Family Practice Grand Rounds

Isoniazid Prophylaxis of Tuberculosis

J. Dennis Mull, MD, MPH
Irvine, California

DR. J. DENNIS MULL (*director, family medicine residency program*): Tuberculin skin testing should be a standard part of every family physician's preventive medicine practice. However, deciding what to do about patients who have positive skin tests can present some interesting challenges. Some of these challenges will be discussed in this Grand Rounds, and the indications for preventive treatment with isoniazid (INH) will be reviewed.

As a focus for today's discussion, Dr. Ben Sonnichsen, Chief Resident, will present five cases that he has seen during the past year. Also with us today are Dr. Michael Golden, staff pediatrician, and Dr. Johanna Shapiro, staff clinical psychologist, and later I will be asking them to share some of their perspectives on prophylactic use of INH. But at the outset, before we get into specific cases, I would like to review some general issues in prophylactic treatment of tuberculosis.

First, with regard to the prevalence of tuberculin skin test positivity, there is considerable heterogeneity in the human species. Prevalence rates vary with such factors as the locus of the population—for example, urban vs rural—or the age or ethnic group. The Public Health Service estimated that in 1973, seven percent of all Americans were tuberculin positive,[1] but there is much variation within this statistic. On the one hand, the Public Health Service figures indicated that in 1971, only 0.7 percent of junior high school students had positive skin tests.[1] On the other hand, we know that skin test positivity increases steadily as a function of increasing age. In fact, if we extrapolate from surveys done in the 1960s, we see that probably 50 percent of Americans now over 50 years old have positive skin tests.[2,3] Even higher rates have been found among Alaskan Eskimos living at a subsistence level in isolated communities: in some of these groups, virtually 100 percent of the people have turned out to be positive.[4]

In contrast, a few years ago, the University of Virginia Hospital did regular tuberculin testing of all its employees and found that about 15 percent had positive tests.[5] Further study showed that approximately two percent of the hospital workers developed positive tuberculin tests in any given

From the Department of Family Medicine, University of California/Irvine, Irvine, California. Requests for reprints should be addressed to Dr. J. Dennis Mull, Department of Family Medicine, College of Medicine, University of California/Irvine, Irvine, CA 92717.

0094-3509/79/030607-07$01.75

Table 1. Isoniazid (INH) Prophylaxis: Comparative Risks and Recommendations*

Age of Patient (years)	Yearly Risk of Active TB (%)	Lifelong Risk of Active TB (%)	Risk of INH Hepatitis (%)	Recommendations
0-6	5	10	Rare	INH mandatory.
7-20	1-5	1-3	Rare	INH highly desirable if no contraindication (Table 2).
21-35	1	Unavailable	0.3	
36-50	0.5	Unavailable	1.2	INH not recommended in absence of additional risk factors.
Over 50	0.5	Unavailable	2.3	

*For patients with positive intermediate PPD greater than 10 mm and clear chest x-ray.

year; most of them had been exposed to a tuberculosis case without knowing it. And the tuberculin testing program here in this hospital has produced statistics generally similar to those of the University of Virginia.

Having noted this heterogeneity, let us now turn to the question of how to decide whether to treat prophylactically with INH when the skin test is positive. I think you are all aware of the phenomenon of hepatitis due to INH, so one of the first questions to answer for each patient is whether the risk from tuberculosis is greater than the risk from the drug. Table 1 compares the relative risks due to disease and drug in different age groups.[6,7]

In the 0 to 6-year age group, the yearly risk of developing tuberculosis is five percent in the first year after conversion; the estimated lifelong risk of active tuberculosis in this group is ten percent. By contrast, the risk of INH hepatitis is very slight. INH therapy is considered mandatory in this group, partly because infants and children are especially susceptible to tuberculous meningitis, which carries an extraordinary risk of serious morbidity or mortality.

In the next group, the 7 to 20-year age group, the yearly risk of tuberculosis is one to five percent, and the lifelong risk is about one to three percent. Since the incidence of INH hepatitis in these young people continues to be quite small—vanishingly small, in fact—INH therapy is highly recommended for them.

And then in the 21 to 35-year age group, there is a one percent risk of developing tuberculosis and a relatively low risk of hepatitis, so it is generally wise to give the drug.

But after the age of 35, the statistical risk of tuberculosis diminishes for people with positive skin tests and the risk of developing INH hepatitis rises steadily. People over 50 years of age, in fact, have a 2.3 percent chance of developing hepatitis on the drug. Prophylactic INH is therefore contraindicated for people over the age of 35 years unless there are additional considerations or risk factors.

DR. MINDY FRIEDMAN (*first year family medicine resident*): When would you treat people over the age of 35?

DR. MULL: Clearly, you would treat people with positive purified protein derivative (PPD) tests who have had recent contact with an infectious case. Such people should be treated exactly as are individuals whose conversion from negative to positive is documented. Just to be safe, assume that they have converted recently, since the risk of going on to develop active tuberculosis is greatest

within the first year after a skin test conversion. That is why, in your practices, you need to record the results of your patients' tuberculosis skin tests and retest negative individuals regularly.

Another group of people with positive skin tests who are at special risk for developing active tuberculosis are those with evidence of inactive disease on their chest x-rays. These people should be treated prophylactically with INH whether or not they are over 35.

Other factors that make development of active tuberculosis likely include diabetes, alcoholism, gastrectomy, silicosis, malignancy, prolonged corticosteroid therapy, or poor nutrition. Anyone with these problems who has positive tuberculin tests should be treated with INH regardless of age unless there are contraindications such as liver disease. More will be said about this later.

Diabetes is a known predisposer to the development of tuberculosis. Alcoholism is known to depress the delayed immune system so that the tuberculosis arises like the phoenix to recur. Gastrectomy is also associated with development of tuberculosis. So is malignancy of any kind, presumably because it is associated with depression of the immune responses. So is prolonged steroid therapy, of course, and poor nutrition.

Another group of people who should be treated prophylactically, whether or not they are over 35 years of age, are those with an abnormal but stable chest scar suggestive of old tuberculosis. All of this has been clearly spelled out by the Center for Disease Control in its official position paper.[7]

DR. EDWARD PELOCHINO (*instructor in family medicine*): Sometimes theory and practice are different. Do you really treat people over 50 if they have a scar with a positive test?

DR. MULL: Yes. I have seen several patients who have developed active tuberculosis in their 60s and 70s who might not have done so if they had been prophylactically treated. One of them was a 70-year-old man who had had tuberculosis in World War I, which had recurred at age 70, nearly 50 years later.

I think whether or not to treat in such cases depends partly on whether the physician is able to monitor the patient carefully. As mentioned before, the risk of INH hepatitis increases with age, so the physician must be in a position to see the patient monthly. We will discuss the monitoring process in a moment.

Now, let us discuss the step-by-step approach to a person presenting with a positive skin test. As many will recall, tuberculin tests are available in several strengths: first strength, 1 tuberculin unit (TU); intermediate strength, 5 TU; and second strength, 250 TU. For screening purposes, always use intermediate strength stabilized PPD (Tween-80). This intermediate test is what I mean whenever I refer to a "positive skin test" in today's presentation.

So what do we actually do with a patient who has a positive skin test? Table 2 summarizes the steps.[7]

If there is a suggestion of active tuberculosis on chest x-ray, you should go ahead and culture. Do not merely put people on INH without doing a culture. For one thing, there is the possibility of their having resistance to INH; if they do, you will want to use some other form of treatment, either as a supplement or instead of INH.

Then question the patient for history of INH treatment to see whether there was a full 12 months of treatment in the past. There are many people who say they have had their tuberculosis treated, but when questioned closely, admit they got bored with pill taking after five or six months, or left the tuberculosis sanatorium against medical advice, and hence never had the full course of treatment.

Then decide whether there are any contraindications to treatment with INH, such as hepatitis, drug fever, or liver disease with INH. Also look for special situations that modify the use of the drug (Table 2). For example, diphenylhydantoin (DPH, Dilantin) is known to modify the metabolism of INH, so use a somewhat lower dose of INH—say 200 mg instead of 300 mg—in a patient who is taking DPH, because DPH keeps the blood level of INH higher over a longer period of time.

Also, daily use of alcohol is associated with a higher risk of INH hepatitis than exists for the nonalcoholic patient. The original cases of INH hepatitis that were fatal were recorded in people who were alcoholics and probably had some underlying liver disease. If you want to give INH to someone who is using alcohol daily, be sure of the liver function and follow it closely. In the presence of any kind of current liver disease, I would not give INH if it can possibly be avoided.

Another special situation that comes up fre-

Table 2. Management of Patients with Positive Tuberculin Skin Tests

Preliminary Steps

A. Get a chest x-ray (and culture for active tuberculosis if x-ray suggests).
B. Question for history of INH treatment to see whether there was a full 12 months of treatment previously.
C. Determine whether there is any contraindication to treatment with INH:
   1. Age (Table 1).
   2. Past INH hepatitis.
   3. Drug fever with INH.
   4. Liver disease with INH.
D. Look for special situations that modify or contraindicate use of INH:
   1. Concurrent diphenylhydantoin (DPH, Dilantin) therapy.
   2. Daily use of alcohol.
   3. Current liver disease.
   4. Pregnancy
   5. History of vague problems with INH.
E. Do baseline liver function tests before INH is begun.

INH Prophylaxis

A. Adults: 300 mg—one dose per day for one year.
B. Children: 10 mg per kg of body weight (not to exceed 300 mg total)—one dose per day for one year.

Note: Ten to 20 percent get elevated SGOT either in first six months of treatment or later. In most cases, there is no need to discontinue the drug.

Monitoring the Patient on INH

A. Do not do liver function tests on a routine basis—not useful.
B. See patients monthly for evidence of liver disease or other toxic effects of the drug: anorexia, nausea, vomiting, fatigue, weakness, persistent dark urine, rash, fever. If these are present, then do liver function tests such as SGOT, bilirubin, and alkaline phosphatase.

quently is that of a pregnant patient who has a positive skin test. I always try to wait until after delivery to begin treatment. In fact, I usually try to wait until after the first trimester even to do a chest x-ray, unless the history or physical examination is very worrisome.

DR. FRIEDMAN: What if you have to treat during pregnancy?

DR. MULL: The literature supports the use of INH and ethambutol during pregnancy in the treatment of active tuberculosis.[8] If the circumstance is sufficiently compelling, I would treat the patient; otherwise, I would wait until the pregnancy was over.

Now, how do we manage INH therapy once it is decided to proceed with active treatment? Table 2 shows the recommended dosage schedules and procedures for monitoring the patient.[7]

The thinking about monitoring has changed over the last few years and at present it is considered essential to see the patient monthly. By contrast, laboratory tests of liver function should not be routinely repeated throughout the course of treatment.

One reason for this is that 10 to 20 percent of all patients on INH develop transient elevations of SGOT during therapy—usually in the first six months, but this is possible at any time.[7] Since in most cases these liver function abnormalities go away spontaneously after a few weeks, they are no cause for alarm. Do not stop the drug unless there is clinical evidence of progression of liver disease. But it is very important to question the patient monthly about clinical signs and symptoms that could indicate persistent liver disease, such as dark urine, fever, itching, nausea, fatigue, and general malaise. If any of these are present, then liver function tests should be ordered.

DR. THOMAS TREADWELL (*first year internal medicine resident*): If a chest x-ray shows old tuberculosis that appears inactive, do you ever do a culture before starting INH?

DR. MULL: Temper your assessment of the x-ray with clinical judgment. I remember a case that illustrates that point very well. A 33-year-old schoolteacher who had emigrated from Hong Kong came in to see me because of fatigue. She had a positive skin test and an apical scar on x-ray.

She insisted that she could not have active disease and said that she had already been treated for her tuberculosis. It was clear that she wanted to keep her new teaching job for financial reasons. Her relatives were worried about her, though, and they told me that she had been losing weight and coughing.

Coincidentally, the radiologist was a chest x-ray specialist, and he was of the opinion that the patient did not have active disease. I said, "Don't be insulted, but I'm going to do some cultures anyway." I did six sputum cultures and the last one was positive, even though none of them were positive on the Ziehl-Neelsen stain. By this time, the patient was back in her teaching job and still losing weight. The moral of this story is that you must use your clinical judgment.

DR. TREADWELL: How was this patient finally treated?

DR. MULL: Her treatment was based on sensitivity studies in vitro. Presumably because of inadequate treatment in the past, her organisms were somewhat resistant and she was treated with INH, ethambutol, and rifampin.

DR. TREADWELL: What happened to the children in her classroom?

DR. MULL: They were all skin tested, and the positives were treated.

A MEDICAL STUDENT: Do you treat people more vigorously when they are in certain occupations like teaching, food handling, or hospital work?

DR. MULL: If the patient were a trumpet player or a schoolteacher, I would lean in the direction of treatment if there were a question about it. As for food handlers, if they are staying in the kitchen handling their food, they are not very likely to be transmitting tuberculosis, because the fact is, you can eat tuberculosis organisms and you will not get the disease unless you lack acid in your stomach. Acid kills tuberculosis organisms. So kitchen-based food handlers do not usually transmit disease, providing they are not waiters going around coughing on people.

A MEDICAL STUDENT: When you treat people with positive skin tests with INH, do they always become negative?

DR. MULL: Interestingly enough, no. In the University of Virginia study mentioned at the beginning of today's program, after the hospital workers received a year of INH therapy, only half reverted to negative. The other half diminished the size of their response but did not convert to negative. This is somewhat analogous to what happens to the serological response when you treat someone for syphilis.

Now let us review cases that Dr. Sonnichsen has been following and talk about how to handle them.

DR. BEN SONNICHSEN (*chief resident, family medicine*): The first patient is a 35-year-old white male who during a routine employment physical claimed to have a positive PPD. He said he had been aware of it for several years but had not been treated. A chest x-ray revealed questionable right apical scarring. He had hypertension controlled with hydrochlorothiazide and was a heavy smoker.

DR. MULL: In this case I would first try to document the positive tuberculin reaction. If I could not obtain his old records, I would put on a first-strength PPD. The usual intermediate dose of PPD might cause too much discomfort in such a patient. Once a positive skin test is demonstrated, in the absence of active disease or any contraindications, I would proceed to treat him prophylactically for a year.

DR. SONNICHSEN: The second case is a 43-year-old Mexican-American female with adult onset diabetes mellitus controlled with chlorpropamide (Diabinese) and diet. She had a past history of presumably adequate treatment for pulmonary tuberculosis: she was treated with triple drug therapy at this hospital for two years starting in 1974. She came to me complaining of nonproductive cough of two weeks duration, but had no fever, chills, weight loss, or night sweats. A chest x-ray revealed scarring in the right upper lung field. Her PPD was positive at 15 mm induration. Her sedimentation rate was 25 mm/hr.

DR. MULL: If you are convinced that this patient has more than a transitory, self-limited cough, then she needs a diagnosis. I would certainly try to get sputum cultures for tuberculosis, but I would also consider other diagnoses and I would follow her closely until a diagnosis was achieved. Because of her age and previous treatment, I would not treat her prophylactically.

DR. SONNICHSEN: The third patient is a three-year-old Laotian male presenting with pneumonia diagnosed by physical examination and chest x-ray. He had a patchy infiltrate that

cleared on treatment with erythromycin. However, he was found to have a tuberculin test positive at 12 mm. A 2 cm scar on his right upper arm raised a question of previous Bacillus Calmette-Guérin (BCG) or smallpox vaccination, but his mother was uncertain about this.

DR. MULL: Since the infiltrate cleared completely with erythromycin, obviously the pneumonia was not due to tuberculosis. However, the positive skin test in a young patient who may have had BCG is a situation we face often. In Mexico and many other third-world countries, BCG is routinely administered at birth. The BCG inoculation site drains for months, forms a scar, and leaves the patient with both resistance to tuberculosis infection and a positive skin test.

This particular case is one that could easily generate debate among physicians. I personally would not treat this patient prophylactically, partly because I would have doubts about being able to get adequate compliance with the medication taking and with follow-up visits. However, if the child were three years older and had this kind of skin test response, I would treat him prophylactically.

The reason for this is that when BCG is given at birth, which is when it is usually given in third-world countries, the body tends to "forget" after about five years and the skin tests are either weak or negative. Consequently, a strong skin test reaction such as the one you have described would make me fear lingering active organisms. There is, after all, a correlation between skin test size and the likelihood of active disease.

The immune responses in the first year of life are not as good or as long lasting as they are after the body becomes more mature. That is why, if you give measles vaccine at less than a year of age, the body "forgets" and the vaccine does not protect later on. A recent Canadian paper reports that in contrast with what I have just said about BCG given at birth, if it is given later on (at six years of age in this Canadian study), the skin test probably remains positive permanently.[9]

DR. SONNICHSEN: Going on to the fourth patient, we have a 38-year-old Mexican-American female who on routine physical examination was found to have a positive PPD at 12-13 mm. She is asymptomatic and has a clear chest x-ray.

DR. MULL: Everything needs a cutoff point. She is over the officially recommended cutoff point of 35 years of age, and since she has no special risk factor that would make me lean in the direction of treatment, I would not give treatment. In fact, I would say that if you did do prophylactic treatment in a case like this, and the patient got a reaction, you could be in trouble with her lawyers.

DR. SONNICHSEN: My last case is a 30-year-old Mexican-American female found on routine examination to have a blistering PPD at 30 mm. Her chest x-ray was negative. What would you do with this patient?

DR. MULL: As I said before, there is a definite and well-established correlation between the magnitude of the reaction and the probability of live tuberculosis organisms residing in the body. Consequently, this patient must be considered to have organisms lurking somewhere in her body and she must be treated. She is under 35 years of age, and in the absence of the contraindications I have already enumerated, she should be treated prophylactically with INH for one year.

DR. DENNIS MACINTOSH (*first year family medicine resident*): I wonder if you would comment about the treatment of extrapulmonary tuberculosis such as scrofula.

DR. MULL: We have seen several cases of extrapulmonary tuberculosis in the family medicine unit during the past year, including two cases of renal tuberculosis presenting as hematuria and one case of dermatologic tuberculosis. As you know, we have also seen patients with tuberculous cervical lymph nodes. The latter condition is usually treated with drugs for a time after appropriate cultures and sensitivity studies have been done. When suppuration and drainage have been reduced, the lymph nodes are then removed surgically, simply because it is very difficult to eradicate this type of infection solely by medical means.

I would prefer not to go further into this rather large subject right now, if there are other questions.

DR. MICHAEL STONE (*assistant professor, family medicine*): You have not mentioned the Tine test. Would you comment on its usefulness?

DR. MULL: The Tine test is a convenient means of testing, but it has a high rate of false positives. The general rule is that if you get a positive Tine test, you ought to go ahead and get a PPD test as well and see whether it is also positive. About 10 to 20 percent of positive Tine testers have negative PPD tests.

Another caveat about the Tine test is that great skill is required to read it, because a 3 mm induration is a positive. Three millimeters is about the size of a BB, and that can be very easy to miss.

DR. SONNICHSEN: How frequently should a person have a PPD test?

DR. MULL: I think the physician must consider the respective risks that people are under. The peak age of susceptibility to tuberculosis in terms of disastrous consequences is in the first six years of life and then again around age 20. Postpartum is another time when the risk of activating tuberculosis becomes a problem, and also when people have diabetes, special risk factors, or simply waning immunity, as in old age. How frequently PPD testing is warranted in your practice will therefore vary with the individual circumstance, but in general, negatives should be tested every couple of years. Dr. Golden, how often do you do tuberculosis testing on schoolchildren?

DR. MICHAEL GOLDEN (*pediatrician and assistant professor, family medicine*): Every other year.

DR. MULL: We have been talking about prophylactic treatment, but in fact, with almost any drug regimen, there is a 30 to 70 percent chance that the patient will not do what you ask him to do, and there are many reasons why this might be so.[10] I would like to ask Dr. Shapiro to talk about some of the things that might help us to keep patients on treatment.

DR. JOHANNA SHAPIRO (*clinical psychologist and assistant professor, family medicine*): I want to say just a few things about eliciting compliant behavior in patients in general.

There are two main barriers to compliance. One is that patients may simply forget. The treatment is not unpleasant in itself, but taking a pill a day over a long period of time is difficult to remember to do, especially if it does not make any difference in the way the patient feels. Also, if it happens that the treatment produces adverse side effects with no concomitant obvious benefits, there is an even more difficult situation. The patient must believe in the benefits of the treatment.

One technique very commonly used to elicit compliance is that of fear arousal: "If I scare him enough, he's going to do what I tell him, if I make it sound bad enough." But this is a dangerous technique to use, because intense fear arousal is usually associated with all kinds of escapism and denial. Generally, if you scare your patient too much, it will not produce the positive effect that you are seeking. Less intense fear arousal is often recommended, but even so, studies with rats show that this less intense arousal will produce a behavior change but will not maintain that change.

I think there is no question that as family doctors, we should involve the family as a whole if possible, so that any drug regimen receives a lot of support from the other family members. That way, it is not just the patient who has the responsibility.

Also, in this kind of situation you are usually dealing with a low-probability behavior, ie, taking a pill, but you can cue the patient to remember it by associating it with a more frequent behavior, such as brushing the teeth or eating.

In children, it is a good idea to link pill taking to a reward system that you can negotiate with them.

Finally, I think that the quality of the relationship with the physician can be extremely important. If you have a positive relationship, the patient will want to please you, and investing time in creating this kind of relationship usually pays off in terms of eliciting compliance.

DR. MULL: Our time is up. Thank you all for your interest and participation today.

References

1. Johnston RF, Wildrick KH: "State of the art" review: The impact of chemotherapy on the care of patients with tuberculosis. Am Rev Respir Dis 109:637, 1974

2. Tuberculosis in the Sixties. A report of the US Department of Health, Education, and Welfare. In Public Health Service (Washington, DC): PHS publication No. 1036. Government Printing Office, 1963

3. Pfuetz KH, Radner DB: Clinical Tuberculosis. Springfield, Ill, Charles C Thomas, 1966, p 382

4. Ferebee SH: Controlled chemoprophylaxis trials in tuberculosis: A general review. Adv Tuberc Res 17:33, 1969

5. Atuk NO, Hunt EH: Serial tuberculin testing and isoniazid therapy in general hospital employees. JAMA 218:1795, 1971

6. FDA Drug Bulletin 8:11, 1978

7. Preventive therapy of tuberculous infection. From the American Thoracic Society, American Lung Association, and the Center for Disease Control. Am Rev Respir Dis 110:371, 1974

8. Bobrowitz ID: Ethambutol in pregnancy. Chest 66:20, 1974

9. Joncas JH, Robitaille R, Gauthier T: Interpretation of the PPD skin test in BCG-vaccinated children. Can Med Assoc J 113:127, 1975

10. Sackett DL, Haynes RB: Compliance with Therapeutic Regimens. Baltimore, Johns Hopkins University Press, 1976