PHARMACOLOGY
TEAM 439

MED439
KING SAUD UNIVERSITY

# Tuberculosis drug therapy

## Objectives:

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

Important

In male and female slides

Only in male slides

Only in female slides

Extra information

Editing file

# Introduction to 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.
- Disease information:
  -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 (top/upper) areas of lung (The mycobacteria survive & multiply within macrophages).
- Renal parenchyma.
- Growing ends of bones.

## Treatment of Tuberculosis

**Tuberculosis treatment**
Drugs are divided into 2 groups:

**First line**

- Rifampin (RIF)
- Isoniazid (INH)
- Pyrazinamide
- Ethambutol

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

- Streptomycin — should not be the 1st line choice

**Second line**

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

- 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 total duration to be reduced to 6 months.
- Periods of treatment (minimum 6 months).
- Drugs combination is important to prevent development of drug resistance.

# 1st line treatment

| | Isoniazid (INH) | Rifampin (RIF) |
|---|---|---|
| **Overview** | -**Bacteriostatic** for resting bacilli<br>-**Bactericidal** for rapidly growing bacilli | **Bactericidal** |
| **Site of Action** | Intracellular bacilli & extracellular bacilli | |
| **MOA** | -Inhibits the synthesis of **mycolic acid** an important component of mycobacterial cell wall -> inhibits cell wall synthesis.<br>-Penetrates into macrophages | -Binds to and inhibits bacterial DNA-dependent RNA polymerase enzyme & thus **inhibits RNA synthesis.** |
| **Clinical Use** | -Treatment of TB<br>-Treatment of latent TB in patients with positive tuberculin skin test<br>-Prophylaxis against active TB in individuals who are in great risk (health care providers). | -Treatment of TB<br>-Prophylaxis<br>-Against other bacterial infection such as meningococcal (meningitis) & staphylococcal infections. |
| **ADRs** | -Peripheral neuritis<br>(pin & needles sensation in the feet)<br>-Optic neuritis & atrophy because INH causes pyridoxine (vitamine B6) deficiency -> Pyridoxine should be given in both cases.<br>-Hepatitis (toxic metabolites)<br>➢ Hepatitis with INH, 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.<br>Can permanently stain contact lenses.<br>-Hepatitis<br>less common compared to INH.<br>-Flu-like syndrome (fever, chills, headache, muscle or body aches, cough, sore throat, runny nose, fatigue, nausea, vomiting, and diarrhea).<br>-Hemolytic anemia. |
| **Drug interactions** | -INH inhibits cytochrome P450 **2C19** isoform (enzyme inhibitor)<br>- Slow & fast acetylators :<br>-slow acetylators -> accumulation of INH -> risk of peripheral neuropathy (neuritis).<br>-Fast acetylators -> results in excess metabolites produced -> risk of hepatitis. | -Rifampicin strongly **induces** most cytochrome P450 isoforms (enzyme inducer)<br>-Clinically significant drug interactions: such as **warfarin**, **methadone** will be metabolized faster.<br>therefore their activity is reduced |

# 1st line treatment

| | Ethambutol | Pyrazinamide(PZA) | Streptomycin |
|---|---|---|---|
| **Overview** | Bacteriostatic | | Bactericidal |
| **Site of Action** | Intracellular & extracellular bacilli | Intracellular bacilli | Extracellular 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 is converted to **pyrazinoic acid** (The active form) which disrupts mycobacterium cell membrane metabolism & transport functions. -Mechanism of action is unknown | -**Inhibitor of protein synthesis** by binding to bacterial 30s ribosomal subunits. |
| **Clinical Use** | Treatment of TB in combination with other drugs | -mycobacterial infections in multi-drug resistance cases. -Important In short-course (6 months) regimen. -Prophylaxis of TB. | Injectable drug used in severe life threatening form of TB as meningitis, disseminated disease |
| **ADRs** | -Impaired visual acuity ( the ability of the eye to see fine detail). -Red-green color blindness . ---------- -**Contraindicated** in children under 5 years. | -Hepatotoxicity (common). -Hyperuricemia (gouty arthritis). -Drug fever and skin rash. | -Ototoxicity . (Vertigo & hearing loss) may be permanent. -Nephrotoxicity. -Neuromuscular block. |

Streptomycin is added to first line regimens because patients that have previously been treated for TB are more likely to have developed some drug resistance.

# 2nd line treatment

- 2nd line drugs are more toxic
- Used in typical & atypical tuberculosis.

## Indication of 2nd line treatment

1.There is contraindication for first line drugs.
2.Failure of clinical response.
3.Resistance to 1st line drugs.

# 2nd line treatment

| | Ethionamide | Fluoroquinolones (ciprofloxacin) | Rifabutin | Para Aminosalicylic acid (PAS) |
|---|---|---|---|---|
| **Overview** | - | - | - | Bacteriostatic |
| **MOA** | Inhibits synthesis of **mycolic acid**<br>Same MAO as INH | Effective against multi drug resistant TB | -RNA inhibitor<br>-Cross-resistance with rifampicin is complete<br>(if mycobacteria is resistant to rifampin it is also resistant to rifabutin).<br>-Enzyme inducer | -Inhibits **folic acid synthesis** thus slows bacterial cell growth & multiplication |
| **Clinical Use** | as a 2nd line agent treatment for TB<br>(po = orally) | - | -effective in Prevention & treatment of TB<br><br>-Prevention & treatment of atypical TB | -as a 2nd line agent in the Treatment of chronic pulmonary & other forms of TB<br><br>-help to slow development of resistance to other drugs especially INH and streptomycin |
| **ADRs** | -Teratogenic<br>-Poorly tolerated because of:<br>-severe gastric irritation<br>-neurological manifestations | - | -GIT intolerance<br><br>-Orange-red discoloration of body secretions | -GIT upset<br><br>-peptic ulceration & hemorrhage<br><br>-Crystalluria<br>( cloudy urine ) |

## TB &...

**Pregnancy**

-Untreated TB is a great risk for pregnant women and their fetus than the treatment.
-1st line drugs (INH ,Ethambutol, rifampin) are given for 9 months in normal doses (monitoring is important).

-Streptomycin is not used? because it can cross the placenta (fetal ototoxicity).

**Breastfeeding**

It is not a contraindication to receive drugs but caution is recommended (monitoring).

# MCQ

| 1- Which of the following is contraindicated in pregnant women? | | | |
|---|---|---|---|
| **A- Isoniazid** | **B- Rifampin** | **C-Streptomycin** | **D-Ethambutol** |

| 2- Which of the following 2nd line drugs inhibits mycolic acid? | | | |
|---|---|---|---|
| **A- Ethionamide** | **B- Streptomycin** | **C-Rifabutin** | **D-PAS** |

| 3-A 45 year-old man complained of blurred vision and inability to distinguish green objects from red objects. The man was recently diagnosed with cavitary pulmonary tuberculosis, has been receiving a drug combination regimen for two months. Which of the following drugs has most likely caused these adverse effects? | | | |
|---|---|---|---|
| **A-Rifampin** | **B-Ethambutol** | **C- Isoniazid** | **D- Streptomycin** |

| 4- Which of the following is a 1st line drug and gives the patient red-orange discoloration of body secretions? | | | |
|---|---|---|---|
| **A- Isoniazid** | **B- Streptomycin** | **C- Rifampin** | **D- Rifabutin** |

| 5- Which of the following should not be used as a 1st line choice drug? | | | |
|---|---|---|---|
| **A- Rifampin** | **B- Isoniazid** | **C- Streptomycin** | **D- Ethambutol** |

| 6- Which of the following is an enzyme inhibitor? | | | |
|---|---|---|---|
| **A- Rifampin** | **B- Streptomycin** | **C- Ethionamide** | **D- Isoniazid** |

# Answers

| 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|
| C | A | B | C | C | D |

# SAQ

Q1) **What are the indications for using 2nd line drugs as a treatment?**

Q2) **Why is streptomycin contraindicated in pregnant women?**

Q3) **Mention 3 Common sites of infections of TB.**

Q4) **Demonstrate How Isoniazid works (MOA).**

Q5) **Mention 2 ADRs of streptomycin.**

# Answers

A1)

- Failure response to 1st line drug
- there is contraindication in 1st line drugs
- there is resistance to 1st line drugs

A2) Because it can cross the placenta easily.

A3) Apical areas of lung, Renal parenchyma and Growing ends of bones.

A4) Inhibits the synthesis of mycolic acid which is an important component of mycobacterial cell wall.

A5) Ototoxicity, Nephrotoxicity and Neuromuscular block

# GOOD LUCK!

## Team Leaders

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