Advanced Concepts in Pediatric TB:
Latent TB Infection

Welcome to the second of eight sessions on Advanced Concepts in Pediatric TB, sponsored by the Southeastern National Tuberculosis Center. Today we present the Latent TB Infection in Pediatric TB. Today's presenter is Dr. Nizar Maraqa. Dr. Maraqa is an Associate Professor of Pediatrics at the University of Florida College of Medicine in Jacksonville and the Fellowship Program Director for Pediatric Infectious Diseases.

He is a Fellow of the Pediatric Infectious Disease Society and practices as a specialist in Pediatric Infectious Disease at UF Health Jacksonville and Wolfson Children's Hospital as well as the University of Florida Center for HIV/AIDS Research, Education and Services (inaudible).

Dr. Maraqa graduated from the Faculty of Medicine at the University of Georgia in 1993 after which he completed his Pediatric residency and Infectious Disease fellowship training at the University of Florida College of Medicine in Jacksonville.

Welcome Dr. Maraqa.

Thank you very much. I appreciate the opportunity to speak to you today. I will be covering the second of the series of webinars, and I will cover latent TB infection in children.

At the end of this presentation, the attendees should be able to identify the high priority groups of children who should be tested for latent TB infection. They should understand the indications for tuberculin skin testing or the use of interferon gamma release assays. And they should correctly interpret the results of those tests as well as describe the management of children with a positive TST or IGRA.

I will go through some instructional cases very briefly, and I want you to keep in mind two questions related to these cases. One is what are the risk factors that the patient has for TB infection or disease? And the second is what would be the appropriate management for the patient? After going through the cases, we will continue with the presentation and come back to these cases at the end of the presentation.

The first is a seven-year-old Hispanic male who moved to the U.S. from Guatemala four years ago. He received a BCG vaccine at the age of one year, and is a known contact of an infectious TB case. His TST is five millimeters of induration. He is asymptomatic and has a normal chest x-ray, CBC, liver enzymes and bilirubin.

The second case is a 12-year-old Asian female who moved to the U.S. from the Philippines more than five years ago. Plans to volunteer at the long-term care facility. Her TST result is negative, zero millimeter induration one year ago. However, prior to volunteering, her TST is now 26 millimeters of induration. Her chest x-ray is normal. She has no symptoms of TB disease, and no known contact of a TB patient.

The third case is a 16-year-old Asian male who moved to the United States from China less than five years ago, received BCG vaccine in China as an infant, and had a quantiFERON test which was positive. The chest x-ray is normal and he has no symptoms of TB disease but is a known contact with a TB patient.

Now let's discuss what latent TB infection is. It is really the presence of mycobacterium tuberculosis organisms, the tubercle bacilli, without any signs or symptoms or radiographic evidence or bacteriologic evidence of TB disease. Infection with such a small number of bacilli that is insufficient to produce clinically manifest TB disease. In fact, latency is an incubation period of undefined duration.

The best available proxy for diagnosing latent TB infection is the identification of an adaptive immune response by the tuberculin skin test or an interferon gamma based assay.

A few studies have actually come out to challenge the fact that latent TB infection is an adaptive immune response, and they are questioning whether latent TB infection status is actually an ongoing infection with

a very, very small number of organisms. However, it is important for clinicians to distinguish between latent infection and TB disease. And as you can see, a latent TB infected individual would have a positive screening test, whether a TST or IGRA, a normal chest x-ray, no symptoms or physical evidence of TB disease. And, if done, the respiratory specimens are going to be smear and culture negative. And this is in contrast to the most common form of TB disease, pulmonary TB, where the TST is usually positive, the chest x-ray is usually abnormal, and the patient may have symptoms of TB disease which includes one or more of the following: fever, cough, hemoptysis, night sweats, weight loss, fatigue, or decreased appetite. And these stations can be culture positive, although not as much in pediatrics as in older individuals.

In the United States, we employ targeted TB testing. And that is a strategy because of the declining rate of TB disease, as you can see in this graph from the Centers for Disease Control and Prevention. Targeted TB testing is used to focus program activities and provider practices on groups that are at highest risk for TB disease.

Targeted TB testing and treatment of latent TB infection are crucial to the control of the spread of TB in the U.S. Treatment of LBTI substantially reduces the risk that persons who are infected with M. TB will progress to TB disease. For more than three decades, this targeted TB testing has been an essential component of TB prevention and control and has been the treatment of persons with LTBI to prevent TB disease.

It is essential TB prevention and control strategy. It detects persons with LTBI who would benefit from treatment. And it de-emphasizes testing of groups that are not at high risk for TB. It can also help reduce the waste of resources and to prevent inappropriate treatment.

Here I will show you the milestones in the guidelines for LTBI treatment in the United States, which started in 65 with the American Thoracic Society recommending treatment for LTBI for those individuals who were previously untreated TB who had TST conversion and who were young. In 1967, the recommendations were expanded to include all those with a positive, more than ten-millimeter induration tuberculin skin test.

In 1974, the CDC and the ATS produced guidelines which established the screening to decrease the risk of hepatitis associated with treatment for latent TB infection. The treatment was recommended for persons who are under 35 years of age.

In 1983, the CDC recommended clinical and laboratory monitoring of people over 35 years of age who require treatment for LTBI.

And it was in 1988 where the CDC recommended two months of rifampin and pyrazinamide as an option for the HIV-infected patients requiring LTBI treatment. This later changed, as I will refer to in later slides.

In the year 2000, the CDC and ATS issued updated guidelines for targeted testing and LBTI treatment. And the preferred regimen for LTBI treatment was nine months of INH, as we will discuss later in more detail.

In the year 2001, due to liver injury and death associated with the two-month regimen of rifampin and pyrazinamide, the use of this option was deemphasized in favor of other regimens. In fact, in 2003, this two-month rifampin-pyrazinamide combined regimen became generally not recommended to be used in patients unless the potential benefits outweigh the risks of severe liver injury and death.

And it wasn't until 2011 that we had – the CDC recommended using a 12 weekly-dose regimen of INH combined with rifapentine as an option that is equal to the standard nine-month INH regimen for certain groups of patients. And we will come to details of this 12-dose regimen later in the presentation.

Moving on to identifying risk factors that put the patient at a high risk for progressing from LTBI to TB disease. We know that the risk of progressing from latent TB infection to TB disease is highest in the first

two years after acquisition of the infection. And this risk declines exponentially by about tenfolds over the first few years. In the initial year, the cumulative risk of progression is two to five percent, or one per 100 person years.

The subsequent risk, however, is one in 1,000 person years. And the lifetime risk for an individual infected with TB to progress to TB disease is ten to 15%. Of note, this risk increases substantially to five to 15% annually in the immune compromised, especially those with HIV infection.

The persons at high risk for developing TB disease after infection fall into two categories: those who have increased likelihood of exposure to persons with TB disease and those with clinical conditions that increase their risk of progressing from LTBI to TB disease.

The increased likelihood of exposure to persons with TB disease applies to close contacts to persons with infections TB disease, especially adult cases of TB disease. Residents and employees of high-risk congregate settings such as correctional facilities, homeless shelters, and healthcare facilities, and also recent immigrants from TB-endemic regions of the world, especially within five years of arrival to the United States.

Children who are five years or younger with a positive tuberculin skin test are also at a higher risk of progression from latent TB infection to TB disease. The risk is largest in the youngest children and drops to one of the lowest in life during primary school, to only increase again with adolescence to a second peak among young adults.

Other individuals at high risk of progression from LTBI to TB disease are HIV-infected persons, those with a history of prior untreated TB or fibrotic lesions on chest x-rays, and those who are underweight or malnourished.

Individuals who are receiving immunomodulators such as tumor necrosis factor alpha antagonists for the treatment of rheumatoid arthritis or inflammatory bowel disease are at increased risk of progressing. Also injection drug users. And those people with underlying medical conditions such as chronic renal failure, solid organ transplantation, diabetes mellitus, gastrectomy, or jejunoileal bypass, silicosis, and those with carcinoma of the head or neck.

In children, certain individuals who have conditions that require them to receive glucocorticoid therapy for an extended period of time are a major group of individuals at a higher risk of progressing from latent TB infection to TB disease.

Now let’s discuss the methods used for testing. Testing for M. TB infection in the United States is available using two testing methods. One is the Mantoux tuberculin skin test, and the second is the interferon gamma release assays, referred to as IGRAs for short. These are tests that measure the adaptive immune responses to mycobacterium tuberculosis. These tests do not exclude latent TB infection or TB disease when negative. And clinical decisions about medical and public health management should include other information and not solely rely on the TST or IGRA results. Those would be physical examination, good history, and other diagnostic studies.

When discussing the tuberculin skin test, this is one of the tests that has been most in use in clinical medicine for over 100 years. It’s a skin test that measures delayed type hypersensitivity reaction to a purified protein derivative of tuberculin. A crude mixture of antigens shared by M. TB, M. bovis, Mycobacterium bovis VCG, and other environmental mycobacterium species.

The multiple puncture tests, such as the tine test, are inaccurate and are no longer recommended for testing.

Regarding administration of the TST, one is supposed to inject 0.1 ML or five tuberculin units of PPD tuberculin solution intradermally on the volar surface of the forearm using a 27 gauge needle. And that should produce a wheel (sp) of six to ten millimeters in diameter using the Mantoux technique.

Universal precautions are recommended when performing the tuberculin skin test, and this should be done within two to eight weeks after exposure when the test is expected to become positive.

We are supposed to measure the induration reaction in 48 to 72 hours. We are to palpate and measure the induration and not the erythema caused by the skin injection. We are to record the reaction in millimeters and to avoid using negative and positives. In fact, when there is no induration, we should record zero millimeters of induration.

The reading of the TST should be done by healthcare professionals who are very well trained in interpretation of the test results. And family members should not be relied on for reading or interpreting the test results.

And induration may start to appear immediately following placement of the purified protein derivative, and this is typically a Type 1 or Type 3 immune reaction. This is not the reaction that we are supposed to measure in 48 to 72 hours of placing the test, which is a Type 4 delayed type hypersensitivity reaction.

From a histopathology standpoint, the perivascular extravasation of lymphocytes into the epidermis and the interstetium (sp) producing that induration that we measure. A strongly positive TST may lead to a persistent skin discoloration, or, very rarely, tissue necrosis.

You should educate the patient and the family regarding the significance of a positive TST result. And we typically say that an intention to test an individual should be an intention to treat that individual if found to be positive.

A positive TST reaction can be measured accurately for up to seven days. A delayed reaction is much more common in children than it is in older individuals.

A negative reaction can be read accurately for only 72 hours and should not be read or recorded past that point in time.

A TST sensitivity and specificity is influenced by the cutoff used for interpretation of the results. A lower cutoff will result in a higher sensitivity and a lower specificity from M. TB infection. The agreed-upon cutoffs in the United States are as follows: a five millimeter induration is interpreted as positive in HIV-infected individuals, close recent contacts of an infectious TB case, persons with a chest x-ray consistent with prior untreated TB, organ transplant recipients, and other immunosuppressed individuals, such as those taking the equivalent of more than 15 milligrams a day of prednisone for more than a month or those taking immunomodulators.

A ten-millimeter induration cutoff is interpreted as positive in recent arrivals from high prevalence countries, children under four years of age, or children and youth exposed to adults at high risk of TB, persons with clinical conditions that place them at high risk for progressing from infection to TB disease, residents or employees of congregate settings, injection drug users, and mycobacteriology laboratory personnel.

A 15-millimeter induration is used a cutoff in persons with no risk factors for TB. And although skin testing programs should be conducted only among those with high risk groups, certain individuals may require testing for employment or school attendance. Diagnostic interpretation and treatment of latent TB infection should always be tied to risk assessment. And the American Academy of Pediatrics and the CDC have risk assessment tools available on their website to help assess the risk of an individual for TB infection or disease.

Now let's discuss some factors that may cause false positive or false negative TST reactions. Factors that cause false positive TSTs include nontuberculous environmental bacteria. The reactions that are caused by nontuberculous mycobacterium are usually under ten millimeters of induration. However, in less than five percent of cases, the TST reaction to nontuberculous mycobacterium could be over 15 millimeters of induration.

A second cause of false positive TST reaction is BCG vaccination. BCG leaves an immunological imprint for a prolonged period of time which usually is for less than five years. However, in some individuals, it may be prolonged for ten or more years. Reactivity in BCG recipients generally wanes over time, and a positive TST result is likely to be due to TB infection if risk factors are present rather than to be attributed to the receipt of BCG vaccine.

There are situations where false negative reactions may occur. And a setting of energy or the inability to react to a TST because of a weakened immune system is one of the common causes of a false negative TST reaction.

The usefulness of energy testing in TST-negative persons who are HIV infected has not been demonstrated and is not routinely recommended.

Other causes of false negative TST reactions include a recent TB infection, because it usually takes less than eight to ten weeks after exposure before the TST reaction can be reliably relied on as a positive test. Overwhelming TB disease is another reason for a false negative reaction, especially with severe miliary disease and TB meningitis. And in the very young, especially newborn and infants less than three months of age, negative TST results can be falsely negative and should not be relied on. However, in a TB contact investigation, an infant with a positive TST result should be evaluated for TB disease and offered the correct management based on that positive TST.

Other causes of false negative TST reaction include live viral vaccination which can temporarily suppress the TST reactivity. This is commonly the scenario when we are placing the PPD test in a patient who recently received an MMR vaccine.

And poor TST administration technique can be a reason for a false negative TST reaction.

Now we will describe a phenomenon called boosting related to the interpretation of the TST results.

Some people with latent TB infection may have a negative TST reaction when tested years after infection because of a waning response. An initial skin test may simulate or boost the ability to react to tuberculin in such individuals. And a subsequent positive, or a boosted reaction to TST, may be misinterpreted as a new infection. So boosting may occur in BCG-vaccinated persons and even in some persons with exposure to nontuberculous environmental mycobacterium.

The two-step testing is a strategy to differentiate between a boosted reaction and a reaction due to a recent infection. If the first test is found to be positive, you consider the individual to be infected. And if negative, you give a second test one to three weeks later. If the second test is positive, then the individual is considered infected. And if negative, the individual is considered uninfected.

Use the two-step test for initial baseline skin testing of adults who will be retested periodically, such as healthcare workers. This flow diagram shows the two-step testing where a baseline skin test is placed, and if the reaction is positive, then the individual probably has a TB infection and follow up of the positive TST with evaluation and LTBI treatment is in order. But if the baseline skin test is negative, then you retest in one to three weeks later. And if the reaction is positive, then this is considered a boosted reaction due to TB infection that occurred a long time ago. That individual requires follow up for positive TST and evaluation for LTBI treatment.

If the second test is negative, then the person is probably not infected with TB, and repeating a TST at regular intervals to detect a positive reaction, which would be an indication of a recent TB infection from there on.

In pregnancy, TST is considered safe and reliable for both the mother and the fetus throughout her pregnancy. Pregnant women who have risk factors for TB infection should be tested. In the case of occupational exposure, such as healthcare workers, the cutoff for TST positivity depends on the prevalence of TB in the facility and the individual's own risk factors for TB. We typically – most institutions would test at hire and then at intervals determined by the annual risk assessment for their individual employees.

Now let's discuss interferon gamma release based assays. IGRAs are ex vivo whole blood tests used to detect the immune response to mycobacterium tuberculosis infection. There are two U.S. FDA-approved IGRAs that are commercially available: the quantiFERON-TB Gold In-Tube test and the T-SPOT.TB test.

How do these tests work? The tests measure and compare the amount of interferon gamma released by blood cells, mainly lymphocytes, in response to antigens. It entails mixing blood samples from the individual with antigens from M. TB and from controls. The T-lymphocytes that recognize the antigens release interferon gamma, and that is picked up using an immunospot or a whole blood ELISA technique. The amount of interferon released in response to mycobacterium tuberculosis antigens is compared to the amount released in response to other antigens and to background signals, positive and negative controls.

IGRA test results are reported as positive, negative, or indeterminate, or equivoco. Of note, the laboratory should provide both quantitative and qualitative results. The quantitative results may be useful for difficult-to-interpret cases in combination with risk factors.

Children with a positive result from an IGRA should be considered infected with mycobacterium tuberculosis complex. A negative IGRA cannot be interpreted universally as the absence of infection. Indeterminate IGRA results have several possible causes that could be related to the patient, to the assay itself, or its performance. And indeterminate results do not exclude M. TB infection and may necessitate repeat testing.

The advantages of IGRAs is that they require a single patient visit to conduct the test. Results can be available within 24 hours. It does not boost responses measured by subsequent tests. They have higher specificity than the tuberculin skin test in populations with higher prevalence of BCG vaccination since the BCG vaccine does not cause a false positive IGRA test.

Very few environmental nontuberculous mycobacterium can cause a false positive IGRA test, and those are limited to mycobacterium marinum, mycobacterium szulgai, and flavescens.

The limitation of IGRAs is that errors in collecting and transporting the blood or in interpreting the assay can decrease its accuracy. Tests may be more expensive than the tuberculin skin test. And there is somewhat limited data on the use of IGRAs for children under five years of age, persons recently exposed to M. TB, the immunocompromised, and those who require serial testing. However, more information is becoming available for individuals who are under five years of age and those with certain immunocompromising situations, which we will talk to in subsequent slides.

There is limited data on the use of IGRAs to predict who will progress from TB infection to TB disease in the future.

So let's talk about which TB test to select in an individual patient. IGRAs are the preferred method of testing for groups of people who have poor rate of returning to have their TST read. And also for persons who have received a BCG vaccine.

A skin test is the preferred method of testing for children under the age of five, especially those under two years of age. Individuals between two and five years of age have a limited data about the reliability of IGRA testing. And until more data is readily available, they are not to be routinely used in that age group.

Either the TST or the IGRA can be used without preference for all other groups, and routine testing with both tests, TST and IGRA, is not recommended.

The American Academy of Pediatrics, in the Red Book, has provided guidance on the strategy for use of TST and IGRA by age and BCG immunization status. As you can see in this flow diagram, if the patient is under five years of age, then the TST is the preferred test. While if the patient is not under five, then you ask whether they have received a BCG vaccination. And if they did, then the IGRA test is the preferred method of testing.

If the patient is not likely to return for TST reading, then an IGRA test is the preferred method of testing.

If the patient is not BCG vaccinated and is likely to return for testing, then either the TST or IGRA are acceptable for testing.

Results from both IGRA and TST may be helpful when the initial test is negative and the patient has high risk of TB infection or disease. Both tests may be used when the initial test is positive and additional evidence is required or desired to insure compliance. And when the initial test is unclear or indeterminate, then there would be value from performing a second different test.

In contact investigations, you should confirm a negative test by retesting eight to ten weeks after the last exposure. Use the same test for repeat testing in order to reduce misclassification of errors.

In the immunocompromised, the use of IGRAs may be better. There is variability seen with the type of immune compromising condition. In HIV, for example, IGRA tests have shown superiority over tuberculin skin testing, especially in high TB burden populations.

For solid organ transplant recipients, there is no clear advantage for IGRA over TST up until this time.

For hematopoietic stem cell transplant recipients, IGRAs have an edge over TST or even maybe combining a TST and IGRA may be the way to go.

In immunosuppressed individuals receiving immunomodulators, either test may be used. And a full analysis of the clinical and epidemiological risk factors will increase the positive predictive value and may improve latent TB infection detection in these immunocompromised population.

To evaluate persons with positive TB test results, TB disease needs to be ruled out, and then the patient is considered for latent TB infection when TB disease is ruled out. If the person accepts and is able to receive treatment of LTBI, you should develop a plan of treatment with the patient to insure their adherence with that plan. If the person refuses or is unable to receive treatment for LTBI, follow-up of TST or IGRA and serial test x-rays are unnecessary. You should educate the patient about signs and symptoms of TB disease.

Close contact with negative TB test results need to be evaluated. These include children who are under four years of age, immunosuppressed persons, and any person at high risk of progressing from TB infection to TB disease once they acquire the infection.

Always rule out TB disease before treating for latent TB infection. A medical evaluation and a chest x-ray should be required in that evaluation.

You should administer latent TB infection for people at high risk of progressing from TB infection to TB disease. This is called window prophylaxis and is most importantly applied to individuals who are under

four years of age. Then retest eight to ten weeks after the last exposure in order to allow for a delayed immune response to occur.

Now let's discuss latent TB infection treatment regimens. Before you initiate treatment, you should rule out TB disease with a good history, physical examination, and a chest x-ray. And when indicated, bacteriologic studies should be performed. You should determine the prior history of treatment for LTBI or TB disease, assess risks and benefits of treatment, determine current and previous drug therapies, and recommend HIV testing.

The treatment regimens for latent TB infection that are recommended for use are as follows: INH for nine months given daily or twice weekly. The nine-month regimen of INH is the standard regimen for treatment of LTBI and has shown a much higher efficacy in preventing progression from infection to disease than the use of six months of INH, which only be reserved to those individuals who cannot and will not complete a nine-month regimen of INH.

INH and rifapentine combined could be used for three months in a once-weekly regimen in a minimum of 12 doses.

And rifampin, especially in individuals who cannot tolerate INH or have INH-resistant rifampin susceptible mycobacterium tuberculosis infection, can receive four months of treatment daily. And this used to be applied for adults with the American Academy of Pediatrics recommending a six-month regimen of rifampin. However, we no longer require six months for children, and they can be treated with four months of rifampin if using this regimen.

It is important to note that the INH nine-month regimen should be a minimum of 270 doses and should be completed within 12 months of treatment. The same applies to the INH rifapentine regimen, which comprises of a minimum of 12 doses and should be completed within a four-month regimen. And for the four-month rifampin regimen, the 120 doses needs to be completed within a six-month period.

Let's discuss in more detail the INH nine-month regimen, which is the preferred regimen for children two to 11 years of age. The six-month regimen, as I alluded to, is less effective in the prevention of progression from TB infection to TB disease and should be reserved for those who are unable to complete nine months of INH.

The INH regimen may be given daily or intermittently, and when used in the twice weekly intermittent regimen, it should be with direct observed therapy. It comprises of 270 doses used within 12 months.

The INH rifapentine regimen is a three-month regimen, which is an option equal to the nine-month preferred INH regimen in LTBI treatment for certain groups such as otherwise healthy people who are 12 years or older and who recently were in contact with infectious TB or had tuberculin skin test conversion or positive blood tests for TB. It must be used with direct observed therapy. It is not recommended for children younger than 12 years of age at the present time.

HIV-infected people taking antiretroviral therapy should not routinely be given INH and rifapentine. It, however, can be used in HIV individuals who are not receiving therapy.

It also should not, and is not recommended for, pregnant women or women who are expecting to be pregnant within the 12-week regimen. INH and rifapentine is given once a week for three months. The regimen is comprised of 12 doses administered within a four-month period.

The rifampin regimen is used daily for four months as an acceptable alternative when treatment with the INH regimen is not feasible. We no longer recommend a six-month duration for the rifampin regimen for treatment of LTBI in children as was proposed by the AAP previously. It is used in situations where rifampin cannot be used. It is allowed to use rifabutin as a substitute.

And the rifampin regimen is comprised of 120 doses that are administered within six months.

In the 2015 edition of the Red Book, additional possible regimens that can be used for treatment of LTBI include the following:

Three months of daily INH and rifampin, with INH dose being the same as when used alone and the rifampin dose of ten to 15 milligrams per kilo per day.

Another option are two months of daily rifampin and pyrazinamide when given as part of rifampin, INH, pyrazinamide and ethambutol RIPE therapy for suspected TB disease which subsequently is determined to be M. TB infection only.

In the HIV-infected individual, it is advised that you consult an expert in managing HIV and TB. INH daily for nine months, rather than six months, is optional and preferred. Two hundred and seventy doses should be administered within a 12-month duration.

Rifampin is generally contraindicated for persons taking protease inhibitors. Rifabutin can sometimes be substituted for rifampin. INH rifapentine is a regimen that is not recommended for HIV-infected individuals who are taking antiretroviral agents.

In individuals with fibrotic lesions suggestive of TB, they should be treated for LTBI if they have a positive TST reaction, with a cutoff of five millimeter induration or a positive IGRA result. No symptoms of infectious disease and no history of treatment for TB disease. You treat only after active disease is excluded with the proper bacteriologic testing. Acceptable regimens include nine months of INH, four months of rifampin, with or without INH, and three months of INH and rifapentine.

In situations when there is multi-drug-resistant TB, contacts of persons with MDR-TB, the risk of progressing from infection to disease needs to be considered before recommending LTBI treatment, and consultation with a TB expert is recommended.

When prescribing treatment for these contacts, consult an expert since dual agent regimens may be necessary. Use of second line antimycobacterial agents is likely. And a longer duration of treatment, and a more closely-done follow up is mandatory.

In the case of pregnancy and breast feeding, latent TB infection treatment should be delayed until after the early post partum period unless the pregnant woman is at high risk of progressing from infection to TB disease, such as a very recent conversion. Nine months of INH given daily or twice weekly, along with vitamin B6 supplementation, should be administered. Pregnant women who are receiving INH should be monitored very carefully as they are at higher risk of developing hepatic toxicity attributed to INH use. If unable to take INH, you should consult with a TB expert.

Breast feeding is not a contraindication to LTBI treatment. However, vitamin B6 supplementation is recommended for nursing women who are receiving INH therapy and for breastfeeding infants of women who are receiving INH therapy.

Latent TB infection is transplant candidates and recipients is another specific situation. Risk assessment in transplant recipients for the development of TB depends on, among other factors, the locally-expected underlying prevalence of infection with M. TB in the target population. In areas where there is high prevalence, preventive LTBI chemotherapy for all transplant recipients may be justified without immunodiagnostic testing while in areas of medium and low prevalence, preventive LTBI chemotherapy should only be offered to candidates who have positive M. TB-specific immune responses.

The diagnosis of TB in transplant recipients can be challenging. Treatment of TB is often difficult due to substantial interaction between the M. TB drugs and the immunosuppressive medications.

Completion of LTBI therapy is based on the total number of doses administered and not the duration of therapy alone.

For patients who have missed doses, extend or restart treatment if the interruptions were frequent or prolonged to preclude completing the minimum number of doses within the recommended duration. When treatment has been interrupted for more than two months, patients should be examined to rule out TB disease before resuming or restarting LTBI treatment.

Direct observed preventive therapy may also be recommended in certain situations.

Clinical monitoring is crucial for the success of LTBI treatment. Educate the patient to report signs and symptoms of adverse drug reactions. These include fever, headache, rash, anorexia, nausea, vomiting, abdominal pain in the right upper quadrant indicating hepatic toxicity, fatigue or weakness, darkening of urine and its discoloration, persistent numbness in the hands and feet indicating peripheral neuropathy. This peripheral neuropathy is typically associated with INH use and occurs in less than .2% of recipients. It is more likely to occur in those with other conditions that predispose to neuropathy, such as diabetes mellitus, HIV infection, and excessive use of alcohol.

Monthly visits should include a brief physical examination and a review of the rationale for treatment, adherence with therapy, symptoms of adverse drug reaction, and the plan for continued treatment.

The incidence of clinical hepatitis in people who are taking INH is lower than previously thought. Hepatitis risk increases with age. It’s quite uncommon in persons under 20. And nearly about two percent of individuals aged between 50 and 60 years.

The risk increases when the individual has an underlying liver disease or with heavy alcohol consumption.

In a study conducted by Chang and Colleagues, hepatic toxicity was seen in 13, or about one percent, of 1,235 children under 18 years of age who completed nine months of INH. There were eight girls and nine Hispanics among those 13 that developed hepatic toxicity. Eleven of those had symptoms and signs, and only two were asymptomatic and had elevation of ALT above five times the upper limit of normal. Three developed hepatic toxicity more than six months after the start of INH therapy.

The ALT dropped to normal in all of those patients after discontinuation of INH. The authors concluded that in children who have latent TB infection, INH hepatic toxicity has low frequency and is typically reversible once INH is stopped.

There is also evidence of late drug-induced liver injury, indicating the importance for monitoring symptoms and (inaudible) throughout the INH therapy course.

Baseline liver function tests are not necessary except for patients who have other risk factors such as HIV infection, underlying liver disease, regular excessive alcohol use, and pregnancy or early post partum period.

Repeat laboratory monitoring should be done in people with abnormal baseline results, those at high risk for adverse reaction, when there are symptoms of adverse reaction, if there is liver enlargement or tenderness during your physical examination, and with current or recent pregnancy.

The asymptomatic elevation of hepatic enzymes can be seen in ten to 20% of people taking INH. The levels usually return to normal after completion of therapy. You should discontinue the INH treatment if transaminase levels are three times or more the upper limit of normal if the patient has symptoms of hepatic toxicity. And when the patient is asymptomatic, elevation above five times the upper limit of normal should lead you to discontinue the treatment.

For every patient, you should asses the TB risk factors, and if risk is present, perform the appropriate testing. If TST or IGRA is positive, you should rule out TB disease, and if that is ruled out, then you should initiate treatment for latent TB infection.

If treatment is initiated, you should take all action necessary to ensure the patient's adherence and completion of the therapy.

I've provided the following additional resources for your reading.

Now let's go back to the instructional cases. The first was a seven-year-old Hispanic male who moved to the U.S. from Bolivia four years ago, received a BCG vaccine at the age of one, is a known contact of an infectious TB case. He has a tuberculin skin test of five millimeters of induration, no symptoms of TB disease, and a normal workup. The two questions that we're keeping in our mind is what risk factors for TB infection or disease the patient has, and what would be the appropriate management.

The patient is a contact of an infectious TB case. He is a recent immigrant to the U.S. from a country with a high prevalence of TB. And the patient emigrated within five years. If the patient has not been a contact, the recent immigration would have made him a candidate for targeted TB testing, but the five millimeter reaction would not be considered positive in a seven year old. As a contact of an active TB case, however, five millimeters of induration is considered positive. This patient should be treated for latent TB infection immediately.

In the second case, we had a 12-year-old Asian female who moved to the U.S. from the Philippines over five years ago. She plans to volunteer at a long-term care facility. Her initial TST a year prior was zero millimeters of induration; however, her current TST is 26 millimeters induration. Chest x-ray was normal, she has no symptoms of TB disease and no known contact of an active TB case. In discussing her risk factors and her management, the patient's TST converted to negative to positive, zero to 21 millimeters of induration within a two-year period. This TST conversion increases her risk of progressing from LTBI to TB disease. She is foreign born, which is less of a risk factor since she immigrated over five years ago. The patient is a recent converter, and as such she is a candidate for treatment for LBTI with the preferred regimen of INH.

In our third case, we had a 16-year-old Asian male who moved to the U.S. from China less than five years ago. Received a BCG vaccine in China as an infant. The quantiFERON test, the IGRA test, is positive. Chest x-ray is normal. The patient is asymptomatic for TB disease, and he is a known contact of a TB patient. In discussing his risk factors, positive IGRA results suggest that M. TB infection is likely. The result is not affected by his receipt of BCG vaccination as an infant. Recent immigrant to the U.S. from a country with a high prevalence of TB is another risk factor. His foreign-born status is a risk factor since he immigrated less than five years ago. And he is a known contact with a TB patient, which is another important risk factor. The patient recently immigrated from a TB endemic country, has a positive quantiFERON result, which is indicative of latent TB infection, is a contact with a TB patient, which could have been the source of his infection, and thus he should be treated for LTBI.

Thank you very much for your attention.