

وَقُلْ رَبِّ زِدْنِي عِلْمًا



RESPIRATORY SYSTEM

HAYAT BATCH



SUBJECT : Pharmacology

LEC NO. : 7

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Lecture 7: Treatment of tuberculosis (TB)

Respiratory system

Second year

Medical school

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Overview

البكتيريا المسببة لل TB

- 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**). *Asymptomatic* ← البكتيريا موجودة بس ما عندو اعراض
- Typical symptoms of active TB: chronic cough with blood-containing mucus, fever, night sweats, and weight loss.
Differential diagnosis is cough with blood-containing mucus
- **Air-borne (active NOT latent).** مع الكحة او العطاس المريض يكون معدي للناس اللي حواليه و لهيك علاج TB
بالاغلب يكون بالمستشفى لانه علاجه فترة طويلة
(minimum 4 months, بالعادة، 6 شهور)

ممکن يعمل outbreak
Also treatment is very difficult to handle
مش زي pneumonia بتعطي دوا بس

(minimum 4 months, بالعادة، 6 شهور)



Signs & Symptoms

Pulmonary:

هاد اللي بهمنا

- 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

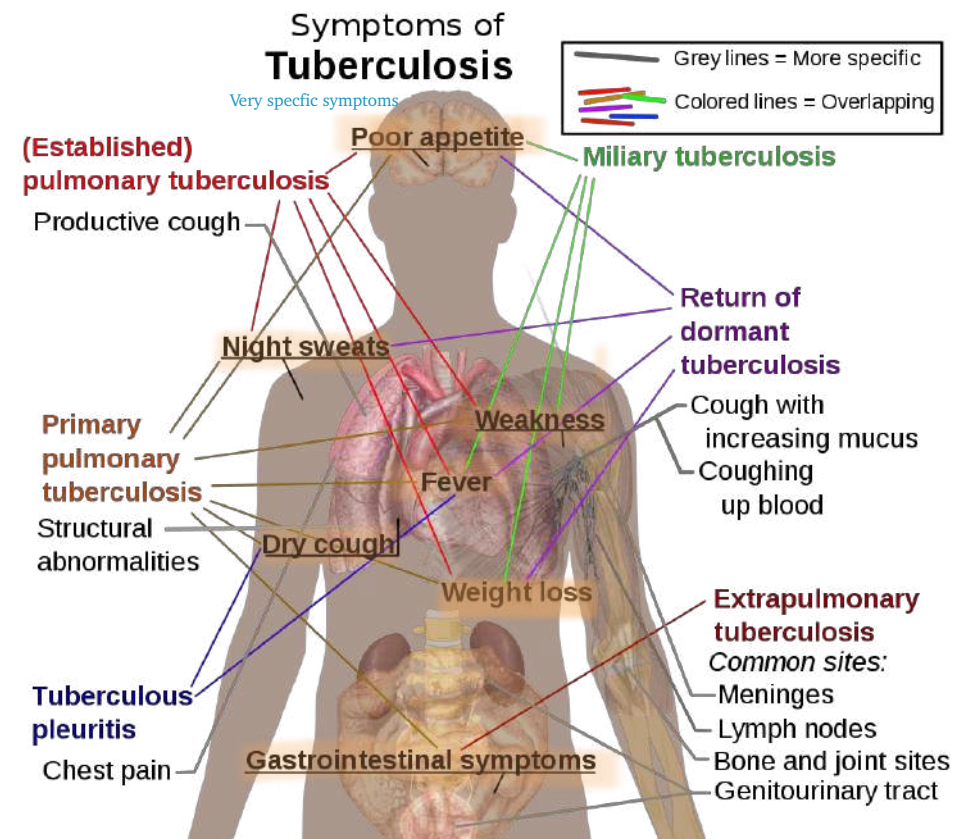
Extrapulmonary:

برا الرئتين more serious

- 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 / GU

معرفة unique symptoms الموجودين في figure





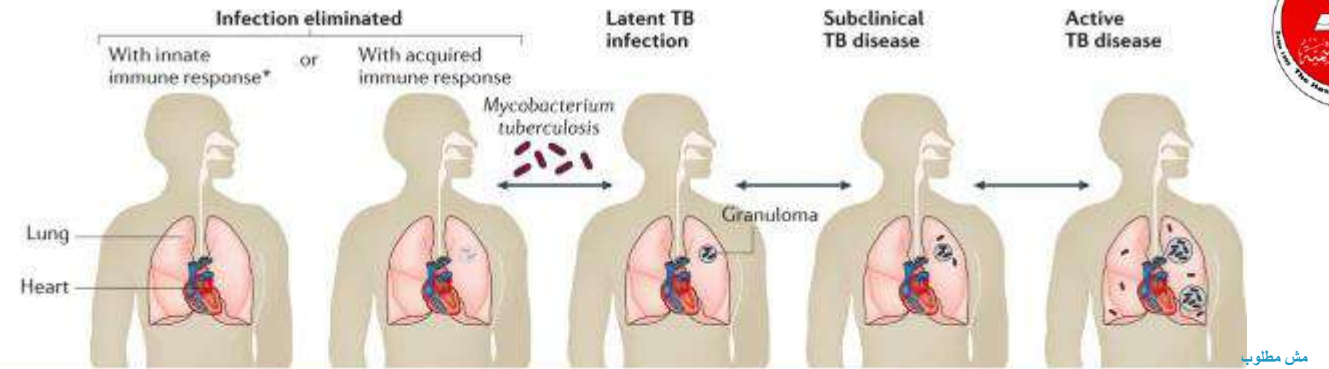
Overview

• **Diagnosis:**

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

Latent TB: blood or skin test

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



مش مطلوب

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



Treatment

- Generally, includes **four** first-line drugs *It starts with four and going up*
اربع ادوية يعطيها مع بعض بالمستشفى وهما first line for TB
- 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**. *If there is resistant with first line or the patient can't tolerate first-line drugs*
- M. tuberculosis grows slowly and requires treatment for **months to years**. *Long-term treatment*
بتبلش من ٤ اشهر و اطلع مش اقل من هيك



TB is very complicated disease

و بالاردن في كثير حالات سل

must be treated with several drugs.



Treatment

✓ Two main regimens for pulmonary TB:

Very basic standard ↴

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

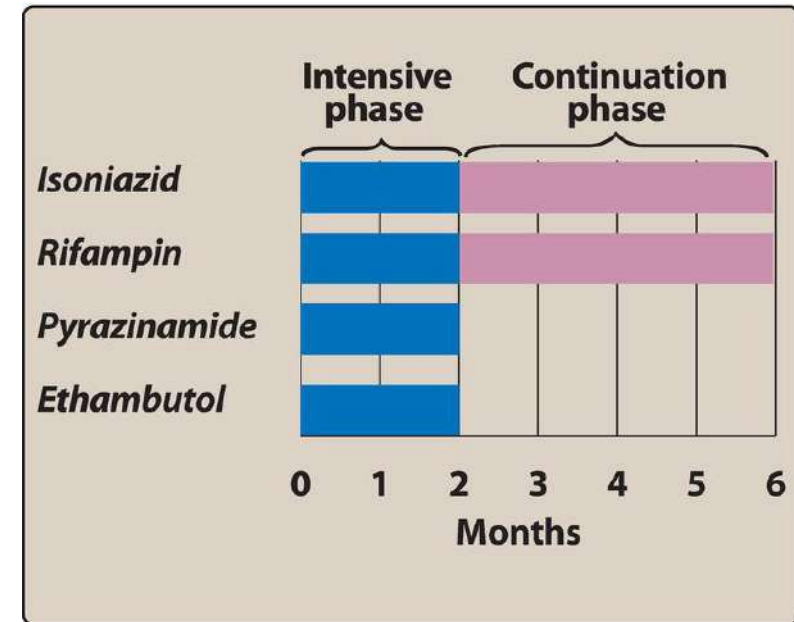
2) Shortened, four-month regimen: isoniazid, rifapentine, pyrazinamide and moxifloxacin

Traditional

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

Shortened

الشرح بالاسلايد اللي جاي



ليش بال shortened regimen ما بنعطي rifampin و ethambutol
لانه يكون more effective in active TB

الفرق بين ال regimen الاول و الثاني :

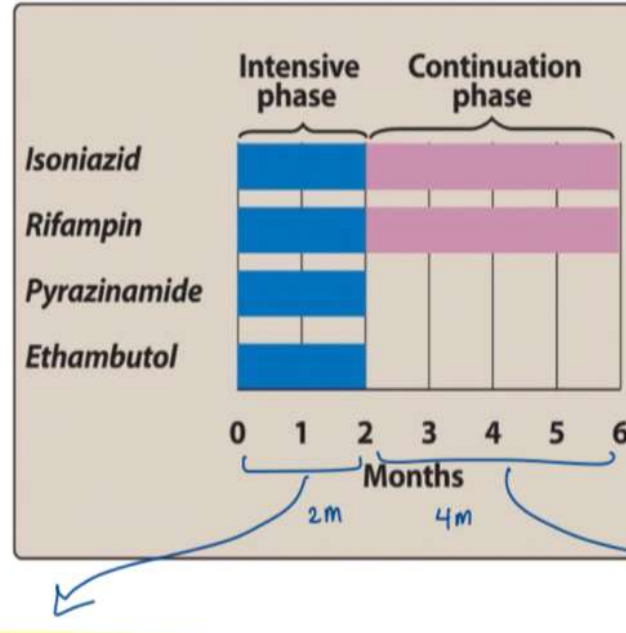
اول اشي المدة بحيث واحد بس اربع اشهر يعني high

compliance و واحد اقل اشي ست اشهر و تاخ الاربع اشهر يعتبر

cheaper مقارنة مع هداك و اخر فرق هما الادوية اللي بالاصفر

بتختلف بكل واحد

بالتالي لو المريض ماشي مع كل الشروط تاخ ال regimen الاربع اشهر ف خلص بخليه يمشي عليه لانو اغلب مواصفاته افضل



هلاء احنا ببداية العلاج بنبلش ب ال 4 ادويه و هاد الحكي هو اول 2 month من العلاج و بنسمي المرحلة هاي ب intensive phase وبعطي فيها اكثر من دوا لانو هاي اكثر مرحلة بكون فيها ال organism كثير و اعراض واضحه و مبينه بحيث المرحلة هاي من العلاج شديده

Isoniazid + Rifampin + pyrazinamide + Ethambutol

بعد الشهرين بدخل ب phase ثاني اسمو ال continuation phase و اللي هي هدفها اضمن القضاء على اي persistent or resistant organisms ضلت من بعد ال intensive phase بحيث ما يصير عندي relapse و مدته 4 اشهر و بعطي بس 2 drugs

Isoniazid + Rifampin

لازم اعرف وين راح ال infection

طيب لو بعد الست اشهر من العلاج اجي المريض و فحصناه و طلعة نتيجته +ve

هون بعرف انو عندو multi drug resistant TB فيلجا على طول ال second line بسلايد 10



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. مقاومة ضد monotherapy رح يصير زيادة بعدد organism

- Multidrug therapy is employed to suppress these resistant organisms (Active disease **always** requires treatment with multidrug regimens) خصوصا active TB اما latent عادي لو اعطيت monotherapy

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



Treatment

حتى لو isoniazid لحاله

- **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

Mutation in these 3 enzymes will make isoniazid resistant (inactive)

① mycobacterial catalase-oxidase (KatG)

>> ② enzymes acyl carrier protein reductase

(InhA) & ③ β -ketoacyl-ACP synthase (KasA)

>> Inhibits mycolic acid >> disruption in the bacterial cell wall.

حكي الدكتور انه رح يجيب بالامتحان اسم الانزيم و الاختصار تاعه، فاحفظوا واحد منهم

ISONIAZID

Active INH

InhA & Kas

Block Mycolic Acid Synthesis

Kat G (catalase peroxidase in mycobacteria)

InhA (acyl carrier protein reductase)

KasA (β ketoAcyl Carrier protein synthetase)

Mutation of KatG/InhA/KasA -> activate mycolic acid-> no disruption in the bacterial cell wall



Isoniazid (INH) 2/4

Antibacterial spectrum

❖ Specific for treatment of *M. tuberculosis*

Resistance (follows chromosomal mutations):

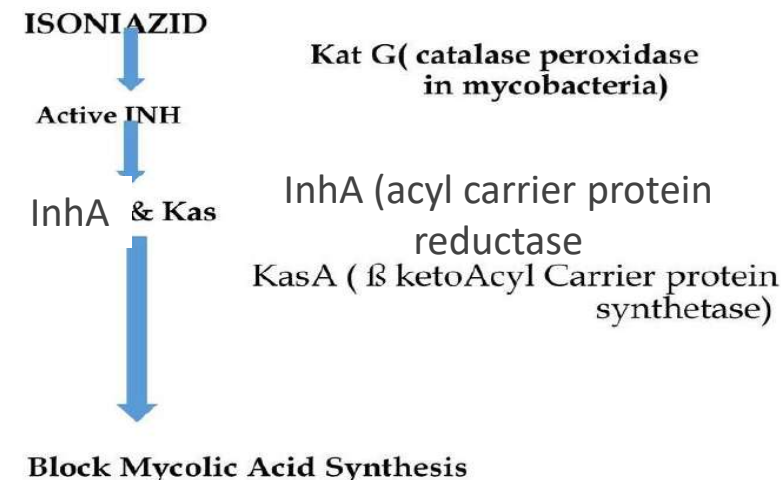
1) mutation or deletion of **KatG** (producing mutants incapable of prodrug activation)

حكينا عنه بالاسلايد اللي قبل

2) varying mutations of the **acyl carrier proteins** (inhA,kasA)

3) overexpression of the target enzyme **InhA**.

يعني صار عندي خلل ادى انا هاي البكتيريا بتصير تزد من عمليات تصنيع هاد الانزيم (زادت عمليات ال transcription and translation لالو) بالتالي لو فرضنا اعطيت جرعه من الدواء عملت تثبيط ل 5 من هاد الانزيم لكن ضل كمان 5 فصار بدني كمان جرعة دواء و رحب اعطي لقيت انا صار عدد الانزيمات 20 فهيك بوصل لمرحلة لو زدت جرعات بوصل لمرحلة ال toxicity بالتالي صار في resistance against isoniazid





Isoniazid (INH) 3/4

Pharmacokinetics

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

Signs that the patient is receiving isoniazid

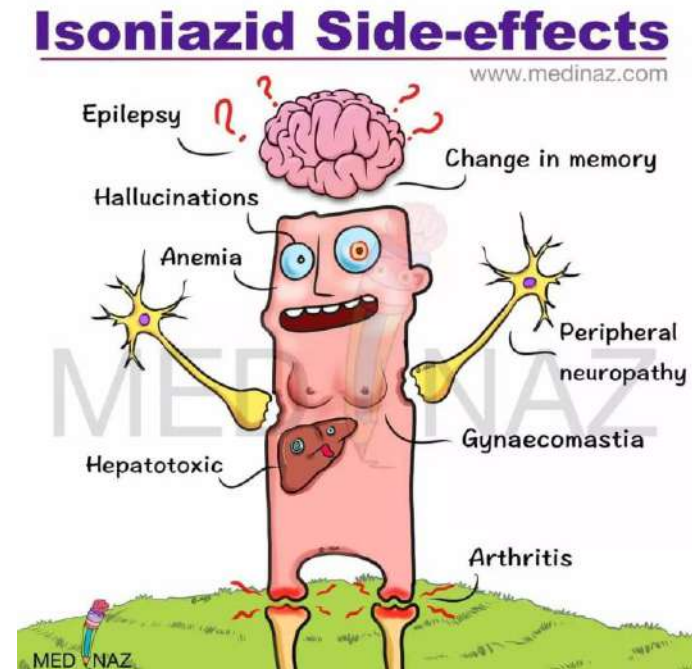
- ❖ Diffuses into ^①all body fluids, ^②cells, and ^③caseous material (**necrotic tissue resembling cheese** that is produced in tuberculous lesions).



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

Isoniazid is specific for TB

❖ 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?

اصلا بال TB ما بنستخدم monotherapy

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. *isoniazid* زي
- Taken up by the **liver** and undergoes enterohepatic recycling.



Rifampin 3/4

Adverse effects

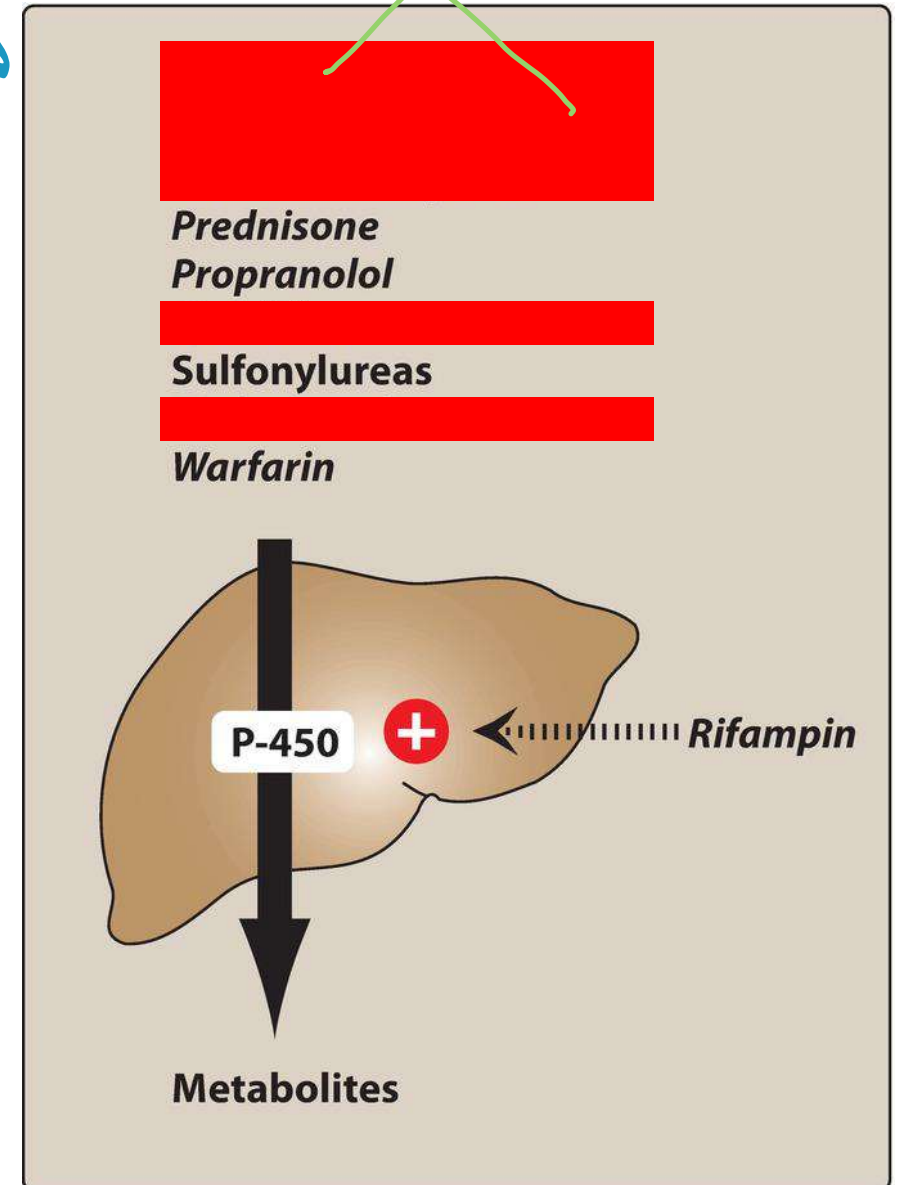
- Urine, feces, and other secretions have an **orange-red** color, so patients should be forewarned. **Tears** may even stain soft contact lenses orange-red.
- **Hepatitis** and death due to liver failure are rare.
- When rifampin is dosed intermittently, especially with higher doses, a **flu-like syndrome** can occur, with fever, chills, and myalgia, sometimes extending to **acute renal failure, hemolytic anemia, and shock**.



Rifampin 4/4 هاد السلايد محذوف

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

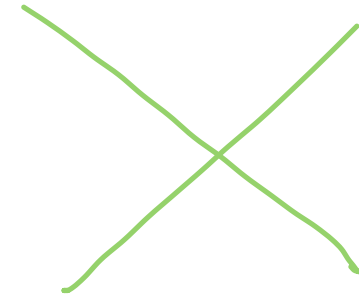
Rifabutin

- ❑ derivative of rifampin: preferred for TB patients **co-infected with HIV** Immunosuppressed
- ❑ Adverse effects similar to those of rifampin بس بدرجة اقل but can also cause uveitis, skin hyperpigmentation, and neutropenia.



Rifapentine

محذوف



- ✓ **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.



2nd line

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.
- That's why patient with cardiovascular disease should not receive bedaquiline*
- نبدل bedaquiline ب drug تاني



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:

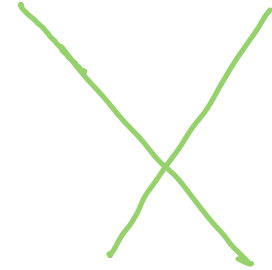
- Greater action against extracellular organisms.
- Infections due to streptomycin-resistant organisms may be treated with kanamycin or amikacin
- AE: Vertigo (feel like the world is spinning), hearing loss and GIs

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

Quiz

1. Which of the following is NOT a first-line drug for the treatment of pulmonary TB?

- a) Isoniazid
- b) Rifampin
- c) Pyrazinamide
- d) Moxifloxacin

Correct answer: d) Moxifloxacin

2. Why is multidrug therapy employed in the treatment of TB?

- a) To reduce treatment duration
- b) To enhance drug effectiveness
- c) To suppress resistant organisms
- d) To simplify treatment regimen

Correct answer: c) To suppress resistant organisms

3. Which drug is a preferred choice for TB patients co-infected with HIV?

- a) Rifampin
- b) Rifabutin
- c) Rifapentine
- d) Pyrazinamide

Correct answer: b) Rifabutin

4. What adverse effect is commonly associated with Isoniazid?

- a) Peripheral neuropathy
- b) Hepatitis
- c) Uveitis
- d) Optic neuritis

Correct answer: b) Hepatitis

5. Rifampin resistance is caused by mutations in which gene?

- a) KatG
- b) InhA
- c) DNA-dependent RNA polymerase
- d) KasA

Correct answer: c) DNA-dependent RNA polymerase

6. What is the main mechanism of action of Ethambutol?

- a) Inhibition of mycolic acid synthesis
- b) Blocking RNA transcription
- c) Disruption of bacterial cell wall
- d) Inhibition of ATP synthase

Correct answer: a) Inhibition of mycolic acid synthesis

7. Which drug is known for its black box warning for QT prolongation?

- a) Cycloserine
- b) Bedaquiline
- c) Linezolid
- d) Ethionamide

Correct answer: b) Bedaquiline

8. What is the primary mode of excretion of Cycloserine?

- a) Feces
- b) Sweat
- c) Urine
- d) Saliva

Correct answer: c) Urine

9. Which second-line drug is a structural analog of isoniazid?

- a) Ethionamide
- b) Streptomycin
- c) Para-aminosalicylic acid
- d) Fluoroquinolones

Correct answer: a) Ethionamide

10. What adverse effect is commonly associated with Fluoroquinolones?

- a) Vertigo
- b) Uveitis
- c) Tendinopathy
- d) Hepatitis

Correct answer: c) Tendinopathy

Quiz ① Which of the following antimycobacterial drugs is inactivated by hepatic acetylation, the rate of which depends on genetic background?

- A. Streptomycin
- B. Ethambutol
- C. Rifampin
- D. Isoniazid
- E. Pyrazinamide

② • A 56-year-old man reports tingling sensation in his limbs and that his arms sometimes feel heavy. He was recently diagnosed with pulmonary tuberculosis and has been receiving isoniazid, rifampin, pyrazinamide and ethambutol for two months. Which of the following drugs would be most appropriate to treat his current symptoms?

- A. Vitamin A
- B. Vitamin C
- C. Folic acid
- D. Pyridoxine
- E. Vitamin E

لأنه عندو PNS فيعطيه B6

لو شلنا ال isoniazid و حطينا