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Acute Forms of Tuberculosis in Adults

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ABSTRACT

Although typically considered a chronic disease, tuberculosis (TB) has protean acute manifestations, the major forms of which are reviewed in this article. The pathogenesis of acute TB, although still incompletely understood, may be related to both epidemiologic and genetic host factors. Miliary TB manifests as a nonspecific clinical syndrome with a high mortality rate. The most well-known form of acute TB is meningitis, characterized by fever, nuchal rigidity, and a lymphocytic pleocytosis of the cerebrospinal fluid. Acute abdominal TB may present with obstruction or less commonly as perforated viscus or peritonitis. Critically ill patients may have acute respiratory distress syndrome, shock, or disseminated intravascular coagulopathy. The spectrum of disease makes diagnosis of acute TB difficult unless clinical suspicion of disease is high, but the high mortality mandates its consideration. Early initiation of therapy is crucial to optimize clinical outcome.

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Despite major medical advances since the discovery of Koch's bacillus, tuberculosis (TB) remains a diagnostic challenge. Given its protean and often nonspecific features, cases often can be missed, especially in areas with a low disease incidence. The patient with pulmonary TB classically presents with several months of both constitutional (fever, weight loss, and night sweats) and localized symptoms (cough and hemoptysis). Although commonly thought of as a chronic pulmonary disease, TB also might present acutely in almost any organ system and mimic other common infectious or noninfectious processes. Many such unusual manifestations have been described, but this article will review the pathophysiology, risk factors, and clinical manifestations of the major forms of acute TB (duration of symptoms/signs $\leq$ 30 days) in adults.

PATHOPHYSIOLOGY AND RISK FACTORS

Once *Mycobacterium tuberculosis* is inhaled into the lungs, a series of immunologic events leads to 3 possible outcomes: eradication, primary infection, or latent infection. Acute TB can arise as a primary disease or from reactivation of latent infection. Primary infection in most individuals is asymptomatic or mild; acute symptomatic disease requiring medical attention develops in only 3% to 10%.[1] Latent TB affects approximately one third of the world's population, all of whom are potentially at risk for reactivation and acute disease. Less commonly, reinfection with TB also might lead to an acute clinical syndrome.

Many host factors contribute to the development of active primary disease. A higher risk of primary disease is associated with age (peaking between the ages of 15 to 29 years), human immunodeficiency virus (HIV) infection, increasing tuberculin skin test size, and inversely from time of exposure.[2] At least two thirds of adult TB cases, and likely most acute presentations, are thought to result from reactivation. Risk factors for reactivation include chronic medical conditions, such as HIV infection, insulin-dependent diabetes, transplantation, or chronic renal failure, and might be affected by older age, ethnicity, and duration of latent infection.[3] Acute TB, including severe extrapulmonary disease, has been reported within 1 week of initiation of infliximab, a tumor necrosis factor-α antagonist.[4]

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The immune status of the patient may play an important role in disease pathogenesis. The exact mechanisms governing the host–pathogen interactions resulting in clinical outcome is complex and remains incompletely understood, although some patterns emerge. For example, young adults have a higher number of lymphoid-rich Peyer's patches, which can explain the higher incidence of intestinal TB between the ages of 15 and 25 years.[5] The rapid clinical course seen in some HIV-infected patients may be explained by a deficient response at the cellular level, resulting in less inflammation with fewer granulomas, more necrosis, and greater numbers of acid-fast organisms on histology. A T-helper 1-mediated response might be an important component in acuity of disease; mice with deficient interferon-γ or tumor necrosis factor-α production have more rapid, progressive disease when exposed to TB.[6] Disease severity and susceptibility might be mediated by mutations and polymorphisms in the interferon-γ response pathway.[7] The contribution to the severity and onset of clinical disease of these and other components of the immunologic response to TB continues to be explored.

Special attention should be given to immunocompromised patients because an altered immune response can result in atypical manifestations. For example, most patients aged 65 years or more have few classic clinical or laboratory features of TB, and patients coinfected with HIV have fewer neurologic signs, lower cerebrospinal fluid (CSF) and serum leukocyte counts, and more frequent extrapulmonary disease and positive microbiology.[8]

CLINICAL SIGNIFICANCE

- Acute tuberculosis can manifest in nearly any organ system, although the most well described forms are miliary, meningeal, abdominal, and pulmonary.
- Consider acute tuberculosis in critically ill patients with enigmatic acute respiratory distress syndrome, shock, or disseminated intravascular coagulation.
- Diagnosis requires a high index of suspicion; clinical, radiographic, pathologic, and laboratory findings individually are often nonspecific, but helpful considered together.
- Early recognition and diagnosis are essential to initiate prompt, appropriate treatment.

ACUTE PRESENTATIONS OF TUBERCULOSIS

Miliary Disease

Two well-defined entities exist at either end of the spectrum of miliary TB: acute miliary TB and nonreactive TB. Acute miliary TB has a severe, rapidly progressive course, usually after acute infection in young adults, and is characterized by caseating granulomas with few organisms, frequently resulting in negative acid-fast bacilli (AFB) stains and cultures. Nonreactive TB usually occurs in older adults with disease reactivation. AFB cultures are frequently positive, and the pathologic hallmark is scattered microabscesses with neutrophils and abundant AFB surrounded by normal parenchyma.[9] One third of patients with nonreactive TB present with less than 4 weeks of symptoms.[10] Nonreactive TB also is called cryptic TB because it may be associated with minimal symptoms and a normal chest film; antemortem diagnosis occurs in as little as 20% of cases.[11] The full spectrum of miliary TB will be discussed below.

Although the peak incidence of miliary TB is in the second to fourth decades of life, it may occur at any age.[12] Up to 20% of those with a chronic form of TB have evidence of acute miliary TB at autopsy. In those dying of acute TB, the disease is diagnosed premortem in approximately 25%.[11] Approximately one third of patients with acute miliary TB have an underlying comorbidity, including diabetes, pregnancy, or chronic corticosteroid use.[10,13] Less than 25% had either exposure to or history of active TB.[11] Mortality is high (up to 33%) and increases with age, underlying medical illness, and the presence of meningitis; there are conflicting reports in the literature whether the duration of symptoms affects mortality.[10,11,14]

The most common symptoms of miliary TB (**Table 1**) are nonspecific: anorexia, fever, cough, and weight loss. However, rapidity of onset and severity might be helpful in establishing the diagnosis.[11] Constitutional and respiratory symptoms are common, but central nervous system symptoms are not.[10,11,14] Nearly all have fever, and most have abnormal chest findings, but sometimes/occasionally is not present at the extremes of age or with meningitis.[10,11,14] Although the spleen or liver is palpable in more than one third of patients, clinically significant organomegaly is found in less than 10% at autopsy.[11] Both choroidal tubercles (bilateral, pale, grayish-white oblong patches with indistinct edges on ophthalmologic examination) and cutaneous findings (*tuberculosis cutis acuta generalisata*) are thought to be highly specific, but not sensitive, for miliary TB.[11] The majority of patients with

Table 1 Clinical Findings in Acute Forms of Miliary Tuberculosis[10,11,14]

Finding	Frequency
Fever	93%
Weight loss	85%
Night sweats	79%
Dyspnea	64%
Cough	82%
Abnormal physical examination results for chest	57%-72%
Splenomegaly*	78%
Hepatomegaly*	35%

*Pathologically significant in <10% at autopsy.

Table 2 Laboratory and Radiological Findings in Acute Forms of Miliary Tuberculosis[10,11,14]

Finding	Frequency
Hematologic abnormalities	
Anemia	68%-84%
Leukopenia	18%-49%
Leukocytosis	16%-29%
Positive tuberculin skin test	~50%
Chest radiography	
Normal	4%-22%
Miliary pattern	39%-50%
Other abnormality	46%

presenting symptoms of abdominal pain or headache have TB at those sites.[13]

Leukocyte counts may vary over the clinical course, with leukocytosis or leukopenia occurring at some point among most patients.[11] Anemia is common, with pancytopenia being less frequent.[11] Elevated alkaline phosphatase and hyponatremia occur in approximately half of patients.[10,14] In autopsy series, the classic miliary pattern is seen on chest radiography in less than half of patients but is clear on admission in approximately one fourth of patients (**Table 2**).[10,14]

Given the nonspecific clinical presentation, the diagnosis of acute forms of miliary TB is difficult to establish, and time to diagnosis averaged 1 month in older studies.[13] The disease is frequently mistaken for viral or bacterial pneumonia, or treated as a fever of unknown origin.[13,14] By using either smear or culture from sputum, bone marrow, CSF, and bronchioalveolar lavage alone, the sensitivity ranges from 30% to 60%; gastric lavage can provide a higher microbiologic yield.[10,11,14] By using a combination of biopsies with stains from multiple sites, rapid diagnosis can be achieved in 83% of all patients; this strategy may be especially useful for nonreactive TB.[10]

MENINGITIS

Meningitis is probably the most well-described acute presentation of TB. Clinical syndromes range from mimicking typical bacterial meningitis to a nonspecific, subacute illness characterized by fever and headache. Typically occurring in the fourth decade of life, meningitis seems to more commonly affect men.[8,15-18] When tested, 43% to 65% of patients are HIV infected and have an average CD4 count less than 200.[8,15,16]

The median duration of symptoms ranges from 12 to 29 days in most major series, and approximately one third of patients have symptoms of less than 1 week.[8,15,17] Few signs or symptoms are consistently present, with only headaches and vomiting in the majority of patients.[15-17,19-21] Other than fever, the most common physical finding is nuchal rigidity.[17-19] Neurologic findings can be summarized as outlined by British Medical Council definitions: fully conscious, nonspecific symptoms (stage I); signs of meningitis, lethargy, or cranial nerve palsies (stage II); stupor, severe illness, gross paralysis, or paresis (stage III). Most patients have some alteration in mental status, and nearly half present with British Medical Council stage III disease.[8,15,17,18,22] The classic finding of cranial nerve palsy, particularly oculomotor nerve dysfunction due to basilar involvement, is relatively frequent.[8,15,17,18,21,23] Other focal neurologic signs, such as hemiparesis, seizure, or Babinski's sign, are present in less than one fourth of patients (**Table 3**).[8,15-18,21,23]

The tuberculin skin test is negative in the majority, but as with other acute forms of TB, a negative tuberculin skin test does not rule out disease.[20] Serum leukocyte counts are typically normal, although anemia, hyponatremia, and elevated inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) are common.[8,15,17] Initial CSF examination may reveal mostly neutrophils, but the paradoxic change from lymphocytic to neutrophilic predominance over 48 hours occurs in up to 25% of patients and may be pathognomic of TB; CSF lymphocytic pleocytosis is common.[8,17,23,24] CSF protein is typically high and usually accompanied by a low, often severely depressed CSF glucose.[8,15-18,21] The results of CSF polymerase chain reaction assays may be diagnostic (**Table 4**).[25]

More than half of patients have an abnormality on chest radiography, but less than one third have the classic millet-seed appearance.[8,16,17,19,23] Computed tomography or magnetic resonance imaging of the head often is usually abnormal, with hydrocephalus being the most common finding, followed by basilar exudates or inflammation, tuberculoma, brain edema, or cerebral infarction.[15-17,19,23] AFB smear and culture are infrequently positive, with less than one third of cases having either a positive CSF smear or culture.[15,17,23] Most cases are diagnosed on the basis of clinical presentation, positive cultures from other sites, and a combination of laboratory and radiographic findings.

Standard anti-tuberculous regimens result in clearance of coma in a median of 7 days and of fever in a median of 8 to 14 days.[8,13,16] The use of corticosteroids in acute TB men-

Table 3 Clinical Findings in Acute Tuberculous Meningitis[8,15-22]

Finding	Frequency
Fever	68%-91%
Headache	83%-100%
Vomiting	77%-81%
Nuchal rigidity	68%-100%
Altered mental status	55%-72%
Cranial nerve palsy[a]	12%-45%
Other focal neurologic signs[b]	<25%
Tuberculin skin test positive	<50%

[a]Most frequently oculomotor nerve.
[b]Includes hemiparesis, seizure, or Babinski's sign.

Table 4 Laboratory and Radiologic Findings in Acute Tuberculous Meningitis[8,15-22]

CSF parameters	
Opening pressure	10-25 cm H_20
Leukocyte count	120-500 $\times$ 10^6 cells/mL
Lymphocytic pleocytosis	70%-92%
Protein	50-200 mg/dL
Glucose	2-48 mg/dL
AFB smear positive	13%-20%
AFB culture positive	10%-30%
Chest radiography	
Abnormality	50%-75%
Miliary pattern	9%-34%
Cranial computed tomography	
Abnormality[a]	68%-94%
Hydrocephalus	23%-55%

CSF = cerebrospinal fluid; AFB = acid-fast bacillus.
[a]Includes hydrocephalus, basilar meningitis, tuberculoma, edema, or infarction.

ingitis has been shown to decrease adverse events, but not mortality or morbidity.[8,17] Surgery can be required in up to 5% for symptomatic hydrocephalus.[17] Of particular interest, new symptoms may develop on therapy in approximately half of patients and may be ameliorated by corticosteroid therapy.[18]

The mortality for TB meningitis remains high, primarily because of delays in diagnosis and is between 10% and 50% at 1 year.[15,16,18,21,23] This rate seems to be related significantly to the severity of illness as measured by British Medical Council disease staging, with mortality of 19% at stage I and 69% at stage III.[8,17,23] Other predictors of mortality include CSF glucose less than 40 mg/dL, CSF protein greater than 1500 mg/dL, HIV infection, foci of TB outside the meninges, and a longer duration of illness.[8] Of those who survive, complete recovery occurs in 31% to 57%, with persistent major sequelae including hemiparesis, blindness, and seizures in up to one third of patients.[8,15,16,23]

ABDOMINAL DISEASE

Abdominal TB generally occurs during the third and fourth decades of life and is more common in women.[26] Between one tenth and one third of abdominal TB cases are acute, with an average duration of symptoms of 1 to 2 weeks.[26,27] Acute forms most commonly manifest in 3 clinical syndromes, often as surgical emergencies: peritonitis or acute abdomen (15%), obstruction (66%), and perforation (17%).[26-29] Gastrointestinal TB most commonly involves the ileocecal area, perhaps because of the high concentration of lymphoid tissue in the area, leading to obstruction (20%), perforation (15%), and bleeding (5%) in patients.[27]

Physical examination findings and laboratory data vary by and reflect the physiopathology typical of the clinical syndrome because signs of TB are often absent. The classic "doughy abdomen" seen in chronic forms is often absent.[26] The largest series of 139 patients with acute abdominal TB reported that 88% had abnormal bowel sounds, mostly hyperactive; distention and tenderness were frequent, but guarding was not.[26] On plain film, three quarters of patients had air fluid levels in the bowel, and 44% with peritonitis had pneumoperitoneum. The majority have abnormalities on plain abdominal films and computed tomography scan.[26]

Surgery for abdominal TB should be limited to emergency presentations and to establish a diagnosis.[30] Mortality after emergency surgery is higher than in elective cases, and conservative therapy with reassessment every 6 hours has been recommended, followed by surgery in approximately 2 weeks.[26] Because the presentations are nonspecific, a nonoperative diagnosis is difficult unless concomitant extraabdominal disease is present. The diagnosis is often based on the histologic finding of caseating granulomas, although the epidemiologic and clinical features of abdominal TB overlap with inflammatory bowel disease, causing misdiagnosis. Recovery of miliary TB is difficult and may be less than 10% because abdominal TB is paucibacillary.[27]

ACUTE TUBERCULOSIS IN THE CRITICAL CARE SETTING

The above manifestations of acute TB may progress in severity requiring care in an intensive care unit in 1% to 3% of cases.[31] Pulmonary TB is most common among these conditions to require critical care, with a resultant hospital mortality of 25% to 33%, and approaching 70% for those requiring mechanical ventilation (**Figure 1**).[32,33] Mechanical ventilation, adult respiratory distress syndrome, sepsis, acute renal failure, pancreatitis, and secondary nosocomial pneumonia are independent risk factors for inpatient mortality.[33] Adult respiratory distress syndrome is a rare complication of TB in both immunocompetent and immunocompromised populations, but it is the most frequent cause of mechanical ventilation in these patients.[32-34] Miliary TB carries the highest risk, but adult respiratory distress syndrome may be a sequela to nonmiliary pulmonary and other forms of TB.[32,34,35] Patients with TB-associated adult respiratory distress syndrome often have concomitant or develop multisystem disease.

TB also can infrequently lead to sepsis and shock, which has been well described in the literature since the original report by Landouzy.[36] Hematogenous dissemination of *M. tuberculosis* may occur with or without miliary disease, the latter known as Landouzy septicemia or *sepsis tuberculosa acutissima.* Disseminated TB from any cause might lead to septic shock with multiorgan failure, termed *sepsis tuberculosa gravissima.* TB-associated sepsis is most common in immunocompromised patients, especially patients with HIV, but may occur in immunocompetent patients.[37,38] These patients' conditions may progress rapidly from shock and multisystem failure to death, often before any specific sign of TB is apparent.[31,39-42]

Disseminated intravascular coagulopathy has been associated with many forms of disseminated TB; however, pa-

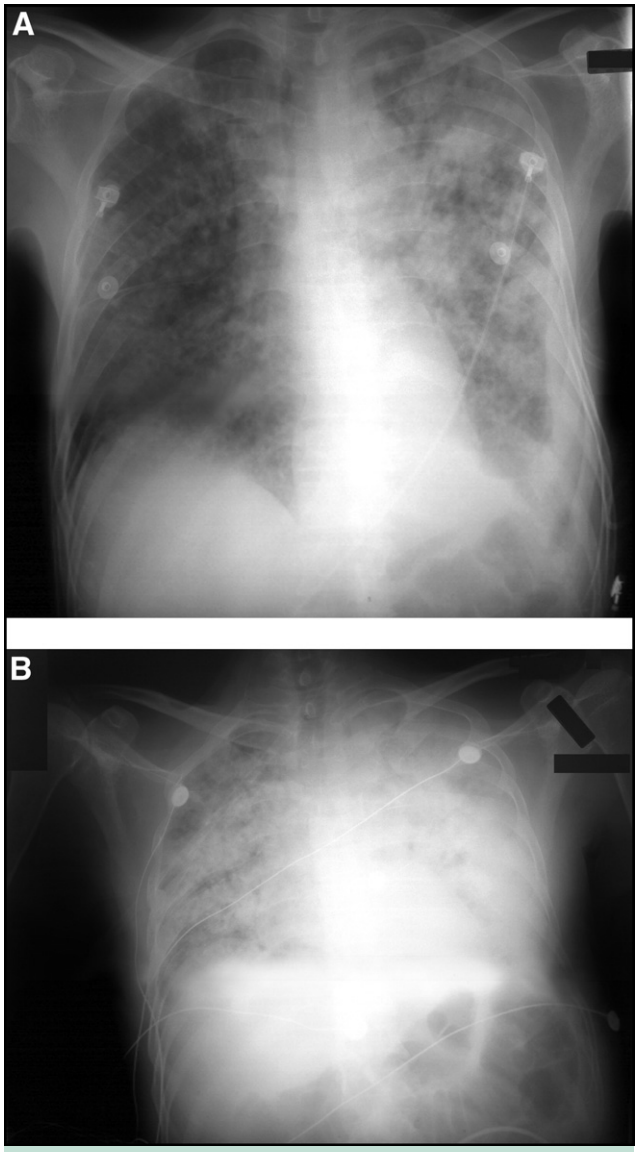

Figure 1 Admission chest radiograph demonstrating bilateral airspace disease and interstitial infiltrates in a patient with acute pulmonary TB **(A)**. Within 24 hours, the patient developed respiratory failure **(B)** requiring intubation.

tients with TB sepsis or TB-associated adult respiratory distress syndrome have a high incidence of disseminated intravascular coagulopathy.[35,41,42] Pancytopenia is often coincident with disseminated intravascular coagulopathy and TB sepsis but may be related to the immunocompromised state of the patient and the pathogenesis.[40] In addition, patients with TB-induced disseminated intravascular coagulopathy have high rates of hemophagocytic syndrome, more than 10% in one series.[43] These hematologic complications portend greater morbidity to patients with TB sepsis.[44]

The underlying pathophysiology of these processes is unknown, but many have postulated that production of tumor necrosis factor-α in response to lipoarabinomannan from *M. tuberculosis* may be a major factor in a patient's rapid deterioration, paralleling the effects of endotoxins such as lipopolysaccharide in bacterial sepsis.[39,45] In addition, *M. tuberculosis* can invade, inflame, and destroy bone marrow and potentially any other organ.

Hypovolemic shock may arise from TB adrenalitis with subsequent insufficiency[41] or massive hemoptysis, which may be associated with a ruptured Rasmussen's aneurysm.[46] Cardiogenic shock can be a consequence of TB myocarditis, endocarditis, pericarditis, or pericardial tamponade.

Recognition and early treatment may decrease mortality and the possible nosocomial spread of TB in the intensive care unit.[44,47] Given the fulminant presentations of acute TB, more typical causes of respiratory failure and sepsis are considered, leading to inadequate antibiotic therapy.[42] Because of the length of time required to identify *M. tuberculosis* and the nonspecific presentations, patients often die having received little or no antimycobacterial agents.[31,32,39-42] However, progression to *sepsis tuberculosa gravissima* and death occurs in patients receiving adequate multidrug therapy, even without any known immunodeficiency.[35,38]

Antimycobacterial therapy is more complex in critically ill patients as a consequence of unpredictable absorption, altered pharmacokinetics, increased side effects, and limited intravenous first-line agents. Second- and third-line agents are used frequently, with little clear data or consensus on their use.[48] Therefore, some have advocated monitoring serum drug levels instead of standard dosing schemes.[49] Adjuvant therapies, such as corticosteroids, and in one reported case, recombinant human activated protein C, have been used with success, but their roles are yet to be defined.[50]

CONCLUSIONS

During the last 2 decades, TB has reemerged in the developing and developed world. The recent development of extensively resistant strains of *M. tuberculosis* concerns clinicians, field workers, and the public health community. Despite improved methods, the diagnosis of acute TB is frequently made postmortem. The increasing number of immunocompromised individuals is expanding the population at risk for acute TB. Although these acute presentations are rare, the morbidity from TB is significant, and the ramifications of delayed therapy are great. Therefore, it remains exceedingly important to consider TB in the differential diagnosis of a variety of clinical syndromes, especially in those patients with prolonged symptoms before admission, negative cultures, and no response to standard therapies. A high level of suspicion for acute TB, supported by clinical, radiologic, pathologic, and laboratory findings should prompt early initiation of anti-tuberculous therapy as both a diagnostic and therapeutic maneuver. In practice, this strategy will benefit patient and systems outcomes from acute forms of TB.

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