Tuberculin Skin Test

Introduction

The **Mantoux tuberculin skin test** (TST) is the standard method of determining whether a person is infected with Mycobacterium tuberculosis. Reliable administration and reading of the TST requires standardization of procedures, training, supervision, and practice.

The diagnosis of tuberculosis in children by demonstration of the bacilli is difficult as the disease is usually paucibacillary. Hence indirect evidence of tests like the Tuberculin test becomes all the more important.

History

Tuberculin has come a long way from Koch's Old Tuberculin (OT) in the 1890s to the current PPDs in use. The Purified Protein Derivative (PPD) was initially derived by TCA precipitation of culture filtrates by Florence Siebert in 1941. That was accepted by the WHO as the standard preparation PPD-S (PPD-Standard). Another preparation of PPD was made by Siebert at the Statens Serum Institute, Copenhagen in 1958, the PPD-RT23. This was accepted as the international standard. Later a detergent, Tween 80 was added to the PPD to prevent its adsorption to glass vials & syringes.

Hence, currently, there are only two standard preparations of PPD: PPD-S and PPD RT23. 1 tuberculin unit (TU) of PPD RT23 is equivalent to 2.5 TU of PPD-S. In India as PPD RT 23 is available, 2 TU of PPD RT23 should be used, as an equivalent to 5 TU of PPD-S, as per international recommendations.

Utility

The usefulness of the test lies not only on proper technique of administering a standard dose of a standard tuberculin and reading of the reactions by trained personnel but also in its careful interpretation.

Method

There are three types of Tuberculin Skin Tests (TST): the multiple puncture, or Heaf test; the Tine test and the intradermal Mantoux test. The Heaf and the Tine test have poor specificity and sensitivity, and are better avoided. For all practical purposes, the intradermal tuberculin skin test is the internationally accepted standard TST for diagnostic and epidemiological purposes. PPD is available in multi-dose vials of 10 or 50 tests that must be refrigerated at 2 – 8 deg C and discarded within 1 month of opening the vial.

Site of Administration

Tuberculin is injected in a measured amount of 0.1 ml intradermally on the mid-volar aspect of the forearm (Mantoux method). Conventionally, the test is given on the left forearm to avoid errors in reading. However, right arm may be used in case of any contra-indication to use the left arm.

Wheal

A satisfactory test should raise a flat pale pea-sized wheal with clear pits of hair follicles and there should be no leakage of tuberculin. If the test is unsatisfactory i.e., the correct amount has not been injected or the injection has been made into the sub-

cutaneous tissue, then another injection can be given either at a sufficient distance from the first injection or on the other forearm. The site chosen for the second test should be appropriately recorded.

It is to be injected on the volar surface of the forearm after thoroughly cleaning the area with alcohol swab. 0.1 ml of the solution is then injected intradermally using a tuberculin syringe, to form a pea-sized wheal of 6mm diameter.

Adverse effects

In some atopic individuals, an urticarial wheal may appear within minutes of injection. It usually disappears in 1-2 hours. The formation of vesicles, bullae, lymphangitis, ulceration or necrosis at the test site, which may occur in a proportion of children, indicates a high degree of tuberculin sensitivity.

There can be some local reactions, in the form of swelling, itching or irritation. The induration at the site is measured in mm in the transverse axis 48 – 72 hrs later using the finger or a ball-point pen to locate the edge of the induration. In case of irregular indurations, the largest diameter is to be recorded.

Reading of the Test

The injection of the tuberculin antigen leads to migration and proliferation of the sensitized T-cell lymphocytes to the test site. These T-cells release lymphokines, which further attract other lymphocytes and monocytes. These reactions along with increased permeability of the local blood capillaries lead to an induration at the test site. Reading has to be done maximum between 48-96 hours after the test. The reading of the test is done by measuring the maximal transverse diameter of this induration during this period. The erythema at the test site due to increased vascular

permeability extends beyond the induration and is not considered for interpretation of the test results. The reading of the test should be done in good day light with flexed forearm, by carefully palpating the site of injection using one finger. Since PPD RT23 with tween 80 has been found to result in softer reactions, the small indurations may be missed if not sought carefully. The transverse margins of the induration are marked with the ballpoint pen and the maximum transverse diameter is measured in millimetres with a transparent ruler, as followed internationally. The test result should never be recorded as 'positive' or 'negative' and must always be recorded in millimeter of size. Indurations upto 40 min in diameter are found in practice. Record should also be made of formation of vesicles, bullae, lymphangitis, ulceration and necrosis at the test site. A very high degree of inter-reader variation has been observed in the measurement of the induration sizes and more commonly, there is a tendency towards under-reading. Therefore, in any institution, the required number of health workers may be appropriately trained in tuberculin testing and reading to perform the test.

A false negative TST

This can occur if the person has a viral infection, severe cases of TB like disseminated or miliary, and other viral (HIV, mumps, measles, chickenpox) and bacterial (typhoid, brucellosis, typhus, leprosy, pertussis) infections; age; stress; and use of corticosteroid and other immunosuppressive drugs. Other factors include improper storage, faulty administration technique and faulty reading of the reports. A negative Mantoux test does not exclude Latent tuberculosis or tubercular disease.

How is the TST Read?

The skin test reaction should be read between 48 and 72 hours after administration. A patient who does not return within 72 hours will need to be rescheduled for another skin test.

The reaction should be measured in millimeters of the induration (palpable, raised, hardened area or swelling). The reader should not measure erythema (redness). The diameter of the indurated area should be measured across the forearm (perpendicular to the long axis).

WHO recommends a cut off of 10mm for positivity. Keeping the value at 15mm increases specificity at the cost of sensitivity. A positive Mantoux test is indicative of infection with Mycobacteium, with only 10% developing disease. However, it does not differentiate between active and latent disease as well as tubercular from non-tubercular mycobacteria.

What Are False-Positive Reactions?

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 nontuberculosis mycobacteria
- Previous BCG vaccination
- Incorrect method of TST administration
- Incorrect interpretation of reaction
- Incorrect bottle of antigen used

What Are False-Negative Reactions?

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

- 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 6 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

Who Can Receive a TST?

Most persons can receive a TST. TST is contraindicated only for persons who have had a severe reaction (e.g., necrosis, blistering, anaphylactic shock, or ulcerations) to a previous TST. It is not contraindicated for any other persons, including infants, children, pregnant women, persons who are HIV-infected, or persons who have been vaccinated with BCG.

How Often Can TSTs Be Repeated?

In general, there is no risk associated with repeated tuberculin skin test placements. If a person does not return within 48-72 hours for a tuberculin skin test reading, a second test can be placed as soon as possible. There is no contraindication to repeating the TST, unless a previous TST was associated with a severe reaction.

What is a Boosted Reaction?

In some persons who are infected with M. tuberculosis, the ability to react to tuberculin may wane over time. When given a 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.

Why is Two-Step Testing Conducted?

Two-step testing is useful for the initial skin testing of adults who are going to be retested periodically, such as health care workers or nursing home residents. This two-step approach can reduce the likelihood that a boosted reaction to a subsequent TST will be misinterpreted as a recent infection.

Can TSTs Be Given To Persons Receiving Vaccinations?

Vaccination with live viruses may interfere with TST reactions. For persons scheduled to receive a TST, testing should be done as follows:

- Either on the same day as vaccination with live-virus vaccine or 4-6 weeks after the administration of the live-virus vaccine
- At least one month after smallpox vaccination

Conclusion

Thus, the Mantoux test is simple to perform and read, but requires two visits to the lab and this results in drop-outs. It is not the final word for diagnosis of TB, the decision needs to be individualised.