INTRODUCTION — The lungs are the major site for *Mycobacterium tuberculosis* primary infection and disease. Clinical manifestations of tuberculosis (TB) include primary TB, reactivation TB, laryngeal TB, endobronchial TB, lower lung field TB infection, and tuberculoma. Pulmonary complications of TB can include hemoptysis, pneumothorax, bronchiectasis, extensive pulmonary destruction, malignancy, and chronic pulmonary aspergillosis.

The clinical manifestations and evaluation of pulmonary TB will be reviewed here. The clinical manifestations of pulmonary TB in children and HIV-infected patients are discussed separately, as are the epidemiology, pathogenesis, laboratory diagnosis, and treatment of pulmonary TB. Extrapulmonary and miliary TB are also discussed separately. (See related topics.)

CLINICAL MANIFESTATIONS

Primary tuberculosis — Primary tuberculosis (TB) is a term that describes new tuberculosis infection or active disease in a previously naïve host. Primary TB was considered to be mainly a disease of childhood until the introduction of effective chemotherapy with isoniazid in the 1950s. Many studies since that time have shown an increased frequency in the acquisition of TB in adolescents and adults [1,2].

Symptoms and signs — The natural history of primary TB was well described in a prospective study of 517 new tuberculin converters living on the Faroe Islands off the coast of Norway from 1932 to 1946 [3]. The study included 331 adults and 186 children; all were followed for more than five years. The clinical manifestations of primary TB varied substantially in this population, and symptoms and signs referable to the lungs were present in approximately one-third of patients. Fever was the most common symptom, occurring in 70 percent of 232 patients in whom fever was not a condition for enrollment in the study. The fever onset was generally gradual and low grade but could be as high as 39°C (102.2°F) and lasted for an average of 14 to 21 days. Fever resolved in 98 percent of patients by 10 weeks.

Fever was not usually accompanied by other symptoms, although approximately 25 percent of patients developed pleuritic or retrosternal pain. One-half of patients with pleuritic chest pain had evidence of a pleural effusion. Retrosternal and dull interscapular pain were ascribed to enlarged bronchial lymph nodes and sometimes worsened with swallowing. Rarer symptoms included fatigue, cough, arthralgias, and pharyngitis. (See "Tuberculous pleural effusions in HIV-uninfected patients" and "Tuberculous pleural effusions in HIV-infected patients").

Radiographic abnormalities — In primary pulmonary TB, the chest radiograph is often normal. In one series including 517 patents with recent skin test conversion, chest radiograph findings were notable for the following [3]:

- Hilar adenopathy was the most common finding, occurring in 65 percent of cases. Hilar changes were visible early as one week after skin test conversion, and within two months in all cases.
- Pleural effusions developed in approximately one-third of patients, typically within the first three to four months after infection but occasionally as late as one year.
- Pulmonary infiltrates were observed in 27 percent of patients; in general, they resolved slowly, over months to years.
  - Perihilar and right-sided infiltrates were the most common, and ipsilateral hilar enlargement was the rule.
  - Contralateral hilar changes sometimes were present; only 2 percent of patients had bilateral infiltrates.
  - Lower and upper lobe infiltrates were observed in 33 and 13 percent of patients, respectively; 43 percent of adults with infiltrates also had effusions.
  - The infiltrates progressed within the first year after skin test conversion in 20 patients (15 percent of cases), reflecting progressive primary TB. The majority of these patients had progression of disease at the original site; four developed cavitation.

Other studies that provide insight into the clinical manifestations of TB have focused retrospectively upon patients with culture-proven TB [4-6]. In one series from Canada, 188 patients were assessed, all of whom were culture positive and had abnormal chest radiographs [3]. Thirty patients (18 percent) were classified clinically as having primary TB. The most common finding was
hilar lymphadenopathy, present in 67 percent. Right middle lobe collapse may complicate the adenopathy but usually resolves with therapy.

Several factors probably favor involvement of the right middle lobe: it is more densely surrounded by lymph nodes, it has a relatively longer length and smaller internal caliber, and it has a sharper branching angle.

In this retrospective series, pleural effusions were present in 33 percent and were the sole abnormality in 23 percent of cases [5]. Pulmonary infiltrates were present in 63 percent of patients, and 85 percent of infiltrates were in the mid- to lower lung fields. Two patients had cavitation and two others had evidence of endobronchial spread.

**Natural history** — After primary infection, 90 percent of individuals with intact immunity control further replication of the bacilli, which may then enter a "latent" phase. The remaining 10 percent of individuals develop a TB pneumonia with expansion of infiltrates at the site of the initial seeding or near the hilum and may have hilar lymphadenopathy or present with disease at more distant sites, commonly with cervical lymphadenopathy, meningitis, pericarditis, or miliary dissemination. Progression to local disease or dissemination occurs more frequently in those with poor immune responses, such as in those with HIV infection, chronic kidney failure, poorly controlled diabetes mellitus, and in those receiving immunosuppressive medications (including transplant recipients) and older adults. (See "Natural history, microbiology, and pathogenesis of tuberculosis", section on 'Natural history of infection'.)

** Reactivation tuberculosis** — Multiple terms have been used to describe reactivation TB: chronic TB, postprimary disease, recrudescent TB, endogenous reinfection, and adult-type progressive TB. Reactivation TB represents 90 percent of adult cases among HIV-uninfected individuals and results from reactivation of a previous focus of mycobacterial containment that was seeded at the time of the primary infection. The apical posterior segments of the upper lobes or the superior segment of the lower lobe of the lung are frequently involved (image 1). The reason for this is uncertain; relatively poor lymphatic flow in the apices may be associated with poor organism clearance. It has also been suggested that *M. tuberculosis* organisms prefer the higher oxygen tensions in the apical area of the lungs, although TB may not be an obligate aerobe [7,8]. The original site of infection may have been previously visible as a small scar called a Simon focus.

**Symptoms** — Reactivation TB may remain undiagnosed and potentially infectious for two to three years or longer, with development of symptoms only late in the course of the disease. The symptoms of reactivation TB have been described retrospectively, mainly in case series of hospitalized patients in single institutions [9-11]. In these series, symptoms typically began insidiously and were present for weeks or months before the diagnosis was made. One-half to two-thirds of patients developed cough, weight loss, and fatigue. Fever and night sweats or night sweats alone were present in approximately one-half. Chest pain and dyspnea each were reported in approximately one-third of patients and hemoptysis in approximately one-quarter. Many patients had vague or nonspecific symptoms; almost one-third of patients had pulmonary TB diagnosed after an admission for unrelated complaints [9].

- Fever is usually low grade at onset but becomes marked with progression of disease. It is classically diurnal, with an afebrile period early in the morning and a gradually rising temperature throughout the day, reaching a peak in the late afternoon or evening. Fever subsides during sleep, but night sweats may occur. Fever and night sweats are more common among patients with advanced pulmonary TB [12].
- Cough may be absent or mild initially and may be nonproductive or productive of only scant sputum. Initially, it may be present only in the morning, when accumulated secretions during sleep are expectorated. As the disease progresses, cough becomes more continuous throughout the day and productive of yellow or yellow-green and occasionally blood-streaked sputum, which is rarely foul smelling. Symptomatic individuals are more likely to have smear-positive sputum [13]. Frank hemoptysis, due to caseous sloughing or endobronchial erosion, typically occurs later in the disease and is rarely massive. Nocturnal coughing is associated with advanced disease, often with cavitation.
- Dyspnea can occur in the setting of extensive parenchymal involvement, pleural effusions, or a pneumothorax. Pleuritic chest pain is not common but, when present, signifies inflammation abutting or invading the pleura, with or without an effusion. Rarely, this can progress to frank empyema.
- In the absence of treatment, patients may present with painful ulcers of the mouth, tongue, larynx, or gastrointestinal tract due to chronic expectoration and swallowing of highly infectious secretions; these findings are rare in the setting of antituberculosis therapy.
- Anorexia, wasting (consumption), and malaise are common features of advanced disease and may be the only presenting features in some patients.
Ambulatory patients with active TB typically have milder and less specific symptoms than hospitalized patients. In a study including 313 TB cases identified among ambulatory patients, cough >2 weeks was observed among 52 percent of patients with pulmonary disease; fever >2 weeks was observed among 29 percent of patients [14]. In addition, clinical symptoms were observed less frequently among patients of Asian ethnicity than among other patients.

Other comorbidities may affect the presentation of reactivation TB; these include diabetes, administration of tumor necrosis factor (TNF)-alpha inhibitors and advanced HIV infection. Such patients present with more symptoms and a higher proportion of smear positivity, cavitation, treatment failure, and non-TB deaths [15]. (See “Epidemiology, clinical manifestations, and diagnosis of tuberculosis in HIV-infected patients” and “Tumor necrosis factor-alpha inhibitors and mycobacterial infections.”)

Presentation in older adults — In nonendemic countries, the incidence of pulmonary TB is two to three times higher among older adults, especially those in old age homes, and the risk of death is higher compared with younger patients [16,17].

Comparative studies have suggested some differences in the manifestations of pulmonary TB between older and younger patients. A meta-analysis including 12 studies noted no significant differences between patients >60 years and patients <60 years with respect to time to diagnosis, prevalence of cough, sputum production, weight loss, or fatigue/malaise [18]. Findings observed less commonly among older adults included fever, sweats, hemoptysis, cavitary disease, and a positive tuberculin skin test, but they were likely to present with the nonspecific symptoms of dyspnea and fatigue. Findings observed more frequently among older adults included hypoalbuminemia, leukopenia, and underlying disorders such as cardiovascular disease, chronic obstructive pulmonary disease (COPD), diabetes, malignancy, and gastrectomy. Cavitary disease is less common, and multilobar and lower lobe involvement more common. Because of comorbidities such as COPD and the nonspecificity of symptoms, the diagnosis in older adults can be delayed or missed [19,20].

Physical findings — Physical findings of pulmonary TB are not specific and usually are absent in mild or moderate disease. Dullness with decreased fremitus may indicate pleural thickening or effusion. Crackles may be present throughout inspiration or may be heard only after a short cough (posttussive crackles). When large areas of the lung are involved, signs of consolidation associated with open bronchi, such as whispered pectoriloquy or tubular breath sounds, may be heard. Distant hollow breath sounds over cavities are called amphoric, after the sound made by blowing across the mouth of jars used in antiquity (amphorae). Extrapulmonary signs include clubbing and findings localized to other sites of involvement. (See “Clinical manifestations, diagnosis, and treatment of extrapulmonary and miliary tuberculosis”.)

Laboratory findings — The approach to diagnosis of tuberculosis is discussed separately. (See “Diagnosis of pulmonary tuberculosis in HIV-uninfected patients” and “Epidemiology, clinical manifestations, and diagnosis of tuberculosis in HIV-infected patients.”)

Routine hematology and biochemistry laboratory studies are frequently normal in the setting of pulmonary TB. The C-reactive protein (CRP) can be elevated in up to 85 percent of patients [21]. Late in the disease, hematologic changes may include normocytic anemia, leukocytosis, or, more rarely, monocytosis. Hyponatremia may be associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [22] or rarely with adrenal insufficiency. Hypoalbuminemia and hypergammaglobulinemia also can occur as late findings.

Radiographic findings — Most patients with reactivation TB have abnormalities on chest radiography, even in the absence of respiratory symptoms [9,23]. Reactivation TB typically involves the apical-posterior segments of the upper lobes (80 to 90 percent of patients), followed in frequency by the superior segment of the lower lobes and the anterior segment of the upper lobes (image 1 and image 2) [9,24-26]. In multiple large series of TB among adults, 70 to 87 percent had upper lobe infiltrates typical of reactivation; 19 to 40 percent also had cavities, with visible air-fluid levels in as many as 20 percent of cases [9,24-26].

Adults without upper lobe infiltrates have “atypical” radiographic patterns (13 to 30 percent of pulmonary TB cases) [4,27,28]. These findings include hilar adenopathy (sometimes associated with right middle lobe collapse), infiltrates or cavities in the middle or lower lung zones, pleural effusions, and solitary nodules. These “atypical” findings are more common in the setting of primary TB and probably represent increasing incidence of primary TB rather than "atypical" forms of reactivation TB. (See “Primary tuberculosis” above.)

Up to 5 percent of patients with active TB present with upper lobe fibrocalcific changes thought to be indicative of healed primary TB. However, such patients should be evaluated for active TB in the setting of pulmonary symptoms or absence of serial films documenting stability of the lesion.

A normal chest radiograph is also possible even in active pulmonary TB. As an example, in one Canadian study of 518 patients with culture-proven pulmonary TB, 25 patients (5 percent) had normal chest radiographs; 23 of these patients had pulmonary...
Endobronchial tuberculosis definition: Endobronchial TB is defined as tuberculous infection of the tracheobronchial tree. It may develop via direct extension to the bronchi from an adjacent parenchymal focus (usually a cavity) or via spread of organisms to the bronchi via infected sputum. Lesions are more likely to be observed in the main and upper bronchi; in 5 percent of patients, the lower trachea is involved.

Prior to the availability of antituberculous therapy, endobronchial TB was relatively common in the setting of primary infection and reactivation TB. In a 1943 study in a TB sanatorium in West Virginia, lesions in the tracheobronchial tree were observed in 15 percent of cases via rigid bronchoscopy and in 40 percent of cases at autopsy. Endobronchial disease was observed more frequently among patients with extensive pulmonary TB, particularly cavitary lesions. Upper lung parenchymal or cavitary disease with bronchogenic spread to the lower lung fields was commonly observed, presumably from pooled infected secretions.

Since the availability of antituberculous therapy, endobronchial TB has been described in 10 to 40 percent of patients with active pulmonary TB. Some degree of bronchial stenosis is observed in 90 percent of cases of endobronchial TB; early diagnosis and prompt treatment prior to development of fibrosis are important to reduce the likelihood of this complication. Endobronchial disease in patients with primary infection has also been associated with impingement of enlarged lymph nodes on the bronchi. Associated inflammation can lead to endobronchial ulceration or perforation. Other complications of endobronchial TB include obstruction, atelectasis (with or without secondary infection), bronchiectasis, and tracheal stenosis.

Symptoms: Symptoms may be acute in onset and be confused with bacterial pneumonia, asthma, or foreign body aspiration. A barking cough has been described in approximately two-thirds of patients with endobronchial disease, often accompanied by sputum production. Rarely, patients develop so-called bronchorrhea, which is production of more than 500 mL/day of sputum. In some cases, caseous material from endobronchial lesions or calcific material from extension of calcific nodes into the bronchi is expectorated, which is known as lithoptysis. Wheezing and hemoptysis may also be observed. Lymph node rupture can be associated with chest pain. The presence of dyspnea may signal obstruction or atelectasis.

Physical findings: Diminished breath sounds, rhonchi, or wheezing may be heard. The wheeze is low pitched, monophonic, and is auscultated consistently over the same area on the chest wall.

Radiographic abnormalities: Because endobronchial lesions can exist without extensive parenchymal abnormalities, a normal chest radiograph is observed in 10 to 20 percent of cases. In such cases, CT scanning may demonstrate endobronchial lesions or stenosis. The most common radiographic finding of endobronchial TB in adults is an upper lobe infiltrate and cavity with ipsilateral spread to the lower lobe and possibly to the superior segment of the contralateral lower lobe. Patchy, small lower lobe infiltrates may progress to confluence or even cavitation. Extensive endobronchial TB can also be associated with bronchiectasis on CT scan.

When endobronchial TB occurs in patients with primary disease, segmental atelectasis may be the only finding; atelectasis is more frequent in the right middle lobe and the anterior segment of the right upper lobe.

Evaluation and approach: The diagnosis of endobronchial TB may be established by bronchoscopy, which may demonstrate erythematous, vascular, and/or ulcerated tissues. Granulation tissue may be bulky or polypoid. Hilar node rupture may be visible as a mass protruding into the bronchial lumen; with perforation of the node into the bronchus, caseous or calcific material may be seen extruding into the lumen. Bronchial stenosis also may be visible. The likelihood of developing stenosis is increased in the setting of a distorted airway or a mass occluding the airway.
Brushings of the lesions or lavage of the distal airways can increase the frequency of positive smears; the yield for cultures of this material is >90 percent [32,37]. (See “Diagnosis of pulmonary tuberculosis in HIV-uninfected patients”, section on “Laboratory studies”.)

Treatment regimens for endobronchial disease are the same as for other forms of pulmonary TB. (See “Treatment of pulmonary tuberculosis in HIV-uninfected adults” and “Treatment of pulmonary tuberculosis in HIV-infected adults”.)

Other manifestations

Laryngeal tuberculosis — Prior to the availability of antituberculous therapy, laryngeal TB was considered a terminal condition, as it usually occurred during progression of pulmonary disease, developing soon before death. Since the availability of antituberculous therapy, laryngeal TB has become rare (<1 percent of TB cases). It can also occur in the absence of pulmonary disease as an extrapulmonary manifestation. Symptoms include dysphonia, cough, dysphagia, odynophagia, stridor, and hemoptysis [30]. The true vocal cords, epiglottis, and false vocal cords are the most common sites involved, and areas of hyperemia, nodules, ulcerations, or exophytic masses can be seen on laryngoscopy.

The similarity of laryngeal TB to chronic laryngitis warrants consideration of TB in the differential diagnosis of inflammatory laryngeal disease in patients with epidemiologic risk factors [51]. (See “Hoarseness in adults”.)

Lower lung field tuberculosis — Lower lung field TB refers to disease involvement below the hila (including the perihilar regions) on chest imaging [52]. The incidence in adults is 2 to 9 percent [9,52]. Consolidation in lower lung field TB tends to be more extensive and homogeneous than upper lobe TB [53-55]. Cavitation may occur, and large cavities have been described. Symptoms in lower lobe TB are generally either subacute in onset (mean of 12 weeks) or chronic (up to 6 months). Lower lobe TB is frequently misdiagnosed initially as viral or bacterial pneumonia, bronchiectasis, or carcinoma.

Lower lobe involvement can be a manifestation of primary TB (with involvement of adjacent lymph nodes), reactivation TB (involving the superior segments of the lower lobes), or endobronchial TB [53,54,56]. Endobronchial TB can affect lower lung fields in both primary infection (especially when adjacent lymph nodes are involved) and reactivation (spread from upper lobe disease can secondarily infect the lower lung fields).

Older adult patients and those with HIV, diabetes, renal or hepatic disease, those receiving corticosteroids, and those with underlying silicosis appear at highest risk for lower lobe TB. However, many patients have no underlying medical illnesses. Studies in nursing homes suggest that lower lobe TB may be a manifestation of active tuberculosis in an older, tuberculin-negative population with significant underlying diseases or anergy [56]. In some cases, the patients are suspected or known to have had previous TB but develop exogenous reinfecion, perhaps due to a loss of demonstrable tissue hypersensitivity.

Tuberculoma — Rounded mass lesions can develop during primary infection or when a focus of reactivation TB becomes encapsulated [55]. Cavitation is rare. The differential diagnosis of pulmonary coin lesions is extensive, and the diagnosis of tuberculoma can be difficult since airway cultures are often negative. Fine needle aspiration or lung biopsy may be necessary for diagnosis. (See “Diagnostic evaluation and management of the solitary pulmonary nodule”.)

COMPLICATIONS OF TUBERCULOSIS — Pulmonary complications of tuberculosis (TB) include hemoptysis, pneumothorax, bronchiectasis, extensive pulmonary destruction (including pulmonary gangrene), malignancy, and chronic pulmonary aspergillosis.

Hemoptysis — Hemoptysis occurs most frequently in the setting of active tuberculosis but may also occur after completion of treatment [57-59]. Many patients with hemoptysis are acid-fast bacilli (AFB) smear positive and usually have cavitary disease. Bleeding usually is of small volume, appearing as blood-streaked sputum. Massive hemoptysis is a rare complication since the advent of chemotherapy. Prior to effective chemotherapy, massive hemoptysis accounted for approximately 5 percent of deaths from TB.

Sources of massive hemoptysis due to TB include the pulmonary artery, bronchial arteries, intercostal arteries, and other vessels supplying the lung. "Rasmussen's aneurysm" is a relatively uncommon cause of hemoptysis; it refers to the formation of an aneurysm in the setting of cavitory infection that extends into the adventitia and media of bronchial arteries, resulting in inflammation and thinning of the vessel wall [60,61]. This aneurysm subsequently ruptures into the cavity, producing massive hemoptysis.

Hemoptysis after the completion of therapy for TB only occasionally represents TB recurrence. Other causes include residual bronchiectasis, an aspergilloma or other fungus ball invading or colonizing an old healed cavity, a ruptured broncholith that erodes through a bronchial artery, a carcinoma, or another infectious or inflammatory process.
Patients with significant hemoptysis should be evaluated promptly to define the source of bleeding and to facilitate immediate intervention. Apart from impending exsanguination (which requires immediate surgical care), bronchial artery embolization is the preferred management approach if feasible [62,63]. In one study including 140 patients with TB and massive hemoptysis (more than 300 mL of blood in 24 hours) who underwent bronchial artery embolization, nearly complete control of hemoptysis was achieved in 73 percent of cases [62]. In the absence of access to appropriate facilities for bronchial artery embolization, other treatments includes bed rest, postural management, volume replacement, cough suppression, and intravenous vasopressin [64]. (See “Massive hemoptysis: Initial management”.)

If embolization and medical management fail, surgical options include ligation of arteries, resection of a lung lobe, and endobronchial tamponade. Both ligation and embolization can be complex because of the frequent presence of multiple feeder arteries often connecting systemic with bronchial circulation [65]. Older studies suggest that after an episode of massive hemoptysis or repeated episodes of severe hemoptysis, surgical intervention improves survival [66-68] and should be considered if embolization fails.

**Pneumothorax** — Prior to the availability of antituberculous therapy, spontaneous pneumothorax was a frequent and dangerous complication of pulmonary TB [69]. Since the availability of antituberculous therapy, spontaneous pneumothorax associated with TB has been reported in about 1 percent of hospitalized patients [70-72]. A case series from Turkey reported pneumothorax in 1.5 percent of cases of pulmonary TB [72]. In regions where TB is endemic, it may be the most common cause of spontaneous pneumothorax [73].

Pneumothorax appears to result from the rupture of a peripheral cavity or a subpleural caseous focus with liquefaction into the pleural space [70,71]. Inflammation can lead to development of a bronchopleural fistula, which can persist or seal off spontaneously. The lung may reexpand if the bronchopleural fistula seals spontaneously, but more commonly chest tube drainage is required.

Factors preventing successful chest tube drainage and expansion include extensive pulmonary parenchymal disease with large fistulas, a long interval between pneumothorax and chest tube insertion, and the development of an empyema due to TB and/or bacterial superinfection. However, successful closure of even extensive air leaks has been reported after as much as six weeks of chest tube drainage accomplished by appropriate antituberculous chemotherapy [74]. (See "Secondary spontaneous pneumothorax in adults").

**Bronchiectasis** — Bronchiectasis may develop following primary or reactivation TB and can be associated with hemoptysis [75-80]. (See "Clinical manifestations and diagnosis of bronchiectasis in adults").

Following primary TB infection, extrinsic compression of a bronchus by enlarged nodes may cause bronchial dilation distal to the obstruction. There may be no evidence of parenchymal TB.

In the setting of reactivation TB, progressive destruction and fibrosis of lung parenchyma may lead to localized bronchial dilation. If endobronchial disease is present, bronchial stenosis may result in distal bronchiectasis. Bronchiectasis is more frequent in the common sites of reactivation TB (apical and posterior segments of the upper lobe) but may be found in other areas of the lung.

**Extensive pulmonary destruction** — Rarely, untreated or inadequately treated TB can cause progressive, extensive destruction of areas of one or both lungs [81,82]. In primary TB, occasionally lymph node obstruction of the bronchi together with distal collapse, necrosis, and bacterial superinfection can produce parenchymal destruction [82]. More commonly, destruction results from chronic reactivation TB, typically in the absence of effective chemotherapy. Symptoms include progressive dyspnea, hemoptysis, and weight loss.

In one series of 18 patients with extensive destruction of one or both lungs, eight died [81]. Causes of death were massive hemoptysis and respiratory failure, sometimes in the presence of active TB or superinfection. Radiographically, patients had large cavities and fibrosis of remaining lung; in some cases, air-fluid levels at the base of the destroyed lung were observed [81,82].

Pulmonary gangrene refers to acute pulmonary destruction [83]. This form of TB progresses rapidly from a homogeneous, extensive infiltrate to dense consolidation. Air-filled cysts develop and coalesce into cavities. Necrotic lung tissue attached to the wall of the cavity may be observed. Pulmonary gangrene may resemble an intracavitary clot, fungus ball, or Rasmussen's aneurysm. Pathology demonstrates arteritis and thrombosis of the vessels supplying the necrotic lung. Mortality usually is high; in one small series, 75 percent of patients died [83]. Resolution with effective therapy has also been reported [84].

**Septic shock** — TB can cause septic shock; the manifestations are similar to bacterial septic shock. Compared with patients with septic shock due to other pathogens, patients with septic shock due to TB have lower mean body mass indices (22 versus 27),
lower mean white blood counts (10.4 versus 16.2), and are more often HIV infected (15 versus 3 percent) [85]. The probability of survival in patients with *M. tuberculosis* septic shock is extremely poor, with an in hospital mortality rate of 79 percent; delayed initiation of appropriate therapy likely played an important role in clinical outcome [85]. Extrapulmonary disease may be observed in more than 50 percent of cases. (See "Sepsis and the systemic inflammatory response syndrome: Definitions, epidemiology, and prognosis").

**Malignancy** — A study conducted by the National Cancer Institute found that pulmonary tuberculosis was associated with an increased risk of lung cancer, after adjustment for active smoking and socioeconomic status (odds ratio [OR] 2.1, 95% CI 1.4-3.1) [86]. The causal relationship is not clear but mycobacterial cell wall components may induce production of nitric oxide and reactive oxygen species, which have been implicated in DNA damage leading to carcinogenesis [87]. Chronic inflammation may also enhance mutagenesis. In addition, immune suppression and radiation therapy for lung cancer may be associated with an increased risk of tuberculosis. Clinical and radiographic similarities between TB and malignancy may lead to a delay in establishing the correct diagnosis.

**Venous thromboembolism** — Tuberculosis, both pulmonary and extrapulmonary, has been suggested as an independent risk factor for venous thromboembolism (VTE), perhaps due to a hypercoagulable state. In one retrospective study including 3485 cases of active TB, the prevalence of VTE was approximately 2 percent [88], which is similar to the rate associated with malignancy and approximately 100 times higher than the incidence of VTE among hospitalized patients in general [89]. The clinical approach to VTE is discussed further separately. (See "Overview of acute pulmonary embolism in adults").

**Chronic pulmonary aspergillosis** — Chronic pulmonary aspergillosis can be a sequela of pulmonary tuberculosis, especially in those with cavitary disease. This is discussed further separately. (See "Clinical manifestations and diagnosis of chronic pulmonary aspergillosis", section on 'Underlying diseases'.)

**DIFFERENTIAL DIAGNOSIS** — The following conditions can cause cavitary pulmonary lesions and symptoms suggestive of tuberculosis (TB) including fever, cough, and weight loss:

- **Nontuberculous mycobacterial infection (NTM)** — Symptoms of NTM include fatigue, dyspnea, and occasional hemoptysis; fever and weight loss occur less frequently than in patients with tuberculosis. Clinical features of *Mycobacterium kansasii* are often very similar to those of TB. NTM is distinguished from TB by culture results and/or molecular diagnostic testing. (See "Overview of nontuberculous mycobacterial infections in HIV-negative patients").
- **Fungal infection** — Fungal pneumonia can present with a range of manifestations including pneumonia, pulmonary nodule, and cavitary lung disease. It is distinguished from TB by epidemiologic exposure and culture results. (See "Diagnosis and treatment of pulmonary histoplasmosis" and "Diagnosis of invasive aspergillosis" and "Mucormycosis (zygomycosis)" and "Clinical manifestations and diagnosis of blastomycosis" and "Epidemiology, clinical manifestations, and diagnosis of Cryptococcus neoformans meningoencephalitis in HIV-infected patients").
- **Sarcoidosis** — Sarcoidosis most commonly presents with diffuse interstitial lung disease. It rarely forms cavities and is distinguished from TB by histopathologic detection of noncaseating granulomas. (See "Clinical manifestations and diagnosis of pulmonary sarcoidosis").
- **Lung abscess** — Lung abscess generally presents with fever, cough, and sputum production but without shaking chills or true rigors. Chest imaging usually shows infiltrates with a cavity. The diagnosis is established based on culture results. (See "Lung abscess").
- **Septic emboli** — Septic emboli to the lung from an extrapulmonary nidus are distinguished from TB by blood culture results and echocardiography. (See "Complications and outcome of infective endocarditis", section on 'Septic embolization'.)
- **Lung cancer** — Lung cancer most commonly presents with cough, hemoptysis, chest pain, and dyspnea. It is distinguished from TB by histopathology. (See "Overview of the risk factors, pathology, and clinical manifestations of lung cancer").
- **Lymphoma** — Lymphoma typically presents with a rapidly growing mass together with fever, night sweats, and weight loss. It is distinguished from TB by histopathology. (See related topics.)

**INFORMATION FOR PATIENTS** — UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.
Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topic (see "Patient information: Tuberculosis (The Basics")
- Beyond the Basics topic (see "Patient information: Tuberculosis (Beyond the Basics")

**SUMMARY**

- Clinical manifestations of pulmonary tuberculosis (TB) include primary TB, reactivation TB, endobronchial TB, lower lung field TB infection, and tuberculosis. (See Introduction above.)
- Among patients with primary tuberculosis, clinical manifestations have been observed in approximately one-third of cases. Symptoms include fever and chest pain. Retrosternal pain and dull interscapular pain have been ascribed to enlarged bronchial lymph nodes. The physical exam is generally normal. The most common chest radiograph abnormality in one large series was hilar adenopathy. Other manifestations include pleural effusions and pulmonary infiltrates. (See Primary tuberculosis above.)
- Reactivation TB refers to reactivation of a previously dormant focus seeded at the time of the primary infection. The apical posterior segments of the lung are frequently involved (image 1). Typically, symptoms are insidious and may include cough, weight loss, fatigue, fever, night sweats, chest pain, dyspnea, and/or hemoptysis; these findings are observed less frequently among patients >60 years. (See Reactivation tuberculosis above.)
- Endobronchial TB may develop via direct extension to the bronchi from an adjacent parenchymal focus (usually a cavity) or via spread of organisms to the bronchi via infected sputum. It can occur in patients with primary TB or reactivation TB and was observed more frequently prior to the antituberculous therapy era. Symptoms may be acute or chronic; a barking cough has been described in approximately two-thirds of patients. (See Endobronchial tuberculosis above.)
- Pulmonary complications of TB include hemoptysis, pneumothorax, bronchiectasis, extensive pulmonary destruction (including pulmonary gangrene), malignancy, venous thromboembolism, and chronic pulmonary aspergillosis. (See Complications of tuberculosis above.)
- The differential diagnosis for pulmonary tuberculosis is broad and includes other causes of chronic infection, inflammatory diseases, and malignancy. (See Differential diagnosis above.)

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**REFERENCES**


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Topic 7026 Version 21.0
Chest radiographs of tuberculosis

Chest radiographs (posteroanterior and lateral views) demonstrating cavitary reactivation of latent tuberculosis infection in the posterior apical segment of the right upper lobe.

Chest radiographs of different presentations of tuberculosis

(A) Primary tuberculosis in a child (note the right-sided hilar adenopathy, right-sided lower lobe infiltrates, and volume loss).(B) Lower lung field tuberculosis infiltration and cavity with air-fluid level in lingula.(C) Reactivated tuberculosis, far-advanced disease with bronchogenic spread.(D) Miliary tuberculosis.
Imaging of cavitary lesions in tuberculosis

Chest radiograph (A) and computed tomography (CT) scan (B), the latter of which more clearly demonstrates two cavitary lesions. A repeated CT scan (C) showed improvement after one month of treatment in a young woman with primary multidrug-resistant tuberculosis.
Clinical manifestations, diagnosis, and treatment of extrapulmonary and miliary tuberculosis

Author
Jo

Section Editor
C Fordham von Reyn, MD

Deputy Editor
Elinor L Baron, MD, DTMH

hn Bernardo, MD

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Literature review current through: Feb 2016. | This topic last updated: Sep 11, 2015.

INTRODUCTION — Miliary tuberculosis (TB) refers to clinical disease resulting from the hematogenous dissemination of Mycobacterium tuberculosis. The term miliary was coined in 1700 by John Jacobus Manget, who likened the appearance of the involved lung, with its surface covered with firm small white nodules, to millet seeds (picture 1). Originally a pathologic and then a radiographic description, the term miliary TB is now used to denote all forms of progressive, widely disseminated hematogenous TB. Miliary TB can arise as a result of progressive primary infection or via reactivation of a latent focus with subsequent spread.

The clinical manifestations, diagnosis, treatment, and prevention of miliary TB, as well as extrapulmonary TB, will be reviewed here. The pathogenesis and epidemiology of miliary TB are discussed separately. (See "Epidemiology and pathology of miliary and extrapulmonary tuberculosis").

CLINICAL MANIFESTATIONS — Several large retrospective series provide much of the data on the clinical features of miliary tuberculosis (TB) (table 1) [1-6]. While these studies include a relatively large number of patients, they differ markedly by year, inclusion criteria, country, and type of medical center, so direct comparison is difficult.

The clinical presentation of miliary TB is highly variable; manifestations can be acute but are more likely to be subacute or chronic. In highly endemic areas, miliary TB may be associated with reinfection. Development of miliary TB during primary infection can present with relatively acute onset and rapid clinical course. Acute disease may be fulminant, including multiorgan system failure [7], a syndrome of septic shock [8], and acute respiratory distress syndrome (ARDS) [9,10].

The subacute or chronic presentations of miliary TB are more common than acute disease. These patients may present with failure to thrive [5], fever of unknown origin [2], or dysfunction of one or more organ systems [11]. The most common extrapulmonary sites of disease include the lymphatic system, bones and joints, and the liver. Night sweats are frequent. Rigors are unusual but have been described [12,13]. In one series including 38 patients, the median duration of illness was two months [2]. Symptoms and signs of miliary TB are described in the Tables (table 2 and table 3).

The diagnosis of miliary TB is often missed due to the nonspecific nature of the presentation. In one review, approximately 20 percent of miliary TB cases in the United States were diagnosed postmortem [14]. Among HIV-infected patients in Africa, previously unrecognized disseminated tuberculosis has been identified at autopsy in as many as 40 percent of hospital deaths [15].

Pulmonary disease — Pulmonary disease is noted in over 50 percent of patients with miliary TB in most series. Patients reported dyspnea or cough and had rales or rhonchi on physical examination. Hypoxemia was common. Pleuritic chest pain with accompanying pleural rub or other signs of a pleural effusion have also been well described.

As noted above, miliary TB is a rare cause of acute respiratory failure and ARDS [9,10,16-18]. In one series from a region endemic for TB in South Africa, it was estimated that 2 percent of cases of ARDS were associated with disseminated TB [19]. Another study suggested that the diagnosis of TB is more likely to be delayed or missed entirely in patients presenting with acute respiratory failure as opposed to more typical symptoms of pulmonary or pleural TB [20]. (See "Clinical manifestations and complications of pulmonary tuberculosis").

Lymphatic disease — Patients with lymphatic TB usually present with signs and symptoms referable to the site of disease, although constitutional symptoms may be the sole complaint. Cervical lymph node enlargement, with or without other symptoms, is a frequent presentation of cervical tuberculous adenitis.

Within the chest, hilar (usually unilateral) and mediastinal lymph node enlargement may reflect either primary TB or reactivation disease. Enlarged intrathoracic nodes may cause extrinsic airway compression leading to focal wheezing or airway obstruction, especially in children. (See "Tuberculous lymphadenitis").
Bone and joint disease — In adults, bone or joint TB should be suspected in individuals at risk for TB who present with bone or joint pain (including back pain) with or without focal swelling or fever [1,6,21]. The course usually is indolent and pain usually is the first presenting symptom. Spinal TB (Pott’s disease) may present in children as scoliosis or a limp [22]. The diagnosis often is delayed and may be difficult to establish. Radiographic findings can be nonspecific; early features may include soft tissue swelling (especially of the anterior portions of the vertebral body) with bone demineralization and preservation of joint surfaces. With chronic disease, complete destruction of bone with local sclerosis may be seen, accompanied by loss of structural support and spinal deformity. Disease is most common in the lower thoracic and lumbar vertebrae. Extension of the infectious process to surrounding soft tissue may create cold abscesses [23]. Involvement of multiple vertebrae is characteristic of Pott’s disease. Computed tomography (CT) and magnetic resonance imaging (MRI) can identify early lesions not seen on plain radiographs. Confirmation of a diagnosis of TB requires aspiration or biopsy and culture of the affected tissue. (See “Skeletal tuberculosis”.)

Gastrointestinal disease — Forms of gastrointestinal involvement include hepatic disease, tuberculous enteritis, and tuberculous peritonitis. Miliary TB may also present as pancreatitis [24] or cholecystitis [25].

The liver is frequently involved in disseminated TB. Signs and symptoms include diffuse abdominal pain or pain localizing to the right upper quadrant, nausea, vomiting, and diarrhea [26]. Histopathologic sections of involved liver demonstrate scattered granulomatous lesions that on gross examination have the appearance of millet seeds (picture 2) [27]. Liver function test abnormalities are common, including elevated alkaline phosphatase and transaminases in 83 and 42 percent of patients, respectively, in one series [1]. Cholestatic jaundice is also well documented in miliary TB. Rarely, fulminant hepatic failure can occur [28]. The diagnosis is established by identifying the organism obtained from a biopsy sample in culture.

Tuberculous enteritis consists of relatively vague, nonspecific symptoms and signs. A presumptive diagnosis can be made in the presence of known active pulmonary TB. However, chest imaging is typically positive (for active or healed TB) in less than half of cases. (See “Tuberculous enteritis”.)

Tuberculous peritonitis usually develops following spread of infection from adjacent organs. It should be suspected in patients at risk for TB who present with ascites. Symptoms of fever, fatigue, and abdominal pain are common. Ascites fluid usually demonstrates lymphocytosis, elevated protein, and elevated inflammatory markers. Culture of ascites fluid or of peritoneal tissue is required to confirm the diagnosis. The surface of the peritoneum may demonstrate miliary lesions on visual examination; biopsy of these lesions demonstrates caseating granulomas, with or without acid-fast staining organisms. (See “Tuberculous peritonitis”.)

Central nervous system disease — Central nervous system (CNS) disease, such as meningitis or tuberculoma, was observed in 15 to 20 percent of patients with TB in two large series [1,3]. Among patients with tuberculous meningitis, about one-third to one-half had miliary TB; in one series, meningeal involvement was evident postmortem in 54 percent of cases of miliary TB [29].

A high index of suspicion is necessary to make a timely diagnosis, since presenting symptoms and findings on examination often are nonspecific. In adults, CNS TB typically presents indolently, with headache, low-grade fever, and/or focal neurological findings. In children or immunocompromised hosts, the disease may present as acute meningitis.

CT with contrast or MRI with gadolinium of the brain may demonstrate hydrocephalus, parenchymal lesions, or leptomeningeal and basal cistern enhancement. Cerebrospinal fluid (CSF) pressure usually is elevated; the fluid usually demonstrates high protein, very low glucose, and lymphocytosis, although polymorphonuclear leukocytes may be seen early in the disease. Isolation of M. tuberculosis by culture confirms the diagnosis (although sensitivity is 50 to 60 percent), and nucleic amplification testing of the CSF may support the diagnosis [30-32]. Nucleic acid amplification by polymerase chain reaction (PCR) for MTb DNA in the CSF is not approved by the US Food and Drug Administration (FDA), although many laboratories offer internally validated PCR testing. However, treatment should be initiated as soon as TB is suspected in order to minimize the risk of long-term neurologic sequelae or death. (See “Central nervous system tuberculosis”.)

Genitourinary and adrenal disease — TB of the urinary tract may present with hematuria, proteinuria, and “sterile” pyuria. In the kidney, the disease frequently localizes to the renal papillae, and characteristic distortion of the collecting system tract may be seen radiographically (image 1). Flank pain, hydrenephrosis, and cystitis indicate more severe disease, and spread to the genitalia may occur. Diagnosis is established by culture of the organism from the
TB of the female genital tract may occur in the setting of primary or reactivation disease. Menstrual abnormalities in the setting of known TB infection should prompt consideration of female genital tract involvement. Ultrasonography or other radiographic studies may be helpful in localizing lesions. The diagnosis is established with open biopsy, dilation and curettage, and/or colposcopy, with histologic examination and culture of biopsy materials [33,34].

Scrotal pain, swelling, and/or epididymal or prostate tenderness in the setting of known TB infection should prompt consideration of male genital tract involvement [35]. Urine culture and/or biopsy of affected tissue for culture are necessary for diagnosis.

Adrenal insufficiency has been associated with miliary TB and involvement of the adrenals may be found in as many as 42 percent of autopsies [4,36]. Overt adrenal insufficiency is less common, occurring in 1 percent of reported cases of miliary TB [1,36]. In a prospective study including 30 patients with miliary TB, adrenal function was abnormal in 1 of 30 patients [37]. Among 55 patients with TB involvement of the adrenal gland in one series, 12 percent presented with clinical manifestations of Addison's disease [36].

Cardiovascular disease — Cardiovascular disease is unusual in miliary TB. Autopsy series report an incidence of less than 10 percent, almost always clinically silent [29,38]. The most common single form of cardiovascular TB is pericarditis [1,39]. Myocardial disease is much less frequent; one patient with sudden cardiac death due to myocardial dissemination has been reported [39]. Tuberculous endocarditis is also very rare [40].

Tuberculous pericarditis generally is a late diagnosis. The chest radiograph usually demonstrates an enlarged cardiac silhouette, and echocardiography may show signs of constriction [41]. A positive tuberculin skin test is observed in more than 85 percent of patients, although this number is lower in the immunocompromised [42-45]. Pericardial fluid and biopsy can be obtained for mycobacterial smear and culture, but the yield from these specimens is not as high as for pleural fluid or tissue. Thus, presumptive therapy often is administered to patients with evidence of constrictive pericardial disease and a positive tuberculin skin test. (See "Tuberculous pericarditis").

Disseminated TB can be associated with mycotic aneurysms of the ascending or descending aorta [46]. Potential mechanisms include spread from a lymph node or from vertebral osteomyelitis to the aorta, followed by hematogenous dissemination. Embolization to the aortic wall vasa vasorum during hematogenous spread from an infected lymph node is possible [47]. Potential mechanisms also include spread from an infected lymph node to the aortic wall vasa vasorum [48]. Pericardial fluid and biopsy can be obtained for mycobacterial smear and culture, but the yield from these specimens is not as high as for pleural fluid or tissue. Thus, presumptive therapy often is administered to patients with evidence of constrictive pericardial disease and a positive tuberculin skin test. (See "Tuberculous pericarditis").

Cutaneous disease — Cutaneous disease is rare in miliary TB. The most common presentation is TB cutis miliaris disseminata, which consists of 5 to 10 mm macules and papules [47]. A generalized rash which resembles a lichenoid tuberculid response has also been described [13]. Advanced HIV may also predispose to skin manifestations of disseminated TB [48]. (See "Cutaneous manifestations of tuberculosis").

Breast disease — TB of the breast is rare [49]. Clinical presentation is usually of a solitary, ill-defined, unilateral hard lump [50]. TB can also present with nipple discharge, skin thickening, or discharging sinuses in the breast or axilla. Breast TB can mimic breast carcinoma or breast abscess, clinically and radiographically [49,50]. Mammographic imaging may show a dense tract connecting an ill-defined breast mass to an area of skin thickening and a skin bulge. Ultrasound may demonstrate a complex, predominantly cystic mass.

Other organ involvement — Autopsy series of miliary TB describe seeding of every organ in the body [29]. Laryngitis [51] and otitis media [52] have been reported as clinical presentations of miliary TB. Involvement of the thyroid gland with clinical hyperthyroidism or hypothyroidism has also been described [53].

One large autopsy series which included eye examinations found tubercles in 50 percent of eyes [29], suggesting that a good dilated examination might be helpful in the diagnosis of hematogenous spread of TB. Choroidal tubercles are said to be specific for miliary TB, although they were rarely found in the large clinical series where dilated examinations were not routinely performed. (See "Tuberculosis and the eye").

LABORATORY FINDINGS — Many laboratory abnormalities may be observed in miliary tuberculosis (TB) [table 4]. Hematologic abnormalities are prominent. Normocytic, normochromic anemia is seen in approximately one-half of the
patients in most series. Most patients have a normal white blood cell count, but leukopenia and leukocytosis occur in a minority of patients with roughly equal frequency. Miliary TB should be considered in the differential diagnosis of patients with a leukocytosis or left shift when initial evaluation does not reveal a typical bacterial etiology, especially when accompanied by anemia. Leukemoid reactions are also described and have even led to a misdiagnosis of leukemia [54,55]. Monocytosis occurs but is less common. Thrombocytopenia and thrombocytosis are also reported.

Pancytopenia is another hematologic manifestation, which should raise concern for miliary TB; this may be due to marrow infiltration alone or may be a manifestation of an underlying hematologic disorder [56]. Cases of the histiocytic hemophagocytic syndrome associated with miliary TB have also been described [57]. Some cases have resolved with antituberculous chemotherapy alone, although associated conditions, such as viral infections, were not always excluded and response to steroids may have been nonspecific.

Overt disseminated intravascular coagulation is rare; it has been described in acute, fulminant disease. Milder coagulation abnormalities have been described more frequently [1]. The erythrocyte sedimentation rate and other acute phase reactants are elevated in the majority of patients with miliary TB. Polyclonal gammaglobulinemia is also common [2].

Hyponatremia is the most common electrolyte abnormality observed in miliary TB. It is presumed to be due to the same problems with regulation of antidiuretic hormone seen in other pulmonary processes, since not all series note a correlation with central nervous system disease [2]. Hypercalcemia is rare but may be seen in miliary TB [58]. (See "Pathophysiology and etiology of the syndrome of inappropriate antidiuretic hormone secretion (SIADH)."

Sterile pyuria was found in 32 percent of patients with miliary TB in one series [2], without positive mycobacterial cultures from the urinary tract. Urine cultures may also be positive for M. tuberculosis in miliary TB, in the absence of an abnormal urine sediment.

RADIOGRAPHIC IMAGING — Two series of cases of miliary tuberculosis (TB) provide the best overview of pulmonary findings, since a miliary pattern on chest radiograph was not required for study inclusion [1,2]. More than two-thirds of patients with the diagnosis of disseminated TB had a chest radiograph with a miliary pattern.

Chest radiography — The classic appearance is a faint, reticulonodular infiltrate distributed fairly uniformly throughout the lungs (image 2). This miliary pattern may only become apparent days or weeks after presentation [1,3,6]. This finding is thought to reflect nodular interstitial spread without significant alveolar involvement, although it has been demonstrated that, by the time the miliary nodules are large enough to be appreciated on a plain chest radiograph, they typically involve the adjacent alveoli [59].

Conversely, pathologic conditions that initially involve alveoli, such as alveolar hemorrhage, pulmonary edema, or inhalational diseases, can appear as early small nodules. These so-called "acinar nodules" are described as larger (5 to 10 mm) and more heterogeneous than classic miliary TB, but overlap occurs, making the appearance of many of these conditions indistinguishable [60]. The differential diagnosis of a miliary chest radiography pattern is summarized in the Table (table 5).

Other chest radiograph abnormalities include pleural reactions, hilar or mediastinal adenopathy, and other evidence of active or healed parenchymal TB (interstitial or alveolar infiltrates or cavities). A miliary pattern can be seen in addition to non-miliary disease. Normal chest radiographs may be observed in up to one-half of patients with disseminated TB [61]. In some cases, abnormalities may be subtle and appreciated only after review with an experienced chest radiologist.

Computed tomography — High-resolution computed tomography (HRCT) of the chest is more sensitive for miliary TB than plain chest radiography and has improved antemortem diagnosis [62]. Numerous 2 to 3 mm nodules can be visualized distributed throughout the lung (image 3). Septal thickening usually accompanies these nodules. These findings are sensitive but not necessarily specific. In series correlating clinical and pathologic findings with HRCT, disseminated nodules were found in many other infections (Haemophilus influenzae, Mycoplasma pneumoniae, Candida albicans) and noninfectious diseases (sarcoidosis, metastatic adenocarcinoma, lymphoma, amyloidosis, hypersensitivity pneumonitis, and pneumoconiosis) [63,64].

Other nonspecific findings on chest CT can be observed in miliary TB. As an example, in one study, ground glass opacities covering >50 percent of the lung field were seen in 20 percent of patients with miliary TB [65].
**Other imaging** — Gallium scans can show diffuse pulmonary and extrapulmonary uptake in miliary TB [66]. However, sensitivity and specificity are limited; patients with miliary TB and evidence of miliary patterns on chest imaging may have negative gallium scans.

Abdominal imaging may also show findings consistent with miliary TB [67]. Contrast-enhanced abdominal computed tomography may demonstrate multiple foci of low attenuation, typically without enhancement after intravenous contrast administration. Ultrasound may reveal multiple echogenic lesions with surrounding hypoechoic halos.

**DIAGNOSIS** — Establishing a diagnosis of miliary tuberculosis (TB) requires sufficient clinical suspicion; the diagnosis can be challenging due to nonspecific clinical symptoms and signs [68]. Careful diagnostic evaluation of extrapulmonary findings is warranted whether systemic disease is suspected in the setting of known pulmonary TB or whether extrapulmonary disease is the initial presenting factor prompting clinical attention. This is important because the nature and scope of extrapulmonary findings observed on diagnostic evaluation may influence the approach to treatment.

**Clinical approach** — Clinical evaluation begins with a thorough history and physical examination (including a dilated funduscopic examination, which can be helpful in the diagnosis of hematogenous spread of TB). In general, an evaluation for pulmonary disease is warranted in all patients in whom disseminated TB is suspected (table 6), including chest radiography (followed by computed tomography, if warranted), sputum for acid-fast smear and culture, and tuberculin skin test. If sputum cannot be obtained, evaluation of bronchoscopy or gastric secretions may be warranted. In addition, mycobacterial blood culture should be performed using a lysis centrifugation or automated broth system designed for mycobacterial culture [69-71]. In regions where available, molecular tests can be useful rapid diagnostic tools. (See "Tuberculin skin test" below and 'Acid-fast smear and culture' below and 'Molecular tests' below and "Diagnosis of pulmonary tuberculosis in HIV-uninfected patients".)

The subsequent diagnostic approach should be tailored to localizing signs or symptoms of disease involvement:

- **Patients with neurologic signs or symptoms** should undergo neuroimaging and lumbar puncture (if feasible). The most common radiographic findings in tuberculous meningitis are basal meningeal enhancement and/or hydrocephalus. Cerebrospinal fluid (CSF) should be analyzed for cell count, protein, and glucose concentrations, as well as acid-fast staining and culture for bacterial and mycobacterial organisms. (See "Central nervous system tuberculosis".)
- **In the setting of pleural effusion, pericardial effusion or ascites, fluid should be obtained for evaluation of cell count, protein, glucose, and LDH concentrations, as well as acid-fast staining and culture for bacterial and mycobacterial organisms.** Pleural biopsy is warranted in the setting of moderate to high suspicion for TB when pleural fluid evaluation is not diagnostic. (See "Tuberculous pleural effusions in HIV-uninfected patients" and "Tuberculous pericarditis" and "Tuberculous peritonitis".)
- **Patients with symptoms referable to the gastrointestinal or genitourinary tract** should undergo radiographic imaging of the involved site(s). Gastrointestinal disease may warrant further endoscopic and/or surgical evaluation. Suspected genitourinary disease should prompt urine acid-fast bacillus (AFB) culture (urine AFB smears are less useful since they can be confounded by other, nontuberculous mycobacteria). (See "Renal disease in tuberculosis".)
- **Patients with symptoms localizing to other extrapulmonary sites** (lymph nodes, bones/joints, skin, and other sites) should undergo evaluation as warranted depending on the involved organ system. Radiographic imaging may be warranted. Tissue biopsy may be required to establish a definitive diagnosis. (See"Tuberculous lymphadenitis" and "Skeletal tuberculosis" and "Cutaneous manifestations of tuberculosis".)

Biopsy specimens from the lung, bone marrow, pericardium, lymph nodes, bones, joints, bowel, liver, brain, or other tissues allow for both histopathologic examination and culture. Liver biopsies are generally associated with the highest yield for diagnosis of extrapulmonary TB. In two series, granulomas were demonstrated more frequently in liver biopsies (91 to 100 percent) than bone marrow biopsies (31 to 82 percent) or transbronchial biopsies (72 and 63 percent) [1,2]. Lymph nodes and serosal biopsies also had high yields in patients in these series. The biopsy yield is likely to be increased in the setting of associated clinical or laboratory abnormalities. Biopsy specimens should be collected with and without fixative; culture requires specimens without fixative. (See 'Histopathology' below.)

There is no role for serologic testing in diagnosis of TB; such tests have very low specificity [72-75]. While large numbers of individuals worldwide have TB antibodies, only about 10 percent of them go on to develop active disease.
Diagnostic tools

**Tuberculin skin test** — The **tuberculin skin test** can be a supportive diagnostic tool if positive, but a negative skin test does not exclude the diagnosis; anergy is observed more frequently among patients with miliary TB than those with pulmonary or isolated extrapulmonary involvement and may be as high as 68 percent [76]. (See "Diagnosis of latent tuberculosis infection (tuberculosis screening) in HIV-uninfected adults", section on ‘Tuberculin skin test’.)

**Acid-fast smear and culture** — Acid-fast culture of tissue, fluid, or drainage from an infected locus is the standard tool for establishing the diagnosis of TB. Acid-fast microscopy may support a diagnosis of TB, especially if organisms or caseating granulomas are seen. The frequency of positive smears or cultures is summarized in the Table (table 7 [1,2]). These data make several important points:

- Smears for acid-fast bacilli were positive in a minority of patients when only a single site was sampled; the probability of a positive smear increased with the number of sites sampled. Thus, when possible, samples of multiple sites (sputum, gastric aspirate, pleural fluid, ascites, urine) should be examined for the presence of acid-fast bacilli.
- Gastric aspirate cultures were frequently positive in these series. However, it was not clear how often they were positive when sputum smears were negative. It is reasonable to obtain gastric aspirates if sputum smears are not available or negative.
- Bronchoscopy may be warranted if acid-fast bacilli are not detected at multiple sites (sputum, gastric aspirate, pleural fluid, ascites, urine); in general, bronchoscopy is most useful when there is evidence of pulmonary involvement on chest radiography [77,78]. In the setting of subacute or chronic presentation with negative sputum smears, it is reasonable to delay bronchoscopy until cultures are negative for one to two weeks, particularly if a rapid diagnostic assay is available. In the setting of acute presentation or in the absence of rapid diagnostic tools, prompt bronchoscopy is warranted. (See 'Molecular tests' below.)

Smears should be stained with the acid-fast fluorochrome dye, auramine-O, which is more sensitive than the conventional Ziehl-Nielsen stain [79]. Rapid probes can be applied to smear-positive sputum specimens to confirm the diagnosis of *M. tuberculosis* (in areas where available) [80]. Specimens should then be inoculated into a commercial automated radiometric detection system (BACTEC, Becton Dickson), which is faster and more sensitive than standard techniques using solid medium for the isolation of *M. tuberculosis* [81]. *M. tuberculosis* can be differentiated from commonly isolated nontuberculous mycobacteria by hybridization using nucleic acid probes on the liquid medium.

Mycobacterial blood cultures (preferably using lysis centrifugation techniques) should be performed in all patients in whom hematogenous dissemination is suspected [69]. Positive blood cultures in disseminated TB are relatively rare though may be observed in immunocompromised patients, including those with HIV infection [71,82].

**Histopathology** — Histopathology of tissue biopsy specimens in the setting of TB typically demonstrates granulomatous inflammation. Granulomas of TB characteristically contain epithelioid macrophages, Langhans giant cells, and lymphocytes. The centers of tuberculous granulomas often have characteristic caseation (“cheese-like”) necrosis; organisms may or may not be seen with acid-fast staining. The demonstration of characteristic caseating granulomas on a tissue section in the appropriate clinical and epidemiologic circumstances strongly supports a diagnosis of active TB, but it is not pathognomonic; culture is required to establish a laboratory diagnosis [83].

**Molecular tests** — In regions where available, molecular tests can be useful rapid diagnostic tools.

**Nucleic acid amplification** — Nucleic acid amplification assays (NAA) are used to amplify the quantity of *M. tuberculosis* DNA in diagnostic specimens where organisms may be present in amounts too small to be seen by routine staining techniques. These techniques are sensitive for rapid detection of *M. tuberculosis* in a variety of specimens, including blood, sputum, and urine [84-90].

Two NAA tests were approved by the US Food and Drug Administration (FDA) as of 2012 but only for use with sputum or respiratory secretions obtained by bronchoscopy. Of these tests, the Amplified MTD test (GenProbe) is approved for AFB smear-positive or smear-negative specimens; Amplicor (Roche) is approved only for smear-positive samples. Sensitivity of these tests is better in smear-positive samples, and a positive test in the appropriate clinical setting likely represents pulmonary TB [91,92].

The primary advantage of these tests is that a positive result to establish a diagnosis may be available within 24 hours. The United States Centers for Disease Control and Prevention (CDC) has published recommendations for the
use of these tests in the diagnosis of TB [93]. (See "Diagnosis of pulmonary tuberculosis in HIV-uninfected patients", section on 'Nucleic acid amplification'.)

**Xpert MTB/RIF assay** — The Xpert MTB/RIF assay is an automated nucleic acid amplification test that can simultaneously identify *M. tuberculosis* and rifampin resistance. The Xpert MTB/RIF assay is approved by the United States Food and Drug Administration only for testing sputum in adults, although it may be applied in a nonapproved indication to non-sputum samples following a validation process for that indication by the laboratory performing the test. (See "Diagnosis of pulmonary tuberculosis in HIV-uninfected patients", section on 'Xpert MTB/RIF assay'.)

The Xpert MTB/RIF assay is useful for detection of extrapulmonary TB in lymph nodes and cerebrospinal fluid, but the sensitivity in pleural fluid is low [94-96]. In a systematic review and meta-analysis including 18 studies, the sensitivity and specificity for the Xpert MTB/RIF assay (compared with culture) in lymph nodes were 83 and 94 percent, respectively, in cerebrospinal fluid were 81 and 98 percent, respectively, and in pleural fluid were 46 and 99 percent, respectively [96].

**Other molecular tests** — Many hospital and clinical laboratories offer nucleic acid amplification testing for *M. tuberculosis* complex using molecular methods (eg, polymerase chain reaction [PCR]) not approved by the FDA but validated internally within the testing laboratory according to a written protocol. These "in-house" tests generally offer high specificity and, if positive, may be useful in supporting a clinical diagnosis of TB.

**DIFFERENTIAL DIAGNOSIS** — The differential diagnosis of miliary tuberculosis is broad and depends on the degree of dissemination and the involvement of specific tissues and organs. The anatomic distribution of granulomatous lesions within the lung on high-resolution computed tomography (CT) scanning can be helpful for distinguishing hematogenously disseminated processes like miliary tuberculosis (which exhibits a random distribution of lesions) from airway-centered disorders (such as inhalational diseases) and lymphatic-centered processes (such as sarcoidosis) [97].

A miliary pattern on chest imaging may be due to many conditions, including (table 5):

- **Histoplasmosis** – Clinical manifestations of histoplasmosis include fever, fatigue, hepatosplenomegaly, and pancytopenia. Pulmonary manifestations may include pneumonia, adenopathy, lung mass, lung nodule(s), and/or cavitary lung disease. The diagnosis is established via histopathology, culture, antigen detection, or serology. (See "Diagnosis and treatment of pulmonary histoplasmosis").
- **Sarcoidosis** – Clinical manifestations of sarcoidosis include cough, dyspnea, chest pain, eye lesions, and/or skin lesions. Bilateral hilar adenopathy is a classic chest radiograph finding; it may be absent and/or occur in combination with parenchymal opacities. The diagnosis is based on compatible clinical and radiographic manifestations and histopathologic detection of noncaseating granulomas. (See "Clinical manifestations and diagnosis of pulmonary sarcoidosis").
- **Hypersensitivity pneumonia** – Subacute or chronic hypersensitivity pneumonitis is characterized by productive cough, dyspnea, fatigue, anorexia, and weight loss. The diagnosis is based upon exposure history, clinical assessment, radiographic and physiologic findings, and the response to avoidance of the suspected etiologic agent. (See "Classification and clinical manifestations of hypersensitivity pneumonitis (extrinsic allergic alveolitis)").
- **Talc granulomatosis** – Clinical manifestations of talc granulomatosis are usually nonspecific such as dyspnea, cough, or an increase in sputum production. Some patients are asymptomatic; night sweats, weight loss, and hemoptysis occur less commonly. Clinical history and radiographic findings are often highly suggestive; when the diagnosis is unclear flexible bronchoscopy with bronchoalveolar lavage is warranted. (See "Foreign body granulomatosis").
- **Pulmonary hemosiderosis** – The clinical presentation of pulmonary hemosiderosis varies from an acute onset illness with hemoptysis and dyspnea to an insidious process characterized by fatigue, anemia, and slowly progressive exertional dyspnea. Radiography demonstrates bilateral ground glass alveolar opacities. Hemosiderin-laden alveolar macrophages may be identified in sputum, bronchoalveolar lavage fluid, and lung biopsy. (See "Idiopathic pulmonary hemosiderosis").
- **Primary bronchoalveolar carcinoma** – Radiographic findings of bronchioloalveolar carcinoma may be variable and range from a solitary or limited number of nodules to more extensive miliary disease or diffuse parenchymal
Miliary tuberculosis (TB) refers to clinical disease resulting from the hematogenous dissemination of *Mycobacterium tuberculosis*. Millary TB can arise as a result of progressive primary infection or via reactivation of a latent focus with subsequent spread. The clinical presentation of miliary TB is highly variable; the factors that contribute to survival in miliary TB are difficult to assess, since the literature is generally limited to disease involving the central nervous system (CNS), some patients with bone or joint disease, and some cases of lymphadenitis (a site of early relapse in anecdotal reports) [99]. Depending on the site(s) and scope of disease, surgical intervention may be needed for diagnostic and/or therapeutic management.

The factors that contribute to survival in miliary TB are difficult to assess, since the literature is generally limited to retrospective case and includes patients with variable clinical and laboratory presentations. However, central nervous system disease appears to be an independent predictor of mortality in most studies [2,3,102]. Pancytopenia or lymphopenia were poor prognostic indicators in some studies [1,56]. Age, late presentation, serious underlying disease, and a nonreactive tuberculin skin test are cited in other studies as predictors of mortality [103].

The clinical course and outcomes of miliary tuberculosis (TB) have improved markedly between the pre-antibiotic and postantibiotic eras [29,102]. In the United States Veteran's Administration study of miliary TB (excluding meningitis), the attributable mortality dropped successively (from nearly 100 percent) with the introduction of each new drug. Mortality dropped with the introduction of streptomycin (to 47 percent), with streptomycin plus paraaminosalicylic acid (to 18 percent), and with isoniazid-based combination therapy (to 5 percent) [102]. Subsequently, two large series noted mortality of approximately 20 percent [1,2]. These studies included relatively diverse populations with a range of underlying diseases and did not exclude meningeal TB. Since the introduction of isoniazid-based therapy, case series have documented shorter duration of fever and more rapid clinical and radiographic improvement. In one study, the median time to defervescence was seven days (range 1 to 55 days); 76 percent of patients were afebrile within 14 days of the initiation of therapy [1].

In general, the approach to antimicrobial therapy for treatment of miliary tuberculosis (TB) is the same as for pulmonary TB [98]. This approach is based upon retrospective review of a relatively small number of patients with extrapulmonary TB, since extrapulmonary TB is much less common than pulmonary TB. While the data suggest that this approach is successful, individualization of regimens may be warranted. (See “Treatment of pulmonary tuberculosis in HIV-uninfected adults” and “Treatment of pulmonary tuberculosis in HIV-infected adults”.)

Prevention — Miliary tuberculosis (TB) can be prevented by treatment of latent TB infection. In addition, childhood administration of Bacillus Calmette-Guérin (BCG) in endemic areas reduces the incidence of miliary TB. A large meta-analysis found a 78 percent protective effect of the vaccine against miliary TB [104]. (See “Treatment of latent tuberculosis infection in HIV-uninfected adults” and “Treatment of latent tuberculosis infection in HIV-infected adults” and “BCG vaccination”.)

Summary

- Miliary tuberculosis (TB) refers to clinical disease resulting from the hematogenous dissemination of *Mycobacterium tuberculosis*. Millary TB can arise as a result of progressive primary infection or via reactivation of a latent focus with subsequent spread. The clinical presentation of miliary TB is highly variable; manifestations can be acute but are more likely to be subacute or chronic. (See ‘Introduction’ above.)
- Acute disease may be fulminant, including multiorgan system failure, a syndrome of septic shock and acute respiratory distress syndrome (ARDS). Patients with subacute or chronic disease may present with failure to

TREATMENT — In general, the approach to antimicrobial therapy for treatment of miliary tuberculosis (TB) is the same as for pulmonary TB [98]. This approach is based upon retrospective review of a relatively small number of patients with extrapulmonary TB, since extrapulmonary TB is much less common than pulmonary TB. While the data suggest that this approach is successful, individualization of regimens may be warranted. (See “Treatment of pulmonary tuberculosis in HIV-uninfected adults” and “Treatment of pulmonary tuberculosis in HIV-infected adults”.)

Modifications to the standard drug regimen may be warranted in the setting of drug-resistant TB. In addition, longer duration of therapy may be warranted for children, immunocompromised hosts, patients with a large organism burden, and patients with a slow microbiologic or clinical response. Longer duration of therapy is also warranted for patients with disease involving the central nervous system (CNS), some patients with bone or joint disease, and some cases of lymphadenitis (a site of early relapse in anecdotal reports) [99]. Depending on the site(s) and scope of disease, surgical intervention may be needed for diagnostic and/or therapeutic management.

Data on the role of corticosteroids in patients with miliary TB are limited; results of case reports and small clinical series using corticosteroids in miliary TB are conflicting [27]. In some circumstances, corticosteroids are warranted for treatment of TB involving the CNS [100] or pericardium [101]. (See “Central nervous system tuberculosis”, section on ‘Glucocorticoids’.)

OUTCOME — The clinical course and outcomes of miliary tuberculosis (TB) have improved markedly between the pre-antibiotic and postantibiotic eras [29,102]. In the United States Veteran’s Administration study of miliary TB (excluding meningitis), the attributable mortality dropped successively (from nearly 100 percent) with the introduction of each new drug. Mortality dropped with the introduction of streptomycin (to 47 percent), with streptomycin plus paraaminosalicylic acid (to 18 percent), and with isoniazid-based combination therapy (to 5 percent) [102]. Subsequently, two large series noted mortality of approximately 20 percent [1,2]. These studies included relatively diverse populations with a range of underlying diseases and did not exclude meningeal TB. Since the introduction of isoniazid-based therapy, case series have documented shorter duration of fever and more rapid clinical and radiographic improvement. In one study, the median time to defervescence was seven days (range 1 to 55 days); 76 percent of patients were afebrile within 14 days of the initiation of therapy [1].

The factors that contribute to survival in miliary TB are difficult to assess, since the literature is generally limited to retrospective case and includes patients with variable clinical and laboratory presentations. However, central nervous system disease appears to be an independent predictor of mortality in most studies [2,3,102]. Pancytopenia or lymphopenia were poor prognostic indicators in some studies [1,56]. Age, late presentation, serious underlying disease, and a nonreactive tuberculin skin test are cited in other studies as predictors of mortality [103].

Prevention — Miliary tuberculosis (TB) can be prevented by treatment of latent TB infection. In addition, childhood administration of Bacillus Calmette-Guérin (BCG) in endemic areas reduces the incidence of miliary TB. A large meta-analysis found a 78 percent protective effect of the vaccine against miliary TB [104]. (See “Treatment of latent tuberculosis infection in HIV-uninfected adults” and “Treatment of latent tuberculosis infection in HIV-infected adults” and “BCG vaccination”.)
thrive, fever of unknown origin, or dysfunction of one or more organ systems. The most common extrapulmonary sites of disease include the lymphatic system, bones and joints, and the liver. The clinical approach to evaluation of TB at extrapulmonary sites is discussed in detail separately. (See ‘Clinical manifestations’ above.)

- The most common laboratory abnormalities include anemia and other hematologic findings. Other laboratory abnormalities may include elevated acute phase reactants, hyponatremia, hypercalcemia and sterile pyuria. The classic chest radiograph appearance is a faint, reticulonodular infiltrate distributed fairly uniformly throughout the lungs (image 2). Other chest radiograph abnormalities include pleural reactions, hilar or mediastinal adenopathy, interstitial or alveolar infiltrates, or cavities. Computed tomography of the chest is more sensitive for evaluation of miliary TB than plain chest radiography (See ‘Laboratory findings’ above and ‘Radiographic imaging’ above.)

- Clinical evaluation begins with a thorough history and physical examination. In general, an evaluation for pulmonary disease is warranted in all patients in whom disseminated TB is suspected. In addition, mycobacterial blood culture should be performed. In regions where available, molecular tests can be useful rapid diagnostic tools. (See ‘Clinical approach’ above.)

- The subsequent diagnostic evaluation should be tailored to localizing signs or symptoms of disease involvement. Patients with neurologic signs or symptoms should undergo neuroimaging and lumbar puncture (if feasible). In the setting of pleural effusion, pericardial effusion, or ascites, fluid should be obtained for evaluation and a biopsy strongly considered. Radiographic imaging of the involved site(s) may be warranted for patients with symptoms referable to the gastrointestinal tract, genitourinary tract, bones/joints, or lymph nodes. Suspected genitourinary disease should prompt urine acid-fast bacillus (AFB) culture. Depending on the involved site(s), tissue biopsy may be required to establish a definitive diagnosis. (See ‘Clinical approach’ above.)

- Biopsy specimens allow for both histopathologic examination and acid-fast culture. Biopsy sites with relatively good yield include the pleura, liver, bone marrow, lymph nodes, and transbronchial biopsies; the yield is likely to be increased in the setting of associated clinical or laboratory abnormalities. Histopathology typically demonstrates granulomatous inflammation. Tuberculous granulomas characteristically contain epithelioid macrophages, Langhans giant cells, and lymphocytes, and the centers often have characteristic caseation (“cheese-like”) necrosis. (See ‘Histopathology’ above.)

- In general, the approach to antimicrobial therapy for treatment of miliary TB is the same as for pulmonary TB, although modifications may be warranted in the setting of drug-resistant TB. In addition, longer duration of therapy may be warranted for children, immunocompromised hosts, patients with a large organism burden, and patients with a slow microbiologic or clinical response. Longer duration of therapy is also warranted for patients with disease involving the central nervous system, some patients with bone or joint disease, and some cases of lymphadenitis. Surgical intervention may be needed for diagnostic and/or therapeutic management in some cases. (See ‘Treatment’ above.)

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REFERENCES


Comparative size of millet seeds

Millet seeds from which the name miliary tuberculosis derives compared to the size of a dime (right) and a centimeter scale (left). These correspond to the approximate size of miliary lesions seen on chest radiograph.
<table>
<thead>
<tr>
<th>First author, year</th>
<th>Years included</th>
<th>Location</th>
<th>Inclusion criteria</th>
<th># of patients</th>
<th>Percent male</th>
<th>Race, percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maartens, 1990</td>
<td>1978 to 1987</td>
<td>Groote Schuur Hospital (community-based teaching hospital in South Africa)</td>
<td>Miliary pattern on CXR plus MTB on culture from any site; or biopsy or autopsy evidence of miliary organ involvement with TB</td>
<td>109</td>
<td>51</td>
<td>African, 45, mixed, 49, white, 6</td>
</tr>
<tr>
<td>Kim, 1990</td>
<td>1975 to 1988</td>
<td>Duke University Medical Center and Durham VA Hospital Durham, North Carolina</td>
<td>Discharge diagnosis of disseminated or miliary TB</td>
<td>38</td>
<td>50</td>
<td>African-American, 50*</td>
</tr>
<tr>
<td>Gelb, 1973</td>
<td>1960 to 1970</td>
<td>UCLA Hospital Los Angeles, California</td>
<td>Miliary pattern on CXR and one or more: 1. MTB on culture 2. Biopsy or autopsy showing caseating granulomas with AFB 3. Clinical presentation and response consistent with TB</td>
<td>109</td>
<td>59</td>
<td>African-American, 81</td>
</tr>
<tr>
<td>Munt, 1971</td>
<td>1954 to 1970</td>
<td>Sanitorium drawing from eastern part of North Carolina</td>
<td>“Acute, diffuse pulmonary and extra-pulmonary dissemination of TB, usually associated with a miliary pattern on CXR, with either MTB by culture or response to TB therapy”</td>
<td>69</td>
<td>65</td>
<td>African-American, 87</td>
</tr>
<tr>
<td>Proudfoot, 1969</td>
<td>1954 to 1967</td>
<td>Edinburgh, Scotland</td>
<td>“Adults diagnosed in Edinburgh as having disseminated TB”</td>
<td>40</td>
<td>40</td>
<td>Non-British, &lt;1</td>
</tr>
<tr>
<td>Biehl, 1957</td>
<td>1951 to 1956</td>
<td>Cincinatti General (city teaching hospital Cincinatti, Ohio)</td>
<td>Bacteriologic or pathologic diagnosis of miliary tuberculosis or probable diagnosis with response to therapy</td>
<td>68</td>
<td>69</td>
<td>African-American, 23</td>
</tr>
</tbody>
</table>

* Excluding VA population.
### Symptoms in patients with miliary tuberculosis

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever and/or night sweats</td>
<td>96*</td>
<td>89</td>
<td>85</td>
<td>83</td>
<td>83</td>
<td>35</td>
</tr>
<tr>
<td>Anorexia</td>
<td>92</td>
<td>78</td>
<td>87</td>
<td>91</td>
<td></td>
<td>42</td>
</tr>
<tr>
<td>Weight loss</td>
<td>92</td>
<td>66</td>
<td>87</td>
<td>85</td>
<td>75</td>
<td>61</td>
</tr>
<tr>
<td>Weakness or malaise</td>
<td>92</td>
<td></td>
<td>92</td>
<td>78</td>
<td></td>
<td>40</td>
</tr>
<tr>
<td>Respiratory (cough, dyspnea, pleuritic chest pain)</td>
<td>72</td>
<td>55</td>
<td>69</td>
<td>78</td>
<td>18</td>
<td>91</td>
</tr>
<tr>
<td>Gastrointestinal (abdominal pain, nausea, vomiting, diarrhea)</td>
<td>21</td>
<td></td>
<td></td>
<td>12</td>
<td></td>
<td>32</td>
</tr>
<tr>
<td>Headache or central nervous system</td>
<td>25</td>
<td>5</td>
<td>16</td>
<td>10</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* All of the numbers recorded are percentages
## Physical signs in patients with miliary tuberculosis

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>96*</td>
<td>90</td>
<td>85</td>
<td>84</td>
<td>82</td>
</tr>
<tr>
<td>Pulmonary (rales, rhonchi, rubs, signs of effusion)</td>
<td>72</td>
<td>50</td>
<td>51</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>52</td>
<td>16</td>
<td>31</td>
<td>36</td>
<td>20</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>15</td>
<td>13</td>
<td>11</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Neurologic (altered mental status, meningismus)</td>
<td>20</td>
<td>32</td>
<td>15</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>Ascites</td>
<td></td>
<td>8</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td></td>
<td>5</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatologic</td>
<td>4</td>
<td>8</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive PPD</td>
<td>42</td>
<td>28</td>
<td></td>
<td>53</td>
<td></td>
</tr>
</tbody>
</table>
Millet seeds are small grains (average diameter <2 mm) that are consumed without their outer layer being removed. Pearl millet (*Pennisetum typhoides*, bajra) is shown here. These grains (inset, upper right) correspond to the approximate size of miliary lesions on the high-resolution computer tomography scan of the chest (inset, lower left).

**Tuberculous ureteric stricture**

Intravenous urogram showing diseased left kidney with hydroureronephrosis because of stricture of lower ureter. The bladder is of small capacity.
### Laboratory findings in patients with miliary tuberculosis

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>52*</td>
<td>38</td>
<td>58</td>
<td>12</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>15</td>
<td></td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>Leukocytosis or left shift</td>
<td>14</td>
<td>61</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>23</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytosis</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>78</td>
<td>68</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Elevated alkaline phosphatase</td>
<td>83</td>
<td></td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Transaminitis</td>
<td>42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>15</td>
<td>8</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Elevated ESR &gt;50</td>
<td>68</td>
<td></td>
<td></td>
<td>97</td>
</tr>
<tr>
<td>Hypoxemia (pO2 &lt;60)</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sterile pyuria</td>
<td>32</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

ESR: erythrocyte sedimentation rate.* Numbers are percentages
A full PA radiograph of the chest shows diffuse involvement (left). The right panel is magnified, illustrating the reticulonodular pattern of miliary tuberculosis.
# Differential diagnosis of febrile illness with miliary chest x-ray infiltrates

<table>
<thead>
<tr>
<th>Infectious Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mycobacterial</strong></td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td>Atypical mycobacteria</td>
</tr>
<tr>
<td><strong>Fungal</strong></td>
</tr>
<tr>
<td>Endemic fungi (histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidioidomycosis)</td>
</tr>
<tr>
<td><strong>Bacterial</strong></td>
</tr>
<tr>
<td><em>Legionella micdadei</em> infection</td>
</tr>
<tr>
<td>Nocardiosis</td>
</tr>
<tr>
<td><em>Staphylococcus aureus, Haemophilus influenzae</em> and other pyogenic bacteria</td>
</tr>
<tr>
<td>Psittacosis</td>
</tr>
<tr>
<td>Tularemia</td>
</tr>
<tr>
<td>Bartonellosis</td>
</tr>
<tr>
<td>Brucellosis</td>
</tr>
<tr>
<td>Melioidosis</td>
</tr>
<tr>
<td><strong>Viral</strong></td>
</tr>
<tr>
<td>Varicella</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Influenza</td>
</tr>
<tr>
<td>Measles</td>
</tr>
<tr>
<td><strong>Parasitic</strong></td>
</tr>
<tr>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td>Strongyloidiasis</td>
</tr>
<tr>
<td>Schistosomiasis</td>
</tr>
<tr>
<td><strong>Neoplastic diseases</strong></td>
</tr>
<tr>
<td>Lymphoma</td>
</tr>
<tr>
<td>Lymphangitic spread of carcinoma</td>
</tr>
<tr>
<td>Mesothelioma</td>
</tr>
<tr>
<td>Other diseases</td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Hypersensitivity pneumonitis</td>
</tr>
<tr>
<td>Pneumoconioses</td>
</tr>
<tr>
<td>Foreign-body induced vasculitis related to injection drug use</td>
</tr>
</tbody>
</table>
High resolution computed tomography of the chest in a patient with miliary tuberculosis

Numerous 2 mm nodules and septal thickening are seen diffusely throughout the lung.

**Guidelines for the evaluation of pulmonary tuberculosis in adults in five clinical scenarios**

<table>
<thead>
<tr>
<th>Patient and setting</th>
<th>Recommended evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any patient with a cough of ≥2 to 3 weeks' duration, with at least one additional symptom, including fever, night sweats, weight loss, or hemoptysis</td>
<td>Chest radiograph: If suggestive of TB*, collect three sputum specimens for AFB smear microscopy and culture. At least one specimen should also be tested using an NAA test.</td>
</tr>
<tr>
<td>Any patient at high risk for TB(^t) with an unexplained illness, including respiratory symptoms, of ≥2 to 3 weeks' duration</td>
<td>Chest radiograph: If suggestive of TB*, collect three sputum specimens for AFB smear microscopy and culture. At least one specimen should also be tested using an NAA test.</td>
</tr>
<tr>
<td>Any patient with HIV infection and unexplained cough and fever</td>
<td>Chest radiograph, and collect three sputum specimens for AFB smear microscopy and culture. At least one specimen should also be tested using an NAA test.</td>
</tr>
<tr>
<td>Any patient at high risk for TB(^t) with a diagnosis of community-acquired pneumonia who has not improved after seven days of treatment</td>
<td>Chest radiograph, and collect three sputum specimens for AFB smear microscopy and culture. At least one specimen should also be tested using an NAA test.</td>
</tr>
<tr>
<td>Any patient at high risk for TB(^t) with incidental findings on chest radiograph suggestive of TB even if symptoms are minimal or absent(^\text{Δ})</td>
<td>Review of previous chest radiographs if available, three sputum specimens for AFB smear microscopy and culture. At least one specimen should also be tested using an NAA test.</td>
</tr>
</tbody>
</table>
TB: tuberculosis; AFB: acid-fast bacilli; NAA: nucleic acid amplification.* Infiltrates with or without cavitation in the upper lobes or the superior segments of the lower lobes.¶ Patients with one of the following characteristics: recent exposure to a person with a case of infectious TB; history of a positive test result for *Mycobacterium tuberculosis*; HIV infection; injection or noninjection drug use; foreign birth and immigration ≤5 years from a region in which incidence is high; residents and employees of high-risk congregate settings; membership in a medically underserved, low-income population; or a medical risk factor for TB (including diabetes mellitus, conditions requiring prolonged corticosteroid and other immunosuppressive therapy, chronic renal failure, certain hematological malignancies and carcinomas, weight >10 percent below ideal body weight, silicosis, gastrectomy, or jejunoileal bypass).Δ Chest radiograph performed for any reason, including targeted testing for latent TB infection and screening for TB disease.

### Frequency of positive smear or culture in patients with miliary tuberculosis

<table>
<thead>
<tr>
<th>Site</th>
<th>Maartens, 1990</th>
<th>Kim, 1990</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum smear</td>
<td>33*</td>
<td>36</td>
</tr>
<tr>
<td>Sputum culture</td>
<td>62</td>
<td>76</td>
</tr>
<tr>
<td>BAL smear</td>
<td>27</td>
<td>9</td>
</tr>
<tr>
<td>BAL culture</td>
<td>55</td>
<td>54</td>
</tr>
<tr>
<td>Gastric aspirate smear</td>
<td>43</td>
<td>0</td>
</tr>
<tr>
<td>Gastric aspirate culture</td>
<td>100</td>
<td>75</td>
</tr>
<tr>
<td>Urine smear</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Urine culture</td>
<td>33</td>
<td>59</td>
</tr>
<tr>
<td>CSF smear</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>CSF culture</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>Serosal smear</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Serosal culture</td>
<td>44*</td>
<td>14Δ</td>
</tr>
</tbody>
</table>

BAL: bronchoalveolar lavage; CSF: cerebrospinal fluid.* All numbers are percentages.¶ 9 ascites, 7 pleural, 2 pericardial.Δ All pleural.