

Current Concepts in the Management of Tuberculosis

IRENE G. SIA, MD, MSc, AND MARK L. WIELAND, MD, MPH

On completion of this article, readers should be able to (1) identify patients at high risk of tuberculosis; (2) accurately and efficiently diagnose active tuberculosis on the basis of clinical presentation, laboratory results, and microbiological tests; and (3) prescribe first-line therapy for latent and active uncomplicated pulmonary tuberculosis.

Tuberculosis (TB) poses a serious threat to public health throughout the world but disproportionately afflicts low-income nations. Persons in close contact with a patient with active pulmonary TB and those from endemic regions of the world are at highest risk of primary infection, whereas patients with compromised immune systems are at highest risk of reactivation of latent TB infection (LTBI). Tuberculosis can affect any organ system. Clinical manifestations vary accordingly but often include fever, night sweats, and weight loss. Positive results on either a tuberculin skin test or an interferon- γ release assay in the absence of active TB establish a diagnosis of LTBI. A combination of epidemiological, clinical, radiographic, microbiological, and histopathologic features is used to establish the diagnosis of active TB. Patients with suspected active pulmonary TB should submit 3 sputum specimens for acid-fast bacilli smears and culture, with nucleic acid amplification testing performed on at least 1 specimen. For patients with LTBI, treatment with isoniazid for 9 months is preferred. Patients with active TB should be treated with multiple agents to achieve bacterial clearance, to reduce the risk of transmission, and to prevent the emergence of drug resistance. Directly observed therapy is recommended for the treatment of active TB. Health care professionals should collaborate, when possible, with local and state public health departments to care for patients with TB. Patients with drug-resistant TB or coinfection with human immunodeficiency virus should be treated in collaboration with TB specialists. Public health measures to prevent the spread of TB include appropriate respiratory isolation of patients with active pulmonary TB, contact investigation, and reduction of the LTBI burden.

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AFB = acid-fast bacilli; BCG = bacille Calmette-Guérin; CFP-10 = culture filtrate protein 10; DOT = directly observed therapy; EMB = ethambutol; ESAT-6 = early-secreted antigenic target 6; HIV = human immunodeficiency virus; IFN- γ = interferon- γ ; IGRA = IFN- γ release assay; INH = isoniazid; LTBI = latent TB; MDR-TB = multidrug-resistant TB; NAA = nucleic acid amplification; PZA = pyrazinamide; RIF = rifampin; TB = tuberculosis; TBI = TB infection; TST = tuberculin skin test; XDR-TB = extensively drug-resistant TB

Effective medical therapy for tuberculosis (TB) has existed for more than half a century, yet TB remains among the most pressing public health issues of our day. Tuberculosis is, in part, a disease of poverty.¹ The fact that it remains the eighth leading cause of death in the world speaks to the challenges facing practitioners and public health officials as they try to control a disease that is so entwined in the cultural and economic fabric of society. Challenges to effective solutions include lack of access to diagnosis and treatment, the frequent coexistence of epidemics of TB and human immunodeficiency virus (HIV), and the

increasing prevalence of multidrug-resistant TB (MDR-TB).² Although a chasm in disease burden exists between resource-rich and poor regions, an increasingly mobile and connected global community has ensured that TB remains highly relevant to practitioners throughout the world. This review highlights key principles in the management of TB. For purposes of definition, TB infection (TBI) occurs when a susceptible person inhales droplets containing *Mycobacterium tuberculosis* nuclei that travel through the respiratory tract to the alveoli. In most patients, an immune response limits propagation of TBI, resulting in an asymptomatic, noninfectious, localized infection that may remain in the body for many years. These patients have positive immunologic test results for *M tuberculosis* and carry a diagnosis of latent TBI (LTBI). A constellation of clinical, radiographic, microbiological, and histopathologic hallmarks are used to diagnose active TB disease.³

EPIDEMIOLOGY

An estimated one-third of the world's population is infected with TB.⁴ Tuberculosis accounted for 1.3 million deaths in 2007, and the prevalence of active disease is estimated at 13.7 million (206 per 100,000 persons).⁵ Incident cases of active TB are highest (≥ 100 cases per 100,000 persons) in sub-Saharan Africa, India and Central Asia, parts of Eastern Europe, Southeast Asia, and Micronesia. Intermediate incidence rates (26-100 per 100,000 persons) are observed in Central and South America, China, and northern Africa. Low rates (< 25 per 100,000 persons) occur in the United States, Canada, Australia, Western Europe, and Japan.^{5,6}

While absolute numbers have been on the rise, the prevalence of TB in relationship to population has trended downward during the past 15 years, and global public

From the Division of Infectious Diseases (I.G.S.) and Division of Primary Care Internal Medicine (M.L.W.), Mayo Clinic, Rochester, MN.

Address correspondence to Irene G. Sia, MD, MSc, Division of Infectious Diseases, 200 First St SW, Rochester, MN 55905 (sia.irene@mayo.edu). Individual reprints of this article and a bound reprint of the entire Symposium on Antimicrobial Therapy will be available for purchase from our Web site www.mayoclinicproceedings.com.

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health efforts have averted an estimated 6 million deaths during this time.² Nevertheless, the emergence of drug resistance coupled with the persistence of HIV and global poverty have thwarted a more substantive break in the TB epidemic. Indeed, 0.5 million cases of MDR-TB, in which the infecting organism is resistant to at least isoniazid (INH) and rifampin (RIF), were reported in 2007, and 55 countries reported at least 1 case of extensively drug-resistant TB (XDR-TB),⁵ in which the organism is resistant to at least INH, RIF, fluoroquinolones, and either aminoglycosides or capreomycin, or both. The magnitude of the problem is particularly overwhelming in parts of the Russian Federation and Central Asia, where the proportion of MDR-TB among incident TB cases ranged from 12% to 28% between 1994 and 2009, compared with 0% to 3% in the United States.⁷

As in the rest of the world, the incidence of TBI in the United States has declined during the past decade, but this decline has been much less pronounced among foreign-born Americans. More than half of active TB cases in the United States currently occur in foreign-born individuals,^{5,8} and most cases result from reactivation of LTBI.^{9,10} The effect of global migration on TB has been seen throughout the developed world, most dramatically in London, where cases of active TB increased by 50% between 1999 and 2009, mostly among foreign-born individuals.¹¹

Sociodemographic risk factors for TBI include recent residence in an endemic region of the world, low socioeconomic position, being a member of a racial or ethnic minority (in the United States), homelessness, residency or employment at high-risk facilities (eg, correctional facilities, homeless shelters, skilled nursing facilities), and employment as a health care worker caring for patients with TB.

TRANSMISSION

Tuberculosis is transmitted through droplet aerosolization by an individual with active pulmonary disease. The highest risk of transmission occurs among patients with cavitary or positive acid-fast bacilli (AFB) smears¹²; however, patients with negative smears but positive cultures may still transmit the disease.¹³

Host factors dramatically influence which of those exposed to TB are most likely to contract primary disease or progress to active disease. Those with greater susceptibility include persons with immune systems that have been compromised through either diseases, such as HIV infection and hematologic and reticuloendothelial malignancies, or through immunosuppressive medications, such as corticosteroids, tumor necrosis factor α inhibitors, calcineurin inhibitors, and cytotoxic chemotherapeutic agents. Furthermore, patients with chronic diseases, such as diabetes,

chronic kidney disease, and silicosis, are at elevated risk. Finally, age younger than 4 years, long-term malnutrition, and substance abuse are independent risk factors for disease.³

CLINICAL MANIFESTATIONS

PULMONARY TB

Primary Pulmonary TB. Symptoms occurring around the time of inoculation are referred to as *primary pulmonary TB*. Symptoms are generally mild and include low-grade fever.^{14,15} Two-thirds of persons with primary pulmonary TB remain asymptomatic. Physical examination findings are generally unremarkable, and the most common radiographic finding is hilar adenopathy.¹⁶ Less common radiographic findings include pulmonary infiltrates in the mid and lower lung field.

Reactivation TB. Approximately 90% of TB cases among adults can be attributed to reactivation TB. Symptoms present insidiously, most commonly with fever, cough, weight loss, fatigue, and night sweats. Less common symptoms include chest pain, dyspnea, and hemoptysis. Physical examination findings are nonspecific and may include rales or signs of pleural effusion (eg, dullness to percussion). Chest radiography demonstrates infiltrates in the apical-posterior segment of the upper lobes, and up to 20% of these infiltrates are associated with cavities characterized by air-fluid levels. Although not specific for TB, apical computed tomographic findings may show a “tree in bud” morphology manifested by centrilobular lesions, nodules, and branching linear densities.^{17,18} Among the roughly 15% of patients who present without upper lung field infiltrates, a variety of radiographic findings have been described, including lower lung infiltrates (especially superior segments), nodules, effusions, and hilar adenopathy. Finally, up to 5% of patients with active pulmonary disease may have normal findings on chest radiography.^{19,20} This is particularly worth noting among patients coinfecting with HIV, who are more likely to have atypical (eg, less predisposition for upper lobes) or normal findings on chest radiography.²¹

Endobronchial TB. Endobronchial TB develops as the direct extension of TB from a pulmonary parenchymal source or sputum inoculation into the bronchial tree.²² Symptoms may include barking cough with sputum production, and examination may reveal rhonchi and wheezing^{23,24}; the wheezing may lead to misdiagnosis of asthma.²⁵ Diagnosis and response to therapy may be assessed through bronchoscopy.²⁶

EXTRAPULMONARY TB

Extrapulmonary TB accounts for roughly 15% of TB cases among immunocompetent hosts²⁷ and for 50% to

TABLE 1. **Diagnosis of Common Extrapulmonary TB Manifestations**

| Site | Diagnostic procedure |
|---------------------------|---|
| Tuberculous lymphadenitis | Excisional biopsy with culture |
| CNS TB | Characteristic CSF exam (see text for details) AFB smear and culture of CSF Polymerase chain reaction for TB of CSF |
| Pleural TB | Pleural biopsy with pathology and culture |
| Tuberculous peritonitis | Laparoscopic peritoneal biopsy with culture |
| Tuberculous pericarditis | Pericardiocentesis with culture |
| Skeletal TB | Needle biopsy and culture |
| Genitourinary TB | Biopsy and culture of masses Culture of urine |
| Miliary (disseminated) TB | Culture of involved sites |

AFB = acid-fast bacilli; CNS = central nervous system; CSF = cerebrospinal fluid; TB = tuberculosis.

70% of cases that occur in the context of coinfection with HIV.²⁸⁻³⁰ In low-incidence countries, immigrants from endemic countries are much more likely to present with extrapulmonary TB.³¹⁻³³ As a rule, TB can present in any organ system; therefore, vigilance and examination for extrapulmonary disease are important for all persons being evaluated for TBI. A summary of the most common presentations of extrapulmonary TB follows (see also Table 1).

Tuberculous Lymphadenitis. Up to 40% of extrapulmonary TB cases are attributable to tuberculous lymphadenitis.²⁷ It presents most commonly in the cervical lymph nodes, followed by the mediastinal and axillary nodes.^{34,35} A typical presenting symptom is long-term, unilateral, nontender lymphadenopathy; systemic symptoms are often absent.³⁶ On examination, the node is typically matted and adherent to surrounding structures.^{36,37} If tuberculous lymphadenitis is clinically suspected, fine-needle aspiration should be pursued, followed by lymph node biopsy if the aspiration is nondiagnostic.^{38,39}

Pleural TB. Accounting for roughly 4% of all TB cases, pleural TB is the second leading cause of extrapulmonary TB.⁴⁰ In addition to constitutional symptoms, patients may present with nonproductive cough and pleuritic chest pain.⁴¹ Chest radiography typically shows a unilateral effusion, and pleural fluid analysis shows lymphocyte-predominant exudative features with low glucose levels and low pH.⁴² Pleural fluid culture is positive in only roughly 30% of cases, whereas the combination of histology and culture from a closed pleural biopsy specimen yields a diagnosis in most cases.⁴³

Central Nervous System TB. A devastating manifestation of the disease, central nervous system TB occurs in approximately 1% of all TB cases.⁴⁴ Tuberculous meningitis is clinically heralded by a 2- to 3-week prodrome

of malaise, headache, low-grade fever, and personality changes. This prodrome is followed first by a meningitic phase that mimics bacterial meningitis (fever, nuchal rigidity, altered mental status) and then by a paralytic phase characterized by rapid progression to stupor, coma, seizures, paralysis, and death.⁴⁵⁻⁴⁷ Diagnosis requires a high index of suspicion, and cerebrospinal fluid analysis demonstrates elevated protein levels (100-150 mg/dL; to convert to g/L, multiply by 10), low glucose levels (<45 mg/dL; to convert to mmol/L, multiply by 0.0555), mononuclear pleocytosis, and an elevated cell count (100-150 cells/ μ L). A less common manifestation of the disease is central nervous system tuberculoma, which is characterized by single or multiple conglomerate caseous foci within the brain that cause focal neurologic symptoms and signs of elevated intracranial pressure. Finally, spinal tuberculous arachnoiditis represents a focal inflammatory disease producing gradual encasement of the cord with associated neurologic deficits.

Tuberculous Peritonitis. The most common manifestation of TB in the gastrointestinal tract is tuberculous peritonitis.^{48,49} Cirrhosis and portal hypertension are associated with an increased proclivity for tuberculous peritonitis.^{50,51} Patients present with insidious onset of ascites (73%), abdominal pain (65%), weight loss (61%), and low-grade fever (59%).⁵² Clinically, tuberculous peritonitis may be mistaken for ovarian carcinoma or peritoneal carcinomatosis.^{53,54} Unexplained lymphocytic ascites should prompt definitive diagnostic testing for peritoneal TB. Culture of tubercles obtained through peritoneal biopsy remains the criterion standard for diagnosis.

Tuberculous Pericarditis. In the developing world, tuberculous pericarditis is likely the most common cause of pericardial effusion and constrictive pericarditis^{55,56}; however, in high-income nations, it is rare.⁵⁷ Patients can present with pericardial effusion, constrictive pericarditis, or a mixed effusive and constrictive condition.⁵⁸ Symptoms are those of effusion or constriction from any cause (dyspnea, cough, orthopnea, edema) in the context of systemic symptoms (night sweats, low-grade fevers, weight loss).⁵⁹

Skeletal TB. Skeletal TB occurs in 1% to 5% of patients with TB⁶⁰ and presents most commonly in the thoracolumbar spine. Patients present with localized pain over the afflicted site; systemic symptoms are often absent.⁶¹ Diagnosis is confirmed through culture of specimens obtained through needle aspiration or biopsy.⁶²

Miliary TB. The lymphatic and hematogenous spread of TB is referred to as *miliary TB*.⁶³ Patient presentation is variable, and systemic symptoms (fever, weight loss, night sweats) are common.⁶⁴ When miliary TB occurs in the context of primary infection, patients may

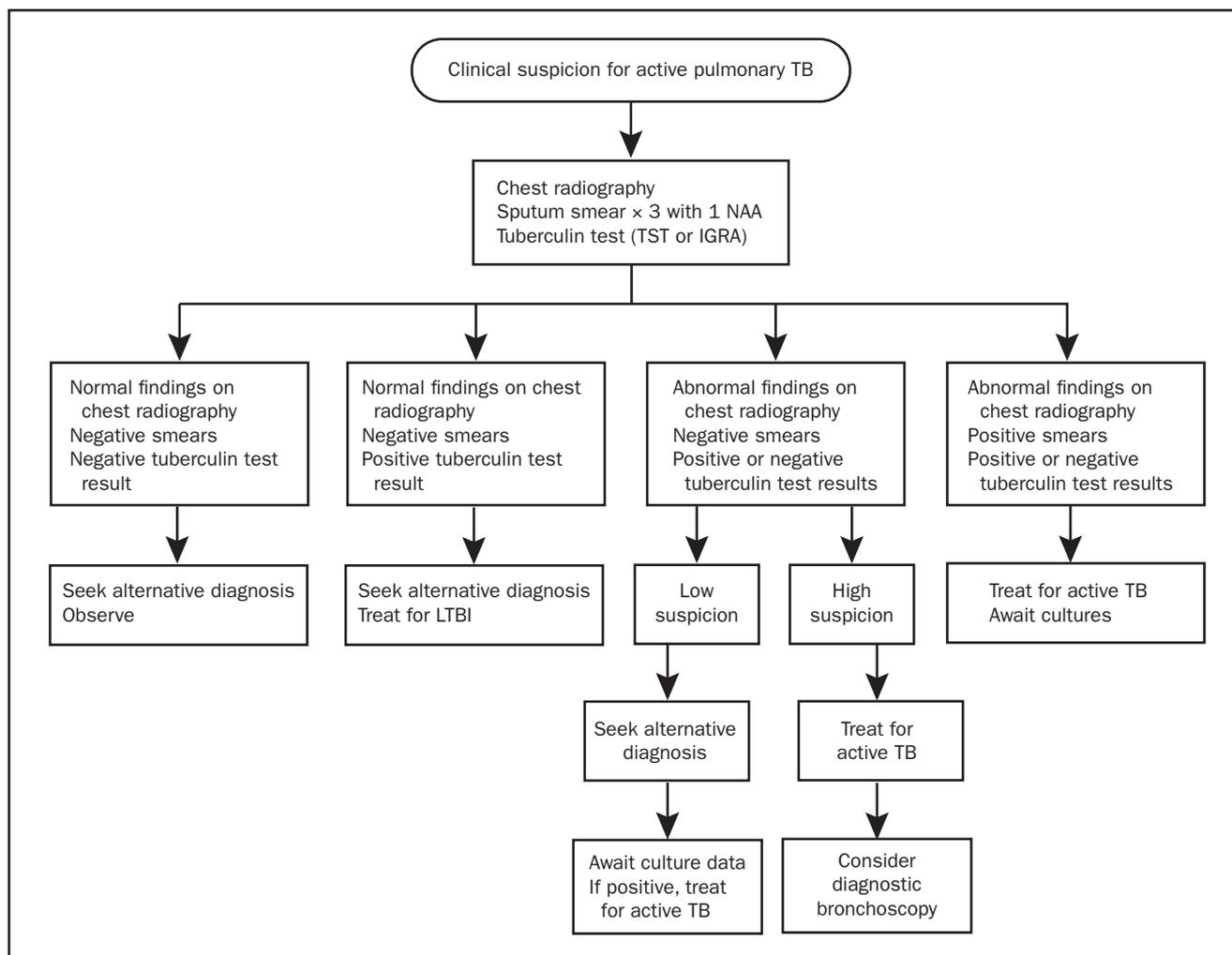


FIGURE. Evaluation and initial management of suspected pulmonary tuberculosis (TB). IGRA = interferon- γ release assay; LTBI = latent TB infection; NAA = nucleic acid amplification; TST = tuberculin skin test.

present with septic shock and acute respiratory distress syndrome.⁶⁵⁻⁶⁷

DIAGNOSIS

The diagnosis of LTBI is established by a positive result on either a tuberculin skin test (TST) or an interferon- γ (IFN- γ) release assay (IGRA), in the absence of active TB. Active TB is diagnosed on the basis of a combination of epidemiological (eg, exposure, travel to or residence in a high prevalence area, previous TB), clinical (eg, cough lasting longer than 2-3 weeks, fever, night sweats, weight loss), radiographic (eg, infiltrates, fibrosis, cavitation), microbiological (eg, positive sputum smear or culture), and histopathologic (eg, caseating granuloma) features. Patients in whom clinical suspicion for TB infections is strong on the

basis of clinical criteria should undergo chest radiography. Patients with chest radiographic findings suggestive of pulmonary TB should submit 3 sputum specimens, preferably obtained on different days, for AFB smears and culture.^{68,69} At least 1 early morning sputum specimen should be submitted. Patients unable to produce sputum spontaneously should undergo sputum induction, which requires inhalation of an aerosol of sterile hypertonic saline (3%-15%) in negative-pressure isolation rooms.^{70,71} Bronchoscopy with bronchoalveolar lavage may be necessary in patients unable to produce adequate expectorated or induced sputum samples. Nucleic acid amplification (NAA) testing should be performed on at least 1 respiratory specimen.⁷² Confirmation of the diagnosis of TB requires laboratory identification of *M tuberculosis* by AFB smear microscopy with NAA test and/or culture (Figure).

TABLE 2. Interpretation of TST Results for Populations at Risk of TB^a

| At-risk populations | Positive TST reaction size (mm) |
|--|---------------------------------|
| Patients with HIV infection | ≥5 |
| Patients receiving immunosuppressive therapy ^b | |
| Abnormal findings on chest radiography consistent with previous TB infection | |
| Persons who have come in close contact with an actively contagious patient | |
| Patients with certain chronic conditions ^c | ≥10 |
| Patients with certain malignancies ^d | |
| Foreign-born persons from high-incidence regions (>25/100,000) | |
| Employees and residents of high-risk facilities ^e | |
| Healthy people at low risk of TB | ≥15 |

^a HIV = human immunodeficiency virus; TB = tuberculosis; TNF = tumor necrosis factor; TST = tuberculin skin test.

^b Immunosuppressive therapies include chemotherapeutic agents, TNF- α inhibitors, and glucocorticoid therapy (>15 mg/d of prednisone equivalent for >1 mo).

^c Diabetes, dialysis-dependent renal failure, silicosis, and being underweight.

^d Leukemia, lymphoma, and cancers of the head, neck, and lung.

^e Health care facilities, prisons, and homeless shelters.

TUBERCULIN SKIN TEST

The TST, also known as the Mantoux test, requires the intradermal injection of 0.1 mL of 5 tuberculin units of purified protein derivative into the volar surface of the forearm. The TST measures cell-mediated immunity manifesting as a delayed-type hypersensitivity to tuberculin purified protein derivative, which contains a mixture of antigens shared by several species of mycobacteria.⁷³ The test result is recorded as the diameter of transverse induration in millimeters 48 to 72 hours after administration. Interpretation of the TST result varies depending on the prevalence of and the risk for progression to TB in different groups. Induration between 5 and 15 mm is considered positive and may be indicative of LTBI (Table 2). The size of induration has some predictive value in that persons with TBI tend to have larger indurations^{74,75}; however, it does not correlate with risk for progression to active TB. An increase of 10 mm or more in the skin test reaction within 2 years in persons with previously negative results (conversion) is indicative of recent *M tuberculosis* infection. The TST cannot discriminate between active TB and LTBI.

Interpretation of skin-test results is the same for bacille Calmette-Guérin (BCG)-vaccinated and non-BCG-vaccinated persons. The estimated interval between *M tuberculosis* infection and skin test reactivity (ie, skin test conversion) is 2 to 12 weeks.^{76,77} Therefore, those in close contact with patients who have active pulmonary TB with initial negative test results should have the test repeated 8 to 12 weeks after exposure. Skin test conversion may also be due to new

delayed-type hypersensitivity after infection with nontuberculous mycobacteria or BCG vaccination.⁷⁸ The phenomenon of reversion (ie, decrease in the size of the tuberculin reaction) may present problems in skin test interpretation when serial TSTs are performed. Therefore, TST should not be performed if a positive TST result has been documented previously or if the patient has been treated for TB. False-positive skin tests can result from BCG vaccination or infection with nontuberculous mycobacteria. False-negative test results may occur because of the following technical and biological limitations: presence of active TB; presence of other bacterial, fungal, and viral (eg, HIV) infections; live virus vaccination; immunosuppressive therapy; long-standing renal failure; malnutrition; lymphoid diseases; and age.

The TST may have a booster effect on immunologic memory in patients with a history of TB, previous BCG vaccination, and exposure to nontuberculous mycobacteria.^{74,79} This results in a positive TST 1 to 4 weeks after initial negative findings on TST. Evaluation for the booster phenomenon with a second TST 1 to 4 weeks after the first test (the 2-step method) should be considered for persons from countries with a high incidence of TB, for those with a history of BCG vaccination, and (as a baseline assessment) for those who need periodic retesting, such as health care workers. Test interpretation is based on the induration observed with the second test.

About 10% of immunocompetent persons with LTBI will develop TB disease over their lifetime, with the greatest risk for progression (5%) being in the first 2 years after infection with *M tuberculosis*.⁸⁰ Approximately 50% of TB cases will occur within 2 years after initial infection.⁸¹ Targeted tuberculin testing identifies persons at high risk of developing TB who would benefit from treatment for LTBI. These include persons at risk of becoming infected with *M tuberculosis* and those with clinical conditions associated with increased risk of progression of TB infection to active TB (Table 2). A joint statement from the American Thoracic Society and the Centers for Disease Control and Prevention provides guidelines on testing and treatment of LTBI in the United States.⁷⁶

INTERFERON- γ RELEASE ASSAY

Serum IGRAs are in vitro tests of whole blood or mononuclear cells that are based on IFN- γ release after T-cell stimulation by *M tuberculosis*-specific proteins (eg, early-secreted antigenic target 6 [ESAT-6] and culture filtrate protein 10 [CFP-10]), which are absent from BCG vaccine strains and most nontuberculous mycobacteria. The QuantiFERON-TB Gold In-Tube test (Cellestis Limited, Carnegie, Victoria, Australia) is an enzyme-linked immunosorbent assay-based whole blood assay that measures and quantifies IFN- γ (IU/mL) released from blood collected in special tubes that are coated with *M tuberculosis*-specific

TABLE 3. Key Features of Tests for TB

| Test | Strengths | Limitations |
|------------------------------------|---|--|
| Tuberculin skin test | High specificity in non-BCG-vaccinated populations Cost-effectiveness | Training required for administration and interpretation Return visit required in 48-72 h for test result Possible booster effect Possible false-positive and false-negative results |
| Interferon- γ release assay | High specificity Only 1 patient visit required Results available in 16-24 h No confounding by BCG vaccination | Blood withdrawal required Indeterminate results in those who are immunosuppressed and in those aged <5 y No capacity to differentiate between latent and active TB High cost |
| Chest radiography | Ready availability Capacity to differentiate latent infection from active TB | Low sensitivity and specificity Not confirmatory |
| Smear microscopy | Ease, speed, and cost-effectiveness of the technique Quantitative estimate of the number of bacilli Usefulness in determining infectiousness and in monitoring treatment progress | Low sensitivity No capacity to differentiate from nontuberculous mycobacteria |
| Nucleic acid amplification test | High specificity Higher sensitivity than smear microscopy Rapid (1-2 d) diagnosis Capacity to differentiate TB from other mycobacteria | Low sensitivity with smear-negative TB Contamination-prone Technical skill and expertise required Results may remain positive in patients who have completed treatment High cost |
| Culture in solid media | Examination of colony morphology possible Quantitative results | Wait of 3-8 wk for result |
| Automated liquid culture | Sensitivity greater than culture in solid media Faster results (1-3 wk) | Contamination-prone Stringent quality assurance systems required Expensive equipment required |

BCG = bacille Calmette-Guérin; TB = tuberculosis.

antigens, including ESAT-6, CFP-10, and TB7.7(p4). The T-SPOT.TB test (Oxford Immunotec Limited, Abingdon, United Kingdom) is an enzyme-linked immunospot assay that uses peripheral blood mononuclear cells incubated with mixtures of peptides containing ESAT-6 and CFP-10 to measure the number of cells secreting IFN- γ (IFN- γ -spot-forming cells). Results of IGRA are reported both qualitatively (positive, negative, indeterminate, or borderline) and quantitatively (IU/mL or IFN- γ -spot-forming cells). Reversion of IGRA test results from positive to negative has been observed, particularly in those with negative results on the initial TST.⁸² Conversion of IGRA (ie, a change in test results from negative to positive within 2 years) has not been associated with an increased risk of subsequent progression to TB disease.⁸³

The IGRA can be used in the same setting as TST⁸³ but has the advantage of being able to differentiate *M tuberculosis* infection from previous BCG vaccination and most nontuberculous mycobacterial infections; it may also be able to discriminate true-negative responses from anergy. However, currently available IGRA, like TST, cannot distinguish active TB from latent infection.^{73,82} Because ESAT-6 and CFP-10 proteins are present in *Mycobacterium marinum*, *Mycobacterium kansasii*, and *Mycobacterium szulgai*, false-positive IGRA results are possible. As with negative

TST findings, negative findings on IGRA may not exclude TB infection in immunosuppressed persons. An IGRA is the preferred method of testing for groups of people who have low rates of returning to have their TST test results read and for those who have received BCG vaccine. The TST is preferred for testing children younger than 5 years. For other groups being tested for LTBI, either TST or IGRA may be used.⁸³ A summary of tests for TB is presented in Table 3.

CHEST RADIOGRAPHY

Chest radiography is indicated for all persons being evaluated for LTBI or active TB. Pulmonary TB as a result of endogenous reactivation of latent infection classically presents with infiltrates in the apical and posterior segments of the right upper lobe, the apical-posterior segment of the left upper lobe, and the superior segment of the lower lobe. Cavitation, fibrosis, and/or enlargement of the hilar and mediastinal lymph nodes may be present. In some cases, pulmonary TB may present as lobar or segmental infiltrates, lung mass, scattered fibronodular lesions ("miliary"), or pleural effusions.

SMEAR MICROSCOPY

Smear microscopy for the detection of AFB is the most rapid and inexpensive method for TB diagnosis. Two commonly

used methods for AFB staining are the carbofuchsin methods (eg, Ziehl-Neelsen and Kinyoun methods) and the fluorochrome procedure using auramine O or auramine-rhodamine dyes. The fluorochrome method with fluorescence microscopy is preferred because it is far more sensitive than the carbofuchsin methods. The finding of AFB on respiratory specimens associated with the appropriate epidemiological, clinical, and radiographic findings is highly suggestive of TB.

NUCLEIC ACID AMPLIFICATION TEST

The NAA test is useful for the rapid detection of *M tuberculosis* in respiratory specimens. The Enhanced Amplified MTD (Mycobacterium Tuberculosis Direct) test (Gen-Probe, San Diego, CA) detects *M tuberculosis* ribosomal RNA directly from AFB smear-positive and AFB smear-negative respiratory specimens from patients with suspected TB. The Amplicor MTB (Mycobacterium Tuberculosis) test (Roche Diagnostic Systems, Branchburg, NJ) detects *M tuberculosis* DNA in AFB smear-positive respiratory specimens.

Interpretation of NAA test results should be correlated with AFB smear results.⁷² Positive findings on the NAA test and a positive sputum AFB smear are strongly indicative of TB.⁸⁴⁻⁸⁶ When NAA and sputum microscopy test results are discordant, physicians should exercise their clinical judgment in deciding whether to start anti-TB treatment while culture results are awaited.⁷² When the clinical suspicion for TB is high, a positive NAA test result in smear-negative cases can be valuable for the early detection of TB in approximately 50% to 80% of cases.^{87,88} Findings on the NAA test often remain positive after cultures become negative during therapy and can remain positive even after completion of therapy⁸⁹; therefore, it should not be used for assessing infectivity or response to treatment.

CULTURE

Culture remains the criterion standard for laboratory confirmation of TB. Three types of culture media are available for the microbiological detection of *M tuberculosis*: egg-based (Löwenstein-Jensen), agar-based (Middlebrook 7H10 or 7H11), and liquid (Middlebrook 7H12 and other commercial broth systems). Mycobacterial growth tends to be slightly better on the egg-based medium but more rapid on the agar medium. Growth in liquid media is faster than growth on solid media and allows detection in 1 to 3 weeks.⁹⁰ The development of automated liquid culture systems for mycobacterial growth detection, such as BACTEC 460TB and BACTEC MGIT960 (Becton Dickinson Microbiology Systems, Sparks, MD), VersaTREK Myco (Trek Diagnostic Systems, Westlake, OH), and BacT/Alert 3D (bioMérieux, Durham, NC), which are faster and more sensitive than solid media, has clearly facilitated TB diagnosis in the past decade.

NEW TECHNOLOGY

Several recently developed tests for TB, including molecular drug resistance, have the potential for providing rapid diagnosis and targeted treatment.^{91,92} These fully automated tests provide rapid drug-resistance testing for RIF and INH; however, they require sophisticated technology and are currently available only at reference laboratories.⁹³

OTHER CONSIDERATIONS

At the start of LTBI therapy, baseline measurements of serum aspartate aminotransferase, alanine aminotransferase, and bilirubin are recommended for patients who have a history of liver disease (eg, hepatitis B or C, alcoholic hepatitis, or cirrhosis), use alcohol regularly, have risk factors for chronic liver disease, are infected with HIV, are pregnant, or have given birth within the past 3 months.⁷⁶ All patients diagnosed as having LTBI should be offered voluntary HIV counseling and testing.

All patients with active TB should receive counseling and be tested for HIV infection. Serologic tests for hepatitis B and C should be performed for patients with risk factors such as injection drug use, foreign birth, and HIV infection. Susceptibility testing for INH, RIF, ethambutol (EMB), and pyrazinamide (PZA) should be performed on any initial culture that is positive. Susceptibility testing to the second-line drugs should be performed on specimens from patients who have had previous therapy, are known to have resistance to first-line drugs, are contacts of patients with drug-resistant TB, or have persistently positive cultures 3 months or more after starting treatment. Baseline measurements of platelet count and serum aspartate aminotransferase, alanine aminotransferase, bilirubin, alkaline phosphatase, and serum creatinine levels are recommended for all patients starting TB treatment.⁶⁸

TREATMENT

LATENT TB INFECTION

Treatment for LTBI is recommended for persons deemed to be at relatively high risk of developing active TB (Table 2) and should be initiated only after active TB has been excluded by clinical and radiographic evaluations. Failure to rule out TB may result in inadequate treatment and development of drug resistance. For most patients, treatment with INH for 9 months is preferred (Table 4).^{76,94} Pyridoxine supplementation (25 mg/d) to INH is recommended for patients at an increased risk of neuropathy, including those with preexisting peripheral neuropathy, nutritional deficiency, diabetes mellitus, HIV infection, renal failure, alcoholism, or thyroid disease and those who are pregnant or breast-feeding. Intermittent treatment (ie, a twice-weekly regimen) should only be performed as directly

observed therapy (DOT). Due to the high rates of hospitalization and death from liver injury, the combination of RIF and PZA is no longer recommended for the treatment of LTBI.⁹⁴

ACTIVE TB

Patients with active TB should be treated with multiple agents to achieve bacterial clearance, to reduce the risk of transmission, and to prevent the emergence of drug resistance. Directly observed therapy, which involves direct observation of patients ingesting anti-TB medications, is the preferred management strategy for all patients being treated for TB. For treatment to be successful, patient-centered case management and close collaboration between health care professionals and local public health programs are imperative.

Medications for treating TB are classified as first- and second-line drugs (Table 5). First-line drugs are INH, RIF, EMB, and PZA. The rifamycin derivatives rifapentine and rifabutin are also considered among the first-line drugs. Second-line drugs include the aminoglycosides streptomycin, kanamycin, and amikacin; the polypeptide capreomycin; p-aminosalicylic acid; cycloserine; the thioamides ethionamide and prothionamide; and several fluoroquinolones (eg, moxifloxacin, levofloxacin and gatifloxacin). The American Thoracic Society, the Centers for Disease Control and Prevention, and the Infectious Diseases Society of America have issued a joint statement on the treatment of TB in the United States.⁶⁸ An overview of this guideline and summary recommendations follow.

Four treatment regimens are recommended for patients with drug-susceptible disease. Although these regimens are broadly applicable, treatment must be individualized on the basis of each patient's clinical situation. Each of the 4 TB treatment regimens has an initial phase of 2 months followed by a continuation phase of 4 or 7 months (Table 6). Treatment in the initial phase is usually empirical because susceptibility data may not be available. To guard against drug resistance and to ensure maximal effectiveness, the initial phase of treatment should include 4 drugs (INH, RIF, PZA, and EMB). If the isolate is susceptible to INH and RIF, EMB can be discontinued. Depending on the regimen chosen, medication in the initial phase may be given daily throughout treatment, daily for 2 weeks then twice weekly thereafter, or 3 times weekly throughout. Susceptibility data should direct treatment in the continuation phase, which lasts for 4 months in most patients. The continuation phase of treatment should be extended to 7 months for the following 3 groups of patients: those with cavitary pulmonary TB whose sputum culture remains positive after 2 months of treatment; those in whom the initial phase of treatment did not include PZA (eg, those

TABLE 4. Treatment Regimens for Latent Tuberculosis Infection

| Medication | Adult dose (maximum) | Interval and duration |
|----------------------|----------------------|-----------------------|
| Preferred regimen | | |
| Isoniazid | 5 mg/kg (300 mg) | Daily for 9 mo |
| Alternative regimens | | |
| Isoniazid | 15 mg/kg (900 mg) | Twice weekly for 9 mo |
| Isoniazid | 5 mg/kg (300 mg) | Daily for 6 mo |
| Isoniazid | 15 mg/kg (900 mg) | Twice weekly for 6 mo |
| Rifampin | 10 mg/kg (600 mg) | Daily for 4 mo |

Data from *MMWR Recomm Rep*.⁷⁶

who have severe liver disease or are pregnant); and those being treated with once-weekly INH and rifapentine whose sputum culture remains positive after 2 months of treatment. Extending the continuation phase of treatment in these situations reduces the rate of relapse. During the continuation phase, medications may be given daily or 2 to 3 times a week with DOT.

The minimum duration of treatment for culture-positive TB is 6 months. If PZA is not included in the initial phase, treatment should be given for 9 months. Smear-negative, culture-negative pulmonary TB may be treated successfully with 4 months of a combination INH-RIF regimen. Completion of anti-TB treatment is determined by both the total number of doses taken and the duration of therapy.

FOLLOW-UP EVALUATION

Patients receiving treatment for TB infection or disease should be counseled about adverse effects and should have clinical evaluations at least once monthly to assess adherence and evaluate for possible adverse effects of anti-TB medications (Table 5). Patients receiving INH for LTBI therapy should be given no more than a 1-month drug supply and should be monitored monthly for drug-induced hepatotoxicity or other adverse effects.⁹⁵ Laboratory monitoring during treatment for LTBI is indicated only for patients with abnormal baseline liver function test results and other risks of liver disease and for evaluation of possible adverse effects during treatment.⁷⁶

Patients being treated for pulmonary TB should have sputum microscopy and culture performed at least once a month until 2 consecutive negative specimens are obtained. Sputum culture after 2 months of treatment is particularly important because a positive result is associated with increased risk of relapse⁹⁶⁻⁹⁹ and requires 7 months of continuation therapy. Platelet counts and measurements of hepatic and renal function are necessary for those with baseline abnormalities or those at increased risk of toxicity (eg, hepatitis B or C infection, alcohol abuse).⁶⁸ When EMB is to be used, visual acuity and red-green color discrimination should be monitored.

TABLE 5. Doses and Adverse Effects of Antituberculosis Medications^a

| Medication | Adult dose (daily maximum) | Important adverse effects | Use in pregnancy | Comments |
|--|---|--|---|--|
| First-line medications | | | | |
| Isoniazid | 5 mg/kg (300 mg) | Hepatitis (risk increases with age), peripheral neuropathy, rash | Safe for fetus; increased hepatotoxicity postpartum | Should be supplemented with pyridoxine in pregnant patients or in patients at risk of neuropathy |
| Rifampin | 10 mg/kg (600 mg) | GI upset, hepatotoxicity, pruritus, orange discoloration of bodily fluids | Safe | Induces hepatic microsomal enzymes, resulting in decreased effectiveness of some drugs; use with caution in women taking oral contraceptives and advise on use of the supplement barrier method; has important interactions with antiretroviral agents |
| Rifapentine | 10 mg/kg (600 mg) continuation phase | GI symptoms, hepatotoxicity, pruritus, orange discoloration of bodily fluids | Insufficient information | Can be used in a once-weekly regimen; not recommended in patients infected with HIV; induces hepatic microsomal enzymes, resulting in increased metabolism of coadministered drugs |
| Rifabutin ^b | 5 mg/kg (300 mg) | Neutropenia, uveitis, polyarthralgia, rash, hepatotoxicity, and orange discoloration of bodily fluids | Limited data; use with caution | Interacts with protease inhibitors and nonnucleoside reverse transcriptase inhibitors |
| Ethambutol | 40-55 kg: 14.5-20.0 mg/kg (800 mg) 56-75 kg: 16.0-21.4 mg/kg (1200 mg) 76-90 kg: 17.8-21.1 mg/kg (1600 mg) | Optic neuritis and peripheral neuropathy | Safe | Can affect visual acuity and color vision and so these should be monitored |
| Pyrazinamide | 40-55 kg: 18.2-25.0 mg/kg (1000 mg) 56-75 kg: 20.0-26.8 mg/kg (1500 mg) 76-90 kg: 22.2-26.3 mg/kg (2000 mg) | Hepatotoxicity, GI symptoms, polyarthralgia, asymptomatic hyperuricemia, gout, rash, dermatitis | Limited data; probably safe | Routine measurement of uric acid not recommended |
| Second-line medications | | | | |
| Cycloserine | 10-15 mg/kg (1.0 g in 2 doses) | Dose-related psychosis, seizures, depression, and headache | Crosses placenta; may be used if necessary | Use with pyridoxine for prevention and treatment of adverse neurotoxic effects; measure serum concentration and perform periodic renal, hepatic, and hematologic tests |
| Ethionamide | 15-20 mg/kg (1.0 g/d in 1 or 2 divided doses) | GI effects, including metallic taste; neurotoxicity, including peripheral and optic neuritis; endocrine effects, including hypothyroidism, gynecomastia, alopecia, and impotence; and hepatotoxicity | Contraindicated | Perform liver function tests, measure thyroid-stimulating hormone monthly |
| Levofloxacin ^b | 500-1000 mg | GI upset, dizziness, tremulousness, insomnia, rash, photosensitivity, QT prolongation | Avoid | Should not be administered within 2 h of antacids and other medications containing divalent cations |
| Moxifloxacin/gatifloxacin ^b | 400 mg | GI upset, dizziness, tremulousness, insomnia, rash, photosensitivity, QT prolongation | Avoid | Should not be administered within 2 h of antacids and other medications containing divalent cations |
| p-Amino-salicylic acid | 8-12 g in 2 or 3 doses | Hepatitis, often severe GI intolerance, malabsorption syndrome, hypothyroidism, and coagulopathy | Has been used safely | Perform liver function and thyroid function tests |
| Streptomycin | 15 mg/kg/d (1 g); in those >59 y, 10 mg/kg (750 mg) | Ototoxicity, neurotoxicity (weakness, circumoral paresthesia), nephrotoxicity | Contraindicated | Perform audiography, vestibular testing, and Romberg testing; measure serum creatinine levels; monitor serum drug concentration |
| Amikacin/kanamycin ^b | 15 mg/kg/d (1 g); in those >59 y, 10 mg/kg (750 mg) | Ototoxicity, nephrotoxicity | Contraindicated | Perform audiography, vestibular testing, and Romberg testing; measure serum creatinine levels; monitor serum drug concentration |
| Capreomycin | 15 mg/kg/d (1 g); in those >59 y, 10 mg/kg (750 mg) | Ototoxicity, nephrotoxicity | Avoid | Perform audiography, Romberg testing, and vestibular testing; measure serum creatinine, potassium, and magnesium levels; monitor serum drug concentration |

^a GI = gastrointestinal; HIV = human immunodeficiency virus.^b Not approved by the Food and Drug Administration for treatment of tuberculosis.

TABLE 6. Treatment Regimens for Drug-Susceptible Pulmonary Tuberculosis

| Initial phase | | | Continuation phase | | |
|---------------|--|--|--------------------|--------------------------|--|
| Regimen | Drugs | Interval and doses (duration) | Regimen | Drugs | Interval and doses (duration) |
| 1 | Isoniazid Rifampin Pyrazinamide Ethambutol ^a | 7 d/wk for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk) | 1a | Isoniazid Rifampin | 7 d/wk for 126 doses (18 wk) or 5 d/wk for 90 doses (18 wk) |
| | | | 1b | Isoniazid Rifampin | Twice weekly for 36 doses (18 wk) |
| | | | 1c | Isoniazid Rifapentine | Once weekly for 18 doses (18 wk) |
| 2 | Isoniazid Rifampin Pyrazinamide Ethambutol ^a | 7 d/wk for 14 doses (2 wk), then twice weekly for 12 doses (6 wk); or 5 d/wk for 10 doses (2 wk), then twice weekly for 12 doses (6 wk) | 2a | Isoniazid Rifampin | Twice weekly for 36 doses (18 wk) |
| | | | 2b | Isoniazid Rifapentine | Once weekly for 18 doses (18 wk) |
| 3 | Isoniazid Rifampin Pyrazinamide Ethambutol ^a | 3 times weekly for 24 doses (8 wk) | 3a | Isoniazid Rifampin | 3 times weekly for 54 doses (18 wk) |
| 4 | Isoniazid Rifampin Ethambutol ^a | 7 d/wk for 56 doses (8 wk); or 5 d/wk for 40 doses (8 wk) | 4a | Isoniazid Rifampin | 7 d/wk for 217 doses (31 wk); or 5 d/wk for 155 doses (31 wk) |
| | | | 4b | Isoniazid Rifampin | Twice weekly for 62 doses (31 wk) |

^a Ethambutol need not be included when the organism is known to be fully susceptible.
Data from *MMWR Recomm Rep*.⁶⁸

Follow-up chest radiography after 2 months and at the completion of treatment is optional. Expert consultation should be sought for the management of patients who develop substantial adverse effects and require alternative treatment regimens.¹⁰⁰⁻¹⁰³

TREATMENT IN SPECIAL SITUATIONS

INFECTION WITH HIV

In general, the treatment of LTBI and TB in HIV-infected adults is the same as in adults not infected with HIV, with a few exceptions. Treatment for TB can be complicated by the interaction between rifamycins, antiretroviral agents, and other anti-infective drugs prescribed for opportunistic infections. In persons receiving antiretroviral therapy, RIF should be avoided or used with caution. Rifabutin, which has fewer problematic drug interactions, may be substituted for RIF. During the continuation phase of treatment, the INH-rifapentine regimen should never be used because of the high relapse rate.

Concurrent initiation of anti-TB and antiretroviral therapy may cause increased adverse effects and paradoxical reactions in patients not already receiving treatment. The term *immune reconstitution inflammatory syndrome* is used to describe this paradoxical reaction, which presents as worsening clinical (eg, high fever, weight

loss, increased lymphadenopathy) and radiographic (eg, increased pulmonary infiltrates) manifestations of TB resulting from the immune reconstitution achieved by antiretroviral therapy.¹⁰⁴⁻¹⁰⁷ The mechanism for these paradoxical reactions is unclear but appears to be immune mediated: lower CD4 counts in patients with HIV infection seem to be associated with a higher risk of developing immune reconstitution inflammatory syndrome.^{104,108} For these reasons, antiretroviral therapy should be delayed for 2 to 8 weeks after starting anti-TB therapy.¹⁰⁹ Treatment of HIV-related TB is complex and is best managed by those with expertise in both HIV infection and TB.

EXTRAPULMONARY TB

The same basic principles for the treatment of pulmonary TB apply to extrapulmonary TB. For TB at any site, a treatment course of 6 to 9 months with regimens that include INH and RIF is recommended; the single exception is meningitis, for which 9 to 12 months of treatment is recommended. The addition of corticosteroids to anti-TB treatment is recommended for patients with TB of the pericardium and central nervous system, including the meninges.

PREGNANCY AND BREAST-FEEDING

For the treatment of TB in pregnant women, the initial regimen should be INH, RIF, and EMB for at least 9 months.

Although teratogenicity data for PZA are limited, it is probably safe to use in pregnancy. Breast-feeding should not be discouraged for women receiving anti-TB treatment. Pyridoxine supplementation (25 mg/d) is recommended for all pregnant and breast-feeding women taking INH.

DRUG-RESISTANT TB

Treatment of drug-resistant TB (resistance of the organism to 1 first-line drug) has become even more complex, difficult, and expensive with the emergence of MDR-TB and XDR-TB. Patients with drug-resistant TB may acquire further drug resistance and are at high risk of treatment failure.^{110,111} These patients should receive prompt expert consultation. General guidelines for treating patients with drug-resistant TB include using multiple (4-6) drugs, including an injectable agent to which the organism is susceptible. Treatment includes second-line drugs that have many adverse effects and are more expensive and less effective than first-line drugs. Careful supervision under DOT is mandatory to ensure adherence to therapy. Treatment is extended to 24 months after culture conversion, with posttreatment follow-up for 24 months. Case series reveal a possible role for surgical therapy in select cases of MDR-TB and XDR-TB.¹¹²

CONTROL AND ELIMINATION

Active TB is frequently treated in the outpatient setting. Patients with active TB should be managed in conjunction with local public health offices and TB control agencies to coordinate visits and maximize adherence. When active TB is suspected, patients should wear a simple surgical mask when they are out of the house or near other people.

Initial treatment in the hospital may be appropriate for patients who are acutely ill, those with substantial comorbid illness, or infectious patients who are nonadherent to therapy.⁶⁸ These patients should be admitted to a negative-pressure isolation room with at least 6 air exchanges per hour.³ Health care professionals should wear a fit-tested N95 mask; those who have not been fit-tested or are unable to use an N95 mask should use a powered air-purifying respirator. Simple surgical masks are more effective than N95 masks at preventing extrusion of respiratory droplets; therefore, patients with TB should wear a simple surgical mask when they are not in their isolation room. Patients may be removed from isolation when clinical improvement is seen on effective therapy and when 3 consecutive sputum samples on separate days are AFB smear-negative.³ If patients with active pulmonary TB are medically stable for discharge but are not yet AFB

smear-negative, they may be discharged only if a definitive plan for outpatient therapy has been coordinated with the local TB control agency, if no children younger than 4 years or no immunocompromised persons live with them, and if they agree to leave their home only for medical appointments.³ The preferred mechanism of therapy for both inpatients and outpatients is DOT.^{113,114}

Treatment of patients with active TB is the top public health priority for TB control, followed by contact investigation of all persons who came into close contact with these patients before initiation of therapy. Such contact investigation should be carried out on all patients with confirmed active pulmonary TB and on selected patients with suspected pulmonary TB before testing is complete.¹¹⁵ Patients with extrapulmonary TB are generally not infectious; therefore, contact investigation is not indicated.

The third priority for TB elimination and control is to reduce the population-based burden of LTBI through targeted testing and treatment. This strategy is particularly important in low-incidence nations, where most TB cases arise from reactivation of LTBI. In high-incidence, resource-poor settings, this strategy is rarely feasible. Testing for LTBI is indicated to detect patients at risk of new infection or at risk of reactivation of LTBI due to underlying medical conditions. Persons at risk of new infection include contacts of patients with active pulmonary TB, employees at facilities with a high risk of exposure (eg, prisons, health care facilities, homeless shelters), and those who have recently immigrated (ie, within the past 5 years) from regions of the world where TB is endemic. Persons at highest risk of reactivation include those taking immunosuppressive medications (ie, chemotherapy, tumor necrosis factor α inhibitors) and those with HIV infection, hematologic malignancy, silicosis, dialysis-dependent renal failure, or changes on chest radiography consistent with previous TB.⁷⁶

CONCLUSION

Tuberculosis remains a devastating disease throughout the world. Efforts to eradicate it have been thwarted by poverty, lack of health care access, drug resistance, immunosuppressed populations (eg, HIV-infected persons), and global migration. Effective management requires prompt recognition using a combination of clinical, radiographic, microbiological, and histopathologic hallmarks and initiation of appropriate multidrug therapy. In addition to effective treatment of patients with active TB, public health management strategies include contact investigation and testing of persons who came into close contact with patients with active TB before initiation of therapy and reduction of the population-based burden of LTBI through targeted testing and treatment.

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