Drug therapy of TB

Dr. Nashwa Aborayah
Associate professor of clinical and experimental pharmacology
Mu‘tah University- Faculty of Medicine
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OBJECTIVES

- The mechanism of action of antitubercolous drugs
- Adverse effects
- Drug interactions
- Contraindication
- Multidrug therapy
- Antituberculous regimens
- Chemoprophylaxis

Introduction

- **Tuberculosis** :chronic granulomatous disease.
- **Epidemiology**: Each year, **1%** of the global population is infected
- **If the body's immune system weakens, tuberculosis can become active and cause disease.**
- **Tuberculosis typically affects the lungs. But in up to one-third of infected people, particularly those with HIV/AIDS, the illness also involves other areas of the body.**
- **Common sites of infection include the lymph nodes, meninges , the joints, the kidneys and peritoneum.**
- Kills 2 million people each year

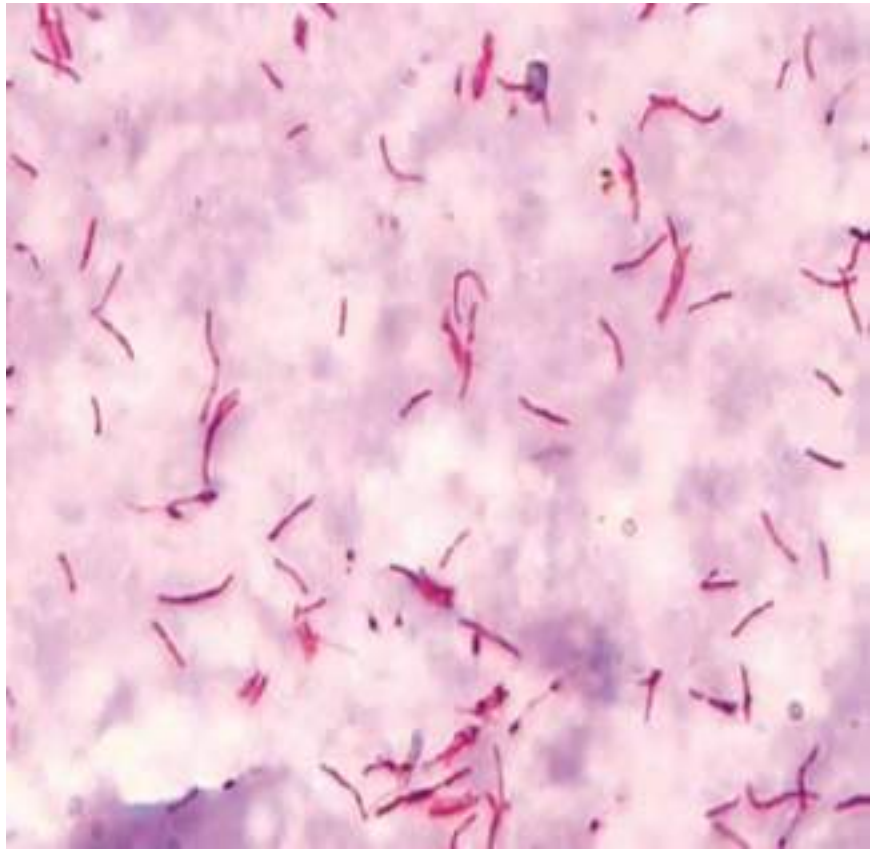
Introduction

•**Mycobacterium** from the Greek word **"mycos,"** refers to **Mycobacteria's waxy appearance**, which is due to the composition of their cell walls.
•More than 60% of the cell wall is lipid, mainly **mycolic acids.**
•**Barriers to therapy:**
•1- This **extraordinary shield** prevents many pharmacological compounds from getting to the bacterial cell membrane or inside the cytoplasm.

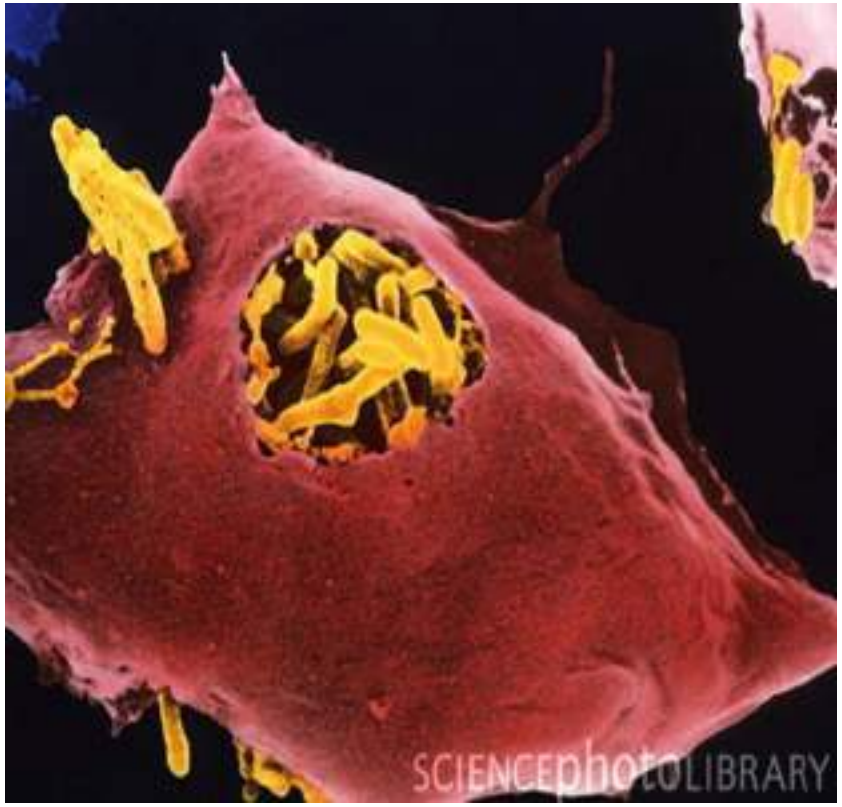
•2- Bacilli are surrounding themselves with an extra physicochemical barrier that antimicrobial agents must cross to be effective: **inside macrophages:**
•**Mycobacteria survive inside macrophages by avoiding the usual pathway where bacteria are destroyed: altering lysosomal function**

Waxy appearance of Mycobacteria

Mycobacteria



Acid fast bacilli (AFB)



Dormant forms in macrophages

Classification of antituberculous drugs

First line

- These drugs have high antituberculous efficacy and low toxicity
- Rifampicin (R)
- Ethambutol (E)
- Pyrazinamide (Z)
- Streptomycin (S)
- INH: isoniazid (H)

Second line

- Aminoglycosides
- Quinolones
- Cycloserine
- Rifabutin & rifapentine
- PAS
- These drugs low anti TB efficacy, but relatively high toxicity.

1ST Line drugs

- **Route of administration**: oral:R#food INH#AL-antacid
- **Metabolism**: liver: R: Mainly liver, enterohepatic: bile: stools
- **Excretion**: kidney: INH:# renal impairment
- **All are bactericidal except: ethambutol, (INH?)**
- **All acting on mycobacterium cell wall except: rifampicin (genome)**
- **Streptomycin: protein synthesis inhibitor**
- **Extra & intracellular: HER**
- **Extracellular: S**
- **Intracellular: Z**

RIFAMPICIN (R)

- **Spectrum:**
- **Antibacterial**: broad spectrum: wide range of gram positive and gram negative bacteria: Staph, Strept., N. meningitides, H. influenza, Legionella, Clostridium difficile (anaerobic).
- **Anti mycobacterial: Mycobacteria tuberculosis and mycobacteria leprae**
- **Antiviral:** poxvirus (small pox): inhibiting virus protein synthesis
- **Bactericidal**
- **Extra & intracellular bacteria**

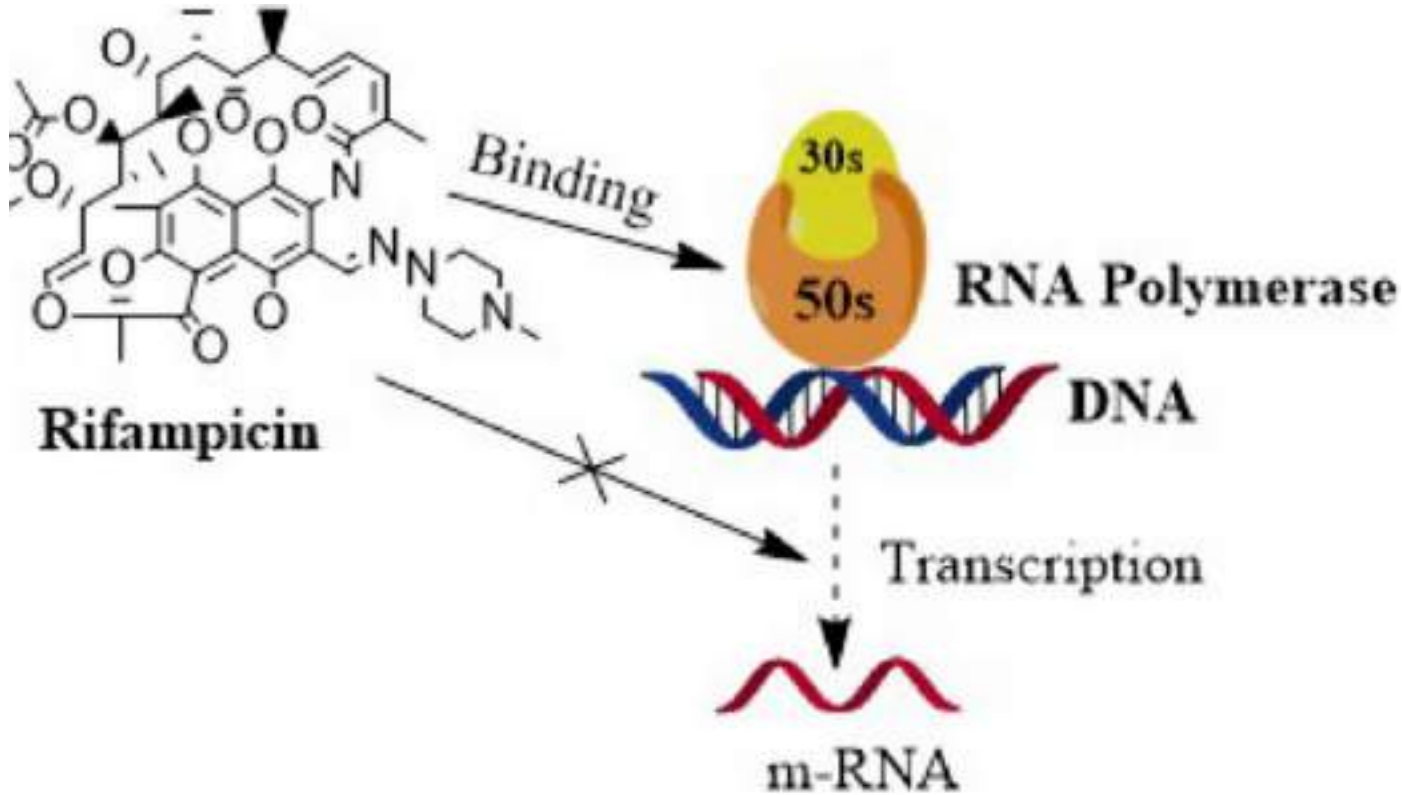
PDs of rifampicin

Mechanism of action:

Rifampicin inhibits synthesis of bacterial R.N.A.: by binding mycobacterial **DNA dependent RNA polymerase** & blocks its polymerizing function.

N.B. Rifampicin does not bind mammalian RNA polymerase (Basis for selectivity).

Antiviral action: Inhibit the replication of poxvirus by blocking the synthesis of virus protein: **by inhibiting viral reverse transcriptase**


Binding
30s
50s
RNA Polymerase
DNA
Rifampicin
Transcription
m-RNA

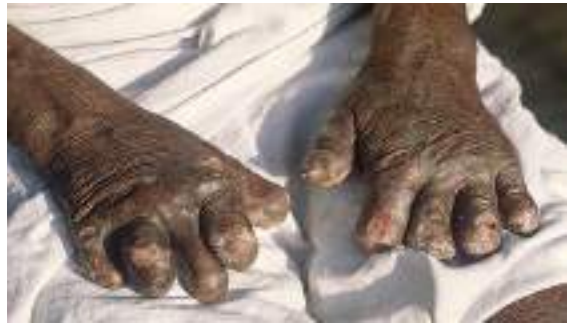
Pks of rifampicin

- **Absorption** Well absorbed orally.
- Food also interferes with absorption: **on empty stomach**
- **Distribution** widely distributed in all body fluids.
- **Penetration intracellularly & enters • tubercular cavities • Caseous masses • placenta**
- **Metabolism**: in liver to an **active** de-acetylated metabolite.
- Rifampicin is a **potent enzyme inducer of the cytochrome P450 oxidase system**, its administration is associated with numerous drug interactions.
- Rifampicin also has an inducer effect on its own hepatic metabolism. Therefore, repeated administration of rifampicin increases its oral clearance (after 2 weeks).
- **Excretion:** mainly in bile some in urine also.
- (30-70%) of the drug and its metabolite undergoes enterohepatic circulation (hepatic metabolism)
- **Metabolites are orange red in color: (red sweat & urine): staining of clothes**

Indications

TBLB

•1- **TB**: prophylaxis and treatment
•2- **Leprosy**
•3- **Osteomyelitis**, **meningitis** and **bacterial endocarditis**



•**Adverse effects:**
•1- **Hepatitis** is a major side effect: due to its metabolites
•2- Interstitial nephritis, acute tubular necrosis
•3- Hemolytic anemia 4- Flue- like symptoms
•5- **Enzyme-inducer** (many drug interactions): Thus enhances its own metabolism as well as of other drugs including:
Warfarin (**oral anticoagulants)** , Corticosteroids, **Contraceptive pills**, Digoxin **(adjust the dose)**

ISONIAZID[INH]: (H)

- Cheapest, the keystone of TB treatment
- **Mycobactericidal**
- **Bactericidal** for rapidly growing bacilli, **non-growing bacilli are only inhibited (static)**
- Extra and intracellular bacilli
- **Mechanism of action**: inhibition of mycobacterial catalase peroxidae ⟶ Inhibition of mycolic acid synthesis

Pks of INH

•**Absorption**: completely absorbed orally

• Aluminum-containing antacids inhibits its absorption

•**Distribution:**

Penetrate all body tissue, tubercular cavities, placenta & meninges **(like R)**

•**Metabolism**: **in liver** by **acetylation (INH acetyltransferase)**

•Side effects are common in **slow acelylators**

•**Excretion**: in urine (decreasing the dose in renal impairment)

INH adverse effects

- **1- Peripheral neuropathy**: neurological manifestations
- **Paresthesia, numbness**: most important dose-dependent toxic effects due to pyridoxine deficiency (vitamin B6)
- **Pyridoxine** given prophylactically (10mg/day) prevents neurotoxicity
- **INH neurotoxicity** is treated by pyridoxine 100mg/day
- **2- Hepatotoxicity** **3- CNS toxicity**: seizures, optic neuritis, memory disturbances and stupor
- **4- Hemolysis** in glucose 6PD deficiency
- **5- SLE- like symptoms**

ETHAMBUTOL (E)

❖**The Only Tuberculostatic** drug among 1st line drugs.

❖**Importance**: Added to TB regimens **to hasten the rate of sputum conversion** and **prevents the development of resistance.**

❖**Acts both extracellular and intracellular**

❖**Mechanism of action**: **inhibits mycolic acid synthesis**

•**Adverse effects:**

•**1- Optic neuritis**: Loss of visual acuity (**reversible**) , loss of color vision (inability to discriminate between red and green)

•Dose & duration-dependent toxicity.

•Pt should be instructed to stop the drug at first indication of visual impairment.

•**Visual toxicity: reversible**

• **2- Hyperuricemia: cause or worsen attacks of gout: competes with uric acid for excretion**

•**Contraindications:**

•1- Children <6yrs 2- Creatinine clearance <50ml/min 3- Hyperuricemia

Streptomycin (S)

- **Bactericidal**
- **Mechanism of action**: **Inhibitors of protein synthesis by binding to 30 S ribosomal subunits.**
- Active mainly **on extracellular bacilli**
- **The only antibiotic among the first line drugs**
- **Uses**: Severe , life-threating forms of T.B. as meningitis, disseminated disease.
- **Adult dose**: 15 mg/Kg/day
- **Child dose**: 20 mg /Kg/ day
- **NOT** exceeding 2 gm/ day in both
- **Adverse effects:**
- Ototoxicity
- Nephrotoxicity
- Neuromuscular block

PYRAZINAMIDE (Z)

✓**Tuberculocidal**

✓**More lethal to intracellular bacteria**

✓**Highly effective during 1st 2 months**

✓**Importance**: By killing the residual intracellular bacteria it has good sterilizing activity

✓Distributed in all body fluids

✓**Mechanism of action**: Inhibits mycolic acid synthesis

✓**Adverse effects:**

✓1- Hepatotoxicity (dose dependent)

✓2- Hyperuricemia; inhibits excretion of urates

2nd line drugs

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

2nd line drugs: aminoglycosides, quinolones & cycloserine

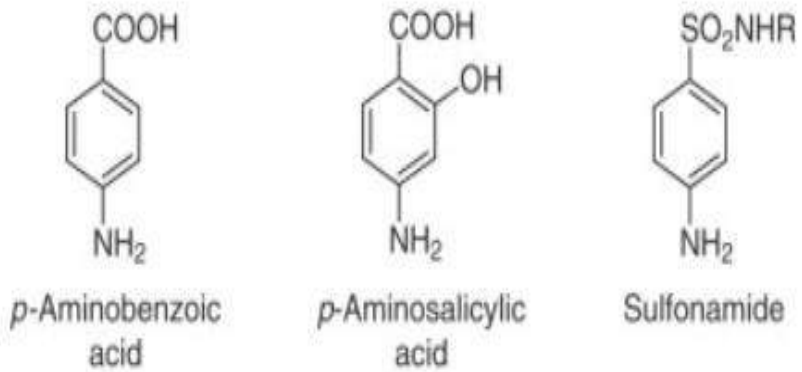
- **Aminoglycosides:** amikacin, kanamycin: **bactericidal**
- Affect both typical and atypical mycobacteria
- **Quinolones**: **bactericidal**: Ciprofloxacin, Ofloxacin and Sparfloxacin
- Combined with 2 or more antituberculous drugs in resistant cases
- **Cycloserine**: Broad spectrum antibiotic (**static**)
- Reaches the CSF well
- Causes CNS side effects

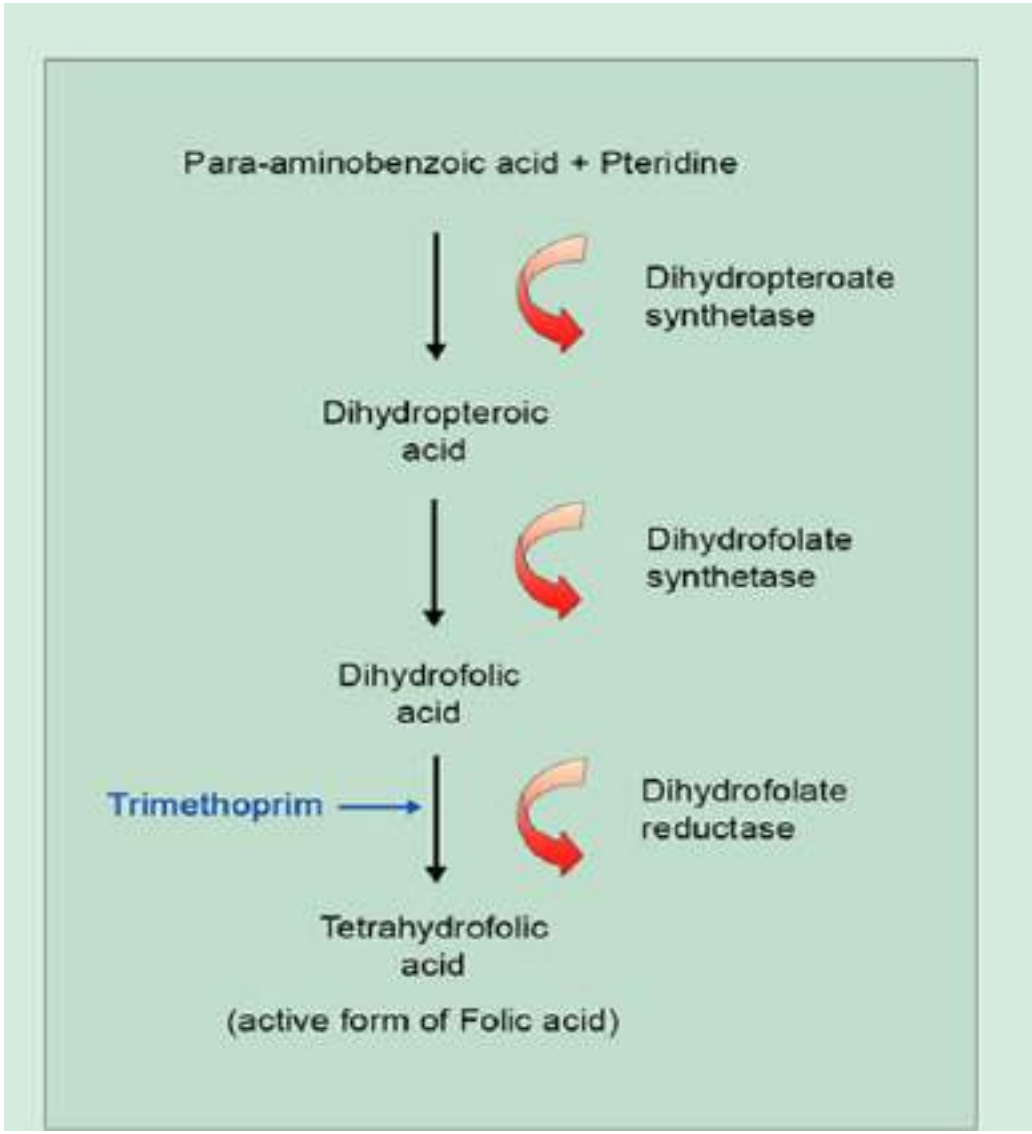
Rifabutin & rifapentine

- **Rifabutin**: **similar to rifampicin in spectrum and action**.
- Has cross tolerance with rifampicin
- **PKs:** absorbed orally and excreted in bile and urine (orange yellow metabolites)
- **Less enzyme inducer** with less drug interactions
- **Rifapentine**: **similar to rifampicin in spectrum, action and toxicity**
- Slower and prolonged action than rifampicin
- **Contraindicated in** HIV patients because its **enzyme-inducing activity destroys antiviral drugs**

Para-aminosalicylic acid (PAS)

- **Least active drugs, only delay the development of resistance.**
- It is **tuberculostatic drug** active **only on TB bacilli** and not on other bacteria.
- **Mechanism of Action** : Competitively **inhibits an enzyme dihydrofolate reductase** as they are structural analogues or antagonists of Para-aminobenzoic acid (PABA), leading to inhibition of synthesis of folic acid.
- **Selectivity for mycobacterial dihydrofolate reductase**
- Not used nowadays due to high doses needed and its side effects


COOH
NH2
p-Aminobenzoic acid
COOH
OH
NH2
p-Aminosalicylic acid
SO2NHR
NH2
Sulfonamide


Para-aminobenzoic acid + Pteridine
Dihydropteroate synthetase
Dihydropteroic acid
Dihydrofolate synthetase
Dihydrofolic acid
Trimethoprim
Dihydrofolate reductase
Tetrahydrofolic acid
(active form of Folic acid)

Why multidrug therapy?

•Use of single drug in tuberculosis results in the emergence of resistant organisms and relapse in almost 75% of patients.

•**Combination:**

•**H & R most potent bactericidal**

1- Combination synergistic

2- Duration of therapy shortened from more than12 months to 9 months

Treatment categories:

1- **Category 1:** new cases

2- **Category 2**: **Previously treated patient**: Did not complete the course, took irregular doses, relapsed after responding or failed to respond

Phases of treatment:

1- **Intensive phase**: **4 drugs for 2 months**: rapidly kills the organism, sputum conversion and symptomatic relief

2- **Continuation phase**: **2 drugs for 4 months**: eliminate remaining bacilli so, no relapse

Ideal TB regimen

- **An ideal TB regimen should be:**
- 1- Of short duration of therapy
- 2- Low drug doses
- 3- Less drug toxicity
- 4- Cost-effective therapy
- 5- Able to target latent and resistant forms of M. tuberculosis

TB regimens

- **2 drugs for at least 6 months in mild cases**
- **Regimen 1**: 4 drugs for 2 months then 2 drugs for 4 months:
- HERZ 2 months, then HR 4 months
- **Regimen 2**: HR 9 months
- **Regimen 3**: HRZ(E or S): miliary TB and HIV till 3 sputum cultures are negative
- **Regimen 4:** safe in pregnancy: HER
- **4 Drug regimen indicated in**: resistance, military TB, extensive pulmonary TB and extrapulmonary TB

Causes of treatment failure

- 1- Irregular or inadequate treatment (poor patient compliance)
- 2- Single drug therapy
- 3- Primary resistance of microorganism
- 4- Drug toxicity or hypersensitivity

- **Indications of chemoprophylaxis**:
- Households, contacts, tuberculin positive persons (> 5mm induration)
- INH: 300mg daily X 6 months Children : 10 mg /Kg
- If INH cannot be used : R X 4 months

References

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Thank you