Diagnosis and Treatment of Latent Tuberculosis Infection

Case Study and Commentary, Edward D. Chan, MD, and Kathryn Chmura, BA

Abstract

• Objective: To review the diagnosis and treatment of latent tuberculosis infection (LTBI).
• Methods: Qualitative assessment of the literature.
• Results: One third of the world's population is latently infected with Mycobacterium tuberculosis. From this pool, approximately 9 million active tuberculosis (TB) cases emerge annually, resulting in 2 to 3 million deaths and making TB the most common cause of death by a single infectious agent in the world. In otherwise healthy individuals with LTBI, the lifetime risk for active TB is 5% within the first year of infection and 5% for the remainder of the lifetime of the individual. Perhaps the single most important host risk factor for reactivation TB is co-infection with HIV, where the estimated rate of reactivation is approximately 5% to 10% per year. Other particularly high-risk individuals include those with upper-lobe fibronodular scarring, recent immigrants from regions endemic for TB, nursing home residents, and persons with silicosis, chronic renal insufficiency, gastrectomy, malnutrition, diabetes mellitus, organ transplantation, or immunosuppressive use. Testing for latent infection involves administering 0.1 mL of 5 tuberculin units of purified protein derivative (or 0.1 mL of 2 tuberculin units of RT-23, available in many places outside the United States) intradermally and measuring the diameter of induration at 48 to 72 hours. There is compelling epidemiologic evidence that treatment for LTBI decreases the development of active TB. The preferred treatment regimen of LTBI is 9 months of isoniazid for those with normal chest radiographs.
• Conclusion: Correctly diagnosing and treating individuals with LTBI are important cornerstones to curbing the scourge of TB.

"[I]n the treatment of Consumption, . . . in the commencement [it] is easy to cure and difficult to understand; but when it has neither been discovered in due time nor treated upon a proper principle, it becomes easy to understand and difficult to cure."

Niccolo Machiavelli (1469-1527)
and China (1.4 million cases per year). In North America, cases occur disproportionately among foreign-born individuals from TB-endemic countries, HIV-infected persons, institutionalized persons, and minorities. The United States saw a decline in TB cases up to the early 1980s due mostly to public health programs, but HIV/AIDS, immigration, and waning TB programs led to a resurgence of TB in the late 1980s and early 1990s [4]. The annual incidence is now declining again, but as TB becomes less frequent in this country, decreased awareness of disease manifestations may lead to delays in diagnosis and treatment.

As indicated by the opening quotation, hundreds of years before the cause of tuberculosis was elucidated it was recognized that tuberculosis may exist in 2 different forms. TB is divided into 2 stages: infection and disease. Infection occurs by airborne transmission of tubercle bacilli from person to person. Primary infection is usually asymptomatic but may present with mild nonspecific symptoms, symptoms of acute pneumonia, or severe disseminated disease. After primary infection, *M. tuberculosis* spreads from the lungs to hilar lymph nodes and then throughout the bloodstream, generally resulting in latent TB infection (LTBI) (Figure 1). Most cases of active TB are due to reactivation of latent infection. Reactivation TB is typically a chronic destructive pneumonia with cavitation and fibrosis involving the lung apices and superior segments of lower lobes. This paper focuses on the diagnosis and treatment of LTBI as opposed to management of active disease. Treatment of active TB is discussed in a recent publication and the latest (2003) guidelines from the American Thoracic Society (ATS)/Centers for Disease Control and Prevention/Infectious Diseases Society of America [5,6].

**CASE STUDY**

**Initial Presentation**

A 50-year-old woman who works as a nursing assistant at a nursing home receives a tuberculin skin test using 5 units of purified protein derivative (PPD) as part of an annual screening program. After 72 hours, the diameter of the induration is 14 mm, whereas it was 3 mm the previous year. She is asymptomatic, healthy, and does not use tobacco or alcohol. She is not on any medications and is HIV-negative.

- What are the exogenous risk factors for TB infection?

Close contact with a person was has pulmonary TB represents the single most important risk factor for TB transmission. Factors associated with a high burden of tubercle bacilli further increase this risk and include exposure to individuals with cavitary pulmonary TB, laryngeal TB, and untreated or inadequately treated TB. Surroundings that facilitate TB transmission include places with indoor crowding such as nursing homes, schools, and prisons.

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**Figure 1.** Graphic representation of a primary tuberculosis (TB) infection and occult dissemination. After ingestion of *M. tuberculosis* by mononuclear phagocytes in the alveoli, a largely asymptomatic dissemination of the tubercle bacilli occurs when infected cells migrate throughout the body, particularly to the lung apices, kidneys, bone growth plates, and the vertebrae, resulting in latent infection. In normal hosts, the risk of progression to active TB in a newly infected individual is ~5% for the first year and ~5% for the remaining lifetime.
LATENT TUBERCULOSIS INFECTION

Table. Criteria for Selecting Individuals for Insoniazid Preventive Therapy Based on Diameter of Tuberculin Reaction

<table>
<thead>
<tr>
<th>Criteria for Positivity</th>
<th>Patient Groups</th>
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<tr>
<td>≥ 5 mm</td>
<td>Recent close contacts to an active case of TB HIV-positive persons Persons with apical fibronodular disease consistent with prior healed TB Organ transplant recipients</td>
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<tr>
<td>≥ 10 mm</td>
<td>≥ 15 mg/day of prednisone use for ≥ 1 month Recent skin test converters (≥ 10 mm increase within 2 yr) Foreign-born persons from high prevalence regions such as Asia, Africa, and Latin America High-risk groups (alcohol abusers, intravenous drug abusers, homeless persons, nursing home patients, prisoners, employees of hospitals or other health care facilities, children) Persons with medical risk factors (diabetes, silicosis, immunosuppressive therapy, prolonged corticosteroid therapy, chronic renal failure, gastrectomy, jejunal-ileal bypass, malnutrition, hematologic malignancies)</td>
</tr>
<tr>
<td>≥ 15 mm</td>
<td>All others; essentially, those who are considered low risk. In general, these individuals should not be tested in the first place.</td>
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- **Who are candidates for tuberculin skin testing?**

  Testing should be performed on groups with a high risk for TB infection. The most important individuals to test are close contacts of an active case of TB, especially if the exposure occurred prior to treatment of the index case. Others include HIV-infected persons, recent immigrants from countries with high rates of TB, homeless persons, health care workers, residents or employees of long-term care facilities, as well as other individuals with the endogenous and exogenous risk factors described above [9]. While there are no prospective studies for screening diabetic patients for LTBI, they are clearly at increased risk and thus it is prudent to perform tuberculin skin testing on diabetics, especially those who are insulin-dependent, poorly controlled, and/or in a population where TB is relatively more prevalent.

  In recently exposed individuals who are historically known to be PPD-positive, preventive therapy can probably be withheld unless the subjects are HIV-positive. The rationale for this is that a number of case studies have shown that previous LTBI appears to protect individuals from developing TB from a new infection. All persons with LTBI should be clinically monitored for signs and symptoms that would indicate progression to active disease such as fever, anorexia, weight loss, and any unexplained respiratory symptoms, whether they are treated or not.

- **What is the general algorithm for screening for latent infection?**

  One important tenet in testing for LTBI is that if the skin test result is positive, treatment usually is indicated (ie, “the decision to test is a decision to treat”). Thus, low-risk individuals (Table) should not be tested because the likelihood that a positive test represents a true TB infection is small based on the combined effects of low pretest probability and the observation that infection with nontuberculous mycobacteria can cause a false-positive PPD. In individuals who are routinely screened for TB infection (eg, health care workers) or in whom infection is a possibility due to a recent contact, the tuberculin skin test should be performed by injecting intradermally 0.1 mL of 5 tuberculin units of PPD into the volar surface of the forearm (Figure 2A). In many countries outside the United States, a tuberculin formulation known as RT-23 at a dose of 2 tuberculin units is often used. A 27-gauge needle is used to produce a wheal 6 to 10 mm in diameter. The diameter of the induration and not erythema is measured...
after 48 to 72 hours (Figure 2B). Only trained personnel should determine the degree of induration, as it has been shown that patients’ own evaluations of their test results are generally inaccurate [10]. Three different diameters of induration are used as threshold values for treatment depending on host risk factors (Table). If both skin test result and review of symptoms are negative, treatment is not indicated (Figure 3) except in 2 instances. One exception is in children younger than 5 years of age or any children with additional risk factors for development of TB and known exposure to an active case (ie, even if the initial PPD skin test and chest radiograph are negative, empiric prophylactic therapy is recommended for at least 3 months) [11]. The tuberculin skin test is then repeated after 3 months and if negative, treatment can be discontinued; if the second tuberculin skin test is positive, isoniazid treatment should be continued for a total of 9 months. The other exception is the HIV-positive individual with a negative PPD who has had a close contact exposure to an active case (ie, because the risk of progression to active disease is so high, these patients should be treated for LTBI despite a negative tuberculin skin test). If either skin test or symptom review is positive, a chest radiograph should be obtained and if abnormal, the individual should be ruled out for active TB with serial sputum for acid-fast staining and culture for mycobacteria (Figure 3). If the chest radiograph is normal in an asymptomatic person with a positive PPD, then the patient is a candidate for LTBI treatment.

The BCG vaccine was developed in 1924 from an attenuated strain of Mycobacterium bovis. It is used in many parts of the world but not in the United States. While BCG may cause a false-positive tuberculin skin test, most noninfected persons vaccinated with BCG are in fact skin test-negative to PPD, especially if they were vaccinated during infancy or early childhood [12]. Thus, it has been recommended that prior BCG vaccination should not be a factor in either initiating or interpreting the skin test (ie, if the tuberculin skin test is positive, it is attributed to M. tuberculosis infection and the history of prior BCG can essentially be ignored).

- What is the booster phenomenon?

The booster phenomenon describes an initial negative skin test that upon subsequent testing is positive even though the person is not newly infected. This apparent conversion is actually a reflection of a prior LTBI in which waning immunity resulted in a false-negative initial skin test. Two-step testing, in which a negative test is followed by a second test 2 weeks later, helps reduce the likelihood that boosted reactions will be interpreted as a new conversion should the person be retested at a later date (as in annual screening programs).

- Can one induce induration in an uninfected person with serial PPD skin testing?

No. PPD is not sensitizing.

Figure 2. (A) The tuberculin skin test is performed by injecting 0.1 mL of 5 tuberculin units of purified protein derivative intradermally. (B) An example of a positive tuberculin skin test on the volar surface of a forearm. The diameter of the induration should be measured and recorded in millimeters. Erroneously measuring the diameter of the erythema instead will overestimate the true reaction size. (Photos obtained and slightly modified from a poster published by the Centers for Disease Control and Prevention.)

- What is the effect of previous bacille Calmette-Guerin (BCG) vaccine on the tuberculin skin test and its interpretation?

The BCG vaccine was developed in 1924 from an attenuated strain of Mycobacterium bovis. It is used in many parts of the world but not in the United States. While BCG may cause a false-positive tuberculin skin test, most noninfected persons vaccinated with BCG are in fact skin test-negative to PPD, especially if they were vaccinated during infancy or early childhood [12]. Thus, it has been recommended that prior BCG vaccination should not be a factor in either initiating or interpreting the skin test (ie, if the tuberculin skin test is positive, it is attributed to M. tuberculosis infection and the history of prior BCG can essentially be ignored).
**Evaluation and Treatment**

The case patient’s induration response to PPD showed an increase of 11 mm. Given her occupational risk of TB infection, the patient is started on treatment for LTBI.

- **What is the epidemiologic basis for treatment of LTBI?**

Based on a number of clinical trials, many of which were double-blind and placebo-controlled, there is compelling epidemiologic evidence that treatment of LTBI is efficacious in preventing disease provided patients adhere to treatment [13]. The rationale for treating LTBI is not only to prevent active TB in the individual but also as a public health measure since most active TB cases are derived from the pool of LTBI. This beneficial public health effect of isoniazid preventive therapy is schematically shown in an initial 1963 Ferebee model [14] updated by Dr. Michael Iseman [13] (Figure 4). As shown in this theoretical model, isoniazid decreases the number of cases of reactivation TB leading to a decrease in secondary TB infection and disease.

- **What is the standard recommended treatment for LTBI?**

The preferred treatment of LTBI is 9 months of isoniazid [7,15]. Two isoniazid regimens may be used: 5 mg/kg (maximum dose, 300 mg) daily for 9 months (preferable for self-administration) or 15 mg/kg (maximum dose, 900 mg) twice weekly for 9 months (preferable for directly observed preventive therapy [DOPT]). For those who are not infected with HIV, do not have fibrotic lesions on chest radiograph, and are older than 18 years, a shorter regimen consisting of 6 months of isoniazid 5 mg/kg (maximum dose, 300 mg) once daily or 15 mg/kg (maximum dose, 900 mg) twice weekly are acceptable but inferior alternatives to the 9-month regimen. For individuals with exposure to isoniazid-resistant TB or who are intolerant to isoniazid, rifampin 600 mg once daily for 4 to 6 months is recommended. While a 2-month regimen of daily or biweekly rifampin plus pyrazinamide (PZA) regimen also has been recommended for isoniazid-resistant TB or for non-adherent individuals, this combination therapy can no longer be recommended for most individuals [16].

**Follow-up**

The patient is nonadherent with her daily isoniazid. Based on the 2000 ATS guidelines [7], an infectious disease consultant recommends rifampin 600 mg once daily and PZA 2 g once daily for 2 months.

- **Would you follow the consultant’s recommendations?**

As alluded to previously, probably not. Initially, based on 3 randomized trials in HIV-infected individuals comparing isoniazid preventive therapy (6 to 12 months) with 2 months of rifampin-PZA, the latter regimen was found to be as efficacious as isoniazid without any apparent increase risk of adverse effects [17–19]. Thus, to help improve compliance by shortening the length of therapy, 2 months of rifampin-PZA once daily or rifampin-PZA twice weekly for 2 to 3 months was recommended as a viable alternative [7]. However, soon after the publication of the 2000 ATS guidelines, this 2-drug regimen was found to have a significantly greater risk of grade 3 hepatitis (liver enzymes > 5 times normal) or grade 4 hepatitis (liver enzymes > 10 times normal or > 5 times normal with compatible symptoms) with an initial report of 5 deaths from severe liver injury [16,20]. As a result, the 2-month regimen of rifampin and PZA can no longer be recommended as initially stated. Indeed, revised guidelines were issued warning that the 2-month rifampin-PZA combination should be used with extreme caution and not be used in patients with alcoholism, chronic liver disease, or those with a history of isoniazid-induced liver toxicity [16]. The most recent recommendation from the Centers for Disease Control and Prevention also emphasize that
rifampin-PZA should generally not be offered for treatment of LTBI [21]. For individuals who are nevertheless put on rifampin-PZA dual therapy, stricter monitoring also was recommended: (1) no more than a 2-week supply of rifampin-PZA should be given, (2) patients should be evaluated closely for symptoms and signs of hepatitis such as anorexia, nausea, emesis, abdominal pain, and jaundice, and (3) liver function tests should be obtained before starting therapy and at 2, 4, and 6 weeks after initiation of treatment, even in asymptomatic individuals [16,22]. Thus, in the case patient, other measures to improve adherence (eg, isoniazid twice weekly under DOPT) should be tried before resorting to the riskier rifampin-PZA regimen.

While it is not clear why the incidence of hepatitis with the rifampin-PZA combination appears to be greater than that with rifampin-PZA plus isoniazid, used for active TB, impaired host immunity during active disease may account for the decreased risk of liver injury even in those who received the triple regimen [23]. A decreased host immune response also is used to explain why in the initial studies examining the use of rifampin-PZA in HIV-positive patients [17–19], treatment was not associated with a relatively alarming risk of hepatitis [23]. While not mutually exclusive, an alternative explanation for the increased risk of hepatitis with rifampin-PZA is that perhaps PZA in the absence of isoniazid may be metabolized to more hepatotoxic metabolites (M. Iseman, personal communication, December 2003). This interesting hypothesis is indirectly supported by the observation that the use of a fluoroquinolone plus PZA for LTBI due to a multidrug-resistant strain of M. tuberculosis in New York City and California also was associated with an unacceptable risk of hepatitis [24,25].

Despite these concerns about rifampin-PZA hepatotoxicity, Stout and coworkers [22] recently suggested that the rifampin-PZA regimen may be useful for high-risk, traditionally nonadherent groups (61% of their 114 patients were homeless and 17% drank alcohol excessively), albeit cautioning the need for close monitoring. However, the rate of confirmed and suspected cases of hepatitis in their cohort was found to be 5.3% [22]. In an accompanying editorial, Jasmer and Daley [23] evaluated 5 separate rifampin-PZA regimen studies comprising over 1300 patients and found the overall frequency of grade 3 or 4 hepatitis to be 5.8%. This relatively high incidence of significant hepatitis is unacceptable as it is 19- to 53-fold greater than that seen with isoniazid preventive therapy, where the incidence of at least grade 3 hepatitis is estimated to be approximately 0.1% to 0.3% [26]. Drs. Jasmer and Daley also questioned the claim of improved compliance with the shorter regimen by identifying a multicenter study that showed that there was no difference in the proportion of patients who completed therapy with 2 months of rifampin-PZA versus the 6 months of isoniazid (61% versus 57%, respectively; \( P > 0.2 \))[20].

**What is the recommended treatment of LTBI due to multidrug-resistant M. tuberculosis in someone with a PPD skin test conversion?**

Prospective studies evaluating the treatment of LTBI caused by a presumed multidrug-resistant TB strain are lacking and thus such treatment is controversial. As previously noted, in high school students and teachers from Orange County, California [25] and health care workers at Lincoln Hospital
LATENT TUBERCULOSIS INFECTION

in Bronx, New York [24] who were exposed to multidrug-resistant TB and were treated with ofloxacin and PZA, there was an unacceptably high risk of hepatitis (approximately 25% to 32%). HIV-negative persons can be treated with drugs to which the tubercle bacilli is susceptible or observed for the development of active TB. HIV-positive persons should be treated with at least 2 drugs to which the strain is susceptible because the risk of progression to active TB is so high in this population. Alternatively, fluoroquinolone monotherapy without PZA may be considered with the caveat that long-term efficacy data on these treatments are lacking [7]. Other recommended options include PZA-ethambutol or fluoroquinolone-ethambutol regimens [27]. Vitamin B₆ (pyridoxine) is not routinely recommended with isoniazid preventive therapy in individuals with adequate nutrition. However, when the diet is suboptimal, as may be seen in homeless persons, alcoholics, or intravenous drug abusers, pyridoxine may decrease the incidence of isoniazid-induced peripheral neuropathy. The dose of pyridoxine should be less than or equal to 10 mg a day, because larger doses may antagonize isoniazid itself [31]. Indeed, very large doses of pyridoxine are recommended as an antidote for isoniazid overdose [32].

• What are the adverse effects of isoniazid and who is at high risk of developing them?

The major adverse effects of isoniazid are hepatitis, peripheral neuropathy, anaphylaxis, and psychosis, while minor side effects include headache, rash, nausea, and nonspecific abdominal pain not necessarily associated with hepatitis [28–30]. Risk of isoniazid-associated hepatitis (defined as symptoms consistent with hepatitis, aspartate aminotransferases [AST] levels ≥ 5 times normal levels, and resolution of signs and symptoms of hepatotoxicity after withdrawal of isoniazid) is 0.1% in persons younger than age 35 years, and approximately 0.2% to 0.3% in persons aged 35 or older [26]. Risk increases with age, current alcohol use, ingestion of other hepatotoxic drugs, and chronic hepatitis B or C infection. For the standard isoniazid regimen for LTBI, baseline and follow-up liver function test is not routinely indicated except for those individuals with HIV infection, pregnancy, or history of chronic liver disease or in those who regularly drink alcohol [7]. Subjects should be evaluated monthly for adherence to the regimen and to uncover any symptoms suggestive of hepatitis. Patients should abstain from alcohol and other potential hepatotoxins. Clinical signs of hepatitis such as fever, fatigue, nausea, vomiting, and jaundice should be monitored. Mild elevations of hepatic transaminases are common and in the absence of symptoms do not necessarily require interruption of medication. If AST and alanine aminotransferases levels are 5 times the upper limit of normal, or if 3 times normal with compatible symptoms, then isoniazid should be discontinued.

• Should vitamin B₆ be given with isoniazid preventive therapy and, if so, what is the recommended dose?

Review of symptoms and physical examinations are the cornerstone of monitoring for drug toxicities with subsequent clinically indicated laboratory testing for confirmation (eg, liver function tests such as AST, alanine aminotransferases, alkaline phosphatase, and bilirubin). However, certain individuals should have liver function testing obtained at baseline and periodically during treatment, including HIV-infected subjects, pregnant women and those at least 3 months postpartum, alcoholics, patients with liver disease, or individuals taking other potentially hepatotoxic medications [7].

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References


EVALUATION FORM: Diagnosis and Treatment of Latent Tuberculosis Infection

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<th>Strongly Agree</th>
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<td>I was provided with new information pertinent to my practice.</td>
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Part 2. Please complete the following sentence.  

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❑ see no need to change my practice.  
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