Pharmacology of drug used in tuberculosis

EDITING FILE

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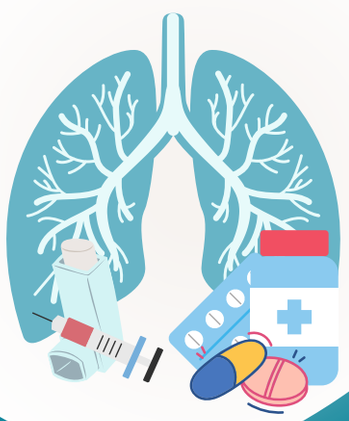

Objectives:

- Discuss the etiology of TB.
- Discuss the common route for transmission of the disease.
- Discusses the outline for treatment of TB.
- Discuss tuberculosis & pregnancy.
- Discuss tuberculosis & breast feeding.
- Discuss the drugs used in the first & second line
  - The mechanism of action.
  - Adverse effects.
  - Drug interactions.
  - Contraindication.

Introduction And Treatment

Tuberculosis

Etiology

❖ Mycobacterium tuberculosis, slow growing, an acid fast bacillus.

❖ Robert Koch was the first to isolate mammalian Mycobacterium tuberculosis with his staining technique in 1882.

Common sites of infections

❖ Apical (top/upper) areas of lung (The mycobacteria survive & multiply within macrophages).
❖ Renal parenchyma.
❖ Growing ends of bones.
❖CNS, bones & joints.

- Four drugs for 2 months then two drugs for four months
- We can use two drugs only like Rifampicin and Isoniazid-but for longer duration - 9 months

Tuberculosis treatment

Drugs are divided into 2 groups:

First Line

- Rifampicin (RIF)
- Isoniazid (INH)
- Pyrazinamide
- Ethambutol
- Streptomycin
  Given by injection -advantage-
  should not be the 1st line choice

Given for first 8 weeks, followed by INH/RIF for 18 weeks

Never use a single drug therapy

isoniazid-Rifampicin combination administered for 9 months will cure 95-98% of cases..

❖ Addition of pyrazinamide/ethambutol for this combination for the first 2 months allows to duration to be reduced to 6 months
❖ Periods of treatment (≥ 6 months).
❖ Drugs combination is important to prevent development of drug resistance.

Second Line

- Ethionamide
- Rifabutin
- Fluoroquinolones (ciprofloxacin)
- Para Aminosalicylic acid (PAS)

Given to Resistant Patients
(Patients themselves aint't Resistant But the bacteria they have is developed)

	Isoniazid (INH) (Only used for TB infection)	Rifampin (RIF) Or Rifampicin
overview	- Bacteriostatic for resting bacilli - Bactericidal for rapidly growing bacilli	-Bactericidal
Site of Action	-Intracellular & extracellular bacilli	
MOA	- Inhibits the synthesis of mycolic acid an important component of mycobacterial cell wall -> inhibits cell wall synthesis. - Penetrates into macrophages.	-Binds to bacterial DNA dependent RNA polymerase enzyme - thus inhibits RNA synthesis.
Clinical uses	-Treatment of TB - Treatment of latent TB in patients with positive tuberculin skin test - Prophylaxis against active TB in individuals who are in great risk (3 month). (Health care providers)	-Treatment of TB - Prophylaxis - Against other bacterial infection such as meningococcal (meningitis) & staphylococcal infections.
ADRs	-Peripheral neuritis (pin & needles sensation in the feet) - Optic neuritis & atrophy because INH causes pyridoxine (vitamine B6) deficiency → Pyridoxine should be give for the ADRs above - Hepatitis, it is age dependent;it is rare in persons younger than 20 years, risk increases with age & alcohol use.	-Harmless red orange discoloration of body secretions (saliva, sweat, urine, tears) tell the patient about this effect. - Can permanently stain contact lenses. - Hepatitis less common compared to INH. - Flu-like syndrome (fever, chills, headache, muscle or body aches, cough, sore throat, runny nose, fatigue, nausea, vomiting, and diarrhea). - Hemolytic anemia.
Drug interactions	INH inhibits cytochrome P450 2C19 isoform (enzyme inhibitor) - Slow & fast acetylators - slow → risk of peripheral neuropathy neuritis. - Fast acetylators→ risk of hepatitis.	-Rifampicin strongly induces most cytochrome P450 isoforms Remember xanthine preparations and antihistamine drugs metabolized by cytochrome p450 -Clinically significant drug interactions: such as warfarin, methadone will be metabolized faster. therefore their activity is reduced.

	Ethambutol	Pyrazinamide (PZA)
overview	-Bacteriostatic	
Site of Action	Intracellular & extracellular bacilli	- Intracellular bacilli
MOA	-Inhibits mycobacterial arabinosyl transferase; essential enzyme for mycobacterial cell wall synthesis (alters the cell barrier) - Thus disrupts the assembly of mycobacterial cell wall	Pyrazinamide (inactive form) is converted to pyrazinoic acid (the active form) which disrupts mycobacterial cell membrane metabolism & transport functions.
Clinical uses	-Treatment of TB in combination with other drugs	-Mycobacterial infections mainly in multi-drug resistance cases. - Important In short course (6 months) regimen. - Prophylaxis of TB.
ADRs	-Impaired visual acuity (the ability of the eye to see fine detail). - Red-green color blindness . في حال استجد الموضوع عند البالغ (عدم التفريق بين الاحمر والاخضر) بيتم تبليغ الدكتور ولكن عند الاطفال قد يكون الطفل من الاساس مايفرق مو من الدواء. - Contraindicated in children under 5 years.	-Hepatotoxicity (common). - Hyperuricemia (gouty arthritis). - Drug fever and skin rash.

Streptomycin (aminogolycosides)	
overview	Bactericidal
Site of Action	Extracellular bacilli
MOA	Irreversible Inhibitor of protein synthesis by binding to bacterial 30s ribosomal subunits.
Clinical uses	Injectable drug used in severe life threatening Clinical form of TB as meningitis, disseminated disease The drug crosses the blood-brain barrier and achieves therapeutic concentrations with inflamed meninges.
ADRs	- Ototoxicity . (Vertigo & hearing loss) may be permanent. -Nephrotoxicity. -Neuromuscular block.

Indication of 2nd line treatment

(When do we use 2nd line treatment)

1. **RESISTANCE TO THE DRUGS OF 1ST LINE**
2. **FAILURE OF CLINICAL RESPONSE**
3. **THERE IS CONTRAINDICATION FOR FIRST LINE DRUGS**
4. **USED IN TYPICAL & ATYPICAL TUBERCULOSIS**

2nd line drugs are more toxic than 1st line drugs.

Second line Treatment

	Ethionamide	Fluoroquinolones (ceprofloxacin)	Rifabutin	Para Aminosalicylic acid (PAS)
Overview	-			Bacteriostatic
MOA	Inhibits synthesis of mycolic acid (same as INH)	Effective against multi-drug resistance TB	- RNA inhibitor - Cross-resistance with rifampicin is complete (if mycobacteria is resistant to rifampin it is also resistant to rifabutin). - Enzyme inducer	Inhibit folic acid synthesis thus slows bacterial cell growth & multiplication.
Clinical use	As a secondary line agent treatment for TB.		Effective in prevention & treatment of typical & atypical TB.	-As a 2nd line agent in treatment of chronic pulmonary & other TB. -Help to slow development of resistance to other drugs especially INH and streptomycin.
ADRs	-Teratogenic (disturb development of fetus) -Poorly tolerated because of : • severe gastric irritation • neurological manifestations		- GIT intolerance (vomiting, nausea, diarrhea) - orange-red discoloration of body secretions.	- GIT upset - Peptic ulceration & hemorrhage - Crystalluria (cloudy urine)

TB and Pregnancy

1

Untreated TB represent a great risk to the pregnant woman & her fetus than the treatment itself.

2

Streptomycin not used, why?

Because It can cross the placenta.

3

First line (INH,RIF and Ethambutol) drugs are given for 9 months in normal doses.

Pyrazinamide is not used because of its teratogenic effect

TB and Breast feeding

> It’s not a contraindication to receive drugs, but caution is recommended.

“ study smarter , not harder “

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summary

MCQs

1 Which of the following drugs causes Hyperuricemia?

- **A** Ethambutol
- **B** Pyrazinamide
- **C** Rifampin
- **D** Ethionamide

2 **What's the mechanism of action of isoniazid?**

- **A** inhibits the protein synthesis
- **B** inhibits RNA synthesis
- **C** inhibits the synthesis of Mycolic acid
- **D** inhibits arabinosyl transferase

3 All of the following are considered 1st line treatment except:

- **A** INH
- **B** RIF
- **C** PAS
- **D** PZA

4 Which of the following drugs causes orange discoloration of body secretions?

- **A** Rifampin
- **B** streptomycin
- **C** Rifabutin
- **D** Both A&C

1-B 2-C 3-C 4-D

MCQs

5 Red-Green color blindness is caused by:

- **A** Ethambutol
- **B** PAS
- **C** Streptomycin
- **D** A & C

6 Which of the following is true about streptomycin?

- **A** MOA: RNA inhibitor
  ADR: GIT intolerance
- **B** MOA: RNA inhibitor
  ADR: Neuromuscular blocker
- **C** MOA: protein synthesis inhibitor
  ADR: hepatotoxicity
- **D** MOA: protein synthesis inhibitor
  ADR: nephrotoxicity

7 Which of the following have both a bacteriostatic and bactericidal activity?

- **A** Rifampin
- **B** Ethambutol
- **C** Pyrazinamide
- **D** Isoniazid

8 Which of the following drugs affects only intracellular bacilli?

- **A** Isoniazid
- **B** Rifampin
- **C** Pyrazinamide
- **D** Ethambutol

5-A 6-D 7-D 8-C

SAQs

1

Which ONE of the following anti-TB drugs causes ototoxicity and nephrotoxicity?

◆ streptomycin

2

Explain the M.O.A. of ethionamide?

◆ inhibit mycolic acid synthesis

3

Mention 2 reasons why a doctor should consider 2nd line treatment.

◆
- Resistance to the drugs of 1st line.
- There is contraindication for first line drugs.

4

A 43-year-old woman is referred to the clinic with a recent diagnosis of tuberculosis, what drugs should be used? (1st line treatment)

◆
1-Rifampicin
2- Isoniazid
3- Pyrazinamide
4- Ethambutol
Streptomycin is also right for severe cases

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