Tuberculosis

What Every Hospitalist Should Know

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KEYWORDS

• Mycobacterium tuberculosis • TB • Latent tuberculosis infection • Extrapulmonary
• Multidrug resistant • Extremely drug resistant

HOSPITAL MEDICINE CLINICS CHECKLIST

1. Tuberculosis (TB) refers to the broad range of clinical illnesses caused by the acid-fast bacillus, *Mycobacterium tuberculosis* (MTB).
2. *M tuberculosis* is transmitted by inhalation of airborne droplets containing tubercle bacilli (MTB organisms) aerosolized by coughing, sneezing, or talking.
3. Latent TB infection (LTBI) is demonstrated by positive tuberculin skin testing (TST) or interferon-gamma release assay (IGRA), without evidence of active disease. Patients with LTBI are noninfectious and asymptomatic.
4. Primary pulmonary TB refers to active infection isolated to the lungs. It presents as one of 4 syndromes: atypical pneumonia; pleuritis with pleural effusion; upper lobe disease; or progression to extrapulmonary disease.
5. Secondary pulmonary TB refers to infection in patients previously sensitized to *M tuberculosis*, usually in the form of reactivation TB, but may occur with reinfection.
6. Extrapulmonary TB refers to disease located at sites in the body other than the lungs; it may affect any organ system.

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7. Miliary TB occurs with widespread hematogenous dissemination of infection. "Miliary" also refers to the reticulonodular pattern sometimes seen on chest radiography in cases of disseminated TB.
8. Multi-drug-resistant TB (MDR-TB) infection is present when a strain is resistant to at least isoniazid (INH) and rifampin (RIF).
9. Extensively drug-resistant TB (XDR-TB) is present when strains are resistant to at least INH, RIF, a fluoroquinolone, and an aminoglycoside.
10. Up to 20% of HIV-infected patients with active pulmonary TB may have normal chest radiographs.
11. The recommended screening tests for LTBI include the Mantoux TST (ie, purified protein derivative or PPD) or one of the available IGRAs. It takes 2 to 8 weeks after exposure to MTB for the immune system to react to TST or IGRAs.
12. TST is not contraindicated in persons who previously received Bacillus Calmette-Guérin (BCG) vaccination and interpretation of a TST in a patient with a history of BCG vaccination is the same as in a person without a history of BCG vaccination.
13. Definitive diagnosis of active TB infection requires mycobacterial cultures and speciation.
14. The American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America guidelines recommend that newly diagnosed cases of drug-susceptible pulmonary TB should be treated with four-drug therapy including INH, RIF, pyrazinamide (PZA), and ethambutol (EMB). INH and RIF are administered for at least 6 months (26 weeks), whereas PZA and EMB are generally administered with INH and RIF during the initial 2 months of therapy.

DEFINITIONS

1. What is tuberculosis and why is it clinically important?

Tuberculosis (TB) refers to the broad range of clinical illnesses caused by the acid-fast bacillus, *Mycobacterium tuberculosis* (less frequently, *Mycobacterium bovis*).[1,2] TB is a life-threatening disease that requires treatment with multiple drugs, for a minimum of 6 months, to achieve clinical cure.[3] Worldwide, with nearly 2 billion people infected (most with latent disease), tuberculosis is the second leading cause of death resulting from an infectious disease after the human immunodeficiency virus (HIV).[4] It is postulated that there is no major disease in which the etiologic agent has taken refuge in as many people throughout the world as that of TB.[5] Since 1993, the World Health Organization (WHO) has considered it a global public health problem.[4]

2. What are the different clinical forms of TB infection?

Latent Tuberculosis Infection

Latent TB infection (LTBI) occurs when a host is infected with *M tuberculosis* and it is contained, but not eradicated, by the host's cell-mediated immune mechanisms.[1,6] LTBI is the most common form of TB and is usually detected by a reaction to tuberculin skin testing (TST) or an interferon-gamma release assay (IGRA). Patients with LTBI are

asymptomatic and noninfectious, but are at risk for active disease later in life (ie, reactivation).[1,7] Treatment of LTBI reduces the risk of progression to active disease. Thus, programs directed at screening for LTBI in at-risk patients is an important and cost-effective method to prevent disease progression.[8,9]

Pulmonary TB

Pulmonary TB is the most commonly encountered form of disease in the United States and is further divided into *primary tuberculosis* (ie, developing soon after infection) and *secondary tuberculosis* (ie, developing after LTBI).[1,6] Secondary disease is also referred to as *reactivation tuberculosis*.

Primary pulmonary TB

Historically, primary pulmonary TB was most commonly encountered in children, but it is now seen with increasing frequency in adults who are immunosuppressed or debilitated because of HIV infection or other immunosuppressive conditions.[1,6] It presents as 1 of 4 syndromes: atypical pneumonia; pleuritis with pleural effusion; upper lobe disease; or progression to extrapulmonary disease. The most common of the 4 presentations is one that resembles atypical pneumonia, with nonproductive cough, fevers, and infiltrates on chest radiography (unilateral, patchy parenchymal infiltrates, lower lobe disease; paratracheal or hilar adenopathy; or both).[1,6]

Secondary pulmonary TB

The most common clinical form of TB is reactivation pulmonary disease (also known as secondary pulmonary TB).[1,6] Onset of symptoms is insidious, progressing over a period of several weeks, and includes cough (nonproductive or productive), fever, night sweats, and weight loss. Hemoptysis is rarely a presenting symptom, but may result from residual tuberculous bronchiectasis, rupture of a dilated vessel in the wall of a cavity (Rasmussen's aneurysm), bacterial or fungal coinfection (eg, *Aspergillus*) in a residual cavity, or erosion of calcified lesions into the lumen of an airway (broncholithiasis).[1,6]

Extrapulmonary TB

Extrapulmonary TB refers to disease located at body sites other than the lungs. Infection may affect any organ system.[6,10] It is the result of dissemination of bacilli soon after formation of initial lesions. The bacteria migrate through blood vessels or lymph ducts, causing hematogenous dissemination, either during primary infection or as the result of reactivation from a site of latent infection. In most cases, the disease is localized to a single organ, causing an array of clinical syndromes, including lymphadenitis, pleuritis, pericarditis, nephritis, osteomyelitis, arthritis, meningitis, peritonitis, or hepatitis. Persons with extrapulmonary TB are not infectious, unless they have disease located in the oral cavity or larynx, at an open body site (especially with aerosolized fluid), or concomitant pulmonary disease.[1]

Miliary (Disseminated) Tuberculosis

Widespread hematogenous dissemination can occur in the young, immunosuppressed, elderly, or malnourished, with the clinical syndrome known as *miliary (disseminated) tuberculosis*.[11] The onset of miliary TB can be acute or insidious. Constitutional symptoms predominate in most patients, consisting of fever, anorexia, night sweats, and weight loss. Most patients also have respiratory symptoms and, on chest radiography, a pattern resembling small millet seed lesions (eg, reticulonodular pattern). Hematologic abnormalities are common, including leukopenia, thrombocytopenia, lymphopenia, and pancytopenia.[12] Without appropriate treatment, the disease is uniformly fatal and, even with appropriate therapy, mortality is as high as 20%.[12–14]

EPIDEMIOLOGY

1. What is the incidence and prevalence of TB?

Globally, TB is a major cause of morbidity and mortality and it remains one of the deadliest diseases in the world, accounting for 1.4 million deaths in 2011.[4] Although the global and local incidence rate is declining, it is estimated that nearly one-third of the world's population (nearly 2 billion persons) are infected. Since 1990, the prevalence of TB has fallen by 36%; however, an estimated 8.7 million new cases were diagnosed in 2011 and approximately 13% of cases were coinfected with HIV.[4] Worldwide, more than 60% of new TB cases occur in Southeast Asia and Africa.[4,15] Together, India and China account for nearly 40% of the world's TB cases.[4] In patients coinfected with HIV, TB has become one of the leading causes of death.[16]

In 2012, the United States reported 9951 new cases of TB, marking the first time since reporting began in 1953 that the number of cases in the United States has dropped to less than 10,000 per year. Since the resurgence of TB in the late 1980s and early 1990s, the United States has documented a decline in the incidence of TB for the 20th consecutive year. Despite these advances in the eradication of TB, the development of future initiatives directed at increasing awareness of the disease and treatment of LTBI will be crucial to TB elimination efforts.[17]

PATHOPHYSIOLOGY

1. How is TB transmitted and what is the pathophysiology of infection?

Humans are the only reservoir for the species *M tuberculosis* and it is most commonly transmitted by inhalation of airborne droplets containing tubercle bacilli from an infected person. It has been reported that a room occupied by a person with pulmonary TB may remain infectious for approximately 30 minutes after the infected person has departed.[1] The initial focus of bacterial replication is usually located in areas of the lungs where higher airflow favors deposition of bacilli (ie, subpleural and in the lower parts of the upper lobes or upper parts of the lower and middle lobes). Once the bacilli are deposited in the respiratory epithelium, alveolar macrophages ingest the bacteria, and pneumonitis slowly develops. In most cases, infection is controlled by the host's defense mechanisms. Tuberculin positivity appears as the result of cell-mediated hypersensitivity, 2 to 8 weeks after initial infection, with resultant granuloma formation. This stage of disease is referred to as LTBI. Persons with LTBI are asymptomatic and noninfectious and their infection is radiographically inapparent, but they are still at risk to develop active disease later in life (termed secondary disease or reactivation TB). In a minority of cases, hypersensitivity results in necrosis of the initial pulmonary focus (the Ghon focus) and ipsilateral draining regional lymph nodes, producing calcification visible on chest radiography, known as a Ranke's complex (calcified parenchymal tuberculoma and ipsilateral calcified hilar node).[1,18] When the immune system cannot keep replication of tubercle bacilli under control, active disease develops.

2. Once infected with TB, what is the natural history of disease progression?

Among immunocompetent persons infected with TB, active disease develops in 5%, within the first 2 years after exposure if left untreated (defined as "primary progressive TB"), and another 5% develop active infection later in life (defined as "*reactivation tuberculosis*").[1] Thus, the cumulative lifetime risk of developing active disease in

immunocompetent persons with LTBI who defer treatment is approximately 10%.[19] The 10-year mortality of untreated cases of smear-positive pulmonary TB is approximately 70% in HIV-negative patients. In cases that are culture-positive (but smear-negative), 10-year mortality rates are approximately 20%.[20]

Risk factors for progression of LTBI to active infection include infection in the last 2 years, chronic disease states such as diabetes and renal failure, and a compromised immune system (**Table 1**). Persons with untreated HIV infection are at the highest risk of developing active disease, with a rate of 7% to 10% annually.[4] Despite the availability of effective treatment agents, many infected individuals still go untreated or discontinue treatment for a variety of reasons, including failure or delay in diagnosis of the disease, ineffective treatment (eg, noncompliance, poor drug absorption, adverse side effects), leading to significant morbidity and mortality.[21] In addition, practitioners are now faced with the introduction of drug-resistant strains of TB, both locally and abroad.

After initiating appropriate treatment for active TB infection, patients soon become noninfectious as cough subsides and the concentration of organisms in sputum decreases.[1] Although the time to become noninfectious varies, evidence suggests that in most circumstances it takes approximately 2 to 3 weeks once proper treatment is started.[22] In health care facilities, the Centers for Disease Control and Prevention (CDC) has established strict guidelines for removing patients from respiratory isolation, including 3 consecutive negative sputum acid-fast bacilli (AFB) smears on specimens obtained at least 8 hours apart, at least one obtained as an early morning specimen.[23]

3. What is the cure rate for LTBI in compliant patients?

Randomized trials evaluating the efficacy of isoniazid (INH) for the treatment of LTBI have shown that completion of a 9-month course of isoniazid decreases the risk of progression to active disease by approximately 90%. Completion of a 6-month course of INH reduces the risk by 60% to 80%.[8]

DRUG RESISTANCE

1. *What is multi-drug resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB)?*

   - Multi-drug resistant TB (MDR-TB) infection is present when a strain is resistant to at least INH and rifampin (RIF).

Table 1
High-risk populations to screen for TB infection

High-Risk Groups	High-Prevalence Groups
• Children less than 4 y of age	• Persons born in countries with high prevalence of TB
• Persons with HIV coinfection	• Groups with poor access to health care
• Close contacts of persons with infectious TB	• Persons who live or spend time in certain facilities (eg, nursing homes, correctional facilities, homeless shelters, drug treatment centers)
• Persons who TST results converted to positive in the past 1–2 y	• Persons who inject drugs
• Persons who have chest radiographs suggestive of old TB infection	
• Persons with certain medical conditions[a]	

[a] Diabetes mellitus, silicosis, prolonged therapy with corticosteroids, immunosuppressive therapy (including TNF-α inhibitors), Hodgkin disease, head and neck cancers, severe kidney disease, certain intestinal conditions, and malnutrition.

Data from Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med 2000;161(4):1376–95.

- Extensively drug-resistant TB (XDR-TB) is present when strains are resistant to at least INH, RIF, any fluoroquinolone, and at least 1 of 3 available second-line injectable aminoglycosides (ie, amikacin, kanamycin, or capreomycin).[24]

Resistance to antituberculosis agents may be present before the initiation of therapy (ie, *primary drug resistance*—due to transmission of a drug-resistant strain) or develops during the course of therapy after at least 1 month of treatment (ie, *secondary drug resistance*). Secondary (acquired) drug resistance is more common and usually occurs as a result of medication noncompliance.[1,25] There is growing concern for the transmission of XDR-TB because of reported outbreaks in South Africa and Iran.[24,26,27] In 2011, nearly 60,000 MDR-TB cases were reported worldwide, accounting for an estimated proportion of 1 in 5 TB cases.[4] A large proportion of MDR-TB cases are accounted for in India, China, the Russian Federation, and South Africa. Furthermore, there is a significant association between HIV-positive status and MDR-TB.[28] XDR-TB is estimated to represent approximately 9% of MDR-TB cases, and as of 2011, it has been reported in 84 countries.[4]

2. What proportion of TB cases in the United States is due to MDR-TB?

Since 1998, the percentage of MDR-TB cases in the United States has remained steady. Among all reported TB cases in the United States in 2011, 1.3% were classified as primary MDR-TB (defined as no previous history of TB disease).[4]

3. What patients are highest risk for TB infection and MDR-TB infection?

In persons not previously exposed to MTB, the most important determinants of infection are proximity to and infectiousness of the source patient (eg, cases with positive sputum smears are more infectious than culture positive cases).[1] Approximately 30% of household contacts of smear-positive cases may become infected; however, the rate of transmission is much higher in closed environments.[29] Other factors that increase the risk of exposure to or development of TB infection include HIV infection, immunosuppression, originating from or traveling to an endemic area (eg, Africa, Asia, or Latin America), and exposure to untreated TB cases in congregate living facilities (eg, imprisonment, nursing homes, homeless shelters, other health care facilities). Patients at risk for active TB once infection has occurred include those with recent TB infection, injection drug users, end-stage renal disease, silicosis, diabetes mellitus, hematologic cancers, receiving immunosuppressive therapy, malnutrition, and history of gastrectomy or jejunoileal bypass surgery.[7] **Box 1** describes the potential risk factors that would raise concern for MDR-TB infection.

Box 1
Risk factors for multidrug-resistant tuberculosis (MDR-TB)

- Exposure to a person with known drug-resistant TB.
- Exposure to a person with active TB previously treated for TB (treatment failure or relapse) and whose susceptibility test results are unknown.
- Exposure to persons with active TB from areas in which there is a high prevalence of drug resistance.
- Exposure to persons who continue to have positive sputum smears after 2 mo of combination therapy.

Data from American Thoracic Society, Centers for Disease Control, Infectious Diseases Society of America. Treatment of tuberculosis. MMWR Recomm Rep 2003;52(RR-11):1–77.

HISTORY AND EXAMINATION

1. What are the most common findings in patients with LTBI and active TB?

Symptoms

Patients with LTBI are generally asymptomatic at presentation.[30,31] Early disease may be discovered incidentally on chest radiography. As the burden of disease progresses, the clinical picture is often reflective of constitutional symptoms (fatigue, anorexia, unexplained weight loss, fevers, chills, and night sweats), accompanied by a prolonged cough (ie, >3 weeks). Progression of the primary complex may lead to bronchial collapse with distal atelectasis or erosion into the bronchial vasculature, producing hemoptysis. Inflammation of the parietal pleura may produce chest pain. Symptoms that may suggest the possibility of extrapulmonary TB include hematuria (TB of the kidney), headache or confusion (TB meningitis), hoarseness (laryngeal involvement), and back pain (TB of the spine).[1,6]

Patient History

It is pertinent to determine the history of the Bacillus Calmette-Guérin (BCG) vaccination and medications that could result in immunosuppression (eg, corticosteroids, tumor necrosis factor-α [TNF-α] antagonists, chemotherapeutic agents). One should investigate risk factors for HIV infection, prior organ transplantation, past TB treatment, as well as prior history of contact with persons with active TB, or occupational exposures. Other potentially useful information that can be obtained from the history includes homelessness, alcoholism, prior incarceration, and immigration from an endemic country within 5 years. It is also important to determine if persons have underlying medical conditions that increase risk of TB disease.[1,6]

Physical Findings

In general, physical findings are often nonspecific. Pleural thickening or fluid may produce dullness to percussion or decreased tactile fremitus. Crackles are sometimes heard on auscultation, and with large lesions, signs of consolidation may be heard. Initial inoculation with the bacterium is followed by tuberculin hypersensitivity, 2 to 8 weeks later and is rarely associated with erythema nodosum[32] or phlyctenular keratoconjunctivitis (severe unilateral inflammation of the eye).[33]

Imaging and Additional Testing

In adults, chest radiographs may depict apical or subapical infiltrates, often accompanied by cavitation, with or without hilar adenopathy. The presence of a patchy or nodular infiltrate in the apical or subapical-posterior areas of the upper lobes or the superior segment of a lower lobe is characteristic of early chronic TB, particularly if it is bilateral or associated with cavitary lesions.[1,6] The chest radiograph can also be normal in a minority of patients. More than 20% of HIV-positive patients with pulmonary TB may have a normal chest radiograph.[34–37] Routine laboratory findings are nonspecific. Patients with advanced, chronic disease may show evidence of hypoalbuminemia or normocytic normochromic anemia with a normal white blood cell count. The presence of sterile pyuria or hematuria should prompt investigation for renal TB. As in other granulomatous diseases, hypercalcemia may be observed, due to production of 1,25-dihydroxycholcalciferol by activated macrophages. Isolated pulmonary disease or adrenal involvement may cause hyponatremia as a result of syndrome of inappropriate antidiuretic hormone secretion or adrenal insufficiency, respectively.[1,6]

SCREENING AND DIAGNOSIS

1. Who should be screened for a prior TB infection and what test is now recommended for screening?

Consider screening high-prevalence and high-risk populations[6] who may have been previously exposed to TB resulting in LTBI, or are at high risk for developing active TB disease (see **Table 1**). The recommended screening tests for TB infection include the Mantoux TST (ie, purified protein derivative or PPD) or one of the commercially available IGRAs, which are described below.[7] Identification of a recent infection occurs when induration from a TST increases by $\geq$10 mm within a 2-year period (ie, "tuberculin conversion"). The risk for developing active disease is highest soon after primary infection; therefore, testing these patients is of utmost importance. However, it takes 2 to 8 weeks after an initial exposure for the immune system to react to TST or IGRAs. To avoid a false-negative TST or IGRA during this "window" period, patients can be retested 8 to 10 weeks after their most recent exposure to allow for delayed immune response. Treatment of LTBI should be considered if the TST or IGRA is interpreted positive, and patients have no symptoms or radiographic evidence to suggest active TB infection.

HIV-positive patients are at particularly high risk for infection with TB, and it is recommended to screen for LTBI (with TST or IGRA) as part of the initial evaluation after diagnosis and annually thereafter.[7] Another high-risk population for TB infection is patients with immune-mediated inflammatory diseases (IMID), such as rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis, and psoriatic arthritis. Patients with IMID are often treated with immunomodulators, such as corticosteroids, and methotrexate or biologic agents, such as TNF-α inhibitors, which have been associated with increased risk for developing active TB disease.[38–40] Before initiating therapy with TNF-α inhibitors for IMID, active TB should be ruled out and screening for LTBI should be performed. It is recommended that screening include a detailed medical history, chest radiography, and IGRA testing.[41]

2. How is TST performed and interpreted?

TST is easily performed by intradermal injection of PPD (0.1 mL, 5 tuberculin units) into the volar surface of the forearm producing a wheal that is 6 to 10 mm in diameter. The test is then interpreted 48 to 72 hours after injection and test positivity (indicating the presence of infection) is defined by the diameter of *induration* by palpation of the injection site. Another suggested method is to use a medium-point ballpoint pen to draw a line starting 1 to 2 cm away from the skin reaction and moving toward its center.[1] The pen is lifted when resistance is felt and the procedure is then repeated from the opposite direction in the same manner. Using this method, the distance between opposing line ends is measured to determine the diameter of induration. The American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) /CDC guidelines on TST recommend targeted testing of persons at high risk for developing TB, and treatment of LTBI if the test is abnormal.[8] Three cutoff levels have been recommended for defining positive TST reactions, depending on individual patient characteristics (**Table 2**).

Because anergy can occur in the setting of active disease or advanced HIV, a negative TST does not exclude active infection. The sensitivity of the TST in immunocompromised individuals is considerably lower, especially in HIV-infected persons with a $CD4^+$ count less than 100 cells/mm^3; however, once anti-retroviral therapy is initiated and the $CD4^+$ count increases to more than 100 cells/mm^3, its reliability improves.[42] In

Table 2
Criteria for a positive TST

Induration (diameter)	Persons Test Considered Positive
≥5 mm	• HIV-infected persons • Persons with organ transplants and other immunosuppressed persons (taking ≥15 mg prednisone/d or equivalent for ≥1 mo or those taking TNF-α inhibitors) • Recent close contact with a person with known infectious TB • Persons with an abnormal chest radiograph consistent with prior TB infection[a]
≥10 mm	• Foreign-born persons recently arrived (<5 y) from a high prevalence country • Injection drug users • Children <4 y of age, or children and youth exposed to adults at high risk • Persons with a medical condition that increases the risk of TB[b] • Members of medically underserved, low-income populations (eg, homeless persons) • Health care workers and residents/staff of long-term care facilities (eg, nursing homes, correctional facilities, homeless shelters) • Persons with conversion on a TST (increase in induration of ≥10 mm within a 2-y period)
≥15 mm	• All others (persons with no known risk factors for TB)[c]

[a] Radiograph demonstrating fibrotic opacities occupying more than 2 cm^2 of the upper lobe; radiographs showing pleural thickening or isolated calcified granulomas are not considered to be suggestive of previous TB.
[b] Silicosis, end-stage renal disease, malnutrition, diabetes mellitus, carcinoma of the head and neck or lung, immunosuppressive therapy (including TNF-α inhibitors), lymphoma, leukemia, loss of >10% ideal body weight, gastrectomy, and jejunoileal bypass.
[c] These persons should not be screened in the absence of an indication.
Data from Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med 2000;161(4):1376–95.

addition, a positive TST does not differentiate between LTBI and active disease (ie, neither TST nor IGRA can distinguish LTBI from active infection).

An abnormal PPD supports the diagnosis of culture-negative pulmonary TB in symptomatic patients, as well as LTBI in persons with stable abnormal chest radiographs consistent with inactive TB. False-positive TST results can occur because of prior BCG vaccination or prior exposure to opportunist environmental nontuberculous mycobacteria. Tuberculin skin testing is not contraindicated for persons who received the BCG vaccination and interpretation of a TST in a patient with a history of BCG vaccination is the same as in a person without a history of BCG vaccination. Less than 10% of patients who receive the BCG vaccination at birth will have an abnormal TST 15 years later.[43]

3. What is the "booster" phenomenon and what is its role in TB screening?

The concept behind the 2-step approach or "booster effect" is to restimulate prior hypersensitivity that has waned. The booster effect is characterized by a positive tuberculin reaction 1 to 4 weeks after a normal TST because the initial test stimulates the host's ability to react to the test.[1] For example, health care workers often undergo 2-step testing at baseline to avoid interpreting a booster effect as a tuberculin

conversion. If the initial TST showed no reaction, a second test should be performed 1 to 4 weeks later and patients with a second TST (ie, booster) response of $\geq$10 mm should be considered to have prior TB infection. Persons who do not have a positive response after 2-step testing, but whose TST reactions change to positive after 1 year, should be considered to have newly acquired TB infection.

4. What is the difference between TST (ie, PPD) and IGRAs?

Before 2001, the TST was the most widely available immunologic test for *M tuberculosis* infection.[6] Currently, 2 IGRAs are approved by the Food and Drug Administration the T-SPOT.*TB* test (Oxford Immunotech) and QuantiFERON-TB Gold In-Tube test (Cellestis).[44–47] The T-SPOT.*TB* test uses purified peripheral blood mononuclear cells with an enzyme-linked immunospot technique. The QuantiFERON-TB Gold In-Tube test uses enzyme-linked immunosorbent assay to detect interferon-γ released by sensitized T cells. A meta-analysis[48] comparing both IGRAs in 2008 reported a specificity for the T-SPOT.*TB* of 93% (95% Confidence Interval [CI], 86%–100%) and sensitivity of 90% (95% CI, 86%–93%). In comparison, the QuantiFERON-TB Gold In-Tube had a specificity of 99% (95% CI, 98%–100%) and sensitivity of 78% (95% CI, 73%–82%).[48]

IGRAs can be used for screening patients in any situation that a TST (eg, PPD) would be appropriate, with the exception of children less than 5 years of age, where TST is preferred.[49] The PPD reaction relies on host immune function, making its sensitivity limited in patients with an impaired immune system. However, current evidence suggests the IGRAs perform similarly to the TST at identifying HIV-infected individuals with LTBI.[50] IGRAs may be used in place of, but not in addition to, TST. Use of IGRA testing may be preferred when testing persons who might not return for TST reading and results are generally available within 24 to 48 hours, if the test is interpreted locally. In addition, prior BCG vaccination will not cause a false-positive IGRA result. Similar to the TST, IGRAs do not differentiate between active TB disease and LTBI. Furthermore, IGRAs are not recommended for testing persons who have a low risk of LTBI or progression to active disease.[49]

The sensitivity of TST/IGRA varies depending on the pretest probability of disease. A free evidence-based calculator designed to estimate whether or not a positive TST or IGRA result is a true positive is available at http://tstin3d.com. The Web-based algorithm was developed in 2008 by Menzies and colleagues.[51] In addition to the positive predictive value of a given TST/IGRA result, the calculator also provides clinically useful information including the annual and cumulative lifetime risk of developing TB in adults with a positive TST or IGRA. It also provides estimates on the risk of drug-induced hepatitis with INH therapy.

5. Are there any clinical situations where IGRAs might be preferred over TST?

IGRAs detect antigens that are not present in the BCG vaccine; therefore, they may be preferred over TST when screening for TB infection in persons with a history of BCG vaccination.[52] Because of the high risk of anergy in HIV-positive patients with $CD4^+$ counts less than 100 cells/mm^3 and patients taking immunomodulators (eg, TNF-α inhibitors) for immune-mediated inflammatory diseases (eg, inflammatory bowel disease, rheumatoid arthritis), IGRA testing may be preferred over TST.[41,42]

6. How should the diagnosis of active TB be approached once it is suspected and what are the preferred methods of diagnosis?

Chest radiography remains central to the diagnosis of TB and the presence of characteristic patterns can often lead to a strong presumptive diagnosis in the appropriate

clinical setting.[1,6] If imaging results are suggestive of active infection, organisms can be detected using sputum microscopy, with characteristic AFB on stained smears. Before performing a diagnostic workup, all TB suspects should be placed empirically in airborne isolation precautions. The sensitivity of sputum AFB smear when compared with culture is approximately 60%.[53] Noncavitary disease and coexisting HIV infection decrease the sensitivity of sputum AFB smears. Collection of a second sputum sample increases the sensitivity by approximately 10%, and another 2% with a third specimen.[54] Thus, collection of 3 sputum specimens, at least 8 hours apart, is recommended (at least one smear should be an early morning specimen). In addition, AFB staining can be used to identify organisms directly from any biologic fluid or material (eg, cerebrospinal fluid, gastric lavage fluid, tissue biopsy or fine-needle aspiration, pleural fluid).[1,6]

If sputum cannot be produced, induction by inhalation of aerosolized (via a nebulizer) hypertonic saline (3%–15%) is effective, with a yield comparable to fiberoptic bronchoscopy.[55] The specimen should be clearly labeled as "induced sputum" so it will not be discarded by the laboratory as an inadequate specimen (appearance is often thin and watery and may be perceived as inadequate). If sputum cannot be produced with aerosol inhalation, gastric aspiration may be necessary; however, this diagnostic method is rarely used in adults. If performed, aspiration of approximately 50 mL of gastric contents should be collected in the early morning, after the patient has fasted for 8 to 12 hours. The specimen should be neutralized immediately after collection per a standardized protocol.[56]

If suspicion for active TB remains high despite inconclusive sputum testing, pulmonary consultation for diagnostic fiberoptic bronchoscopy with bronchoalveolar lavage, with or without transbronchial biopsy, should be considered. This approach should also be considered in patients with AIDS. However, it only confers a rapid diagnosis in approximately one-third of cases; thus, it does not entirely exclude active pulmonary TB in patients with AIDS.[57–59]

Examination of pleural, peritoneal, and pericardial fluids can also be useful in the diagnosis of TB. A high protein (>50% of serum protein concentration), low glucose, and lymphocytosis are characteristic for TB infections, but neither their presence nor absence is diagnostic. Adenosine deaminase levels may also be useful and are often elevated in sites with TB infection.[60–63] Mycobacterial cultures of pleural fluid are abnormal in less than 25% of cases. Biopsy of the pleura will show granulomatous inflammation in approximately 60% of patients; however, diagnosis can be made in up to 90% of cases when 3 consecutive pleural biopsy specimens are obtained in combination with acid-fast culture and microscopic examination.[64]

Culture remains the gold standard for detecting mycobacteria, and all specimens suspected of containing mycobacteria should be cultured to obtain speciation and drug susceptibility testing. On standard solid media, visible growth of *M tuberculosis*, requires 3 to 8 weeks.[1,6] Rapid identification of *M tuberculosis* can be achieved with use of DNA probes (ie, nucleic acid amplification testing); however, these methods do not differentiate *M tuberculosis* from other members of the complex (ie, *M bovis*, *M africanum*, and *M microti*) and can also identify species from the *M avium* complex, *M kansasii*, and *M gordonae*.[65] For smear-positive specimens, the sensitivity and specificity of nucleic acid amplification are greater than 95%; for smear-negative cases, the sensitivity ranges from 40% to 70%, whereas the specificity remains greater than 95%.[66] Drug susceptibility testing for INH, RIF, and EMB should be performed on the initial isolate of *M tuberculosis* obtained from all patients. Drug susceptibility testing should be repeated in patients who do not respond to therapy or have positive cultures despite 3 months of adequate therapy.[3]

Diagnosis of active TB remains a challenging task; however, a recently developed nucleic acid amplification assay shows promise to revolutionize the diagnosis of TB. The rapid nucleic acid amplification assay is known commercially as the GeneXpert MTB/RIF assay (Cepheid) and it can simultaneously detect MTB complex and RIF resistance, with a turn-around time of approximately 90 minutes.[67] In addition, the sensitivity of MTB detection with the GeneXpert MTB/RIF assay is greater than that of standard sputum smear microscopy, with a reported sensitivity of 98% in smear-positive cases and 72% in smear-negative, culture-positive cases.[67,68] The GeneXpert MTB/RIF assay was endorsed by the World Health Organization for use in TB endemic countries in December 2010.[69] It is also currently being used in Europe and pending approval for use in the United States.

7. Once a diagnosis of TB is made, how is it classified, and which patients should be reported to the local health department?

The classification system for TB is based on the organism's pathogenesis and was designed to help clinicians track the development of TB in patients (**Table 3**). Cases of class 3 or 5 TB should be reported to local health departments. Persons should not be labeled with class 5 TB for longer than 3 months.[6]

MANAGEMENT

1. What initial recommendations are suggested if a patient is suspected of having active pulmonary TB?

Initial management of hospitalized patients with suspected or known active TB should always include isolation with airborne precautions in a negative pressure room.[3] All visitors entering the room should wear a properly fitted N95 respirator mask and/or other suitable personal protective equipment. Consultation with an infectious disease specialist is generally recommended before initiating empiric therapy in cases where the possibility of MDR-TB exists (see **Box 1**). The decision to initiate antituberculosis therapy should be based on clinical, pathologic, and radiographic findings in addition to the results of diagnostic specimens (ie, AFB stains, cultures, or biopsy specimens). It is recommended that all patients with TB have counseling and testing for HIV infection. Patients with risk factors for hepatitis B or C viruses (eg, injection drug use, foreign birth in Asia or Africa, HIV infection) should have serologic testing for these viruses. Guidelines published in conjunction with the ATS, the CDC, and the IDSA

Table 3
TB classification system

Class	Stage of Disease
0	No exposure, no infection
1	Exposure, no evidence of infection
2	TB infection, no disease
3	TB, clinically active
4	TB, not clinically active
5	TB suspect

Data from Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med 2000;161(4):1376–95.

are periodically updated and provide outlines on the recommended treatment regimens (**Table 4**).[3]

2. What is the treatment for LTBI and how long should it be continued?

The mainstay of treatment of LTBI has been INH for nearly 50 years. Nine months of INH therapy is currently recommended for treatment of LTBI (270 doses within 12 months).[71] When this regimen is completed properly, it is curative in more than 90% of cases. Patients undergoing treatment for LTBI should receive regular follow-up

Table 4
Recommended treatment regimens for tuberculosis in adults

LTBI	Comments
Isoniazid 300 mg daily for 9 mo[a] (270 doses within 12 mo)	***Preferred regimen*** (including in persons infected with HIV taking anti-retrovirals and pregnant women)
Isoniazid 300 mg daily for 6 mo[a] (180 doses within 9 mo)	***Alternative regimen*** for HIV-negative adults and pregnant women ***Not recommended*** for HIV-infected persons, individuals with fibrotic lesions on chest radiograph, or <18 y of age
Isoniazid 900 mg + rifapentine 900 mg once weekly for 3 mo[a,b]	Only recommended for use with DOT ***Not recommended*** for persons infected with HIV taking anti-retrovirals, pregnant women, or women trying to get pregnant
Rifampin 600 mg daily for 4 mo[b] (120 doses within 6 mo)	***Alternative regimen*** for persons with contraindications or unable to tolerate INH and individuals with exposure to INH-resistant, RIF-susceptible TB
Drug-Susceptible Active Tuberculosis Infection	**Comments**
Initial phase (2 mo): Isoniazid, rifampin ethambutol, and pyrazinamide daily (Alternative: Daily for 2 wk, then twice weekly for 6 wk if receiving DOT)[c] ***Continuation phase (4 mo)***: Isoniazid and rifampin *daily (Alternative: 3 times weekly if receiving DOT)*	*Continuation phase* should be lengthened from 4 to 7 mo (9 mo total) in the following circumstances: 1. Cavitation is seen on initial chest X-ray and sputum cultures are positive after initial 2 months of therapy are completed; 2. Once-weekly isoniazid and rifapentine used in continuation phase, and culture is positive at end of initial phase; or 3. Initial phase excluded pyrazinamide (e.g., due to severe liver disease, gout, or pregnancy).

[a] Pyridoxine supplementation (25–50 mg/d) is recommended in patients taking isoniazid to prevent peripheral neuropathy and CNS effects (especially in those with pregnancy, alcoholism, diabetes, HIV, and seizure disorders).
[b] Rifapentine and rifampin causes red/orange discoloration of urine and tears, and can stain contact lenses; they are also a strong CYP3A4 inducers. Use of RIF is contraindicated with some combinations of anti-retroviral therapy.
[c] Sputum AFB smears and cultures should be obtained after completion of the initial phase to identify patients at high risk of relapse.
Data from Refs.[3,8,70]

examinations after their initial clinical evaluation. It is recommended that no more than a 1-month supply of medication should be dispensed at a time.

Before treating patients for LTBI, clinicians should:

- Exclude the possibility of active TB disease (ie, chest radiograph, medical evaluation for signs or symptoms of active disease);
- Determine if contraindications to treatment exist;
- Recommend testing for HIV infection;
- Determine if the patient has been previously treated for LTBI or active disease; and
- Obtain information about current and prior drug therapy, including adverse reactions or allergies.

During follow-up, patients should be questioned about side effects related to the medication and advised to discontinue INH if they experience symptoms consistent with hepatitis (eg, jaundice, nausea, fatigue, loss of appetite, abdominal pain). At monthly follow-up appointments, patients should be questioned about their adherence to the prescribed regimen as well as signs and symptoms of active TB disease. Periodic measurement of liver function tests (LFTs) is recommended in patients with pre-existing LFT abnormalities, chronic liver disease (eg, monthly LFTs), HIV infection, and women who are pregnant or in the immediate postpartum period. INH should be discontinued if levels of alanine aminotransferase or aspartate aminotransferase exceed 5 times normal in asymptomatic patients or 3 times normal in symptomatic patients.[71]

3. What empiric treatment should be started in patients newly diagnosed with drug-susceptible active TB infection and how long should it be continued?

The ATS/CDC/IDSA guidelines recommend that newly diagnosed cases of drug-susceptible active pulmonary TB should be treated with 4-drug therapy, including INH, RIF, pyrazinamide (PZA), and ethambutol (EMB).[3] **Table 5** describes the dosage, adverse effects, and monitoring required for drugs used in the treatment of drug-susceptible TB. The regimen can be administered daily or intermittently by the use of directly observed therapy (DOT).

The *initial phase* of the 6-month regimen for adults should consist of a 2-month period of INH, RIF, PZA, and EMB, followed by a *continuation phase* of treatment with INH and RIF for a minimum of 4 months (18 weeks). EMB can be discontinued before the end of the initial 2-month period if susceptibility testing reveals sensitivity to INH, RIF, and PZA. PZA should be continued for the entirety of the 2-month initial phase. During treatment, sputum specimens should be obtained for microscopic examination and culture at a minimum of monthly intervals until 2 consecutive specimens are normal on culture.[3] Treatment of children, pregnant patients, HIV-infected individuals, and those with MDR-TB or XDR-TB is beyond the scope of this article and it is suggested that it should be completed in conjunction with a specialist in infectious disease or other experienced personnel. Guidelines for treatment in these circumstances are listed below in the section, “Clinical Guidelines.”

4. What patients should be considered for DOT?

There is no reliable way to predict which patients will be adherent to therapy; therefore, all patients with active TB disease should be considered for DOT. Use of DOT is recommended in patients with the following conditions/circumstances: pulmonary TB with positive sputum smears; treatment failure; drug resistance; relapse; HIV

Table 5
First-line drugs used in the treatment of active pulmonary TB

Drug	Dosage (Maximum)	Adverse Effects	Monitoring
Isoniazid (INH)	5 mg/kg (300 mg) by mouth daily[a]	Hepatitis (fatal), elevation of liver enzymes, peripheral neuropathy (prevented with pyridoxine 50 mg/d [vitamin B_6] co-administration), lupus-like syndrome	LFTs at baseline and then monthly if baseline abnormalities or concomitant liver disease
Rifampin (RIF)	10 mg/kg (600 mg) by mouth daily[a]	GI upset, orange discoloration of bodily fluids (sputum, urine, sweat, tears), hepatitis, fever, hypersensitivity, drug interactions	LFTs at baseline and then monthly if baseline abnormalities or concomitant liver disease
PZA	25 mg/kg (2000 mg) by mouth daily[a]	Hepatitis, hyperuricemia (gout), arthritis, rash	LFTs at baseline and then monthly if baseline abnormalities or concomitant liver disease
EMB	15–25 mg/kg (1600 mg) by mouth daily[a]	Optic neuritis (doses >20 mg/kg/d, renal insufficiency, and duration >2 mo)	Monthly assessment of visual acuity and color discrimination

[a] Dosing should be based on lean body weight.
Data from American Thoracic Society, Centers for Disease Control, Infectious Diseases Society of America. Treatment of tuberculosis. MMWR Recomm Rep 2003;52(RR-11):1–77.

infection; previous treatment of either active or LTBI; current/prior substance abuse; psychiatric illnesses; memory impairment; or previous nonadherence to therapy. To limit resistance, patients who are not started on DOT should be given combination pills to deter noncompliance and decrease the risk of acquired drug resistance. In the United States, 2 combination formulations are approved for use: INH, RIF, and PZA (Rifater) and INH and RIF (Rifamate). Representatives of the public health system are usually the best referral source when considering DOT.[3,71]

5. What infection control measures should be taken in patients hospitalized with active TB infection?

All patients suspected of having TB should be immediately isolated until it is determined they are no longer infectious or until TB has been excluded.[23,72] Suspected or confirmed TB cases must be reported to the local or state health department in accordance with laws and regulations. Airborne precautions should be implemented and isolation rooms should have negative air pressure with at least 6 cycles per hour to prevent spread of infection. All individuals caring for the patient or entering isolation should wear N95 masks to prevent inhalation of infectious particles when working in the enclosed room. Strict guidelines exist regarding removal from airborne isolation while patients are in health care facilities. Airborne precautions can be discontinued when infectious TB disease is considered unlikely and either (1) the clinical syndrome is explained by another diagnosis or (2) 3 normal AFB sputum smear results

are completed. At least 1 of the 3 sputum specimens should be an early morning specimen, and consecutive AFB sputum samples should be collected at least 8 to 24 hours apart.[23,72]

6. What patients are at risk for treatment failure and relapse of infection?

Treatment failure is defined by positive culture after 4 months of treatment and relapse is defined by recurrent TB at any time after completion of treatment and apparent cure.[3] Patients with cavitation on the initial chest radiograph and positive sputum cultures after completion of 2 months of therapy (the initial phase) are at high risk for relapse. It is recommended that patients with these features receive a prolonged continuation phase of 7 months (total treatment period of 9 months) due to significantly higher relapse rates. This recommendation highlights the importance of obtaining sputum cultures 2 months after initiation of treatment, and those with positive cultures at that time should undergo evaluation to determine the cause. After 2 months of treatment with a standard 4-drug regimen, approximately 80% of patients with drug-susceptible pulmonary TB will have negative sputum cultures.[3] The authors recommend consultation with an infectious disease specialist or other experienced personnel if this situation arises to determine the appropriate duration of therapy and evaluate for the presence of drug-resistant infection or other potential causes of treatment failure.

7. What drugs are available for the treatment of MDR-TB and XDR-TB?

Second-line anti-TB drugs currently available for use in the United States include cycloserine, ethionamide, levofloxacin, moxifloxacin, gatifloxacin, ρ-aminosalicylic acid, streptomycin, amikacin/kanamycin, and capreomycin. Only cycloserine, ethionamide, ρ-aminosalicylic acid, streptomycin, and capreomycin are Food and Drug Administration–approved for this indication.[3] Linezolid has also been used off-label in the treatment of XDR-TB; however, its role of use in this setting has not been well established.[73,74]

CLINICAL GUIDELINES

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