Medscape

Tuberculosis (TB)

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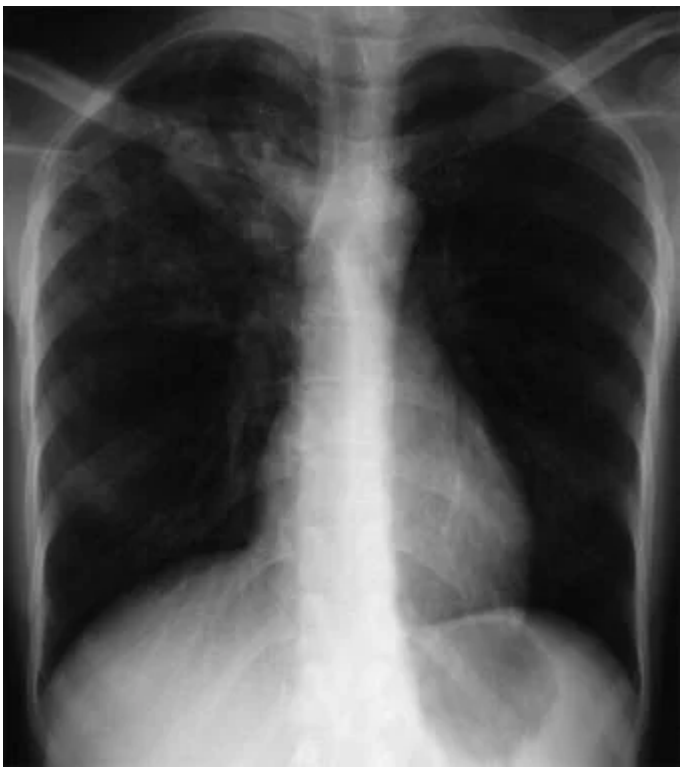
Overview

Practice Essentials

Tuberculosis (TB) (see the image below), 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.



Anteroposterior chest radiograph of a young patient who presented to the emergency department (ED) with cough and malaise. The radiograph shows a classic posterior segment right upper lobe density consistent with active tuberculosis. This woman was admitted to isolation and started empirically on a 4-drug regimen in the ED. Tuberculosis was confirmed on sputum testing. Image courtesy of Remote Medicine (remotemedicine.org).

See 11 Travel Diseases to Consider Before and After the Trip, a Critical Images slideshow, to help identify and manage infectious travel diseases.

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 testwith 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[1]

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[2, 3]
- 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[4]
- In patients with higher CD4+ T-cell counts, it may be reasonable to defer antiretroviral therapy until the continuation phase of TB treatment[5]

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:

- Segmentectomy (rarely used)
- Lobectomy
- Pneumonectomy
- Pleurectomy for thick pleural peel (rarely indicated)

Latent TB

Recommended regimens for isoniazid and rifampin for latent TB have been published by the US Centers for Disease Control and Prevention (CDC)[6, 7, 8] : An alternative regimen for latent TB is isoniazid plus rifapentine as self-administered or directly observed therapy (DOT) once-weekly for 12 weeks[9, 10] ; it is not recommended for children under 2 years, pregnant women or women planning to become pregnant, or patients with TB infection presumed to result from exposure to a person with TB that is resistant to 1 of the 2 drugs.

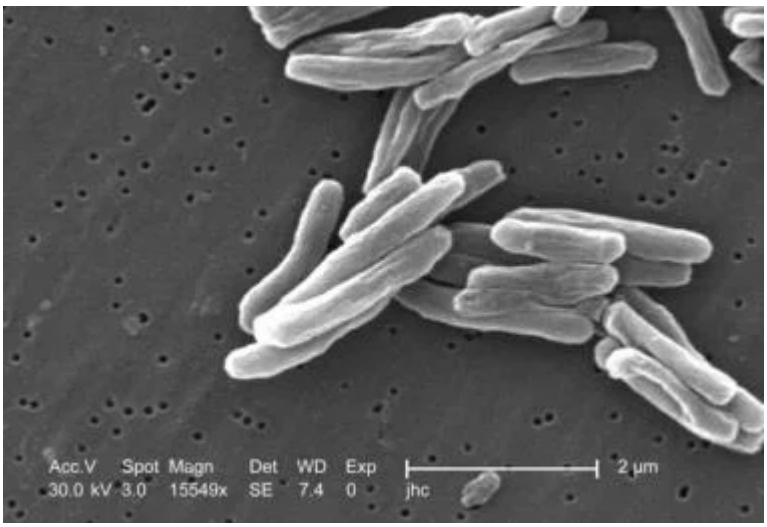
See Treatment and Medication for more detail.

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.[11] (See Epidemiology.)[12]

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.[13] (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.



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,[14] 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.[15] Correspondingly, TB is the leading cause of mortality among persons infected with HIV.[16]

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.[16] 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).[11] XDR-TB resistant to all anti-TB drugs tested has been reported in Italy, Iran, and India.[17]

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.[18]

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.[19]

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.[20]

XDR-TB is becoming increasingly significant.[19] 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.[16] The estimated cure rate for XDR-TB is 30-50%.[11] 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.[21] 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.[22] 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.[23]

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.

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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.

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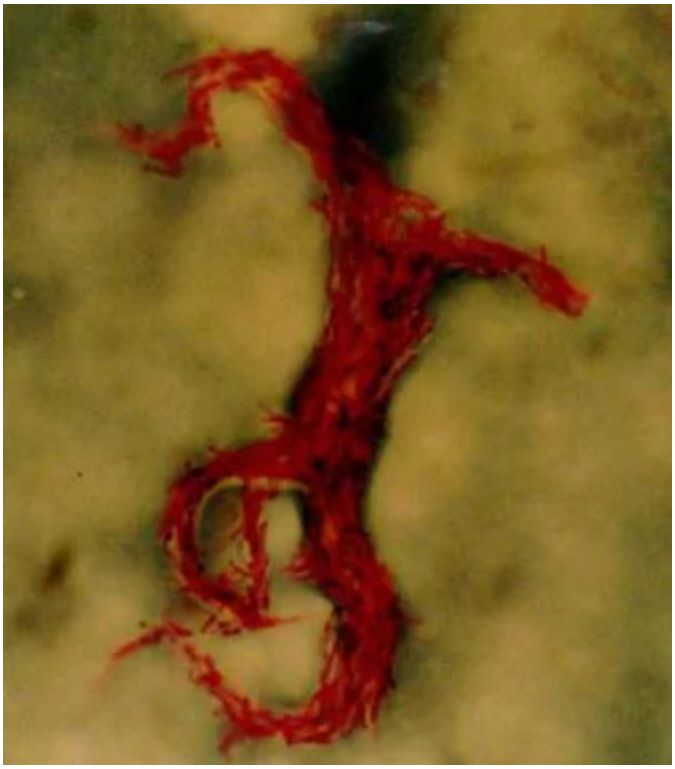
Etiology

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.



Acid-fast bacillus smear showing characteristic cording in Mycobacterium tuberculosis.

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.[24] 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[25]
- Smoking - Smokers who develop TB should be encouraged to stop smoking to decrease the risk of relapse[26]
- 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.[27] 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.[28]

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-q13 are associated with increased risk, although an exact mechanism or candidate gene has not yet been found.

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.[29] The association of NRAMP1 with risk of TB has been replicated in subsequent studies.[30, 31]

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.[32]

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.[33]

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.[34]

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.[35]

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.[36] Subsequent sequencing of the gene showed a nonsense mutation that resulted in a nonfunctional gene product.[37]

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 again invasive pneumococcal disease, bacteremia, malaria, and TB.[38]

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.[39]

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.[20]

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 (15%). However, blacks/African Americans represented 39% of TB cases in US-born persons.[20]

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.[40] 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.[41]

Overall, the WHO noted the following[41] :

- 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%. [41]

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[20] :

- 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.[41] TB is uncommon in children aged 5-15 years.

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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%.[42] In countries with low TB rates, recurrences usually occur within 12 months of treatment completion and are due to relapse.[43] In countries with higher TB rates, most recurrences after appropriate treatment are probably due to reinfection rather than relapse.[44]

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.[45]

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Presentation

History

The following factors increase the likelihood that a patient will have tuberculosis (TB):

- HIV infection
- History of a positive purified protein derivative (PPD) test result
- History of prior TB treatment

- TB exposure
- Travel to or emigration from an area where TB is endemic
- Homelessness, shelter-dwelling, incarceration

Classic clinical features associated with active pulmonary TB are as follows:

- Cough
- Weight loss/anorexia
- Fever
- Night sweats
- Hemoptysis
- Chest pain
- Fatigue

Chest pain in patients with TB can also result from tuberculous acute pericarditis. Pericardial TB can lead to cardiac tamponade or constriction.

Elderly individuals with TB may not display typical signs and symptoms of TB infection, because they may not mount a good immune response. Active TB infection in this age group may manifest as nonresolving pneumonitis.

Signs and symptoms of extrapulmonary TB may be nonspecific. They can include leukocytosis, anemia, and hyponatremia due to the release of ADH (antidiuretic hormone)-like hormone from affected lung tissue.

Tuberculous meningitis

Patients with tuberculous meningitis may present with a headache that has been either intermittent or persistent for 2-3 weeks. Subtle mental status changes may progress to coma over a period of days to weeks. Fever may be low grade or absent.

Skeletal TB

The most common site of skeletal TB involvement is the spine (Pott disease); symptoms include back pain or stiffness. Lower-extremity paralysis occurs in up to half of patients with undiagnosed Pott disease.

Tuberculous arthritis usually involves only 1 joint. Although any joint may be involved, the hips and knees are affected most commonly, followed by the ankle, elbow, wrist, and shoulder. Pain may precede radiographic changes by weeks to months.

Genitourinary TB

Symptoms of genitourinary TB may include flank pain, dysuria, and frequent urination. In men, genital TB may manifest as a painful scrotal mass, prostatitis, orchitis, or epididymitis. In women, genital TB may mimic pelvic inflammatory disease. TB is the cause of approximately 10% of sterility cases in women worldwide and of approximately 1% in industrialized countries.

Go to Tuberculosis of the Genitourinary System and Imaging of Genitourinary Tuberculosis for complete information on these topics.

Gastrointestinal TB

Any site along the gastrointestinal tract may become infected. Symptoms of gastrointestinal TB are referable to the infected site and include the following:

Nonhealing ulcers of the mouth or anus

Difficulty swallowing - With esophageal disease

Abdominal pain mimicking peptic ulcer disease - With stomach or duodenal infection

Malabsorption - With infection of the small intestine

Pain, diarrhea, or hematochezia - With infection of the colon

Physical Examination

Physical examination findings associated with TB depend on the organs involved. Patients with pulmonary TB have abnormal breath sounds, especially over the upper lobes or involved areas. Rales or bronchial breath signs may be noted, indicating lung consolidation.

Signs of extrapulmonary TB differ according to the tissues involved. They may include the following:

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

Lymphadenopathy in TB occurs as painless swelling of 1 or more lymph nodes. Lymphadenopathy is usually bilateral and typically involves the anterior and posterior cervical chain or supraclavicular nodes.

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. Up to 20% of patients with active TB may deny symptoms. Therefore, sputum sampling is essential when chest radiographic findings are consistent with TB.

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DDx

Diagnostic Considerations

Tuberculosis (TB) is well known for its ability to masquerade as other infectious and disease processes. For example, congenital TB can mimic congenital syphilis or cytomegalovirus (CMV) infection. Along with the differentials listed in the next section, conditions with a presentation that may resemble pulmonary TB include the following:

- Blastomycosis
- Tularemia
- Actinomycosis
- Mycobacterium avium-intracellulare infection
- M chelonae infection
- M fortuitum infection
- M gordonae infection
- M kansasii infection
- M marinum infection
- M xenopi infection
- Squamous cell carcinoma

Conditions to be included in the differential diagnosis of extrapulmonary TB include the following:

- Blastomycosis
- Tularemia
- Actinomycosis
- Hidradenitis suppurativa
- Eosinophilic granuloma

- M avium-intracellulare infection
- M chelonae infection
- M fortuitum infection
- M gordonae infection
- M kansasii infection
- M marinum infection
- M xenopi infection
- Endemic syphilis
- Erythema induratum (nodular vasculitis)
- Erythema nodosum
- Leishmaniasis
- Leprosy
- Cat scratch disease
- Syphilis
- Syringoma
- Rheumatoid arthritis

Dermatologic differential diagnosis

Diagnosis of skin infection with M tuberculosis involves the following:

- Differentiate primary-inoculation TB from ulceroglandular complexes and mycobacterioses
- Differentiate TB verrucosa cutis from diseases such as North American blastomycosis, chromoblastomycosis, iododerma and bromoderma, chronic vegetative pyoderma, verruca vulgaris, verrucous carcinoma, verrucous atypical mycobacterial infection, and verrucous lupus vulgaris
- Differentiate miliary TB of the skin (which appears as small, noncharacteristic, erythematous, papular or purpuric lesions) from drug reactions
- Differentiate scrofuloderma from suppurative lymphadenitis with sinus-tract formation, such as blastomycosis or coccidioidomycosis
- Differentiate TB cutis orificialis from glossitis, apotheosis, and deep fungal infections
- Differentiate lupus vulgaris from lupoid rosacea, deep fungal or atypical mycobacterial infection, chronic granulomatous disease, granulomatous rosacea, and Wegener granulomatosis
- Differentiate erythema induratum from nodular panniculitides (eg, Weber-Christian disease) and nodular vasculitides (eg, syphilitic gumma, nodular pernio)
- Differentiate papulonecrotic tuberculid from other papulonecrotic entities, such as leukocytoclastic vasculitis, lymphomatoid papulosis, papular eczema, and prurigo simplex with neurotic excoriation
- Differentiate lichen scrofulosorum from keratosis spinulosa, lichenoid sarcoid, and lichenoid secondary syphilis

Differential Diagnoses

- Actinomycosis
- Aspergillosis
- Bronchiectasis
- Constrictive Pericarditis
- Fungal Pneumonia

- Histoplasmosis
- Lung Abscess
- Nocardiosis
- Non-Small Cell Lung Cancer (NSCLC)
- Pott Disease (Tuberculous [TB] Spondylitis)

Workup

Approach Considerations

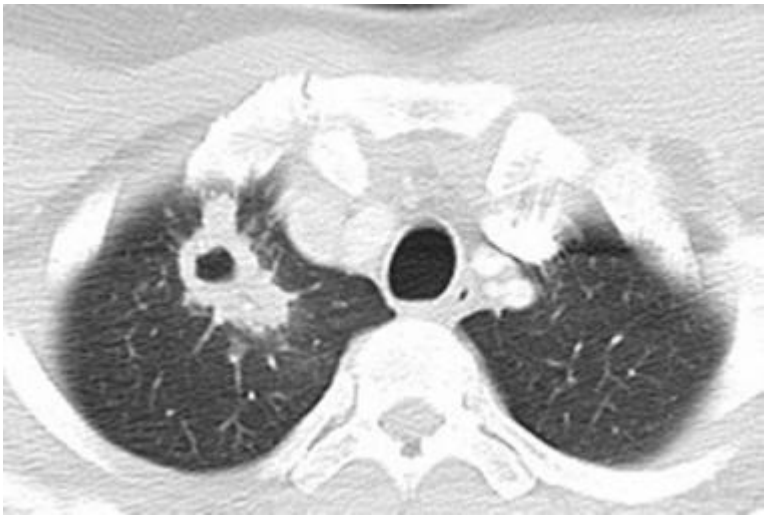
The primary screening method for tuberculosis (TB) infection (active or latent) is the Mantoux tuberculin skin test with purified protein derivative (PPD). An in vitro blood test based on interferon-gamma release assay (IGRA) with antigens specific for Mycobacterium tuberculosis can also be used to screen for latent TB infection. IGRA assays offer certain advantages over tuberculin skin testing.[46, 47]

Obtain the following laboratory tests for patients with suspected TB:

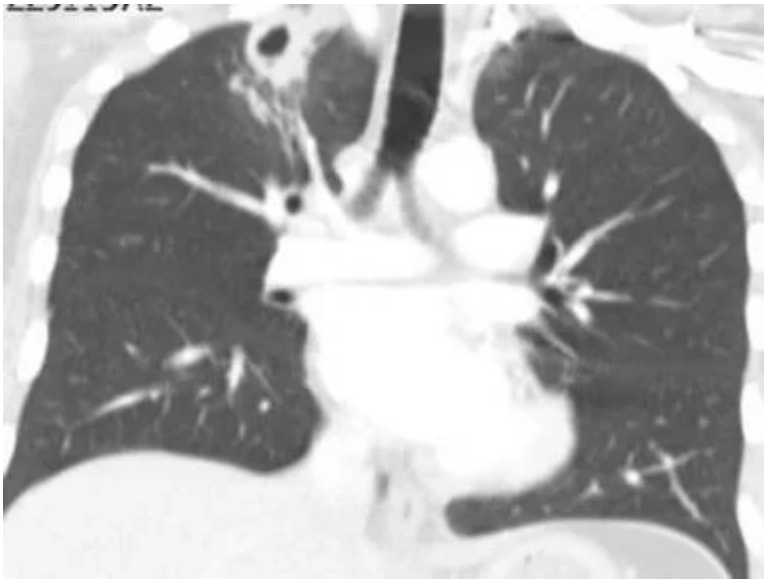
- Acid-fast bacilli (AFB) smear and culture - Using sputum obtained from the patient
- HIV serology in all patients with TB and unknown HIV status

AFB stain is quick but requires a very high organism load for positivity, as well as the expertise to read the stained sample. This test is more useful in patients with pulmonary disease. Other diagnostic testing may need to be considered, as a delay in diagnosis can increase patient mortality. Traditional mycobacterial cultures require weeks for growth and identification. Newer technologies allow identification within 24 hours.

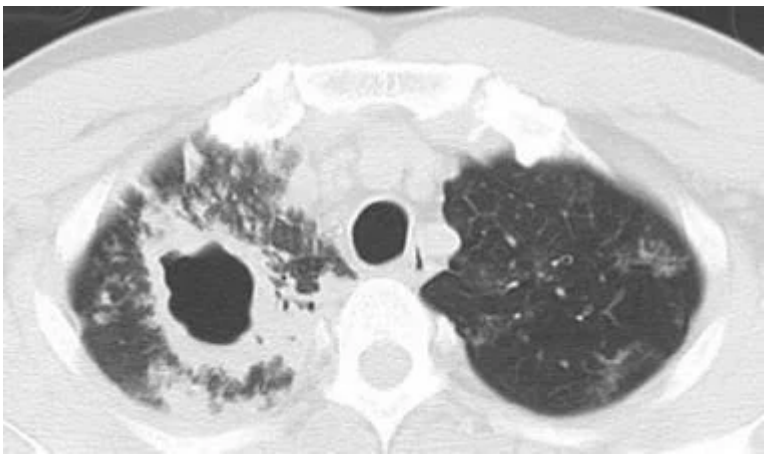
Obtain a chest radiograph to evaluate for possible associated pulmonary findings. If chest radiography findings suggest TB and a sputum smear is positive for AFB, initiate treatment for TB. A computed tomography (CT) scan of the chest may help to better define abnormalities in patients with vague findings on chest radiography. See the images below.



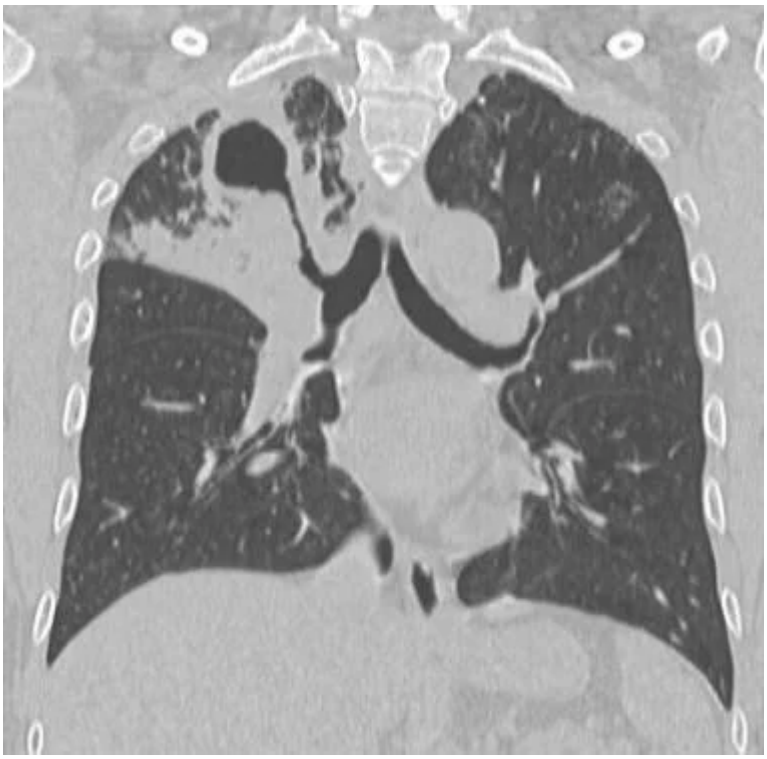
Axial noncontrast enhanced computed tomography with pulmonary window shows a cavity with an irregular wall in the right apex of a 37-year-old man who presented with cough and fever (same patient as above).



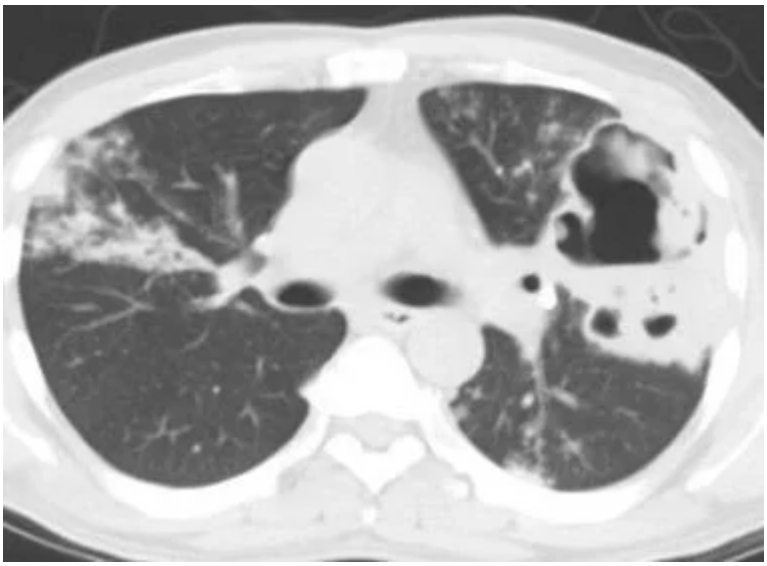
Coronal reconstructed computed tomography image shows the right apical cavity in a 37-year-old man who presented with cough and fever (same patient as above).



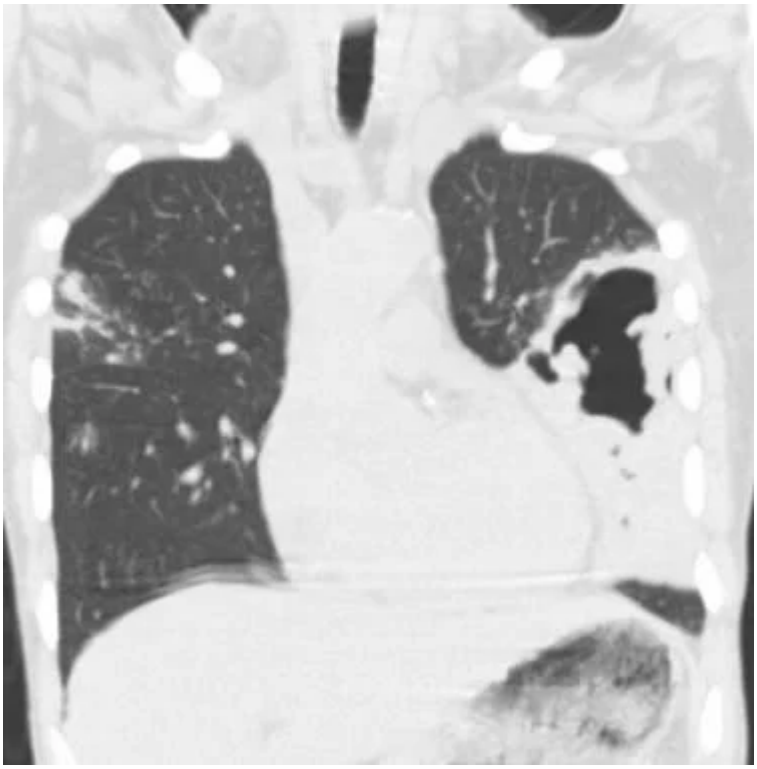
Axial chest computed tomography without intravenous contrast with pulmonary window setting shows a right apical thick-walled cavity and surrounding lung consolidation in a 43-year-old man who presented with cough and fever (same patient as above).



Coronal reconstructed computed tomography image shows the consolidated, partially collapsed right upper lobe with a cavity that is directly connected to a bronchus in a 43-year-old man who presented with cough and fever (same patient as above).



Axial chest computed tomography without intravenous contrast with pulmonary window setting through the mid-chest shows a large, irregular-walled cavity with nodules and air-fluid level and two smaller cavities in a 43-year-old man who presented with cough and hemoptysis (same patient as above). Small, patchy peripheral opacities are also present in the left lower lobe. In the right mid-lung, nodular opacities are in a tree-in-bud distribution, suggestive of endobronchial spread.



Coronal reconstructed computed tomography image shows the lingular cavity with irregular nodules and right mid-lung nodular opacities in a 43-year-old man who presented with cough and hemoptysis (same patient as above).

Technetium-99m (99m Tc) methoxy isobutyl isonitrile single-photon emission CT (SPECT) scanning for solitary pulmonary nodules yields a high predictive value for distinguishing TB from malignancy. Therefore, it has the potential to serve as a low-cost alternative when positron emission tomography (PET) scanning is not available, especially in endemic areas.[48]

Symptoms and radiographic findings do not differentiate multidrug-resistant TB (MDR-TB) from fully susceptible TB. Suspect MDR-TB if the patient has a history of previous treatment for TB, was born in or lived in a country with a high prevalence of MDR-TB, has a known exposure to an MDR-TB case, or is clinically progressing despite standard TB therapy.

Extrapulmonary TB

Extrapulmonary involvement occurs in one fifth of all TB cases, although 60% of patients with extrapulmonary manifestations of TB have no evidence of pulmonary infection on chest radiograph or sputum culture. Biopsy of bone marrow, liver, or blood cultures is occasionally necessary and may be helpful. Ocular TB can be especially difficult to identify, owing to its mimicry of other disorders and its lack of accessible sampling; a high index of suspicion is required.

The hallmark of extrapulmonary TB histopathology is the caseating granuloma, consisting of giant cells with central caseating necrosis. Rarely, if ever, are any TB bacilli seen.

Altered mental status, neck stiffness, decreased level of consciousness, increased intracranial pressure, and cranial nerve involvement can indicate tuberculous meningitis or tuberculoma. If these conditions are suspected, performing a lumbar puncture for evaluation of the cerebrospinal fluid is necessary. In addition, a tuberculoma can be substantiated on the basis of an increase in intracranial pressure and findings on CT or magnetic resonance image (MRI) scans.

If vertebral (Pott disease) or brain involvement is suspected, it is important to consider that a delay in treatment could have severe repercussions for the patient (ie, compression of the spinal cord and/or paraplegia). Consequently, further evaluation is necessary with CT scanning or MRI.

Urinalysis and urine cultures can be obtained for patients with genitourinary complaints. Although patients are often asymptomatic, significant pyuria and/or hematuria with no routine bacterial organisms mean that a urine culture for acid-fast bacilli should be obtained.

Pregnancy

Pregnancy provides an opportunity to screen for TB; all pregnant women can undergo tuberculin skin testing. If the results are positive, chest radiography can be performed with lead shielding. Chest radiography should not be delayed during the first 3 months of pregnancy in patients with suggestive symptoms.

TB in children

For congenital TB, the best diagnostic tests are the pathologic and histologic examination of the placenta, as well as a placental culture. Mycobacterial blood cultures of the newborn may also be helpful. Treatment may be necessary until placental culture results are negative.

Postnatal TB in infants is contracted via the airborne route. The most common findings of postnatal TB include adenopathy and a lung infiltrate. However, the chest radiographic findings may be normal in infants with disseminated disease.

Chest radiographs in children with TB may show only hilar lymphadenopathy or a patchy infiltrate. Gastric aspirates or biopsies are not necessary if positive cultures have been obtained from the source case. Go to Pediatric Tuberculosis for complete information on this topic.

Patients with HIV infection

Individuals infected with HIV are at increased risk for TB, beginning within the first year of HIV infection.[49] All patients who are diagnosed with active TB and who are not known to be HIV positive should be considered for HIV testing.

The initiation of antiretroviral therapy (ART) decreases the risk of developing TB in these patients,[50] although the TB risk remains higher in the first 3 months of ART. The highest risk is in patients with the following factors[51] :

- Baseline CD4+ count of less than 200/µL
- Higher baseline HIV-1 ribonucleic acid (RNA) level - Relative hazard 1.93 for every log increase in baseline HIV-1 RNA
- History of injection drug use
- Male sex

In a study from Durban, South Africa, nearly 20% of patients starting ART had undiagnosed, culture-positive pulmonary TB. Neither cough nor acid-fast bacillus smear were sufficiently sensitive for screening. TB sputum cultures should be attempted before ART initiation in areas with a high prevalence of TB.[52]

Patients with TB must be tested for HIV, and patients with HIV need periodic evaluation for TB with tuberculin skin testing and/or chest radiography. Patients with HIV and a positive tuberculin skin test result develop active TB at a rate of 3-16% per year.

Patients with TB and HIV are more likely to have disseminated disease and less likely to have upper lobe infiltrates or classic cavitary pulmonary disease. Patients with a CD4 count of less than 200/µL may have mediastinal adenopathy with infiltrates.

Sputum Smear

Patients suspected of having TB should submit sputum for AFB smear and culture. Sputum should be collected in the early morning on 3 consecutive days. In hospitalized patients, sputum may be collected every 8 hours.[53] Early-morning gastric aspirate may also produce a good specimen, especially in children.

In patients without spontaneous sputum production, sputum induction with hypertonic saline should be attempted.[54] Fiberoptic bronchoscopy with bronchoalveolar lavage (and perhaps transbronchial biopsy) can be used if other attempts at obtaining sputum specimens are unsuccessful.

Ziehl-Neelsen staining of sputum is a simple 5-step process that takes approximately 10 minutes to accomplish. While highly specific for mycobacteria, however, this stain is relatively insensitive, and detection requires at least 10,000 bacilli per mL; most clinical laboratories currently use a more sensitive auramine-rhodamine fluorescent stain (auramine O).

TB detection following negative smear

The absence of a positive smear result does not exclude active TB infection. Approximately 35% of culture-positive specimens are associated with a negative smear result.

Jafari et al found that an M tuberculosis –specific enzyme-linked immunospot (ELISpot) assay can be used to differentiate TB cases with negative sputum smears from latent TB infection. In a prospective study of 347 patients suspected of having active TB who were unable to produce sputum or who had AFB-negative sputum smears, ELISpot testing of bronchoalveolar lavage fluid displayed a sensitivity and specificity of 91% and 80%, respectively, for the diagnosis of active pulmonary TB.[55]

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Nucleic Acid Amplification Tests

Deoxyribonucleic acid (DNA) probes specific for mycobacterial ribosomal RNA identify species of clinically significant isolates after recovery. In tissue, polymerase chain reaction (PCR) amplification techniques can be used to detect M tuberculosis -specific DNA sequences and thus, small numbers of mycobacteria in clinical specimens.[56, 57]

Ribosomal RNA probes and DNA PCR assays allow identification within 24 hours. The DNA probes are approved for direct testing on smear-positive or smear-negative sputa. However, smear-positive specimens yielded higher sensitivity.

The CDC recommends performing one of these nucleic acid amplification tests when the diagnosis of pulmonary TB is being considered but has not yet been established, and when the test result would alter case management or TB control activities, such as contact investigations. The CDC recommends performing the test on at least 1 respiratory specimen.[58]

A retrospective cohort analysis of 2140 patients with suspected pulmonary TB found that Mycobacterium tuberculosis direct (MTD) nucleic acid amplification testing (NAAT) yielded improved diagnostic accuracy, shortened time to diagnosis, and reduced unnecessary treatment. In all study subpopulations examined (HIV-infected, homeless, substance abuser, and foreign-born), MTD had higher positive predictive value, sensitivity, and negative predictive value than no MTD, and in all subpopulations except homeless patients, MTD had higher specificity. In HIV-infected or homeless patients, MTD substantially reduced the cost of diagnosing or excluding TB, and in substance abusers, it cut the cost of excluding TB in those with smear-negative specimens.[59, 60]

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Culture

Culture for AFB is the most specific test for TB and allows direct identification and determination of susceptibility of the causative organism. Access to the organisms, however, may require lymph node/sputum analysis, bronchoalveolar lavage, or aspirate of cavity fluid or bone marrow. In addition, obtaining the test results is slow (3-8 wk), and they have a very low positivity in some forms of disease.

Routine culture uses a nonselective egg medium (Lowenstein-Jensen or Middlebrook 7H10) and often requires more than 3-4 weeks because of the 22-hour doubling time of M tuberculosis. Radiometric broth culture (BACTEC radiometric system) of clinical specimens was found to significantly reduce the time (10-14 days) for mycobacterial recovery.

Newer broth culture media and systems for isolation, based on a fluorescent rather than a radioactive indicator, are available for use in clinical laboratories. The indicator is inhibited by oxygen; as mycobacteria metabolize substrates in the tubes and use the oxygen, the tube begins to fluoresce.[61]

Blood cultures

Blood cultures using mycobacteria-specific, radioisotope-labeled systems help to establish the diagnosis of active TB. However, mycobacterial bacteremia (bacillemia) is detectable using blood cultures only if specialized systems are used; these bacilli have specific nutrient growth requirements not met by routine culture systems.

Such blood cultures should be used for all patients with HIV infection who are suspected of having TB, because bacillemia is particularly prevalent in this population. If available, in fact, these cultures should be used for any patient highly suspected of having active TB.

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Drug Susceptibility Testing

Positive cultures should be followed by drug susceptibility testing. Symptoms and radiographic findings do not differentiate MDR-TB from fully susceptible TB. Suspect MDR-TB if the patient has a history of previous treatment for TB, was born in or lived in a country with a high prevalence of MDR-TB, has a known exposure to an MDR-TB case, or is clinically progressing despite standard TB therapy. Susceptibilities should be repeated if cultures remain positive after 2 months, even when initial susceptibilities have not revealed any resistance.

DNA sequencing

Because conventional drug susceptibility tests for M tuberculosis take at least 3-8 weeks, Choi et al recommend direct DNA sequencing analysis as a rapid and useful method for detecting drug-resistant TB. In their clinical study, turnaround time of the direct DNA sequencing analysis was 3.8 +/- 1.8 days. The sensitivity and specificity of the assay were 63.6% and 94.6% for isoniazid, 96.2 and 93.9% for rifampin, 69.2% and 97.5% for ethambutol, and 100% and 92.6% for pyrazinamide, respectively.[62]

Automated molecular testing

An automated molecular test that uses sputum samples for the detection of M tuberculosis and resistance to rifampin has been developed. In studies conducted in low-income countries, the sensitivity for TB was 98.3% using a single smear-positive sputum sample. Sensitivity with a single smear-negative sputum sample was 76.9%, but it increased to 90.2% when 3 samples were tested. The test correctly identified 94.4% of rifampin-resistant organisms and 98.3% of rifampin-sensitive organisms.[63, 64]

MODS and TLA assays

Microscopic-observation drug susceptibility (MODS) and thin-layer agar (TLA) assays are inexpensive, rapid alternatives to conventional and molecular methods of TB drug susceptibility testing. The WHO has endorsed the MODS assay as a direct or an indirect test for rapid screening of patients with suspected MDR-TB. The evidence is insufficient to recommend the use of the TLA assay for rapid screening, but this assay is a promising diagnostic technique.[65]

Additional rapid tests

Other rapid tests are also available, such as BACTEC-460 (Becton-Dickinson), ligase chain reaction, and luciferase reporter assays (within 48 h) (Franklin Lakes). These tests have been developed for rapid drug-susceptibility testing, and results from these can be available within 10 days. Drug-resistance tests such as the FASTPlaque TB-RIF for rifampin resistance can be used after growth in semiautomated liquid cultures such as BACTEC-460; rifampin resistance can be used as a surrogate marker for isoniazid resistance.

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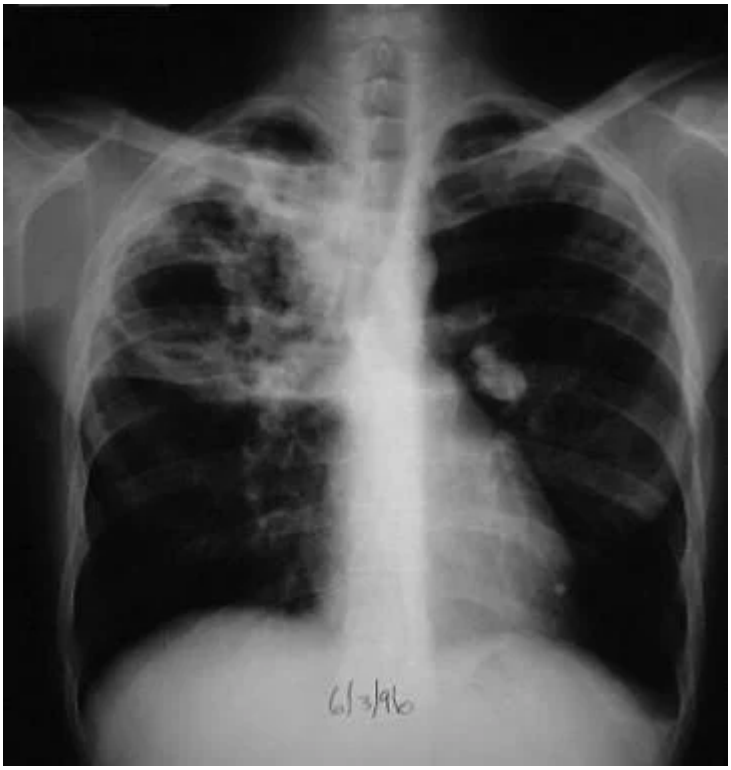
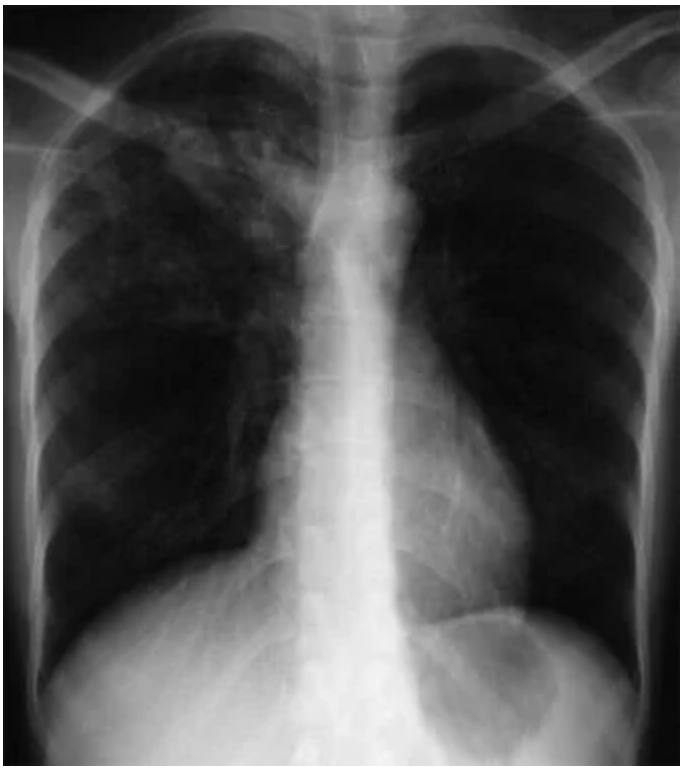
Chest Radiography

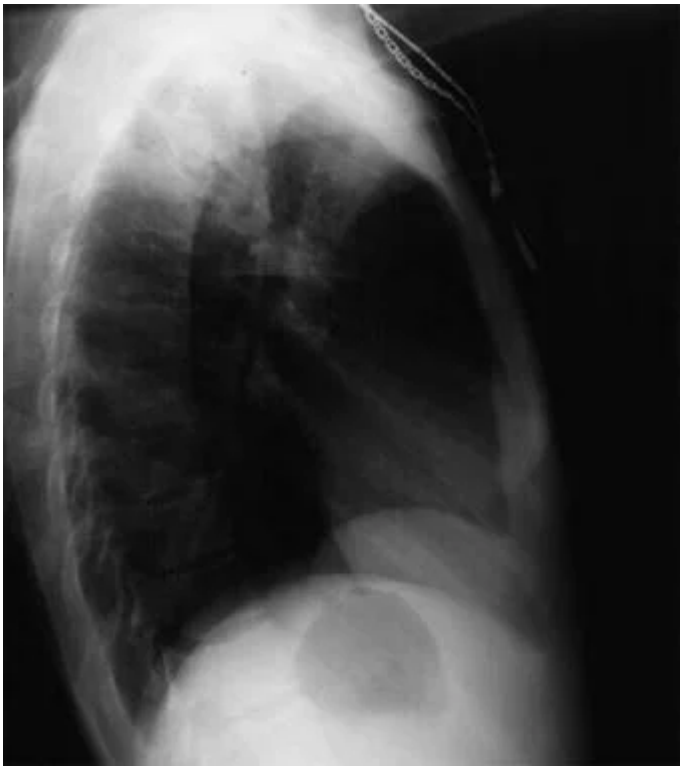
Obtain a chest radiograph to evaluate for possible TB-associated pulmonary findings (demonstrated in the images below). A traditional lateral and posteroanterior (PA) view should be ordered. In addition, an apical lordotic view may permit better visualization of the apices and increase the sensitivity of chest radiography for indolent or dormant disease.



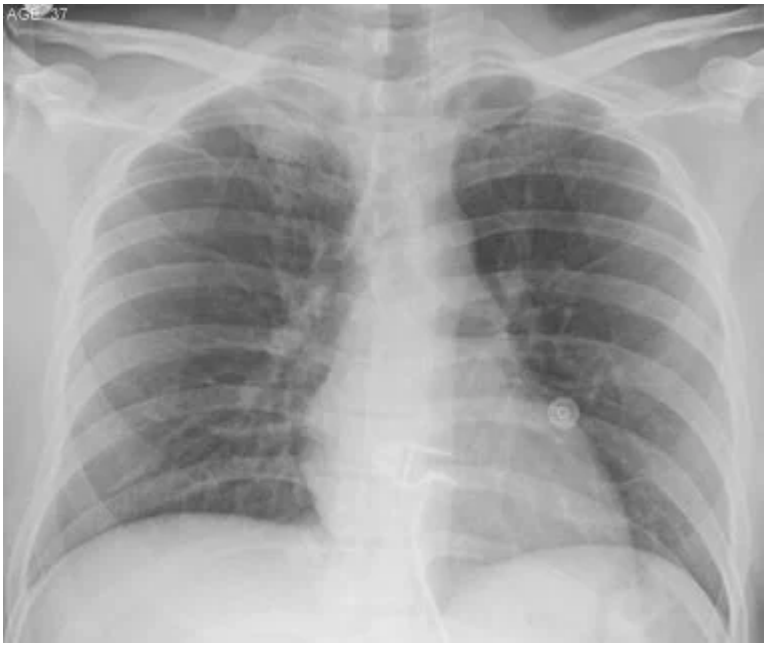
This radiograph shows a patient with typical radiographic findings of tuberculosis.



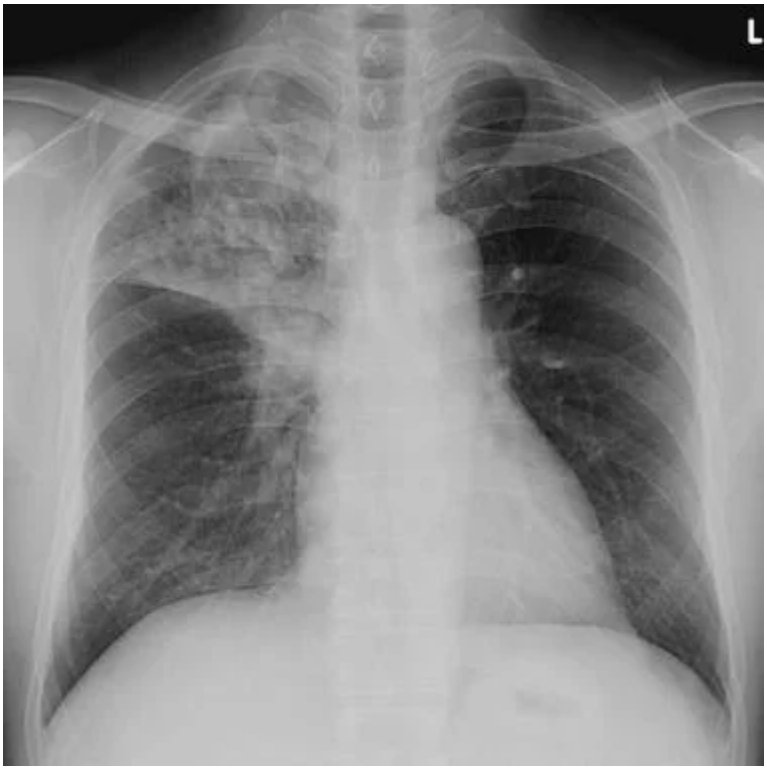
Anteroposterior chest radiograph of a young patient who presented to the emergency department (ED) with cough and malaise. The radiograph shows a classic posterior segment right upper lobe density consistent with active tuberculosis. This woman was admitted to isolation and started empirically on a 4-drug regimen in the ED. Tuberculosis was confirmed on sputum testing. Image courtesy of Remote Medicine (remotemedicine.org).



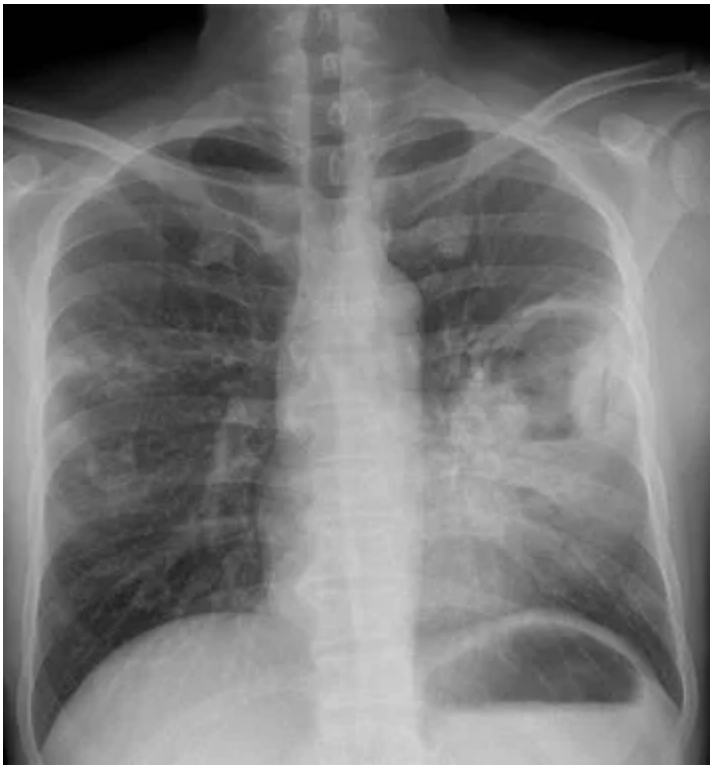
Lateral chest radiograph of a patient with posterior segment right upper lobe density consistent with active tuberculosis. Image courtesy of Remote Medicine (remotemedicine.org).



This chest radiograph shows asymmetry in the first costochondral junctions of a 37-year-old man who presented with cough and fever. Further clarification with computed tomography is needed.



This posteroanterior chest radiograph shows right upper lobe consolidation with minimal volume loss (elevated horizontal fissure) and a cavity in a 43-year-old man who presented with cough and fever.



The posteroanterior chest radiograph shows a large cavity with surrounding consolidation in the lingular portion of the left upper lobe in a 43-year-old man who presented with cough and hemoptysis. There are also a few nodular opacities in the right mid-lung zone.

The chest film is also useful to screen for sarcoidosis, which closely imitates the clinical course of ocular TB. Radiologists look more decisively for signs of TB or sarcoid if the requesting physician specifies an interest in these.

Chest radiographs may show a patchy or nodular infiltrate. TB may be found in any part of the lung, but upper lobe involvement is most common. The lordotic view may better demonstrate apical abnormalities.

The following patterns may be seen on chest radiographs:

- Cavity formation - Indicates advanced infection and is associated with a high bacterial load

- Noncalcified round infiltrates - May be confused with lung carcinoma
- Homogeneously calcified nodules (usually 5-20 mm) - Tuberculomas; represent old infection rather than active disease
- Miliary TB - Characterized by the appearance of numerous small, nodular lesions that resemble millet seeds on chest radiography (go to Miliary Tuberculosis for complete information on this topic)

Chest radiography consistent with TB indicates active disease in the symptomatic patient even in the absence of a diagnostic sputum smear. Similarly, normal chest radiographic findings in the symptomatic patient do not exclude TB, particularly in a patient who is immunosuppressed.

Primary TB

In primary active TB, radiographic features of pulmonary tuberculosis are nonspecific, sometimes even normal. The chest radiograph typically shows a pneumonialike picture of an infiltrative process in the middle or lower lung regions, often associated with hilar adenopathy and/or atelectasis.

Primary TB is more likely to mimic the appearance of routine community-acquired pneumonia (CAP) on chest radiography than is reactivation TB. Studies have shown that primary TB and CAP may be associated with pleural effusion and cavitation.

Reactivation TB

In classic reactivation TB, pulmonary lesions are located in the posterior segment of the right upper lobe, the apicoposterior segment of the left upper lobe, and the apical segments of the lower lobes. Cavitation is most common; healing of tubercular regions results in the development of a scar, with loss of lung parenchymal volume and calcification.

TB and HIV infection

In patients with HIV infection or another immunosuppressive disease, lesions are often atypical. Up to 20% of HIV-positive patients with active TB have normal chest radiographic findings.

Healed and latent TB

Old, healed TB presents a different radiographic appearance, with dense pulmonary nodules, with or without calcifications, in the hilar or upper lobes. Smaller nodules, with or without fibrotic scars, can be seen in the upper lobes. Nodules and fibrotic lesions are well demarcated, have sharp margins, and are dense.

Patients with nodular or fibrotic scars on chest radiography and positive PPD results should be treated as latent carriers. Calcified nodular lesions (granulomas) or apical pleural thickening indicate a lower risk of conversion.

Miliary TB

In disseminated/miliary TB, the chest radiograph commonly shows a miliary pattern, with 2-mm nodules that, histologically, are granulomas disseminated like millet seeds throughout the lung. However, chest radiographic patterns can vary and can include upper lobe infiltrates with or without cavitation.

Pleural TB

In pleural tuberculosis, the pleural space can be involved in 2 ways: (1) a hypersensitivity response can cause pleuritic pain and fever, or (2) an empyema can be present that can be seen on chest radiographs, with associated pleural effusions.

See the following articles for more information on TB imaging studies:

- Imaging of CNS Tuberculosis
- Imaging of Primary Pulmonary Tuberculosis
- Imaging of Gastrointestinal Tuberculosis
- Imaging of Genitourinary Tuberculosis

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Screening

Tuberculin skin test

The primary screening method for TB infection (active or latent) is the Mantoux tuberculin skin test with PPD. Tuberculin sensitivity develops 2-10 weeks after infection and usually is lifelong. Tuberculin skin testing is based on the fact that TB infection induces a strong, cell-mediated immune response that results in a measurable delayed-type hypersensitivity response to intradermal inoculation of tuberculin PPD.

The PPD test involves an intradermal injection of 5 units of PPD (0.1 mL), preferably with a 26-, 27-, or 30-gauge needle. The results should be read between 48 and 72 hours after administration. In immunologically intact individuals, induration of less than 5 mm constitutes a negative result.

Population-based criteria for PPD positivity are as follows:

- Cutoff of 5 mm or more induration - Patients who are HIV positive, have abnormal chest radiographic findings, have significant immunosuppression, or have had recent contact with persons with active TB
- Cutoff of 10 mm or more induration - Patients who are intravenous drug users, residents of nursing homes, prisoners, impoverished persons, or members of minority groups
- Cutoff of 15 mm or more induration - Patients who are young and in good health

Reactions in patients who have received the bacillus Calmette-Guérin (BCG) vaccine should be interpreted in the same way as the reactions above, regardless of BCG history, according to guidelines from the CDC.[66]

Interferon-gamma release assay

An in vitro blood test based on IGRA with antigens specific for M tuberculosis can also be used to screen for latent TB infection and offers certain advantages over tuberculin skin testing.[46, 47] The 2 currently available tests are (1) QuantiFERON-TB Gold In-Tube (QFT-GIT), an enzyme-linked immunosorbent assay (ELISA) based on ESAT-6, CFP-10, and TB 7.7 antigens, and (2) T-SPOT.TB, an enzyme-linked immunosorbent spot (ELISpot) assay based on ESAT-6 and CFP-10 antigens.

IGRA tests measure T-cell interferon-gamma response to antigens that are highly specific for M tuberculosis and absent from the BCG vaccine and M avium.[67] Overall, sensitivity and specificity of IGRA are comparable to those of tuberculin skin testing; however, unlike tuberculin skin testing, these tests do not require a second visit for a reading. Results are reported as positive, negative, or indeterminate. Patients with an indeterminate result may have evidence of immunosuppression and may be nonreactive on skin testing.[68]

Advantages of IGRA compared with PPD include the following:

- Only a single patient visit required
- Ex vivo tests
- No booster effect
- Independent of BCG vaccination

Disadvantages of IGRA include the following:

- High cost
- More laboratory resources required
- Complicated process of lymphocyte separation
- Lack of prospective studies

Screening test accuracy

Neither tuberculin skin testing nor IGRA testing is sufficiently sensitive to rule out TB infection.[69] Approximately 20% of patients with active TB, particularly those with advanced disease, have normal PPD test results. In addition, caution is recommended on the interpretation of these tests in infants and in patients with immunosuppressive conditions.[67]

A systematic review of QuantiFERON-TB Gold (QFT-G)/Gold in-Tube (QFT-GIT) and T-SPOT.TB by Chang and Leung concluded that QFT-G had the highest positive likelihood ratio (48.1) for latent TB infection and that T-SPOT.TB had the best negative likelihood ratio (0.10). A negative T-SPOT.TB result in middle-aged and older patients makes active TB very unlikely.[70]

Results from a study by Leung et al indicated that tuberculin skin testing is not predictive of the subsequent development of active TB.[71] The authors followed 308 men with increased risk of TB because of silicosis. A positive T-SPOT.TB finding was associated with a relative risk of 4.5 for subsequent TB in the group overall and a relative risk of 8.5 among the men

who did not receive preventive treatment for latent TB. The CFP-10 spot count was more predictive than the ESAT-6 spot count.

In a study by Diel et al, all subjects who developed active TB within 4 years after exposure to a smear-positive index case had positive results using QFT-GIT. These researchers concluded that QFT-GIT was more reliable than tuberculin skin testing for identifying patients, especially children, who will soon progress to active TB.[72]

In a study of kidney-transplant recipients, positive ELISpot assays predicted the subsequent development of TB in patients who did not have a significant tuberculin skin test reaction or risk factors for TB infection. Active TB developed after kidney transplantation in 4 of 71 patients (6%) with positive ELISpot assays, but in none of the 201 patients with negative or indeterminate ELISpot results[73]

Treatment

Approach Considerations

Isolate patients with possible tuberculosis (TB) infection in a private room with negative pressure (air exhausted to outside or through a high-efficiency particulate air filter). Medical staff must wear high-efficiency disposable masks sufficient to filter the tubercle bacillus. Continue isolation until sputum smears are negative for 3 consecutive determinations (usually after approximately 2-4 wk of treatment). Unfortunately, these measures are neither possible nor practical in countries where TB is a public health problem.

Drug therapy

For initial empiric treatment of TB, start patients on a 4-drug regimen: isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin. Once the TB isolate is known to be fully susceptible, ethambutol (or streptomycin, if it is used as a fourth drug) can be discontinued.[1]

Patients with TB who are receiving pyrazinamide should undergo baseline and periodic serum uric acid assessments, and patients with TB who are receiving long-term ethambutol therapy should undergo baseline and periodic visual acuity and red-green color perception testing. The latter can be performed with a standard test, such as the Ishihara test for color blindness.

After 2 months of therapy (for a fully susceptible isolate), pyrazinamide can be stopped. Isoniazid plus rifampin are continued as daily or intermittent therapy for 4 more months. If isolated isoniazid resistance is documented, discontinue isoniazid and continue treatment with rifampin, pyrazinamide, and ethambutol for the entire 6 months. Therapy must be extended if the patient has cavitary disease and remains culture-positive after 2 months of treatment.

Directly observed therapy (DOT) is recommended for all patients. With DOT, patients on the above regimens can be switched to 2- to 3-times per week dosing after an initial 2 weeks of daily dosing. Patients on twice-weekly dosing must not miss any doses. Prescribe daily therapy for patients on self-administered medication.

Monitoring

Patients diagnosed with active TB should undergo sputum analysis for Mycobacterium tuberculosis weekly until sputum conversion is documented. Monitoring for toxicity includes baseline and periodic liver enzymes, complete blood cell (CBC) count, and serum creatinine.

Seizures from isoniazid overdose

A special regimen exists for patients with TB who are actively seizing or who have overdosed on antimycobacterial medication. In these patients, overdose with isoniazid should be suspected. The administration of diazepam can be attempted to control seizure activity, but IV pyridoxine is the drug of choice, in a gram-for-isoniazid-ingested-gram dose. If the ingested dose is unknown, 5 g of pyridoxine can be used empirically. For patients who are awake and alert, an oral dose of activated charcoal (1 g/kg) with sorbitol can be administered.

Treatment During Pregnancy

Pregnant women with active TB should be treated, even in the first stage of pregnancy. Isoniazid, rifampin, and ethambutol may be used. In the United States, pyrazinamide is reserved for women with suspected multidrug-resistant TB (MDR-TB).

Elsewhere in the world, pyrazinamide is commonly used in pregnant women with TB. Streptomycin should not be used, because it has been shown to have harmful effects on the fetus.

Preventive treatment is recommended during pregnancy, especially in the following types of patients:

- Pregnant women with a positive tuberculin skin test result who are HIV seropositive or who have behavioral risk factors for HIV infection but who decline HIV testing
- Pregnant women with a positive tuberculin skin test result who have been in close contact with a patient who is smear-positive for pulmonary TB
- Pregnant women who had a documented tuberculin skin test conversion during the previous 2 years

Pregnant women are at an increased risk for isoniazid-induced hepatotoxicity and should undergo monthly alanine aminotransferase (ALT) monitoring while on treatment. This risk continues 2-3 months into the postpartum period. Pyridoxine should also be administered to pregnant women receiving isoniazid.

Breastfeeding can be continued during preventive therapy. Many experts recommend supplemental pyridoxine for the breastfed infant.

Lin et al reported that women diagnosed with TB during pregnancy are at an increased risk of having babies who are of low birthweight and are small for their gestational age. However, preterm birth was not more common in women with TB.[74]

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Treatment in Children

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, many experts increase the treatment duration to 9 or 12 months because of the possible impaired immune system in children younger than 12 months. Bacillus Calmette-Guérin (BCG) vaccine is not recommended in infants in the United States but is commonly used around the world.

Isoniazid tablets may be crushed and added to food. Isoniazid liquid without sorbitol should be used to avoid osmotic diarrhea, which can cause decreased absorption.

Rifampin capsules may be opened and the powder added to food. If rifampin is not tolerated, it may be taken in divided doses 20 minutes after light meals.

Ethambutol is often avoided in young children because of difficulties monitoring visual acuity and color perception. However, studies show that ethambutol (15 mg/kg) is well tolerated and can prevent further resistance if the child is infected with a resistant strain. Go to Pediatric Tuberculosis for complete information on treatment of children.

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Treatment in HIV-Infected Patients

Treatment regimens for active or latent TB in patients with HIV infection are similar to those used in HIV-negative patients, but dose adjustments may be necessary.[2, 3] The most significant differences involve the avoidance of rifampin in patients who are on protease inhibitors. Rifabutin may be used in place of rifampin in such patients.

Antiretroviral therapy

Patients with HIV and TB may develop a paradoxical response (immune reconstitution inflammatory syndrome [IRIS]) when starting antiretroviral therapy. This response has been attributed to a stronger immune response to M tuberculosis. Clinical findings include fever, worsening pulmonary infiltrates, and lymphadenopathy.

However, in an open-label, randomized trial, Abdool Karim et al concluded that the initiation of antiretroviral therapy during TB therapy significantly improved patient survival. In this study, the mortality rate with simultaneous initiation of antiretroviral therapy and TB therapy was 5.4 deaths per 100 person-years (25 deaths in 429 patients), compared with 12.1 deaths per 100 person-years (27 deaths in 213 patients) with antiretroviral therapy started after the completion of TB therapy, a relative reduction of 56%.[4]

Subsequent studies by these and other researchers found that starting antiretroviral therapy early (eg, within 4 weeks after the start of TB treatment) reduced progression to AIDS and death. In patients with higher CD4+ T-cell counts, however,

deferring initiation of antiretroviral therapy until the continuation phase of TB treatment may be a reasonable strategy, because the risks of IRIS and of adverse events that necessitate switching of antiretroviral drugs are lower with later initiation of antiretroviral therapy.[5]

Treatment length and recurrence rate

Swaminathan et al reported a significantly lower bacteriologic recurrence rate with 9 months, instead of 6 months, of an intermittent (3 times/wk) 4-drug regimen in patients with HIV infection and newly diagnosed TB. Mortality was similar in both groups. The rate of acquired rifampin resistance was high in both groups and was not altered by the longer TB treatment.[2]

Tuberculous meningitis

In patients with tuberculous meningitis, dexamethasone added to routine 4-drug therapy reduces complications.

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Treatment of Multidrug-Resistant TB

When MDR-TB is suspected, because of a relevant history or epidemiologic information, treatment is initiated after sputum specimens are drawn for culture and sensitivity testing; however, treatment must be started empirically before culture results become available. Once results are known, the regimen is modified according to susceptibilities. (Costs are many times higher for the treatment of MDR-TB.)

The complexity of MDR-TB treatment lies in the futility of using isoniazid and rifampin. Isoniazid has the strongest antibactericidal action and significantly contributes to making patients rapidly noninfectious; rifampin has unique antibacterial properties against dormant bacilli that are no longer in the active phase of replication.

When initiating treatment, utilize at least 3-5 previously unused drugs for which there is in vitro susceptibility. Levofloxacin, which is a fluoroquinolone, has been shown to be best suited long-term and should be included in the regimen.

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 - Ie, streptomycin, amikacin, capreomycin, kanamycin
- A fluoroquinolone - Ie, levofloxacin, ciprofloxacin, ofloxacin
- A thioamide - Eg, ethionamide, prothionamide
- Pyrazinamide
- Ethambutol
- Cycloserine
- Terizidone
- Para-aminosalicylic acid
- A diarylquinoline: Bedaquiline

Consider rifabutin as a substitute for rifampin, as approximately 15% of rifampin-resistant strains are rifabutin sensitive.

Successful MDR-TB treatment is more likely in association with such factors as lower prior patient exposure to anti-TB drugs, a higher number of anti-TB drugs to which the infection is still susceptible, and a shorter time since the first TB diagnosis (indicating less advanced disease).

Continue treatment for MDR-TB for 18-24 months after sputum culture conversion. The drugs should be prescribed daily (no intermittent therapy), and the patient should always be on DOT. Weekend DOT may not be possible; therefore, giving self-administered oral drugs on Saturdays and Sundays may be reasonable. All patients should be closely observed for 2 years after completion of treatment, with a low threshold for referral to TB centers.

Novel drugs for TB are currently under development and may prove valuable for treatment of MDR-TB. 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 ($p = 0.014$).[75, 76]

In another phase II study by Diacon et al, 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%).[77]

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 multidrug-resistant tuberculosis, 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.[78, 79]

The diagnosis of extensively drug-resistant TB (XDR-TB) is established with an isolate that is resistant to isoniazid, rifampin, at least 1 of the quinolones, and at least 1 injectable drug. Treatment options for XDR-TB are very limited, and XDR-TB carries a very high mortality rate.

A CDC analysis of the prevalence, trends, and risk factors for initial resistance to pyrazinamide in Mycobacterium tuberculosis complex (MTBC) cases in the United States showed that such resistance increased from 2% in 1999 to 3.3% in 2009. Pyrazinamide monoresistance was associated with younger age, Hispanic ethnicity, HIV infection, extrapulmonary disease, and normal chest radiograph and inversely associated with Asian and Black race, substance use, homelessness, and residence in a correctional facility.[80, 81]

In the same CDC analysis, pyrazinamide polyresistance was associated with Hispanic ethnicity, Asian race, previous TB diagnosis, and normal chest x-ray and inversely associated with age 45 years and older. Pyrazinamide resistance in multidrug-resistant cases was associated with female sex and previous TB diagnosis. Bacterial lineage, rather than host characteristics, was the primary predictor of pyrazinamide resistance ijn M tuberculosis cases.[80, 81]

Surgical resection

Surgical resection of an infected lung may be considered to reduce the bacillary burden in patients with MDR-TB. Surgery is recommended for patients with MDR-TB whose prognosis with medical treatment is poor. Surgery can be performed with a low mortality rate (< 3%), with prolonged periods of a chemotherapeutic regimen used for more than 1 year after surgery.

Procedures include segmentectomy (rarely used), lobectomy, and pneumonectomy. Pleurectomies for thick pleural peel are rarely indicated.

Intraoperative infection of uninvolved lung tissue has been observed in resections. Complications include the usual perioperative complications, recurrent disease, and bronchopleural fistulas.

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Treatment of Latent TB

The antimycobacterial rifapentine (Priftin), which was previously approved for use against active pulmonary TB caused by Mycobacterium tuberculosis, has now been approved by the US Food and Drug Administration (FDA) for use, in combination with isoniazid, in the treatment of latent TB infection. Therapy was approved for patients aged 2 years or older who are at high risk of progression to TB disease.[82, 9]

FDA approval for the new indication was partially based on a randomized study of more than 6000 patients in which a 12-dose, once-weekly regimen of directly observed therapy (DOT) with rifapentine plus isoniazid was compared with a regimen consisting of 9 months of self-administered daily isoniazid. The cumulative rate of tuberculosis disease development was 0.16% in the rifapentine-isoniazid group (5 out of 3074 patients), compared with 0.32% in the isoniazid group (10 out of 3074 patients).[82, 9]

Patients with a clinically significant result on tuberculin skin testing or a positive interferon-gamma release assay (IGRA) result should receive a course of therapy for latent TB, once active infection and disease are ruled out. Recommended regimens for latent TB published by the US Centers for Disease Control and Prevention (CDC) are as follows[6, 10] :

- Isoniazid 300 mg - Daily for 9 months
- Isoniazid 900 mg - Twice weekly for 9 months (administered as DOT)
- Isoniazid 300 mg - Daily for 6 months (should not be used in patients with fibrotic lesions on chest radiography, patients with HIV infection, or children)
- Isoniazid 900 mg - Twice weekly for 6 months (administered as DOT; should not be used in patients with fibrotic lesions on chest radiography, patients with HIV infection, or children)
- Rifampin 600 mg - Daily for 4 months
- Rifapentine 900 mg plus isoniazid 900 mg - Once-weekly for 12 weeks (self-administered or as DOT)

- No longer recommended - Rifampin plus pyrazinamide daily for 2 months (increased liver toxicity)

Self-administered therapy versus directly observed therapy

A 2017 study has reported that self-administered therapy for latent tuberculosis infection (LTBI) may be a viable option for patients when direct medical oversight is unavailable.[83]

As part of an open-label, phase 4 randomized clinical trial, researchers enrolled 1002 patients from outpatient TB clinics in the United States, Spain, Hong Kong, and South Africa between September 2012 and April 2014. Patients with active TB, prior treatment for TB lasting more than 1 week, contact with someone with a resistant form of TB, or prior intolerance to anti-TB agents were excluded. Most enrolled patients (n = 774) were in the United States; however, participants were demographically similar between groups. The median age was 36 years, and 48.1% of the patients were women.

Patients were randomly assigned to receive isoniazid or rifapentine once weekly by directly observed therapy (DOT), self-administered therapy (SAT) with weekly text message reminders, or SAT without reminders. The primary objective of the study was to compare treatment adherence, defined as completion of 11 or more doses of medication within 16 weeks. All participants were counseled on correct pill-taking and symptoms of drug toxicity. All patients had monthly follow-up visits both during therapy and for 28 days after the last dose to assess adherence and monitor for adverse events.

The researchers documented overall completion rates of 87.2% (95% confidence interval [CI], 83.1% - 90.5%) in the DOT group, 74.0% (CI, 68.9% - 78.6%) in the SAT group, and 76.4% (CI, 71.3% - 80.8%) in the SAT with reminders group.

Specifically, among US patients, the researchers noted treatment completion rates of 85.4% (CI, 80.4% - 89.4%), 77.9% (CI, 72.7% - 82.6%), and 76.7% (CI, 70.9% - 81.7%), respectively. Using a 15% difference to define noninferiority, the researchers found SAT without reminders to be noninferior to DOT in the United States.

The researchers also found that adverse events were similar among all 3 groups.[83]

Isoniazid plus rifapentine

This combination, approved by the FDA in November 2014, is indicated for patients aged 2 years and older who are at high risk for developing active TB disease (including those in close contact with active TB patients, patients who have had a recent conversion to a positive tuberculin skin test, HIV-infected patients, and those with pulmonary fibrosis on radiograph).

Consider using this 12-dose regimen among populations that are unlikely to complete longer courses of therapy with isoniazid alone. This regimen is not recommended for children under 2 years, pregnant women or women planning to become pregnant, or patients whose TB infection is presumed to be the result of exposure to a person with TB disease that is resistant to 1 of the 2 drugs.

The PREVENT TB Study compared this regimen with 9 months of self-administered, daily isoniazid (300 mg) therapy for latent tuberculosis. The combination therapy was shown to be as effective as isoniazid alone in preventing tuberculosis and had a higher treatment-completion rate.[9]

Isoniazid therapy in children

Children younger than 12 years should receive isoniazid for 9 months. In addition, children younger than 5 years who have close contact with a person who has active TB should be started on isoniazid, even if the results on skin testing are negative; preventive therapy can be stopped if the results on repeat skin testing are negative 2-3 months after last contact with a culture-positive source case. Alternatively, children aged 2-11 years may receive DOT with weight-base dosing of once-weekly rifapentine plus isoniazid for 12 weeks.[84, 9]

MDR-TB and patient contacts

Household contacts of patients with MDR-TB have a particularly high risk for tuberculosis, 7.8% within 4 years in a study from Lima, Peru.[85] Limited data are available on regimens for the treatment of patients exposed to MDR-TB. However, if treatment is initiated, at least 2 drugs should be given, and the index isolate should be susceptible to all drugs used

Therapy in patients with HIV infection

Recommended regimens in patients with HIV infection include rifampin alone daily for 4 months or isoniazid, daily or twice weekly, for 9 months. Patients on antiretroviral therapy may need rifabutin instead of rifampin because of potential drug interactions.

Prevention and Consultations

The BCG vaccine continues to be used throughout much of the world and usually provides protection until early childhood. Immunity begins to wane, however, as early as 3 months after administration.[86] As previously noted, use of the BCG vaccine is not recommended in infants in the United States.

In a meta-analysis of eight 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 (P = 0.004). However, isoniazid had no effect in children who initiated treatment at 4 months of age or earlier. When those patients were excluded, isoniazid prophylaxis reduced the risk of developing TB by 59% (RR, 0.41; P< 0.001).[87]

The public health sector should be notified and involved in cases of TB. Local county health departments are expert and funded in the care of TB infection. Consultation with a primary care, pulmonology, internal medicine, or infectious disease specialist prior to initiating therapy is helpful, and it may be appropriate for this consultant to manage the antituberculous chemotherapy. Consult an expert on MDR-TB in cases of multidrug resistance.

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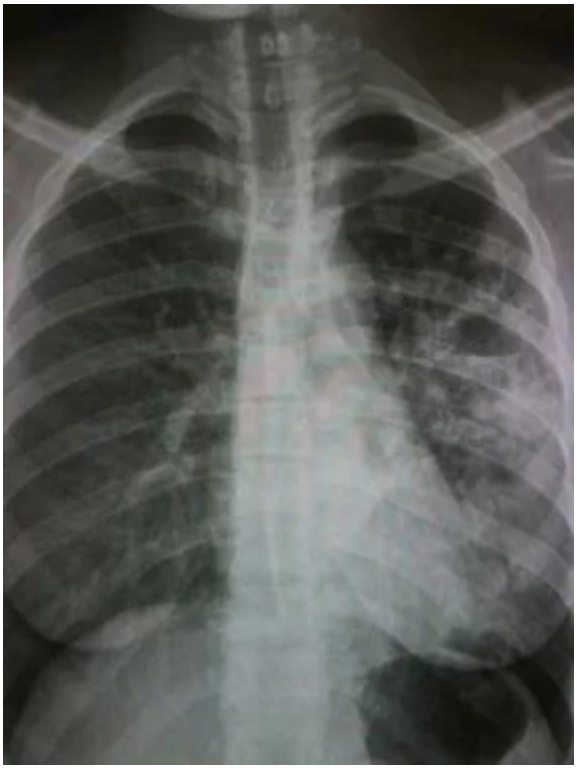
Long-Term Monitoring

After completion of treatment for pulmonary TB, patients remain at risk for late complications, which include relapse, aspergilloma, bronchiectasis, broncholithiasis, fibrothorax, and possibly carcinoma. A copy of the chest radiograph at the time of completion of therapy should be provided to the patient to facilitate the diagnosis of late complications.

The relapse rate following appropriate completed therapy is only 0-4% and occurs within the first 2 years after completion. Aspergilloma is a fungus ball that develops in a residual lung abnormality (eg, pneumatocele, bulla, bleb, cyst). It may appear as a crescent sign on chest radiographs. Other superinfections may manifest with an air-fluid level (seen in the image below) and often contain mixed bacteria, including anaerobes.



Pulmonary tuberculosis with air-fluid level.

Hemoptysis is the most common late complication. Bleeding from submucosal bronchial veins is usually self-limited.

Other complications include the following:

- Broncholithiasis - The result of spontaneous lymph node migration into the bronchial tree; may be associated with postobstructive pneumonia or esophageal perforation
- Chronic obstructive pulmonary disease (COPD) - Bronchiectasis may progress to COPD
- Fibrothorax - The development of trapped lung due to pleural fibrosis and scarring
- Cancer - The risk of carcinoma is controversial but should be considered with newly developing clubbing

Adverse effects of antibiotic therapy in TB can be severe. They include the following:

- Hepatitis
- Peripheral neuropathy
- Retrobulbar optic neuropathy

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Medication

Medication Summary

The treatment of tuberculosis (TB) must satisfy the following basic therapeutic principles:

- Any regimen must use multiple drugs to which Mycobacterium tuberculosis is susceptible
- The medications must be taken regularly
- The therapy must continue for a period sufficient to resolve the illness

New cases are initially treated with four drugs: isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin. After 2 months, they are then treated with a continuation phase of 4 months with isoniazid and rifampin. Patients requiring retreatment should initially receive at least 5 drugs, including isoniazid, rifampin, pyrazinamide, and at least 2 (preferably 3) new drugs to which the patient has not been exposed.[1]

In three phase III trials, shorter TB treatment regimens were not as effective as standard 6-month regimens.[88, 89, 90, 91, 92] In all of the trials, one of the standard treatment drugs was replaced with a fluoroquinolone. In the first study, ethambutol was replaced with gatifloxacin for 2 months of intensive treatment followed by a 2-month continuation phase. In the shorter regimen group, 21.0% of patients had unfavorable outcomes, compared with 17.2% of patients in the standard regimen group. Rates of recurrence were 14.6% and 7.1% in the two groups, respectively.[89]

The second study involved a 4-month treatment regimen in which moxifloxacin was substituted for isoniazid for 2 months, followed by moxifloxacin and rifapentine twice weekly for 2 months. This shorter regimen was inferior to both a 6-month regimen with moxifloxacin and to a standard 6-month treatment regimen.[90]

In the third study, ethambutol or isoniazid was replaced with moxifloxacin. Favorable outcomes were seen in 85% and 80% of the two moxifloxacin groups, compared with 92% of the standard treatment group.[91]

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Antitubercular agents

Class Summary

The goals of TB treatment are to shorten the clinical course of TB, prevent complications, prevent the development of latency and/or subsequent recurrences, and decrease the likelihood of TB transmission. In patients with latent TB, the goal of therapy is to prevent disease progression.

Isoniazid

This is the drug of choice for use in preventive therapy and the primary drug for use in combination therapy for active TB. It is also used in combination with rifapentine for adults and children aged 2 years or older with latent TB as once-weekly DOT therapy for 12 weeks. Its mechanism of action is not fully known, but isoniazid may inhibit the synthesis of mycolic acid, resulting in disruption of the bacterial cell wall. In patients receiving treatment for active TB, pyridoxine 25-50 mg orally once daily should be coadministered to prevent peripheral neuropathy.

Rifampin (Rifadin)

Rifampin is used in combination with at least 1 other antituberculous drug for the treatment of active TB. It inhibits DNA-dependent RNA polymerase activity in bacterial cells but not in mammalian cells. Cross-resistance may occur.

In most susceptible cases, the patient undergoes 6 months of treatment. Treatment lasts for 9 months if the patient's sputum culture result is still positive after 2 months of therapy.

Pyrazinamide

This is a pyrazine analog of nicotinamide that is either bacteriostatic or bactericidal against M tuberculosis, depending on the concentration of drug attained at the site of infection. Pyrazinamide's mechanism of action is unknown. Administer the drug for the initial 2 months of a 6-month or longer treatment regimen for drug-susceptible TB. Treat drug-resistant TB with individualized regimens.

Ethambutol (Myambutol)

Ethambutol diffuses into actively growing mycobacterial cells (eg, tubercle bacilli). It impairs cell metabolism by inhibiting the synthesis of 1 or more metabolites, which in turn causes cell death. No cross-resistance has been demonstrated.

Mycobacterial resistance is frequent with previous therapy. In such cases, use ethambutol in combination with second-line drugs that have not been previously administered. Administer every 24 hours until permanent bacteriologic conversion and maximal clinical improvement are observed. Absorption is not significantly altered by food.

Adverse effects of ethambutol include optic neuritis, which is usually reversible with discontinuation of the drug. During the period when the patient is on a daily dose of 25 mg/kg, monthly eye exams are recommended.

Streptomycin

Streptomycin sulfate, an aminoglycoside, is used for the treatment of susceptible mycobacterial infections. Use this agent in combination with other antituberculous drugs (eg, isoniazid, ethambutol, rifampin).

Although the total period of treatment for TB is a minimum of 6 months, streptomycin therapy is not commonly used for the full duration of therapy, because of toxicity concerns. The drug is recommended when less potentially hazardous therapeutic agents are ineffective or contraindicated.

Levofloxacin (Levaquin)

Levofloxacin, a second-line antituberculous drug, is used in combination with rifampin and other antituberculous agents in treating most cases of multidrug-resistant TB (MDR-TB). A good safety profile with long-term use among the fluoroquinolones has made levofloxacin the preferred oral agent for treating MDR-TB caused by organisms resistant to first-line drugs. Levofloxacin elicits its action through inhibition of bacterial topoisomerase IV and DNA gyrase, which are required for DNA replication, transcription, repair, and recombination.

Moxifloxacin (Avelox)

Moxifloxacin, a second-line antituberculous drug, inhibits the A subunits of DNA gyrase, resulting in inhibition of bacterial DNA replication and transcription. Moxifloxacin can be used for MDR-TB caused by organisms known or presumed to be sensitive to fluoroquinolones or when first-line drugs cannot be used because of intolerance.

Rifapentine (Priftin)

This agent is used twice weekly as part of a multiple drug regimen for 2 months during the intensive phase of TB treatment, then once weekly for 4 months, along with isoniazid or an appropriate agent for susceptible organisms. It is also indicated for adults and children aged 2 years or older with latent TB in combination with isoniazid as once-weekly therapy for 12 weeks. Rifapentine inhibits DNA-dependent RNA polymerase in susceptible strains of M tuberculosis organisms. It should not be used to treat active tuberculosis in individuals with HIV infection or with positive TB cultures after 2 months of treatment.

Ethionamide (Trecator)

Ethionamide is a second-line drug that is bacteriostatic or bactericidal against M tuberculosis, depending on the concentration of the drug attained at the site of infection. It is recommended if treatment with first-line drugs (isoniazid, rifampin) is unsuccessful. Ethionamide can be used to treat any form of active TB. However, it should be used only with other effective antituberculous agents.

Amikacin

Amikacin is a second-line drug used to treat patients with MDR-TB or those who do not tolerate first-line therapies. This agent irreversibly binds to the 30S subunit of bacterial ribosomes, blocking the recognition step in protein synthesis and causing growth inhibition.

Cycloserine

Cycloserine, a second-line TB drug, inhibits cell wall synthesis in susceptible strains of gram-positive and gram-negative bacteria and in M tuberculosis. It is a structural analogue of D-alanine, which antagonizes the role of D-alanine in bacterial cell wall synthesis, inhibiting growth. Like all antituberculosis drugs, cycloserine should be administered in conjunction with other effective TB drugs and not as the sole therapeutic agent

Capreomycin (Capastat)

Capreomycin, which is obtained from Streptomyces capreolus, is a second-line drug that is coadministered with other antituberculous agents in pulmonary infections caused by capreomycin-susceptible strains of M tuberculosis. Capreomycin is used only when first-line agents (eg, isoniazid, rifampin) have been ineffective or cannot be used because of toxicity or the presence of resistant tubercle bacilli.

Rifabutin (Mycobutin)

This is an ansamycin antibiotic derived from rifamycin S. Rifabutin inhibits DNA-dependent RNA polymerase, preventing chain initiation. It is used for TB treatment in individuals on specific HIV medications, when rifampin is contraindicated (most protease inhibitors).

Clofazimine (Lamprene)

Clofazimine inhibits mycobacterial growth, binding preferentially to mycobacterial DNA. It has antimicrobial properties, but its mechanism of action is unknown. It is rarely used to treat MDR-TB. Like all drugs for TB, clofazimine is always used with other antituberculous agents. Clofazimine is available only on a single-patient basis, to physicians who submit an Investigational New Drug (IND) application to the US Food and Drug Administration (FDA).

Para-aminosalicylic acid (Paser)

This is a bacteriostatic agent that is useful as a second-line agent against M tuberculosis. It is most commonly used for MDR-TB or when therapy with isoniazid or rifampin is not possible. It inhibits the onset of bacterial resistance to streptomycin and isoniazid. Administer this agent with other antituberculous drugs.

Bedaquiline (Sirturo)

Bedaquiline is a diarylquinoline that inhibits mycobacterial adenosine 5'-triphosphate (ATP) synthase, an enzyme essential for the generation of energy in Mycobacterium tuberculosis. It is indicated as part of a 22-week multidrug regimen (with at least 4 other antitubercular drugs) in adults with pulmonary MDR-TB. Therapy with bedaquiline is reserved for use when an effective treatment regimen cannot otherwise be provided. It is not indicated to treat latent, extrapulmonary, or drug-sensitive tuberculosis.

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Questions & Answers

Overview

What is tuberculosis (TB) (consumption)?

What are the signs and symptoms of pulmonary tuberculosis (TB) (consumption)?

What are the symptoms of tuberculous (TB) meningitis?

What are the symptoms of skeletal tuberculosis (TB)?

What are the symptoms of genitourinary tuberculosis (TB)?

What are the symptoms of gastrointestinal tuberculosis (TB)?

What are the physical findings of pulmonary tuberculosis (TB) (consumption)?

What are the signs and symptoms of extrapulmonary tuberculosis (TB)?

Does the absence of significant physical findings exclude active tuberculosis (TB) (consumption)?

Which tests are used to screen for tuberculosis (TB) (consumption)?

Which lab tests should be performed in suspected tuberculosis (TB)?

Which tests are performed to determine drug susceptibility following a positive culture for tuberculosis (TB) (consumption)?

Which radiography findings are diagnostic for tuberculosis (TB) (consumption)?

Which tests should be performed in the diagnosis of extrapulmonary tuberculosis (TB)?

Which infection prevention and control measures should be implemented for patients with active tuberculosis (TB) (consumption)?

What is the initial pharmacologic therapy for tuberculosis (TB) (consumption)?

How is tuberculosis (TB) treated in pregnant women?

How is tuberculosis (TB) treated in children?

How is tuberculosis (TB) treated in patients with HIV infection and AIDS?

What are the treatment options for multidrug-resistant tuberculosis (MDR-TB)?

Which surgical interventions are indicated for multidrug-resistant tuberculosis (MDR-TB)?

What are the CDC treatment recommendations for latent tuberculosis infection (LTBI)?

What is the global burden of tuberculosis (TB) (consumption)?

Which comorbidity has contributed to the emergence and spread of drug-resistant tuberculosis (TB)?

Which infectious agent causes tuberculosis (TB) (consumption)?

What is the most common site for the development of tuberculosis (TB)?

What is the primary screening test for tuberculosis (TB) infection?

What is the usual treatment regimen for tuberculosis (TB) (consumption)?

What are the typical communicable-disease control laws for tuberculosis (TB)?

What is the early history of tuberculosis (TB) (consumption)?

What caused the historical increase in the global prevalence of tuberculosis (TB) (consumption)?

What caused a resurgence of tuberculosis (TB) in the 1980s in the US?

What is the prevalence of coinfection with tuberculosis (TB) and HIV infection/AIDS?

Where is tuberculosis (TB) most prevalent and what factors have contributed to its spread?

What is multidrug-resistant tuberculosis (MDR-TB)?

Which factors contribute to the high prevalence of multidrug-resistant tuberculosis (MDR-TB)?

What is the global proportion of multidrug-resistant tuberculosis (MDR-TB) cases?

What population group has the highest rate of resistant tuberculosis (MDR-TB) in the US?

What is the prevalence of extensively drug-resistant tuberculosis (XDR-TB) in the US?

What is the cure rate for multidrug-resistant tuberculosis (MDR-TB)?

Is directly observed therapy (DOT) effective in reducing the incidence of multidrug-resistant tuberculosis (MDR-TB)?

Is there a standard triage protocol for treatment of tuberculosis (TB) in the emergency department (ED)?

Which emergency department (ED) patients are at increased risk for active tuberculosis (TB)?

What is the incidence of extrapulmonary tuberculosis (EPTB)?

What is the prevalence of cutaneous tuberculosis (TB)?

Which physical findings suggest ocular tuberculosis (TB)?

What are the symptoms of ocular tuberculosis (TB)?

What is the incidence of ocular tuberculosis (TB)?

Where can patients find information on tuberculosis (TB)?

How does M tuberculosis infection occur?

What causes the antigenicity of mycobacteria in tuberculosis (TB)?

What is the pathogenesis of latent tuberculosis infection (LTBI)?

What is the most common site for the development of tuberculosis (TB)?

What are the most common sites of extrapulmonary tuberculosis (TB)?

What is the principal cause of tissue destruction due to M tuberculosis infection?

What is the pathogenesis of tuberculosis (TB)-related uveitis?

What is the pathogenesis of tuberculosis (TB) lesions?

What are the features of early tubercles in tuberculosis (TB)?

What is the disease course of tuberculosis (TB) lesions?

What inhibits the growth of tubercle bacillus in tuberculosis (TB)?

What is the disease course in hosts unable to arrest the initial infection of tuberculosis (TB)?

How do lesions initially develop in tuberculosis (TB)?

How do proliferative lesions develop in tuberculosis (TB)?

How do exudative lesions develop in tuberculosis (TB)?

What is the etiology of tuberculosis (TB)?

What are the characteristics of Mycobacterium tuberculosis (M tuberculosis)?

How is Mycobacterium tuberculosis transmitted?

How frequently does exposure to Mycobacterium tuberculosis result in active tuberculosis (TB)?

In the US, what percentage of tuberculosis (TB) is caused by reactivation of latent infection?

Does isoniazid-resistant tuberculosis (TB) have higher or lower transmissibility than fully-susceptible TB?

How does Mycobacterium tuberculosis spread to extrapulmonary sites?

Which groups are at increased risk for developing disseminated (primary miliary) tuberculosis (TB)?

Which factors determine the transmissibility of Mycobacterium tuberculosis infection?

Which settings increase the risk for transmission of Mycobacterium tuberculosis infection?

Which factors increase an individual's risk of acquiring active tuberculosis (TB)?

Which medications significantly increase the risk for tuberculosis (TB)?

Does immunosuppressive therapy increase the risk for tuberculosis (TB)?

What are the possible complications of tuberculosis (TB) in children younger than 5 years?

Do children with tuberculosis (TB) commonly infect other children?

Are there genetic factors related to tuberculosis (TB)?

What role does the NRAMP1 gene have in tuberculosis (TB)?

What role does the SP110 gene have in tuberculosis (TB)?

Which lab tests are performed in suspected tuberculosis (TB)?

What is the role of acid-fast bacilli (AFB) staining in the diagnosis of tuberculosis (TB)?

When are imaging studies indicated in the diagnosis of tuberculosis (TB)?

What is the role of technetium-99m (99m Tc) methoxy isobutyl isonitrile SPECT scanning in the diagnosis of tuberculosis (TB)?

Is radiography useful in the diagnosis of multidrug-resistant tuberculosis (MDR-TB)?

Which tests are used to diagnose extrapulmonary tuberculosis (TB)?

Which factors make ocular tuberculosis (TB) especially difficult to diagnose?

What is the histopathology of extrapulmonary tuberculosis (TB)?

Which symptoms suggest tuberculous (TB) meningitis or tuberculoma, and what tests are performed to confirm diagnosis?

Which testing is needed when vertebral (Pott disease) or brain involvement is suspected in tuberculosis (TB)?

When are urinalysis and urine cultures indicated in the diagnosis of tuberculosis (TB)?

Which tests should be performed if tuberculosis (TB) is suspected during pregnancy?

Which diagnostic tests are indicated for suspected congenital tuberculosis (TB)?

How is postnatal tuberculosis (TB) in infants contracted?

Which chest radiographic findings may suggest tuberculosis (TB) in children?

When is HIV testing indicated in patients with tuberculosis (TB)?

Among HIV-positive patients, who is at increased risk for developing tuberculosis (TB)?

Which tuberculosis (TB) screening test should be performed prior to initiation of antiretroviral therapy (ART) in patients with HIV infection?

Which tests should be performed in patients with tuberculosis (TB) and HIV infection?

What are the increased health risks for patients with tuberculosis (TB) and HIV infection?

What is the role of a sputum smear in the diagnosis of tuberculosis (TB)?

How are sputum samples collected in patients with suspected tuberculosis (TB)?

What is the role of Ziehl-Neelsen staining in the diagnosis of tuberculosis (TB)?

How often are culture-positive specimens associated with a negative smear result for tuberculosis (TB)?

What can be used to differentiate tuberculosis (TB) with negative sputum smears from latent TB infection (LTBI)?

What is the role of nucleic acid amplification tests (NAAT) in the diagnosis of tuberculosis (TB)?

What are the CDC recommendations for use of nucleic acid amplifications in the diagnosis of pulmonary tuberculosis (TB)?

How accurate is nucleic acid amplification testing (NAAT) in diagnosing tuberculosis (TB)?

Which test is the most specific for tuberculosis (TB)?

What is the role of acid-fast bacilli (AFB) cultures in the diagnosis of tuberculosis (TB)?

Are broth cultures available for use in clinical labs for the diagnosis of tuberculosis (TB)?

What is the role of blood cultures in the diagnosis of tuberculosis (TB)?

When is drug susceptibility testing indicated in the diagnosis of tuberculosis (TB)?

What is the efficacy of DNA sequencing analysis for detecting drug-resistant tuberculosis (TB)?

What is the efficacy of automated molecular testing for the detection of tuberculosis (TB)?

What is the role of microscopic-observation drug susceptibility (MODS) and thin-layer agar (TLA) assays in the diagnosis of multidrug-resistant tuberculosis (MDR-TB)?

Which rapid drug susceptibility tests are used to diagnose multidrug-resistant tuberculosis (MDR-TB)?)?

What is the role of chest radiography in the diagnosis of tuberculosis (TB)?

When is chest radiography used to screen for sarcoidosis in patients with suspected tuberculosis (TB)?

Which chest radiography findings suggest tuberculosis (TB)?

In a symptomatic patient with normal chest radiographic findings, is tuberculosis (TB) excluded?

How do radiographic findings differentiate primary tuberculosis (TB) from reactivation TB?

Which chest radiographic findings suggest reactivation tuberculosis (TB)?

Which chest radiographic findings suggest tuberculosis (TB) with HIV infection?

Which chest radiographic findings suggest healed tuberculosis (TB)?

Which chest radiographic findings suggest miliary tuberculosis (TB)?

Which chest radiographic findings suggest pleural tuberculosis (TB)?

What is the primary screening test for tuberculosis (TB) infection?

How is the Mantoux tuberculin skin test with purified protein derivative (PPD) administered in patients with suspected tuberculosis (TB)?

What are the population-based criteria for purified protein derivative (PPD) positivity in tuberculosis (TB) testing?

What are the population-based criteria for purified protein derivative (PPD) positivity in tuberculosis (TB) testing for patients who have received the Bacillus Calmette–Guérin (BCG) vaccine?

What is the role of interferon-gamma release assay (IGRA) in the diagnosis of tuberculosis (TB)?

Are interferon-gamma release assays (IGRA) effective for the diagnosis of tuberculosis (TB)?

What are the advantages and disadvantages of interferon-gamma release assays (IGRA)?

What is the accuracy of tuberculin skin testing and interferon-gamma release assay (IGRA) for tuberculosis (TB) infection?

What are the highest positive and negative likelihood ratios for latent tuberculosis infection (LTBI)?

How accurate is skin testing in predicting the subsequent development of tuberculosis (TB)?

Which tests may be more reliable than skin testing for identifying patients who will progress to active tuberculosis (TB)?

Treatment

Which infection prevention and control measures should be implemented for patients with active tuberculosis (TB) (consumption)?

What is the initial empiric treatment of tuberculosis (TB)?

What baseline assessments are required for patients with tuberculosis (TB) who receive pyrazinamide or long-term ethambutol therapy?

How long should drug therapy for tuberculosis (TB) be continued?

When is directly observed therapy (DOT) indicated in the treatment of tuberculosis (TB)?

How should active tuberculosis (TB) be monitored?

What is the treatment for patients with tuberculosis (TB) who are actively seizing or who have overdosed on antimycobacterial medication?

How should pregnant women with active tuberculosis (TB) be treated?

When is preventive treatment for tuberculosis (TB) recommended in women who are pregnant?

What are the risks of isoniazid therapy in pregnant and postpartum women with tuberculosis (TB)?

Should women breastfeed during preventive therapy for tuberculosis (TB)?

Does tuberculosis during pregnancy increase the risk of preterm birth?

How is tuberculosis (TB) treated in children?

What is the duration of treatment for postnatal tuberculosis (TB)?

How is isoniazid administered in the treatment of tuberculosis (TB) in children?

How is rifampin administered in the treatment of tuberculosis (TB) in children?

What is the role of ethambutol in the treatment of tuberculosis (TB) in children?

How does the treatment regimen for tuberculosis (TB) differ in patients with HIV infection?

What is immune reconstitution inflammatory syndrome (IRIS) in patients receiving treatment for tuberculosis (TB) and HIV infection?

What are the benefits of early antiretroviral therapy (ART) in patients with HIV infection and tuberculosis (TB)?

What is the treatment length and recurrence rate of treatment for tuberculosis (TB) in patients with HIV infection?

Which medication reduces complications in the treatment of tuberculous meningitis?

When is treatment initiated when multidrug-resistant tuberculosis (MDR-TB) is suspected?

What are the benefits of combining isoniazid and rifampin in the treatment of multidrug-resistant tuberculosis (MDR-TB)?

Which drugs should be used when initiating multidrug-resistant tuberculosis (MDR-TB) treatment?

Which medications are used for the treatment of multidrug-resistant tuberculosis (MDR-TB)?

Which agent can be substituted for rifampin in multidrug-resistant tuberculosis (MDR-TB) treatment?

Which factors increase the likelihood of successful multidrug-resistant tuberculosis (MDR-TB) treatment?

How long should treatment be continued for multidrug-resistant tuberculosis (MDR-TB)?

Is bedaquiline (Sirturo) effective for the treatment of multidrug-resistant tuberculosis (MDR-TB)?

What are the CDC guidelines for the use of bedaquiline in the treatment of multidrug-resistant tuberculosis (MDR-TB)?

How is the diagnosis of extensively drug-resistant tuberculosis (XDR-TB) established?

According to the CDC, which groups have the highest risk for pyrazinamide-resistant tuberculosis (TB)?

When is surgical resection of an infected lung indicated in the treatment of multidrug-resistant tuberculosis (MDR-TB)?

What are the possible complications of surgical resection in multidrug-resistant tuberculosis (MDR-TB)?

Is rifapentine (Priftin) an effective treatment for latent tuberculosis infection (LTBI)?

What are the CDC guidelines for the treatment of latent tuberculosis infection (LTBI)?

How effective is self-administered therapy versus directly observed therapy in the treatment of latent tuberculosis infection (LTBI)?

How is isoniazid plus rifapentine administered in the treatment of latent tuberculosis infection (LTBI)?

When are longer isoniazid plus rifapentine regimens indicated in the treatment of latent tuberculosis infection (LTBI)?

When are isoniazid plus rifapentine regimens contraindicated in the treatment of latent tuberculosis infection (LTBI)?

How does combination isoniazid plus rifapentine therapy compare to isoniazid alone for treatment of latent tuberculosis infection (LTBI)?

Should children with latent tuberculosis infection (LTBI) receive isoniazid therapy?

When is treatment indicated for individuals exposed to multidrug-resistant tuberculosis (MDR-TB)?

What is the recommended treatment for patients with HIV infection and latent tuberculosis infection (LTBI)?

Does the Bacillus Calmette–Guérin (BCG) vaccine offer protection against tuberculosis (TB)?

Does isoniazid prophylaxis reduce the risk of tuberculosis (TB) in children?

Which specialist consultations are indicated in the treatment of tuberculosis (TB)?

Medications

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