TARGETED TESTING AND TREATMENT OF LATENT TUBERCULOSIS INFECTION (LTBI)

OBJECTIVES

Upon completion of this session, participants will be able to:

1. Identify persons at high risk for TB infection
2. Describe populations most likely to progress from LTBI to TB disease
3. Recognize CDC population preferences in the use of the TST and IGRA
4. Describe current regimens for the treatment of LTBI

INDEX OF MATERIALS

1. Targeted testing and treatment of latent tuberculosis infection (LTBI) – slide outline
   Presented by: April King-Todd, RN, BSN, MPH

REFERENCE MATERIALS

SUPPLEMENTAL READING MATERIALS

- Centers for Disease Control and Prevention, Division of TB Elimination. Fact Sheets: Testing, Diagnosis and Treatment of TB Infection available at:

Targeted Testing and Latent TB infection

Tuberculosis Case Management & Contact Investigation Intensive

April King-Todd, BSN, MPH
Nurse Manager
Los Angeles County TB Control Program

Targeted Testing and Latent TB infection

- What is targeted testing
- TB screening tests
- Evaluation for TB disease
- Candidates for treatment of TB infection
- LTBI treatment regimens
- Monitoring for adherence and drug toxicity

Objectives

Upon completion of this session, participants will be able to:

1. Identify persons at high risk for TB infection
2. Describe populations most likely to progress from LTBI to TB disease
3. Recognize CDC population preferences in the use of the TST IGRA
4. Describe current regimens for the treatment of LTBI
Identifying High-Risk Groups for *M. tb* Testing

- Health-care providers should find and test
  - Uninfected persons at high risk for LTBI, and/or
  - Persons at high risk for progression to TB disease
- Flexibility needed in defining high-risk groups
- Risk for TB or LTBI in current high-risk groups may decrease over time, and groups currently not at risk may subsequently become high risk

Source: CDC. Core Curriculum on Tuberculosis

Evaluation of Persons with Positive TB Tests

- Facilities should consult with local health department before starting testing program to ensure evaluation and treatment resources are available
- Persons with positive TST or IGRA should be evaluated for disease
- If disease is ruled out, consider for LTBI treatment
- If patient not willing or able to take treatment, educate on TB signs and symptoms

Source: CDC. Core Curriculum on Tuberculosis

Methods for Detecting *M. tb* Infection in U.S.

- Mantoux tuberculin skin test (TST)
- IGRA:
  - QuantIFERON-TB Gold In-Tube (QFT-GIT)*, and
  - T-Spot.*TB*
- These tests do not exclude LTBI or TB disease
- Decisions about medical/public health management should include other info/data, and not rely only on TST/IGRA results

Source: CDC. Core Curriculum on Tuberculosis
Mantoux Tuberculin Skin Test (TST)

- Purified protein derivative (PPD), derived from tuberculin, is injected between skin layers using the Mantoux technique.
- Infected person's immune cells recognize TB proteins in PPD, respond to site, causing wheal to rise.
- Takes 2-8 weeks after exposure and infection for the immune system to react to PPD.
- Reading and interpretation of TST reaction must be done within 48-72 hours.

Source: CDC. Core Curriculum on Tuberculosis.

Administering the TST

- Inject 0.1 ml of PPD (5 tuberculin units) into forearm between skin layers.
- Produce wheal (raised area) 6–10 mm in diameter.
- Follow universal precautions for infection control.

Source: CDC. Core Curriculum on Tuberculosis.

Reading the TST

- Trained health care worker assesses reaction 48–72 hours after injection.
- Palpate (feel) injection site to find raised area.
- Measure diameter of induration across forearm; only measure induration, not redness.
- Record size of induration in millimeters; record “0” if no induration found.

Source: CDC. Core Curriculum on Tuberculosis.

Targeted Testing and Latent TB infection
Interpreting the TST Reaction

- ≥5 mm induration is classified as positive in
  - HIV-infected persons
  - Recent contacts of infectious TB
  - Persons with fibrotic changes on chest radiograph consistent with prior TB
  - Patients with organ transplants and other immunosuppressed patients

Source: CDC. Core Curriculum on Tuberculosis

---

Interpreting the TST Reaction (cont.)

- ≥10 mm induration is classified as positive in
  - Recent arrivals from high-prevalence countries
  - Injection drug users
  - Residents and employees of high-risk congregate settings

Source: CDC. Core Curriculum on Tuberculosis

---

Interpreting the TST Reaction (cont.)

- ≥10 mm induration is classified as positive in
  - Mycobacteriology laboratory personnel
  - Persons with conditions that increase risk for progressing to TB
  - Children <5 years of age, or children and youth exposed to adults at high risk

Source: CDC. Core Curriculum on Tuberculosis
Interpreting the TST Reaction (cont.)

≥15 mm is classified as positive in

- Persons with no known risk factors for TB

Targeted skin testing should only be conducted among high-risk groups

Targeted Testing and Latent TB infection

≥15 mm is classified as positive in

- Persons with no known risk factors for TB

Targeted skin testing should only be conducted among high-risk groups

Factors that May Affect the Skin Test Reaction

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Possible Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>False-positive</td>
<td>• Nontuberculous mycobacteria</td>
</tr>
<tr>
<td></td>
<td>• BCG vaccination</td>
</tr>
<tr>
<td></td>
<td>• Problems with TST administration</td>
</tr>
<tr>
<td>False-negative</td>
<td>• Anergy</td>
</tr>
<tr>
<td></td>
<td>• Viral, bacterial, fungal co-infection</td>
</tr>
<tr>
<td></td>
<td>• Recent TB infection</td>
</tr>
<tr>
<td></td>
<td>• Very young age: advanced age</td>
</tr>
<tr>
<td></td>
<td>• Live-virus vaccination</td>
</tr>
<tr>
<td></td>
<td>• Overwhelming TB disease</td>
</tr>
<tr>
<td></td>
<td>• Renal failure/disease</td>
</tr>
<tr>
<td></td>
<td>• Lymphoid disease</td>
</tr>
<tr>
<td></td>
<td>• Low protein states</td>
</tr>
<tr>
<td></td>
<td>• Immunosuppressive drugs</td>
</tr>
</tbody>
</table>

- Problems with TST administration

Special Considerations When Using TST

Boosting

- Some may have negative (waned) TST reaction when tested years after infection (e.g., older adults)
- Initial skin test may stimulate (boost) ability to react to PPD
- Subsequent positive boosted reaction may be misinterpreted as a new infection
- May still be considered for treatment if currently at high risk for TB disease
Special Considerations When Using TST (cont.)

Two-Step Testing
- Used for initial skin testing of adults to be retested periodically, to reduce likelihood that boosted reaction will be misinterpreted as recent infection
- If 1st test positive, consider infected; if negative, give 2nd test 1–3 weeks later
- If 2nd test positive, consider infected; if negative, consider uninfected

Source: CDC. Core Curriculum on Tuberculosis

Special Considerations When Using TST (cont.)

Pregnant women
- TST is safe and reliable for mother and fetus throughout pregnancy
- Give TST to pregnant women who have risk factors for infection or disease

Source: CDC. Core Curriculum on Tuberculosis

Special Considerations When Using TST (cont.)

Occupational Exposure to TB
- Cutoff for defining a positive TST reaction depends on
  - Individual risk factors for TB
  - Prevalence of TB in the facility
- High-risk sites should test residents and staff at entry and hire and at intervals determined by annual risk assessment

Source: CDC. Core Curriculum on Tuberculosis
Interferon Gamma Release Assays (IGRAs)

- IGRAs detect *M. tb* infection by measuring immune response in blood
- Cannot differentiate between TB and LTBI; other tests needed
- May be used for surveillance/screening, or to find those who will benefit from treatment
- FDA-approved IGRAs are QFT Gold In-Tube and T-Spot.TB test

General Recommendations for Using IGRAs

- May be used in place of, but not in addition to, TST
- Preferred when testing persons
  - Who might not return for TST reading
  - Who have received BCG vaccination
- Generally should not be used to test children <5 years of age, unless used in conjunction with TST

General Recommendations for Using IGRAs (cont.)

- May be used in place of TST to test recent contacts of infectious TB
- Detect *M. tb* infection with greater specificity than TST
- Data are limited on ability to predict subsequent TB
- In contact investigations, confirm negative via retest 8–10 weeks postexposure
- Use same test for repeat testing to reduce misclassification errors

Source: CDC. Core Curriculum on Tuberculosis
General Recommendations for Using IGRAs (cont.)

- May be used for periodic screening, e.g., for health-care workers
- IGRAs do not boost subsequent test results; administered with one patient visit
- Results from both IGRA and TST may be useful when initial test is
  - Negative, and patient has high risk of TB infection or disease
  - Positive, and additional evidence is required/desired
  - Unclear or indeterminate

Source: CDC. Core Curriculum on Tuberculosis

BCG Vaccination

- Vaccine made from live, attenuated (weakened) strain of M. bovis
- Early version first given to humans in 1921
- Many TB-prevalent countries vaccinate infants to prevent severe TB disease

Source: CDC. Core Curriculum on Tuberculosis

Recommendations for BCG Vaccination

- BCG not generally recommended in the U.S.
- However, its use may be considered in very limited circumstances
- Use BCG only after consultation with local health department and TB experts

Source: CDC. Core Curriculum on Tuberculosis
Recommendations for BCG Vaccination (cont.)

Infants and Children
- Can be considered for infant or child with negative skin-test result who
  - Is continually exposed to untreated or ineffectively treated adult
  - Will be continually exposed to adult with MDR TB
- BCG vaccination not recommended for HIV-infected children

Health-Care Workers
Should be considered on individual basis for health-care workers in settings in which
- High percentage of MDR TB patients has been found,
- Transmission of drug-resistant TB strains and subsequent infection are likely, and
- Comprehensive TB infection-control precautions implemented but not successful.

BCG Contraindications
- Contraindicated in persons with impaired immune response from
  - HIV infection, congenital immunodeficiency
  - Leukemia, lymphoma, generalized malignancy
  - High-dose steroid therapy
  - Alkylating agents
  - Antimetabolites
  - Radiation therapy
- BCG vaccination should not be given to pregnant women
Treatment for Latent Tuberculosis Infection

- Over 11 million persons in U.S. estimated to have LTBI (4% of population)
  - 5%-10% will develop TB disease if untreated
- Treatment of LTBI essential to controlling and eliminating TB disease
- Reduces risk of LTBI to TB disease progression
- Use targeted testing to find persons at high risk for TB who would benefit from LTBI treatment
- Several treatment regimens available

Source: CDC. Core Curriculum on Tuberculosis

Candidates for Treatment of LTBI

- High-risk persons with positive IGRA test or TST reaction of ≥5 mm:
  - HIV-infected persons
  - Recent contacts of persons with infectious TB
  - Persons with fibrotic changes on chest radiograph consistent with prior TB
  - Patients with organ transplants and other immunosuppressed patients

Source: CDC. Core Curriculum on Tuberculosis
Candidates for Treatment of LTBI (cont.)

High-risk persons with positive IGRA test or TST reaction of ≥10 mm:
- Recent arrivals (<5 yrs) from high-prevalence areas (e.g., Asia, Africa, Eastern Europe, Latin America, and Russia)
- Injection drug users
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, homeless shelters, hospitals, and long term care facilities)
- Mycobacteriology laboratory personnel

Source: CDC. Core Curriculum on Tuberculosis

Candidates for Treatment of LTBI (cont.)

High-risk persons with positive IGRA test or TST reaction of ≥10 mm (cont.):
- Persons with conditions that increase risk for TB:
  - Silicosis
  - Diabetes mellitus
  - Chronic renal failure
  - Certain cancers (e.g., leukemia and lymphomas, or cancer of the head, neck, or lung)
  - Gastrectomy or jejunooileal bypass
  - Weight loss of at least 10% below ideal body weight
  - Young children <5 years of age; children/adolescents exposed to adults in high-risk categories

Source: CDC. Core Curriculum on Tuberculosis

Candidates for Treatment of LTBI (cont.)

Low-risk persons with positive IGRA test or TST reaction of ≥15 mm:
- Persons with no known risk factors for TB generally should not be tested
- Targeted testing programs should only be conducted among high-risk groups
- If low-risk persons are tested and have positive IGRA test or TST reaction ≥15 mm, evaluate for LTBI treatment

Source: CDC. Core Curriculum on Tuberculosis
Close Contacts with Negative IGRA or TST Result

- Some contacts should be evaluated and treated for LTBI even with negative TB test results:
  - Young children <5 years of age
  - Immunosuppressed persons
  - Others at risk for rapid progression to TB disease once infected
- Always rule out TB disease with chest radiograph and medical evaluation before treating for LTBI
- Give LTBI treatment (window prophylaxis) regardless of test result
- Retest 8–10 weeks after last exposure to allow for delayed immune response

Source: CDC. Core Curriculum on Tuberculosis

LTBI Treatment Regimens

Isoniazid (INH)

- 9-month daily regimen is preferred: 270 doses within 12 months
  - Effective for HIV-infected as well as HIV-uninfected persons
  - Can be given twice weekly via DOT: 76 doses within 12 months
  - Preferred for children 2–11 years of age

Source: CDC. Core Curriculum on Tuberculosis

LTBI Treatment Regimens

INH (cont.)

- 6-month regimen also generally acceptable: 180 doses within 9 months
  - Can be given twice weekly via DOT: 52 doses within 9 months
  - Shorter regimen not recommended for children, immunosuppressed persons, persons whose x-rays suggest previous TB
LTBI Treatment Regimens

INH-rifapentine (RPT) regimen (12-dose regimen)
- INH and RPT given in 12 once-weekly doses under DOT
- Offers equal option to 9 months daily INH, but does not replace other treatment options for LTBI (Table 5.3)
- Recommended for treating LTBI in otherwise healthy people ≥12 years of age who had recent contact with infectious TB, or who had a tuberculin skin test conversion or a positive blood test for TB infection

Source: CDC. Core Curriculum on Tuberculosis

LTBI Treatment Regimens

INH-RPT regimen (12-dose regimen) (cont.)
- Can be considered for specific groups that would benefit (e.g., need to complete treatment in short time)
- 12-dose regimen is *not* recommended for children <2 years, HIV-infected persons on ART drugs, patients with presumed INH or RIF resistance, women who are or might become pregnant during treatment
- Patients should be monitored monthly; ask about side effects and assess for signs of adverse effects

Source: CDC. Core Curriculum on Tuberculosis

LTBI Treatment Regimens

Dosage for 12-dose INH and RPT:
- Isoniazid: 15 mg/kg rounded up to the nearest 50 or 100 mg, with a 900 mg maximum
- Rifapentine:
  - 10.0-14.0 kg: 300 mg
  - 14.1-25.0 kg: 450 mg
  - 25.1-32.0 kg: 600 mg
  - 32.1-49.9 kg: 750 mg
  - ≥ 50.0 kg: 900 mg maximum
- Keep RPT sealed until it is used

Source: CDC. Core Curriculum on Tuberculosis
Adverse Reactions to INH

Use of INH is associated with some adverse reactions:
- Peripheral neuropathy – give vitamin B₆ if patient has risk factors, or if signs/symptoms develop
- Fatal hepatitis – pregnant/postpartum women at increased risk; monitor closely
- Elevated liver enzymes – discontinue INH if liver enzyme levels exceed 3X normal with symptoms, or 5X upper limit of normal with no symptoms
  - Closely monitor if signs/symptoms of liver injury, or liver enzyme levels are elevated but less than above

Source: CDC. Core Curriculum on Tuberculosis

Rifampin (RIF)

- Alternative to INH is 4 months daily RIF: 120 doses within 6 months
- Should not be used in HIV-infected persons being treated with some antiretroviral therapy (ART)
- In some instances where RIF cannot be used, rifabutin can be substituted

Source: CDC. Core Curriculum on Tuberculosis

Recommendation Against the RIF/PZA Regimen

- LTBI regimen of 2 months of RIF/PZA is no longer recommended owing to associated severe liver injury.
- PZA should not be offered to persons with LTBI, but should continue to be included in multidrug regimens for treatment of TB disease.

Source: CDC. Core Curriculum on Tuberculosis
LTBI Treatment Regimens for Specific Situations

HIV-Infected Persons
- Consult an expert in managing HIV and TB
- INH daily for 9 mos, rather than 6 mos, is optimal: 270 doses within 12 months
- HIV-infected persons on ART drugs should not take the 12-dose regimen; drug interactions not known
- HIV-infected persons on some ART drugs, such as protease inhibitors or delavirdine, should not take RIF
- Rifabutin with dose adjustments can sometimes be substituted for RIF

Source: CDC. Core Curriculum on Tuberculosis

LTBI Treatment Regimens for Specific Situations (cont.)
Persons with Fibrotic Lesions Suggesting Previous TB
- Should be treated for LTBI if they have
  - A positive TST reaction (at least 5 mm) or IGRA result
  - No symptoms of infectious TB disease
  - No history of treatment for TB disease
- Evaluate with sputum smear and culture, and treat only after TB disease excluded by negative culture
- Acceptable regimens include
  - 9 months of INH
  - 4 months of RIF (with or without INH)
- Persons with evidence of primary, healed TB not at increased risk for TB

Source: CDC. Core Curriculum on Tuberculosis

LTBI Treatment Regimens for Specific Situations (cont.)
Contacts of Persons with Multidrug-Resistant (MDR) TB
- Consider risk for progressing to MDR disease before recommending LTBI treatment
- When prescribing treatment for these contacts, consult an MDR TB expert

Source: CDC. Core Curriculum on Tuberculosis
LTBI Treatment Regimens for Specific Situations (cont.)

Pregnancy and Breast-Feeding
- 9 months of INH daily or twice weekly; give with vitamin B₆
- If cannot take INH, consult with TB expert
- 12-dose INH-RPT regimen not recommended for pregnant women; its safety in pregnancy is not known
- Women at high risk for progression to TB disease, especially HIV infected or diabetic, should not delay LTBI treatment; monitor carefully
- Breast-feeding not contraindicated

Patient Monitoring

Before starting treatment for LTBI, clinicians should
- Exclude possibility of disease (symptoms, chest radiograph)
- Determine if patient has history of prior treatment for LTBI or disease
- Determine if any contraindications to treatment
- Obtain information about current and previous drug therapy, including adverse reactions
- Recommend HIV testing, unless the patient declines (opt-out screening)

Patient Monitoring (cont.)

Establish rapport with patient and emphasize
- Benefits of treatment
- Importance of adherence to treatment regimen
- Possible adverse side effects of regimen
- Establishment of optimal follow-up plan
Patient Monitoring (cont.)

- Baseline laboratory testing not routinely indicated for all patients
- Baseline hepatic measurements are indicated for
  - Patients with a liver disorder or liver disease
  - Patients with HIV infection
  - Pregnant women and those in immediate postpartum period
- Patients with abnormal baseline tests should be monitored regularly

Source: CDC. Core Curriculum on Tuberculosis

Patient Monitoring (cont.)

At least monthly, evaluate for

- Adherence to prescribed regimen
- Signs and symptoms of TB disease
- Signs and symptoms of adverse effects, especially hepatitis
  - Jaundice, loss of appetite, fatigue, and/or muscle and joint aches

Source: CDC. Core Curriculum on Tuberculosis

Treatment of LTBI

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Duration</th>
<th>Total Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>300 mg/day</td>
<td>6 months</td>
<td>3600 doses</td>
</tr>
<tr>
<td>RIF</td>
<td>600 mg/day</td>
<td>9 months</td>
<td>5400 doses</td>
</tr>
<tr>
<td>SM</td>
<td>15 mg/kg/day</td>
<td>6 months</td>
<td>5400 doses</td>
</tr>
<tr>
<td>PZA</td>
<td>20 mg/kg/day</td>
<td>6 months</td>
<td>5400 doses</td>
</tr>
</tbody>
</table>

Table III.B: Dosages of Anti-Tuberculosis Medications for Latent Tuberculosis Infection Treatment
References


- ATS/CDC. Targeted tuberculin testing and treatment of latent TB infection. Adobe PDF file. MMWR 2000;49(No. RR–6). [PDF]

- Tuberculosis Nursing: A Comprehensive Guide to Patient Care 3rd Edition

- CDC. Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium Tuberculosis Infection. MMWR 2011;60:1650-1653.

- Latent Tuberculosis Infection: A Guide for Primary Health Care Providers