Pulmonary Tuberculosis: Role of Radiology in Diagnosis and Management[1]

Arun C. Nachiappan, MD
Kasra Rahbar, MD
Xiao Shi, MD
Elizabeth S. Guy, MD
Eduardo J. Mortani Barbosa, Jr, MD
Girish S. Shroff, MD
Daniel Ocazionez, MD
Alan E. Schlesinger, MD
Sharyn I. Katz, MD
Mark M. Hammer, MD

Tuberculosis is a public health problem worldwide, including in the United States—particularly among immunocompromised patients and other high-risk groups. Tuberculosis manifests in active and latent forms. Active disease can occur as primary tuberculosis, developing shortly after infection, or postprimary tuberculosis, developing after a long period of latent infection. Primary tuberculosis occurs most commonly in children and immunocompromised patients, who present with lymphadenopathy, pulmonary consolidation, and pleural effusion. Postprimary tuberculosis may manifest with cavities, consolidations, and centrilobular nodules. Miliary tuberculosis refers to hematogenously disseminated disease that is more commonly seen in immunocompromised patients, who present with miliary lung nodules and multiorgan involvement. The principal means of testing for active tuberculosis is sputum analysis, including smear, culture, and nucleic acid amplification testing. Imaging findings, particularly the presence of cavitation, can affect treatment decisions, such as the duration of therapy. Latent tuberculosis is an asymptomatic infection that can lead to postprimary tuberculosis in the future. Patients who are suspected of having latent tuberculosis may undergo targeted testing with a tuberculin skin test or interferon-γ release assay. Chest radiographs are used to stratify for risk and to assess for asymptomatic active disease. Sequelae of previous tuberculosis that is now inactive manifest characteristically as fibronodular opacities in the apical and upper lung zones. Stability of radiographic findings for 6 months distinguishes inactive from active disease. Nontuberculous mycobacterial disease can sometimes mimic the findings of active tuberculosis, and laboratory confirmation is required to make the distinction. Familiarity with the imaging, clinical, and laboratory features of tuberculosis is important for diagnosis and management.

Abbreviations: AFB = acid-fast bacilli, HIV = human immunodeficiency virus, PA = posteroanterior

RadioGraphics 2017; 37:52–72

Published online 10.1148/rg.2017160032

Content Codes: CH CT

[1]From the Department of Radiology, University of Pennsylvania, 3400 Spruce St, 1 Silverstein, Suite 130, Philadelphia, PA 19104 (A.C.N., E.J.M.B., S.I.K., M.M.H.); Mallinckrodt Institute of Radiology, Washington University School of Medicine, St Louis, Mo (K.R.); Department of Radiology (X.S.) and Department of Medicine, Section of Pulmonary and Critical Care Medicine (E.S.G.), Baylor College of Medicine, Houston, Tex; Department of Diagnostic Radiology, University of Texas MD Anderson Cancer Center, Houston, Tex (G.S.S.); Department of Diagnostic and Interventional Imaging, University of Texas Medical School at Houston, Houston, Tex (D.O.); and Department of Radiology, Texas Children's Hospital, Houston, Tex (A.E.S.). Presented as an education exhibit at the 2014 RSNA Annual Meeting. Received February 28, 2016; revision requested May 17 and received July 28; accepted August 9. For this journal-based SA-CME activity, the authors, editor, and reviewers have disclosed no relevant relationships. **Address correspondence to** A.C.N. (e-mail: *arun.nachiappan@uphs.upenn.edu*).

SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Describe the clinical and radiologic appearances of primary and postprimary tuberculosis.
- Explain the differences between active tuberculosis and latent tuberculosis, particularly the results of the different laboratory tests used to evaluate for each.
- Discuss the role of imaging in the management of patients with tuberculosis.

See www.rsna.org/education/search/RG.

Introduction

Tuberculosis is caused by mycobacterial species in the *Mycobacterium tuberculosis* complex. *M tuberculosis* is the species responsible for the vast majority of cases, but other species can cause similar disease, including *Mycobacterium bovis*, *Mycobacterium africanum*, *Mycobacterium microti*, and *Mycobacterium canettii* (1). Airborne mycobacteria are transmitted by droplets 1–5 μm in diameter, which can remain suspended in the air for several hours when a person with active tuberculosis coughs, sneezes, or speaks (1). Not all individuals exposed to tuberculosis get infected. The probability of transmission to another individual depends on the infectiousness of the tuberculosis source, the environment and duration of exposure, and the immune status of the exposed individual (1). The airborne droplets reach the terminal airspaces by means of inhalation, where the droplets infect alveolar macrophages. In approximately 5% of infected individuals, the immune

TEACHING POINTS

- Primary tuberculosis demonstrates radiologic findings that include lymphadenopathy, consolidation, pleural effusion, and miliary nodules. Postprimary tuberculosis demonstrates consolidations that are predominant in the apical and upper lung zones, nodules, and cavitation.
- Lymphadenopathy in tuberculosis typically demonstrates a low-attenuation center with peripheral rim enhancement on contrast material–enhanced CT images, findings that are due to central caseous necrosis with peripheral granulomatous inflammatory tissue.
- It is important to note that the tuberculin skin test and interferon-γ release assays are not designed to evaluate subjects for active tuberculosis.
- Patients with active tuberculosis who have cavitation on the initial chest radiograph and who, at the completion of the initiation phase of treatment, still demonstrate positive 2-month tuberculosis cultures are at a high risk of relapse and should continue therapy for a total of 9 months.
- Classic (cavitary) nontuberculous mycobacterial infection can have an appearance and clinical manifestations indistinguishable from those of postprimary tuberculosis; classic nontuberculous mycobacterial infection is characterized by upper lobe cavitary lesions and centrilobular and tree-in-bud nodules.

system is inadequate at controlling the initial infection, and active tuberculosis develops within the first 1–2 years (2); this category is referred to as primary tuberculosis. In another 5% of infected individuals, the immune system is effective at controlling the initial infection, but viable mycobacteria remain dormant and reactivate at a later time (2); this category is referred to as postprimary or reactivation tuberculosis. The remaining 90% of individuals will never develop symptomatic disease and will harbor the infection only at a subclinical level, which is referred to as latent tuberculosis infection. These individuals are asymptomatic and noncontagious. In latent infection, the host immune response prevents the multiplication and spread of mycobacteria (1). The immune response to mycobacteria has important implications for the clinical and imaging appearance of tuberculosis, particularly in immunocompromised patients.

Tuberculosis infects an estimated one-third of the world's population, thereby making the disease a major public health issue (3). Nine million people become infected and 1.5 million people die of tuberculosis every year (1). In the United States, the rate of active tuberculosis cases was three cases per 100 000 in 2013 (1). Ethnic minorities are disproportionately affected in the United States, where 65% of active tuberculosis cases in 2013 were in foreign-born persons (1).

Imaging plays a pivotal role in the diagnosis and management of tuberculosis. In this article, the radiologic appearance of pulmonary tuberculosis is discussed, with an emphasis on the role of imaging within the clinical context. Laboratory testing for tuberculosis is also reviewed, to guide the radiologist in how laboratory findings are combined with clinical and imaging findings to diagnose tuberculosis and manage patients.

Risk Factors

Clinical suspicion for tuberculosis may be heightened in patients with various risk factors. Thus, any individual at increased risk is eligible for targeted tuberculosis testing to identify and treat those with latent infection, prevent the development of active disease, and prevent further spread of tuberculosis (1). Risk factors for tuberculosis can be grouped into two categories: those that cause increased risk of exposure to tuberculosis, and those that increase the risk of developing active disease, once a person is infected.

Individuals at increased risk of exposure include immigrants from endemic regions (Asia, Africa, Russia, Eastern Europe, and Latin America), those with a low income and limited access to health care, intravenous drug users, people who live or work in high-risk residential centers (nursing homes, correctional facilities, and homeless shelters), and health care workers (1). In the United States, immigrants from endemic areas represent an increasing proportion of tuberculosis cases (4).

Risk factors associated with a higher risk of progression to active tuberculosis include *(a)* age younger than 4 years, *(b)* intravenous drug use, *(c)* recent tuberculosis infection or test conversion within the past 2 years, and *(d)* immunodeficiencies, such as those resulting from human immunodeficiency virus (HIV)/AIDS infection, organ transplantation, and treatment with immunosuppressive drugs. HIV infection is the strongest known risk factor for developing active tuberculosis, with a risk of 7%–10% per year (1). Patients treated with biological agents, such as therapy with tumor necrosis factor α inhibitors for autoimmune disorders, have a higher risk of reactivation (5); the increasing use of these drugs means that radiologists will need to assess for tuberculosis in these patient populations. Other conditions that can increase the risk of active disease include diabetes mellitus, silicosis, chronic renal failure, low body weight, prior gastrectomy or jejunoileal bypass, alcohol or tobacco abuse, and certain malignancies (leukemia, head and neck carcinoma, and lung carcinoma) (1).

Clinical Features

The classification of pulmonary tuberculosis is based on clinical and radiologic factors (Table 1) (6). Active disease may manifest with symptoms that are only minimal initially but then

Table 1: Classification of Tuberculosis on the Basis of Clinical and Radiologic Findings

Class	Definition	Clinical History	Laboratory Test Results	Chest Radiographic Findings
0	No exposure to tuberculosis; no infection	No history of exposure	Negative results of tuberculin skin test or interferon-γ release assay	No radiographic evidence of disease
1	Exposure to tuberculosis; no infection	History of exposure	Negative results of tuberculin skin test or interferon-γ release assay (done at least 10 weeks after exposure)	No radiographic evidence of disease
2	Latent tuberculosis infection; no tuberculosis disease	No clinical evidence of disease	Positive results of tuberculin skin test or interferon-γ release assay; negative results of bacteriologic examinations (if done)	No radiographic evidence of active disease
3	Active tuberculosis disease (current)	Meets criteria for active clinical case	Meets current laboratory criteria (eg, positive culture)	Radiographic evidence of active disease
4	Previous tuberculosis disease (inactive)	Medical history of tuberculosis disease; no evidence of active tuberculosis disease	Positive results of tuberculin skin test or interferon-γ release assay, negative results of bacteriologic examinations (if done)	Abnormal but stable radiographic findings; no radiographic evidence of active tuberculosis disease
5	Tuberculosis suspected; diagnosis pending	Ongoing evaluation for active tuberculosis on the basis of clinical, laboratory, and/or radiographic findings	…	…

develop during the course of several months (7). Typical symptoms of active tuberculosis include a productive cough, hemoptysis, weight loss, fatigue, malaise, fever, and night sweats (7). The insidious and nonspecific nature of the symptoms means that physicians caring for these patients must maintain a high index of suspicion that is based on the risk factors. Radiologists can aid in diagnosis by performing imaging examinations, sometimes even incidentally in the absence of clinical suspicion.

Extrapulmonary tuberculosis results from hematogenous spread or direct extension from adjacent organs and may involve the larynx, lymph nodes, pleura, gastrointestinal tract, genitourinary tract, central nervous system, or bones. Most extrapulmonary disease is not contagious, with the exception of laryngeal tuberculosis. No evidence of tuberculosis may be seen on chest radiographs. Immunocompromised individuals and young children are at higher risk of extrapulmonary disease. Miliary tuberculosis is a hematogenously disseminated disease characterized by numerous tiny lesions, measuring 1–3 mm, which can involve multiple organs such as the lungs, liver, spleen, and central nervous system.

Active Tuberculosis

Imaging has an important role in the initial evaluation of patients suspected of having active tuberculosis. An algorithm for the evaluation of such a patient is presented in Figure 1 (8). If the chest radiograph is negative and the patient is HIV negative, no further workup may be needed. If the chest radiograph is positive for findings of active tuberculosis or if the patient is HIV positive, then laboratory evaluation for active tuberculosis should be performed. For HIV-positive patients, a chest radiograph should be obtained, but the results of the chest radiograph do not guide immediate management, because radiographic findings may be normal in this population, despite active disease.

If tuberculosis is not initially suspected clinically but radiographic or computed tomographic (CT) findings are concerning for active tuberculosis, then further workup for active tuberculosis is warranted. Regardless of the indication, any radiologic finding that raises the possibility of active tuberculosis should prompt immediate communication with the referring provider, so that patients may be placed in respiratory isolation until negative results of sputum staining are obtained.

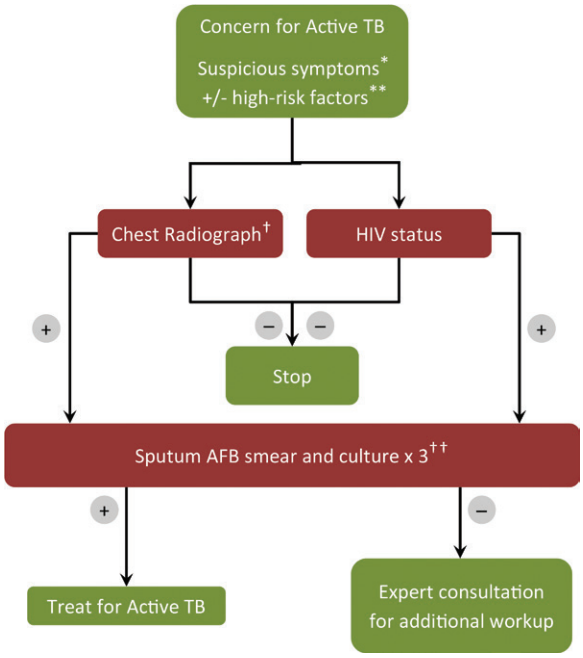


Figure 1. Diagram of an algorithm for the evaluation of patients who are suspected of having active tuberculosis *(TB)* (concern for active tuberculosis). Note that if the chest radiograph and HIV status are both negative, then stop; however, if either of them is positive, the next step is obtaining sputum. * = fever, cough, night sweats, weight loss, hemoptysis; ** = high-risk factors for tuberculosis exposure or reactivation (eg, immigration from endemic area, recent exposure and conversion within the past 2 years, HIV-positive status, and immunosuppression); † = positive chest radiograph refers to findings that may represent active tuberculosis; †† = send one of the sputum specimens for a nucleic acid amplification test, where available. *AFB* = acid-fast bacilli.

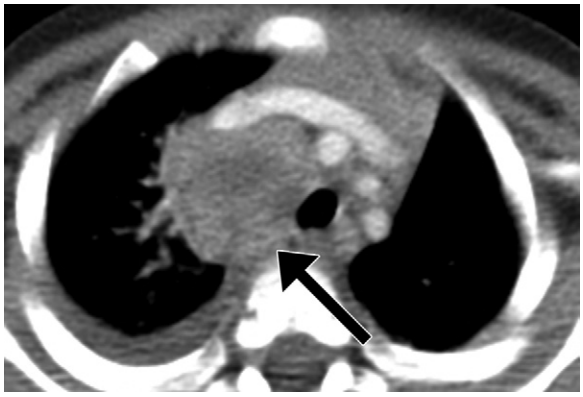


Figure 2. Lymphadenopathy from primary tuberculosis in a 6-month-old male infant. Axial contrast-enhanced chest CT image shows necrotic mediastinal lymphadenopathy (arrow) and a small right-sided pleural effusion.

Infection prevention personnel should also be notified, where such a system is in place, to ensure that patients with active tuberculosis and their close contacts are managed appropriately.

Primary tuberculosis demonstrates radiologic findings that include lymphadenopathy, consolidation, pleural effusion, and miliary nodules (9). Postprimary tuberculosis demonstrates consolidations that are predominant in the apical and upper lung zones, nodules, and cavitation (2). Traditionally, primary tuberculosis was considered a disease of childhood, and postprimary tuberculosis was believed to always represent reactivation of latent infection in adults. However, a better understanding of the disease reveals these notions to be somewhat inaccurate. Because of more-effective therapies and the declining prevalence of tuberculosis in developed countries, 23%–34% of adult tuberculosis cases in developed countries are actually primary tuberculosis (10,11). With regard to postprimary tuberculosis, evidence suggests that patients in endemic areas are more likely to be infected by a second strain of tuberculosis than to experience reactivation of a previously infected strain (12,13). In contrast, reactivation causes the majority of cases of postprimary tuberculosis in developed countries, although a second infection is responsible for a small fraction of cases (14). The clinical and imaging manifestations of tuberculosis may be related more to host factors, particularly immunosuppression, than to the mechanism of infection (15). Overall, although there are several different forms of active tuberculosis, it is more important to distinguish between active and latent tuberculosis (Table 1) than to distinguish between primary and postprimary tuberculosis.

Primary Tuberculosis

Lymphadenopathy.—Mediastinal and hilar lymphadenopathy is the most common radiologic manifestation of primary tuberculosis (2). Lymphadenopathy in tuberculosis typically demonstrates a low-attenuation center with peripheral rim enhancement on contrast material–enhanced CT images (Fig 2), findings that are due to central caseous necrosis with peripheral granulomatous inflammatory tissue (Fig 3) (16). The differential diagnosis of necrotic lymphadenopathy includes nontuberculous mycobacterial

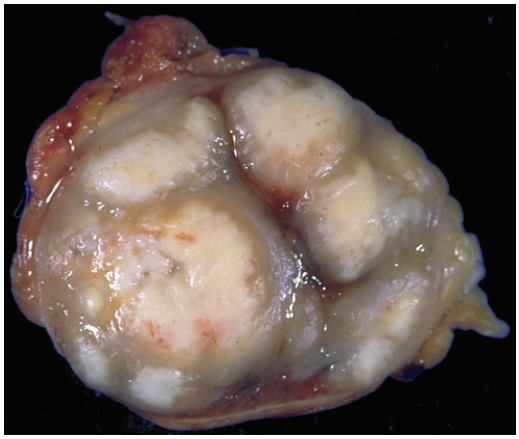


Figure 3. Photograph of a gross pathologic specimen shows tuberculous lymphadenitis with central caseous necrosis. (Courtesy of Yale Rosen, MD, Winthrop University Hospital, Mineola, NY, under a CC BY-SA 2.0 license.)

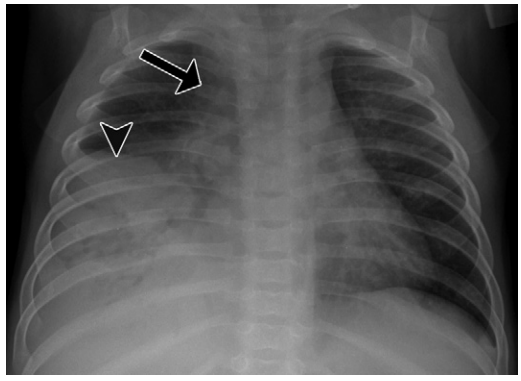


Figure 4. Lymphadenopathy and consolidation in a 6-month-old male infant with primary tuberculosis (same patient as shown in Fig 2). Frontal chest radiograph shows thickening of the right paratracheal stripe, consistent with lymphadenopathy (arrow), and consolidation (arrowhead) in the right middle and lower lobes.

infection, lymphoma, and metastatic carcinoma (17). Lymphadenopathy is seen in 83%–96% of pediatric cases of primary tuberculosis and 10%–43% of adult cases and typically involves the right paratracheal and hilar lymph nodes (Fig 4) (2,18). Within the pediatric population, mediastinal and hilar lymphadenopathy may be the only radiologic finding (9). At resolution of lymphadenopathy, calcified normal-sized lymph nodes may remain.

Parenchymal Disease.—Parenchymal disease most frequently manifests as consolidation depicted as an area of opacity in a segmental or lobar distribution (Fig 4) (2,19). There is no strong lobar predilection in primary tuberculosis (19). Cavitation occurs in a minority of patients with primary tuberculosis (29% in one series [19]); and when cavitation occurs, it is known as progressive primary disease (2). This cavitation occurs within existing consolidation and thus does not demonstrate an upper lung zone predominance, in contrast to postprimary disease (2). Parenchymal disease often appears similar to bacterial pneumonia, but the presence of lymphadenopathy can be a clue that points toward primary tuberculosis. Resolution of pulmonary consolidation is generally slow, taking as long as 2 years; and in many cases, residual opacities are seen (9,20). After resolution, residual parenchymal scarring can be seen at sites of prior consolidation in 15%–18% of patients and is referred to as a Ghon focus, or Ghon tubercle (9,20).

Pleural Effusion.—Pleural effusion is seen in approximately 25% of primary tuberculosis cases in adults, with the vast majority of such effusions being unilateral (Fig 5) (19). Pleural effusion is less common in children and may only appear

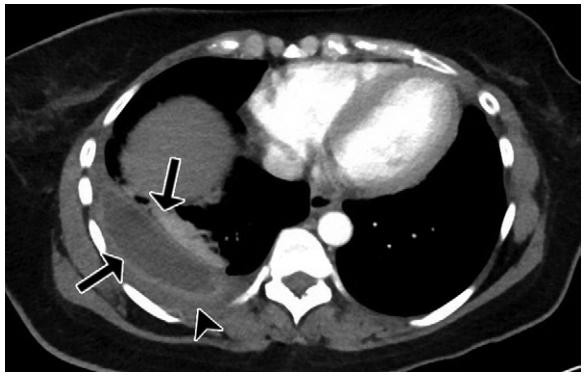


Figure 5. Tuberculous empyema in a 40-year-old woman presenting with weight loss, malaise, and chills. Axial contrast-enhanced chest CT image shows a loculated right-sided pleural effusion with thickened, enhancing pleura (arrows) as well as infiltration of the extrapleural fat (arrowhead).

in 6%–11% of pediatric cases, with increasing prevalence with age (2,20). Pleural effusion is also less common in postprimary disease (approximately 18% of cases) (9). Tuberculous pleural effusions usually result from hypersensitivity to tuberculous protein, rather than frank pleural infection; and therefore, isolation of *M tuberculosis* from pleural fluid is uncommon. Cytologic examination of the pleural fluid typically reveals predominantly lymphocytes; certain fluid studies, such as determining the fluid level of adenosine deaminase, a marker of monocytes and macrophages, are useful in the diagnosis of tuberculous effusions (21). If the results of fluid analysis are not definitive, the addition of pleural biopsy can increase the diagnostic yield in these patients (22). Pleural specimens can be examined for granulomas at histopathologic examination and can be cultured for organisms.

Tuberculous empyemas are typically loculated and associated with pleural thickening and enhancement, findings that represent involvement

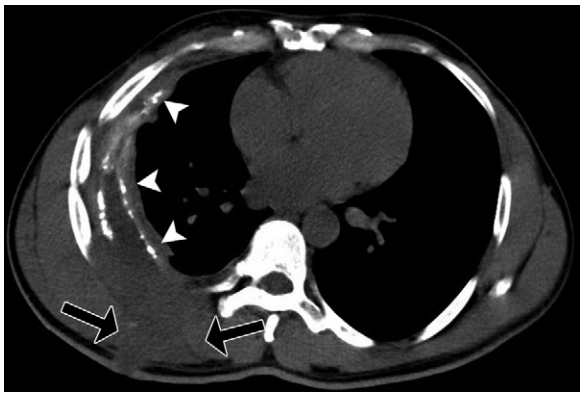
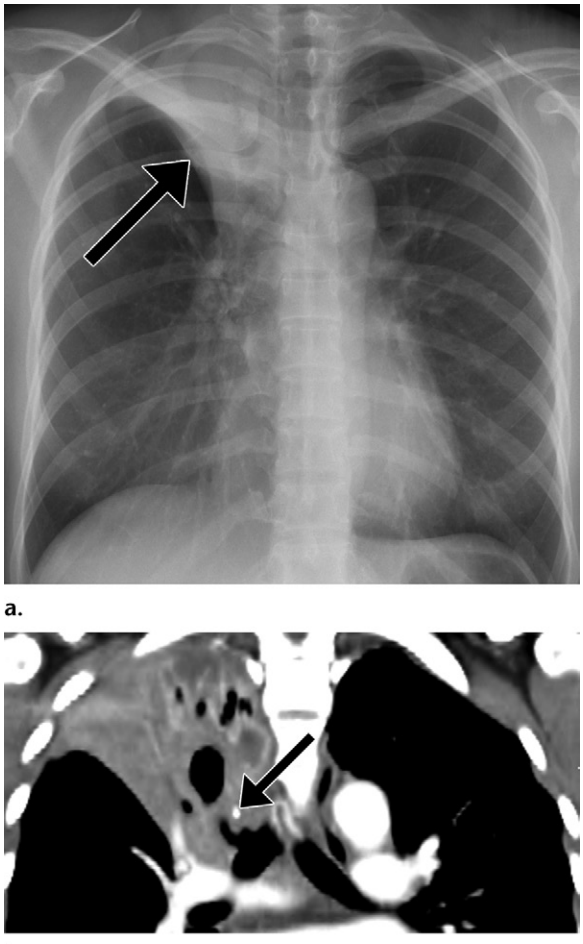


Figure 6. Empyema necessitatis in a 35-year-old man with chronic empyema related to tuberculosis. Axial nonenhanced chest CT image shows pleural calcifications (arrowheads), a loculated pleural effusion with marked pleural thickening, and extension into the chest wall (arrows).



a.

b.

Figure 7. Airway involvement with tuberculosis in a 41-year-old woman. **(a)** Posteroanterior (PA) chest radiograph shows right upper lobe collapse (arrow). **(b)** Coronal contrast-enhanced reformatted chest CT image at the level of the central bronchi shows irregular thickening of the right upper lobe bronchus (arrow), as well as right upper lobe volume loss.

of the pleura. If not treated early, tuberculous empyemas may be complicated with bronchopleural fistula or extension into the chest wall (empyema necessitatis) (Fig 6) (16,23). An air-fluid level within an empyema in the absence of instrumentation is suggestive of a bronchopleural fistula (20). After treatment and healing, residual pleural thickening with calcification can develop, potentially leading to fibrothorax (9,16).

Airway Disease.—Bronchial wall involvement may be seen in primary and postprimary tuberculosis, although it is more common in the former (16,24). Bronchial stenosis occurs in 10%–40% of patients with active tuberculosis and is due to direct extension from tuberculous lymphadenitis by means of endobronchial or lymphatic dissemination (16). The main radiographic features of proximal airway involvement are indirect, including segmental or lobar atelectasis (Fig 7a), lobar hyperinflation, mucoid impaction, and postobstructive pneumonia (16). At CT, airway involvement can manifest as long segment narrowing with irregular wall thickening, luminal obstruction, and extrinsic compression (Figs 7b, 8) (9).

Miliary Tuberculosis

Hematogenous dissemination results in miliary tuberculosis, especially in immunocompromised and pediatric patients. Miliary disease may occur in primary or postprimary tuberculosis. In primary tuberculosis, miliary disease often manifests as an acute, severe illness with high mortality (25). Miliary tuberculosis may also manifest insidiously, such as with a fever of unknown origin or failure to thrive, also with relatively high mortality (26). On the chest radiograph or CT image, miliary disease manifests as diffuse 1–3-mm nodules in a random distribution (Fig 9). Miliary tuberculosis is spread by hematogenous seeding, as demonstrated by the finding of a miliary nodule centered on a small blood vessel (Fig 10).

Postprimary Tuberculosis

Postprimary tuberculosis is typically thought to result from reactivation of dormant *M tuberculosis*

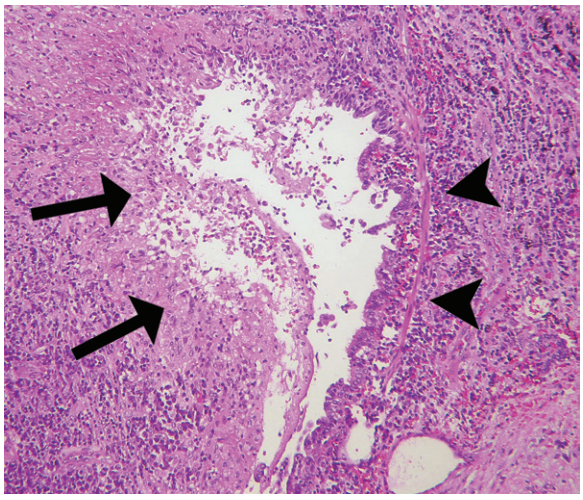


Figure 8. Airway involvement with tuberculosis in a 41-year-old woman. Photomicrograph shows granulomatous destruction of a bronchial wall on the left (arrows). The airway epithelium is intact but inflamed on the right (arrowheads). (Hematoxylin-eosin stain; original magnification, ×100.) (Courtesy of Yale Rosen, MD, Winthrop University Hospital, Mineola, NY, under a CC BY-SA 2.0 license.)

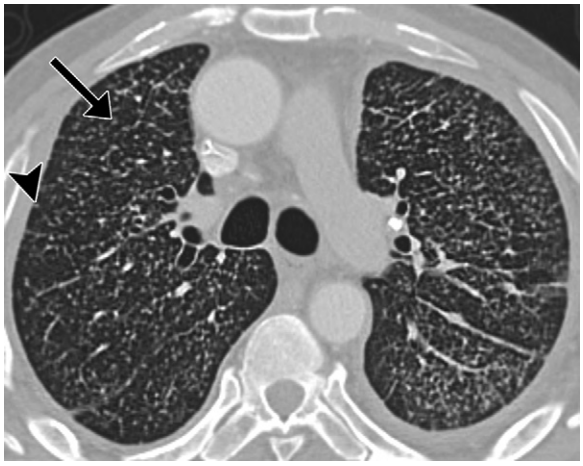


Figure 9. Miliary tuberculosis in a 53-year-old man. Axial chest CT image shows numerous micronodules in a random distribution. Note subpleural (arrowhead) and centrilobular (arrow) nodules.

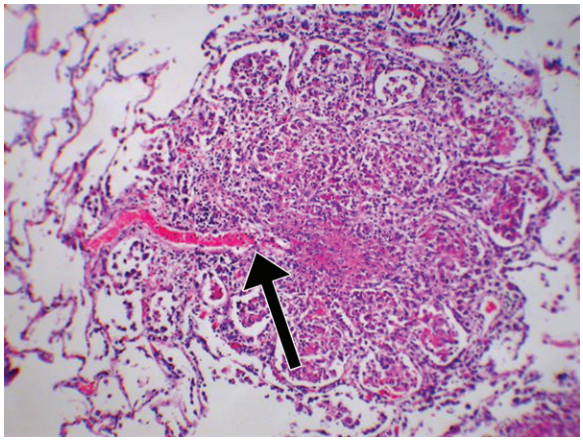
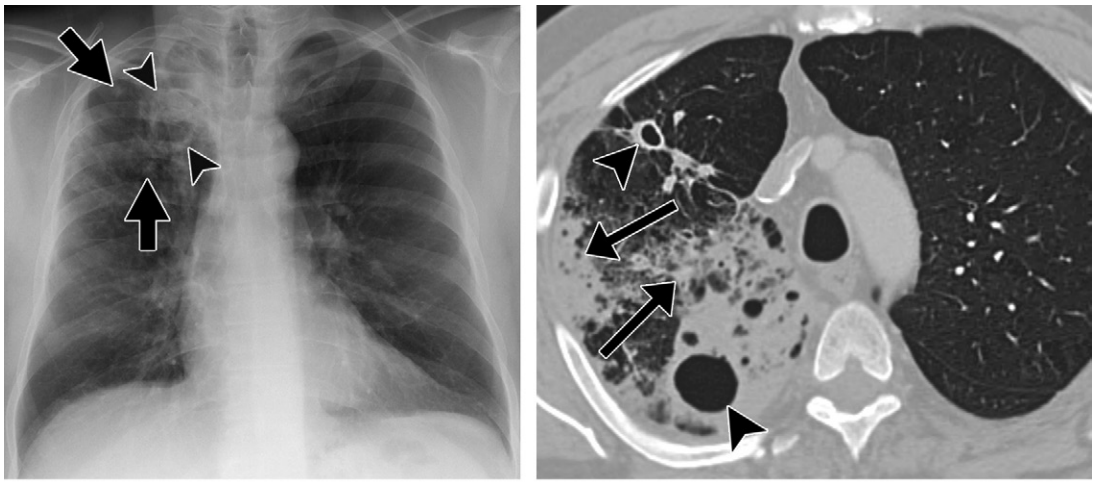


Figure 10. Miliary tuberculosis in a different 53-year-old man (different patient from Fig 9). Photomicrograph shows granulomatous inflammation centered around a small blood vessel (arrow), reflecting hematogenous seeding. (Hematoxylin-eosin stain; original magnification, ×150.) (Courtesy of Yale Rosen, MD, Winthrop University Hospital, Mineola, NY, under a CC BY-SA 2.0 license.)

infection but may also result from a second infection with a different strain, especially in endemic areas (12,13). The apical and upper lung zone predominance may be related to the relatively reduced lymphatic drainage and increased oxygen tension in these regions, factors that facilitate bacillary replication (16,27). Patients typically present with insidious fever, cough, weight loss, and night sweats. A chest radiograph is typically obtained to evaluate for findings of active disease. Chest CT may be useful in identifying active tuberculosis even if the chest radiograph is negative, although chest CT is not the standard of practice (28).

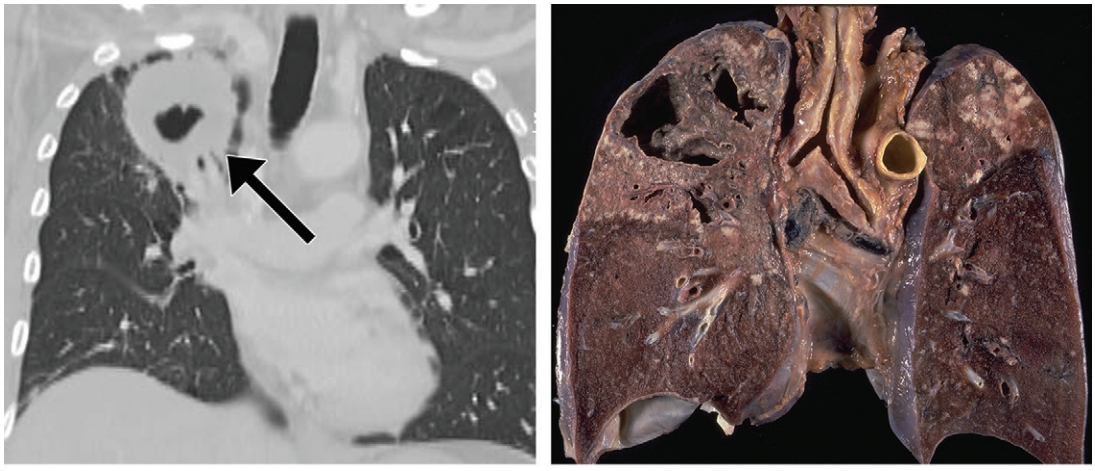
Consolidation and Cavitation.—Patchy, poorly marginated consolidation is an early and consistent feature of postprimary tuberculosis (Fig 11). Consolidation and cavitation have a strong predilection for the apical and posterior segments of the upper lobes as well as the superior segments of the lower lobes in postprimary tuberculosis (16). Isolated involvement of the lung bases is rare and is seen in only approximately 5% of postprimary tuberculosis cases (2). In 3%–6% of cases of postprimary tuberculosis, a noncalcified nodule known as a tuberculoma (ranging from 5 mm to 40 mm in largest dimension) may be the predominant manifestation; these tuberculomas are typically solitary and may occur with small satellite nodules (2).

In postprimary tuberculosis, cavitation is a common finding, seen in 20%–45% of patients on chest radiographs. Cavities can be several centimeters in largest dimension and can develop thick and irregular walls (Figs 12, 13) (16). Cavitary lesions are often seen within areas of consolidation and may be multifocal (Fig 11b) (16). Residual cavities may persist after treatment, findings that predispose to bacterial superinfection, mycetoma formation, or erosion



a. b.

Figure 11. Postprimary tuberculosis in a 50-year-old man. **(a)** PA chest radiograph shows patchy airspace opacities (arrows) in the right upper lobe, with a cavitary lesion (arrowheads). **(b)** Axial chest CT image shows right upper lobe consolidation (arrows) with associated cavitation (arrowheads).



12. 13.

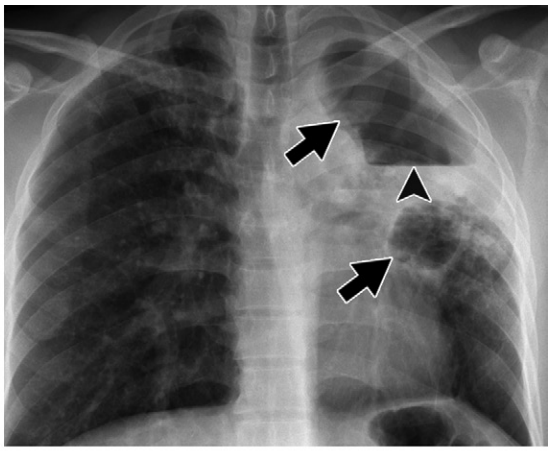
Figures 12, 13. **(12)** Postprimary tuberculosis in a 63-year-old man. Coronal chest CT image shows a thick-walled cavitary lesion (arrow) in the right upper lobe. **(13)** Postprimary tuberculosis in a different patient from the one shown in Figure 12. Photograph of a gross lung specimen shows necrotizing consolidation in the right upper lobe, which has developed several cavities. Consolidation is also noted in the left upper lobe. (Courtesy of Yale Rosen, MD, Winthrop University Hospital, Mineola, NY, under a CC BY-SA 2.0 license.)

of adjacent vasculature resulting in hemoptysis (Fig 14) (16). The presence of an air-fluid level within a cavity may be related to the tuberculosis itself or to bacterial superinfection (16,29).

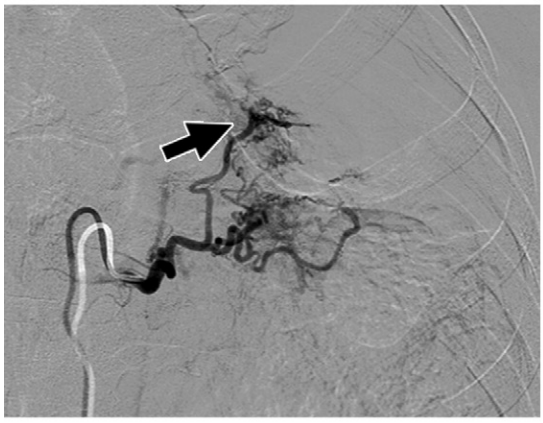
Centrilobular Nodules.—Active tuberculosis often communicates with the bronchial tree, which results in endobronchial spread (2). Histologically, caseous necrosis and granulomatous inflammation fill respiratory bronchioles and alveolar ducts (Fig 15). This histologic finding manifests radiologically as centrilobular nodules and the tree-in-bud sign (Fig 16). At CT, centrilobular nodules are seen in approximately 95% of cases of active tuberculosis (2). Unlike cavitary lesions and consolidation, centrilobular nodules may be seen in the lower lobes, distant from the cavitary lesions (16). Involvement of the airways and pleura is less common in postprimary than in primary tuberculosis but shows similar imaging features.

Tuberculosis in Immunocompromised Patients

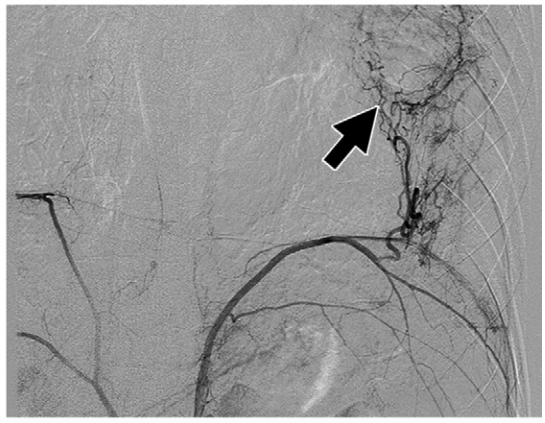
Immunocompromised patients are at a higher risk of developing primary and postprimary tuberculosis. For example, HIV-positive patients with latent tuberculosis infection are 20–30 times more likely to develop active tuberculosis, when compared with HIV-negative patients (30). Although most tuberculosis cases in immunocompromised individuals are related to reactivation of latent tuberculosis, the radiologic and clinical manifestations



a.



b.



c.

Figure 14. Tuberculous cavity in a 32-year-old man with hemoptysis. **(a)** PA chest radiograph shows two left-sided cavitary lesions (arrows), with an air-fluid level in the larger lesion (arrowhead), and scattered reticulonodular opacities. **(b)** Bronchial artery angiographic image shows blush of contrast material around the cavitary lesions (arrow). The patient subsequently underwent bronchial artery embolization. **(c)** Phrenic artery angiographic image shows recruitment of additional vasculature (arrow). Embolization of the superior branch of the phrenic artery was also performed.

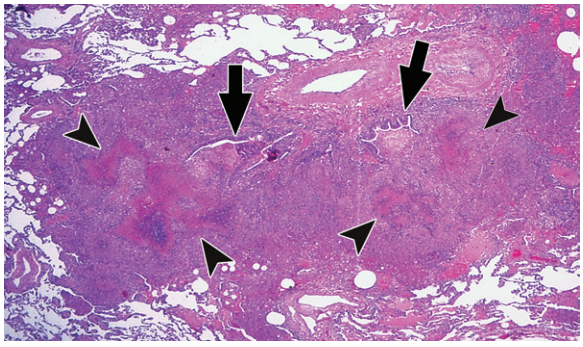


Figure 15. Airway dissemination of tuberculosis. Photomicrograph shows multiple granulomas (arrowheads) localized around airways (arrows). (Hematoxylin-eosin stain; original magnification, ×40.) (Courtesy of Yale Rosen, MD, Winthrop University Hospital, Mineola, NY, under a CC BY-SA 2.0 license.)

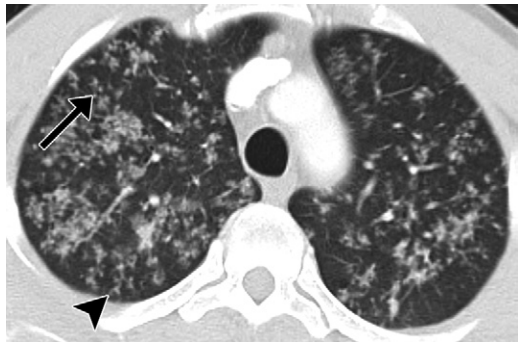


Figure 16. Airway dissemination of tuberculosis in an 86-year-old man with active tuberculosis (different patient from Fig 15). Axial chest CT image shows centrilobular (arrow) and tree-in-bud (arrowhead) nodules, as well as more confluent areas of consolidation.

more closely resemble those of primary tuberculosis (ie, with consolidation and lymphadenopathy) (Fig 17a). In severely immunosuppressed patients with pulmonary tuberculosis, chest radiographs may be normal 10%–40% of the time. Miliary tuberculosis also occurs at a higher rate in patients with severe immunosuppression.

Treatment of patients with HIV infection by using highly active antiretroviral therapy in patients infected with tuberculosis may result in a paradoxical worsening of pulmonary disease, an entity known as the immune reconstitution inflammatory syndrome (31). This phenomenon reflects a delayed and often vigorous immune response to a previously subclinical infection and affects 10%–25% of patients with AIDS, typically within 60 days after the initiation of highly active antiretroviral therapy (32). Tuberculosis-associated immune reconstitution inflammatory syndrome is more common with CD4 cell counts of less than

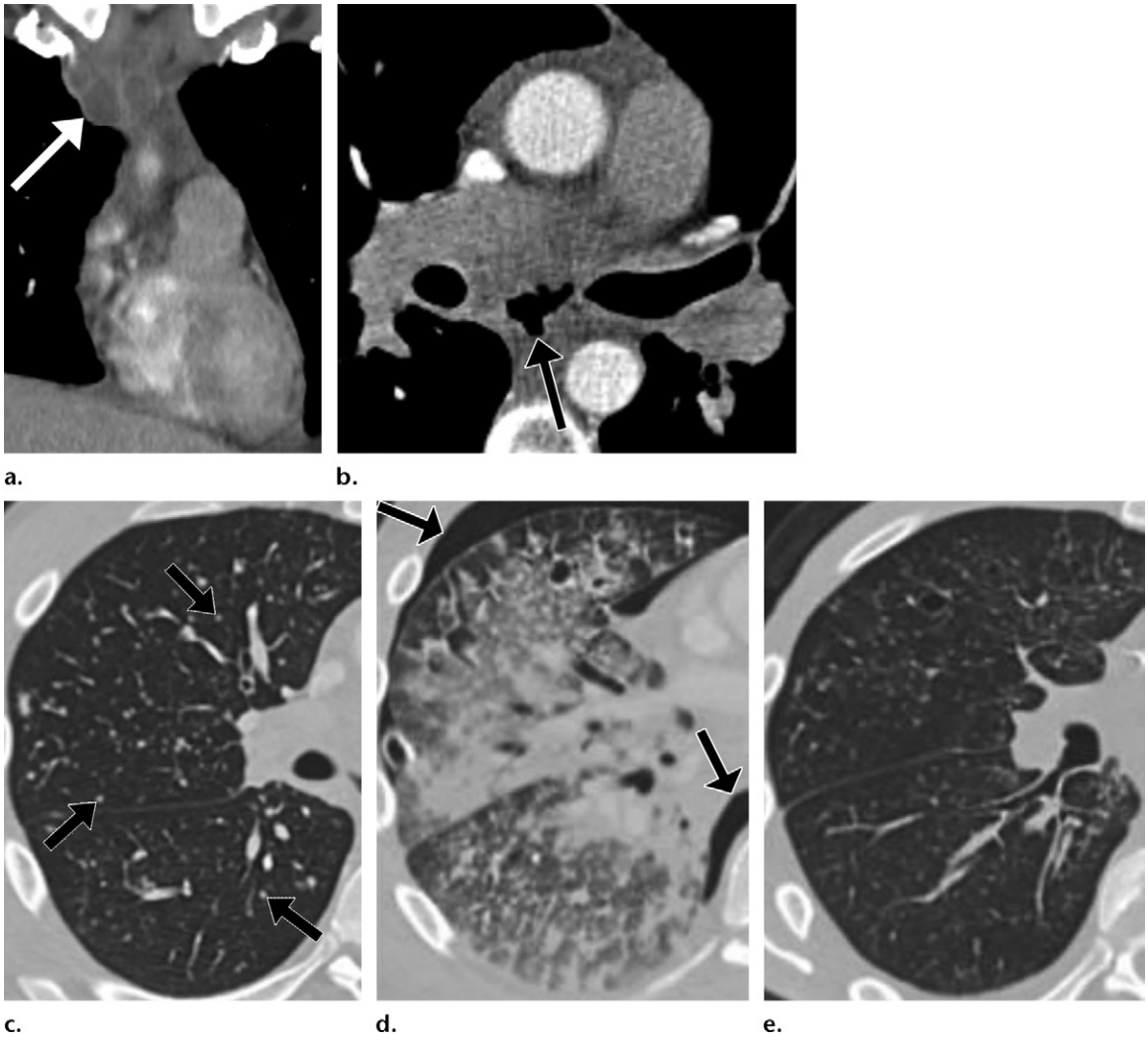


Figure 17. Primary tuberculosis in a 39-year-old man with AIDS. **(a, b)** Magnified contrast-enhanced chest CT images from the same CT examination. **(a)** Coronal reformatted image (soft-tissue window) at the level of the clavicular heads shows necrotic lymphadenopathy (arrow). **(b)** Axial chest CT image (soft-tissue window) at a level just below the carina shows an air collection in the subcarinal region, a finding that represents esophageal perforation with a fistula or sinus tract (arrow) to a necrotic lymph node. **(c–e)** Sequential magnified axial chest CT images (lung window) at a level just below the carina. **(c)** Three weeks after the onset of administration of highly active antiretroviral therapy, the CT image shows multiple centrilobular nodules (arrows). **(d)** One week later, diffuse consolidation has developed, representing tuberculosis-associated immune reconstitution inflammatory syndrome. A pneumothorax (arrows) is also depicted. **(e)** One month later, after antituberculous treatment, the consolidation has resolved, and the nodules have markedly improved. (Fig 17b–17e reprinted from reference 35 under a CC BY 3.0 license.)

50/μL but can occur even in patients with CD4 cell counts of more than 200/μL (33,34). In addition to *M tuberculosis* complex, other infectious agents such as atypical mycobacteria may result in immune reconstitution inflammatory syndrome. Tuberculosis-associated immune reconstitution inflammatory syndrome often demonstrates worsening lymphadenopathy and pulmonary consolidations and/or nodules (Fig 17) (35). Treatment of patients with tuberculosis-associated immune reconstitution inflammatory syndrome involves continuing therapy with antituberculous drugs. In severe cases, corticosteroid therapy may be used, or highly active antiretroviral therapy may be discontinued (36).

Pediatric Tuberculosis

The manifestation of tuberculosis in pediatric patients differs from that in adult disease. The most common form of active tuberculosis in children is primary disease (37). The likelihood of developing active tuberculosis decreases with age. Older children and adolescents with active tuberculosis are more likely to show an adult pattern of disease, with postprimary tuberculosis being more common than primary tuberculosis (38).

Diagnosis of tuberculosis presents several challenges in children. Bacteriologic confirmation is less frequent in children than in adults because of the lower frequency of cavitation and the decreased number of bacteria (39). Without

Table 2: Sensitivity and Specificity of Sputum Tests for Active Tuberculosis Disease

Test	Sensitivity (%)	Specificity (%)	False Positives
Culture	80–85	98	Rarely; contamination
Nucleic acid amplification test			
When smear is positive	95	98	Rarely
When smear is negative	48–53	95	Rarely
AFB smear ×3	68–72	77–98*	Nontuberculous mycobacteria; rarely, other bacteria

*Specificity varies on the basis of population (ie, prevalence of nontuberculous mycobacteria).

a positive culture, a recent history of exposure to an infected adult is often critical in establishing the diagnosis. The diagnostic approach to a child suspected of having tuberculosis should include obtaining a history and performing a physical examination, HIV testing, tuberculin skin testing, interferon-γ release assay, culture, and imaging (37). In many cases, empirical therapy must be initiated with a presumed diagnosis that is based on the clinical and imaging findings without laboratory confirmation; treatment may be guided by the results of cultures from the adult exposure source.

Hilar and mediastinal lymphadenopathy is the radiologic hallmark of pediatric tuberculosis and may be transiently seen in asymptomatic patients (Fig 2). Earlier in childhood (ages 0–3 years), nearly 50% of cases can manifest as isolated lymphadenopathy, as compared with only 9% of cases later in childhood (ages 5–14 years) (20). Extrinsic compression of adjacent bronchi may cause symptoms related to airway compression or postobstructive pneumonia.

Laboratory Evaluation of Active Tuberculosis

It is important for radiologists to have a basic understanding of laboratory testing in patients who are suspected of having tuberculosis and to integrate the relevant laboratory findings and clinical context, to optimize communication with the referring providers and provide the best patient care. The limitations of laboratory testing in the form of false positives and false negatives should be considered in offering a differential diagnosis. The sensitivity and specificity of relevant laboratory tests are summarized in Table 2 (40,41).

Patients suspected of having active tuberculosis should be placed in respiratory isolation. Laboratory evaluation begins with obtaining sputum for smear and culture (Fig 1). Three successive sputum samples should be obtained at 8–24-hour intervals, preferably in the early morning (42). The results of a sputum smear are generally available within 1 day. The number of bacilli identified on the smear correlates with the patient's degree of infectiousness (1). In instances in which the patient cannot produce sputum, expectoration of sputum may be induced with administration of nebulized hypertonic saline. In children, who commonly swallow sputum, gastric washings obtained in the early morning with nasogastric aspiration have a diagnostic yield of approximately 40% in those with radiographic signs of pulmonary disease (43). If sputum cannot be obtained, bronchoscopy is the next step in evaluation. In cases of sputum smear–negative pulmonary tuberculosis, bronchial washing has a sensitivity of 73% and a negative predictive value of 93% (44). In addition, if there is mediastinal lymphadenopathy, endobronchial ultrasound (US)–guided transbronchial needle aspiration may be helpful for diagnosis (45).

Staining

Once a sputum sample is obtained, it is processed by using an acid-fast staining method. Mycobacteria have a lipid-rich cell wall (rich in mycolic acids) that binds basic fuchsin dyes, and the staining is resistant to removal with acid and alcohol. Therefore, these mycobacteria are termed *AFB* (Fig 18). Several acid-fast staining techniques are available, such as the older Ziehl-Neelsen stain and newer fluorescent stains with improved sensitivity (46). Of note, acid-fast staining occurs in both *M tuberculosis* complex and nontuberculous mycobacteria, as well as a number of other bacterial organisms, including *Nocardia* organisms (47). The sensitivity of the smear for AFB with three successive expectorated sputum specimens is 68%–72% in patients with culture-positive tuberculosis (48–50) and 62% in HIV-positive patients (48). Thus, the clinical context and imaging findings are important to determine the need for empirical antituberculous therapy, as compared with awaiting culture confirmation. Respiratory isolation can be concluded after three successive negative smears for AFB, even while the culture results are pending (51).

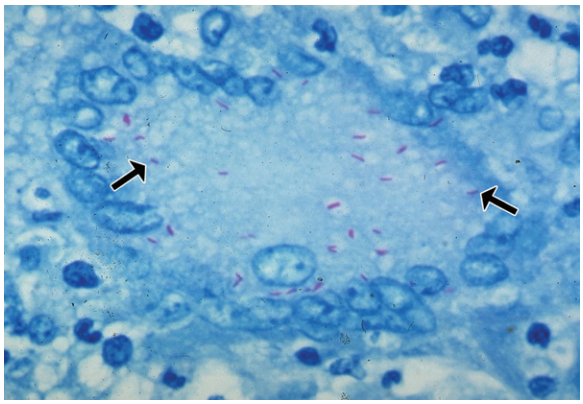


Figure 18. Acid-fast staining for active tuberculosis. Photomicrograph of lung tissue shows numerous AFB (arrows) in the cytoplasm of a giant cell. (Ziehl-Neelsen AFB stain; original magnification, ×400.) (Courtesy of Yale Rosen, MD, Winthrop University Hospital, Mineola, NY, under a CC BY-SA 2.0 license.)

Culture

Culture can detect as few as 10 mycobacteria per milliliter of sample, whereas at least 5000 mycobacteria per milliliter are required for a positive smear (52). Traditionally, solid culture media can take as long as 6 weeks for the growth of mycobacteria to be detected, whereas the use of liquid culture media can shorten this time to 2 weeks (1). Once growth is detected, the mycobacterial species can be identified, allowing the distinction of *M tuberculosis* from other nontuberculous mycobacteria.

Mycobacterial culture remains the reference standard for diagnosing active tuberculosis, with a sensitivity of 80%–85% and a specificity of 98%. In 10% of adult cases, confirmation is never established with culture findings (6). The rate of culture confirmation is even lower in children, at approximately 28% (6). Thus, clinical judgment must be used in empirically treating culture-negative patients. Cultures should be obtained monthly until two consecutive negative results are obtained, which is known as culture conversion (1). Culture conversion is an important event in monitoring the treatment response and affects the length and type of treatment.

Culture studies are also important in determining the drug susceptibility of the organism. In developing countries, *multidrug-resistant strains*—which are resistant to isoniazid and rifampin therapy—and *extensively drug-resistant strains*—which are resistant to therapy with isoniazid, rifampin, any fluoroquinolone drug, and one of the injectable antituberculous drugs—are emerging (1). Although imaging findings cannot be used to distinguish multidrug-resistant strains, extensively drug-resistant strains, and susceptible strains of tuberculosis, at least one group of investigators has suggested that extensively drug-resistant tuberculosis has more-extensive parenchymal findings than multidrug-resistant tuberculosis (53).

Nucleic Acid Amplification Test

The nucleic acid amplification test is a molecular test that can rapidly detect genetic material of tuberculous mycobacteria from sputum samples within 48 hours (41). According to current guidelines, at least one respiratory specimen from a patient suspected of having active tuberculosis should be tested with the nucleic acid amplification test, concurrently with an AFB smear (Fig 1) (54). If both the nucleic acid amplification test and sputum smear yield positive findings, this combination is sufficient for confirmation of tuberculosis, and treatment should be started (6). Note that the nucleic acid amplification test cannot be used to follow the clinical response to treatment, because the test can also detect nonviable tuberculous mycobacteria (6).

Latent Tuberculosis

Latent tuberculosis is a somewhat broad term that, when used in the discussion of patient treatment, may encompass latent tuberculosis infection and previous (inactive) tuberculosis, as defined in Table 1. More narrowly defined, *latent infection* refers to positive findings on laboratory screening tests in the absence of radiographic or clinical evidence of active disease. By definition, *previous (inactive) disease* demonstrates radiographic or clinical evidence of previous tuberculosis but no evidence of currently active tuberculosis (Table 1) (6).

Inactive tuberculosis is characterized by stable fibronodular changes, including scarring (peribronchial fibrosis, bronchiectasis, and architectural distortion) and nodular opacities in the apical and upper lung zones (Fig 19). Fibronodular change is associated with a considerably higher risk of developing tuberculosis reactivation (55). In contrast, calcified granulomas (Figs 20, 21) and calcified lymph nodes are associated with an extremely low risk of reactivation and are commonly seen in other granulomatous diseases, such as endemic fungal infections and sarcoidosis (55). Healed tuberculous cavities may persist after active disease resolves and can be complicated by hemoptysis, bacterial infection, or mycetoma.

An algorithm for the evaluation of latent tuberculosis is presented in Figure 22. As the algorithm indicates, for a patient suspected of having latent tuberculosis, the most appropriate initial test is either a tuberculin skin test or an interferon-γ release assay. An asymptomatic patient with positive results on a tuberculosis screening test should undergo chest radiography

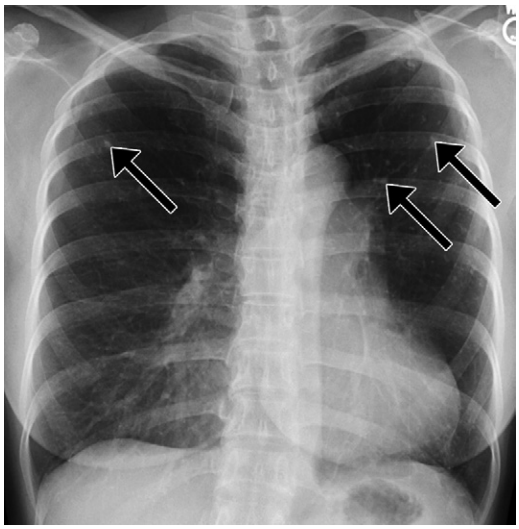
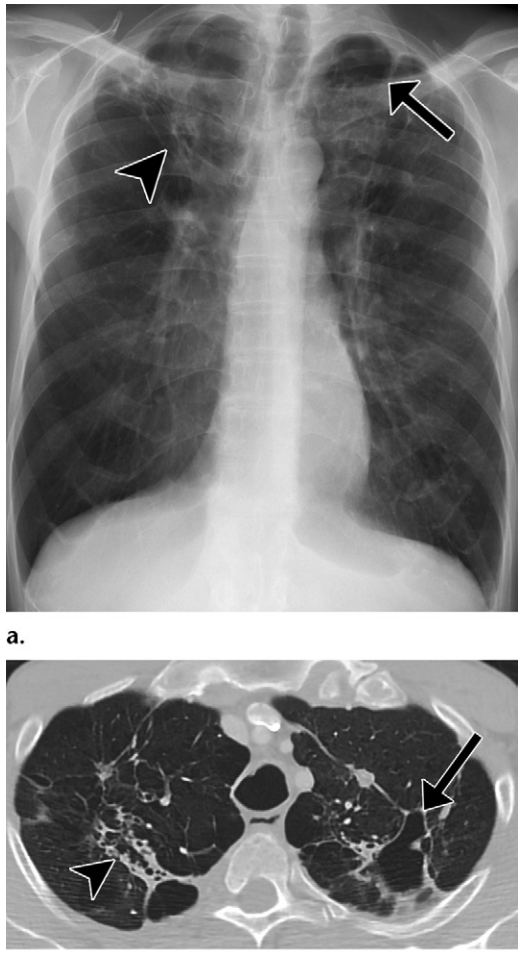


Figure 20. Calcified nodules from an old granulomatous infection in a 52-year-old woman with a positive tuberculin skin test before initiation of biological therapy for inflammatory arthritis. PA chest radiograph shows scattered calcified nodules (arrows).



a.

b.

Figure 19. Fibronodular scarring at the lung apices in a 46-year-old man with previous (inactive) tuberculosis. **(a)** PA chest radiograph shows upper lobe fibrosis (arrowhead) and volume loss with a residual cavity (arrow). **(b)** Axial CT image shows peribronchial fibrosis (arrowhead) and architectural distortion in the lung apices, with a residual cavity (arrow).

to evaluate for the presence of active or inactive tuberculosis (Table 3) (6). If the chest radiograph shows normal findings or demonstrates calcified granulomas, the patient may or may not be treated for latent tuberculosis, depending on the presence of risk factors for reactivation. Treatment of patients with latent tuberculosis is typically single-drug therapy with isoniazid or rifampin (1). If the chest radiograph demonstrates fibronodular changes, treatment of patients with latent tuberculosis is appropriate if these findings have been stable for at least 6 months or if the results of a workup for active tuberculosis are negative (16). If 6-month stability cannot be established, for example, owing to a lack of prior examinations, then further clinical and laboratory evaluation for active tuberculosis is required. Patients with equivocal radiographic findings, such as ill-defined nodules or questionable cavitation, for which 6-month stability cannot be established, should similarly undergo further evaluation for active tuberculosis. Chest CT may be helpful for better characterization of radiographic findings, particularly when no prior imaging results are available. If the chest radiograph demonstrates cavities or consolidation suggestive of active tuberculosis, patients will need to undergo further clinical and laboratory evaluation. If the results of the workup are positive, initial four-drug therapy for active tuberculosis is required, instead of single-drug therapy for latent tuberculosis (56).

Incidental radiographic findings of fibronodular change (and not merely calcified granulomas) should warrant a test for infection, if the patient does not have a history of antituberculous treatment. If the test for infection is positive, these patients should be managed according to the algorithm for evaluation for latent tuberculosis (Fig 22). Occasionally, high-risk patients with normal test results may be started on therapy for latent tuberculosis, for example, if the last exposure to tuberculosis is recent (within the past 8–10 weeks) (1).

Chest radiographs are important in the evaluation and risk stratification of patients suspected of having latent or inactive tuberculosis. Radiology reports should describe whether the radiograph shows entirely normal findings, shows calcified granulomas, shows fibronodular scarring (noting the duration of stability), or shows findings that raise concern for active tuberculosis. A sample template for the radiology report is shown in Table 4. It is important to remember that any

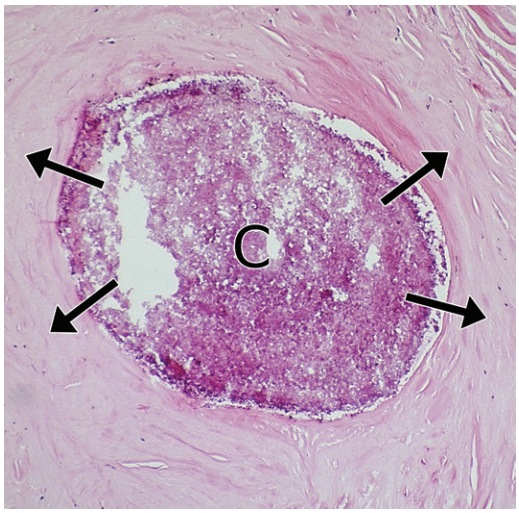


Figure 21. Calcified nodules from an old granulomatous infection in a different patient from the one shown in Figure 20. Photomicrograph shows an old healed fibrocalcific granuloma. The center *(C)* represents the calcific remnant of the granuloma with surrounding fibrosis (arrows). (Hematoxylin-eosin stain; original magnification, ×150.) (Courtesy of Yale Rosen, MD, Winthrop University Hospital, Mineola, NY, under a CC BY-SA 2.0 license.)

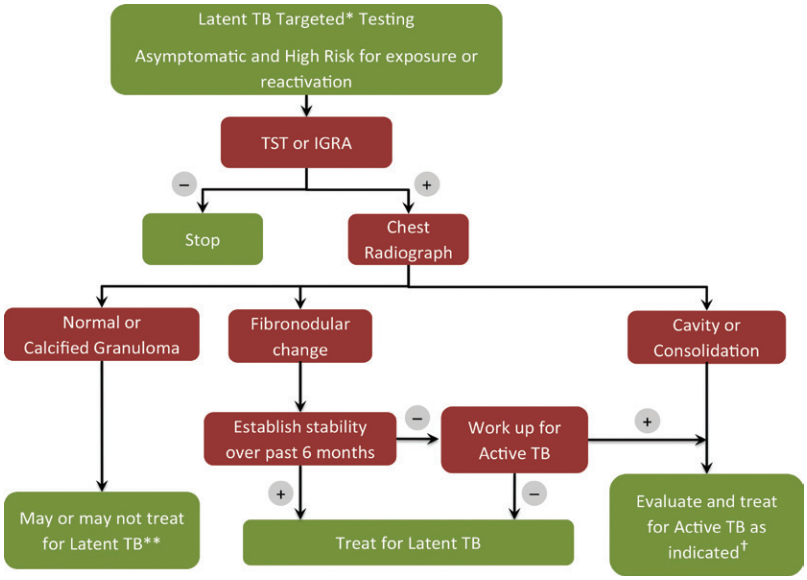


Figure 22. Diagram of an algorithm for the evaluation and treatment of patients who are suspected of having latent tuberculosis *(TB)* (concern for latent tuberculosis infection). * = targeted testing implies that there is an indication to treat if the test results are positive; ** = may treat for latent tuberculosis, particularly if patient is at high risk for reactivation (eg, HIV positive and immunosuppression, recent exposure within past 2 years); † = for radiographic finding of a cavity or consolidation, if workup for active tuberculosis yields negative findings, then expand the investigation and differential diagnosis. *IGRA* = interferon-γ release assay, *TST* = tuberculin skin test.

finding that raises the possibility of active tuberculosis should prompt communication with the referring provider and placement of the patient in respiratory isolation, as detailed earlier.

Tests for Infection

Testing for latent tuberculosis is advised for *(a)* individuals without symptoms, but who are at high risk of exposure or reactivation, and *(b)* individuals with incidental imaging findings suggestive of inactive tuberculosis. Asymptomatic individuals without any risk factors should generally not be tested. Testing is important because patients with latent tuberculosis are at risk for developing active tuberculosis later: a risk of approximately 0.1% per year for healthy patients with normal chest radiographs, and up to 10% per year in patients with HIV infection (57). A number of different tests are available; the sensitivities and specificities of these tests are summarized in Table 5 (58).

Tuberculin Skin Test

The most commonly used test for latent tuberculosis is the tuberculin skin test, also known as the purified protein derivative (PPD) or Mantoux test. A dose of protein extracted from *M tuberculosis* is injected intradermally, and a delayed cell-mediated hypersensitivity immune response is mounted against the bacterial proteins. The size of any resulting induration is measured at 48–72 hours. Depending on patient risk factors, different size thresholds of induration are used, with a trade-off between sensitivity and specificity (6). A threshold of more than 5 mm of induration is used for extremely high-risk patients, such as *(a)* patients with radiographic findings of previous tuberculosis, *(b)* those with recent contacts with persons with infectious tuberculosis, and *(c)* immunocompromised patients with HIV infection, organ transplants, or therapy with immunosuppressive drugs, such as prolonged corticosteroid therapy or

Table 3: Imaging Findings of Active Tuberculosis and Previous (Inactive) Tuberculosis

Active tuberculosis
Cavitation
Consolidation
Centrilobular and tree-in-bud nodules
Miliary nodules
Lymphadenopathy
Pleural effusion
Previous (inactive) tuberculosis
Fibronodular scarring*
Peribronchial fibrosis
Well-defined nodular opacities
Traction bronchiectasis
Apical and upper lung zone volume loss
Calcified granulomas or lymph nodes†

*Findings must be stable for at least 6 months.
†If calcified granulomas or lymph nodes are the only finding, this finding would represent latent tuberculosis infection.

Table 4: Sample Report Template for Chest Radiograph in the Setting of Suspected Latent or Active Tuberculosis

FINDINGS:
There is [no] cavitation, consolidation or nodular pattern. There are [no] fibronodular changes. [Mention if depicted: calcified granulomas, calcified lymph nodes, mediastinal or hilar lymphadenopathy, pleural effusion.]
IMPRESSION [Pick one:]:
– No evidence of active or previous tuberculosis.
– Calcified granulomas, consistent with old granulomatous infection.
– Stable fibronodular opacities for 6 months, consistent with inactive tuberculosis.
– Fibronodular changes suggestive of tuberculosis of uncertain activity. Recommend comparison with prior images. Recommend clinical evaluation for possible active tuberculosis. Findings communicated to [ ].
– Findings likely represent active tuberculosis. Recommend respiratory isolation and sputum sampling. Findings communicated to [ ].

Table 5: Sensitivity and Specificity of Tests for Latent Tuberculosis Infection

Test	Sensitivity (%)	Specificity (%)	False Positives
Tuberculin skin test	77–80	Up to 97*	Nontuberculous mycobacteria; BCG vaccine
Interferon-γ release assays			
QuantiFERON-TB Gold In-Tube (Cellestis, Carnegie, Australia)	70–80	96–99	Rarely, nontuberculous mycobacteria
T-SPOT.*TB* (Oxford Immunotec, Marlborough, Mass)	90	93	Rarely, nontuberculous mycobacteria

*The specificity of the tuberculin skin test is 35%–60% in populations with high rates of BCG vaccination.

therapy with tumor necrosis factor α inhibitor. In patients at high risk, such as immigrants from endemic regions, drug abusers, those with exposure in high-risk congregate settings, those with certain medical conditions, and certain pediatric patients, a threshold of more than 10 mm of induration is used. In the absence of any risk factors, a threshold of more than 15 mm of induration is used.

False-positive reactions to the tuberculin skin test may occur because of exposure to nontuberculous mycobacteria (59). In addition, vaccination with BCG vaccine in childhood can cause lasting tuberculin skin test positivity in some individuals, particularly if they were vaccinated after 1 year of age (59). False-negative reactions may occur in patients with recent tuberculosis infection within the past 8–10 weeks, in infants younger than 6 months, in those with recent live-virus vaccination, and in immunocompromised patients (1). A patient's tuberculin skin test positivity can revert to negative with time, at a rate of about 5% per year after initial exposure. As a result, a substantial proportion of the elderly population will have a negative reaction despite previous exposure to tuberculosis (60). In these patients, a repeat test performed 1–3 weeks later will generally be positive owing to the "booster phenomenon."

Interferon-γ Release Assays

An alternative to the tuberculin skin test for the evaluation of patients suspected of having latent tuberculosis is the interferon-γ release assay; two versions of the interferon-γ release assay are currently approved in the United States (QuantiFERON-TB Gold In-Tube; and

T-SPOT.*TB*) (58,61,62). A patient's blood is exposed to *M tuberculosis* antigen, and the resulting interferon-γ immune response is measured. In comparison with the tuberculin skin test, interferon-γ release assays require only one visit to conduct the test, with the results available within 24 hours. As with the tuberculin skin test, a negative reaction cannot absolutely exclude tuberculosis infection. Limited data are available with regard to the use of interferon-γ release assays in immunocompromised individuals (eg, those with HIV infection) to suggest that there may be an increase in false-negative or indeterminate results (63). Interferon-γ release assays do not cross-react with BCG vaccination or with most strains of nontuberculous mycobacteria (64).

Screening Tests in Patients with Active Tuberculosis

It is important to note that the tuberculin skin test and interferon-γ release assays are not designed to evaluate subjects for active tuberculosis. The sensitivity of both tests is limited for active tuberculosis, particularly because of the time that it takes for the cell-mediated immune response to develop after the initial infection (65). Although a positive result of these tests supports the diagnosis of active tuberculosis, the positive result should not be used alone for diagnosis. A negative result of these tests, as discussed, does not exclude tuberculosis. Thus, although many experts may consider the use of screening tests in cases of suspected active tuberculosis as a diagnostic aid, such tests should not be regarded as providing a definitive answer (8,66).

Role of Imaging in Diagnosis and Management

Imaging plays a critical role in the diagnosis and treatment of active tuberculosis. A chest radiograph is generally obtained at the time of diagnosis; typically, a single PA view is adequate. Adjunctive views, such as a lordotic view or dual-energy radiography with bone subtraction, can improve the depiction of the lung apices (67). Imaging findings suggestive of active tuberculosis, whether it is clinically suspected or not, should prompt immediate communication with the referring provider and placement of the patient in respiratory isolation until negative sputum samples are obtained.

Treatment of patients with active tuberculosis has two phases: *(a)* an initiation phase, also known as the bactericidal or intensive phase, and *(b)* a continuation phase, also known as the sterilizing phase (56). The bactericidal phase typically lasts for 2 months and requires administration of a four-drug regimen of isoniazid, rifampin, ethambutol, and pyrazinamide. The length of the continuation phase can vary, depending on the risk of relapse of the patient. Isoniazid and rifampin are typically administered together in the continuation phase.

A treatment algorithm for active tuberculosis, highlighting the role of imaging in management, is shown in Figure 23 (68). Patients with active tuberculosis who have cavitation on the initial chest radiograph and who, at the completion of the initiation phase of treatment, still demonstrate positive 2-month tuberculosis cultures are at a high risk of relapse and should continue therapy for a total of 9 months. Thus, careful examination of the initial chest radiograph should be made for cavitary disease (Figs 11a, 14a). Although CT is twice as sensitive as chest radiography in the detection of cavities (69) and may be useful in raising suspicion for active tuberculosis, the decision about the length of treatment in the algorithm is based on the presence of cavities on the chest radiograph, rather than on the CT images. Patients without cavitation on the initial chest radiograph and patients with a negative 2-month culture may need therapy for a total of only 6 months. A chest radiograph should be obtained in all patients at the completion of treatment to establish a new baseline (Fig 24).

When treatment is indicated for latent tuberculosis, the principal treatment regimen is 9 months of therapy with isoniazid. If the patient is HIV negative and if the chest radiograph shows normal findings, then 6 months of therapy with isoniazid may be sufficient. For patients who cannot tolerate isoniazid therapy or have been exposed to isoniazid-resistant *M tuberculosis*, 4 months of rifampin therapy is recommended. The results of new studies have shown that weekly therapy with isoniazid and rifapentine for 3 months is an acceptable alternative in selected patients (70).

Nontuberculous Mycobacteria

Nontuberculous mycobacteria are a diverse group of mycobacterial species other than *M tuberculosis* complex, which are ubiquitous in the environment, including the soil and water. Nontuberculous mycobacterial disease in the lungs is most commonly seen with *Mycobacterium avium* complex—also referred to as *Mycobacterium avium-intracellulare* complex—and *Mycobacterium kansasii* (71). The prevalence of pulmonary nontuberculous mycobacterial disease is two- to threefold that of tuberculosis (72). Nontuberculous mycobacterial disease manifests in two major forms: classic (cavitary) and nonclassic (bronchiectatic) (73,74).

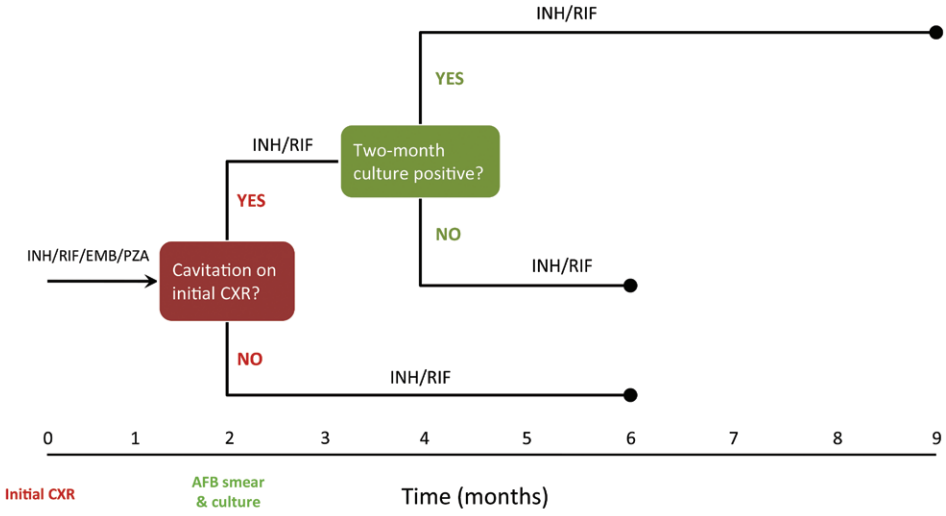
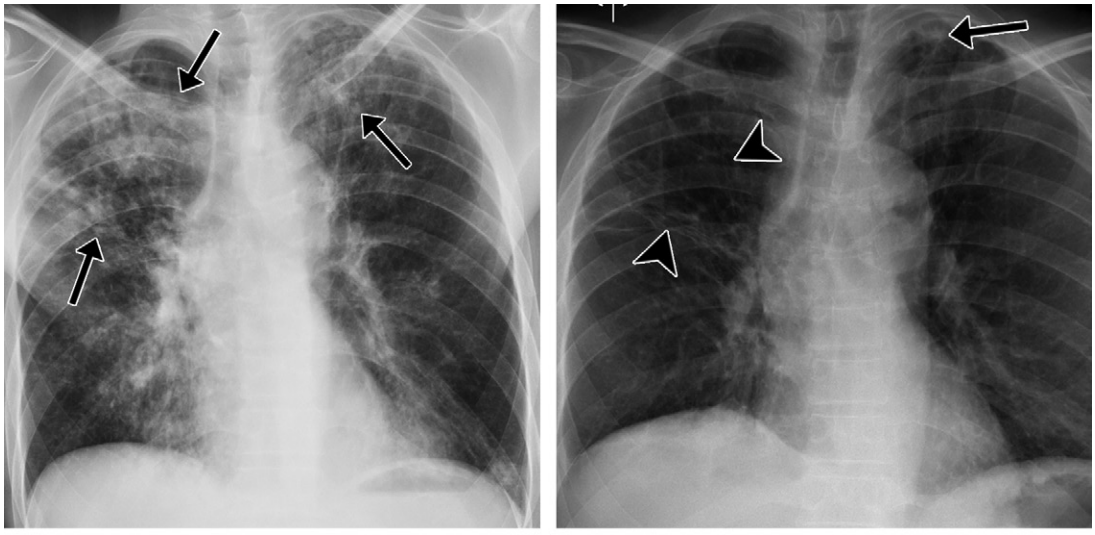


Figure 23. Diagram of a treatment algorithm for active tuberculosis. *CXR* = chest x-ray, *EMB* = ethambutol, *INH* = isoniazid, *PZA* = pyrazinamide, *RIF* = rifampin.

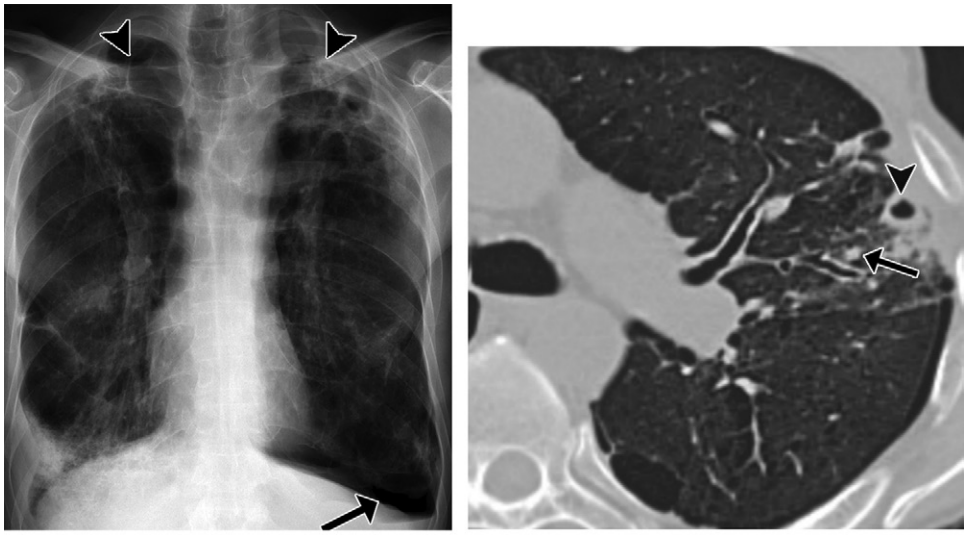


a. **b.**

Figure 24. Pre- and posttreatment images in a 53-year-old man with tuberculosis. **(a)** Pretreatment PA chest radiograph shows nodules and consolidations (arrows), predominantly in the bilateral apical and upper lung zones. **(b)** Posttreatment PA chest radiograph shows residual fibrosis (arrowheads) and nodular opacities (arrow), findings that represent this patient's new baseline.

Classic (cavitary) nontuberculous mycobacterial infection can have an appearance and clinical manifestations indistinguishable from those of postprimary tuberculosis; classic nontuberculous mycobacterial infection is characterized by upper lobe cavitary lesions and centrilobular and tree-in-bud nodules (Fig 25) (73,74). Upper lobe architectural distortion is often also depicted. Classic nontuberculous mycobacterial infection most commonly affects elderly men with chronic lung disease (typically, emphysema). When compared with tuberculosis, classic nontuberculous mycobacterial infection tends to progress more slowly, and cavities tend to be smaller with thinner walls (74). However, substantial overlap exists between the manifestations of tuberculous and nontuberculous mycobacterial infections. Both types of infections yield AFB on smears, and thus a sputum culture is necessary for definitive diagnosis.

In contrast, nonclassic (bronchiectatic) nontuberculous mycobacterial infection manifests as chronic bronchiectasis and bronchiolitis with a mid to lower lung zone predominance (74). This form of nontuberculous mycobacterial infection is most commonly seen in elderly women without predisposing factors. It is generally not mistaken for tuberculosis, given the midlung zone distribution and bronchiectasis. However, if there is more bronchiolitis than bronchiectasis, this infection could mimic active postprimary tuberculosis. The



a. b.

Figure 25. Classic nontuberculous mycobacterial infection with *M kansasii* in a 64-year-old man with emphysema. **(a)** PA chest radiograph shows patchy consolidation in the right lower lobe and the apices (arrowheads), with possible cavitation. A left-sided basilar pneumothorax (arrow) is incidentally depicted. **(b)** Axial chest CT image shows a cavitary lesion (arrowhead), with surrounding centrilobular nodules (arrow), in the left lung.

lack of upper lung zone predominance should help distinguish these two entities.

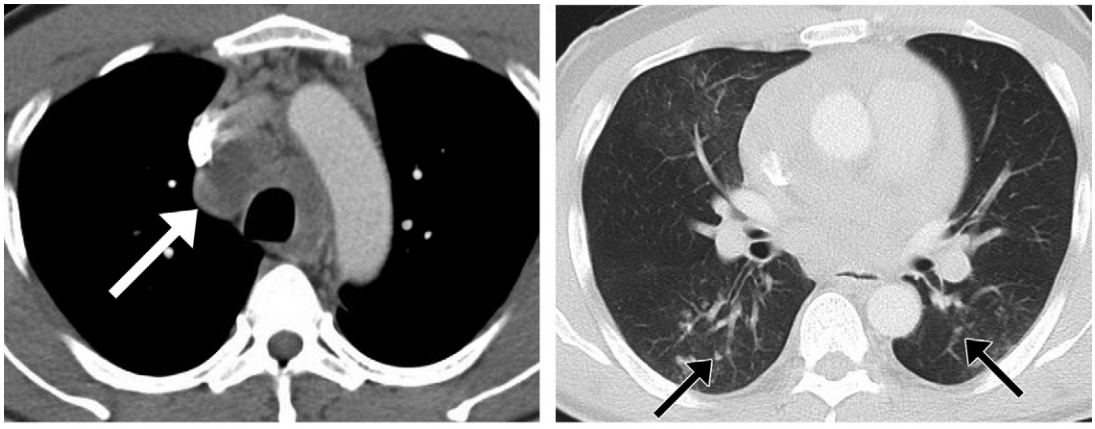
In immunocompromised patients, the clinical and radiologic findings of nontuberculous mycobacterial infection are nonspecific and may overlap with those of tuberculosis or other disseminated infections (74). Typical symptoms include fever, weight loss, fatigue, and cough. Disseminated nontuberculous mycobacterial infection occurs particularly in AIDS patients with CD4 cell counts of less than 70/μL, affecting the bone marrow, liver, spleen, and lymph nodes. Lymphadenopathy, particularly the necrotic type, is the most frequent finding at imaging (Fig 26). Pulmonary findings may include centrilobular nodules (Fig 26), miliary micronodules, and cavitation (75). AFB can be demonstrated from sputum and lymph node sampling (Fig 27). Given the substantial degree of overlap in clinical and imaging manifestations between nontuberculous mycobacterial infection and tuberculosis in HIV-positive patients, who are predisposed to infection with both types of mycobacteria, culture studies are necessary for a definitive diagnosis and to guide therapy.

Unlike *M tuberculosis,* nontuberculous mycobacteria can colonize human airways. In patients with chronic lung disease, false-positive cultures caused by the presence of colonizing mycobacteria may be misleading. Thus, guidelines recommend *(a)* obtaining at least three sputum samples, with two positive sputum cultures or *(b)* a single positive culture from bronchoalveolar lavage fluid or lung biopsy to establish the diagnosis (76). In patients without cavitary disease, the diagnostic yield is lower, so false negatives may delay diagnosis.

Prolonged antibiotic therapy, usually until at least 1 year after a negative sputum culture, is necessary to eradicate nontuberculous mycobacterial infection (76). For infection with *M avium* complex, triple therapy with rifampin (or rifabutin), azithromycin (or clarithromycin), and ethambutol is used. For *M kansasii* infection, combination therapy with rifampin, isoniazid, and ethambutol is used. Patients with an incomplete response to medical therapy may benefit from surgical resection (76).

Conclusion

Tuberculosis is an important public health issue in both developing and developed countries. Radiologists need to be familiar with the imaging findings of pulmonary tuberculosis. Awareness of certain risk factors, such as vulnerability to exposure, altered immunity, pediatric age, and comorbidities, that can influence the likelihood and appearance of disease is essential. It is also important to be aware of the role and limitations of laboratory testing, alongside imaging and clinical evaluation, in establishing a diagnosis. In patients with positive findings on a tuberculin skin test or interferon-γ release assay, imaging plays an important role in risk stratification by helping to distinguish latent infection, previous inactive disease, and active disease. Imaging findings, such as the presence of cavitation, affect treatment decisions, such as the length of a course of therapy for active disease. Nontuberculous mycobacterial infection can



a. b.

Figure 26. Atypical mycobacterial infection in a 44-year-old HIV-positive man (CD4 cell count, 20/μL). **(a)** Axial chest CT image (mediastinal windows) shows necrotic mediastinal lymphadenopathy (arrow). **(b)** Axial chest CT image (lung windows) shows centrilobular nodules (arrows). Cultures grew *Mycobacterium mucogenicum*.

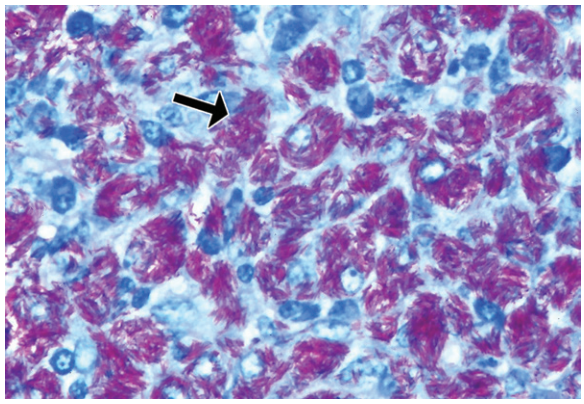


Figure 27. Acid-fast staining in a 30-year-old man with HIV infection. Photomicrograph of an axillary lymph node shows multiple large histiocytes, each filled with many AFB (arrow), which were proven to be *M avium* complex. (Ziehl-Neelsen stain; original magnification, ×200.) (Courtesy of Yale Rosen, MD, Winthrop University Hospital, Mineola, NY, under a CC BY-SA 2.0 license.)

mimic the findings of pulmonary tuberculosis and frequently affects immunosuppressed patients who are also at risk for tuberculosis. Distinguishing nontuberculous mycobacterial disease from tuberculosis is important, because the treatment regimens are different. The radiologist should be familiar with the imaging findings of pulmonary tuberculosis, as well as the clinical features, risk factors, laboratory tests, and treatment algorithms, to contribute more effectively to patient care.

Acknowledgments.—The authors wish to thank Yale Rosen, MD, Department of Pathology, Winthrop University Hospital, Mineola, NY, for the pathologic images and Barbarah Martinez, RN, BSN, Bureau of Tuberculosis Control, Houston Department of Health and Human Services, Houston, Tex, for clinical guidance.

References

1. Self-study modules on tuberculosis. Centers for Disease Control and Prevention website. http://www.cdc.gov/tb/education/ssmodules/. Updated May 11, 2016. Accessed June 14, 2016.
2. Leung AN. Pulmonary tuberculosis: the essentials. Radiology 1999;210(2):307–322.
3. Lönnroth K, Raviglione M. Global epidemiology of tuberculosis: prospects for control. Semin Respir Crit Care Med 2008;29(5):481–491.
4. Cain KP, Benoit SR, Winston CA, Mac Kenzie WR. Tuberculosis among foreign-born persons in the United States. JAMA 2008;300(4):405–412.
5. Jauregui-Amezaga A, Turon F, Ordás I, et al. Risk of developing tuberculosis under anti-TNF treatment despite latent infection screening. J Crohns Colitis 2013;7(3):208–212.
6. Diagnostic standards and classification of tuberculosis in adults and children: official statement of the American Thoracic Society and the Centers for Disease Control and Prevention. Am J Respir Crit Care Med 2000;161(4 pt 1):1376–1395.
7. Arango L, Brewin AW, Murray JF. The spectrum of tuberculosis as currently seen in a metropolitan hospital. Am Rev Respir Dis 1973;108(4):805–812.
8. Bernardo J. Diagnosis of pulmonary tuberculosis in HIV-uninfected patients. UpToDate website. http://www.uptodate.com/contents/diagnosis-of-pulmonary-tuberculosis-in-hiv-uninfected-patients. Updated April 27, 2016. Accessed June 14, 2016.
9. Burrill J, Williams CJ, Bain G, Conder G, Hine AL, Misra RR. Tuberculosis: a radiologic review. RadioGraphics 2007;27(5):1255–1273.
10. McAdams HP, Erasmus J, Winter JA. Radiologic manifestations of pulmonary tuberculosis. Radiol Clin North Am 1995;33(4):655–678.
11. Madkour MM. Primary tuberculosis in adults. In: Madkour MM, ed. Tuberculosis. Berlin, Germany: Springer, 2004;265–272.
12. Marais BJ, Parker SK, Verver S, van Rie A, Warren RM. Primary and postprimary or reactivation tuberculosis: time to revise confusing terminology? [letter]. AJR Am J Roentgenol 2009;192(4):W198–W200.
13. Verver S, Warren RM, Beyers N, et al. Rate of reinfection tuberculosis after successful treatment is higher than rate of new tuberculosis. Am J Respir Crit Care Med 2005;171(12):1430–1435.
14. Bandera A, Gori A, Catozzi L, et al. Molecular epidemiology study of exogenous reinfection in an area with a low incidence of tuberculosis. J Clin Microbiol 2001;39(6):2213–2218.
15. Asimos AW, Ehrhardt J. Radiographic presentation of pulmonary tuberculosis in severely immunosuppressed HIV-seropositive patients. Am J Emerg Med 1996;14(4):359–363.
16. Curvo-Semedo L, Teixeira L, Caseiro-Alves F. Tuberculosis of the chest. Eur J Radiol 2005;55(2):158–172.
17. Moon WK, Im JG, Yeon KM, Han MC. Mediastinal tuberculous lymphadenitis: CT findings of active and inactive disease. AJR Am J Roentgenol 1998;170(3):715–718.

18. Im JG, Song KS, Kang HS, et al. Mediastinal tuberculous lymphadenitis: CT manifestations. Radiology 1987;164(1):115–119.
19. Woodring JH, Vandiviere HM, Fried AM, Dillon ML, Williams TD, Melvin IG. Update: the radiographic features of pulmonary tuberculosis. AJR Am J Roentgenol 1986;146(3):497–506.
20. Leung AN, Müller NL, Pineda PR, FitzGerald JM. Primary tuberculosis in childhood: radiographic manifestations. Radiology 1992;182(1):87–91.
21. Valdés L, Alvarez D, San José E, et al. Tuberculous pleurisy: a study of 254 patients. Arch Intern Med 1998;158(18): 2017–2021.
22. Gopi A, Madhavan SM, Sharma SK, Sahn SA. Diagnosis and treatment of tuberculous pleural effusion in 2006. Chest 2007;131(3):880–889.
23. Hulnick DH, Naidich DP, McCauley DI. Pleural tuberculosis evaluated by computed tomography. Radiology 1983;149(3):759–765.
24. Moon WK, Im JG, Yeon KM, Han MC. Tuberculosis of the central airways: CT findings of active and fibrotic disease. AJR Am J Roentgenol 1997;169(3):649–653.
25. Maartens G, Willcox PA, Benatar SR. Miliary tuberculosis: rapid diagnosis, hematologic abnormalities, and outcome in 109 treated adults. Am J Med 1990;89(3):291–296.
26. Kim JH, Langston AA, Gallis HA. Miliary tuberculosis: epidemiology, clinical manifestations, diagnosis, and outcome. Rev Infect Dis 1990;12(4):583–590.
27. Goodwin RA, Des Prez RM. Apical localization of pulmonary tuberculosis, chronic pulmonary histoplasmosis, and progressive massive fibrosis of the lung. Chest 1983;83(5):801–805.
28. Lee SW, Jang YS, Park CM, et al. The role of chest CT scanning in TB outbreak investigation. Chest 2010;137(5): 1057–1064.
29. Cohen JR, Amorosa JK, Smith PR. The air-fluid level in cavitary pulmonary tuberculosis. Radiology 1978;127(2):315–316.
30. Luetkemeyer A. Tuberculosis and HIV. HIV InSite website. http://hivinsite.ucsf.edu/InSite?page=kb-05-01-06. Published January 2013. Accessed June 14, 2016.
31. Rajeswaran G, Becker JL, Michailidis C, Pozniak AL, Padley SP. The radiology of IRIS (immune reconstitution inflammatory syndrome) in patients with mycobacterial tuberculosis and HIV co-infection: appearances in 11 patients. Clin Radiol 2006;61(10):833–843.
32. Venkatanarasimha N. HIV, HAART, and IRIS: tuberculosis versus malignancy [letter]. AJR Am J Roentgenol 2010;195(5):W376.
33. Luetkemeyer AF, Kendall MA, Nyirenda M, et al. Tuberculosis immune reconstitution inflammatory syndrome in A5221 STRIDE: timing, severity, and implications for HIV-TB programs. J Acquir Immune Defic Syndr 2014;65 (4):423–428.
34. Ratnam I, Chiu C, Kandala NB, Easterbrook PJ. Incidence and risk factors for immune reconstitution inflammatory syndrome in an ethnically diverse HIV type 1–infected cohort. Clin Infect Dis 2006;42(3):418–427.
35. Valentin L, Dinardo A, Chiao E, Woc-Colburn L, Nachiappan A. Tuberculosis IRIS: a mediastinal problem [version 2; referees: 3 approved]. F1000 Res 2013;2:54. doi:10.12688/f1000research.2-54.v2.
36. Murdoch DM, Venter WD, Feldman C, Van Rie A. Incidence and risk factors for the immune reconstitution inflammatory syndrome in HIV patients in South Africa: a prospective study. AIDS 2008;22(5):601–610.
37. Stop TB Partnership Childhood TB Subgroup. Guidance for National Tuberculosis Programmes on the management of tuberculosis in children: chapter 1—introduction and diagnosis of tuberculosis in children. Int J Tuberc Lung Dis 2006;10(10):1091–1097.
38. Cruz AT, Hwang KM, Birnbaum GD, Starke JR. Adolescents with tuberculosis: a review of 145 cases. Pediatr Infect Dis J 2013;32(9):937–941.
39. TB in children in the United States. Centers for Disease Control and Prevention website. http://www.cdc.gov/tb/topic/populations/tbinchildren/default.htm. Updated October 10, 2014. Accessed June 14, 2016.
40. Morgan MA, Horstmeier CD, DeYoung DR, Roberts GD. Comparison of a radiometric method (BACTEC) and conventional culture media for recovery of mycobacteria from smear-negative specimens. J Clin Microbiol 1983;18(2): 384–388.
41. Shinnick TM, Good RC. Diagnostic mycobacteriology laboratory practices. Clin Infect Dis 1995;21(2):291–299.
42. Craft DW, Jones MC, Blanchet CN, Hopfer RL. Value of examining three acid-fast bacillus sputum smears for removal of patients suspected of having tuberculosis from the "airborne precautions" category. J Clin Microbiol 2000;38(11): 4285–4287.
43. Starke JR. Pediatric tuberculosis: time for a new approach. Tuberculosis (Edinb) 2003;83(1-3):208–212.
44. Anderson C, Inhaber N, Menzies D. Comparison of sputum induction with fiber-optic bronchoscopy in the diagnosis of tuberculosis. Am J Respir Crit Care Med 1995;152(5 pt 1): 1570–1574.
45. Madan K, Mohan A, Ayub II, et al. Initial experience with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) from a tuberculosis endemic population. J Bronchology Interv Pulmonol 2014;21(3):208–214.
46. Steingart KR, Henry M, Ng V, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis 2006;6(9):570–581.
47. Reynolds J, Moyes RB, Breakwell DP. Appendix 3H: differential staining of bacteria—acid fast stain. Curr Protoc Microbiol 2009;appendix 3:appendix 3H. Wiley Online Library website. http://onlinelibrary.wiley.com/doi/10.1002/9780471729259.mca03hs15/abstract. Published online November 1, 2009.
48. Leonard MK, Osterholt D, Kourbatova EV, Del Rio C, Wang W, Blumberg HM. How many sputum specimens are necessary to diagnose pulmonary tuberculosis? Am J Infect Control 2005;33(1):58–61.
49. Mathew P, Kuo YH, Vazirani B, Eng RH, Weinstein MP. Are three sputum acid-fast bacillus smears necessary for discontinuing tuberculosis isolation? J Clin Microbiol 2002;40 (9):3482–3484.
50. Taegtmeyer M, Beeching NJ, Scott J, et al. The clinical impact of nucleic acid amplification tests on the diagnosis and management of tuberculosis in a British hospital. Thorax 2008;63(4):317–321.
51. Dooley SW Jr, Castro KG, Hutton MD, Mullan RJ, Polder JA, Snider DE Jr. Guidelines for preventing the transmission of tuberculosis in health-care settings, with special focus on HIV-related issues. MMWR Recomm Rep 1990;39(RR-17): 1–29.
52. Hobby GL, Holman AP, Iseman MD, Jones JM. Enumeration of tubercle bacilli in sputum of patients with pulmonary tuberculosis. Antimicrob Agents Chemother 1973;4(2):94–104.
53. Lee ES, Park CM, Goo JM, et al. Computed tomography features of extensively drug-resistant pulmonary tuberculosis in non-HIV-infected patients. J Comput Assist Tomogr 2010;34(4):559–563.
54. Centers for Disease Control and Prevention. Updated guidelines for the use of nucleic acid amplification tests in the diagnosis of tuberculosis. MMWR Morb Mortal Wkly Rep 2009;58(1):7–10.
55. Grzybowski S, Fishaut H, Rowe J, Brown A. Tuberculosis among patients with various radiologic abnormalities, followed by the chest clinic service. Am Rev Respir Dis 1971;104(4): 605–608.
56. Blumberg HM, Leonard MK Jr, Jasmer RM. Update on the treatment of tuberculosis and latent tuberculosis infection. JAMA 2005;293(22):2776–2784. [Published correction appears in JAMA 2005;294(2):182. Dosage error in article text.]
57. Pai M, Menzies D. Diagnosis of latent tuberculosis infection (tuberculosis screening) in HIV-infected adults. UpToDate website. http://www.uptodate.com/contents/diagnosis-of-latent-tuberculosis-infection-tuberculosis-screening-in-hiv-uninfected-adults. Updated March 25, 2016. Accessed June 14, 2016.
58. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection—an update. Ann Intern Med 2008;149(3):177–184.
59. Farhat M, Greenaway C, Pai M, Menzies D. False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria? Int J Tuberc Lung Dis 2006;10(11):1192–1204.
60. Stead WW. Tuberculosis among elderly persons, as observed among nursing home residents. Int J Tuberc Lung Dis 1998;2(9 suppl 1):S64–S70.

61. Pai M, Denkinger CM, Kik SV, et al. Gamma interferon release assays for detection of *Mycobacterium tuberculosis* infection. Clin Microbiol Rev 2014;27(1):3–20.
62. Mori T, Sakatani M, Yamagishi F, et al. Specific detection of tuberculosis infection: an interferon-γ-based assay using new antigens. Am J Respir Crit Care Med 2004;170(1):59–64.
63. Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro, K. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection: United States, 2010. MMWR Morb Mortal Wkly Rep 2010;59(RR05):1–25. Centers for Disease Control and Prevention website. https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm. Updated June 25, 2010.
64. Adams LV, Waddell RD, Von Reyn CF. T-SPOT.*TB* Test® results in adults with *Mycobacterium avium* complex pulmonary disease. Scand J Infect Dis 2008;40(3):196–203.
65. Rangaka MX, Wilkinson KA, Glynn JR, et al. Predictive value of interferon-γ release assays for incident active tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis 2012;12(1):45–55.
66. Tuberculosis (TB): testing & diagnosis. Centers for Disease Control and Prevention website. http://www.cdc.gov/tb/topic/testing/. Updated April 14, 2016. Accessed June 14, 2016.
67. Sharma M, Sandhu MS, Gorsi U, Gupta D, Khandelwal N. Role of digital tomosynthesis and dual energy subtraction digital radiography in detection of parenchymal lesions in active pulmonary tuberculosis. Eur J Radiol 2015;84(9):1820–1827.
68. American Thoracic Society; CDC; Infectious Diseases Society of America. Treatment of tuberculosis. MMWR Recomm Rep 2003;52(RR-11):1–77. [Published correction appears in MMWR Recomm Rep 2005;53(51):1203. Dosage error in article text.]
69. Im JG, Itoh H, Shim YS, et al. Pulmonary tuberculosis: CT findings—early active disease and sequential change with antituberculous therapy. Radiology 1993;186(3):653–660.
70. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med 2011;365(23):2155–2166.
71. Woodring JH, Vandiviere HM. Pulmonary disease caused by nontuberculous mycobacteria. J Thorac Imaging 1990;5(2):64–76.
72. Prevots DR, Shaw PA, Strickland D, et al. Nontuberculous mycobacterial lung disease prevalence at four integrated health care delivery systems. Am J Respir Crit Care Med 2010;182(7):970–976.
73. Miller WT Jr. Spectrum of pulmonary nontuberculous mycobacterial infection. Radiology 1994;191(2):343–350.
74. Erasmus JJ, McAdams HP, Farrell MA, Patz EF Jr. Pulmonary nontuberculous mycobacterial infection: radiologic manifestations. RadioGraphics 1999;19(6):1487–1505.
75. Martinez S, McAdams HP, Batchu CS. The many faces of pulmonary nontuberculous mycobacterial infection. AJR Am J Roentgenol 2007;189(1):177–186.
76. Diagnosis and treatment of disease caused by nontuberculous mycobacteria: official statement of the American Thoracic Society. Am J Respir Crit Care Med 1997;156(2 pt 2):S1–S25.