in the clinic

Tuberculosis

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The content of In the Clinic is drawn from the clinical information and education resources of the American College of Physicians (ACP), including PIER (Physicians’ Information and Education Resource) and MKSAP (Medical Knowledge and Self-Assessment Program). Annals of Internal Medicine editors develop In the Clinic from these primary sources in collaboration with the ACP’s Medical Education and Publishing Division and with the assistance of science writers and physician writers. Editorial consultants from PIER and MKSAP provide expert review of the content. Readers who are interested in these primary resources for more detail can consult http://pier.acponline.org and other resources referenced in each issue of In the Clinic.

The information contained herein should never be used as a substitute for clinical judgment.

CME objective: To review the screening and prevention, diagnosis, treatment, and practice improvement for tuberculosis.

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One third of the world population has *Mycobacterium tuberculosis* infection (1). Despite recent progress in the United States, tuberculosis infection remains prevalent in immigrants, immunosuppressed persons, and other high-risk groups (3). Latent tuberculosis infection (LTBI) is the most prevalent form of tuberculosis in the United States (2). LTBI can progress to active tuberculosis disease, especially in individuals with a suppressed cell-mediated immunity. Active tuberculosis disease in immunosuppressed patients can be difficult to diagnose and can progress to disseminated forms of tuberculosis disease associated with high mortality (4). New methods of diagnosing tuberculosis disease have entered practice in recent years (5), but the diagnosis of LTBI can be challenging in some high-risk populations (6, 7). The introduction of directly observed therapy with first-line antituberculosis regimens (8) was an important advance in therapy, but multidrug-resistant tuberculosis (MDR-TB) and the extensively resistant form of MDR-TB remain significant threats to international and local tuberculosis control efforts (9, 10).

Who should be screened for tuberculosis?
Clinicians should screen all individuals at risk for tuberculosis infection, including close contacts of persons who have active pulmonary tuberculosis. Table 1 identifies asymptomatic individuals who should be screened because they are at high risk for exposure to active tuberculosis or at high risk for disease once infected.

What tests are used to screen for tuberculosis?
The tuberculin skin test (TST) with purified protein derivative (PPD) and the Mantoux method have been in use for more than 100 years to screen for tuberculosis. The TST result may not become positive for 8 to 10 weeks after exposure to active tuberculosis. The TST can give false-positive results in patients with previous bacille Calmette–Guérin (BCG) vaccination or other mycobacterial infections and false-negative results in anergic or immunosuppressed patients; however, previous BCG vaccination should not change the interpretation of the TST in most adults. The newer interferon-γ release assays (IGRAs), including the 2 U.S. Food and Drug Administration–approved commercial tests (T-SPOT.TB [Oxford Immunotec, Oxford, United

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Table 1. Risk Factors for Tuberculosis Infection or Progression to Disease After Infection

<table>
<thead>
<tr>
<th>Persons positive for HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with other immunocompromising conditions, including those with organ transplants and other conditions that require immunosuppressive therapy (the equivalent of ≥15 mg/d prednisone for ≥4 weeks, which includes most people on tumor necrosis factor-α antagonists)</td>
</tr>
<tr>
<td>Recent contact with a person with active tuberculosis</td>
</tr>
<tr>
<td>Persons with fibrotic changes on chest radiography consistent with old tuberculosis</td>
</tr>
<tr>
<td>Recent arrivals from high-prevalence countries (&lt;5 years)</td>
</tr>
<tr>
<td>Mycobacteriology laboratory personnel</td>
</tr>
<tr>
<td>Residents or employees of high-risk settings, such as prisons and jails, nursing homes and other long-term facilities for elderly persons, hospitals and other health care facilities, residential facilities for patients with acquired immunodeficiency syndrome, and homeless shelters</td>
</tr>
<tr>
<td>Injection drug users, users of other drugs (for example, crack cocaine), and tobacco smokers</td>
</tr>
<tr>
<td>Persons with clinical conditions that put them at high-risk for active disease (including diabetes mellitus, silicosis, intestinal bypass or gastrectomy, cancer of the head and neck, chronic malabsorption syndromes, end-stage renal disease, hematologic malignant conditions, and body weight 10% or more below ideal body weight)</td>
</tr>
<tr>
<td>Children age &lt;4 years exposed to adults in high-risk categories</td>
</tr>
</tbody>
</table>
The commercially available IGRAIs also have limitations; indeterminate results can occur in immunocompromised patients, more so with QuantiFERON TB Gold than T-SPOT.TB (6). Discordant results between TST and IGRA testing also occur in about 20% of individuals (13), which could be related, at least in part, to differences in performance characteristics of these tests (5) and to characteristics of the studied populations, such as the prevalence of persons previously vaccinated with BCG and the proportion of persons born outside the United States (15, 16). In addition to their improved specificity compared with TST, IGRAIs have several practical advantages. They do not require a second visit for reading and they do not trigger amnestic responses. Longitudinal data supporting the predictive value of IGRA testing is limited, however, in contrast to the many studies of TST for predicting active tuberculosis (17).

A recent study from a high-incidence area of tuberculosis in Africa found that initial test results were positive in only 56% of TST testing and 52% of IGRA testing in close household contacts who developed active tuberculosis during 2 years of follow up. Of these close household contacts who developed active tuberculosis, 71% had a positive result with either TST or IGRA during their initial evaluations (18).

Another prospective study (19) from a country with a low incidence of tuberculosis suggests that IGRA testing could be more accurate than TST for diagnosing LTBI and for detecting individuals who will progress to active tuberculosis, but more longitudinal data are needed, especially in immunocompromised individuals.

What can patients do to reduce their likelihood of becoming infected with tuberculosis?

Tuberculosis is mainly transmitted by the airborne route from a patient with respiratory symptoms, and its ability to infect others decreases significantly after 2 weeks of effective therapy (20–22). Therefore, prevention of tuberculosis transmission involves promptly identifying and treating patients with active tuberculosis.

For hospitalized patients, prevention includes isolating patients with tuberculosis from other patients and strictly applying other hospital infection control practices (23, 24). Patients usually can be removed from airborne infection isolation when they are no longer considered infectious. Patients are no longer infectious when they are on adequate tuberculosis drug therapy, have had a significant clinical response to therapy, and have had negative results on 3 consecutive sputum smears for acid-fast bacilli (AFB).

Some patients can be isolated from outsiders at home after appropriate evaluation and the initiation of outpatient treatment. Isolation of patients at home assumes that household contacts already have been exposed and that further exposure will not affect their outcomes.

Two studies, one in India and one in Arkansas, showed similar rates of disease or infection in exposed household contacts whether the patient was admitted to the hospital or allowed to remain at home for initial treatment (25, 26). However, if household contacts of the patients with infectious tuberculosis are at high risk (for example, infants or immunocompromised persons), housing the patient elsewhere until he or she meets noninfectious criteria should be strongly considered.
Hospitalization may be required until housing can be obtained (27).

Educating health care workers to evaluate exposed persons for active tuberculosis by obtaining sputum for AFB testing when they have respiratory symptoms has been shown to improve the case detection rates in primary care settings (28).

What should clinicians tell patients with active tuberculosis to protect household members and other contacts from infection?

Clinicians should teach patients to cough into disposable tissues and to cover their nose and mouth when coughing or sneezing to contain droplet nuclei before they are expelled into the air. Patients who are placed in airborne infection isolation rooms should be educated about the transmission of tuberculosis, the reasons for isolation, and the importance of staying in their rooms. Every effort should be made to help the patient follow the isolation policy (29).

Screening and Prevention... Clinicians should screen persons who have close contact with a person who has active pulmonary tuberculosis, and screen other persons who are at high risk for infection or for progression to disease once infected. Clinicians should screen with TST or IGRAs and should prevent infection by identifying and treating persons with active pulmonary tuberculosis. Patient airborne infection isolation is an important part of early treatment and prevention of transmission. Persons who provide care to patients with active pulmonary tuberculosis should wear particulate respirators. Clinicians should notify public health authorities about patients with suspected active tuberculosis.

**CLINICAL BOTTOM LINE**

Diagnosis

What signs and symptoms suggest active tuberculosis?

Although tuberculosis can cause disease in many parts of the body, this article focuses on pulmonary tuberculosis because it is the most common form of the disease. Clinicians should consider a diagnosis of pulmonary tuberculosis and evaluate patients for tuberculosis if the patient has constitutional or pulmonary signs and symptoms, such as cough longer than 2 to 3 weeks (may not be productive until later in course of disease), hemoptysis (more likely with cavitation and rarely a presenting symptom), chest pain, fever, chills, night sweats, weight loss, easy fatigability, or anorexia. Some patients have classic signs and symptoms, but it is rare for someone to have most of the classic signs and symptoms except in advanced disease, and many patients will have few of them. Some patients with active pulmonary tuberculosis infection can be fairly asymptomatic. Table 2 shows some of the main findings from the history and the physical...
examination that are associated with active tuberculosis disease.

One study reviewed 101 patients admitted to respiratory isolation to rule out tuberculosis. The patients were unlikely to have tuberculosis if they had symptoms of cough with sputum production and weight loss of less than 2 weeks' duration and absence of typical findings on chest radiograph (31).

The lung examination may be minimally abnormal with only the presence of a few crackles, unless advanced disease is present (32). Patients with HIV or those who are immunocompromised may not have classic signs and symptoms of disease, and immunosuppression increases the likelihood of active tuberculosis disease presenting as disseminated or extra pulmonary disease (33).

In one study, some delays did occur in tuberculosis treatment among HIV-infected or other immunocompromised patients because of atypical presentations, but more delays were the result of an incomplete diagnostic work-up (34).

What diagnostic tests should clinicians perform when they suspect active tuberculosis?

Persons suspected of having active pulmonary tuberculosis usually receive chest radiography and serial sputum smears and cultures for AFB. Table 3 describes the performance characteristics of these and other tests frequently used to diagnose and manage active tuberculosis disease.

Clinicians should perform chest radiography in all patients with suspected pulmonary or extrapulmonary tuberculosis. Look for classic changes of endogenous reactivation, which include upper lobe abnormalities, such as infiltrates; cavitation; volume loss; and pleural

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**Table 2. Findings from the History and Physical Examination in Patients with Active Tuberculosis**

<table>
<thead>
<tr>
<th>Element of the History</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of tuberculosis exposure, infection, disease, or treatment</td>
<td>Patients with recent exposure to tuberculosis are more likely to develop disease. A known exposure is not necessary to have tuberculosis. Clinicians may contact their local health department to learn if a patient has received tuberculosis treatment in the past and what regimen was used.</td>
</tr>
<tr>
<td>History of HIV infection or other medical conditions, or demographic factors that may increase the risk for or change the presentation of tuberculosis</td>
<td>HIV patients with latent tuberculosis infection have 100 times the risk for progression to active tuberculosis compared with patients without HIV. Signs and symptoms of other concurrent medical conditions may mask signs and symptoms of tuberculosis.</td>
</tr>
<tr>
<td>Fever</td>
<td>Less likely to be present in elderly persons. Absence of fever does not rule out tuberculosis. Patients may report feeling feverish without having fever.</td>
</tr>
<tr>
<td>Malaise</td>
<td>Although a classic symptom of tuberculosis, may only be present in disease of long duration</td>
</tr>
<tr>
<td>Night sweats</td>
<td>Most common symptom in pulmonary tuberculosis. Patients with extrapulmonary disease only are unlikely to have cough.</td>
</tr>
<tr>
<td>Cough</td>
<td>Pelvic pain, menstrual irregularities, or infertility are the most common symptoms.</td>
</tr>
<tr>
<td>Gynecologic symptoms</td>
<td>Elements of the Physical Examination</td>
</tr>
</tbody>
</table>

**Systemic signs**

- Fever, wasting, hepatomegaly, pulmonary findings, lymphadenopathy, and splenomegaly can be present.
- Weight loss is more common in advanced or disseminated disease.
- Hoarseness.

**Throat examination**

- May be palpable with pulmonary or disseminated disease.
- Generally not helpful but may include rales, signs of consolidation, or findings consistent with effusion, often unilateral pleural effusion (including pleuritic pain).
- Tachycardia, increased venous pressure, hepatomegaly, pulsus paradoxus, and friction rub.
- Ascites, doughy abdomen, or abdominal mass. Hepatosplenomegaly in disseminated disease.
- Recurrent UTI with no organisms on culture. In men, beaded vas deferens on palpation, draining scrotal sinus, epididymitis or induration of prostate or seminal vesicles.
- Joint swelling, gibbus deformity, or localized pain.

**Abdominal examination**

- Ascites, doughy abdomen, or abdominal mass. Hepatosplenomegaly in disseminated disease.

**Neurologic examination**

- Abnormal behavior, headache, convulsions.

**UTI = urinary tract infection.**

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Table 3. Laboratory and Other Studies for Diagnosing and Managing Tuberculosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest radiography</td>
<td></td>
<td></td>
<td>Infiltrates with or without cavity in the apical-posterior segments of the upper lung and superior segments of the lower lobe are common findings of tuberculosis reactivation. However, active tuberculosis disease may present in any region of the lung. Immunosuppressed patients, including patients with AIDS, can have atypical chest radiography findings, including infiltrates without cavities in any lung zone, and mediastinal or hilar lymphadenopathy with or without accompanying infiltrates or cavities. Chest radiography may be normal in patients with endobronchial disease, peribronchial node with fistula, or symptomatic HIV infection with active tuberculosis. In disseminated disease, 50% to 90% can have a miliary pattern.</td>
</tr>
<tr>
<td>Smear of sputum for acid-fast bacilli</td>
<td>50–96</td>
<td></td>
<td>At least 5000 to 10 000 organisms should be present for a smear to be positive. The more acid-fast bacilli seen, the more infectious the patient is. Induced sputum or gastric washings may be obtained if the patient does not have a productive cough. Nontuberculous mycobacteria may produce positive smears. Nocardia are acid-fast on modified acid-fast staining. Sensitivity improves with multiple specimens. May be obtained from any site with suspected infection by <em>Mycobacterium tuberculosis</em>.</td>
</tr>
<tr>
<td>Nucleic acid amplification of smear-positive sputum</td>
<td>95</td>
<td>98</td>
<td>Results available in a few hours. False-positive results only on laboratory contamination, although test does not indicate if bacteria are alive or dead (i.e., the test may remain positive for some time after treatment).</td>
</tr>
<tr>
<td>Nucleic acid amplification of smear-negative sputum</td>
<td>48–53</td>
<td>95</td>
<td>Increased sensitivity based on increased signs and symptoms of tuberculosis. See nucleic acid amplification of smear-positive sputum.</td>
</tr>
<tr>
<td>Culture of sputum for acid-fast bacilli (LJ Media)</td>
<td>67–82</td>
<td>99–100</td>
<td>Solid media cultures in conjunction with liquid media are frequently the gold standard for diagnosis. The only false-positive results that occur are caused by laboratory error or contamination of specimen. False-negative results do occur and are often due to nontuberculous mycobacterial overgrowth and antibiotic treatment. May be used on specimen taken from any site.</td>
</tr>
<tr>
<td>Liquid culture media for acid-fast bacilli (7H-12 Bactec)</td>
<td>93–97</td>
<td>98</td>
<td><em>M. tuberculosis</em> growth indicators may be positive in as little as 2 weeks. Considered the gold standard when used with solid media cultures. Increased rate of recovery with positive acid-fast bacilli smear specimens. Sensitivity based on cultures is the gold standard. May be used on specimen taken from any site.</td>
</tr>
<tr>
<td>Nucleic acid probes of liquid or solid media that have evidence of bacilli</td>
<td>99</td>
<td>99</td>
<td>Used to identify bacilli after organism has grown in liquid or solid media. Test result available in a few hours. Sensitivity and specificity change with risk factor of patient, established cut-off point for that risk factor and history of BCG vaccination. Positive test may be indication of LTBI, but test cannot differentiate LTBI from active tuberculosis. False-positive results can occur from nontuberculous mycobacteria or past BCG vaccination. False-negative results occur in immunosuppressed and anergic patients and in up to 25% of active cases. Therefore, a negative reaction to the tuberculin skin test does not exclude the diagnosis of tuberculosis, especially for patients with severe tuberculosis illness, immunosuppression, or infection with HIV. Measure induration not erythema.</td>
</tr>
<tr>
<td>TST</td>
<td>59–100</td>
<td>44–100</td>
<td>Sensitivity and specificity change with risk factor of patient, established cut-off point for that risk factor and history of BCG vaccination. Positive test may be indication of LTBI, but test cannot differentiate LTBI from active tuberculosis. False-positive results can occur from nontuberculous mycobacteria or past BCG vaccination. False-negative results occur in immunosuppressed and anergic patients and in up to 25% of active cases. Therefore, a negative reaction to the tuberculin skin test does not exclude the diagnosis of tuberculosis, especially for patients with severe tuberculosis illness, immunosuppression, or infection with HIV. Measure induration not erythema.</td>
</tr>
<tr>
<td>Interferon-γ release assays</td>
<td>70–90</td>
<td>93–99</td>
<td>Quantiferon-TB Gold and its In-Tube version have been approved by the FDA for the diagnosis of LTBI in immunocompetent patients. T-Spottb has been approved for individuals with immunosuppression.</td>
</tr>
<tr>
<td>Chest CT scan</td>
<td></td>
<td></td>
<td>Chest CT can further characterize less obvious pulmonary involvement, including the presence of small cavities, nodules, miliary pattern, bronchiectasis, fibrosis, mediastinal involvement, small pleural effusions, and “tree-in-bud” infiltrates. CT is also more sensitive and specific than chest radiography in detecting mediastinal lymphadenopathy in pediatric patients.</td>
</tr>
<tr>
<td>Sputum induction</td>
<td>87</td>
<td>100</td>
<td>In one study, sputum induction was more sensitive than bronchoscopy with a comparative predictive value. Sensitivity increases with obtaining an adequate specimen.</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>73–94</td>
<td>92–100</td>
<td>Bronchoscopy is especially helpful in patients with a negative smear or patients with a nonproductive cough when an early diagnosis would aid treatment decisions. The combination of bronchial alveolar lavage plus bronchial washing plus postbronchoscopy sputum had a higher sensitivity for <em>M. tuberculosis</em> in 1 study.</td>
</tr>
</tbody>
</table>

(continued on next page)
effusions, which may indicate pleural tuberculosis. Primary tuberculosis has radiologic findings that include infiltrates in any part of the lung similar to those seen in bacterial pneumonia with ipsilateral hilar adenopathy or isolated hilar adenopathy. Note that radiologic presentation may be absent or atypical in immunocompetent patients but is often absent or atypical in patients with HIV or other immunocompromised patients.

**What other diseases should clinicians consider when they suspect active tuberculosis?**

Clinicians should test sputum from patients with symptoms and signs of tuberculosis for other bacterial pathogens, including nontuberculous mycobacteria and fungal pathogens. Local prevalences of these diseases should guide the choice of specific test. Table 4 indicates these and some of the other differential diagnoses commonly considered during assessments of patients with suspected active pulmonary tuberculosis.

### Table 4. Laboratory and Other Studies for Diagnosing and Managing Tuberculosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postbronchoscopy sputum</td>
<td>46</td>
<td></td>
<td>Test is done in patients with negative sputum and smears by other procedures. The procedure itself will probably induce sputum production, and samples should be obtained for smear and culture. Postbronchoscopy specimens may be positive even if the bronchoscopy specimens are not. Acid-fast bacilli may be nontuberculous or nocardia. The differential diagnosis of caseating granulomas includes tuberculosis, nontuberculous mycobacteria fungal disease, and such bacteria as <em>Bartonella</em>. Identifies over 50 mycobacterial species. Requires specimen from pure culture. Pleural fluid analysis is useful for the diagnosis of tuberculosis pleuritis. Pleural fluid usually is an exudate with increased cell count and lymphocyte predominance. Increased protein and decreased glucose are common. Pleural fluid acid-fast bacilli smear and cultures have a low diagnostic yield. Pleural biopsy specimen showing necrotizing granulomas along with acid-fast bacilli culture of those biopsies have the highest diagnostic yield. Lymphocyte activity markers, such as adenosine deaminase and interferon-γ, levels, are usually increased in tuberculosis pleuritis. CSF analysis is useful for the diagnosis of tuberculosis meningitis. CSF usually has an increased cell count with lymphocyte predominance. Increased polymorphonuclear leukocytes could occur early in the disease course. Protein is usually elevated. Normal CSF glucose, protein, or cell count does not rule out tuberculosis meningitis. CSF acid-fast bacilli smear has a very low diagnostic yield, and CSF acid-fast bacilli culture using a semi-automated radiometric system and liquid media (BACTEC) has the highest diagnostic yield.</td>
</tr>
<tr>
<td>Biopsy histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-performance liquid chromatography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural effusion analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*BCG = bacille Calmette–Guérin; CT = computed tomography; CSF = cerebrospinal fluid; FDA = U.S. Food and Drug Administration; LTBI = latent tuberculosis infection; TST = tuberculin skin test.*

When should clinicians refer patients with suspected active tuberculosis to an expert?

Clinicians who rarely care for patients with tuberculosis should consult a physician who is a tuberculosis expert in the following situations: if the patient has negative AFB smear and culture results and pulmonary tuberculosis is still suspected clinically, if a patient has MDR-TB, or if the patient has had previous treatment for tuberculosis. Delay in treatment or inappropriate treatment may lead to prolonged transmission of disease or acquisition of drug resistance. Consultation also is recommended if drug resistance is acquired during treatment, adverse reactions prevent continuation of first-line therapy, or sputum culture results fail to convert from positive to negative after 3 months of treatment. In addition, consultation is advisable when the patient is pregnant, the patient has HIV co-infection, symptoms progress during treatment, or when nonstandard treatment regimens are required.


### Table 4. Differential Diagnosis of Active Pulmonary Tuberculosis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristic</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nontuberculous mycobacterium</td>
<td>Signs and symptoms may be the same as for <em>Mycobacterium tuberculosis</em></td>
<td>Usually less fever and weight loss than in patients with <em>M. tuberculosis</em>. Presence of multiple nodules with bronchiectasis on computed tomography of the lung was highly specific for <em>M. avium</em> complex in one study.</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Dyspnea and cough. Diffuse infiltrative lung disease with bilateral hilar adenopathy on chest radiography. Noncaseating granulomas on biopsy.</td>
<td>Diagnosis is made after exclusion of other possibilities.</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>May have indolent course. Radiologic infiltrates are more common in dependent areas.</td>
<td>May have decrease in mental status or evidence of reduced gag reflex. Barium swallow testing could be helpful.</td>
</tr>
<tr>
<td>Lung abscess</td>
<td>Frequently occurring posterior upper segment of upper lobes. May be acute or indolent. Sputum usually foul-smelling.</td>
<td>Obtain anaerobic bacterial cultures.</td>
</tr>
<tr>
<td>Pulmonary fungal infections (such as histoplasmosis or coccidiomycosis)</td>
<td>May have fever, cough, or night sweats. These diseases are usually geographically specific. Chest radiography may be miliary (histoplasmosis) or even cavitary.</td>
<td>Review geographic likelihood of disease. Obtain fungal stains and cultures and fungal serology.</td>
</tr>
<tr>
<td>Wegener granulomatosis</td>
<td>Fever and cough. Necrotizing granulomas in the lung and necrotizing glomerulonephritis. Chest radiography shows a cavitary lesion up to 70% of the time.</td>
<td>Obtain cytoplasmic antineutrophilic cytoplasmic antibody titers, or autoantibodies for myeloperoxidase and proteinase-3</td>
</tr>
<tr>
<td>Actinomycosis</td>
<td>Cough, hemoptysis, and draining sinuses are characteristic. Indolent course may have respiratory symptoms up to 5 months before diagnosis.</td>
<td>Sulfur granules should be in material draining from sinuses.</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>May have same symptoms as tuberculosis (for example, weight loss and cough). Primary lung cancer, lymphoma, metastasis.</td>
<td>Cytology or biopsy. Patients may have neoplasm and <em>M. tuberculosis</em>.</td>
</tr>
</tbody>
</table>

**What concurrent diseases should clinicians be alert for in patients with active tuberculosis?**

Signs and symptoms of concurrent medical conditions may mask signs and symptoms of tuberculosis, potentially delaying prompt diagnosis and treatment (35). HIV co-infection and other immunosuppressive states (for example, solid-organ transplant, tumor necrosis factor [TNF]-α antagonist therapy, and prednisone therapy) can be associated with atypical pulmonary involvement on presentation and disseminated or extra pulmonary forms of active tuberculosis disease. Pleural disease caused by other infections, inflammation, or malignant conditions can mimic tuberculosis pleuritis. Extra pulmonary forms of active tuberculosis can also mimic other conditions, for example, tuberculosis lymphadenitis can be confused with other infections or lymphoma.

**Diagnosis...** Consider evaluating patients for tuberculosis when they have cough longer than 2 to 3 weeks, hemoptysis, chest pain, fever, chills, night sweats, weight loss, easy fatigability, or anorexia. Perform chest radiography and either TST or IGRA in all patients with suspected tuberculosis, and obtain serial sputum smears and cultures in patients with suspected pulmonary tuberculosis. Test sputum for tuberculosis and for bacterial pathogens other than tuberculosis. Refer patients to a tuberculosis expert when the primary physician is inexperienced in taking care of patients with tuberculosis, the presentation is not straightforward, drug resistance is present, or the patient does not respond to therapy.

**CLINICAL BOTTOM LINE**

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What can patients with latent tuberculosis do to reduce their risk for active disease?
Latent tuberculosis is diagnosed when a TST or an IGRA for tuberculosis is positive and there is no evidence of active disease. Clinicians should always rule out active culture–negative tuberculosis before starting treatment for latent tuberculosis and evaluate the person for HIV disease. The preferred treatment regimen is isoniazid for 9 months, and one alternative treatment is rifampin for 4 months. Discuss the risks and benefits and the patient’s perceptions of LTBI treatment to optimize adherence to treatment and the completion of therapy. Table 5 identifies the therapeutic options and levels of evidence that support the treatment of LTBI.

What is the usual drug treatment for active tuberculosis before bacteriologic confirmation?
Bacteriologic confirmation of active tuberculosis disease is often achieved initially by identification of AFB in a sputum smear with confirmation with a nucleic acid amplification test in the appropriate clinical context (38). If a nucleic acid amplification test is not available, *M. tuberculosis* culture results could take about 1 to 2 weeks when using liquid media with rapid radiometric systems (for example, BACTEC system), or about 4 to 8 weeks when conventional testing is done with solid media (32). Patients suspected of having active tuberculosis should be placed on empirical antituberculosis medication before bacteriologic culture confirmation and susceptibility testing.

Modern antituberculous drug regimens for active pulmonary tuberculosis usually include intensive therapy with isoniazid, rifampin, pyrazinamide, and ethambutol daily or 3 times weekly during the first 2 months, followed by isoniazid and rifampin daily, 3 times weekly, or twice weekly for the continuation phase (24). Twice-weekly regimens are not indicated for patients coinfected with HIV, especially ones with CD4 counts $0.100 \times 10^9$ cells/L or less, because of an increased risk for drug resistance (39). Ethambutol can be stopped at any time if drug susceptibility testing indicates pansensitive *M. tuberculosis*. The continuation phase of treatment can last 4 months if the patient does not have cavitary disease and sputum cultures become negative during the first 2 months of therapy. If the patient has cavitary disease and sputum remains culture-positive after 2 months of therapy, the continuation phase should be extended to 7 months, for a total of 9 months of therapy (24), because these patients have an increased risk for relapse if treated for only 6 months (40). The risk for relapse is also increased if patients with cavitary disease are treated twice weekly during the continuation phase (41).

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Duration, mo</th>
<th>Interval</th>
<th>Rating (Evidence)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9</td>
<td>Daily</td>
<td>HIV–: A (2), HIV+: A (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice Weekly</td>
<td>HIV–: B (2), HIV+: B (2)</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>6</td>
<td>Daily</td>
<td>HIV–: B (1), HIV+: C (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice Weekly</td>
<td>HIV–: B (2), HIV+: C (1)</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4</td>
<td>Daily</td>
<td>HIV–: B (2), HIV+: B (3)</td>
</tr>
<tr>
<td>Rifapentin and isoniazid†</td>
<td>3</td>
<td>Weekly</td>
<td>HIV–: I (1), HIV+: –</td>
</tr>
</tbody>
</table>

*A = preferred; B = acceptable alternative; C = offer when A and B cannot be given; I = investigational regimen; 1 = randomized, clinical trial; 2 = data from clinical trials that were not randomized or were conducted in other populations; 3 = expert opinion.


When should patients with suspected active tuberculosis be hospitalized?

Consider hospitalizing patients with tuberculosis who cannot be managed in an outpatient setting. In most cases, do not hospitalize patients solely for respiratory isolation (29); however, hospitalization may be required when housing is not immediately available or the patient needs to be removed from a congregate setting, such as a nursing home or a prison, to respiratory isolation.

In particular, consider hospitalizing patients with tuberculosis complicated by malnutrition, respiratory distress, significant hemoptysis, or other usual signs or symptoms of a systemic disease that require hospital support.

Also, hospitalize patients with adverse reactions to drugs that cannot be managed at home, for example, drug-induced hepatitis, drug fever, and severe skin lesions (36). Health care facilities should work closely with the health department to develop an appropriate discharge plan, including arrangements for directly observed therapy and follow-up care (29).

What is the best way to monitor the results of treatment for active tuberculosis?

All patients should be monitored for clinical response. For patients whose sputum cultures are positive before treatment, the best way to measure the effectiveness of therapy is to obtain sputum specimens for culture monthly until the cultures become negative. Patients whose sputum cultures are negative after 2 months of treatment should have at least one additional sputum smear and culture during the completion of therapy (29).

Most sputum conversions occur within the first 2 months of therapy, and often within a few weeks.

Patients with cavitary disease and persistence of AFB in either sputum smear or culture after 2 months should be closely monitored clinically and radiologically and assessed for drug resistance. Radiographic evaluations during treatment are of less importance than sputum evaluation. However, a chest film at completion of treatment provides a baseline for comparison with any future evaluation (42).

In patients with negative sputum cultures before treatment, the major indicators of response to therapy are the chest radiography and the clinical evaluation. If the chest radiography does not improve after the patient has received at least 2 months of treatment, the abnormality may be the result of either previous tuberculosis or another process (42).

What are the main side effects of drugs for tuberculosis and what is the best way to monitor for their occurrence?

Monitoring for adverse reactions to tuberculosis medications must be individualized. The type and frequency of monitoring should depend on the drugs used and the patient’s risk for adverse reactions because of age, alcohol use, pregnancy, or HIV co-infection, among other factors. Patients should be seen at least monthly during therapy and questioned by medical personnel about adverse reactions. Patients should be instructed to look for symptoms associated with the most common reactions to the medications they are taking, for example, hepatitis with pyrazinamide, rifampycins, and isoniazid, and to seek medical attention urgently should symptoms occur. If the symptoms suggest adverse reactions, drug therapy should be stopped and an evaluation should be performed.

Antituberculosis treatment regimens with first-line agents are usually well tolerated. Hepatotoxicity is a potential side effect of most antituberculous drugs, especially pyrazinamide, rifampycins, and isoniazid (36). In general, adults treated for tuberculosis should have baseline measurements of hepatic enzymes, bilirubin, and serum creatinine or
blood urea nitrogen, as well as complete blood and platelet counts. Serum uric acid should be measured if pyrazinamide is used, and a baseline examination of visual acuity should be obtained for patients who will be taking ethambutol (42). While patients are on therapy, measure hepatic enzymes if clinical evaluation indicates the possibility of acute or chronic liver disease, and monitor hepatic enzymes at least monthly if the patient is infected with HIV, is pregnant (especially if she is within 3 months of delivery) uses alcohol regularly, or takes drugs that might cause hepatotoxicity or interact with antituberculous medication.

**What should be done when the patient does not respond to initial treatment?**

Adherence to therapy is necessary to achieve optimal treatment outcomes, but adherence can be difficult because of the length of therapy and because patients' symptoms frequently improve early during treatment. Directly observed therapy helps achieve optimal adherence to therapy, and it decreases treatment failures and development of drug resistance (43). In adherent patients who do not respond clinically to appropriate therapy within the first 2 months, initial drug susceptibility testing results should be reexamined for primary drug resistance. Patients whose cultures have not become negative or whose symptoms have not resolved after 3 months of therapy should be reevaluated for drug resistance and for nonadherence. If the patient is receiving self-administered therapy, the remainder of treatment should be directly observed (42). Also, consider assessing drug blood levels for possible medication malabsorption (44). Consider also assessing for drug resistance if the patient has risk factors for MDR-TB (for example, a history of tuberculosis therapy, immigration from an area endemic for MDR-TB, or contact with patients who have MDR-TB) (45). If drug resistance is suspected, respiratory isolation should be considered. The immune reconstitution syndrome should be suspected if symptoms recur or worsen in the absence of bacteriologic relapse, especially in patients with significant immunosuppression or HIV co-infection (45).

**What is the approach to treatment of HIV infection and active tuberculosis?**

Management of HIV-related tuberculosis is complex and must be individualized. Care for patients with tuberculosis and HIV co-infection often requires consultation with experts in both tuberculosis and HIV (46). Rifampin-based regimens for tuberculosis can have potential interactions with several antiretroviral agents. Risk for the immune reconstitution syndrome is also increased with the initiation of HIV antiretroviral therapy when immunosuppression is severe (CD4 cell count <0.100 × 10^9 cells/L) (47). Treatment for active tuberculosis must be started immediately for patients with HIV co-infection and who are not taking antiretroviral drugs. The optimal time to start antiretroviral therapy in this situation has not been determined, but some experts recommend basing the decision on CD4 cell counts. If the CD4 cell count is more than 0.350 × 10^9 cells/L, treatment for HIV can be delayed until treatment for active tuberculosis is completed. If the CD4 cell count is less than 0.350 and greater than 0.200 × 10^9 cells/L, treatment for HIV can be started some time during the maintenance phase of tuberculosis therapy. If the CD4 cell count is between 0.200 and 0.100 × 10^9 cells/L, treatment for HIV should be considered after completion of the 2-month induction phase of tuberculosis therapy. If the CD4 cell count is less than 0.100 × 10^9 cells/L, some experts recommend starting antiretroviral therapy after 2 or more weeks of tuberculosis therapy to reduce the risk of overlapping toxicities and the immune reconstitution syndrome (47). Treatment for active tuberculosis can have potential interactions with several antiretroviral agents.

### Table 6. Drug Treatment for HIV-Related Tuberculosis Disease

<table>
<thead>
<tr>
<th>Total Duration, months</th>
<th>Induction Phase</th>
<th>Continuation Phase</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drugs</td>
<td>Interval and Duration*</td>
<td>Drugs</td>
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</table>
|                        | Daily for 8 wk or daily for 2 wk and then 2 times per wk for 6 wk |                | Daily or 2 times per wk for 18 weeks or 2 times per wk for 18 wk† | Concurrent administration of rifabutin is contraindicated with hard-gel saquinavir and delavirdine. A 20%-25% increase in the dose of PIs or NNRTIs might be necessary. Patient should be monitored carefully for rifabutin toxicity (arthralgia, uveitis, leukopenia) if rifabutin is used concurrently with PIs or NNRTIs. Evidence of decreased antiretroviral drug activity should be assessed periodically with HIV RNA levels. No rifabutin with NRTIs. If the patient is also taking nevirapine, efavirenz, or NRTIs, the daily dose of rifabutin is decreased from 300 mg to 150 mg. The 2 times per wk dose of rifabutin (300 mg) remains the same. If the patient is taking ritonavir or lopinavir/ritonavir, the dose of rifabutin is decreased to 150 mg 2 times per wk. If the patient is also taking efavirenz, the daily dose of rifabutin is increased from 300 mg to 450 mg or 600 mg. 3 times per wk dosing for rifabutin has not been studied and cannot currently be recommended. Can be used concurrently with antiretroviral regimens that include PIs, NRTIs, and NNRTIs. Streptomycin is contraindicated for pregnant women. Every effort should be made to continue administering streptomycin for the total duration of treatment. When streptomycin is not used for the recommended 9 months, ethambutol should be added to the regimen and the treatment duration should be prolonged from 9 months (38 wk) to 12 months (52 wk). | }

|                        | Isoniazid, rifabutin, pyrazinamide, ethambutol† |                | Isoniazid, rifabutin |                | Rifampin can be used for the treatment of active tuberculosis for patients whose antiretroviral regimen includes the NNRTI efavirenz and 2 NRTIs or the PI ritonavir and 1 or more NRTIs. Rifampin should not be used with ritonavir and either saquinavir hard-gel capsule or saquinavir soft-gel capsule. NRTIs may be administered concurrently with rifampin. If appropriate, patients should be assessed every 3 mo to evaluate the decision to initiate antiretroviral therapy. A 2-wk "P-450 induction wash-out" period may be necessary between the last dose of rifampin and the first dose of PIs or NNRTIs. Streptomycin is contraindicated for pregnant women. Rifampin can be used for the treatment of active tuberculosis for patients whose antiretroviral regimen includes the NNRTI efavirenz and 2 NRTIs or the PI ritonavir and one or more NRTIs. Rifampin should not be used with the combination of ritonavir saquinavir hard-gel capsule or saquinavir soft-gel capsule. NRTIs may be administered concurrently with rifampin. If appropriate, patients should be assessed every 3 mo to evaluate the decision to initiate antiretroviral therapy. A 2-week "P-450 induction wash-out" period may be necessary between the last dose of rifampin and the first dose of PIs or NNRTIs. Streptomycin is contraindicated for pregnant women. | }

|                        | 3 times per wk for 8 wk or ethambutol, or streptomycin§ |                | 3 times per wk for 18 wk |                | Rifampin can be used for the treatment of active tuberculosis for patients whose antiretroviral regimen includes the NNRTI efavirenz and 2 NRTIs or the PI ritonavir and one or more NRTIs. Rifampin should not be used with the combination of ritonavir saquinavir hard-gel capsule or saquinavir soft-gel capsule. NRTIs may be administered concurrently with rifampin. If appropriate, patients should be assessed every 3 mo to evaluate the decision to initiate antiretroviral therapy. A 2-week "P-450 induction wash-out" period may be necessary between the last dose of rifampin and the first dose of PIs or NNRTIs. Streptomycin is contraindicated for pregnant women. | }

NNRTI = Nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

Consult a tuberculosis or HIV expert for current guidelines in the management of HIV drugs and antituberculous medication. For all patients, if susceptibility results show resistance to any of the first-line drugs, if the patient remains symptomatic, or if smear or culture are positive after 3 months, consult a tuberculosis medical expert. Directly observed therapy is recommended for all treatment regimens.


* Patients with CD4+ cell counts <0.100 × 10⁹ cells/L should receive daily or 3 times weekly treatment (regimen 1/1a or regimen 3/3a) (see Table 5)

† Duration of therapy should be prolonged for patients with delayed response to therapy. Criteria for delayed response should be assessed at the end of 2-month induction phase and should include either a lack of conversion of the Mycobacterium tuberculosis culture from positive to negative or a lack of resolution or progression of signs or symptoms of tuberculosis.

‡ Continue pyrazinamide and ethambutol for the total duration of the induction phase (8 wk).

§ Continue pyrazinamide for the total duration of the induction phase (8 wk). Ethambutol can be stopped if the isolate is susceptible to isoniazid and rifabutin.

NNRTI = Nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.
tuberculosis should also be started immediately in patients with HIV co-infection who are already on antiretroviral therapy, but this therapy should be modified to avoid drug interactions while maintaining effective control of HIV infection. Rifamycin-based regimens generally are recommended for patients who have not started antiretroviral therapy and for those who will not receive protease inhibitors or nonnucleoside reverse transcriptase inhibitors (NNRTIs). Recent guidelines recommend that rifampin not be used with protease inhibitors. Initiation of antiretroviral therapy with efavirenz or nevirapine is preferred because they have fewer interactions with rifampin. Some experts also recommend that antiretroviral drug levels be monitored when rifamycin is used to treat tuberculosis (47). For patients receiving protease inhibitors or NNRTIs that cannot be used with rifampin, rifampin may be replaced with rifabutin during the initial treatment phase. However, delavirdine should not be used with either rifampin or rifabutin (47). An alternative initial treatment regimen includes a combination of isoniazid, ethambutol, pyrazinamide, and streptomycin (24, 48). Audiometry is recommended with prolonged use of streptomycin, and monitoring of renal function should be considered in older patients. Table 6 shows some recommended treatment regimens for tuberculosis and HIV co-infection.

**What are the indications for directly observed therapy of active tuberculosis?**

Consider initiating directly observed therapy in all patients with active tuberculosis disease, but especially for patients with HIV infection and for intermittent tuberculosis regimens.

In a study from Texas, directly observed therapy was shown to decrease rates of drug resistance and relapse (49). Another study showed that, in one city, tuberculosis decreased 51.7% more than did in other comparable cities that did not routinely use directly observed therapy (50). Directly observed therapy also has been shown to be cost-effective when intermittent regimens are used (51, 52). However, 2 randomized clinical trials in countries with a high incidence of tuberculosis showed no benefits of directly observed therapy over self-administered therapy (53, 54). One meta-analysis showed similar rates of cure and treatment completion among patients treated under directly observed therapy compared with those treated by self-administered treatments (55).

Nevertheless, the Centers for Disease Control and Prevention recommend that directly observed therapy be considered for all patients, in part because clinicians are inaccurate in predicting which patients will adhere to medication regimens (43, 56). Directly observed therapy can be done in public health clinics, private offices, or other locations.
What do professional organizations recommend regarding the care of patients with tuberculosis?
The American Thoracic Society and Centers for Disease Control and Prevention have created guidelines for the management of patients with tuberculosis (24, 32). One study in Virginia from 1995 to 1998 showed that among 770 laboratory-confirmed patients with tuberculosis, 28.7% did not receive an initial treatment recommended by these guidelines (37). The Division of Tuberculosis Elimination of the Centers for Disease Control and Prevention has developed additional guidelines on a variety of specific topics related to tuberculosis and updates them frequently. These guidelines and other resources are available at www.cdc.gov/tb/.

What measures do stakeholders use to evaluate the quality of care for patients with tuberculosis?
The Centers for Medicare & Medicaid Services through the Physician Quality Reporting Initiative (PQRI) has established 186 eligible quality measures (www.cms.hhs.gov/PQRI/). None of these measures applies to the care of patients with tuberculosis.
WHAT YOU SHOULD KNOW ABOUT TUBERCULOSIS

What is tuberculosis?

Tuberculosis is a disease caused by bacteria. The bacteria usually attack the lungs but can attack any part of the body.

There are 2 kinds of tuberculosis:

- Active tuberculosis. (You feel sick and you can give it to others.)
- Latent tuberculosis. (You do not feel sick and it does not spread to others. Some people with latent tuberculosis infection get active tuberculosis later on.)

How does tuberculosis spread?

Tuberculosis is spread through the air. This happens when a person with active tuberculosis disease of the lungs or throat coughs, sneezes, speaks, or sings. People nearby may catch it.

How is tuberculosis found?

A doctor can check for tuberculosis by doing a skin test called a purified protein derivative (PPD). A PPD skin test shows if you have been infected with the tuberculosis bacteria.

If your PPD skin test is positive, it means you have been infected. Your doctor will check you and give you a chest X-ray. This will help your doctor know if you have active tuberculosis that can spread to other people. Keep in mind that most people who have a positive skin test do not have active tuberculosis.

What are the symptoms of tuberculosis?

Symptoms of active tuberculosis in the lungs include:

- A new cough that lasts 2 to 3 weeks or longer
- Weight loss
- Coughing up blood or mucus
- Weakness or feeling tired
- Fever and chills
- Night sweats

If not treated properly, tuberculosis can be deadly. But usually, active tuberculosis can be cured by taking several medicines for a long time.

People with latent tuberculosis can take medicine to keep from getting active tuberculosis.

For More Information

Web Sites With Information on Tuberculosis

www.cdc.gov/tb/faqs/
Centers for Disease Control and Prevention
National Library of Medicine
familydoctor.org/online/famdocen/home/common.html
American Academy of Family Physicians
www.lungusa.org/site/c.dvLUK900E/b.4294231/k.7AE3/Lung_Diseases_A_to_Z.htm
American Lung Association
CME Questions

1. A 40-year-old man is evaluated because of a positive tuberculin skin test after a preemployment physical examination. There is a local reaction with induration measured at 22 mm. Chest radiograph is essentially normal. He is asymptomatic except for an occasional dry cough. He has no shortness of breath.

Which of the following is the best next step in this patient's management?
A. Treatment for latent tuberculosis
B. Sputum induction
C. Isoniazid therapy for 9 months
D. Rifampin and pyrazinamide therapy for 6 months
E. Computed tomography of the chest

2. A 78-year-old man is hospitalized because of a 3-week history of fever, night sweats, and cough productive of blood-tinged sputum. On physical examination, he seems chronically ill. Temperature is 37.8°C (100º F), pulse rate is 96/min, and blood pressure is 120/60 mm Hg. Crackles are auscultated over the right upper posterior lobe. A chest radiograph shows a right upper lobe infiltrate and cavity. Stained sputum specimens for acid-fast bacilli are positive.

Physical examination is normal except for changes related to rheumatoid arthritis. A complete blood count shows mild normochromic, normocytic anemia with normal leukocyte and platelet counts. A recent chest radiograph was normal.

Which of the following tests would be most appropriate before starting therapy with etanercept?
A. Nitroblue tetrazolium dye test
B. Measurement of quantitative serum immunoglobulins
C. Skin testing with mumps and Candida antigens
D. Tuberculin skin testing
E. Measurement of total hemolytic complement level (CH 50)

3. A 25-year-old man is evaluated for a 2-month history of low-grade fevers, cough, night sweats, fatigue, pleuritic chest pain, and weight loss. The patient emigrated from Mexico almost 2 years ago and now lives in central California. On physical examination, his temperature is 38°C (100.4º F), pulse rate is 96/min and regular, respiration rate is 22/min at rest, and oxygen saturation is 94% on room air. There is diminished breath sound and vocal fremitus over the right hemithorax. The left lung is clear.

Peripheral blood leukocyte count is 9 × 10⁹ cells/L, with 60% neutrophils and 35% lymphocytes. Liver function test results are normal. Chest radiograph shows a moderate right-sided pleural effusion with layering of 3 cm of free-flowing pleural fluid and no parenchymal infiltrates on right lateral decubitus chest radiograph.

Thoracentesis yields 1.0 L of minimally turbid, yellow fluid with pleural fluid cell count: leukocyte count 3 × 10⁹ cells/L with 5% neutrophils, 85% lymphocytes, 1% mesothelial cells, and 1% macrophages; total protein: 5.5 mg/dL; lactate dehydrogenase: 290 U/L; glucose: 4.44 mmol/L (80 mg/dL); and pH: 7.36.

Pleural fluid Gram stain, fungal stain, and acid-fast bacilli stain are negative. Tuberculin skin test is pending. Serologic tests for fungal organisms are negative. Cytologic evaluation for malignant cells is negative.

Which of the following is the most likely diagnosis?
A. Tuberculosis
B. Pneumococcal parapneumonic effusion
C. Pulmonary embolism
D. Malignant pleural effusion
E. Pleural effusion due to coccidioidomycosis

4. A 40-year-old retired public health nurse with a 2-year history of rapidly progressive rheumatoid arthritis is evaluated before starting etanercept. Her disease has been inadequately controlled on diclofenac, methotrexate, and prednisone. She was in good health before developing rheumatoid arthritis.

Which of the following tests would be most appropriate before starting therapy with etanercept?
A. Begin empirical therapy with isoniazid
B. Begin empirical therapy with isoniazid, pyrazinamide, ethambutol, and rifampin
C. Obtain sputum for acid-fast stain and culture
D. Repeat the tuberculin skin test
E. Begin empirical therapy with intravenous ceftriaxone and azithromycin

5. A 44-year-old woman is evaluated because of a 3-week history of cough and fever. Six months ago, when she was working as a hospital nurse, her annual tuberculin skin test result was positive for the first time at 15 mm of induration. She was advised to take isoniazid prophylaxis but declined because of concerns about her age and the risk for hepatotoxicity. Subsequently, she decided to seek employment in a non–health care setting.

On physical examination, temperature is 38.3°C (100.4º F); other vital signs are normal. Crackles are heard over the left posterior chest. A chest radiograph confirms a density in the posterior left upper lobe.

Which of the following is the most appropriate management at this time?
A. Begin empirical therapy with isoniazid
B. Begin empirical therapy with isoniazid, pyrazinamide, ethambutol, and rifampin
C. Obtain sputum for acid-fast stain and culture
D. Repeat the tuberculin skin test
E. Begin empirical therapy with intravenous ceftriaxone and azithromycin

Questions are largely from the ACP’s Medical Knowledge Self-Assessment Program (MKSAP). Go to www.annals.org/intheclinic/ to obtain up to 1.5 CME credits, to view explanations for correct answers, or to purchase the complete MKSAP program.