**FIRST LINE DRUGS**

* **Isoniazide: INH: H: 5 mg/kg**
* **Rifampicin: RMP: R: 10 mg/kg**
* **Ethambutol: EMB: E: 15-25 mg/kg**
* **Pyrazinamide: PZA: Z: 25-35 mg/kg**
* **Streptomycin: SM: S: 15-20 mg/kg**

**Remember “ IRESP ”**

**CAT 1 :**

1) New smear positive pulmonary TB

2) New smear negative pulmonary TB with extensive parenchymal involvement.

3) New cases of severe forms of extrapulmonary TB.

2(HRZE)3 + 4(HR)3 : 6months duration

* **CAT 2:**

1. Smear positive failure
2. Relapse
3. Default

2(HRZES)3 + 1(HRZE)3 + 5(HRE)3 : 8 months

**Treatment failure** : A patient whose sputum smear or culture is positive at 5 months or later during treatment.

**Realpse** : A patient declared cured from any form of TB in the past after receiving one full course of chemotherapy and now has become sputum positive or clinically active TB.

**Default** : A patient whose treatment was interrupted for 2 consecutive months or more.

**A REGIMEN**

* Specific combination of drugs prescribed in specific doses, specific rhythm and for a specific time duration is defined as a regimen.

**PECULARITIES OF AN ANTI-TB REGIMEN**

* More than one drugs are used. Always a combination chemotherapy
* Both bactericidal and bacteriostatic drugs are used together
* There is a an intensive and a continuation phase
* The drugs are given on daily or alternate basis regardless of the half life of the drug
* The treatment is prolonged.

**COMBINATION CHEMOTHERAPY**

* Monotherapy shown to cause failure
* Natural resistant mutants in a bacterial population:  
  1 per 1 lakh: resistant to SM  
  1 per 10 lakhs: resistant to INH etc
* Addition of bacteriostatic drugs prevents occurrence of drug resistant mutants

**PROLONGED THERAPY**

* Subgroups of bacteria are:   
  Rapid multipliers  
  Intracellular dormants (Intermittent growers)  
  Extracellular dormants (Intermittent growers)  
  Persisters (Occasional growers)
* Bacterial population reduces to less than 5% within 2 months.
* Bactericidal drugs act only when the bacteria is actively multiplying

**STEPS IN STARTING TREATMENT**

1. Confirm the diagnosis
2. Disclose the diagnosis to the patient
3. Do thorough counseling of patient and relatives
4. Categorize the patient
5. Start proven regimen in correct dosages and rhythm and give for recommended duration
6. Avoid un-necessary co-prescriptions
7. Monitor closely

**ISONIAZID (INH).**

* Isonicotinic acid hydrazide – INH
* Tuberculocidal drug.
* Fast multiplying organisms are rapidly killed, but quiescent ones are only inhibited.
* It acts on extracellular & intracellular TB
* Equally active on acidic and alkaline medium.
* Most atypical mycobacteria are not inhibited by INH
* **MOA** -: inhibition of synthesis of mycolic acids which are unique components of mycobacterial cell wall.
* **Highly selective** – not active against other microorganism.
* INH is completely absorbed orally and penetrates all body tissues tubercular cavities,placenta,meninges.
* Metabolized in liver.
* T ½ 1hr(fast acetylators) 3hr slow acetylators.
* **Ineteractions:** aluminium hydroxide inhibits INH absorption.
* INH inhibits phenytoin,carbamazepine,diazepam and warfarin metabolism : may raise their levels.
* **Dose** - : 5mg/kg/day,maximum 300mg. 10mg/kg three times weekly,maximum 900mg
* **Side effects: Peripheral neuritis**, other neurological manifestations like parasthesias , numbness, mental disturbances, rarely convulsions.
* Due to interference with utilization of pyridoxine and its increased excretion in urine.
* Pyridoxine (10mg/day) given prophylactically with higher doses of ATT.
* Not recommended routinely.
* INH neurotoxicity is treated by pyridoxine 100mg/day.
* **Hepatitis,Fever,rashes,acne,arthralgia,lupus like syndrome.**

**RIFAMPICIN (R)**

* Semisynthetive derivative of rifamycin B obtained from streptomyces mediterranei.
* Bactericidal to M.tuberculosis and many other gram positive and gram negative bacteria.
* Acts best on slowly or intermittently dividing ones and on many atypical mycobacteria.
* Extra and intracellular organisms affected.
* Rifampicin inhibits DNA dependent RNA synthesis.
* Resistance is due to mutation in repo B gene.
* Well absorbed orally and widely distributed in the body,penetrates cavities,caseous masses,placenta and meninges.
* Metabolized in liver and excreated mainly in bile and in urine also.
* **Interactions**: microsomal enzyme inducer – increases several CYP450 isoenzymes.
* Enhances its own metabolism as well as many other drugs including warfarin,OCP,corticosteroids,digitoxin,sulphonyl ureas,NNRTIs,metoprolol,ketoconazole.
* Contraceptive failures have occurred.
* **Adverse effects:**

1. Hepatitis
2. Respiratory syndrome : breathlesness which may be associated with shock and collapse.
3. Cutaneous syndrome : flushing,pruritis,rash (especially on face and scalp),redness and watering of eyes.
4. Flu like syndrome : with chills,fever,headache,malaise,bone pain.
5. Abdominal syndrome : nausea,vomitting,abdominal cramps with or without diarrhoea.
6. Urine and secretions may become orange red – this is harmless.

* **Dose** -: 10mg/kg/day or, 3 times weekly,maximum 600mg.
* **Other uses :**

1. Leprosy
2. Prophylaxis of meningococcal and H influenzae meningitis and carrier state.
3. Second/third choice drug for MRSA,diphtheroids and legionella infections.
4. Combination of doxycycline and rifampicin is 1st line therapy for brucellosis.

**PYRAZINAMIDE (Z)**

* Weakly tuberculocidal more active in acidic medium.
* More lethal to intracellularly located bacilli and those at sites showing inflammatory response.
* Highly active during 1st 2 months of therapy.
* **MOA**-: similar to INH,it inhibits mycolic acid synthesis.
* Absorbed orally, has good penetration to CSF
* Metabolized in liver and excreted in urine.
* Plasma t ½ 6-10hrs.
* **Dose** : Adults 25mg/kg(20-30mg/kg) daily.
* 35mg/kg(30-40mg/kg) 3 times weekly.

**Adverse effects:**

1. Hepatotoxicity.
2. Hyperuricemia – due to inhibition of uric acid secretion in kidney (gout)
3. Arthralgia,flushing,rash, fever and loss of diabetes control

**ETHAMBUTOL**

* Selectively **tuberculostatic.**
* Clinically active against fast multiplying bacilli.
* More susceptibile are many atypical mycobacteria.
* **MOA -**: is not fully understood,found to inhibit arabinosyl transferases involved in arabinogalactan synthesis and to interfere with mycolic acid incorporation in mycobacterial cell wall.
* About 3/4th of an oral dose of E is absorbed.widely distributed but penetrates meninges incompletly and temporarily stored in RBCs.
* Excreated in urine.
* **Dose** : 15mg/kg(15-20mg/kg)daily.
* 30mg/kg(25-35mg/kg)3 times daily.
* **Side effects** :Patient acceptability of E is very good and side effects are few.
* Loss of visual acuity/colour vision, field defects due to **optic neuritis** is most important dose and duration of therapy dependant toxicity.
* **Nausea,rashes,fever.**
* **Hyperuricemia** due to interference with urate excretion.
* **STREPTOMYCIN**
* Tuberculocidal drug,but less effective than INH or rifampicin.
* Acts only on extracellular bacilli(because of poor penetration into cells)
* It penetrates tubercular cavities,but does not cross CSF and has got poor action in acidic medium.
* **Dose** :- 15mg/kg(12-18mg/kg)daily or 3 times weekly maximum daily dose is 1000mg
* **Side effects**: ototoxicity,nephrotoxicity. Should not be used in pregnancy,causes auditory nerve impairment and nephrotoxicity in fetus.

**MDR TB** :- Multi drug resistant tuberculosis is defined as a strain of tuberculosis with a documented resistance in vitro to at least isoniazid and rifampin.

* **XDR TB** :- Extensively drug resistant tuberculosis has been defined a strain of tuberculosis with a documented resistance in vitro to all first line antituberculous agents as well as an injectable agent and a fluroquinolone.

**New WHO Classification**

* Group 1:Isoniazid,Rifampicin,Ethambutol,Pyrizinamide
* Group2:Injectables i.eStreptomycin,Kanamycin, Amikacin 15mg/kg
* Group 3 : Quinolones like Levofloxacin, Moxifloxacin 10-15mg/kg
* Group 4 : Other bacteriostatic second line drugs like
  + Ethionamide,Prothionamide 15-20mg/kg,Cycloserine 15-20mg/kg,PAS 150mg/kg
* Group 5 : Agents with unclear role like Linezolide,Amox-

Clav,Imp-cilastin High dose INH

* Use minimum of 4 drugs and maximum of 7 drugs in treatment of MDR TB.
* Use any one group 1 drug,one effective amynoglycoside,use one fluroquinolone and remaining group 4 drugs.
* Intensive phase : The recommended duration of treatment is guided by smear and culture conversion.The minimal recommendation is that the injectable agent should be continued for atleast 6 months and at least 4 months after the patient first becomes and remains sputum smear negative or culture negative.
* The minimum recommendation is that treatment should last for atleast 18 months after culture conversion.
* Treatment can be extended to 24 months in chronic cases.