CME CREDIT

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New guidelines: What to do about an unexpected positive tuberculin skin test

ABSTRACT

The 2000 recommendations for tuberculosis testing from the American Thoracic Society and the Centers for Disease Control and Prevention advocate a shift in focus from screening the general population to testing only patients at increased risk of developing tuberculosis.

KEY POINTS

In people at low risk, a tuberculin skin test is now considered positive only if the induration is at least 15 mm; in people at moderate risk the cut point is 10 mm, and in people at high risk the cut point is 5 mm.

Ten percent to 25% of people with active tuberculosis have false-negative test results, especially early in treatment. Some people who are not infected have a reaction due to infection with other mycobacterial species or to bacille Calmette-Guérin vaccine.

For people found to have latent tuberculosis infection, the new guidelines recommend therapy with isoniazid for 9 months. Other options are isoniazid for 6 months, rifampin for 4 months, or rifampin and pyrazinamide for 8 weeks.

Isoniazid-induced hepatitis is uncommon, but when it occurs, it resolves completely if therapy is stopped early enough.

PATIENT INFORMATION
If your tuberculosis skin test is positive, page 56

A 38-YEAR-OLD WOMAN who lives in the suburbs of a large city comes to your office for a tuberculin skin test. She will be volunteering at her daughter's elementary school cafeteria, and the school district requires tuberculosis testing. You perform a tuberculin skin test, and in 2 days she returns for a reading. You measure 12 mm of induration. She has no history of tuberculosis exposure, has no underlying medical conditions, and has never been tested previously. She was born in the United States.

Is the reaction significant? What should you do?

NEW NUMBERS, NEW RECOMMENDATIONS

To eliminate tuberculosis, we must identify people with latent tuberculosis infection and treat them. However, the prevalence of tuberculosis infection in the general population is declining, and therefore so is the positive predictive value of our best screening tool, the tuberculin skin test.

Faced with these changes, in 2000 the American Thoracic Society and the US Centers for Disease Control and Prevention (CDC) revised their recommendations.[1] The new recommendations provide different cut points for interpreting the tuberculin skin test reaction, depending on the risk of tuberculosis infection in the person tested. In brief, a person at low risk needs to have a larger test reaction than a person at high risk for the test to be considered positive.

Other changes in the 2000 recommendations:

Nomenclature. For people who test positive but do not have active tuberculosis, old guidelines spoke of "preventive therapy"; the new recommendations call this "treatment of latent tuberculosis infection." The change is meant to encourage physicians and patients to take positive test results more seriously and consider treatment in this situation.

Treatment options for latent tuberculosis infection have changed somewhat (see below).

Primary care physicians perform most of the tuberculin skin tests in the United States and therefore should be aware of current recommendations. This article reviews:

- Characteristics of the tuberculin skin test
- Who should be tested
- How to interpret the tuberculin skin test
- How to evaluate and treat a patient with latent tuberculosis infection.

PREVALENCE

In the United States, 5% to 10% of the general population and less than 1% of children entering school are infected with tuberculosis.[1] Most of these have latent infections: only 5% to 10% of those infected develop active tuberculosis.

We are fortunate: The World Health Organization estimates that one third of the world population is infected. Most of these people live in parts of the world where active tuberculosis is common.

Induration < 15 mm is not significant in low-risk patients

HOW TUBERCULIN SKIN TESTS WORK

Robert Koch first developed tuberculin from culture filtrates of *Mycobacterium tuberculosis* as a treatment for active tuberculosis. It didn't work as a cure, but patients with and without tuberculosis were found to have different responses to tuberculin injection. As a result, tuberculin skin testing has been used since the 1930s to diagnose M *tuberculosis* infection.[2]

Two formulations of tuberculin are available in the United States: old tuberculin and purified protein derivative (PPD). Old tuberculin is used in veterinary medicine and in the multiple-puncture (tine) screening test. PPD (a solution containing tuberculin protein) is used in the Mantoux skin test, which involves intracutaneous or intradermal injection of 0.1 mL of PPD.

The multiple-puncture test is limited by variation in the amount of antigen introduced during administration.[2] For this reason, the Mantoux or intradermal method is preferred for screening. The test should be read 48 to 72 hours after administration, and the amount of induration should be measured and recorded in millimeters.

INTERPRETING THE TUBERCULIN SKIN TEST

To interpret a patient's skin test response, it is important to understand the characteristics of the test and to know the prevalence of tuberculosis infection in the local community.

The induration that occurs in a tuberculin skin test is a delayed hypersensitivity response to the antigens in PPD. After initial infection with M *tuberculosis*, there is an average incubation period of 6 to 8 weeks, during which the skin test may give a negative result.[3] After that period, the skin test is usually positive.

Sensitivity and specificity

Like many other diagnostic tests, the tuberculin skin test is neither 100% sensitive nor 100% specific. As many as 10% to 25% of people with active tuberculosis have false-negative test results, especially early in treatment.[2]

In addition, some people who are not infected react to the skin test. These reactions may be due to infection with other mycobacterial species (eg, *Mycobacterium avium* complex) or to bacille Calmette-Guérin (BCG) vaccine. These cross-reactions tend to result in small reactions to PPD (< 6 mm), but larger reactions can occur.

The specificity of the test therefore ranges from 95% to 99%, depending on the prevalence of nontuberculous mycobacterial infection in the region. Specificity decreases as the risk of cross-reactions increases.

A specificity of 95% sounds reasonable, until we examine the test characteristics in light of the prevalence of disease in the community. An estimated 5% to 10% of US adults are infected with tuberculosis. If we test this whole group and consider an induration of 10

mm or larger to be a positive response, only 50% to 67% of those with a positive reaction are actually infected with *M tuberculosis*.[2] This is the positive predictive value. In children the prevalence of latent tuberculosis infection is only 1%, so the positive predictive value of a 10-mm reaction is even lower.

We could improve the specificity of the test by increasing the cut point to 15 mm. However, in active tuberculosis infection, the median PPD response is 16 mm. By choosing 15 mm as our cut point, we would miss almost half of those infected.

Testing should target people at risk

The new recommendations address these limitations. First, they shift the focus of tuberculosis control programs from mass screening to targeted testing: identifying and testing people at risk for developing tuberculosis who would benefit by treatment of latent tuberculosis infection if it is detected. Persons at low risk of tuberculosis infection should not be tested.[1]

Those at risk of developing tuberculosis fall into two broad categories (TABLE 1):

- Those at risk of recent exposure to tuberculosis
- Those with underlying medical conditions that increase their risk of developing active tuberculosis if infected.

Size of induration

Whether the tuberculin skin test is positive—and whether follow-up care is needed—now depends on the size of the skin induration *and* the patient's risk profile (TABLE 2).

Patients at high risk of developing active tuberculosis are considered to have latent tuberculosis infection if the skin induration measures 5 mm or greater. This group includes people:

- Infected with human immunodeficiency virus (HIV), regardless of CD4 count
- In recent contact with someone with active tuberculosis
- With fibrosis on a chest radiograph that is consistent with prior tuberculosis infection
- Receiving immunosuppressive treatment equivalent to prednisone 15 mg/day or greater.

TABLE 1

Risk factors for tuberculosis

Factors that increase the probability of recent infection

- Contact with someone with active tuberculosis
- Immigration within the last 5 years from a country with a high prevalence of tuberculosis
- Intravenous drug use
- Confinement or employment in a jail, nursing home, hospital, homeless shelter, or other congregate setting
- Occupational exposure to tuberculosis in a laboratory

Factors that increase the risk of progression to active tuberculosis

- Human immunodeficiency virus infection
- Immunosuppressive drug therapy (eg, in a transplant recipient)
- Fibrosis on chest radiography
- Silicosis, diabetes mellitus, chronic renal failure, leukemia, lymphoma, cancer of the head, neck, or lung, excessive weight loss
- Gastrectomy or jejunoileal bypass

Patients at moderate risk. A skin induration of 10 mm or larger is considered positive.

This risk category includes many types of patients, such as recent immigrants (< 5 years); people with diabetes, chronic renal failure, and some cancers; intravenous drug users; and employees and residents of hospitals, nursing homes, and jails. For a complete list, see TABLE 2.

Patients at low risk. An induration of 15 mm or larger is considered positive. These people have no risk factors.

A reaction ≥ 5 mm is significant in high-risk patients

FREQUENCY OF TUBERCULIN TESTING

The recommendations do not address how often we should screen patients for latent tuberculosis infection. However, some suggestions can be made.

No testing is recommended in low-risk patients.

One-time testing. Patients with medical conditions that increase the risk of progression to active tuberculosis (eg, diabetes, silicosis, chronic renal failure) should have a

TABLE 2

What is a positive PPD test? Indications for chest radiography and treatment

RISK GROUP	SIZE OF INDURATION FOR POSITIVE TEST
Low	≥ 15 mm
(None of the following risk factors)	
Moderate	≥ 10 mm
Recent immigrant (within 5 years)	
Intravenous drug abuser	
Child < age 4	
Resident or employee of hospital, nursing home, jail, shelter	
Patient with diabetes, silicosis, chronic renal failure, leukemia, lymphoma, cancer of the head or neck or lung	
Patient with excessive weight loss	
Patient with gastrectomy or jejunoileal bypass	
High	≥ 5 mm
Human immunodeficiency virus infection	
Fibrosis on chest radiograph	
Recent contact with someone with active tuberculosis	
Immunosuppression	

BCG vaccine does not make all PPD tests positive

single screening test if ongoing exposure to tuberculosis is not a concern. The exception might be those with immunosuppression or HIV infection, who may be anergic at the time of the initial test. A repeat test may be advisable when immunosuppressives have been stopped or when the CD4 count responds to treatment.

Annual testing. People at risk for ongoing exposure to tuberculosis should be tested regularly. Health care workers are generally tested annually. Residents and employees of other congregate settings (eg, jails, nursing homes, homeless shelters) may also be tested at regular intervals.

If a patient who is to undergo annual testing has not been tested within the past year, a two-step procedure is recommended. If the first step is negative, a second step should be performed 1 to 3 weeks later. The two-step procedure may uncover a tuberculosis infection that occurred in the distant past: the first dose of PPD boosts the patient's immune memory, and the second may produce a positive result.

This is good to know. For example, a 70-year-old man who was infected as a child may have a negative result on his initial skin test, but the test may boost his immune response. If the initial test is not repeated, then a year later his annual test might be positive, and the physician might incorrectly conclude that the patient had acquired tuberculosis in the interval.

A person with recent infection has a 5% chance of developing active tuberculosis within the next 2 years. This person is a clear candidate for treatment of latent tuberculosis infection. The treatment of a 70-year-old patient with no other risk factors is more controversial.

SPECIAL SITUATIONS

Prior BCG vaccination

A number of myths persist about the safety and interpretation of the tuberculin skin test in people who have received BCG vaccine. Many who have received the vaccine, including physicians, believe it will cause them to react to the skin test. Some believe that the skin test is unsafe for them. The BCG vaccine is used in most of the developing world and in Eastern Europe, where it is given a few days after birth and is sometimes repeated in early childhood.

Despite these fears, tuberculin skin testing is not contraindicated in people who have received BCG vaccine, and many who have received BCG vaccine have no reaction to the skin test.

The challenge is how to interpret a reaction when it occurs: Is it due to the vaccination or to infection with *M tuberculosis*? Unfortunately, current testing cannot reliably discriminate between the two. The CDC recommends that the results of the tuberculin skin test be interpreted in light of the person's risk factors for recent infection or underlying medical conditions (TABLE 1).

In the future, more specific immunologic testing may resolve this issue. A blood test shows some promise in distinguishing those with latent tuberculosis infection from those who have received BCG vaccine but are not infected with tuberculosis.[4] This test measures gamma interferon in whole blood that is incubated overnight in PPD and in control antigens.

Pregnancy

The tuberculin skin test can be given at any time during pregnancy. Routine screening of all pregnant women is not recommended, but pregnant women in high-risk groups (TABLE 1) should be tested.

Immunosuppressive therapy

A recent report of tuberculosis in patients receiving infliximab for rheumatoid arthritis highlights the importance of doing the tuberculin skin test before starting potent immunosuppressive therapy.[5] Those who test positive should start isoniazid or another regimen (see below) before starting immunosuppressive therapy.

There are no guidelines for interpreting a skin test reaction in these patients, but it is reasonable to consider an induration of 5 mm or larger as positive.

EVALUATING FOR ACTIVE TUBERCULOSIS

Once the tuberculin skin test has been given, measured, and interpreted as significant, the patient should be evaluated for active tuberculosis. This should include an interview with the patient to ask about signs or symptoms of active tuberculosis, and a chest radiograph.

Signs of active tuberculosis include:

- Persistent, productive cough
- Hemoptysis
- Unexplained fever and night sweats
- Unexplained weight loss.

The possibility of active extrapulmonary tuberculosis should also be considered; the most common manifestations are pleural disease and lymphadenitis.

Patients with signs or symptoms or an abnormal chest radiograph require further evaluation, which is beyond the scope of this article. Those with no signs or symptoms and a normal chest radiograph should be offered treatment for latent infection.

ISONIAZID TREATMENT OF LATENT TUBERCULOSIS

Isoniazid is the mainstay of treatment of latent tuberculosis infection. It was first used to treat active tuberculosis in the early 1950s. In the 1960s a number of trials worldwide compared isoniazid given for 12 months against placebo in the treatment of latent tuberculosis. While efficacy rates among these trials varied, in compliant patients isoniazid for 12 months gave a 90% protective effect[1] (ie, there was a 90% reduction in active cases of tuberculosis in people who took isoniazid vs those who did not). On the basis of these results, the American Thoracic Society began recommending isoniazid therapy for latent tuberculosis in 1965.

A later, landmark European trial[6] comparing 3, 6, or 12 months of isoniazid therapy against placebo found that, if patients were compliant, 3 months of treatment gave no protection against developing active tuberculosis, 6 months gave 69% protection, and 12 months gave 93% protection.[6] In 1994, on the basis of this study and a subsequent cost-effectiveness analysis, the CDC recommended a course of 6 to 12 months.

Six months of isoniazid rapidly became the standard course in the community, with a few groups receiving isoniazid for 9 to 12 months, including children, people who had recently converted, and people with underlying medical problems.

In 2000, the CDC and the American Thoracic Society changed the recommended duration of isoniazid therapy to 9 months, although 6 months is still acceptable. The reasons for this change were:

- To simplify the treatment regimens, since isoniazid for 9 months can be used for everyone, including children and HIV-positive patients
- To address the concerns of some groups of public health professionals that 6 months of isoniazid was too little, and that data from the US Public Health Service trials supported 9 months of isoniazid as the optimal regimen.

Signs of active TB:

- **Cough**
- **Hemoptysis**
- **Fever**
- **Night sweats**
- **Weight loss**

Monitoring for isoniazid-induced hepatitis

Isoniazid-induced hepatitis was not fully recognized until 1970, when 2,300 people working on Capitol Hill were exposed to several cases of active tuberculosis. After they were started on isoniazid, 19 developed clinical hepatitis, and 2 died.[7]

The US Public Health Service then conducted a trial in 13,000 people to determine the risk of isoniazid-induced hepatitis.[8] They

TABLE 3

Regimens for latent tuberculosis infection

REGIMEN	DURATION	COMMENTS
Isoniazid		
Adults: 300 mg daily or 900 mg twice a week Children: 10–20 mg/kg daily, up to 300 mg	9 months	The preferred regimen Use with pyridoxine in pregnancy, diabetes, neuropathy, alcohol abuse
	6 months	Not appropriate for children or patients with human immunodeficiency virus (HIV) infection
Rifampin		
Adults: 600 mg daily or twice weekly Children: 10–20 mg/kg daily, up to 600 mg	4 months	Monitor aminotransferase levels and complete blood count in liver disease, HIV infection, pregnancy
Rifampin and pyrazinamide		
Rifampin 600 mg daily or twice weekly Pyrazinamide 15–20 mg/kg daily or 50 mg/kg twice weekly	8 weeks	For adults only Obtain baseline aminotransferase levels, then monitor every 2 weeks during treatment

found that the rates of clinical hepatitis were extremely low in people under age 35, 1% for ages 35 to 50, and 2% for those over age 50. Daily alcohol drinkers had the highest rates of isoniazid-induced hepatitis.[8]

Advise patients on isoniazid to watch for signs of hepatitis

In view of the risk, we need to remind patients taking isoniazid to watch for signs and symptoms of hepatitis and to stop taking isoniazid if these should occur:

- Nausea and vomiting
- Loss of appetite
- Flulike illness with myalgias
- Jaundice
- Change in urine to tea color
- Excessive tiredness.

The CDC does not recommend routine monitoring of liver function (serum aspartate aminotransferase, alanine aminotransferase, and bilirubin levels) during isoniazid therapy except in cases of HIV infection, pregnancy, early postpartum status, underlying liver disease, or regular alcohol use.[1] However, it is reasonable to test these levels at baseline and to monitor them monthly for several months in those age 35 and older.

Isoniazid can cause transient, mild elevations in aminotransferase levels that resolve spontaneously. However, if levels rise to more that 3 to 4 times normal, isoniazid should be stopped, and the patient should avoid alcohol and acetaminophen until these levels normalize. Isoniazid-induced hepatitis resolves completely if isoniazid is stopped early enough.

Contraindications to isoniazid

Do not give isoniazid to patients with a history of isoniazid-induced hepatitis or allergy. Do not give isoniazid to patients who are unavailable for clinical monitoring (eg, traveling outside the country for more than 2 weeks).

Isoniazid therapy can be used with caution in patients with active viral hepatitis; however, baseline and monthly liver function testing is advised. Patients with mildly elevated baseline aminotransferase levels (40–70 U/L) can still be offered isoniazid, but liver function should be checked again 2 weeks after starting isoniazid.

RIFAMPIN

Rifampin can also be used to treat latent tuberculosis infection (TABLE 3). A regimen of rifampin daily for 4 months is generally well tolerated and is the first choice when isoniazid cannot be used.

The advantage of rifampin over isoniazid therapy is its shorter treatment duration. The disadvantages are the risks of drug interactions and toxicity, and high cost ($8.99 for a 30-day supply of isoniazid vs $108 for rifampin).

Drug interactions with rifampin

Rifampin induces cytochrome P450 enzymes and therefore can decrease the plasma concentrations of many drugs, notably barbiturates, benzodiazepines, beta-blockers, chloramphenicol, cyclosporine, digoxin, estrogens, ketoconazole, methadone, mexiletine, oral contraceptives, quinidine, sulfonylureas, theophylline, tocainide, verapamil, warfarin, and zidovudine.

Toxicity of rifampin

Hepatitis due to rifampin is rare. However, the rifampin-pyrazinamide regimen has been associated with several cases of fatal hepatitis, so strict monitoring of serum aminotransferase levels is recommended in patients receiving it (ie, at baseline and at 2, 4, and 6 weeks). Rifampin-pyrazinamide should be reserved for patients who cannot take isoniazid due to allergy, gastrointestinal intolerance, or isoniazid-resistant infection, or in whom the duration of isoniazid therapy is impractical.[9]

Rifampin can stain secretions orange.

DIRECTLY OBSERVED THERAPY

Direct observation of patients taking their antituberculosis drug for treatment of latent infection is advisable in homeless people, children living with someone with active tuberculosis, and patients with some psychiatric diagnoses. Direct observation is recommended for all patients with active tuberculosis. The availability of outreach workers to provide direct observation varies across the country. County health departments can provide information about local availability.

CASE CONTINUED

Our school volunteer is at low risk of exposure and progression to tuberculosis, so she would not have been tested except for the school district's requirement. Her 12-mm reaction should be interpreted as unlikely to represent tuberculosis infection. No further medical evaluation is indicated by current guidelines. However, many agencies and physicians do not yet recognize the 15-mm cutoff for low-risk groups and might consider her reaction to be significant.

While obtaining a chest radiograph for her volunteer post would be wise, I would not offer her isoniazid therapy.

Rifampin: shorter treatment duration but more costly

REFERENCES

1. **The American Thoracic Society and the Centers for Disease Control and Prevention.** Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2000; 161:S221–S247.
2. **Huebner RE, Schein MF, Bass JB Jr.** The tuberculin skin test. Clin Infect Dis 1993; 17:968–975.
3. **Reichman LB.** Tuberculin skin testing. The state of the art. Chest 1979; 76:764–770.
4. **Mazurek GH, LoBue PA, Daley CL, et al.** Comparison of a whole-blood interferon gamma assay with tuberculin skin testing for detecting latent *Mycobacterium tuberculosis* infection. JAMA 2001; 286:1740–1747.
5. **Keane J, Gershon S, Wise RP, et al.** Tuberculosis associated with infliximab, a tumor necrosis factor alpha neutralizing agent. N Engl J Med 2001; 345:1098–1104.
6. **International Union Against Tuberculosis Committee on Prophylaxis.** Efficacy of various durations of isoniazid preventive therapy for tuberculosis: 5 years of follow-up in the IUAT trial. Bull WHO 1982; 60:555–564.
7. **Garibaldi RA, Drusin RE, Ferebee SH, Gregg MB.** Isoniazid-associated hepatitis. Report of an outbreak. Am Rev Respir Dis 1972; 106:357–365.
8. **Kopanoff DE, Snider DE Jr, Caras GJ.** Isoniazid-related hepatitis. A US Public Health Service cooperative surveillance study. Am Rev Respir Dis 1978; 117:991–1001.
9. **Centers for Disease Control and Prevention.** Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations—United States, 2001. MMWR 2001; 50:733–735.

SUGGESTED BROWSING

Centers for Disease Control and Prevention, Division of Tuberculosis Elimination
http://www.cdc.gov/nchstp/tb/default.htm

World Health Organization, Tuberculosis Control and Prevention
http://www.who.int/gtb/misc/sitemap.htm

American Thoracic Society Statements
http://www.thoracic.org/statements/

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