CHAPTER 25

Tuberculosis in Travelers and Immigrants

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Approximately 2 billion people, one-third of the world's population, are infected with *Mycobacterium tuberculosis*, and the majority of burden is in developing countries. The World Health Organization (WHO) estimates that the annual incidence of active tuberculosis (TB) cases was 9 million worldwide with mortality of 1.5 million in 2013 (WHO, 2014).

In 2013, 65% of reported TB cases in the United States were foreign born; the case rate among the foreign born (15.6 cases per 100,000 persons) was 13 times higher than that of US-born persons (1.2 cases per 100,000). In this chapter, we briefly review the standard approach to evaluate patients for TB and address unique aspects in evaluation and management of TB among travelers and immigrants.

TRANSMISSION AND PATHOGENESIS

TB is caused by bacteria of the *Mycobacterium tuberculosis* complex, which belong to the family Mycobacteriaceae and the order Actinomycetales. Among the species of the *M. tuberculosis* complex, *M. tuberculosis* is the most common in human disease. The *M. tuberculosis* complex also includes *Mycobacterium bovis* (see section on *Mycobacterium bovis* and Nontuberculous Mycobacterial Infection). *M. tuberculosis* is characterized by a waxy component of the cell wall, mycolic acid, which is neutral on Gram stain. The designation of *M. tuberculosis* as the "acid-fast bacillus" derives from its distinctive staining property: resistance to decolorization by acid alcohol after stained with basic fuchsin.

The typical mode of transmission is inhalation and deposition of droplet nuclei containing *M. tuberculosis* on the respiratory bronchiole or alveolus, located beyond the protective mucociliary blanket of the respiratory tree. When droplet nuclei are deposited in the terminal airway passages, bacilli are asymptomatically engulfed by alveolar macrophages. *M. tuberculosis* survives within alveolar macrophages and proliferates intracellularly. Thereafter, bacilli are transported to hilar lymph nodes and then, via thoracic duct, spread systemically to other organs. In the majority of hosts, cell-mediated immunity effectively contains bacilli by formation of granulomas in 2-10 weeks after acquisition of *M. tuberculosis*, and subsequently TB infection becomes latent. Latent TB infection (LTBI) is marked by a positive tuberculin skin test (TST) or a positive interferon-gamma release assay (IGRA). A small proportion of infected individuals show fibrotic or fibronodular lesions in the upper lung fields on chest radiographs (CXRs), presumably as a result of self-limited pulmonary disease that may have been sub-clinical in the past. Persons with these radiologic findings, however, are at greater risk of reactivation and should be encouraged to take treatment for LTBI (see section on Treatment). In addition, a conventional notion was that once someone has LTBI, this person is protected against further acquisition of *M. tuberculosis*. Studies showed that reinfection can occur in high-incidence settings, especially among human immunodeficiency (HIV)-infected individuals (Sonnenberg et al. 2001). Reinfection is uncommon in low-incidence settings, especially among immunocompetent hosts (Jasmer et al. 2004).

TABLE 25.1 Tuberculosis Risk Assessment: Factors Increasing the Risk of LTBI Reactivation

- Recent exposure to an infectious case
- Silicosis
- Diabetes mellitus
- Chronic renal failure/hemodialysis
- Intravenous drug use
- Gastrectomy and jejunoileal bypass
- Tobacco smoking
- Immunocompromising diseases (e.g., HIV infection) or treatment (e.g., corticosteroids, TNF inhibitors, organ transplant) associated with suppression of cell-mediated immunity
- Malnutrition and extremely low body weight

HIV, Human immunodeficiency virus; *LTBI,* latent tuberculosis infection; *TNF,* tumor necrosis factor.

Most cases of active TB arise from reactivation of dormant foci of infection. All the factors that determine the small proportion of individuals whose TB infections will become reactivated are not known. However, certain conditions are known to increase the risk of reactivation. (**Table 25.1**)

When TB is "reactivated" at a later time, pulmonary TB is the most common form, but TB in extrapulmonary sites can be seen (see section on Extrapulmonary Tuberculosis).

Those who have spent substantial time indoors with an infectious TB case may become infected with *M. tuberculosis*. The infection rate among the household contacts of sputum acid-fast bacilli (AFB) smear-positive pulmonary TB cases is around 30-40%. At least 8 hours in a confined indoor space is considered the minimal duration for raising concern about TB transmission.

Persons with LTBI are not infectious and cannot spread TB infection to others. The rate of progression from LTBI to active TB is around 5% within the first 2 years of acquisition and, thereafter, approximately 0.1% per year in immunocompetent adults. Age less than 5 years and immunocompromised status, especially HIV infection, increase the risk of progression to active TB (Horsburgh 2004).

EPIDEMIOLOGY

The global epidemiology of TB has been affected by the acquired immunodeficiency syndrome (AIDS) epidemic. Most of the estimated TB cases in 2013 occurred in Asia (56%) and the African region (29%). Incidence rates vary from high in sub-Saharan Africa and in South and Southeast Asia to fewer than 10/100,000 population in the United States, Canada, and most of Western Europe (**Table 25.2**) (WHO 2014).

CONDITIONS MIMICKING TUBERCULOSIS

In evaluating patients with symptoms of pulmonary TB, clinicians should be reminded that TB may simulate many other diseases. Pneumonia, lung abscess, neoplasm, and fungal and parasitic infections may be mimicked by TB. The patient who originates from or who has traveled to a foreign country presents an additional diagnostic challenge. For example, as coccidioidomycosis is prevalent in persons from northern Mexico, it should be considered in the differential diagnosis of fibrosing, cavitary pulmonary disease in Mexican immigrants. While deep tissue fungal infections are rare in refugees from Southeast Asia, paragonimiasis is often confused with TB. Paragonimiasis is endemic in Asian countries and should be considered, particularly when raw crawfish consumption is reported. The diagnosis is made by identifying the parasite in sputum or in lung biopsy specimens (Chapter 48).

TABLE 25.2 Tuberculosis Incidence Rates in 2013[a]

Region/Nation	Case Rate per 100,000 Population
Sub-Saharan Africa	
South Africa	862
Mozambique	552
Zimbabwe	552
Nigeria	338
Democratic Republic of the Congo	326
Kenya	268
Ethiopia	224
Uganda	166
South and Southeast Asia	
Cambodia	400
Myanmar	373
Philippines	292
Pakistan	275
Bangladesh	224
Afghanistan	189
Indonesia	183
India	171
North America and Western Europe	<10

[a]Globally, 13% of new TB cases in 2013 were HIV co-infected.

MYCOBACTERIUM BOVIS AND NONTUBERCULOUS MYCOBACTERIAL INFECTION

M. bovis and other nontuberculous mycobacterial infections may be seen in immunocompetent patients who have lived or traveled abroad. Generally, *M. bovis* infection is acquired by consumption of unpasteurized milk from infected cows. Human infections with *M. bovis* have been essentially eliminated in developed countries as a result of the pasteurization of milk and TB-control programs for cattle. TB caused by *M. bovis* is almost exclusively recognized in immigrants to the United States from the regions where these two control measures are absent (Barnett and Walker 2008).

Mycobacteria other than *M. tuberculosis*, or nontuberculous mycobacteria (NTM), can cause pulmonary and extrapulmonary diseases. Most cases of cervical adenitis in refugee or immigrant children from African or Asian countries should be presumed to be *M. tuberculosis* disease rather than NTM, whereas cervical adenitis caused by *Mycobacterium avium* complex would be more likely in US-born children.

TUBERCULOSIS IN TOURISTS

Despite the high incidence of TB in many parts of the world, tourists from the United States, Canada, or western European countries to TB-endemic areas do not seem to be at significant risk of exposure when the purpose of their trip is business, tourism, missionary, research, or volunteering (Boggild et al. 2014; Monge-Maillo et al. 2014; Schlagenhauf et al. 2015). Epidemiologic studies have shown that casual contact with an infectious TB case usually does not result in transmission of infection. The important determinants of transmission consist of (1) infectiousness of the index case, (2) environment where TB exposure occurs (e.g., a confined, small space with poor ventilation increases the risk of transmission), and (3) cumulative hours of exposure (e.g., at least 6–8 hours in a confined space even if the index case is highly infectious). TB transmission is typically seen among

the family members or within a close social network. Although transmission might occur during long air travel exceeding 8 hours, the public health risk from this is considered very low. Therefore, visitors to TB-endemic areas who follow normal tourist routes for a period of less than 2-3 weeks are unlikely to experience sufficient personal contact with infectious TB cases to acquire TB infection. TB in persons with foreign travel histories is more likely to occur in those who have traveled or lived abroad for several months or years, as is the case with students and expatriates.

Other travel scenarios more relevant to concern for TB transmission include health professionals providing medical aid work in high-risk settings and outbound medical tourists who obtain services in hospitals where TB patients may also be cared for.

TB Risk in Tourists

Lower Risk	Higher Risk
• Standard tourist routes or business trips • Trips lasting 2-3 weeks	• Visiting friends and relatives for several weeks • Healthcare workers providing medical aid work • Receiving medical services in hospitals where TB patients are also cared for

CLINICAL FEATURES

Pulmonary Tuberculosis

The onset of symptoms and signs of TB is usually gradual, over a period of weeks or months. The first symptoms are often nonspecific, consisting of fatigue, anorexia, weight loss, night sweats, or low-grade fever. Pulmonary symptoms usually include a cough, which slowly progresses over weeks to become more frequent and producing mucoid or mucopurulent sputum. Hemoptysis or chest pain may develop when the pulmonary process is advanced. Dyspnea is uncommon in the absence of pleural or advanced disease.

Extrapulmonary Tuberculosis

Extrapulmonary TB (EPTB) is TB outside the lungs. EPTB includes lymphadenitis (often cervical), pleuritis, meningitis, abdominal TB including peritonitis, skeletal TB such as Pott disease (spine), and genitourinary (renal) TB. Miliary TB results from hematogenous spread of *M. tuberculosis* and affects both pulmonary and extrapulmonary sites. Approximately 10% of all TB cases have both pulmonary and extrapulmonary TB, and an additional 20% have EPTB without pulmonary involvement (CDC 2014). HIV-infected patients, especially with low CD4 counts, have higher rates of EPTB. Children are more likely to have EPTB than adults.

In general, EPTB is more difficult to diagnose than pulmonary TB and often requires invasive procedures to obtain tissue and/or fluid specimens. Besides possible fever and weight loss, the symptoms and signs of EPTB often relate specifically to the affected organ system. Lymphatic TB, which appears to be frequently seen in Asians and Africans, can involve any regional lymph nodes but often affects those of the neck and supraclavicular regions (scrofula). TB of the bones and joints usually causes persistent localized pain and swelling. An exception may be Pott disease of the spine, which can progress insidiously and become advanced with neurologic deficits before diagnosis is made. Meningeal TB typically presents with headache and, if advanced, altered mental status or other neurologic deficits.

Tuberculosis in Children

While only a small fraction of children entering school in the United States have a TST, immigrants of comparable age from TB-endemic countries have a higher rate of TST positivity due to increased prevalence of true LTBI as well as influence of overseas bacillus

Calmette-Guérin (BCG) vaccination. BCG vaccine for infants is routinely used in many countries outside the United States. The primary benefit of the vaccine is prevention of severe forms of TB, particularly TB meningitis, in children. Evaluations of BCG's efficacy on prevention of pulmonary TB have yielded inconsistent results. Regardless of BCG history, small children (aged <5 years) with active TB are generally not transmitters of TB.

Tuberculosis in Persons with HIV Infection

The clinical presentation of TB in persons with HIV infection may be similar to those in HIV-negative patients, particularly if CD4 counts are still relatively preserved (e.g., >200/μL). On the other hand, the symptoms of TB may be indistinguishable from other respiratory diseases, such as *Pneumocystis jiroveci* pneumonia, bacterial pneumonia, and even progressive HIV infection itself. In advanced HIV (e.g., CD4 <200/μL), TB disease is more likely to be extrapulmonary and to involve serous cavities and regional lymph nodes (particularly thoracic and retroperitoneal). A high index of suspicion for the diagnosis must be maintained. Miliary and meningeal TB occurs with increased frequency in persons with HIV infection. These two forms of TB are uniformly lethal if not recognized and treated promptly. Consequently, they must be included in the differential diagnosis when HIV-infected patients experience a severe, abrupt illness with nonspecific signs, neurologic symptoms, or headache. In Africa, a high proportion of patients with "slim disease," the wasting syndrome attributed to AIDS, who come to autopsy are found to have had unsuspected TB.

DIAGNOSIS

Radiographic Findings

Immunocompetent patients with pulmonary TB who have disease sufficient to cause symptoms will virtually always have an abnormal CXR. Pulmonary opacities are usually seen in the apical and/or posterior segments of the upper lobes or in the superior segments of the lower lobes. HIV-infected patients with pulmonary TB are associated with a wide variety of radiographic abnormalities, including hilar, paratracheal, or mediastinal adenopathy; lobar consolidation; patchy pneumonitis; and diffuse miliary infiltration. Cavitation is infrequent, and CXRs can be even normal in advanced HIV infection with very low CD4 counts (e.g., <200/μL).

Hilar and mediastinal adenopathies are not commonly seen with pulmonary TB in immunocompetent adults. When these findings are noted, another diagnosis, such as lymphoma, should be considered. In children, however, active primary TB commonly includes hilar or mediastinal adenopathy or both. The adenopathy on the radiograph is usually unilateral and in approximately half the cases is associated with parenchymal opacities.

Tuberculin Skin Testing

The TST using purified protein derivative (PPD) is a time-honored diagnostic aid in the evaluation of a patient with suspected TB infection, but its limitations must be understood. TST measures T-cell response to TB antigens and thus has limited sensitivity in those with impaired T-cell function. Furthermore, the test is unable to differentiate LTBI from active TB disease. However, when used appropriately, TST can yield valuable epidemiologic information and identify individuals who may be at high risk for progression to active TB disease.

It is recommended to use different cutoff points between a positive and negative test depending on either the risk of TB infection or the risk of progression to TB disease (**Table 25.3**) (CDC 2000b). The lowest cutoff point, a diameter of induration of 5 mm, should apply to those at highest risk of disease progression (e.g., HIV-infected patients, solid organ transplant recipients) and close contacts of an infectious TB case. The highest cutoff point, a diameter of induration of 15 mm, should apply to those who lack all identified risk factors.

TABLE 25.3 Criteria for Tuberculin Positivity by Risk Group[a]

≥5 mm Induration	≥10 mm Induration	≥15 mm Induration
HIV infection	Recent immigrants (<5 years of arrival) from high-prevalence countries	Persons without risk factors listed in previous two columns.
Recent close contacts of a patient with infectious TB	Injection drug users	
Persons whose chest radiograph shows fibrotic lesions likely to represent untreated yet healed tuberculosis	Residents and employees of high-risk settings: prisons and jails, nursing homes and long-term care facilities, hospitals, homeless shelters	
Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of 15 mg/day of prednisone for ≥1 month)	Persons with medical conditions reported to increase risk of tuberculosis once infection has occurred, e.g., silicosis, gastrectomy, jejunoileal bypass, chronic renal failure, diabetes mellitus, immunosuppressive therapy, and some hematologic disorders and malignancies, and weight loss >10% of ideal body weight	
Persons receiving treatment with TNF-α antagonist therapy	Mycobacteriology laboratory personnel	
	Children <4 years or older children exposed to adults at high risk.	

[a]Test performed by intradermal injection of 0.1 mL of PPD-S, containing 5 TU, usually into forearm, with reading at 48-72 h. Induration is measured across the forearm, ignoring any erythema.
HIV, Human immunodeficiency virus; *TNF-α,* tumor necrosis factor alpha.
From CDC 2000b.

Interferon-γ Release Assays

Recently, IGRAs have been developed as an alternative to TST (CDC 2010). Two FDA-approved tests, QuantiFERON-Gold (Qiagen, Venlo, Netherlands) and T-SPOT.*TB* (Oxford Immunotec, Marlborough, MA) are available in the United States. These tests measure the ex vivo production of interferon-gamma from T cells that are stimulated with the TB-specific antigens (peptides called ESAT-6 and CFP-10). ESAT-6 and CFP-10 are not present in BCG nor most of the commonly encountered nontuberculous mycobacteria (with the exception of *M. kansasii*, *M. szulgai*, and *M. marinum*). Conversely, TST uses whole extracts of TB (i.e., PPD) as a stimulant, and positive results may represent cross-reactivity to BCG and nontuberculous mycobacteria that share some of the antigens present in PPD. Therefore, the specificity of IGRA is higher (>90%) than TST, especially among BCG-vaccinated populations (Pai et al. 2008). The sensitivity of IGRAs to detect TB infection is similar to that of TST, but T-SPOT.*TB* appears to have slightly higher sensitivity.

There are a few concerns about the use of IGRAs. While high cost and limited availability were problematic in the initial roll-out of IGRAs, most clinical settings are now served by a clinical or reference laboratory that can provide the test at a reasonable price. Except for children <5 years of age, the CDC recommends that IGRAs can be used in all other settings where TST is currently utilized.

AFB Smear and Culture

The recovery of *M. tuberculosis* organisms in culture from clinical specimens is essential for the definitive diagnosis of TB and drug susceptibility testing. A patient suspected of having active TB disease based on epidemiologic information, signs, symptoms, and compatible abnormalities on radiographs should have the appropriate specimens submitted for AFB smear and culture. Most patients with pulmonary TB are able to produce specimens of sputum that yield *M. tuberculosis* on culture. Respiratory specimens should be examined microscopically for the presence of AFB (smear). The sensitivity of AFB microscopy is only 50-60% in pulmonary TB cases, but it is inexpensive, has short turn-around time (within a day), and correlates with infectiousness of the case.

Although sputum smears are positive for AFB among patients with pulmonary TB who have advanced symptoms and extensive radiographic abnormalities and for virtually all those with cavitary pulmonary TB, negative AFB smears should *not* lead the clinician away from the diagnosis of TB, especially when epidemiologic information and radiographic findings are consistent with active TB. At least one-third of patients with pulmonary TB who produce positive sputum cultures have negative sputum smears.

Invasive procedures, such as bronchoscopy and lung biopsy, are usually not necessary to establish the diagnosis of pulmonary TB but may be performed to rule out other etiologies such as malignancy. Children with hilar and mediastinal lymphadenopathy typically have negative sputum smears, and a positive culture may not be required for the diagnosis in appropriate settings (e.g., household exposure and clinical response to empirical TB treatment). Because of similarity in the onsets, symptoms, and radiographic appearances of several AIDS-associated respiratory diseases, bronchoscopy may be necessary to obtain additional specimens in HIV-infected patients to arrive at the correct diagnosis and to begin appropriate therapy as rapidly as possible.

Compared with most bacteria, *M. tuberculosis* multiplies very slowly, dividing every 18-24 hours. Using the most modern method of culture, the isolation and identification of the causative organism require 2-6 weeks.

When EPTB is suspected on clinical grounds, it is usually necessary to obtain tissue or other body fluids from the affected sites to establish the diagnosis. Whenever possible, both tissue and fluid obtained from either open or closed biopsy should be submitted for AFB smear and culture. The yield on culture will be improved by submission of multiple specimens. This is particularly true with pleural and lymphatic TB, in which culture of tissue gives a greater yield than culture of aspirated fluid.

Nucleic Acid Amplification Testing

To distinguish among the more than 100 mycobacterial species, laboratories have traditionally used biochemical methods. More recently, nucleic acid amplification testing (NAAT) has been increasingly used for species identification, since it is more timely and specific (e.g., GeneXpert, Cepheid). Amplification techniques can be applied to specimens before the organism grows in culture to determine whether *M. tuberculosis* is present. At least one specimen submitted for AFB smear and culture should also be submitted for NAAT as part of the initial evaluation for active TB. In some laboratories, NAAT is also being used to identify common mutations conferring drug resistance before culture-based drug susceptibility testing results become available.

TREATMENT OF ACTIVE TUBERCULOSIS

The goals of TB treatment are (1) to cure illness caused by TB in a patient and (2) to interrupt transmission of TB in a community. With available chemotherapeutic agents, both goals are readily achievable if drug susceptible. The treatment of TB generally requires at least 6 months, and thus adherence to the treatment is challenging.

The four most commonly used antituberculous drugs—isoniazid, rifampin, ethambutol, and pyrazinamide—are described in **Table 25.4**. Second-line agents may be used in case

TABLE 25.4 Chemotherapeutic Agents Commonly Used to Treat Tuberculosis

Drug	Daily Dose	Side Effects	Interactions	Remarks
Isoniazid	5-10 mg/kg up to 300 mg p.o.	Hepatitis, peripheral neuritis, rash, dizziness	Potentiation of phenytoin, Antabuse	Inexpensive
Rifampin	10-15 mg/kg up to 600 mg p.o.	Hyperbilirubinemia, fever, purpura	Inhibition of many drugs: oral contraceptives, warfarin, methadone, many antiretrovirals (e.g., protease inhibitors), azole antifungal agents, sulfonylurea hypoglycemics, some statins, calcium channel blockers, and immunosuppressive agents (e.g., corticosteroids, cyclosporine)	Colors urine and other body secretions orange
Ethambutol	15-25 mg/kg p.o.	Optic neuritis (rare at 15 mg/kg), rash		Use with caution in patients with renal disease
Pyrazinamide	20-25 mg/kg up to 2 g p.o.	Hyperuricemia, rash, hepatitis		When used for the first 2 months with isoniazid and rifampin, can shorten total duration of therapy to 6 months

p.o., By mouth.

of drug-resistant TB or intolerance to first-line agents. They include fluoroquinolones, streptomycin, capreomycin, amikacin, ethionamide, cycloserine, para-aminosalicylic acid, linezolid, and bedaquiline. The second-line agents are better used under the guidance of experts in this field, as these are less potent against *M. tuberculosis* (with the exception of fluoroquinolones and injectables) and are difficult to administer because of frequent and/or serious side effects.

To prevent development of acquired drug resistance, it is critical to treat active TB with at least two drugs known to be potent against the infecting organism. Susceptibility testing of *M. tuberculosis* isolates is an essential component of optimum management of a case of active TB. Throughout the United States, susceptibility testing of TB is available free of cost through local or state health departments.

The initial empiric treatment regimen should consist of four drugs for the first 2 months: isoniazid, rifampin, pyrazinamide, and ethambutol. This regimen gives excellent results in pulmonary, extrapulmonary, and primary TB. The regimen should be adjusted after the results of sensitivity testing on the patient's isolate are known.

A number of factors influence the decision regarding the total duration of therapy. For patients who have a negative sputum culture at 2 months, have a fully susceptible organism, and do not have cavitation on their CXR, therapy can be completed in 6 months (2 months of initiation phase [four first-line drugs] and 4 months of continuation phase [isoniazid and rifampin]). Patients with cavitation on CXR whose sputum cultures remain positive at 2 months have high relapse rates if they are treated for only 6 months. As a result, 9 months of therapy is recommended in this setting. The patient with persistently positive sputum cultures despite initial four-drug therapy should be suspected of non-adherence, having a drug-resistant strain, or malabsorption of TB medications.

Most HIV-infected TB patients respond well to routine TB treatment. Nevertheless, some authorities recommend extending the TB treatment for 3 additional months (a total of 9 months), because of the possibility of relapse resulting from impaired immunity in HIV-infected patients. The authors recommend that treatment of TB in HIV-infected patients be individualized and that the patient be monitored closely throughout the course of treatment to ensure that the response is satisfactory.

Drug-Resistant TB

Whereas the prevalence of resistance to any of the four first-line antituberculous drugs in **Table 25.4** is <10% among active cases of TB in those born in the United States, resistance is more common in *M. tuberculosis* isolates from other parts of the world. For example, the prevalence of isoniazid resistance among TB patients who immigrated from Southeast Asian is 10-15%; among Filipino immigrants, it is 15-25%.

Emergence of increasingly resistant strains of *M. tuberculosis* has been reported and necessitates complex treatment options. Multidrug-resistant (MDR) TB is resistant to at least both isoniazid and rifampin. More recently, MDR TB strains with additional resistance to key second-line medications (i.e., fluoroquinolones and injectables), known as extensively drug-resistant (XDR) TB, have been reported. Challenges of treatment of MDR TB include the need to use more expensive, less effective second-line drugs, frequent serious side effects, and the risk of increased mortality from less effective treatment.

Globally, 3.5% of new and 20.5% of previously treated TB cases were estimated to have been MDR TB in 2013. This translates into an estimated 480,000 people having developed MDR TB in 2013. WHO has recommended the use of Xpert MTB/RIF, the first automated molecular test that both confirms the presence of *M. tuberculosis* and detects mutation suggestive of rifampin-resistance. Because most rifampin-resistant isolates are also isoniazid-resistant, detection of a rifampin-resistance mutation indicates MDR TB. While Xpert MTB/RIF is very useful in developing countries with high incidence of TB and MDR TB, its use and results in developed countries with low incidence of MDR TB should be carefully interpreted (Sohn et al. 2014).

When applying available information on drug resistance to the management of the individual TB patient, several important principles of treatment should be emphasized:

- When there is a reasonable possibility that a TB patient acquired the infection in a country with high drug-resistance rates, drug susceptibility testing is absolutely essential.
- Before the results of susceptibility testing become available (usually 3-6 weeks from the time of specimen collection), treatment regimens must include at least two drugs to which the infecting organism is likely to be susceptible. A treatment regimen using the four recommended first-line drugs (i.e., isoniazid, rifampin, pyrazinamide, and ethambutol) is recommended for TB patients in the United States, regardless of national origin, and it should be adequate in >98% of patients.
- When susceptibility test results indicate that the organism is susceptible to isoniazid and rifampin, ethambutol can be discontinued. Pyrazinamide may be withdrawn after 2 months, and the total length of treatment should be 6-9 months. If the organism is resistant to isoniazid, the other three agents of the original regimen (rifampin, pyrazinamide, and ethambutol) should be continued for 6-9 months. In patients with isoniazid-resistant TB, the response to therapy must be monitored carefully.
- When susceptibility test results indicate resistance to isoniazid and rifampin or extensive drug resistance, consultation with a TB expert is recommended.

The predominant risk factor for MDR TB in the United States is foreign birth. Therefore, clinicians who are involved in the healthcare of immigrants, refugees, and travelers at high risk of TB infection must be aware of global trends of MDR TB. In addition, treatment of MDR TB is exceedingly difficult and has significant public health implications. Care of such patients should be coordinated by a local health department.

Treatment Precautions

Three of the first-line TB drugs are safe for use in pregnancy: isoniazid, rifampin, and ethambutol. The safety of pyrazinamide during pregnancy has not been verified. Streptomycin and other injectables may be nephrotoxic and should be used carefully in persons with renal disease. In addition, ethambutol is excreted via the kidneys, and thus the dosing should be adjusted when used in patients with renal disease; serum drug levels may be necessary to determine appropriate dosing. As isoniazid, rifampin, and pyrazinamide can be hepatotoxic, they should be used cautiously by patients with underlying liver disease or persons at risk of hepatitis (e.g., excessive alcohol use).

With the advancement of antiretroviral therapy for patients with HIV infection, treatment of TB in persons with HIV infection has become complex. For example, rifampin—the key drug that determines the effectiveness of TB treatment—may not be readily used along with some antiretrovirals because rifampin accelerates the metabolism of those agents and lessens their antiretroviral effect. Conversely some antiretrovirals affect drug levels of rifampin substantially. Given the increasing complexity of TB treatment of HIV-infected patients, it is ideal for a clinician with expertise in managing both HIV infection and TB to supervise the HIV and TB treatment in such patients. At a minimum, it is crucial to emphasize communication and coordination between HIV and TB care providers.

Adherence to TB Treatment

Because of the long duration of the drug therapy that is required to cure a case of active TB, patient adherence (i.e., the ability of patients to take their medications and complete the treatment as advised) is a major issue. When treatment is based on susceptibility testing, as described earlier, failure to eradicate the infection is commonly due to non-adherence, even in patients with HIV infection.

Many non-adherent patients are discovered when they fail to return for follow-up clinic visits. While adherence should be monitored in all TB patients, it must be emphasized particularly among patients with mental illness, substance abuse, or homelessness. When the patient comes from an ethnic culture that stigmatizes TB or when the understanding of medical advice is difficult due to a language barrier, non-adherence may occur.

Non-adherence with anti-TB medications undermines both the personal and public health goals of TB treatment. Non-adherent patients should be reported to the local health department for appropriate evaluation and management. Most public health TB control programs in the United States require directly observed therapy (DOT), if not for all cases, then at least for pulmonary cases. DOT is a practice of observing patients swallow their medications. Because of the key role of drug therapy in terminating the spread of TB and in preventing development of drug resistance during TB treatment, DOT is the standard of care especially for infectious TB cases in the United States.

PREVENTION

Although medical practice has traditionally focused on curing human disease, there has been a wide interest in disease prevention and health maintenance. In this context, clinicians who provide medical care to foreign-born patients have both the opportunity and the responsibility to practice preventive medicine with respect to TB in that population.

Review of the pathogenesis of TB reveals that there are two targets for prevention of TB: (1) prevention of acquiring TB infection in uninfected persons and (2) prevention of progression from latent TB infection to active TB disease in those who already have latent TB infection. The primary way to prevent the acquisition of latent TB infection is to eliminate the excretion of tubercle bacilli from infectious patients. This is achieved, as noted previously, by administering effective chemotherapy to persons with pulmonary TB.

A second means of preventing TB is vaccination with BCG, a live vaccine made from an attenuated strain of *M. bovis*. BCG has been used for decades for the prevention of severe forms of TB in infants and children in many parts of the world. However, because of uncertainty regarding its efficacy and its interference with interpretation of the TST, it was never chosen for use in TB control programs in the United States (see Chapter 5).

The second line of approach to prevention of TB—preventing disease in those with latent TB infection—has a place in modern medical practice. A number of studies by the US Public Health Service in the 1950s and 1960s showed that administration of isoniazid 300 mg/day, for 9 months, had a 50-80% efficacy rate in preventing TB disease in persons with latent TB infection. The protective effect of isoniazid preventive therapy is believed to be lifelong if the patient is immunocompetent. In addition to isoniazid, two other regimens for LTBI are used: rifampin self-administered daily for 4 months and isoniazid-and-rifapentine directly observed once weekly for 12 weeks (WHO 2015).

Treatment should be offered in the following situations:

1. The patient may have been recently infected with *M. tuberculosis*. Recent infection is likely in close contacts of an infectious case of TB and in young children with diagnosis of LTBI.
2. The patient has one (or more) of the following medical conditions that raise the risk of progression from latent TB infection to active TB: HIV infection; treatment with immunosuppressive medications such as corticosteroids or TNF inhibitors; diabetes mellitus; certain malignancies; conditions associated with low weight, such as malnutrition, gastrectomy, and intestinal bypass surgery; and fibrotic pulmonary lesions consistent with untreated yet healed pulmonary TB.
3. The patient is under 50-60 years of age and has an estimated cumulative lifetime risk of reactivation that exceeds the risk of significant adverse effects from LTBI therapy.

One tool for patient-centered decision making is to first calculate lifetime risk of developing active TB (e.g., www.tstin3d.com). Then, clinicians inform the patient of a balance between benefits and risks of LTBI treatment options. Shared decision making may increase the engagement of the patients and thus potentially increase adherence with LTBI treatment.

Patients receiving LTBI treatment should be evaluated monthly during treatment and given prescriptions for 1-month supplies of medicine at each follow-up appointment. Personal interviews for adherence and side effects should be performed at these monthly intervals. The most important side effect of isoniazid is hepatotoxicity. Although potentially

fatal, the frequency of this side effect appears to be low. Every patient who starts LTBI treatment should be educated about the symptoms of hepatotoxicity and instructed to stop treatment immediately if such symptoms develop. Patients capable of following these instructions do not require laboratory monitoring of liver-related enzymes during LTBI treatment. However, it is recommended to conduct baseline and periodic monitoring of liver function tests in patients with co-existing chronic liver disease or who are at increased risk of drug-induced hepatitis (e.g., excessive alcohol use, hepatitis B or C infection, concurrent use of other hepatotoxic drugs, and pregnancy). A 2-month regimen of rifampin-pyrazinamide was previously recommended as an alternative to isonicotinic acid hydrazide for treating latent TB. However, significant rates of serious hepatotoxicity were observed with this combination, and it is no longer recommended.

TB RISK ASSESSMENT

Figure 25.1 illustrates each step of TB risk assessment when a clinician evaluates a person for TB infection. The first two steps are to assess significant TB exposure and potential TB acquisition. At minimum, we consider TB exposure significant when someone spends more than 8 hours in a confined indoor space with someone who has infectious TB. When a person has an immature or impaired immune system (e.g., an infant or someone with HIV infection), rapid progression to active TB disease must be ruled out after significant TB exposure. Otherwise, risk of reactivation TB and an opportunity for prevention (i.e., treatment of latent TB infection) should be addressed. In rare circumstances, those with latent TB infection or a history of cured TB may be reinfected with a different strain of *M. tuberculosis* after substantial TB exposure. Diagnosis of reinfection and prevention of post reinfection disease has not been established yet.

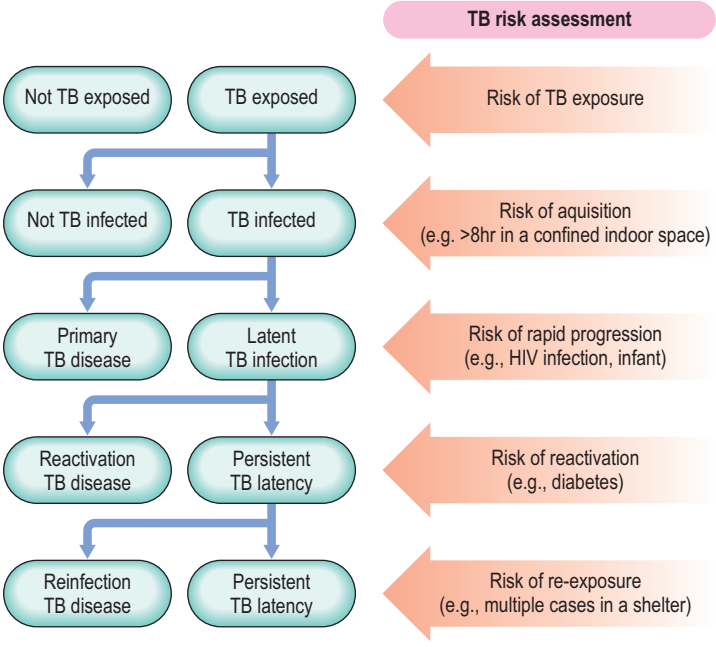

Fig. 25.1 **Tuberculosis risk assessment.**

EVALUATION OF IMMIGRANTS FOR TB

Evaluation of immigrants from TB-endemic countries is crucial for TB control in the United States. There are two steps. First, to exclude active TB disease and to evaluate for LTBI; second, to treat appropriately. Those who apply for permanent resident status ("a green card") have to undergo CXR. If abnormal, sputum examination for AFB smear and culture is completed prior to emigration. Refugees are also screened in this way, but those with student, work, or tourist visas generally do not undergo health screening, including TB screening. While treatment of active TB is mandatory, treatment of LTBI is not required for immigration purposes.

EVALUATION OF TRAVELERS WHO VISIT TB-ENDEMIC COUNTRIES

Pre-Travel

While sensitivity of TST and IGRA to detect TB infection is reasonably high (~80%), positive predictive values of TST and IGRA in a population with low prevalence of TB infection are concerning (**Table 25.5**). Both tests, especially IGRA, appear to have limited reproducibility when used in a low-LTBI prevalence group. This raises concerns because of consequences of positive TST or IGRA (e.g., CXR, possible treatment for LTBI especially after conversion). Knowledge of positive predictive values in BCG-vaccinated and nonvaccinated populations with various likelihoods of TB infection should help a clinician whether LTBI testing is beneficial or not (**Table 25.5**). At this point, the authors do not recommend testing a US-born traveler for LTBI prior to a trip to TB-endemic countries

TABLE 25.5 Positive Predictive Values of Latent Tuberculosis Infection Testing[a]

Non-BCG Vaccinated			
	TST	QFT-G	
	Sensitivity 77%	Sensitivity 78%	
LTBI Prevalence	Specificity 97%	Specificity 99%	
1%	20%	44%	
3%	44%	70%	
5%	57%	80%	
10%	74%	90%	
BCG Vaccinated			
	TST	QFT Gold	TSpot
	Sensitivity 77%	Sensitivity 78%	Sensitivity 90%
LTBI Prevalence	Specificity 59%	Specificity 96%	Specificity 93%
5%	9%	51%	40%
10%	17%	68%	59%
20%	32%	83%	76%
30%	45%	89%	85%

[a]Based on the sensitivities and specificities published in a systematic review.
BCG, Bacillus Calmette-Guérin; *LTBI,* latent tuberculosis infection; *QFT-G,* QuantiFERON-TB Gold test; *TST,* tuberculin skin test.

when the purpose of the travel is business, tourism, missionary, research, or volunteer work in nonhealthcare settings. If foreign-born persons plan to visit their families and friends in TB-endemic countries, the information on prior TST or IGRA is helpful. If a negative result had been documented, we recommend considering pre- and post-travel LTBI testing especially if the duration of the trip is longer than a few weeks. Detailed interview of anticipated activities in TB-endemic countries (e.g., being a healthcare volunteer in a TB hospital) can be used to help determine the need for pre- and post-travel LTBI testing. The following recommendations may be given to travelers:

- Avoid places where people at high risk for TB congregate (e.g., hospitals, jails, prisons, homeless shelters)
- Use mitigating measures (e.g., augmentation of airflow or ventilation, N-95 mask) if high-risk exposure cannot be avoided
- Consider pre- and post-travel testing for LTBI if high-risk TB exposure is unavoidable or if the stay in a TB-endemic country is over 3 months. Be mindful of poor positive predictive value of TST and IGRA when the likelihood of acquisition of TB infection is remote.

Some experts suggest a single dose of BCG as a pre-travel preventive measure when healthcare and humanitarian workers have high risk of exposure to MDR or XDR TB, especially in settings where the TB infection control measures are not fully implemented (Seaworth et al. 2014).

Post-Travel

Urgent evaluation is indicated if the traveler has signs or symptoms consistent with active TB disease. Otherwise, a test for TB infection (TST or IGRA) should be obtained 8-10 weeks after return to the United States for high-risk travelers. If the stay exceeds 3 months, repeat testing for TB infection overseas (i.e., prior to return) may be appropriate.

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