Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY

Respiratory Block

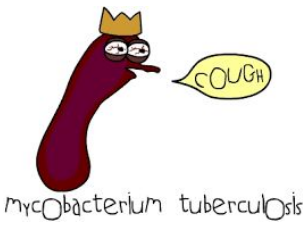
7 Antimycobacterial Drugs

Objectives :

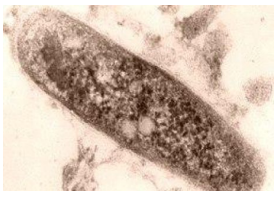
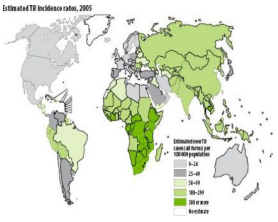
1. Discuss the etiology of tuberculosis.
2. Discuss the common route for transmission of the disease.
3. Discusses the out line for treatment of tuberculosis.
4. Discuss the drugs used in the first & second line.
5. Regarding :
    a. The mechanism of action
    b. Adverse effects
    c. Drug interactions
    d. Contraindication
6. Discuss tuberculosis & pregnancy
7. Discuss tuberculosis & breast feeding

Color index:
Red: important
Grey: Notes or extra information

تمت المراجعة
غيداء آل مهمع
&
عبدالرحمن الخيسوني



Tuberculosis

Etiology	-Mycobacterium tuberculosis: slow growing and an acid-fast bacilli. -Robert Koch was the first to isolate mammalian Mycobacterium tuberculosis with his staining technique in 1882 
Disease information	❖ Each year 1% of the global population is infected. 
Common sites of infections	1. Apical areas of lung (because this area is rich in oxygen). The mycobacteria survives and multiply within macrophages 2. Renal parenchyma 3. Growing ends of bones

Treatment of Tuberculosis	• Drugs combination is important to prevent development of drug resistance.
	• Periods of treatment → minimum 6 months
	• Drugs are divided into 2 groups:
	  ○ First line
	  ○ Second line

First line drugs	1. Isoniazid (INH) 2. Rifampin 3. Ethambutol 4. Pyrazinamide 5. Streptomycin (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:

INH/RIF combination administered for 9 months will cure 95-98% of cases

Addition of pyrazinamide/ethambutol for this combination for the first 2 months allows total duration to be reduced to 6 months

1st line drugs

1 Isoniazid (INH)

About Drug	• Bacteriostatic for resting bacilli. • Bactericidal for rapidly growing bacilli. • **Site of action:** Effective against intracellular bacilli and extracellular bacilli.
MOA	• Inhibits the synthesis of mycolic acid, an important component of mycobacterial cell wall. • Penetrates into macrophages & is active against both intracellular & extracellular organisms.
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 (e.g. HIV and diabetic patients) .
ADRs	• **Peripheral neuritis** (pin & needles sensation in the feet)  • **Optic neuritis & atrophy** (Pyridoxine* should be given in both cases) • **Hepatitis (toxic metabolites)** Hepatitis with INH, is age dependent; it is rare in persons younger than 20 years, risk increases with age & alcohol use.
Drug interaction	• INH inhibits cytochrome P450 2C19 isoform (enzyme inhibitor) • Slow & fast acetylators.

*** pyridoxine= vitamin B6**

Isoniazid interferes competitively with pyridoxine metabolism by inhibiting the formation of the active form of the vitamin B6. So it's results in peripheral neuritis, optic neuritis & atrophy. **And we use it to prevent the development of peripheral neuritis, optic neuritis & atrophy in patients receiving isoniazid.**

2 Rifampin

About Drug	• Bactericidal for rapidly • **Site of action:** Effective against intracellular bacilli and extracellular bacilli.
MOA	Binds to bacterial DNA- dependent RNA polymerase enzyme & thus inhibits RNA synthesis.
Clinical uses	• Treatment of TB. • Prophylaxis. • Against other bacterial infection such as meningococcal & staphylococcal infections.
ADRs	• **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. • Hemolytic anemia.Rare
Drug interaction	• Rifampicin strongly induces most cytochrome P450 isoforms • Clinically significant drug interactions: warfarin, methadone will be metabolized faster.

3 Ethambutol

MOA	• Bacteriostatic • Inhibits mycobacterial arabinosyl transferase; essential enzyme for mycobacterial cell wall synthesis. Thus disrupts the assembly of mycobacterial cell wall. • **Site of action:** Intracellular & extracellular bacilli
Clinical uses	• Treatment of TB in combination with other drugs.
ADRs	• **Impaired visual acuity** • **Red-green color blindness**
Contraindication	• Ethambutol is contraindicated in children under 5 years.

4 Pyrazinamide (PZA)

MOA	• Bacteriostatic • Pyrazinamide is converted to pyrazinoic acid—the active form which disrupts mycobacterial cell membrane, metabolism & transport functions. • **Site of action:** Active against intracellular Bacilli.
Clinical uses	• Mycobacterial infections mainly in multidrug resistance cases • It is important in short –course (6 months) regimen • Prophylaxis of TB.
ADRs	• Hepatotoxicity (common) • **Hyperuricemia** (gouty arthritis) • Drug fever & skin rash.

5 Streptomycin

MOA	• Bactericidal • Inhibitors of protein synthesis by binding to 30S ribosomal subunits • Active mainly against extracellular bacilli
Clinical uses	• Injectable drug used in severe, life-threatening form of T.B. as meningitis, disseminated disease.
ADRs	• **Ototoxicity (Vertigo & hearing loss) may be permanent** • **Nephrotoxicity** • **Neuromuscular block**

2nd line drugs

1 Ethionamide

MOA	• Inhibits the synthesis of mycolic acid. (Similar to INH)
Clinical uses	• As a secondary line agent for treatment of TB (po). (P.O.) means orally
ADRs	• Teratogenic. Teratogenic: Able to disturb the growth and development of an embryo or fetus. Contraindicated in pregnant women. • Poorly tolerated, because of: ○ Severe gastric irritation. ○ Neurological manifestations.

2 Fluoroquinolones (Ciprofloxacin)

Clinical uses	Effective against multidrug-resistant TB.

3 Rifabutin

MOA	• RNA inhibitor. • Cross –resistance with rifampin is complete. • Enzyme inducer.
Clinical uses	• Effective in prevention & treatment of TB. • In prevention & treatment of atypical TB.
ADRs	• GIT intolerance. • Orange-red discoloration of body secretions.

4 Para AminoSalicylic acid (PAS)

MOA	• Bacteriostatic. • Inhibits folic acid synthesis thus slows bacterial cell growth & multiplication.
Clinical uses	• As a second line agent is used in the treatment of chronic pulmonary & other forms of TB. • Help to slow development of resistance to other drugs, especially INH & streptomycin.
ADRs	• GIT upset, peptic ulceration & hemorrhage. • Crystalluria. Prevent it by take large amount of water

Indication of 2nd line treatment

- Resistance to the drugs of 1st line.
- Failure of clinical response
- There is contraindication for first line drugs
- Used in typical & atypical tuberculosis.
- 2nd line drugs are more toxic than 1st line drugs

Tuberculosis and pregnancy

1. Untreated TB represents a great risk to the pregnant woman & her fetus than the treatment itself.
2. First line (INH, ethambutol & rifampicin) drugs are given for 9 months in normal doses.
3. Streptomycin not used??
   Because it can pass the placenta easily and cause permanent damage in the ear and balance of the fetus.

Tuberculosis and breastfeeding

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

MCQs

1-Which of the following is the correct drug regimen for a newly diagnosed patient with pulmonary tuberculosis? :

A. 2 months of Streptomycin, Rifampicin, Isoniazid, Pyrazinamide and Ethambutol followed by 4 months of Rifampicin and Isoniazid
B. 8 months of Rifampicin, Isoniazid and Ethambutol
C. 2 months of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol followed by 4 months of Rifampicin and Isoniazid
D. 6 months of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol

2-Which of the following drugs has no hepatotoxicity potential?

A. Rifampicin
B. Pyrazinamide
C. Isoniazid
D. Ethambutol

3-Which of the following is a risk factor for ATT induced hepatitis?:

A. Advancing age
B. Malnutrition
C. chronic alcohol consumption
D. All of the above

4-Pyridoxine(vitamin B6) deficiency can occur due to treatment of which anti-TB drug?

A. Rifampicin
B. Isoniazid
C. Ethambutol
D. Pyrazinamide

5- Which of the following drugs that could inhibit mycobacterial arabinosyl transferase ?

A. Rifampicin
B. Pyrazinamide
C. Isoniazid
D. Ethambutol

6- Which of the following drugs that can lead to bleeding due to their interaction ?

A. Rifampicin
B. Pyrazinamide
C. Isoniazid
D. Ethambutol

7- A patient went to see his doctor, told him that he noticed changes in his urination, as it looked kind of cloudy, which of the following drugs is responsible for that ?

A. Rifabutin
B. Aminosalicylic Acid (PAS)
C. Fluoroquinolones
D. Ethionamide

SAQ

1. Which of the following drugs is active only against Intracellular Bacilli ?
2. What is the mechanism of action of this drug?
3. List the major side effect of this drug.

Answers:
1. C
2. D
3. D
4. B
5. D
6. A
7. B

Answers:
1. Pyrazinamide
2. Pyrazinamide is converted to pyrazinoic acid—the active form which disrupts mycobacterial cell membrane, metabolism & transport functions.
3. A. Hepatotoxicity (common)
B. Hyperuricemia (gouty arthritis)
C. Drug fever & skin rash

Good Luck & Thank you !

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