Diagnosis and Treatment of Active and Latent Tuberculosis

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INTRODUCTION

Globally, tuberculosis remains a leading cause of morbidity and mortality due to a curable infectious disease. The World Health Organization (WHO) estimated that worldwide there were 8.7 million new cases and 1.4 million deaths due to tuberculosis in 2011. Until recently, the global burden of tuberculosis had been increasing, driven largely by areas with high rates of HIV co-infection in sub-Saharan Africa. Current estimates have shown a modest decline in tuberculosis rates, demonstrating the success of extensive efforts to improve global tuberculosis control.

A major threat to continued progress, however, is the increasing rate of drug resistance. Multidrug-resistant (MDR) tuberculosis is defined as resistance to isoniazid and rifampin, and extensively drug-resistant (XDR) tuberculosis is MDR plus resistance to fluoroquinolones and second-line injectable medications like amikacin. The prevalence of MDR and XDR tuberculosis has increased in many areas of the world, although accurate assessments are difficult since many high-burden areas are unable to perform culture and drug-susceptibility testing. The increasing reports of drug-resistant disease, particularly XDR, is concerning because few options exist for treatment and these reports have been associated with high mortality rates.

In the United States, tuberculosis rates have been declining since 1992, reaching a historical low in 2012 when 9951 new patients were diagnosed. Meanwhile, the proportion of tuberculosis patients who are foreign-born has progressively increased, and racial/ethnic minorities suffer from disproportionately higher rates of disease in the United States. MDR and XDR tuberculosis are rare in the United States, with most patients having received prior tuberculosis treatment. Increasingly, the epidemiology of tuberculosis in the United States is a reflection of tuberculosis internationally. Therefore, continued progress towards elimination of tuberculosis in the United States will depend upon effective tuberculosis control strategies globally.

CASE PRESENTATIONS

CASE PATIENT 1

A 45-year-old man presents to the hospital complaining of a cough for 3 weeks with...
fevers and occasional hemoptysis. He denies night sweats and weight loss but admits to some shortness of breath. He is U.S.-born, has a history of diabetes and alcoholism, and was previously homeless. On physical exam, he is febrile at 38.5°C and tachycardic at 110 beats/min, and has an oxygen saturation of 89% on room air. A chest radiograph shows a lobar opacity in the right upper lung.

- Should this patient be placed in respiratory isolation and evaluated for active tuberculosis?

INITIAL EVALUATION

The decision to work-up a patient for possible tuberculosis requires careful consideration of the presenting symptoms, the clinical findings, and the patient’s risk for tuberculosis. The history of present illness often provides the first suggestion that a patient may have tuberculosis, but the symptoms are variable and depend upon the site and extent of disease. Pulmonary tuberculosis is the most common form, occurring in approximately 80% of patients diagnosed in the United States each year.5 Classically, patients present with a chronic cough and fevers lasting longer than 3 weeks. Other symptoms suggestive of pulmonary tuberculosis include hemoptysis, dyspnea, and weight loss.6

Extrapulmonary tuberculosis is more common among patients infected with HIV, but the lungs are still involved in more than 70% of HIV-infected tuberculosis patients.7,8 Common sites for extrapulmonary disease include lymph nodes, pleura, peritoneum, pericardium, genitourinary tract, and meninges. The symptoms often include localized pain and evidence of inflammation at the site. Patients may also report fever, night sweats, or weight loss. Delays in diagnosis are common, and symptoms can be present for months or even years before the diagnosis is made. The exceptions are meningeal and pericardial tuberculosis, which generally present with more acute severe disease.

Failure to diagnose pulmonary tuberculosis early increases transmission in the community and can result in irreversible lung damage for patients. Extrapulmonary tuberculosis is typically noninfectious, although patients can progress to pulmonary disease. There have been reports of tuberculosis being transmitted during autopsies and in operating rooms when using instruments that can aerosolize small particles, such as bone saws and pulse lavage.9,10

The history of a chronic, progressive illness with fever, night sweats, and weight loss, with or without a cough, should raise concerns about possible tuberculosis. However, obtaining an accurate history can be difficult, and many patients will report the acute onset of symptoms. Physical exam findings are helpful for localizing the disease but are not sensitive or specific enough to definitively diagnose or exclude tuberculosis. Similarly, a variety of laboratory abnormalities have been reported, including anemia, hypoalbuminemia, elevated alkaline phosphatase, and hyponatremia, but none is sensitive or specific.6

Chest radiography is an invaluable tool for diagnosing tuberculosis. Radiographs are able to detect most active pulmonary tuberculosis cases, particularly those with extensive parenchymal disease and cavitation, which are the most infectious. Radiographs can also demonstrate fibrosis from previously active tuberculosis, which identifies patients at higher risk for reactivation, and can provide clues to the diagnosis in patients with extrapulmonary disease. Pulmonary tuberculosis can present with a variety of radiographic findings dependent primarily upon the duration of illness and the host’s immune function. The classic radiographic finding is a fibrotic, cavitary upper lobe opacity (Figure 1). Other common radiographic appearances which
have been seen alone or in combination are alveolar opacities, mixed alveolar-interstitial infiltrates, a diffuse nodular pattern (miliary), unilateral pleural effusion, and intrathoracic adenopathy.\textsuperscript{11,12} In the presence of advanced immunodeficiency, there is greater variation in the radiographic patterns, with more frequent lower lobe involvement, diffuse infiltrates, hilar or mediastinal adenopathy, and pleural effusions.\textsuperscript{13}

**RISK ASSESSMENT**

Given the variability of presenting signs and symptoms, a rapid risk assessment is important for deciding whether to initiate a work-up for tuberculosis. The risks can be divided into 3 categories: risk for infection, risk for reactivation, and risk for transmission if not promptly diagnosed. Most active tuberculosis results from reactivation of a prior infection. The greatest risk factor for infection is living in a country where tuberculosis is more common than in the United States. The regions with the highest tuberculosis rates include Africa, Asia/Pacific Islands, Eastern Europe, and Central/South America. Within these regions, the risk will differ by country, the length of time spent in the country, and social factors such as type of work and living conditions while there. Additional risk factors for tuberculosis infection in the United States include current or prior history of homelessness, incarceration, and being a U.S.-born child of foreign-born parents. Older U.S.-born persons are also at increased risk because tuberculosis was more common domestically when they were young. Working in health care or living in a congregate setting confers a small risk that is continually decreasing as the overall number of U.S. tuberculosis cases declines.

Among otherwise healthy people who are infected with tuberculosis, the estimated lifetime risk of reactivation is 10%.\textsuperscript{14} However, there are many comorbid medical conditions that will increase this risk. HIV co-infection is the greatest risk factor for tuberculosis reactivation as evidenced by the high incidence in sub-Saharan Africa. Other risk factors include recent infection, diabetes, end-stage renal disease, fibrotic scarring on a chest radiograph, and other immunosuppressing conditions such as solid organ or bone marrow transplants. Tumor necrosis factor-α inhibitors and other biologic agents are increasingly being used to treat patients and increase the risk for tuberculosis reactivation.\textsuperscript{15}

The third risk category to consider when deciding whether to pursue a tuberculosis diagnosis is the risk of transmission to others. Knowing basic details about a patient’s closest contacts is important for assessing the risk from a missed or delayed diagnosis. For example, young children under 5 years old and immunocompromised indi-
Individuals are at much greater risk of acute, severe and potentially life-threatening tuberculosis if infected. Therefore, the threshold to evaluate a person for tuberculosis should be lower in someone who has frequent contact with children or other high-risk individuals. Similarly, the work-up should be initiated sooner in someone who lives or sleeps in a congregate setting, such as a nursing home or homeless shelter, where a delayed diagnosis has a high risk for transmitting tuberculosis. The local health department is an important resource for assessing the public health risk of a patient with possible tuberculosis and should be notified early about patients with possible tuberculosis even when the diagnosis has not been confirmed.

**CASE 1 CONTINUED**

The patient has symptoms that are concerning for tuberculosis, including a cough with hemoptysis and fevers for 3 weeks. His prior history of homelessness and alcoholism place him at risk for tuberculosis infection, and diabetes increases his risk of reactivation. Based on these risks, he is placed in respiratory isolation and started on ceftriaxone and azithromycin to treat possible community-acquired pneumonia. He is given a tuberculin skin test (TST) and the reaction is read as 11 mm of induration. An interferon-gamma release assay (IGRA) is positive. Three sputum smears are negative.

- **What is the role of the TST and IGRA for diagnosing active tuberculosis?**

  The TST, commonly called a PPD, had been the only licensed test for detecting tuberculosis infection for decades. While helpful, the TST has several well characterized limitations, including the need for 2 patient visits within 48 to 72 hours, only moderate sensitivity for active disease, and decreased specificity in people who have received the bacille Calmette-Guérin (BCG) vaccine against tuberculosis. More recently, IGRA have been approved by the U.S. Food and Drug Administration (FDA) for diagnosing tuberculosis infection. The 2 licensed, commercially available tests in the United States are QuantiFERON-TB Gold In-tube (Qiagen, Germantown [MD]) and T-SPOT.TB (Oxford Immunotec, Marlborough [MA]).

  For diagnosing active tuberculosis, the TST and IGRA are useful adjunctive tests but must be interpreted with caution. A positive result indicates the patient has been infected and may increase the clinical suspicion for active disease but alone is nondiagnostic. Similarly, a negative test does not rule out active tuberculosis. Among patients with culture-confirmed disease, approximately 30% have a negative TST and 15% have a negative IGRA. Anergy testing to detect patients with false-negative results is of no diagnostic value and is no longer recommended for any patient population.

  **How sensitive are acid-fast bacilli smears for diagnosing active tuberculosis?**

  Definitively diagnosing tuberculosis relies upon the collection of samples for acid-fast bacilli (AFB)
smear and culture. For suspected pulmonary, pleural, or disseminated disease, a minimum of 3 sputa or other lower respiratory tract specimens should be collected. The current recommendation is to collect the respiratory samples 8 to 24 hours apart, with at least 1 early morning specimen.\textsuperscript{18} The overall sensitivity of sputum smears is only about 50%, and the proportion of hospitalized tuberculosis patients having positive sputum smears ranges between 35% and 65%.\textsuperscript{19,20} Bronchoscopy specimens are not better than sputa and should not be considered a replacement for sputum samples. The sensitivity of sputum or bronchoscopy specimens is not high enough to exclude tuberculosis based on a negative result. Because smear-negative patients can transmit infection, hospitalized patients at high risk for tuberculosis should be kept in respiratory isolation despite negative smears until an alternative diagnosis is made or the patient is cleared by the local health department.

For extrapulmonary tuberculosis, the AFB smears and cultures from nonrespiratory samples are less sensitive than sputum is for pulmonary disease. Specimens from lymph nodes, pleural or peritoneal fluid, urine, and cerebrospinal fluid are rarely smear-positive due to a low burden of organisms and subsequently can be difficult specimens to culture AFB.\textsuperscript{21} Obtaining tissue for pathology evaluation and AFB cultures increases the likelihood of definitively diagnosing tuberculosis and should be pursued early in patients at high risk. Tissue is not easily obtained from patients with suspected tuberculosis meningitis, and the morbidity and mortality from delayed treatment is high. Culturing a large volume of cerebrospinal fluid for AFB prior to starting empiric tuberculosis treatment will maximize the likelihood of getting a confirmed diagnosis.

\textbf{CASE 1 CONTINUED}

The patient improves after 3 days on ceftriaxone and azithromycin with decreased cough and resolution of his fevers and hypoxia. He is diagnosed clinically with community-acquired pneumonia and is discharged home.

- \textbf{Should the patient be treated for latent tuberculosis infection?}

Patients are diagnosed with latent tuberculosis infection (LTBI) based on a positive TST or IGRA in the absence of any findings for active tuberculosis. Generally, this occurs when patients are asymptomatic and have a normal chest radiograph. Since the TST and IGRAs cannot differentiate infection from active disease, symptomatic patients should only be diagnosed with LTBI after a thorough evaluation has excluded active tuberculosis. This diagnosis should be made after the symptoms have resolved or an alternative diagnosis has been made, and all cultures for AFB are negative. Most tuberculosis cultures will grow in 2 weeks using conventional liquid-based systems, but the growth can take as long as 6 weeks. As a result, LTBI is rarely diagnosed and treated during a hospitalization. LTBI treatment should generally be initiated by primary care providers or through a tuberculosis control program at the health department.

Treating LTBI is beneficial for individuals and the public by preventing future tuberculosis cases and subsequent transmission. An individual’s lifetime risk of active tuberculosis depends on his or her age at the time of infection and the presence of comorbidities associated with reactivation. The decision to treat LTBI is made by weighing the future risk of active tuberculosis versus the current risk of drug toxicity. Therefore, treatment guidelines emphasize targeted testing and treatment of LTBI.
Diagnosis and Treatment of Active and Latent Tuberculosis

Isoniazid daily for 9 months has long been the recommended regimen for treating LTBI. When taken completely, isoniazid reduces the risk of tuberculosis reactivation by 90%, but the effectiveness has been limited due to poor completion rates. Serious toxicity due to isoniazid is rare, with serious drug-induced liver injury occurring in less than 1% of patients. Nevertheless, the length of therapy coupled with minor side effects such as headache and fatigue reduce the overall effectiveness. Rifampin daily for 4 months is a second-line regimen for LTBI treatment that has better completion rates than isoniazid. The efficacy of rifampin has not been established, but a randomized clinical trial is ongoing.

A newer regimen using once-weekly isoniazid and rifapentine for 12 weeks by directly observed therapy was shown to be safe and effective compared to 9 months of isoniazid in a randomized controlled trial. The completion rates with the 12-dose regimen were 82% versus 69% with the 9-month treatment course (P < 0.001). The primary limitation to expanded use of this regimen is the need to give directly observe therapy. Adherence to once-weekly isoniazid and rifapentine by self-administered therapy is being studied and may lead to greater use of this combination for LTBI treatment in the future.

CASE 1 CONCLUSION

The patient was scheduled for a follow-up visit at the local tuberculosis clinic after discharge. LTBI treatment was deferred until his symptoms had resolved and the sputum cultures were finalized as no growth at 6 weeks. He was then offered and accepted LTBI therapy. Due to ongoing alcoholism and unstable housing, he was treated with once-weekly isoniazid and rifapentine and successfully completed 12 weeks of treatment.

CASE PATIENT 2

A 21-year-old woman originally from India who has been living in the United States for 2 years presents to an urgent care clinic with a cough. She is febrile at 38.4°C and is noted to have a right upper lobe infiltrate on chest radiograph (Figure 2). She is prescribed amoxicillin/clavulanate for 10 days and is seen shortly after by her primary care provider, who notes improvement in her symptoms. A TST is placed and is negative.

One week later, she presents to an emergency department complaining of increased symptoms including cough, fevers, night sweats, and weight loss. Her physical exam is notable for a temperature of 39.3°C, heart rate of 115 beats/min, and rales
over the right upper lobe. Her oxygen saturation is 95% on room air. A repeat chest radiograph shows a worsening right upper lobe opacity (Figure 3). She is admitted to the hospital and placed in respiratory isolation to obtain sputum samples for AFB smears and cultures.

- What antibiotic(s) should be used to treat community-acquired pneumonia in patients who are at risk for tuberculosis?

The current Infectious Diseases Society of America and American Thoracic Society guidelines for the treatment of community-acquired pneumonia in non-ICU patients recommend using a β-lactam plus a macrolide or using a fluoroquinolone. However, fluoroquinolones have excellent activity against tuberculosis and are an integral part of the management of MDR tuberculosis. Use of fluoroquinolones for the treatment of community-acquired pneumonia has been demonstrated to delay the diagnosis of Mycobacterium tuberculosis infection. A delayed diagnosis has been associated with worsened outcomes, including death. Additionally, repeated courses of fluoroquinolones may be associated with the development of fluoroquinolone-resistant tuberculosis, potentially further compromising clinical outcomes. For non-hospitalized patients, azithromycin or doxycycline are preferred when tuberculosis has not been excluded.

Linezolid also has substantial antituberculosis activity and is one of the many agents utilized to treat drug-resistant tuberculosis. There are no studies to date that have clearly demonstrated that linezolid treatment delays the diagnosis of tuberculosis, but the possibility exists. Unless there is a clear indication for its use, linezolid should be avoided in patients who are at increased risk of tuberculosis. For patients where staphylococcal pneumonia is a concern, vancomycin or an anti-staphylococcal penicillin is preferred.

In the patient described, tuberculosis remains high on the differential diagnoses, so the optimal regimen to treat bacterial pneumonia without compromising the tuberculosis evaluation would be a β-lactam with a macrolide. Of note, patients with tuberculosis who are treated with regimens that do not contain a fluoroquinolone may experience some improvement in symptoms. Symptomatic improvement does not rule out tuberculosis, highlighting the need for diligence and the importance of maintaining an appropriate level of suspicion in patients at risk.

CASE 2 CONTINUED

The sputum smears are reported positive for AFB.
How long will it take to confirm if the patient has active tuberculosis and whether it is resistant to any medications?

AFB smears cannot differentiate tuberculosis from nontuberculous mycobacterium. In areas with a low burden of tuberculosis, the predictive value of a positive AFB smear is only 50% to 80% for tuberculosis. Culture is the gold standard for diagnosis, but conventional liquid cultures take an average of 2 weeks to grow and can take as long as 6 weeks. More traditional solid media cultures can take 1 to 2 months. In the acutely ill or coughing patient, awaiting culture confirmation would lead to unnecessary delays in treatment, compromising individual and public health outcomes.

NUCLEIC ACID AMPLIFICATION TESTS

Nucleic acid amplification tests (NAAT) can identify tuberculosis within 24 hours on either smear-negative or smear-positive sputum specimens. Current Centers for Disease Control and Prevention (CDC) recommendations are to perform NAAT on at least 1 specimen from individuals in whom tuberculosis remains high on the differential and where the result would alter management. The sensitivity of NAAT is greater than 95% in smear-positive specimens, but only 50% to 80% in smear-negative, culture-positive specimens. Similar to sputum smears, a negative NAAT does not rule out tuberculosis, and empiric treatment should be considered when an alternative diagnosis has not been made and the possibility of tuberculosis remains high.

DRUG SUSCEPTIBILITY TESTING

Once the diagnosis is established through culture or NAAT, determining susceptibilities of the organism is important for ensuring the best medications are given and the duration of treatment is appropriate. Isoniazid resistance occurs in about 10% of patients diagnosed in the United States. Pyrazinamide resistance is less common but important to know because the therapy should be extended. While isolated rifampin resistance is uncommon, more than 90% of rifampin-resistant tuberculosis is also isoniazid resistant, making rifampin resistance a good marker for MDR tuberculosis.

Automated liquid cultures can yield drug susceptibility results in 4 to 14 days after tuberculosis is isolated in culture. This is the current gold standard for detecting resistance to first-line drugs. However, rapid molecular tests which detect the presence of genetic mutations associated with resistance can give results in a few hours to a few days. Molecular tests also offer the advantage that many of them can be performed directly on patients’ sputum specimens without waiting for a traditional culture to grow. A disadvantage of genetic testing is that silent mutations can label an organism as resistant when it is phenotypically susceptible.

Several different molecular tests have been developed that differ in their technical difficulty to perform, laboratory requirements, and the genetic regions assessed. Rifampin susceptibility or resistance is determined by the \textit{rpoB} gene, making it the most accurate target for molecular testing. Determining susceptibility to other medications is more complex and is controlled by more than one genetic region, which decreases the accuracy of the molecular tests. Line probe assays utilize DNA probes to amplify genetic mutations that then undergo reverse hybridization with probes that can detect both rifampin and isoniazid resistance. The GenoType MTBDR\textit{plus} (Hain Lifescience, Nehren, Germany) detects resistance to isoniazid and rifampin while MTBDR\textit{sl} can detect resistance to fluoroquinolones, aminoglycosides/cyclic peptides,
and ethambutol with good correlation to culture-based drug susceptibility testing. Probes using molecular beacons such as GeneXpert MTB/RIF assay (Cepheid, Sunnyvale [CA]) will emit light when tuberculosis is present and can detect rifampin resistance. None of the molecular tests for drug resistance are currently FDA approved, but some labs have developed in-house assays or validated the commercial tests internally. Check with your local lab or tuberculosis control program to determine which tests are available in your area.

• Should empiric tuberculosis treatment be started, and what other factors should be considered?

EMPIRIC THERAPY

Empiric therapy should be considered for all patients undergoing a work-up for tuberculosis. The goals of empiric treatment are to prevent disease progression in the individual and to prevent further transmission in the community. The decision to start treatment depends on the overall clinical findings, the risks to the patient of early versus delayed therapy, and the risk to their contacts if treatment is delayed. The public health implications associated with delayed diagnosis make tuberculosis relatively unique compared to other illnesses, where nearly all the risk/benefit rests with the patient. Generally, empiric treatment should not be started until after cultures have been obtained, but urgent treatment may be required for critically ill patients in whom tuberculosis is highly likely.

The choice of medications for empiric therapy requires consideration of the risk for drug resistance. MDR tuberculosis is rare in the United States, with 98 cases reported to the Centers for Disease Control and Prevention (CDC) in 2011. However, the global burden has been increasing and was estimated to be 310,000 in 2011, according to the WHO. The primary risk factor for drug resistance is prior treatment with antituberculosis therapy. Globally, 3.7% of new tuberculosis cases are found to be MDR, which rises to 20% among retreatment cases. Additional risk factors include contact with another case of MDR tuberculosis, living in a community with high incidence of MDR, and in some settings, underlying immunodeficiency or malabsorption. If drug-resistant tuberculosis is suspected, consult with a tuberculosis expert.

Standard treatment for drug-susceptible tuberculosis is with 4 medications: isoniazid, rifampin, pyrazinamide, and ethambutol. Pyridoxine (vitamin B6) is often added to decrease the risk of isoniazid-related peripheral neuropathy. Combination therapy helps ensure effective treatment since susceptibilities are not usually known at the start of treatment. The specific benefit from each drug differs, but together the combination protects against acquired resistance if the organism happens to have primary resistance to one of the other drugs. The role of each drug, standard dosing, and common side effects are listed in Table 1.

Tuberculosis treatment consists of an initiation phase and a continuation phase. Four drugs are given for 2 months during the initiation phase to rapidly decrease the burden of organisms and subsequently the infectiousness of the patient. During the continuation phase, pyrazinamide and ethambutol are stopped while isoniazid and rifampin are continued for a minimum of 4 months. Most treatment will last a total of 6 months, but may be extended in patients who have resistance or intolerance to first-line medications, those with more extensive disease including large cavities, and those with a positive sputum culture at 2 months. Treatment is also given longer for children and immunocompromised patients with tuberculosis.
meningitis and other severe forms of extrapulmonary disease.

All tuberculosis treatment should be given by directly observed therapy (DOT). DOT began as a strategy to ensure patient adherence and evolved to represent a comprehensive patient-centered approach to care. DOT became standard of care in the United States after a resurgence of tuberculosis between 1985 and 1992 revealed that many patients were failing to complete therapy, resulting in relapses and drug resistance. Following success in the United States, the WHO adopted directly observed therapy, short course (DOTS) as the title for their plan to reduce the global burden of tuberculosis.

Early treatment is administered daily, but later therapy can be given intermittently with good efficacy. Intermittent therapy reduces the burden of DOT for patients and health providers, and can result in fewer days per week that patients experience side effects. The main challenge with intermittent therapy is that the number of pills per dose increases and the number of pills is more than some patients are able to tolerate. Patients who are in a hospital, nursing home, or jail should remain on daily therapy to maximize both the efficacy and adherence. In addition, patients who are HIV-infected with CD4 counts below 100 cells/µL or who have cavitary disease are not candidates for highly intermittent treatment due to increased relapse rates and the risk of acquired rifampin resistance.

Table 1. Standard First-line Medications for Tuberculosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Role in Eradication</th>
<th>Usual Adult Dose</th>
<th>Adverse Effects</th>
<th>Important Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH or I)</td>
<td>Early bactericidal activity against rapidly dividing bacilli</td>
<td>5 mg/kg (max 300 mg) daily</td>
<td>Hepatitis, peripheral neuropathy, rash (rare)</td>
<td>May increase serum concentrations of carbamazepine and phenytoin</td>
</tr>
<tr>
<td>Rifampin (RIF or R)</td>
<td>Early bactericidal activity against rapidly dividing bacilli; semi-dormant bacilli, important for sterilization</td>
<td>10 mg/kg (max dose 600 mg) daily</td>
<td>Orange discoloration of body fluids, pruritus, rash, nausea, hyperbilirubinemia, hepatitis, immune reaction—rare (thrombocytopenia, hemolytic anemia, acute renal failure, TTP)</td>
<td>Several: decreases concentrations of methadone, oral contraceptives, warfarin, protease inhibitors, antiepileptics, immunosuppressive agents (Consult CDC website*)</td>
</tr>
<tr>
<td>Pyrazinamide (PZA or Z)</td>
<td>Dormant or semi-dormant bacilli within macrophages or acidic environments</td>
<td>20–25 mg/kg (max dose 2000 mg) daily</td>
<td>Hepatitis (most hepatotoxic of first-line medications), nausea/vomiting, arthralgias, rash, hyperuricemia, gouty flare</td>
<td>No substantial drug interactions; review on case-by-case basis</td>
</tr>
<tr>
<td>Ethambutol (ETH or E)</td>
<td>Prevent emergence of rifampin resistance if INH resistance may be present</td>
<td>15–20 mg/kg (max dose 1600 mg) daily</td>
<td>Optic neuritis, peripheral neuropathy (rare)</td>
<td>No substantial drug interactions; review on case-by-case basis</td>
</tr>
</tbody>
</table>

*www.cdc.gov/nchstp/tb/

TTP = thrombotic thrombocytopenic purpura.

• What are the common drug-related side effects and how are they managed?

Although severe drug toxicity is rare, medication side effects are common during tuberculosis
treatment. The more common or more severe side effects are listed in Table 1. Minor adverse effects such as headaches, fatigue, or myalgias do not warrant cessation of therapy but require symptom management to ensure good adherence. Maculopapular rash with or without pruritus can usually be treated with oral antihistamines and topical steroids without discontinuing treatment. Gastrointestinal side effects like nausea, vomiting, and loss of appetite are common even in the absence of drug-induced hepatitis. Gastrointestinal symptoms should be managed early and aggressively to prevent patients from developing anticipatory symptoms prior to each dose. Once a patient has developed a strongly negative psychological association with taking treatment, completing standard therapy becomes much more difficult. Antiemetics should be used as needed. The antihistamine hydroxyzine also has anxiolytic and antiemetic properties, which can be an effective and inexpensive way to control symptoms.

Drug-induced hepatitis is the most feared complication from tuberculosis therapy. While transient elevations in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) occur in approximately 20% of patients on therapy, severe drug-induced liver injury is rare. With standard 4-drug therapy, pyrazinamide is most often the cause of elevated transaminases, followed by isoniazid. Rifampin is less commonly the cause of liver injury, but is more likely to present with elevated bilirubin and alkaline phosphatase, similar to the pattern observed with biliary obstruction. Ethambutol is not typically associated with drug-induced hepatitis. Of note, patients with disseminated tuberculosis may have abnormal liver function tests due to granulomatous hepatitis. This can usually be identified by checking baseline labs prior to starting tuberculosis treatment.

Patients who are asymptomatic with elevated transaminases can safely continue standard therapy unless the AST or ALT increases more than 5 times the upper limit of normal. For patients with gastrointestinal symptoms, medications should be held if the transaminases exceed 3 times the upper limit of normal. In either case, isoniazid, pyrazinamide, and possibly rifampin should be stopped. If more than 3 drugs are thought to be implicated, the entire regimen should be discontinued to avoid monotherapy with ethambutol. For patients with severe hepatitis or who cannot interrupt tuberculosis treatment, such as in the setting of substantial cavitary disease or severe disseminated disease, a “liver sparing” regimen can be administered, which consists of ethambutol, a fluoroquinolone, and an aminoglycoside with activity against tuberculosis. After the transaminases improve, medications can be slowly reintroduced every few days, beginning with rifampin followed by isoniazid. When rifampin, ethambutol, and isoniazid have been successfully restarted, pyrazinamide may or may not be reintroduced, dependent upon the peak severity of the drug-induced hepatitis. For additional questions regarding hepatotoxicity, refer to the CDC guidelines and consult with a provider specializing in tuberculosis.

To assess the risk of drug toxicity, baseline labs should be checked at the start of treatment, including a test for HIV-infection, liver function tests, serum creatinine, and a complete blood count. Patients with abnormal baseline liver function tests should also be evaluated for chronic hepatitis B and C infection. Ethambutol and pyrazinamide require dose adjustments in the setting of renal insufficiency when the creatinine clearance falls below 30 mL/min. Because ethambutol can cause optic neuritis, all patients taking ethambutol should have their visual acuity and red-green color perception
assessed at baseline and at least once monthly, or sooner if symptoms occur.

• When can patients with tuberculosis be safely removed from isolation and discharged from the hospital?

Patients with active tuberculosis do not all require hospital admission. Many patients are isolated at home while completing their work-up and starting tuberculosis treatment. Hospitalized patients can be discharged when they are medically stable if they can be safely isolated at home. Infectiousness decreases rapidly after starting therapy, so the risk of transmission to household contacts after a patient starts treatment is far less than their risk prior to the diagnosis. In addition, household contacts to pulmonary tuberculosis patients should be evaluated for active or latent disease and treated, if appropriate. For hospitalized patients, they should generally remain on airborne precautions in a negative pressure room until discharge. Patients who require an extended hospitalization or who will be discharged to a congregate setting such as a nursing home should remain in isolation until they have received at least 2 weeks of effective medications with evidence of clinical response and sputum smears are negative. Although sputum AFB smears and NAATs can remain positive for months and do not differentiate between living and dead organisms, hospitalized patients with a positive smear should have negative sputum smears or cultures documented before discontinuing isolation.

CASE 2 CONCLUSION

Three sputum smears and cultures were collected over 24 hours. The patient was medically stable and had a home where she could be safely isolated until she was no longer contagious, so she was discharged the next day.

The patient’s risks for tuberculosis were living in a high-burden country and clinical findings consistent with tuberculosis including her symptoms, chest radiographs, and positive AFB smear. A NAAT was not ordered to confirm tuberculosis because the likelihood of a non-tuberculosis mycobacteria infection was low and the result would not have changed her initial treatment. Molecular tests that include a screen for resistance were not available at the time she was diagnosed but would have been ordered if they had been available. She had not previously been treated for tuberculosis, so her risk of drug resistance was low. The local tuberculosis control program started empiric treatment with isoniazid, rifampin, pyrazinamide, and ethambutol the day of discharge. Two weeks later, cultures confirmed tuberculosis and susceptibility to first-line drugs was reported 1 week after the positive culture.

CASE PATIENT 3

A 32-year-old man originally from Malawi who has been living in the United States for 3 years presents to his primary care provider with cough for several days associated with subjective fevers and chills. He is given a 5-day course of azithromycin for presumed community-acquired pneumonia and sent home. His symptoms do not improve, and 1 week later he presents to an emergency department. A chest radiograph demonstrates right middle lobe consolidation with ipsilateral hilar adenopathy (Figure 4). He is discharged from the emergency department with a 7-day course of amoxicillin/clavulanate. He returns to the emergency department several days later with continued symptoms of cough and fevers that have progressed to include night sweats, a 15-lb weight
loss, and a “lump” on his neck. Chest radiograph shows worsening right middle lobe consolidation with persistent hilar adenopathy (Figure 5).

The patient’s vital signs are normal except for a maximum temperature of 40.9°C. On physical exam, he is diaphoretic but in no acute distress. He does have enlarged cervical lymph nodes and rales over the right mid lung. The remainder of his exam is normal. A rapid HIV test is positive. He is admitted to the hospital and placed on ceftriaxone and azithromycin.

Three sputum specimens are collected for AFB smears, which are negative. A TST and IGRA are also negative. His symptoms continue, including daily fevers to 41°C. Antibiotics are changed to vancomycin and cefepime. A bronchoscopy is performed and AFB smears are again negative. On hospital day 13, he undergoes mediastinoscopy, which identifies purulent fluid in the lymph nodes. Antimicrobial coverage is empirically broadened to meropenem, linezolid, and voriconazole. The purulent fluid is subsequently AFB smear-positive and he is started on isoniazid, rifampin, pyrazinamide, and ethambutol. He is also initiated on trimethoprim-sulfamethoxazole for Pneumocystis jirovecii pneumonia prophylaxis. His cough improves within 2 days and his fevers resolve by day 4 of tuberculosis treatment.

- How does tuberculosis differ in patients with HIV co-infection?

TUBERCULOSIS IN PATIENTS WITH HIV

HIV infection has had a devastating impact on the tuberculosis epidemic globally and is a major risk factor for tuberculosis infection.50 In South Africa, 60% to 80% of tuberculosis patients have underlying HIV disease. It is the leading cause of death.
among HIV-infected individuals globally and the leading cause of morbidity in HIV-infected individuals.\textsuperscript{51} Tuberculosis can accelerate progression of HIV disease by increasing viral load and accelerating decline in CD4 count.\textsuperscript{52,53} As illustrated by the case, tuberculosis can be extremely difficult to diagnose in HIV-infected individuals. Tuberculosis can present as an acute pneumonia or as a more typical subacute illness in immunocompromised patients. HIV-infected patients without symptoms have also been found to have subclinical, culture-positive tuberculosis that if untreated will progress to symptomatic respiratory disease within several weeks.\textsuperscript{54–57} Cavitary disease can occur but is less common at lower CD4 counts. Individuals with CD4 counts below 100 cells/µL are more likely to present with disseminated disease with 2 or more sites of disease.

Typical signs and symptoms include fevers, night sweats, weight loss, hepatosplenomegaly, lymphadenopathy, and in some patients, sepsis and respiratory failure.\textsuperscript{58–60} Cough may not be a prominent feature and/or may be of less than 2 weeks’ duration.\textsuperscript{61} Tuberculosis bacteremia is common in HIV-infected individuals in areas of high tuberculosis incidence and can be documented in up to 50% of patients.\textsuperscript{56,60,62} HIV-infected patients are also more likely to present with smear-negative pulmonary disease even when severely ill.\textsuperscript{63} Chest radiograph findings vary tremendously from normal appearing films to hilar lymphadenopathy, diffuse infiltrates, and lobar consolidation. TSTs and IGRAs are often negative and serve as poor screening tools for active disease.\textsuperscript{64}

Delays in tuberculosis treatment are a major contributor to excess mortality in HIV-infected patients.\textsuperscript{51} The need for early empiric treatment in acutely ill HIV-infected individuals cannot be overstated. The WHO published guidelines in 2007 to help guide clinicians in the management of HIV-infected individuals suspected of having tuberculosis.\textsuperscript{50} While WHO guidelines are developed for low-resource settings, these guidelines have some relevance in the United States when managing patients with HIV who have lived or traveled to areas with a high burden of tuberculosis. Remembering tuberculosis in your differential, being vigilant in pursuing a diagnosis, and starting empiric therapy early are all important when treating HIV-infected individuals to avoid turning a treatable disease into a lethal one.

- **When should antiretroviral therapy be initiated in a patient with tuberculosis?**

Initiating antiretroviral therapy in patients with HIV and tuberculosis co-infection requires careful consideration for patients and providers. Combination therapy for both diseases should not be started simultaneously because of the overlapping toxicity profiles among the medications. Side effects that are common to groups include rash, gastrointestinal symptoms, and drug-induced hepatotoxicity. If severe side effects occur after starting 4 drugs for tuberculosis and 3 drugs for HIV, determining the exact cause often requires stopping all medications, which compromises the patient’s health. Another challenge with co-administration of tuberculosis and HIV treatment include the drug-drug interactions between rifampin and antiretrovirals. Additionally, patients are at risk for immune reconstitution inflammatory syndrome (IRIS), which can be severe or even fatal and is more common in patients with baseline CD4 counts less than 100 cells/µL. However, delays in antiretroviral therapy increase the risk of other HIV-associated opportunistic infections and death. This has been demonstrated among patients with low CD4 counts in
areas of high tuberculosis incidence, where mortality rates as high as 35 per 100 person-years have been reported.65 Experts agree that tuberculosis treatment should be started first and be tolerated before adding HIV treatment.

The optimal timing for antiretrovirals has been controversial, but 3 recent trials have greatly improved our understanding of this issue. The CAM-ELA trial enrolled individuals with pulmonary and extrapulmonary tuberculosis; the median CD4 count was 25 cells/µL. Patients were randomly assigned to initiate antiretroviral therapy within 2 weeks of starting tuberculosis treatment or after 8 weeks. There was a marked reduction in overall mortality within the group who initiated at 2 weeks.66 A multicenter trial by the AIDS Clinical Trials Group (ACTG) randomized patients with opportunistic infections, including tuberculosis, to initiate antiretroviral therapy within 2 weeks or at 8 weeks. The median CD4 count in that study was 77 cells/µL. There was no overall difference in mortality; however, those patients with CD4 counts less than 50 cells/µL did have a reduction in mortality at 30 days.67 Finally, the SAPIT trial enrolled patients with a median CD4 count of 150 cells/µL and randomly assigned them to 3 arms: antiretroviral therapy started within the first 4 weeks of the initiation phase (integrated earlier), during the first 4 weeks of the consolidation phase (integrated later), or at the end of tuberculosis treatment (sequential). The evaluation of the sequential arm was stopped early due to a reduction in mortality in the integrated treatment arms (both early and later).68 In the remaining arms, there was no difference in mortality between starting within 4 weeks of initiating tuberculosis treatment or within 4 weeks of the consolidation phase of tuberculosis treatment.69 Similar to the ACTG trial, patients with CD4 counts less than 50 cells/µL who initiated antiretroviral therapy within 4 weeks of tuberculosis treatment did have a reduced mortality.

In all 3 trials, the risk of IRIS was the highest in the group with CD4 counts less than 50 cells/µL, but IRIS was not associated with excess mortality. The optimal time to initiate antiretroviral therapy in patients with CD4 counts greater than 50 cells/µL remains uncertain. However, these data support that starting antiretroviral therapy after a patient has taken 2 weeks of tuberculosis treatment is reasonable. For some patients, the structure provided by DOT for tuberculosis improves the early adherence to HIV treatment. Prior to starting HIV treatment, a careful assessment of the patient’s readiness and ability to adhere to treatment should be made. Poor adherence to HIV treatment causes increased HIV resistance, making it more difficult to treat in the future.

• **What antiretroviral medications are safe and effective in patients undergoing tuberculosis treatment?**

Rifampin induces metabolism of protease inhibitors, non-nucleoside reverse transcriptase inhibitors, integrase inhibitors, and CCR5 inhibitors. Of these drug interactions, co-administration of efavirenz and rifampin is the best characterized, and there seems to be little clinical impact of increased metabolism of efavirenz. Therefore, efavirenz-based regimens are the first choice for treatment of HIV in patients taking rifampin as part of tuberculosis treatment. Nevirapine metabolism is more profoundly impacted by co-administration with rifampin, with one study demonstrating an increased risk of virologic failure.70 For this reason, nevirapine is not recommended for HIV patients co-infected with tuberculosis in the United States.

Rifampin should not be co-administered with protease inhibitors due to the profound reductions
in protease inhibitor levels. If a protease inhibitor is needed for HIV treatment, rifabutin should be substituted for rifampin but will require dose adjustment of rifabutin. Current adult dosing for rifabutin is 300 mg daily. However, if a ritonavir-boosted protease inhibitor is given, the rifabutin should be reduced to 150 mg daily. In resource-limited settings where rifabutin is not available, lopinavir/ritonavir is administered with rifampin by doubling the dose of lopinavir/ritonavir. However, there are reports of increased drug-induced hepatotoxicity, so this is not currently recommended practice in countries where rifabutin is widely available.71,72

Table 2 contains a summary of the drug-drug interactions and dose adjustments for patients taking antiretroviral therapy while undergoing tuberculosis treatment.

- What is the role for corticosteroids in treating tuberculosis and preventing IRIS?

### Table 2. Recommendations for Co-administering Antiretroviral Medications with Rifamycins

<table>
<thead>
<tr>
<th>Antiretroviral Drug Class</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-nucleoside reverse transcriptase inhibitors</td>
<td></td>
</tr>
<tr>
<td>Efavirenz*</td>
<td>None*</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Do not co-administer</td>
</tr>
<tr>
<td>Nevirapine†</td>
<td>Do not co-administer†</td>
</tr>
<tr>
<td>Protease Inhibitors</td>
<td></td>
</tr>
<tr>
<td>Atazanavir/ritonavir</td>
<td>Do not co-administer</td>
</tr>
<tr>
<td>Darunavir/ritonavir</td>
<td>Do not co-administer</td>
</tr>
<tr>
<td>Fosamprenavir/ritonavir</td>
<td>Do not co-administer</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Do not co-administer</td>
</tr>
<tr>
<td>Other PIs (saquinavir, indinavir, amprenavir, tipranavir)</td>
<td>Do not co-administer</td>
</tr>
<tr>
<td>Integrase Inhibitors</td>
<td></td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Increase raltegravir dose to 800 mg twice daily</td>
</tr>
<tr>
<td>Elvitegravir/cobicistat (with tenofovir/emtricitabine)</td>
<td>Do not co-administer</td>
</tr>
<tr>
<td>CCR5 Receptor Antagonist</td>
<td></td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Co-administration is not recommended If necessary, use 600 mg twice daily If co-administered with a strong CYP3A inhibitor, use maraviroc 300 mg twice daily If used without strong CYP3A inhibitor, use maraviroc 300 mg twice daily; if used with a strong CYP3A inhibitor, use maraviroc 150 mg twice daily</td>
</tr>
</tbody>
</table>

*Some clinicians advocate for increasing the dose of efavirenz to 800 mg daily in patients >60 kg. However, we do not advocate this approach.

†Some clinicians in resource-limited settings would advocate for starting at full-dose nevirapine if rifampin is started prior to initiation of ART. This approach is commonly used in resource-limited settings where rifabutin is not available and there are relative contraindications to use of efavirenz, such as the first trimester of pregnancy.
Patients with isolated pulmonary tuberculosis do not routinely require the addition of corticosteroids. However, corticosteroids are associated with a reduction in mortality among patients with tuberculosis meningitis and improvement in clinical outcomes in patients with tuberculosis pericarditis.73–75 Steroids may also be beneficial in patients with severe IRIS. IRIS is defined as clinical deterioration after starting antiretroviral therapy, usually with a rapid decline in HIV viral load and/or a rising CD4 count.76 The symptoms of IRIS may occur as early as a few days after the initiation of antiretroviral therapy, but most symptoms present after 2 to 12 weeks, with 75% of cases occurring within 90 days of starting antiretroviral therapy. Patients with lower CD4 counts at baseline are at greatest risk, with estimates that 10% to 25% of individuals with a CD4 count less than 100 cells/µL develop some form of IRIS.77,78 Mortality related to tuberculosis-associated IRIS is estimated to be 3.2%, and IRIS is particularly dangerous in patients with tuberculosis lesions in the brain.79 Symptoms may mimic the initial presentation of tuberculosis or may manifest with new symptoms. Enlarging lymphadenopathy is a common manifestation, while respiratory distress is rare.

Nonsteroidal anti-inflammatory agents are recommended for treatment of mild IRIS, but there have been no clinical trials that have demonstrated clear efficacy.80 Up to 25% may require hospitalization, and corticosteroids are often given when the inflammatory responses cause severe organ dysfunction or become life-threatening.81 The optimal dose of corticosteroids is unknown, but one study evaluating steroid use for tuberculosis-associated IRIS noted decreased morbidity when using prednisone (prednisolone) at 1.5 mg/kg for 2 weeks followed by 0.75 mg/kg for 2 weeks.76 Preferably, the antiretroviral therapy should be continued while managing the symptoms associated with IRIS. As demonstrated in the studies, patients taking antiretroviral therapy had better short-term survival in part due to the reduced risk of other opportunistic infections. In life-threatening situations where the response to corticosteroids may be delayed or unknown, stopping antiretroviral treatment may be necessary.

**SUMMARY**

Nearly one third of the world’s population is thought to be infected with tuberculosis, most of whom have latent disease. Despite effective medications to prevent and treat most patients with tuberculosis, the disease remains a leading cause of infectious disease–related morbidity and mortality worldwide. The increasing global burden of tuberculosis has been fueled by the HIV epidemic, and tuberculosis is the leading cause of death among HIV-infected patients. Coordinated efforts have halted the progressive increase in global tuberculosis, but continued success is threatened by rising rates of drug resistance, poor diagnostic tests, and limited options for second-line therapy.

Delays in diagnosis are common and occur due to a lack of clinical suspicion, empiric treatment of respiratory and other symptoms with antibacterial agents that have activity against tuberculosis, and false reassurance from negative initial tests like TSTs, IGRA, and AFB smears. Tuberculosis treatment is long and challenging for patients. As a result, DOT has proven to be an effective strategy as the backbone of a comprehensive, patient-centered approach. Achieving the goal of tuberculosis elimination requires continued efforts to maximize current tools while searching for better diagnostic tests and shorter, well-tolerated therapy for both active and latent disease. Additionally, increased access to antiretroviral therapy for HIV-infected patients reduces their risk of developing...
active tuberculosis and the risk of transmitting tuberculosis in their community.

**BOARD REVIEW QUESTIONS**

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**REFERENCES**


