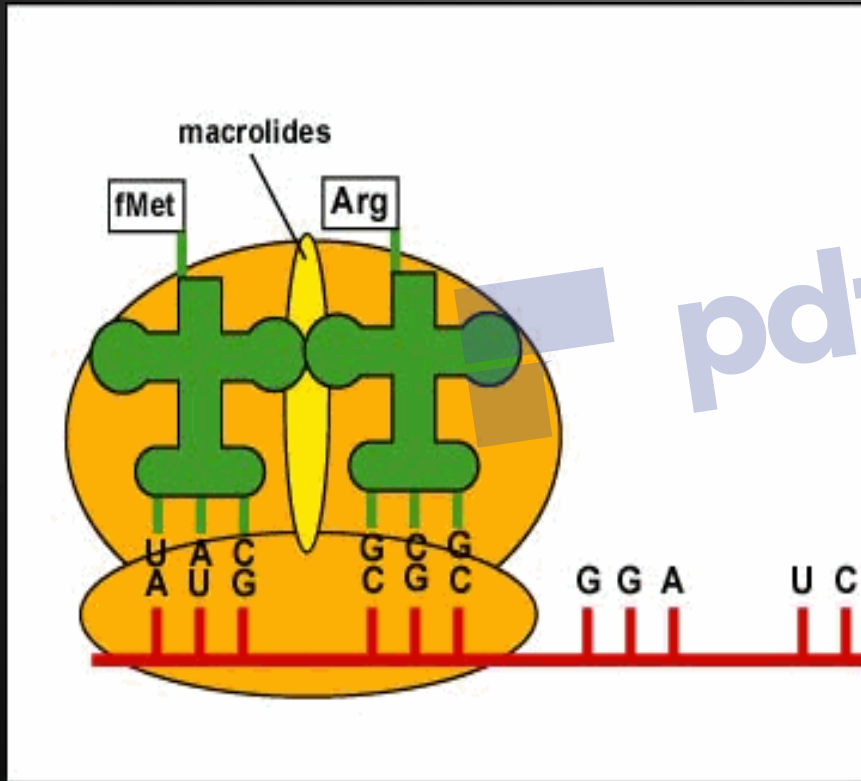
- × inhibit protein synthesis by binding reversibly to 50S ribosomal subunits at or very near the site that binds chloramphenicol .
- × Inhibits transpeptidation
- × inhibits the translocation step wherein a newly synthesized peptidyl tRNA molecule moves from the acceptor site on the ribosome to the peptidyl donor site.

- ▶ It can **inhibit elongation of the protein** by blocking the translocation of the ribosome to the next codon on the mRNA
- ▶ **Gram-positive bacteria** accumulate about 100 times more erythromycin than do gram-negative bacteria.

MECHANISM OF ACTION



Macrolide Antibiotics



RESISTANCE TO MACROLIDES

- (1) **drug efflux** by an active pump mechanism
- (2) production of methylase enzymes, which modify the ribosomal target and **decrease drug binding**
- (3) **macrolide hydrolysis** by esterases produced by bacteria .

PHARMACOKINETICS

	<i>Erythro- mycin</i>	<i>Clarithro- mycin</i>	<i>Azithro- mycin</i>	<i>Telithro- mycin</i>
Oral absorption	Yes	Yes	Yes	Yes
Half-life (hours)	2	3.5	>40	10
Conversion to an active metabolite	No	Yes	Yes	Yes
Percent excretion in urine	15	50	12	13

**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***



PHARMACOKINETICS

- × *Administration:*
- × erythromycin base is destroyed by **gastric acid**.
- × Thus, either **enteric-coated tablets** or esterified forms of the antibiotic are administered.
- × All are **adequately absorbed** upon oral administration
- × intravenous administration of erythromycin is associated with a high incidence of **thrombophlebitis**.

- × **Distribution:**
- × Erythromycin distributes well to all body fluids **except the CSF.**
- × Azithromycin has the **longest half-life** and largest volume of distribution of the four drugs.

- × **Fate:** Erythromycin and telithromycin are extensively metabolized and are known to inhibit the oxidation of a number of drugs.
- × **Excretion:** Erythromycin and azithromycin are primarily concentrated and excreted in an active form in the **bile**.
- × In contrast, **clarithromycin** and its metabolites are eliminated by the kidney
- × **Active metabolites.**

ANTIBACTERIAL SPECTRUM

- × *Erythromycin*:
- × Spectrum same as penicillin G therefore
- × used in patients who are allergic to the penicillins.

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Erythromycin

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- ▶ usually bacteriostatic but may be bactericidal .
- ▶ effective against aerobic gram positive bacilli and cocci
- ▶ *S. pyogenes*
- ▶ *Streptococcus viridans*
- ▶ *Clostridium perfringens*
- ▶ *Corynebacterium diphtheria*
- ▶ *Listeria monocytogenes*
- ▶ Less activity against gram negative including *H. influenzae*, *N. meningitidis*.

Antibacterial Activity (Erythromycin)

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- ▶ Good against *N. gonorrhoeae*
- ▶ *Pasteurella multocida*, *Borrelia*
- ▶ *Bordetella pertussis*
- ▶ *Compylobacter jejuni*
- ▶ *M. pneumoniae*, *Legionella pneumophila*
- ▶ *C. Trachomatis*
- ▶ Atypical mycobacteria.

Therapeutic Uses (Erythromycin)

- ▶ Mycoplasma pneumoniae infections
- ▶ Legionnaires' disease.
 - Drug of choice in pneumonia caused by legionella sp.
- ▶ Chlamydial infections
- ▶ Diphtheria
- ▶ Pertussis (drug of choice)
- ▶ Streptococcal infections
- ▶ Staphylococcal infections
- ▶ Campylobacter infections
- ▶ Tetanus
- ▶ Prophylactic use:
 - It may be used prophylactically as an alternate to Benzyl penicillin in recurrence of rheumatic fever / during dental procedures

Clarithromycin

- ▶ It is derived from erythromycin by adding a **methyl group** and has **improved acid stability** and oral absorption compared with erythromycin.
- ▶ **Spectrum** is Similar to erythromycin in addition it is more active against
 - **mycobacterium avium.**
 - M. leprae

Clarithromycin

- × *Clarithromycin*: similar to that of erythromycin

- ▶ The advantages of clarithromycin compared with erythromycin are
 - lower frequency of gastrointestinal intolerance and
 - less frequent dosing.

- × *Haemophilus influenzae*.

- × intracellular pathogens, *Chlamydia*, *Legionella*, *Moraxella*, and *Ureaplasma* species and *Helicobacter pylori*, is higher than that of erythromycin.

Therapeutic uses of Clarithromycin

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- ▶ **Helicobacter pylori infections**
- ▶ **Mycobacterial infections (first line therapy)**
- ▶ Tetanus
- ▶ Syphilis
- ▶ Campylobacter infections
- ▶ Streptococcal infections: Pharyngitis, scarlet fever etc
- ▶ Staphylococcal infections, but can not be relied upon.
- ▶ Legionella infections
- ▶ Mycoplasma infections
- ▶ Prophylactic uses as described in erythromycin

Azithromycin

- × *Azithromycin*
- × more active against respiratory infections due to *H. influenzae* and *Moraxella catarrhalis*.
- × It is now the preferred therapy for urethritis caused by *Chlamydia trachomatis*.
Mycobacterium avium-intracellulare complex in patients with acquired immunodeficiency syndrome and disseminated infections.

×

Azithromycin

- ▶ **SPECTRUM**
- ▶ Similar to erythromycin with **more activity against H. influenzae and campylobacter**, very active against M. catarrhalis, Chlamydia, M. Pneumoniae, L. pneumophila, B. burgdorferi, Fusobacterium and N. gonorrhoeae.
- ▶ Enhanced activity against **M. avium-intracellulare** as well as some **protozoa e.g.**, Toxoplasma gondii, Cryptosporidium, and plasmodium.

Therapeutic uses

- ▶ Chlamydial infections:
 - Azithromycin is specifically recommended as an alternative to doxycycline in patients with uncomplicated urethral, endocervical, rectal, or epididymal infections.
 - Pneumonia caused by Chlamydial pneumoniae
- ▶ Diphtheria:
 - Erythromycin is more effective

- ▶ **Mycobacterial Infections:**
 - Azithromycin or Clarithromycin are first line of therapy against prophylaxis and treatment of disseminated infections caused by *M. avium-intracellulare* in AIDS pts. And treatment of pulmonary disease in non-HIV-infected patients.
- ▶ Other infections:
 - Treatment and prophylaxis of toxoplasmosis encephalitis and diarrhea due to *Cryptosporidium*.

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 occurring during pregnancy.

CORYNEBACTERIUM DIPHTHERIAE

- *Erythromycin* or *penicillin* is used to eliminate the carrier state.

LEGIONNAIRES' DISEASE (LEGIONELLOSIS)

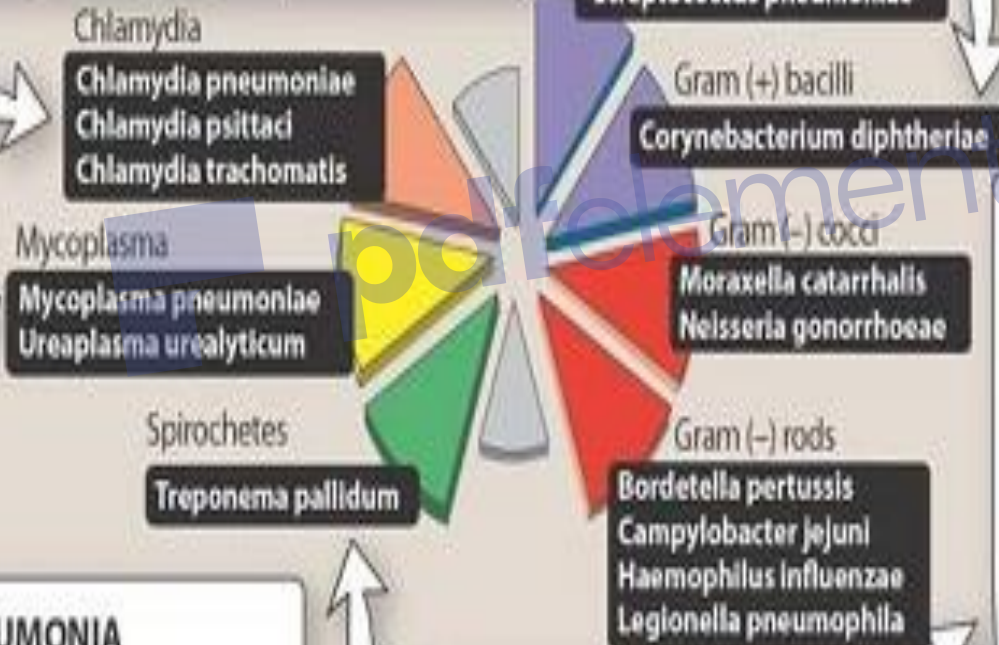
- Legionellosis represents 0.5 to 2.0 percent of all pneumonia in the United States. Undiagnosed or asymptomatic infections are common.
- *Azithromycin* is the therapy of choice.

MYCOPLASMAL PNEUMONIA

- Called "atypical" pneumonia because causative mycoplasma escape isolation by standard bacteriologic techniques.
- *Erythromycin* or *tetracycline* is effective.

SYPHILIS

- *Erythromycin* is used to treat syphilis in patients who are allergic to *penicillin G*.



- ▶ *Telithromycin*: This ketolide drug has an antibacterial spectrum similar to that of azithromycin.
- ▶ Many **macrolide-Resistant strains** are vulnerable due to structural modification which renders ability to resist efflux-pump

Pharmacokinetics

- ▶ Absorption:
 - Absorbed from GIT
- ▶ Distribution:
 - distributed in tissues and intracellular penetration is good.
- ▶ Elimination:
 - Metabolized in the liver and eliminated by combination of biliary and urinary routes.
- ▶ Dose: 800mg single daily dose.

Indications:

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- ▶ Respiratory tract infections including
 - community-acquired bacterial pneumonia,
 - acute-on-chronic bronchitis,
 - sinusitis,
 - streptococcal pharyngitis.

Adverse effects:

- Cardiac effects more pronounced like erythromycin

ADVERSE EFFECTS



GI disturbance



Jaundice



Ototoxicity

ADVERSE EFFECTS

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- × *GIT Effects:*
 - + Anorexia, nausea, vomiting and diarrhea – oral administration
- × *Liver Toxicity:*
 - + Erythromycin particularly can produce acute cholestatic hepatitis (fever, jaundice, impaired liver functions) probably as a hypersensitivity reaction.

- × **Hypersensitivity reactions:**
 - + Fever, eosinophilia and skin eruptions.

- × **Cardiac**
 - + Erythromycin has been reported to cause cardiac arrhythmias, including QT prolongation.

- × **Transient auditory Impairment:**
 - + Potential complication of treatment with erythromycin followed by I/V administration

DRUG INTERACTIONS

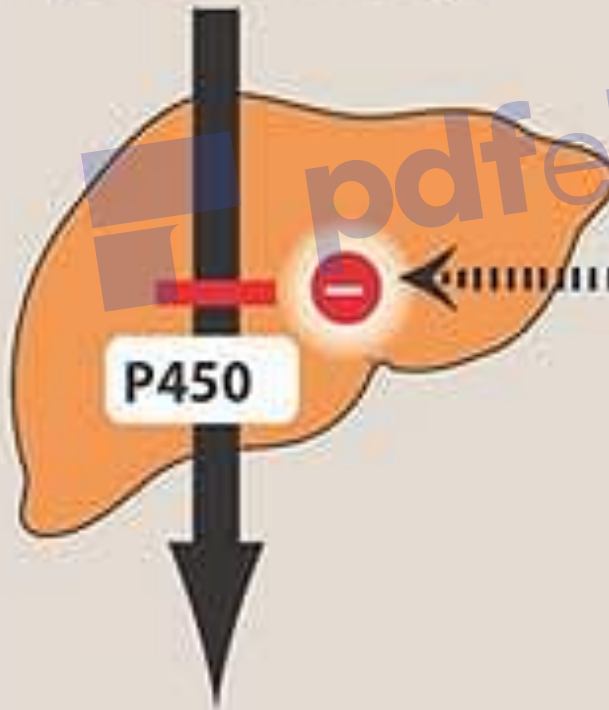
- ▶ Interactions: Erythromycin, telithromycin, and clarithromycin **inhibit the hepatic metabolism** of a number of drugs, which can lead to toxic accumulations of these compounds.

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Atorvastatin
Carbamazepine
Cyclosporine
Simvastatin
Theophylline
Valproate
Warfarin
plus other drugs



Serum
concentration
increases



Erythromycin
Clarithromycin
Telithromycin

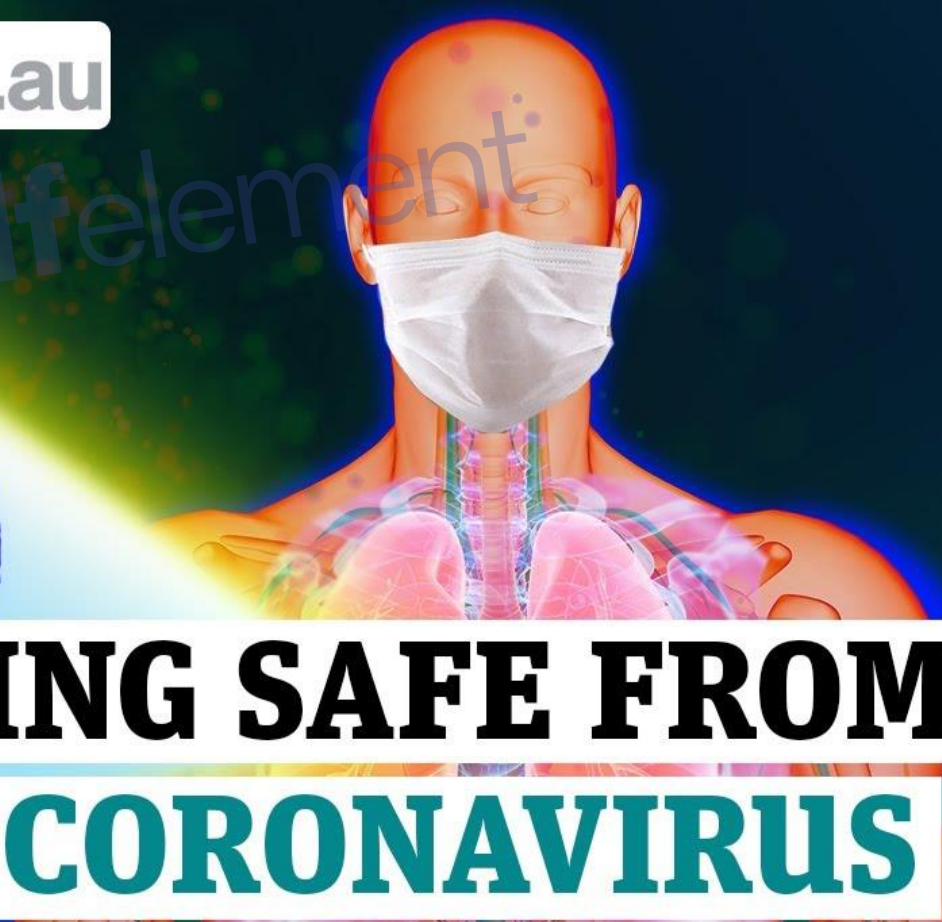
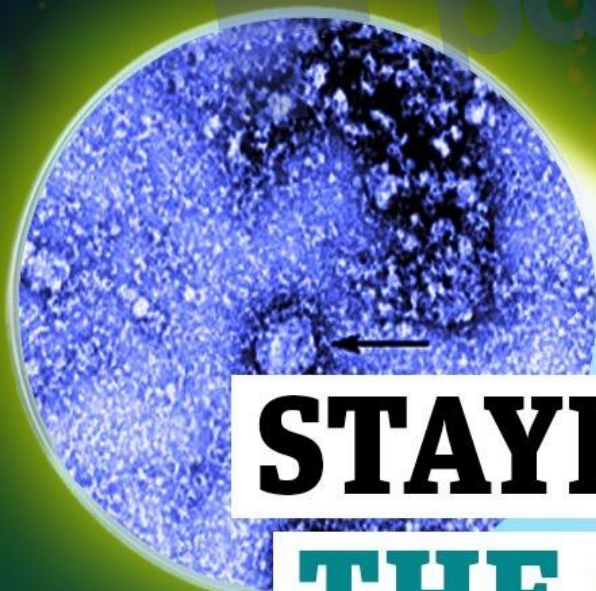
Metabolites

- ▶ *Advantages of newer macrolides*
- ▶ To overcome limitations of erythromycin
- ▶ Narrow spectrum
- ▶ Gastric acid lability
- ▶ Low oral bioavailability
- ▶ Poor tissue penetration
- ▶ Short half life
- ▶ (roxithromycin, clarithromycin, azithromycin)

POINTS TO REMEMBER

- ▶ **MACROLIDES ARE BACTERIOSTATIC but are bactericidal at higher conc.**
- ▶ **THESE BIND TO 50-S RIBOSOMAL SUBUNIT.**
- ▶ **ENZYME INHIBITORS**
- ▶ **CAUSE CHOLESTATIC JAUNDICE**

Thank you



**STAYING SAFE FROM
THE CORONAVIRUS**

MECHANISM OF ACTION(CHORAMPHENICOL)

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