Latent Tuberculosis Infection: The Basics

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Latent Tuberculosis Infection (LTBI): The Basics - Overview

**NTCA/CDC LTBI Guidelines:** Guidelines for the Treatment of Latent Tuberculosis infection *(February 2020 MMWR; prior 2000!)*

*Testing and Treatment of Latent Tuberculosis Infection in the United States: Clinical Recommendations* *(February 2021, NTCA)*

- LTBI epidemiology
- *(Words we use matter)*
- Pathophysiology
- Who to target for testing:
  - TB risk groups
TB is Global

- Approx. **one-quarter** of the world’s population is infected with TB
- 10 million cases active TB/yr
- 1.4 million TB deaths/yr

WHO 2020 Global Tuberculosis Report (2019 data)
TB is Local: U.S.

Only the “tip of the iceberg” → 7163 active TB cases*
(2.2 per 100,000 population)

Estimated 10-15 million persons with Latent TB infection
(NHANES 2012: 13.2 million with 4.7% prevalence)

Approx. 80% of active cases due to reactivation
(Shea KM et al, Am J Epidemiol 2014)

*TB in the United States – CDC 3.2021 report

Preventable!
Targeted Testing and Latent Tuberculosis Infection

Fundamental Principles:
- As a low incidence country, targeted testing and treatment of LTBI is an essential component of the strategic plan towards **TB elimination** in the US

→ **Focus on high-risk individuals**

*Goal:* Reduce reservoir of latent TB

“A Decision to Test is a Decision to Treat (think)”
## US Prevalence

**LTBI: Subgroups**

*Horsburgh NEJM 2011*

<table>
<thead>
<tr>
<th>Group and Study</th>
<th>Expected Prevalence (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign-born persons</td>
<td></td>
</tr>
<tr>
<td>Bennett et al.</td>
<td>18.7 (13.5-25.2)</td>
</tr>
<tr>
<td>Close contacts of persons</td>
<td></td>
</tr>
<tr>
<td>with infectious TB</td>
<td></td>
</tr>
<tr>
<td>Marks et al.</td>
<td>37.1 (35.7-38.5)</td>
</tr>
<tr>
<td>Homeless persons</td>
<td></td>
</tr>
<tr>
<td>Kong et al.</td>
<td>12.8 (12.2-13.5)</td>
</tr>
<tr>
<td>Moss et al.</td>
<td>32.4 (30.5-34.4)</td>
</tr>
<tr>
<td>Injection drug users</td>
<td></td>
</tr>
<tr>
<td>Riley et al.</td>
<td>16.1 (12.5-22.4)</td>
</tr>
<tr>
<td>Grimes et al.</td>
<td>27.7 (19.3-37.5)</td>
</tr>
<tr>
<td>Brassard et al.</td>
<td>22.4 (17.7-28.5)</td>
</tr>
<tr>
<td>Salomon et al.</td>
<td>14.0 (11.4-17.1)</td>
</tr>
<tr>
<td>Prisoners</td>
<td></td>
</tr>
<tr>
<td>Lobato et al.</td>
<td>17.0 (16.8-17.1)</td>
</tr>
<tr>
<td>US-born, no other risk</td>
<td></td>
</tr>
<tr>
<td>Bennett et al.</td>
<td>1.8 (1.4-2.1)</td>
</tr>
</tbody>
</table>
US TB Cases, 2019; (N=8,905)

Non-U.S.-born (Rate: 14.2 per 100,000)

Oklahoma: 0.9 per 100,000

29%

71%

CDC data: Countries of birth among non-US born reported TB 2019

Mexico, 19%

Philippines, 12%

India, 9%

Vietnam, 8%

Honduras, 3%

Guatemala, 4%

China, 6%
But look at what’s happening in your own area......

Proportion of TB cases by country of origin, 2019, King County, WA

- China 29%
- Other 25%
- USA 14%
- Phillipines 12%
- Vietnam 8%
- Guatemala 4%
- Honduras 4%
- India 16%
- Other Countries 25%
- Mexico 4%
- China 5%
- Ethiopia 7%
- Cambodia 8%
- Vietnam 9%

....compared to San Francisco, CA 2018

- China 29%
- Other 25%
- USA 14%
- Phillipines 12%
- Vietnam 8%
- Guatemala 4%
- Honduras 4%
- India 16%
- Other Countries 25%
your home, your priorities, your practice....
Case: Is it something I said?

• Mr. X is a recent immigrant with LTBI. I tell him that his positive PPD means that he has been exposed to TB and I think that he should start preventive treatment.

• He explains to me that since he has only “been exposed” and doesn’t have the disease that he graciously declines.
“Latent TB Infection” = TB infection

Rather than saying:
- “You have been exposed to TB…”
- “We would like to give you preventative/prophylactic treatment for TB…”

Say this:

“You are infected with TB, but it is in a dormant state now (“sleeping TB” or what we call latent TB infection). We would like to treat the infection now before it has a chance to “wake-up” and become active…"
What are your favorite words to use to explain LTBI to your patients
TB Pathophysiology: from infection to active disease

a Latent infection

- Mycobacterium tuberculosis
- Alveolar macrophage
- Monocyte
- Phagosome
- Dendritic cell
- Migration to the lymph nodes for T cell priming

b Active disease

- Granuloma
- Lymph node
- Infected lymph node
- T cell
- B cell
- Interstitial macrophage
- Epithelial cell

TB Primer Nature Reviews, Pai 2016
## Compare LTBI vs Active TB

<table>
<thead>
<tr>
<th></th>
<th>Latent TB Infection</th>
<th>Active TB Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TST</strong></td>
<td>Positive</td>
<td>Usually positive</td>
</tr>
<tr>
<td><strong>IGRA</strong></td>
<td>Positive</td>
<td>Usually positive</td>
</tr>
<tr>
<td><strong>Culture</strong></td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td><strong>Sputum smear</strong></td>
<td>Negative</td>
<td>Positive or negative</td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>None</td>
<td>Mild to severe</td>
</tr>
<tr>
<td><strong>Preferred treatment</strong></td>
<td>Preventive therapy</td>
<td>Multidrug therapy</td>
</tr>
</tbody>
</table>

Adapted: TB Primer Nature Reviews, Pai 2016
Are the bugs truly “sleeping”…….? 
Probably not a true binary “latent vs. active”-----> spectrum

- Clinical disease
  - Bacterial replication maintained at a subclinical level by the immune system
  - Infection controlled with some bacteria persisting in non-replicating form
  - Infection eliminated in association with T cell priming
  - Infection eliminated without priming antigen-specific T cells

- Disease
  - Acquired immune response
  - Innate immune response

Barry C et al. Nature Reviews 2010 (modified)
Evidence of activity: PET/CT LTBI vs active TB

- Macaque monkey
- Inoculated with TB via bronchoscopy
- Followed with PET/CT over 6 mo.
- At 6 mo., classified as LTBI vs. TB disease
  - Clinical
  - Radiographic
  - Microbiologic (BAL)
  - Inflammatory markers (ESR)
Moving forward – so much yet to learn....

Primate model: PET CT following active lesions: both *grow/regress*

Battle of good vs. evil: what are the chances?
LTBI: Lifetime risk for (active) TB Disease

- In general: 5-10% lifetime risk of Active TB

5% first year, 2-3% second year

90% no disease thereafter

~0.1% per year thereafter
Figure 1. Lifetime Risk of Active Tuberculosis among Persons with a Non-conversion Positive Tuberculin Skin Test.
Risks were calculated with the assumption of a decrease in risk of 10 percent per decade.
# Lifetime Risk for TB: Effect of Age on Co-factors

**Table 2. Lifetime Risk of Reactivation Tuberculosis.**

<table>
<thead>
<tr>
<th>Size of Induration on Skin Test and Age</th>
<th>Nonconversion Positive Skin Test</th>
<th>Recent Conversion of Skin Test</th>
<th>Immunosuppressive Therapy</th>
<th>Old, Healed Tuberculosis</th>
<th>Advanced HIV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induration of ≥15 mm</td>
<td>percent (95 percent confidence interval)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–5 Yr</td>
<td>13 (10–16)</td>
<td>17 (12–24)</td>
<td>25 (7–87)</td>
<td>66 (34–100)</td>
<td>100 (88–100)</td>
</tr>
<tr>
<td>6–15 Yr</td>
<td>7 (6–8)</td>
<td>8 (6–10)</td>
<td>14 (4–46)</td>
<td>37 (21–67)</td>
<td>70 (52–92)</td>
</tr>
<tr>
<td>16–25 Yr</td>
<td>8 (5–15)</td>
<td>13 (8–21)</td>
<td>17 (3–84)</td>
<td>44 (15–100)</td>
<td>83 (39–100)</td>
</tr>
<tr>
<td>26–35 Yr</td>
<td>7 (4–13)</td>
<td>12 (8–19)</td>
<td>15 (3–74)</td>
<td>39 (14–100)</td>
<td>73 (35–100)</td>
</tr>
<tr>
<td>36–45 Yr</td>
<td>4 (2–7)</td>
<td>7 (5–12)</td>
<td>8 (2–39)</td>
<td>21 (8–57)</td>
<td>40 (20–79)</td>
</tr>
<tr>
<td>46–55 Yr</td>
<td>3 (2–6)</td>
<td>6 (4–10)</td>
<td>6 (1–32)</td>
<td>17 (6–46)</td>
<td>32 (16–44)</td>
</tr>
<tr>
<td>56–65 Yr</td>
<td>3 (2–4)</td>
<td>3 (1–7)</td>
<td>5 (1–23)</td>
<td>13 (5–33)</td>
<td>25 (14–46)</td>
</tr>
<tr>
<td>≥66 Yr</td>
<td>2 (1–3)</td>
<td>2 (1–5)</td>
<td>4 (1–17)</td>
<td>9 (4–24)</td>
<td>18 (10–33)</td>
</tr>
</tbody>
</table>

Horsburgh NEJM 2004
Targeted Testing

TB controllers
How birds see the world
TARGETED TESTING.....

Should we just screen everyone?
TARGETED TESTING.....

Only target if higher risk for TB

↑ higher risk for recent infection

↑ higher risk for progression
Target: Risk of recent infection

- Close contacts of infectious TB cases
- Immigrants from TB endemic countries
- Employees/residents of high-risk congregate settings
  - Homeless shelters, correctional facilities, nursing homes, and residential homes for people living with HIV [where TB is more common]
    - [Healthcare Personnel -> see new HCP recommendations]

➔ Look at local data & demographic risk groups......

CDC: Latent TB Infection Testing & Treatment: Summary of U.S. Recommendations; Feb 2019
https://www.cdc.gov/tb/publications/ltbi/ltbiresources.htm
[Note: ATS/IDSA/CDC 2017 Guidelines: Diagnosis of TB adds Mycobacteriology Lab personnel]
Target: Risk of recent infection (2)

Foreign-born persons:

- ~80% of U.S. TB cases are foreign-born
- Target those born in or who frequently travel to countries with high TB prevalence
- High and intermediate incidence countries include: Mexico, Philippines, Vietnam, India, China, Haiti, & Guatemala (countries of origin for ↑ cases in U.S.)

[Again, good to know local demographics & risk groups]
Target: Risk of progression → HIV

HIV infection:

- Screen as early as possible (anergy increases if HIV disease advances)
- Screen as part of standard medical care - depends on TB exposure risks
- Exceptionally high rate of reactivation (7-10% per year) ➔ rapid development to active disease once newly infection
Target: Risk of progression → TB4

TB4: Individuals with abnormal chest x-ray compatible with past TB. If untreated:

- Risk of active disease is 5x that of person with normal x-ray and no other risk factors
- Higher underlying bacillary load
- TB test and sputum part of initial screening in spite of stability of chest x-ray before LTBI treatment
  - Must rule out active TB disease with cultures before starting LTBI treatment
Target: Risk of progression → other

- Infants and young children < 5 yrs. age
  (“Sentinels of transmission”)
- Specific medical conditions
  
  HIV, diabetes, immunosuppression - includes TNF-alpha inhibitors & corticosteroids (>15mg/d for >2wks), organ transplants, renal failure, head & neck CA, silicosis, alcoholism, IVDU, tobacco use, gastrectomy/jejunoileal bypass, low body weight
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced untreated HIV</td>
<td>9.9 (8.7-11)</td>
</tr>
<tr>
<td>Close Contacts</td>
<td>6.1 (5.5-6.8)</td>
</tr>
<tr>
<td>CXR c/w prior healed TB</td>
<td>5.2 (3.4-8.0)</td>
</tr>
<tr>
<td>Prednisone ≥15mg/day</td>
<td>2.8 (1.7-4.6)</td>
</tr>
<tr>
<td>Chronic Renal Failure</td>
<td>2.4 (2.1-2.8)</td>
</tr>
<tr>
<td>TNF alpha inhibitor</td>
<td>2.0 (1.1-3.5)</td>
</tr>
<tr>
<td>Poorly controlled diabetes</td>
<td>1.7 (1.5-2.2)</td>
</tr>
<tr>
<td>Weight &lt;10% below normal</td>
<td>1.6 (1.1-2.2)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.5 (1.1-2.2)</td>
</tr>
</tbody>
</table>
**Recommendation**

The USPSTF recommends screening for latent tuberculosis infection (LTBI) in populations that are at increased risk.

<table>
<thead>
<tr>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults who are at increased risk for tuberculosis:</td>
</tr>
<tr>
<td>• persons born in, or former residents of, countries with increased tuberculosis prevalence</td>
</tr>
<tr>
<td>• persons who live in, or have lived in, high-risk congregate settings (such as homeless shelters and correctional facilities)</td>
</tr>
</tbody>
</table>
Screening Tools: Keep it Simple!
CA Risk Assessment Tool
(Adult, pediatric, school, university versions available)

LTBI testing is recommended if any of the boxes below are checked.

- **Birth, travel, or residence** in a country with an elevated TB rate for at least 1 month
  - Includes any country other than the United States, Canada, Australia, New Zealand, or a country in western or northern Europe
  - If resources require prioritization within this group, prioritize patients with at least one medical risk for progression (see the California Adult Tuberculosis Risk Assessment User Guide for this list).
  - Interferon Gamma Release Assay is preferred over Tuberculin Skin Test for non-U.S.-born persons ≥2 years old

- **Immunosuppression**, current or planned
  - HIV infection, organ transplant recipient, treated with TNF-alpha antagonist (e.g., infliximab, etanercept, others), steroids (equivalent of prednisone ≥15 mg/day for ≥1 month) or other immunosuppressive medication

- **Close contact** to someone with infectious TB disease during lifetime

Treat for LTBI if LTBI test result is positive and active TB disease is ruled out.

- **None**: no TB testing is indicated at this time.

[www.cdph.ca.gov/Programs/CID/DCDC/Pages/TB-Risk-Assessment.aspx](http://www.cdph.ca.gov/Programs/CID/DCDC/Pages/TB-Risk-Assessment.aspx) or Curry website
Frequency of HCP screening: 2019 Changes

Updated CDC/NTCA recommendations for US health care personnel (HCP) screening, testing & treatment; MMWR, Sosa et al, May 17, 2019

- Review of US Surveillance data: 1995-2007 HCP TB incidence rates similar to general population
- 2018 retrospective cohort study (40,000 HCP, low incidence state) found low rate TST conversion (0.3%) from 1998-2014; Clin Inf Dis, Dobler et al, Feb 10, 2018

HCP Retesting: Need to correlate with local epidemiologic data

- Past wording: CDC Guidelines 12/05: Serial testing → “Institutional decision based on setting’s risk classification” (Low, medium, or high ongoing risks); MMWR Dec. 30, 2005

2019 - Frequency of testing HCP dependent on ongoing risk of TB exposure
In support of new HCP Recommendations:

- Relatively low proportion (3%–5%) of U.S. HCP test positive for *M. tuberculosis* at baseline
- <1% of U.S. HCP previously testing negative convert to a positive test result during serial testing
- Nearly 50% of U.S. HCP previously testing positive revert to a negative test result during serial testing
- Insufficient evidence to assess incidence and transmission of TB disease among HCP
  - No cases of TB disease reported among the ~64,000 U.S. HCP included in the studies reviewed

*Slide credit: Lynn Sosa, Aug.2019 HCP Webinar*
<table>
<thead>
<tr>
<th>Category</th>
<th>2019 Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (pre-placement) screening and testing</td>
<td>TB screening of all HCP, including a symptom eval. and test (IGRA or TST) for those without documented prior TB disease or LTBI (unchanged); <strong>individual TB risk assessment (new)</strong></td>
</tr>
<tr>
<td>Post-exposure screening and testing</td>
<td>Sx eval. for all HCP when an exposure is recognized. For HCP with a baseline neg TB test and no prior TB disease of LTBI, perform a test (IGRA or TST) when the exposure is identified. If that test is negative do another test 8-10 weeks after the last exposure (unchanged)</td>
</tr>
<tr>
<td>Serial screening and testing for HCP without LTBI</td>
<td><strong>Not routinely recommended (new);</strong> can consider for selected HCP groups (unchanged); <strong>recommend annual TB education for all HCP (unchanged) including information about TB exposure risks for all HCP (new emphasis)</strong></td>
</tr>
<tr>
<td>Evaluation and treatment of positive test results</td>
<td><strong>Treatment is encouraged for all HCP</strong> with untreated LTBI, unless medically contraindicated (new)</td>
</tr>
</tbody>
</table>
CDC/NTCA: HCP Baseline Risk assessment tool

Health care personnel should be considered to be at increased risk for TB if they answer “yes” to any of the following statements.

1. **Temporary or permanent residence (for ≥1 month) in a country with a high TB rate** (i.e., any country other than Australia, Canada, New Zealand, the United States, and those in western or northern Europe); Or

2. **Current or planned immunosuppression**, including human immunodeficiency virus infection, receipt of an organ transplant, treatment with a TNF-alpha antagonist, chronic steroids (equivalent of prednisone ≥15 mg/day for ≥1 month), or other immunosuppressive medication; Or

3. **Close contact** with someone who has had infectious TB disease since the last TB test

† Adapted from a tuberculosis risk assessment form developed by the California Department of Public Health
• LTBI identification and treatment is fundamental to US TB elimination strategy

• “Latency” may be dynamic process

• Identifying target high risk groups is key
http://www.currytbccenter.ucsf.edu

Curry International TB Center

http://www.currytbccenter.ucsf.edu
(Check out their Warmline!)