

Utility of Mantoux and Interferon-gamma Release Assays

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ABSTRACT

India has the highest burden of tuberculosis (TB). This article presents a review of the diagnostic utility and various limitations of the Mantoux and the interferon-gamma release assays (IGRA) tests in this high TB endemic setting. While both the tests cannot differentiate between latent and active TB, recent guidelines from WHO strongly recommends against the use of IGRA as an alternative to Mantoux test for India.

Keywords: Mantoux, Interferon-gamma release assays, Tuberculosis.

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INTRODUCTION

In today's era where drug-resistant strains of *Mycobacterium tuberculosis* (MTB) are highly prevalent in India, there is a major drive in the standard recommendations towards initiating TB treatment in a clinically suspected TB after confirmatory evidence through microbiological/molecular testing rather than collaborative evidence of exposure. The significance of the century-old Mantoux test in the diagnostic workup of pediatric TB is compared with the modern IGRA test in India.

MANTOUX TEST

Mantoux test or tuberculin skin test (TST) is done by intradermal injection of 0.1 mL 2 TU RT23 tuberculin in the ventral forearm, 2–4 inches below the elbow joint to raise a wheel of about 6 mm. The induration palpated with the help of fingertips or ballpoint is then read after 48–72 hours with a scale held in transverse axis over the induration.

The test is defined as positive if there is 10 mm or more induration after 48 hours when no more than 2 TU RT23 tuberculin is used.

Each part of the above definition is crucial, and it is the size of induration and not erythema that is read; 10 mm is cut off for a positive result except in HIV infected where the lower cutoff of 5 mm is acceptable. Patients presenting beyond 72 hours but within 7 days need repeat testing if negative and is labeled as positive if still above 10 mm and beyond 7 days require repeat testing. Repeat testing if indicated, should be on the other forearm. The strength of the tuberculin test of 2TU is extremely important as false positive results are greater with the use of greater strength. Under no circumstances should strength beyond 5TU be used.¹ Finally, the test is read as either positive or negative and has no further grades of positivity, i.e., skin necrosis, vesiculation, ulceration, or the extent of induration have no significance.

Pitfalls of TST Test

Errors in technique, underlying host immune suppressed condition due to primary or acquired immune deficiency, malnutrition, steroids, viral infections, or energy caused by severe TB itself can result in false-negative results. False positive results are known with BCG vaccination and infection with non-tubercular mycobacteria (NTM). However, the timing of BCG vaccination is important as there is the least interference with TST if the vaccine given at birth. TST can remain positive even after the clearance of infection.²

INTERFERON-GAMMA RELEASE ASSAYS TEST

While TST employs a skin test to demonstrate the delayed hypersensitivity to tuberculin antigen, IGRA test is a whole blood

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test which is based on the principle that IFN- γ are released when the TB sensitized T lymphocytes are mixed with antigens derived from MTB. The two commercially available tests are QuantiFERON-TB Gold In-Tube test (QFT-G-IT) which uses enzyme-linked immunosorbent assay (ELISA) and (T SPOT.TB) which involves an enzyme-linked immunosorbent assay. While Quantiferon-Gold measures the amount of interferon-gamma produced in response to three *M. tuberculosis* antigens (QFT-G:ESAT-6 and CFP-10; QFT-GIT: ESAT-6, CFP-10, and TB7.7), T-SPOT.TB measures the number of peripheral mononuclear cells that produce IFN- γ after stimulation with ESAT-6 and CFP-10.

The advantage of IGRA over Mantoux test is that the antigens utilized are not present in BCG vaccine and most nontubercular mycobacteria (NTM), other than *M. marinum*, *M. kansasii*, *M. szulgai*, and *M. flavescens*. It is a rapid test as the only a single visit is required to the laboratory.

Pitfalls of Interferon-gamma Release Assays Test

The technique is more complicated, thereby much costlier and requires processing within hours of collection of blood so that lymphocytes remain viable at the time of testing. The sensitivity and specificity are varied, and there is no superiority established of either IGRA test over TST in the diagnosis of active TB in high TB endemic area.³ It is not recommended in young children less than 5 years, and immune-compromised.⁴

Current Role of TST and IGRA

Both these tests with their respective limitations can only detect latent tubercular infection (LTBI). It cannot distinguish between latent and active disease. Both tests rely on T cell-mediated response and have low sensitivity in immunocompromised patients. IGRA has been widely used in high-income countries for detection of LTBI where the TB burden is low. There are conflicts about utility between the tests even in low TB burden countries. An example of

such a conflict is in BCG vaccinated young children where IGRA is preferable over TST especially if BCG vaccine has been given after infancy, while TST is preferable over IGRA in less than 5 years).⁴ IGRA test–Not endorsed for India

On reviewing the evidence of its specificity and sensitivity over TST for children in high endemic country like India, the expert committee of WHO strongly recommends against its use as an alternative to TST in pediatric TB for the diagnosis of latent TB infection, or as an alternative to TST in the workup of a diagnosis of active TB disease in children, irrespective of HIV status).³ TST test as a supportive tool in the workup for TB diagnosis

Though the TST test still continues to be used by pediatricians in diagnostic workup for tuberculosis, its role is very limited. Clinical and radiological leads are more important to decide about the need for further investigations for confirmatory evidence.

For example, in the diagnostic algorithm of a suspected case of tuberculosis lymph node swelling, if FNAC of the lymph node is suggestive of a granuloma/non-caseating granuloma without AFB, an alternative diagnosis or lymph node biopsy should be resorted for diagnosis, irrespective of Mantoux test being positive or negative.¹

Role in Prevention of TB Disease

The lifetime risk of a general population who have latent TB infection to develop active TB is 5–10% whereas the risk in HIV / immunocompromised or young children is 10% every year.⁵ In high TB endemic countries, the risk of exposure to TB and being latently infected is high, and the majority of the healthy population do not progress to active disease. Also, the predictive value of the LTBI tests in identifying those with the highest risk of progression is low.² Therefore, it is prudent to offer LTBI treatment with Isoniazid prophylaxis (10 mg/kg/day) for 6 months to the specific group of children where the risk of progression to active TB is definitely high and will have maximum benefit from preventive treatment. These are:¹

- HIV infected children who either had a known exposure to an infectious TB case or are tuberculin skin test (TST) positive (≤ 5 mm induration) but have no active TB disease, and

- TST positive children who are receiving immunosuppressive therapy (e.g., as in nephrotic syndrome, acute leukemia, etc.).
- The other two indications for chemoprophylaxis which is regardless of TST positivity are asymptomatic contacts (under 6 years of age) of a smear-positive case, after ruling out active disease and irrespective of their BCG or nutritional status, and a child born to mother who was diagnosed to have TB in pregnancy after congenital TB has been ruled out.

CONCLUSION

Both Mantoux (TST) test and IGRA have a role only in detecting latent tubercular infection, and positive results cannot confirm the active disease. IGRA is not recommended by WHO for use as an alternative to TST test in high TB endemic country. TST test has a limited role in the diagnostic algorithm of clinically suspected TB in the present times in the background of availability of improved microbiological and molecular tests and the high prevalence of drug resistance. TST positivity result can be utilized for initiating chemoprophylaxis in immune-suppressed children without active TB.

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