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Abbreviations:
BCG = bacille Calmette-Guérin
CDC = Centers for Disease Control and Prevention
HIV = human immunodeficiency virus
MDR = multidrug resistant
TB = tuberculosis

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Pulmonary Tuberculosis: The Essentials[1]

The association between tuberculosis (TB) and man predates written history (1). Aristotle is usually credited as being the first to recognize the contagious nature of the disease (2). Discovery of the specific infectious agent, the tubercle bacillus (*Mycobacterium tuberculosis*), did not occur for several more centuries until it was isolated by Robert Koch in 1882. The discoveries of streptomycin in 1944, paraamino salicylic acid in 1946, and isoniazid in 1952 led to the first effective cure for TB. Descriptions of airborne transmission of infection and of reactivation of dormant infection in the 1960s by Riley et al (3) and Stead and colleagues (4,5), respectively, furthered our understanding of the spread and pathogenesis of this disease.

On the basis of these past achievements, as we approach the new millennium, medical knowledge and technology have advanced to the point that TB can now be regarded as a treatable, preventable, and eradicable disease (6). However, largely because it has been neglected as a global public health issue for many years, TB remains the major cause of death from a single infectious agent among adults in developing nations. In 1993, the World Health Organization declared TB to be a global emergency (7). At current control levels, it is estimated that between 1997 and 2020, nearly 1 billion people will become newly infected and 70 million people will die from the disease (C. Dye, WHO, personal communication, 1998).

EPIDEMIOLOGY

Morbidity and mortality associated with TB are greatest in developing nations, where 95% of all cases and 98% of all deaths associated with TB occurred in 1990 (7). The highest prevalence and estimated annual risk of infection are found in Southeast Asia (rate, 237 per 100,000) and sub-Saharan Africa (rate, 191 per 100,000) (7). Of the 3.3 million cases of TB notified to the World Health Organization in 1995, 78% were from Asia, sub-Saharan Africa, and island regions (8). By contrast, during these same time periods, industrialized countries (Western Europe, Australia, Canada, Japan, New Zealand, and United States) had an average annual incidence of 23 per 100,000 and accounted for only 4% of total notified cases (7,8).

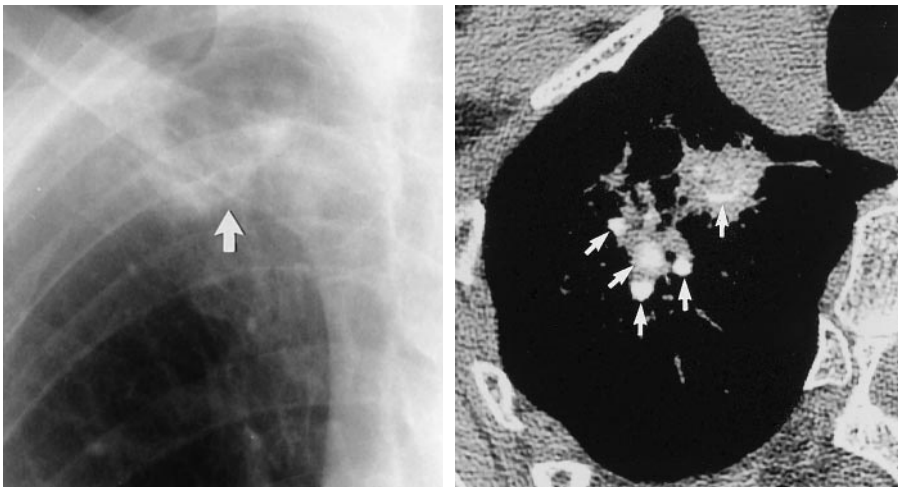
Distinct differences in the epidemiology of TB are observed between developing and industrialized nations. In countries where the standard of living is low and health resources are scarce, the risk of recent infection is high and 80% of cases involve persons in their productive years (15–59 years of age) (7). In economically developed countries where progressive declines in the incidence of TB have been achieved, the annual risk of infection is low. The majority of TB cases arise as a result of endogenous reactivation of remote infection acquired when TB was more prevalent; this results in disease rates highest in the elderly (≥65 years of age). Active disease manifesting in younger patients usually arises in racial and ethnic minorities or in association with human immunodeficiency virus (HIV) infection (7).

In the United States, a total of 21,337 cases of TB (rate, 8.0 per 100,000) were reported to the Centers for Disease Control and Prevention (CDC) in 1996, representing the lowest number and rate of reported TB cases since national reporting began in 1953 (9). This was the fourth consecutive year that the number of reported TB cases had declined and improvements in TB-prevention and TB-control programs that resulted directly from increased federal resources provided to the states in the early 1990s were credited with reversing the increasing trend observed from 1985 to 1992 (9). California, New York, Texas, Florida, and Illinois were the five states that reported the highest number of cases.

During 1996, the number of reported cases in the United States decreased in each age group and in all racial and ethnic groups. Rates continued to be highest among the elderly (rate, 15.1 per 100,000). Seventy-four percent of reported cases occurred among nonwhite

racial and ethnic groups. During the past decade, a steady increase in the percentage of cases affecting foreign-born persons has been observed—from 22% of total reported cases in 1986 to 37% in 1996 (9,10). Seven countries of origin (China, Haiti, India, Korea, Mexico, Philippines, and Vietnam) accounted for 66% of the foreign-born cases in 1996.

Global emergence of multidrug-resistant (MDR) strains of *M tuberculosis* in recent years has greatly complicated the management and control of transmission of active cases (11,12). Although relatively few drug resistance surveys have been conducted outside industrialized nations, areas reporting high rates of MDR TB include Nepal (48%); Gujarat, India (33.8%); Bolivia (15.3%); and Korea (14.5%) (12,13). In the United States, MDR TB accounted for 1.6% of all cases with susceptibility testing results (90% of total reported cases) reported to the CDC in 1996 (14). In this CDC survey, which extended from 1993 to 1996, MDR TB cases were documented from 42 states and the District of Columbia; New York City reported 38% of all cases. Risk factors associated with drug resistance included history of TB, foreign country of birth, and co-infection with HIV (14).



a. **b.**

Figure 1. Sputum culture–positive TB in an 82-year-old Asian woman. **(a)** Close-up radiographic view of right upper lobe shows an ill-defined area of increased opacity (arrow) associated with calcification in the retroclavicular region. **(b)** Corresponding thin-section CT scan obtained with 1-mm collimation shows nodular opacities containing foci of calcification (arrows) in the apical segment. The remainder of the thoracic CT study (not shown) obtained at 7 mm collimation revealed no other abnormalities that could account for the positive culture.

PATHOGENESIS

M tuberculosis, the infectious agent of TB, is a thin, slightly curved bacillus that is an obligate aerobe. In comparison to other bacteria, *M tuberculosis* has a cell wall with a very high lipid content that resists staining by the usual Gram method. However, it accepts basic fuchsin dyes and is not easily discolorized even with acid-alcohol; this resistance to decolorization by acid-alcohol is termed acid-fast. As this property is shared only by members of the mycobacterial family and a few other organisms (*Nocardia*, *Rhodococcus*, and *Corynebacterium* species), it forms the basis for the simple, rapid, and relatively specific traditional technique of identification by means of an acid-fast smear (15).

M tuberculosis is transmitted via airborne droplet nuclei that are produced when persons with pulmonary or laryngeal TB cough, sneeze, speak, or sing (16). The particles, which measure 1–5 μm in size, can be kept airborne by normal air currents for prolonged periods of time, resulting in dispersion throughout a room or building. The presence of acid-fast bacilli in the sputum smear is the main indicator of potential for transmission (17); other source patient characteristics that increase the probability of transmission include positive sputum culture for *M tuberculosis*, presence of cavitation on the chest radiograph, presence of TB laryngitis, and high-volume and watery respiratory secretions (17).

Infection occurs when a susceptible person inhales droplet nuclei that contain tubercle bacilli. As the distribution of inhaled droplet nuclei is determined by the ventilatory pattern and volumes of the various lung lobes, the site of implantation preferentially occurs in the middle and lower lung zones, although any lobe may be affected (18,19). Once lodged in the alveolus, *M tuberculosis* is ingested by alveolar macrophages. Resistance to establishment of tuberculous infection is known to be under genetic control (20), and the course of infection depends on the interaction between the inherent microbicidal power of the alveolar macrophage and the virulence of the ingested bacillus (21). If the alveolar macrophage cannot destroy or inhibit *M tuberculosis*, the bacilli multiply within its intracellular environment, causing the host macrophage or its progeny to burst. The cycle continues as released bacilli are ingested by other alveolar macrophages and monocytes are recruited from the blood. During this period of rapid growth, tubercle bacilli are spread through lymphatic channels to regional hilar and mediastinal lymph nodes and through the bloodstream to more distant sites in the body. The logarithmic phase of bacillary growth is arrested with the development of cell-mediated immunity and delayed-type hypersensitivity at 2–10 weeks after the initial infection (21,22).

Development of specific immunity is usually adequate to limit further multiplication of the bacilli; the host remains asymptomatic; and the lesions heal (22). Some of the bacilli remain dormant and viable for many years, and this condition—referred to as latent TB infection—may be detectable only by means of a positive purified protein derivative tuberculin skin test or radiologically identifiable calcification at the site of the primary lung infection or in regional lymph nodes (1,16). In approximately 5% of infected individuals, immunity is inadequate and clinically active disease develops within 1 year of infection (22); in another 5% of the infected population, endogenous reactivation of latent infection occurs remote from time of initial infection (22).

Co-infection with HIV and *M tuberculosis* is the strongest known risk factor for both immediate and delayed progression from infection to active TB (23). The risk of progression to disease for co-infected persons is 5%–10% per year compared with a 5%–10% lifetime risk for HIV-negative persons (24,25). Other known risk factors for development of active TB include conditions that are associated with defects in T-lymphocyte and/or macrophage function, such as malnutrition, drug and alcohol abuse, coexistent medi-

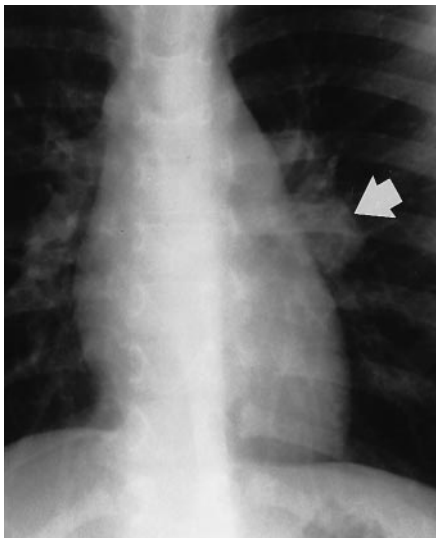


Figure 2. Chest radiograph obtained in a 4-year-old girl shows isolated left hilar lymphadenopathy (arrow) without associated parenchymal involvement.

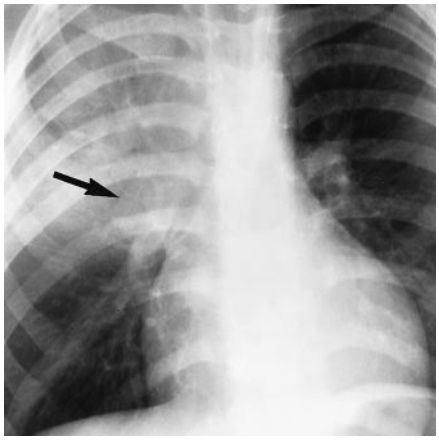


Figure 3. Chest radiograph obtained in a 4-year-old boy shows right hilar lymphadenopathy (arrow) associated with right upper lobe consolidation. Right paratracheal lymphadenopathy (not shown) was also present.

cal conditions (eg, chronic renal failure, diabetes mellitus, silicosis, jejunoileal bypass, and subtotal gastrectomy), and corticosteroid or other immunosuppressive therapy (16,26).

Postprimary TB occurs in a person who has previously been infected and has retained a degree of acquired immunity; it can result from endogenous reactivation or, less commonly, exogenous reinfection (27). Although delayed progression of latent infection may occur at any seeded site in the body, lung foci account for the majority of cases (22). Predilection of postprimary disease to involve the

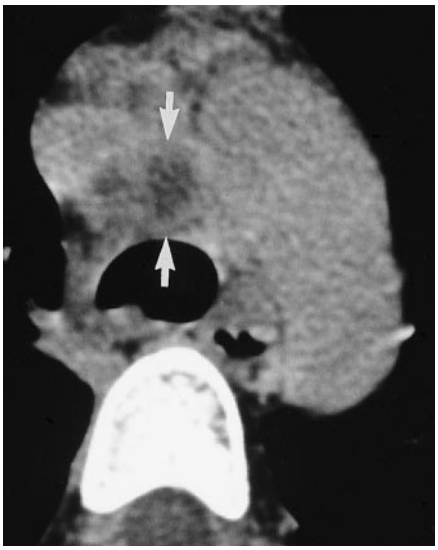


Figure 4. Delayed thin-section CT scan obtained with 1-mm collimation after administration of intravenous contrast material in a 29-year-old Asian woman shows typical appearance of tuberculous lymphadenitis with central low attenuation and peripheral rim enhancement (arrows).

upper lung zones is likely due to a combination of factors including the relatively higher oxygen tension and impaired lymphatic drainage in this region (19,28).

Local control and resolution of pulmonary TB is always accompanied by some destruction of involved tissues (19). While cell-mediated immunity controls TB by activating macrophages to kill ingested bacilli, delayed-type hypersensitivity causes caseous necrosis that results in killing of bacilli-laden macrophages at the expense of destruction of nearby tissues (21). In primary and postprimary disease, the extent of necrosis and cavitation is dependent on the relative efficacy of each of these two immunologic processes in inhibiting multiplication of *M tuberculosis*. Progressive primary TB refers to local progression of parenchymal disease with development of cavitation (at the site of initial infection or hematogenously seeded foci); this progression occurs in a small percentage of patients with primary disease and is similar in morphology and course to postprimary disease (19). Healing of TB occurs with resorption of caseous material accompanied by deposition of collagen (fibrosis) (29). Dystrophic calcification occurs commonly at sites of caseous necrosis but is not a reliable marker for lesion sterility (19,29). Viable tubercle bacilli may persist, and in the preantibiotic era, *M tuberculosis* could be grown from up to 20% of calcified lesions at autopsy (19).

Endobronchial TB, defined as infection of the tracheobronchial tree as documented by microbiologic and histopathologic proof, usually occurs in association with pulmonary involvement and is believed to result most commonly from the implantation of organisms from infected sputum in persons with cavitary (progressive primary and postprimary) disease (30,31). In the absence of parenchymal cavitation, possible sources include direct extension from adjacent parenchymal infection, lymph node erosion, hematogenous spread, and extension to the peribronchial region via lymphatic drainage (31). Airway lesions typically evolve from submucosal sites of infection associated with ulceration to hyperplastic inflammatory polyps that eventually heal by fibrosis and result in circumferential stenosis (30,31).

Pleural involvement may occur at any time after the initial infection. In primary TB, effusions typically develop 3–6 months after infection (32) and are believed to result from a hypersensitivity response to a small amount of tuberculoprotein released into the pleural space (22,33). Because of the paucity of organisms, pleural fluid will yield positive cultures in only 20%–40% of cases; a single closed needle biopsy of the pleura substantially increases the diagnostic yield to approximately 65%–75% (33). Pleural effusions are less commonly a manifestation of postprimary disease in which a large number of organisms are spilled into the pleural space from rupture of a cavity or adjacent parenchymal focus. In true empyemas, acid-fast smears and mycobacterial cultures are usually positive (33).

Miliary spread of TB may also occur during either primary or postprimary stages of disease. It results when a focal collection of tubercle bacilli discharges into a blood or lymph vessel, releasing a large number of viable bacilli that embolize to capillary beds in multiple organs (34). The lung is the most commonly involved organ (34). Because sputum contains acid-fast bacilli in the minority of cases, bronchoscopy with transbronchial biopsy is often necessary for diagnosis (34,35).

CLINICAL SIGNS AND SYMPTOMS

The clinical signs and symptoms of pulmonary TB in an infected adult are often nonspecific; complete absence of symptoms occurs in approximately 5% of active adult cases (36). Systemic manifestations include low-grade fever, anorexia,

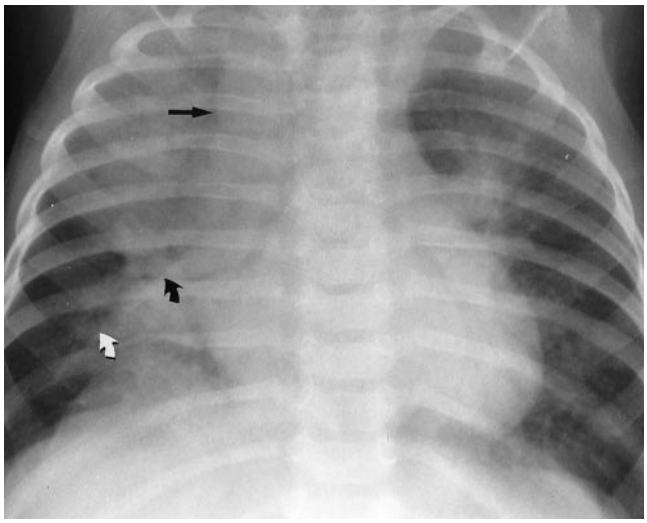


Figure 5. Chest radiograph obtained in a 7-month-old Hispanic boy shows right paratracheal lymphadenopathy (straight arrow) with multilobar consolidation predominating in the right lung. Moderate right lower lobe atelectasis with inferior displacement of major fissure (curved arrows) is associated. Right hilar lymphadenopathy (not shown) was also present.

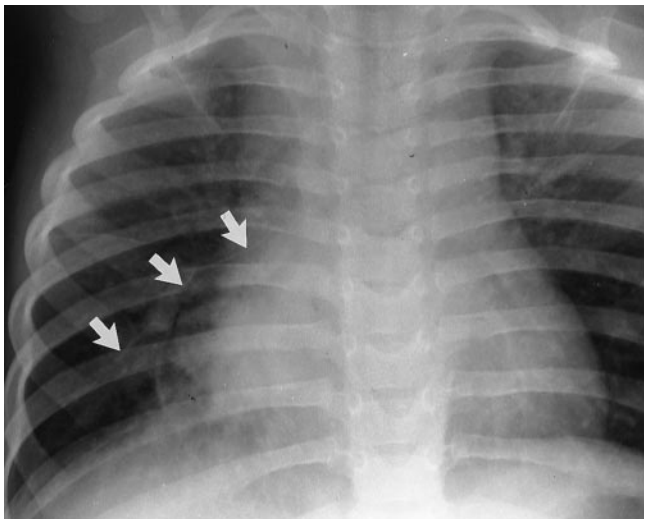


Figure 6. Chest radiograph obtained in a 3-year-old Hispanic boy shows mediastinal and right hilar lymphadenopathy. Atelectasis of the right lower lobe is present with depression of the major fissure (arrows).

fatigue, night sweats, and weight loss that may persist for weeks to months (22). Erythema nodosum may occur with the acute onset of TB and typically manifests at the time of development of specific immunity (22,32). The most common hematologic manifestations associated with TB are raised peripheral blood leukocyte count and anemia, each of which occurs in approximately 10% of patients (33). Hyponatremia, caused by production of an antidiuretic hormonelike substance within affected lung tissue, may occur in up to 11% of patients (37).

Cough is the most frequent symptom referable to the site of lung infection (22,33). Early in the disease, it may be nonproductive, but subsequently there usually is production of mucoid or mucopurulent sputum. Hemoptysis may also occur. Inflammation adjacent to a pleural surface can cause pleuritic chest pain; dyspnea is unusual unless extensive lung involvement is present. Rarely, patients with miliary disease may present with symptoms of respiratory failure (38).

Specific clinical manifestations of TB are influenced by the age and immune status of the infected person (32,33). Congenital TB is a rare entity associated with high mortality rates, partly because the correct diagnosis is often missed (39). Clinical presentation is similar to that caused by bacterial sepsis and other congenital infections; the most common signs are fever, failure to thrive, lymphadenopathy, hepatomegaly, and splenomegaly (39,40).

Up to 60% of children with pulmonary TB are asymptomatic and found solely through contact investigation (41). Because of the narrower diameter of their airways, younger children are more likely to have respiratory symptoms, which include cough and wheezing or rales over the involved region (42,43).

Diagnosis of TB in the elderly (≥65 years of age) is frequently delayed (44,45). In comparison to younger adults, the elderly are less likely to present with classic symptoms of cough, hemoptysis, fever, and night sweats (36). A cryptic presentation—fever of unknown origin often accompanied by pancytopenia or leukemoid reaction—is particularly common because of the greater frequency of hematogenous dissemination in this age group (36,45).

The clinical features of TB in HIV-infected persons are dependent on the severity of their immunosuppression (46,47). Persons with relatively intact cellular immune function present with symptoms similar to the non–HIV-infected individuals, and TB generally remains localized to the lung. In persons with advanced HIV disease (CD4 T-lymphocyte count, $<200/mm^3$), pulmonary TB is often accompanied by extrapulmonary involvement, which most commonly takes the form of lymphadenitis or miliary disease (23,48). Depending on the sites of involvement, systemic or localized symptoms may predominate.

RADIOLOGY

Radiographic Screening

The purpose of screening chest radiographs is to identify persons with active TB (16). Although radiography is often used in conjunction with tuberculin skin testing, it is the initial screening method of choice when tuberculin skin test results may be unreliable, when reading of the skin test may be impractical, and/or when the risks of transmission of an undiagnosed case are high as occurs in institutional settings (jails, hospitals, long-term care facilities) (17).

Because of the considerable morbidity and mortality associated with congenital and perinatal transmission of TB, the CDC recommends that pregnant women in high-risk groups or from areas with a high prevalence of both HIV infection and TB undergo screening. In a pregnant woman with a positive tuberculin skin test, a chest radiograph with shielding of the abdomen should be performed after the 12th week of gestation (49); radiographic evaluation should be performed earlier if the woman has symptoms suggestive of pulmonary TB (49).

Radiographic screening for active TB in high-risk populations may demonstrate findings consistent with prior and/or current infection. A Ghon focus refers to the initial site of parenchymal involvement at the time of first infection; a Ranke complex is the combination of a Ghon focus and enlarged or calcified lymph

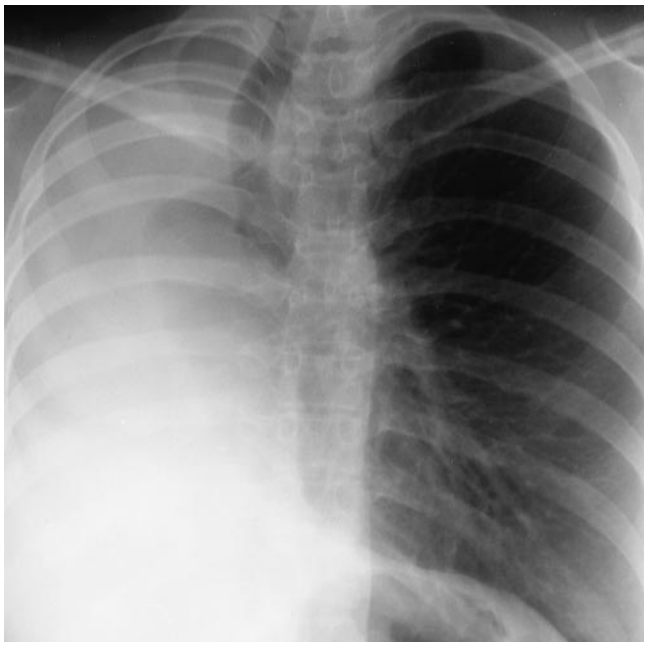


Figure 7. Chest radiograph obtained in a 25-year-old Asian woman shows volume loss of the right lung with mediastinal shift to right. At bronchoscopy, severe stenosis of right main and upper lobe bronchi was identified.

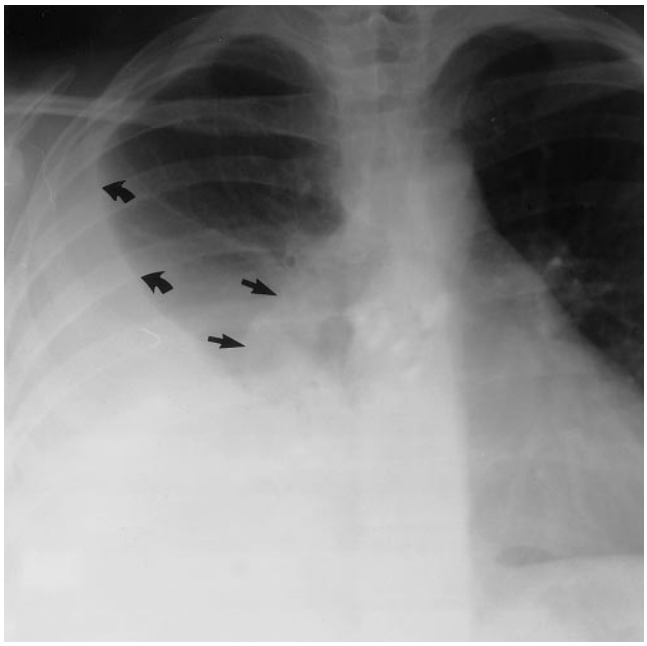


Figure 8. Chest radiograph obtained in a 19-year-old woman shows a large right-sided pleural effusion (curved arrows) associated with right hilar lymphadenopathy (straight arrows).

nodes; and Simon foci are apical nodules that are often calcified and result from hematogenous seeding at the time of initial infection (19).

According to a joint statement issued by the American Thoracic Society and the CDC (22), persons infected with *M tuberculosis*, as evidenced by a positive tuberculin skin test, should be classified on the basis of clinical, bacteriologic, and radiographic evaluation into one of the three following categories: (*a*) TB infection, no disease; (*b*) TB infection, clinically active; and (*c*) TB infection, clinically inactive. A normal chest radiograph has a high negative predictive value for the presence of active TB. However, the frequency of false-negative examinations is approximately 1% in the adult immunocompetent population (36,50) and increases to 7%–15% in HIV-seropositive individuals (51–53).

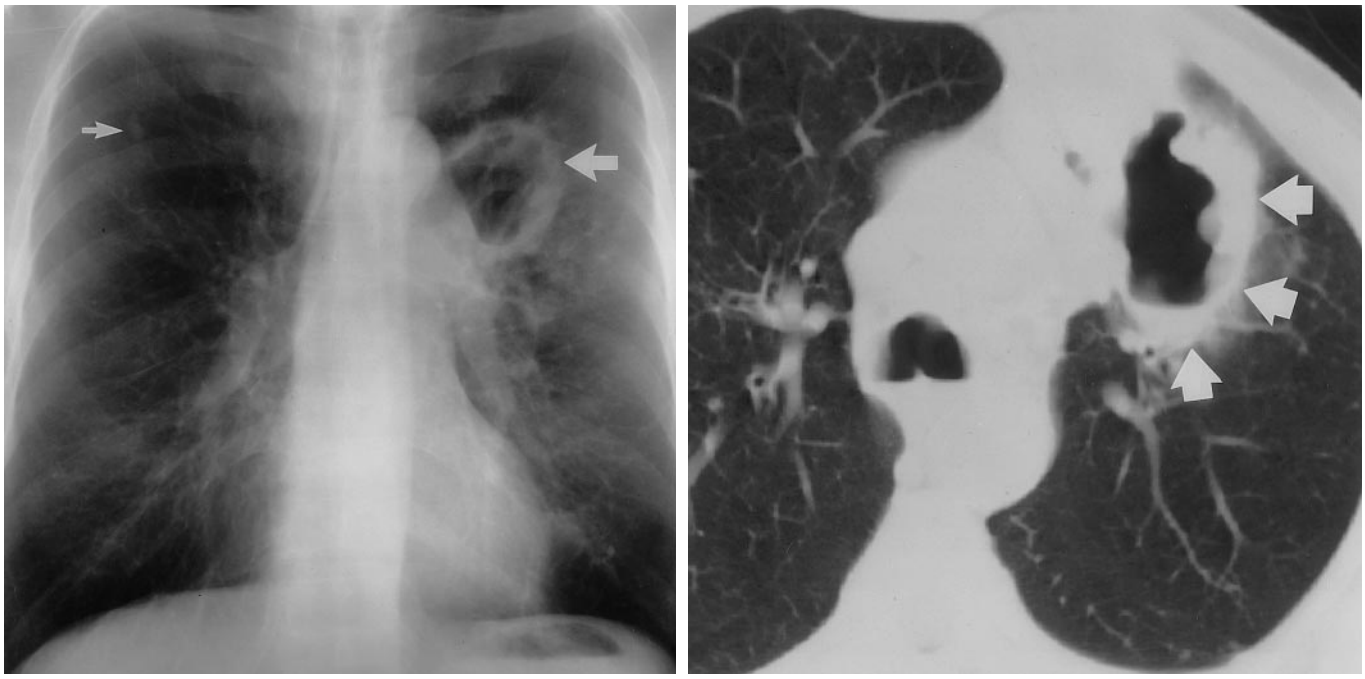
On a single screening chest radiograph, detection of any abnormality—parenchymal, nodal, or pleural—with or without associated calcification, should result in an interpretation of indeterminate disease activity (54,55) (Fig 1). Radiographic differentiation between active and inactive disease can only be reliably made on the basis of temporal evolution (22,56,57). Lack of radiographic change over a 4- to 6-month interval generally indicates inactive disease (22,56). However, because even long-term stability of radiographic findings may occasionally be associated with culture-positive disease, Miller and MacGregor (56) emphasize that such findings should be described as ''radiographically stable'' rather than ''inactive.''

Disease Manifestations

Radiologic manifestations of pulmonary TB are dependent on several host factors, including prior exposure to TB, age, and underlying immune status. In persons with normal immune function, radiologic manifestations can be logically categorized into the two distinct forms of primary and postprimary disease that develop in individuals without and with prior exposure and acquired specific immunity.

Primary disease.—Lymphadenopathy is the radiologic hallmark of primary TB (Fig 2). While enlarged nodes occur in 83%–96% of pediatric cases (58–60), the prevalence of lymphadenopathy decreases with increasing age (59). In a retrospective study of 191 children with TB, Leung et al (59) found that children 0–3 years of age (63 of 63 [100%]) had a significantly ($P < .01$) higher prevalence of lymphadenopathy than that of children 4–15 years of age (112 of 128 [88%]). This age-related trend appears to continue into adulthood during which a much lower frequency of lymphadenopathy has been reported, ranging from 43% (16 of 37) in a series (5) composed primarily of young adults under 35 years of age to 10% (10 of 103) in an older population of median age in the 6th decade (61).

The right paratracheal and hilar stations (Fig 3) are the most common sites of nodal involvement in primary TB, although any combination, including bilateral hilar or isolated mediastinal lymphadenopathy, may also occur (59,60,62). On contrast material–enhanced computed tomographic (CT) scans, mediastinal tuberculous lymphadenitis, particularly when nodal size exceeds 2 cm in diameter, may have a characteristic appearance consisting of central areas of low attenuation associated with peripheral rim enhancement and obliteration of surrounding perinodal fat (60,62) (Fig 4). With CT-histologic correlation, excised nodes exhibiting this pattern of enhancement have been found to contain complete central necrosis in association with a highly vascular, inflammatory, capsular and perinodal reaction (63). Although Im and colleagues (62) have suggested that this pattern of nodal enhancement is sufficiently characteristic to support a diagnosis of TB in younger patients, confirmation is necessary because similar findings may also be caused by atypical mycobacterial infection (64); lymphoma (62); metastases, particularly from testicular carci-



a. **b.**

Figure 9. Atypical distribution of postprimary TB in a 62-year-old man. **(a)** Chest radiograph shows a 5-cm cavitary mass with a thick, irregular wall (large arrow) and surrounding adjacent nodular opacities in the left upper lobe. An ill-defined 5-mm nodule (small arrow) is present in the contralateral, right upper lobe. **(b)** CT scan obtained with 7-mm collimation shows the location of the cavitary mass (arrows) in the anterior segment of left upper lobe.

noma (65); and benign conditions such as Whipple and Crohn diseases (63).

Parenchymal opacities occur in association with and affect the same side as nodal enlargement in approximately two-thirds of pediatric cases of primary TB (59). In contrast to the age-related trend observed with lymphadenopathy, Leung et al (59) found that the prevalence of radiographically detectable parenchymal involvement was significantly ($P < .001$) lower in children 0–3 years of age (32 of 63 [51%]) as compared to that in older children (100 of 128 [78%]) in whom the prevalence is similar to the 78%–84% previously reported in adults (5,61). Because of these two opposing age-related trends in frequency of radiographic manifestations, parenchymal involvement in the absence of lymphadenopathy occurs in only approximately 1% of pediatric cases (59), whereas this nonspecific pattern is observed in 38%–81% of adults with primary disease (5,61).

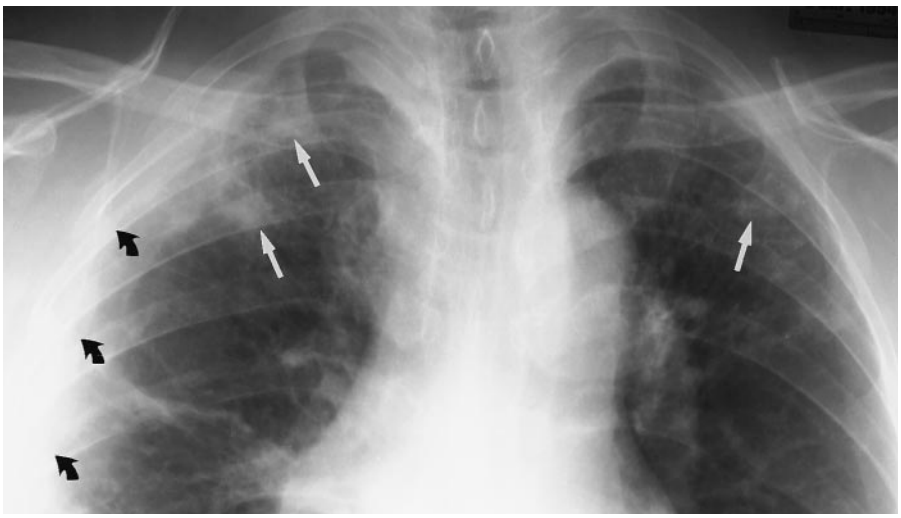


Figure 10. Close-up radiographic view of the upper lung zones in a 56-year-old Hispanic man shows ill-defined parenchymal opacities (white arrows) associated with nodular and linear components in the periphery of the bilateral upper lobes. A loculated right pleural effusion (black arrows) is present.

Parenchymal involvement in primary pulmonary TB most commonly appears as an area of homogeneous consolidation (59,61,66), although patchy, linear (58), nodular (67), and masslike (56,68) forms have also been described. Consolidation typically occurs in a segmental or lobar distribution; multifocal involvement is identified radiographically (Fig 5) in 12%–24% and found at autopsy in 16% of the affected population (18,59,66). There is no consensus as to the most common site of parenchymal involvement in primary TB, with different reports documenting upper (5,58), lower (66), or no regional predominance (59,61). However, a right-sided predominance in the distribution of Ghon foci and Ranke complexes is well recognized (5,58,59,61) and presumably reflects the greater statistical probability of an airborne infection involving the right lung.

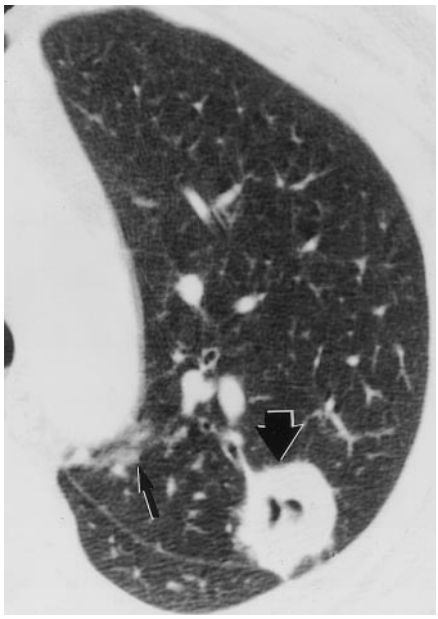


Figure 11. Targeted 1.5-mm-collimation CT scan of the left upper lobe in a 40-year-old woman shows an irregularly marginated, 2-cm tuberculoma (large arrow) demonstrating central cavitation and associated with small, adjacent nodules (small arrow).

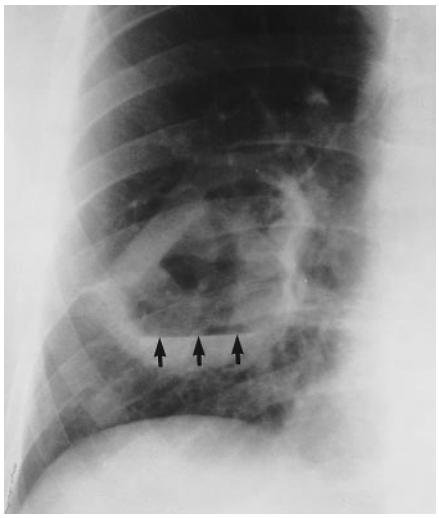


Figure 12. Chest radiograph obtained in a 39-year-old Asian man shows an air-fluid level (arrows) within an 8-cm cavitary mass located in the superior, lateral basal, and posterior basal segments of the right lower lobe.

Obstructive atelectasis and overinflation resulting primarily from compression by adjacent enlarged nodes have been reported to occur in 9%–30% and 1%–5% of children with primary TB, respectively (58,59). Distribution is typically right-sided with obstruction occurring at the level of the lobar bronchus or bronchus intermedius (58) (Fig 6). Extrinsic airway obstruction occurs much less frequently in the adult population because of their larger caliber airways and lower prevalence of lymphadenopathy. However, airway involvement by endobronchial TB in adults with primary disease may manifest radiologically as atelectasis (Fig 7) and endoluminal or peribronchial masses simulating neoplastic disease (30,68). Consolidation confined to the lower lung zones (69,70) and normal findings (30,69) are other atypical radiographic patterns well documented to be associated with endobronchial TB.

Pleural effusion is an uncommon manifestation of primary TB in infants and young children (<2 years of age) (32). The prevalence of effusion increases with age and is reported to be 6%–11% in children (58,59) and 29%–38% in adults (5,61). A pleural effusion usually develops on the same side as the site of initial tuberculous infection and is typically unilateral (32) (Fig 8). Bilateral effusions occur in 12%–18% of cases with pleural involvement (59,61,66). Although usually observed in association with parenchymal and/or nodal abnormalities, pleural effusion is the only radiographic finding indicative of the presence of primary TB in approximately 5% of adult cases (61).

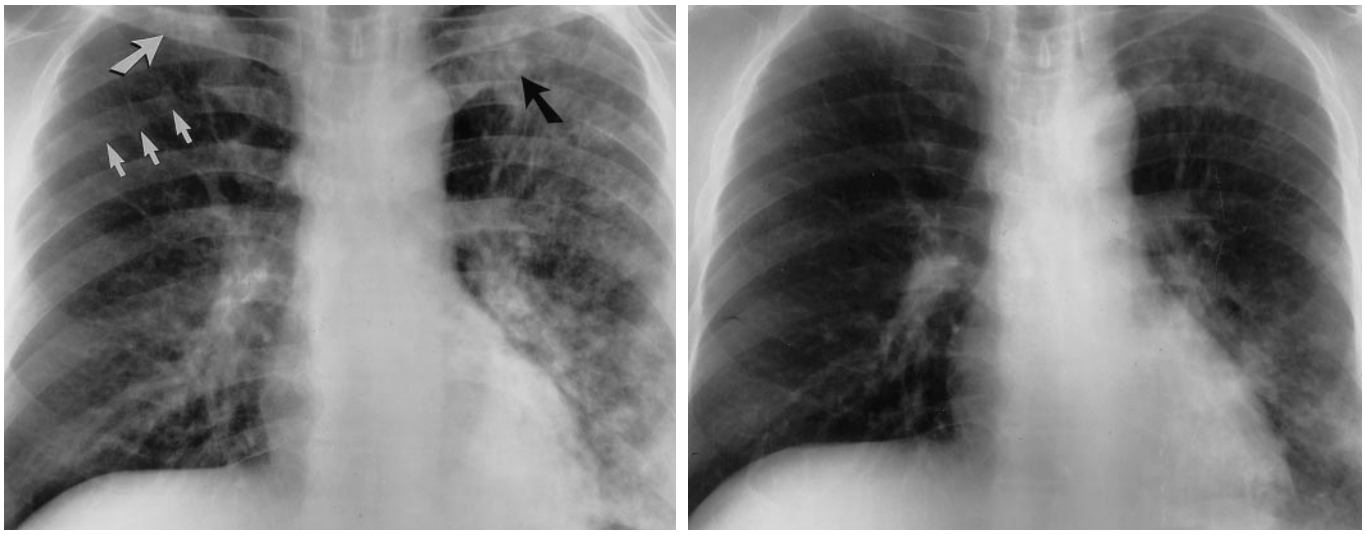
Postprimary disease.—Parenchymal opacities situated in the apical and posterior segments of the upper lobes and the superior segment of the lower lobes, often associated with cavitation, are the characteristic radiographic manifestations of postprimary TB. In two large series consisting of 204 and 500 affected persons, the sites of cavitary disease were found to involve the apical and/or posterior segments of the upper lobes in 83%–85% and the superior segments of the lower lobes in 11%–14% (71,72). Parenchymal involvement occurs in more than one segment in the majority of cases (66,73); although parenchymal disease outside of typical locations is common, this distribution is usually observed in association with concomitant abnormalities in characteristic sites (50,66). An atypical distribution of disease with parenchymal opacities isolated to the anterior segment of the upper lobes or basilar segments of the lower lobes has been reported to occur in approximately 5% of cases of postprimary TB (66,72,74) (Fig 9). Prior reports (45,70,75,76) suggesting that patients with diabetes mellitus and the elderly are predisposed to atypical distributions of postprimary disease have not been confirmed with subsequent case-control studies (36,73,77).

Parenchymal involvement in postprimary TB most commonly manifests radiographically as heterogeneous opacities. In the early stages, an ill-defined area of increased opacity often associated with nodular and linear components is observed radiating outward from the hilum or in the periphery of the lung (55,56) (Fig 10). With disease progression, additional opacities develop that may coalesce and are sometimes seen in association with distortion of adjacent bronchovascular and mediastinal structures (55,56). In 3%–6% of cases of postprimary disease, tuberculomas (defined as round or oval, sharply marginated lesions usually measuring between 0.5–4.0 cm) are the predominant parenchymal manifestation (56,57,74). Tuberculomas are typically solitary but may be multiple (67), have regular or irregular margins (57), and often demonstrate calcification as well as proximity to adjacent small ''satellite'' nodules (57,67) (Fig 11).

Cavitation in single or multiple sites is evident radiographically in 40%–45% of cases of postprimary TB (66,78). Walls of cavities may range from thin and smooth to thick and nodular (66,78); air-fluid levels have been reported to occur in 9%–21% of tuberculous cavities (66,78) (Fig 12). Bronchogenic spread of disease occurs when an area of caseous necrosis liquefies and communicates with the bronchial tree. Radiographically, bronchogenic spread is identified in approximately 20% of cases of postprimary TB (50) and manifests as multiple, ill-defined, 5- to 10-mm nodules distributed in a segmental or lobar distribution, distant from the site of cavity formation and typically involving the lower (dependent) lung zones (50,79,80) (Fig 13).

On CT scans, bronchogenic spread of infection can be identified in 95% of persons with postprimary TB (79,81). According to Im and colleagues (79,82), the most common thin-section CT findings of early bronchogenic spread are 2- to 4-mm centrilobular nodules and sharply, marginated linear branching opacities (Fig 14) which, with thin-section CT–pathologic correlation, have been shown to represent caseous necrosis within and around terminal and respiratory bronchioles (82,83). Other thin-section CT findings, in decreasing order of frequency, include 5- to 8-mm poorly defined nodules, lobular consolidation, and interlobular septal thickening (82).

Endobronchial involvement occurs in approximately 2%–4% of persons with pulmonary TB (30,68); main, upper, and lower lobe bronchi account for three-



a. **b.**

Figure 13. Postprimary pattern of TB in a 54-year-old Hispanic man. **(a)** Radiograph obtained at presentation shows focal areas of confluent consolidation (large arrows) in the bilateral upper lobes. In the right lung, multiple ill-defined, 5–8-mm nodules (small arrows) can be identified; in the more severely affected left lung, a bronchopneumonia pattern is present predominating in the lower lobe. **(b)** Radiograph obtained 3 months after initiation of treatment shows that improvement has occurred, with resolution of right lung nodules. Reticulonodular opacities persist in bilateral upper and left lower lung zones.

quarters of the involved sites (68). Associated parenchymal opacities predominating in the upper lobes and segmental or lobar atelectasis are radiographically apparent in 65%–75% and 18%–25% of cases, respectively (30,68). On CT scans, endobronchial TB typically manifests as irregular or smooth circumferential bronchial narrowing associated with mural thickening (84,85) (Fig 15).

Hilar and mediastinal lymphadenopathy are uncommon manifestations of postprimary TB and occur in only approximately 5% of cases (66). Tuberculous pleural effusion, although usually regarded as a manifestation of primary disease, may occur in association with postprimary disease in up to 19% of detected cases (86). Pleural effusion is observed radiographically in 16%–18% of persons with postprimary TB and is typically unilateral in distribution (66,74,86). Although parenchymal abnormalities in characteristic locations are common associated findings, the ruptured parenchymal focus may be radiographically occult (87) (Fig 16a). Occasionally, an air-fluid level may be demonstrable within the pleural cavity, indicating the presence of a bronchopleural fistula (66,74). Contrast-enhanced CT evaluation of postprimary tuberculous effusions typically reveals smooth thickening of visceral and parietal pleural surfaces separated by a variable amount of fluid—the ''split pleura'' sign (88,89) (Fig 16b). Tuberculous effusions are typically loculated and may be stable in size for years; detection of persistent fluid within a calcified fibrothorax at CT should raise concern for active disease and chronic tuberculous empyema (87,90).

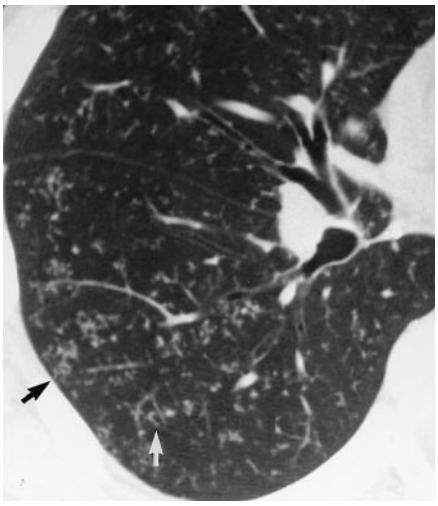


Figure 14. Thin-section CT scan obtained with 1-mm collimation in a 26-year-old Hispanic man shows multiple 2–4-mm centrilobular nodules and linear, branching opacities (arrows) in the superior segment of right lower lobe.

Radiographic evidence of the original primary infection in the form of calcified lymph nodes and nodules and/or upper lobe fibrotic changes is found in approxi-

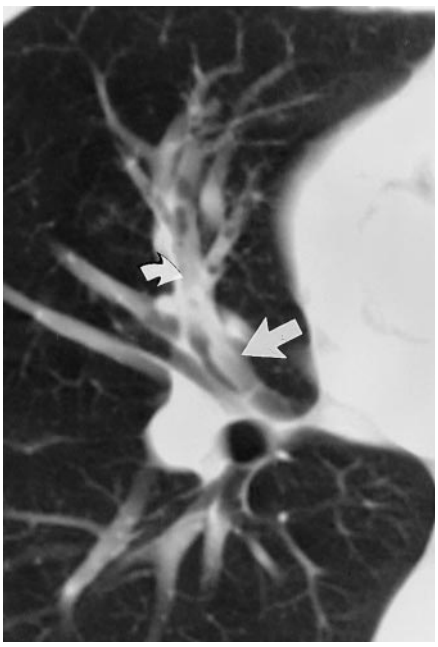
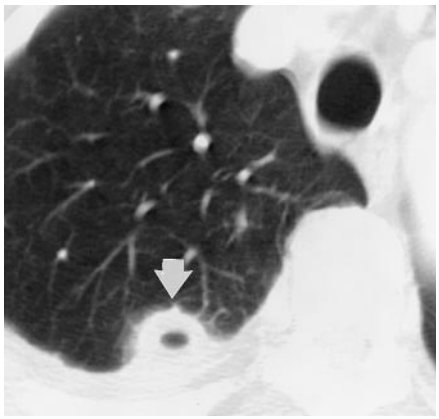
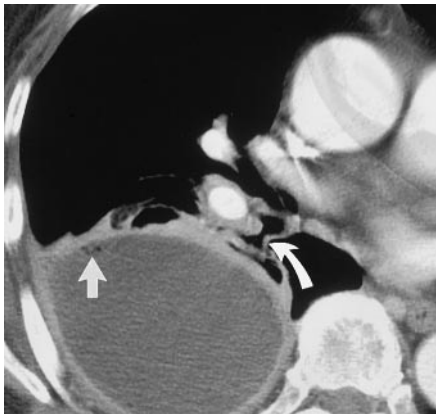


Figure 15. CT scan obtained with 8-mm collimation in a 41-year-old man shows eccentric mural thickening (straight arrow) involving the proximal aspect of the medial segmental bronchus of the right middle lobe associated with endobronchial secretions (curved arrow) more distally. The patient's symptoms at presentation were a mild, nonproductive cough with right-sided wheezing. Bronchial biopsy specimens contained areas of necrotizing granulomatous inflammation from which *M tuberculosis* was grown on culture.



a.



b.

Figure 16. Tuberculous empyema in a 77-year-old Asian man. **(a)** Seven-millimeter-collimation CT scan of the right upper lobe shows a 2-cm nodule (arrow) with central cavitation in the posterior subpleural region that was not detected at radiography. **(b)** Seven-millimeter-collimation contrast-enhanced CT scan obtained at the level of the superior segmental bronchus (curved arrow) shows a roughly elliptical fluid collection bordered by thickened and enhancing visceral and parietal pleura. The small amount of air (straight arrow) seen in the nondependent region indicates the presence of a bronchopleural fistula.

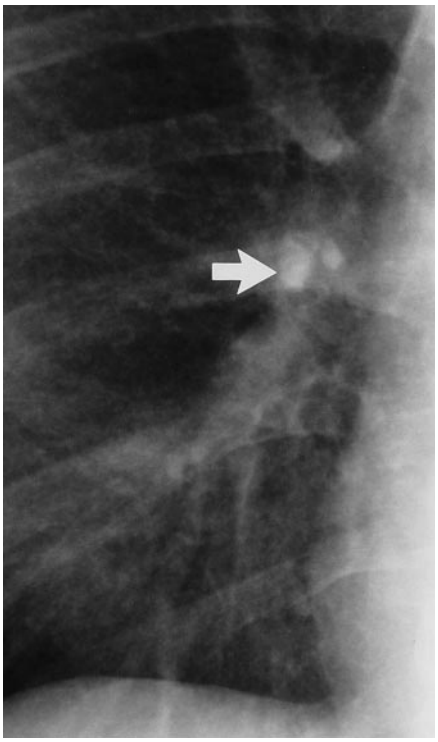


Figure 17. Close-up radiographic view of the right lung of a 35-year-old HIV-seropositive man shows innumerable, 1–3-mm nodules scattered diffusely through the lung parenchyma, with associated calcified right hilar nodes (arrow).

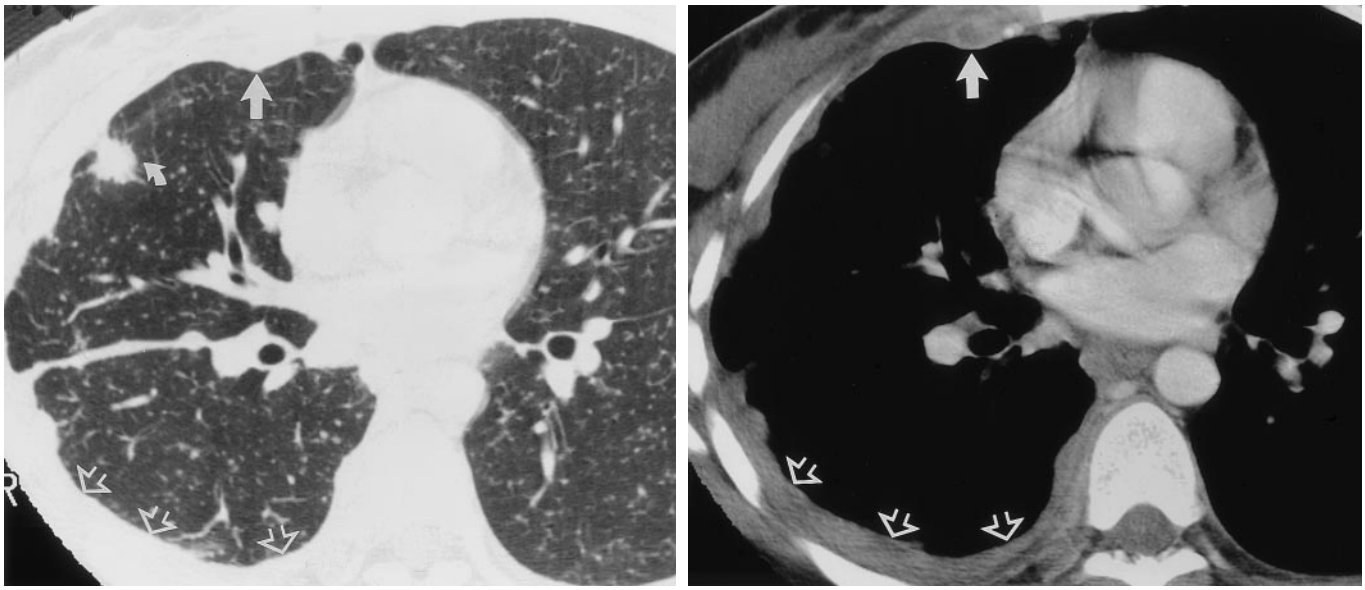
mately 20%–40% of individuals with active, postprimary disease (66,74). Because architectural distortion (fibrosis) and calcification are features found in both healed and active disease, radiographic determination of disease status based on their presence is unreliable (54,55,74) (Fig 1).

The utility of CT in the differentiation of active from inactive TB has been investigated in two case-control studies (81,91). In the larger study by Lee et al (91), thin-section CT findings identified in 89 patients with active disease included centrilobular branching linear opacities (92%), lobular consolidation (62%), acinar nodule (61%), cavity (36%), and ground-glass attenuation (35%). These same findings were also observed in 95%, 35%, 47%, 22%, and 22% of the 57 patients with inactive disease, respectively (91). On the basis of a constellation of findings, these investigators accurately diagnosed active and inactive disease in 80% and 89% of cases, respectively (91). A lesser overlap of thin-section CT findings was observed in the study by Hatipoglu and colleagues (81); centrilobular nodules, tree-in-bud appearance, nodules 5–8 mm in diameter, and consolidation were found in 91%, 71%, 69%, and 14%, respectively, of 32 patients with active disease and in none of 34 patients with inactive disease. The results of these two studies suggest that although CT evaluation may be helpful in determination of disease activity in some patients, definitive diagnosis still requires isolation and identification of *M tuberculosis* in clinical specimens.

Miliary disease.—The characteristic radiographic findings of miliary TB consist of innumerable, 1–3-mm, noncalcified nodules scattered throughout both lungs, with mild basilar predominance (92) (Fig 17). Associated radiographic findings that may suggest the diagnosis of TB are present in up to 30% of affected persons and include consolidation, cavitation, calcified lymph nodes, and lymphadenopathy (92). Normal radiographic findings in the early stages of disease are well recognized and occur in 25%–40% of persons at initial presentation (92–94); typical miliary lesions may not be visible until 3–6 weeks after hematogenous dissemination (94). Rarely, a diffuse alveolar pattern is observed in patients with associated adult respiratory distress syndrome (95). CT can demonstrate miliary disease before it becomes radiographically apparent (96,97). At thin-section CT, a mixture of both sharply and poorly defined, 1–4-mm nodules are seen in a diffuse, random distribution often associated with intra- and interlobular septal thickening (97,98) (Fig 18).

TB in acquired immunodeficiency syndrome.—The radiographic manifestations of HIV-associated pulmonary TB are dependent on the level of immunosuppression at the time of overt disease (99–101). Persons with relatively intact cellular immune function demonstrate radiographic findings similar to those of non–HIV-infected individuals (47). At severe levels of immunosuppression, 10%–20% of co-infected persons have normal radiographs (51,52,100) or demonstrate findings usually associated with primary disease, regardless of prior TB exposure status (46,102) (Fig 19). In a prospective multicenter study that included 128 HIV-seropositive patients with TB in whom both chest radiographs and CD4 T-lymphocyte data were available, a significantly higher prevalence ($P = .01$) of mediastinal and/or hilar lymphadenopathy and a lower prevalence ($P = .08$) of cavitation were identified in 98 patients with a CD4 T-lymphocyte count of less than 200/mm^3 as compared to 30 patients with a CD4 T-lymphocyte count equal to or greater than 200/mm^3 (100). A miliary pattern of disease has also been reported to be associated with severe immunosuppression (46,51,103) (Fig 17).

CT evaluation of pulmonary TB in HIV-seropositive persons with normal radiographs usually demonstrates subtle abnormalities (51). In six patients with normal radiographs drawn from a series of 42 co-infected individuals, Leung et al (51) identified three patterns of disease on CT scans; these patterns consisted of multiple nodules ($n = 3$, two miliary and one endobronchial), tuberculoma ($n = 2$, 5 and 10 mm); and lymphadenopathy ($n = 1$, right paratracheal, hilar, and subcarinal stations). CT evaluation demonstrates



a. b.

Figure 18. Miliary tuberculosis in a 27-year-old Asian woman. Thin-section CT scans obtained at 1-mm collimation and displayed at **(a)** lung and **(b)** mediastinal windows show innumerable, sharply marginated, 1–2-mm nodules in a diffuse and random distribution. The associated findings, which include an irregularly marginated right middle lobe tuberculoma (curved arrow), loculated right pleural effusion (open arrows), and internal mammary lymphadenopathy (straight arrow), suggest that miliary dissemination occurred as a result of primary TB.

mediastinal and/or hilar lymphadenopathy in up to 60%–75% of HIV-seropositive persons with pulmonary TB (51,104). As in the immunocompetent population, Pastores and colleagues (105) reported that tuberculous lymphadenitis in the HIV-seropositive population may also be associated with central low attenuation and peripheral enhancement on contrast-enhanced CT scans.

Response to Treatment

Evaluation of the response of pulmonary TB to antibiotic treatment is best assessed by means of repeated sputum examinations in patients with positive bacteriology (106); radiographic evaluation is of lesser importance, although a baseline radiograph at the completion of treatment may be useful for future comparison purposes (106). In persons with negative pretreatment sputum, radiographic and clinical evaluation become the major indicators of response to therapy and are the most common methods used in children, in whom bacteriologic confirmation is possible in only about one-third of cases (59,106).

Regression of radiographic abnormalities in pulmonary TB is a slow process (55,59) (Fig 13). In the first 3 months of treatment, worsening of radiographic findings consisting of extension of parenchymal involvement and development or enlargement of nodes may be observed in up to one-third of pediatric patients receiving appropriate therapy (59); a similar trend with progression of nodal disease has also been observed in adults with tuberculous lymphadenitis (107). The cause of the disease progression in primary TB is unknown but may be related to the effects of the hypersensitivity reaction that normally occurs 2–10 weeks after initial infection (59). In the majority of patients, parenchymal and nodal abnormalities usually regress in parallel (59). In adults, failure of radiographic findings to improve after 3 months of chemotherapy suggest drug-resistant organisms or a superimposed process (106). Resolution of parenchymal abnormalities has been observed to require from 6 months to 2 years on radiographs (59) and up to 15 months on CT scans (82). Lymphadenopathy may persist for several years after treatment (59,107).

Complications

Bronchiectasis and residual cavities (Fig 20a) are sequelae of pulmonary TB that typically involve the upper lobes and are identifiable in 71%–86% and 12%–22% of persons with prior disease on thin-section CT scans, respectively (19,81,91). An ectatic bronchus or, more commonly, a residual tuberculous cavity may be colonized by *Aspergillus* species; the fungus ball or aspergilloma consists of a cluster of intertwined hyphae matted together with a variable amount of mucus and cellular debris. Hemoptysis is the most clinically important consequence of aspergilloma and occurs in 50%–70% of affected patients, resulting in death in up to 5% (108). Radiographically, an aspergil-

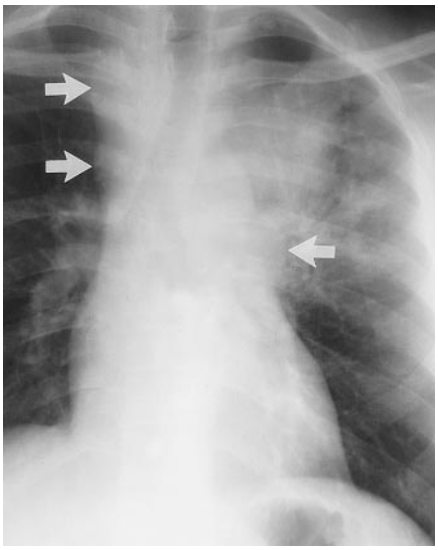


Figure 19. Chest radiograph obtained in a 28-year-old HIV-seropositive man shows consolidation in the left upper lobe associated with mediastinal (double arrows) and left hilar (single arrow) lymphadenopathy.

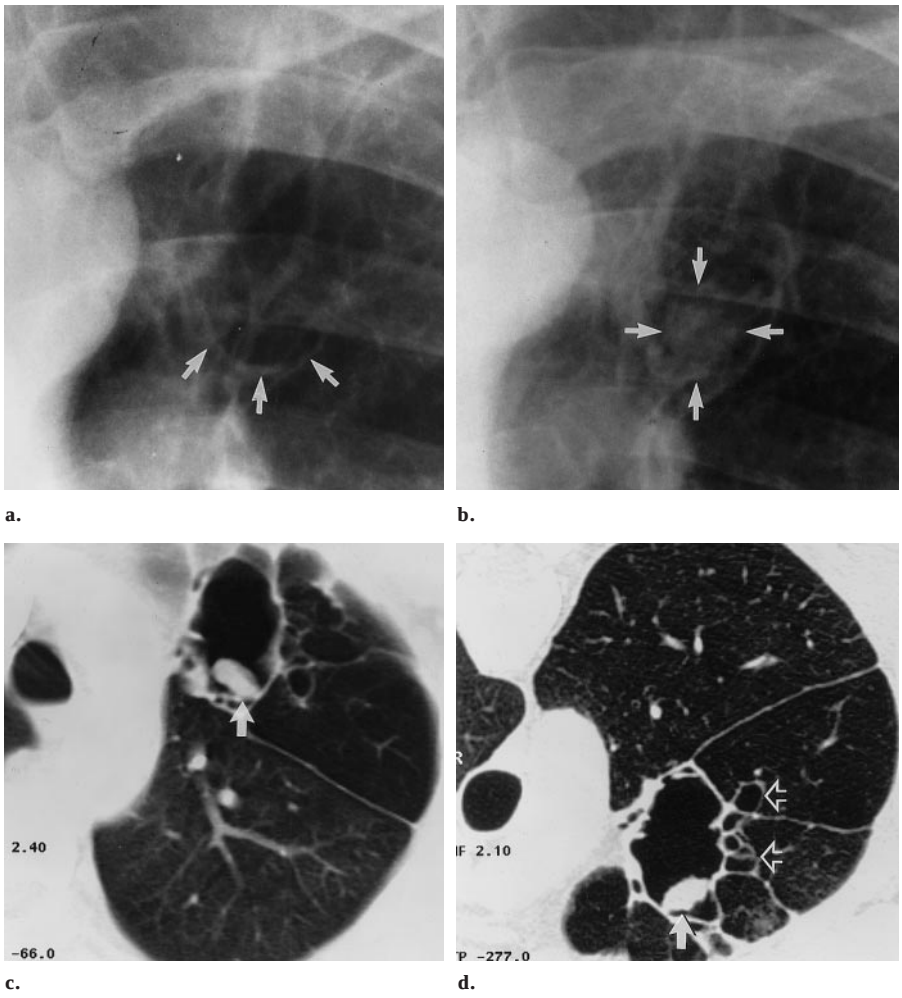


Figure 20. Complications of childhood TB causing recurrent hemoptysis in a young black man. **(a)** Detailed radiographic view obtained when the patient was 28 years old shows a cavity (arrows) in the left upper lobe. **(b)** Eleven years later, detailed radiographic view shows development of a nodule (arrows) in the cavity. **(c, d)** Corresponding 8-mm-collimation, supine and 1-mm-collimation, prone CT scans show the dependency of the mobile fungus ball (solid arrow) relative to patient positioning. Bronchiectasis (open arrows) adjacent to the cavity and atelectasis of the left upper lobe are present.

loma appears as a roughly spherical nodule or mass separated by a crescent-shaped area of decreased opacity from the adjacent cavity wall (108) (Fig 20b). The characteristic CT features consist of a mobile intracavitary nodule or mass that is usually surrounded by air but may completely fill the cavity (109). On prone and supine CT images, the aspergilloma will gravitate to the dependent position (Fig 20c, 20d).

A Rasmussen aneurysm is a pseudoaneurysm of a pulmonary artery caused by erosion from an adjacent tuberculous cavity (110); these pseudoaneurysms are uncommon and may form months to years after formation of the cavity (111). Hemoptysis is the usual presenting symptom, which may be massive (>300 mL/24 hours) and life threatening (111,112). Arterial embolization has been demonstrated as an effective method to achieve primary control of bleeding associated with chronic tuberculous cavities (112, 113).

Broncholithiasis is an uncommon complication of pulmonary TB that is characterized by calcified peribronchial nodes that either erode into or cause considerable distortion of an adjacent bronchus (114). Presenting symptoms may include cough, hemoptysis, wheezing, or evidence of recurrent pneumonia (114). Although any bronchus may be involved, a right-sided predominance has been observed (114). In addition to the presence of calcified peribronchial nodes, radiologic findings may include segmental or lobar atelectasis, obstructive pneumonitis, branching opacities in a ''V'' or ''Y'' configuration (obstructive bronchocele), and rarely, focal hyperinflation (114,115).

OTHER DIAGNOSTIC TESTS

Tuberculin Skin Test

Although neither 100% sensitive nor specific, the tuberculin skin (Mantoux) test remains the best method for detecting infection with *M tuberculosis* (22). In persons with reactive tuberculin tests, the major confounding factors are infection with and hypersensitivity to mycobacteria other than *M tuberculosis* and prior vaccination with bacille Calmette-Guérin (BCG). In general, the larger the reaction, the greater the probability that the reaction represents infection. False-negative tuberculin skin test reactions (anergy) is a problem among debilitated persons and other immunocompromised hosts, particularly those with advanced HIV infection (22). Delayed-type hypersensitivity can be assessed with skin test antigens such as tetanus toxoid or *Candida* species to which most healthy persons in the population are already presensitized; however, the scientific basis for anergy testing is tenuous (116).

The criteria endorsed jointly by the American Thoracic Society and the CDC for use in interpretation of the Mantoux test are intended to increase the likelihood that persons at high risk for TB will be candidates for therapy and that persons having tuberculin reactions not caused by *M tuberculosis* will not receive unnecessary diagnostic evaluation or therapy (116). Induration of 5 mm or greater is classified as positive in persons with recent close contact with a person with active TB, persons with HIV risk factors or proved HIV infection, and persons with radiographic evidence of prior TB. Induration of 10 mm or greater is classified as positive in persons belonging to other well-recognized high-risk groups, which include foreign-born persons who have recently arrived from countries with a high prevalence of TB; high-risk racial or ethnic minority populations; persons with medical conditions reported to increase the risk of active TB; and residents and employees of high-risk congregate settings (prisons and jails, nursing homes, and homeless shelters) (116). Induration of 15 mm or greater is classified as positive in all other persons.

Specimens

The diagnosis of pulmonary TB requires isolation and identification of *M tuberculosis* in a sputum or other clinical specimens. The main diagnostic procedure in persons with a productive cough

consists of smear and culture of three sputum specimens collected on different days. Sputum smears that fail to demonstrate acid-fast bacilli do not exclude the diagnosis of TB; positive acid-fast bacilli smears are found in only approximately 60% of persons with culture-positive sputum (16). This percentage decreases in the HIV-seropositive population because of their lower propensity to develop cavitary disease.

For individuals such as children who are unable to produce sputum (natural or induced), aspiration of gastric contents in the early morning may be performed; however, this method is successful in only 30%–40% of cases of pediatric TB (59). In the absence of a positive culture, the strongest evidence for TB in a child is recent exposure to an adult with active disease (117). The tuberculin skin test and chest radiography may be used to provide supportive information.

Invasive procedures may become necessary when noninvasive methods do not permit a diagnosis. In miliary TB, sputum contains acid-fast bacilli in the minority of cases, and bronchoscopy with transbronchial biopsy is often necessary for diagnosis (34,35). Percutaneous needle biopsy is often indicated when parenchymal involvement occurs in the form of a tuberculoma. In a patient with primary TB, culture of pleural fluid will yield positive cultures in only 20%–40% of cases; a single closed needle biopsy of the pleura substantially increases the diagnostic yield (33). Pleural effusions in patients with postprimary TB are true empyemas, and in this setting, acid-fast smears and mycobacterial cultures are usually positive (33).

Laboratory Identification Methods

Staining and microscopic examination.—The initial step in the laboratory diagnosis of TB is microscopic examination of smears stained by means of an acid-fast procedure. Two types of acid-fast stains are commonly used. The first is a basic fuchsin stain (Ziehl-Neelsen or Kinyoun methods) that when used in combination with light microscopy requires an average examination time of 15 minutes (118). The second and preferred method is use of an auramine-rhodamine fluorochrome stain in combination with fluorescent microscopy. The yellowish fluorescence of this acid-fast stain when taken up by *M tuberculosis* allows faster and more sensitive detection of the bacilli in smears (118).

Cultivation and identification of mycobacteria.—Expeditious diagnosis of TB by isolation of *M tuberculosis* is hampered by the slow growth rate of tubercle bacilli. Standard culture methods with specially developed media such as the Löwenstein-Jensen agar usually require 3–6 weeks for adequate growth to allow identification (119). Radiometric methods represent an important advance in the technology of mycobacterial identification. The most widely used system is BACTEC (Becton Dickson, Sparks, Md), which consists of a growth-optimized broth matrix containing carbon 14–labeled palmitic acid, a substrate that is almost specific for mycobacteria (22,119). The radiolabeled palmitic acid is metabolized by mycobacteria, resulting in release of $^{14}CO_2$, which is quantified to identify presence and growth of the bacteria. The BACTEC system allows detection of *M tuberculosis* growth with a mean detection time of 7–13 days for smear-positive and 14–22 days for smear-negative sputum specimens (119).

Radiometric DNA probes and high-performance liquid chromatography are two methods that allow identification of cultures at the species level in 2–4 hours; each requires 10^7 bacilli for reliable, reproducible results (118). When either of these methods are used in conjunction with a radiometric system for primary culture, detection and identification of *M tuberculosis* in clinical specimens are achievable in about 2 weeks, under the best of circumstances (118,120).

Polymerase chain reaction, or PCR, is the most widely studied of the nucleic acid amplification techniques aimed at direct detection of *M tuberculosis* in clinical specimens without the need for prior culture. Polymerase chain reaction relies on the exponential amplification and subsequent detection of a fragment of DNA that is specific for *M tuberculosis*, by using a thermostable DNA polymerase (119,120). Its acceptance into the clinical setting has been hampered by reports of both false-negative and false-positive reactions caused by the presence of inhibitors and contaminants in samples, respectively (119,120).

Restriction fragment length polymorphism, or RFLP, analysis, also referred to as ''DNA fingerprinting,'' is a molecular biology technique that allows differentiation of unrelated strains of *M tuberculosis* by demonstration of nucleotide sequence differences at selected sites in their DNA genome (120,121). RFLP is a powerful epidemiologic tool that allows study of the patterns of infection within a population, with identification of the points of transmission.

Susceptibility testing.—Because of the widespread emergence of MDR *M tuberculosis*, drug susceptibility testing should be performed on organisms initially isolated in all patients with newly diagnosed TB (106). Testing is repeated if the patient continues to produce culture-positive sputum after 2 months of treatment (106). The direct-drug susceptibility test is performed by inoculating digested, concentrated clinical specimens onto drug-containing culture medium and comparing the growth on this to the growth on non–drug-containing medium. The best method to test susceptibility to first-line antituberculous drugs is by using the BACTEC system, which allows interpretation in as little as 5 days (118).

PREVENTIVE THERAPY AND TREATMENT

Bacille Calmette-Guérin

BCG was derived from a strain of *Mycobacterium bovis* attenuated through years of serial passage in culture at the Pasteur Institute in France. The effectiveness of the BCG vaccine in preventing development of active TB has been shown to vary from 0% to 80% (106). Because the ability of BCG to prevent adult forms of TB remains controversial, it is not recommended for widespread use in the United States, where the risk of infection in the general population is low (17). BCG vaccination may protect infants and young children from more severe forms of TB such as meningitis and miliary disease; in this age group, BCG vaccination is strongly recommended for those who are at high risk of acquiring infection (106).

Chemoprophylaxis

The main purpose of preventive therapy is to prevent latent infection from progressing to active TB. Taken for 6–12 months, preventive therapy with isoniazid is highly effective and can reduce risk of developing active disease by up to 90% (17,26). Because isoniazid is associated with a number of side effects, including hepatitis, recommendations for its use select candidates with positive tuberculin skin test results so as to maximize the benefit and minimize the risk to the individual (26). Patient groups who are recommended to undergo preventive therapy are outlined in a joint statement by the American Thoracic Society and the CDC (106) and include persons with HIV infection, close contacts of persons with newly diagnosed TB, recent tuberculin skin test converters, and persons

with underlying medical conditions reported to increase risk of TB.

Treatment for TB

There are five first-line antituberculous medications: isoniazid, rifampin, streptomycin, ethambutol, and pyrazinamide. Drug resistance in *M tuberculosis* results from spontaneous chromosomal mutations conferring resistance to antituberculous medications (12). Primary drug resistance is defined as resistance occurring in a patient who is not known to have had previous treatment with antituberculous drugs and presumably results from transmission of a drug-resistant strain. Secondary or acquired drug resistance is defined as documented, increasing levels of resistance to one or more drugs in a strain recovered from a patient undergoing inadequate therapy. Because the sites of resistance for individual drugs are not linked, multidrug therapy is always used to ensure that organisms remain susceptible and to prevent the emergence of resistant strains (12).

A 6-month regimen consisting of isoniazid, rifampin, and pyrazinamide given for 2 months followed by isoniazid and rifampin for 4 months is the preferred treatment for all patients, regardless of HIV status, with fully susceptible organisms (106). Ethambutol or streptomycin is included in the initial regimen until the results of drug susceptibility testing are available. After 2 months of treatment, the results of sputum cultures in more than 85% of patients should have converted from positive to negative (106).

Treatment of MDR TB (resistance to the two most potent drugs, isoniazid and rifampin) is a difficult therapeutic problem. Treatment regimens that are more toxic, more expensive, and not as successful must be individualized on the basis of susceptibility studies and should be planned in consultation with an expert in management of TB (17,106).

CONTROL

Effective control of TB requires early identification, isolation, and treatment of persons with active TB. Early identification is particularly important within congregate settings to prevent transmission; the CDC has reported a number of hospital and institutional outbreaks in which TB spread among hospitalized patients and employees, resulting in several deaths due to occupationally acquired MDR TB (122–124).

Early identification of active TB requires vigilance on the part of physicians to consider this diagnosis when a patient presents with nonspecific constitutional or pulmonary symptoms for which no cause can be found. In two hospital-based studies of 32 and 85 patients with active pulmonary TB, 30% and 20% of patients, respectively, either died or were discharged before the diagnosis was made (125,126). Cited factors contributing to delayed diagnosis included low use of tuberculin skin tests and misinterpretation of chest radiographs (126). Six radiographic patterns of pulmonary TB that have been repeatedly found in association with delayed diagnosis are (*a*) normal findings (56,66,126,127), (*b*) nodule or mass (56,66,125,126), (*c*) parenchymal abnormalities attributed to ''old'' or ''inactive'' disease (56,66,125), (*d*) isolated pleural effusion (126,127), (*e*) isolated lymphadenopathy (126,127), and (*f*) parenchymal opacities located in sites other than the usual postprimary sites (56,66). Nonspecific radiographic findings, as exemplified by the latter three patterns, are typical of primary TB, a form that is increasing in incidence among adults in developed countries (61).

Because of the critical importance of rapid identification in limiting disease transmission, the most rapid and reliable diagnostic tests for *M tuberculosis* should be used in clinical laboratories (128,129). With respect to turnaround times from receipt of specimen in the laboratory to reporting results, the CDC recommends 24 hours for the acid-fast bacilli smear, 10–14 days for detection and identification of mycobacteria, and 15–30 days for susceptibility tests (128).

The degree and duration of isolation imposed on patients with active TB are dependent on the estimated degree of infectiousness, the nature of the patient's usual activities, and the group at risk as a consequence of transmission (17). Infectious persons can usually remain at home because the additional risk of transmission to household members previously exposed is low (17). In the hospital setting, isolation of infectious individuals is mandatory to protect susceptible patients and employees from infection. Although the exact point at which patients with drug-susceptible organisms become noninfectious is difficult to define, most become noninfectious within a few days to weeks after initiation of appropriate anitituberculous drugs. Three consecutive negative sputum smear examinations collected on separate days indicate an extremely low risk of transmission, and a negative culture ensures virtually no risk of transmission (17).

Noncompliance with therapy is a major problem in TB control and can lead to treatment failure, development of drug resistance, and continuing transmission. Because patient compliance cannot be predicted on the basis of demographic factors or subjective judgment of personality traits (130,131), the CDC currently recommends that all patients with TB be considered for directly observed therapy (106). Directly observed therapy means observation of the patient by a health care provider or other responsible person as the patient ingests antituberculous medications; directly observed therapy can be achieved with daily, twice weekly, or thrice weekly administration of drugs. Its implementation has been shown to be an effective method to promote patient compliance (130,132). In a small number of patients, typically homeless persons or alcoholics, who are refractory to directly observed therapy and other compliance-enhancing methods, short-term incarceration has been performed in the interests of public health (133).

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