

Latent Tuberculosis Infection (Updated 2-9-07)

NOMENCLATURE

The CDC has recommended a change in the terminology in this area. The terms “chemoprophylaxis” and “preventive therapy” will no longer be used. Instead, the phrase treatment of “latent tuberculosis infection (LTBI)” is recommended because it more accurately describes the intended intervention (4). This change is meant to promote greater understanding of the concept for both patients and providers, resulting in better compliance with the TB control strategy. An emphasis on the diagnosis and treatment of LTBI represents a basic shift in the approach to TB control.

CLINICAL COURSE

Tuberculosis infection occurs usually by airborne transmission, often resulting with as few as one to five bacilli depositing in the terminal alveolus. Primary tuberculosis itself is often a self-limited, respiratory illness that often goes undiagnosed.

Depended on the immune status of the host and the nature of the exposure, only 10 percent of patient will go on to progress to active infection; about 5 percent of patients exposed with progress to active infection within two years, while another 5 percent will progress at some later point in their lives.

Symptoms of active disease include fever, night sweats, anorexia, weight loss and weakness. Such non-specific symptoms often resulting in delayed diagnosis. Chest radiographs often show infiltrates in the middle or lower lung zones, often with ipsilateral lymphadenopathy, in primary TB, and upper lobe infiltrates in reactivation TB. Although 85 % of cased of active tuberculosis are pulmonary in nature, it is important to remember that active TB can be extrapulmonary, the most common sites being lymph nodes, pleura and bones/joints (1).

PPD TESTING

Targeting tuberculin testing in LTBI is a strategic component of TB control. Testing should focus only on persons who are at high risk for infection and would benefit from treatment. This includes patients in three broad categories:

1. Recent infection with *Mycobacterium tuberculosis*
2. Conditions associated with an increased progression to LTBI to active TB*
3. High risk group for exposure to TB (HIV patients, the homeless, immigrants, health care professionals, inmates, IVDU or alcoholics and residents of nursing homes)

*High risk of progression includes (4):

- Infection < 1 year

- HIV infection
- IVDU
- Silicosis
- Radiographic evidence of fibronodular disease consistent with old TB
- Solid organ transplantation
- Jejunioileal bypass
- CRF
- Carcinoma of the head and neck
- Gastrectomy
- DM
- Weight loss of > 10% Ideal Body Weight

Skin testing in low risk patients is discouraged. High-risk patient who are found to be positive should be offered LTBI irrespective of age.

PPD INTERPRETATION

The tuberculin skin test is the most reliable method for establishing the diagnosis of *M. tuberculosis* infection in the absence of clinical symptoms. The 5 tuberculin units (TU), or intermediate strength tuberculin, applied by the Mantoux (intradermal) technique should always be used.

The PPD is read 48 to 72 hours after placement of the test. Reading should be based on palpating the skin for induration borders. One should NOT use the extent of erythema on the arm. One method often employed is use of a pen to facilitate measurement of induration. A single measurement of the induration diameter presents transverse to the long axis of the forearm should be recorded (e.g. not a reading of 12 by 8 mm).

A prior history of vaccination with the bacille Calmette-Guérin (BCG) is frequently cited as a reason not to perform a tuberculin skin test, because of problems in interpretation of the result. However, given most persons who have received the vaccine come from high prevalence parts of the world, the CDC recommends that previous infection should be ignored (3).

The definition of a positive test depends on one's risk factors. The American Thoracic Society and Centers for Disease Control (ATS/CDC) recommends the following interpretation of the tuberculin test with three defined cutoff values for significant reactions (or positive tests)(4):

1. ≥ 5 mm induration:

- Recent contacts of an active TB
- HIV infection
- Abnormal chest radiograph consistent with TB disease
- Immunosuppressed individuals

- All inmates (this is a California provision from the Calif. Dept of Corrections) (5)

2. ≥ 10 mm of induration:

- All persons except in the 5 mm category.

The CDC recommends a 15 mm cutoff for low risk patients. However, in California is considered a high-risk state, and also the prevalence of nontuberculous mycobacterial infections in lower in this state (5).

A positive TB skin conversion is defined as > 10 mm of increase from a negative TB test to a positive one within a two year period.

In patients that require serial testing (i.e. nursing home patients), especially in patients who have experienced a long delay between exposure and presentation, a two-step test is recommended. It is well known that such patients may initially have a “negative” test because of an initial weakened immune response placement of the PPD. However, the placement of the Mannatoux will cause a reinvigorated immune response to a subsequent test. The “booster effect” describes the phenomenon that a follow-up PPD will then be “positive,” and may be interpreted as a new conversion. To avoid this misinterpretation, a repeat PPD should be placed in these patients two weeks after the original “negative” test. If the resultant test becomes positive, then the infection is long standing, and thus will not be interpreted as a recent conversion in subsequent testing.

POSITIVE PPD CONVERSION TO ACTIVE TUBERCULOSIS

Overall, between 5 and 10% of all tuberculin reactors will develop active tuberculosis during their lifetime. Thus, the decision to treat a patient is based on their cumulative risk of developing active tuberculosis versus their risk of developing an adverse reaction to isoniazid.

The rates of conversion to active to tuberculosis are listed below (6):

| | |
|--------------------------------------|--|
| Adults with positive PPD, normal CXR | 5% > 2 years 5% < 2 years |
| Household contact of active case | 2 to 5% 1st year (30 % lifetime for heavily exposed persons) |
| Positive PPD, HIV infection | 10 % per year |

These risks are mitigated by the underlying conditions that increase these percentages. These range anywhere from 2 time the relative risk (diabetes mellitus) to 40 times the relative risk (transplantation).

In every patient, with a positive test, a symptom review should be performed as well as a chest radiograph. If the chest x-ray is negative and the patient is asymptomatic, treatment of LTBI may be indicated. If the chest x-ray is abnormal or the patient is symptomatic, the patient must have bacteriologic studies to exclude active disease, and therapy with LTBI should be delayed until final cultures are obtained.

LTBI ELIGIBILITY

The CDC guidelines for 2000 have been primarily modified to extend the patients eligible for treatment and the duration of therapy. This is based a series of studies that have shown that 9 months of therapy reduced the incidence of subsequent active disease 93%, as compared to 70% at 6 month. Nine months was shown to be similar in efficacy to 12 months of therapy from the earlier studies (7).

Los Angeles County Department of Health Services have modified this somewhat (5). The following are a list ten categories of the patients in whom are eligible for LTBI:

- I. Abnormal CXR with parenchymal changes consistent with active TB, a positive PPD, but negative bacteriologic changes (regardless of age).
- II. Persons with HIV (regardless of age)
- III. Persons with close contact to persons with active TB (regardless of age).
- IV. Recent TB skin test converters (regardless of age).
- V. Persons form countries with high TB rates:
 - i. Immigrants in the US less than 3 years (regardless of age).
 - ii. Immigrants in the US more than 3 years – UNDER AGE 35. *
- VI. Conditions associated with an increased risk of TB:
 - DM (especially insulin-dependent)
 - Silicosis
 - ESRD
 - Transplantation
 - Immunosuppression
 - Chronic steroids (>15 mg/day for 1 month or more)
 - Hematologic or Reticuloendothelial diseases
 - Malnutrition
 - Head and Neck cancer
 - Intestinal bypass or gastrectomy
 - Chronic malabsorption
 - >10 % below ideal body weight
- VII. Children and adolescents under 18, with exposure to TB.
- VIII. Residents and employees in high risk settings (regardless of age):
 - Prisons
 - Nursing homes and other long-term facilities for the elderly

- Residential facilities for those with AIDS
 - Homeless and homeless shelters
 - Hospital and other health care employees
- IX. Those who abuse alcohol, cocaine, and IV drugs.
- X. All others who are test not in categories I – IX, UNDER AGE 35. *

* This is specific to LA County

RECOMMENDED THERAPY FOR THE TREATMENT OF LTBI

The CDC revised the guidelines for TB prophylaxis are listed below. Before initiating therapy, a history should be taken to document any previous treatment of active disease or previous treatment of LTBI, medical conditions (especially HIV infection) and current medications that may interact with TB medications. In addition, as previously stated, a chest radiograph must be performed on ALL patients to exclude the possibility of active TB.

1. INH alone*:

- A. 6 months INH is the minimum requirement (9 months preferred) for all immuno-competent adults.
- B. 9 months for children and adolescents (up to age 18).
- C. 9 months for all persons with HIV infection.
- D. 9 months in all persons with evidence of evidence of old TB

* May be given twice weekly if given with direct observed treatment (DOT).

2. Rifampin and Pyrazinamide for 2 months:

This regimen must **ONLY** be after approval with the LA County TB Program. This regimen is really only for HIV patients who are risk for active TB who are unlikely to take 9 months of INH. This regimen is more hepato-toxic than INH alone.

3. Rifampin for 4 months:

This regimen is for INH intolerant patients.

CLOSE CONTACTS

In the case of close contacts, of patients with active TB, the initial PPD may be negative. It may take 2-12 weeks to develop a positive PPD in this situation. Clearly if patient's PPD is positive (i.e. 5 mm or more), a chest X-ray should be obtained and, if active disease is excluded, LTBI should be initiated as above.

However, if the PPD is initially negative, and the chest X-ray is negative, INH therapy should also be initiated when the risk of infection is high. This also applies in the case of a child under 5 years of age, or immunosuppressed patient. After 10 –12 weeks of therapy, if the PPD is again negative, therapy may be discontinued. If the patient converts to a positive PPD, completion of full therapy of LTBI is, of course recommended.

In the case of HIV infected close contacts, treatment should be completed regardless of the result of the repeat test.

MONITORING THERAPY

After the decision has been made to initiate LTBI, patients should receive a clinical evaluation monthly. This evaluation should include a review of side effects associated with the medications, particularly hepatitis (i.e. anorexia, abdominal pain, jaundice, fever, nausea, vomiting, dark urine.) Baseline and periodic laboratory testing are not routinely indicated for all persons starting LTBI. This change in the prior recommendation is due to a new report that determined the incidence of INH related hepatitis to be only 1 case in 1000 persons. However, baseline and periodic liver function test are indicated in the following groups:

- 1. HIV infection**
- 2. History of chronic liver disease**
- 3. Alcoholism**
- 4. Ingestion of other hepatotoxic medications**
- 5. Pregnant women and those in the first 6 months post-partum**

If a regimen of INH is interrupted, the patient should be given an additional three months of therapy (4). If the lapse in treatment is greater than three months, the regimen should be restarted.

Peripheral neuropathy occurs in up to two percent of patients taking the drug. It is caused by interference with the metabolism of pyridoxine and can be effectively prevented by pyridoxine supplementation (Vitamin B6 - 25 – 50 mg).(8) Pyridoxine should be given to patients who are high risk for neuropathy.

CONCLUSION

In conclusion, testing and treatment of latent tuberculosis infection (LTBI) has changed in the past few years to try and target high-risk populations. PPD testing should try to target those at high risk of exposure and those whose medical conditions increase their risk to progress to active disease if exposed. Low risk groups should not be routinely tested. PPD interpretation should be based on the guidelines above, remembering that everyone in California is now considered at increased risk. The 9-month regimen of INH has been advocated as the new standard duration of treatment by the CDC for all patient who qualify, but in Los Angeles this should be focus on children and adolescents, HIV infected persons, and those with evidence of old TB. In all other immunocompetent adults, the County of Health considers a 6-month regimen acceptable. Clinical monitoring is still recommended monthly, but routine testing is not recommended unless the patient is in a high-risk category.

REFERENCES:

- 1. Division of Tuberculosis Elimination. Surveillance reports: report tuberculosis in the United States, 2000. Atlanta. CDC, 2001.**
- 2. Core curriculum on tuberculosis: what the clinician should know. 4th Ed. Atlanta: Centers for Disease Control and Prevention, 2000.**
- 3. Dye C., et al. Consensus statement: global burden of tuberculosis: estimated incidence, prevalence, and mortality by country: WHO Global Surveillance and Monitoring Project. JAMA 1999; 282:677-86.**
- 4. Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. ATS Official Statement. Am. J. Respir. Crit. Care Med. 2000; 161: 1376-95.**
- 5. Targeted Skin Testing and Treatment of Latent Tuberculosis Infection in Adults and Children. County of Los Angeles Department of Health Services TB Program. Position Paper. 10/2001.**
- 6. Small, P., et al. Management of Tuberculosis in the United States. N Engl J Med 2001; 345: 189-200.**
- 7. Comstock, G. How Much Isoniazid is needed for Prevention of Tuberculosis? Int J Tuberc Lung Dis 1999; 3: 847-50.**
- 8. Snider, D. Pyridoxine supplementation during isoniazid therapy. Tubercle 1980; 61:191-6.**