

Editorial

Management of latent tuberculosis infection: An evidence-based approach

Most individuals who get exposed to *Mycobacterium tuberculosis* (MTB) manage to eliminate or contain the infection using host T-cell immune defenses. However, some MTB bacilli may remain viable (latent) and “reactivate” later to cause active TB disease. This state is called latent TB infection (LTBI). Although LTBI and active TB disease are part of a dynamic spectrum,^[1] people with LTBI are asymptomatic and not infectious. For example, nearly 50% of doctors and health care workers in India will test positive on the Mantoux tuberculin skin test, but a majority will not display any TB symptoms, or develop active TB disease.^[2] Such individuals, presumably, have LTBI. However, some health care workers may go on to develop symptoms, and if found to have active TB require the standard four-drug short course anti-TB therapy.

Identification and treatment (i.e. preventive therapy or prophylaxis) of LTBI can substantially reduce the risk of development of active disease (by as much as 60%), and is an important TB control strategy in low-TB incidence settings where reactivation disease usually accounts for the majority of non-imported TB disease.^[3] For example, LTBI screening and treatment is a major component of TB control programs in both USA and Canada, and large numbers of individuals are tested for LTBI and treated with isoniazid for 9 months.

The goal of testing for LTBI is to identify individuals who are at an increased risk for the development of active TB; these individuals would benefit most from treatment of LTBI. There is no diagnostic gold standard for LTBI and all existing tests are immunological tests that provide indirect evidence of sensitization of the host to TB antigens.

There are two available tests for identification of LTBI: Tuberculin skin test (TST) and interferon-gamma release assays (IGRA). TST is usually performed using the Mantoux skin test method, and purified protein derivative (PPD) is the antigen injected intradermally. Skin induration is read after a period of 48-72 h.

IGRAs are done in vitro, and instead of PPD, they use highly specific peptides from two main antigens—early secreted antigenic target (ESAT6) and culture filtrate protein (CFP10). Commercial IGRAs include QuantiFERON-TB Gold In Tube (Qiagen, Valencia, CA, USA), and T-SPOT. TB (Oxford Immunotec, UK). Both TST and IGRA depend on cell-mediated immunity (memory T-cell response), and a positive result suggests that the patient has been exposed and sensitized to MTB in the past.

A detailed recent review of these tests is available elsewhere.^[4] Briefly, published data suggest that both TST and IGRA are acceptable, but somewhat imperfect tests. Both represent indirect markers of MTB exposure and measure a cellular immune response to MTB (read as mm induration with the TST, and amount of interferon-gamma released by T-cells in IGRAs). Neither test can accurately differentiate between LTBI and active TB. Neither test can resolve the various stages within the spectrum of MTB infection.

Both TST and IGRA have reduced sensitivity in immunocompromised patients (e.g., people living with HIV/AIDS), and have low predictive value for progression to active TB. In other words, a majority of individuals with positive TST or IGRA results will not progress to active TB disease.^[5]

Tuberculin skin test surveys in India show a very high annual risk of TB infection.^[6] Given the very high TB burden of active TB in India, it is not surprising that nearly 40% of Indians are estimated to be latently infected.^[7] Given the large number of latently infected individuals in the country, the Revised National TB Control Program (RNTCP) does not give priority to LTBI detection and treatment in the public sector. This is true for most high TB burden countries around the world.

For high-burden countries such as India, what should be the approach toward the management of LTBI? In 2014, World Health Organization (WHO) published its first comprehensive guideline on management of latent TB infection.^[8] This guideline offers a clear, evidence-based algorithm [Figure 1].^[8]

As shown in the algorithm, WHO recommends that only selected risk groups should be evaluated for LTBI.^[8] These include people living with HIV, adult and child contacts of pulmonary TB cases, patients initiating anti-tumor necrosis factor (TNF-alpha) treatment, patients with end-stage renal failure on dialysis, patients preparing for organ or hematologic transplantation, and patients with silicosis.

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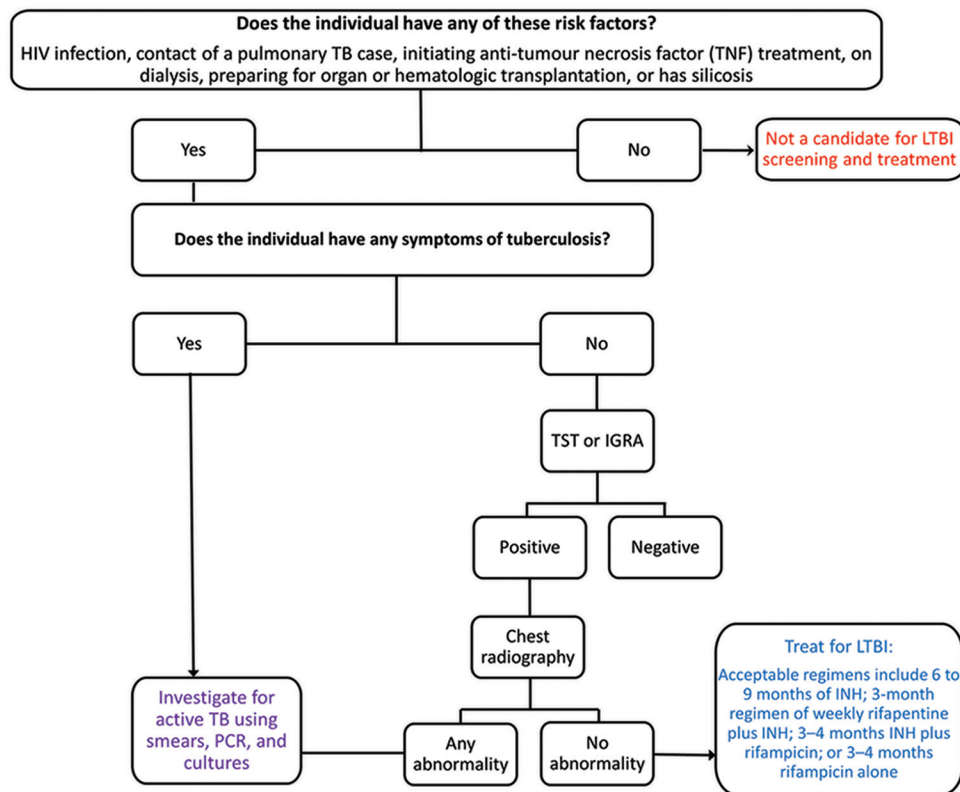


Figure 1: World Health Organization algorithm for latent tuberculosis infection management. Source: Adapted from WHO, Geneva⁸

The rationale for giving priority to these subgroups is that they are at a very high risk of progressing from latent infection to active disease, and this progression could be prevented by treating LTBI.

If an individual has any of the above risk factors, the WHO algorithm requires that they be assessed for TB symptoms. If any TB symptom is present (e.g., cough, fever, weight loss, hemoptysis, night sweats), then the focus should be on diagnosing active TB using WHO and RNTCP-endorsed microbiological tests such as smear microscopy, TB cultures, and molecular tests as Xpert MTB/RIF (Cepheid Inc, Sunnyvale, CA, USA), and line probe assays as Genotype MTBDR *plus* (Hain Life Science, Nehren, Germany). Chest radiography can also be used as part of the work-up for active TB. If the individual has no symptoms, then WHO recommends that either TST or an IGRA be used to test for LTBI in high-income and upper middle-income countries with estimated TB incidence less than 100 per 100 000. TST is preferred and IGRA should not replace TST in low-income and other middle-income countries.^[8]

If either TST or IGRA is positive, then the next step is to rule out active disease, before starting LTBI treatment. This is done by getting chest radiography done. If the radiogram shows any abnormalities, then it is critical to investigate for active TB, using smear microscopy, TB cultures, and molecular tests. If the radiogram is normal and the individual has no symptoms, then the

likelihood of active TB is very low, and LTBI treatment can be initiated.

What are the drug regimens available for LTBI treatment? Unlike active TB where four drugs are required in the intensive phase, the burden of bacteria in LTBI is quite low. So, even a single TB drug is sufficient. As shown in the WHO algorithm, treatment options recommended by WHO include 6–9 months of isoniazid, 3-month regimen of weekly rifapentine plus isoniazid, or 3–4 months isoniazid plus rifampicin, or 3–4 months rifampicin alone.^[8] All regimens are known to be efficacious, but adherence can be poor with longer regimens such as 9 months of isoniazid.^[3] Rifampicin containing regimens may be more suitable in populations with a high background level of isoniazid monoresistance.

Regardless of the regimen used for LTBI, it is important to ensure adherence, and provide patients adequate counseling about why they are being treated for LTBI (despite not having symptoms), likely adverse events, and monthly follow-up visits. The risk of toxicity is highest with isoniazid, especially in older individuals, and those who consume alcohol.^[3]

In India, there is concern that tests such as Mantoux and IGRAs (e.g., TB Gold, TB Platinum) are being misused for active TB diagnosis.^[9] The WHO algorithm clearly shows that when doctors suspect active TB, they should test for active TB, not screen for LTBI. In fact, the Standards for TB Care in India (STCI) clearly state that both TST and IGRAs should not be used for the diagnosis of active TB in high

endemic settings such as India.^[10] If IGRAs are used for active TB diagnosis, this will result in significant overdiagnosis of TB, because of the high background prevalence of LTBI in India. In children, STCI suggests that the Mantoux test may have some value as a test for infection, in addition to chest radiography, symptoms, history of contact, and other microbiological investigations (e.g., gastric juice acid fast bacilli and Xpert MTB/RIF).^[10]

In conclusion, LTBI screening must be restricted to specific high-risk populations in India, where the benefits of LTBI treatment outweigh any risks. Although either TST or IGRA can be used for LTBI screening, it is important to make sure that these tests are not used for active TB diagnosis. For persons with symptoms or abnormal chest radiograms, physicians should order smears, cultures, and molecular tests (these tests are now available in the public sector, and made more affordable in the private sector in India via the Initiative for Promoting and Affordable Quality TB Tests (IPAQT - www.ipaqt.org)). If LTBI is diagnosed, then physicians must rule out TB disease with chest radiography before starting one of the recommended drug regimens. It is important to ensure adherence, and provide adequate counseling to ensure that patients do not stop therapy prematurely.

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