Diagnosis of Latent TB Infection

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Disclosures: None
Objectives

- Explain use of TST
- Explain use of IGRA testing
TB Nomenclature

- **Latent TB Infection (~90% TB infections):**
  - Positive TST (or IGRA eg, QFT-G)
  - No symptoms
  - Negative or chronic CXR changes
  - Can not transmit disease to others.

- **Active TB Infection (~10% TB infections):**
  - TST (or IGRA) may be positive
  - Symptoms present
  - CXR changes & sputum smear positive in most cases
  - Disease transmission to others

- Treatment for **both** latent and active infections
- Avoid terms: Prophylaxis, Preventive therapy
Infection (LTBI)

- 3-4% First Year
- 1-2% Second Year
- ~0.1% per year thereafter

Disease (Active Infection)

- No Active Disease (~90%)
Epidemiology of Tuberculosis
TB in Foreign-Born Immigrants to US

- Proportion of TB cases foreign-born increased from <25% to 57% (1986-2006)
- US-born TB cases decreased by 45% (1993-2006)
- ~70% MDR TB occur among Foreign-born
  - Anticipate XDR TB & TDR TB
- SE Asians, Sub-Saharan Africans, & Latin Americans
- Concentrated in NY, NJ, Ca, Fl, IL, Tx
- Active cases most often arise from prior infection
- ~55% occur within 5 yrs of immigration
  - ≤ 2 yrs in US 75/100,000
  - > 2 yrs in US 16/100,000

CDC; Cain et al: JAMA 2008
Foreign-Born ⇒ US
TB Cases & Case Rates vs. Years in US

~30% Foreign-born coming into US unscreened...

Cain et al: JAMA 2008
Refugee & Immigrant TB Screening

• Within Country of Origin
  – Adults: Evaluated for Active TB only
  – Children (<15 yrs) & TB contacts screened (TST) in some countries but no LTBI Rx
• Arrival within US
  – TB Suspects are expected to f/u w/ local health dept (not mandated)
  – Applicants for adjustment of status evaluated for LTBI (Rx not mandated)
• Not evaluated...Estimates ~30%
  – Visitors, Temp Workers, Undocumented
  – Student visa

Immigration process doesn’t deal with LTBI for you...
“Tuberculosis is a social disease with medical implications”

–Sir William Osler
How do Rural TB rates compare to the National TB rates?
US vs. Foreign-Born TB Cases – Iowa 2012

US: 3.2 /100,000
Iowa: 1.5 /100,000
~1/yr drug resistant
Focus of TB Control in the US: Targeted Testing & Rx for LTBI

- Few cases due to transmission from other active cases (↓ HIV related cases)
- High rates of TB among foreign-born immigrants to US (including rural locales) from high incident countries
- "Targeted tuberculin testing" is the theme of the LTBI guidelines
- One of the main targets must be the foreign-born immigrants from high incident countries
## Relative TB Risk

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Risk Estimate (vs. control w/ +TST)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced HIV</td>
<td>9.9</td>
</tr>
<tr>
<td>Anti-TNF Rx</td>
<td>7.9</td>
</tr>
<tr>
<td>Old, healed TB</td>
<td>5.2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.1</td>
</tr>
<tr>
<td>Tobacco abuse</td>
<td>2.7</td>
</tr>
<tr>
<td>Chronic Renal Failure</td>
<td>2.4</td>
</tr>
<tr>
<td>Silicosis</td>
<td>1.7</td>
</tr>
<tr>
<td>Underweight (10% &lt; IBW)</td>
<td>1.6</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Targeted TB Testing
Decision to Test = Decision to Treat

- Patients at highest risk for progression to active TB
- Patients with medical conditions that increase risk for active TB
- Patients in whom active TB is more prevalent
Targeted TB Testing

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Targeted TB Testing

Decision to Test = Decision to Treat

Patients at highest risk for progression to active TB

- HIV infection, or risk factors for HIV infection
- Receiving TNFα antagonist for RA or Crohn’s
- Fibrotic lesion on CXR c/w prior pulmonary TB
- Close contact of persons with infectious TB (e.g., pulmonary, laryngeal TB)
- New TB infection (TST conversion within prior 2 years)
- IV drug abuser (HIV negative)
Targeted TB Testing

Decision to Test = Decision to Treat

- Patients at highest risk for progression to active TB
- Patients with medical conditions that increase risk for active TB
- Patients in whom active TB is more prevalent
Targeted TB Testing

Decision to Test = Decision to Treat

Medical conditions ↑ risk for progression to active TB

- Diabetes mellitus
- Tobacco abuse (NEW)
- Silicosis
- Jejunoileal bypass surgery or gastrectomy
- Solid organ transplant (e.g. renal, heart)
- Chronic renal failure/hemodialysis
- Head/neck carcinoma
- Hematologic malignancies (e.g. leukemia, Hodgkin’s)
- Immunosuppressed, particularly steroid treatment (≥15 mg/day, ≥ 1 month)
- Substantial weight loss: >10% ideal body weight
Targeted TB Testing
Decision to Test = Decision to Treat

- Patients at highest risk for progression to active TB
- Patients with non-HIV medical conditions that increase risk for active TB
- Patients in whom active TB is more prevalent
Targeted Skin Testing

Decision to Test = Decision to Treat

Patients in whom active TB is more prevalent

- Recent arrivals (< 5 years) from high TB prevalence countries (Africa, SE Asia, Pacific Isles, Latino, E. Europe, Russia)

- Resident or employee of high-risk congregate settings: prisons/jails, nursing homes/other long term facilities, hospitals/other health care facilities, residential facilities for AIDS patients, and homeless shelters

- Mycobacteriology lab workers
Case S. B.

- 56 yo female
- Asymptomatic
- TST+ (estranged husband had TB 20 years ago)
- On no drugs, no HIV risk factors, no EtOH
- Chest x-ray unremarkable
What is the diagnosis?

Latent TB Infection (LTBI)
New technology replacing old…
Mantoux Tuberculin Skin Test (TST)

- Standard (old) method of skin testing for *M. tuberculosis* infection
- Produces delayed-type hypersensitivity reaction
- TST is useful for:
  - Detecting LTBI
  - Contact investigation: Determining how many people in a group are infected
  - Evaluating persons who have symptoms of active TB
Administering the TST

- Inject 0.1 ml of 5 TU PPD tuberculin solution intradermally on volar surface of lower arm using a 27-gauge needle
- Produce a wheal 6 to 10 mm in diameter
Low (Old) Tech...TST
Delayed-type Hypersensitivity Reaction @ 48-72 hrs

- Positive: 18 mm **Induration**
- A positive test may be measured up to 7 days out
- A negative reaction can be read accurately @ 48-72 hrs
Reading a TST

- Measure induration, not erythema by 48 to 72 hours
- Record induration size in millimeters, in addition to interpretation (“negative” or “positive”)
- Ensure trained health care professional measures & interprets the TST
- Educate patient & family about the significance of a positive test
TST Interpretation

Positive classification based on pre-test probability of TB:

$\geq 5\text{ mm} = \text{ positive}$
- HIV positive
- Household or close contact to patient with infectious, active TB
- CXR consistent with old/healed TB
- Organ transplant or other immunosuppressed patient

$\geq 10\text{ mm} = \text{ positive}$
- Foreign born (e.g. Africa, SE Asia, Hispanic, India, China, E Europe)
- IV drug abusers
- Residents or employee of high risk congregate setting
- Non-immunosuppressive medical conditions known to increase risk of active TB
- Mycobacteriology lab workers

$\geq 15\text{ mm} = \text{ positive}$
- Persons in regions of low TB incidence
Limitations for TST

• Interpretation variability; False positives: NTM, BCG…

• BCG Vaccine effect on TST Interpretation
  – Induces 3-19 mm TST reaction in 1st few mos.
    • Reaction wanes significantly by 10 years
    • Reaction size does not correlate with protection
  – Positive TST most likely due to TB infection:
    • Persons from regions of high TB prevalence (eg. hispanic, asian)
    • Large reaction (>15 mm)
  – Prior BCG, should be Tested and Treated if positive

• Booster Phenomenon
  – False negative TST, becomes positive as a result of skin testing
  – Most common situations:
    • Initial TB infection many years previous
    • Prior BCG immunization
  – Two Step Skin Testing (TST x 2, one week apart)
    • Elderly nursing home population
    • Prior BCG immunization
LTBI Testing Upgrade…
Interferon Gamma Release Assay (IGRA)

Measures interferon-gamma (IFN-γ) released by lymphocytes in response to specific TB antigens: ESAT-6, CFP-10

• QuantiFERON® Family:
  – QuantiFERON®-TB test 1999
  – QuantiFERON® - TB Gold 2005
  – QuantiFERON® - TB Gold In-Tube (GIT) 2007
    Added 3rd antigen TB7.7 (RD4) & travel time

• T-Spot. TB® Aug 2008:
TST vs IGRA

Presentation of TB antigens
• TST (Multiple = PPD)
• IGRA (Specific = ESAT-6, CFP-10)

IGRA Results include control wells
• Negative (Nil) – no antigen (subtract from pt value)
• Positive – mitogen stimulation

### IGRA vs TST

<table>
<thead>
<tr>
<th>IGRA</th>
<th>TST</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>In vitro</em></td>
<td><em>In vivo</em></td>
</tr>
<tr>
<td>Specific antigens</td>
<td>Multiple antigens</td>
</tr>
<tr>
<td>Unaffected by BCG</td>
<td>BCG affects results</td>
</tr>
<tr>
<td>No boosting</td>
<td>Boost occurs</td>
</tr>
<tr>
<td>One patient visit</td>
<td>Two pt visits</td>
</tr>
<tr>
<td>No inter-reader variability</td>
<td>Inter-reader variability</td>
</tr>
<tr>
<td>One standard result for all</td>
<td>Different thresholds based on risk</td>
</tr>
</tbody>
</table>
QFT vs T-Spot.TB

- **Quantiferon TB (QFT):** Whole blood incubated w/ TB specific antigens. ELISA measures IFN-γ release

- **T-Spot.TB:** Lymphocytes (T) incubated w/ specific antigens. ELISPOT-method counts IFN-γ releasing cells
## IGRA Interpretation

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
<th>Gray Zone</th>
<th>Indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>QFT-TB</strong> Gold &amp; IT version</td>
<td>≥0.35*</td>
<td>&lt;0.35*</td>
<td>None</td>
<td>Controls fail:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• High Nil</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Mitogen response</td>
</tr>
<tr>
<td><strong>T Spot.TB</strong></td>
<td>≥8 spots*</td>
<td>&lt;8 spots*</td>
<td>5-7 spots*</td>
<td>Same as above</td>
</tr>
</tbody>
</table>

*TB Ag – Nil, assuming appropriate control response
IGRA CDC Guidelines 2010

- IGRA may substitute for TST
- IGRA preferred:
  - BCG vaccinated persons
  - Clients unlikely to return for TST reading
  - Low risk persons
- TST preferred in children <5
- Clinical judgment required when interpreting IGRA among immunosuppressed, children <5, & TB suspects
- Lab should be reporting quantitative results
Indeterminate IGRA Results

- Poor response to mitogen that resolves with repeat assay
  - Delayed specimen processing
  - Technical errors
- Persistent poor response to mitogen
  - Anergy from immunosuppression
  - May occur in healthy persons
- High background IFN-γ levels (high NIL response)
  - Often persistent, reasons unclear
  - IGRA not useful
Interpreting IGRA Results

- Contact investigation: If initial IGRA negative, Repeat test at 8-10 wks as one would with TST
- IGRA conversion = change from neg to positive
- Indeterminate result: Repeat IGRA or do nothing (don’t recommend TST generally)

Areas of uncertainty:
- Quantification of IGRA conversion (serial testing)
- Possible quantitative assessment of Rx response
Host Factors Creating False Negative TST & IGRA

- HIV (low CD4, no HART)
- <10 wks since TB infection
- Other infections (viral, fungal, bacterial)
- Lymphoma
- Live virus vaccination (eg, measles, smallpox)
- Immunosuppressive Rx
- Overwhelming TB (eg, miliary TB)
- Age (newborn, very old)
TST False Positives

- Cross reaction w/ NTM or BCG
- Immediate hypersensitivity misinterpreted as positive
- TST product switch (Tubersol vs Aplisol)

IGRA False Positives

- Cross reaction NTM: *M. kansasii*, *M. szulgai*, & *M. marinum*
- Product failure such as endotoxin traces in tubes
- Lab error
Can IGRA Replace TST?

- Contact investigation: YES
- BCG vaccine Hx: YES
- Low risk person: yes
- Screening homeless & other unreliable persons: YES
- Serial Testing: Yes, but…
Real Life with IGRA

• Significant reduction in positive rate vs TST
• Increased frequency of retesting

• Serial testing issues:
  – Unexpected positives that require further review (eg, repeat testing, assessing quantitative results)
  – “Wobblers” = results hovering around cut point
LTBI: TST & IGRA ≠ Gospel

- Reassess TB risk factors
- Review symptoms
- Review CXR... evidence suggest old TB (Upper lobe fibrosis, Gohn lesion, Hilar Ca++)

- LTBI Rx decision should be based on complete certainty that active TB not present
Key Recent References


Summary Points

• Screen persons at high risk for TB (eg, foreign born)
• Seek to distinguish active vs. latent TB infection
• LTBI diagnosis reviewed
  – Decision to test = Decision to treat!
  – Highest risk subgroups identified
• Role for IGRA: QFT-Gold, T-Spot. TB
Factors Causing False-Negative TST

- **Anergy** = Weakened immune system ⇒ Inability to react to TST
  - **Anergy testing** utility in TST-negative persons not demonstrated in clinical trials
- New TB infection (eg, 2-10 weeks post exposure)
- Newborns
- Live virus vaccination (eg, measles, smallpox) suppresses TST response
- Overwhelming disease (eg, miliary TB)
- Poor TST administration technique
A 35-year-old woman is referred to you from the employee health service of a skilled nursing facility to evaluate for a positive tuberculin skin testing of 10 mm induration. She is a recent immigrant from India. She denies fever, fatigue, productive cough, hemoptysis, night sweats and HIV risk factors. Her chest x-ray is normal. Which of the following is the MOST appropriate NEXT step?

A. Repeat tuberculin skin test in 2 weeks
B. Start Isoniazid, Rifampin, pyrazinamide and Ethambutol
C. Recommend Isoniazid therapy for 9 months
D. Check sputum AFB stain and culture
E. Bring in household contacts for tuberculin testing
A patient is coming to clinic to decide on a recent positive IGRA test. He is a medical student from Iowa who has traveled extensively to remote areas in Mexico and India as part of a medical volunteer mission. He had an IGRA test 3 years ago prior to enrolling in medical school, which was negative. He is afebrile, continues to run daily, and denies weight loss or hemoptysis. A chest radiograph is normal. Which is the MOST appropriate interpretation of this positive test?

A. He has active TB and should be started on quadruple therapy.
B. Repeat the IGRA since it is likely falsely positive.
C. Start on treatment for latent tuberculosis.
D. Collect sputum for AFB smear, NAAT, and culture
E. A PPD should be placed to confirm the result.