A 20-Year-Old Man With Cough of Two Months Duration

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A 20-year-old man with no significant past medical history presented to the emergency department complaining of cough for two months. The cough, productive of green-yellow sputum, had gradually worsened over the two months prior to presentation. He also complained of subjective fevers, night sweats, fatigue, and a 15-pound weight loss over this period. The patient denied any history of hemoptysis, recent sick contacts, or prior incarcerations. The remainder of the patient’s review of systems was negative.

The patient had no significant surgical or family history. He denied smoking, alcohol use, and illicit drug use. The patient worked as a parking valet and was not taking any prescription medications.

On physical examination, the patient’s vital signs were all within the normal range and included a respiratory rate of 18/min and a systemic arterial oxygen saturation of 100% breathing air. Lung examination revealed only decreased breath sounds in both upper lung zones. The remainder of the patient’s physical exam was normal. Plain radiograph of the chest demonstrated bilateral upper lobe infiltrates with cavitory lesions (Figure 1).

Upon admission, the patient was placed in respiratory isolation and started on rifampin, isoniazid, pyrazinamide, ethambutol, and pyridoxine daily for empiric treatment of pulmonary tuberculosis. A non-contrast computed tomogram (CT) of the chest also showed extensive upper lobe disease with areas of bronchiectasis, consolidation, lobular nodules, and cavitation (Figure 2). Sputum stains revealed acid fast bacilli (AFB), and sputum cultures grew Mycobacterium tuberculosis. After four days of hospitalization...
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the patient was discharged home with directly observed therapy for pulmonary tuberculosis.

**EPIDEMIOLOGY**

It is estimated that about one-third of the world’s population (over two billion people) are infected with tuberculosis (TB), and it ranks as the second most common cause of death from an infectious agent.\(^1,2\) In the United States in 2009, the Centers for Disease Control and Prevention reported a total of 11,540 cases of TB with a rate of 3.8 cases per 100,000, which was the lowest recorded rate since the beginning of national TB surveillance dating back to 1953. Foreign-born persons and ethnic minorities account for a disproportionate number of cases with rates in foreign-born persons at 21.5 cases per 100,000 (Figure 3).\(^3,4,5\) Immunocompromised individuals with human immunodeficiency virus (HIV), although only accounting for approximately 9% of total cases, are critical to identify because they are at greatest risk for progression of latent disease to active disease, including disseminated disease, and are five times as likely to die during treatment.\(^6\) Tuberculous infection can be divided into two broad categories, active and latent (LTBI). Active TB can be further subdivided into primary TB and reactivation TB (from the latent state). In the United States, LTBI is the most prevalent so identification at this stage is critical to minimizing reactivation and spread of the disease throughout the population.\(^7\)

In the United States, four states account for more than 50% of reported TB cases: New York, Florida, Texas, and California (Figure 4).\(^8\) Louisiana is ranked seventh for rate of TB in the United States (5.1 per 100,000 in 2008). In 2009, Orleans Parish and Jefferson Parish reported 34 cases and 26 cases respectively.\(^9\)

**RISK FACTORS**

Tuberculosis has several important risk factors which can be broadly divided into host and environmental factors. Host factors include substance abuse (intravenous drugs, tobacco, and alcohol use), poor nutritional status, and immunocompromising conditions, including HIV infection and treatment with glucocorticoids and TNF-\(\alpha\) inhibitors.\(^11,12\) Environmental risk factors for TB include recent exposure to an individual with active TB; birth in a TB-endemic area; work or residence in facilities such as hospitals, correctional facilities, nursing homes, and homeless shelters; and low socioeconomic status.\(^13\)

**CLINICAL PRESENTATION**

Active TB can involve many different organ systems but the most common is the pulmonary system. Symptoms typically begin insidiously over the course of several weeks. The most common symptoms of pulmonary TB include cough, weight loss, fever, chills, and night sweats; chest pain, hemoptysis, and dyspnea are also seen, although less frequently.\(^14\) Some patients can remain relatively asymptomatic, however, with fever and/or night sweats as the only symptoms and a relatively normal lung examination.\(^15\) The cough of TB typically begins as an intermittent, mild, non-productive cough that slowly progresses to a more continuous and productive cough with sputum that may contain blood.

Physical findings of mild-to-moderate pulmonary TB tend to be nonspecific, if present at all. Rales may be heard throughout inspiration, and dullness to percussion and decreased fremitus may indicate a pleural effusion. Radiographic abnormalities are classically localized to the apical-posterior segments of the upper lobes of the lung; however, atypical, non-upper lobe radiographic patterns, including hilar adenopathy, lower or middle lung zone involvement, pleural effusions, and solitary nodules may
be present in approximately 20% of patients, particularly in those who are immunocompromised.\textsuperscript{15,16} Classic radiographic presentations include upper lobe cavitation or infiltrate, and pleural effusions.

**DIAGNOSIS**

High-risk populations are generally screened for tuberculosis with a tuberculin skin test (TST) with purified protein derivative (PPD) using the Mantoux technique which involves an intradermal injection of PPD which is measured 48-72 hours later by the amount of induration, not erythema. The criteria for a positive TB skin test varies with each individual’s risk factors. For immunocompromised patients (ie, those with HIV infection or organ transplantation or those receiving corticosteroids, TNF-alpha inhibitors, or chemotheraphy), patients who have close contact with an active TB case, or patients with a chest radiograph suggestive of old TB, the tuberculin skin test is considered positive if the induration is \geq 5mm in diameter. In other high-risk populations, such as injection drug users, recent arrivals from high-prevalence countries, residents or employees of high-risk congregate settings (eg, hospitals, nursing homes, prisons, homeless shelters), or persons with clinical conditions that put them at high risk (eg, diabetes, leukemia, end-stage renal disease), an induration of \geq 10mm is considered positive. For all other populations, an induration \geq 15mm is considered positive.\textsuperscript{17}

Newer interferon-γ release assays (IGRAs), T-SPOT.TB and QuantiFERON-TB, can also used as screening tests.\textsuperscript{18} The Quantiferon test is preferred for patients that have a low probability of returning to get a TST read. It is also the preferred method for patients who have previously been vaccinated for bacille Calmette-Guerin (BCG) because of its lower false positive rate compared to TSTs. TST is generally preferred for testing children aged \leq 5 years. Use of both TST and Quantiferon should be considered when patients who are at high risk for infection or progression or in whom active tuberculosis is initially suspected test negative with one of the two screening tests. If a patient needs extra proof to reinforce compliance with treatment, either test may be used to confirm a positive result in the other one (eg, proving that it is not a false positive due to a BCG vaccine). Also, in patients at low risk for both infection and progression, whose initial TST or Quantiferon is positive, the physician may consider obtaining the other test to confirm the diagnosis, thereby preventing unnecessary treatment if the other test is negative. If one test result is indeterminate, the other test may be used to elucidate a result. In most other cases, either TST or quantiferon is acceptable. Remember, these tests can not differentiate between active or latent tuberculosis. In order to differentiate latent from active tuberculosis, the history, physical, and further studies will be required.

Since these tests cannot differentiate LTBI from active tuberculosis infection, persons with LTBI should undergo clinical evaluation including chest radiography and when indicated, sputum (or other clinical specimens) smears, and cultures for AFB. These cultures typically use solid and liquid media and are considered the gold standard for diagnosis with sensitivities and specificities approaching 80% and 95%, respectively.\textsuperscript{19} Nucleic acid amplification testing can be used in conjunction with a positive AFB smear to provide a rapid diagnosis of TB; when combined, the tests have a positive predictive value of over 95%.\textsuperscript{20}

Physicians need to notify public health authorities about all patients suspected of having active tuberculosis. This will help identify further cases in the community and prevent further transmission.

**TREATMENT**\textsuperscript{21}

For LTBI, active disease should be ruled out with AFB cultures before starting treatment. The preferred treatment for LTBI is isoniazid with pyridoxine for nine months. An alternative treatment is rifampin for four months.

For presumed active tuberculosis, empiric treatment should be started before bacteriologic culture confirmation. The most common treatment regimen is a combination of rifampin, isoniazid, pyrazinamide, and ethambutol daily or three times weekly during the first two months followed by isoniazid and rifampin daily, three times weekly, or twice weekly for the continuation phase. In HIV patients, the twice weekly regimen is contraindicated due to an increased risk for resistance. For patients without a cavitary lesion and whose cultures become negative during the first two months, the continuation phase is only four months. For the patients with cavitary lesions or with the positive cultures after two months, the continuation phase is seven months. For any patient on isoniazid, the physician should also prescribe pyridoxine 50 mg daily to help prevent neuropathy.

Approximately two weeks of effective therapy is needed to significantly decrease the rate of infecting others. If the patient is hospitalized, airborne respiratory isolation should be continued until effective therapy has been initiated and three consecutive sputum smears are negative for AFB. Not every patient needs to be hospitalized for isolation. Hospitalization is typically an option in patients who are without housing or who reside in a congregate setting such as a nursing home or prison. Also, patients whose care is complicated by other problems such as malnutrition, respiratory distress, or hemoptysis should be considered for initiation of treatment in an inpatient setting. Some of these patients may need arrangements for direct observe therapy with the healthcare department. Patients can also be isolated in their home assuming that the household members were already exposed and none of them are infants or immunocompromised hosts.

Sputum cultures should be checked monthly to monitor efficacy of treatment. For patients who were already culture negative when treatment was started, physicians should monitor for clinical improvement and follow chest radiographs for signs of improvement. If patients
are not responding to initial therapy, nonadherence with treatment should be considered. For this reason, the CDC recommends that all patients be considered for directly observed therapy. For patients who are compliant with treatment, but not responding clinically after two months, drug susceptibility testing should be re-examined to check for primary drug resistance. If symptoms are still present or cultures remain positive after three months of treatment, physicians should reevaluate the patients for drug resistance and place them on directly observed therapy. Other causes for poor clinical response include reduced drug absorption, which can be assessed by checking drug blood levels. Immune reconstitution syndrome should be considered in HIV-infected patients receiving highly active antiretroviral therapy.

All patients should be monitored for adverse reactions on a monthly basis, at a minimum. The most common reaction is hepatotoxicity. For this reason, it is recommended that a set of baseline labs, such as hepatic enzymes, bilirubin, serum creatinine, and a CBC, be drawn before starting treatment. Hepatic enzymes should be monitored monthly in patients who are pregnant, infected with HIV, alcoholic, or on additional drugs that can also cause hepatotoxicity. People on ethambutol should be screened with a baseline eye exam.

The hardest group of patients to treat is those who are co-infected with HIV and TB. The treatment depends on the level of immunosuppression and may also be affected by concomitant highly active antiretroviral therapy (HAART). For patients with active tuberculosis who are not on HAART, TB treatment should be started immediately. It is not yet established as to when would be the best time to start antiretroviral therapy on these patients, although some recent data suggest that on initiating HAART early during antituberculous therapy (ie, combined therapy) has survival benefit.\(^\text{22}\) In patients already on antiretroviral therapy, treatment should be started immediately for active TB, but it should be modified to avoid interactions between the two treatments. Though rifampin should not be dosed with protease inhibitors, rifabutin can be used.

REFERENCES


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