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Tuberculosis- Overview

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ABSTRACT

Tuberculosis (TB) remains one of the world's deadliest communicable diseases. TB is an airborne infectious disease caused by organisms of the Mycobacterium tuberculosis complex. Although primarily a pulmonary pathogen, M. tuberculosis can cause disease in almost any part of the body. Infection with M. tuberculosis can evolve from containment in the host, in which the bacteria are isolated within granulomas (latent TB infection), to a contagious state, in which the patient will show symptoms that can include cough, fever, night sweats and weight loss. Only active pulmonary TB is contagious. In many low-income and middle-income countries, TB continues to be a major cause of morbidity and mortality. Although several TB diagnostics have been developed, including skin test, sputum test, chest x-ray etc. Treatment usually requires a prolonged course of multiple antimicrobials, stimulating efforts to develop shorter drug regimens. TB requires at least six months of treatment. If treatment is incomplete, patients may not be cured and drug resistance may develop. Directly Observed Therapy (DOT) is a specific strategy, endorsed by the World Health Organization, to improve adherence by requiring health workers, community volunteers or family members to observe and record patients taking each dose. The final goal is to minimize the risk of TB in India and evaluate as to what extent the National TB Control program is being implemented and extent of its effectiveness.

Key words: Tuberculosis (TB), Multi-drug resistant (MDR-TB), Directly Observed Therapy (DOT), Extensively-drug resistant (XDR-TB), Revised National Tuberculosis Programme (RNTCP)

Introduction

Tuberculosis is one of the most ancient diseases of mankind and has co-evolved with human for many thousands of years or perhaps for several million years.[1] TB commonly was known as "consumption" because of the pronounced weight loss that it caused. Other common names included "wasting disease" and the "white plague".[2] Tuberculosis remains one of the world's deadliest communicable diseases.[3] In 1882, the bacillus causing tuberculosis, Mycobacterium Tuberculosis, was discovered by Robert Koch.[4] It is a chronic disease caused by the bacillus Mycobacterium Tuberculosis and spreads from person to person through air. TB usually affects the lungs but also affects other parts of the body such as Brain, Intestines, Kidneys or the Spine.[5] Two forms of this disease exist- Pulmonary Tuberculosis and Extra Pulmonary Tuberculosis.[6] Today, the principal cause of human tuberculosis is Mycobacterium Tuberculosis. Other members of the M. tuberculosis complex that can cause TB include M. bovis, M. microti, and M.africanum. M.microti does not cause TB in humans, infection with M.africanum is very rare while M.bovis has a wider host range & is the main. Humans become infected by M.bovis usually via milk, milk products or meat from an infected animal.[7,8]

TB can affect people of any age and individuals with weakened immune system eg. with HIV infection, are at increased risk.[9] Children younger than 2 years and adults over 65 years of age have 2 to 5 time greater risk for active disease compared to other age groups.[2] Urbanization and Industrialization lead to

poverty, overcrowding, insanitation and malnutrition which provide a conducive environment for the bacteria to flourish inside the human body.[10] Other conditions that may pose a high risk for susceptibility to MTB infection are Diabetes, long term use of corticosteroids, TNF-α blockers, polymorphism in vitamin D receptors, poly morphism in IL-12 & IFN -γ genes etc.[11,12]

Men are more commonly affected than women. The case notification in most countries are higher in males than in females.[13] According to WHO, TB is a worldwide pandemic.[14] Tuberculosis remains one of the major global health threats leading to morbidity and mortality.[15,16] The WHO reported that "one- third of the world's population has been infected with TB"[17] Tuberculosis still is one of the deadliest diseases in the world killing nearly 2 million people every year.[18] India has one of the highest tuberculosis burdens globally accounting for 20% of new 8.6 million TB cases annually.[19,20] TB is one of the top 3 infectious killer disease in the world. [14] Globally 3.7% of new cases and 20% of previously treated cases are estimated to have **Multidrug Resistance-TB (MDR-TB).** In India, the estimated annual incidence of MDR-TB is around 99,000, the highest in the world. India had launched National TB Control Program (NTP) in 1962. It was one of the best TB control programs in the world well planned & designed to suit the social, cultural and economic features of the country.[10] In 1993, WHO declared TB to be a global emergency and devised the DOTS strategy & recommend that all countries adopt this strategy.[21]

ETIOLOGY OF TUBERCULOSIS

The main cause of TB is Mycobacterium Tuberculosis a small, aerobic, nonmotile bacillus.[22] Mycobacteria are rod- shaped, non–spore forming, slow growing (4 to 6 weeks), aerobic and acid fast tubercle bacilli.[23] It divides every 16 to 20 hours, which is an extremely slow rate compared with other bacteria, which usually divide in less than one hour,[22] which doubles about every 30 minutes.[2] The most common acid fast staining techniques are Ziehl -Neelsen stain and the Kinyon stain, which dye acid fast bacilli a bright red that stands out against a blue background. Auramine–rhodamine staining,[22] Fluorescent method, Immunohistochemical stain ,culture method, Molecular method , serologic test [24] are also used. Other members of Mycobacterium complex include M.africanum and M.ulcerans ,which are also primarily human pathogens and M.bovis which causes TB primarily in cattle and other animals; however, M.bovis can cause human disease through extensive contact with infected animals or can be transmitted by unpasteurized milk .[25] M.microti is also rare and is seen almost only in immunodeficient people. Other "nontuberculous mycobacteria" such as M.kanasii, M.fortuitum ,M.leprae [22], M..AviumComplex(MAC) cause infection in patients with other medical problems, especially the Acquired Immunodeficiency Syndromes (AIDS).[2]

MODE OF TRANSMISSION [24, 26]

- **Inhalation** of organisms present in fresh cough droplets, sneeze or in dried sputum from an open case of pulmonary tuberculosis.
- **Ingestion** of the organism leads to development of tonsillar or intestinal tuberculosis. This mode of infection of human tubercle bacilli is from self-swallowing of infected sputum.
- **Inoculation** of the organisms into the skin may rarely occur from infected postmortem tissue.
- **Transplacental** route is rare mode of transmission and may cause congenital tuberculosis in foetus from mother.
- TB is not transmitted by fomites such as dishes and articles used by patients.

o Spread of Tuberculosis:[36]

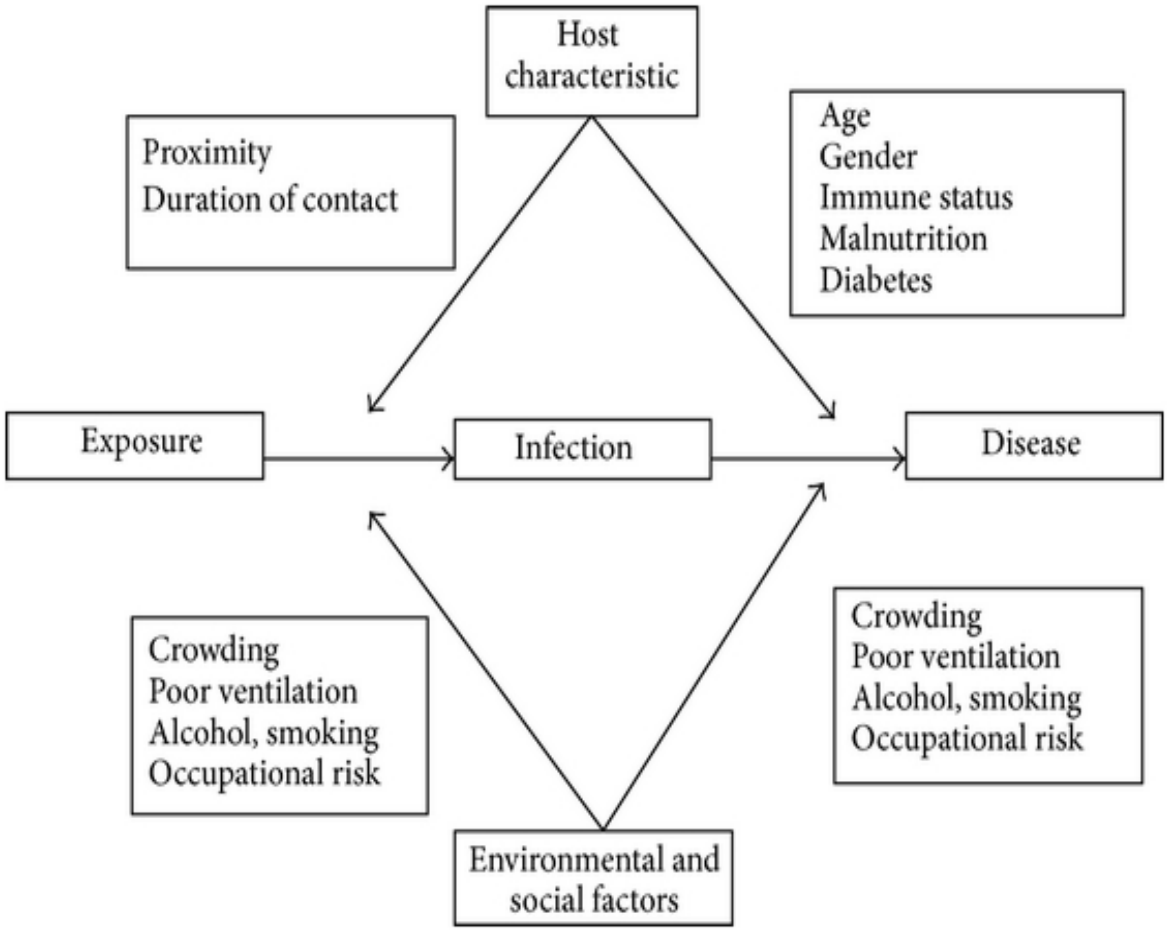
The disease spreads in the body by various routes:

- **Local spread:** This takes place by macrophages carrying the bacilli into the surrounding tissue.
- **Lymphatic spread:** Tuberculosis is primarily an infection of lymphoid tissue. The bacilli may pass into lymphoid follicles of pharynx, bronchi, intestines or regional lymph nodes resulting in regional tuberculous lymphadenitis which is typical of childhood infections
- **Haematogenous spread:** This occurs either as a result of tuberculosis bacillaemia because of the drainage of lymphatics into the venous system or due to caseous material escaping through ulcerated wall of a vein. This produces milisary tuberculosis characterized by millet seed sized lesions in different organs of the body such as lungs, kidney, bones, and other tissues.

INCUBATION PERIOD OF TUBERCULOSIS [26, 27]

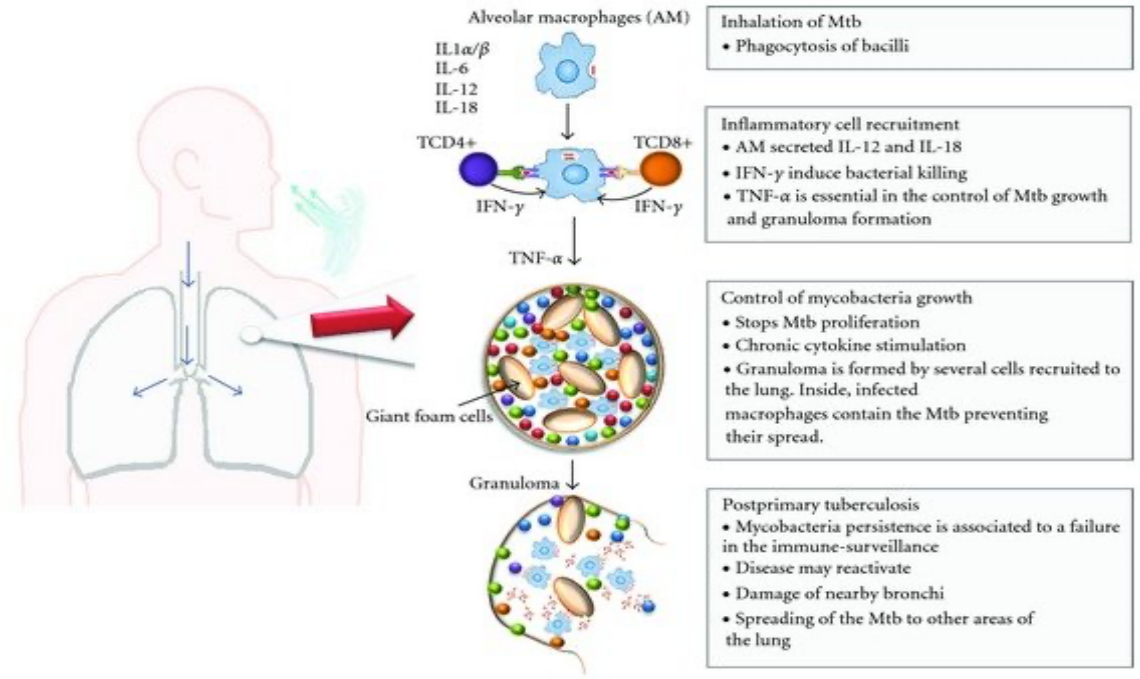
- The incubation period from infection to demonstrable primary lesions or significant tuberculin reaction ranges from 2-10 weeks. Thus the incubation period may be weeks, months, or years. HIV infection appears to shorten the interval for the development of clinically apparent tuberculosis.

RISK FACTORS OF TUBERCULOSIS:



[Figure 1: Risk factor of tuberculosis] [28]

PATHOGENESIS OF TUBERCULOSIS



[Figure 2: Pathogenesis of tuberculosis] [25]

FORMS OF TUBERCULOSIS[22, 23, 25, 29, 30, 31]

As per site/ location of infection in body

1. **Pulmonary Tuberculosis:** Occurs in about 90% of cases and commonly involves the lungs. Puilmonary TB can be further categorized as **primary or post primary (secondary).**

(a) Primary pulmonary disease results from initial infection with M. Tuberculosis and often occurs in children with impaired Immunity, with localization in the middle and lower lung zones.

(b) Post primary disease is also referred to as adult type reactivation or secondary TB and occurs most frequently from reactivation of latent infection. This form of pulmonary disease tends to be localized to the apical and posterior segments of the upper lobes.

The upper lobes of lungs are more frequently affected by Tuberculosis than the lower ones.

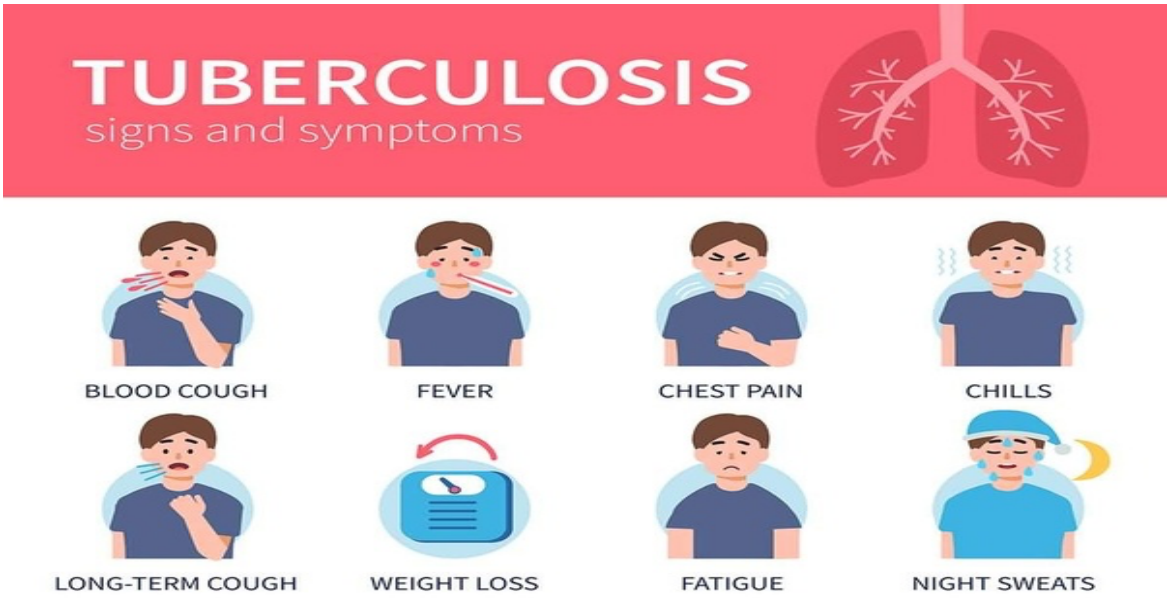
2. **Extrapulmonary Tuberculosis:** In 15-20% of active cases, the infection spreads outside the lungs, causing other kinds of TB. These are collectively denoted as "**Extrapulmonary Tuberculosis**".
Notable extrapulmonary infection sites are the Pleura, Lymph nodes, Genitourinary tract, Bone and Joints, Spine, Peritoneum, and CNS (Tuberculous Meningitis).

As per nature

1. **Latent Tuberculosis:** A person can have TB bacteria in their body and never develop symptoms.
2. **Miliary Tuberculosis or Disseminated Tuberculosis:** Miliary tuberculosis is a rare form of active disease that occurs when TB bacteria find their way into the blood stream.
3. **Active Tuberculosis :** Active tuberculosis is an illness in which the TB bacteria are rapidly multiplying and invading different organs of the body. Symptoms are same as Pulmonary TB.

SIGNS AND SYMPTOMS OF TUBERCULOSIS[22]

1. Chest pain
2. Prolonged cough
3. Cough with blood in sputum (Haemoptysis)
4. Evening Fever
5. Chills
6. Night sweat
7. Weight loss
8. Anorexia
9. General malaise



[Figure 3: Sign and symptoms of tuberculosis]

DIAGNOSIS OF TUBERCULOSIS

1. **Blood test:** [32, 33, 34] A TB blood test is a reliable indicator of a TB infection. There are currently two types of blood test technology:

(a) QuantiFERON-TB Gold blood test : is a simple blood test that aids in the detection of MTB. It is used as a modern alternative to the tuberculin skin test. It cannot distinguish between active TB disease and latent TB infection.

(b) T-SPOT test: It isan in vitro diagnostic test for the detection of effector T cells that respond to stimulation by MTB antigen. **2. Sputum test:** sputum sample may be looked at under microscope and if TB germs are visible, it indicates an active TB infection in the lungs.

3. Staining for TB smear: [24, 26]

(a) Acid fast (Ziehl- Neelsen) Staining: The acid fastness of the TB is due to mycolic acids, cross- linked fatty acids and other lipids in the cell wall of organism making it impermeable to the usual stains. It takes up stain by heated carbol fuchsin and resists decolourisation by weak acids and alcohol

(b) Fluoresent method: Traditional method employs fluorescent dyes such as Auramine and Rhodamine to detect presence of Mycobacteria as indicated by appearance of fluorescence.

4. Mycobacterial culture: [24, 26, 35, 36] Mycobacteria from sputum or from any other material can be cultured in Lowenstein – Jensen medium by conventional method and has high specificity, but the growth is slow and takes 4-8 weeks.

Skin test: Tuberculin Test: The TB skin test also called the Montoux Tuberculin Skin Test (TST) is performed by injecting a small amount of fluid into the skin on the lower part of the arm. Injection should produce a pale wheal of the skin, 6 to 10 mm in diameter. The result of the test is read after 48-96 hours but 72 hours (3rd day) is the ideal. Tuberculin reaction

consists of erythema and induration. Reactions exceeding 10 mm are considered "positive".

BCG Skin Test: On re-exposure to mycobacterium a peculiar accelerated body reaction is observed called Kock's phenomenon. When BCG is given to such a sensitized person skin changes appear in rapid sequence which are basis of accelerated BCG skin reaction. BCG Skin response has been found to be highly sensitive compared with tuberculin test but does not differentiate between active or inactive disease. Negative test may rule out exposure to mycobacterium. Positive test may be more reliable than tuberculin test.

5. Chest radiology: [31] A chest x-ray can identify damage to the lungs, an indicator of pulmonary TB.

[Figure 4: Chest x-ray of advance tuberculosis] [22]

6. Antigen based diagnostic tests: [35] Radio-Immunoassay (RIA), Enzyme Linked Immunosorbent Assay (EIA), Haemagglutination and latex agglutination test are used to detect mycobacterial antigen in sputum, cerebrospinal, pleural and ascetic fluids.

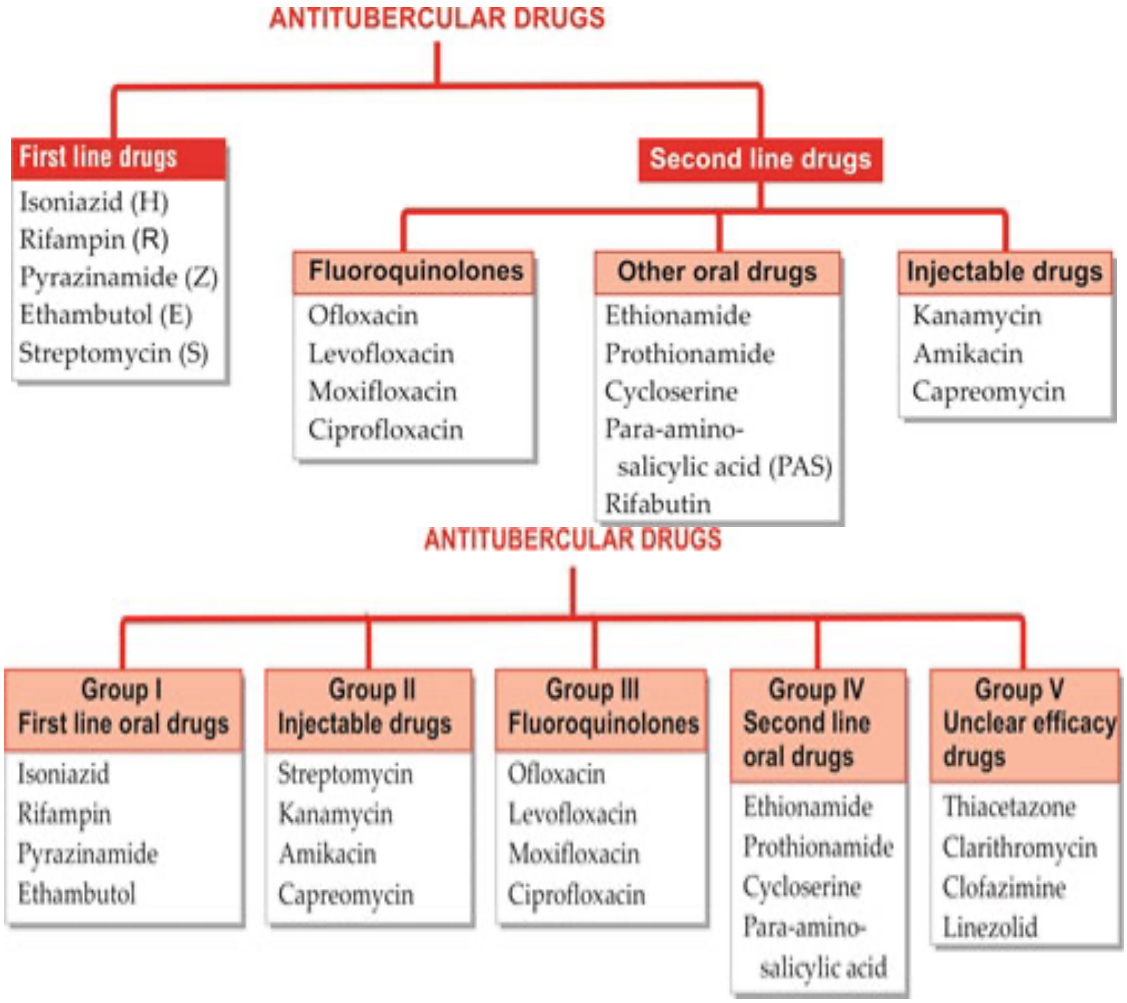
7. Antibody based diagnostic tests: [35] A variety of methods are employed to detect antibodies in sera, though such techniques lack required specificity and sensitivity. These include Compliment fixation test, Haemagglutination test, Precipitation test, Gel diffusion test and Kaolin agglutination tests. More sensitive and preferable tests include RIA, EIA and Soluble Antigen Fluorescent Antibody Tests (SAFA).

TREATMENT OF TUBERCULOSIS

General principles: [37]

- Drug treatment is the cornerstone of TB management. A minimum of two drugs, and generally three or four drugs, must be used simultaneously.
- Drug treatment is continued for at least 6 months and up to 2 to 3 years for some cases of multi drug resistant TB (MDR-TB).
- Measures to assure adherence, such as Directly Observed Therapy (DOTS), are important.
- Patients with active disease should be isolated to prevent spread of the disease.
- Public health departments are responsible for preventing the spread of TB has already spread using contact investigation.
- Debilitated patients may require therapy for other medical conditions, including substance abuse and HIV infection, and some may need nutritional support.
- Surgery may be needed to remove destroyed lung tissue, space- occupying lesions, and some extra pulmonary lesions

Classification of tubercular drugs:



[Figure 5: Classification of tubercular drugs] [38]

Domiciliary treatment: [26]

The self-administration of drugs (generally oral drugs) by the patients themselves without recourse to hospitalization is called **domiciliary or ambulatory treatment**.

A. Long course regimens:

The classical (long-course) conventional chemotherapeutic regimens depend upon the use of INH along with one or two bacteriostatic or "companion" drugs.

TABLE 1: Daily regimens[38]

Drug	Daily dose(mg/kg)
1.Isoniazid(H)	5(4-6)
2.Rifampin(R)	10(8-12)
3.Pyrazinamide(Z)	25(20-30)
4.Ethambutol(E)	15(15-20)
5.Streptomycin(S)	15(12-18)

II. Biweekly/Intermittent regimen: [36]

Isoniazid + Rifampicin + Pyrazinamide + Ethambutol given 3 times weekly.

B. Short course chemotherapy:[26]

I. Initial intensive phase with 4 drugs INH, Rifampicin and Pyrazinamide, supplemented

by either Streptomycin or Ethambutol for a period of 2 months.

II. Followed by 2 drugs in the **continuation phase** INH + Rifampicin or Thioacetazone given daily or intermittently.

Directly observed treatment (DOTS): [26]

Short course chemotherapy DOTS is a strategy to ensure cure by providing the most effective medicine and confirming that it is taken. In DOTS, during the intensive phase of treatment a health worker or other trained person watches as the patient swallows the drug in his presence. During continuation phase, the patient is issued medicine for one week in a multi blister combi -pack, of which the first dose is swallowed by the patient in the presence of health worker or trained person. The consumption of medicine in the continuation phase is also checked by return of empty multi blister combi-pack, when the patient comes to collect medicine for the next week. The drugs are provided in patient-wise boxes with sufficient shelf-life. In the programme alternate-day treatment is used.

TABLE 2: DOTS regimen

Category	Types Of Patient	Regimen	Duration in Months	Test at Month
Category I Color of box: RED	New Sputum Smear Positive New Sputum Smear Negative New Extra Pulmonary New Other	$2(HRZE)_3$, $4(HR)_3$	6	2
Category II Color of box: BLUE	Sputum Positive Relapse Sputum Positive Failure Sputum Positive Treatment after Default	$2(HRZES)_3$, $1(HRZE)_3$, $5(HRE)_3$	8	3

*H: Isoniazide R: Rifampicin Z: Pyrazinamide E: Ethambutol

Dots-plus treatment for MDR-TB:[38]

Recognizing that the diagnosis and treatment of MDR-TB is complex, **Revised National Tuberculosis Programme (RNTCP)** has developed national guidelines based on the WHO recommended International DOTS-Plus guidelines. After diagnosis, the treatment of MDR-TB is initiated at designated DOTS-Plus sites, which are established in tertiary care centres (like medical colleges, large speciality hospitals) at least one in each state. The DOTS-Plus sites have qualified staff available to manage patient; using DOTS-Plus regimen; using the second-line drugs, given under DOT and standardized follow-up protocol; and have system in place to deliver ambulatory DOT after an initial short period of in-patient care to stabilize the patient.

- **Regimen for MDR-TB : [26]**

This regimen comprises of 6 drugs Kanamycin, Levofloxacin, Ethionamide, Pyrazinamide, Ethambutol and Cycloserine during 6-9 months of the intensive phase and 4 drugs-Levovfloxacin, Ethionamide, Ethambutol and Cycloserine during the 18 months of the continuation phase.

- **Drug dosage and administration:**

All drugs should be given in a single daily dosage under Directly Observed Treatment (DOT) by a DOT provider, on 6 days of the week. On Sunday, the oral drugs will be administered unsupervised whereas injection Kanamycin will be omitted. If intolerance occurs to the drugs, Ethionamide, Cycloserine and PAS may be split into two dosages and the morning dose administered under DOT. The evening dose will be self-administered. The empty blister packs of the self-administered

doses will be checked the next morning during DOT. Pyridoxine should be administered to all patients on regimen for MDR-TB.

- **Treatment Duration For MDR- TB:**[26]

The treatment is given in two phases, the intensive phase (IP) and the continuation phase (CP). The total duration of treatment for regimen for MDR-TB is 24-27 months, depending on the IP duration. IP should be given for at least six months. After 6 months of treatment, the patient will be reviewed and the treatment changed to CP if the 4th or 5th month culture result in solid or liquid culture is negative respectively. The IP can be extended upto a maximum of 3 months after which the patient will be initiated on the CP irrespective of the culture result. The recommended duration for CP is 18 months.

Discharge from DR-TB Centres and transition to decentralized supervised treatment - Patients admitted at the DR-TB centre, if clinically appropriate, may be discharged 7 days after treatment initiation to their district of residence with a maximum of 7 day supply of drugs and arrangement for injections in transit.

- **Regimen for extensively drug resistant TB (XDR-TB):**[26]

All XDR-TB patients should also be subject to a repeat full pre-treatment evaluation, but also including consultation by a thoracic surgeon for consideration of surgery. MDR-TB patients diagnosed as XDR-TB would be given an outcome of "Switched to regimen for XDR-TB". The decision and initiation of regimen for XDR-TB is to be taken by the concerned DR-TB centre committee.

- The Intensive Phase (6-12 months) consists of 7 drugs - Capreomycin (Cm), PAS, Moxifloxacin (Mfx), High dose INH, Clofazimine, Linezolid, and Amoxyclav.
- The Continuation Phase (18 months) consists of 6 drugs - PAS, Moxifloxacin (Mfx), High dose INH, Clofazimine, Linezolid, and Amoxyclav.

PREVENTION[37]

Vaccination:

BCG is a vaccine against TB that is prepared from a strain of the attenuated live bovine TB, M. bovis, that has lost its virulence in humans by being specially subcultured (230 passages) in an artificial medium for 13 years, and also prepared from MTB. The bacilli have retained enough strong antigenicity to become a somewhat effective vaccine for the prevention of human TB. At best, the BCG vaccine is 80% effective in preventing TB for duration of 15 years; however, its protective effect appears to vary according to geography. BCG is given as a single intradermal injection at the insertion of the deltoid.

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