Latent Tuberculosis Infection: The Basics

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Latent Tuberculosis Infection (LTBI): The Basics - Overview

ATS/CDC LTBI Guidelines: Targeted tuberculin testing and treatment of latent tuberculosis infection (April 2000 AJRCCM)

- LTBI epidemiology
- Nomenclature
- Who to target for testing: TB risk groups
- Online algorithm tool (tst3D.com) - preview
TB is Global

- Approx. one-third of the world’s population is infected with TB
- 10.4 million cases active TB/yr
- 1.8 million TB deaths/yr

WHO 2016 Global Tuberculosis Report (2015 data)

TB is Local

Only the “tip of the iceberg” → 9287 active TB cases*
(2.9 per 100,000 population)

Estimated 10-15 million persons with Latent TB infection (NHANES 2000: 11 million)

Approx. 85% of active cases due to reactivation (France AM et al, Am J Epidemiol 2015)

*TB in the United States – CDC 2016 report
LTBI epidemiology: U.S.
Bennett AJRCCM 2008

National survey (NHANES) 1999-2000:
- Included TST >7000 participants
- Estimated prevalence LTBI 4.2%
  (down from 14.3% in 1971-72)
- Only 25.5% were diagnosed, 13.2% given rx
- Higher prevalence:
  - 18.7% Foreign-born
  - 7% Non-Hispanic/Black
  - 9.4% Mexican American
  - 6.1% individuals living in poverty

US Prevalence
LTBI: Subgroups
Horsburgh NEJM 2011

<table>
<thead>
<tr>
<th>Group and Study</th>
<th>Expected Prevalence (95% CI)</th>
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<tbody>
<tr>
<td>Foreign-born persons</td>
<td>18.7 (13.5–25.2)</td>
</tr>
<tr>
<td>Close contacts of persons with infectious tuberculosis†</td>
<td>37.1 (35.7–38.5)</td>
</tr>
<tr>
<td>Homeless persons</td>
<td>12.8 (12.2–13.5)</td>
</tr>
<tr>
<td>Injection-drug users</td>
<td>32.4 (30.5–34.4)</td>
</tr>
<tr>
<td>Prisoners</td>
<td>16.1 (12.5–22.4)</td>
</tr>
<tr>
<td>U.S.-born, no other risk</td>
<td>17.0 (16.8–17.1)</td>
</tr>
<tr>
<td>Bennett et al.⁴</td>
<td>1.8 (1.4–2.1)</td>
</tr>
</tbody>
</table>
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.”

your home, your priorities, your practice....
Case: Is it something I said?

- Mr. X is an 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 patiently to me via translator that since he has only been exposed and doesn’t have the disease that he graciously declines.

Nomenclature: “Latent TB Infection” (2)

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 (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…”
Nomenclature: “Latent TB Infection”

In the near future??

TB Infection

Are the bugs truly “sleeping”.......?

Probably not a true binary “latent vs. active”----- spectrum

Barry C et al. Nature Reviews 2010
Moving forward – so much yet to learn....

Primate model: PET CT can follow active lesions (grow/regress)

[Can also demonstrate active lesions in LTBI (not pictured here)]


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

~0.1% per year thereafter

*Figure: Esmial and Barry Drug discovery 2012*

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**Lifetime risk: Age matters (non-converters)**

*Horsburgh NEJM 2004*

*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.
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>11 (9–16)</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
With current budget cuts, which screening program would be the lowest priority for targeted TB testing?

A. Annual testing of all HIV patients in continuity clinic
B. All new residents to a local nursing home
C. All new teachers upon hire in school district
D. Annual screening of all clinical / administrative staff in hospital

Who should be screened: “TARGETED TESTING”

Screening should be targeted to those at higher risk of TB ➔ NOT the general population.

Target populations with:
- Increased rates of recent TB infection
- Increased risk of progression to active TB

Goals:
- Identify active TB cases
- Identify LTBI that would benefit from rx
- Surveillance
Target: Risk of recent infection

- Close contacts of infectious TB cases
- Recent immigrants (< 5 years) TB endemic countries
- Residents/employees of high-risk congregate settings
  - Healthcare, Correctional, Long-term care facilities
- Medically underserved (consider local demographics)
  - Homeless
  - Migrant workers
  - Low-cost hotel dwellers or crowded living conditions
  - Persons with substance use disorders
  - Racial and ethnic minorities
  - Children with parents that have these TB risk factors

Recent infection (contacts and converters):
- 4-5% risk of developing active disease within the first 1-2 years

CDC definition of “Converter”:
>10 mm increase in PPD within 2 year period
Target: Risk of recent infection

Foreign-born persons:

- ~68% of U.S. TB cases are foreign-born
- Emphasis on newcomers to the U.S. (<5 years), TB incidence rates similar to country of origin for first several years (rules may change)
- High and intermediate incidence countries (Asia and Pacific Islands, Africa, Central and South America, Eastern Europe, Middle East)

Target: Risk of progression

- HIV
- Individual with abnormal CXR compatible with past TB
- Infants and young children < 5 yrs. age
- Specific medical conditions
**Target: Risk of progression → HIV**

**HIV infection:**
- Screen as early as possible (anergy increases as HIV disease advances)
- Screen every 6-12 months (depends on lifestyle and environmental TB 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 5-10x that of a person with a normal x-ray and no other risk factors
- Higher underlying bacillary load
- *TB test and sputum part of screening in spite of stability of chest x-ray and history of treatment, must rule out active TB disease with cultures before starting LTBI treatment
Target: Risk of progression (2)

- Infants and young children < 5 yrs. age
  - (“Sentinels of transmission”)
  - Risk may double if <4 years old
  - 40% progression to disease in infants < 1 year old
- Specific medical conditions
  - Diabetes, Immunosuppression (includes TNF-alpha inhibitors), Renal failure, Lymphoma/Leukemia, Head and neck CA, Silicosi, Alcoholism, IVDU, Tobacco use, Gastrectomy/Jejunoileal bypass, Malnutrition

Which LTBI (PPD+) patient has a higher risk of progression to active disease over the next 1 year?

A. Healthy adult contact to 4+ smear positive case
B. Pregnant/healthy woman in first trimester
C. Recent immigrant from India with abnormal CXR suggesting old TB
D. HIV+ patient with CD4 100
## Risk of Developing Active TB

**Horsburgh NEJM 2011**

<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 &gt;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>

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**tstin3d.com**

[http://www.tstin3d.com](http://www.tstin3d.com)

Online resource tool

→ algorithm combines risk factors and TST vs. IGRA performance

(Will cover later in case)
Frequency of screening

Retesting:

Frequency dependent on ongoing risk of TB exposure
- Annual testing*: health care workers, long-term care residents, shelter or homeless program or substance recovery program staff
- Q 6 month testing*: TB clinic frontline staff, ER workers, pulmonologists performing bronchoscopy

*Need to correlate with local epidemiologic data.

CDC Guidelines 12/05: Serial testing → “Institutional decision based on setting’s risk classification” (Low, medium, or high ongoing risks)  

LTBI Basics: Summary

- LTBI identification and treatment is fundamental to US TB elimination strategy
- “Latency” may be dynamic process
- Identifying target high risk groups is key