UNIT NO. 2

LATENT TB INFECTION

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ABSTRACT

Latent TB infection (LTBI) is defined as a state of persistent immune response to stimulation by M. tuberculosis antigens without evidence of clinically manifested active TB. Current methods for LTBI detection are the tuberculin skin test (TST) and the interferon-gamma release assays (IGRAs). Both these tests indicate prior host immunosensitisation to M. tuberculosis antigens and do not provide information regarding viability of the organism within the host. Around 10 percent of immunocompetent adults with LTBI develop active TB in their lifetime: of these, approximately half (i.e. 5%) develop disease within 2 to 5 years of acquiring the infection. The risk of progression of LTBI to active TB disease is increased in HIV/AIDs, in very young children, and in persons with solid and haematological transplant, end-stage renal failure on haemodialysis, silicosis, head and neck malignancies, and diabetes. Isoniazid preventive therapy has been shown to reduce the risk of developing active TB by 60–90 percent. However, it is associated with a risk of hepatoxicity, which increases with age. It is recommended that LTBI testing be targeted at groups/persons with a high risk of progression to active disease (e.g. close contacts, those with HIV infection) and/or for whom the benefit of PT outweighs the risk of hepatotoxicity.

Keywords: Mycobacterium tuberculosis; LTBI, Tuberculin Skin Test; Interferon-gamma Release Assay;

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INTRODUCTION

TB, an airborne infectious disease caused by Mycobacterium tuberculosis (M. tuberculosis), has afflicted man for millennia. It is transmitted via cough aerosols generated by persons with active pulmonary or laryngeal TB; these aerosols which carry M. tuberculosis bacilli in microdroplet nuclei may remain suspended in the air for several hours, and be inhaled into the alveoli of persons in prolonged, close proximity with the infectious index case. Most healthy contacts are able to eliminate the pathogen via their innate or adaptive immunity. Others are able to contain the bacilli within granulomas in the host tissues and remain in a disease-free state. This is referred to as latent TB infection (LTBI), and defined by the World Health Organization (WHO) as "a state of persistent immune response to stimulation by M. tuberculosis antigens without evidence of clinically manifested active TB" .[1,2] Persons with LTBI are asymptomatic, have normal chest radiographs, and are not infectious to others. Around 10 percent of immunocompetent adults with LTBI develop active TB in the course of their lifetime; of these, approximately half (i.e. 5%) develop disease within 2 to 5 years of acquiring the infection.[3] The risk of developing active TB disease is increased in certain medical conditions, the most important being HIV/AIDs. Other risk groups for progression of LTBI to active disease include very young children, and persons with solid and haematological transplant, end-stage renal failure on haemodialysis, silicosis, head and neck malignancies, and diabetes (Table 1).[4,5]

It should be noted that LTBI encompasses a spectrum which, depending on the interaction between the host immune system and bacteria, may range from subclinical TB of low-grade activity, to complete dormancy of the organism.[6,7]

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TESTS FOR LTBI

There is no gold standard test for LTBI. There are currently two methods available for LTBI detection: the century-old **tuberculin skin test (TST)** and the **interferon-gamma release assays (IGRAs)**. Both these tests indicate prior host immunosensitisation to M. tuberculosis antigens and do not provide information regarding viability of the organism within the host[8].

Tuberculin Skin Test (TST)

The TST elicits a delayed-type hypersensitivity reaction to an intradermal injection of PPD (purified protein derivative), which is a crude mixture of proteins obtained from the sterile supernatant of liquid cultures of M. tuberculosis which also contain antigens from non-tuberculous mycobacteria (NTM) and the M. bovis bacille Calmette-Guerin (BCG) substrain. The skin induration is read in millimetres at 48–72 hours after inoculation. The interpretation of the TST (i.e. the cut-off value above which PT is recommended) is dependent on the person's risk of acquiring TB infection or the risk of progression to TB disease if infected.[4] A major drawback of the TST is its low specificity, as a positive reaction may also be caused by previous BCG vaccinations or infection with NTM. The TST may also be falsely negative, especially in immunocompromised patients due to cutaneous anergy. The TST requires personnel trained in the intradermal application of the test and measurement of induration to obtain standardised results; the reading of the test is also subject to inter- and intra-reader variability. Other drawbacks of the TST include the need for a return visit to read the test, and the occurrence of the booster phenomenon.

Interferon-gamma Release Assays (IGRAs)

The IGRAs are commercially available as the **QuantiFERON Gold In-tube (QFT-GIT)** (Qiagen, Hilden, Germany) and **T-SPOT.TB** (Oxford Immunotec, Abingdon, UK) assays. These blood tests measure the production of interferon gamma

(IFN-γ) after overnight stimulation of lymphocytes with M. tuberculosis-specific antigens ESAT-6 and CFP-10 which are encoded in the RD-1 genomic region of M. tuberculosis that is not present in the M. bovis BCG strain and most NTM species.[9]

The major advantage of the IGRAs is their increased specificity compared to the TST in BCG-vaccinated populations. Other advantages over the TST are the utilisation of negative and positive controls to internally control for antigen-nonspecific reactivity or general immune-function, respectively; having a technical readout which is not subject to intra/inter-reader variability; and no requirement for a return visit in 48–72 hours. Although the T-SPOT.TB and QFT-GIT are based on the same principle, these tests utilise different technology platforms. The T-SPOT requires the isolation of peripheral blood mononuclear cells (PBMCs) and the standardisation of 250,000 PBMCs in each of 4 test wells (negative control, positive control, ESAT-6, and CFP-10). After overnight incubation, the number of IFN-γ producing cells ("spot-forming cells") are measured using the enzyme-linked immunospot (ELISPOT) assay. The QFT-GIT is technically less demanding than the T-SPOT. It is a whole-blood assay in which 1ml of blood is drawn into each of a nil-control tube, a positive-control tube, and a tube coated with TB antigens which stimulate CD4 lymphocytes. After an overnight incubation, the cells are spun down and the concentration of IFN-γ in the supernatant is measured using the ELISA assay.

Meta-analyses of the performance of TST and IGRAs have shown the superior specificity of IGRAs to the TST in BCG-vaccinated individuals.[9,10] The IGRAs also show better correlation with M. tuberculosis exposure, and are of similar or even superior sensitivity as compared to TST.[10] Studies on IGRAs in very young children have shown a high percentage of indeterminate results, hence the US Centers for Disease Prevention and Control (CDC) currently recommend the TST in children under the age of 5 years old.[4,11]

It can take 2 to 8 weeks (the "window period") after initial TB infection for the host immune system to manifest a response to M. tuberculosis antigens and for the TST or IGRA to detect the infection. The TST and IGRAs are positive in both LTBI and active disease, and quantitative measurements of these tests are not helpful in indicating disease activity. These tests also do not distinguish recent infection from that acquired in the remote past. A negative test result does not exclude the diagnosis of LTBI or TB disease.

The QFT-GIT assay has very recently been replaced by the 4th generation **QuantiFERON-TB Gold Plus.** This assay includes an additional antigen tube which stimulates both CD4 and CD8 lymphocytes. This is in recognition of the role of CD8+ T cells in TB immunity. TB-specific CD8+ T cells that produce IFN-γ have been shown to be more frequently detected in those with active TB disease vs latent infection,[12,13] to be associated with recent TB exposure,[14] to be detectable in active TB subjects with HIV co-infection and young children,[15,16] and observed to decline when patients are exposed to anti-TB treatment.[17] Studies using this assay are awaited to see if it can indeed improve sensitivity and fulfil currently unmet clinical needs in identifying those with active disease, those with recent LTBI, and for the monitoring of response to anti-TB treatment.

LTBI TREATMENT (PREVENTIVE THERAPY)

Singapore's National TB Control Programme uses a 6-month course of isoniazid as standard treatment for LTBI. This is based on randomised controlled studies by the US Public Health Services during the 1950s and 1960s in close contacts and TB-endemic populations which demonstrated the efficacy of isoniazid monotherapy in reducing progression of LTBI to active TB by 60–90 percent.[18,19,20,21] A similar protective effect has also been shown in HIV-TB co-infected persons.[22] Other preventive therapy (PT) regimens include rifampicin for 4 months (which is reserved for selected cases under Singapore's TB Control Programme), and a regimen comprising 12 doses of once-weekly rifapentine and isoniazid given under directly-observed therapy.[23,24]

Decisions pertaining to medical management should not be based on the TST or IGRA result alone, but should take into account the epidemiology, the history and other clinical factors of the person tested. Persons with positive test results must be screened for active TB with chest radiograph and sputum examination where appropriate. Failure to exclude active TB before commencing PT may result in the generation of drug resistance as a result of monotherapy of active disease. The prescribing physician should be aware of the risk of isoniazid hepatotoxicity, which increases with age.[25,26] Persons on PT should be counselled regarding signs and symptoms of hepatotoxicity and monitored at least monthly for any medication adverse effects and for adherence to treatment.

Targeted Testing for LTBI

It is recommended to only test for LTBI in groups/persons with a high risk of progression to active disease and/or for whom the benefit of PT outweighs the risk of hepatotoxicity.[27] WHO guidelines for high/upper middle-income countries with TB incidence <100/100,000 population recommend the systematic testing and treatment of LTBI in people living with HIV, adult and child contacts of pulmonary TB cases, patients initiating anti-tumour necrosis factor (TNF) treatment, patients receiving dialysis, patients preparing for organ or haematologic transplantation, and patients with silicosis.[1]

Persons at low risk of TB or progression of LTBI to active disease should not be tested, as screening such persons diverts resources from higher-priority TB control activities and increases the number of false positive results. The sensitivity and specificity of any test depends on the prevalence of the condition in the population screened. When applied to a low-risk group, increased rates of false positive results will occur. In the case of LTBI, low-risk persons who test falsely positive will be unnecessarily exposed to the risk of drug toxicity.

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Table 1: Risk Factors for Development of Active TB among Persons with LTBI

Estimated risk for TB relative to persons with no known risk factor	
AIDS	110-170 times
HIV infection	50-110
Solid Organ Transplant	20-74
Silicosis	30
Recent TB infection (<2 years)	15
Chronic renal failure requiring haemodialysis	10-25
Carcinoma of head and neck	16
Abnormal chest radiograph with upper lobe fibro nodular disease typical of healed TB infection	6-19
TNF Alpha inhibitor therapy	1.7-9
Glucocorticoid therapy	4.9
Children 0-4 years old	2.2-5
Diabetes mellitus (all types)	2-3.6
Underweight (BMI <20)	2-3
Smoker (1 pack/ day)	2-3
Person with no known risk factor	1

Source: Lobue P, Menzies D. Treatment of latent tuberculosis infection: An update. Respirology. 2010; 15: 603-22.

LEARNING POINTS

- **Latent TB infection (LTBI) is defined as a state of persistent immune response to stimulation by M. tuberculosis antigens without evidence of clinically manifested active TB. Persons with LTBI are asymptomatic, have normal chest radiographs, and are not infectious to others.**
- **Current methods for LTBI detection are the tuberculin skin test (TST) and the interferon-gamma release assays (IGRAs). Both these tests merely indicate prior host immunosensitisation to M. tuberculosis antigens and do not provide information regarding viability of the organism within the host.**
- **Persons at low risk of TB or progression of LTBI to active disease should not be tested, as screening such persons diverts resources from higher-priority TB control activities and increases the number of false positive results which may lead to unnecessary treatment and exposure to risk of isoniazid hepatotoxicity.**