Lecture 7: Treatment of tuberculosis (TB)

Respiratory system
Second year
Medical school
Hashemite University
2nd semester 23/24
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Overview

- Caused by Mycobacterium tuberculosis (MTB) bacteria (infectious).
- Generally, affects the lungs, but it can also affect other parts of the body.
- Most infections show no symptoms= latent tuberculosis (**LTB**).
- Typical symptoms of active TB: chronic cough with blood-containing mucus, fever, night sweats, and weight loss.
- Air-borne (active **NOT** latent).

Signs & Symptoms

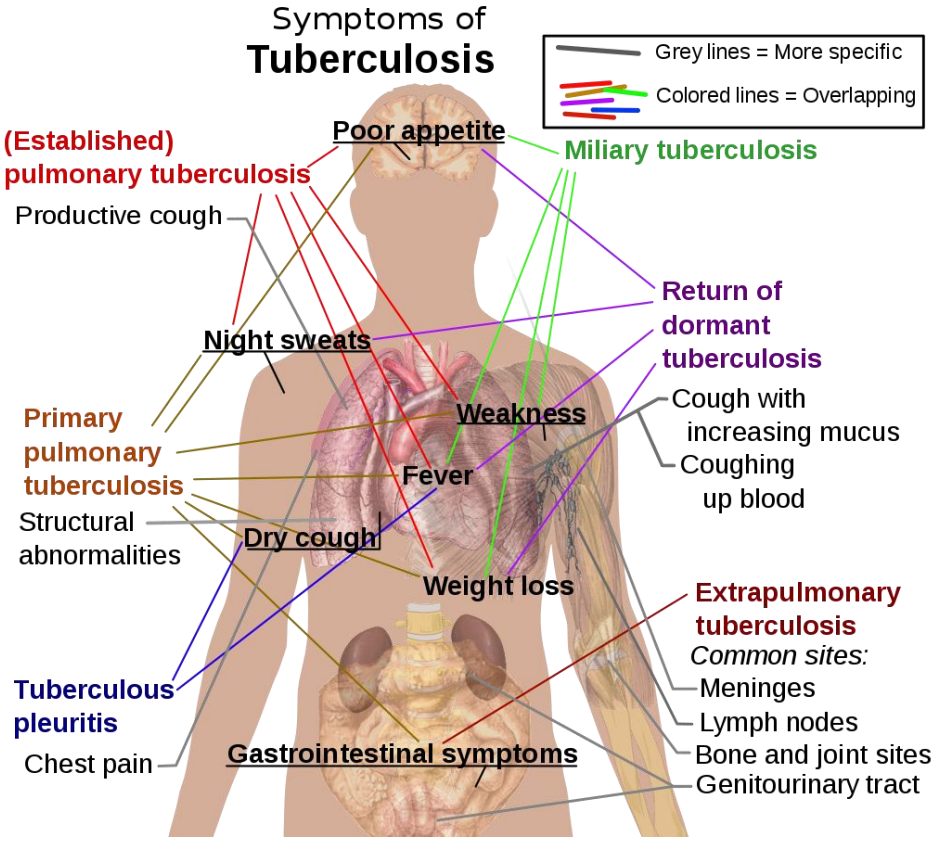
Pulmonary:

- Chest pain, prolonged cough producing sputum
- About 25% of people may not have any symptoms
- **Upper** lung lobes are more frequently affected by tuberculosis than the lower ones

Extrapulmonary:

- In 15–20% of active cases, the infection spreads outside the lungs
- Extrapulmonary TB occurs more commonly in people with a **weakened immune** system and **young** children.

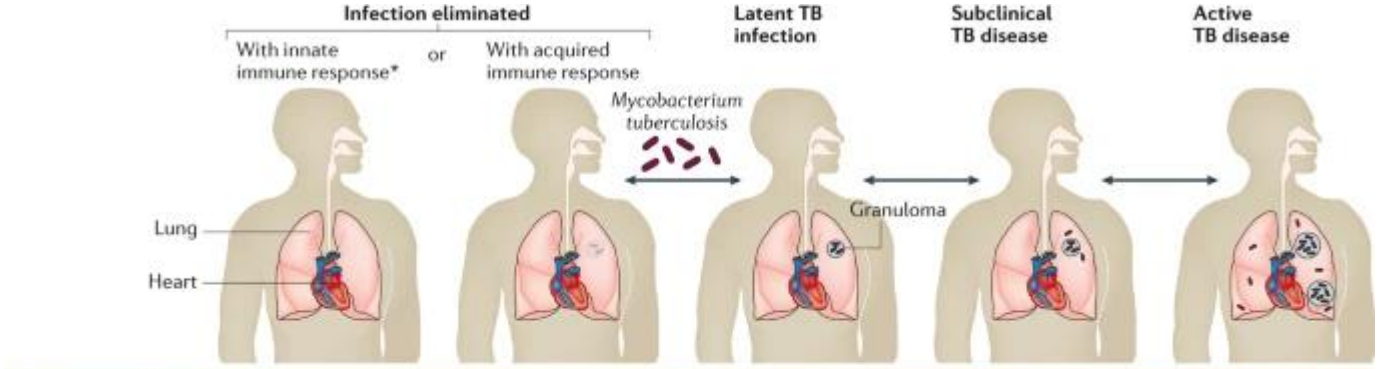
Tuberculous meningitis: CNS



Overview

- **Diagnosis**:

active TB: chest X-rays, microscopic examination and culture of body fluids.



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Nature Reviews | Disease Primers

- **Prevention**: vaccination with the bacillus Calmette-Guérin (BCG) vaccine.

Treatment

- Generally, includes **four** first-line drugs
- Second-line drugs are typically **less effective**, **more toxic**, and less extensively studied.
- Second-line used for patients who **cannot tolerate** the first-line drugs or who are infected with **resistant TB.**
- M. tuberculosis grows slowly and requires treatment for **months to years.**

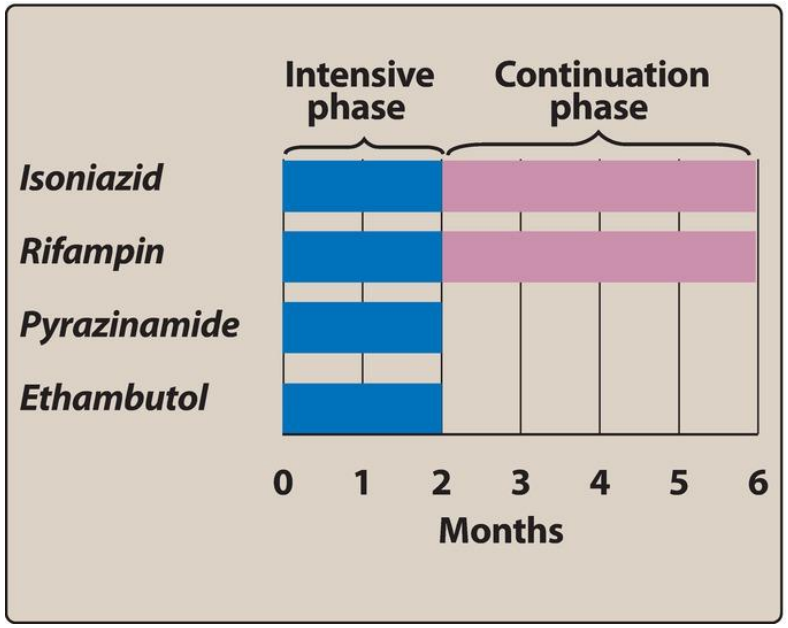
must be treated with several drugs.

Treatment

✓Two main regimens for pulmonary TB:

1) Traditional regimen (≥6 months): isoniazid, rifampin, pyrazinamide, and ethambutol

2) Shortened, four-month regimen: isoniazid, rifapentine, pyrazinamide and moxifloxacin



Both regimens have two treatment phases: 2 months then 4. and 8 weeks then 9 weeks

Strategies for addressing drug resistance

- Under selective pressure from inadequate treatment, (monotherapy), small number of organisms (naturally resistant to a particular drug) can emerge as the dominant population.

- Multidrug therapy is employed to suppress these resistant organisms (Active disease **always** requires treatment with multidrug regimens)

- Therapy should continue for longer time even if clinical improvement occurred, Why? **to eradicate persistent organisms and to prevent relapse.**

Treatment

- **Second-line regimens for MDR-TB (TB resistant to at least isoniazid and rifampin): at least four drugs should be used**

Standard: Fluoroquinolone (levofloxacin or moxifloxacin) + Bedaquiline + Linezolid
Add one or two: Clofazimine OR Cycloserine OR Pyrazinamide OR Ethambutol

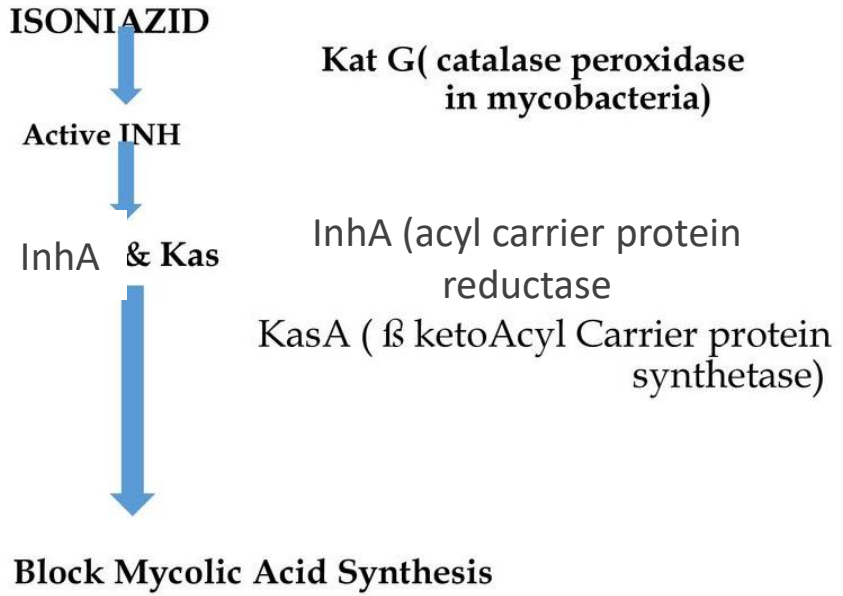
Capreomycin, kanamycin, macrolides: no longer recommended for inclusion in MDR-TB regimens

Isoniazid (INH) 1/4

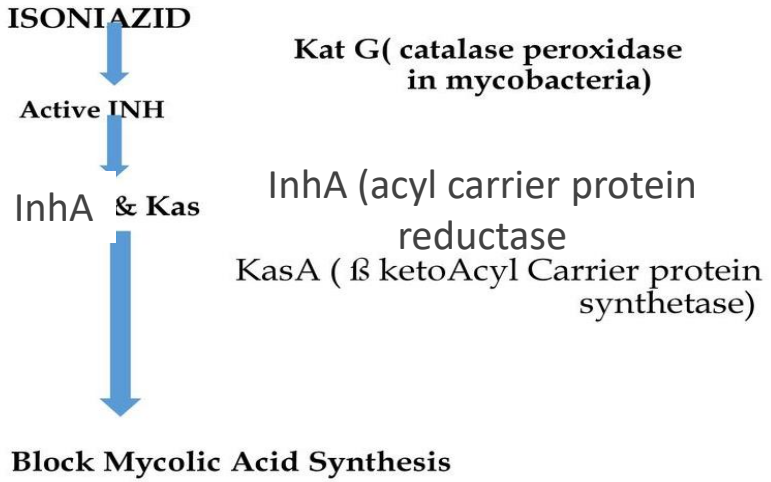
InhA & KasA are essential for the synthesis of mycolic acid

MOA:

Isoniazid (pro-drug) >> activated by a **mycobacterial catalase–peroxidase** (KatG) >> enzymes acyl carrier protein reductase (**InhA**) & β-ketoacyl-ACP synthase (KasA) >> Inhibits mycolic acid >> <u>disruption in the bacterial cell wall.</u>



Isoniazid (INH) 2/4



Antibacterial spectrum

❖**Specific** for treatment of **M. tuberculosis**

Resistance (follows chromosomal mutations):

1) mutation or deletion of **KatG** (producing mutants incapable of prodrug activation)
2) varying mutations of the **acyl carrier proteins**
3) overexpression of the target enzyme InhA.

Isoniazid (INH) 3/4

Pharmacokinetics

❖readily absorbed after oral administration **(impaired if taken with food)**

❖Diffuses into **all** body fluids, cells, and caseous material (**necrotic tissue resembling cheese** that is produced in tuberculous lesions).

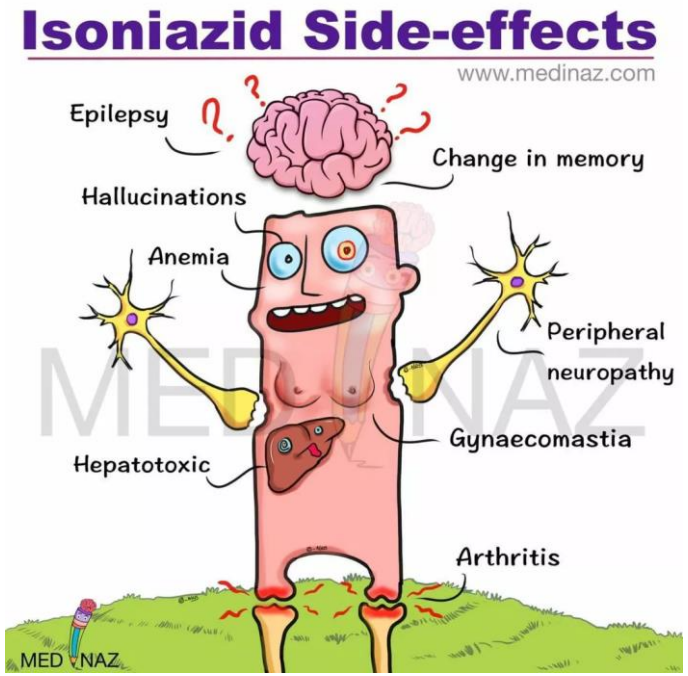
Isoniazid (INH) 4/4

Adverse effects

- **Hepatitis** (most serious adverse effect), If hepatitis goes unrecognized, and if isoniazid is continued >> fatal.

- **Peripheral neuropathy** (paresthesia of the hands and feet) >> relative pyridoxine deficiency caused by isoniazid (can be avoided by daily supplementation of pyridoxine (vitamin B6).

- **CNS** convulsions in patients prone to seizures.



Rifampin 1/4

- broader antimicrobial activity **than isoniazid** and can be used as part of treatment for several different bacterial infections.
- **Never** given as a single agent in the treatment of active tuberculosis, why?

Because resistant strains rapidly emerge during monotherapy

- Used prophylactically for individuals exposed to **meningitis caused by meningococci or H. influenzae**.

MOA: blocks RNA transcription by interacting with the **β subunit** of mycobacterial DNA-dependent RNA polymerase.

Rifampin 2/4

Resistance: caused by mutations in the affinity of the bacterial DNA-dependent RNA polymerase gene for the drug.

Pharmacokinetics (oral**)**

- Distribution to **all** body fluids and organs.
- Taken up by the **liver** and undergoes enterohepatic recycling.

Rifampin 3/4

Adverse effects

- Urine, feces, and other secretions have an **orange-red** color, so patients should be forewarned. **Tears** may even stain soft contact lenses orange-red.

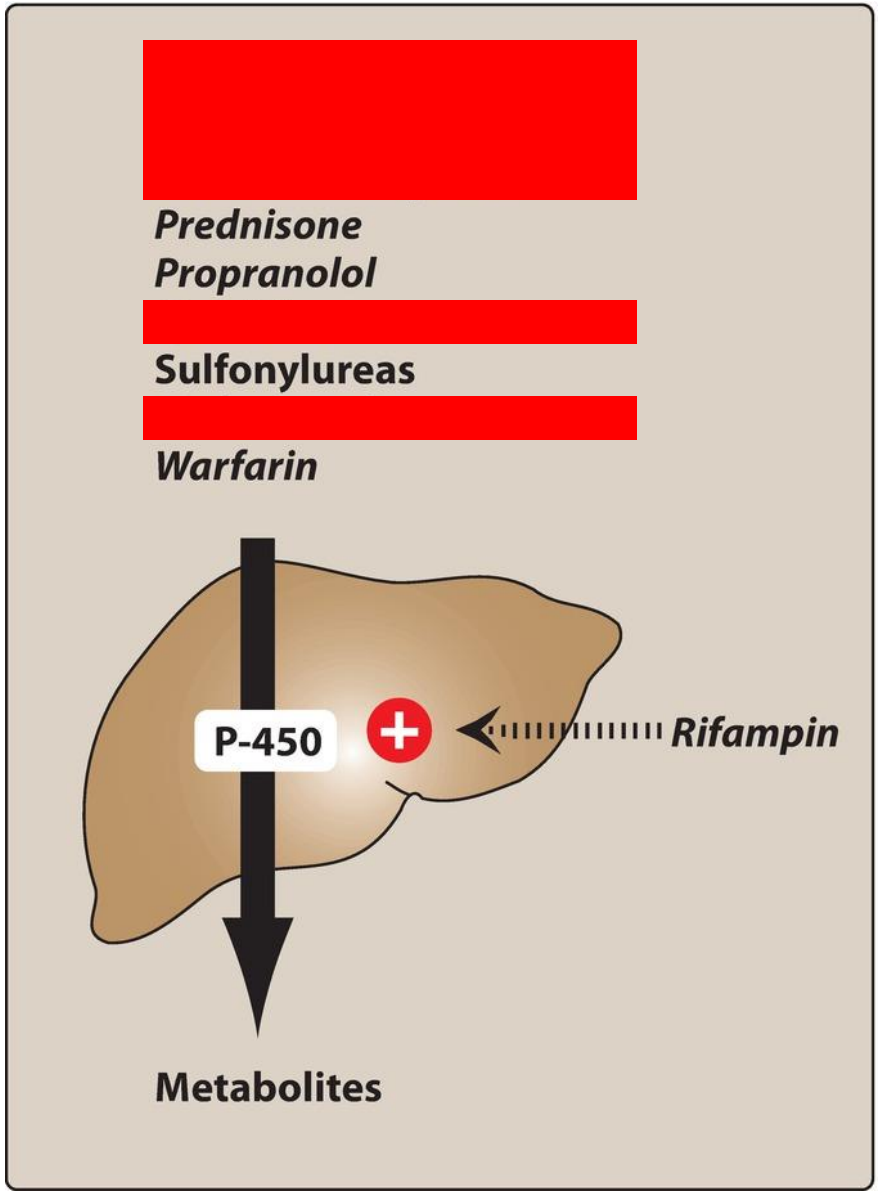
- **Hepatitis** and death due to liver failure are rare.

- When rifampin is dosed intermittently, especially with higher doses, a **flu-like syndrome** can occur, with fever, chills, and myalgia, sometimes extending to **acute renal failure, hemolytic anemia, and shock**.

Rifampin 4/4

Drug interactions

induces a number of phase I cytochrome P450 enzymes and phase II enzymes >> it can decrease the half-lives of co-administered drugs that are metabolized by these enzymes



Rifabutin

Rifabutin

- derivative of rifampin: preferred for TB patients **co-infected with HIV**

- Adverse effects similar to those of rifampin but can also cause uveitis, skin hyperpigmentation, and neutropenia.

Rifapentine

- ✓**longer half-life** than that of rifampin.
- ✓In combination with isoniazid, rifapentine may be used once weekly in patients with **LTBI** and in select **HIV-negative patients with minimal pulmonary TB.**

Pyrazinamide

- Orally. short-course agent used in **combination** with isoniazid, rifampin, and ethambutol.
- MOA: **unclear!**
- Active against **tuberculosis bacilli**
- Penetrating the CSF.
- May contribute to **liver toxicity**.
- Most of the clinical benefit from pyrazinamide **occurs early in treatment**. Therefore, this drug is usually **discontinued after 2 months of a 6-month** regimen.

Ethambutol

- Specific for mycobacteria
- It inhibits arabinosyl transferase (enzyme important for the synthesis of the mycobacterial cell wall).
- Used in combination with pyrazinamide, isoniazid, and rifampin pending culture and susceptibility data.
- If the isolate is determined to be susceptible to isoniazid, rifampin, and pyrazinamide>> discontinue ethambutol
- adverse effect: **optic neuritis**>> diminished visual acuity and loss of ability to discriminate between red and green.
- The risk of optic neuritis **increases** with **higher doses** and in patients with **renal impairment**.
- Visual acuity and color discrimination should be tested prior to initiating therapy and periodically thereafter.

Cycloserine

- Disrupts d-alanine incorporation into the bacterial cell wall.
- Primarily excreted unchanged in urine. (accumulation in renal insufficiency)
- Adverse effects: CNS disturbances (difficulty concentrating, anxiety, and suicidal tendency), and seizures may occur.

Bedaquiline

- an ATP synthase inhibitor.
- **Black box** warning for QT prolongation, and monitoring of the electrocardiogram is recommended.
- Elevations in liver enzymes have also been reported and liver function should be monitored during therapy.

Linezolid

- inhibits bacterial protein synthesis by preventing the fusion of 30S and 50S ribosomal subunits
- an alternative to vancomycin in inpatient settings, particularly MRSA.
- AE: myelosuppression, neuropathy and hypoglycemia

Alternate second-line drugs: Streptomycin & Para-aminosalicylic acid

Streptomycin:

- Greater action against extracellular organisms.
- Infections due to streptomycin-resistant organisms may be treated with kanamycin or amikacin
- AE: Vertigo (feel like the world is spinning), hearing loss and GIs

Para-aminosalicylic acid

- works via folic acid inhibition.
- PAS remains an important component of many regimens for MDR-TB.

Alternate second-line drugs: Ethionamide & Fluoroquinolones

Ethionamide

- Structural analog of isoniazid that also disrupts mycolic acid synthesis.
- Metabolism is extensive, most likely in the liver, to active and inactive metabolites.
- Adverse effects: nausea, vomiting, and hepatotoxicity. Hypothyroidism, gynecomastia, alopecia, impotence, and CNS effects also have been reported.

Fluoroquinolones

- Like moxifloxacin and levofloxacin, have an important place in the treatment of multidrug-resistant tuberculosis.
- AE: tendinopathy, GIs and Peripheral neuropathy