Targeted Testing and Diagnosis of Latent TB Infection

Chris Spitters, MD, MPH
19 November 2015

Learning Objectives

• Identify patients for whom TB infection testing is indicated.
• Request and interpret appropriate TB infection testing according to national guidelines.
• For patients with positive TB infection testing results, conduct an appropriate evaluation to exclude active TB.
• Provide individualized estimates for future risk of active TB when counseling patients about benefits and risks of treatment.

Tuberculosis Mortality
United States, 1860-1960
Why Test for LTBI?

![Graph showing TB Incidence Rates, 2005-2014]


Percentage of TB Cases Among Foreign-born Persons, United States*

2000  2010

*Updated as of July 21, 2015.

Targeted Testing—Race/Ethnicity Surrogate for Foreign-Birth*

Tuberculosis Disease Burden by Race/Ethnicity

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>2014 Cases</th>
<th>2014 %Total</th>
<th>2012-2014 Rate/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>85</td>
<td>43.6</td>
<td>17.8</td>
</tr>
<tr>
<td>Black</td>
<td>31</td>
<td>15.9</td>
<td>12.5</td>
</tr>
<tr>
<td>Hispanic</td>
<td>30</td>
<td>15.4</td>
<td>3.6</td>
</tr>
<tr>
<td>White</td>
<td>23</td>
<td>11.8</td>
<td>0.5</td>
</tr>
<tr>
<td>NHOP</td>
<td>19</td>
<td>9.7</td>
<td>27.7</td>
</tr>
<tr>
<td>AI/AN</td>
<td>5</td>
<td>2.6</td>
<td>4.2</td>
</tr>
</tbody>
</table>

75-80% of active TB in Washington State

Table 1. Estimated TB Rates\(^1\) by Race/Ethnicity, Yakima County, 2004-2013

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>Rate</th>
<th>Relative Risk</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White, non-Hispanic</td>
<td>17</td>
<td>1.5</td>
<td>1.0</td>
<td>Referent</td>
</tr>
<tr>
<td>Hispanic</td>
<td>55</td>
<td>5.0</td>
<td>3.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Native American</td>
<td>24</td>
<td>22.7</td>
<td>15.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>2.8</td>
<td>1.9</td>
<td>0.30 (NS)</td>
</tr>
</tbody>
</table>

\(^1\)Cases per 100,000 per year  
\((s)\)National incidence rate for Native Americans in 2012: 6.3  
\(\)Not statistically significant  
\(\)Cases with any of the following risk factors were excluded: foreign birth, recent contact to a known case, homelessness, heavy alcohol use, long-term care residence, methamphetamine or injection drug use, and incarceration.

Yakima Health District Bulletin, February 2014
Addressing TB in Our Communities  
November 19, 2015  
Curry International Tuberculosis Center

In incidence of Active TB among Immigrants with Normal Visa CXRs

California-bound Filipino immigrants, 2001-2010. 

Risk of Reactivation Re-visited

This study measured the rate of TB occurring among persons with a positive tuberculin skin test in a southeastern United States population. The rate, 0.040 to 0.058 per 100 person-years, was substantially lower than rates measured during the 1950s and 1960s. This decrease is likely due to the disappearance of old, healed but untreated TB in the U.S. population. If these lower rates are representative of other areas of the United States, treatment of latent TB infection may not be as cost-effective as previously reported.


Relative risk of TB reactivation by medical condition

Horsburgh, NEJM 2004 350; 20: 2060-7
Addressing TB in Our Communities  
November 19, 2015  
Curry International Tuberculosis Center

Targeted Testing and Diagnosis of Latent TB Infection

### Cost-Effectiveness of LTBI Screening & Treatment: IGRA vs. TST

Linas BP, et al. AJRCCM 2011;184:590

### Priority Groups for LTBI Dx & Rx

**Medical**
- Fibrosis
- Immunosuppressed
  - Diabetes
  - ESRD
  - HIV
  - Iatrogenic (e.g., TNF-alpha blockade, organ transplant)
- Malabsorption
- Rapid weight loss

**Epidemiologic**
- Recent contacts
- Recently infected
- Foreign-born from high incidence countries
  - Younger-older
  - Africa & Asia > Latin America & Europe
- Recent vs. remote arrival
- Native Americans
- Homeless
LTBI Evaluation-1

- History
  - Symptoms
  - Prior TB diagnosis and treatment
  - Risk factors for acquisition and reactivation
  - PMH (reactivation risk, safety issues)

LTBI Evaluation-2

- TST or IGRA
- Chest radiograph (positive test results or TB sx)
- Sputum x3 for AFB smear-and-culture ONLY if abnormality suggestive of current or prior active TB (induce x2 if unable to raise)
- Nucleic acid amplification testing not recommended when no suspicion for active TB.
- Follow-up CXR when cultures negative
- If sputum is collected, DO NOT START therapy for LTBI until cultures are negative and follow-up radiograph is demonstrated to be stable.

Tuberculin Skin Test

A technician correctly places a tuberculin

Purified protein derivative 5U intradermally
Addressing TB in Our Communities
November 19, 2015
Curry International Tuberculosis Center

Quantiferon TB Gold In Tube

- Nil, positive controls, and TB Ag readings (1 for each tube)
- Result = TB Ag – Nil (“positive” ≥ 0.35; usually >1.00)
- Mitogen should be >0.5 (usually >10)
- Nil should be <8.0 (usually <0.10)

Quantiferon Interpretation

<table>
<thead>
<tr>
<th>Interpretation</th>
<th>Nil</th>
<th>Nil Response</th>
<th>Mitogen Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>0.0</td>
<td>&lt;0.35</td>
<td>Any</td>
</tr>
<tr>
<td>Negative**</td>
<td>0.0</td>
<td>&lt;0.35 + &lt;20% of Nil</td>
<td>25.5</td>
</tr>
<tr>
<td>Indeterminate*</td>
<td>0.0</td>
<td>&lt;0.35 + &lt;20% of Nil</td>
<td>&gt;25.5</td>
</tr>
<tr>
<td>Positive</td>
<td>&gt;0.5</td>
<td>Any</td>
<td>Any</td>
</tr>
</tbody>
</table>

CDC, 2010.
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm

TSpot

Targeted Testing and Diagnosis of Latent TB Infection
Targeted Testing and Diagnosis of Latent TB Infection

**TSpot**

- Negative control = 0 spots
- Panel A > 20 spots
- Panel B = 7 spots
- Positive control > 20 spots

Positive: A-Neg or B-Neg = 8+ spots
Negative: Both <5 spots
Indeterminate: either 5-7 spots

**TST vs IGRA**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TST</th>
<th>IGRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigens used</td>
<td>Mant, PPD, 2 ESAT-6 or 1 ESAT-6</td>
<td>IS961- and M. tuberculosis specific</td>
</tr>
<tr>
<td>Sample type</td>
<td>Transdermal injection</td>
<td>Blood draw</td>
</tr>
<tr>
<td>Patient visits required</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Distinct between TB and TB disease</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cross-reactivity with BCG</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cross-reactivity with M. avium</td>
<td>Yes</td>
<td>Only in cases of infection</td>
</tr>
<tr>
<td>Differentiation by risk</td>
<td>Yes (TB+ risk)</td>
<td>No</td>
</tr>
<tr>
<td>Cause; beading</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Subject to boosting and previous TST</td>
<td>Yes</td>
<td>Paradox</td>
</tr>
<tr>
<td>Stability over time vs. potential with or without treatment</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>Difficult with test reproducibility</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Relative cost</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>Location of need for trained staff</td>
<td>“Routinely”</td>
<td>Laboratory</td>
</tr>
<tr>
<td>Estimated specificity in BCG-vaccinated children</td>
<td>75% to 85%</td>
<td>90% to 95%</td>
</tr>
<tr>
<td>Estimated specificity in BCG-vaccinated adults</td>
<td>75% to 85%</td>
<td>90% to 95%</td>
</tr>
<tr>
<td>Estimated sensitivity in TB disease</td>
<td>75% to 85%</td>
<td>90% to 95%</td>
</tr>
<tr>
<td>Estimated sensitivity in Normal TB disease</td>
<td>50% to 70%</td>
<td>85% to 90%</td>
</tr>
</tbody>
</table>

* M. avium, M. kansasii, M. gordonae, and M. flavescens


**IGRA vs. PPD in TB Contacts**

Arends et al., AJRCCM 2007
Targeted Testing and Diagnosis of Latent TB Infection
**Addressing TB in Our Communities**

**November 19, 2015**

**Curry International Tuberculosis Center**

---

**Age-dependent risk of future TB reactivation**

![Graph showing age-dependent risk of TB reactivation](image)

- **Horsburgh R.** *NEJM* 2004

---

**Rate of Progression to Active TB**

<table>
<thead>
<tr>
<th>QFT</th>
<th>No. untreated contacts</th>
<th>Progressed to active TB</th>
<th>Progression rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>147</td>
<td>19</td>
<td>12.9%</td>
</tr>
<tr>
<td>Negative</td>
<td>756</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>TST (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-5</td>
<td>344</td>
<td>2</td>
<td>0.6%</td>
</tr>
<tr>
<td>&gt; 5</td>
<td>555</td>
<td>17</td>
<td>3.1%</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>207</td>
<td>10</td>
<td>4.8%</td>
</tr>
<tr>
<td>&gt; 15</td>
<td>63</td>
<td>2</td>
<td>3.2%</td>
</tr>
</tbody>
</table>


---

**AAP Recommendations**

![Flowchart of AAP recommendations](image)

- **Starke J (AAP).** *Pediatrics* 2014;134(6)e1736

---

**Targeted Testing and Diagnosis of Latent TB Infection**
TST or IGRA for LTBI Diagnosis in HIV?

- No evidence based argument for promoting one over another
- IGRA less prone to perturbation by immunosuppression
- Consider dual testing and acceptance of any positive result as evidence of infection

_Cattamanchi A, et. al. JAIDS 2011;56(3):230-238._

- If baseline TST or IGRA negative and CD4 <200, retest for LTBI when CD4>200.

_DHHS OI Guidelines, 2015_

What if the CXR is Abnormal?

- Indications for sputum AFB smr/culture and follow-up CXR (to demonstrate stability) prior to launching treatment for inactive TB:
  - Fibrotic or fibro-nodular opacities
  - Upper zone
  - Volume loss
- Abnormalities which do not merit further evaluation before starting treatment for LTBI:
  - Calcified granulomata
  - Pleural scarring
  - Non-TB abnormalities

Principles of LTBI Evaluation and Management

- Generally not urgent
- Criteria for initiating LTBI treatment
  - Active TB excluded
  - Baseline health status
  - Reasonable chance of completing therapy
  - Benefits warrant risks, costs and inconvenience
  - www.tstin3d.com
### Latent TB Infection

**To treat or not to treat?**

- TST+, HIV-negative, no fibrosis, not recently infected:
  - Historical incidence: 0.10-0.16% per year
  - More recent data: 0.04-0.056% per year
- Think about future benefit (age) and...
- Dominant risk factors:
  - HIV, SOT, TNF-blockade, other immunosuppression
  - Fibrosis
  - Recent acquisition
  - Diabetes, ESRD and other key medical conditions

### LTBI Treatment Decision Making

**Benefit-Risk Assessment**

- Annual risk of reactivation * life expectancy = cumulative lifetime risk of reactivation
- Risk of treatment depends on regimen selected and, for use of isoniazid, age of patient

### Case 1

- 27 y/o household contact to smear-positive cavitary pulmonary TB
- Asymptomatic
- PMH benign
- QFT positive (TB Ag – Nil = 1.57)
- PA CXR normal
Case 1

- Estimated risk of reactivation:
  - Next 2 years: 5%
  - Thereafter: 0.1% per year
  - Cumulative lifetime to age 80:
    - $5\% + 0.1\%(50\text{ years}) = \sim 10\%$

Case 2

- 70 y/o Mexico-born woman
- Immigrated 2004
- Routine screening; asymptomatic
- Father had TB when she was 5 y/o
- PMH: HTN, hypercholesterolemia, CAD
- No DM or immunosuppression
- PA CXR normal

Case 2

- Estimated risk of reactivation
  - $0.1\% \times 10-15 = 1.0-1.5\%$
### Case 3
- 56 y/o Mexican
- Change of immigration status exam
- Asymptomatic
- DM-II
- Tspot positive (A 17 spots, B 9 spots)
- PA CXR normal

### Case 3
- Estimated risk of reactivation to age 80
  \[1.7 \times \text{RR for DM} \times 0.1\% \text{/year} \times 24 \text{yr} = 4\%\]
- Change of immigration status exam
- Asymptomatic
- DM-II with Hgb A1c 9%
- Tspot positive (A 17 spots, B 9 spots)
- PA CXR normal

### Case 4
- 63 y/o male Filipino immigrant
- Asymptomatic
- PMH otherwise benign
- QFT positive (TB Ag – Nil = 0.87)
- CXR...
Case 4

- Sputum AFB smears and cultures negative x 3
- Follow-up CXR stable
- Remains asymptomatic
- Annual risk of reactivation up to age 80:
  \[ 1 - 0.99^{17} = 16\% \text{ (~1\% * 17 = 17\%)} \]