Chapter 67: Tuberculosis

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INTRODUCTION AND EPIDEMIOLOGY

Tuberculosis remains an important worldwide infection, with more than one third of the overall population harboring the bacterium. It is the second leading cause of death among infectious diseases and a major cause of death among those with human immunodeficiency disease (HIV), especially in countries with limited resources.[1,2] Despite therapeutic progress over the past 20 years, drug resistance and HIV coinfection continue to challenge the global control of tuberculosis.[2]

Tuberculosis has been on the decline in the United States, with an average 3.8% decrease each year from 2000 to 2010.[3] This reduction is primarily due to tuberculosis control programs targeting high-risk individuals. In addition, improved infection control policies, increased vigilance among physicians, implementation of directly observed therapy, and standardized drug regimens all contributed to the decline of tuberculosis rates. Although overall national cases have decreased, the incidence in foreign-born patients remains 12 times that of U.S.-born persons.[3] In foreign-born patients, clinical tuberculosis is usually from reactivation of latent disease. Overall, reactivation of latent tuberculosis is responsible for 70% of active tuberculosis cases.[4]

Continued improvement in tuberculosis control and prevention requires recognition and treatment of high-risk populations (**Table 67-1**). Screening and treatment of latent infection in high-risk individuals are key to reducing tuberculosis in the United States.[4]

TABLE 67-1

Patients with a High Prevalence of Tuberculosis (Highest to Lowest Risk)

Immigrants from high-prevalence countries
Patients with the human immunodeficiency virus
Residents and staff of prisons or shelters for the homeless
Alcoholics and illicit drug users
Elderly and nursing home patients

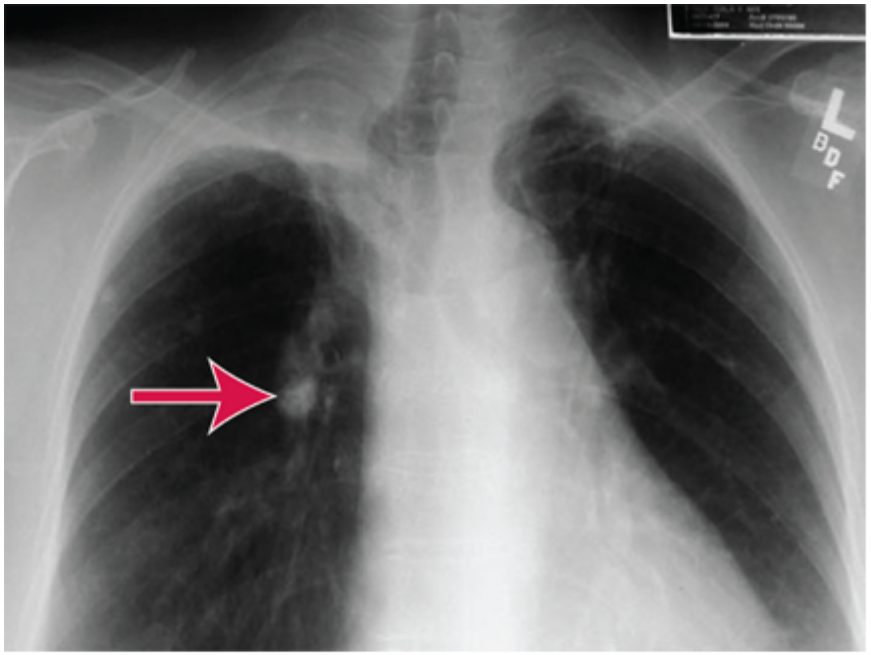
PATHOPHYSIOLOGY

Mycobacterium tuberculosis is a slow-growing aerobic rod that has a multilayered cell wall containing lipids that account for its acid-fast staining property. Because the organism is an obligate aerobe, it settles in areas of high oxygen content and blood flow. Transmission from person to person occurs through inhalation of droplet nuclei into the lungs. Persons with active tuberculosis who excrete mycobacteria in saliva or sputum are the most infectious.[5] Only 30% of patients actually become infected after a droplet exposure.[6]

PRIMARY AND LATENT INFECTION

Once the organisms reach the lungs, host defenses are activated. Some organisms survive and are transported to the regional lymph nodes, where the host cell-mediated immunity is activated to contain the infection. Granulomas, known as tubercles, form as a result of this process, which involves activated macrophages and T lymphocytes in addition to active bacteria in most cases. Tubercles are a sign of primary infection and may progress to caseation necrosis and calcification. In the lung, the **Ghon complex** (**Figure 67-1**) is a manifestation, appearing as calcified hilar lymph nodes.

FIGURE 67-1.
Primary Ghon complex (arrow).



Source: J.E. Tintinalli, J.S. Stapczynski, O.J. Ma, D.M. Yealy, G.D. Meckler, D.M. Cline: Tintinalli's Emergency Medicine: A Comprehensive Study Guide, 8th Edition
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If the tubercle fails to contain the infection, the mycobacteria may spread by hematogenous, lymphatic, or direct mechanical routes. The tendency is for survival in areas of high oxygen content or blood flow, such as the apical and posterior segments of the upper lobe and the superior segment of the lower lobe of the lung, the renal cortex, the meninges, the epiphyses of long bones, and the vertebrae. In these areas, the mycobacteria can remain dormant for years. During dormancy (or latent infection), the disease is detected by a positive tuberculin skin test. **The skin test generally becomes positive 1 to 2 months after initial exposure.** Only 1% to 13% of otherwise healthy patients will go on to develop active postprimary disease. However, children and HIV patients have a higher risk, approaching a 20% frequency of postprimary infection.[5,7]

REACTIVATION TUBERCULOSIS

Whether latent infection progresses to recurrently active (or "reactivation") tuberculosis is dependent on the immune status of the host.[5,6] As the host defense system weakens, it is no longer capable of containing the foci of previous hematogenous spread, and active tuberculosis may develop. The risk for reactivation is higher among HIV-infected persons and those more than 50 years old.[6] In 5% of p to active disease within 2 years after initial exposure, with another 5% developing disease later in

life.[5,7] In immunocompromised hosts, spread often occurs rapidly, and progression of early active disease is more frequent. HIV-infected patients are at particularly high risk, with progression reported at 7% to 10% per year.[5] Other groups at risk for developing tuberculosis activation include those immunocompromised from carcinoma of solid organs, leukemia, transplantation, or medications such as antagonists of tumor necrosis factor-α (etanercept or infliximab) or corticosteroids. Those with select chronic diseases such as diabetes, chronic renal failure requiring hemodialysis, psoriasis, and silicosis are also at increased risk for tuberculosis activation.[5,8]

CLINICAL FEATURES

PRIMARY TUBERCULOSIS

The initial infection is usually asymptomatic, often detected only by a positive screening tuberculin skin test or by abnormalities on chest radiograph. When the infection is primary and active, common symptoms include fever, malaise, weight loss, and chest pain.[5] Infrequently, a pneumonitis that is similar to a viral or bacterial infection appears. Hilar adenopathy is present but rarely massive. In some cases, especially in immunocompromised patients, the primary infection may be rapidly progressive and fatal.

REACTIVATION TUBERCULOSIS

When latent infection progresses to tuberculosis reactivation, symptoms may be systemic or pulmonary. The most common reactivation symptoms are similar to those of primary tuberculosis and include fever, night sweats, malaise, fatigue, and weight loss. Productive cough, hemoptysis, dyspnea, and pleuritic chest pain develop as the infection spreads within the lungs. Physical examination is generally unremarkable, although rales may be noted in areas of pulmonary infection.

Although most cases of active tuberculosis involve the lungs, up to 20% of cases will have extrapulmonary manifestations.[5] The most common extrapulmonary site of tuberculosis is the lymphatic system—painless lymphadenopathy (i.e., scrofula, cervical lymphadenitis). Other extrapulmonary manifestations include abdominal pain due to hepatosplenomegaly, peritoneal tubercles, prostatitis, epididymitis, or orchitis; adrenal insufficiency; bone pain with arthritis, osteomyelitis, or Pott's disease (bony destruction, often in the spine); hematuria and sterile puree; and meningitis. Tuberculosis can also cause pericarditis, which can lead to tamponade and constrictive symptoms. One key extrapulmonary tuberculosis axiom is that it can mimic many other common diseases, especially in the elderly and HIV patients.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

With the aging population, consider tuberculosis in all patients over 50 years old with a pneumonia-like presentation or prominent respiratory complaint.[5,6] Similarly, consider the disease in those with HIV or on immunosuppressive medications (notably after transplantation or with a connective tissue disease). The variable clinical presentation and the time required to culture the organism make diagnosis in the ED challenging. The goal is to have considered and begun testing for tuberculosis and to start respiratory precautions while awaiting results.

The ED is the point of entry into the healthcare system for many patients.[9] Prehospital and ED personnel should think of potential tuberculosis in higher-risk patients with lung symptoms, institute appropriate respiratory precautions, and notify healthcare providers about the possibility of tuberculosis. Place patients with suspected tuberculosis in separate waiting areas, provide them with surgical masks, and instruct them to cover the mouth and nose when coughing. Immunocompromised patients with respiratory symptoms should be evaluated promptly and isolated until tuberculosis can be excluded based on a chest radiograph.[10] A negative-pressure room is ideal for isolation when available.

During triage or initial assessment, consider the diagnosis of tuberculosis in any patient with a persistent cough (weeks or months) that has not improved despite appropriate treatment. Tuberculosis can mimic community-acquired pneumonia; clues that suggest tuberculosis include hemoptysis, night sweats, and weight loss. On chest radiograph, look carefully for upper lung field involvement, fibrocalcific changes, pleural capping, or a calcified Ghon complex.[5]

Once tuberculosis is suspected, give empiric antibiotics for pneumonia, admit the patient to an isolation bed, and institute airborne precautions. The evaluation should include sputum culture and tuberculosis skin testing and should also include HIV testing if the patient's HIV status is unknown.

MANTOUX OR TUBERCULIN SKIN TEST

The most common method for screening for exposure to M. tuberculosis is a skin test. The Mantoux test uses intracutaneous injection of 0.1 mL of **purified protein derivative** into the forearm. The test relies on a delayed-type hypersensitivity reaction that is triggered in those with past infection or those with a significant recent exposure to tuberculosis. The test is read between 48 and 72 hours after administration by measuring the extent of skin induration at the test site; erythema or other skin changes are not assessed (**Table 67-2**).[10] All persons with a new positive skin test or recent conversion should be referred for treatment of latent tuberculosis.

TABLE 67-2

Interpretation of a Purified Protein Derivative Skin Test*

≥5-mm induration is positive in: Patients with the human immunodeficiency virus Patients with close contact with a tuberculosis-infected individual Patients with abnormal chest radiograph suggestive of healed tuberculosis Patients with organ transplants and other immunosuppressed patients receiving the equivalent of prednisone >15 milligrams per day for >1 month
≥10-mm induration is positive in patients not meeting the above criteria but who have other risks: Injection drug users High-prevalence groups (immigrants, long-term care facility residents, persons in local high-risk areas) Patients with conditions that increase the risk of progression to active disease (silicosis, diabetes, carcinoma of the head, neck, or lung) Children <4 y of age
≥15-mm induration is positive in all others
Detection of newly infected persons in a screening program: ≥10-mm induration increase within any 2-y period is positive if <35 y ≥15-mm induration increase within any 2-y period is positive if >35 y If the patient is anergic, other epidemiologic factors must be considered

*A positive reaction does not necessarily indicate disease.

In a few situations, a positive skin test is not diagnostic of tuberculosis. Those who received **Bacillus Calmette-Guérin (BCG)** immunization for tuberculosis prevention will often have a positive skin test response in absence of infection. Exposure to nontuberculosis mycobacteria also can result in a false-positive test. False-negative skin test results occur with improper administration or reading, very early in the disease, or with profound underlying immunosuppression (notably in HIV).[7,8,11]

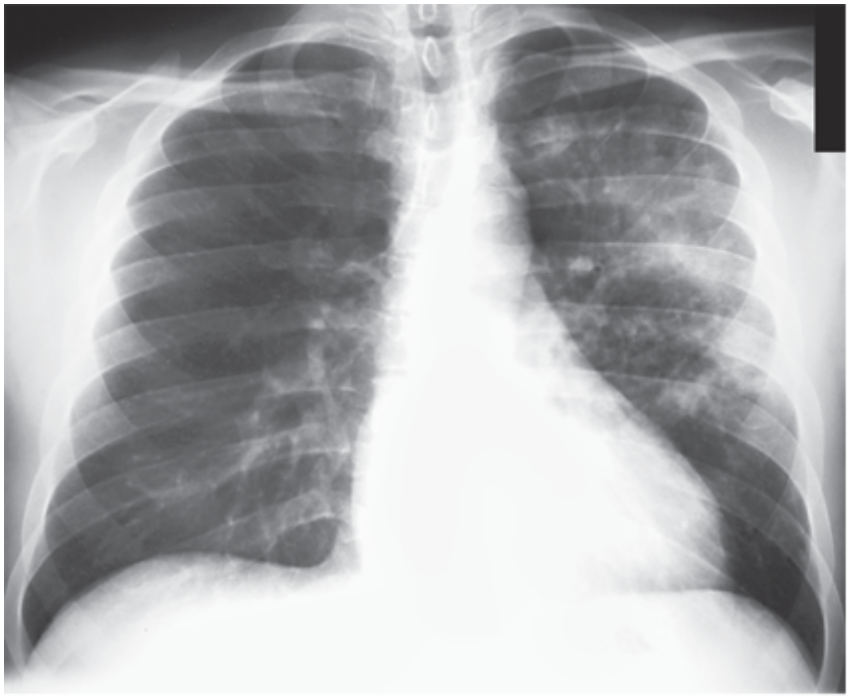
BLOOD TESTS

Interferon-gamma release assays (IGRA) are blood tests that indirectly assess for tuberculosis. The test seeks the response to peptides present in all M. tuberculosis proteins, which trigger the release of interferon-gamma by the infected host.[11] These proteins are absent in the BCG vaccine and in most nontuberculous mycobacteria, making IGRA more specific than skin testing.[8,11] IGRA is used in conjunction with a history, chest radiograph, and culture in those with suspected active tuberculosis.[11,12] Currently used IGRA tests give results in 16 to 24 hours. These tests are especially helpful when follow-up care compliance is a concern, notably in the homeless or drug-abusing patient, and can aid in those patients in whom skin testing is not helpful for the previously mentioned reasons or with known previous exposure (e.g., a healthcare worker).[8,11]

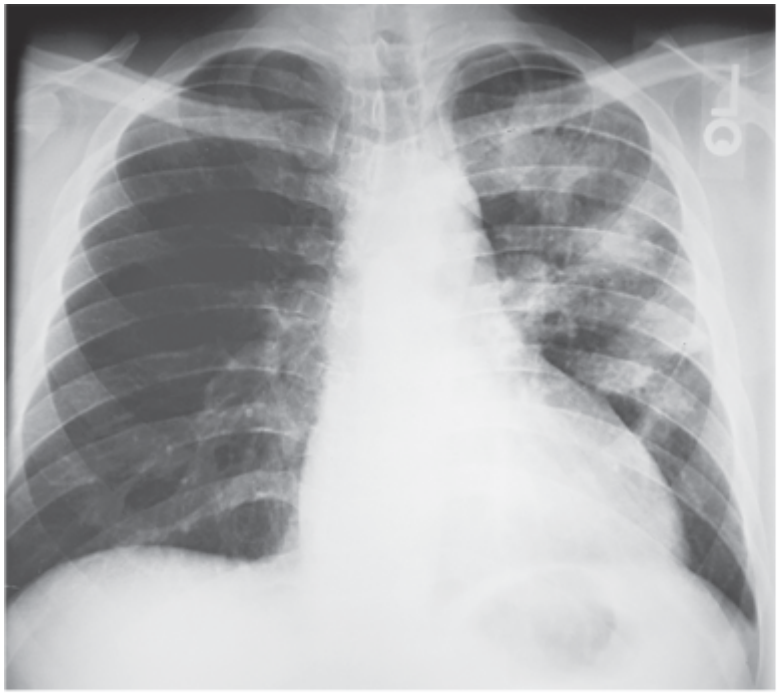
CHEST RADIOGRAPH

The chest radiograph is used to identify disease in those with pulmonary symptoms or after a positive skin test. No singular findings are pathognomonic for primary tuberculosis,[13] and the most common finding is a normal chest radiograph.[5] In primary infection, parenchymal infiltrates in any area of the lung may be found (**Figure 67-2**). Isolated ipsilateral hilar or mediastinal adenopathy is sometimes the only finding. Pleural effusions are usually unilateral and occur alone or in association with parenchymal disease. During primary infection, younger patients are more likely to have enlarged hilar lymph nodes, whereas adults more frequently have parenchymal abnormalities and effusions. The enlarged lymph nodes commonly encountered in children may cause external compression, leading to bronchial obstruction, atelectasis, and postobstructive hyperinflation. Because tuberculosis has a wide variety of appearances on chest radiographs, comparison with previous films is extremely helpful in determining the significance of an abnormal or unusual finding.[5,13]

FIGURE 67-2.
Reactivation tuberculosis. **A**. This elderly patient was treated with antibiotics for community-acquired pneumonia. **B**. When the patient did not respond, a past history of asymptomatic exposure to tuberculosis was elicited. Infiltrates were noted to be worse on hospital day 5 when tuberculosis skin test turned positive, diagnosing reactivation pulmonary tuberculosis.



A



B

In **latent tuberculosis**, nonspecific findings include upper lobe or hilar nodules and fibrotic lesions, which may be calcified. Other findings are bronchiectasis, volume loss, and pleural scarring. Healed primary areas of infection appear as Ghon foci, areas of scarring, and calcification (see Figure 67-1).

Reactivation infections often have the classic findings of tuberculosis: cavitary or noncavitary lesions in the upper lobe or superior segment of the lower lobe of the lungs (**Figures 67-3 and 67-4**).

FIGURE 67-3.
Cavitary tuberculosis of the right upper lobe.

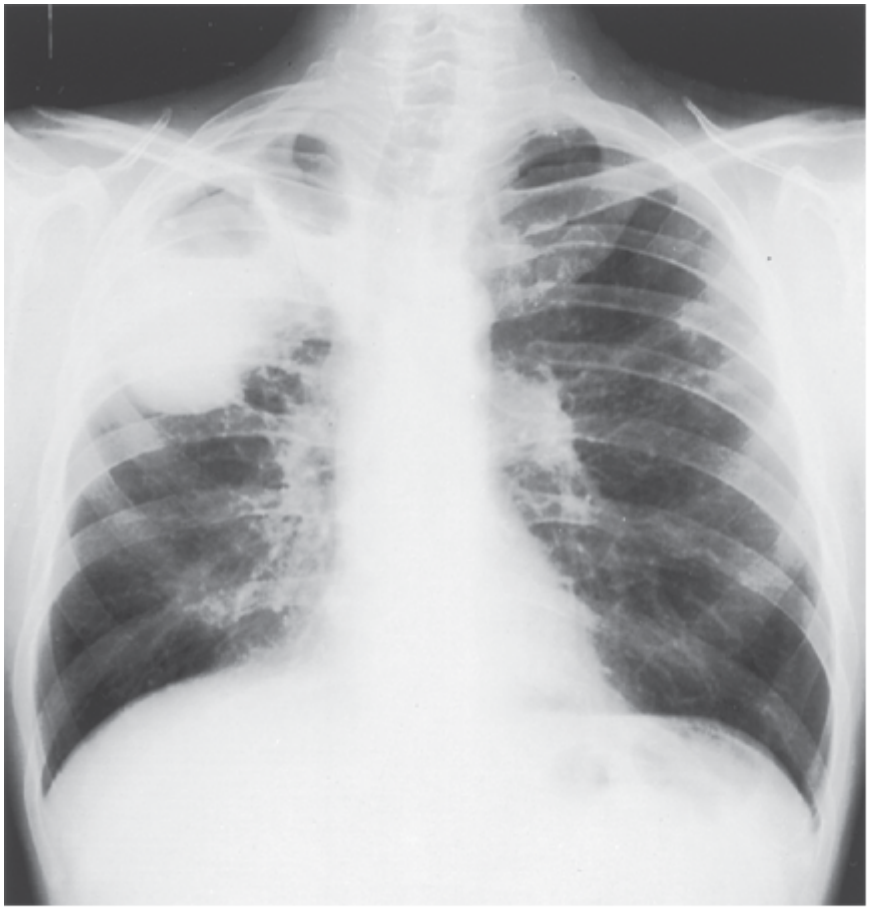
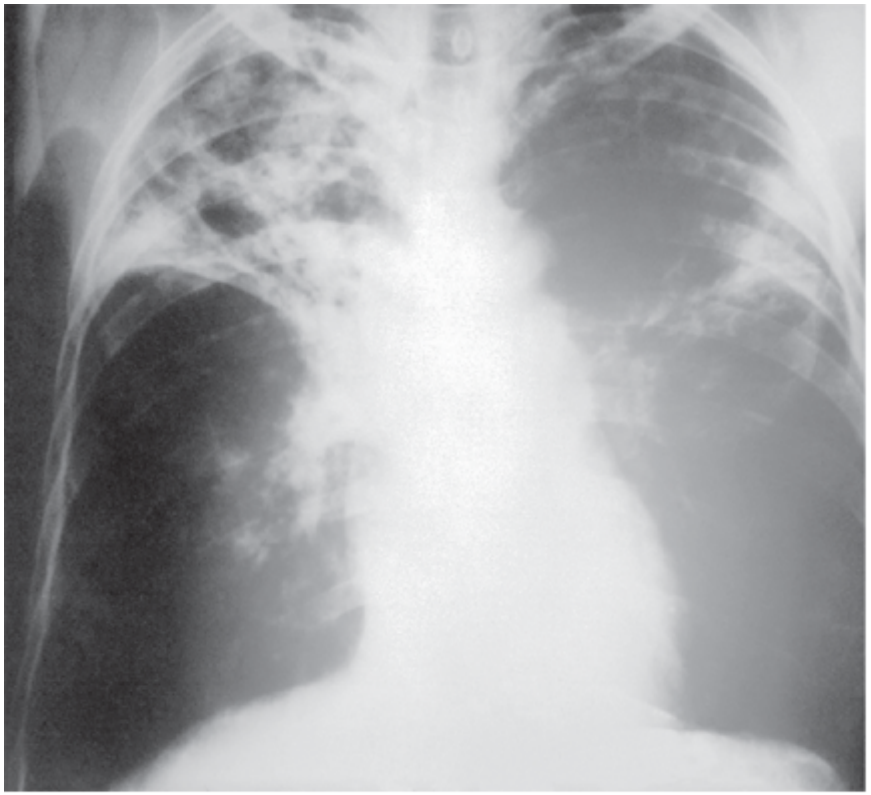


FIGURE 67-4.

Advanced pulmonary tuberculosis involving apex and upper lobe.



The radiographic appearance of tuberculosis is often dependent on the integrity of the immune system rather than the stage of tuberculous disease, with classic findings seen in the immunocompetent patient. Thus, immunocompromised patients are more likely to have radiographic findings traditionally considered findings of primary disease.[13,14] The frequency of classic findings on chest radiographs is directly related to the degree of immunosuppression; those HIV patients with low CD4 counts have more atypical findings on radiographs. Normal radiographs occur in up to 22% of tuberculosis patients with advanced HIV.[14,15]

MICROSCOPY/CULTURES

Sputum is normally collected to detect the presence of M. tuberculosis. In the absence of a satisfactory sputum sample, gastric aspirates, pleural and other body fluids, or tissue samples may be used for culture and other diagnostic tests. The samples are typically s[illegible]in or a fluorochrome procedure followed by exposure to an acidic agent. Mycobacteria will not lose the stain despite being rinsed with an acidic chemical. Hence, the term "**acid-fast bacilli**" is used to describe the appearance on

microscopic smears. Unfortunately, the staining procedure is not sufficiently sensitive or specific to confirm or exclude the diagnosis of tuberculosis.[2] Negative smears are found in approximately 60% of culture-positive cases of tuberculosis. This number may be even higher in children and HIV patients.[13,15]

Cultures for M. tuberculosis are the best method of confirming diagnosis. Cultures also can aid detecting resistance to treatment regimens. However, culture results are not available for weeks, thus creating the need for newer adjunctive tests to expedite diagnosis and treatment. The **nucleic acid amplification test (NAAT)** can yield results within 1 day. In patients with positive smears, it has a reported sensitivity of greater than 95%. Patients with positive smears and positive NAAT should receive treatment pending culture results.[2] However, a negative NAAT result cannot rule out tuberculosis. For these cases, treatment may depend on further testing and should be guided by clinical suspicion and culture results.[13]

TREATMENT

TREATMENT OF ACTIVE TUBERCULOSIS

Active tuberculosis treatment requires the use of a combination of antituberculous medications to overcome resistance (**Table 67-3**).[12] Initial therapy includes first-line medications (isoniazid [INH], rifampin [RIF], pyrazinamide [PZA], ethambutol) for 8 weeks, followed by two-drug continuation treatment for 18 to 31 weeks based on culture results. Second-line medications are used for drug-resistant cases or when side effects from initial therapy are not tolerable. In the ED, patients are either admitted to the hospital to determine the need for antituberculous medications or referred to specialists in the community for follow-up if compliance is likely. In most cases, antituberculous medications will not be started in the ED unless done in consultation and for classic cases. The recommended Centers for Disease Control and Prevention regimens are as follows[12]:

TABLE 67-3

Antituberculous Medications

First-Line	Second-Line
Isoniazid	Cycloserine
Rifampin	Ethionamide
Rifapentine	Fluoroquinolones
Ethambutol	Streptomycin
Pyrazinamide	Amikacin
Rifabutin	Capreomycin

Daily four-drug (INH, RIF, PZA, ethambutol) therapy for 8 weeks, followed by either INH/RIF or INH/rifapentine for 18 weeks OR

Daily four-drug therapy for 2 weeks, followed by two times per week for 6 weeks, with subsequent INH/RIF or INH/rifapentine for 18 weeks OR

Three times weekly four-drug therapy for 8 weeks, followed by INH/RIF three times weekly for 18 weeks OR

Daily three-drug therapy (INH, RIF, ethambutol) for 8 weeks followed by INH/RIF for 31 weeks

More prolonged therapy is recommended for immunocompromised patients or for those with extrapulmonary disease. Initial therapy may be modified once drug susceptibilities are available. The importance of directly observed therapy is paramount in select patients where compliance is a concern; the Centers for Disease Control and Prevention recommends that all regimens of two or three times per week be given by directly observed therapy.[2,12]

Although the standard medications used to treat tuberculosis are generally effective and safe, side effects or drug interactions may occur (**Table 67-4**). Hepatotoxicity, or hepatitis, is the major adverse effect of INH. Preexisting liver disease, pregnancy, ethanol use, HIV, and hepatitis C infection have been associated with an increased risk for hepatotoxicity from INH. Those with preexisting medical conditions requiring multiple medications may be at higher risk for drug interactions with antituberculous agents.[2,12,15]

TABLE 67-4

Treatment of Tuberculosis (Adults)*

Drug	Daily (maximum)	Three Times Weekly DOT (maximum)	Two Times Weekly DOT (maximum)	Potential Side Effects and Comments
Isoniazid	5 milligrams/kg PO* (300 milligrams)	15 milligrams/kg PO (900 milligrams)	15 milligrams/kg PO (900 milligrams)	Hepatitis, peripheral neuropathy, drug interactions.
Rifampin (RIF)	10 milligrams/kg PO* (600 milligrams)	10 milligrams/kg PO (600 milligrams)	10 milligrams/kg PO (600 milligrams)	Hepatitis, thrombocytopenia, GI disturbances, drug interactions.
Rifapentine	Not given daily	Not given 3 times weekly	600 milligrams PO twice weekly in adults; not approved in children <12 y old	Hepatitis, thrombocytopenia, exacerbation of porphyria. Recommended by Centers for Disease Control and Prevention for continuation therapy only for human immunodeficiency virus–negative patients.
Rifabutin	5 milligrams/kg PO (300 milligrams)	5 milligrams/kg PO (300 milligrams)	5 milligrams/kg PO (300 milligrams)	Similar to RIF; used for patients who cannot tolerate RIF.

Drug	Daily (maximum)	Three Times Weekly DOT (maximum)	Two Times Weekly DOT (maximum)	Potential Side Effects and Comments
Ethambutol	15–20 milligrams/kg PO (1.6 grams)	25–30 milligrams/kg PO (2.5 grams)	50 milligrams/kg PO (2.5 grams)	Retrobulbar neuritis, peripheral neuropathy.
Pyrazinamide	15–30 milligrams/kg PO (2 grams)	50 milligrams/kg PO (3 grams)	50 milligrams/kg PO (2 grams)	Hepatitis, arthralgia, hyperuricemia.

Abbreviation: DOT = directly observed therapy.

*See http://www.cdc.gov.une.idm.oclc.org/tb for more accurate weight-based protocols and dosages for children.

A portion of patients being treated for tuberculosis will clinically worsen after the initiation of antituberculous medications.[10,15,16] This effect is called a paradoxical reaction or immune reconstitution syndrome and can be seen in any patient receiving treatment for tuberculosis, although it is more commonly seen in those with HIV infection. Signs and symptoms include fever, worsening respiratory status, lymphadenopathy, hepatosplenomegaly, ascites, meningitis, and new or worsening CNS lesions. **Hypercalcemia** is a unique finding in paradoxical reactions. Because treatment of tuberculosis and HIV both improve immune function, the paradoxical reaction is thought to be a result of improvement in the body's ability to mount an inflammatory response as mycobacteria are cleared. The dilemma is differentiating this from treatment failures, drug resistance, and medication noncompliance. (See the Special Populations section.)

TREATMENT OF LATENT TUBERCULOSIS

Treatment of latent infection with INH alone is started in those with recent asymptomatic skin test conversion (see Table 67-2), any person in close contact with an actively infected patient, and anergic patients with known tuberculosis contact.[11,12] Unless contraindicated, therapy is for a minimum of 9 months for adults, children, and HIV-infected persons. Monitor those at risk for INH hepatotoxicity by serial laboratory assessment. For those exposed to INH-resistant strains or those who are intolerant, use RIF and PZA for 2 months with hepatotoxicity monitoring.[12]

DISPOSITION AND FOLLOW-UP

OUTPATIENT CARE

Most patients with tuberculosis can be treated initially as outpatients. If planning discharge or transfer for other nonmedical care, start or maintain therapy while awaiting smear and culture results on all with suspicious findings of active tuberculosis, notably cavitary lesions or known previous infection with new weakness or fevers.

Contact primary care physicians or public health services and arrange for long-term care before patient discharge. Discharge instructions include home isolation procedures and follow-up at the appropriate clinic to receive medication and ongoing care. **Antituberculosis medications should not be instituted in the ED unless there is joint agreement with the consultant and follow-up providers.**

HOSPITAL ADMISSION

Hospital admission should be done for the following cases: ill-appearing, hypoxemic, or dyspneic patients; if the diagnosis is uncertain; if noncompliance is likely or if the social situation makes it difficult to complete evaluation and start care; or patients with active drug-resistant tuberculosis. Hospitalized patients with suspected tuberculosis require respiratory isolation in a negative-pressure room (**Table 67-5**). An alternative to admission for therapy compliance alone is a court-ordered drug observation program (if available), where scheduled outpatient contacts to ensure medication use occur for the course of therapy.[2]

TABLE 67-5

Engineering Controls to Reduce the Transmission of Tuberculosis

High airflow (at least 6 room air changes per hour) with external exhaust
High-efficiency particulate filters on ventilation system
Ultraviolet germicidal irradiation
Negative-pressure isolation rooms
Personal respiratory protection: high-efficiency particulate filter masks or respirators

SPECIAL POPULATIONS

PATIENTS WITH TUBERCULOSIS AND HUMAN IMMUNODEFICIENCY VIRUS

HIV infection is the strongest known risk factor for tuberculosis, and the incidence of tuberculosis in HIV-positive patients is much higher than in the general population. Patients with a new diagnosis of tuberculosis are almost 20 times more likely to have HIV, and HIV patients are 20 to 30 times more likely to develop tuberculosis. Tuberculosis (pulmonary and extrapulmonary) often can be the initial clinical manifestation of immunodeficiency and is a defining event in the acquired immunodeficiency syndrome. Once active tuberculosis has developed, the risk of rapid progression and drug resistance is much higher in the HIV patient. Successful treatment with antiretroviral therapy lowers the rate of tuberculosis and reduces the incidence of extrapulmonary involvement.[17] **For these reasons, physicians considering a diagnosis of tuberculosis should obtain HIV testing to provide early diagnosis and therapy.**

Treatment of tuberculosis in HIV-positive patients is generally effective and not markedly different from others with the infection. However, due to the number of medications taken by patients with HIV, potential drug interactions are common, and compliance may become an issue. There is no consensus statement on the timing of antiretroviral therapy when treating both diseases. Recent studies support early antiretroviral therapy in combination with antituberculous medications, especially in those who are severely immunocompromised.[1,18]

Immune reconstitution inflammatory syndrome or paradoxical reaction (see Treatment of Active Tuberculosis) is a condition in which HIV patients clinically worsen as the immune system recovers after the initiation of antiretroviral therapy or antituberculous medications. The

ideal timing of antiretroviral therapy in those with active tuberculosis is uncertain.[1,18] See chapter 154, Human Immunodeficiency Virus Infection.

MULTIDRUG-RESISTANT TUBERCULOSIS

Multidrug-resistant tuberculosis is defined as tuberculosis with isolates that demonstrate resistance to at least INH and RIF. M. tuberculosis becomes resistant by spontaneous genetic mutation, often as a result of inadequate drug therapy or noncompliance with initial treatment. While resistance is usually not confirmed until culture and sensitivity data are available, certain historical and clinical features raise the level of suspicion for multidrug-resistant tuberculosis. These include a history of tuberculosis treatment in the past, exposure to multidrug-resistant tuberculosis, known INH resistance in the community above 4%, and persistent symptoms or persistently positive sputum cultures despite 4 months of standard treatment.[19]

Extensive drug-resistant tuberculosis is a more intense worldwide threat to public health and tuberculosis control. Extensive drug-resistant tuberculosis is defined as disease resistant to INH and RIF, plus resistance to any fluoroquinolone, and resistance to at least one injectable second-line medication. It is associated with poor outcomes and higher mortality.

Treatment of multidrug-resistant tuberculosis depends on sensitivity patterns from culture. Some countries may use standardized regimens based on known local resistance patterns. Usually a combination therapy with four to six medications, including the more toxic and less potent second-line medications, is administered for up to 2 years. Success rates rarely exceed 75%.[20] In refractory cases, resectional surgery may be necessary in addition to ongoing medical therapy.[19]

The "Global Plan to Stop Tuberculosis" calls for new medications to fight against the problem of multidrug-resistant tuberculosis. In addition to testing and better current therapy compliance, new medications show promise, especially **delamanid**.[20]

CHILDREN

Tuberculosis in children occurs in the same risk groups as in the adult population (see Table 67-1). The clinical course and disease manifestations in children have several unique aspects. Although children are at greater risk for developing rapidly progressive and disseminated disease, their presenting signs and symptoms can be subtle. Primary tuberculosis in children is often asymptomatic and only identified through screening programs or contact tracing.[21] Children may be asymptomatic even with abnormal radiographs. Or, c

, wheezing, poor feeding, and fatigue. The classic symptoms of fever, night sweats, and weight

loss may be seen in older children; however, in those younger than 5 years, presentation may be that of miliary tuberculosis (see below), meningitis, or a pneumonia that does not respond to therapy. The most common extrapulmonary presentation is **cervical lymphadenitis,** but other regions may be involved including the meninges, pericardium, abdomen, bone, joints, kidneys, skin, and eyes.

The yield of sputum smears and cultures is lower in children because of difficulty in obtaining adequate samples in addition to the lower incidence of cavitary disease.[22,23] Traditionally, obtaining three early morning consecutive gastric lavage or gastric aspirate samples has been standard procedure. However, this is invasive, unpleasant, and often requires an overnight admission and trained staff. Sputum induction using bronchodilators, followed by nebulized saline and expectoration of mucus, can improve sampling.[23]

The diagnosis of tuberculosis in children is confirmed by culture in only 30% to 40% of cases.[13] The newer tests, IGRA and NAAT, are not recommended for children less than 5 years old. The immune response differs in this age group, making the tests less reliable.[11] Often, treatment is initiated based on a skin test or on clinical grounds (symptoms, a history of exposure, or abnormal radiographs), and the diagnosis is presumed based on response to treatment.[22] Multidrug therapy is currently recommended for all children considered to have active disease, whereas monotherapy is used for latent infections.

MILIARY TUBERCULOSIS

Miliary tuberculosis is a historic term used in reference to the gross appearance of the lung during disseminated tuberculosis. In such cases, the lung is often covered with multiple small lesions resembling millet seeds. Classic miliary tuberculosis shows diffuse nodules on radiographs (1 to 3 mm) in a patient with positive laboratory testing or by demonstration of mycobacteria in multiple organs. The classic radiographic findings may not appear on films until the disease has progressed over time. A miliary pattern on radiographs can be found in conditions other than tuberculosis including histoplasmosis, malignancy, siderosis, and sarcoidosis.[24]

Today, miliary tuberculosis refers to wide hematogenous spread during the primary or reactivation disease, and it is associated with higher mortality. Children, the elderly, and immunocompromised patients are all at increased risk of developing miliary disease.

Miliary disease during primary tuberculosis is generally more rapid and severe, often presenting with multiorgan failure, shock, and acute respiratory distress syndrome. Conversely, miliary reactivation often manifests with a chronic, nonspecific clinical course affecting any number of organ systems. Fever, anorexia, night sweats, cough, weight loss, splenomegaly, lymphadenopathy, and signs of multisystem illness should cause one to suspect miliary disease. Cutaneous involvement, seen more often in HIV patients, manifests as papules or

vesiculopapules (tuberculosis cutis miliaris disseminata or tuberculosis cutis acuta generalisata). Choroidal tubercles found on ocular exam are pathognomonic for miliary tuberculosis.

TUBERCULOUS MENINGITIS

Tuberculous meningitis is often seen in children, although those with HIV or others who are immunocompromised may also be afflicted. The challenge is the subtle and subacute presentation over days to weeks, with gradual fever, headache, and cognition or sensorium changes that often are not accompanied by neck stiffness or irritation, in contrast with those seen in other forms of bacterial meningitis. Focal neurologic deficits or cranial nerve palsies may also be evident. Suspecting the infection and requesting tuberculosis cultures and smear are key to making a diagnosis, because other diagnostics are not helpful.[25] Long-term neurologic dysfunction is common, with ventriculoperitoneal shunting needed in 25% of patients for hydrocephalus. Tuberculous meningitis often seeds after a miliary infection. Treatment parallels other forms of tuberculosis.

PRACTICE GUIDELINES

The American Thoracic Society, Infectious Disease Society (http://www.idsociety.org), and Centers for Disease Control and Prevention (http://www.cdc.gov.une.idm.oclc.org) have issued recent joint guidelines for the management of tuberculosis.

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USEFUL WEB RESOURCES

1. Centers for Disease Control and Prevention Interactive Core Curriculum on Tuberculosis Web-Based Course (2004)—
http://www.cdc.gov.une.idm.oclc.org/tuberculosis/publications/Cont_Core_Curr_Course.htm

2. Centers for Disease Control and Prevention resources for tuberculosis including drug recommendations and dosages—
http://www.cdc.gov.une.idm.oclc.org/tb

3. National Institute of Allergy and Infectious Diseases: New research and development at the National Institutes of Health—
www.niaid.nih.gov

4. World Health Organization Tuberculosis: This Web site describes the work of the Stop Tuberculosis Department—
http://www.who.int.une.idm.oclc.org/tuberculosis/en

5. WHO Tuberculosis Epidemiology and Surveillance Virtual Workshop—
http://www.who.int.une.idm.oclc.org/tuberculosis/surveillanceworkshop