Antitubercular drugs

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Tuberculosis

- Tuberculosis, or TB, is an infectious bacterial disease caused by Mycobacterium tuberculosis, which most commonly affects the lungs.
- It is transmitted from person to person via droplets from the throat and lungs of people with the active respiratory disease.
- The symptoms of active TB of the lung are coughing, sometimes with sputum or blood, chest pains, weakness, weight loss, fever and night sweats.
- Types: Pulmonary and Extra-pulmonary TB

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Anti-tuberculosis drugs

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)
2. Rifampin (R)
3. Pyrazinamide (Z)
4. Ethambutol (E)
5. Streptomycin (S)

Second line drugs

1. Thiacetazone (Tzn)
2. Paraaminosalicylic acid (PAS)
3. Ethionamide (Etm)
4. Cycloserine (Cys)
5. Kanamycin (Kmc)
6. Amikacin (Am)
7. Capreomycin (Cpr)

Newer drugs

1. Ciprofloxacin
2. Ofloxacin
3. Clarithromycin
4. Azithromycin
5. Rifabutin

Isoniazid (isonicotinyl hydrazide; INH or H)

MOA: inhibits the synthesis of mycolic acid which is a unique fatty component of mycobacterial cell wall. Fast multiplying organisms are rapidly killed.

Adverse Effect

- Peripheral neuritis and a variety of neurological manifestations (paresthesias, numbness, mental disturbances, rarely convulsions) are the most important dose-dependent toxic effects. This may be due to increased excretion of pyridoxine. → Vit B6 supplement.
- Hepatitis, a major adverse effect.
- Other side effects are rashes, fever, acne and arthralgia.

Rifampicin (R)

- Rifampin is bactericidal to M. tuberculosis and many other gram-positive and gram-negative bacteria.

MOA

- Rifampicin binds strongly to the β-subunit of *DNA-dependent RNA polymerase and* thereby inhibits RNA synthesis from DNA and kill the bacteria.

Adverse effect

- Hepatitis; jaundice
- Nausea, vomiting abdominal pain
- Flu- syndrome: fever, headaches, malaise
- *Urine and secretion (sweat, saliva or tears) may be* **orange-red color**→ harmless

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Pyrazinamide (Z)

- Bacteriostatic
- More active in acidic medium

MOA

- Pyrazinamide is a prodrug converted by pyrazinamidase to pyrazinoic acid that stops the growth of M. tuberculosis.
- inhibits mycolic acid synthesis, but by interacting with a different fatty acid synthase and thus disrupts cell wall function.

Adverse Effect

- Hepatotoxicity
- Hyperuricemia
- Others: arthralgia, flushing, rashes, fever

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Ethambutol (E)

- Bacteriostatic

MOA

- It interferes with mycolic acid incorporation in cell wall and inhibits RNA synthesis.

Adverse Effect

- Loss of visual acuity/ colour vision, field defects due to optic neuritis
- nausea, rashes, fever, neurological changes are infrequent.
- Hyperuricemia is due to interference with urate excretion

Streptomycin (S)

- It is tuberculocidal, but less effective than INH or rifampin
- acts only on extracellular bacilli (because of poor penetration into cells).

MOA

- It binds with the 30s subunit of ribosome and induce misreading of mRNA thus inhibits protein synthesis.

Adverse Effect

- Ototoxicity
- nephrotoxicity

Treatment of Tuberculosis

- Prevent and control TB.
- WHO recommend the use of MDT (multi drug therapy)
- Objective of MDT are:
  - ✓ To make the patient noninfectious as early as possible
  - ✓ To prevent the development of drug resistance
  - ✓ To prevent relapse
  - ✓ To reduce the total duration of effective therapy

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Short course chemotherapy

- WHO introduced 6-8 month MDT "short course chemotherapy" in 1995 under DOTS programme.
- This regimen have two phases- intensive and continuation phase.
- National tuberculosis center for Nepal launched 6 month short course chemotherapy.

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Phases for treatment of TB

1. Intensive phase.
Includes three or more drugs for 2-3 months, which kill most of the TB bacteria quickly so that patient becomes non-infectious quickly.
Examples- Isoniazid (300mg) + Rifampicin (600mg) + Pyrazinamide (1.5g) + Ethambutol (1g) / streptomycin (1g)

2. Continuous phase.
Includes two or more drugs for 4-6 months. These kill off any remaining bacteria in the body.
Examples- Isoniazid (300 mg) + Rifampicin (600mg) + Rifampicin (600mg)

Treatment guideline of NTC, Nepal

Categories of Treatment and their Anti-TB Drug Regimens

Type of TB		Intensive Phase	Continuation phase
New TB cases - Adult and childhood - Bacteriological or clinically diagnosed - Pulmonary or extra-pulmonary		2HRZE	4HR
Complicated/Severe EP cases (CNS TB, TB Pericarditis, Musculoskeletal TB, Miliary TB etc)		2HRZE	7-10HRE*
Retreatment cases All forms: 1st Rapid DST with Xpert MTB/RIF testing should be done to see the status of resistance of Rifampicin. Rifampicin sensitive for Isoniazid (INH) resistance status	Xpert MTB/RIF - Rifampicin sensitive LPA-Isonizaid sensitive	2HRZE	4HR
	Xpert MTB/Rif-Rifampicin sensitive LPA-Isoniazid Resistant and FQ sensitive	6 (H) RZE + Levofloxacin (Full Duration)	
	Xpert MTB/Rif-Rifampicin sensitive LPA-Isoniazid Not known because of no access to LPA	6 HRZE (Full duration)	
	Rifampicin sensitive INH resistance and FQ resistant **	6 HRZE	
DR TB	Refer no national guidelines on DR-TB management (2019)		

- LPA- line probe assay: rapid diagnostic test for detection of R and H resistance
- DST- Drug susceptibility test

Multidrug resistance (MDR-TB)

- The bacteria that cause tuberculosis (TB) can develop resistance to the antimicrobial drugs used to cure the disease.
- MDR-TB - does not respond to at least **isoniazid and rifampicin**, the two most powerful anti-TB drugs.
- Anti-tuberculosis (TB) drug resistance is a major public health problem that threatens progress made in TB care and control worldwide.
- The reasons why multidrug resistance continues to emerge and spread are mismanagement of TB treatment and person-to-person transmission.

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Multidrug resistance (MDR-TB)

- Inappropriate or incorrect use of antimicrobial drugs, or use of ineffective formulations of drugs (e.g. use of single drugs, poor quality medicines or bad storage conditions), and premature treatment interruption can cause drug resistance, which can then be transmitted, especially in crowded settings such as prisons and hospitals.
- Solutions to control drug-resistant TB are to:
  1. cure the TB patient the first time around;
  2. provide access to diagnosis;
  3. ensure adequate infection control in facilities where patients are treated;
  4. ensure the appropriate use of recommended second-line drugs.

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DOTS (Directly Observed treatment Short Course)

- is the name given to the tuberculosis control strategy recommended by the WHO.
- According to WHO, "The most cost-effective way to stop the spread of TB in communities with a high incidence is by curing it. The best curative method for TB is known as DOTS".
- First DOTS program initiated in Nepal- 1996
- DOTS demonstrated center in 4 district; Bhaktapur, Parsa, Nawalparasi and Kailali
- Before DOTS: 35% of the patient were cured
- After DOTS: 90% are cured