ILOs:

1. Outline the classification of anti-tuberculous drugs.

2. Describe the mechanism of action of different anti-tuberculous drugs.

3. Identify the adverse reactions and contraindications of anti-tuberculous drugs.

4. Outline the therapeutic regimen for treatment of TB case.

background

Tuberculosis

- About a quarter of the global population is estimated to have been infected with TB bacteria.
- About 5–10% of people infected with TB will eventually get symptoms and develop TB disease.
- A total of 1.6 million people died from TB in 2021.
- Worldwide, TB is the 13th leading cause of death and the second leading infectious killer after COVID-19 (above HIV and AIDS).

- The causative organism of pulmonary tuberculosis (TB) is Mycobacterium tuberculosis .

Classification of anti-tuberculous drugs

First line drugs (RIPE)

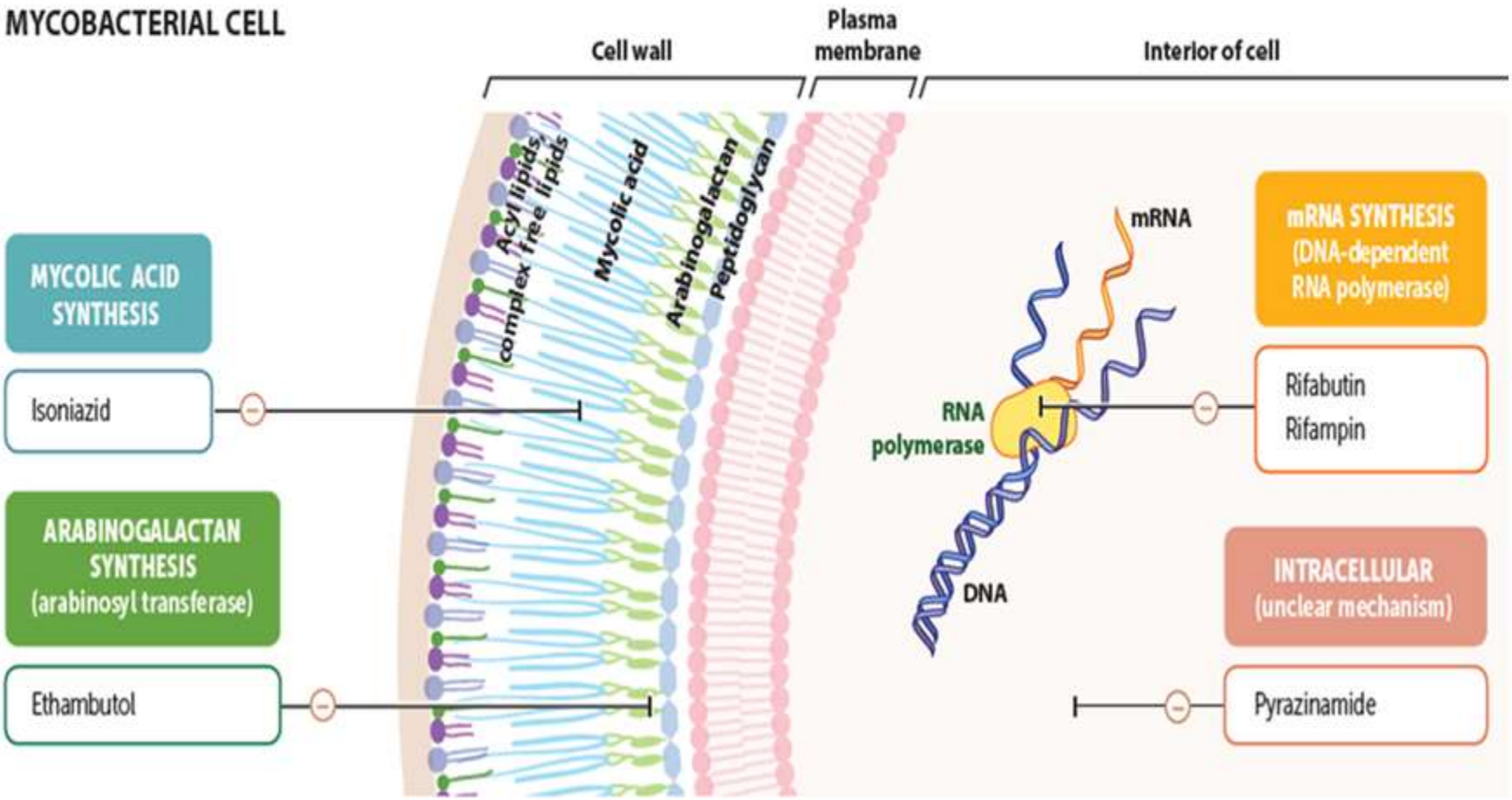
1-Rifampin
2-Isoniazid (INH)
3-Pyrazinamide
4-Ethambutol

Second line drugs

1- Streptomycin and other aminoglycosides like capreomycin, amikacin and kanamycin
2- Ethionamide
3- p-aminosalicylic acid (PAS)
4- Imipenem-cilastatin
5- Fluroquinolones.
6-Cycloserine

N.B. Streptomycin
Even though streptomycin is no longer a first-line drug for TB, it has historical significance as the first drug to be discovered that could cure tuberculosis.

Sites of action of (RIPE) anti-TB drugs



Rifampin (Rifampicin)

- **Rifampin** (U.S) or **rifampicin** (Europe) is one of the Rifamycins (drug group which includes Rifampin and rifabutin)

- Rifamycins **Inhibit** DNA-dependent **RNA polymerase** in the bacteria leading to inhibition of RNA formation.

- Bacterial Mutations which reduce rifampin binding to RNA polymerase lead to resistance.

Clinical uses of Rifampin

1- Treatment of **Mycobacterium tuberculosis** infection (used in combination with other drugs). Monotherapy rapidly leads to resistance.

2- Treatment of **leprosy** (Rifampin delays resistance to dapsone when used for leprosy).

3-Used for **meningococcal prophylaxis** and chemoprophylaxis in contacts of children with H. influenzae type b.

Adverse effects of rifampin

1- Minor hepatotoxicity. However, serious hepatic injury rarely occur.

2-Drug interactions: Rifampin induces cytochrome P-450 leading to accelerated metabolism of different drugs including; warfarin, hormonal contraceptives, antiretroviral drugs, theophyllin and others.

N.B: Rifabutin favored over Rifampin in patients with HIV infection due to less cytochrome P-450 stimulation.

N.B: Rifampin causes nonhazardous orange body fluids.

- Rifampin may change the color of urine, sweat, saliva, or tears to (yellow, orange, red, or brown).
- This effect is harmless and will disappear when the medication is stopped.
- However, teeth and contact lens staining may be permanent.

Remember
Rifampin's 4 R's

1. **R**NA polymerase inhibitor.
2. **R**amps up microsomal cytochrome P-450.
3. **R**ed/orange body fluids
4. **R**apid resistance if used alone

N.B. Rifapentine is an antibacterial drug similar to Rifampin but has longer half-life than

Isonicotinylhydrazide
(INH) or
Isoniazid

Mechanism of action:

- Isonicotinylhydrazide (INH) or Isoniazid decreases the synthesis of mycolic acids (one of mycobacterial cell wall components).

- Bacterial catalase-peroxidase (encoded by KatG) is needed to convert INH to the active antibacterial metabolite.

- This explains the activity of INH on certain bacterial cells like mycobacterial tuberculosis.

Clinical uses of Isoniazid

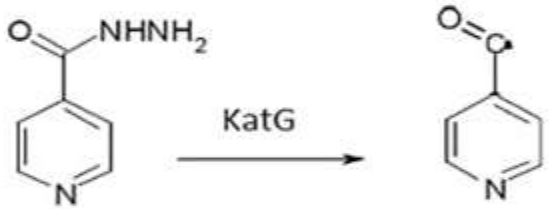
1- **Treatment** of Mycobacterium **tuberculosis infections** (with Rifampin and other drugs).

2- Isoniazid is the only agent that can be used as solo **prophylaxis** against T.B among contacts to patients suffering from tuberculosis.

3- Isoniazid can be used as Monotherapy for **latent TB control.**

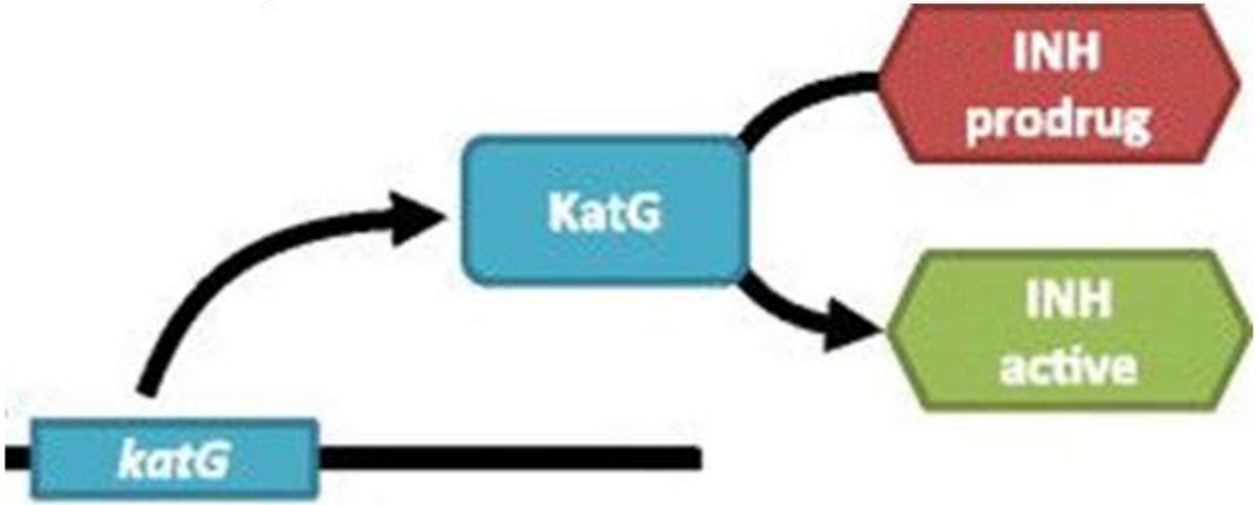
How mycobacterial cell could resist INH??

Through Mutations leading to under-expression of KatG. This will lead to decrease bioactivation of INH (prodrug) to the active form (Isonicontinyl radical).



INH

Isonicotinyl radical



- Isoniazid is metabolized via acetylation and hydrolysis

- Some populations are slow acetylators leading to accumulation of Isoniazid and toxicity

Adverse effects of isoniazid

1- **Hepatotoxicity**.

2- **Drug interactions** (Isoniazid inhibit cytochrome P-450).

3-Drug-induced **systemic lupus erythematous** (SLE).

4-Metabolic **acidosis**.

5-Vitamin B6 deficiency (which may lead to peripheral **neuropathy** and anemia).

6-Seizures (with high doses of INH, and usually refractory to benzodiazepines).

Isoniazid and vit. B6

Pyridoxine (B6) should be given with isoniazid to avoid certain adverse effects like neuropathy especially in slow acetylates (Where INH half life is greater than fast acetylators).

Contraindications

Isoniazid is contraindicated in patients with acute liver failure, severe uncontrolled diabetes, anemia from pyruvate kinase and G6PD deficiencies and severe neuropathy.

Pyrazinamide

Mechanism: uncertain.
Pyrazinamide is a prodrug that is converted to the active compound **pyrazinoic acid**. It works best at acidic pH (e.g, in host **phagolysosomes**).

Clinical use: Mycobacterium tuberculosis (with other drugs).

Adverse effects: Hyperuricemia, hepatotoxicity.

Ethambutol

Mechanism of action:

It decreases carbohydrate polymerization of mycobacterium cell wall by blocking arabinosyl-transferase.

Clinical uses: Mycobacterium tuberculosis (with other drugs).

Adverse effects:

1-Optic neuropathy (red-green color blindness, may be reversible).

2-Hyperuricemia.

Second line drugs for treatment of tuberculosis

1- Streptomycin

- Mechanism of action: Like other aminoglycosides (irreversible inhibition of bacterial protein synthesis).
- Adverse effects: ototoxicity (tinnitus, vertigo, ataxia), and nephrotoxicity.
- Contraindicated in pregnancy and renal failure.

2 - **Capreomycin**: It is a peptide antibiotic given by intramuscular injection. Its principal mechanism of action is thought to be through binding to the 70S ribosomal unit thereby inhibiting protein synthesis, but it may have other effects on the bacterial cell membrane.

Adverse effects include damage to the kidney and to the auditory nerve

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3- **Cycloserine** is a broad-spectrum agent.

- It inhibits an early stage of peptidoglycan synthesis.
- Used orally, it penetrates the CSF.
- Adverse effects affect mostly the central nervous system.

4- **Ethionamide** is chemically related to Isoniazid.

- It blocks the synthesis of mycolic acids.
- It is available only for oral use.
- It is metabolized by the liver.
- Ethionamide is also hepatotoxic.
- Neurologic symptoms may be alleviated by pyridoxine.

5- Fluoroquinolone

- Ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin inhibit strains of M tuberculosis.
- They are also active against atypical mycobacteria.
- Moxifloxacin is the most active against M tuberculosis *in vitro*.

6- Aminosalicylic Acid.

- **It is structurally similar to p-amino-benzoic acid (PABA).**
- Aminosalicylic acid is a folate synthesis antagonist (similar mechanism of action to the sulfonamides)
- Active against TB
- **Gastrointestinal symptoms are common** but occur less frequently with the delayed-release granules; they may be diminished by giving the drug with meals and with antacids.
- Peptic ulceration and hemorrhage may occur.
- Hypersensitivity reactions manifested by fever, joint pains, skin rashes, hepatosplenomegaly, hepatitis, adenopathy, and granulocytopenia often occur after 3–8 weeks of PAS therapy, making it necessary to stop administration temporarily or permanently.

7- Bedaquiline

- Bedaquiline inhibits adenosine 5'-triphosphate (ATP) synthase in mycobacteria.
- It has *in vitro* activity against both replicating and non-replicating bacilli.
- It is highly protein-bound (>99%), is metabolized chiefly through the cytochrome P450 system, and is excreted primarily via the feces. .
- The most common adverse effects, occurring at rates of 25% or more, are nausea, arthralgia, and headache.
- Bedaquiline has been associated with hepatotoxicity and cardiac toxicity.
- The **FDA has issued a black-box warning related to the risk of QT prolongation and associated mortality.**

Therapeutic regimens for treating TB

1- **Latent** tuberculosis infection (individuals with a positive PPD but no active disease) generally treated for 9 months by only **INH** (Add pyridoxine).

2- Six months regimen for active TB.

- For initial empiric treatment of TB, start patients on a 4-drug regimen: isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin.
- After 2 months of therapy (for a fully susceptible isolate), Isoniazid plus rifampin are continued as daily or intermittent therapy for 4 more months.
- Add pyridoxine

First 2 months (RIPE)

1. **Rifampin**
2. **INH**
3. **Pyrizynamide**
4. **Ethambutol**

Then

Four months treatment with

1. Rifampin
2. INH

3- The short 4 months regimen for treating susceptible TB

For adults with or without HIV who have drug-susceptible active TB (DS-TB), the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) in 2023 recommend a 4-month regimen of rifapentine (RPT), moxifloxacin (MOX), isoniazid (INH), and pyrazinamide (PZA) for 2 months followed by 2 months of RPT, MOX, and INH.

First 2 months

1. **Rifapentine**
2. **INH**
3. **Moxifloxacin**
4. **Pyrazinamide**

Then

Four months treatment with

1. **Rifapentine**
2. **INH**
3. **Moxifloxacin**

Remember: Add Vitamin B 6 (Pyridoxine)

4- The treatment of drug-resistant TB

Multidrug-resistant TB (MDR-TB) refers to isolates that are resistant to both Isoniazid and Rifampin (and possibly other drugs). The extensively drug-resistant (XDR) tuberculosis. XDR-TB is additionally resistant to several second-line therapies.

• Administer at least 5 drugs for the initial phase of treatment and at least 4 drugs for the continuation phase .

N.B. The selection of drugs depends heavily on culture sensitivities.

Drugs used for the resistant TB

1. A fluoroquinolone: levofloxacin or moxifloxacin preferred
2. Bedaquiline
3. Linezolid
4. Clofazimine
5. Cycloserine
6. An aminoglycoside: streptomycin or amikacin preferred
7. Ethambutol
8. Pyrazinamide
9. Delamanid
10. Ethionamide
11. Para-aminosalicylic acid
12. Imipenem- cilastatin


Thank
You !