Antitubercular Agents

Tuberculosis often called TB, is chronic bacterial infection caused by Mycobacterium Tuberculosis. It is a chronic disease

The bacteria contain unusual cell wall which contain high lipid contents so highly hydrophobic in nature & resistant to alcohol, Acids, Alkalies.

The bacteria mainly infects lungs and almost other tissues ~~also~~ also such as brain, circulatory system, genitourinary system bones by formation of nodular bodies or tubercules thats why the ~~disease~~ disease called ~~tuberculosis~~.

The person affected with TB, when sneeze & cough the droplet in air can infects other healthy person.

The other strain of TB bacteria is M. bovis mainly found in cattles. (cow, buffalos, etc)

Mode of transmission: Inhalation, Ingestion, Innoculation & Transplacental

Classification - Based on treatment / Clinical

Antitubercular Drug

I st line drugs

High activity
Low toxicity
routinely used

- Isoniazid
- Rifampin
- Pyrazinamide
- Ethambutol

these 4 drugs are essential drug for TB

[Streptomycin (Antibiotic) ~~Essential~~ supplimentary drug for TB]

II nd Line drugs

Low efficacy
High Toxicity

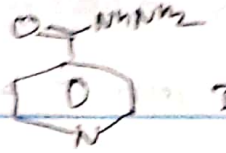
- Paraaminosalicylic Acid
- Cycloserin
- Kanamycin
- Amikacin
- Ciprofloxacin
- Ofloxacin
- Clarithromycin
- Azithromycin
- Capriomycin
- Ethionamide

antibiotics

Third line drug in special Clinical situation : such as resistant to any candidate of first or second line drugs.

ex Amoxicillin / Clavulanate, Meropenem, imipenam
Linezolide

~~300 mg OD~~ 300 mg OD



5 mg/kg/d – OD – 6 months

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Isoniazid: Isonicotinic acid hydrazide

Most active drug
Freely water soluble

Act against actively growing tubercle bacilli

Penetrate in to macrophages & active against both intracellular & extracellular organism

MoA → inhibit synthesis of Mycolic acid which is essential component of mycobacterium cell wall.

→ It is prodrug – activated by Catalase-peroxidase

⇒ Mutation causes inhibition of this enzyme — Drug Resistance

Always given in Combination

10mg/kg/d – OD for 6 months Category - Aminoglycosides

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Also called Rifampicin

⇒ **Rifampin** : Semi synthetic derivative of rifamycin

produced by Streptomyces mediterranei

active against G⊕ & G⊖

Must be used in combination

MOA :- bind ~~Inhibit~~ DNA dependent RNA polymerase (Bind to β subunit of DNA/RNA channel away from active site)

↓

inhibit RNA synthesis (mRNA, tRNA, rRNA)

↓

No protein → No bacterial growth

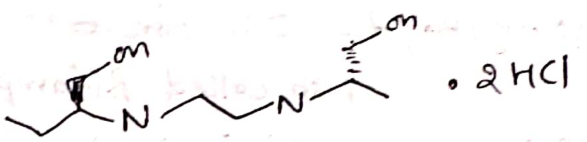
Resistance → Mutation reduce binding to DNA depend RNA Polym

Uses → TB
Leprosy
Meningococcal infection
H. influenza type B

Rifabutin :- Category - Aminoglycosides

MOA :- Also Inhibit DNA dependent RNA polymerase (bacterial enzyme)

15-25 mg/kg/d — OD



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Ethambutol :-

- water soluble, heat stable

Given in combination with Isoniazid, Rifampin & pyrazinamide

MOA : Inhibit mycobacterial **Arabinosyl transferase enzyme**

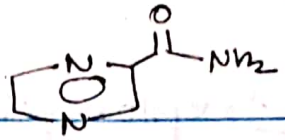
↓

essential component of cell wall

Resistance : → due to mutation in gene for enzyme

→ Due to monotherapy, so always use in combination

40 - 50 mg/kg/ - Thrice weekly → 6 month

Pyrazinamide:-  Stable & Slightly Soluble in H_2O

Inactive at 7 pH

active at ph 5.5

Taken by macrophages & exert activity

→ Highly effective at 2 month of therapy

MoA:- pyrazinamide (converted to) → pyrazinoic Acid (active) ↓ By Mycobacterial pyrazinamidase enzyme

Resistance:- ↓ uptake of drug

mutation of enzyme

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Streptomycin

Aminoglycoside antibiotics

Act only on extracellular bacilli,
poor penetration in cell

MOA:- Irreversible inhibitor of protein synthesis
bind on bacterial 30S subunit of ribosome
loss of bacterial protein required for growth

IV - ~~30-60~~ 20-40 mg/kg/d for several weeks

IInd line

PAS :=D (Para amino salicylic Acid)

Given with Isoniazid

↓ hepatic acylation of Isoniazid

So ↑ Isoniazid level also

→ Also inhibit synthesis of DNA precurser required for bacterial nucleic acid formation

Limited to MDR tuberculosis

Structural Analog of PABA → Interfere insertion of PABA into folic Acid → Inhibit folic Acid synthesis in bacteria

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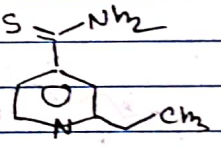
Ethionamide :



15 mg/Kg/d

MoA : Related to ~~Eto~~ Isoniazid —

Block Mycolic Acid synthesis (Cell wall synthesis)

Capriomycin :- used when resistance to Streptomycin & ~~Rifampicin~~ Amikacin

Chemical Class :- Cyclic peptides

Used in injection (15mg/Kg/day) IM

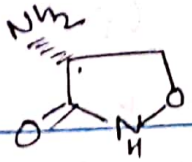
inhibit protein synthesis

Obtained from S. capreolus

active against drug resistant TB

It is nephrotoxic & ototoxic

Cycloserin:

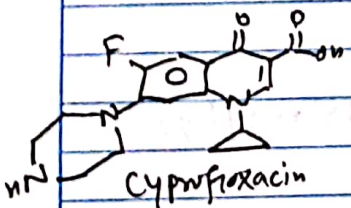


0.5-1 gm/d two divided dose

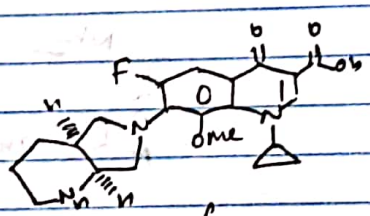
inhibit cell wall synthesis of M. Tuberculosis

Fluoroquinolones:

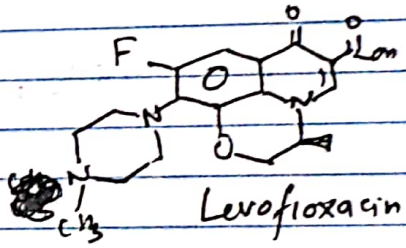
Ciprofloxacin, Moxifloxacin, Levofloxacin



Ciprofloxacin



Moxifloxacin



Levofloxacin

Mode of Action: Inhibit bacterial DNA gyrase (Topoisomerase-II) enzyme, They also inhibit Topoisomerase-IV enzyme. So In place of complete complete DNA formation, there are formation of DNA fragments. & also stop genetic material Segregation in to new bacterial daughter cell.

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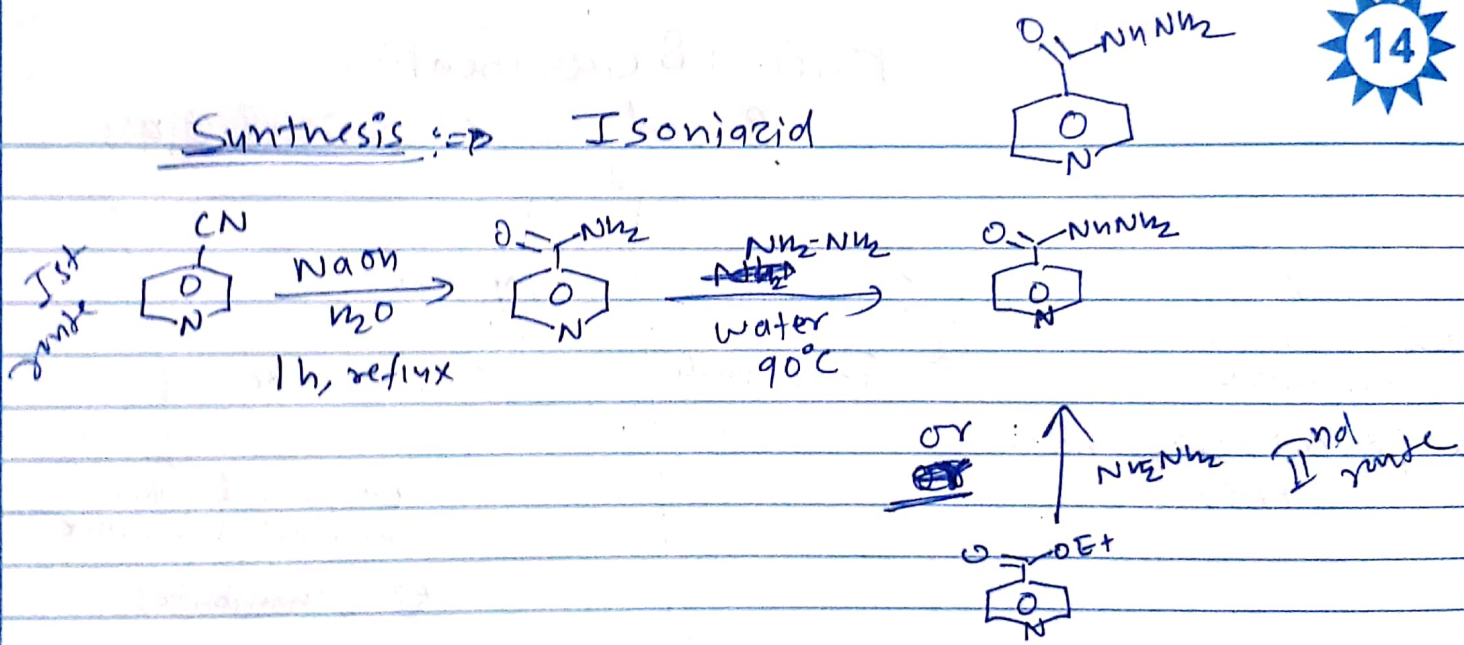
Anti-TB Classification Based on Chemical Class

- Salicylic Acid Derivative
  - ex Para Amino Salicylic Acid (PAS)
- Pyridine derivatives
  - ex Isoniazid, Ethionamide
- Pyrazine derivative
  - ex Pyrazinamide
- Ethylene diamino butanol derivative
  - ex Ethambutol
- Fluoroquinolones
  - ex → Ciprofloxacin
  - → Moxifloxacin
- Antibiotics
  - ex Streptomycin, Cycloserin, Rifampin (Rifampicin), Kanamycin, Amikacin, Capreomycin, Rifabutin

Synthesis :- Isoniazid



Synthesis : Para Amino Salicylic Acid