Targeted Testing and Diagnosis of Latent TB Infection

Jeremy Clain, MD
Pulmonary & Critical Care Medicine | Mayo Clinic
November 13, 2017
Disclosures

• No relevant financial relationships
• No conflicts of interest
Objectives

• Describe the importance of targeted testing for latent tuberculosis infection (LTBI)

• Explain use of the tuberculin skin test (TST)

• Explain use of the interferon gamma release assay (IGRA)
Foundations

• Role of LTBI in the *pathogenesis* of TB disease
• Importance of identifying and treating LTBI as part of an effective TB *control* program
• Principles of efficient *screening* protocols
Foundations

• Role of LTBI in the **pathogenesis** of TB disease
• Importance of identifying and treating LTBI as part of an effective *TB control* program
• Principles of efficient **screening** protocols
Pathogenesis of TB Disease

Exposure to infectious particles
- No infection (70%)
  - Innate immunity
    - Adequate
      - Containment (95%)
    - Inadequate
      - Infection (30%)
      - Adaptive (T-cell) immunity
        - Adequate
          - Continued containment (90%)
        - Inadequate
          - Late progression (5%)
      - Inadequate
        - Early progression (5%)

Inadequate
Pathogenesis of TB Disease

Features of LTBI:
1. Engages the adaptive immune system
2. Generates immune memory

Foundations

• Role of LTBI in the pathogenesis of TB disease
• Importance of identifying and treating LTBI as part of an effective TB control program
• Principles of efficient screening protocols
Foundations

• Role of LTBI in the pathogenesis of TB disease

• Importance of identifying and treating LTBI as part of an effective TB control program

• Principles of efficient screening protocols
Identification and Treatment of LTBI

Exposure to infectious particles

- Adequate
  - No infection (70%)
  - Innate immunity
    - Containment (95%)
      - Adequate
        - Adaptive (T-cell) immunity
        - Continued containment (90%)
          - Adequate
            - Late progression (5%)
          - Inadequate
            - Early progression (5%)
        - Inadequate
          - Adaptive (T-cell) immunity
      - Inadequate
        - Infection (30%)
    - Inadequate
      - Infection (30%)
A Case

OUTBREAK OF TUBERCULOSIS AMONG REGULAR PATRONS OF A NEIGHBORHOOD BAR

Susan E. Kline, M.D., Linda L. Hedemark, M.D., and Scott F. Davies, M.D.

Abstract  Background. Outbreaks of tuberculosis have been reported in prisons, nursing homes, urban homeless shelters, and other crowded settings. We report a nonresidential outbreak of tuberculosis that originated in a neighborhood bar.

Methods. A homeless patient with highly infectious pulmonary tuberculosis was a regular patron of a neighborhood bar during a long symptomatic interval before diagnosis. We investigated 97 other regular customers and employees of the bar through interviews, tuberculin skin testing, and chest roentgenography. We performed DNA fingerprinting on isolates from the index patient and 11 other patients.

Results. The index patient apparently infected 41 of 97 contacts (42 percent), resulting in 14 cases of active tuberculosis and 27 cases of infection but no disease (indicated by positive tuberculin skin tests). Four other cases of active tuberculosis occurred among regular customers of the bar who were missed by the contact investigation. There were also two secondary cases. Radiographic findings in active cases included upper-lobe disease in seven cases (three cavitary) and negative chest films at the time of diagnosis in four cases. All 12 culture isolates we tested had the same chromosomal-DNA restriction pattern.

Conclusions. The spread of tuberculosis in a neighborhood bar can be a major public health problem. The high rate of infection and disease among the contacts was unexpected and was not due to coinfection with the human immunodeficiency virus. Possible explanations include heavy alcohol use among the contacts, high infectivity of the index case, or both. Sputum cultures must be performed in tuberculin-positive contacts who have symptoms, even if the chest films are normal. (N Engl J Med 1995;333:222-7.)

Case History

• 48-year-old man presented to HCMC in Minneapolis in 1992 with progressive respiratory and symptoms for 6 months

• Symptoms included:
  • Frequent coughing
  • Intermittent hemoptysis
  • 31 kg weight loss
Case Outcome

- Sputum smear densely positive for AFB+ organisms
- Sputum culture positive for MTB

A Case Continues – Contact Investigation

- Patient frequented a neighborhood bar
- 41 of 97 contacts infected
- 20 active cases linked back to the original patient

Figure 2. Flow-Chart Overview of the Contact Investigation and Origin of the 20 Active Cases of Tuberculosis That Resulted from Infection in the Index Patient. 

Identification and Treatment of LTBI

- Ultimate goal: reduce the number of cases of active TB disease
- Contacts of an index patient with infectious TB:
  - 1% active TB
  - 23% LTBI
- LTBI generates a reservoir of MTB in the population which can generate further TB disease and further dispersion of the organism

*MMWR Recomm Rep 2000; 49:1–51*
Public Health Benefit of Identifying and Treating Latent TB Infection

- Individual Exposed to MTB
- Contact with Public
- LTBI
- Progression to Active TB
Foundations

• Role of LTBI in the pathogenesis of TB disease

• Importance of identifying and treating LTBI as part of an effective TB control program

• Principles of efficient screening protocols
Foundations

- Role of LTBI in the **pathogenesis** of TB disease
- Importance of identifying and treating LTBI as part of an effective **control** program
- Principles of efficient **screening** protocols
Goals of Screening Program

• Identify asymptomatic disease
• Transition those found to have preclinical disease to disease-modifying treatment
• Avoid undue harm
Principles of Screening

• Target populations likely to benefit
  • At risk of having asymptomatic disease
  • At risk of progression to clinically-relevant, difficult-to-treat disease

• Be prepared to provide an intervention to those who screen positive

• Be aware of the risks of false-positive screening results and how to best account for them
Practical Considerations for LTBI Screening

• Choose individuals and populations to screen wisely
• Choose the screening test wisely
• Interpret test results wisely
Screening for LTBI Wisely: Factors that Favor LTBI Testing

- Elevated risk of infection with MTB
- Elevated risk of progression to active TB
Elevated risk of infection with MTB

- Residents and employees of high risk congregate settings
- Immigrants from high-burden countries (> 20 cases / 100,000 population)
- Mycobacteriology lab personnel
- Household contact or recent exposure
Elevated risk of progression to active TB

- Diabetes
- Chronic renal failure
- Intravenous drug use
- HIV infection
- Immunosuppressive therapy
- CXR consistent with prior TB
- Silicosis
- Age less than 5
Screening for LTBI Wisely: When to Avoid LTBI Testing

• LTBI testing generally not recommended for those at low risk for MTB infection \textit{and} low risk for disease progression

• (Acknowledging that testing may be mandated by law or credentialing bodies)
Choosing the LTBI Screening Test Wisely

• Options:
  • Tuberculin Skin Test (TST)
  • Interferon Gamma Release Assay (IGRA)
    • QuantiFERON Test
    • T-Spot
• Considerations:
  • Testing specificity
  • Practical concerns
What LTBI Screening Tests Do Not Do

- Directly assess the presence of MTB infection
- Distinguish between active TB disease and latent TB infection
Tuberculin Skin Test (TST)

- Traditional means of detecting MTB exposure
- Tests for cell-mediated immune recognition of MTB antigens by assessing for delayed-type hypersensitivity reaction
- Requires two visits:
  1. TST placement
     [...48-72 hours...]
  2. TST read
- Has suboptimal specificity
How a TST Works

• A purified protein derivative (PPD) is prepared by precipitation of proteins from heat-killed cultures of *M. tuberculosis*

• The resulting PPD is a mixture of complex antigens that is poorly defined and contains many individual proteins

• The PPD is injected intradermally, and presence or absence of a delayed-type hypersensitivity reaction is assessed after a 48-72 hour delay

Delayed-Type Hypersensitivity Reaction
Delayed-Type Hypersensitivity Reaction
How a TST Works

Presentation of mycobacterial antigens

Antigen presenting cell

Memory T cell

Measurement of induration and erythema

IFN-γ

TNF-α

IL-8, etc

Skin test

Lancet 2000;356:1099–104

Mayo Clinic Center for Tuberculosis
How a TST is Read

• Quantitative result:
  • Measure of induration, not erythema

• Qualitative result
  • Dependent on risk factors for MTB infection and disease progression
  • Three cut-points depending on risk factors: 5, 10, or 15 mm
# TST Interpretation

<table>
<thead>
<tr>
<th>Groups with Increased Likelihood of Infection with Mtb</th>
<th>Benefit of Therapy</th>
<th>LTBI Testing Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Household contact or recent exposure of an active case</td>
<td>Yes</td>
<td>Likely to be Infected Low to Intermediate Risk of Progression (TST ≥ 10mM)</td>
</tr>
<tr>
<td>Mycobacteriology laboratory personnel</td>
<td>Not demonstrated</td>
<td>Likely to be Infected High Risk of Progression (TST ≥ 5mM)</td>
</tr>
<tr>
<td>Immigrants from high burden countries (&gt;20 / 100,000)</td>
<td>Not demonstrated</td>
<td></td>
</tr>
<tr>
<td>Residents and employees of high risk congregate settings</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>Not demonstrated</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk of Developing Tuberculosis if Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Intermediate (RR 1.3 -3)</td>
</tr>
<tr>
<td>High (RR 3-10)</td>
</tr>
<tr>
<td>No risk factors</td>
</tr>
<tr>
<td>Clinical predisposition</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>Intravenous drug use</td>
</tr>
<tr>
<td>Children age less than 5</td>
</tr>
<tr>
<td>HIV infection</td>
</tr>
<tr>
<td>Immunosuppressive therapy</td>
</tr>
<tr>
<td>Abnormal CXR consistent with prior TB</td>
</tr>
<tr>
<td>Silicosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benefit of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not demonstrated</td>
</tr>
<tr>
<td>Yes</td>
</tr>
</tbody>
</table>

*CID* 2017;64:e1–e33

Mayo Clinic Center for Tuberculosis

©2014 MFMER | slide-34
TST Benefits

• Simplicity
  • No phlebotomy, no laboratory
  • Low cost

• Longstanding experience in serial screening programs

• Well-defined cut points
TST Limitations

• Programmatic issues
  • Two step process is burdensome

• Interpretation issues
  • Inaccurate measurement is common

• Specificity issues
  • PPD consists of multiple antigens
  • Cross-reactivity with BCG and some nontuberculous mycobacteria

• Sensitivity issues
  • TST reaction may wane over time
Interferon Gamma Release Assay (IGRA)

- Newer assays to assess for sensitization to MTB antigens
- In contrast to TST:
  - *In vitro* test (rather than *in vivo*)
  - T cell-based assay (rather than an assay of a coordinated response by multiple cell types)
  - Utilizes highly specific MTB antigens (rather than the multitude of antigens in PPD)
How an IGRA Test Works

Lancet 2000;356:1099–104
Available IGRA Tests

- QuantiFERON Assays
  - Several generations (QFT, QFT-Gold, QFT-GIT, QFTPlus)
- T-SPOT.TB Assays
QuantiFERON Assays

- Whole blood is drawn directly into heparinized tubes coated with lyophilized antigen (plus control tubes, mitogen and nil)
- After incubation for 16-24 hours at 37°C, plasma is collected from each tube and the concentration of IFN-gamma is determined for each by ELISA
- Generates “TB minus nil” quantitative result, with single qualitative cut point
- Also generates mitogen control of generic response

CID 2017;64:e1–e33
T-SPOT.TB Assays

• Whole blood is collected and must be processed within a defined time frame

• Mononuclear cells are separated using density gradient centrifugation, enumerated, and then added to microtiter wells that have been coated with monoclonal antibodies to IFN-gamma

• Antigen is added to the wells and incubated for 16-20 hours

• Wells are washed, additional step is performed to detect “captured” IFN-gamma, producing “spots”
T-SPOT.TB Assays – Interpretation

• Quantitative Result:
  • Number of spots

• Qualitative Result:
  • 0-4 spots: negative
  • 5-7 spots: borderline
  • ≥ 8 spots: positive
Indeterminate IGRA Results

- IGRA tests will produce indeterminate results if there is a high negative control (nil) response or a low positive control (mitogen) response.

- Usually reflects one of the following:
  - Immunosuppression
  - Anergy
  - Incorrect test procedures
## IGRA Results

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
<th>Borderline</th>
<th>Indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>QFT-Gold</strong></td>
<td>≥ 0.35 IU/ml</td>
<td>&lt; 0.35 IU/ml</td>
<td>N/A</td>
<td>High nil response or Low mitogen response</td>
</tr>
<tr>
<td><strong>QFT-GIT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T-SPOT.TB</strong></td>
<td>≥ 8 spots</td>
<td>≤ 4 spots</td>
<td>5-7 spots</td>
<td>High nil response or Low mitogen response</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
IGRA Benefits

- Single patient visit
- Enhanced test specificity
- Standardized laboratory testing reduces errors
IGRA Limitations

• Cost
• Test complexity
  • Need for phlebotomy and laboratory analysis
• Inconsistent test reproducibility
• Interpretation challenges
  • Cut points not well established
  • Problems with variability near the positive/negative threshold
IGRA - TST Comparison

**IGRA**
- *In vitro*
- Specific antigens
- Unaffected by BCG
- No boosting
- One patient visit
- No inter-reader variability
- One standard result for all

**TST**
- *In vivo*
- Multiple antigens
- BCG affects results
- Boost occurs
- Two patient visits
- Inter-reader variability
- Different thresholds based on risk
Choosing the Right Test

• IGRA preferred when:
  • Individual is unlikely to return for 2\textsuperscript{nd} visit
  • Individual has a history of BCG vaccination

• TST preferred when:
  • Individual is ≤ 5 years old

• In most cases either test is acceptable, choice depends on:
  • Availability, programmatic concerns, staff expertise, prevalence of BCG vaccination
Choosing the Right Test

<table>
<thead>
<tr>
<th>Group</th>
<th>Testing Strategy</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely to be Infected</td>
<td>Adults: IGRA OR TST</td>
<td>Prevalence of BCG vaccination</td>
</tr>
<tr>
<td>High Risk of Progression</td>
<td>Acceptable: dual testing where a positive result</td>
<td>Expertise of staff and/or laboratory</td>
</tr>
<tr>
<td></td>
<td>from either result would be considered positive</td>
<td>Test availability</td>
</tr>
<tr>
<td></td>
<td>Children ≤ 5 years of age:</td>
<td>Patient perceptions</td>
</tr>
<tr>
<td></td>
<td>Preferred: TST</td>
<td>Staff perceptions</td>
</tr>
<tr>
<td></td>
<td>Acceptable: IGRA OR TST</td>
<td>Programmatic concerns</td>
</tr>
<tr>
<td>Likely to be Infected</td>
<td>Consider dual testing where a positive result</td>
<td></td>
</tr>
<tr>
<td>Low to Intermediate Risk of Progression</td>
<td>from either would be considered positive¹</td>
<td></td>
</tr>
<tr>
<td>(TST ≥ 10mM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unlikely to be Infected</td>
<td>Preferred: IGRA where available</td>
<td></td>
</tr>
<tr>
<td>(TST &gt; 15mM)</td>
<td>Acceptable: Either IGRA OR TST</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Testing for LTBI is not recommended</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If necessary:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Preferred: IGRA where available.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acceptable: Either IGRA OR TST</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For serial testing:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Preferred: Either IGRA OR TST</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acceptable: Either IGRA OR TST</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider repeat or dual testing where a negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>result from either would be considered negative²</td>
<td></td>
</tr>
</tbody>
</table>

¹: Consider the use of IGRA or TST based on local guidelines and resource availability.
²: Consider the use of IGRA or TST based on local guidelines and resource availability.

CID 2017;64:e1–e33

Mayo Clinic Center for Tuberculosis
Interpreting Results Wisely

• How to manage an unlikely positive test result
• When to be skeptical of a negative test result
The Unlikely Positive Test Result

• Due to policy mandates, LTBI testing is occasionally performed on individuals with low likelihood of MTB infection and low risk of disease progression

• If an IGRA or TST is positive in such an individual, consider a repeat test with the other test, and interpret a negative result from either test as a true-negative
When to be Skeptical of a Negative Result

- HIV (low CD4, no HART)
- Immunosuppressive Rx
- Lymphoma
- Live virus vaccination (eg, measles, smallpox)
- Other infections (viral, fungal, bacterial)
- Overwhelming TB (eg, miliary TB)
- <10 wks since TB infection
- Extremes of age (newborn, very old)
Question 1

All of the following are true regarding a comparison of TST and IGRA tests EXCEPT:

A. IGRA tests offer enhanced specificity for TB infection
B. TST tests offer advantages with respect to cost and technical simplicity
C. TST tests more often produce indeterminate results
D. IGRA tests suffer from variability of results that are close to positive/negative cut points
Question 1

All of the following are true regarding a comparison of TST and IGRA tests EXCEPT:

A. IGRA tests offer enhanced specificity for TB infection

B. TST tests offer advantages with respect to cost and technical simplicity

C. **TST tests more often produce indeterminate results**

D. IGRA tests suffer from variability of results that are close to positive/negative cut points
Question 2

Which of the following tests may produce a “borderline” result?

A. TSTs
B. QuantiFERON Assays
C. T-SPOT.TB Assays
D. Both B & C
E. All of the above
Question 2

Which of the following tests may produce a “borderline” result?

A. TSTs
B. QuantiFERON Assays
C. T-SPOT.TB Assays
D. Both B & C
E. All of the above
Summary of LTBI Testing

• Think before you test. Testing most useful in an individual with some likelihood of being infected or increased risk of experiencing disease progression.

• TST and IGRA tests have inherent benefits and limitations, and testing properties differ.

• In most cases either test is acceptable, but IGRA tests are preferred for those with a history of BCG vaccination or a low likelihood of returning for a second clinic visit.
Thank you!
clain.jeremy@mayo.edu