Pharmacology Team

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Red	**Important**
Purple	Extra Notes
Orange	General Explanation
Black	From the slides

Objectives:

Discuss the etiology of tuberculosis

Discuss the common route for transmission of the disease

Discusses the outline for treatment of tuberculosis

Discuss the drugs used in the first & second line

The mechanism of action

Adverse effects

Drug interactions

Contraindication

Discuss tuberculosis & pregnancy

Discuss tuberculosis & breast feeding

Treatment of tuberculosis:

- A thereby of **multiple drugs** should be used so the bacteria doesn't devolp risistance.
- The thereby lasts for a **minimum of 6 months**.

The drugs are divided into two groups:

First-line drugs and second-line drugs.

First-line drugs:

Ethambutol (EMB),

isoniazid (INH),

pyrazinamide (PZA),

rifampicin (RMP),

Streptomycin (is no longer considered as a first line drug by ATS/IDSA/CDC because of high rates of resistance).

Note:

Isoniazid –rifampin combination administered for 9 months will cure 95--98% of cases.

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

Drug	General Information	Mechanisim of action	Clinical uses	Advers effects	Drug interaction
isoniazid (INH)	1--- bacteriostatic for resting bacilli. 2--- bactericidal for rapidly dividing bacilli. 3--- is effective against both intracellular and extracellular bacilli.	1---is a prodrug (inactive) then activated by mycobacterial enzyme (enzyme produced by the organism). 2--- inhibits the synthesis of mycobacterial cell wall by inhibiting the synthesis of mycolic acidwhich is anessential component of the bacterial cell wall.	1---mycobacterial infections. 2--- latent tuberculosis in patients with positive tuberculin test. 3---**prophylaxis** against active TB in individuals who are in great risk. ** it is **very effective** in treatment of latent TB .	1--- Peripheral neuritis (inflamition of nerve) (pin & needle sensation in the feet) 2--- Optic neuritis & atrophy. *Pyridoxine (vitamin B6) should be given in both cases as prophylactic from neuritis) 3--- Hepatitis.	Enzyme inhibitor (inhibits the hepatic microsomal enzyme especially cytochrome P450). Enzyme inhibitor = inhibit metabolism of other drugs.

Drug	Genral Information	Mechanisim of action	Clinical uses	Advers effects	Drug interaction
rifampicin (RMP)	1--- bactericidal. 2--- effective against intracellular and extracellular bacilli. 3--- inhibit RNA synthesis	inhibits RNA synthesis by binding to DNA dependent RNA polymerase enzyme.	1--- mycobacterial infections 2--- prophylaxis of active tuberculosis. 3--- treatment of serious staphylococcal infections. 4--- meningitis by highly resistant penicillin pneumococci.	1--- Harmless red--- orange discoloration of body secretions. 2--- flu---like syndrome 3--- Hemolytic anemia. 4--- Hepatitis.	Enzyme inducer of hepatic microsomal enzymes (cytochrome P450).

Drug	General information	Mechanisim of action	Clinical uses	Advers effects
Ethambutol (EMB)	1--- bacteriostatic. 2---effective against intracellular and extracellular bacilli	inhibits mycobacterial cell wall synthesis bins to (arabinosyl transferase) (alters the cell barrier). فتاح الابواب *which is an enzyme produsing substance called (arabinoglycan)on the bacterial cell wall as cell barrier→ to inhibit the crossing of the drug . SO,by inhibiting this enzyme the drug facilate crossing of drug on the bacterial cell wall.	treatment of tuberculosis **in combination** with other drugs.	1--- impaired visual acuity. 2--- red---green color blindness. 3--- contraindicated in children under 5 years *Usually the doctor make periodic visual acuity examination to the patient and if any changes happened the doctor will shift the drug and it is difficult to make these examination to a child under 5 years that's why it is contraindicated for them.

Drug	General information	Mechanisim of action	Clinical uses	Advers effects
pyrazinamide (PZA)	1---bactericidal 2--- prodrug 3--- active against intracellular bacilli only.	Unknown.	1---mycobacterial infections mainly in multidrug resistance cases. 2--- it is important in short – course (6 months) regimen. 3--- Prophylaxis of TB.	1--- hepatotoxicity 2--- hyperuricemia (precipitate gouty arthritis). 3--- drug fever and skin rash.

Drug	*General information*	*Mechanisim of action*	*Clinical uses*	*Advers effects*
Streptomycin	1--- Bactericidal. 2--- activates mainly on extracellular bacilli.	nhibitors of protein synthesis by binding to 30s ribosomal subunits.	severe, life---threating form of TB as meningitis , disseminated disease	1--- ototoxicity. 2--- nephrotoxicity. 3--- neuromuscular block.

Notes:

- Mycolic acid= an important component that forms the cell wall
- Deficiency in vitamin B6 is the cause of peripheral and optic neuritis
- Streptomycin is the last choice we think of in case of tuberculosis (in case of disseminated TB)
- Neuromuscular block= muscle paralysis. Streptomycin contraindicated before surgeries because the 2 muscle relaxants will potentiate each other and may cause respiratory failure
- Streptomycin is also contraindicated in pregnancy because it may pass through the placenta and cause deafness to the

child.

2nd line treatment of tuberculosis:

- Used when there is resistance to the drugs of 1st line
- Failure of clinical response
- There is contraindication for the 1st line drug
- Used in typical and atypical tuberculosis

Drug	*Ethionamide*	*Fluoroquinolones (ciprofloxacin)*	*Refabutin*	*Aminosalicylic acid (PAS)*
General Information	inhibits the synthesis of mycobacterial cell wall through inhibition of mycolic acid	effictive against multidrug- --resistant tuberculosis	1--- RNA inhibitor 2--- cross---resistance with Rifampin is complete 3--- enzyme inducer for cytochrome P450	1--- bacterostatic 2--- inhibits folic acid synthesis which is important for the growth of bacteria.
Clinical uses	as a secondary line agent		effective in prevention and treatment of typical and atypical TB	As a second line agent in treatment of pulmonary and other forms of TB
Advers effects	Poorly tolerated because of: • Severe gastric irritation • Neurological manifistations		1--- GIT intolerance 2--- orange---red discoloration of body secretions	1--- GIT upset 2--- hypersensitivity reactions 3--- crystalluria. *when the drug is excreted it deposit and crystallized , the crystals make injury to the bladder and ureters thats why the doctor always advice the patient to drink alot of water.

Notes:

- Ethionamide: isn't from the first line drug because of its side effect although it is similar to INH .
- Folic acid is responsible for the growth of the organism
- Rifabutin have same mechanism and advers effect of Rifambin but it is less potent .
- Fluoroquinolones (ciprofloxacin) is no longer used

***TB and pregnancy*:**

• *Untreated TB represents a great risk to the pregnant women and her fetus than the treatment itself*

• First line drugs are given for 9 months in normal doses

• Streptomycin is the last alternative in treatment because it leads to the death of the fetus, but we give whole the First line .

***TB and breast feeding*:**

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

Q: what is the most common rout and site of TB infection?

Q:Why is multiple drugs used for the treatment of TB?

Q:which drug cause the flu-like syndrom as an advers effect?

Q:Which drug shouldn't be used in children under 5 years old?

Q:What are the drugs that have both inracelluraly and extracellulary action?

Q:Which drug should be use in severe life-threatening TB?

Q:Which drug is contraindicated in pregnancy?

A1: Common route of infection is air.

Common site of infection:

Apical areas of lung

Renal parenchyma

Growing ends of bones.

A2: so the bacteria doesn’t devolp risistance.

A3: rifampicin (RMP).

A4: Ethambutol (EMB).

A5: Ethambutol (EMB), isoniazid (INH), rifampicin (RMP).

A6: Streptomycin.

A7: Streptomycin

Good luck