Tuberculosis (TB), a multisystemic disease with myriad presentations and manifestations, is the most common cause of infectious disease–related mortality worldwide. Although TB rates are decreasing in the United States, the disease is becoming more common in many parts of the world. In addition, the prevalence of drug-resistant TB is increasing worldwide.

**Essential update: Prophylactic isoniazid reduces TB risk in children**

In a meta-analysis of 8 randomized controlled studies involving a total of 10,320 patients aged 15 years or younger, Ayieko et al found that isoniazid prophylaxis reduced the risk of developing TB, with a pooled risk ratio (RR) of 0.65 (95% confidence interval [CI], 0.47-0.89; \( P = .004 \)).

Various subgroup analyses were done, but participant age was the only factor associated with substantial differences in the summary estimate of efficacy. Isoniazid had no effect in children who initiated treatment at 4 months of age or earlier. When these patients were excluded, isoniazid prophylaxis reduced the risk of developing TB by 59% (RR, 0.41; 95% CI, 0.31-0.55; \( P < 0.001 \)).
Signs and symptoms

Classic clinical features associated with active pulmonary TB are as follows (elderly individuals with TB may not display typical signs and symptoms):

- Cough
- Weight loss/anorexia
- Fever
- Night sweats
- Hemoptysis
- Chest pain (can also result from tuberculous acute pericarditis)
- Fatigue

Symptoms of tuberculous meningitis may include the following:

- Headache that has been either intermittent or persistent for 2-3 weeks
- Subtle mental status changes that may progress to coma over a period of days to weeks
- Low-grade or absent fever

Symptoms of skeletal TB may include the following:

- Back pain or stiffness
- Lower-extremity paralysis, in as many as half of patients with undiagnosed Pott disease
- Tuberculous arthritis, usually involving only 1 joint (most often the hip or knee, followed by the ankle, elbow, wrist, and shoulder)

Symptoms of genitourinary TB may include the following:

- Flank pain
- Dysuria
- Frequent urination
- In men, a painful scrotal mass, prostatitis, orchitis, or epididymitis
- In women, symptoms mimicking pelvic inflammatory disease

Symptoms of gastrointestinal TB are referable to the infected site and may include the following:

- Nonhealing ulcers of the mouth or anus
- Difficulty swallowing (with esophageal disease)
- Abdominal pain mimicking peptic ulcer disease (with gastric or duodenal infection)
- Malabsorption (with infection of the small intestine)
- Pain, diarrhea, or hematochezia (with infection of the colon)

Physical examination findings associated with TB depend on the organs involved. Patients with pulmonary TB may have the following:

- Abnormal breath sounds, especially over the upper lobes or involved areas
- Rales or bronchial breath signs, indicating lung consolidation
Signs of extrapulmonary TB differ according to the tissues involved and may include the following:

- Confusion
- Coma
- Neurologic deficit
- Chorioretinitis
- Lymphadenopathy
- Cutaneous lesions

The absence of any significant physical findings does not exclude active TB. Classic symptoms are often absent in high-risk patients, particularly those who are immunocompromised or elderly.

See Clinical Presentation for more detail.

**Diagnosis**

Screening methods for TB include the following:

- Mantoux tuberculin skin test with purified protein derivative (PPD) for active or latent infection (primary method)
- In vitro blood test based on interferon gamma release assay (IGRA) with antigens specific for *Mycobacterium tuberculosis* for latent infection

Obtain the following laboratory tests for patients with suspected TB:

- Acid-fast bacilli (AFB) smear and culture using sputum obtained from the patient: Absence of a positive smear result does not exclude active TB infection; AFB culture is the most specific test for TB
- HIV serology in all patients with TB and unknown HIV status: Individuals infected with HIV are at increased risk for TB

Other diagnostic testing may warrant consideration, including the following:

- Specific enzyme-linked immunospot (ELISpot)
- Nucleic acid amplification tests
- Blood culture

Positive cultures should be followed by drug susceptibility testing; symptoms and radiographic findings do not differentiate multidrug-resistant TB (MDR-TB) from fully susceptible TB. Such testing may include the following:

- Direct DNA sequencing analysis
- Automated molecular testing
- Microscopic-observation drug susceptibility (MODS) and thin-layer agar (TLA) assays
- Additional rapid tests (eg, BACTEC-460, ligase chain reaction, luciferase reporter assays, FASTPlaque TB-RIF)

Obtain a chest radiograph to evaluate for possible associated pulmonary findings. The following patterns may be seen:
• Cavity formation: Indicates advanced infection; associated with a high bacterial load
• Noncalcified round infiltrates: May be confused with lung carcinoma
• Homogeneously calcified nodules (usually 5-20 mm): Tuberculomas, representing old infection
• Primary TB: Typically, pneumonialike picture of infiltrative process in middle or lower lung regions
• Reactivation TB: Pulmonary lesions in posterior segment of right upper lobe, apicoposterior segment of left upper lobe, and apical segments of lower lobes
• TB associated with HIV disease: Frequently atypical lesions or normal chest radiographic findings
• Healed and latent TB: Dense pulmonary nodules in hilar or upper lobes; smaller nodules in upper lobes
• Miliary TB: Numerous small, nodular lesions that resemble millet seeds
• Pleural TB: Empyema may be present, with associated pleural effusions

Workup considerations for extrapulmonary TB include the following:
• Biopsy of bone marrow, liver, or blood cultures
• If tuberculous meningitis or tuberculoma is suspected, perform lumbar puncture
  • If vertebral (Pott disease) or brain involvement is suspected, CT or MRI is necessary
• If genitourinary complaints are reported, urinalysis and urine cultures can be obtained
See Workup for more detail.

Management

Physical measures (if possible or practical) include the following:
• Isolate patients with possible TB in a private room with negative pressure
• Have medical staff wear high-efficiency disposable masks sufficient to filter the bacillus
• Continue isolation until sputum smears are negative for 3 consecutive determinations (usually after approximately 2-4 weeks of treatment)

Initial empiric pharmacologic therapy consists of the following 4-drug regimens:
• Isoniazid
• Rifampin
• Pyrazinamide
• Either ethambutol or streptomycin

Special considerations for drug therapy in pregnant women include the following:
• In the United States, pyrazinamide is reserved for women with suspected MDR-TB
• Streptomycin should not be used
Preventive treatment is recommended during pregnancy
Pregnant women are at increased risk for isoniazid-induced hepatotoxicity
Breastfeeding can be continued during preventive therapy

Special considerations for drug therapy in children include the following:

Most children with TB can be treated with isoniazid and rifampin for 6 months, along with pyrazinamide for the first 2 months if the culture from the source case is fully susceptible.
For postnatal TB, the treatment duration may be increased to 9 or 12 months
Ethambutol is often avoided in young children

Special considerations for drug therapy in HIV-infected patients include the following:

Dose adjustments may be necessary[3, 4]
Rifampin must be avoided in patients receiving protease inhibitors; rifabutin may be substituted
Considerations in patients receiving antiretroviral therapy include the following:
Patients with HIV and TB may develop a paradoxical response when starting antiretroviral therapy
Starting antiretroviral therapy early (eg, < 4 weeks after the start of TB treatment) may reduce progression to AIDS and death[3]
In patients with higher CD4+ T-cell counts, it may be reasonable to defer antiretroviral therapy until the continuation phase of TB treatment[3]

Multidrug-resistant TB

When MDR-TB is suspected, start treatment empirically before culture results become available, then modify the regimen as necessary. Never add a single new drug to a failing regimen. Administer at least 3 (preferably 4-5) of the following medications, according to drug susceptibilities:

An aminoglycoside: Streptomycin, amikacin, capreomycin, kanamycin
A fluoroquinolone: Levofloxacin (best suited over the long term), ciprofloxacin, ofloxacin
A thioamide: Ethionamide, prothionamide
Pyrazinamide
Ethambutol
Cycloserine
Terizidone
Para-aminosalicylic acid
Rifabutin as a substitute for rifampin
A diarylquinoline: Bedaquiline

Surgical resection is recommended for patients with MDR-TB whose prognosis with medical treatment is poor. Procedures include the following:
Latent TB

Recommended regimens for isoniazid and rifampin for latent TB have been published by the US Centers for Disease Control and Prevention (CDC)\(^2\): An alternative regimen for latent TB is isoniazid plus rifapentine\(^8\); it is not recommended for children under 2 years, pregnant women or women planning to become pregnant, HIV-infected persons taking antiretrovirals, or patients with TB infection presumed to result from exposure to a person with TB that is resistant to 1 of the 2 drugs.

See Treatment and Medication for more detail.

Background

Tuberculosis (TB), a multisystemic disease with myriad presentations and manifestations, is the most common cause of infectious disease–related mortality worldwide. The World Health Organization (WHO) has estimated that 2 billion people have latent TB and that globally, in 2009, the disease killed 1.7 million people.\(^9\) (See Epidemiology.)\(^10\)

Although TB rates are decreasing in the United States, the disease is becoming more common in many parts of the world. In addition, the prevalence of drug-resistant TB is also increasing worldwide. Coinfection with the human immunodeficiency virus (HIV) has been an important factor in the emergence and spread of resistance.\(^11\) (See Treatment.)

*Mycobacterium tuberculosis*, a tubercle bacillus, is the causative agent of TB. It belongs to a group of closely related organisms—including *M africanum, M bovis,*
and *M microti* — in the *M tuberculosis* complex. (See Etiology.) An image of the bacterium is seen below.

![Image of M tuberculosis bacterium](https://example.com/image.jpg)

Under a high magnification of 15549x, this scanning electron micrograph depicts some of the ultrastructural details seen in the cell wall configuration of a number of Gram-positive Mycobacterium tuberculosis bacteria. As an obligate aerobic organism, *M. tuberculosis* can only survive in an environment containing oxygen. This bacterium ranges in length between 2-4 microns, with a width between 0.2-0.5 microns. Image courtesy of the Centers for Disease Control and Prevention/Dr. Ray Butler.

The lungs are the most common site for the development of TB; 85% of patients with TB present with pulmonary complaints. Extrapulmonary TB can occur as part of a primary or late, generalized infection. (See Pathophysiology and Presentation.)

The primary screening method for TB infection (active or latent) is the Mantoux tuberculin skin test with purified protein derivative (PPD). An in vitro blood test based on interferon-gamma release assay (IGRA) with antigens specific for *M tuberculosis* can also be used to screen for latent TB infection. Patients suspected of having TB should submit sputum for acid-fast bacilli (AFB) smear and culture. (See Workup.)

The usual treatment regimen for TB cases from fully susceptible *M tuberculosis* isolates consists of 6 months of multidrug therapy. Empiric treatment starts with a 4-drug regimen of isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin; this therapy is subsequently adjusted according to susceptibility testing results and toxicity. Pregnant women, children, HIV-infected patients, and patients infected with drug-resistant strains require different regimens. (See Treatment and Medication.)

Laws vary from state to state, but communicable-disease laws typically empower public health officials to investigate suspected cases of TB, including potential contacts of persons with TB. In addition, patients may be incarcerated for noncompliance with therapy.

New TB treatments are being developed, and new TB vaccines are under investigation. (See Epidemiology and Treatment.)

**Historical background**

TB is an ancient disease. Signs of skeletal TB (Pott disease) have been found in remains from Europe from Neolithic times (8000 BCE), ancient Egypt (1000 BCE), and the pre-Columbian New World. TB was recognized as a contagious disease by the time of Hippocrates (400 BCE), when it was termed "phthisis" (Greek from *phthinein*, to waste away). In English, pulmonary TB was long known by the
term “consumption.” German physician Robert Koch discovered and isolated *M tuberculosis* in 1882.

The worldwide incidence of TB increased with population density and urban development, so that by the Industrial Revolution in Europe (1750), it was responsible for more than 25% of adult deaths. In the early 20th century, TB was the leading cause of death in the United States; during this period, however, the incidence of TB began to decline because of various factors, including the use of basic infection-control practices (eg, isolation).

**Resurgence of TB**

The US Centers for Disease Control and Prevention (CDC) has been recording detailed epidemiologic information on TB since 1953. Beginning in 1985, a resurgence of TB was noted. The increase was observed primarily in ethnic minorities and especially in persons infected with HIV. TB control programs were revamped and strengthened across the United States, and rates again began to fall. (See Epidemiology.)

As an AIDS (acquired immunodeficiency syndrome)—related opportunistic infection, TB is associated with HIV infections, with dual infections being frequently noted. Globally, coinfection with HIV is highest in South Africa, India, and Nigeria. Persons with AIDS are 20-40 times more likely than immunocompetent persons to develop active TB. Correspondingly, TB is the leading cause of mortality among persons infected with HIV.

Worldwide, TB is most common in Africa, the West Pacific, and Eastern Europe. These regions are plagued with factors that contribute to the spread of TB, including the presence of limited resources, HIV infection, and multidrug-resistant (MDR) TB. (See Epidemiology.)

**Drug-resistant TB**

MDR-TB is defined as resistance to isoniazid and rifampin, which are the 2 most effective first-line drugs for TB. In 2006, an international survey found that 20% of *M tuberculosis* isolates were MDR. A rare type of MDR-TB, called extensively drug-resistant TB (XDR-TB), is resistant to isoniazid, rifampin, any fluoroquinolone, and at least one of 3 injectable second-line drugs (ie, amikacin, kanamycin, or capreomycin). XDR-TB resistant to all anti-TB drugs tested has been reported in Italy, Iran, and India.

Multiple factors contribute to the drug resistance of *M tuberculosis*, including incomplete and inadequate treatment or adherence to treatment, logistical issues, virulence of the organism, multidrug transporters, host genetic factors, and HIV infection. A study from South Africa found high genotypic diversity and geographic distribution of XDR-TB isolates, suggesting that acquisition of resistance, rather than transmission, accounts for between 63% and 75% of XDR-TB cases.
Statistics

In a 2008 report by the WHO, the proportion of TB cases in which the patient was resistant to at least 1 antituberculosis drug varied widely among different regions of the world, ranging from 0% to over 50%; the proportion of MDR-TB cases ranged from 0% to over 20%. The WHO calculated that the global population-weighted proportion of MDR-TB was 2.9% in new TB cases, 15.3% in previously treated patients, and 5.3% in all TB cases.[17]

In the United States, the percentage of MDR-TB cases has increased slowly, from 0.9% of the total number of reported TB cases in 2008 to 1.3% of cases in 2011. Although the percentage of US-born patients with primary MDR-TB has remained below 1% since 1997, the proportion of cases in which the patient was foreign born increased from 25.3% in 1993 to 82.7% in 2011.[18]

XDR-TB is becoming increasingly significant.[17] According to the US National TB Surveillance System (NTSS), between 1993 and 2006 a total of 49 cases (3% of evaluable MDR-TB cases) met the revised case definition for XDR-TB. The largest number of XDR-TB cases was found in New York City and California.

Cure rate

The cure rate in persons with MDR-TB is 50-60%, compared with 95-97% for persons with drug-susceptible TB.[14] The estimated cure rate for XDR-TB is 30-50%.[9] In people who are also infected with HIV, MDR-TB and XDR-TB often produce fulminant and fatal disease; time from TB exposure to death averages 2-7 months. In addition, these cases are highly infectious, with conversion rates of as much as 50% in exposed health-care workers.

Global surveillance and treatment of TB

As previously stated, multidrug resistance has been driven by poor compliance with TB therapies, resulting in difficulties in controlling the disease. Consequently, a threat of global pandemic occurred in the late 1980s and early 1990s. Reacting to these signals, the WHO developed a plan to try to identify 70% of the world’s cases of TB and to completely treat at least 85% of these cases by the year 2000.

Out of these goals were born major TB surveillance programs and the concept of directly observed therapy (DOT), which requires a third party to witness compliance with pharmacotherapy. With worldwide efforts, global detection of smear-positive cases rose from 11% (1991) to 45% (2003), with 71-89% of those cases undergoing complete treatment.

Approach to TB in the emergency department

Despite the importance of early isolation of patients with active TB, a standardized triage protocol with acceptable sensitivities has yet to be developed.[19] Moran et al demonstrated that among patients with active TB in the emergency department (ED), TB was often unsuspected, and isolation measures were not used.[20] The
difficulty in establishing such a protocol only highlights the importance of the
emergency physician’s role in the prompt identification and isolation of active TB.

A large percentage of ED patients are at increased risk for having active TB,
including homeless/shelter-dwelling patients, travelers from endemic areas,
immunocompromised patients, health-care workers, and incarcerated patients.
Therefore, emergency physicians must consider the management and treatment of
TB as a critical public health measure in the prevention of a new epidemic.  

For high-risk cases,prehospital workers can assist in identifying household contacts
who may also be infected or who may be at high risk of becoming infected.

Prehospital workers should be aware that any case of active TB in a young child
indicates disease in 1 or more adults with close contact, usually within the same
household. TB in a child is a sentinel event indicating recent transmission.

**Extrapulmonary involvement in TB**

Extrapulmonary involvement occurs in one fifth of all TB cases; 60% of patients with
extrapulmonary manifestations of TB have no evidence of pulmonary infection on
chest radiographs or in sputum cultures.

**Cutaneous TB**

The incidence of cutaneous TB appears low. In areas such as India or China, where
TB prevalence is high, cutaneous manifestations of TB (overt infection or the
presence of tuberculids) have been found in less than 0.1% of individuals seen in
dermatology clinics.

**Ocular TB**

TB can affect any structure in the eye and typically presents as a granulomatous
process. Keratitis, iridocyclitis, intermediate uveitis, retinitis, scleritis, and orbital
abscess are within the spectrum of ocular disease. Choroidal tubercles and
choroiditis are the most common ocular presentations of TB. Adnexal or orbital
disease may be seen with preauricular lymphadenopathy. Because of the wide
variability in the disease process, presenting complaints will vary.

Most often, patients will complain of blurry vision that may or may not be associated
with pain and red eye. In the rare case of orbital disease, proptosis, double vision, or
extraocular muscle motility restriction may be the presenting complaint. Preseptal
cellulitis in children with spontaneous draining fistula may also occur. In cases of
both pulmonary and extrapulmonary TB, there may be ocular findings without ocular
complaints.

In patients with confirmed active pulmonary or active, nonocular extrapulmonary TB,
ocular incidence ranges from 1.4-5.74%. In HIV patients, the incidence of ocular TB
may be higher, with a reported prevalence of from 2.8-11.4%.
Patient education

Patient information on TB can be found at the following sites:

- CDC [Tuberculosis (TB)]
- World Health Organization [Tuberculosis]

For patient education information, see the [Infections Center], as well as [Tuberculosis].

Pathophysiology

Infection with *M. tuberculosis* results most commonly through exposure of the lungs or mucous membranes to infected aerosols. Droplets in these aerosols are 1-5 μm in diameter; in a person with active pulmonary TB, a single cough can generate 3000 infective droplets, with as few as 10 bacilli needed to initiate infection.

When inhaled, droplet nuclei are deposited within the terminal airspaces of the lung. The organisms grow for 2-12 weeks, until they reach 1000-10,000 in number, which is sufficient to elicit a cellular immune response that can be detected by a reaction to the tuberculin skin test.

Mycobacteria are highly antigenic, and they promote a vigorous, nonspecific immune response. Their antigenicity is due to multiple cell wall constituents, including glycoproteins, phospholipids, and wax D, which activate Langerhans cells, lymphocytes, and polymorphonuclear leukocytes.

When a person is infected with *M. tuberculosis*, the infection can take 1 of a variety of paths, most of which do not lead to actual TB. The infection may be cleared by the host immune system or suppressed into an inactive form called latent tuberculosis infection (LTBI), with resistant hosts controlling mycobacterial growth at distant foci before the development of active disease. Patients with LTBI cannot spread TB.

The lungs are the most common site for the development of TB; 85% of patients with TB present with pulmonary complaints. Extrapulmonary TB can occur as part of a primary or late, generalized infection. An extrapulmonary location may also serve as a reactivation site; extrapulmonary reactivation may coexist with pulmonary reactivation.

The most common sites of extrapulmonary disease are as follows (the pathology of these lesions is similar to that of pulmonary lesions):

- Mediastinal, retroperitoneal, and cervical (scrofula) lymph nodes - The most common site of tuberculous lymphadenitis (scrofula) is in the neck, along the sternocleidomastoid muscle; it is usually unilateral and causes little or no pain; advanced cases of tuberculous lymphadenitis may suppurate and form a draining sinus
- Vertebral bodies
- Adrenals
- Meninges
GI tract

Infected end organs typically have high regional oxygen tension (as in the kidneys, bones, meninges, eyes, and choroids, and in the apices of the lungs). The principal cause of tissue destruction from *M. tuberculosis* infection is related to the organism's ability to incite intense host immune reactions to antigenic cell wall proteins.

Uveitis caused by TB is the local inflammatory manifestation of a previously acquired primary systemic tubercular infection. There is some debate with regard to whether molecular mimicry, as well as a nonspecific response to noninfectious tubercular antigens, provides a mechanism for active ocular inflammation in the absence of bacterial replication.

**TB lesions**

The typical TB lesion is an epithelioid granuloma with central caseation necrosis. The most common site of the primary lesion is within alveolar macrophages in subpleural regions of the lung. Bacilli proliferate locally and spread through the lymphatics to a hilar node, forming the Ghon complex.

Early tubercles are spherical, 0.5- to 3-mm nodules with 3 or 4 cellular zones demonstrating the following features:

- A central caseation necrosis
- An inner cellular zone of epithelioid macrophages and Langhans giant cells admixed with lymphocytes
- An outer cellular zone of lymphocytes, plasma cells, and immature macrophages
- A rim of fibrosis (in healing lesions)

Initial lesions may heal and the infection become latent before symptomatic disease occurs. Smaller tubercles may resolve completely. Fibrosis occurs when hydrolytic enzymes dissolve tubercles and larger lesions are surrounded by a fibrous capsule. Such fibrocaseous nodules usually contain viable mycobacteria and are potential lifelong foci for reactivation or cavitation. Some nodules calcify or ossify and are seen easily on chest radiographs.

Tissues within areas of caseation necrosis have high levels of fatty acids, low pH, and low oxygen tension, all of which inhibit growth of the tubercle bacillus.

If the host is unable to arrest the initial infection, the patient develops progressive, primary TB with tuberculous pneumonia in the lower and middle lobes of the lung. Purulent exudates with large numbers of acid-fast bacilli can be found in sputum and tissue. Subserosal granulomas may rupture into the pleural or pericardial spaces and create serous inflammation and effusions.

With the onset of the host immune response, lesions that develop around mycobacterial foci can be either proliferative or exudative. Both types of lesions develop in the same host, since infective dose and local immunity vary from site to site.
Proliferative lesions develop where the bacillary load is small and host cellular immune responses dominate. These tubercles are compact, with activated macrophages admixed, and are surrounded by proliferating lymphocytes, plasma cells, and an outer rim of fibrosis. Intracellular killing of mycobacteria is effective, and the bacillary load remains low.

Exudative lesions predominate when large numbers of bacilli are present and host defenses are weak. These loose aggregates of immature macrophages, neutrophils, fibrin, and caseation necrosis are sites of mycobacterial growth. Without treatment, these lesions progress and infection spreads.

Etiology

TB is caused by *M tuberculosis*, a slow-growing obligate aerobe and a facultative intracellular parasite. The organism grows in parallel groups called cords (as seen in the image below). It retains many stains after decoloration with acid-alcohol, which is the basis of the acid-fast stains used for pathologic identification.

Mycobacteria, such as *M tuberculosis*, are aerobic, non–spore-forming, nonmotile, facultative, curved intracellular rods measuring 0.2-0.5 μm by 2-4 μm. Their cell walls contain mycolic, acid-rich, long-chain glycolipids and phospholipoglycans (mycocides) that protect mycobacteria from cell lysosomal attack and also retain red basic fuchsin dye after acid rinsing (acid-fast stain).

Transmission

Humans are the only known reservoir for *M tuberculosis*. The organism is spread primarily as an airborne aerosol from an individual who is in the infectious stage of TB (although transdermal and GI transmission have been reported).

In immunocompetent individuals, exposure to *M tuberculosis* usually results in a latent/dormant infection. Only about 5% of these individuals later show evidence of clinical disease. Alterations in the host immune system that lead to decreased immune effectiveness can allow *M tuberculosis* organisms to reactivate, with tubercular disease resulting from a combination of direct effects from the replicating infectious organism and from subsequent inappropriate host immune responses to tubercular antigens.
Molecular typing of *M tuberculosis* isolates in the United States by restriction fragment-length polymorphism analysis suggests more than one third of new patient occurrences of TB result from person-to-person transmission. The remainder results from reactivation of latent infection.

Verhagen et al demonstrated that large clusters of TB are associated with an increased number of tuberculin skin test–positive contacts, even after adjusting for other risk factors for transmission.\[22\] The number of positive contacts was significantly lower for index cases with isoniazid-resistant TB compared with index cases with fully-susceptible TB. This suggests that some TB strains may be more transmissible than other strains and that isoniazid resistance is associated with lower transmissibility.

**Extrapulmonary spread**

Because of the ability of *M tuberculosis* to survive and proliferate within mononuclear phagocytes, which ingest the bacterium, *M tuberculosis* is able to invade local lymph nodes and spread to extrapulmonary sites, such as the bone marrow, liver, spleen, kidneys, bones, and brain, usually via hematogenous routes.

Although mycobacteria are spread by blood throughout the body during initial infection, primary extrapulmonary disease is rare except in immunocompromised hosts. Infants, older persons, or otherwise immunosuppressed hosts are unable to control mycobacterial growth and develop disseminated (primary miliary) TB. Patients who become immunocompromised months to years after primary infection also can develop late, generalized disease.

**Risk factors**

The following factors help to determine whether a TB infection is likely to be transmitted:

- Number of organisms expelled
- Concentration of organisms
- Length of exposure time to contaminated air
- Immune status of the exposed individual

Infected persons living in crowded or closed environments pose a particular risk to noninfected persons. Approximately 20% of household contacts develop infection (positive tuberculin skin test). Microepidemics have occurred in closed environments such as submarines and on transcontinental flights. Populations at high risk for acquiring the infection also include hospital employees, inner-city residents, nursing home residents, and prisoners.

The following factors increase an individual’s risk of acquiring active tuberculosis:

- HIV infection
- Intravenous (IV) drug abuse
- Alcoholism
• Diabetes mellitus (3-fold risk increase)
• Silicosis
• Immunosuppressive therapy
• Tumor necrosis factor–alpha (TNF-α) antagonists
• Cancer of the head and neck
• Hematologic malignancies
• End-stage renal disease
• Intestinal bypass surgery or gastrectomy
• Chronic malabsorption syndromes
• Low body weight - In contrast, *obesity* in elderly patients has been associated with a lower risk for active pulmonary TB\(^\text{[23]}\)
• Smoking - Smokers who develop TB should be encouraged to stop smoking to decrease the risk of relapse\(^\text{[24]}\)
• Age below 5 years

**TNF antagonists and steroids**

Treatment with tumor necrosis factor–alpha (TNF-α) antagonists, which is used for rheumatoid arthritis, psoriasis, and several other autoimmune disorders, has been associated with a significantly increased risk for TB.\(^\text{[25]}\) Reports have included atypical presentations, extrapulmonary and disseminated disease, and deaths. Patients scheduled to begin therapy with a TNF-α antagonist should be screened for latent TB and counseled regarding the risk of TB.

Immunosuppressive therapy includes long-term administration of systemic steroids (prednisone or its equivalent, given >15 mg/day for ≥4 wk or more) and/or inhaled steroids. Brassard and colleagues reported that inhaled steroids, in the absence of systemic steroids, were associated with a relative risk of 1.5 for TB.\(^\text{[26]}\)

**TB in children**

In children younger than 5 years, the potential for development of fatal miliary TB or meningeal TB is a significant concern. Osteoporosis, sclerosis, and bone involvement are more common in children with TB than in adults with the disease. The epiphyseal bones can be involved because of their high vascularity.

Children do not commonly infect other children, because they rarely develop cough and their sputum production is scant. However, cases of child-child and child-adult TB transmission are well documented. (See [Pediatric Tuberculosis](#) for complete information on this topic.)

**Genetic factors**

The genetics of tuberculosis are quite complex, involving many genes. Some of those genes involve important aspects of the immune system, while others involve more specific mechanisms by which the human body interacts with mycobacterium species. The genes that follow have polymorphisms that are associated with either susceptibility to or protection from tuberculosis. Additionally, regions such as 8q12-
NRAMP1

In a study from Africa, 4 different polymorphisms of the NRAMP1 gene were associated with an increased risk for TB. Subjects who possessed a certain 2 of those polymorphisms (located in an intron and in a region upstream from the coding region) were at particular risk for contracting TB. [27] The association of NRAMP1 with risk of TB has been replicated in subsequent studies. [28, 29]

SP110

The product of this gene interacts with the interferon system and as such is an important aspect of the immune response. A study of 27 different polymorphisms in this gene found 3 that were associated with increased risk of TB; 2 of these polymorphisms were intronic and the third was a missense mutation in exon 11. [30]

CISH

The product of this gene functions to suppress cytokine signaling, which is important for inflammatory signaling. One study found that a single-nucleotide polymorphism upstream from CISH was associated with susceptibility to TB, malaria, and invasive bacterial disease. The same study found that leukocytes of persons who had the risk variant for CISH had a decreased response to interleukin 2. [31]

IRGM

The expression of this gene is induced by interferon, and the product is involved in the control of intracellular mycobacteria. One study found that homozygosity for a particular polymorphism in the promoter region of IRGM confers protection against TB, but only in persons of European ancestry. In vitro analyses showed increased expression of the IRGM gene product with the promoter variant, further underscoring the importance of this gene in the immune response to mycobacterial infection. [32]

IFNG

Interferon gamma is a cytokine that has an important role in the immune response to intracellular infections, including viral and mycobacterial infections. One particular polymorphism near a microsatellite in this gene is associated with increased expression of the IFNG gene and increased production of interferon gamma. An association study found evidence that this polymorphism was related to protection against TB. [33]

IFNGR1

The product of IFNGR1 is part of a heterodimeric receptor for interferon gamma. This has important implications for the response of this part of the immune system in the defense against certain infections.
A region of homozygosity in the region of the *IFNGR1* gene has been found in a group of related children in southern Europe who were known to have a predisposition to mycobacterial infection; this predisposition, which had resulted in death in three children and chronic mycobacterial infection in a fourth, was felt to be autosomal recessive. Subsequent sequencing of the gene showed a nonsense mutation that resulted in a nonfunctional gene product.

*TIRAP*

The *TIRAP* gene produces a protein that has several functions in the immune system. A study of 33 polymorphisms in the *TIRAP* gene found that heterozygosity for a serine-to-leucine substitution was associated with protection against invasive pneumococcal disease, bacteremia, malaria, and TB.

*CD209*

The product of the *CD209* gene is involved in the function of dendritic cells, which are involved in the capture of certain microorganisms. An association was found between susceptibility to TB and a polymorphism upstream from the *CD209* gene in a multiracial South African population.

**Epidemiology**

**Occurrence in the United States**

With the improvement of living conditions and the introduction of effective treatment (streptomycin) in the late 1940s, the number of patients in the United States reported to have TB began to steadily decline (126,000 TB patients in 1944; 84,000 in 1953; 22,000 in 1984; 14,000 in 2004), despite explosive growth in the total population (140 million people in 1946, 185 million in 1960, 226 million in 1980).

On a national level, the incidence of TB is at an all-time low. Since the 1992 TB resurgence peak in the United States, the number of TB cases reported annually has decreased by 61%.

In 2011, 10,528 TB cases (a rate of 3.4 cases per 100,000 population) were reported in the United States, representing a 5.8% decline in the number of reported TB cases and a 6.4% decline in the case rate, compared with 2010.

California, New York, Texas, and Florida accounted for half of all TB cases reported in the United States in 2011. Cases in foreign-born persons made up 62% of the national case total; foreign-born Hispanics and Asians together represented 80% of TB cases in foreign-born persons and accounted for 50% of the national case total. The top five countries of origin for foreign-born persons with TB were Mexico, the Philippines, India, Vietnam, and China.

Among racial and ethnic groups, the largest percentage of total cases was in Asians (30%), followed by Hispanics (29%) and non-Hispanic blacks/African Americans.
However, blacks/African Americans represented 39% of TB cases in US-born persons.\textsuperscript{18}

There were 529 deaths from TB in 2009, the most recent year for which these data are available.

**International statistics**

Globally, more than 1 in 3 individuals is infected with TB.\textsuperscript{39} According to the WHO, there were 8.8 million incident cases of TB worldwide in 2010, with 1.1 million deaths from TB among HIV-negative persons and an additional 0.35 million deaths from HIV-associated TB. In 2009, almost 10 million children were orphaned as a result of parental deaths caused by TB.\textsuperscript{39}

Overall, the WHO noted the following:\textsuperscript{39}:

- The absolute number of TB cases has been falling since 2006 (rather than rising slowly, as indicated in previous global reports)
- TB incidence rates have been falling since 2002 (2 years earlier than previously suggested)
- Estimates of the number of deaths from TB each year have been revised downwards

The 5 countries with the highest number of incident cases in 2010 were India, China, South Africa, Indonesia, and Pakistan. India alone accounted for an estimated 26% of all TB cases worldwide, and China and India together accounted for 38%.\textsuperscript{39}

**Race-related demographics**

In 2011, only 16% of TB cases in the US occurred in non-Hispanic whites; 84% occurred in racial and ethnic minorities, as follows:\textsuperscript{18}:

- Hispanics - 29%
- Asians - 30%
- Non-Hispanic blacks/African Americans - 23%
- American Indians/native Alaskans - 1%
- Native Hawaiians/other Pacific Islanders – 1%

However, race is not clearly an independent risk factor, as foreign-born persons account for 77% of TB cases among Hispanics and 96% of TB cases among Asians, but only 29% of TB cases among blacks. This skewed distribution is most likely due to socioeconomic factors.

**Sex-related demographics**

Despite the fact that TB rates have declined in both sexes in the United States, certain differences exist. TB rates in women have declined with age, but in men, rates have increased with age. In addition, men are more likely than women to have a positive tuberculin skin test result. The reason for these differences may be social, rather than biologic, in nature.
The estimated sex prevalence for TB varies by source, from no sex prevalence to a male-to-female ratio in the United States of 2:1.

**Age-related demographics**

Higher rates of TB infection are seen in young, nonwhite adults (peak incidence, 25-40 y) than in white adults. In addition, white adults manifest the disease later (peak incidence, age 70 y) than do nonwhite persons.

In the United States, more than 60% of TB cases occur in persons aged 25-64 years; however, the age-specific risk is highest in persons older than 65 years. TB is uncommon in children aged 5-15 years.

**Prognosis**

Full resolution is generally expected with few complications in cases of non-MDR- and non-XDR-TB, when the drug regimen is completed. Among published studies involving DOT treatment of TB, the rate of recurrence ranges from 0-14%. In countries with low TB rates, recurrences usually occur within 12 months of treatment completion and are due to relapse. In countries with higher TB rates, most recurrences after appropriate treatment are probably due to reinfection rather than relapse.

Poor prognostic markers include extrapulmonary involvement, an immunocompromised state, older age, and a history of previous treatment. In a prospective study of 199 patients with TB in Malawi, 12 (6%) died. Risk factors for dying were reduced baseline TNF-α response to stimulation (with heat-killed *M. tuberculosis*), low body mass index, and elevated respiratory rate at TB diagnosis.

**Pediatric Tuberculosis**

- **Overview of Tuberculosis**
- **TB Risk Factors**
- **Mechanism of TB Infection**
- **TB Incidence and Prevalence**
- **ATS Staging Criteria of Pediatric TB**
- **Overview of Pediatric TB Evaluation**
- **Evaluation of Pediatric Pulmonary TB**
- **Evaluation of Pediatric Extrapulmonary TB**
- **Tuberculin Skin Test**
- **Specimen Collection for Analysis**
- **AFB Staining**
- **Mycobacterium Cultures**
Overview of Tuberculosis

Tuberculosis (TB) is the most common cause of infection-related death worldwide. In 1993, the World Health Organization (WHO) declared TB to be a global public health emergency.

Tubercle bacilli belong to the order Actinomycetales and family Mycobacteriaceae. *Mycobacterium tuberculosis* is the most common cause of this disease, and it is seen in the image below. Other rare causes include *M. bovis* and *M. africanum*.

The acid-fast characteristic of the mycobacteria is their unique feature. *M. tuberculosis* is an aerobic, non-spore-forming, nonmotile, slow-growing bacillus with a curved and beaded rod-shaped morphology. It is a very hardy bacillus that can survive under adverse environmental conditions. Humans are the only known reservoirs for *M. tuberculosis*. 
Acid-fast bacillus smear showing characteristic cording in Mycobacterium tuberculosis.

Most persons infected with *M tuberculosis* do not develop active disease. In healthy individuals, the lifetime risk of developing disease is 5-10%. In certain instances, such as extremes of age or defects in cell-mediated immune (CMI) response (e.g., human immunodeficiency virus [HIV] infection, malnutrition, administration of chemotherapy, prolonged steroid use), TB may develop. For patients with HIV infection, the risk of developing TB is 7-10% per year.

For patient education information, see eMedicineHealth's Infections Center. Also, see eMedicineHealth's patient education article Tuberculosis.

Go to Medscape Reference articles Tuberculosis, Miliary Tuberculosis, Primary Tuberculosis Imaging, Pediatric HIV Infection, and HIV Disease for more information on these topics.

**TB Risk Factors**

Risk factors for the acquisition of tuberculosis (TB) are usually exogenous to the patient. Thus, likelihood of being infected depends on the environment and the features of the index case. However, the development of TB disease depends on inherent immunologic status of the host.

Tuberculosis has been reported in patients treated for arthritis, inflammatory bowel disease, and other conditions with tumor necrosis factor (TNF)-alpha blockers/antagonists.

**Factors in acquiring TB infection**

The number of bacilli in the inoculum and the relative virulence of the organism are the major factors determining transmission of the disease. TB is transmitted by inhaling the tubercle bacilli.

The infectiousness of the source case is of vital importance in determining likelihood of transmission. Bacillary population of TB lesions varies and depends on the morphology of the lesion. Nodular lesions have 100-10,000 organisms, whereas cavitary lesions have 10 million to 1 billion bacilli. Thus, persons with cavitary lesions are highly infectious. Also, contacts of persons with sputum-positive smears have an
increased prevalence of infection as opposed to contacts of those with sputum-negative smears.

Persons who have received anti-TB drugs are much less infectious than those who have not received any treatment. This decline in infectiousness is due primarily to reduction in the bacillary population in the lungs.

Environmental factors also contribute to the likelihood of acquiring the infection. The concentration of bacilli depends on the ventilation of the surroundings and exposure to ultraviolet light. Thus, overcrowding, congregation in prison settings, poor housing, and inadequate ventilation predispose individuals to the development of TB.

**Factors in acquiring TB disease**

Defects in cell-mediated immunity (CMI) and level of immunocompetence are major determinants for development of disease. In fact, infection with human immunodeficiency virus (HIV) is one of the most significant risk factors for TB infection. Case rates for persons who are dually infected with HIV and *M. tuberculosis* exceed the lifetime risk of persons with TB infection who are not infected with HIV.

Steroid therapy, cancer chemotherapy, and hematologic malignancies increase the risk of TB. In addition, malnutrition interferes with the CMI response and therefore accounts for much of the increased frequency of TB in impoverished patients.

Non-TB infections, such as *measles*, *varicella*, and *pertussis*, may activate quiescent TB.

Individuals with certain human leukocyte antigen (HLA) types have a predisposition to TB. Hereditary factors, including the presence of a *Bcg* gene, have been implicated in susceptibility to acquisition of this disease.

**Mechanism of TB Infection**

Tuberculosis (TB) occurs when individuals inhale bacteria aerosolized by infected persons. The organism is slow growing and tolerates the intracellular environment, where it may remain metabolically inert for years before reactivation and disease. The main determinant of the pathogenicity of TB is its ability to escape host defense mechanisms, including macrophages and delayed hypersensitivity responses.

**Virulence factors and infective droplets**

Among the several virulence factors in the mycobacterial cell wall are the cord factor, lipoarabinomannan (LAM), and a highly immunogenic 65-kd *M. tuberculosis* heat shock protein. Cord factor is a surface glycolipid present only in virulent strains that causes *M. tuberculosis* to grow in serpentine cords in vitro. LAM is a heteropolysaccharide that inhibits macrophage activation by interferon (IFN)-
gamma and induces macrophages to secrete TNF-alpha, which causes fever, weight loss, and tissue damage.

The infective droplet nucleus is very small, measuring 5 µm or less, and may contain approximately 1-10 bacilli. Although a single organism may cause disease, 5-200 inhaled bacilli are usually necessary for infection. The small size of the droplets allows them to remain suspended in the air for a prolonged time period. Primary infection of the respiratory tract occurs as a result of inhalation of these aerosols. The risk of infection is increased in small enclosed areas and in areas with poor ventilation. Upon inhalation, the bacilli are deposited (usually in the midlung zone) into the distal respiratory bronchiole or alveoli, which are subpleural in location. Subsequently, the alveolar macrophages phagocytose the inhaled bacilli. However, these naïve macrophages are unable to kill the mycobacteria, and the bacilli continue to multiply unimpeded.

**Seeding**

Transportation of the infected macrophages to the regional lymph nodes then occurs. Lymphohematogenous dissemination of the mycobacteria travels to other lymph nodes, the kidney, epiphses of long bones, vertebral bodies, juxtaependymal meninges adjacent to the subarachnoid space, and, occasionally, to the apical posterior areas of the lungs. In addition, chemotactic factors released by the macrophages attract circulating monocytes to the site of infection, leading to differentiation of the monocytes into macrophages and ingestion of free bacilli. Logarithmic multiplication of the mycobacteria occurs within the macrophage at the primary site of infection.

**Immune response**

A cell-mediated immune (CMI) response terminates the unimpeded growth of the *M. tuberculosis* 2-3 weeks after initial infection. CD4 helper T cells activate the macrophages to kill the intracellular bacteria with resultant epithelioid granuloma formation. CD8 suppressor T cells lyse the macrophages infected with the mycobacteria, resulting in the formation of caseating granulomas. Mycobacteria cannot continue to grow in the acidic extracellular environment, so most infections are controlled.

TNF is a potent inflammatory cytokine that plays an important role in immune defense against *M. tuberculosis*. TNF-mediated innate immune responses, including phagolysosomal maturation and cell-mediated responses (eg, IFN-gamma secretion by memory T cells, complement-mediated lysis of *M. tuberculosis* –reactive CD8+ T cells) are important immune responses in *M. tuberculosis* infection.

Evidence of infection includes a positive tuberculin skin test (TST) result (see Tuberculin Skin Test) or a positive IFN-gamma release assay (IGRAs) finding. However, the initial pulmonary site of infection and its adjacent lymph nodes (ie, primary complex or Ghon focus) sometimes reach sufficient size to develop necrosis and subsequent radiographic calcification.
Disease progression

Progression of the primary complex may lead to enlargement of hilar and mediastinal nodes with resultant bronchial collapse. Progressive primary TB may develop when the primary focus cavitates and organisms spread through contiguous bronchi.

Lymphohematogenous dissemination, especially in young patients, may lead to miliary TB when caseous material reaches the bloodstream from a primary focus or a caseating metastatic focus in the wall of a pulmonary vein (Weigert focus). TB meningitis may also result from hematogenous dissemination. Bacilli may remain dormant in the apical posterior areas of the lung for several months or years, with later progression of disease resulting in the development of reactivation-type TB (ie, endogenous reinfection TB).

Go to Miliary Tuberculosis, and Tuberculous Meningitis for more information on these topics.

TB Incidence and Prevalence

Globally, the World Health Organization (WHO) reports more than 9 million new cases of tuberculosis (TB) occur each year, and an estimated, 19-43.5% of the world's population is infected with *M* tuberculosis. This disease occurs disproportionately among disadvantaged populations, such as homeless individuals, malnourished individuals, and those living in crowded areas. Most cases of TB occur in the South-East Asia (35%), African (30%), and Western Pacific (20%) regions.

In the United States, approximately 15 million people are infected with *M* tuberculosis. The number of US cases reported annually dropped 74% between 1953 and 1985 (84,304 to 22,201), but there was a subsequent resurgence, peaking at 26,673 cases in 1992. Unfortunately, although the incidence of TB increased by approximately 13% in all ages from 1985-1994, the rate among children younger than 15 years increased by 33%.

This resurgence was attributed to the human immunodeficiency virus (HIV) epidemic, which increased the risk of developing active TB among persons infected with HIV and those latent TB infection. Other contributory factors included emigration from developing countries and transmission in settings such as endemic hospitals and prisons. In addition, the development of multidrug-resistant (MDR) organisms and deterioration of the public health infrastructure for TB services further contributed to the rise in the number of cases.

Go to Tuberculosis, HIV Infection, and HIV Disease for more information on these topics.

Factors contributing to decline in US cases

Since 1992, the US case numbers of TB has declined. Increased awareness of the disease, the institution of more aggressive preventive measures, improvement in
healthcare strategies (eg, prompt identification and treatment of patients with TB), and highly active antiretroviral therapy (HAART) for individuals with HIV infection have contributed to this decline. However, a huge reservoir of individuals who are infected with \textit{M tuberculosis} remains.

According to the Centers for Disease Control and Prevention (CDC), a total of 12,898 new cases of TB were reported in the United States in 2008, representing a rate of 4.2 cases per 100,000 population. This was the lowest rate recorded since national reporting began in 1953. However, the rate of the decline has slowed since 2000, influenced by the rate of TB of foreign origin, which increased 5% from 1993-2004, whereas the rate of affected US-born individuals declined 62% over the same period.

\textbf{ATS Staging Criteria of Pediatric TB}

Although the natural history of tuberculosis (TB) in children follows a continuum, the American Thoracic Society (ATS) definition of stages is useful.\cite{6,7,8,9,10}

\textbf{Stage 1}

Exposure has occurred, implying that the child has had recent contact with an adult who has contagious TB. The child has no physical signs or symptoms and has a negative tuberculin skin test (TST) result (see Tuberculin Skin Test). Chest radiography does not reveal any changes at this stage.

Not all patients who are exposed become infected, and the TST result may not be positive for 3 months. Unfortunately, children younger than 5 years may develop disseminated TB in the form of miliary disease or TB meningitis before the TST result becomes positive. Thus, a very high index of suspicion is required when a young patient has a history of contact.

Go to \textit{Miliary Tuberculosis}, and \textit{Tuberculous Meningitis} for more information on these topics.

\textbf{Stage 2}

This second stage is heralded by a positive TST result. No signs and symptoms occur, although an incidental chest radiograph may reveal the primary complex.

\textbf{Stage 3}

In stage 3, TB disease occurs and is characterized by the appearance of signs and symptoms depending on the location of the disease. Radiographic abnormalities may also be seen.

\textbf{Stage 4}

Stage 4 is defined as TB with no current disease. This implies that the patient has a history of previous episodes of TB or abnormal, stable radiographic findings with a
significant reaction to the TST and negative bacteriologic studies. No clinical findings suggesting current disease are present.

**Stage 5**

TB is suspected, and the diagnosis is pending.

**Overview of Pediatric TB Evaluation**

Any patient with pneumonia, pleural effusion, or a cavitary or mass lesion in the lung that does not improve with standard antibacterial therapy should be evaluated for tuberculosis (TB). Also, patients with fever of unknown origin, failure to thrive, significant weight loss, or unexplained lymphadenopathy should be evaluated for TB.

**Congenital TB**

Congenital disease is rare. Symptoms typically develop during the second or third week of life and include poor feeding, poor weight gain, cough, lethargy, and irritability. Other symptoms include fever, ear discharge, and skin lesions.

Signs of congenital TB include failure to thrive, icterus, hepatosplenomegaly, tachypnea, and lymphadenopathy.

**Asymptomatic infection**

Patients with asymptomatic infection have a positive tuberculin skin test (TST) result, but they do not have any clinical or radiographic manifestations. Children with asymptomatic infection may be identified on a routine well-child physical examination, or they may be identified subsequent to TB diagnosis in household or other contacts (eg, children who recently have immigrated, adopted children).

Primary TB is characterized by the absence of any signs on clinical evaluation. As discussed above, these patients are identified by a positive TST result. Tuberculin hypersensitivity may be associated with erythema nodosum and phlyctenular conjunctivitis.

**Evaluation of Pediatric Pulmonary TB**

Pulmonary tuberculosis (TB) may manifest itself in several forms, including endobronchial TB with focal lymphadenopathy, progressive pulmonary disease, pleural involvement, and reactivated pulmonary disease. Symptoms of primary pulmonary disease in the pediatric population are often meager. Fever, night sweats, anorexia, nonproductive cough, failure to thrive, and difficulty gaining weight may occur. Signs of disease depend on the site involved (pulmonary or extrapulmonary).

**Endobronchial TB with lymphadenopathy**

Endobronchial disease with enlargement of lymph nodes is the most common variety of pulmonary TB. Symptoms are the result of impingement on various
structures by the enlarged lymph nodes. Enlargement of lymph nodes and persistent cough may result in signs suggestive of bronchial obstruction or hemidiaphragmatic paralysis, whereas difficulty swallowing may result from esophageal compression. Vocal cord paralysis may be suggested by hoarseness or difficulty breathing and may occur as a result of local nerve compression. Dysphagia due to esophageal compression may also be observed.

**TB pleural effusion**

Pleural effusions due to TB usually occur in older children and are rarely associated with miliary disease. The typical history reveals an acute onset of fever, chest pain that increases in intensity on deep inspiration, and shortness of breath. Fever usually persists for 14-21 days.

Signs include tachypnea, respiratory distress, dullness to percussion, decreased breath sounds, and, occasionally, features of mediastinal shift.

**Progressive primary TB**

Progression of the pulmonary parenchymal component leads to enlargement of the caseous area and may lead to pneumonia, atelectasis, and air trapping. This is more likely to occur in young children than in adolescents. The child usually appears ill with symptoms of fever, cough, malaise, and weight loss.

This condition presents with classic signs of pneumonia, including tachypnea, nasal flaring, grunting, dullness to percussion, egophony, decreased breath sounds, and crackles.

**Reactivation TB**

Reactivation of TB disease usually has a subacute presentation with weight loss, fever, cough, and, rarely, hemoptysis. This condition typically occurs in older children and adolescent and is more common in patients who acquire TB at age 7 years and older.

Physical examination results may be normal or may reveal posttussive crackles.

**Evaluation of Pediatric Extrapulmonary TB**

Extrapulmonary tuberculosis (TB) includes peripheral lymphadenopathy, TB meningitis, miliary TB, skeletal TB, and other organ involvement. Other unusual sites for TB include the middle ear, gastrointestinal (GI) tract, skin, kidneys, and ocular structures.

Go to Scrofula, Tuberculosis of the Genitourinary System, Miliary Tuberculosis, and Tuberculous Meningitis for more information on these topics.

**Lymphadenopathy**
Patients with lymphadenopathy (ie, scrofula) may have a history of enlarged nodes. Fever, weight loss, fatigue, and malaise are usually absent or minimal. Lymph node involvement typically occurs 6-9 months following initial infection by the tubercle bacilli. More superficial lymph nodes commonly are involved. Frequent sites of involvement include the anterior cervical, submandibular, and supraclavicular nodes. TB of the skeletal system may lead to involvement of the inguinal, epitrochlear, or axillary lymph nodes.

Typically, infected lymph nodes are firm and nontender with nonerythematous overlying skin. The nodes are initially nonfluctuant. Suppuration and spontaneous drainage of the lymph nodes may occur with caseation and the development of necrosis.

**TB meningitis**

One of the most severe complications of TB is TB meningitis, which develops in 5-10% of children younger than 2 years; thereafter, the frequency drops to less than 1%. A very high index of suspicion is required to make a timely diagnosis because of the insidious onset of the disease.

A subacute presentation usually occurs within 3-6 months after the initial infection. Nonspecific symptoms such as anorexia, weight loss, and fever may be present. After 1-2 weeks, patients may experience vomiting and seizures or alteration in the sensorium. Deterioration of mental status, coma, and death may occur despite prompt diagnosis and early intervention.

Three stages of TB meningitis have been identified. Stage 1 is defined by the absence of focal or generalized neurologic signs. Possibly, only nonspecific behavioral abnormalities are found.

Stage 2 is characterized by the presence of nuchal rigidity, altered deep tendon reflexes, lethargy, and/or cranial nerve palsies. TB meningitis most often affects the sixth cranial nerve due to the pressure of the thick basilar inflammatory exudates on the cranial nerves or to hydrocephalus; this results in lateral rectus palsy. The third, fourth, and seventh cranial nerves may also be affected. Funduscopic changes may include papilledema and the presence of choroid tubercles, which should be carefully sought.

Stage 3, the final stage, comprises major neurologic defects, including coma, seizures, and abnormal movements (eg, choreoathetosis, paresis, paralysis of one or more extremities). In the terminal phase, decerebrate or decorticate posturing, opisthotonus, and/or death may occur. Patients with tuberculomas or TB brain abscesses may present with focal neurologic signs. Spinal cord disease may result in the acute development of spinal block or a transverse myelitis–like syndrome. A slowly ascending paralysis may develop over several months to years.

**Miliary TB**
This is a complication of primary TB in young children. Miliary TB may manifest subacutely with low-grade fever, malaise, weight loss, and fatigue. A rapid onset of fever and associated symptoms may also be observed. History of cough and respiratory distress may be obtained.

Physical examination findings include lymphadenopathy, hepatosplenomegaly, and systemic signs including fever. Respiratory signs may evolve to include tachypnea, cyanosis, and respiratory distress. Other signs, which are subtle and should be carefully sought in the physical examination, include papular, necrotic, or purpuric lesions on the skin or choroidal tubercles in the retina.

**Bone or joint TB**

Skeletal TB may present acutely or subacutely. Vertebral disease may go unrecognized for months to years because of its indolent nature. Common sites involved include the large weightbearing bones or joints, including the vertebrae (50%), hip (15%), and knee (15%).

Destruction of the bones with deformity is a late sign of TB. Manifestations may include angulation of the spine (gibbus deformity) and/or Pott disease (severe kyphosis with destruction of the vertebral bodies). Cervical spine involvement may result in atlantoaxial subluxation, which may lead to paraplegia or quadriplegia.

**Diagnostic Overview**

Making the diagnosis of tuberculosis (TB) in children is extremely challenging because of the difficulty in isolating *M tuberculosis*. Definitive TB diagnosis depends on isolation of the organism from secretions or biopsy specimens. Despite innovations in rapid diagnosis, many of the classic diagnostic tools remain useful and continue to be used in the evaluation of patients with TB.

To make a diagnosis of congenital TB, the infant should have proven TB lesions and at least one of the following:

- Skin lesions during the first week of life, including papular lesions or petechiae
- Documentation of TB infection of the placenta or the maternal genital tract
- Presence of a primary complex in the liver
- Exclusion of the possibility of postnatal transmission

**Differentials**

The following conditions should also be considered in cases of suspected TB:

- Actinomycosis
- Aspergillosis
- Bronchiectasis
- Bronchopulmonary Dysplasia
- Brucellosis
- Chronic Granulomatous Disease
Tuberculin Skin Test

The tuberculin skin test (TST) is a widely used diagnostic test for evaluation of patients who have symptoms of tuberculosis (TB) or in whom infection with *M. tuberculosis* is suspected. The sensitivity and the specificity of the TST is approximately 90%. Interferon gamma release assays (IGRA) are now replacing the TST as the preferred test for screening and testing for tuberculosis.

**AAP guidelines for pediatric testing**

According to the American Academy of Pediatrics (AAP), immediate skin testing is indicated for the following children:

- Those who have been in contact with persons with active or suspected TB
- Immigrants from TB-endemic countries (eg, Asia, Middle East, Africa, Latin America) or children with travel histories to these countries
- Those who have radiographic or clinical findings suggestive of TB

An annual TST is indicated for the following children:

- Children who are infected with human immunodeficiency virus (HIV) or those living in a household with persons infected with HIV
- Incarcerated adolescents

Testing at 2-year to 3-year intervals is indicated if the child has been exposed to high-risk individuals including those who are homeless, institutionalized adults who are infected with HIV, users of illicit drugs, residents of nursing homes, and incarcerated adolescents or adults.

Testing when children are aged 4-6 years and 11-16 years is indicated for the following children:

- Children without risk factors residing in high-prevalence areas
- Children whose parents emigrated from regions of the world with a high prevalence of TB or who have continued potential exposure by travel to the endemic areas and/or household contact

Performing an initial TST before the initiation of immunosuppressive therapy is recommended in any patient.
Administration of TST

The recommended TST is the Mantoux test. The dosage of 0.1 mL or 5 tuberculin units [TU] of purified protein derivative (PPD) should be injected intradermally into the volar aspect of the forearm using a 27-gauge needle. A detergent called Tween 80 to prevent loss of efficacy on contact and adsorption by glass stabilizes the PPD. A wheal should be raised and should measure approximately 6-10 mm in diameter.

Skilled personnel should always read the test 48-72 hours after administration. Measure the amount of induration and not erythema. This should be measured transverse to the long axis of the forearm.

Multiple puncture tests (eg, tine test, Heaf test) lack sensitivity and specificity and hence are not recommended.

Interpretation of TST results

The Centers for Disease Control and Prevention (CDC) and the AAP provided recommendations regarding the size of the induration created by the TST that is considered a positive result and indicative of disease. The TST is interpreted on the basis of 3 "cut points": 5 mm, 10 mm, and 15 mm.

Induration of 5 mm or more is considered a positive TST result in the following children:

- Children having close contact with known or suspected contagious cases of the disease, including those with household contacts with active TB whose treatment cannot be verified before exposure
- Children with immunosuppressive conditions (eg, HIV) or children who are on immunosuppressive medications
- Children who have an abnormal chest radiograph finding consistent with active TB, previously active TB, or clinical evidence of the disease

Induration of 10 mm or more is considered a positive TST result in the following children:

- Children who are at a higher risk of dissemination of TB disease, including those younger than 5 years or those who are immunosuppressed because of conditions such as lymphoma, Hodgkin disease, diabetes mellitus, and malnutrition
- Children with increased exposure to the disease, including those who are exposed to adults in high-risk categories (eg, homeless, HIV infected, users of illicit drugs, residents of nursing homes, incarcerated or institutionalized persons); those who were born in or whose parents were born in high-prevalence areas of the world; and those with travel histories to high-prevalence areas of the world

Induration of 15 mm or more is considered a positive TST result in children aged 5 years or older without any risk factors for the disease.

False-positive and false-negative results
False-positive reactions and false-negative results can have various causes. False-positive reactions are often attributed to asymptomatic infection by environmental non-TB mycobacteria (due to cross-reactivity).

False-negative results may be due to vaccination with live-attenuated virus, anergy, immunosuppression, immune deficiency, or malnutrition. Other factors that may cause a false-negative result include improper administration (eg, subcutaneous injection, injection of too little antigen), improper storage, and contamination. PPD has been recognized to have an initial false-negative rate of 29%.

**Previous BCG vaccination**

Some important points regarding administering the TST to previous recipients of the bacille Calmette-Guérin (BCG) are briefly discussed.

Immunization with BCG is not a contraindication to the TST. BCG vaccination is used in many parts of the world, especially in developing countries.

Differentiating tuberculin reactions caused by vaccination with BCG versus reactions caused by infection with *M tuberculosis* is difficult. History of contact with a person with contagious TB or emigration from a country with a high prevalence of TB suggests that the positive results are due to infection with *M tuberculosis*. However, multiple BCG vaccinations may increase the likelihood that the positive TST result is due to the BCG vaccination. The positive reactivity caused by BCG vaccination generally wanes with the passage of time. With the administration of TST, this positive tuberculin reactivity may be boosted.

A previous BCG vaccination does not affect interpretation of a TST result for a person who is symptomatic or in whom TB is strongly suspected.

**Specimen Collection for Analysis**

The initial step in detection and isolation of the mycobacterium is to obtain appropriate specimens for bacteriologic examination. Examination of sputum, gastric lavage, bronchoalveolar lavage, lung tissue, lymph node tissue, bone marrow, blood, liver, cerebrospinal fluid (CSF), urine, and stool may be useful, depending on the location of the disease.

Decontamination of other microorganisms in the specimens obtained may be performed by the addition of sodium hydroxide, usually in combination with *N*-acetyl-L-cysteine. Other body fluids (eg, CSF, pleural fluid, peritoneal fluid) can also be centrifuged; the sediment can be stained and evaluated for presence of acid-fast bacilli (AFB). CSF smear results are positive in fewer than 10% of patients in some series. Enhancement of the yield may be possible by staining any clot that may have formed in standing CSF specimens, as well as using the sediment of a centrifuged specimen. Increased yield may also be obtained from cisternal or ventricular fluid.

**Sputum specimens**
Sputum specimens may be used in older children, but not in very young children (<6 y), who usually do not have a cough deep enough to produce sputum for analysis. In those younger than 6 years, gastric aspirates are used.

Nasopharyngeal secretions and saliva are not acceptable. In older children, bronchial secretions may be obtained by the stimulation of cough by an aerosol solution of propylene glycol in 10% sodium chloride (see Bronchial secretions).

**Gastric aspirates**

Gastric aspirates are used in lieu of sputum in children younger than 6 years.

Using the correct technique for obtaining the gastric lavage is important because of the scarcity of the organisms in children compared with adults. An early morning sample should be obtained before the child has had a chance to eat or ambulate, because these activities dilute the bronchial secretions accumulated during the night.

Initially, the stomach contents should be aspirated, and then a small amount of sterile water is injected through the orogastric tube. This aspirate should also be added to the specimen.

Because gastric acidity is poorly tolerated by the tubercle bacilli, neutralization of the specimen should be performed immediately with 10% sodium carbonate or 40% anhydrous sodium phosphate. Even with careful attention to detail and meticulous technique, the tubercle bacilli can be detected in only 70% of infants and in 30-40% of children with disease.

**Bronchial secretions**

Bronchoalveolar lavage may be used in older children (6 y or older). Bronchial secretions may be obtained by the stimulation of cough by an aerosol solution of propylene glycol in 10% sodium chloride. This technique may also be used to provide bronchial secretions for detection of tubercle bacilli.

**Urine specimens**

Obtain overnight urine specimens in the early morning. Send immediately for analysis, because the tubercle bacilli poorly tolerate the acidic pH of urine.

**AFB Staining**

Because *M tuberculosis* is an acid-fast bacilli (AFB), AFB staining provides preliminary confirmation of the diagnosis. Conventional methods include the Ziehl-Neelsen staining method. The Kinyoun stain is modified to make heating unnecessary. Fluorochrome stains, such as auramine and rhodamine, are variations of the traditional stains. The major advantage of these methods is that slides can be screened faster, because the acid-fast material stands out against the dark, nonfluorescent background. However, fluorochrome-positive smears must be confirmed by Ziehl-Neelsen staining.
Staining can also give a quantitative assessment of the number of bacilli being excreted (eg, 1+, 2+, 3+). This can be of clinical and epidemiologic importance in estimating the infectiousness of the patient and in determining the discontinuation of respiratory isolation. However, for reliably producing a positive result, smears require approximately 10,000 organisms/mL. Therefore, in early stages of the disease or in children in whom the bacilli in the respiratory secretions are sparse, the results may be negative. A single organism on a slide is highly suggestive and warrants further investigation.

A significant drawback of AFB smears is that they cannot be used to differentiate *M. tuberculosis* from other acid-fast organisms such as other mycobacterial organisms or *Nocardia* species.

**Mycobacterium Cultures**

Culture of mycobacterium is the definitive method to detect bacilli. It is also more sensitive than examination of the smear. Approximately 10 acid-fast bacilli (AFB) per millimeter of a digested concentrated specimen are sufficient to detect the organisms by culture.

Another advantage of culture is that it allows specific species identification and testing for recognition of drug susceptibility patterns. However, because *M. tuberculosis* is a slow-growing organism, a period of 6-8 weeks is required for colonies to appear on conventional culture media.

**Conventional growth techniques**

Conventional solid media include the Löwenstein-Jensen medium, which is an egg-based medium, and the Middlebrook 7H10 and the 7H11 media, which are agar-based media. Liquid media (eg, Dubos oleic-albumin media) are also available, and they require incubation in 5-10% carbon dioxide for 3-8 weeks. These media usually have antibacterial antibiotics, which are slightly inhibitory for tubercle bacilli.

**Rapid growth techniques**

Because mycobacteria require 6-8 weeks for isolation from conventional media, automated radiometric culture methods (eg, BACTEC) are increasingly used for the rapid growth of mycobacteria. The methodology uses a liquid Middlebrook 7H12 medium that contains radiometric palmitic acid labeled with radioactive carbon-14 (\(^{14}\)C). Several antimicrobial agents are added to this medium to prevent the growth of nonmycobacterial contaminants. Production of \(^{14}\)CO\(_2\) by the metabolizing organisms provides a growth index for the mycobacteria. Growth is generally detected within 9-16 days.

Another rapid method for isolation of mycobacteria is SEPTICHEK. This nonradiometric approach has a biphasic broth-based system that decreases the mean recovery time versus conventional methods.
Mycobacterial growth indicator tubes (MGITs), which presently are used as a research tool, have round-bottom tubes with oxygen-sensitive sensors at the bottom. MGITs indicate microbial growth and provide a quantitative index of *M tuberculosis* growth.

**Species Identification**

*M tuberculosis* can be reliably differentiated from other species on the basis of culture characteristics, growth parameters, and other empiric tests. *M tuberculosis* produces heat-sensitive catalase, reduces nitrates, produces niacin, and grows slowly. Serpentine cording is demonstrated on smears prepared from the BACTEC system.

Addition of *p*-nitro-acetyl-amino-hydroxy-propiophenone (NAP) inhibits the growth of *M tuberculosis* complex (including *M bovis* and *M africanum*) but does not inhibit growth of other mycobacteria. This provides the basis for the NAP differentiation test.

Chromatographic analysis of mycobacterial cell wall lipids can provide further speciation. The most useful approaches include gas-liquid chromatography and high-performance liquid chromatography (HPLC). The unique mycolic acid pattern associated with the species can be detected by the chromatographic separation of the ester.

A significant drawback of these chromatographic methods is the requirement of bacterial colonies grown in conventional solid media, a process that takes at least 3 weeks. However, the recent combination of HPLC with fluorescence detection has made the method more sensitive; thus, BACTEC broth culture can be used instead of conventional solid media. This may make the method comparable to the NAP and AccuProbe tests (see Nucleic Acid Probes). The expense of the initial equipment limits the availability of HPLC.

**Nucleic Acid Probes**

Because biochemical methods are time-consuming and laborious, nucleic acid hybridization using molecular probes has become widely accepted. The basic principle is the use of a chemiluminescent, ester-labeled, single-strand DNA probe. A luminometer is used to assess the chemiluminescence.

Commercially available probes, including the AccuProbe technology, help advance identification of the *M tuberculosis* complex. Sensitivity and specificity approach 100% when at least 100,000 organisms are present.

Positive test results should be reported as *M tuberculosis* complex, because the probe does not reliably differentiate between *M tuberculosis* and other members of the complex (eg, *M bovis*). In addition, final identification to species level is required, because pyrazinamide should not be included in the treatment regimen if the isolate is *M bovis*. 
Niacin production, nitrate reduction, pyrazinamidase, and susceptibility to thiophene-2-carboxylic acid hydrazide can help differentiate between *M. bovis* and *M. tuberculosis*.

**Nucleic Acid Amplification Tests**

Nucleic acid amplification techniques (eg, polymerase chain reaction [PCR]) allows the direct identification of *M. tuberculosis* in clinical specimens, unlike the nucleic acid probes, which require substantial time for bacterial accumulation in broth culture.

The US Food and Drug Administration (FDA) has approved at least 2 tests, the amplified *M. tuberculosis* direct test and the AMPLICOR *M. tuberculosis* test. The amplified *M. tuberculosis* direct test is an isothermal transcription-mediated amplification that targets RNA. The AMPLICOR test targets the DNA. The most commonly used target sequence for the detection of *M. tuberculosis* has been the insertion sequence IS6110.

Although amplification techniques are promising tools for the rapid diagnosis of tuberculosis (TB), several caveats remain. Contamination of samples by products of previous amplification and the presence of inhibitors in the sample may lead to false-positive or false-negative results.

Although the sensitivity and specificity of the nucleic acid techniques in smear-positive cases exceed 95%, the sensitivity of smear-negative cases varies from 40% to 70%. Thus, discordance between the acid-fast smear result and the nucleic acid amplification techniques requires careful clinical appraisal and judgment.

**Immunoassays**

IFN-gamma plays a critical role in regulating cell-mediated immune responses to *M. tuberculosis* infection. This resulted in the development of IGRAs to aid clinicians in diagnosing *M. tuberculosis* infection (latent infection and active infection).

IGRAs detect sensitization to *M. tuberculosis* by measuring IFN-gamma release in response to antigens that represent *M. tuberculosis*. Available assays include the QuantiFERON-TB test (QFT), the QuantiFERON-TB Gold test (QFT-G), the QuantiFERON-TB Gold In-Tube test (QFT-GIT), and the T-SPOT.TB test (T-Spot).

The use of IGRAs in children is subject to the following limitations:

- Studies evaluating IGRAs performance in children are scant.
- Indeterminate results for children are a potential limitation to implementing IGRAs into clinical practice. The frequencies of indeterminate IGRA results in children vary (range, 0–17%) and most are attributable to a low mitogen response as a result of a lack of immunologic maturity. A study of 761 children by Critselis et al confirmed that indeterminate results from the QFT-IT assay occur more frequently among younger children.13
Difficulties in collecting blood for these tests and the need for a relatively large volume of blood from small children (especially for infants) are also limitations. Because of the above limitations, a TST is preferred for testing children younger than 5 years. Regardless, sensitivity of IGRAs in children is expected to be comparable to TST. Specificity of IGRAs in children is expected to be high. However, additional studies are needed to evaluate the performance of IGRAs in children.

Situations in which an IGRA is preferred but a TST is acceptable include the following:

- Testing patients who have low rates of returning for TST
- Testing persons who have received BCG as a vaccine or for cancer therapy to increase diagnostic specificity and improve acceptance of treatment for latent infection

M tuberculosis Drug Susceptibility

Because of the emergence of multidrug-resistant (MDR) organisms, determination of the drug susceptibility panel of an isolate is important so that appropriate treatment can be ensured.

Numerous chromosomal mutations are associated with drug resistance. Genotypic methods now being evaluated to identify these mutations include DNA sequencing, solid phase hybridization, and polymerase chain reaction (PCR)-single-strand combination polymorphism analysis.

Mutations of the catalase peroxidase gene katG, the inhA gene involved in fatty acid biosynthesis, the ahpc gene, and the oxyR gene have been identified as major determinants for isoniazid (INH) resistance.

Resistance to rifampin is determined by mutations in the rpoB gene encoding the beta subunit of the RNA polymerase.

Phenotypic susceptibility assays, which are still under investigation, use mycobacteriophages to type the mycobacteria grown in the presence of antituberculous agents.

Rapid molecular detection of TB and drug resistance using an automated molecular test for *M tuberculosis* and resistance to rifampin (Xpert MTB/RIF), by PCR assay to amplify an *M tuberculosis*--specific sequence within the rifampin resistance--determining region has been studied in countries with a high TB burden. Overall, the findings suggest use of MTB/RIF test in low-resource countries may be feasible to allow to early diagnosis and treatment. This test can be performed using nasopharyngeal specimens in settings where induced sputum and culture are not practical.\[14\]

Serology
*M. tuberculosis* increases the levels of antibody titers in the serum. However, there is no available serodiagnostic test for tuberculosis (TB) that has an adequate sensitivity and specificity for routine use in diagnosing TB in children.

**Management Overview**

The American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC) have provided standard guidelines for the treatment of tuberculosis (TB). The ultimate goal of treatment is to achieve sterilization of the TB lesion in the shortest possible time. The general rule is strict adherence to TB treatment regimens for a sufficient time period. To prevent the emergence of resistance, the regimens for the treatment of TB always should consist of multiple drugs.

**Pharmacotherapy considerations**

Anti-TB medications kill mycobacteria, thereby preventing further complications of early primary disease and progression of disease. However, disappearance of caseous or granulomatous lesions does not occur even with therapy. These drugs are classified as first-line and second-line drugs. First-line drugs have less toxicity with greater efficacy than second-line drugs. All first-line agents are bactericidal with the exception of ethambutol.

First-line agents include rifampin, isoniazid (INH), pyrazinamide, ethambutol, and streptomycin. Second-line agents are capreomycin, ciprofloxacin, cycloserine, ethionamide, kanamycin, ofloxacin, levofloxacin, and para-aminosalicylic acid.

INH and rifampin are effective against bacilli in necrotic foci and intracellular populations of mycobacteria. Streptomycin, aminoglycosides, and capreomycin have poor intracellular penetration. Multidrug-resistant (MDR) TB is defined as resistance to at least INH and rifampin (see Multidrug-Resistant TB). The emergence of drug-resistant strains has necessitated the use of second-line agents.

Naturally drug-resistant organisms occur with a frequency of approximately $10^{-6}$; however, individual resistances may vary. The resistance to streptomycin is $10^{-5}$, to INH is $10^{-6}$, and to rifampin is $10^{-8}$. The chance that an organism is naturally resistant to both INH and rifampin is on the order of $10^{-14}$. Because populations of this size do not occur in patients, organisms naturally resistant to 2 drugs are essentially nonexistent. If only a single medication is administered to a patient with TB, the subpopulations susceptible to that medication are destroyed, but the other categories continue to multiply. Thus, the use of multiple agents in the treatment of TB is essential.

**Adverse drug effects**

Adverse effects of isoniazid (INH) (eg, hepatitis) are rare in children; therefore, routine determination of serum aminotransferase levels is not necessary. Consider
monthly monitoring of hepatic function tests in the following patients: (1) those with severe or disseminated TB; (2) those with concurrent or recent hepatic disease; (3) those receiving high daily doses of INH (10 mg/kg/d) in combination with rifampin, pyrazinamide, or both; (4) women who are pregnant or within the first 6 weeks postpartum; (5) those with clinical evidence of hepatotoxic effects; and (6) those with hepatobiliary tract disease from other causes.

Bed rest

The advisability of bed rest varies with the type and severity of the disease. No limitation of activity is required in patients with TB infection or asymptomatic primary pulmonary TB. Severely ill patients with miliary TB, TB meningitis, or disseminated TB may require complete bed rest; these individuals may also need transfer to the intensive care unit until their condition is stabilized.

Consultations

An infectious diseases consultation may be helpful in managing affected patients.

Treatment of Pulmonary TB

Recommendations for the treatment of pulmonary tuberculosis (TB) include a 6-month course of isoniazid (INH) and rifampin, supplemented during the first 2 months with pyrazinamide. Ethambutol (or streptomycin in children too young to be monitored for visual acuity) may need to be included in the initial regimen until the results of drug susceptibility studies are available.

Drug susceptibility studies may not be required if the risk of drug resistance is not significant. Significant risk factors include residence in a community with greater than 4% primary resistance to INH, history of previous treatment with anti-TB drugs, history of exposure to a drug-resistant case, and origin in a country with a high prevalence of drug resistance. The purpose of this recommendation is to decrease the development of multidrug-resistant (MDR) TB in areas in which primary INH resistance is increased.

Another treatment option is a 2-month regimen of INH, rifampin, and pyrazinamide daily, followed by 4 months of INH and rifampin twice a week. Effective treatment of hilar adenopathy when the organisms are fully susceptible is a 9-month regimen of INH and rifampin daily or a 1-month regimen of INH and rifampin once a day, followed by 8 months of INH and rifampin twice a week.

Because poor adherence to these regimens is a common cause of treatment failure, directly observed therapy (DOT) is recommended for treatment of TB. DOT means a healthcare provider or other responsible person must watch the patient ingest the medications. Intermittent regimens should be monitored by DOT for the duration of therapy, because poor compliance may result in inadequate drug delivery.

Another initiative recently launched by the World Health Organization (WHO) is the DOTS-plus strategy, which is based on finding appropriate treatment strategies for
MDR TB and drug susceptibility testing, as well as judicious usage of second-line drugs. This initiative also focuses on community involvement and a good recording and reporting system.

Treating Extrapulmonary TB

Most cases of extrapulmonary tuberculosis (TB), including cervical lymphadenopathy, can be treated with the same regimens used to treat pulmonary TB. Exceptions include bone and joint disease, miliary disease, and meningitis. For these severe forms of drug-susceptible disease, the recommendation is a regimen of 2 months of isoniazid (INH), rifampin, pyrazinamide, and streptomycin once a day, followed by 7-10 months of INH and rifampin once a day.

Another recommended regimen is 2 months of INH, rifampin, pyrazinamide, and streptomycin, followed by 7-10 months of INH and rifampin twice a week. Streptomycin may be administered with initial therapy until drug susceptibility is known. Consider administering capreomycin or kanamycin instead of streptomycin in patients who may have acquired TB in areas in which resistance to streptomycin is common.

Managing TB With HIV Coinfection

Optimal therapy for tuberculosis (TB) in children with human immunodeficiency virus (HIV) infection has not been established. According to the guidelines provided by the Centers for Disease Control and Prevention (CDC), effective treatment of TB for patients infected with HIV should include directly observed therapy (DOT) and consultation with a specialist.

A regimen that uses rifabutin instead of rifampin has been advised when simultaneously treating HIV disease and TB. This situation may occur (1) when antiretroviral treatment is recommended for a newly diagnosed HIV infection in a patient with active TB or (2) when a patient with active TB has established HIV infection and continuation of antiretroviral therapy is recommended. This recommendation is based on the fact that the use of rifampin with protease inhibitors or nonnucleoside reverse transcriptase inhibitors is contraindicated.

The treatment regimen for TB should initially include at least 3 drugs and should be continued for at least 9 months. Isoniazid (INH), rifampin, and pyrazinamide with or without ethambutol or streptomycin should be administered for the first 2 months. Treatment of disseminated disease or drug-resistant TB may require the addition of a fourth drug (see Multidrug-Resistant TB).

Multidrug-Resistant TB

Infection caused by multidrug resistant (MDR) organisms, defined as organisms resistant to at least isoniazid (INH) and rifampin, has reached critical levels worldwide. The median prevalence of resistance to any of the 4 antituberculosis (TB) drugs in an update by the World Health Organization (WHO) and the
International Union Against Tuberculosis and Lung Disease (IUATLD) was reported to be 10.2% (range 0-57.1%). \[16, 17\]

The diarylquinoline antimycobacterial, bedaquiline (Sirturo), was approved by the FDA in December 2012 as part of a 22-week multidrug regimen for pulmonary MDR-TB. Approval was based on phase 2 data that showed bedaquiline significantly improved time to sputum culture conversion and included 2 consecutive negative sputum cultures collected at least 25 days apart during treatment. At week 24, sputum culture conversion was observed in 77.6% of patients in the bedaquiline treatment group compared with 57.6% of patients in the placebo treatment group. \[18, 19\]

In another phase 2 study, researchers found bedaquiline (TMC207) added to standard therapy for MDR-TB reduced the time to conversion to a negative sputum culture compared with placebo and increased the proportion of patients with conversion of sputum culture (48% vs 9%). \[20\]

Provisional guidelines from the Centers for Disease Control and Prevention (CDC) include use of bedaquiline for FDA-approved and off-label uses. In addition to the approved indication as part of at least a 4-drug regimen for treatment of MDR-TB, the guidelines include use on a case-by-case basis for children, HIV-infected persons, pregnant women, persons with extrapulmonary MDR-TB, and patients with comorbid conditions on concomitant medications when an effective treatment regimen cannot otherwise be provided. \[21\]

**Categories of TB drug resistance**

Primary and secondary resistance are 2 categories of drug resistance recognized. Primary resistance is defined as the occurrence of resistance to anti-TB treatment in an individual who has no history of previous treatment. Secondary resistance involves the emergence of resistance during the course of ineffectual anti-TB therapy.

In 2006, the WHO Global Task Force defined another category of MDR TB termed extensively drug-resistant (XDR) TB. \[22\]. This is defined as resistance to first-line drugs, including resistance to at least rifampicin and isoniazid (INH), in addition to resistance to any fluoroquinolone and at least one of following second-line anti-TB drugs: capreomycin, kanamicin, and amikacin. This usually occurs as a result of mismanagement of MDR TB.

**Risk factors for TB drug resistance**

Risk factors for the development of primary drug resistance include patient contact with drug-resistant contagious TB, residence in areas with a high prevalence of drug-resistant *M. tuberculosis*, birth outside the United States, ethnicity other than non-Hispanic white, young age, human immunodeficiency virus (HIV) infection, and the use of intravenous drugs. Secondary drug resistance reflects patient
nonadherence to the regimen, inappropriate drug regimens, and/or interference with absorption of the drug.

**MDR TB management principles**

Guidelines endorsed by the Centers for Disease Control and Prevention (CDC) state that if a child is at risk of or has disease resistant to INH, then at least 2 drugs to which the isolate is susceptible should be administered. Another important management principle is to never add a single drug to an already failing regimen. The resistance pattern, toxicities of the drugs, and patients' responses to treatment determine duration and the regimen selected.

The initial treatment regimen for patients with MDR TB should include 4 drugs. At least 2 bactericidal drugs (eg, INH, rifampin), pyrazinamide, and either streptomycin or another aminoglycoside (also bactericidal) or high-dose ethambutol (25 mg/kg/d) should also be incorporated into the regimen.

Six-month treatment regimens are not advocated for patients with strains resistant to INH or rifampin. Intermittent therapy with twice-a-week regimens is also not recommended. In isolated INH resistance, the 4-drug, 6-month regimen should be initially started for the treatment of pulmonary TB. INH should be discontinued when resistance is documented. Continue pyrazinamide for the entire 6-month course of treatment.

In the 9-month regimen, INH should be discontinued upon the documentation of isolated INH resistance. If ethambutol was included in the initial regimen, continue treatment with rifampin and ethambutol for a minimum of 12 months. If ethambutol was not included, then repeating susceptibility tests is advocated, as are discontinuation of INH and the addition of 2 new drugs (eg, ethambutol and pyrazinamide).

Resistance to both INH and rifampin presents a complex problem that often necessitates consultation with a specialist. Continuing the initial drug regimen (with 2 drugs to which the organism is susceptible) until bacteriologic sputum conversion is documented is preferable; then administer at least 12 months of 2-drug therapy. The role of new agents such as quinolone derivatives and amikacin in MDR cases remains unclear.

**Neonates With Household Contacts With TB**

The American Academy of Pediatrics (AAP) and Centers for Disease Control and Prevention (CDC) guidelines advocate avoidance of separation of the mother and infant, if possible. Authorities have endorsed recommendations regarding different clinical scenarios.

**Mother with a positive TST result and no evidence of current disease**

Because the positive tuberculin skin test (TST) result may be evidence of an unrecognized case of contagious tuberculosis (TB) within the household, careful
screening and evaluation of the other members of the household should be performed. Perform a Mantoux test when the infant is aged 4-6 weeks and 3-4 months. Consider administration of isoniazid (INH) (10 mg/kg/d) to the infant if the family cannot be promptly tested.

**Mother has current disease but is noncontagious at delivery**

In this situation, separation of the mother and infant is not necessary, and the mother can breastfeed the infant. Evaluation of the infant includes chest radiography and Mantoux test at age 4-6 weeks; if the Mantoux test is negative, a repeat test is warranted at ages 3-4 months and 6 months. INH should be administered even if the TST result and chest radiography do not suggest TB, because sufficient cell-mediated immunity (CMI) to prevent progressive disease may not develop until age 6 months.

**Mother has current disease and is contagious at delivery**

In this situation, separation of the mother and infant is recommended until the mother is noncontagious. The rest of the management is the same as for the mother with current disease but who is noncontagious at delivery.

**Mother with hematogenous spread**

Congenital TB is possible in this scenario. Promptly perform a Mantoux test and chest radiography, and immediately begin treatment for the infant. INH should be administered until the infant is aged 6 months, at which time evaluation of the infant with a TST should be repeated. If the TST result is positive, the infant should be treated with INH for a total of 9 months.

**Surgical Management of TB**

Pulmonary resection in patients with tuberculosis (TB) may be required in drug-resistant cases because of the high likelihood of failure of the medication regimen. Surgical resection may also be required in patients with advanced disease with extensive caseation necrosis. Hemoptysis, although rare in children, may necessitate surgical intervention. TB abscesses and bronchopleural fistulae also should be surgically removed.

**Complications of TB Disease**

Miliary disease and tubercular (TB) meningitis are the earliest and most deadly complications of primary TB. A high index of suspicion is required for prompt diagnosis and management of these conditions. Pulmonary complications include the development of pleural effusions and pneumothorax. Complete obstruction of a bronchus can result if caseous material extrudes into the lumen. This can lead to atelectasis of the involved lung. Bronchiectasis, stenosis of the airways, bronchoesophageal fistula, and endobronchial disease caused by penetration through an airway wall are other catastrophes that may occur with primary TB.
Perforation of the small bowel, obstruction, enterocutaneous fistula, and the development of severe malabsorption may complicate TB of the small intestine.

Pericardial effusion can be an acute complication or can resemble chronic constrictive pericarditis.

Renal complications including hydronephrosis and autonephrectomy usually do not occur in children. Paraplegia may complicate Pott disease of the spine (ie, TB spondylitis) (see Pott Disease [Tuberculous Spondylitis]).

Outcomes of TB Disease
The prognosis of tuberculosis (TB) varies according to the clinical manifestation. Poor prognosis is associated with disseminated TB, miliary disease, and TB meningitis.

The prognosis of TB meningitis varies according to the stage of the disease at the time treatment is started (see TB Meningitis in Evaluation of Pediatric Extrapulmonary TB). Stage 1 has a good prognosis, whereas patients with stage 3 usually have sequelae such as deafness, blindness, paraplegia, mental retardation, movement disorders, and diabetes insipidus.

The US mortality rate from TB is about 0.6 deaths per 100,000 individuals, which represents approximately 1,700 deaths per year and an annual mortality rate of approximately 7% per newly identified case. In 1953, the mortality rate was 12.5 deaths per 100,000 individuals. This decrease in mortality is attributed to improved health care and prompt initiation of therapy. However, multidrug-resistant TB cases have a reported fatality rate of greater than 70%. Worldwide, deaths due to TB are estimated to be 3 million per year.

Higher mortality rates occur in children younger than 5 years (20%) and in those with a illness lasting longer than 2 months (80%).

Patient Surveillance
Public health authorities should be notified of all cases of tuberculosis (TB).

Directly observed therapy (DOT) is mandatory for the treatment of patients with coexistent human immunodeficiency virus (HIV) disease, those with multidrug-resistant (MDR) TB, and those who may be noncompliant.

A regular follow-up appointment every 4-8 weeks should be scheduled to ensure compliance and to monitor the adverse effects of and response to the medications administered. Adherence to the regimen is of vital importance to its success. Therefore, every measure should be taken to provide language-specific and culturally appropriate material to ensure compliance. Clear and written instructions regarding the timing of medication and the quantity to be administered should be provided.
Monitoring of liver function test results is not indicated routinely. However, it may be required in the treatment of patients with miliary TB, TB meningitis, and coexistence of other hepatic disorders or with concomitant hepatotoxic drug therapy. In the rare event the patient has symptoms of hepatitis, discontinue the regimen and evaluate liver function. If the tests are normal or return to normal, then a decision to restart the medications may be made. Reintroduce the drugs one by one.

Follow-up chest radiography may be performed after 2-3 months of therapy to observe the response to treatment in patients with pulmonary TB. However, hilar lymphadenopathy may take several years to resolve. Thus, a normal chest radiography finding is not required for termination of therapy.

**Prevention of TB Disease**

The key method of preventing tuberculosis (TB) is prompt identification and treatment of patients with TB. Other strategies include patient education, treatment of latent infection, and vaccination.

The World Health Organization (WHO) launched the Stop TB strategy in 2006 (modelled after the directly observed therapy [DOT] strategy) and the core components include pursuing high-quality DOT expansion and enhancement; addressing TB and human immunodeficiency (HIV) infection, multidrug-resistant (MDR) TB, and other challenges; contributing to health system strengthening; engaging all care providers; empowering people with TB; and enabling and promoting research.

**Patient education**

Thoroughly educate patients regarding compliance to therapy, adverse effects of medications, and follow-up care.

**Treatment of latent TB infection**

Recommendations for preventive therapy are based on a comparative analysis of the risk of administration of isoniazid (INH) versus the risk of acquiring the disease. Adults with a positive tuberculin skin test (TST) result and no clinical or radiographic manifestations who are receiving INH therapy have been demonstrated to have 54-88% protection against the development of the disease, whereas children have been shown to have 100% protection.

The risk of acquisition of TB is particularly high in very young children (< 5 y) and in the adolescent population. Thus, patients in these age groups with a positive TST result and no other manifestations should receive INH therapy. Active TB should be carefully excluded before the initiation of preventive therapy.

For recent contacts of patients with contagious TB (ie, in the past 3 mo), INH therapy is indicated even if the TST result is negative. This is especially true for contacts who are infected with HIV or for household contacts younger than 5 years.
Household contacts of any age should be considered for INH therapy if they are from a high-prevalence area, even if the TST result is negative.

The recommendations from the American Academy of Pediatrics (AAP) are to administer 9 months of therapy. The drug of choice is INH. A treatment period of 12 months is recommended for patients with HIV infection. For the management of contacts of INH-resistant cases, rifampin is recommended for 6 months in children.

In case of a high probability of infection with MDR TB, observation is recommended, because none of the other drugs have been evaluated for preventive therapy. Several drugs have been used in these circumstances, including pyrazinamide, fluoroquinolones, and ethambutol, depending on the susceptibility patterns.

**Vaccination**

The [bacille Calmette-Guérin (BCG) vaccine](https://en.wikipedia.org/wiki/Bacille_Calmette-Guérin) is available for the prevention of disseminated TB. BCG is a live vaccine prepared from attenuated strains of *M bovis*. The major role of BCG vaccination is the prevention of serious and life-threatening disease such as disseminated TB and TB meningitis in children. The BCG vaccine does not prevent infection with *M tuberculosis*.

Although the BCG vaccine has been in use since 1921 and approximately 3 billion doses have been administered, its efficacy continues to be debated. Several trials have been performed to assess the efficacy of the vaccine, and results vary. However, 2 meta-analyses of the various trials concluded that the vaccine is efficacious against miliary and meningeal TB. Controversy surrounds the efficacy of BCG vaccination against pulmonary TB.

The WHO’s Expanded Program on Immunization recommends the administration of BCG at birth. The vaccine is used in more than 100 countries. In the United States, BCG vaccination is currently recommended only in certain situations, including the following:

- Child has negative HIV and TST results, is exposed to persons with contagious MDR (resistant to INH and rifampin) pulmonary TB, and cannot be removed from the exposure
- Child has negative HIV and TST results, is exposed to persons with untreated or ineffectively treated contagious pulmonary TB, and cannot be removed from the exposure or treated with anti-TB medication

From birth to age 2 months, administration of BCG does not require a previous TST. Thereafter, a TST is mandatory before vaccination.

Adverse reactions due to the vaccine include subcutaneous abscess formation and the development of lymphadenopathy. Rare complications, such as osteitis of the epiphyses of the long bones and disseminated TB, may necessitate administration of anti-TB therapy, except for pyrazinamide.
Contraindications to the administration of the vaccine include immunosuppressed conditions such as primary or secondary immunodeficiency, including steroid use and HIV infection. However, in areas of the world where the risk of TB is high, the WHO recommends using the BCG vaccine in children who have asymptomatic HIV infection.

**Special Considerations**

Tuberculosis (TB) presents a potential health hazard to the public; therefore, public health authorities should be notified of all cases of TB.

Legal measures have been initiated in several states in the United States that allow for civil or criminal detention of patients with active TB disease and persistent noncompliance with directly observed therapy (DOT).

TB can cause significant morbidity in the pregnant woman and the fetus; hence, pregnant women must be carefully evaluated and be placed on prophylaxis or treatment as indicated. Hematogenous spread of the bacilli through the umbilical vein and the placenta to the fetal liver or aspiration of tubercle bacilli from infected amniotic fluid may lead to the development of congenital TB.

First-line agents recommended by the American Academy of Pediatrics (AAP) include isoniazid (INH), rifampin, and ethambutol. No significant teratogenicity on the fetus has been observed. Streptomycin is contraindicated, because it may lead to the development of deafness in the fetus. Data regarding the use of pyrazinamide, cycloserine, and ethionamide are not available; avoid these drugs if possible.

Treatment should be started as soon as the diagnosis of TB is confirmed or after the first trimester in women younger than 35 years with recent tuberculin skin test (TST) conversion. Strict adherence to the treatment protocol is essential to prevent the development of congenital TB and maternal morbidity.

Breastfeeding should not be discouraged, because the amount of drug in breast milk is very small, and no adverse effects have been documented. All pregnant women on INH therapy should receive pyridoxine.

**Tuberculosis Screening**

- **Overview**
- Selecting Individuals to Screen
- Selecting a Test
Overview

Latent tuberculosis infection is a condition in which a person is infected with *Mycobacterium tuberculosis* -complex but does not have active tuberculosis disease. People with latent tuberculosis infection are at risk of progressing to active tuberculosis. Therefore, it is essential that individuals at high risk of progression to active tuberculosis are identified through screening.

Nearly one-third of the world’s population has latent tuberculosis infection. Risk of progression varies based on age and comorbid conditions. The greatest risk for progression to active disease occurs within the first 2 years of infection, during which time about 5% of individuals progress to tuberculosis disease. After the first 2 years following infection, the risk of developing active disease over an individual’s lifetime is 5-10%.

There is no direct test to detect the presence of latent tuberculosis infection in an individual. The screening tests for latent tuberculosis infection rely on measurements of adaptive host immune responses to the bacteria. The tuberculin skin test measures an individual’s response to a solution of *Mycobacterium tuberculosis* -complex antigens, known as purified protein derivative.

Until the early 2000s, the tuberculin skin test was the standard for screening for latent tuberculosis infection. However, the test has limitations, including precise intradermal administration, the need for a follow-up visit to interpret the results, specific criteria for interpretation of the results, and the possibility of false-positive results with Bacillus Calmette-Guerin vaccination or other environmental mycobacteria. Because of this, interferon-gamma release assays are gaining acceptance as an alternative screening test. Because interferon-gamma release assays are performed in the laboratory, requiring one blood draw and only one patient visit to obtain results, they are significantly distinct from the traditional tuberculin skin test.

Selecting Individuals to Screen

The selection of individuals for screening of latent tuberculosis infection should be based on clinical, social, and environmental risk factors. Screening should be performed with the intent to treat positive test results.

There are two main categories of people who should be screened for latent tuberculosis infection: 1) individuals at risk for exposure to persons with active
tuberculosis disease, and 2) individuals with conditions or other factors associated with progression from latent tuberculosis infection to tuberculosis disease.\[9\]

Individuals at risk for exposure to persons with tuberculosis disease include the following:\[10\]:

- Known close contacts of a person with infectious tuberculosis disease
- Immigrants from tuberculosis-endemic regions of the world (e.g., Africa, Asia, Eastern Europe, Latin America, and Russia)
- Employees or residents of facilities or institutions with people who are at high risk for tuberculosis, such as hospitals, homeless shelters, correctional facilities, nursing homes, or residential facilities for patients with acquired immunodeficiency syndrome

Conditions and other factors associated with progression from latent tuberculosis infection to tuberculosis disease include the following:\[10\]:

- Human immunodeficiency virus infection
- Receipt of immunosuppressive therapy, such as tumor necrosis factor antagonists, systemic corticosteroid doses ≥15 mg of prednisone per day, or organ transplantation
- Recently infected with *M. tuberculosis* within the past 2 years
- Radiographic evidence of prior healed tuberculosis
- History of prior untreated or inadequately treated tuberculosis
- Low body weight (10% below ideal body weight)
- Infants and children under 5 years old with positive tuberculosis test
- Cigarette smoking
- Drug abuse, including alcohol abuse and injection drug use
- Silicosis
- Diabetes mellitus
- Chronic renal failure or on hemodialysis
- Gastrectomy
- Jejunoileal bypass
- Solid organ transplantation
- Head and neck cancer
- Lung cancer

Individuals with a prior positive test or who have had a severe reaction to tuberculin skin test in the past, including skin necrosis, blistering, ulceration, or anaphylactic shock,\[9\] should not be screened again.

Selecting a Test

There is considerable controversy regarding the appropriate test to use for tuberculosis screening. Data on interferon-gamma release assays (IGRAs) is evolving and its validity in specific patient populations is not as well established as the tuberculin skin test (TST). The Centers for Disease Control and Prevention (CDC) issued updated guidelines in 2010 evaluating the role of screening for
tuberculosis with IGRAs. Overall, both IGRAs and TSTs have been endorsed. IGRAs may be used in place of TSTs whenever testing is indicated. The guidelines also indicate preferred tests in certain situations, but routine use of either TST or IGRAs is acceptable practice.

IGRAs are recommended for individuals who may not return for a TST reading, such as those with a history of drug abuse or who are homeless. IGRAs are also recommended for individuals who have received Bacille Calmette-Guerin vaccination. TST is the preferred test for children younger than 5 years.

The CDC recommends against routine use of simultaneous or sequential TST and IGRA for the same patient, although there are exceptions. For example, if the initial TST is negative, repeat testing with IGRA (or vice versa) can be performed if the patient is at high risk for infection, progression, or poor outcome or if there is a high clinical suspicion for active tuberculosis. A positive result from a second test increases the sensitivity for detecting tuberculosis in higher risk patients, although multiple negative tests cannot exclude a diagnosis of tuberculosis. Sequential testing also can be considered if the initial test is borderline or indeterminate.

In the setting of multiple tests, clinicians may be faced with discordant findings (i.e., one positive test and one negative test). The CDC recommends an individualized approach with careful consideration to the quality of each test, the patient’s specific response to testing (e.g., size of induration or values for antigens, positive and negative controls on the IGRA) and the risk of testing or treating a given patient.

For patients who are at low risk for infection and progression, deeming a positive result to be falsely positive is reasonable given the overall low incidence of tuberculosis in the United States. TST reactions of less than 15 mm in size in otherwise healthy, low-risk patients who have received a Bacille Calmette-Guerin vaccination and who have a negative IGRA can be considered to be a false-positive TST reaction. However, for patients who are at high risk of acquisition or progression of tuberculosis, one positive test result can be considered as evidence for infection.

Differing conclusions are presented in the guidelines developed by Canadian, U.K., and U.S. expert panels regarding the use of IGRAs. Given the evolving data and the varied public health priorities, this assessment is not surprising. The choice of a specific test should be based on the local epidemiology of tuberculosis as well as the risk factors of each individual.

**Tuberculin Skin Test Technique**

The tuberculin skin test (TST) measures an individual’s cell-mediated immune response to a solution of more than 200 *M. tuberculosis* complex antigens, known as purified protein derivative (PPD).
Testing equipment for the TST includes a purified protein derivative solution, tuberculin syringe, 27-gauge needle, and alcohol swabs.

PPD solution should be stored in the dark and refrigerated at 36-46°F. To minimize reduction in potency by adsorption, the PPD solution should not be transferred from one container to another.

In the United States, 5 tuberculin units (TUs) are used, whereas in most European countries, 2 TUs are used. Skin tests should be given immediately after the syringe is filled.

The Mantoux technique is the standard method of administration of PPD solution, in which intradermal injection of tuberculin material on the inner surface of the forearm is used. The test is performed as followed:

- Inject 0.1 mL of 5 TU PPD solution intradermally on the volar surface of the lower arm using a 27-gauge needle and tuberculin syringe.
- Produce a wheal 6-10 mm in diameter.
- The arm in which the test was administered is noted.
- The skin test should be read 48-72 hours after administration.
- The area of induration (not erythema) is measured in millimeters in the axis perpendicular to the long axis of the arm.

**Interpretation**

The immune reaction to administered antigen is a type 4 delayed (cellular) hypersensitivity reaction. T cells primed by the prior infection are recruited to the test area, where they release lymphokines leading to local vasodilatation, edema, fibrin deposition, and recruitment of other inflammatory cells leading to induration of the involved skin.

Because this test is an indirect measurement of latent tuberculosis infection, it has certain limitations. Bacillus Calmette-Guerin vaccine, which protects infants and young children from meningeal and miliary tuberculosis, may affect results. The vaccine is not offered in the United States, but foreign-born residents who have been vaccinated may develop a positive PPD reaction. Because it is difficult to distinguish whether the reaction is a true-positive result (indicating latent tuberculosis infection) or a false-positive result (indicating history of Bacillus Calmette-Guerin vaccination), individuals with known or suspected Bacillus Calmette-Guerin vaccination with a positive PPD should be treated as if they have a positive test result.

Some individuals with latent tuberculosis infection have an initial negative skin test reaction when tested years after infection because the TST becomes less sensitive over time. For individuals who have a negative initial TST, a second test should be administered (two-step testing) using the same methods and interpretation paradigm. The initial TST serves as a boost to stimulate a response.
Sensitivity and specificity of the TST is influenced by different cutoff values for positivity in different clinical settings. Table 1 shows the degree of induration required for a positive test in selected population groups.

Table 1. Interpretation of tuberculin skin test results (Open Table in a new window)

<table>
<thead>
<tr>
<th>Degree of induration required for a positive result</th>
<th>Patient population</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5 mm</td>
<td>Individuals with HIV infection</td>
</tr>
<tr>
<td></td>
<td>Individuals who have had close contact with a patient with infectious tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Individuals with chest radiographs that are consistent with prior untreated tuberculosis (fibrotic changes)</td>
</tr>
<tr>
<td></td>
<td>Organ transplant recipients</td>
</tr>
<tr>
<td></td>
<td>Other immunosuppressed patients (taking the equivalent of &gt;15 mg/day of prednisone or tumor necrosis factor antagonists)</td>
</tr>
<tr>
<td>&gt;10 mm</td>
<td>Recent immigrants (within the last 5 years) from tuberculosis-endemic countries</td>
</tr>
<tr>
<td></td>
<td>Injection drug users</td>
</tr>
<tr>
<td></td>
<td>Residents or employees of congregate settings (e.g., prisons, long-term care facilities for the elderly, homeless shelters)</td>
</tr>
<tr>
<td></td>
<td>Mycobacteriology laboratory personnel</td>
</tr>
<tr>
<td></td>
<td>Children younger than 4 years</td>
</tr>
<tr>
<td></td>
<td>Infants, children, and adolescents who have been exposed to high-risk adults</td>
</tr>
<tr>
<td>&gt;15 mm</td>
<td>Individuals with no known risk factors for tuberculosis</td>
</tr>
</tbody>
</table>

Table 2 lists false-positive and false-negative reactions of which the clinician should be aware. (9, 17)

Table 2. Causes of false-positive and false-negative reactions for the tuberculin skin test (Open Table in a new window)

<table>
<thead>
<tr>
<th>False-positive reactions</th>
<th>False-negative reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection with non-tuberculosis mycobacteria</td>
<td>Cutaneous anergy due to a lack of an appropriate immune response (e.g.,</td>
</tr>
</tbody>
</table>
Interferon-gamma Release Assays

Two interferon-gamma release assays (IGRAs) are currently approved by the U.S. Food and Drug Administration (FDA) in the United States:

- QuantiFERON-TB Gold In-Tube test (QFT-GIT)
- T-SPOT.TB test (T-Spot)

**QuantiFERON-TB Gold In-Tube Test**

The QFT-GIT uses three specialized blood collection tubes, each holding 1 mL of blood:

- Grey: Negative control
- Red: Tuberculosis antigens
- Purple: Mitogen control

Immediately after blood collection, all tubes of blood must be vigorously shaken 10 times to ensure the entire inner surface of the tube has been coated with blood. Appropriate mixing is essential to ensure the antigens embedded in the tube walls interact with the blood.\[8\]

Tubes must be incubated within 16 hours at 37°C for 16-24 hours. After incubation, an enzyme-linked immunosorbent assay (ELISA) is performed on separated plasma using a specially developed QFT-GIT microwell plate. The optical density is measured and a software algorithm using FDA-approved cutoff values compares the negative control, positive control, and the antigen wells.\[8, 6\] A qualitative response of positive, negative, or indeterminate is generated from these values.

Indeterminate results may occur for several reasons. The positive control optical density may be below the threshold, indicating the patient’s blood did not react with the mitogen and suggesting an anergic response. The negative control optical density may exceed the threshold value, suggesting high background interferon-gamma levels.
Common clinical reasons for indeterminate results include relative anergy and immunosuppression (specifically limiting interferon gamma production in the positive control), extremes of age, active infection, or antimycobacterial treatment. Technical reasons for indeterminate results include prolonged transit time after draw and before incubation, insufficient mixing, and incomplete washing of the ELISA plates.

**T-SPOT.TB Test**

For the T-Spot test, whole blood is collected in lithium heparin or sodium citrate anticoagulated tubes (or specialized Leucosep or Cell Preparation Tubes), holding 8 mL of blood. Anticoagulated or nonanticoagulated ethylenediaminetetraacetic acid tubes are inappropriate for testing and should not be used.

After blood is collected, samples should be processed within 8 hours of collection unless processed with T-Cell Xtend reagent, which extends the hold time up to 32 hours after venipuncture.

In the laboratory, peripheral blood mononuclear cells (PBMCs) are separated, washed, and counted. After preparation, isolated PBMCs are placed into a specially prepared microtiter plate and exposed to the positive control, a negative control, and two tuberculosis antigens. The positive control contains phytohemagglutinin, which nonspecifically stimulates T-cell production of interferon-gamma.

After a 16- to 20-hour incubation period, secreted interferon-gamma binds to the antibodies coating the base of the plate. A second antibody conjugated to alkaline phosphatase binds to the interferon-gamma and a final substrate is added, which is cleaved by the enzyme to form an insoluble spot on the plate. These spots are counted and then interpreted using FDA-approved interpretation criteria. Notably, the FDA approved a “borderline” criterion, which increases the specificity and sensitivity of the assay by reducing the false-positive and false-negative results near the breakpoint.

As with the QFT-GIT, indeterminate results can occur because of either a lack of positive control response or a high background level of interferon-gamma. Both technical and clinical factors can lead to indeterminate results, including improper testing procedures and washings, as well as patient anergy or immunosuppression.

**Follow-up**

Individuals with positive screening result need further testing to determine if positivity is due to latent tuberculosis infection or active tuberculosis disease. A clinical evaluation and chest radiograph should be performed on all patients with a positive screening test to assess for active tuberculosis disease. If the patient does not have clinical signs or symptoms and the chest radiograph does not have findings suggestive of active tuberculosis, the patient should be diagnosed with latent tuberculosis infection and offered a treatment course to diminish the risk of progressing to active tuberculosis.
Primary Tuberculosis Imaging

- Overview
- Radiography
- Computed Tomography
- Show All

Multimedia Library
References

Overview

Preferred examination

If patients with primary tuberculosis undergo imaging, a conventional chest radiograph may be sufficient for diagnosis in the appropriate clinical setting.

In patients with progressive primary or postprimary tuberculosis, computed tomography scanning is often performed, in addition to chest radiography. Magnetic resonance imaging may be used to evaluate complications of thoracic disease, such as the extent of thoracic wall involvement with empyema, but is of limited value in the evaluation of patients with pulmonary tuberculosis.

Typically, ultrasonography is not useful in imaging pulmonary disease. This modality may be used for thoracentesis guidance or to evaluate the pericardium for secondary tuberculous involvement.

Angiography is not used in the diagnosis of pulmonary tuberculosis. Angiographic techniques, such as bronchial arteriography and embolization in patients with hemoptysis, may be used to treat the complications of cavitary pulmonary tuberculosis.

Patients with postprimary tuberculosis may also undergo bronchoscopy to evaluate endobronchial disease and to obtain sputum specimens for microbacteriologic cultures. [1, 2, 3, 4, 5]

Mycobacteria
Traditionally, the term tuberculosis has been used to indicate infections caused by *Mycobacterium tuberculosis* and *M. bovis*; however, a multitude of causative mycobacteria are recognized. A case of primary pulmonary tuberculosis is depicted in the image below.

![Image of a chest x-ray showing a focal opacity in the left lower lobe.](image)

Young male patient with fever and cough has a focal opacity in the left lower lobe that looks like a pneumonia. This is a case of primary tuberculosis in an adult.

Tuberculosis may involve multiple organs such as the lung, liver, spleen, kidney, brain, and bone. In endemic regions, the normal **host immune response** may be sufficient to contain the infection and prevent clinical presentation. Uncontrolled or uncontained infection may result in great morbidity and mortality.

**Limitations of techniques**

Conventional radiography is limited in its sensitivity and specificity. As many as 15% of patients with primary tuberculosis have normal chest radiographic findings. Clinical suspicion must remain high for prompt diagnosis in these individuals. Chest radiographic results are not specific for tuberculosis, and other entities must remain in the differential diagnosis. [6, 7, 8]

**Intervention**

**Interventional** radiologists may be consulted to perform diagnostic and therapeutic bronchial artery studies, and interventional **radiologic** techniques may be used to confirm the diagnosis with percutaneous lymph node aspiration or biopsy to obtain material for culture, cytologic, or histologic studies.

Radiologists may perform stent placement with fluoroscopic and/or CT guidance in collaboration with the bronchoscopist, and they often obtain fluid for evaluation by performing ultrasonography- or CT-guided thoracentesis.

**Radiography**

The radiographic characteristics of primary and postprimary pulmonary tuberculosis are displayed in the section images below.
Young male patient with fever and cough has a focal opacity in the left lower lobe that looks like a pneumonia. This is a case of primary tuberculosis in an adult. Posteroanterior chest radiograph in a young patient shows a right upper lobe and right lower lobe consolidation and a small pleural effusion on the right side.

A middle-aged man presents with a cough and fever lasting several weeks. Posteroanterior chest radiograph shows a prominent paratracheal area on the right, lymphadenopathy, a cavitary opacity in the right upper lobe, and a focal consolidation in the middle lung zone on the right. The patient was ultimately found to have primary progressive tuberculosis.

**Pulmonary imaging findings in individuals with primary tuberculosis are nonspecific.** Common findings include segmental or lobar airspace consolidation, ipsilateral hilar and mediastinal lymphadenopathy, and/or pleural effusion. Atelectasis may occur in primary pulmonary tuberculosis, often as a consequence of tuberculous airway involvement.

Note that chest radiographic findings may be normal in as many as 15% of patients with primary pulmonary tuberculosis.

**Parenchymal consolidation in primary pulmonary tuberculosis**
Parenchymal consolidation may be observed. Although consolidation may occur in any segment or lobe or in multiple segments or lobes, the disease has a predilection for the lower lobes, for the middle lobe and lingula, and for the anterior segments of the upper lobes.

Airspace consolidation tends to be homogeneous, with ill-defined margins. If the consolidation abuts a fissure, a well-defined margin may be identified. Cavitation within parenchymal opacity is distinctly uncommon in primary infection. As the host immune response continues, healing begins. Caseous necrosis occurs centrally within the lung parenchymal opacity, decreasing its size.

The lung opacity tends to become rounded with healing, and it continues to shrink until only a small nodule remains. Subsequently, the nodule may become calcified or ossified, resulting in a calcified granuloma. Note that although a granuloma may calcify, this does not necessarily reflect an absence of bacilli. The organisms may remain quiescent within this nodule, serving as a possible source for reactivation of disease.

**Lymphadenopathy in primary pulmonary tuberculosis**

Lymphadenopathy is a common manifestation of primary pulmonary tuberculosis. The presence of hilar and mediastinal lymphadenopathy may distinguish primary from postprimary tuberculosis, because lymphadenopathy is conspicuously absent in postprimary tuberculosis. Lymphadenopathy may be symptomatic if it secondarily involves the airways.

Lymphadenopathy without a parenchymal opacity may occur as the only manifestation of primary pulmonary tuberculosis. This is seen most often in the population with human immunodeficiency virus (HIV) infection. (In adults with HIV infection, adenopathy is common.)

As expected, adenopathy is most common in the ipsilateral hilar region. Hilar lymphadenopathy is seen in approximately 60% of children with primary tuberculosis, paratracheal adenopathy is seen in 40%, and subcarinal lymphadenopathy is seen in 80%.

In adults, lymphadenopathy is unusual in an immunocompetent host but it does occur, particularly in blacks and Asians.

The pattern of lymphadenopathy is indistinguishable from that of sarcoid or lymphoma.

With an appropriate immune response or with adequate chemotherapy, enlarged necrotic lymph nodes may diminish in size and commonly calcify. The presence of calcified lymph node and a granuloma represents the Ranke complex.

**Airway involvement in primary pulmonary tuberculosis**
Airway involvement is frequently present in primary tuberculosis and may take any of the following forms:

- Airway compression by adjacent lymphadenopathy with resultant atelectasis
- Mucosal infection with resultant ulceration and long-term stricture formation
- Broncholithiasis, ie, extrinsic erosion of a bronchus by adjacent lymphadenopathy, with extrusion of calcified material into the bronchus
- Endobronchial spread of infection
- Bronchiectasis

Atelectasis is most notable within the anterior segments of the upper lobes and the medial segment of the middle lobe. Atelectasis may resolve as lymphadenopathy regresses with host response. A sudden resolution of atelectasis may represent perforation of an infected lymph node into the airway, which relieves the bronchial obstruction.

A possible long-term sequela of infection is tracheobronchial stenosis. The airways may be involved by tuberculosis in a variety of ways, including direct mucosal involvement from infected sputum, direct extension from perforating lymphadenopathy or adjacent parenchymal infection, and hematogenous or lymphatic drainage.

The endobronchial spread of infection may be seen with tuberculous tracheobronchial disease. Bacilli from the infected airways disseminate into more distal bronchi and bronchioles and subsequently enter the alveoli, where they become deposited. The resultant radiographic appearance is one of small ill-defined acinar shadows and small nodules.

Endobronchial tuberculosis may lead to bronchiectasis, either from bronchial stenosis or secondary to traction from fibrosis. Bronchiectasis is more frequently seen in postprimary tuberculosis (see Postprimary tuberculosis below).

**Pleural involvement in primary pulmonary tuberculosis**

Pleural involvement is uncommon in children with primary tuberculosis, occurring in approximately 10% of these patients. Pleural involvement is seen more frequently in adults with primary pulmonary tuberculosis, and it is even more frequently identified in postprimary tuberculosis.

**Postprimary pulmonary tuberculosis**

The findings of reactivation tuberculosis typically become radiographically apparent within 2 years of the initial infection. Pleural effusions develop if the infection remains untreated. Tuberculous empyema is a much less common finding.

**Parenchymal manifestations of postprimary pulmonary tuberculosis**

Postprimary tuberculosis may have any of a number of parenchymal manifestations. Patchy or confluent airspace opacities are opacities that involve the apical and posterior segments of the upper lobes and the superior segments of the lower lobes.
In postprimary tuberculosis, cavitary disease is secondary to caseous necrosis within the opacity. The debris from the lesion is expelled via the tracheobronchial tree with which the cavity is in communication. The cavities, similar to airspace opacities in reactivation tuberculosis, are commonly within the upper lung zones. The cavities demonstrate a thick outer wall with a smooth inner contour. Air-fluid levels may be present. Superinfection by *Aspergillus* organisms may occur, leading to a mycetoma.

Tuberculomas are rounded discrete nodules that are known to harbor bacilli. They may be present in primary or postprimary tuberculosis and radiographically appear as discrete nodules, typically within the upper lobes. Tuberculomas may calcify. Satellite lesions (ie, small discrete nodules in the vicinity of the tuberculoma) are present in as many as 90% of patients.

Endobronchial spread of infection with acinar opacities occurs as a consequence of infected material passing into the tracheobronchial tree from an infected portion of the lung. The organisms pass via the airways into previously uninvolved portions of the lung. The radiographic appearance is one of widespread ill-defined acinar shadows. Foci may become confluent and mimic bacterial pneumonia. Spread from the upper lobes to the lower lobes is common and called the upstairs-downstairs pattern.

Pulmonary miliary tuberculosis is a consequence of hematogenous spread of organisms to the pulmonary parenchyma. Radiographically, miliary spread can be recognized by circumscribed nodules less than 1-2 mm in diameter located diffusely throughout both lungs.

**Lymphadenopathy in postprimary pulmonary tuberculosis**

In contrast to primary tuberculosis, lymphadenopathy is notably absent in patients with postprimary tuberculosis, with the exception of patients with HIV or AIDS.

**Airway involvement in postprimary pulmonary tuberculosis**

Tracheobronchial stenosis may not be directly visualized on conventional chest radiographs. Airway stenosis may result in atelectasis in the segments of the lung supplied by that bronchus.

Bronchiectasis may be visualized on radiographs as dilated air-containing structures, with a tram-track appearance representing the parallel walls of the dilated airway. Dilated bronchi may be irregular in caliber and varicoid in appearance or may be cystic. Traction bronchiectasis may occur as well, as a consequence of fibrosis.

**Pleural involvement in postprimary pulmonary tuberculosis**

Pleural involvement is seen more commonly in postprimary tuberculosis than in primary infection. Pleural effusions may occur and may progress to empyema. An empyema may require emergent surgical intervention because the infection is
maintained within a closed space and because it may result in rapid destruction of surrounding structures (eg, lung parenchyma, osseous structures of the thorax).

If infection extends from the pleural space to involve the chest wall, it is called empyema necessitans. Osseous destruction and, possibly, air within subcutaneous tissues may be identified radiographically, or the empyema may present as a palpable soft-tissue mass.

**Degree of confidence**

The imaging features of primary tuberculosis are nonspecific, and they may mimic those of other infectious processes. A finding that differentiates primary tuberculosis from other infectious processes is lymphadenopathy, which is typically absent in bacterial pneumonia.

Postprimary tuberculosis may be recognized more readily with the presence of fibrocavitary disease and a history of prior tuberculosis exposure or infection. Radiologic findings of postprimary tuberculosis are highly suggestive of, but not pathognomonic for, the disease. Inactive disease cannot be established without prior radiographs, regardless of the pattern.

**False positives/negatives**

As many as 15% of conventional chest radiographs may be normal in primary tuberculosis. In the immunocompromised population, lymphadenopathy occasionally may occur in isolation, and it may not be detected on conventional radiographs. Additional imaging with CT is often required, because CT is more sensitive in depicting lymphadenopathy.

**Computed Tomography**

The CT scan characteristics of primary and postprimary tuberculosis are displayed in the images below.

![CT scan in a young patient, obtained with the pulmonary window setting, demonstrates consolidation in the right upper lobe, ground-glass opacities in the right lower lobe, and a pleural effusion on the right side. This patient has extensive tuberculous pneumonia and is immunocompromised.](image)
A middle-aged man presents with a cough and fever lasting several weeks. CT scan obtained with the pulmonary window setting in the right upper lobe shows an irregular, thick-walled cavity with some increased markings around it. A nearby nodule is also shown.

CT scan obtained with pulmonary window setting in the right middle lobe (same patient as in the previous image) shows a focal area of consolidation with what may be tiny nodules. This patient has primary progressive tuberculosis with radiographic manifestations of mediastinal adenopathy, cavitary process, and endobronchial spread that occurs over a short period. He had a history of alcohol abuse.

**Primary pulmonary tuberculosis**

CT scanning helps confirm the presence of an ill-defined parenchymal infiltrate, as well as lymphadenopathy.\(^\text{[14, 15, 16, 17, 18, 19, 20]}\)

CT is the examination of choice for evaluating lymphadenopathy and involvement of the tracheobronchial tree. Lymphadenopathy causing bronchial compression can be identified, and airway compromise can be monitored during chemotherapy. CT scans may demonstrate enlarged lymph nodes typically measuring more than 2 cm.

Lymph nodes demonstrate central hypoattenuation with peripheral rim enhancement with the administration of contrast material. This appearance reflects central necrosis within the node. Broncholiths may be identified in rare cases.

Morphologically, the stenoses in active disease are areas of irregular luminal narrowing with circumferential wall thickening. Associated mediastinitis and even mediastinal abscesses may be present. Small pleural effusions are detected more readily on CT scans than on other images. Contrast enhancement may be useful in identifying evolution into an empyema.

**Postprimary pulmonary tuberculosis**

CT scans may be helpful in evaluating parenchymal involvement, satellite lesions, bronchogenic spread of infection, and miliary disease.

Cavitation is best demonstrated on CT scans. The outer wall of the cavity tends to be thick walled and irregular, whereas the inner wall tends to be smooth. An air-fluid level may be identified. The connection of the cavity to the airway may be visualized.
Complications of cavitary disease may become apparent with mycetoma formation, which appears as an intraluminal collection of material with a crescent of surrounding air. Changes in patient positioning demonstrate a change in the position of the mycetoma relative to the cavity.

Tuberculomas can be identified on CT scans as rounded nodules that usually have surrounding associated satellite lesions. The bronchogenic spread of tuberculosis is recognized on CT scans by the presence of acinar shadows and nodules of varying sizes in a peribronchial distribution. The lesions are seen throughout both lungs.

Miliary tuberculosis is characterized by randomly distributed tiny nodules (1-2 mm), which tend to be smooth and well marginated. Calcification is notably absent; this observation may aid in differentiating tuberculosis from metastatic diseases such as thyroid carcinoma.

CT scans may aid in the evaluation of uncommon complications of miliary tuberculosis, such as acute respiratory distress syndrome (ARDS) and pulmonary hemorrhage resulting from disseminated intravascular coagulopathy. Both ARDS and pulmonary hemorrhage may manifest as alveolar filling in a background of miliary nodules.

**Airway involvement**

CT scanning is the examination of choice for evaluating the tracheobronchial tree. Lymphadenopathy is a feature of primary infection; however, calcified lymph nodes may cause persistent extrinsic compression on the bronchi.

Bronchial stenosis is more common in postprimary disease than in primary tuberculosis. In fibrocavitary tuberculosis, the proximal bronchi are more typically involved than the peripheral airways. Variable areas of stenosis are demonstrated. Wall thickening tends to be less marked than in primary tuberculosis.

Bronchiectasis is a well-known sequela of postprimary disease. Bronchiectasis tends to occur in the upper lobes and often manifests as traction bronchiectasis on the basis of fibrotic disease with subsequent traction on the airways. Recurrent infections and hemoptysis may result from traction bronchiectasis.

**Pleural involvement**

Empyema is visualized on contrast-enhanced CT scans with enhancement of the parietal and visceral pleurae. They may demonstrate enhancing septa within the pleural fluid collections. The pleural fluid collections are characterized by low attenuation; however, they do not have attenuation values consistent with simple fluid. Empyemas demonstrate the so-called split pleura sign. This sign consists of the pleural fluid collection tracking between the abnormally enhancing parietal and visceral pleura.
Spontaneous pneumothorax is an uncommon complication of disease; it may be secondary to peripherally located lesions. Involvement of the pericardium and spine may be demonstrated on CT images.

**Degree of confidence**

CT is sensitive in the identification of pulmonary parenchymal and pleural disease. The pattern of disease and distribution of nodules is delineated clearly by using modern CT techniques. Lymphadenopathy may be diagnosed with a high degree of confidence, even without the use of intravenous contrast material.

Pericardial disease can be imaged with CT scanning or MRI, although calcification related to prior tuberculous pericarditis is more readily apparent on CT images.

Osseous involvement is well delineated on CT scans; however, MRI is often necessary to evaluate the disk and the spinal canal.

**Association Between Tuberculin Skin Test Result and Clinical Presentation of Tuberculosis Disease**

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**Abstract**

**Background:** The tuberculin skin test (TST) is used to test for latent tuberculosis (TB) infection and support the diagnosis of active TB. However, little is known about the relationship between the TST result and the clinical presentation of TB disease.

**Methods:** We analyzed US TB surveillance data, 1993–2010, and used multinomial logistic regression to calculate the association between TST result (0–4 mm [negative], 5–9 mm, 10–14 mm, and ≥ 15 mm) and clinical presentation of disease (miliary, combined pulmonary and extrapulmonary, extrapulmonary only, non-cavitary pulmonary, and cavitary pulmonary). For persons with pulmonary disease, multivariate logistic regression was used to calculate the odds of having acid-fast bacilli (AFB) positive sputum.

**Results:** There were 64,238 persons with culture-confirmed TB included in the analysis, which was stratified by HIV status and birthplace (US- vs. foreign-born). Persons with a TST ≥ 15 mm were less likely to have miliary or combined pulmonary and extrapulmonary disease, but more likely to have cavitary pulmonary disease than non-cavitary pulmonary disease. Persons with non-cavitary pulmonary disease with a negative TST were significantly more likely to have AFB positive sputum.
Conclusions: Clinical presentation of TB disease differed according to TST result and persons with a negative TST were more likely to have disseminated disease (i.e., miliary or combined pulmonary and extrapulmonary). Further study of the TST result may improve our understanding of the host-pathogen relationship in TB disease.

Background
The tuberculin skin test (TST) is primarily used to identify latent tuberculosis (TB) infection in persons who may be at risk of progression to active disease and to support the diagnosis of active TB disease. A positive TST result, consisting of measurable skin induration after the injection of tuberculin purified protein derivative, is part of a delayed-type hypersensitivity response of host immune system memory T cells sensitized by prior mycobacterial exposure. However, the TST is an imperfect marker of TB infection and previous reports indicate that 10–25% of persons with active TB disease have a negative TST result.

At the same time, it is well recognized that the host immune system is an important determinant of the clinical presentation of active TB disease, and patients with an immature or suppressed immune system often have faster disease progression and more disseminated disease. Likewise, persons with genetic mutations in the interferon-gamma or interleukin-12 cytokine pathways can present with widely disseminated TB disease. At the other end of the spectrum, patients with a recovering immune system, such as persons with HIV who are initiating antiretroviral therapy or persons stopping anti-tumor necrosis factor therapy, can have an overexuberant immune response to TB infection characterized by extensive cavitary lung lesions and necrotic lymph nodes.

While TST reactivity is recognized to be an indicator of TB infection following exposure to persons with TB disease and has been widely studied in the context of latent TB infection, we are not aware of any large studies that describe the pattern of TST results among persons with different clinical presentations of active TB disease. Understanding the association between the TST and clinical manifestations of TB disease may provide insight into the host-pathogen relationship and how factors such as HIV infection may influence that relationship. We analyzed national surveillance data from the United States to explore whether the TST result correlates with differences in the clinical presentation of active TB among a large cohort of persons with bacteriologically-confirmed TB disease.

Methods
We analyzed reports of persons with culture-confirmed TB in the National Tuberculosis Surveillance System of the Centers for Disease Control and Prevention (CDC) during January 1, 1993 through December 31, 2010. The analysis included persons with a documented TST result, anatomical site of disease, HIV status, and
birthplace (US- or foreign-born). Cases of pulmonary TB without a chest radiograph result were excluded to allow for evaluation of the association between radiograph findings and TST result. Reports from California were also excluded because HIV status was not routinely reported from that jurisdiction prior to 2011.[15]

Based on CDC guidelines for the classification of TST reactions, the TST result was divided into categories of 0–4 mm, 5–9 mm, 10–14 mm, and ≥ 15 mm.[14] A TST result of 0–4 mm was considered negative and a result ≥ 5 mm was considered positive. Pearson's chi-square statistic was used to assess differences in the distribution of TST results for sociodemographic and clinical characteristics. Clinical presentation of disease was defined as one of the following mutually exclusive categories: miliary disease, combined pulmonary and extrapulmonary disease, extrapulmonary only disease, and pulmonary only disease which was further divided into non-cavitary pulmonary disease and cavitary pulmonary disease. A designation of miliary disease was based on either clinical impression or a miliary radiographic pattern on either chest radiograph or CT scan.

Multinomial logistic regression was used to examine the association between TST result category and clinical presentation of disease category and to calculate odds ratios and 95% confidence intervals. Non-cavitary pulmonary disease was the largest clinical presentation category and was used as the referent outcome category. A TST of 0–4 mm (negative) was used as the referent category for TST result. Persons with non-cavitary pulmonary disease with a TST of 0–4 mm served as the comparison group to calculate odds ratios for each of the respective clinical presentation/TST result category combinations (e.g., cavitary pulmonary disease with TST ≥ 15 mm or miliary disease with TST 10–14 mm were all compared to non-cavitary pulmonary disease with a TST of 0–4 mm). We examined the following covariates for effect modification or confounding: sex, age, race and ethnicity (self-designated), HIV status, birthplace, incarceration at the time of diagnosis, homelessness in the 12 months prior to diagnosis, and excessive alcohol or illicit drug use in the 12 months prior to diagnosis. Finally, we conducted an additional analysis restricted to persons with exclusively pulmonary disease who had a documented sputum smear result at baseline. Multivariate logistic regression was used to calculate odds ratios and 95% confidence intervals to quantify the odds of having a positive sputum smear (vs. negative) result for acid-fast bacilli (AFB) for each TST category (TST 0–4 mm referent).

As data were collected as part of routine TB surveillance by the CDC, this analysis was not considered research involving human subjects, and institutional review board approval was not required.
Distribution of TST Results

During 1993 through 2010, there were 308,740 cases of tuberculosis reported in the United States, of which 244,413 (79%) were culture-confirmed (Figure 1). Of these cases, 125,026 (51%) had a TST result reported (see Additional file 1, in the online supplement for a comparison of sociodemographic and clinical characteristics of persons with and without a TST result reported, which shows significant differences between persons with and without TST results for all characteristics) of which 64,238 persons with culture-confirmed TB were eligible for inclusion in the analysis. Among these persons, 15.9% had a TST of 0–4 mm (negative), 2.6% had a TST of 5–9 mm, 21.9% had a TST of 10–14 mm, and 59.7% had a TST ≥ 15 mm (). The proportion of persons with a negative TST was greater in those with age > 45 years, male sex, non-Hispanic white race/ethnicity, who were born in the US, infected with HIV, or who had a positive sputum smear result for AFB at baseline. The distribution of TST results was significantly different among persons with and without HIV: 12.5% of persons without HIV had a negative TST while 38.2% of persons with HIV had a negative TST. Persons with miliary disease and combined pulmonary and extrapulmonary disease also had high rates of TST negativity, 36.7% and 22.9%, respectively, whereas persons with extrapulmonary only, or cavitary pulmonary disease had lower rates of a negative TST with 13.8% and 13.0%, respectively. The distributions of TST results within each sociodemographic and clinical characteristic comparison were statistically significant with a P-value < 0.001.

Table 1. Tuberculin skin test (TST) result and characteristics of selected culture-confirmed TB cases reported in the United States, 1993–2010 (N = 64,238)

<table>
<thead>
<tr>
<th></th>
<th>TST 0–4 mm (n,%): 10,181 (15.9)</th>
<th>TST 5–9 mm (n,%): 1,635 (2.6)</th>
<th>TST 10–14 mm (n,%): 14,049 (21.9)</th>
<th>TST ≥ 15 mm (n,%): 38,737 (59.7)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4</td>
<td>52 (9.3)</td>
<td>30 (5.4)</td>
<td>169 (30.2)</td>
<td>308 (55.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>5–14</td>
<td>29 (5.7)</td>
<td>9 (1.8)</td>
<td>102 (20.0)</td>
<td>369 (72.5)</td>
<td></td>
</tr>
<tr>
<td>15–24</td>
<td>658 (7.6)</td>
<td>213 (2.5)</td>
<td>1,891 (21.8)</td>
<td>5,923 (68.2)</td>
<td></td>
</tr>
<tr>
<td>25–44</td>
<td>4,288 (15.0)</td>
<td>656 (2.3)</td>
<td>6,235 (21.8)</td>
<td>17,450 (61.0)</td>
<td></td>
</tr>
<tr>
<td>Age Group</td>
<td>45–64</td>
<td>65+</td>
<td>Total</td>
<td></td>
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</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7,445 (17.5)</td>
<td>1,149 (2.7)</td>
<td>9,483 (22.3)</td>
<td>24,441 (57.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female</td>
<td>2,731 (12.6)</td>
<td>485 (2.2)</td>
<td>4,563 (21.0)</td>
<td>13,916 (64.1)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>2,203 (14.7)</td>
<td>404 (2.7)</td>
<td>3,500 (23.4)</td>
<td>8,856 (59.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>American Indian</td>
<td>114 (14.0)</td>
<td>20 (2.5)</td>
<td>133 (16.3)</td>
<td>550 (67.3)</td>
<td></td>
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<tr>
<td>Asian</td>
<td>673 (6.9)</td>
<td>255 (2.6)</td>
<td>2,153 (22.2)</td>
<td>6,630 (68.3)</td>
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<tr>
<td>Black</td>
<td>4,164 (16.7)</td>
<td>529 (2.1)</td>
<td>5,162 (20.7)</td>
<td>15,113 (60.5)</td>
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</tr>
<tr>
<td>Native Hawaiian</td>
<td>46 (6.8)</td>
<td>18 (2.7)</td>
<td>158 (23.3)</td>
<td>455 (67.2)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2,944 (23.1)</td>
<td>400 (3.1)</td>
<td>2,870 (22.5)</td>
<td>6,546 (51.3)</td>
<td></td>
</tr>
<tr>
<td>Birthplace</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US-born</td>
<td>6,853 (19.8)</td>
<td>881 (2.5)</td>
<td>7,438 (21.4)</td>
<td>19,530 (56.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Foreign-born</td>
<td>3,328 (11.3)</td>
<td>754 (2.6)</td>
<td>6,611 (22.4)</td>
<td>18,843 (63.8)</td>
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</tr>
<tr>
<td>HIV status</td>
<td></td>
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</table>


<table>
<thead>
<tr>
<th></th>
<th>Negative</th>
<th>Positive</th>
<th>Clinical presentation of disease</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(12.5)</td>
<td>(2.5)</td>
<td>Miliary</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Negative</td>
<td>6,997</td>
<td>3,184</td>
<td>Pulmonary/extrapulmonary</td>
<td>465 (40.4)</td>
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<tr>
<td></td>
<td>(12.5)</td>
<td>(38.2)</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Positive</td>
<td>1,409</td>
<td>226</td>
<td>Extrapulmonary</td>
<td>1,691 (20.3)</td>
</tr>
<tr>
<td></td>
<td>(2.5)</td>
<td>(2.7)</td>
<td></td>
<td>3,242 (38.9)</td>
</tr>
<tr>
<td></td>
<td>12,358</td>
<td>1,691</td>
<td>Non-cavitary pulmonary</td>
<td>4,284 (23.0)</td>
</tr>
<tr>
<td></td>
<td>(22.1)</td>
<td>(20.3)</td>
<td></td>
<td>11,403 (61.3)</td>
</tr>
<tr>
<td></td>
<td>35,131</td>
<td>3,242</td>
<td>Cavitary pulmonary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(62.9)</td>
<td>(38.9)</td>
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<td></td>
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<table>
<thead>
<tr>
<th></th>
<th></th>
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<th>Sputum smear</th>
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<tr>
<td>Negative</td>
<td>3,350</td>
<td>570</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>(13.7)</td>
<td>(2.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>5,111</td>
<td>854</td>
<td></td>
<td>18,147 (58.2)</td>
</tr>
<tr>
<td></td>
<td>(16.4)</td>
<td>(2.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Pearson's chi-square test.
Selection of United States TB cases reported to CDC during 1993 through 2010 for inclusion in the analysis of the relationship between tuberculin skin test (TST) results and clinical presentation. *CXR = chest radiograph.

*TST Result and Clinical Category of Disease

In general, we found that persons with a TST \( \geq 15 \text{ mm} \) were less likely to have miliary or combined pulmonary and extrapulmonary disease, but more likely to have
cavitary pulmonary disease relative to non-cavitary pulmonary disease (and Figure 2). However, we found statistical interaction between TST result and the covariates of age, sex, HIV status, and birthplace. Because of an *a priori* interest in the potential for HIV status and birthplace to influence immune system priming and immune status, we chose to stratify the analysis by HIV status and birthplace (and Figure 2). Age and sex were retained in the subsequent regression models but in the interest of presenting a focused analysis we did not stratify on them. The other covariates did not appreciably impact the regression models.

Table 2. Multinomial associations between clinical presentation of disease and tuberculin skin test (TST) result stratified by HIV status and birthplace and adjusted for age and sex among selected culture confirmed TB cases reported in the United States, 1993–2010 (N = 64,238)

<table>
<thead>
<tr>
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<th>Cavitary pulmonary disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aOR* 95% CI*</td>
<td>aOR 95% CI</td>
<td>aOR 95% CI</td>
<td>aOR 95% CI</td>
</tr>
<tr>
<td><strong>HIV+/US</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4 mm</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>5–9 mm</td>
<td>0.96 0.47, 1.95</td>
<td>0.72 0.42, 1.22</td>
<td>1.29 0.81, 2.06</td>
<td>1.11 0.64, 1.94</td>
</tr>
<tr>
<td>10–14 mm</td>
<td>0.72 0.51, 1.01</td>
<td>0.81 0.65, 1.01</td>
<td>1.23 1.00, 1.53</td>
<td><strong>1.36</strong> 1.07, 1.72</td>
</tr>
<tr>
<td>≥ 15 mm</td>
<td><strong>0.50</strong> 0.37, 0.68</td>
<td>0.86 0.72, 1.03</td>
<td>1.09 0.91, 1.31</td>
<td><strong>1.56</strong> 1.29, 1.90</td>
</tr>
<tr>
<td><strong>HIV+/FB</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0–4 mm</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>5–9 mm</td>
<td>0.18 0.02, 1.29</td>
<td>0.93 0.49, 1.79</td>
<td>1.01 0.53, 1.94</td>
<td>1.68 0.75, 3.75</td>
</tr>
<tr>
<td>10–14 mm</td>
<td>0.66 0.42, 1.04</td>
<td>0.80 0.60, 1.08</td>
<td>0.96 0.71, 1.28</td>
<td><strong>1.85</strong> 1.27, 2.69</td>
</tr>
<tr>
<td></td>
<td>0–4 mm</td>
<td>5–9 mm</td>
<td>10–14 mm</td>
<td>≥ 15 mm</td>
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</tr>
<tr>
<td><strong>HIV-/US</strong></td>
<td>Ref</td>
<td>0.77</td>
<td>0.49</td>
<td>0.41</td>
</tr>
<tr>
<td>0–4 mm</td>
<td>Ref</td>
<td>0.43</td>
<td>0.37</td>
<td>0.32</td>
</tr>
<tr>
<td>5–9 mm</td>
<td>1.09</td>
<td>0.78</td>
<td>0.64</td>
<td>0.80</td>
</tr>
<tr>
<td>10–14 mm</td>
<td></td>
<td>1.05</td>
<td>0.92</td>
<td>1.11</td>
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<td></td>
<td>1.32</td>
<td>1.11</td>
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</tr>
<tr>
<td><strong>HIV-/FB</strong></td>
<td>Ref</td>
<td>0.56</td>
<td>0.22</td>
<td>0.19</td>
</tr>
<tr>
<td>0–4 mm</td>
<td>Ref</td>
<td>0.34</td>
<td>0.16</td>
<td>0.15</td>
</tr>
<tr>
<td>5–9 mm</td>
<td>0.61</td>
<td>0.43</td>
<td>0.42</td>
<td>0.56</td>
</tr>
<tr>
<td>10–14 mm</td>
<td></td>
<td>0.82</td>
<td>0.74</td>
<td>1.03</td>
</tr>
<tr>
<td>≥ 15 mm</td>
<td></td>
<td>0.84</td>
<td>0.92</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Non-cavitary pulmonary disease, with the largest number of cases, is the referent clinical category and 0–4 mm (negative) is the referent TST category for all comparisons.

* *aOR* adjusted odds ratio, 95% CI 95% Confidence Interval.

Note: Numbers in bold represent significant 95% confidence intervals.
Table 2. Multinomial associations between clinical presentation of disease and tuberculin skin test (TST) result stratified by HIV status and birthplace and adjusted for age and sex among selected culture confirmed TB cases reported in the United States, 1993–2010 (N = 64,238)

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<td>aOR 95% CI</td>
<td>aOR 95% CI</td>
</tr>
<tr>
<td>HIV+/US</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4 mm</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
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</tr>
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<tr>
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<td>0.96 0.71, 1.28</td>
<td>1.85 1.27, 2.69</td>
</tr>
<tr>
<td>≥ 15 mm</td>
<td>0.59 0.40, 0.86</td>
<td>0.65 0.50, 0.84</td>
<td>1.16 0.92, 1.47</td>
<td>2.20 1.60, 3.02</td>
</tr>
<tr>
<td>HIV-/US</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4 mm</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
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</tr>
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</tr>
</tbody>
</table>
Non-cavitary pulmonary disease, with the largest number of cases, is the referent clinical category and 0–4 mm (negative) is the referent TST category for all comparisons.

*aOR* adjusted odds ratio, *95% CI* 95% Confidence Interval.

Note: Numbers in bold represent significant 95% confidence intervals.
Figure 2.

Association between TST result and clinical presentation of disease relative to a TST of 0–4 mm and relative to non-cavitary pulmonary disease, stratified by HIV status and birthplace and adjusted for age and sex (N = 64,238). The log of the adjusted odds ratio and their 95% confidence intervals are presented.

Across all strata, persons with a TST ≥ 15 mm had significantly decreased odds of miliary disease relative to non-cavitary pulmonary disease. (Non-cavitary pulmonary
The inverse relationship between a positive TST and miliary disease was strongest among persons without HIV for whom those with a TST \(\geq 15\) mm had 59–81\% lower odds of having miliary disease (US-born adjusted odds ratio [aOR] 0.41 [95\% confidence interval [CI] 0.32, 0.53]; foreign-born aOR 0.19 [95\% CI 0.15, 0.25]) (and Figure 2). Persons with HIV who had a TST \(\geq 15\) mm had 41–50\% lower odds of having miliary disease (US-born aOR 0.50 [95\% CI 0.37, 0.68]; foreign-born aOR 0.59 [95\% CI 0.40, 0.86]). Persons with a TST of 5–9 mm or 10–14 mm also had decreased odds of miliary disease; however, the associations were not consistently statistically significant.

Table 2. Multinomial associations between clinical presentation of disease and tuberculin skin test (TST) result stratified by HIV status and birthplace and adjusted for age and sex among selected culture confirmed TB cases reported in the United States, 1993–2010 (N = 64,238)

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<th>Extrapulmonary only disease</th>
<th>Cavitary pulmonary disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aOR*</td>
<td>95% CI*</td>
<td>aOR</td>
<td>95% CI</td>
</tr>
<tr>
<td>HIV+/US</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4 mm</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>5–9 mm</td>
<td>0.96</td>
<td>0.47, 1.95</td>
<td>0.72</td>
<td>0.42, 1.22</td>
</tr>
<tr>
<td>10–14 mm</td>
<td>0.72</td>
<td>0.51, 1.01</td>
<td>0.81</td>
<td>0.65, 1.01</td>
</tr>
<tr>
<td>(\geq 15) mm</td>
<td>0.50</td>
<td>0.37, 0.68</td>
<td>0.86</td>
<td>0.72, 1.03</td>
</tr>
<tr>
<td>HIV+/FB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4 mm</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>5–9 mm</td>
<td>0.18</td>
<td>0.02, 1.29</td>
<td>0.93</td>
<td>0.49, 1.79</td>
</tr>
<tr>
<td>10–14 mm</td>
<td>0.66</td>
<td>0.42, 1.29</td>
<td>0.80</td>
<td>0.60, 1.08</td>
</tr>
</tbody>
</table>
Non-cavitary pulmonary disease, with the largest number of cases, is the referent clinical category and 0–4 mm (negative) is the referent TST category for all comparisons.

*aOR* adjusted odds ratio, 95% CI 95% Confidence Interval.

Note: Numbers in bold represent significant 95% confidence intervals.

Persons with a positive TST were also less likely to have combined pulmonary and extrapulmonary disease. However, the associations were not as strong as those seen with miliary disease (and Figure 2). Persons without HIV who had a TST ≥ 15
mm were significantly less likely to have combined pulmonary and extrapulmonary disease and the strength of association was stronger among foreign-born persons than US-born persons (foreign-born aOR 0.56 [95% CI 0.48, 0.67]; US-born aOR 0.80 [95% CI 0.70, 0.93]). Among persons with HIV, the association between TST result and having combined pulmonary and extrapulmonary disease was significant for foreign-born persons with a TST of ≥ 15 mm (aOR 0.65 [95% CI 0.50, 0.84]) but not for US-born persons (aOR 0.86 [95% CI 0.72, 1.03]).

Table 2. Multinomial associations between clinical presentation of disease and tuberculin skin test (TST) result stratified by HIV status and birthplace and adjusted for age and sex among selected culture confirmed TB cases reported in the United States, 1993–2010 (N = 64,238)

<table>
<thead>
<tr>
<th></th>
<th>Miliary disease</th>
<th>Pulmonary &amp; Extrapulmonary disease</th>
<th>Extrapulmonary only disease</th>
<th>Cavitary pulmonary disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aOR*</td>
<td>95% CI*</td>
<td>aOR</td>
<td>95% CI</td>
</tr>
<tr>
<td>HIV+/US</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4 mm</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>5–9 mm</td>
<td>0.96</td>
<td>0.47, 1.95</td>
<td>0.72</td>
<td>0.42, 1.22</td>
</tr>
<tr>
<td>10–14 mm</td>
<td>0.72</td>
<td>0.51, 1.01</td>
<td>0.81</td>
<td>0.65, 1.01</td>
</tr>
<tr>
<td>≥ 15 mm</td>
<td>0.50</td>
<td>0.37, 0.68</td>
<td>0.86</td>
<td>0.72, 1.03</td>
</tr>
<tr>
<td>HIV+/FB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4 mm</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>5–9 mm</td>
<td>0.18</td>
<td>0.02, 1.29</td>
<td>0.93</td>
<td>0.49, 1.79</td>
</tr>
<tr>
<td>10–14 mm</td>
<td>0.66</td>
<td>0.42, 1.04</td>
<td>0.80</td>
<td>0.60, 1.08</td>
</tr>
<tr>
<td>≥ 15 mm</td>
<td>0.59</td>
<td>0.40, 0.65</td>
<td>0.65</td>
<td>0.50, 0.84</td>
</tr>
</tbody>
</table>
Non-cavitary pulmonary disease, with the largest number of cases, is the referent clinical category and 0–4 mm (negative) is the referent TST category for all comparisons.

*aOR adjusted odds ratio, 95% CI 95% Confidence Interval.

Note: Numbers in bold represent significant 95% confidence intervals.

US-born persons without HIV and all persons with HIV who had a TST ≥ 15 mm were significantly more likely to have cavitary pulmonary disease. The strength of association was greatest for foreign-born persons with HIV where those with a TST of ≥ 15 mm had an aOR of 2.20 (95% CI 1.60, 3.02) for having cavitary pulmonary disease. In contrast, foreign-born persons without HIV who had a positive TST were
less likely to have cavitary pulmonary disease (aOR 0.81 [95% CI 0.73–0.90] for TST ≥ 15 mm).

With regard to extrapulmonary only disease, there were no consistent differences between the odds of extrapulmonary disease and non-cavitary pulmonary disease by TST result.

**TST Result and Sputum Smear Positivity**

Among persons with exclusively pulmonary disease, 50% of those with non-cavitary disease and 83% of those with cavitary disease had a positive sputum smear (>). For persons with non-cavitary pulmonary disease, the odds of having a positive sputum smear result for AFB were significantly decreased among those with a TST ≥ 10 mm. Foreign-born persons with HIV who had a TST ≥ 15 mm had half the odds of having a positive sputum smear when compared to those with a negative TST (aOR 0.50 [95% CI 0.39–0.65]). However, among persons with cavitary pulmonary disease, TST had no consistent association with sputum smear status.

**Table 3. Association between TST result and sputum smear result for AFB among persons with culture-confirmed pulmonary TB, stratified by HIV status and birthplace and adjusted for age and sex (N = 46,680)**

<table>
<thead>
<tr>
<th></th>
<th>Non-cavitary pulmonary disease</th>
<th></th>
<th></th>
<th>Cavitary pulmonary disease</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Smear-positive (%)</td>
<td>aOR*</td>
<td>95% CI*</td>
<td>Total</td>
<td>Smear-positive (%)</td>
</tr>
<tr>
<td>HIV+/US</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4 mm</td>
<td>1,073</td>
<td>651 (61)</td>
<td>Ref</td>
<td></td>
<td>183</td>
<td>135 (74)</td>
</tr>
<tr>
<td>5–9 mm</td>
<td>79</td>
<td>44 (56)</td>
<td>0.78</td>
<td>0.49, 1.24</td>
<td>16</td>
<td>14 (88)</td>
</tr>
<tr>
<td>10–14 mm</td>
<td>603</td>
<td>317 (53)</td>
<td>0.72</td>
<td>0.59, 0.88</td>
<td>139</td>
<td>117 (84)</td>
</tr>
<tr>
<td>≥ 15 mm</td>
<td>1,182</td>
<td>545 (46)</td>
<td>0.56</td>
<td>0.47, 0.66</td>
<td>320</td>
<td>245 (77)</td>
</tr>
<tr>
<td>Sub-total</td>
<td>2,937</td>
<td>1,557 (53)</td>
<td>Ref</td>
<td></td>
<td>658</td>
<td>511 (78)</td>
</tr>
<tr>
<td>HIV+/FB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–4 mm</td>
<td>522</td>
<td>325 (62)</td>
<td>Ref</td>
<td></td>
<td>62</td>
<td>48 (77)</td>
</tr>
<tr>
<td>Size Range</td>
<td>Count</td>
<td>Cases (%)</td>
<td>Hazard Ratio</td>
<td>95% CI</td>
<td>Count</td>
<td>Cases (%)</td>
</tr>
<tr>
<td>------------</td>
<td>-------</td>
<td>-----------</td>
<td>--------------</td>
<td>--------</td>
<td>-------</td>
<td>-----------</td>
</tr>
<tr>
<td>5–9 mm</td>
<td>36</td>
<td>24 (67)</td>
<td>1.20</td>
<td>0.59, 2.47</td>
<td>7</td>
<td>4 (57)</td>
</tr>
<tr>
<td>10–14 mm</td>
<td>267</td>
<td>140 (52)</td>
<td>0.67</td>
<td>0.50, 0.91</td>
<td>61</td>
<td>37 (61)</td>
</tr>
<tr>
<td>≥ 15 mm</td>
<td>483</td>
<td>217 (45)</td>
<td>0.50</td>
<td>0.39, 0.65</td>
<td>130</td>
<td>102 (78)</td>
</tr>
<tr>
<td>Sub-total</td>
<td>1,308</td>
<td>706 (54)</td>
<td></td>
<td></td>
<td>260</td>
<td>191 (73)</td>
</tr>
</tbody>
</table>

### HIV-/US

<table>
<thead>
<tr>
<th>Size Range</th>
<th>Count</th>
<th>Cases (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>Count</th>
<th>Cases (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4 mm</td>
<td>2,051</td>
<td>1,195 (58)</td>
<td>Ref</td>
<td></td>
<td>1,430</td>
<td>1,232 (86)</td>
<td>Ref</td>
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<tr>
<td>5–9 mm</td>
<td>285</td>
<td>159 (56)</td>
<td>0.89</td>
<td>0.69, 1.14</td>
<td>273</td>
<td>236 (86)</td>
<td>0.99</td>
<td>0.68, 1.44</td>
</tr>
<tr>
<td>10–14 mm</td>
<td>2,759</td>
<td>1,504 (55)</td>
<td>0.84</td>
<td>0.74, 0.94</td>
<td>2,137</td>
<td>1,795 (84)</td>
<td>0.78</td>
<td>0.64, 0.95</td>
</tr>
<tr>
<td>≥ 15 mm</td>
<td>7,576</td>
<td>3,745 (49)</td>
<td>0.69</td>
<td>0.62, 0.76</td>
<td>5,960</td>
<td>5,027 (84)</td>
<td>0.80</td>
<td>0.68, 0.95</td>
</tr>
<tr>
<td>Sub-total</td>
<td>12,671</td>
<td>6,603 (52)</td>
<td></td>
<td></td>
<td>9,800</td>
<td>8,290 (85)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### HIV-/FB

<table>
<thead>
<tr>
<th>Size Range</th>
<th>Count</th>
<th>Cases (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>Count</th>
<th>Cases (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4 mm</td>
<td>831</td>
<td>468 (56)</td>
<td>Ref</td>
<td></td>
<td>600</td>
<td>482 (80)</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>5–9 mm</td>
<td>314</td>
<td>159 (51)</td>
<td>0.78</td>
<td>0.60, 1.02</td>
<td>180</td>
<td>150 (83)</td>
<td>1.23</td>
<td>0.79, 1.91</td>
</tr>
<tr>
<td>10–14 mm</td>
<td>2,702</td>
<td>1,338 (50)</td>
<td>0.74</td>
<td>0.63, 0.87</td>
<td>1,790</td>
<td>1,466 (82)</td>
<td>1.10</td>
<td>0.87, 1.39</td>
</tr>
<tr>
<td>≥ 15 mm</td>
<td>7,992</td>
<td>3,626 (45)</td>
<td>0.62</td>
<td>0.54, 0.72</td>
<td>4,637</td>
<td>3,754 (81)</td>
<td>1.03</td>
<td>0.83, 1.28</td>
</tr>
</tbody>
</table>
Probability modeled is of sputum AFB smear positivity.

*aOR* adjusted odds ratio, 95% CI 95% Confidence Interval.

Note: Numbers in bold represent significant 95% confidence intervals.

**Discussion**

In this analysis of TB cases in the United States, 15.9% of persons with culture-confirmed TB had a negative TST result, and clinical presentation of disease differed by TST result. Overall, persons with a negative TST result were significantly more likely to have miliary or combined pulmonary and extrapulmonary disease, which is consistent with reports from smaller cohorts.\(^1,16,17\) At the same time, persons with a positive TST were typically more likely to have cavitary pulmonary disease as compared to non-cavitary pulmonary disease. A similar relationship has been seen in a rabbit model of aerosolized TB infection whereby more cavities were present in rabbits with strong tuberculin reactions.\(^16\) Importantly, the associations between TST result and clinical presentation of disease were substantially impacted by HIV status and birthplace.

We found that half of persons with non-cavitary pulmonary disease had positive sputum smear results, and this smear positivity was significantly associated with having a negative TST. This association between sputum smear result and TST result was not seen in persons with cavitary pulmonary disease. Our findings support the notion that there may be several mechanisms for the buildup of sufficient bacteria to be visualized by smear microscopy, and smear positive disease in the absence of cavities may be associated with some aspect of immune function that is assayed by the TST.\(^19\) Additionally, several recent studies suggest that *Mycobacterium tuberculosis* (*M. tuberculosis*) benefits from a more active immune response and postulate that direct engagement of *M. tuberculosis* with the human immune system favors cavity formation thereby increasing the likelihood of subsequent aerosol transmission.\(^20–23\) Taken together with our results, this suggests a complex interaction between *M. tuberculosis* and the host immune system that results in different disease manifestations and potential for transmission.

Our finding that HIV status and birthplace impacted the association between TST result and clinical presentation of disease is noteworthy. Associations between TST result and clinical presentation were generally consistent across all strata with the exception of cavitary pulmonary disease. Persons with HIV and US-born persons without HIV who had a TST ≥ 15 mm were significantly more likely to have cavitary
pulmonary disease while foreign-born persons without HIV who had a TST ≥ 15 mm were significantly less likely to have cavitary pulmonary disease.

The basis of these differences according to birthplace is not known; however, US- and foreign-born persons with TB in the US differ in several notable respects. One difference in these populations is in the likelihood of previous exposure to *M. tuberculosis* complex. Most foreign-born cases of TB in the US are among persons from countries with high rates of TB and thus potential for repeated exposure in their country of origin. Additionally, BCG vaccination as a child is virtually universal among immigrants to the US from medium and high TB burden countries. Thus, foreign-born persons who develop TB in the US are substantially more likely to have had prior exposure to mycobacteria (TB and/or BCG) with resultant sensitization of their immune system and the potential for pre-existing immune function directed against mycobacteria. This immune priming may serve to limit more disseminated forms of TB disease (i.e., miliary and combined pulmonary and extrapulmonary), in a manner potentially analogous to BCG vaccination where vaccinated children have decreased incidence of disseminated disease.

Another potential difference between US- and foreign-born persons may be the timing of disease relative to infection. Disease among US-born persons is more often associated with recent transmission whereas TB among foreign-born persons in the US is thought to be primarily due to reactivation of latent TB. Hence, cavitation may represent a vigorous, but locally damaging immune response more commonly associated with recent infection. The lower risk of cavitation seen among foreign-born persons without HIV who had a positive TST may represent a "survivor effect" related to different disease manifestations in the setting of reactivation disease. It is also possible that US- and foreign-born persons have differences in their likelihood of undergoing TB screening or different social or nutritional factors that impact both their immune response and their presentation of disease.

This analysis utilized cross-sectional data and so we could not determine the relative timing of clinical disease presentation and TST result. Prospective studies are needed to determine whether the immune response represented by the TST is a driver of clinical disease presentation or a consequence of infection where, for example, greater presence of mycobacteria may trigger a larger TST response. Although numerous reviews cite disseminated infection as a potential cause of a negative TST in the setting of active disease, it is also possible that disseminated infection occurs as a result of a diminished or impaired host immune response as assayed by the TST.

By limiting our analysis to persons with a documented TST result, we excluded nearly half of the TB cases reported in the United States during the study period. Statistically significant differences were found between the included and excluded populations for all sociodemographic and clinical variables. Therefore, there is a possibility that the population studied was not representative of the entire US surveillance cohort. Nevertheless, we were still able to include a very large cohort of
persons with culture-confirmed TB. We also limited our analysis to persons with a known HIV status because we found that the relationship between TST result and clinical presentation varied by HIV status. Similarly, data from California, which accounts for approximately 20% of TB cases in the United States, were excluded because HIV results were not routinely reported to CDC. However, results of a sensitivity analysis including cases reported from California were not appreciably different (data not shown).

Conclusions
Overall, this analysis provides recent population-level data about the relationship between TST result, a marker of host immune response, and the clinical presentation of active TB disease. Our findings suggest that the significance of the TST result may extend beyond its traditional role as a marker of infection and may be relevant to the pathophysiology and presentation of active disease, even among persons without overt immune dysfunction. The differences in site of disease by TST result may indicate that the TST could be a useful adjunct for identifying patients with different underlying immune system susceptibility to and interaction with *M. tuberculosis*. A better understanding of these differences may provide insight into differential responses to vaccine candidates or TB treatment. Our finding that persons with a positive TST result were less likely to have disseminated disease may parallel the effect of BCG immunization which usually results in transient TST positivity and decreased risk of disseminated disease in children.[31] Future vaccine trials may want to consider including both TST result and clinical presentation of TB disease in their study outcomes since immunization may impact the likelihood of cavity formation or of disseminated disease, both of which would have implications for TB transmission and mortality. Broader incorporation of tuberculin skin testing in TB trials and prospective studies may prove informative as part of the ongoing effort to better understand the relationship between the immune system and *Mycobacterium tuberculosis*.

References


Authors' contributions

SCA, ESC, CMH, RM, KPC, GPB, and WRM substantially contributed to the study conception and design. SCA performed the statistical analyses and wrote the first draft of the manuscript. CMH provided statistical oversight and guidance. ESC, CMH, RM, KPC, GPB, and WRM critically revised the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript.

Acknowledgment

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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**Miliary Tuberculosis**

- **Overview of Miliary Tuberculosis**
Miliary tuberculosis (TB) is the widespread dissemination of *Mycobacterium tuberculosis* via hematogenous spread. Classic miliary TB is defined as milletlike (mean, 2 mm; range, 1-5 mm) seeding of TB bacilli in the lung, as evidenced on chest radiography. This pattern is seen in 1-3% of all TB cases.\(^1\,2\,3\,4\,5\)

Miliary TB may occur in an individual organ (very rare, < 5%), in several organs, or throughout the entire body (>90%), including the brain. The infection is characterized by a large amount of TB bacilli, although it may easily be missed and is fatal if left untreated.

Up to 25% of patients with miliary TB may have meningeal involvement. In addition, miliary TB may mimic many diseases. In some case series, up to 50% of cases are undiagnosed antemortem. Therefore, a high index of clinical suspicion is important to obtain an early diagnosis and to ensure improved clinical outcomes.

Early empirical treatment for possible but not yet definitive miliary TB increases the likelihood of survival and should never be withheld while test results are pending. On autopsy, multiple TB lesions are detected throughout the body in organs such as the lungs, liver, spleen, brain, and others.

### Pathophysiology of Miliary TB
Following exposure and inhalation of TB bacilli in the lung, a primary pulmonary complex is established, followed by development of pulmonary lymphangitis and hilar lymphadenopathy. Mycobacteremia and hematogenous seeding occur after the primary infection. After initial inhalation of TB bacilli, miliary tuberculosis may occur as primary TB or may develop years after the initial infection. The disseminated nodules consist of central caseating necrosis and peripheral epithelioid and fibrous tissue. Radiographically, they are not calcified (as opposed to the initial Ghon focus, which is often visible on chest radiographs as a small calcified nodule).

Etiology of Miliary TB
Risk factors for miliary tuberculosis involve immunosuppression and include, but are not limited to, the following:

- Cancer
- Transplantation
- \textbf{HIV infection}\cite{6,7}
- Malnutrition
- Diabetes
- \textbf{Silicosis}
- End-stage renal disease
- Major surgical procedures - Occasionally may trigger dissemination

Epidemiology of Miliary TB
Of all patients with TB, 1.5% are estimated to have miliary tuberculosis. The World Health Organization reports that 2-3 million patients die with or from all forms of TB each year.\cite{1,8,9}

The incidence of miliary TB may be higher in African Americans in the United States because of socioeconomic risk factors and may be more common in men than in women because of socioeconomic and medical risk factors. No genetic predisposition has been identified.

Miliary disease is more difficult to detect in patients who are very young or very old. Children younger than 5 years who acquire miliary TB are more likely to develop life-threatening miliary and/or meningeal TB. The disease usually follows primary infection, with no or only a short latency period. Adults older than 65 years have a higher risk of miliary TB. Clinically, it may be subacute or may masquerade as a malignancy. If undiagnosed, the disease is detected at autopsy.

Clinical Manifestations of Miliary TB
Patients with miliary tuberculosis may experience progressive symptoms over days to weeks or occasionally over several months.\cite{10,11} Symptoms include the following:

- Weakness, fatigue (90%)
- Weight loss (80%)
- Headache (10%)
Signs of miliary TB include the following:

- Subtle signs, such as low-grade fever (20%)
- Fever (80%)
- Cough (60%)
- Generalized lymphadenopathy (40%)
- Hepatomegaly (40%)
- Splenomegaly (15%)
- Pancreatitis (< 5%)
- Multiorgan dysfunction, adrenal insufficiency

**Differential Diagnosis of Miliary TB**

The differential diagnosis of miliary tuberculosis includes the following:

- Acute respiratory distress syndrome
- Addison disease
- Ascites
- Blastomycosis
- Cardiac tamponade
- Disseminated intravascular coagulation
- Epididymal tuberculosis
- Hypersensitivity pneumonitis
- *Pneumocystis carinii* pneumonia
- Bacterial pneumonia
- Community-acquired pneumonia
- Fungal pneumonia
- Viral pneumonia

Other problems to be considered include the following:

- Fungal infection
- Histiocytosis X (Langerhans cell histiocytosis)
- HIV-related pulmonary opportunistic infections
- Lymphangitic spread of cancer (eg, thyroid carcinoma, malignant melanoma)
- Measles
- Pancreatic abscess
- Pulmonary alveolar microlithiasis
- Talc granulomatosis

**Laboratory Studies for Miliary TB**

**Chemistry**

A decrease in sodium levels may correlate with disease severity, and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or hypoadrenalism may complicate tuberculosis (TB). In approximately 30% of cases, alkaline phosphatase levels are elevated.
Elevated levels of transaminases suggest liver involvement or, if treatment has been initiated, drug toxicity.

**Complete blood count**

Leukopenia/leukocytosis may be present in miliary tuberculosis. Leukemoid reactions may occur; patients may have anemia; and thrombocytopenia or, rarely, thrombocytosis may be present.

**Erythrocyte sedimentation rate**

The erythrocyte sedimentation rate is elevated in approximately 50% of patients.

**Cultures for mycobacteria**

Cultures, as available, may include those of the sputum, blood, urine, or cerebral spinal fluid. Sensitivity testing is essential for all positive isolates, and consider investigation for multidrug-resistant TB (MDR-TB) in all cases. Negative sputum smear results (even 3 negatives) do not exclude the possibility of TB.

For mycobacterial blood cultures, findings are positive in approximately 5% of patients who do not have HIV infection. Findings are positive in many patients who have HIV infection. One study yielded an 85% positivity rate.

**Lumbar puncture** should be strongly considered, even with normal brain MRI findings, and may reveal any of the following:

- Leukocytes: Approximately 65% of patients have WBC counts with 100-500 mononuclear cells/μL.
- Lymphocytic predominance (70%)
- CSF lactic acid levels are mildly elevated.
- Elevated protein levels (90%)
- Low glucose levels (90%)
- RBCs are common
- Acid-fast bacilli (≥40% with serial spinal taps)

**Coagulation studies**

Measure the prothrombin time/activated partial thromboplastin time (PT/aPTT) prior to biopsy.

**Tuberculin skin test**

The tuberculin skin test with purified protein derivative (PPD) often yields negative results in patients with miliary TB. This may be explained by the large number of TB antigens throughout the body. Negative tuberculosis skin testing results do not exclude the possibility of TB.

**Nucleic acid probes**
Specificity for smear-negative and culture-negative specimens is lower than 100% (false-negative results). False-positive TB cultures are of concern, and the rate is estimated to be approximately 5%. This may be due to laboratory contamination.

Polymerase chain reaction testing of the blood may yield positive results in most cases of HIV-related disseminated TB; the yield is low in non-HIV miliary TB.

**Imaging Studies for Miliary TB**

**Chest radiography**
Findings are typical in 50% of cases. A bright spotlight helps to reveal miliary nodules. Bilateral pleural effusions indicate dissemination versus localized and unilateral pleural TB. This may be a useful clinical clue. Nodules characteristic of miliary TB may be better visualized on lateral chest radiography (especially in the retrocardiac space).

**Chest CT scanning**
Chest CT scanning has higher sensitivity and specificity than chest radiography in displaying well-defined randomly distributed nodules. High-resolution CT scanning with 1-mm cuts may be even better. It is useful in the presence of suggestive and inconclusive chest radiography findings.

**Ultrasonography**
Ultrasonography may reveal diffuse liver disease, hepatomegaly, splenomegaly, or para-aortic lymph nodes.

**Head CT scanning with contrast and/or MRI of the brain**
Use this to assess for suspected TB lesions. Hydrocephalus or a cerebral mass lesion (tuberculoma) may increase the risk of herniation if lumbar puncture is performed.

**Abdominal CT scanning**
Abdominal CT scanning may reveal para-aortic lymph nodes, hepatosplenomegaly, or tuberculous abscess.

**Echocardiography**
Echocardiography is the most sensitive test for pericardial effusion.

**Additional Tests and Procedures for Miliary TB**
Additional tests and procedures for miliary tuberculosis include the following:

- Funduscopy may reveal retinal tubercles
- Electrocardiography helps evaluate for pericardial effusion; right ventricular hypertrophy may indicate pulmonary hypertension prior to lung biopsy
Miliary TB in a child indicates recent transmission, and contact investigation could identify the source case and associated susceptibilities; contact investigation of child index cases should be conducted quickly, and thoroughly evaluate household contacts by means of tuberculin skin testing and, if the test results are positive, chest radiography.

- Sputum induction has low sensitivity, and findings are smear-negative and culture-negative in 80% of patients because of hematogenous spread.
- Fiberoptic bronchoscopy is the most effective procedure for obtaining cultures (bronchoalveolar lavage).
- The culture yield for transbronchial biopsies is 90%.
- Bone marrow biopsy yield is approximately 50%, without serious adverse effect.
- In liver biopsy, liver bleeding is a serious and potentially life-threatening complication estimated to occur in approximately 10% of cases.
- For abdominal involvement, laparoscopy is useful to obtain tissue and material for culture.

Histologic Findings of Miliary TB

Necrotizing granulomas are the hallmark of TB, and staining for acid-fast bacilli reveals rodlike structures in approximately 80% of specimens (see the image below). The disseminated nodules consist of central caseating necrosis and peripheral epithelioid and fibrous tissue. Radiographically, the nodules are not calcified.

Treatment Overview for Miliary TB

Miliary TB with meningeal involvement may require prolonged treatment (up to 12 mo). Early treatment of patients with suspected miliary tuberculosis decreases the likelihood of mortality and improves outcome. Surgical treatment is rarely necessary. Occasionally, a ventriculoatrial shunt is indicated for hydrocephalus. Consultations may include the following:

- Pulmonary and critical care specialists
- Infectious disease specialist
- Neurologist - Steroids for meningitis or paradoxically increasing tuberculomas...
• TB expert
• Health department notification
• Appropriate infection control measures
• Failure to involve a TB specialist may lead to acquired resistant TB.

Adequate attention to nutrition is important. Many patients with miliary TB are debilitated by the disease, and malnutrition can contribute to a weakened immune system.

Once the patient receives several weeks of effective therapy, experiences significant clinical improvement, and has negative sputum acid-fast bacillus smears, restrictions are minimal. However, one must be certain that the patient truly is no longer contagious. The absence of sputum positivity does not guarantee others protection against exposure. Directly observed therapy is optimal for assuring compliance and preventing relapse.

Paradoxical enlargement of the lymph nodes or intracerebral tuberculomas during adequate treatment may require steroids. Hydrocephalus may require neurosurgical decompression.

Pharmacological Therapy for Miliary TB

Early empirical therapy for suspected miliary tuberculosis is prudent. A delay of even 1-8 days contributes to a high mortality rate. Steroids are warranted for hypotension due to presumed adrenal insufficiency after an adrenocorticotropic hormone (ACTH) stimulation test.

For susceptible organisms, the treatment period is 6-9 months. For meningitis, it is 9-12 months. For miliary TB with meningeal involvement, daily medications for the entire length of therapy are recommended.

Three basic rules apply in the prevention of entirely "doctor-made" resistant TB:

1. Rifampin is the drug of choice for treatment; in most cases, the treatment duration is at least 18 months without rifampin

2. Ethambutol (EMB) is used to prevent rifampin resistance if the organism is resistant to isoniazid (INH); EMB can be discontinued as soon as the organism is found to be susceptible to rifampin and INH

3. Pyrazinamide is used for the first 2 months of treatment to decrease the treatment duration from 9 months to 6 months if the organism is susceptible to rifampin and INH

For MDR-TB, use a minimum of 1 susceptible injectable and at least 3 additional susceptible drugs to prevent the development of additional resistance. Treat MDR-TB with the consultation of an expert in the care of TB.
Intermittent-type therapies have not been established. If MDR-TB test results are pending, increasing the number of drugs is reasonable. For example, use 6 or 7 initial drugs, including an injectable.

Further Inpatient Care for Miliary TB

If the infected patient lives in a home with immunocompromised persons (eg, with HIV infection) or with children younger than 5 years, or if the patient lives in a communal residence type of facility (eg, homeless shelter, senior citizen facility, jail, prison), keep him or her hospitalized until sputum stain results are negative and significant clinical improvement is shown.

Evaluate all close contacts who might have been infected prior to initiation of effective therapy for evidence of tuberculosis (TB). Contagiousness is low because miliary TB spreads hematogenously, not via the endobronchial system. Cavitary lesions are highly unlikely.

Further Outpatient Care for Miliary TB

Patients may start and continue treatment in an outpatient setting if no children or immunocompromised persons are in the home or if the patient is not in a communal residence facility.

Each patient should be offered directly observed therapy in the clinic, home, or workplace.

Miliary TB and Pregnancy

Miliary tuberculosis during pregnancy can be treated safely with RIE (ie, rifampin, INH, vitamin B-6 [25 mg/d] and ethambutol (EMB) [15 mg/kg/d]), but miliary TB in a newborn of a mother with TB is difficult to diagnose.

Placenta examination by the pathologist is imperative. In a newborn, 3 gastric aspirates of the newborn are helpful, but tuberculin skin testing of the newborn during the first 6 months is rarely helpful because of the limited immune response of the newborn. Lumbar puncture is indicated if the newborn does not thrive. Bacille Calmette-Guérin vaccine clouds the interpretation of a positive tuberculin skin test result after age 6 months.

Transfer of Patients with Miliary TB

The patient is usually removed from isolation when 3 consecutive sputum smear results are negative and clinical improvement is shown. The patient must not be confined with immunosuppressed patients prior to the establishment of negative sputum cultures. Place the patient in a negative pressure room or in adequate respiratory isolation.
Patients who discontinue medication may be subject to public health laws. Patients may be remanded to custody and ordered to continue therapy if judged to be a public health hazard.

When ordered compliance is not successful, the health department may obtain an order of detention.

**Prognosis of Miliary TB**

If left untreated, the mortality associated with miliary tuberculosis is assumed to be close to 100%. With early and appropriate treatment, however, mortality is reduced to less than 10%. The earlier the diagnosis, the better the likelihood of a positive outcome. Early treatment for suspected TB has been shown to improve outcome.

Most deaths occur within the first 2 weeks of admission to the hospital. This may be related to delayed onset of treatment. Up to 50% of all cases of disseminated TB detected at autopsy were missed antemortem in reported case series.

The relapse rate is 0-4% with adequate therapy and directly observed therapy, although results from studies vary. Most relapses occur during the first 24 months after completion of therapy.

**Patient Education**

Educate the patient and contacts about the mode of transmission.

For patient education information, see [Bacterial and Viral Infections Center](https://www.medscape.com), as well as [Tuberculosis](https://www.medscape.com).

**READ MORE ABOUT MILIARY TUBERCULOSIS ON MEDSCAPE**

**RELATED REFERENCE TOPICS**

- Myelophthisis Anemia
- Pediatric Tuberculosis

**RELATED NEWS AND ARTICLES**

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- Moxifloxacin Struggles Against Current TB Drugs: REMox Trial
- Diabetes Set to Undermine Success in Global TB Control

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Diagnostic Studies and Therapeutic Regimens

Provided below are recommendations for diagnostic testing for tuberculosis as well as first-line, second-line, and alternative treatment regimens; treatment recommendations for extrapulmonary and for latent disease; special considerations; and monitoring parameters.

**Appropriate cultures**

- Tuberculosis is caused by *Mycobacterium tuberculosis*, and attempts should be made to culture respiratory secretions from all persons with suspected tuberculosis
- When possible, sputum should be collected in the early morning on 3 consecutive days
- In hospitalized patients, sputum can be collected every 8h to obtain information more quickly
- In persons unable to spontaneously produce sputum for culture, other methods for obtaining a respiratory specimen include the following: sputum induction via inhalation of hypertonic saline; gastric lavage (used primarily in young children); and bronchoscopy with bronchial washings
- In the appropriate clinical setting, mycobacterial cultures should be obtained from pleural fluid, lymph nodes, cerebrospinal fluid, or any other tissue that is clinically suspected of involvement
- DNA-based tests provide rapid identification of tuberculosis; DNA probes are approved for direct testing on smear-positive or smear-negative sputa

**Other diagnostic testing**

- Human immunodeficiency virus (HIV) testing should be performed in all patients with tuberculosis and an unknown HIV status
- Drug susceptibility testing for all first-line medications should be obtained
- Tuberculin skin testing (TST) (purified protein derivative [PPD] skin test; Mantoux test) is used primarily to diagnose latent tuberculosis infection (LTBI); TST has limited sensitivity in screening for active tuberculosis

**TST interpretation:**

Cut-offs for interpreting the TST are based on tuberculosis risk factors.

Wheal ≥ 5 mm:

- Close contacts to persons with tuberculosis
- Persons with HIV infection or other significant immunosuppression
- Persons with apical radiographic abnormalities that are suspicious for tuberculosis

Wheal ≥ 10 mm:
- Patients with underlying medical conditions such as diabetes, end-stage renal disease, or severe malnutrition
- Recent immigrants from countries with high tuberculosis incidence
- Recent converters (within 2y)
- Employees or residents of institutional settings, including hospitals, nursing homes, homeless shelters, and correctional facilities

Wheal ≥ 15 mm (with none of the above risk factors):

- Whole blood assay based on interferon-gamma release (IGRA) is an alternative test to TST
- Available tests include QuantiFERON-TB GIT and T-SPOT.TB
- Sensitivity and specificity are similar to TST
- Antigens used for the IGRA tests do not cross-react with BCG

**First-line treatment recommendations (pulmonary disease)**

*Initial-phase therapy*: \(^{2,3,4}\)

- Tuberculosis is caused by organisms that are resistant to isoniazid; therefore, a 4-drug regimen is necessary in the initial phase
- Generally, all adults with previously untreated tuberculosis should get 2-mo initial-phase therapy of the following:
  - **Isoniazid** (INH) 5 mg/kg/day (maximum [max] 300 mg/day, 10 mg/kg/day in children) PO plus
  - **Rifampin** (RIF) 10 mg/kg/day (max 600 mg/day, 15 mg/kg/day in children) PO plus
  - **Pyrazinamide** (PZA) 25 mg/kg/day (max 2 g/day, 35 mg/kg/day in children per World Health Organization [WHO] guidelines, 15-30 mg/kg/day in children per Centers for Disease Control and Prevention [CDC] guidelines) PO plus
  - **Ethambutol** (EMB) 15 mg/kg/day (max 1.6 g/day, 20 mg/kg/day in children) PO

- If PZA cannot be included in the initial phase of treatment, or if the isolate is resistant to PZA alone (an unusual circumstance), the initial phase should consist of INH, RIF, and EMB given daily for 2 mo; examples of circumstances in which PZA may be withheld include severe liver disease, gout, and, perhaps, pregnancy.

**Duration of therapy:**

- The initial phase may be given daily for 2 wk and then twice weekly for 6 wk, or 3 times weekly throughout
- For patients receiving daily therapy, EMB can be discontinued as soon as the results of drug susceptibility studies demonstrate the isolate is susceptible to INH and RIF
- For drug-susceptible tuberculosis, INH, RIF, PZA, and EMB are given until susceptibilities become available; then, EMB can be discontinued
Regardless of the initial therapy, the continuation phase is 4mo with INH plus RIF based on clinical parameters

Intermittent dosing (only for use in patients on directly observed therapy [DOT]):

- INH 20 mg/kg (max 900 mg) PO 3 times weekly plus
- RIF 10 mg/kg (max 600 mg) PO 3 times weekly plus
- PZA 35 mg/kg (max 3000 mg) PO 3 times weekly plus
- EMB 30 mg/kg (max 2800 mg) PO 3 times weekly

Second-line treatments (for drug-resistant tuberculosis or intolerance to first-line drugs)

- Amikacin 15-20 mg/kg IV daily or
- Capreomycin 15-30 mg/kg (max 1000 mg) IV or IM daily or
- Cycloserine 15 mg/kg (max 1000 mg) PO daily (may divide into 2 doses) or
- Ethionamide 250 mg PO BID/TID or
- Levofloxacin 500-1000 mg PO daily or
- Linezolid 600 mg PO BID or
- Moxifloxacin 400 mg PO daily or
- Para-aminosalicylic acid (PAS) 4 g PO TID

Continuation-phase therapy

Treatment should be based on chest x-ray and sputum culture results after 2-mo initial-treatment phase

No cavitation on chest x-ray:

- If negative sputum culture: INH 5 mg/kg/day (max 300 mg/day, 10 mg/kg/day in children) PO plus RIF 10 mg/kg/day (max 600 mg/day, 15 mg/kg/day in children) PO for 4mo or
- INH 5 mg/kg/day (max 300 mg/day, 10 mg/kg/day in children) PO plus rifapentine 300 mg PO once a week for 4mo, which is a treatment option only for nonpregnant, HIV-negative adults without cavitary or extrapulmonary disease who are smear-negative at 2mo
- If positive sputum culture: INH 5 mg/kg/day (max 300 mg/day, 10 mg/kg/day in children) PO plus RIF 10 mg/kg/day (max 600 mg/day, 15 mg/kg/day in children) PO for 4mo or
- INH 5 mg/kg/day (max 300 mg/day, 10 mg/kg/day in children) PO plus rifapentine 300 mg PO once a week for 7mo, which is a treatment option only for nonpregnant, HIV-negative adults without cavitary or extrapulmonary disease who are smear-negative at 2mo

Cavitation on chest x-ray:

- If negative sputum culture: INH 5 mg/kg/day (max 300 mg/day, 10 mg/kg/day in children) PO plus RIF 10 mg/kg/day (max 600 mg/day, 15 mg/kg/day in children) PO for 4mo
If positive sputum culture: INH 5 mg/kg/day (max 300 mg/day, 10 mg/kg/day in children) PO plus RIF 10 mg/kg/day (max 600 mg/day, 15 mg/kg/day in children) PO for 7mo

**Duration of therapy:**

- The continuation phase is given for either 4 or 7mo; the 4-mo treatment is more commonly prescribed
- The 7-mo continuation phase is recommended for 3 groups: (1) patients with cavitary pulmonary tuberculosis caused by drug-susceptible organisms and whose sputum culture obtained at the time of completion of 2mo of treatment is positive; (2) patients whose initial phase of treatment did not include PZA; and (3) patients being treated with once weekly INH and rifapentine and whose sputum culture obtained at the time of completion of the initial phase is positive
- The continuation phase may be given daily, 2 times weekly by DOT, or 3 times weekly by DOT

**Alternative-treatment recommendations**

- Intermittent regimens with rifapentine may be considered for selected patients to avoid relapse or to avoid rifamycin resistance (patients who are HIV positive should not receive rifapentine)
- Rifapentine may be used once weekly with INH in the continuation phase (rifapentine 10 mg/kg [max 600 mg] PO once weekly plus INH 15 mg/kg [max 900 mg] PO once weekly); rifapentine 600 mg PO twice weekly (induction phase)
- Rifabutin can be used as a substitute for rifampin; the recommended dose of rifabutin is 5 mg/kg (max 300 mg) PO daily
- Streptomycin has been shown to be as effective as EMB; general dosing recommendations of streptomycin are 15 mg/kg (max 1000 mg) IM or IV daily given 5-7 times a week and reduced to 2-3 times a week after the first 2-4mo or after culture conversion; streptomycin 10 mg/kg IM or IV is recommended in persons > 59y

**Treatment recommendations for extrapulmonary disease**

- Principles used in the treatment of pulmonary tuberculosis also apply to extrapulmonary tuberculosis
- Treatment with INH and RIF is preferred for a duration of 6mo for most cases of extrapulmonary disease—except for bone and joint disease, which is generally treated for 6-9mo, and neurotuberculosis, which is generally treated for 9-12mo

**Treatment of LTBI**

- Preferred regimen includes INH 300 mg PO daily for 9mo or
- RIF 600 mg PO daily for 4 mo
- INH 900 mg PO plus rifapentine 900 mg PO weekly for 12 weeks (must be administered as directly observed therapy)
- Patients diagnosed with LTBI should have a significant reaction to TST or have a positive blood assay; active tuberculosis should be ruled out

**Special considerations**
• PZA can be given at the usual dose with mild to moderate renal impairment, but the dosing needs to be reduced in patients with severe renal impairment; generally avoid use of PZA during pregnancy, unless the patient has HIV or drug-resistant tuberculosis

• Dosing for streptomycin must be adjusted with any degree of renal impairment and should not be given during pregnancy

• EMB dosing should be decreased with mild to moderate renal impairment; EMB should generally be avoided in patients with severe renal impairment

• Many of the drugs used to treat tuberculosis are potentially hepatotoxic; increased monitoring of hepatic signs and symptoms is important

• Liver enzymes should be monitored at least monthly and more often in patients with severe hepatic impairment; liver enzymes must be monitored at least monthly in patients on tuberculosis therapy

• Renal function should be checked periodically in patients on medications requiring dose adjustments for renal insufficiency

• Hospitalized patients with suspected or documented tuberculosis must be placed in appropriate isolation; this includes a private room with negative pressure and adequate air exchanges; persons entering the room must wear masks or respirators capable of filtering droplet nuclei

• Regimens for the treatment of persons coinfected with HIV and tuberculosis must account for the numerous potential drug-drug interactions between antiretroviral and antituberculosis medications

Monitoring parameters

• Sputum smear and culture should be assessed every 2-4wk until negative

• Therapy should be extended to 9mo if the patient has cavitary disease and remains culture-positive after 2mo of treatment

• Chest radiographs should be reassessed in patients who are not improving clinically

• Serum uric acid should be monitored in patients who require long-term PZA therapy

• Patients who are receiving long-term EMB therapy should undergo periodic visual acuity and red-green color-perception testing