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REVIEW ON PATHOPHYSIOLOGY AND TREATMENT OF TUBERCULOSIS

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ABSTRACT:

Tuberculosis is a hypersensitive granulomatous infectious disease that mainly affects the lungs. Mycobacterium tuberculosis (M. tuberculosis) is the etiological agent of TB and currently more than one-third of the world population is suffering from TB. So need of knowledge about T.B, pathophysiology and treatment of T.B. to people or society. Pathophysiology means, when a human being or animal being suffering from a disease this is because deranged or change in function on that organ or human body. Infection is caused by airborne droplets of organisms person to person.For the treatment of TB, administration of multiple antibiotics such as isoniazid, rifampicin, pyrazinamide and ethambutol is required for long time period to kill the bacteria. Therefore antibiotic resistance is the emerging problem in multiple drug-resistant tuberculosis (MDR TB) infections. World Health Organization (WHO) has developed a new strategy called DOTS (directly observed treatment, short-course), in which specific combination of anti-TB drugs are given, to control TB.The main object of this project is how to diagnose and how it is cure or treat. In this, we have provided the valuable information about first and second line anti TB drugs, DOTS and novel drug delivery systems to be used against M. tuberculosis.

Keywords: *Tuberculosis (TB), Pathogenesis, Diagnostic Studies, Treatment, DOTS.*

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INTRODUCTION:

Tuberculosis (TB) is the most prevalent infectious disease of human beings, which causes illness and large number of deaths worldwide [1]. This contagious disease is mainly caused by the bacterium known as Mycobacterium tuberculosis (M. tuberculosis). TB primarily affects the lungs, but it can also influence the central nervous system. lymphatic and circulatory system [2-4]. The diagnosis process of active contagious TB mainly involves radiology techniques such as chest X-rays but also includes microscopic examination and microbiological culture of body fluids like multiple sputum cultures. However in case of latent TB, where the bacteria present in the body remain inactive and produce no symptoms, the diagnosis relies on the Mantoux tuberculin skin test and/or Interferon gamma release assays (IGRAS) of the blood samples [5]. Prevention of TB mainly includes screening programs and vaccination such as Bacillus Calmette Guerin (BCG) vaccine [6].

Etiology of Tuberculosis [7]:

Mycobacterium tuberculosis-most common cause

Other than tuberculosis-includes:

- M. aviumintracellulare
- M. kansasi
- M. scrofulaceum
- M. marinum
- M. ulcerence
- M. fortuitum
- M. chelonel

Sites involved [8]:

a. Pulmonary tb-85% of all TB cases
b. Extra pulmonary sites
c. Lymph node22
d. Genitourinary tract
e. Bones & joints
f. Meninges
g. Intestine
h. Skin

Characteristics of Mycobacterium Tb [7]:

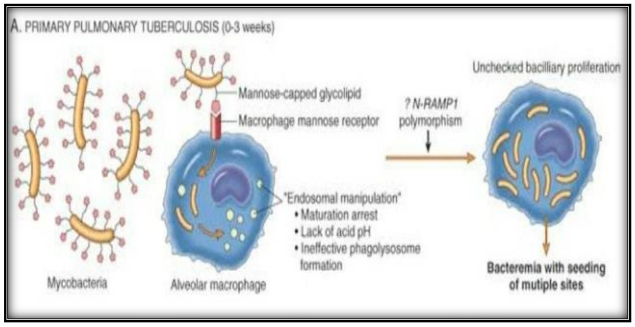
a. Rod shape, 0.2-0.5 in D, 2-4 in L.
b. My colic acid present in its cell wall, makes it acid fast,
c. So it resists decolourization with acid & alcohol.
d. Aerobic and non-motile.
e. Multiplies slowly.
f. Can remain dormant for decades.

How is TB Transmitted [8]:

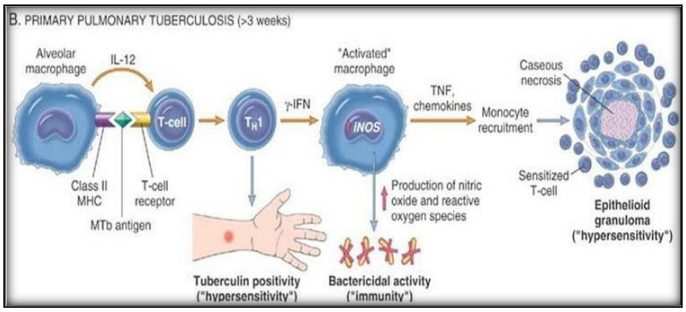
a. Person-to-person through the air by a person with active TB disease of the lungs
b. Less frequently transmitted by
   1. Ingestion of Mycobacterium bovis found in unpasteurized milk products or auto ingestion
   2. Inoculation (in skin tuberculosis).
   3. Trans placental route (rare route).

PATHOGENESIS OF TUBERCULOSIS [7]:

1. M. tuberculosis starts hypersensitivity immune reaction inside the lung which damages the lung tissue while killing the foreign microorganism.
2. Pathologic manifestation of tuberculosis like caseating granuloma and cavitation are result of hypersensitivity that develops in concert with the protective host immune response.
3. Macrophages are the primary cells infected by M. tuberculosis.



During the earliest stage of primary tuberculosis (<3 weeks) in the non- sensitized individual, bacteria proliferate in the pulmonary alveolar macrophages and air spaces, resulting in bacteremia and seeding of multiple sites. Despite the bacteremia, most people at this stage are asymptomatic or have a mild flu-like illness



Morphology of TB:

Primary tuberculosis [7]

1. Form of disease that develops in a previously unexposed person.
2. Almost always begins in lungs.
3. Inhaled bacilli implant in the distal airspaces of lower part of upper lobe or upper partof lower lobe.
4. It forms a small sub pleural parenchymal lesion in the mid zone of the lung (ghon focus inflammation + caseous necrosis)
5. Tubercle bacilli drain to the regional lymph node which also often undergo caseousnecrosis.
6. Parenchymal lung lesion+ Nodal involvement= Ghon's complex.

Histologically:

Granulomatous inflammation forms both caseating and non caseating tubercles. Tuberculous Granuloma has the following characteristics:

1. Central caseous necrosis.
2. Transformed macrophages called epithelioid cells.
3. Lymphocytes, plasma cells, and fibroblasts
4. Langhans giant cells

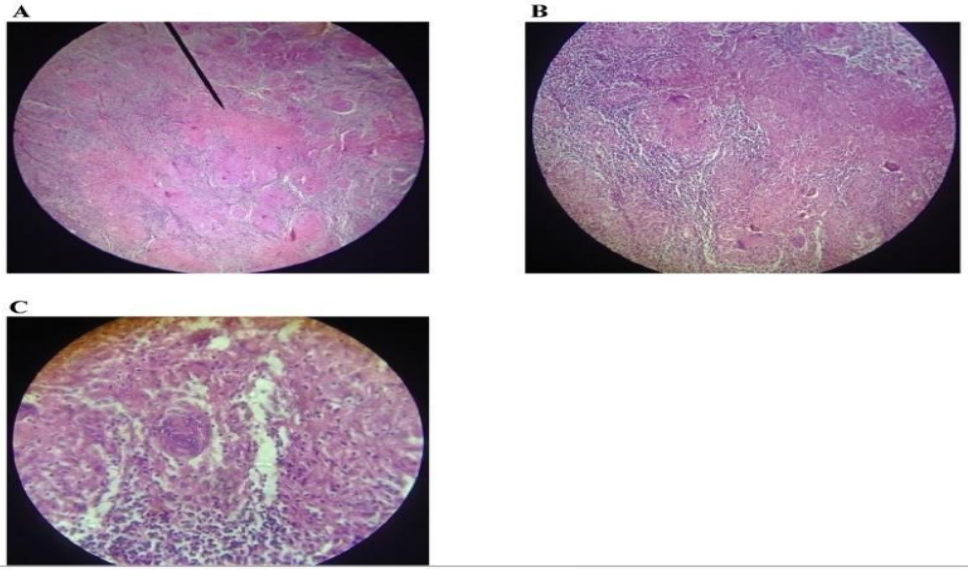


Figure 1: (A) Caseous necrosis. (B) Granuloma surrounded by lymphocytes. (C) Multinucleated giant cells and lymphocytes in tubercular granuloma.

Symptoms of Tuberculosis [9]:

If a patient has any of the following, consider him a 'Tuberculosis Suspect":

1. Cough for over 3 weeks.
2. Haemoptysis.
3. Pain in the chest for over 3 weeks
4. All these can be due to some other diseases but sputum must be tested if any of the symptoms are present. Cough and sputum is very common everywhere. Much of this is due to acute respiratory infections and lasts only a week or two.

There is also much chronic cough due to chronic bronchitis (sometimes called 'Chronic Obstructive Pulmonary Disease' (COPD or other names). This is mostly due to tobacco smoking, but may also occur from atmospheric pollution (either due to cooking or heating fires or in some places due to industrial pollution). [8]

- General Symptoms: [8]

1. Loss of weight.
2. Fever and sweating.
3. Loss of appetite.
4. Breathlessness.
    a. Respiratory Symptoms:
5. Cough
6. Sputum.
7. Blood-spitting.
8. Tiredness.
9. Amenorrhea.
10. Arrhythmia
11. Hoarseness.

Diagnosis [9]:

1. Cough > 2 weeks
2. Fever > 2weeks
3. Exposure to TB
4. Chronic immune suppression
5. Endemic country
6. Abnormal physical exam

Laboratory and Diagnostic Studies:

Active tuberculosis may be considered as a possible diagnosis when findings on a chest radiograph of a patient being evaluated for respiratory symptoms are abnormal, as occurs in most patients with pulmonary tuberculosis. The radiographs may show the characteristic findings of infiltrates with cavitation in the upper and middle lobes of the lungs[10] (Figure). However, specific groups of patients, such as the elderly and patients with advanced infection by human immunodeficiency virus, may not have these typical findings. Compared with other patients, both groups have the classic cavitation less often and may have lower-lobe infiltrates as a prominent finding. [11,10] Although abnormal findings on a chest radiograph may suggest tuberculosis, they are not diagnostic for the disease. [12]

Traditionally, the first laboratory test used to detect active tuberculosis in a patient with abnormal findings on chest radiographs is examination of a sputum smear for the presence of acid-fast bacilli (Table 1). Also, because the bacilli have entered the sputum, the patient is infectious to others. According to the Centers for Disease Control and Prevention, [12]3 sputum specimens should be used for detection of pulmonary tuberculosis, with specimens collected in the morning on consecutive days. However, recently, investigators have questioned the need for 3 specimens. Leonard et al[13] concluded that examination of 2 specimens is just assensitive.

For the test, sputum is smeared on a slide, stained, dried, and then treated with alcohol. Any bacilli that are present will remain red because they will not destain. The test is not specific for tuberculosis, because other mycobacteria give the same results, but it does provide a quick method to determine if respiratory precautions should be maintained while more definitive testing is performed. Results of sputum smears should be available within 24 hours of the specimen collection. [12]

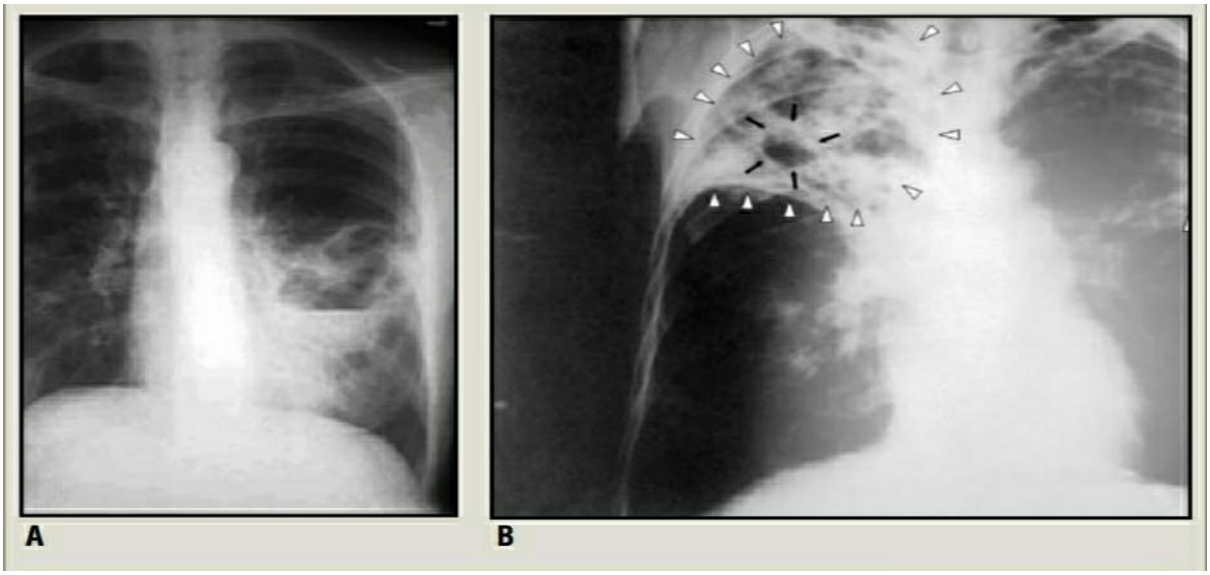


Figure 2: Chest radiographs in pulmonary tuberculosis. A, Infiltrates in left lung. B,Bilateral advanced pulmonary tuberculosis and cavitation in apical area of right lung.[14]

Table 1. Diagnostic tests for identifying tuberculosis

Variable	Sputum smear	Sputum culture	Polymerase chain reaction	Tuberculin skin test	QuantiFERON-TB test	Chest radiography
Purpose of test orstudy	Detect acid-fast bacilli	Identify Mycobacterium tuberculosis	Identify M tuberculosis	Detect exposure to mycobacteria	Measure immune reactivity to M tuberculosis	Visualize lobar infiltrates with cavitation
Time required for results	<24 hours	3-6 weeks with solid media, 4-14 days with high-pressure	Hours	48-72 hours	12-24 hours	Minutes

Treatment of TB:

First Line Anti-TB Drugs:

The most commonly used standard chemotherapeutic regime for treatment of TB consists of first line drugs such as isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB) for an initial 2-month phase followed by a continuation phase with INH and RIF for 4 months (Table 2). Streptomycin is a bactericidal antibiotic that affects polypeptide synthesis but is no longer considered as a first line drug because of high rates of resistance [15,16].

Second Line Anti-TB Drugs:

The second line drugs are often used for treatment of TB in special conditions such as extensively drug-resistant tuberculosis (XDR-TB) or multidrug-resistant tuberculosis (MDR-TB). Various classes of second-line drugs (SLDs) used for the treatment of TB are given in (Table 3). The second-line drugs differ from first-line ones as they may be less effective than the first-line drugs (e.g., p-amino salicylic acid); or may have toxic side-effects (e.g, cycloserine); or may be unavailable in many developing countries (e.g... fluoroquinolones) [16,17].

- Fluoroquinolones: Ofloxacin, Levofloxacin, Moxifloxacin, Ciprofloxacin
- Other Oral Drugs: Ethionamide, Prothionamide, Cycloserine, Terizidone, Paraamino- salycylic acid (PAS), Rifabutine, Rifapentine
- Injectable Drugs : Kanamycin, Amikacin, Capreomycin

DOTS (Directly Observed Treatment, Short-Course):

Drug resistance is more relevant in TB and is contributed by the poor management of chemotherapy, which makes the treatment more complex, increases its length and side effects[18]. Multidrug-resistance (MDR) is mainly concerned with the resistance of M. tuberculosis strains to both isoniazid and rifampicin, regardless of the sensitivity/resistance to other drugs. MDR-TB is alarming due to the high risk of death associated with it while resistance to either drug may be managed with other first-line drugs or second-line drugs underDOTS Plus[19]. Extensively drug-resistant TB (XDR TB) strains have been recently reported byvarious Centers for Disease Control (CDC) with resistance to at least three out of the six classes of second-line drugs (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine, and p-amino salicylic acid). Almost 20% of MDR-TB cases were classified as XDR-TB in some regions, raising concerns over a future epidemic of virtually untreatable TB[20]. DOTS is the most effective strategy available for controlling TB.

It plays a major role in global plans of WHO to stop TB on the basis of five main principles that include

1. Political commitment to control TB (establishing a centralized and prioritized system of TB monitoring, recording and training).
2. Case detection by sputum smear microscopy examination
3. Anti-TB drugs to be given under the direct observation of the health care provider/community DOT provider.
4. Regular, uninterrupted supply of anti-TB drugs.
5. Systematic recording and reporting system that allows assessment of treatment results ofeach and every patient during the whole TB control programme [21].

Table 2. Basic regimens for the treatment of TB.

Preferred Reimen	**Alternative Regimen**	**Alternative Regimen**
Initial Phase Daily INH, RIF, PZA, and EMB for 56 dose (8 weeks)	Initial Phase Daily INH, RIF, PZA. andEMB for 14 doses (2 weeks), then twice weeklyfor 12 doses (6 weeks)	Initial Phase Thrice-weekly INH, RIF, PZA, and EMB for 24 doses(8 weeks)
Continuation Phase Daily INH and RIF for 126doses (18 weeks) or Twice- weekly INH and RIF for 36 doses (18 weeks)	Continuation Phase Twice-weekly INH and RIFfor 36 doses (18 weeks)	Continuation Phase Thrice-weekly INH and RIFfor 54 doses (18 weeks)

Novel Drug Delivery Systems

Patient non-compliance is the most important reason of drug resistance in TB patients. Secondly, for multidrug resistant TB, patients must take second-line anti-TB drugs for 18-24 months. Novel drug delivery systems seem to be the most promising option for advancement in the treatment of TB. NDDSS reduce the dosing frequency, shorten the treatment period, are biocompatible and release the drug in a sustained manner. This helps in improving patient compliance. Inhalation of drugs to treat both local and systemic pathologies has gained much attention in the last decade. Recently developed new drug delivery systems are detailed in Table 3.

Table 3. Novel drug delivery systems developed for controlling TB.

S. No.	Drug Delivery System	Method of Preparation	Remarks	Ref
A.	Site directed drug delivery system			
1	Isoniazid + rifampicin	Emulsion Method	Reduce dose and dosing frequency	[22]
2	Capromycin	Spray drying	Enhance local tissue concentration and is aneffective alternative to capromycin injection	[23]
B.	Nanoparticle based drug delivery system			
1	Rifampicin-pyrazinamide + Isoniazid with PLG nanoparticles	Double emulsion	Plasma drug level maintained above MIC for6-9 days	[24, 25]
2	Ethambutol with PLG nanoparticles	Double emulsion	Plasma level maintained for7 days	[26]
3	Rifampicin nano emulsion	O/W type	99% entrapment efficiency	[27]
4	Clofazimine suspension	Nano crystalline Suspension	Overcomes low solubility	[28]
5	Rifampicin nano suspension	Supercritical carbon dioxide-assisted atomization	Localized delivery to lungs	[29]
6	RIF, INH and streptomycin within PBCA and PIBCA nano capsules	PNP	Longer stability	[30]
7	Moxifloxacin-loaded PBCA NPS	Anionic polymerization	Increased intracellular concentration	[31]
8	Isoniazid-poly(ethylene-glycol)-poly (aspartic acid) conjugates	Polymeric micelles	5.6 Fold increase in anti-tubercular activity	[32]
9	Clofazimine liposomes	Encapsulation	In vivo reduced toxicity	[33]
10	Rifabutine liposomes	Encapsulation	Increased therapeutic activity	[34]

CONCLUSION:

Tuberculosis (TB) is an infectious disease caused by the bacillus Mycobacterium tuberculosis (M-Tb). Tuberculosis is a chronic granulomatous infectious disease. Infection occurs via aerosol, and inhalation of a few droplets containing M. tuberculosis bacilli. Most cases of TB are pulmonary and acquired by person to person transmission of air-borne dropletsof organisms. It can be diagnosed by PPD, IGRA, Sputum studies, X-rays and Biopsies.

Tuberculosis remains a leading cause of mortality worldwide even in 21st century. The high proportion of drug-resistant TB among new cases across the countries indicates transmission of alarming levels of drug-resistant forms of TB and is a major cause of worry which needs to be addressed. All the countries in the world should join hands to make a coordinated effort to control multidrug-resistant tuberculosis (MDR) and extensively drug- resistant tuberculosis (XDR-TB). XDR-TB can only be treated with a handful of drugs, whichare more expensive and have additional side-effects in comparison to those used to treat MDR-TB. Further synergy of this disease with HIV worsens the situation. It is extremely important to develop new methods to detect and monitor drug-resistant tuberculosis quickly, particularly for HIV infected patients. There is a dire need to increase efforts to measure resistance to second-line anti-tuberculosis drugs worldwide. Current efforts to control the disease should be accelerated to have an impact in what appears to be a growing epidemic of drug-resistant tuberculosis. Monitoring of drug resistance should be made as a part of routine surveillance. The currently available drugs used to fight TB were discovered by chance. Consequently, there is a global need to develop novel and potent leads that could reach the clinics in the form of drugs and can treat multidrug-resistant tuberculosis. Usage of first and second line anti-TB drugs, DOTS strategy and novel drug delivery systems in accordance with the latest WHO, CDC guidelines might be effective for complete management of TB. To strengthen the current treatment regimens, especially in developing countries, addition of therapeutic vaccines is required. New vaccines are being developed to curb latent TB infections. Several Research and academic institutions are actively involved in the development of new anti TB drugs acrossthe world. As an outcome of the strenuous efforts of researchers in this direction, many novel molecules are in various stages of drug discovery pipe line. Effective implementation of DOTS as well as adherence to a scientific attitude by physicians and patients is must for curbingthis socioeconomically significant disease.

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