

Mantoux test and its interpretation

Surajit Nayak, Basanti Achariya

Department of Skin
and VD, MKCG Medical
College and Hospital,
Berhampur, Orissa, India

ABSTRACT

The tuberculin skin test is one of the few investigations dating from the 19th century that are still widely used as an important test for diagnosing tuberculosis. Though very commonly used by physicians worldwide its interpretation always remains difficult and controversial. Various factors like age, immunological status coexisting illness etc influence its outcome, so also its interpretation. Utmost care is required while interpreting the result and giving an opinion. This article has been written with the purpose of elucidating the performance and interpretation of the standard tuberculin test.

Key words: Interpretation, Mantoux test, tuberculosis

INTRODUCTION

Tuberculosis (TB) remains a leading cause of morbidity and mortality in the world, especially in developing countries. A combination of factors including high costs, limited resources and the poor performance of various diagnostic tests make the diagnosis of TB difficult in developing countries. Short of demonstrating viable organisms in body tissues and fluids the tuberculin skin test (TST) is the only method of detecting *M. tuberculosis* infection in an individual and is used in the diagnosis of TB in individual patients, as well as in epidemiological settings, to measure the prevalence of tuberculous infection in populations.

It was developed by Koch in 1890 but the intradermal technique currently in use was described in 1912 by Charles Mantoux, a French physician who developed on the work of Koch and Clemens von Pirquetto^[1] to create his test in 1907. After such a long history it is surprising that the interpretation of the test remains controversial.

However, various factors both in the host and inherent in the test lower both its specificity and sensitivity. Consequently, its application in any group of patients will usually yield a wide range of results, from the presence of a reaction in uninfected children to the complete absence of a reaction in some children with confirmed TB disease. The distribution of results generally falls into one of two patterns depending on the

rate of false-positive (cross-reactions from other mycobacterial infections) in the population.

The tuberculin most widely used is purified protein derivative (PPD), which is derived from cultures of *M. tuberculosis*. The "old tuberculin" is no longer used for this purpose; instead, a more standardized product called PPD-S (purified protein derivative, prepared according to the method described by Siebert, from *M. tuberculosis* is used. PPD of non-tuberculous (i.e. atypical) mycobacterium are identified by a letter other than S. PPD-A is from *M. avium*; PPD-G from the Gause strain of schotochromogen; PPD-B from the nonphotochromogen Battey bacilli; PPD-F from the rapid grower *M. fortuitum* and PPD-Y from the yellow photochromogen *M. kansasii*. It is PPD-RT (Research Tuberculin) 23 that is commonly used Indian clinician, are not easily available and may have different interpretation parameters.

IMMUNOLOGIC BASIS FOR THE TUBERCULIN REACTION

The reaction to intracutaneously injected tuberculin is the classic example of a delayed (cellular) hypersensitivity reaction. T-cells sensitized by prior infection are recruited to the skin site where they release lymphokines. These lymphokines induce induration through local vasodilatation, edema, fibrin deposition, and recruitment of other inflammatory cells to the area. Features of the reaction include (1) its

Access this article online

Website: www.idoj.in

DOI: 10.4103/2229-5178.93479

Quick Response Code:



Address for correspondence:

Dr. Surajit Nayak,
Department of Skin
and VD, MKCG Medical
College, Berhampur,
Orissa, India.
E-mail:
surajitnyk@yahoo.co.in

delayed course, reaching a peak more than 24 h after injection of the antigen; (2) its indurated character; and (3) its occasional vesiculation and necrosis.

ADMINISTRATION

A standard dose of five tuberculin units (TU) (0.1 ml) is injected intradermally (into the skin) and read 48 to 72 h later. PPD-RT 23 with Tween 80 of strength 1 TU and 2 TU are standardized tuberculins available in India supplied by the Bacillus Calmette-Guérin (BCG) vaccine Laboratory, Guindy, Chennai. Other tuberculins available in the market are not standardized. Tween 80 is a detergent added to tuberculin to prevent its adsorption on glass or plastic surface. Presently, all tuberculins are manufactured and standardized with Tween 80.

A person who has been exposed to the bacteria is expected to mount an immune response in the skin containing the bacterial proteins. For the sake of standardization of reading and interpretation of results, 5 TU of tuberculin PPD RT23 is used almost universally. It is to be injected strictly intradermally, using 28 or 26-gauge needle and tuberculin syringe from which 0.1 ml can be delivered accurately. A discrete, pale elevation of the skin (a wheal) 6 to 10 mm in diameter should be produced when the injection is given correctly. If it is recognized that the first test was improperly administered, another test dose can be given at once, selecting a site several centimeters away from the original injection. A note in the record should indicate the site chosen for the second test.

Conventionally, the test is given on the left forearm to avoid errors in reading. However, right arm may be used in case of any contraindication to use the left arm. The volar aspect of the forearm is the preferred site of test. After having a TB skin test, it is extremely important to make sure that the patient keeps the appointment to have the test reaction read. The patient is instructed to keep the test site clean, uncovered, and to not scratch or rub the area. The Mantoux skin test should be read between 48 and 72 h after administration. Reading should be performed in a good light, with the forearm slightly flexed at the elbow. The basis of reading is the presence or absence of induration, which may be determined by inspection (from a side view against the light as well as by direct light) and by palpation. For standardization, the diameter of induration should be measured transversely to the long axis of the forearm and recorded in millimeters.^[2,3] Reliable reading of the Mantoux skin test requires standardization of procedures, training, supervision, and practice. This may also include periodic standardized reliability testing. The exact measurement of the induration in millimeters (mm) should be recorded. Erythema (redness) should not be measured.

ADVERSE EFFECTS

Though rare there have been reports of anaphylactic reaction^[4]

and foreign body reaction^[5] involving a Mantoux test site. There is a very slight risk of having a severe reaction to the test, including swelling and redness of the arm, particularly in people who have had TB or been infected previously and in those who have previously had the BCG vaccine. Allergic reactions are also rare complications. Live bacteria are not used in the test so there is no chance of developing TB from the test. Local reactions such as regional lymphangitis and adenitis may also occur on rare occasions.

INTERPRETATION OF TUBERCULIN REACTION

The Mantoux test does not measure immunity to TB but the degree of hypersensitivity to tuberculin. There is no correlation between the size of induration and likelihood of current active TB disease but the reaction size is correlated with the future risk of developing TB disease. The test has a poor positive predictive value for current active disease.^[6] There is no correlation between the size of post-vaccination Mantoux reactions and protection against TB disease and routine post-BCG Mantoux testing serves no purpose.

The results of this test must be interpreted carefully. The person's medical risk factors determine the size of induration the result is positive (5 mm, 10 mm, or 15 mm).

A record should also be made of formation of vesicles, bullae, lymphangitis, ulceration and necrosis at the test site. The formation of vesicles, bullae or necrosis at the test site indicates high degree of tuberculin sensitivity and thus presence of infection with tubercle bacilli.^[7]

Five mm or more is positive in

- HIV-positive person
- Recent contacts of active tuberculosis cases
- Persons with nodular or fibrotic changes on Chest X-ray consistent with old healed TB
- Organ transplant recipients and other immunosuppressed patients who are on cytotoxic immune-suppressive agents such as cyclophosphamide or methotrexate.
- Patients on long term systemic corticosteroid therapy (> than six weeks) and those on a dose of prednisone ≥ 15 mg/day or equivalent.
- End stage renal disease

Ten mm or more is positive in

- Recent arrivals (less than five years) from high-prevalence countries
- Injectable drug users
- Residents and employees of high-risk congregate settings (e.g., prisons, nursing homes, hospitals, homeless shelters, etc.)

- Mycobacteriology lab personnel
- Persons with clinical conditions that place them at high risk (e.g., diabetes, prolonged corticosteroid therapy, leukemia, end-stage renal disease, chronic malabsorption syndromes, low body weight, etc.)
- Children less than four years of age, or children and adolescents exposed to adults in high-risk categories
- Infants, children, and adolescents exposed to adults in high-risk categories

Fifteen mm or more is positive in

- Persons with no known risk factors for TB. Reactions larger than 15 mm are unlikely to be due to previous BCG vaccination or exposure to environmental mycobacteria.

False-positive result

Some persons may react to the TST even though they are not infected with *M. tuberculosis*. The causes of these false-positive reactions may include, but are not limited to, the following:

- Infection with non tuberculous mycobacteria
- Previous BCG vaccination
- Incorrect method of TST administration
- Incorrect interpretation of reaction
- Incorrect bottle of antigen used

Due to the test's low specificity, most positive reactions in low-risk individuals are false-positives.^[6] A false-positive result may be caused by nontuberculous mycobacteria or previous administration of BCG vaccine. Prior vaccination with BCG may result in a false-positive result for many years later.^[9]

False-negative result

A negative Mantoux result usually signifies that the individual has never been exposed to *M. tuberculosis*. However, there are factors that may cause a false-negative result or diminished ability to respond to tuberculin.^[10,11]

- Cutaneous anergy (anergy is the inability to react to skin tests because of a weakened immune system)
- Recent TB infection (within 8-10 weeks of exposure)
- Very old TB infection (many years)
- Very young age (less than six months old)
- Recent live-virus vaccination (e.g., measles and smallpox)
- Overwhelming TB disease
- Some viral illnesses (e.g., measles and chicken pox)
- Incorrect method of TST administration
- Incorrect interpretation of reaction, insufficient dose and inadvertent subcutaneous injection.

The absence of cell mediated immunity to tuberculin may be due to the lack of previous sensitization or due to a false-negative result for various reasons or due to anergy because of immune suppression. Most children with negative result have

not been infected with *M. tuberculosis*. A small proportion of otherwise normal children with *M. tuberculosis* infection remain PPD-negative for unknown reasons. From the time of infection to the development of CMI there is a window period of some two to six weeks, when the Mantoux test would be negative. Those that are immunologically compromised, especially those with HIV and low CD4 T-cell counts, frequently show negative results from the PPD test. This is because the immune system needs to be functional to mount a response to the protein derivative injected under the skin.

Negative tests can be interpreted to mean that the person has not been infected with the TB bacteria or that the person has been infected recently and not enough time has elapsed for the body to react to the skin test. A repeat test is not advocated before one week as the tuberculin injected for the first test has a booster effect on the subsequent dose. TST may convert to positive \leq eight weeks after *Mycobacterium tuberculosis* infection, an interval that is usually referred to as the "window period". A negative TST obtained $<$ eight weeks before does not exclude infection, and a second test is recommended after eight weeks.^[12] Also, because it may take longer than 72 h for an elderly individual to develop a reaction, it may be useful to repeat the TB skin test after 96 h and again at one week to adequately screen these individuals. Immunocompromised persons may be unable to react sufficiently to the Mantoux test, and either a chest X-ray or sputum sample may be required.

Interpretation in children: A correctly applied Mantoux test can be invaluable in the assessment of a child with suspected TB. The interpretation of the result, however, is often difficult, with different workers using different induration sizes to indicate a positive reaction. Although the test itself is neither 100% sensitive nor 100% specific, the predictive value of a positive reaction is very high in such a group. Malnutrition has previously been shown to affect the results of tuberculin testing. As in other studies, underweight children in this study were significantly more likely to have a negative Mantoux result [Table 1].

Table 1: Cutoff size of reaction for a positive Mantoux test in children

≥ 5 mm	≥ 10 mm	≥ 15 mm
Children in close contact with patients with infectious TB	Children with increased risk of disseminated disease	Children with no risk factors
Children with clinical evidence of possible TB	Children with increased risk of exposure to TB	
Children with radiological features suggestive of previous or active TB		
Children with immunosuppressive conditions (including HIV)		

TB: Tuberculosis

As in many other studies, the majority of children did not have any reaction to tuberculin despite having received BCG immunization soon after birth. The reasons for this are not always clear but clearly whatever tuberculin sensitivity BCG might have caused could not have been significant or persistent. This agrees with the current recommendation that for patients with a high risk for TB the history of BCG vaccination should not be a consideration in the interpretation of the tuberculin test.

THE BOOSTER EFFECT

In some persons who are infected with *M. tuberculosis*, the ability to react to tuberculin may wane over time. When given TST years after infection, these persons may have a false-negative reaction. However, the TST may stimulate the immune system, causing a positive or boosted reaction to subsequent tests. Giving a second TST after an initial negative TST reaction is called two-step testing. When sensitization to mycobacteria has occurred many years earlier, an initial intradermal injection of tuberculin may produce a negative or weakly positive response due to there being too few sensitized lymphocytes in circulation to produce a significant local response. If the test is repeated, a larger reading may be obtained due to the immune response being 'recalled' or 'boosted' by the first test. The second boosted reading is the correct one – that is, the result that should be used for decision-making or future comparison. Boosting is maximal if the second test is placed between one and five weeks after the initial test, and it may continue to be observed for up to two years.

MANTOUX REVERSION

Reversion is defined as the change to a negative Mantoux result following a previous positive result. Generally this phenomenon is uncommon in healthy individuals, occurring in less than 10% of such people with a previously positive Mantoux.

Reversion is more common^[13]

- in older adults (estimated at 8% per year)
- when the initial Mantoux is < 14 mm
- in those where the initial positive reaction was a boosted result (identified by two-step testing).

MANTOUX CONVERSION

Whereas boosting is a recall of the hypersensitivity response in the absence of new Infection, conversion is the development of new or enhanced hypersensitivity due to infection with tuberculous or non-tuberculous mycobacteria, including BCG vaccination.

Mantoux conversion is defined^[14] as a change (within a two-year period) of Mantoux reactivity which meets *either of the*

following criteria:

- a change from a negative to a positive reaction
- an increase of ≥ 10 mm.
- Conversion has been associated with an annual incidence of TB disease of 4% in adolescents^[15] or 6% in contacts of smear-positive cases.^[16]

There is debate about the time required for the immunological changes that produce Mantoux conversion following infection. After inadvertent vaccination with *M. tuberculosis* (the Lubeck disaster), children developed positive reactions in three to seven weeks. Other studies have shown clinical illness, with a positive tuberculin test, from 19 to 57 days after exposure, with a mean of 37 days.^[1]

Therefore, when testing TB contacts for conversion, the second tuberculin test is done eight weeks after the date of last contact with the source case. (In the past, the traditional window period, or interval, of 12 weeks was used.)

BACILLUS CALMETTE-GUÉRIN VACCINE AND THE MANTOUX TEST

There is disagreement about the role of Mantoux testing in people who have been vaccinated. The US recommendation is that TST is not contraindicated for BCG-vaccinated persons and that prior BCG vaccination should not influence the interpretation of the test.

According to the US guidelines latent TB infection (LTBI) diagnosis and treatment for LTBI is considered for any BCG-vaccinated person whose skin test is 10 mm or greater, if any of these circumstances are present:

- Was in contact with another person with infectious TB
- Was born or has lived in a high TB prevalence country
- Is continually exposed to populations where TB prevalence is high.

SITUATIONS WHERE MANTOUX TESTING IS NOT RECOMMENDED

Mantoux testing is not recommended in the following situations:

- Past Mantoux reactions ≥ 15 mm: repeating the test will provide no new diagnostic information and will create discomfort
- Previous TB disease: no useful diagnostic information will be gained and significant discomfort is likely
- Infants under 12 weeks old: a positive reaction is very important, but a negative reaction may indicate that the child is too young to mount a response, and the test will need to be repeated if exposure has occurred. Pre-vaccination Mantoux testing before 12 weeks of age is not necessary unless the baby has been exposed to TB.

RECENT DEVELOPMENTS

The Mantoux test is technically difficult to administer and read, so false readings may occur if the tester has insufficient skill. It may require four visits by the patient if a two-step test is performed, and compliance with this is sometimes difficult. A test that can be done on a single patient visit, such as a blood test, would be easier.

The Food and drug administration FDA approved a novel diagnostic test (QuantiFERON-TB GOLD, made by Cellestis, Inc.) for TB. The blood test detects the presence of *Mycobacterium tuberculosis* (TB) infection by measuring interferon-gamma (IFN- γ) harvested in plasma from whole blood incubated with the *M. tuberculosis*-specific antigens, ESAT-6(QFT-RD1) and CFP-10. This new immunodiagnostic test has been launched as an aid in the diagnosis of LTBI. The combination of ESAT-6 and CFP10 was found to be highly sensitive and specific for both *in vivo* and *in vitro* diagnosis. In humans, the combination had a high sensitivity (73%) and a much higher specificity (93%) than PPD (7%). QFT-RD1 test is sensitive for diagnosis of TB, especially in patients with negative microscopy and culture. Despite the fact that antigens such as ESAT-6 and CFP10 are not restricted to *M. tuberculosis*, they hold promise for the specific detection of *M. tuberculosis* infection and, could be a very useful supplementary tool for the diagnosis of TB.

Guidelines for the use of the QuantiFERON test were released by the [Center For Disease control] in December 2005. At present the position of QuantiFERON-TB in the diagnosis of LTBI is not clear. It may be possible in future to replace the skin test with this, or an alternative *in vitro* assay.

REFERENCES

- Menzies D. Tuberculin skin testing. In: Reichman LB, Hershfield ES, editors. Tuberculosis: A comprehensive international approach. New York: Marcel Dekker, 2000. p. 279-322.
- Howard A, Mercer P, Nataraj HC, Kang BC. Bevel-down superior to bevel-up in intradermal skin testing. *Ann Allergy Asthma Immunol* 1997;78:594-6.
- American Thoracic Society. The tuberculin skin test, 1981. *Am Rev Respir Dis* 1981;124:346-51.
- Sanofi Pasteur Limited, Health Canada's Health Products and Food Branch, Public Health Agency of Canada. Risk of serious allergic reactions following Tubersol [tuberculin purified protein derivative (Mantoux)] administration [Dear Health Care Professional letter]. Ottawa: Health Canada; 2005.
- Kim Y, Dawes-Higgs E, Zagarella S. Foreign body reaction involving a Mantoux test site. *Australas J Dermatol* 2005;46:169-71.
- Al Zahrani K, Al Jahdali H, Menzies D. Does size matter? Utility of size of tuberculin reactions for the diagnosis of mycobacterial disease. *Am J Resp Crit Care Med* 2000;162:1419-22.
- American Thoracic Society. The tuberculin skin test statement of American Thoracic Society, Medical Section of the American Lung Association. *Am Rev Respir Dis* 1981;124:356-63.
- Starke JR. Tuberculosis skin testing: New schools of thought. *J Am Acad Pediatr* 1996;98:123-5.
- Chaturvedi N, Cockcroft A. Tuberculosis screening among health service employees: Who needs chest X-rays?. *Occup Med (Lond)* 1992;42:179-82.
- American Thoracic Society. Diagnostic standards and classification of tuberculosis in adults and children. *Am J Respir Crit Care Med* 2000;161:1376-95.
- American Thoracic Society/Centers for Disease Control. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000;161:S221-47.
- Anibarro L, Trigo M, Villaverde C, Pena A, Cortizo S, Sande D, *et al*. Interferon- γ release assays in tuberculosis contacts: is there a window period? *Eur Respir J* 2011;37:215-7.
- Menzies D. Interpretation of repeated tuberculin tests. Boosting, conversion, and reversion. *Am J Respir Crit Care Med* 1999;159:15-21.
- Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. *MMWR Recomm Rep* 2000;49:1-51.
- Sutherland I. The evolution of clinical tuberculosis in adolescents. *Tubercle* 1966;47:308.
- Veening GJ. Long term isoniazid prophylaxis. Controlled trial on INH prophylaxis after recent tuberculin conversion in young adults. *Bull Int Union Tuberc* 1968;41:169-71.

Cite this article as: Nayak S, Acharjya B. Mantoux test and its interpretation. *Indian Dermatol Online J* 2012;3:2-6.

Source of Support: Nil, **Conflict of Interest:** None declared.

Announcement

iPhone App



Download
iPhone, iPad
application

FREE

A free application to browse and search the journal's content is now available for iPhone/iPad. The application provides "Table of Contents" of the latest issues, which are stored on the device for future offline browsing. Internet connection is required to access the back issues and search facility. The application is Compatible with iPhone, iPod touch, and iPad and Requires iOS 3.1 or later. The application can be downloaded from <http://itunes.apple.com/us/app/medknow-journals/id458064375?ls=1&mt=8>. For suggestions and comments do write back to us.