Drug therapy of TB

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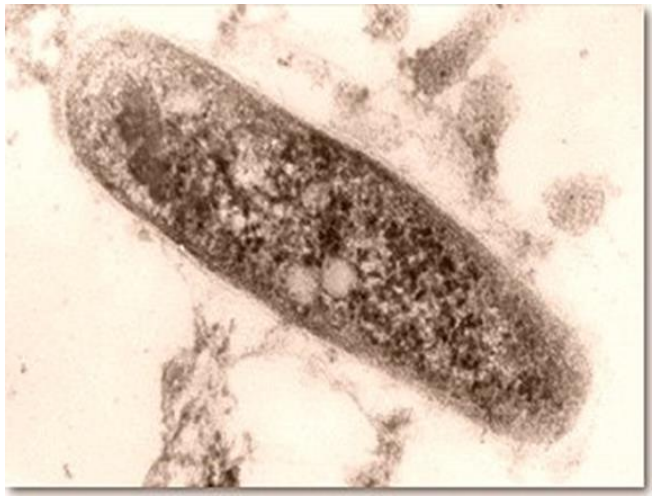
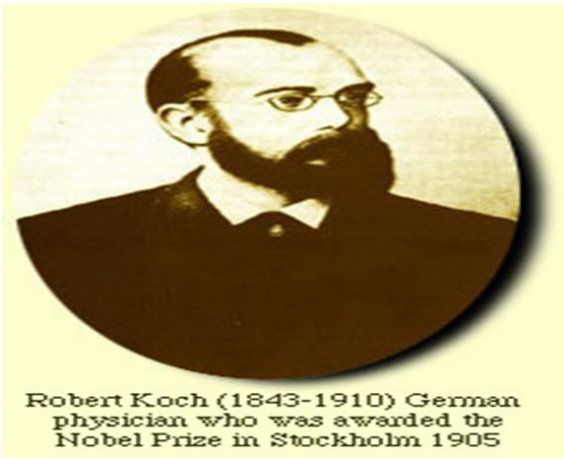
OBJECTIVES

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

Introduction

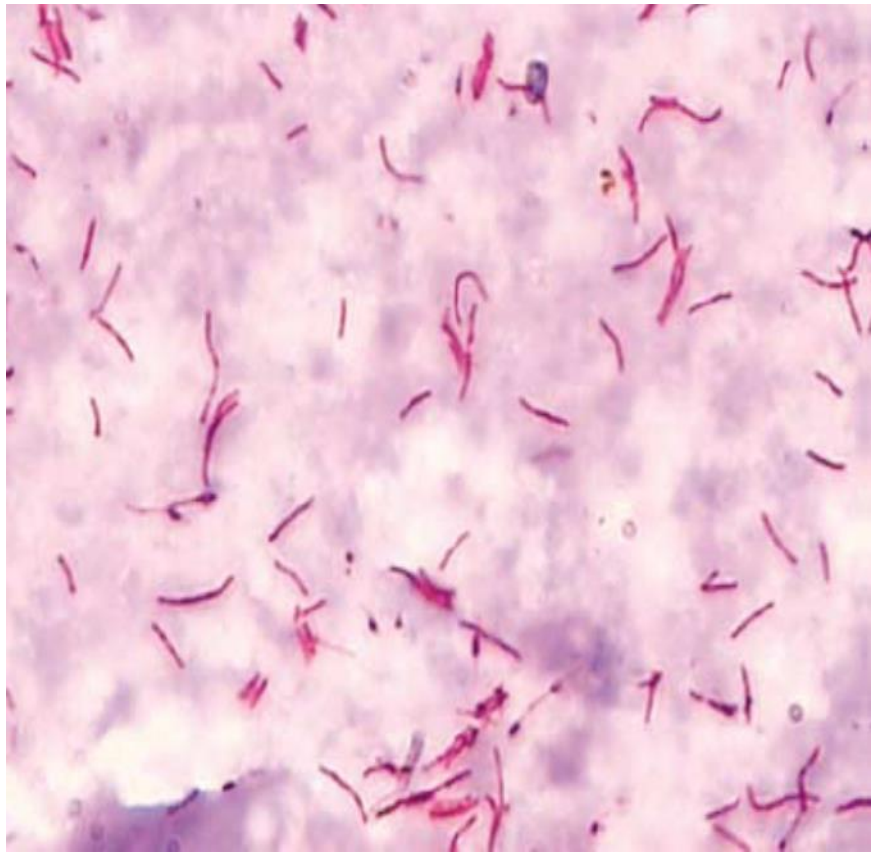
- Tuberculosis :chronic granulomatous disease.
- **Each year, 1% of the global population is infected**
- Kill 2 million people each year
- Increase incidence due to HIV associated Mycobateria
- Mycobacterium tuberculosis, slowly growing, an acid fast aerobic bacillus
- Robert Koch was the first to see *Mycobacterium tuberculosis* with his staining technique in 1882.



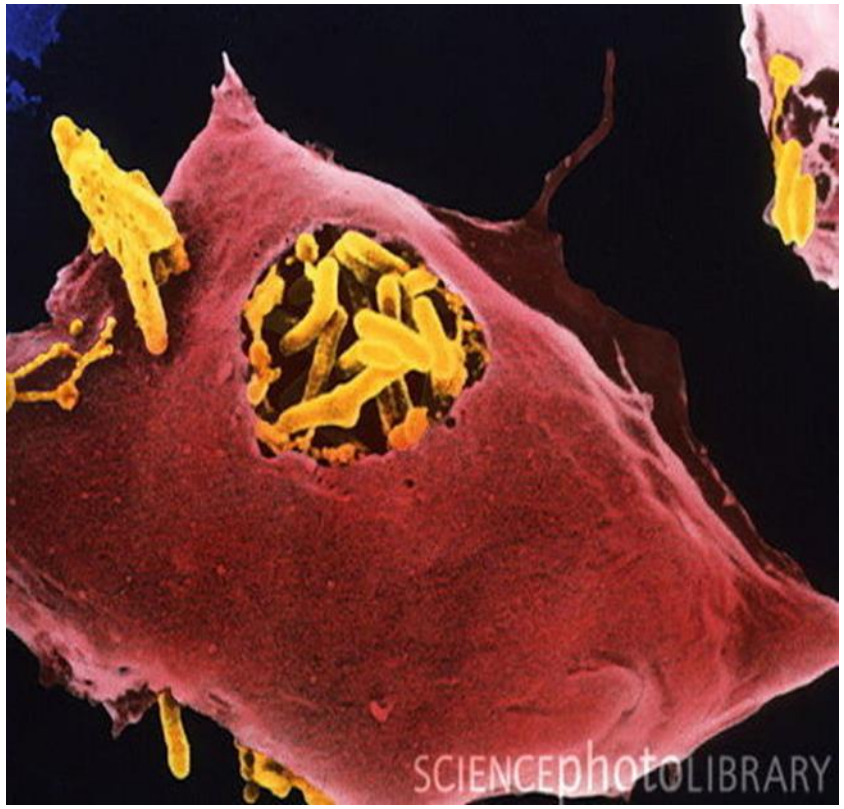


Robert Koch (1843-1910) German physician who was awarded the Nobel Prize in Stockholm 1905

Mycobacteria



- **Acid fast bacilli**



Dormant forms in macrophages

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.
•This extraordinary shield prevents many pharmacological compounds from getting to the bacterial cell membrane or inside the cytoplasm.

•Another barrier is the property of some of the bacilli to hide inside the patient's cells, thereby surrounding themselves with an extra physicochemical barrier that antimicrobial agents must cross to be effective.

Waxy appearance of Mycobacteria

Transmission & common sites

- **Pulmonary TB**: droplet infection
- Patients with the active disease (bacilli) expel them into the air by:
- **coughing**
- **Sneezing**
- **Extrapulmonary:**
- **Cows (bovine):** consumption of raw milk or milk products contain bacilli or droplet infection from infected animal (long exposure) **and birds (avian)**
- **Much less common**

Common sites of infections

- **Apical areas of lung**
- **Renal parenchyma**
- **Growing ends of bones**
- **Liver**
- **Brain**

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

RIFAMPICIN (R)

- **Spectrum:**
- **Antibacterial**: broad spectrum: wide range of gram positive and gram negative bacteria: Staph, N. meningitides, H. influenza, E.coli, Kleibseilla, Psuedomonas, Proteus, Legionella
- **Mycobacteria tuberculosis and mycobacteria leprae**
- **Antiviral:** poxvirus (small pox): inhibiting virus protein synthesis
- **Bactericidal: Bactericidal efficacy**
- **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

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 Chiefly in liver to an active deacetylated metabolite.

•Which is excreted mainly in bile some in urine also.

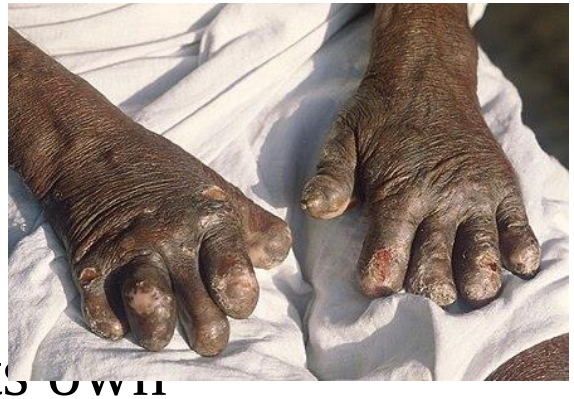
•(30-70%) of the drug and its metabolite undergoes enterohepatic circulation

•Metabolites are orange red in colour

➢**$T_{1/2}$ varies from 2-5 hrs**

Indications

•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

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
- Equally active in acidic & alkaline medium.
- 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

•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

• Paresthesias, 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)

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

❖Added to TB regimens to hasten the rate of sputum conversion and prevents the development of resistance. Primarily added for this reason.

❖Acts both extracellular and intracellular

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

•**Side 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

•**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
- **Side effects**:
- Ototoxicity
- Nephrotoxicity
- Neuromuscular block

PYRAZINAMIDE (Z)

- ✓**Tuberculocidal**
- ✓**More lethal to intracellular bacteria**
- ✓Highly effective during 1st 2 months
- ✓By killing the residual intracellular bacteria it has good sterilizing activity
- ✓Distributed in all body fluids
- ✓**Mechanism of action**: Inhibits mycolic acid synthesis
- ✓**Side effects**:
- ✓1- Hepatotoxicity (dose dependent)
- ✓2- Hyperuricemia; inhibits excretion of urates
- ✓3- Arthralgia, nausea, vomiting

2nd line treatment

- **Indications:**
- Resistance to the drugs of 1st line.
- Failure of clinical response
- There is contraindication for first line drugs.
- **Used in typical & atypical tuberculosis**
- **Most 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

Paraaminosalicylic 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

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

Combination synergistic

Duration of therapy shortened from >12 months to 9 months

Treatment categories:

1- **Category 1:** new cases

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

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

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:
- HRZE 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: HRE
- **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

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Thank you