Tuberculosis Screening in Urgent Care Medicine

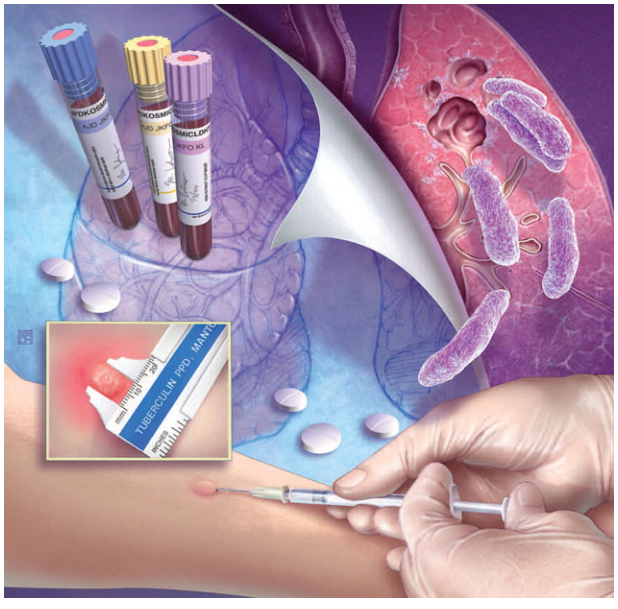
Urgent message: Often placed in the role of first-line clinicians with respect to testing for and treating infectious disease, urgent care practitioners are ideally suited to provide screening services for tuberculosis.

Jacqualine Dancy, PA-C, MPAS

Introduction

In addition to urgent care services, many of us also offer occupational medicine and provide post-offer/pre-employment evaluations. As such, urgent care clinicians play a key role in screening for tuberculosis (TB). In fact, understanding the complexity of the screening process is essential to our specialty.

This article will provide an overview of screening tests and clinical assessment of TB.



Disease Overview

Tuberculosis is a communicable disease caused by the bacteria *Mycobacterium tuberculosis*. While this bacterium most often attacks the lungs, TB can infect many areas in the body, such as the kidneys, spine, and brain.

Tuberculosis is spread primarily by aerosol droplets person-to-person.

The clinical spectrum ranges from non-infectious, asymptomatic, latent TB infection (LTBI) to highly contagious pulmonary infections with significant morbidity and even death.

For the purpose of this article, we will focus on pulmonary tuberculosis.

According to the Centers for Disease Control, the incidence of TB in the United States has declined over the past 50 years from 63,534 in 1958 to 12,906 in 2008.

Similarly, the number of deaths from TB has also declined dramatically; in 1958, 12,417 Americans died from TB. Mortality in 2006, the last year for which deaths have been reported, was 644 people. Continuing to increase understanding of the disease process and appropriate screening tools can only help this trend continue.

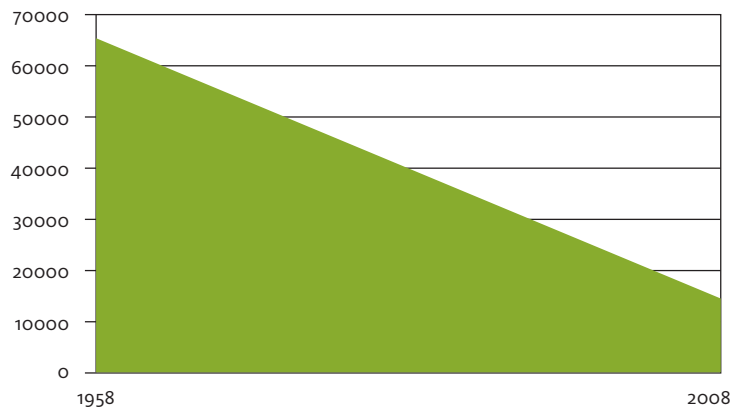
Active vs. Latent Tuberculosis

We will focus our discussion on two disease states: active TB and latent tuberculosis infection (LTBI).

In active TB infection, the bacteria multiply, and the patient will eventually demonstrate signs of active disease. The most common signs and symptoms of active TB include:

- anorexia

U.S. Incidence of TB



Source of data: Centers for Disease Control and Prevention.

Table 1. Interpreting TST Tests

Induration of	is classified as a positive in patients
≥5 mm	• who are HIV positive (especially with AIDS and a low CD4 count) • who have had a recent close contact with a known or suspected TB-infected person • who have had an organ transplant and other immunosuppressed patients (the equivalent of 15 mg/day of prednisone/day or more for >1 month is considered immunosuppressed) • who are receiving specialized treatment for rheumatologic or immunological disease • with fibrotic changes and calcific changes on chest x-ray consistent with old TB.
≥10 mm	• who do not meet the any of the above criteria, but belong to one or more of the following groups having moderate risk for TB: – who are foreign-born, recently arrived to U.S. (i.e., within 5 years) from area with high incidence of TB – who inject illicit drugs – who reside or, who work in high-risk congregate settings: prison and jails, nursing homes, long-term care facilities for the elderly and the young (<4-years-old), healthcare facilities and homeless shelters – who are mycobacteriology laboratory personnel – who have medical conditions known to increase the risk for progressing from LTBI to active TB infection; these medical conditions include: diabetes, silicosis, prolonged corticosteroid therapy, other immunosuppressive therapy, cancer of the head/neck, hematological and reticuloendothelial disease, end-stage renal disease, intestinal bypass or gastrectomy, chronic malabsorption, or weight of more than 10% below ideal body weight – <4-years-old, or children and adolescents exposed to adults in high-risk categories.
≥15 mm	who do not meet any of the above criteria.

- weight loss
- malaise
- fevers
- chills
- night sweats
- cough (which may include hemoptysis and pleuritic chest pain).

Affected patients often have an abnormal chest radiograph and a positive acid-fast bacilli sputum stain and culture in addition to, often, a positive tuberculin skin test (TST).

The patient diagnosed with active tuberculosis must be considered contagious and needs antibiotics, along with public health intervention to minimize the spread of disease.

In cases of LTBI, the patient usually has a positive TST but does not exhibit any signs or symptoms of illness. These patients are not contagious. The bacteria live in the host, whose immune system has been able to halt the bacterial replication process (at least temporarily). Should these LTBI patients become immunocompromised, the bacteria may begin to replicate and cause active TB disease.

Treatment of LTBI is intended to lessen the chance of subsequent conversion to active disease. Among the many drugs currently available to treat tuberculosis are:

- isoniazid
- rifampin
- rifabutin
- rifapentine
- pyrazinamide
- ethambutol
- cycloserine
- ethionamide
- streptomycin
- capreomycin
- p-aminosalicylic acid
- the fluoroquinolone class.

We will focus on screening for, rather than treating, active and latent tuberculosis.

Screening Tests

The TST is the most widely used screening test for tuberculosis infections. It cannot differentiate between active and latent in-

fections, however. Rather, its purpose is to identify patients who have been infected with TB.

The test can also be used to monitor for potential infection in those exposed to TB; the usual recommendation is to test two and six weeks after exposure. Interpretation can be difficult if there is not an established history of a negative TST, however.

The most commonly used screening tool in the United States is the Mantoux tuberculin skin test, commonly referred to as purified protein derivative (PPD). This test is performed by injecting 0.1 ml of solution intradermally on the volar aspect of the forearm. The test is interpreted between 48 to 72 hours after the injection.

Interpretation is based on induration, not erythema; the indurated area is measured transversely to the long axis of the forearm. Diagnostic criteria are detailed in **Table 1**.

Who Should Be Screened—and How Often

Anyone at risk for developing tuberculosis should be screened with a TST. Such candidates for TST screening include:

- recent immigrants
- injection drug users
- residents and employees of prison and jails
- healthcare workers, including part-time volunteers
- children <4-years-old
- people with chronic disease
- people entering a group living situation.

Establishing a baseline before entering a high-risk employment or residential situation is of particular value. The frequency of subsequent screening for tuberculosis is usually annually or biannually, depending on risk stratification.

Two-step TST

The two-step TST is used to identify people who have had tuberculosis in the past and who now have diminished immune response and skin test reactivity. This procedure is designed to reduce the likelihood that a booster reaction, also called the "booster phenomenon," is later interpreted as a new infection.

The two-step technique is employed as the initial TST for adults who will be retested periodically (e.g., healthcare workers). This helps ensure that any future positive TST can be interpreted as being caused by a new infection rather than simply a boosted reaction to an old infection.

The procedure for the two-step is as follows:

Step 1

Place PPD and read within 48-72 hours.
If *positive,* consider the person infected.
If *negative*, proceed to step 2.

Step 2

Place a second PPD one to three weeks later and read within 48-72 hours.
If *positive*, consider the person *previously* infected.
If *negative,* consider the person uninfected.

Potential Errors with TST

The TST is not a true gold standard. The sensitivity is about 95% in healthy patients; however, it can be as low as 80% in immunocompromised patients. The 20% false-negative rate is due to a combination of factors causing immunosuppression. This, in turn, may be due to an acute illness, poor nutrition, medications, or underlying disease.

False negatives

False-negative reactions occur when a patient is immunologically compromised—even secondary to a highly active tuberculosis infection. The immune system needs to be competent to mount a response to the purified protein derived in the TST. Anytime the immune system is significantly strained, a false-negative TST test may occur.

Some scenarios in which higher rates of false-negative TST results might be most likely to occur include:

- patients <6 months or >70 years of age
- leukocytosis
- fever
- irradiation
- live viral vaccine
- viral infections
- sarcoidosis and any other immune-compromising disease process.

False positives

False-positive reactions occur when a patient has been infected with a non-tuberculosis mycobacterium (e.g., mycobacterium avium complex) or by previous administration of the bacille Calmette-Guerin (BCG) vaccine. Highly sensitive people may react to the PPD as a hypersensitive "foreign protein" reaction without an identifiable cause.

Special Testing

Special tuberculin blood tests include interferon-gamma

Table 2. Screening Tool: Assessing Risk of Active Disease

Answer Yes, No, or Unknown to each of the following questions:

Past Medical History
History of positive TB test?
History of TB/treatment?
History of TB exposure?
History of BCG vaccine?
Immune-suppressing disease?
Immune-suppressing therapy?
Pulmonary (lung) problems?
Family history of TB?

Review of Systems
Recurrent fevers?
Night sweats?
Weight loss?
Hemoptysis?
Pleuritic chest pain?

Social Risk Factors
Homeless/shelter?
Institutionalized/prison?
Nursing home?
Alcohol or drug abuse?
Contact with TB patient?
Significant foreign travel?

release assays (IGRAs) that the Federal Drug Administration approved in 2005. This blood test detects the release of interferon-gamma from sensitized persons when incubated with two proteins in *M tuberculosis*. IGRAs provide greater specificity than is possible with tests using purified protein derivative.

These tests are considered by some to be more accurate than the TST test and measure how the immune system reacts to two of the proteins in the bacteria causing tuberculosis. The superiority over TST is well established with active TB when measured against the gold standard of sputum culture.

In LTBI, there is no gold standard and there is only indirect evidence that it is better than TST. Accurate measures of the sensitivity and specificity of IGRAs are not available with LTBI.

The IGRA tests can be used in all circumstances in which TST is used. Many practitioners feel these serological tests are particularly helpful in patients with a positive TST who have received the BCG vaccine (to be discussed).

The commercially available IGRA tests are the QuantiFERON-TB test (QFT-G) and QuantiFeron-TB Gold (QFT-Gold). These tests may also be helpful in patients with dermatological conditions, a probable false-positive, or apparent allergic reactions to PPD.

The results of the IGRAs are qualitative, and a positive result indicates that an infection with *M tuberculosis* is likely; inversely, a negative result indicates that a tuberculosis infection is not likely.

One could consider replacing TST with IGRA testing; however, the value added is not well established and the increased costs are significant, currently.

Diagnostic Testing

Chest radiographs

In patients who have their first positive TST after known negatives (also known as converters), a one-view anterior-posterior chest radiograph should be performed to assess if there is radiographic evidence of active tuberculosis. Chest x-ray is also indicated if the first known TST is positive.

There have been no reliable, evidence-based studies to establish the value of subsequent screening chest radiographs. Annual screening chest x-rays for patients with known positive TSTs have not been shown to be of significant value in the absence of known TB exposures and symptoms or findings consistent with active TB. The cumulative radiation when employed as an annual screening test is noteworthy.

The clinician should evaluate each individual patient and make a thoughtful recommendation based on a focused history and physical to assess the risk of active disease. An example of the screening tool used in our urgent care center is shown in **Table 2**.

Any positive response requires further consideration about risk.

Acid-fast Bacilli (AFB) sputum examination

The gold standard for TB diagnosis is a sputum culture; however, it can be expensive and time-consuming.

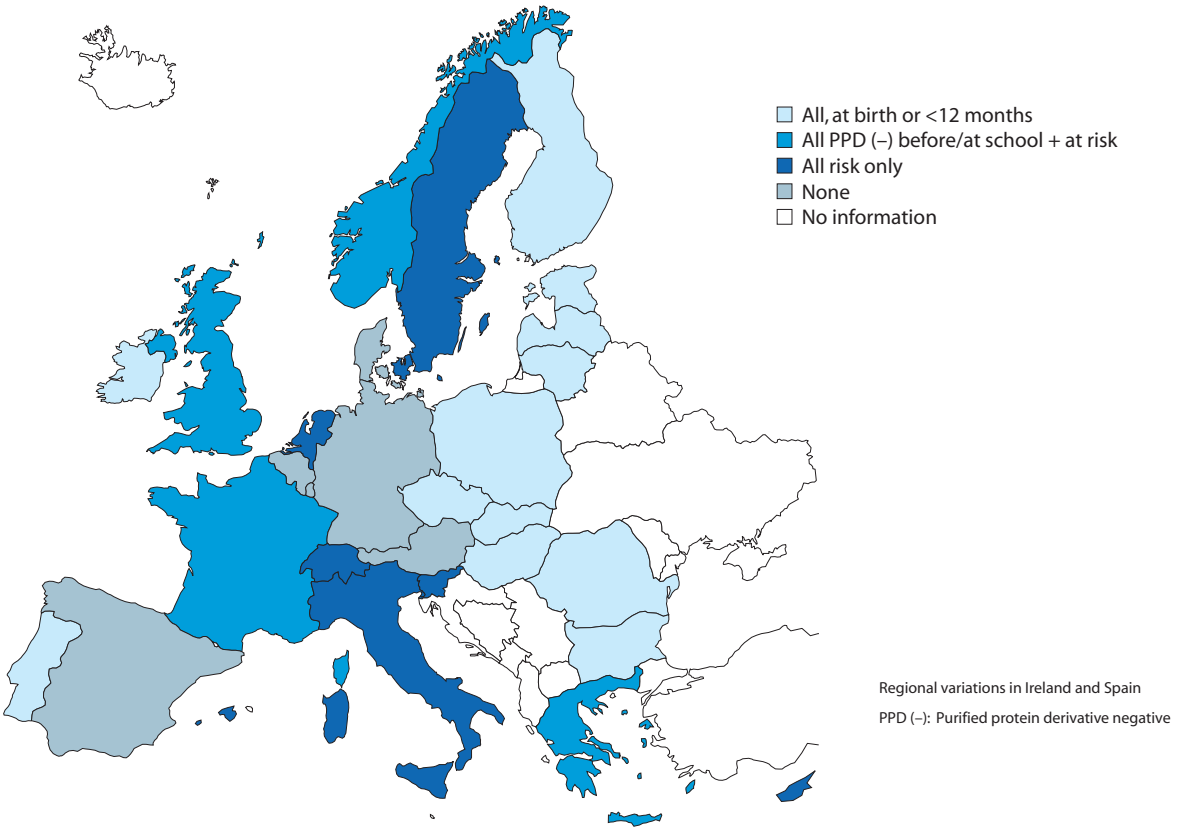
Pulmonary tuberculosis can be diagnosed adequately in the right clinical setting using a chest x-ray and identifying AFB on sputum smear before isolating the organism in a culture. Large quantities of sputum and first morning expectorant may yield higher diagnostic accuracy. Sputum is usually collected over three consecutive days. AFB sputum examination can be used in patients where the diagnosis of active TB should be established before culture results are available.

Special considerations: BCG vaccine

BCG is a vaccine used to prevent tuberculosis. Many foreign-born people, especially those from areas endemic with tuberculosis, have received the vaccine.

The BCG vaccine can interfere with TSTs, causing a

Figure 1. Groups of Children Target for BCG in National Recommendations*, in Europe 2005



false-positive test result.

The fact that BCG vaccine is used in areas with high prevalence of TB makes interpretation of a positive TST problematic. A positive TST may represent a true positive or a vaccine-associated false positive.

Serological IGRA testing is not affected by prior BCG vaccination and is the screening test of choice in a patient with a positive PPD and a history (known or presumed) of BCG vaccination. It need only be done once.

Some of the TB-endemic areas that use the BCG vaccine include: Latin America, Caribbean, Africa, Asia, Eastern Europe, and Russia (**Figure 1** and **Table 3**).

BCG vaccine is usually administered in the first year of life. Currently, revaccination is not widely used, employed only in some areas with higher prevalence of disease.

One study from the pulmonary journal *Chest*, published in 2007, evaluated more than 1,000 Canadian aboriginal children vaccinated with BCG before 1 year of age and found that after four years the effect on TSTs was minimal; after 10 years, the vaccine had no demonstrable effect on TSTs.

IGRA serology testing can be useful in assessment of a positive PPD in a person with a history of BCG vaccine. IGRA testing can be expensive, however, which may be a prohibitive factor in this diagnostic strategy.

Some institutions, such as Brown University Health Services, do not consider BCG vaccine history when interpreting a TST reaction; they assume a positive TST is a true positive and then assess for active versus latent disease.

In a 2004 article published in *Clinical Medicine & Research*, Ayub, et al, write that the majority of TSTs in persons previously BCG-vaccinated are negative—92% of the time. This was particularly prevalent in subjects who received the vaccine in infancy or early childhood. The recommendation is that a previous history of BCG vaccine be ignored when interpreting tuberculin skin test results.

Given the lack of high-quality data on the effect of BCG vaccine on TST results over time for a patient with a history of BCG vaccination and a positive PPD, in our

Table 3. TB Notification Rates Per 100,000, BCG Recommendations in Children, and BCG Coverage in Europe

	TB notification rates, 2003			Groups of children targeted for BCG vaccination, 2005						BCG coverage	
Country	Overall	Children	Rate ratio (adults: children)	All, at birth or <12 months	All, older age	Parents from/birth in high incidence areas	Travel to high incidence areas	Family history of contact with TB case	No systematic use	%	Year
Bulgaria	41.3	16.1	2.8	x*						n/a	–
Czech Republic	11.3	0.7	18.9	x*						98.8	2003
Estonia	47.1	1.9	29.3	x						92.0	2004
Finland	8.0	0.4	24.0	x						98.0	2002
Hungary	27.8	0.6	15.0	x						99.5	2003
Ireland	10.6	2.8	4.5	x	x (r)	x (r)	x (r)	x (r)		90.2	2004
Latvia	74.8	30.3	2.7	x						99.3	2004
Lithuania	81.9	20.3	4.7	x						96.9	2004
Poland	26.2	1.5	20.0	x*						95.0	2003
Portugal	41.1	5.0	8.0	x						83.0	2003
Romania	41.6	43.3	3.7	x						95.6	2003
Slovakia	18.2	2.1	10.3	x*						98.1	2003
Malta	3.8	3.3	3.5	x						87.0	2004
France	9.8	2.7	4.3	x						85.0	1997
Norway	7.5	2.0	4.4	x	x	x				>94.0	2002
United Kingdom	12.3	3.4	4.2	x	x					75.0	n/a
Greece	5.6	1.1	6.5	x		x				31.3	2003
Sweden	4.6	1.1	4.9		x	x	x			88.0	2004
Netherlands	8.2	2.0	4.8	x	x					60-90	2000-04
Slovenia	14.8	3.1	5.4							70-90	2004
Switzerland	8.7	2.1	4.7		x					n/a	–
Cyprus	4.4	0.0	*			x				n/a	–
Italy	7.9	2.2	3.9			x				n/a	–
Andorra	32.6	0.8	-			x				–	–
Austria	32.1	3.2	4.3			x				–	–
Belgium	10.9	4.0	3.1						x	–	–
Denmark	7.3	3.3	2.5			x				–	–
Germany	8.7	2.3	4.3			x				–	–
Luxembourg	11.9	1.2	12.0			x				–	–
Spain	18.2	8.2	2.4	x (r)			x			–	–

(r), regional policy; n/a, not available, *revaccination also recommended

clinic we recommend IGRA serology testing for clarification, when possible.

If the IGRA is positive, we assume a true positive TST.

If the IGRA is negative, we assume the TST was a false positive.

If IGRA testing is not a viable option, consider the BCG-vaccinated patient with a new or first positive PPD as a *new* converter and proceed clinically.

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Public Health Concerns

In most areas of the United States, it is mandatory and appropriate to notify the Public Health Department of potentially active TB. Refer the patient to an appropriate treatment center, which may be your public health department.

Conclusion

It is imperative that the urgent care clinician become an expert on tuberculosis screening to maintain the health and safety of our patients and communities. Interpreting the current recommendations on TB screening and applying them to our diverse pool of patients can be challenging, as there are few comprehensive guidelines available. We must be well informed, diligent in our focused evaluations, and able to interpret a wide spectrum of data. Tuberculosis screening is a patient-specific paradigm.

Summary

BCG vaccine and effect on TST

- Given in countries with high incidence of tuberculosis
- Can affect TST
- TST effect wanes over time (when vaccine given before 1 year of life, the BCG effect on TST is usually gone in 10 years)
- If positive history of BCG vaccine and a positive TST consider IGRA testing **OR** treat as a new converter

New converters (patients with a positive TST)

- Complete a focused history and physical for symptoms and signs of tuberculosis
- Obtain a one-view chest x-ray
- Assess for radiographic evidence of tuberculosis
  - If asymptomatic with a negative x-ray or findings consistent with "old" non- active TB, treat as latent TB and refer them to their primary care provider for further evaluation of LTBI and treatment options.
  - If symptomatic and an X-ray with findings that could represent active TB, obtain a sputum for AFB stain and culture and arrange for evaluation and treatment of potentially active TB.
  - If chest x-ray is completely negative, refer patient to their primary care provider for evaluation of a positive TST.

Resources

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