



Deep Insight to Mycobacterium Tuberculosis (Mtb): Causes, Symptoms, Diagnostics, Treatment, Risk Assessment & Recent Advances

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Abstract

Nearly ¼ TH of world's population is affected by the bacteria that is causing TB, but only 1/10 TH of them affecting TB disease called "Mycobacterium Tuberculosis" (Mtb). It can be two forms namely active and latent. Tuberculosis is ranked by WHO as "One of the top 10 leading causes of death". This is true both before and after COVID-19 pandemic^[3]. This paper discusses about TB causes, microscopic analysis, Infection, symptoms, diagnosis, treatment, and complexities.

Keywords: TB, M Tuberculosis, Drug Resistance TB, TB infection with co-infection.

Introduction

Johann Schonlein coined the term "tuberculosis" in the 1834, though Archaeologist have found TB in the bones of ancient bison in Wyoming. These bison lived over 17,000 years ago. Tuberculosis (TB) was named "phthisis" in ancient Greece, "tabes" in ancient Rome, and "schachepheth" in ancient Hebrew. *Mycobacterium tuberculosis* (Mtb) was discovered by Dr. Robert Koch on 24TH March 1882^[1,2].

Mycobacterium Tuberculosis Microscopic Review

Mycobacterium tuberculosis is the etiologic agent of tuberculosis (TB) in humans. Humans are the only reservoir for the bacterium. *Mycobacterium bovis* is the etiologic agent of TB in cows and rarely in humans. Both cows and humans can

serve as reservoirs for *Mycobacterium bovis*. Humans can also be infected by the consumption of unpasteurized milk. *Mycobacterium Tuberculosis* is aerobic, non-sporing, non-motile and non-Capsulated bacteria. They measure 0.5um X 3um in size. It can appear straight or slightly curved thin rod-shaped bacilli and live in single, pairs or small clumps. Since it is aerobic, prefers to go to lungs. It can divide in 18 – 24 hours. It falls under the category of mycobacterium because it had mycolic acid in its cell wall. Mycolic acid is rich in lipid. This makes it resistant to gram stain. That why it is also called acid fast bacilli. It can survive against week disinfectants^[4]. It needs oxygen to grow, and it falls into category of "Aerobic Bacterium" that's why it prefers to go to lungs and it only travels through air by cough.

The cell wall envelope of mycobacteria is structurally distinct from that of both Gram-positive and Gram-negative bacteria. In *Mycobacterium tuberculosis*, this cell wall has unique structural features and plays a crucial role in drug resistance and macrophage survival under stress conditions. Peptidoglycan is the major constituent of this cell wall, with an important structural role, giving structural strength, and counteracting the osmotic pressure of the cytoplasm. Synthesis of this complex polymer takes place in three stages that occur at three different locations in the cell, from the cytoplasm to the external side of the cell membrane, where polymerization occurs. A fine balance of peptidoglycan synthesis and degradation is responsible for a plethora of molecular mechanisms which are key to the pathogenicity of *Mycobacterium tuberculosis* (Mtb). Enlargement of mycobacterial cells can occur through the synthesis of new peptidoglycan, autolysis of old peptidoglycan, or a combination of both processes^[4].

Transmission

Mycobacterium tuberculosis is transmitted normally by air-borne route. When infected person with active TB disease talks, sings, coughs, sneezes, etc droplets containing the Mtb is expelled into the environment and the person who inhales it gets infected. However, concentration of mycobacterium in the droplets, frequency and strength of cough, dilution of the droplets in the atmosphere, exposure in the sun light, frequency and strength of the exposure, ventilation, virulence of the strain of mycobacterium tuberculosis exposed in atmosphere, duration of the exposure, are some of the important factors determining the transmission. Usually after transmission, it does not become active and will be latent inside the lungs. When it gets opportunity such as immunosuppression in become active. It rarely become active after transmission. Therefore, a person with latent TB cannot spread the

mycobacterium whereas the person with active TB can spread the mycobacterium^[5].

Pathophysiology

Primary infection prefers to go lower lobe of lung but latent infection prefers upper lobe since upper lobe has high V / O ratio (ratio between ventilation and absorption of oxygen in blood). As soon as the mycobacterium enters the lung alveolar macrophage phagocytose it. Due to its various virulence factor, the macrophage is unable to digest the mycobacteria. *Mycobacterium tuberculosis* has three major virulence factors namely, catalase peroxidase, sulfides and trehalose dimycolate. Catalase peroxidase prevents oxidation of cells. So the mycobacterium grows inside the macrophage and then kills the macrophage. After some time the macrophage blasts and the mycobacterium get spread to the whole lung which results granuloma formation. Granuloma is bacteria surrounded by all immune cells. It is a step-in order to prevent spreading of the infection. After this the lung tissue inside the granuloma dies which is called ghon focus caseating necrosis, the mycobacterium may travel to near lymph node and caseating necrosis may occur there. Lymph necrosis in addition to Ghon Focus is known as Ghon complex. Ghon complex may undergo fibrosis and calcification to form scar tissues. This stage is called Ranke complex. From there are two ways to proceed further. One way is immune system clears the infection successfully. The other is it may become latent and after getting immunosuppression becomes reactivated. Memory T cells release cytokines as an attempt to contain the mycobacteria. But this result to mere caseating necrosis in the lung. Now the infection gets dispersed throughout the lung. It may go to lymphatics and spread cell over the lungs. This may cause bronchopneumonia. These mycobacteria may also spread through lymphatic system and vascular system to all parts of our body. This is called miliary TB. It affects macrophages and can go into other cells when required. It produces catalase peroxidase which

prevents oxidation of cells. It produces sulfide that affects macrophages and prevents phagosome activation and phagosome lysosome fusion. It also produces trehalose dimycolate which evades immune response, cytokine release and granuloma formation. It has long pathogenetic chain. It may also spread to other parts which is called Miliary TB. Patients should be tested for TB before giving immunosuppressant drugs. The central necrosis in granulopoiesis promotes mycobacterium transmission is hallmark characteristics of sever TB cases. One of the recent studies reveals that mycobacterium tuberculosis induced necrosis accelerates the growth of the bacteria within dead cell. Hence, Mycobacterium tuberculosis (Mtb) induced cell death plays an important role in the pathogenesis. Mycobacterium tuberculosis (Mtb) Caused granulomatous inflammation’s patterns are Necrotizing and Non-Necrotizing granulomas^[1,6,7].

TB Prevention

TPT is a drug or a set of drugs which is used to protect someone from TB infection. It does not work during TB disease. This is being given first to the risky population who have higher risk of getting infected with TB infection and easily progress from infection to disease. BCG (bacillus Calmette-Guerin) vaccination plays a critical role in the preventive management, however difference in opinion is raised by experts on the efficacy of the BCG. WHO recognises the efficacy of the BCG. It is widely accepted that it

reduces the risk of childhood TB with an 85% reduction in TB meningitis and miliary TB^[8]. Vaccination can be classified into preventive Pre-exposure, Post exposure and therapeutic. Vaccines can also be classified based on their biochemical forms namely live attenuated, inactivated, protein subunit or recombinant which targets various cells or subcellular components of TB pathogenesis^[9]. About two dozen of tuberculosis vaccines are under various stages of trail which gives hope for the possible future vaccine with improvised protection. Some of the promising candidates are MIP, RhMCV,ChadOx1 / PPE15, AEC/BC02, H1:IC31, M72/AS01E, RUTI, BCG – Zmp 1, SapM, CysVac2, VMP1002, Ad5-CEAB, Ad35, GaM.tb, H4:IC31, H56:IC31, ID93/GLA-SE, DAR, MTBvac, V7, Vaccae, DAR-901, Immuvac,MVA84A,AD5Ag85A, etc^[10].

Screening & Diagnosis:

Screening:

There are more than 40 tools for screening namely symptoms screening and chest radiography, c-reactive protein, and rapid molecular test available. Symptom screening involves checking a person for TB symptoms and TB symptom include weight loss, hemoptysis, fever, high heart rate and respiratory rate ^[1,11-16]. The symptoms screen is summarised in the table-I below. Clinician shall exercise caution on symptoms which can mimic age related illness, or some patients may not exhibit critical symptoms.

Table I: Symptom Screening Summary Table

TB Type	Symptoms
Latent	
Latent	No symptom
Active TB Based on Body Part Affected	
Pulmonary TB	Cough with or without blood / phlegm, chest pain, shortness of breath.
TB Lymphadenitis	Fever, Fatigue, Unexplained weight loss, Night sweats, Swollen Lymph nodes.
Skeletal TB	Active TB symptoms, Severe back pain, Stiffness, swelling, abscesses, bone deformities
TB Pericarditis	Chest pain. Fever, Palpitation, Shortness of breath, cough
Cutaneous TB	Lesions (flat, painless, purplish or brownish red, wart like appearance & small bumps and sores.
TB Meningitis	aches, Pains, loss of appetite, Persistent headache, low grade fever, nausea, vomiting, severe headaches, sensitivity to light, neck stiffness
Gastrointestinal	Nausea, Vomiting, Loss of appetite, fever, ascites buildup of fluids in the abdomen (abdominal

Tract TB	swelling, bolting & tenderness), abdominal pain, changes in bowel habits, abdominal mass which can be felt.
Liver TB	Liver enlargement, Jaundice, High grade fever, upper abdominal pain,
Genito urinary TB	Testicular swelling, Painful urination, decreased or interrupted flow of urine, pelvic pain, back pain, decreased semen volume, infertility.
TB Lymphadenitis	Fever, Fatigue, Unexplained weight loss, Night sweats, Swollen Lymph nodes.
Transverse Myelitis	Weight loss, asthenia, intermittent fever, night sweat, lower limb weakness, neck stiffness, positive Brudzinski and Kernig’s sign, areflexia lower limbs, paraparesis, severe headache, inability to walk, urinary incontinence.
TB-IRIS	Shortness of breath, cough, fever, weight loss, night sweat.
Miliary TB	Fever of several weeks duration with morning temperature spikes, anorexia, weight loss, lassitude, dry cough with phlegm, coughing up blood in phlegm, night sweat, skin reactions, abdominal pain, symptoms of hepatosplenomegaly

Diagnosis:

Radiographical tools and laboratory test tools can be effectively used along with clinical trial, pros, and cons of various radiographical, and laboratory test tools are presented in the table-II. Chest X-ray is highly sensitive tool. Artificial Intelligent (AI)

backed advanced radiography machines can identifies abnormalities. C-Reactive Protein is a general marker of inflammation in the body. Rapid Molecular Test is less sensitive tool and requires follow up test. Access for the diagnostic test to be ensured.

Table II: Pros & Cons of Analytical tools

Test	Pros	Cons
Tuberculin skin test	High specificity in non-BCG-vaccinated populations	Training required for administration and interpretation
	Cost-effectiveness	Return visit required in 48–72 hours for test result Possible false-positive and false-negative results
Interferon- γ release assay	High specificity	Blood withdrawal required
	Only one patient visit required	Indeterminate results in those who are immunosuppressed
	Results available in 16–24 hours	No capacity to differentiate between latent and active TB
	No confounding by BCG vaccination	High cost
Chest radiography	Ready availability	Low sensitivity and specificity
	Capacity to differentiate latent infection from active TB	Not confirmatory
Smear microscopy	Ease, speed, and cost-effectiveness of the technique	Low sensitivity
	Quantitative estimate of the number of bacilli	No capacity to differentiate from nontuberculous mycobacteria
	Usefulness in determining infectiousness and in monitoring treatment progress	
Conventional culture using solid media	Examination of colony morphology possible	Wait of 3–8 weeks for result
	Quantitative results	
Automated liquid-culture systems	Sensitivity greater than culture in solid media	Contamination-prone
	Faster results (1–3 weeks)	Stringent quality-assurance systems required Expensive equipment required
Nucleic acid amplification test (NAATs)	High specificity	Low sensitivity with smear-negative TB
	Higher sensitivity than smear microscopy	Contamination-prone
	Rapid (1–2 days) diagnosis	Technical skill and expertise required
	Capacity to differentiate TB from other mycobacteria	High cost

TB Classification and Treatment:

TB can be classified into three, namely Drug susceptible, drug resistance and miliary. Drug resistance can be further classified into five, namely mono drug Resistant, Poly Drug Resistant, Multi Drug Resistant (MDR-TB), Pre-Extensively Drug Resistant (Pre-XDR TB) and Extensively Drug Resistant (XDR-TB). Miliary TB occurs when bacilli enter the bloodstream and dispersed throughout the body. It is rare and risk to life. Treatment shall be in accordance with WHO guidelines or local health authority guidelines. Effectiveness of the TB treatment is depending on prompt diagnosis of TB, recognition of drug resistance, patient’s adherence on drug regimens, contact tracing and prophylactic treatment of contacts, screening of TB infection in high-risk group. Patients with co-infection and co-morbid disease often call for multidisciplinary comprehensive support and treatment [10,12,14,17-20].

Role of Nutrition

Lack of nutrition in the body leads to blunt immune response on pathogens. This is a very dangerous to them because nothing will be there to destroy the pathogen. A study showed that vitamin A deficiency in household contacts increased 10 times progression from infection to disease. It also showed that vitamin E and D deficiency increased 2 times and 5 times chances of progression from infection to disease respectively[21,22]. Body Mass Index (BMI) plays an important role in this. Multiple studies shows that undernutrition likely increases severity and worsens treatment outcome. Zinc protects our body from free radicals and prevents lung damage by hypoxia[23,24]. Table-III represent the simplified clinical interpretation of BMI index; caution should be exercised by the clinician based on clinical trial and other analytical results.

Table-III: Clinical Interpretation

BMI, Kg/m ²	Interpretation
<16	Undernutrition
16 – 15.9	Moderate undernutrition
17 – 18.5	Mild undernutrition
25 - 30	Over-weight
>30	Obese

Risk Assessment

Lab analysis along with clinical trial can be corelated with epidemiological data to get an insight on adverse side effects, drug interaction, concurrent diseases, etc should be considered for the development of the treatment plan. The following factors plays a critical role in the risk assessment of MDRTB^[19].

- Exposure to known MDR – TB patients
- HIV co-infection / patient with immune suppression treatment, diabetes, malnutrition.
- Healthcare providers with high prevalence of MDR-TB
- Discontinued treatment with first line regimen
- Failure to respond to first line regimen.
- Relapse after a full course of treatment with first line regimen.
- Living in aerosol countries with high prevalence of MDRTB

Management of side effects due to anti-TB drugs plays a vital role in the success of treatment. Second line anti-TB drugs have many side effects than first line anti-TB drugs. Manging the side effects is normal part of the treatment and it responsibility of clinician to diagnose and treat it. Suspending any drug due to side effects should be based on the weighting the risk of continued side effect against chances of curing a deadly disease. Nephrotoxicity, Hypothyroidism, neurotoxicity, electrolyte wasting (similar to Fanconi’s syndrome) & ototoxicity due to injectables shall

be monitored as part of the treatment. Second line drugs are known to cause birth defects, for this reason all women of childbearing age should use reliable method of contraception during multi drug resistant TB treatment. Capreomycin may increase risk of ototoxicity, may be used when necessary. Ethionamide generally avoided because of increased risk of nausea and vomiting associated with pregnancy. The risk of birth defects in MDR-TB treatment is highest in the first trimester of pregnancy, so the gestational age of the fetus shall be confirmed before taking these drugs. In some cases, mother does not accept the risk of the treatment and clinically stable, treatment can be delayed until the second trimester after comprehensive multidiscipline specialist opinion [4,17,19,20,25,26].

Pulmonary TB can be associated with various long-term complications such as scarring (fibrosis), bronchiectasis, chronic pulmonary aspergillosis (CPA), air way stenosis and chronic obstructive pulmonary disease (COPD). In one of the studies on 51 numbers of patient successfully treated with multi drug resistance TB, reveals 78% of them had persistent respiratory symptoms, 98% had residual radiological sequelae, 96% had ventilatory defects with 66% with ventilatory defects exhibiting a mixed type of ventilatory abnormality while 19% had pure restriction and 11% had pure obstruction after completion of treatment. Aspergillus lung disease may exhibit in three ways: Invasive Aspergillosis, a serious life-threatening lung disease that present pneumonia; Allergic bronchopulmonary aspergillosis (ABPA) presenting as syndrome of severe asthma with fungal sensitization often with central bronchiectasis and CPA which in post TB patients commonly present as an Aspergilloma / mycetoma. In post TB CPA, the fungus, most commonly Aspergillus fumigatus, colonizes cavities in the lung left behind by the TB^[25,26].

Older TB patients may not exhibit classical clinical symptoms such as cough, hemoptysis, fever, night sweats or weight loss. Dyspnoea is

more common, and haemoptysis is less common. The symptoms can mimic age related illness such as reduced functional capacity, chronic fatigue, cognitive impairment, anorexia, or pyrexia of unknown origin. It often difficult to obtain the basic data from elder patients due to poor memory, hearing, sight and speech difficulties [27,28,29].

Some studies report abnormal liver enzymes, hypoalbuminemia, hyponatraemia, hypokalaemia, and normocytic normochromic anaemia. One of the recent studies reveals increased mortality in older patients (28% in those ≥ 84 years) was observed within 60 days of treatment initiation and increased number of adverse events occurred in older patients despite the common practice of excluding the pyrazinamide (PZA) from initial regimen for many patients aged 80 years or above. It should be noted that immune system undergoes remodelling and decline as age advances. Special care to provide for elderly patients [19,28,29,35,36].

Central nervous system (CNS) TB is associated with high mortality and morbidity. Tuberculous myelopathy is rare form of neurological TB. Spinal cord involvement manifests like intramedullary tuberculoma, leptomeningitis, extradural TB and rarely transverse myelitis (TM). Direct bacillary invasion, vascular thrombosis, immunological mechanism, or mechanism related to treatment may cause TM. Transverse myelitis is a focal inflammatory disorder of spinal cord, often associated with infectious disease and can lead to permanent paraplegia or quadriplegia^[17,32-34].

In Tuberculosis meningitis paradoxical inflammatory reaction are very difficult to predict and may result in morbidity and death. It is believed that the cause is excessive host immune response to dead or dying mycobacteria. Host directed therapies such as corticosteroids can reduce the cause of permanent neurological damages. However, detailed investigation shall be carried out before starting the treatment^[33].

Peripheral neuropathy (PN) is a serious condition affecting the nerves are common for TB patients.

In this condition nerves are affected, compromising the replay of information from different parts of body. It can affect sensory nerves, motor nerves or autonomic nerves. Causes of PN in patients with TB are TB itself, co-morbid conditions, malnutrition, diabetes mellitus, anti-TB medications, etc. Suspected patients need to be monitored carefully^[31].

Another adverse effect of anti-TB drug is Tuberculosis-immune reconstitution inflammatory syndrome (TB-IRIS)^[30]. It may occur during or even after completion of anti-TB therapy. It is an abnormal, excessive immune response against alive or dead mycobacteria tuberculosis that may occur in either HIV infected or more rarely uninfected patients. Paradoxical and unmasking forms are the most common forms of IRIS. Paradoxical IRIS is defined as recurrent, new, or worsening symptoms of treated case. Unmasking IRIS is an antiretroviral (ART) associated inflammatory manifestation of a subclinical infection with a hastened presentation. Pulmonary TB patients may exhibit paradoxical TB-IRIS as a worsening or recurrence of respiratory and constitutional symptoms and often new or expanding infiltrates on chest x-ray images. Lymph node paradoxical IRIS generally represent with rapid enlargement followed by suppuration. Neurological TB-IRIS generally presents with new or worsening meningitis and or features of raised intracranial pressure due to enlarge cerebral tuberculomas or intracranial abscesses; mortality rate is high and can go up to 25%. It may also present with spondylitis, epidural abscesses and radiculomyelopathy. Abdominal TB-IRIS present as granulomatous hepatitis, retroperitoneal lymphadenopathy, and peritonitis whereas musculoskeletal form manifests as mono or poly arthritis. Unmasking TB-IRIS is not well defined, can vary in the degree of clinical presentation, two-third of unmasking form present with lung involvement, often severe pulmonary tuberculosis leading to

acute respiratory distress syndrome or bronchiolitis obliterans organising pneumonia^[37]. Miliary TB is common in infants and children younger than 5 years of age and immunocompromised persons which can be detected in the radiograph appearance of millet seeds scattered throughout the lung. Miliary TB may be found in individual organs including brain, several organs or throughout the whole body. Up to 25% of patients with miliary TB may have meningeal involvement^[35].

Transplantation is available globally. Due to immunosuppression, transplant recipients are at high risk of re-activating latent TB from within themselves or from the transplanted donors. Several guidelines are available however precaution of TB infection of both donor and recipient to be checked^[38,39].

Co-infection of parasitic diseases will normally increase the complication of TB treatment. Co-infections such as HIV, helminth increases the risk of active TB and aids progression of TB^[40].

TB infection will be potential etiology for those have pulmonary diseases such as pneumonia, COPD and lung cancer. Auto-immune disease such SLE (systemic lupus erythematosus) and sarcoidosis will activate the TB because of immune suppressive therapy. The metabolic diseases such as diabetes mellitus, atherosclerosis and hypovitaminosis D will promote / increase the risk of TB progression^[41].

A negative culture status six months after treatment initiation, no positive culture thereafter and no relapses within 1 year after treatment completion need to be confirmed for the cured cases of TB. Terminating the treatment in the mid will have adverse impact of health and will be the cause for MDR-TB^[11].

Recent Advances

The use of host-directed therapeutics (HDTs) is intended to increase the success of TB treatment by immunomodulation and / or immune augmentation. Here, immunomodulation alludes

to down-regulating non-productive inflammation and modifying immune response^[42]. In contrast, immune augmentation is considered in the framework of synergizing with anti-TB treatment regimens of drug susceptible (DS) and drug resistant (DR) tuberculosis to improve long term outcome and promote cure. It should be noted that these approaches are at conceptual or laboratory level.

There are many drugs such as OTB-658, FNDR 20364, TB47, GSK839, MBX-4888A, TB-09, GSK-286, TBAJ-587, TBI-223, BVK-GSK098, GSK-286, Macozinone, TBAJ-587/ 876, / 976, TBI-166 / 223, BTZ-043, Delpazolid, GSK-656, OPC-167832, SPR720, SQ-109, Sutezolid, TBA-7371, Telacebec, delamanid, pretomanid, Sanfetrinem, Sudapyridine, clofazimine, Nix-TB, ZeNix, Simplici TB, TB-Practecal, etc. under various stages of trial promising the possible shorter treatment regime, reduced adverse side effects, decreased risk of relapse and evolution of drug resistance, etc^[11,43-47].

Conclusion

Mycobacterium tuberculosis is one of the bacterial diseases that affect the mankind in decades and WHO pledged to eradicate this disease from the world. Measures have been taken to eradicate before 2047. Many vaccines and drugs which are under different stages of development are also promising the end of tragic TB era. However, optimism should be tempered with caution. Policymakers, researchers, clinicians, patient, corporates cooperation is highly solicited for sustained progress in the eradication of TB. Mycobacterium tuberculosis treatment often requires multidisciplinary specialist for complicated and co-morbid patients.

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