

# ANTITUBERCULOTIC DRUGS

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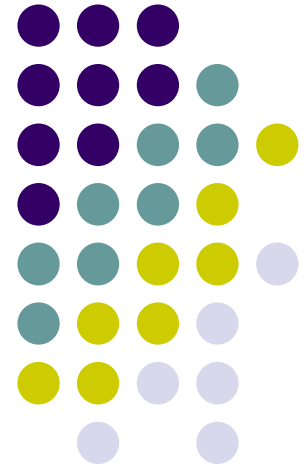
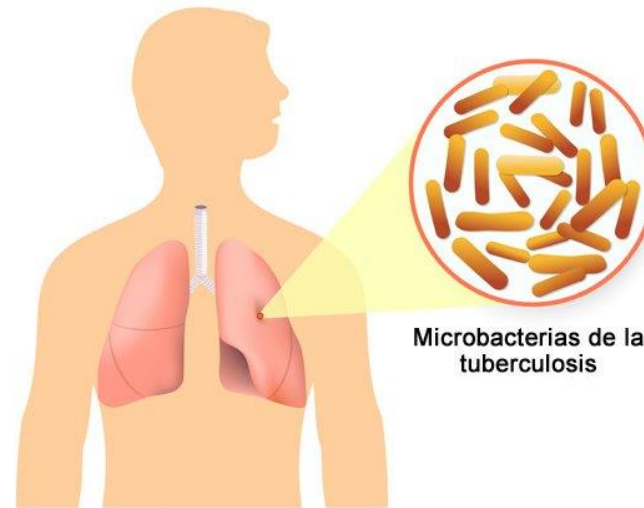
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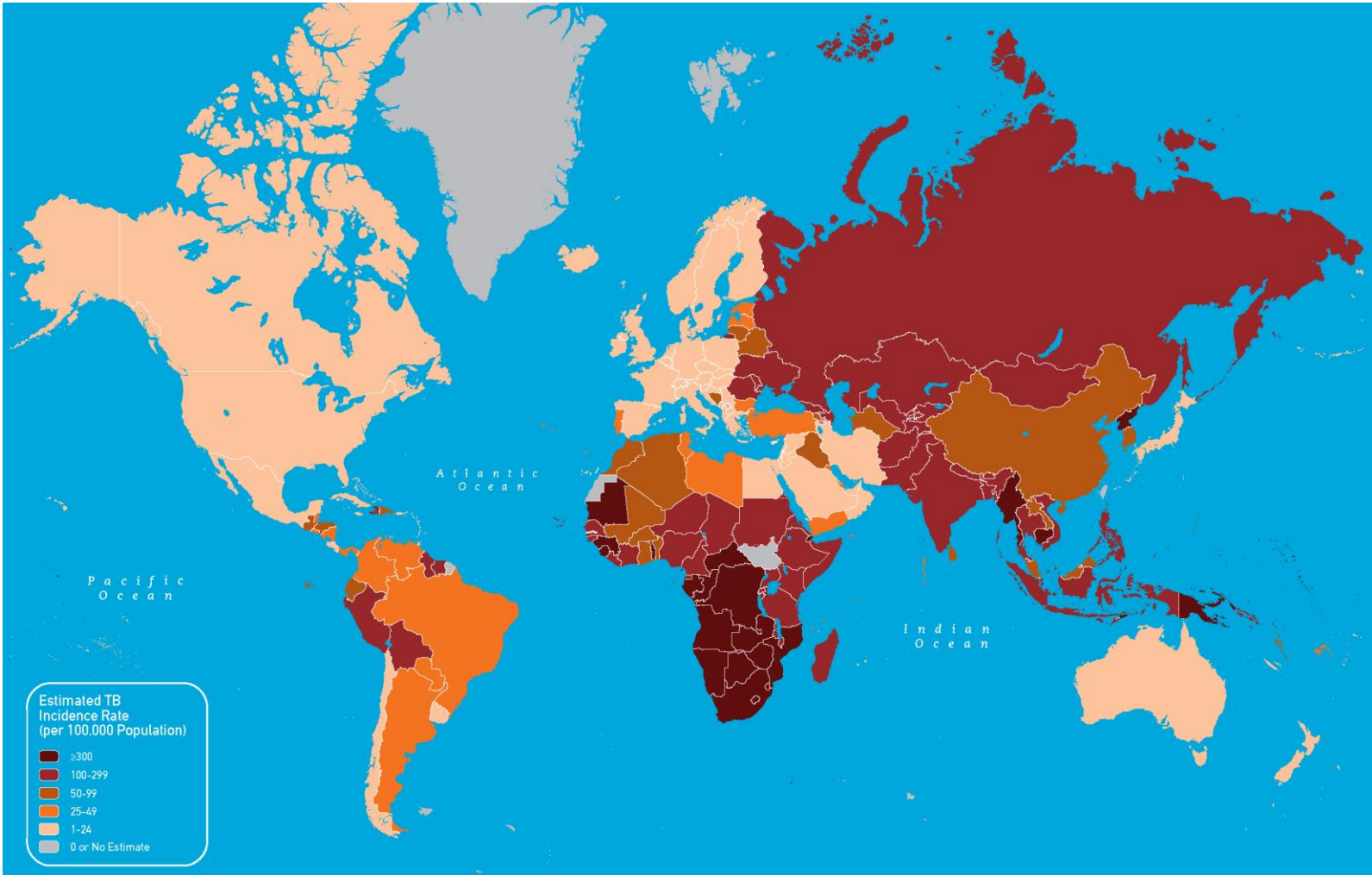
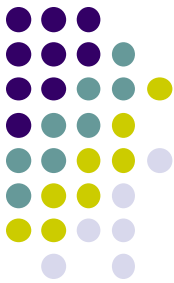
Department of Pharmacology

Košice

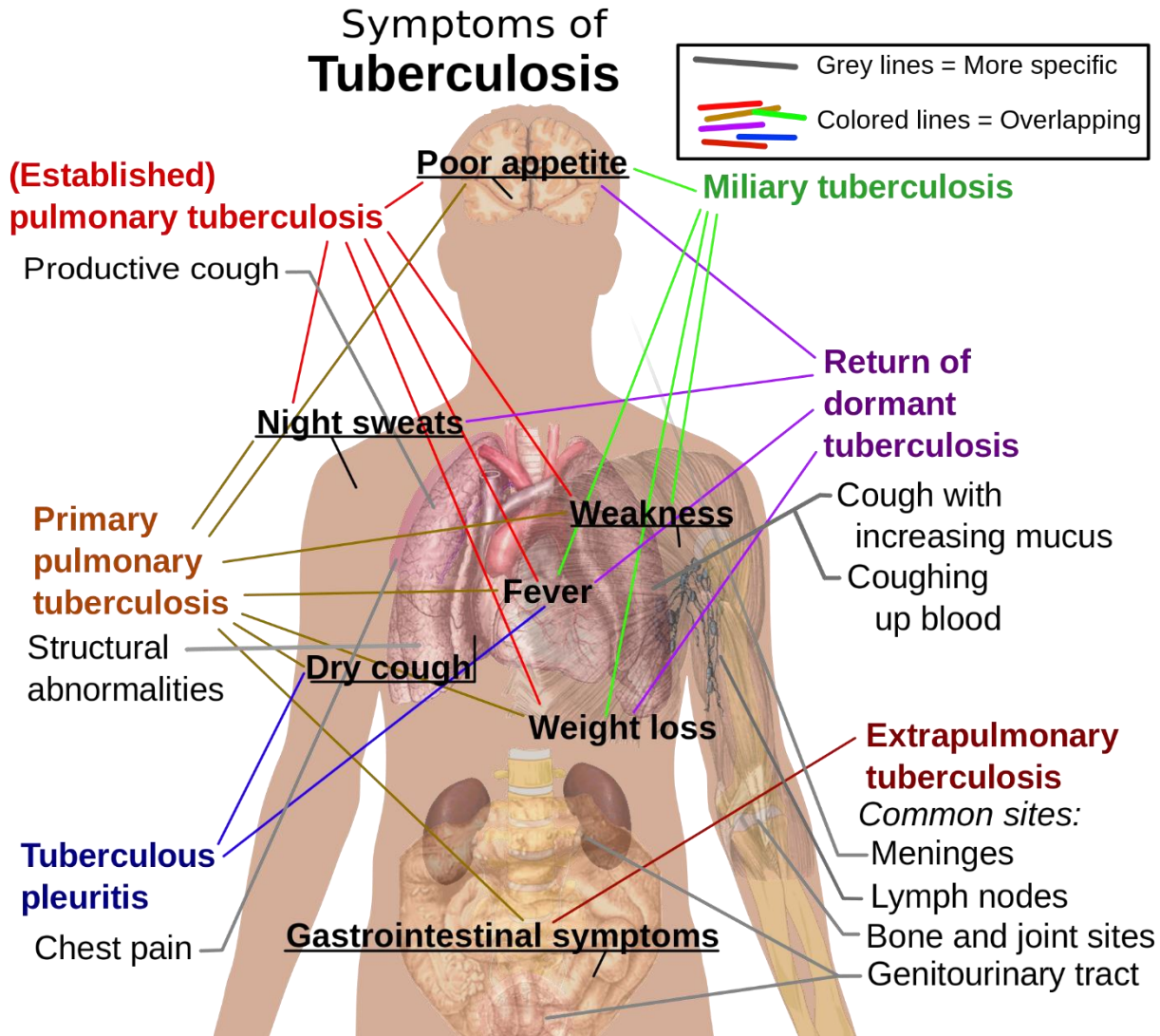
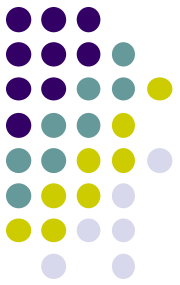
## TUBERCULOSIS



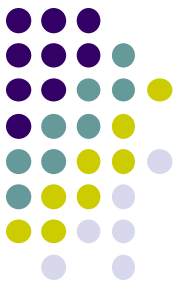
# TBC incidence in the world 2013



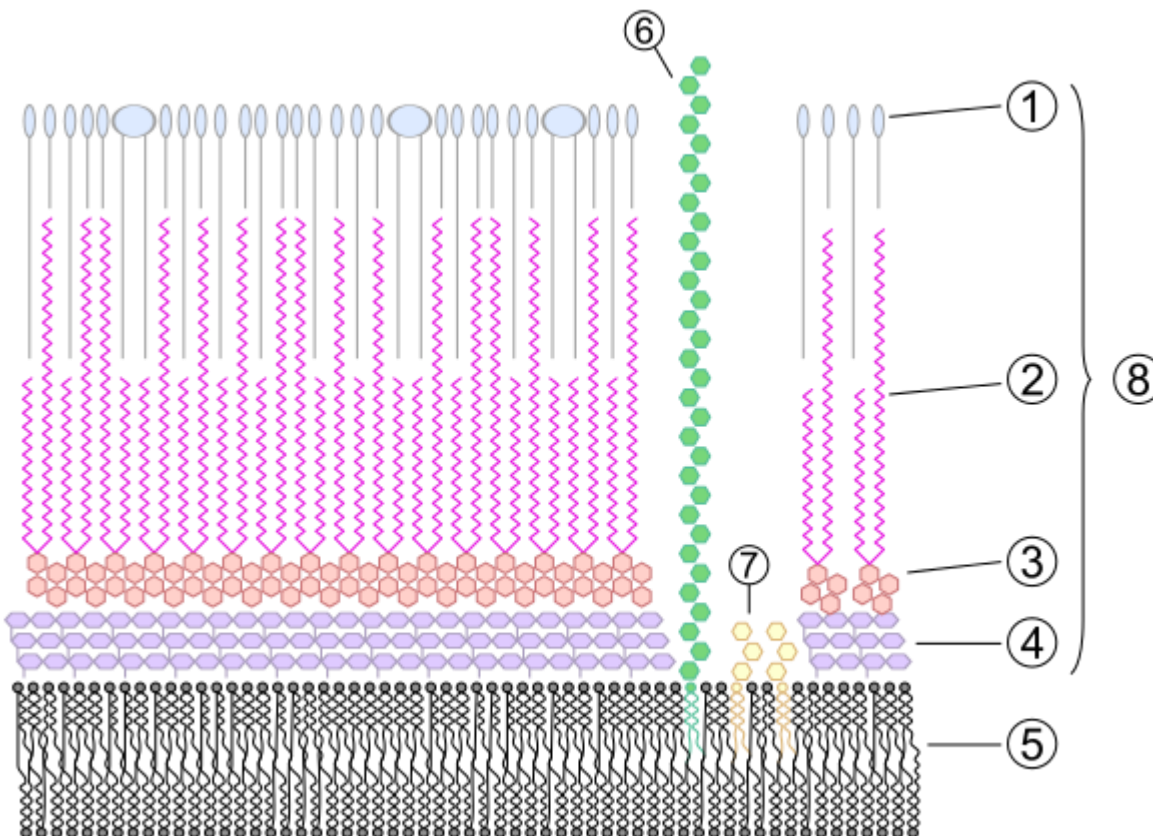
# Symptoms of TBC



# Mycobacterial cell wall



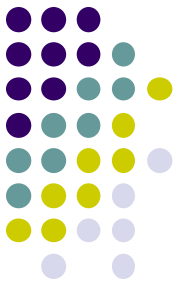
- ***Mycobacteria*** produce a thick **mycolate-rich** outer covering  
- it functions as an **exceptionally efficient barrier**



## Mycobacterial cell wall:

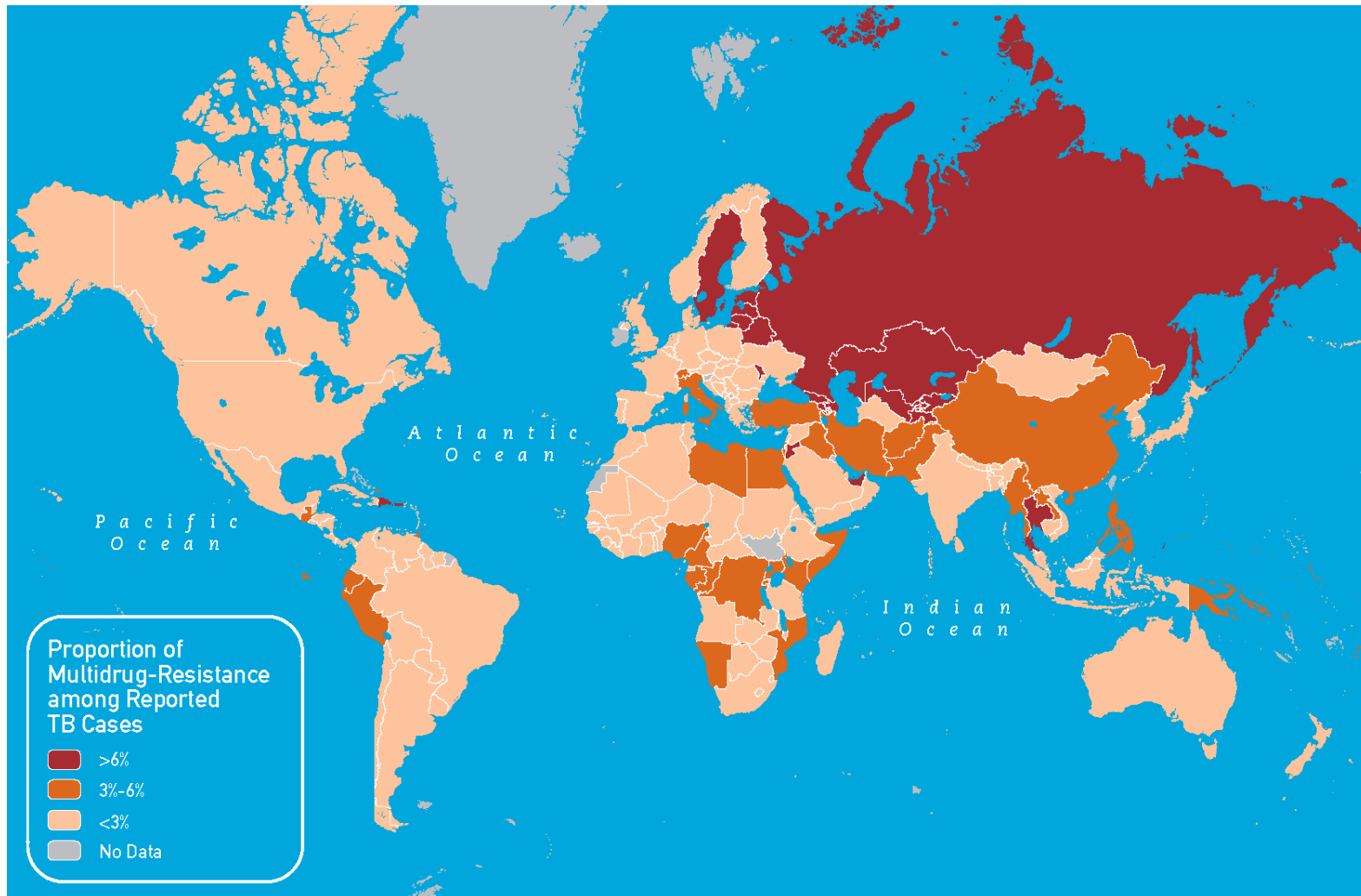
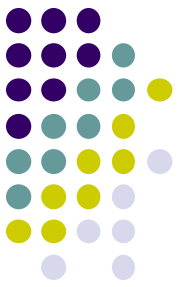
1. outer lipids
2. mycolic acid
3. polysaccharides (arabinogalactan)
4. peptidoglycan
5. plasma membrane
6. lipoarabinomannan (LAM)
7. phosphatidylinositol mannoside
8. cell wall skeleton

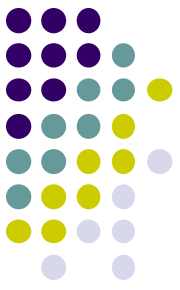
# Principles of TBC treatment



- **Always treat with more than one drug**
- **Six month** regimens are effective for susceptible isolates
- Consider treating all patients with **Directly Observed Therapy, Short-course** (DOTS), which consists of an initial intensive phase & a later continuation phase
- Extrapulmonary disease is treated like pulmonary disease
- Children are treated like adults with dose adjustments for weight
- Pediatric exceptions: miliary, bone/joints, meningitis
- Add 2 new drugs to a failing regimen

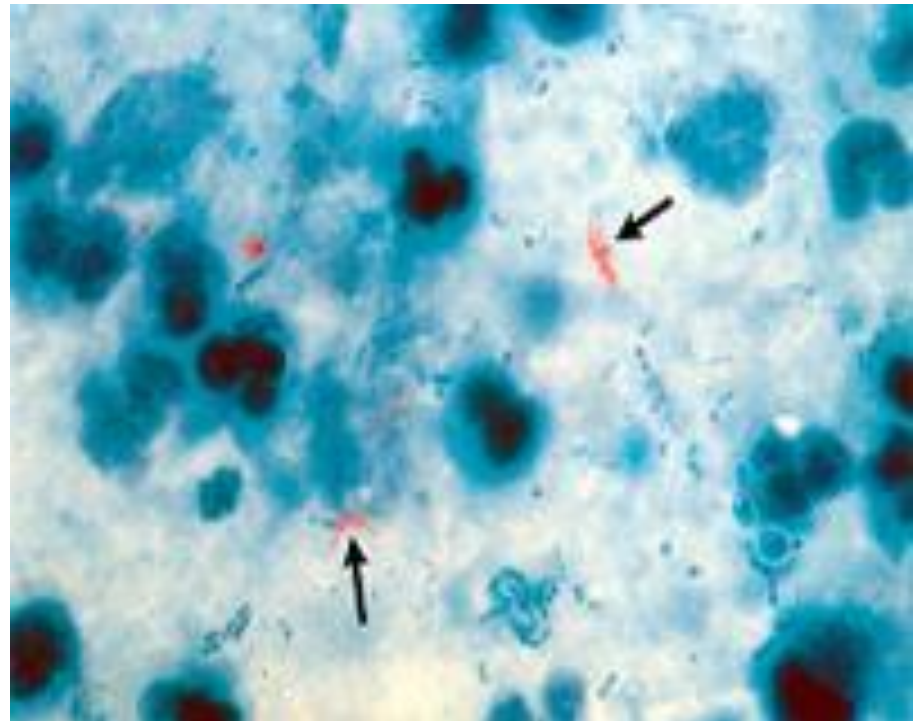
# TBC multi-resistance



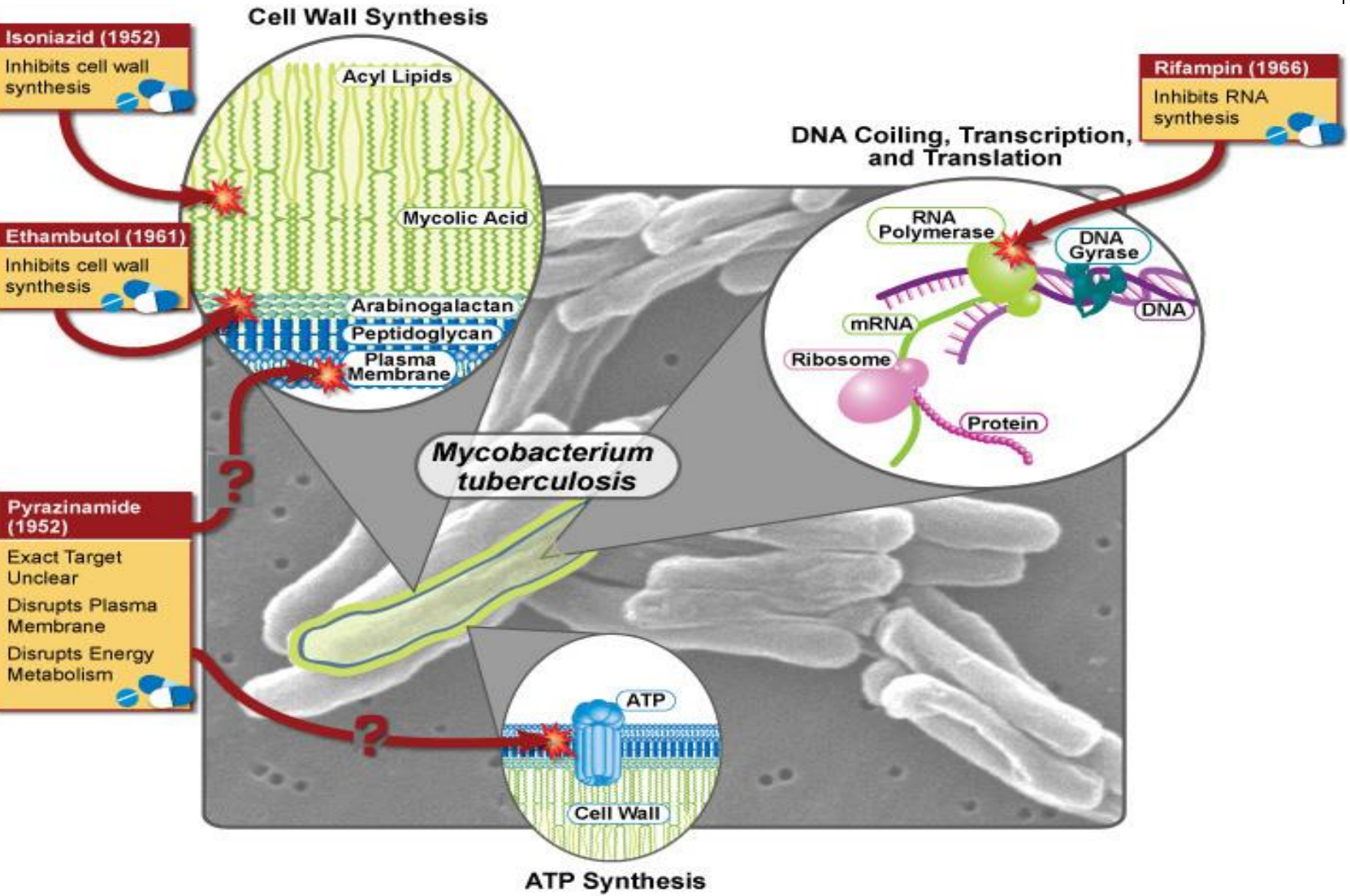


# First line antituberculous drugs

- ***isoniazid (INH)***
- ***rifampicin***
- ***ethambutol***
- ***pyrazinamide***
- ***streptomycin***

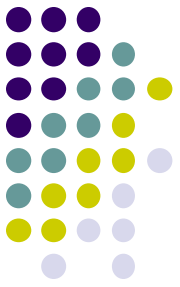


# MOA – 1st line





# INH



## MOA

- **bacterial cell wall inhibition**
- bactericidal (growth phase)
- bacteriostatic (steady phase)

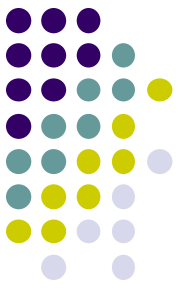
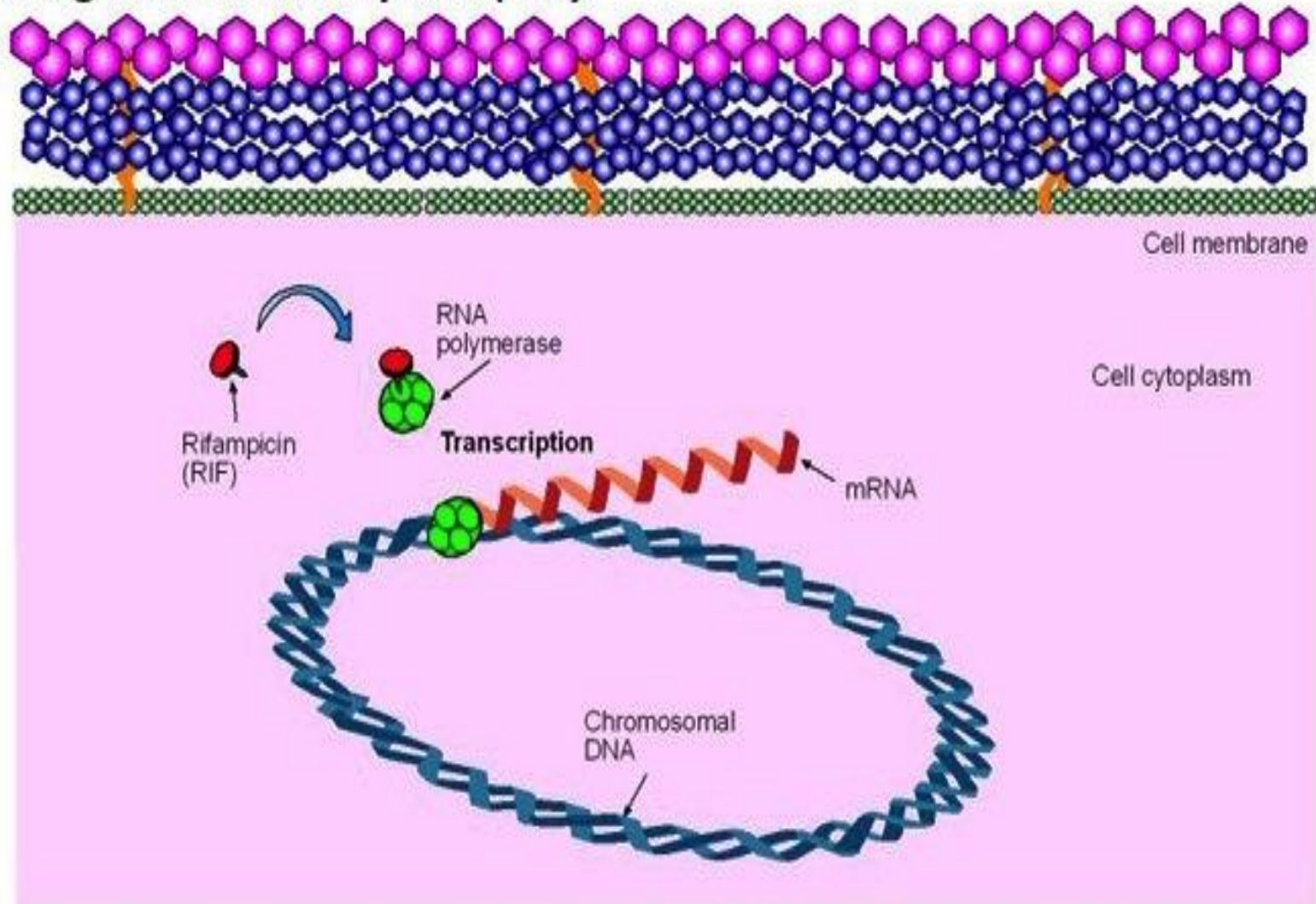
## Kinetics

- good resorption, tissue penetration, intracellular localization, necrotic lesion penetration as well as CNS
- genetically determined acetylation

## SE

- relatively low toxicity
- **pyridoxin deficiency**  
↑ **neurotoxicity risk**  
(*pyridoxin* substitution)
- hepatotoxicity  
#
- no cross resistance with other antituberculotics

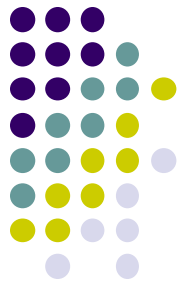
## Drug action: Rifampicin (RIF)



The first-line antibiotic drug rifampicin (RIF) interferes with RNA transcription in *Mycobacterium tuberculosis*. RIF binds to the  $\beta$ -subunit of the DNA-dependent RNA polymerase enzyme complex and inhibits transcription of messenger RNA (mRNA). The mRNA transcripts are essential requirements for protein synthesis (translation).

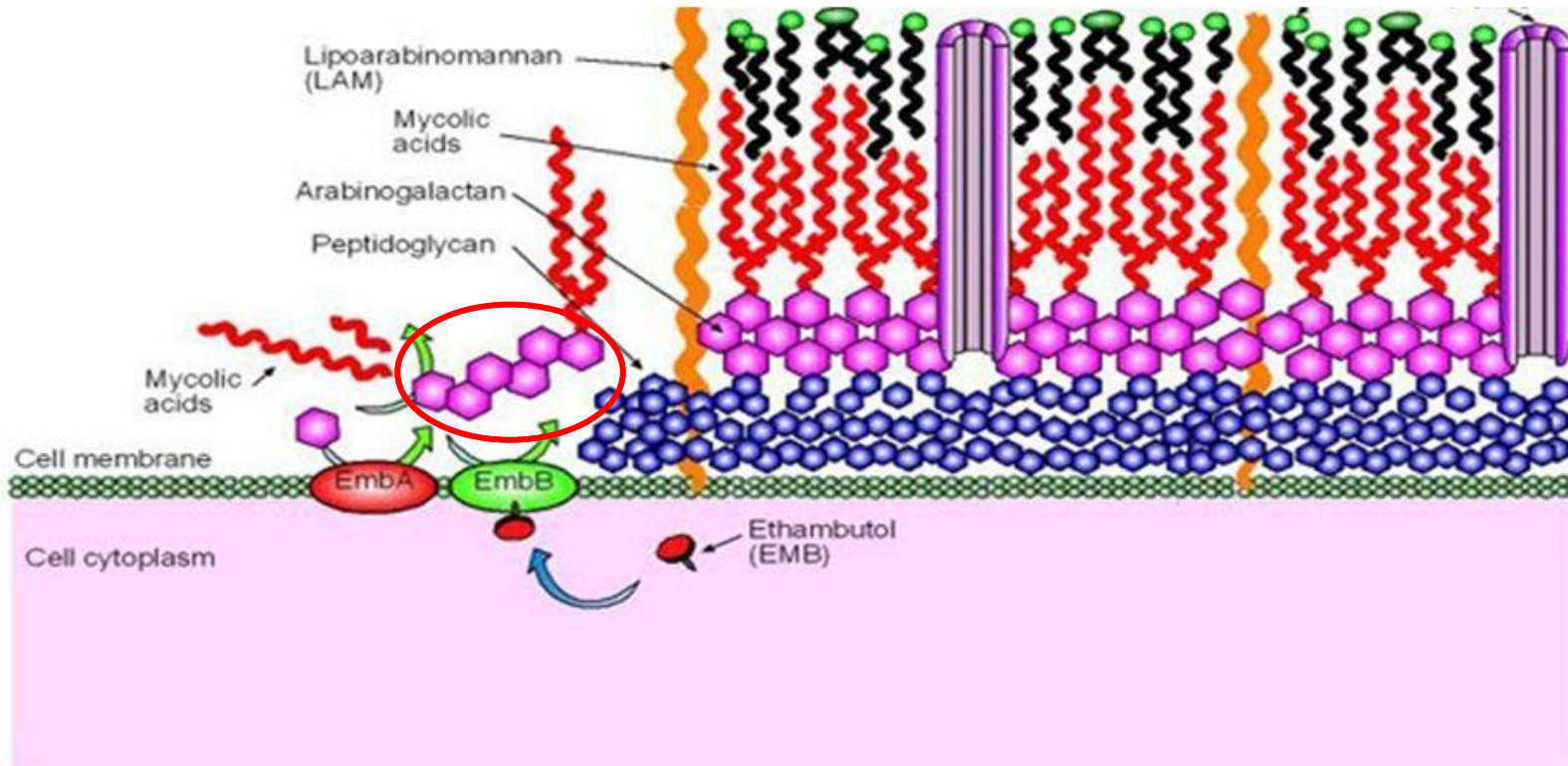
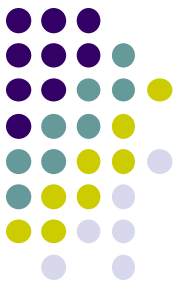
- Mycobacterial RNA-polymerase inhibition

# Rifampicin



- **Good tissue & poor CNS penetration** (but sufficient not only for TBC of the CNS, but also for CNS staphylococcal & listerial infections)
- **Microsomal enzyme induction**
- **Irregular side effects:**
  - **cutaneous** (flushing, pruritus, rash, hyperpigmentation)
  - **respiratory** (breathlessness)
  - **abdominal** (nausea, vomiting, abdominal cramps, diarrhea)
  - **flu-like symptoms** (chills, fever, headache, malaise)
  - **hepatotoxicity** (severe liver damage possible)
  - orange-red urine color (benign)
- **Fast resistance development possible** (arises from mutations that alter residues of the *rifampicin* binding site on RNA polymerase)

# Ethambutol (EMB) inhibits arabinosyl-transferase (EmbB) and blocks arabinogalactan synthesis



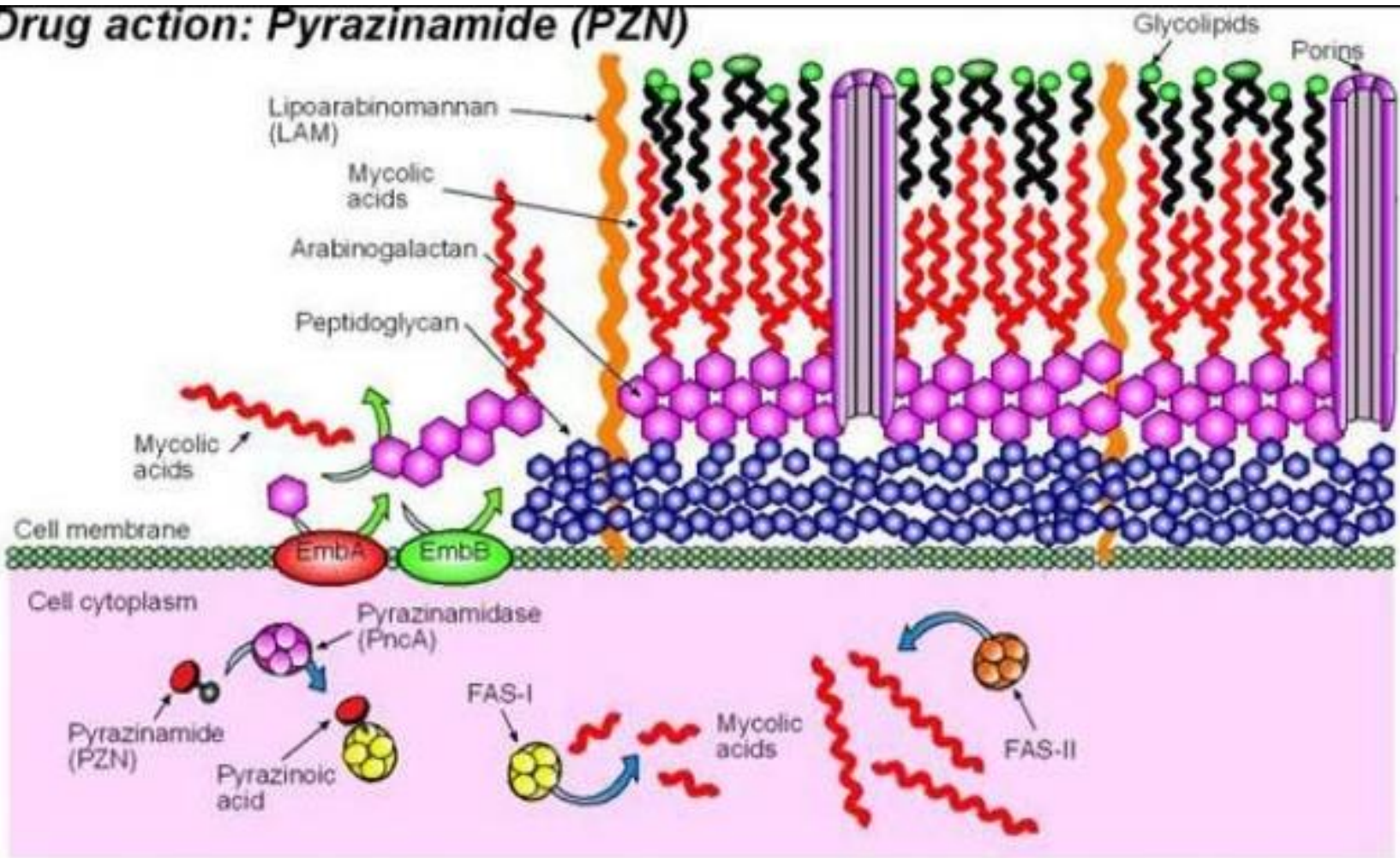
*Ethambutol* (EMB) interferes with cell wall biosynthesis in *Mycobacterium tuberculosis*. EMB ↓ the action of arabinosyl transferase (EmbB - a membrane-associated enzyme involved in the synthesis of arabinogalactan). Arabinogalactan is an essential structural component of the mycobacterial cell wall.

# Ethambutol



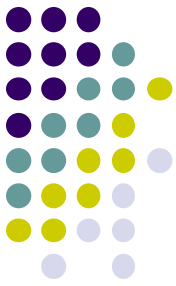
- Regarded as the **least toxic** of the 1. line anti-TBC drugs - **irregular side effects**:
  - possible optic neuritis (considered to be **reversible** following prompt withdrawal - red-green color blindness)
  - peripheral neuropathy
  - arthralgia
- **It is a rare cause** of acute, symptomatic **liver injury** (the addition of *ethambutol* to *isoniazid*, *rifampicin* or *pyrazinamide* does not appear to ↑ the rate of **transient ALT elevations**)
- **Good CNS distribution** (in TBC meningitis)
- Fast resistance development possible
- **Not used in children below 6 years** of age (it is difficult to detect *ethambutol* induced visual impairment)

# Drug action: Pyrazinamide (PZN)



The first-line antibiotic drug pyrazinamide (PZN) interferes with cell wall biosynthesis in Mycobacterium tuberculosis. PZN is a prodrug and is converted to an active form (pyrazinoic acid) by a nicotinamidase-peroxidase enzyme known as pyrazinamidase (PncA). Pyrazinoic acid inhibits the action of fatty acid synthetase I (FAT-I). FAT-I is involved in the synthesis of short-chain mycolic acids. Mycolic acids are essential structural components of the mycobacterial cell wall and are attached to the arabinogalactan layer.

# Pyrazinamide



- **Active only in acidic pH**
- Affects mycobacteria in fagozomes of macrophages (acidic pH)
- **CNS penetration**

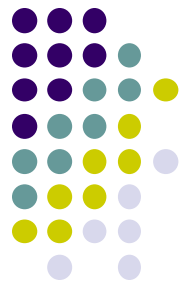
## SE

- ↑ plasma urates
- hepatotoxicity in high doses
- fast resistance development



# Streptomycin

## Aminoglycoside



- **Aminoglycoside**

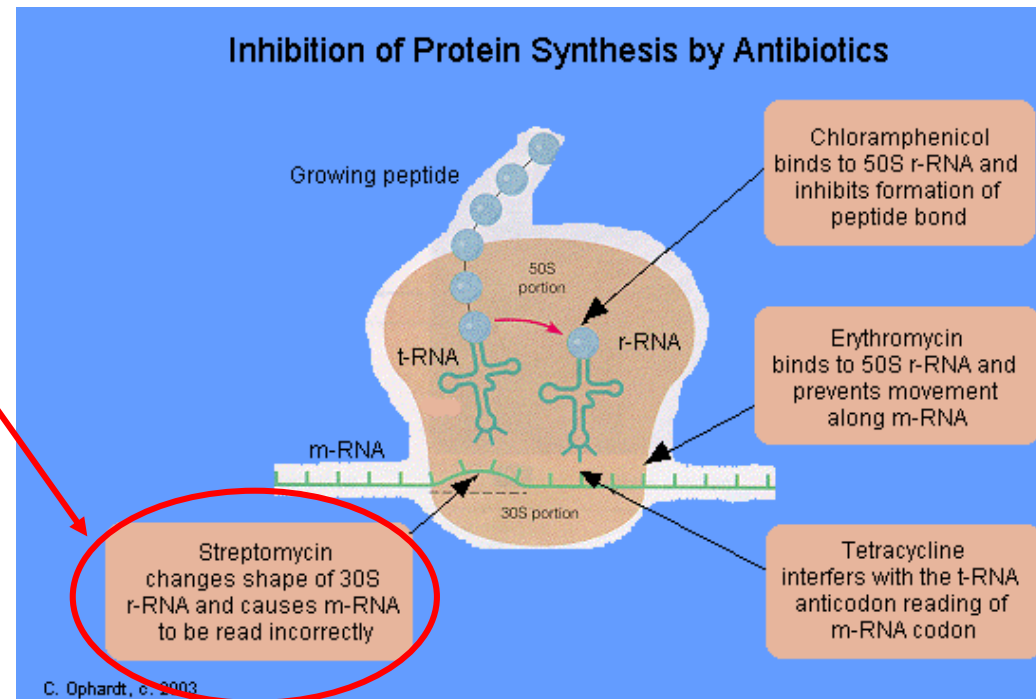
(historically first antituberculous – obsolete because of less toxic alternatives – *capreomycin*, *amikacin*)

- **Bacterial proteosynthesis** ↓↓

- **i.m. application**

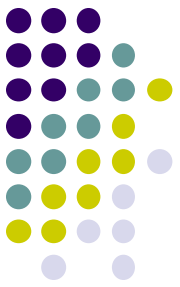
## Side effects

- ototoxicity
- nephrotoxicity





# Summary of SE of the 1st line antituberculoitics



## Tuberculosis Drugs

R-I-P-E-S

Major  
Side Effects

Rifampicin

Red-orange secretions  
and urine

Isoniazid

Peripheral neuritis

Pyrazinamide

↑ uric acid

Ethambutol

Visual problems

Streptomycin

Ototoxic

# Second line antituberculous drugs



- ***capreomycin***
- ***cycloserine***
- ***amikacin***
- ***claritromycin***
- ***levofloxacin***



# Capreomycin



- **Peptide ATB**  
(*Streptomyces capreolus*)

- Proteosynthesis inhibitor

- **Important for drug-resistant TBC**

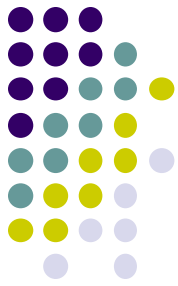
- i.m. application

## Side effects

- nephrotoxicity
- loss of hearing
- ataxia
- hypokalemia
- hypomagnesemia



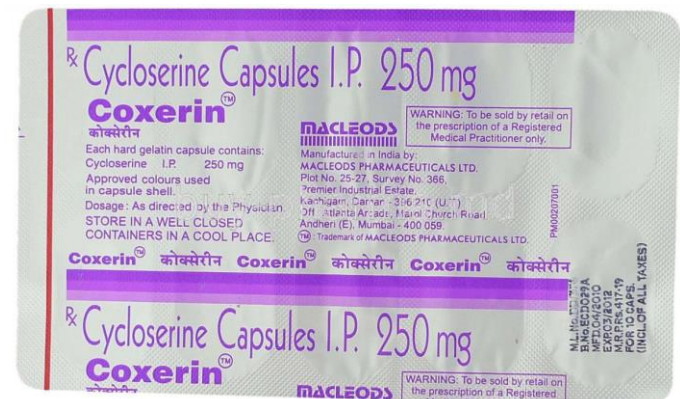
# Cycloserine



- Broad spectrum ATB
- Competitive ↓ of cell wall synthesis
- **Good tissue distribution including CNS**
- Majority of drug **eliminated unchanged in urine**

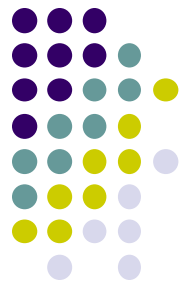
## Side effects

- **Mainly CNS - neurological side effects** (headache, irritability, depression, cramps, psychotic status)
- **In TBC resistant to other drugs**



# Amikacin

## Aminoglycoside

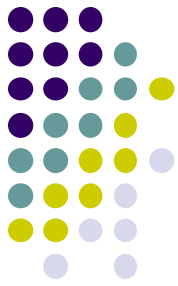


- Irreversibly binds to to 30S subunit of bacterial ribosome:
  - blocks recognition step in proteosynthesis
- Primarily in extracellular fluid (highly hydrophylic):
  - penetrates BBB when meninges inflammed
- i.v. infusion
- Prevalence to *amikacin resistance is low* (most MDR remain susceptible)
- It is active against **atypical mycobacteria:**
  - also for **Gram-** infections **resistant to gentamicin or tobramycin**



# Clarithromycin

## Macrolide



### Sensitivity:

- Most ***Mycobacterium avium*** complex (MAC) bacteria consisting of:
  - *Mycobacterium avium*
  - *Mycobacterium intracellulare*
- Isolated from both **AIDS & non-AIDS patients**

### Uses:

- **Disseminated mycobacterial infections** due to:
  - *Mycobacterium avium* or
  - *Mycobacterium intracellulare*
  - also in AIDS patients



# Levofloxacin

## Fluoroquinolone



### Uses:

- **Tuberculous meningitis (TBM):**
  - guidelines generally recommend treatment with *rifampicin*, *INH*, *pyrazinamide* & *streptomycin* or *ethambutol* (for 3 months in the intensive phase, followed by at least a 6-month period of treatment with *rifampicin* & *INH*)
  - however, CSF penetration of *rifampicin* (the key drug in TBM treatment), ethambutol & streptomycin **is poor**; *INH* & *pyrazinamide* penetrate **more readily**
  - **levofloxacin** - excellent CSF penetration, with  $AUC_c/AUC_p = 75\%$  (compared with *gatifloxacin* 35% & *ciprofloxacin* 14%)
  - it has also demonstrable *in vitro* activity, tolerability, good bioavailability & ease of administration
  - **in combination with above mentioned anti-TBC agents**



**Hello!**

**My name is Sergeant Bobby Bacteria.**

**I am a member of an army that is avidly fighting the**

**War on Drugs**