

## Lurking in the dark: Latent Tuberculosis infection

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### ABSTRACT

A subset of the tuberculous population has latent tuberculosis infection (LTBI). It is a condition wherein the affected individual is infected with Mycobacterium tuberculosis, but does not have any signs or symptoms of tuberculosis nor is he infectious to others. Risk of progression to active tuberculous infection is influenced by co-morbidities like HIV, diabetes, malignancy requiring chemotherapy, infants and children in close contact with susceptible individuals, and healthcare workers. Early diagnosis of LTBI is paramount. In addition to tuberculin test, Interferon gamma release assay (IGRA) is the new diagnostic modality that can be used for this purpose. Quantiferon-TB Gold In-Tube (QFT-GIT) and T-SPOT TB are the two currently available IGRAs, of which the latter is slightly more preferred. More recently, TB PCR (Polymerase Chain Reaction) has aided accurate and early diagnosis of all forms of TB. While treating LTBI, it is observed that Isoniazid (INH) has stood the test of time and still prevails as the treatment of choice for active infection and for LTBI. Of course, adverse effects of INH and need for regular laboratory monitoring persist. Recently, moxifloxacin has been used as a substitute for INH. Newer drugs like rifapentine, nitromidazopyran, metronidazole and nitrofurans have all been tried with variable success and several clinical limitations, depending on co-morbid conditions. India's burden of extensive prevalence of TB is compounded by paucity of data on the same. The World Health Organization has estimated a mortality of 36 million by 2020 due to TB. This projection should encourage aggressive research into this entity.

**Keywords:** Quantiferon-TB Gold In-Tube, T-SPOT TB, TB PCR, isoniazid

### Introduction

Efforts have been put into elimination of tuberculosis (TB) for decades and yet today, as estimated by the World Health Organization, more than one third of the entire world's population or approximately 2 billion people are infected by TB and can be considered as its carriers. <sup>[1]</sup> A chunk of this population is constituted by cases of 'Latent tuberculosis', which go undetected and progress to active TB. Latent tuberculosis infection (LTBI) is a condition in which the patient is infected with Mycobacterium tuberculosis (M.

tuberculosis), but does not have active tuberculosis disease. He does not have any signs or symptoms of TB and is not infectious. However, 5 to 10% of persons with LTBI are at risk of progressing to active disease. <sup>[2]</sup> Hence identification and treatment of these patients is an important step in limiting the spread of tuberculosis and its eradication. Nearly 2 million people in India develop tuberculosis, thus emphasizing the need for TB control. <sup>[3]</sup> Some researchers consider latent tuberculosis as the mass of the iceberg of TB below sea level which is not seen, which

is dormant but can progress to active infection. Indeed LTBI has compounded the problem of TB eradication.

## Discussion

### Etiopathogenesis

Infection with *M. tuberculosis* occurs on inhalation of infected droplet nuclei, which then reach the pulmonary alveoli. Here they adhere to inactivated macrophages resulting in granuloma formation.<sup>[4]</sup> Sometimes following this infection; infected macrophages containing the bacilli remain in the scar tissue and go into latency. *M. tuberculosis* is an obligate aerobe and requires oxygen to grow. However, it has the capability to change its metabolic state in conditions of oxygen depletion and enter into a state of prolonged dormancy. It can remain dormant for decades, often until death of the individual host, unless there is impairment in host immunity and there is progression to active TB. Thus it implies that the state of microbial latency is maintained by the individual host's cell-mediated immunity. Thus, any factor impairing the immunity can cause reactivation of *M. tuberculosis*. Reactivation is the process where *M. tuberculosis* reverts back to its normal metabolic state, moves out of macrophages, multiplies, and continues the process of infection in pulmonary TB.<sup>[5]</sup>

### Susceptible populations

Accurate diagnosis of LTBI is critical as it has been found that 50% of infants and 15% of older children progress to active TB.<sup>[6]</sup> Risk is higher in persons infected with HIV, diabetes and other chronic conditions, and in those on immunosuppressant drugs such as patients with malignancy on

chemotherapy.<sup>[7]</sup> The characteristic granuloma formation as a reaction to TB is primarily composed of macrophages and T cells. Tumor Necrosis Factor (TNF- $\alpha$ ) plays an important role in granuloma formation and immune defense against TB. Use of TNF- $\alpha$  inhibitors like infliximab in the treatment of autoimmune disorders such as rheumatoid arthritis, ankylosing spondylitis and others causes reactivation of TB. Hence the practice to test for LTBI before starting with TNF- $\alpha$  inhibitors is important.

Additional pool of persons at high risk is constituted by persons in close contact with someone known or suspected to have active TB; infants, children and adolescents in close contact with susceptible individuals, medically underserved and low income population, immigrants from countries with high prevalence of tuberculosis, employees and residents of congregate living facilities such as prison, homeless shelters, rehabilitation centers; employees of long-term care centers including hospitals, clinics, medical laboratories; persons on injectable drug abuse (e.g. cocaine), tobacco users, alcoholics and those with malignancy.<sup>[2, 7, 8]</sup>

### Detection of LTBI

LTBI is asymptomatic, thus progression to active TB presents with typical signs and symptoms of pulmonary TB. These include fever, night sweats, cough, chest pain and weight loss. Physical examination may reveal abnormal breath sounds on the affected side. Chest x-ray shows pulmonary infiltrates with or without cavitation.<sup>[9]</sup> Thus patients presenting with these signs and symptoms, alongwith the risk factors mentioned above should raise suspicion of

active TB. Screening tests of high-risk individuals and persons suspected of having LTBI is an important part of TB control. This is called as targeted testing.<sup>[10]</sup> Once diagnosed with LTBI, treatment should be started immediately, thus preventing progression into active TB. Tuberculin skin test (TST) is the commonest and simplest screening test for tuberculosis. It is performed by intradermal injection of 0.1ml of purified protein derivative of tuberculin containing 5TU, usually on the volar surface of the forearm using a 27-gauge needle with a plastic or glass syringe. The injection should be made just below the skin surface, producing a wheal of 6-10mm in diameter. This test is read in 48 to 72 hours. Interpretation of TST is done by measuring the transverse diameter of induration, not erythema, in millimeters. The widest diameter of the induration should be measured over the forearm, perpendicular to the long axis. Induration more than 5mm is considered significant and greater than 15mm indicates definite tuberculosis.<sup>[11]</sup> TST however, lacks sensitivity for LTBI as there is cross-reaction with BCG vaccine and environmental mycobacteria.<sup>[12]</sup> Hence there are increased numbers of false positives.

Interferon gamma release assay (IGRAs) is the new diagnostic tool for LTBI. It is a surrogate marker for tuberculosis infection and indicates cellular immune response to *M. tuberculosis*. IGRAs are in-vitro blood tests that measure T-cell release of interferon gamma upon stimulation of antigens specific to *M. tuberculosis*. Quantiferon-TB Gold In-Tube (QFT-GIT) and T-SPOT TB are the two currently available IGRAs. IFN- $\gamma$  concentration is measured

when whole blood is incubated with TB antigen stimulation in TB antigen tube and is measured again when incubated without antigen in the nil tube. QFT-GIT measures difference in the interferon gamma (IFN- $\gamma$ ) concentration response. Test is interpreted based on pre-defined cut-off values.<sup>[13, 14]</sup> T-SPOT TB test processes peripheral blood mononuclear cells and measures IFN- $\gamma$  producing cells (spots).<sup>[15]</sup> IGRAs have greater sensitivity than TST as IFN- $\gamma$  that is measured is released from antigen-specific T cells on stimulation with *M. tuberculosis* antigens. This release is absent from BCG vaccine and most non-tuberculous mycobacteria. Thus, IGRAs can also be used to diagnose LTBI in people with history of BCG vaccination. IGRAs, however, cannot distinguish between LTBI and active TB. Sensitivity of QFT-GIT is further compromised in high-risk groups such as individuals infected with HIV, immunocompromised patients, children.<sup>[14, 15]</sup> Negative results, like TST, cannot by themselves exclude *M. tuberculosis* infection and requires careful clinical assessment of the patient. High risk individuals may require follow up TST or IGRAs.

Several attempts have been made to increase the sensitivity of IGRAs such as simultaneous measurement of IFN- $\gamma$  and biomarkers downstream of IFN- $\gamma$  signaling pathway, with marginal improvement.<sup>[16,17]</sup> In latest advancement, it has been found that in vitro immunomodulation of whole blood IGRA (QFT-GIT) increases the sensitivity of T-cell to tuberculosis antigens in individuals with LTBI. Immunomodulation with Toll-like receptor agonists PRR ligands, lipopolysaccharides and imiquimod of

whole blood in patients with LTBI have shown enhanced sensitivity of IGRAs.<sup>[18]</sup>

It has been found that T-SPOT gives lesser number of indeterminate results compared to QFT-GIT. T-SPOT test uses an enzyme-linked immunospot assay to detect increase in the number of cells that secrete IFN- $\gamma$  (represented as spots in each test well) after stimulation with antigen as compared to the media control (Nil). It also includes a borderline category for interpretation of TB response, thus increasing its sensitivity and specificity compared to QFT-GIT.<sup>[15]</sup> T-Spot TB test is the preferred assay to detect LTBI in patients with rheumatic disease before starting with immunosuppressant medication including TNF- $\alpha$  inhibitors.<sup>[17]</sup> Latest advancement in detection of LTBI is the use of TB PCR (Polymerase Chain Reaction) technique as a faster and reliable test. This technique measures IFN- $\gamma$  mRNA from respiratory and non-respiratory specimens. TB PCR is almost 100 percent specific, thus helps in immediate initiation of treatment of latent tuberculosis.<sup>[18,19]</sup> PCR technique targets and amplifies the repetitive sequence IS6110, specific for M. tuberculosis complex. An alternative approach utilizes amplification of 16S ribosomal RNA gene with subsequent colorimetric detection of amplified products. These assays have been developed in Western countries. But the genetic make-up of mycobacterial species is different according to geographic areas. Recent reports suggests that mycobacterial isolates from some geographic regions such as Indian Subcontinent, have less number of copies of the target sequence IS6110, thus lowering its specificity in these TB endemic

areas. This has lead to the introduction of highly specific PCR based technique which amplifies a portion of DNA which codes for a specific protein, MPB64, specific to M. tuberculosis complex of Indian Subcontinent.<sup>[19]</sup> PCR techniques give results within 24 hours, hence rapid diagnosis with greater specificity. PCR is emerging as the new diagnostic tool for tuberculosis.<sup>[20]</sup>

### Treatment

Every patient diagnosed with LTBI can be treated irrespective of age and previous BCG vaccination status. Before initiating treatment, active TB should be ruled out by clinical assessment, chest radiograph and sputum examination.

Isoniazid (INH) is the drug of choice for treating LTBI. Recommended duration of treatment for adults is atleast six months, preferably nine months; daily or twice weekly (under DOTS). For immunocompromised patients and children between 2 to 11 years, INH is recommended daily for nine months. In pregnant women, the nine month INH course may be delayed until delivery, unless there is risk of progression to active TB. In this case, treatment should be initiated during pregnancy with close monitoring for INH toxicity.<sup>[21]</sup> Breast feeding is not contraindicated during INH treatment. Major adverse effects of INH are hepatotoxicity and pyridoxine deficiency. Thus patient should be monitored for signs of peripheral neuropathy and hepatitis. Patients with relevant signs and symptoms should be further evaluated with liver function tests. In patients with neuropathy such as diabetics, alcoholism, HIV, persons

with seizure disorder and pregnant women, pyridoxine supplement is advised at a dose of 10 to 15mg daily. Another option equal to INH regimen is the directly observed 12 dose, once weekly regimen of isoniazid and rifampentine. Rifampentine is rifamycin with half life that is five times longer than rifampin, thus allowing once a week treatment. This regimen however, is not recommended for children less than 2 years of age, people with HIV on antiretroviral therapy, pregnant women and patients suspected of MDR-TB. <sup>[21, 22]</sup>

A 4-month regime of Rifampin can be given in patients who cannot tolerate INH or who have been exposed to INH-resistant TB. <sup>[23]</sup> Drug trials are being performed to formulate new regimens for LTBI. Contacts of INH resistant and MDR-TB are difficult to treat. MDR-TB cases are recommended to receive six months of Pyrazinamide and quinolone; however, studies have reported very high rates of toxicity and intolerance resulting in poor compliance to therapy. The current practice is to give moxifloxacin or levofloxacin alone for six months. Moxifloxacin can substitute INH in treatment of active tuberculosis. <sup>[22, 24]</sup> Other newer drugs found useful for dormant bacilli are nitromidazopyran, metronidazole and nitrofurans. <sup>[25, 26]</sup> However, isoniazid remains the treatment of choice.

### Conclusion

In summary, the understanding of LTBI is challenging due to insufficient data. According to current statistics approximately, 36 million people will die of TB by 2020 if it is not controlled, emphasizing the need for more

information. Scientific community continues its research efforts to learn more from this disease in order to develop more treatment options

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