

# **TUBERCULOSIS**

Pulmonary TB

## **Drug therapy**

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# OBJECTIVES



At the end of lecture, the students should:

- ❖ Discuss the etiology of TB
- ❖ Discuss the common route for transmission of the disease
- ❖ Discusses the outline for treatment of TB
- ❖ Discuss the drugs used in the first & second line



# OBJECTIVES (Cont')

## Drugs

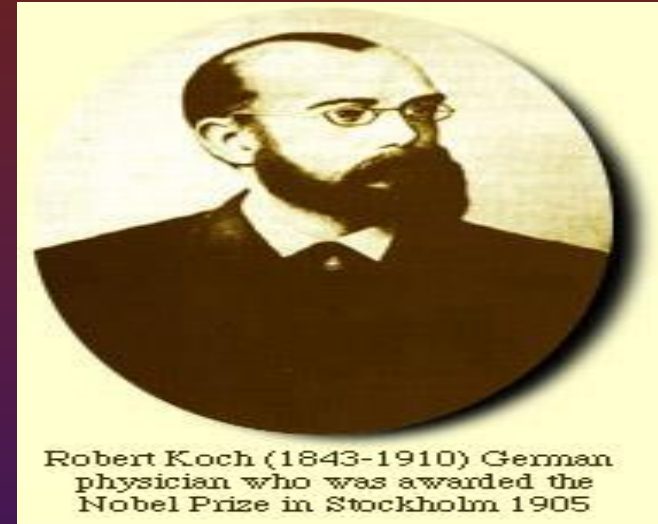
- ❖ The mechanism of action
- ❖ Adverse effects
- ❖ Drug interactions
- ❖ Contraindication
- ❖ Discuss tuberculosis & pregnancy
- ❖ Discuss tuberculosis & breast feeding.



# 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.



Robert Koch (1843-1910) German physician who was awarded the Nobel Prize in Stockholm 1905





# COVER UP! YOUR COUGHS AND SNEEZES

Actual photograph of a sneeze



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THE ANNUAL SALE OF *Christmas Seals* MADE THIS POSTER POSSIBLE



# Tuberculosis

## Common sites of infections

- ❖ **Apical areas of lung. The mycobacteria survive & multiply within macrophages**
- ❖ **Renal parenchyma**
- ❖ **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:
  1. First line
  2. Second line.



# Antimycobacterial drugs

## First line


1- Isoniazid (INH)

2- Rifampin

3- Ethambutol

4- Pyrazinamide

5- Streptomycin (should not be the 1<sup>st</sup> line choice).



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





# Never use a single drug therapy

- ❖ INH –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.



# INH

- ❖ Bacteriostatic for resting bacilli
- ❖ Bactericidal for rapidly growing bacilli
- ❖ Effective against intracellular & extracellular bacilli.

## Mechanism of Action

- ❖ 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.



# ADRs

INH

## ❖ 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.





INH

# Drug Interactions

- ❖ INH inhibits cytochrome P450 2C19 isoform (enzyme **inhibitor**)
- ❖ Slow & fast acetylators.



# Rifampin

❖ **Bactericidal**

❖ **Mechanism of action:**

**Binds to bacterial DNA- dependent RNA polymerase enzyme & thus inhibits RNA synthesis.**

## Site of Action (similar to INH)

- ❖ Intracellular bacilli
- ❖ Extracellular bacilli

## 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.**



# Drug Interactions

❖ **Rifampicin** strongly induces most cytochrome P450 isoforms

**Clinically significant drug interactions: warfarin, methadone will be metabolized faster.**



# Ethambutol

❖ **Bacteriostatic**

❖ **Inhibits mycobacterial arabinosyl transferase; essential enzyme for mycobacterial cell wall synthesis**

**Thus disrupts the assembly of mycobacterial cell wall.**



# **Site of Action (similar to INH)**

**Intracellular & extracellular bacilli**

## **Clinical uses**

**Treatment of TB in combination with other drugs.**



# ADRs

❖ **Impaired visual acuity**

**Red-green color blindness**

❖ **Ethambutol is contraindicated in children under 5 years.**



# Pyrazinamide (PZA)

❖ **Bacteriostatic**

❖ **Mechanism of action:** 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.**



PZA

## ADRs

- ❖ **Hepatotoxicity (common)**
- ❖ **Hyperuricemia (gouty arthritis)**
- ❖ **Drug fever & skin rash.**



# Streptomycin

- ❖ Bactericidal
- ❖ Inhibits of protein synthesis by binding to bacterial 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.**



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

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





# Ethionamide

**Mechanism of action:** Inhibits the synthesis of mycolic acid.

**Clinical uses:**

As a secondary line agent for treatment of TB (po).



# ADRs of Ethionamide

**Teratogenic**

**Poorly tolerated**

**Because of :**

- ❖ **Severe gastric irritation &**
- ❖ **Neurological manifestations.**



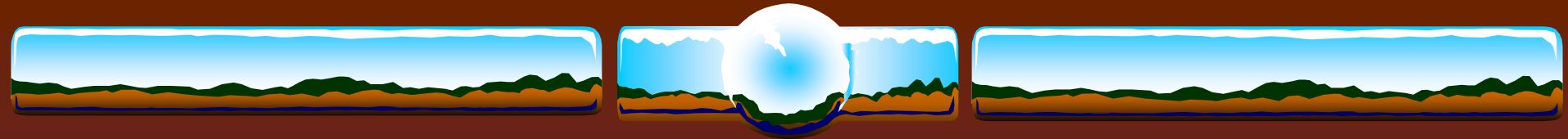
# Fluoroquinolones (Ciprofloxacin)

Effective against multidrug- resistant TB.



# Rifabutin

- ❖ RNA inhibitor
- ❖ Cross –resistance with rifampin is complete
- ❖ Enzyme inducer.



# Clinical uses of Rifabutin

- ❖ Effective in prevention & treatment of TB
- ❖ In prevention & treatment of atypical TB.

## ADRs

- ❖ GIT intolerance
- ❖ Orange-red discoloration of body secretions.



# Para AminoSalicylic acid (PAS)

- ❖ 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.**



# TB & Pregnancy

- ❖ **Untreated TB represents a great risk to the pregnant woman & her fetus than the treatment itself.**
- ❖ **First line (INH, ethmabutol & rifampicin) drugs are given for 9 months in normal doses**
- ❖ **Streptomycin not used ??**





# TB & Breast Feeding

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

# FIGHT TUBERCULOSIS



WPA FEDERAL ART PROJECT

# OBEDY

THE RULES OF HEALTH