Transmission, Diagnosis, & Treatment of LTBI
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Areas of Concern

• TB cases continue to be reported in every state

• Drug-resistant cases reported in almost every state

• Estimated 10-15 million persons in U.S. infected with *M. tuberculosis*
  - Without intervention, about 10% will develop TB disease at some point in life

Transmission and Pathogenesis
Transmission of *M. tuberculosis*

- Spread by droplet nuclei
- Expelled when person with infectious TB coughs, sneezes, speaks, or sings
- Close contacts at highest risk of becoming infected
- Transmission occurs from person with infectious TB disease (not latent TB infection)

Probability TB Will Be Transmitted

- Infectiousness of person with TB
- Environment in which exposure occurred
- Duration of exposure
- Virulence of the organism
Pathogenesis

• 10% of infected persons with normal immune systems develop TB at some point in life

• HIV strongest risk factor for development of TB if infected
  - Risk of developing TB disease 7% to 10% each year

• Certain medical conditions increase risk that TB infection will progress to TB disease

Conditions That Increase the Risk of Progression to TB Disease

• HIV infection
• Substance abuse
• Recent infection
• Chest radiograph findings suggestive of previous TB
• Diabetes mellitus
• Silicosis
• Prolonged corticosteroid therapy
• Other immunosuppressive therapy
Conditions That Increase the Risk of Progression to TB Disease (cont.)

- Cancer of the head and neck
- Hematologic and reticuloendothelial diseases
- End-stage renal disease
  - Intestinal bypass or gastrectomy
- Chronic malabsorption syndromes
- Low body weight (10% or more below the ideal)

Common Sites of TB Disease

- Lungs
- Pleura
- Central nervous system
- Lymphatic system
- Genitourinary systems
- Bones and joints
- Disseminated (miliary TB)
Drug-Resistant TB

- Drug-resistant TB transmitted same way as drug-susceptible TB
- Drug resistance is divided into two types:
  - Primary resistance develops in persons initially infected with resistant organisms
  - Secondary resistance (acquired resistance) develops during TB therapy

Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection, 2005

Applying CDC/ATS Guidelines in Your Clinical Practice

Division of Tuberculosis Elimination
Centers for Disease Control and Prevention
Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection

As tuberculosis (TB) disease rates in the United States (U.S.) decrease, finding and treating persons at high risk for latent TB infection (LTBI) has become a priority.

Latent TB Infection (LTBI)

LTBI is the presence of *M. tuberculosis* organisms (tubercle bacilli) without symptoms or radiographic evidence of TB disease.
### Terminology

- **“Treatment of latent TB infection”** replaces the terms “preventive therapy” and “chemoprophylaxis” to promote greater understanding of the concept for both patients and providers.

- **Targeted tuberculin testing** is used to focus program activities and provider practices on groups at the highest risk for TB.

### LTBI vs. Pulmonary TB Disease

<table>
<thead>
<tr>
<th>Latent TB Infection</th>
<th>Pulmonary TB Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST* or QFT† positive</td>
<td>TST or QFT usually positive</td>
</tr>
<tr>
<td>Negative chest radiograph</td>
<td>Chest radiograph may be abnormal</td>
</tr>
<tr>
<td>No symptoms or physical findings suggestive of TB disease</td>
<td>Symptoms <em>may</em> include one or more of the following: fever, cough, night sweats, weight loss, fatigue, hemoptysis, decreased appetite</td>
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<tr>
<td>Respiratory specimens <em>may</em> be smear or culture positive</td>
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</tbody>
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* TST (tuberculin skin test)
† QFT (QuantiFERON-TB and QuantiFERON-Gold) is a blood test to detect *M. tuberculosis* infection.
Targeted Tuberculin Testing

• Detects persons with LTBI who would benefit from treatment
• De-emphasizes testing of groups that are not at high risk for TB
• Can help reduce the waste of resources and prevent inappropriate treatment

Treatment of LTBI – Milestones (1)

For more than 3 decades, an essential component of TB prevention and control in the U.S. has been the treatment of persons with LTBI to prevent TB disease.
Treatment of LTBI – Milestones (2)

1965: American Thoracic Society (ATS) recommends treatment of LTBI for those with previously untreated TB, tuberculin skin test (TST) converters, and young children.

1967: Recommendations expanded to include all TST positive reactors (≥10 mm).

Treatment of LTBI – Milestones (3)

1974: CDC and ATS guidelines established for pretreatment screening to decrease risk of hepatitis associated with treatment

– Treatment recommended for persons ≤ 35 years of age
Treatment of LTBI – Milestones (4)

1983: CDC recommends clinical and laboratory monitoring of persons ≥ 35 who require treatment for LTBI

1998: CDC recommends 2 months of rifampin (RIF) plus pyrazinamide (PZA) as an option for HIV-infected patients (later changed)

Treatment of LTBI – Milestones (5)

2000: CDC and ATS issue updated guidelines for targeted testing and LTBI treatment\(^1\)

- 9-month regimen of isoniazid (INH) is preferred
- 2-month regimen of RIF and PZA and a 4-month regimen of RIF recommended as options (later changed)

\(^1\) MMWR June 9, 2000; 49(No. RR-6)
Treatment of LTBI – Milestones (6)

2001: Owing to liver injury and death associated with 2-month regimen of RIF and PZA, use of this option de-emphasized in favor of other regimens.2

2003: 2-month regimen of RIZ and PZA generally not recommended — to be used only if the potential benefits outweigh the risk of severe liver injury and death.3

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What’s New (1)

Tuberculin skin testing

• Emphasis on targeting persons at high risk

• 5-mm induration cutoff level for organ transplant recipients and other immunosuppressed patients being treated with prednisone or TNF-α antagonists.4

• Skin-test conversion defined as increase of ≥ 10 mm of induration within a 2-year period, regardless of age

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2 MMWR August 31, 2001; 50(34): 733-735
3 MMWR August 8, 2003; 52(31): 735-739
4 MMWR August 61, 2004; 53(33): 683-686
What’s New (2)

Treatment of LTBI

• HIV-negative persons – INH for 9 months preferred regimen

• HIV-positive persons and those with fibrotic lesions on chest x-ray (consistent with previous TB) – INH should be given for 9 months

• For all persons – RIF for 4 months is an option

What’s New (3)

Clinical and laboratory monitoring

• Routine baseline and follow-up monitoring not required except for
  – HIV-infected persons
  – Pregnant women or those in early postpartum period
  – Persons with chronic liver disease or who use alcohol regularly

• Monthly monitoring for signs or symptoms of possible adverse effects
Identifying Risk Factors That Lead to Development of TB Disease

Persons at Risk for Developing TB Disease

Persons at high risk for developing TB disease fall into 2 categories

• Those who have been recently infected

• Those with clinical conditions that increase their risk of progressing from LTBI to TB disease
Recent Infection as a Risk Factor (1)

Persons more likely to have been recently infected include

• Close contacts to person with infectious TB
• Skin test converters (within past 2 years)
• Recent immigrants from TB-endemic regions of the world (within 5 years of arrival to the U.S.)

Recent Infection as a Risk Factor (2)

• Children ≤ 5 years with a positive TST
• Residents and employees of high-risk congregate settings (e.g., correctional facilities, homeless shelters, health care facilities)
Increased Risk for Progression to TB Disease (1)

Persons more likely to progress from LTBI to TB disease include

- HIV-infected persons
- Those with a history of prior, untreated TB or fibrotic lesions on chest radiograph

Increased Risk for Progression to TB Disease (2)

- Underweight or malnourished persons
- Injection drug users
- Those receiving TNF-α antagonists for treatment of rheumatoid arthritis or Crohn’s disease
Increased Risk for Progression to TB Disease (3)

- Persons with certain medical conditions such as
  - Silicosis
  - Diabetes mellitus
  - Chronic renal failure or on hemodialysis
  - Solid organ transplantation (e.g., heart, kidney)
  - Carcinoma of head or neck
  - Gastrectomy or jejunoilial bypass

Tuberculin Testing
Purpose of Targeted Testing

• Find persons with LTBI who would benefit from treatment
• Find persons with TB disease who would benefit from treatment
• Groups that are not high risk for TB should not be tested routinely

Groups That Should Be Tested for LTBI
Persons at higher risk for exposure to or infection with TB

• Close contacts of a person known or suspected to have TB
• Foreign-born persons from areas where TB is common
• Residents and employees of high-risk congregate settings
• Health care workers (HCWs) who serve
Groups That Should Be Tested for LTBI (cont.)

Persons at higher risk for exposure to or infection with TB

- Medically underserved, low-income populations
- High-risk racial or ethnic minority populations
- Children exposed to adults in high-risk categories
- Persons who inject illicit drugs

Groups That Should Be Tested for LTBI (Cont.)

Persons at higher risk for TB disease once infected

- Persons with HIV infection
- Persons recently infected with *M. tuberculosis*
- Persons with certain medical conditions
- Persons who inject illicit drugs
- Persons with a history of inadequately treated TB
**Testing for \textit{M. tuberculosis} Infection**

\textbf{Mantoux tuberculin skin test (TST)}

Skin test that produces delayed-type hypersensitivity reaction in persons with \textit{M. tuberculosis} infection

\textbf{QuantiFERON® -TB test and QuantiFERON® - Gold}

Blood test that measures and compares amount of interferon-gamma (IFN-\(\gamma\)) released by blood cells in response to antigens

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**Mantoux Tuberculin Skin Test**

- Preferred method of skin testing for \textit{M. tuberculosis} infection
- TST is useful for
  - Determining how many people in a group are infected (e.g., contact investigation)
  - Examining persons who have symptoms of TB
- Multiple puncture tests (e.g., Tine Test) are inaccurate and not recommended
Administering the TST

- Inject 0.1 ml of 5 TU PPD tuberculin solution intradermally on volar surface of lower arm using a 27-gauge needle
- Produce a wheal 6 to 10 mm in diameter

Reading the TST (1)

- Measure reaction in 48 to 72 hours
- Measure induration, not erythema
- Record reaction in millimeters, not “negative” or “positive”
- Ensure trained health care professional measures and interprets the TST
Reading the TST (2)

- Educate patient and family regarding significance of a positive TST result
- Positive TST reactions can be measured accurately for up to 7 days
- Negative reactions can be read accurately for only 72 hours

TST Interpretation (1)

5-mm induration is interpreted as positive in
- HIV-infected persons
- Close contacts to an infectious TB case
- Persons with chest radiographs consistent with prior untreated TB
TST Interpretation (2)

5-mm induration is interpreted as positive in (cont.)

• Organ transplant recipients

• Other immunosuppressed patients (e.g., those taking the equivalent of >15 mg/d of prednisone for 1 month or those taking TNF-α antagonists)

TST Interpretation (3)

10-mm induration is interpreted as positive in

• Recent immigrants

• Injection drug users

• Residents or employees of congregate settings

• Mycobacteriology laboratory personnel
TST Interpretation (4)

10-mm induration is interpreted as positive in (cont.)

- Persons with clinical conditions that place them at high risk
- Children < 4 years; infants, children, and adolescents exposed to adults at high-risk

TST Interpretation (5)

15-mm induration is interpreted as positive in

- Persons with no known risk factors for TB.*

*Although skin testing programs should be conducted only among high-risk groups, certain individuals may require TST for employment or school attendance. Diagnosis and treatment of LTBI should always be tied to risk assessment.
Factors That May Cause False-Positive TST Reactions

• Nontuberculous mycobacteria
  – Reactions caused by nontuberculous mycobacteria are usually ≤ 10 mm of induration

• BCG vaccination
  – Reactivity in BCG vaccine recipients generally wanes over time; positive TST result is likely due to TB infection if risk factors are present

Factors That May Cause False-Negative TST Reactions (1)

• Anergy
  – Inability to react to a TST because of a weakened immune system
  – Usefulness of anergy testing in TST-negative persons who are HIV infected has not been demonstrated
Factors That May Cause False-Negative TST Reactions (2)

• Recent TB infection
  – Defined as 2 to 10 weeks after exposure
• Very young age
  – Newborns

Factors That May Cause False-Negative TST Reactions (3)

• Live-virus vaccination
  – For example, measles or smallpox
  – Can temporarily suppress TST reactivity
• Overwhelming TB disease
• Poor TST administration technique
  – For example, TST injection too shallow or too deep, or wheal is too small
Boosting

- Some people with LTBI may have a negative skin test reaction when tested years after infection because of a waning response.

- An initial skin test may stimulate (boost) the ability to react to tuberculin.

- Positive reactions to subsequent tests may be misinterpreted as new infections rather than “boosted” reactions.

Two-Step Testing (1)

- A strategy to determine the difference between boosted reactions and reactions due to recent infection.
  - If first TST is positive, consider the person infected
  - If first TST is negative, give second TST 1–3 weeks later
  - If second TST is positive, consider the person infected
  - If second TST is negative, consider the person uninfected at baseline
Two-Step Testing (2)

- Use two-step tests for initial baseline skin testing of adults who will be retested periodically (e.g., health care workers).

QuantiFERON®-TB Test and QuantiFERON®-Gold Test (1)

- Whole-blood test used to detect *M. tuberculosis* infection
- Approved by the U.S. Food and Drug Administration (FDA)
- Entails mixing blood samples with antigens from *M. tuberculosis, M. avium complex*, and controls and incubating for 16 to 24 hours
QuantiFERON®-TB Test and QuantiFERON®-Gold Test (2)

- Cells that recognize the antigen release interferon-γ
- Amount of interferon released in response to tuberculin is compared to amount released in response to other antigens⁵


LTBI Treatment Regimens
Initiating Treatment

Before initiating treatment for LTBI

- Rule out TB disease (i.e., wait for culture result if specimen obtained)
- Determine prior history of treatment for LTBI or TB disease
- Assess risks and benefits of treatment
- Determine current and previous drug therapy

Isoniazid Regimens (1)

- 9-month regimen of isoniazid (INH) is the preferred regimen
- 6-month regimen is less effective but may be used if unable to complete 9 months
- May be given daily or intermittently (twice weekly)
  – Use directly observed therapy (DOT) for intermittent regimen
Isoniazid Regimens (2)

• INH daily for 9 months
  
  (270 doses within 12 months)

• INH twice/week for 9 months
  
  (76 doses within 12 months)

• INH daily for 6 months
  
  (180 doses within 9 months)

• INH twice/week for 6 months
  
  (52 doses within 9 months)

Rifampin Regimens (1)

• Rifampin (RIF) given daily for 4 months is an acceptable alternative when treatment with INH is not feasible.

• In situations where RIF cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted.
Rifampin Regimens (2)

• RIF daily for 4 months
  (120 doses within 6 months)

• RIF and PZA for 2 months should generally not be offered due to risk of severe adverse events\(^6\)

\(^6\)MMWR August 8, 2003; 52 (31): 735-739

Completion of Therapy

Completion of therapy is based on the total number of doses administered, not on duration alone.
Management of Patient Who Missed Doses

- Extend or re-start treatment if interruptions were frequent or prolonged enough to preclude completion
- When treatment has been interrupted for more than 2 months, patient should be examined to rule out TB disease
- Recommend and arrange for DOT as needed

Monitoring During Treatment
Clinical Monitoring (1)

Instruct patient to report signs or symptoms of adverse drug reactions

- Rash
- Anorexia, nausea, vomiting, or abdominal pain in right upper quadrant
- Fatigue or weakness
- Dark urine
- Persistent numbness in hands or feet

Clinical Monitoring (2)

Monthly visits should include a brief physical exam and a review of

- Rationale for treatment
- Adherence with therapy
- Symptoms of adverse drug reactions
- Plans to continue treatment
Clinical Monitoring (3)

- Incidence of hepatitis in persons taking INH is lower than previously thought (0.1 to 0.15%)
- Hepatitis risk increases with age
  - Uncommon in persons < 20 years old
  - Nearly 2% in persons 50 to 64 years old
- Risk increased with underlying liver disease or heavy alcohol consumption

Laboratory Monitoring (1)

Baseline liver function tests (e.g., AST, ALT, and bilirubin) are not necessary except for patients with the following risk factors:

- HIV infection
- History of liver disease
- Alcoholism
- Pregnancy or in early postpartum period
Laboratory Monitoring (2)

Repeat laboratory monitoring if patient has

- Abnormal baseline results
- Current or recent pregnancy
- High risk for adverse reactions
- Symptoms of adverse reaction
- Liver enlargement or tenderness during examination

Laboratory Monitoring (3)

- Asymptomatic elevation of hepatic enzymes seen in 10%-20% of people taking INH
  - Levels usually return to normal after completion of treatment
- Some experts recommend withholding INH if transaminase level exceeds 3 times the upper limit of normal if patient has symptoms of hepatotoxicity, and 5 times the upper limit of normal if patient is asymptomatic.}

1 MMWR June 9, 2000; 49(No. RR-6): 39
Meeting the Challenge of TB Prevention

For every patient

• Assess TB risk factors
• If risk is present, perform TST or QFT
• If TST or QFT is positive, rule out active TB disease
• If active TB disease is ruled out, initiate treatment for LTBI
• If treatment is initiated, ensure completion

Additional Resources

For additional information on TB, visit the CDC Division of Tuberculosis Elimination Website at

http://www.cdc.gov/tb
Guidelines Available Online

• CDC’s Morbidity and Mortality Weekly Report
  http://www.cdc.gov/mmwr

• American Thoracic Society
  http://www.thoracic.org/statements/

Case Studies
Case Study A (1)

Patient history

• 29-year-old African-American female
• History of diabetes
• 35 weeks pregnant
• TST = 20 mm of induration
• No symptoms of TB disease
• CXR, CBC, LFTs normal
• No known contact with TB patient

Case Study A (2)

Questions

1. What are this patient’s risk factors for TB infection or disease?

2. What is the appropriate management for this patient?
Case Study A (3)

Discussion of risk factors

- Persons with diabetes mellitus are 2 to 4 times more likely to develop TB disease than those without diabetes
- Risk may be higher in insulin-dependent diabetics and those with poorly controlled diabetes

Case Study A (4)

Discussion of management

- Pregnancy has minimal influence on the pathogenesis of TB or the likelihood of LTBI progressing to disease
- Pregnant women should be targeted for TB testing only if they have specific risk factors for LTBI or progression to disease
Case Study A (5)

Discussion of management

• Some experts prefer to delay treatment until after the early postpartum period, unless the person has recent TB infection or HIV infection

Case Study B (1)

Patient history

• 47-year-old Hispanic male
• Moved to U.S. from Bolivia 4 years ago
• Known contact of infectious TB case
• TST = 5 mm of induration
• 3 months later TST = 23 mm of induration
• No symptoms of TB disease
• Normal CXR, CBC, AST, and bilirubin
Case Study B (2)

Questions
1. What are the patient’s risk factors for TB infection or disease?

2. Has the management of this patient to date been appropriate?

Case Study B (3)

Discussion of risk factors
• Patient is a contact of an infectious TB case
• Recent immigrant to the U.S. from a country with a high prevalence of TB
Case Study B (4)

Discussion of risk factors

• If the patient had not been a contact, the recency of his immigration (less than 4 years) would have made him a candidate for TB testing, but the 5-mm reaction would not be considered positive

• Persons who immigrate from TB-endemic countries have increased rates of TB

Case Study B (5)

Discussion of risk factors

• Rates of TB approach those of their countries of origin for 5 years after arrival in the U.S.

• These increased rates most likely result from recent *M. tuberculosis* infection in their native country
Case Study B (6)

Discussion of management

• Should be treated for LTBI if TST reactions $\geq 10$ mm of induration

• As a contact of an active TB case, 5 mm of induration is considered positive

• This patient should have been treated for LTBI immediately after the first TST

Case Study C (1)

Patient history

• 36-year-old Asian female
• Moved to U.S. from Philippines $> 15$ years ago
• Plans to work in a correctional facility
• TST result negative 1 year ago
• TST for pre-employment physical = 26 mm of induration
• CXR normal
• No symptoms of TB disease
• No known contact with a TB patient
Case Study C (2)

Questions
1. What are the patient’s risk factors for TB infection or disease?

2. What is the appropriate management for this patient?

Case Study C (3)

Discussion of risk factors
• Patient’s TST converted from negative to positive (within a 2-year period)
• TST conversion increases risk for progressing from LTBI to TB disease
• Foreign-born status is less of a risk factor, i.e., she immigrated more than 5 years ago
Case Study C (4)

Discussion of management

• Patient’s TST conversion indicates failure to identify this person as high risk for recent exposure to TB

• Patient may have had extended travel to her country of origin or other high-prevalence parts of the world

Case Study C (5)

Discussion of management

• Patient is a recent converter and, as such, is a candidate for treatment of LTBI with INH