ANTITUBERCULAR DRUGS

Tuberculosis is a chronic granulomatous disease and a major health problem in developing countries. A new dimension got added in the 1980s due spread of HIV with high prevalence of tuberculosis and Mycobact. avium complex (MAC) infection among these patients. India has a large Load of HIV infected subjects, and these patients are especially vulnerable to severe forms of tubercular /MAC infection

According to their clinical utility the anti-TB drugs can be divided into:

First line: These drugs have high antitubercular efficacy as well as low toxicity; are used routinely.

Second line: These drugs have either low antitubercular efficacy or high toxicity or both; are used in special circumstances only.

First line drugs

1. Isoniazid (H) 4. Ethambutol (E)
2. Rifampin (R) 5. Streptomycin (S)
3. Pyrazinamide

(Z)Second line drugs

1 . Thiacetazone (Tzn)	Newer drugs
2. Paraaminosalicylic Ciprofloxacinacid (PAS)	1. 2. Ofloxacin
3. Ethionamide (Etm)	3. Clarithromycin
4. Cycloserine (Cys)	4. Azithromycin
5. Kanamycin (Kmc)	5. Rifabutin
6. Amikacin (Am)	
7. Capreomycin (Cpr)	

Mechanism of action: *Isoniazid*, often referred to as *INH*, is a prodrug that is activated by a mycobacterial catalase-peroxidase (KatG). Genetic and biochemical evidence has implicatedat least two different target enzymes for *isoniazid* within the unique Type II fatty

acid synthase system involved in the production of mycolic acids.

Antibacterial spectrum: For bacilli in the stationary phase, *isoniazid* is bacteriostatic, but for rapidly dividing organisms, it is bactericidal. It is effective against intracellular bacteria. *Isoniazid* is specific for treatment of M. tuberculosis, although Mycobacterium kansasii (an organism that causes three percent of the clinical illness known as tuberculosis) may be susceptible at higher drug levels. When it is used alone, resistant organisms rapidly emerge.

Resistance: This is associated with several different chromosomal mutations, each of which results in one of the following: mutation or deletion of KatG (producing mutants incapable of prodrug activation), varying mutations of the acyl carrier proteins, or overexpression of InhA. Cross-resistance does not occur between *isoniazid* and other antitubercular drugs.

Rifampin (Rifampicin, R) It is a semisynthetic derivative of rifamycin B obtained from Streptomyces mediterranei. Rifampin is bactericidal to M. tu berculosis and many other gram-positive and gram-negative bacteria. Rifampin inhibits DNA dependent RNAsynthesis. Probably, the basis of selective toxicity is that mammalian RNA polymerase does not avidly bind rifampin

Mechanism of action: *Rifampin* blocks transcription by interacting with the subunit of bacterial but not human DNA-dependent RNA polymerase.

Pyrazinamide

Pyrazinamide is a synthetic, orally effective, bactericidal, antitubercular agent used in combination with *isoniazid, rifampin*, and *ethambutol*. It is bactericidal to actively dividing organisms, but the mechanism of its action is unknown.

Mechanism of action *Pyrazinamide* must be enzymatically hydrolyzed to pyrazinoic acid, which is the active form of the drug. Some resistant strains lack the pyrazinamidase. *Pyrazinamide* is active against tubercle bacilli in the acidic environment of lysosomes as well as in macrophages. *Pyrazinamide* distributes throughout the body, penetrating the CSF. It undergoes extensive metabolism.

Ethambutol

Ethambutol is bacteriostatic and specific for most strains of M. tuberculosis and M. kansasii.

Mechanism of action: *Ethambutol* inhibits arabinosyl transferase an enzyme that is important forthe synthesis of the mycobacterial arabinogalactan cell wall. Resistance is not a serious

problem if the drug is employed with other antitubercular agents. *Ethambutol* can be used in combination with *pyrazinamide*, *isoniazid*, and *rifampin* to treat tuberculosis. Absorbed on oral administration, *ethambutol* is well distributed throughout the body. Penetration into the centra nervous system (CNS) is therapeutically adequate in tuberculous meningitis.

Streptomycin: This is the first antibiotic effective in the treatment of tuberculosis and is discussed with the aminoglycosides. Its action is directed against extracellular organisms. Infections due to *streptomycin*-resistant organisms may be treated with *kanamycin* or *amikacin*, to which these bacilli remain sensitive.

Capreomycin: This is a peptide that inhibits protein synthesis. It is administered parenterally. *Capreomycin* is primarily reserved for the treatment of multidrug-resistant tuberculosis. Careful monitoring of the patient is necessary to prevent its nephrotoxicity and ototoxicity.

***Cycloserine*:** is an orally effective, tuberculostatic agent that appears to antagonize the steps in bacterial cell wall synthesis involving D-alanine. It distributes well throughout body fluids, including the CSF. *Cycloserine* is metabolized, and both parent and metabolite are excreted in urine. Accumulation occurs with renal insufficiency. Adverse effects involve CNS disturbances, and epileptic seizure activity may be exacerbated.

Ethionamide: This is a structural analog of *isoniazid*, but it is not believed to act by the same mechanism. *Ethionamide* can inhibit acetylation of *isoniazid*. It is effective after oral administration and is widely distributed throughout the body, including the CSF. Metabolism is extensive, and the urine is the main route.

Daily dose 3 x per week dose

DRUG mg/kg For > 50 kg mg/kg For > 50 kg

Isoniazid (H) 5 (4-6) 300 mg 10 (8-12) 600 mg

Rifampin (R) 10 (8-12) 600 mg 10 (8-12) 600 mg

Pyrazinamide (Z) 25 (20-30) 1500 mg 35 (30-40) 2000 mg

Ethambutol (E) 15 (15-20) 1000 mg 30 (25-35) 1600 mg

Streptomycin (S) 15 (12-18) 1000 mg' 15 (12-18) 1000 mg

Category I This category includes:

• New (untreated) smear-positive pulmonaty TB.

• New smear-negative pulmonary TB with extensive parenchymal involvement.

• New cases of severe forms of extra pulmonary TB, viz . meningitis, miliary, pericarditis, peritonitis, bilateral or extensive pleural effusion, spinal, intestinal, genitourinaryTB.

Initial phase Four drugs HRZ + E or S are given daily or thrice weekly for 2 months.

- The revised national tuberculosis control programme (RNTCP) has been launched in India in 1997, which is implementing DOTS*. Out of the WHO recommended regimens, the RNTCP has decided to follow thrice weekly regimen, since it is equally effective, saves drugs and effort, and is more practical.
- The RNTCP recommends that if the patient is still sputum-positive at 2 months, the intensive phase should be extended by another month; then continuation phase is started regardless of sputum status at 3 months