DIAGNOSING AND TREATING LATENT TUBERCULOSIS INFECTION (LTBI)

LEARNING 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

<table>
<thead>
<tr>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diagnosing and treating latent tuberculosis infection (LTBI) – slide outline</td>
</tr>
</tbody>
</table>

Presented by: Gayle Schack, PHN, MS

SUPPLEMENTAL MATERIAL

None
ADDITIONAL REFERENCES


Objectives

- Upon completion of this session, participants will be able to:
  - Identify persons at high risk for TB infection
  - Describe populations most likely to progress from LTBI to TB disease
  - Recognize CDC population preferences in the use of the TST and IGRA
  - Describe current regimens for the treatment of LTBI
Current Terms and Definitions

- **Latent TB infection (LTBI)** - presence of *M. tb* organisms without symptoms or radiographic evidence of TB disease
- **Treatment of LTBI** - essential in controlling and eliminating TB in the U.S. as it substantially reduces the risk that TB infection will progress to TB disease.
- **Targeted testing** - testing groups at high risk for LTBI and identifying those who would benefit from treatment

Transmission and Pathogenesis

[Images of transmission and pathogenesis]
Transmission of TB

- A person with infectious pulmonary TB (PTB) who coughs, sneezes, or speaks
- Tiny particles of water (droplet nuclei) containing the TB bacteria enter the air and can remain suspended in the air for several hours
- The bacteria can then be inhaled by others sharing the same air space

Pathogenesis

- 10% of 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 7-10% each year
- Certain medical conditions increase risk that TB infection will progress to TB disease
Chance of INFECTION Increases when...

- The concentration of TB bacteria circulating in the air is greater
  - Coughing; smear-positive; cavitary disease
  - Poor ventilation; small enclosed space
- More time is spent with the infectious person (frequency and duration)
- Exposure occurs in an area where the bacteria can easily survive (no UV light)

DISSEMINATION: Spread of TB to Other Parts of the Body

1. Lungs (85% all cases)
2. Pleura
3. Central nervous system (spine, brain, meninges)
4. Lymph nodes
5. Genitourinary system
6. Bones and joints
7. Disseminated (miliary)
Persons at Risk for Developing TB Disease

- Persons at highest 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

- Persons more likely to have been recently infected include:
  - Close contacts to person with infectious TB
  - Skin test or IGRA 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 TB test
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, homeless shelters, healthcare facilities)

Persons at Risk for Progression to TB Disease

- HIV-infected persons
- Persons with a history of prior, untreated TB or fibrotic lesions on x-ray
- Underweight or malnourished persons
- Injection drug users
- Extremes of age (very young or very old)
Persons at Risk for Progression to TB Disease (2)

- Persons with certain medical conditions:
  - Silicosis
  - Diabetes mellitus
  - Chronic renal failure or on hemodialysis
  - Solid organ transplantation
  - Carcinoma of head or neck
  - Gastrectomy or jejunoileal bypass

Persons at Risk for Progression to TB Disease (3)

- Persons taking immunosuppressive agents:
  - Steroids
  - Cancer chemotherapy
  - Cyclosporine

- Persons taking blocking agents against Tumor Necrosis Factor-Alpha:
  - Etanercept (Enbrel®)
  - Infliximab (Remicade®)
  - Adalimumab (Humira™)
LTBI
Diagnosis and Treatment

TB Tests
Tuberculin Skin Test & Interferon Gamma Release Assay

Then
Now
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

- 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)

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

TST Interpretation

<table>
<thead>
<tr>
<th>&gt; 5 mm</th>
<th>&gt; 10 mm</th>
<th>&gt; 15 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Recent immigrant</td>
<td>No risk</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Living/working in high risk congregate setting</td>
<td></td>
</tr>
<tr>
<td>- ≥ 15 mg/day prednisone X 1 month</td>
<td>Injection drug use</td>
<td></td>
</tr>
<tr>
<td>- TNF α antagonist</td>
<td>Children &lt; 5 years</td>
<td></td>
</tr>
<tr>
<td>Recent contact to</td>
<td>Mycobacteriology lab personnel</td>
<td></td>
</tr>
<tr>
<td>infectious TB case</td>
<td>High risk medical condition</td>
<td></td>
</tr>
<tr>
<td>Abnormal CXR</td>
<td>• Silicosis</td>
<td></td>
</tr>
<tr>
<td>Organ transplant</td>
<td>• Chronic renal failure</td>
<td></td>
</tr>
</tbody>
</table>
Factors That May Cause False-positive TST Reactions

- Nontuberculous mycobacteria
- BCG vaccination
  - Consider a positive TST result to indicate TB infection if risk factors are present (CDC)

Factors That May Cause False-negative TST Reactions

- Anergy
  - the inability to react to a TST because of a weakened immune system
- Recent TB infection
  - 2 to 10 weeks after exposure
- Very young age
  - newborns
Factors That May Cause False-negative TST Reactions (2)

- Live-virus vaccination
  - measles or smallpox
- Overwhelming TB disease
- Poor TST administration technique
  - TST injection too shallow or too deep, or wheal too small, drawing up syringe and not administering immediately

Two-Step Testing

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).

BCG and TST

- Tuberculin skin testing not contraindicated for BCG vaccinated persons
- LTBI diagnosis and treatment for LTBI considered for any BCG vaccinated person whose TST is positive, especially if any of these circumstances are present:
  - Contact of another person with infectious TB
  - Born or resided in high TB prevalence country
  - Continually exposed to populations where TB prevalence is high
BCG Atlas

- Detailed information on current and past BCG policies and practices for over 180 countries
- Useful resource for clinicians, policymakers and researchers
- May be helpful for better interpretation of TB diagnostics as well as design of new TB vaccines

Interferon Gamma Release Assays (IGRAs)

- Indirect test for *M. tuberculosis* infection using whole blood
- Test for Cell Mediated Immune response, not Antibody response
- *In vitro* test – lab setting
IGRAs

- QuantiFERON®-TB Gold In-Tube
  (Cellestis LTD, Victoria, Australia
  - Measures interferon-gamma (IFN-γ)
- T-Spot.TB
  (Oxford Immunotec Ltd, Oxford, UK)
  - Measures peripheral blood mononuclear cells that produce IFN-γ

Advantages of IGRA’s

- BCG-vaccinated population
- Screening hard to reach populations
  - One patient visit
  - No need for 2-step testing
Disadvantages of IGRAs

- Requires blood draw
- Requires access to sophisticated lab
- Indeterminate rate may be higher in practice than in studies

IGRA Guidelines

CDC - 2010

- IGRA can be used in place of but not in addition to the TST in all situations in which CDC recommends TST as an aid in diagnosing *M. tuberculosis* infection with preferences and special considerations.
IGRA Preferred

- Groups that historically have low rates of return for TST reading
  - Homeless
  - Drug users
  - Persons who have received BCG

TST Preferred

- Children aged <5 years
TST or IGRA without Preference

- Recent contacts
- Periodic screening
  - Health care workers
  - 2-step testing not needed

Consider Both TST and IGRA

- Risk for progression to disease and poor outcomes are increased
  - HIV
  - Children < 5 and at increased risk for Mtb
  - Clinical suspicion for TB disease
Consider Both TST and IGRA (2)

- Confirmation of test to encourage patient compliance
- Healthy person who is at low risk for infection (false positive)
- Result is indeterminate, borderline or invalid and reason for testing persists

Online TST/IGRA Interpreter

- Estimates the risk of active TB
- TST reaction of ≥5mm
- Based on person's clinical profile
- Intended for adults tested with standard TST and/or IGRA
- http://www.tstin3d.com/
Treatment of Latent TB Infection (LTBI)

LTBI Diagnosis and Treatment

- **Latent Tuberculosis Infection**
- Why treat?
  - TB remains a disease with a mortality rate of 7-9%
  - Treating LTBI can break the cycle of progression to TB and spread to new contacts
Initiating Treatment

- Before initiating treatment for LTBI:
  - Rule out TB disease: CXR, sputum samples (wait for culture result if sputum samples obtained)
  - Determine prior history of treatment for LTBI or TB disease
  - Obtain HIV antibody test
  - Assess risks and benefits of treatment (e.g., medical history, medications, adverse effects)

12 INH/Rifapentine – 3hp

- 12 week INH and rifapentine once weekly by DOT
- Consider in persons
  - 2 years and older
  - Contacts
  - Radiographic findings of healed pulmonary TB
  - HIV infected persons NOT on antiretrovials
Rifampin Regimens

- Rifampin (RIF) daily for 4 months
  - adults & children
- If RIF cannot be used (HIV-infected persons receiving antiretroviral agents), use rifabutin
- RIF and PZA for 2 months should generally not be given (risk of severe liver injury and death*

*MMWR August 8, 2003; 52 [31]: 735-739

INH Regimens

- 9-month regimen of Isoniazid (INH)
- 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
Completion of Treatment

- Count doses, not months
  - 3 months INH/rifapentine – 11 doses within 16 weeks
  - 9 mo INH -- minimum of 270 doses w/in 12 mo
  - 6 mo INH -- 180 doses w/in 9 mo
  - RIF x 4 mo -- 120 doses w/in 6 mo

Clinical Monitoring

- 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
Laboratory Monitoring

- Baseline liver function tests (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 post-partum period
  - For 3hp - consider in older persons taking medications for chronic medical conditions

INH Liver Toxicity

- Asymptomatic LFT elevation (up to 3Xnormal) in up to 20% on INH
  - Resolves with continued treatment
- Age related incidence of symptomatic liver toxicity
  - <0.5% under age 35
  - 2% over age 50
Adverse Events

- Report severe side effects and adverse events to the TB Control Branch
- Report adverse events to the FDA MedWatch at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm

Other Considerations
HIV-infected Individuals

- Treat with 3 months of INH/rifapentine if not on antiretrovirals
- Treat with 9 months of INH
- RIF is contraindicated if patient also being treated with certain antiretroviral drugs
- Even if TST- or IGRA-negative, treat when person has had recent, prolonged exposure to infectious TB or ongoing risk for exposure

Pregnancy

- TST has no adverse effect on pregnant mother or fetus
- Test only if risk factors present
- If positive test, obtain CXR using shielding
- Consider treatment while pregnant if HIV infected or recent contact
- Supplementation with B6 is recommended
Breastfeeding

- May take INH
- Supplementation with B6 is recommended
- Amount of INH secreted in breast milk is inadequate for treatment of infants exposed to TB

LTBI and Drug Resistance

- If person exposed to known INH-resistant TB, treat with 4 months of RIF (6 months for immunocompromised and children)
- If person exposed to known MDR/XDR TB, consult an expert
Re-treatment of LTBI

- Re-infection may occur
- Consider
  - Severity of exposure
  - Health and of person
  - Willingness to complete treatment

Management of Patients Who Miss 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
Summary

- Conduct targeted testing activities in high-risk persons to halt progression of TB disease.
- Always rule out TB disease before starting treatment for LTBI.
  - Wait for culture results if sputum collected
- Consider best regimen for patient
- Encourage completion of therapy