Topics in Primary Care Medicine

Chemoprophylaxis Against Tuberculosis

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Mycobacterium tuberculosis can persist in a dormant state in asymptomatic infected people for years. These infected persons remain at risk throughout their lives for subsequent reactivation of the tubercle bacillus and, therefore, for the development of tuberculous disease. Chemoprophylaxis with isoniazid can prevent future tuberculous disease from developing in infected persons.

Benefits of Isoniazid Chemoprophylaxis

Isoniazid has been tested in more than a dozen prospective, randomized, placebo-controlled trials involving more than 100,000 people. These trials have been conducted for several populations including household contacts, tuberculin skin test converters, infected persons with stable radiographic lesions and negative bacteriologic examinations and child and adolescent skin-test reactors. Twelve months of taking isoniazid daily confers 70% to 90% protection against future tuberculosis; six months of therapy provides 50% to 60% protection. This protection has lasted 20 years and is likely to last a lifetime.

Preventive therapy with isoniazid is practical because both screening for the infected state and treatment with isoniazid are efficacious, inexpensive and safe. Screening for tuberculous infection is done by the tuberculin skin test.

The Tuberculin Skin Test

The tuberculin skin test is the most sensitive and specific means available for diagnosing infection due to *M tuberculosis* in the absence of culture-documented disease. Skin testing with purified protein derivative (PPD) using 0.1 ml of the 5 TU strength, administered by the Mantoux (intradermal) method, is the only standard technique recommended. Multiple-puncture techniques such as Tine testing are less reliable. The skin test should be read at 48 to 72 hours and recorded as millimeters of induration (not erythema) and not simply as "positive" or "negative."

No clear point of separation between significant and nonsignificant skin test reaction sizes can be defined to cover all clinical and epidemiologic circumstances. In most circumstances in the United States, a reaction size of 10 mm or more of induration is accepted as being specific and sensitive enough for an accurate diagnosis of tuberculous infection. The larger the reaction size, the greater the certainty that the reaction is due to sensitization from *M tuberculosis.*

The ability of a given size of tuberculin reaction—such as 10 mm—to predict infections with *M tuberculosis* is also increased when (1) the prevalence of exposure to cross-reacting mycobacteria is low, such as in Alaska where nontuberculous (atypical) mycobacteria are uncommon; and (2) in situations where the prevalence of *M tuberculosis* infection is high —for instance, when there are close contacts with patients who have active pulmonary tuberculosis. In these circumstances, reaction sizes of less than 10 mm of induration may have the same predictive value that 10 mm of induration has for the general population in the United States. Specifically, for persons who are close contacts of patients who have active pulmonary

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TABLE 1.—*Risk of Future Tuberculous Disease Among Tuberculin Reactors*

Group I	
No Additional Risk Factors	
Reactive PPD* of unknown duration, patient older than 5 years of age, normal chest film	0.1% per year
Group II	
Newly Infected	
Recent skin test converter	3%-5% in first year
Household contact	
Positive skin test initially	5.0% in first year
Overall	2.5% in first year
Group III	
Large Residual Bacillary Load	
Reactive PPD, abnormal chest film, inadequate past therapy	1%-4.5%† per year
Group IV	
Special Medical Circumstances‡	
Silicosis, insulin-dependent diabetes mellitus, hematologic or reticuloendothelial malignancy, gastrectomy, ileal bypass, dialysis for chronic renal failure, prolonged glucocorticoid or immunosuppressive therapy	

*PPD = tuberculin skin test with purified protein derivative.
†Higher if prior activity within last five years or if no prior therapy.
‡Risk increased but generally accepted estimates not available.

tuberculosis, skin test readings of 5 mm or more of induration should be interpreted as significant.

Tuberculin reactivity following bacille Calmette-Guérin (BCG) vaccination varies greatly. Because there is no reliable way to differentiate a reaction due to prior BCG vaccination from that due to natural infection with *M tuberculosis,* it is prudent in most situations to ignore a history of BCG vaccination when interpreting a tuberculin skin test reading.

Interpretation of tuberculin skin test conversions is frequently confusing. Skin test conversion is defined as an increase in the size of a reaction by 6 mm or more from less than 10 mm to more than 10 mm within two years. The importance of a skin test conversion is that it allows identification of newly infected persons. Not all apparent conversions represent recent infection, however. First, falsely depressed reactions (even to no induration) occur for many reasons, including poor skin test administration or reading technique, patient immunosuppression or coexisting diseases such as viral infections. If the factor(s) responsible for the falsely depressed reaction are corrected or reversed, and a repeat test is found to be reactive, persons may be mistakenly considered newly infected.

Second, tuberculin reactivity may wane in older persons because of the long interval between their initial infection and their subsequent skin test. In this situation, greater reactivity may be seen on a repeat test because of the "resensitization" that results from the first test. This greater reactivity is called the booster effect and does not represent a new tuberculous infection. When annual skin testing is anticipated (such as in hospital employees), two-step testing at the initial evaluation is recommended. Nonreactors are retested one to two weeks after the first skin test. Those that react on the second test have exhibited a booster effect and should be classified as skin test reactors but not as skin test converters.

In general, those skin test converters who are young (that is, younger than 20 years of age) or who are household contacts of patients with active pulmonary tuberculosis, should be considered newly infected.

Risks of Future Tuberculous Disease

The risk for development of tuberculous disease can be approximated for four groups of infected persons (Table 1). First, tuberculin reactors of unknown duration without additional risk factors have an annual rate of subsequent tuberculous disease occurring of approximately 0.1% per year. This small annual risk becomes significant when expected lifetime cumulative risk is considered. For example, a 20-year-old reactor expected to live an additional 55 years has a calculated lifetime disease risk of 5.5%.

Second, newly infected patients including recent skin test converters and household contacts of patients with active pulmonary tuberculosis have a much greater risk of tuberculous disease developing during the first year after becoming infected (2.5% to 5%) than reactors of unknown duration have per year.

Third, infected persons who harbor large residual numbers of tubercle bacilli have a greater yearly risk of tuberculous disease developing (1.0% to 4.5%) than reactors of unknown duration (Table 1). This group includes infected patients with both reactive skin tests and chest film changes consistent with prior tuberculosis. The presence of calcified granulomas or localized pleural changes on the chest film does not, however, indicate significantly increased risk. Fourth, reactors who have special medical circumstances, as listed in Table 1, are frequently cited as being at increased risk for subsequent tuberculous disease, though generally accepted risk estimates are not available.

Risks of Isoniazid Prophylaxis

Serious adverse reactions to isoniazid given for chemoprophylaxis are uncommon. Mild central nervous system intolerance including minor difficulties with concentration and feelings of dizziness or minor depression or euphoria are the most frequent type of adverse re-

TABLE 2.—*Groups of Persons With Reactive Tuberculin Skin Tests for Whom Isoniazid Preventive Therapy Is Recommended*

Group I
Preventable lifetime risk of tuberculosis >risk of isoniazid toxicity
<5 years old—mandatory
5-20 years old—highly recommended
21-35 years old—controversial
Group II
Newly infected persons
Recent skin test converter (within 2 years)
Household contact
Group III
Persons with presumed large residual bacillary load
Reactive PPD*, abnormal chest film, inadequate past therapy
Prior active disease, inadequate past therapy
Group IV
Special circumstances
Patients with silicosis, insulin-dependent diabetes mellitus, hematologic or reticuloendothelial malignancy, prior gastrectomy or ileal bypass, renal failure requiring dialysis or prolonged use of glucocorticoid or immunosuppressive therapy
Infected persons whose reactivation may have severe public health consequences (for example, school teachers)

*PPD = tuberculin skin test with purified protein derivative.

action to isoniazid. Taking the drug at bedtime instead of in the morning usually alleviates these symptoms.

Although elevated levels of serum amino transferases may be found in 10% to 20% of persons receiving isoniazid chemoprophylaxis, clinical hepatitis that requires discontinuation of isoniazid is infrequent. Patient age is the major risk factor for the development of clinical hepatitis. It occurs in 0.3% of patients 20 to 34 years old, 1.2% of patients 35 to 49 years old and 2.3% of patients 50 to 64 years old. Alcohol use and the presence of chronic liver disease may enhance the risk slightly. Acetylation phenotype does not appear to modify risk estimates.

Isoniazid hepatitis presents as a nonspecific gastrointestinal or flulike illness. Symptoms are most common in the first four to eight weeks of therapy but may occur any time. Only 10% of patients present with jaundice. Fever, rash and splenomegaly are uncommon. Up to 20% of patients have a leukocytosis; eosinophilia is rare. Serum aspartate and alanine amino transferase values are both elevated; however, there is no consistent relationship between the levels of these two amino transferases. When isoniazid is promptly discontinued, isoniazid hepatitis resolves (usually within days) without sequelae. Death can result from continued drug administration, but this is extremely rare now because of improved physician awareness and patient education about this problem.

Patients should be instructed to seek medical attention if they have more than two to three days of anorexia, malaise, nausea, vomiting or other nonspecific symptoms. If symptoms are severe, a patient should discontinue isoniazid therapy. Serum amino transferase levels should be measured. Even if symptoms are mild, if the aspartate amino transferase value is increased, isoniazid should be discontinued. Other causes of hepatitis such as viral should also be sought. Usually a patient's symptoms are mild and transient, not due to isoniazid and amino transferase values are found to be normal.

Most experts do not recommend routine determination of serum amino transferase levels before starting or during isoniazid chemoprophylaxis. For persons with habitual alcohol consumption or suspected chronic liver disease, however, one pretreatment aspartate amino transferase value may help to prevent confusion if symptoms arise later.

A pyridoxine-responsive peripheral neuropathy is seen in less than 1% of persons receiving isoniazid. Pyridoxine hydrochloride therapy (5 to 10 mg daily) is recommended for pregnant women, for elderly patients and for patients who are severely malnourished, a predisposition for peripheral neuropathy to develop (such as persons with diabetes, alcoholism or uremia) or seizure disorders.

Isoniazid interacts with both phenytoin (Dilantin) and disulfiram (Antabuse). Isoniazid interference with the metabolism of phenytoin may result in phenytoin toxicity. Therefore, five to ten days after initiating isoniazid preventive therapy, a patient should be reevaluated and the phenytoin concentration should be measured. The dosage of phenytoin will frequently need to be decreased; the dosage of isoniazid should not be changed. The combination of isoniazid and disulfiram may cause behavioral changes as a result of their additive effects on dopamine metabolism. Introducing the new drug at gradually increasing doses may help allow early detection of such behavioral changes.

Rarely, isoniazid can cause fever, skin rashes or a lupus erythematosus-like syndrome.

Recommendations for Therapy

Isoniazed chemoprophylaxis for tuberculosis is recommended for infected persons who have a high risk of subsequent tuberculous disease when the expected benefit of isoniazid therapy (a reduction of 70% to 90% of total future risk) is greater than the risk of a significant adverse reaction to isoniazid (primarily hepatitis). When considering cumulative lifetime risks for tuberculosis, most experts agree that the risk of preventable tuberculosis is far greater than that of hepatitis for reactors younger than 21 years of age (Table 2). Thus, isoniazid chemoprophylaxis is recommended for all persons younger than 21 years even in the absence of additional risk factors. Chemoprophylaxis is considered mandatory for reactors younger than 5 years old because tuberculous infection in these young patients progresses more often to life-threatening illness (progressive pulmonary, miliary and meningeal disease) than in older children.

Controversy surrounds the recommendations for isoniazid prophylaxis for the 21- to 35-year-old reactor with no additional risk factors. For this group, the risk of preventable tuberculous disease is greater than the risk of isoniazid-hepatitis. However, both risks are

TABLE 3.—*Before Beginning Isoniazid Preventive Therapy*

Exclude active pulmonary tuberculosis
Chest film
If chest film abnormal, sputum smears and cultures for *Mycobacterium tuberculosis*
Identify contraindications to therapy
Prior adequate therapy
Prior adverse reaction to isoniazid
Acute liver disease
Identify possible complicating situations
Habitual alcohol abuse
Chronic liver disease
Pregnancy
Other drugs—phenytoin, disulfiram

small. Tuberculosis is treatable and isoniazid-hepatitis is reversible in a patient who discontinues taking isoniazid promptly if symptoms occur. Tuberculosis has consequences that may involve the health of family members and other close contacts. However, effective isoniazid prophylaxis requires a year of daily pill taking by the reactor. Patients differ greatly in their own assessment of the consequences of these competing risks. We prefer to actively involve reactors in this age range in the isoniazid therapeutic decision.

The additional risk factors listed in Table 1 increase a reactor's chance of tuberculosis developing so much so that isoniazid preventive therapy is justified for them at almost any age. Isoniazid preventive therapy is therefore recommended for recent (within two years) skin test converters and household contacts of patients with active pulmonary tuberculosis (newly infected persons), for tuberculin reactors with inadequate (or no) prior therapy who have an abnormal chest film examination compatible with prior active tuberculosis (persons who presumably harbor large residual numbers of tubercle bacilli) and for persons with special medical circumstances (Table 2). Isoniazid preventive therapy should also be considered on an individual basis for skin test reactors older than 21 years of age when, because of special circumstances of employment, tuberculous disease developing in them may have severe public health consequences, such as in the case of nursery school teachers.

Because household contacts of patients with active pulmonary tuberculosis are at such increased risk for tuberculosis developing, isoniazid prophylaxis should be initiated even for those contacts whose initial skin test is nonreactive (less than 5 mm in this circumstance), if the index case is smear positive, the contact's exposure was intense or if the contact is very young (younger than 5 to 10 years of age). Contacts with nonreactive skin tests should be retested in two to three months. If the skin test remains nonreactive, a contact's isoniazid regimen can be discontinued if the index case has been receiving chemotherapy or if the index case no longer has household contact with the nonreactor. If a contact's repeat skin test becomes 5 mm or more, isoniazid therapy should be continued for a year.

Recommendations for isoniazid preventive therapy during pregnancy are controversial. Isoniazid appears to be safe in pregnancy. No excess fetal loss, premature births, low-birth-weight infants or congenital malformations have been seen in more than 1,400 pregnancies during which isoniazid was used. However, because preventive therapy is elective, we recommend deferring administering the drug until after delivery for reactors of unknown duration without additional risk factors. For higher risk patients (for instance, those with household contact, recent skin test converters or those with abnormal findings on chest film), we believe isoniazid preventive therapy should be given without delay. In these situations the primary goal is to prevent active disease from developing in a mother and *M tuberculosis* being transmitted to her infant. Undetected disease in an infant can be catastrophic.

Initiating Isoniazid Preventive Therapy

Before beginning isoniazid preventive therapy, active tuberculosis must be excluded and contraindications to therapy or possible complicating medical situations must be identified (Table 3). A chest film should be taken on all skin test reactors. If the findings are abnormal and consistent with tuberculous disease, prior chest films should be reviewed and three sputum specimens should be stained and cultured for tuberculosis. In this situation, it is usually advisable to begin therapy with two or more antituberculous medications for possible active disease if chest film abnormalities are extensive, if a reactor is symptomatic or if small children are in the home. If bacteriologic evaluation is negative and no clinical or radiologic response occurs after two to three months, active tuberculosis is unlikely and therapy can be reduced to isoniazid only for prophylaxis.

Taking a detailed history will identify patients with contraindications to isoniazid preventive therapy and with possible complicating medical problems. In most circumstances, patients should not receive isoniazid preventive therapy if they have already received adequate therapy for active disease or for prophylaxis, if they have had previous adverse reactions to isoniazid or if they have acute liver disease of any cause. Patients who use alcohol habitually or who have chronic liver disease should be identified and a pretreatment serum aspartate amino transferase determination should be done. Women should be questioned about possible pregnancy and all patients should be thoroughly questioned about the use of other medications.

For preventive therapy in adults, isoniazid is given once a day as a single 300-mg tablet for one year. Children should be given 5 to 10 mg per kg of body weight a day to a maximum of 300 mg, for one year. Suspensions of isoniazid in sorbitol can be prepared for children who cannot take tablets. Patients should be educated about the symptoms of isoniazid hepatitis at their initial visit and they should be reminded during return visits. A symptom checklist may be useful for physicians or clinics that commonly prescribe isoniazid. Return visits should be scheduled every one to three months depending on a staff's perception of a patient's ability to recognize and report symptoms suggestive of

an adverse reaction to isoniazid. At the end of 12 months of isoniazid therapy, patients can be discharged without the need for additional follow-up. Routine radiographic studies at the completion of therapy are not necessary.

Chemoprophylaxis for Suspected Isoniazid-Resistant Infection

Preventive treatment of suspected isoniazid-resistant *M tuberculosis* infection is a controversial problem. Isoniazid resistance is found in 8% to 20% of sputum isolates in patients from Mexico, Central America and Asia with pulmonary tuberculosis. Although some experts believe isoniazid could still be useful to prevent tuberculous disease in persons infected with resistant organisms, many failures have been reported. No drug other than isoniazid has yet been tested for chemoprophylaxis although most experts believe rifampin will prove effective. For most foreign-born reactors who are candidates for chemoprophylaxis, isoniazid is still recommended. For young children who are close contacts of patients with pulmonary tuberculosis due to known isoniazid-resistant organisms, it may be safest to treat with rifampin (with or without isoniazid).

Screening for Tuberculosis in an Ambulatory Setting

Because of the relatively low prevalence of tuberculosis in the United States, most departments of public health no longer screen or recommend screening for tuberculosis in the general outpatient population. Instead, screening efforts are concentrated in groups with a higher prevalence of disease such as immigrants and close contacts of people with active pulmonary tuberculosis.

For most healthy outpatients, skin testing should be done if a reactive test would change the management of the patient. Therefore, for children younger than 5 years of age, annual skin testing is recommended. The finding of a reactor younger than 5 years of age should prompt further investigation to find the source of the infection. For persons aged 5 to 20 years old, tuberculin skin tests should be done every one to four years. For most persons older than 20 years of age, periodic skin testing is not necessary.

GENERAL REFERENCES

American Thoracic Society: Treatment of tuberculosis and other mycobacterial diseases. Am Rev Respir Dis 1983 Jun; 127:790-796

American Thoracic Society: The tuberculin skin test. Am Rev Respir Dis 1981 Sep; 124:356-363

Comstock GW, Edwards PQ: The competing risks of tuberculosis and hepatitis for adult tuberculin reactors. Am Rev Respir Dis 1975; 111:573-577

Farer LS: Chemoprophylaxis. Am Rev Respir Dis 1982 Mar; 125 (Pt 2): 102-107

Ferebee SH: Controlled chemoprophylaxis trials in tuberculosis—A general review. Adv Tuberc Res 1970; 17:28-106

Kopanoff DE, Snider DE Jr, Caras GJ: Isoniazid-related hepatitis. A US Public Health Service Cooperative Surveillance Study. Am Rev Respir Dis 1978 Jun; 117:991-1001

Snider DE, Layde PM, Johnson MW, et al: Treatment of tuberculosis during pregnancy. Am Rev Respir Dis 1980; 122:65-77

Snider DE Jr: Pyridoxine supplementation during isoniazid therapy. Tubercle 1980; 61:191-196