



# PHARMACOLOGY

## Drugs used in TUBERCULOSIS

### Objectives:

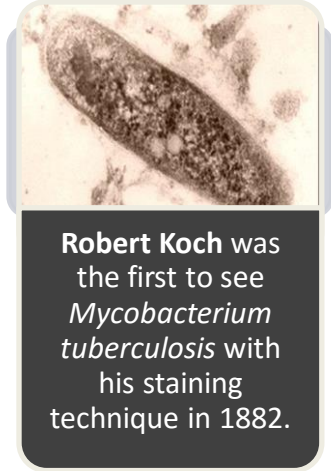
- **Discuss the etiology of tuberculosis**
- **Discuss the common route for transmission of the disease**
- **Discusses the out line for treatment of tuberculosis**
- **Discuss the drugs used in the first & second line Regarding :**
  - The mechanism of action
  - Adverse effects
  - Drug interactions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



# Tuberculosis:

## Etiology:

*Mycobacterium tuberculosis*, slow growing, an acid fast bacillus  
Mycobacteria are intracellular rod-shaped aerobic bacilli that multiply slowly, consequently, infections are often chronic and therapy may be required for as long as 2 years. Resistance to the drug develops rapidly. Their cell walls contain mycolic acids, which give the genus its name.



## Epidemiology:

- Each year, 1% of the global population is infected.
- More than one third of the world's population has tuberculosis.

## Common sites of infections :

- Apical areas of lung, because MTB is aerobic and favors sites of oxygen
- Renal parenchyma
- Growing ends of bones

## Common route for transmission of the disease:

TB is primarily an airborne disease. The bacteria are spread from person to person in tiny microscopic droplets when a TB sufferer coughs, sneezes, speaks, sings, laughs, or spits in public. Only people with active TB can spread the disease to others.

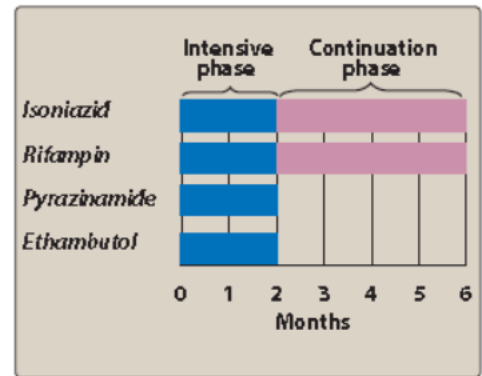
## Treatment Of Tuberculosis :

- Preventing development of drug resistance is the most important reason to use drug combination.
- Periods of treatment ( minimum 6 months)
- Drugs are divided into two groups:  
1-First line                      2. Second line

## Antimycobacterial drugs (First line)

- **Isoniazid (INH)**
- **Rifampin (RIF)**
- **Ethambutol**
- **Pyrazinamide**
- **Streptomycin** (should not be the first line choice)

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



**Figure 41.3**

One of several recommended multidrug schedules for the treatment of tuberculosis.

## Never use a single drug therapy.

- Isoniazid – Rifampin 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.

# 1<sup>st</sup> line treatment

	Isoniazid (INH)	Rifampin (RIF)
Overview	<ul style="list-style-type: none"> <li>• <b>Bacteriostatic</b> → works on resting bacilli</li> <li>• <b>Bactericidal</b> → works on rapidly growing bacilli</li> </ul>	<b>Bactericidal</b>
Site of action	intracellular & extracellular bacilli	
Mechanism of action	Inhibits the synthesis of mycobacterial <b>cell wall</b> (mycolic acid)	Inhibits <b>RNA</b> synthesis by binding to DNA dependent RNA polymerase enzyme.
Clinical use	<ul style="list-style-type: none"> <li>• Treatment of TB</li> <li>• Treatment of <u>Latent</u> TB in patients with Positive tuberculin skin test</li> <li>• <u>Prophylaxis</u> against active TB in individuals who are in great risk</li> </ul>	<ul style="list-style-type: none"> <li>• Treatment of TB</li> <li>• <u>Prophylaxis</u></li> </ul>
ADRs	<ul style="list-style-type: none"> <li>• <b>Peripheral neuritis:</b> (pin &amp; needles sensation in the feet)</li> <li>• <b>Optic neuritis &amp; atrophy.</b></li> </ul> <p><u>pyridoxine</u> (vitamin B6) should be given in both cases</p> <ul style="list-style-type: none"> <li>• <b>Hepatitis</b> (due to toxic metabolites)</li> </ul> <p>Hepatitis with INH is age dependent; it is rare in persons younger than 20 years , risk increases with age and alcohol use</p>	<ul style="list-style-type: none"> <li>• Harmless red-orange discoloration of body secretions (saliva, sweat, urine...). <b>Tell the patient about this effect, as it may permanently stain the contact lenses.</b></li> <li>• <b>Hepatitis</b> (less common compared to INH)</li> <li>• Flu-like syndrome</li> <li>• <b>Hemolytic anemia</b></li> </ul>
Drug interaction	<ul style="list-style-type: none"> <li>• Enzyme inhibitor: decrease metabolism and thus increase duration of action &amp; toxicity of co-administered drugs.</li> </ul>	<ul style="list-style-type: none"> <li>• Enzyme inducer: warfarin, methadone will be metabolized faster</li> </ul>
Pharmacokinetics	Metabolized by: Slow and fast acetylators: Isoniazid is metabolized by the liver by N-acetylation. The rate of acetylation shows a genetic variance among humans; it can be fast in 1 hour or slow in 3 hours.	
Extra	To remember: isoniazid ( <b>INH</b> ): <b>I</b> NH : enzyme <b>I</b> NH <b>I</b> tor <b>N</b> : neuritis <b>H</b> : hepatitis	To remember: rifampin ( <b>RIF</b> ): <b>R</b> : red-orange discoloration + <b>R</b> NA inhibitor <b>I</b> : Enzyme <b>i</b> nducer <b>F</b> : Flu-like syndrome

# 1<sup>st</sup> line treatment cont.

	Ethambutol	Pyrazinamide	Streptomycin (aminoglycoside)
Overview	<b>Bacteriostatic</b>	<b>Bacteriostatic</b>	<b>Bactericidal</b>
Site of action	intracellular & extracellular bacilli	<b>Intracellular</b> Bacilli	<b>extracellular</b> bacilli. it is polar, can't cross lipid membrane
Mechanism Of Action	Inhibits mycobacterial <u>arabinosyl transferase</u> (alters the cell barrier) which disrupts the assembly of mycobacterial <b>cell wall</b> .	<b>unknown</b>	Inhibitor of <b>protein</b> synthesis by binding to <b>30S ribosomal subunit</b> <b>irreversibly</b>
Clinical use	Treatment of TB in combination with other drugs.	<ul style="list-style-type: none"> <li>Mycobacterial infections mainly in <b>multidrug resistance</b> cases.</li> <li>It is important in <b>short course</b> (6 months) regimen combined with INH &amp; RIF</li> <li><b>Prophylaxis</b> of TB .</li> </ul>	<b>Used for Severe life-threatening</b> forms of T.B. as meningitis, disseminated disease.
Adverse effects	Ethambutol = eye <ul style="list-style-type: none"> <li><b>Impaired visual acuity.</b></li> <li><b>Red-green color blindness.</b> (loss of ability to discriminate between red and green)</li> <li>it is <b>contraindicated in children</b> under 5 years old due to toxicity &amp; retinal damage</li> </ul>	<ul style="list-style-type: none"> <li><b>Hepatotoxicity</b> (common)</li> <li><b>Hyperuricemia</b> (gouty arthritis)</li> <li><b>Drug fever &amp; skin rash</b></li> </ul>	<ul style="list-style-type: none"> <li><b>Ototoxicity</b> (ear poisoning)</li> <li><b>Nephrotoxicity</b> (renal poisoning)</li> <li><b>Neuromuscular block</b> (in high doses)</li> </ul>

## 2<sup>nd</sup> line treatment:

2<sup>nd</sup> line drug are **more toxic** than 1<sup>st</sup> line drugs· thus only used in these cases:

- 1) Resistance to 1<sup>st</sup> line drugs**
- 2) Contraindication to 1<sup>st</sup> line drugs**
- 3) Failure of clinical response**
- 4) Used in typical & atypical tuberculosis**

# 2<sup>nd</sup> line treatment

	Ethionamide <i>structural analog of isoniazid</i>	Flouro-quinolones (ciprofloxacin)	Rifabutin (derivative of rifampin)	Para-Aminosalicylic acid (PAS)
action	-	-	Extracellular and intracellular bacilli.	- <b>Bacteriostatic.</b>
Mechanism of action	Inhibit <b>mycolic acid</b> synthesis (cell wall)	-	RNA inhibitor. cross-resistance (1) with <b>rifampin</b> is completed.	- Inhibit <b>foli</b> c acid synthesis.
Clinical uses	2 <sup>nd</sup> line treatment of TB.	Effective against <b>multidrug-resistant</b> tuberculosis.	prevention and treatment of TB & <u>atypical</u> TB (2) .	2 <sup>nd</sup> line treatment of pulmonary & other forms of TB.
ADRs	<ul style="list-style-type: none"> <li>• <b>Teratogenic</b> (interfering with the development of a fetus)</li> <li>• <b>poorly tolerated</b>, due to severe <u>Gastric irritation</u> &amp; <u>neurological manifestation</u></li> </ul>	-	<ul style="list-style-type: none"> <li>- enzyme inducer (less potent than rifampin)</li> <li>- GIT intolerance.</li> <li>- Orange-<b>red</b> discoloration of body secretions.</li> </ul>	<ul style="list-style-type: none"> <li>- GIT upset (shouldn't be used on empty stomach)</li> <li>- <b>Crystalluria</b> (3)</li> </ul>

(1) Cross-resistance is the tolerance to a usually toxic substance as a result of exposure to a similarly acting substance.

(2) Atypical TB: diseases caused by nontuberculosis mycobacteria (NTM). E.g. *M. leprae* causes leprosy.

(3) Crystalluria: the excretion of crystals in the urine, causing irritation of the kidney.

## TB and Pregnancy:

- Although it may be harmful to the fetus, TB should be treated with the same drugs because untreated TB is more harmful than the treatment itself.
- **Streptomycin is not used.**
- First line drugs (INH, Ethambutol and rifampicin) are given for 9 months.

## TB and breast feeding:

There's no contraindication to receive drugs but caution is recommended

# TB Drugs summary

Drug	Type	Site	Mechanism	Clinical use	ADRs
<i>Isoniazid</i>	Bacteriostatic & Bactericidal Enzyme inhibitor	intracellular & extracellular bacilli	Inhibition of cell wall (mycolic acid)	<ul style="list-style-type: none"> <li>- Treatment</li> <li>- Latent TB</li> <li>- Prophylaxis</li> </ul>	<ul style="list-style-type: none"> <li>- Peripheral neuritis</li> <li>- Optic neuritis &amp; atrophy</li> <li>- Hepatitis</li> </ul>
<i>Rifampin</i>	Bactericidal Enzyme inducer		Inhibits RNA synthesis	<ul style="list-style-type: none"> <li>- Treatment of TB</li> <li>- Prophylaxis</li> </ul>	<ul style="list-style-type: none"> <li>- red-orange discoloration</li> <li>- Hepatitis</li> <li>- Flu-like syndrome</li> <li>- Hemolytic anemia</li> </ul>
<i>Ethambutol</i>	Bacteriostatic		Inhibition of cell wall (arabinosyl transferase)	Treatment of TB in combination with other drugs	<ul style="list-style-type: none"> <li>- Impaired visual acuity.</li> <li>- Red-green color blindness.</li> <li>- <b>Contraindicated</b> in children</li> </ul>
<i>Pyrazinamid</i>	Bacteriostatic	Intracellular	unknown	<ul style="list-style-type: none"> <li>- multidrug resistance cases.</li> <li>- short course regimen</li> <li>- Prophylaxis</li> </ul>	<ul style="list-style-type: none"> <li>- Hepatotoxicity</li> <li>- Hyperuricemia</li> <li>- Drug fever &amp; skin rash</li> </ul>
<i>Streptomycin</i>	Bactericidal	extracellular	Inhibitor of protein synthesis	for Severe life-threatening forms of TB (meningitis, disseminated)	<ul style="list-style-type: none"> <li>- Ototoxicity</li> <li>- Nephrotoxicity</li> <li>- Neuromuscular block</li> </ul>
<i>Ethionamide</i>			Inhibition of cell wall (mycolic acid)	2nd line treatment	<ul style="list-style-type: none"> <li>- Teratogenic</li> <li>- Gastric irritation</li> <li>- Neurological manifestations</li> </ul>
<i>ciprofloxacin</i>				multidrug-resistant TB	
<i>Rifabutin</i>	Enzyme inducer	Extracella & intracellular	RNA inhibitor.	prevention and treatment of TB & atypical TB	<ul style="list-style-type: none"> <li>- GIT intolerance</li> <li>- Orange-red discoloration</li> </ul>
<i>(PAS)</i>	Bacteriostatic		Inhibit folic acid synthesis.	2nd line treatment of pulmonary TB & other forms	<ul style="list-style-type: none"> <li>- GIT upset</li> <li>- Crystalluria</li> </ul>

# QUIZ

THANK YOU FOR CHECKING OUR WORK  
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