OVERVIEW OF TESTING FOR LATENT TUBERCULOSIS INFECTION

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Disclosure and Objectives

• Disclosure: No conflicts of interest

• Objectives

  • Discuss latent TB infection diagnosis
  • Understand how to interpret IGRA and PPD tests
  • Explain new USPSTF guidelines on screening for latent TB infection
Targeted TB Testing and Treatment of Latent TB Infection

- As TB disease rates in the United States decrease, finding and treating persons at high risk for latent TB infection (LTBI) has become a priority.
- Targeted TB testing is used to focus program activities and provider practices on groups at the highest risk for TB.
- Treatment of LTBI substantially reduces the risk that persons infected with *M. tuberculosis* will progress to TB disease.
Number of Active Tuberculosis Cases in New York City, According to Birthplace, 1992–2013.
Latent TB Infection (LTBI)

LTBI is the presence of *M. tuberculosis* organisms (tubercle bacilli) without signs and symptoms or radiographic or bacteriologic evidence of TB disease.
LTBI vs. Pulmonary TB Disease – 1

Latent TB Infection

- Positive TST* or IGRA† result
- Chest radiograph normal

Pulmonary TB Disease

- TST or IGRA is usually positive
- Chest radiograph is usually abnormal

*tuberculin skin test  †Interferon-Gamma Release Assay
LTBI vs. Pulmonary TB Disease – 2

Latent TB Infection

- No symptoms or physical findings suggestive of TB
- If done, respiratory specimens are smear and culture negative

Pulmonary TB Disease

- Symptoms *may* include one or more of the following: fever, cough, night sweats, weight loss, fatigue, hemoptysis, decreased appetite
- Respiratory specimens are usually culture positive (smear positive in about 50% of patients)
Treatment of LTBI – Milestones - 7

2011:  CDC recommends 12-doses (3 months) of isoniazid (INH) and rifapentine (RPT) as an option (3HP) equal to the standard 9-month INH regimen for certain groups*

2016:  U.S. Preventive Services Task Force recommends testing for TB as a part of standard preventive care for certain at-risk groups**

*MMWR . Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w
**USPSTF. Latent Tuberculosis Infection: Screening
Latent Tuberculosis Infection: Screening

Recommendation Summary

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade</th>
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<tbody>
<tr>
<td>Asymptomatic adults at increased risk for infection</td>
<td>The USPSTF recommends screening for latent tuberculosis infection (LTBI) in populations at increased risk.</td>
<td>B</td>
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</tbody>
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Release Date: September 2016
USPSTF Recommendation

No copay or deductible for TB screening under Affordable Care Act…

Emphasis on expanded screening of immigrant population in USA

Mobile application AHRQ ePSS
Transmission

Primary Tuberculosis

Latent Tuberculosis

“Reactivation” Tuberculosis

Skin-test conversion in 6 to 8 weeks

Spontaneous healing in 6 months

Progression after 2 years, 5%

Progression within 2 years, 5%

Progression with concurrent HIV infection, 10% each year

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 an increased likelihood of exposure to persons with TB disease
- Those with clinical conditions that increase their risk of progressing from LTBI to TB disease
Increased Likelihood of Exposure to Persons with TB Disease

Persons at risk for exposure to persons with TB disease include:

- Close contacts to person with infectious TB
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, homeless shelters, health care facilities)
- Immigrants from TB-endemic regions of the world (except North America, western Europe)
Foreign-born residents

Metro Detroit’s foreign-born population helps offset slow growth and increase economic power. Detroit lags, with a foreign-born population under 5 percent and limited to a few small areas of the city.

Metro Detroit’s foreign-born population

<table>
<thead>
<tr>
<th>KEY</th>
<th>Percentage Range</th>
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<tbody>
<tr>
<td>Light green</td>
<td>0% - 1%</td>
</tr>
<tr>
<td>Light red</td>
<td>61% - 7%</td>
</tr>
<tr>
<td>Green</td>
<td>7.1% - 16%</td>
</tr>
<tr>
<td>Medium red</td>
<td>16.1% - 24%</td>
</tr>
<tr>
<td>Dark red</td>
<td>24.1% - 32%</td>
</tr>
<tr>
<td>Maroon</td>
<td>32.1% - 60%</td>
</tr>
</tbody>
</table>

Average: 9.3%

Sources: Global Detroit, 2007-11 six-year American Community Survey, 2010 Census
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
- Children ≤ 5 years with a positive TST
Increased Risk for Progression to TB Disease - 2

Persons more likely to progress from LTBI to TB disease include:

- Underweight or malnourished persons
- Substance abusers (such as smoking, alcohol abusers, or injection drug use)
- Those receiving TNF-α antagonists for treatment of rheumatoid arthritis or Crohn’s disease
Increased Risk for Progression to TB Disease - 3

Persons more likely to progress from LTBI to TB disease include:

- Those 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
Testing for *M. tuberculosis* Infection
Testing for *M. tuberculosis* Infection

- There are two testing methods available for the detection of *M. tuberculosis* infection in the United States:
  - Mantoux tuberculin skin test (TST)
  - Interferon-gamma release assays (IGRA)

- These tests do not exclude LTBI or TB disease
- Decisions about medical and public health management should include other information, and not rely only on TST or IGRA results
Administering the TST

- **Inject 0.1 ml of 5 TU PPD tuberculin solution intradermally on volar surface of lower arm using a 27-guage 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
- Organ transplant recipients
- Other immunosuppressed patients (e.g. > 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
- 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 $\leq 10$ 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
PPD can React with BCG and Atypical AFB
IGRA Tests More Specific Than PPD

- IGRA
- BCG
- ATYPICALS
Factors That May Cause False-Negative TST Reactions -1

- Anergy
  - Inability to react to a TST because of a weakened immune system

- Recent TB Infection
  - Defined as less than 10 weeks after exposure

- Very young age
  - Newborns (< 6 months)
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.

- Only use two-step tests for initial baseline skin testing of adults who will be retested periodically (e.g., health care workers).
Interferon-Gamma Release Assays (IGRAs)
Interferon-Gamma Release Assays (IGRAs)

- Whole-blood test used to detect *M. tuberculosis* infection
- Two U.S. Food and Drug Administration (FDA) approved IGRAs are commercially available in the U.S.:
  - QuantiFERON®-TB Gold-in-tube test (QFT-GIT)
  - T.SPOT®. *TB* test (T-Spot)
How IGRAs Work - 1

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

- Entails mixing blood samples with antigens from *M. tuberculosis* and controls
How IGRAs Work - 2

- Cells that recognize the antigen release interferon-γ

- Amount of interferon released in response to *M. tuberculosis* antigens is compared to amount released in response to other antigens
Administering IGRAs

- Confirm and arrange for delivery of blood sample within specific time-frame to ensure viability of blood samples
- Draw blood sample according to test manufacturer’s instructions
- Schedule a follow up appointment to receive test results, medical evaluation and possible treatment if needed
## Interpretation of IGRA Test Results

<table>
<thead>
<tr>
<th>IGRA Test</th>
<th>Results Reported as</th>
</tr>
</thead>
<tbody>
<tr>
<td>QFT-GIT</td>
<td>Positive, negative, indeterminate</td>
</tr>
<tr>
<td>T-Spot</td>
<td>Positive, negative, indeterminate, borderline</td>
</tr>
</tbody>
</table>

Note: Laboratory should provide both quantitative and qualitative results
Advantages of IGRAs

- Requires a single patient visit to conduct test
- Results can be available within 24 hours
- Does not boost responses measured by subsequent tests
- Prior BCG vaccination does not cause false-positive IGRA test result
Disadvantages/Limitations of IGRAs - 1

- Errors in collecting and transporting blood, or in interpreting assays can decrease accuracy of IGRAs
- Limited data on use of IGRAs to predict who will progress to TB disease in the future
Disadvantages/Limitations of IGRAs - 2

- Tests may be expensive
- Limited data on the use of IGRAS for
  - Children < 5 years of age;
  - Persons recently exposed to *M. tuberculosis*;
  - Immunocompromised persons; and
  - Serial testing
TB Test Selection
Selecting a Test to Detect TB Infection - 1

- IGRAs are preferred method of testing for
  - Groups of people who have poor rates of returning to have TST read
  - Persons who have received BCG vaccine

- TST is the preferred method of testing for
  - Children under the age of 5
Selecting a Test to Detect TB Infection - 2

Before initiating treatment for LTBI

- Either TST or IGRA can be used without preference for other groups that are tested for LTBI
- Routine testing with TST and IGRA is _NOT_ recommended
Evaluation of Persons with Positive TB Test Results
Evaluation of Persons with Positive TB Test Results

Person has a positive test for TB infection

TB disease ruled out

Consider for LTBI treatment

Person accepts and is able to receive treatment of LTBI

Develop a plan of treatment with patient to ensure adherence

If person refuses or is unable to receive treatment for LTBI, follow-up TST or IGRA and serial chest radiographs are unnecessary

Educate patient about the signs and symptoms of TB disease
Next talk after the break….

• How to treat latent TB infection

• New CDC guidelines on treatment of active TB