Latent Tuberculosis Infection (LTBI)
Background, Definition, and Diagnosis

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Disclosures

- I cry when I watch The Sound of Music
- I have no financial or other conflicts of interest that are relevant to this talk

LTBI Background, Definition, and Diagnosis Goals

Upon completion of this session, participants will be able to:
1) Understand the context for a renewed focus on LTBI
2) Define LTBI
3) Use a logical approach to diagnosing LTBI
Latent Tuberculosis Infection (LTBI)

- Background
- Definition
- Diagnosis

Features of TB Infection vs. Disease

**TB Infection (LTBI)**
- Positive TST or IGRA
- No symptoms
- Normal CXR
- Negative sputum smears and cultures (if done)

**TB Disease**
- Symptomatic
- Abnormal CXR
- Positive sputum AFB smears and/or cultures
- Positive TST or IGRA (in some)

Example LTBI Case

- 34 year old woman immigrant from Guatemala (age 22)
- Grandfather had TB but 25 years ago
- TST shows 6 mm induration
- No symptoms or abnormal exam findings
Example TB Disease Case

- 54 year old incarcerated man, known IDU
- Known recent TB exposure
- TST shows 17mm induration
- Cachectic, chronic productive cough, asking for cigarettes

If only it were that simple...

Life Cycle of Tuberculosis: Exposure, Infection, and Disease

- No TB Infection Evident
- Defenses Maintained (TB Remains Latent/Dormant/Dead)
- Infection Contained (Latent TB Infection)
- Maintenance of Acquired Defenses
- Defenses Not Maintained (Reactivation TB Disease)

- TB Exposure
- Adequacy of Innate Defenses
- Primary TB Infection (Silent Dissemination)
- Development of Acquired Defenses
- Infection Not Contained (Primary TB Disease)

TRANSMISSION
LTBI: Definition
Latent TB Infection (LTBI)

- Positive tuberculin skin test or IGRA
- No symptoms
- Normal CXR
- Negative AFB smears and cultures (if done)

Latent Tuberculosis Infection (LTBI)

- It’s TB infection, not merely exposure
- It’s not TB disease or active TB
- It’s not contagious at this stage
- It’s latent, or dormant, or maybe even completely dead (we can’t tell)
- It’s the HUGE (submerged) part of the global TB iceberg
LTBI: Diagnosis

• Available Tests
• Targeting test strategies
• Interpretative strategies

Available Tests for Latent TB Infection

• Tuberculin skin test (TST)
  Skin test that produces delayed-type hypersensitivity reaction (induration) in persons with *M. tuberculosis* infection
• QuantIFERON® - Gold In Tube
  Blood test that measures and compares amount of interferon-gamma (IFN-γ) released by blood cells in response to TB antigens
• T-SPOT®.TB Test
  Blood test that measures number of T-cells that secrete IFN-γ in response to TB antigens

Tuberculin Skin Test (TST)

• Uses Purified Protein Derivative (PPD)
• Intracutaneous injection of defined PPD dose
• Allow time for immune response (2-3 days)
• Measure millimeters of induration (not redness)
• Interpret according to complex algorithm incorporating TB risk factors and size of induration
• Not useful for diagnosing active TB disease
Tuberculin Skin Test
inject PPD intracutaneously
read induration 48-72 hours later

TST Interpretation – The Ideal World

Not TB Infected
"negative"
TB Infected
"positive"

Percent of Population

TST Induration (mm)

TST Results in the Real World

“false positive”
“true positive”

Percent of Population

TST Induration (mm)
Interferon gamma release assay (IGRA) -- Blood Tests for LTBI

- Two major types: QFT and T-Spot.TB
- Rely on M. tuberculosis-specific antigens that are not present in BCG or most NTMs
- Appealing specificity but still requires complex interpretation
- Susceptible to blood collection and handling practices
- Not useful for diagnosing active TB disease
- More to follow …

Choosing Between TST & IGRA

<table>
<thead>
<tr>
<th>TST</th>
<th>IGRA</th>
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<tbody>
<tr>
<td>Pros:</td>
<td></td>
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<tr>
<td>PPD nonspecific</td>
<td></td>
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<tr>
<td>Fair sensitivity</td>
<td></td>
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<tr>
<td>Familiarity</td>
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<td>Cons:</td>
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<td>Two visits</td>
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<td>Lack of specificity</td>
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<td>Complex interpretation</td>
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<td>Lack of familiarity</td>
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<td>Complex interpretation</td>
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Traditional (1999) LTBI Test Targeting Strategies

- Test Groups at Risk for Having TB Infection
- Test Groups at Risk, if Infected, for Progressing to Active TB Disease

Groups at High Risk for Having Tuberculosis Infection

Risks of Exposure and Infection
- Close contacts of TB cases
- Foreign-born in endemic areas
- Medically “underserved”
- Institutionalized or Incarcerated
- Injection drug users
- Occupational TB exposure
- Locally-identified risk groups
  (e.g. Homeless, Native American ethnicity, other)

Groups at High Risk of Developing Tuberculosis Disease

Risk of Progression, if Infected
- HIV infection
- Recent TB infection
- Injection drug users
- History of inadequate TB treatment
- Underlying medical conditions
  • Immunosuppressive therapy (steroids, anti-TNF, etc.)
  • Substance abuse
  • Malnutrition
  • Renal failure and other medical problems
  • Other
Newer Test Targeting Concepts

- Quantitative Risk Estimation According to Risk Factors
- Estimation of Residual Lifetime Risk of Reactivation TB


Lifetime Risk of Reactivation TB by Age (In Non-converters)

Lifetime Risk of Reactivation TB by TB Risk Factor (TST ≥15mm)
Old LTBI Pearls

- No new diagnostic tests in over a hundred years
- 10% lifetime risk of progression to TB disease
- Prior BCG vaccination does not affect subsequent TST results
- A decision to test is a decision to treat

Old LTBI Pearls

- No New TB Tests in 100 years
  - Quantiferon
  - T-Spot.TB
  - Others
- Lifetime Risk of Active TB is 10%
  - Advanced HIV Disease = 60%
  - Old Healed TB = 42%
  - Immunosuppression = 18%

### Annual Rate of Reactivation TB (%)

<table>
<thead>
<tr>
<th>Size of Induration on TST</th>
<th>0-5</th>
<th>6-15</th>
<th>16-30</th>
<th>30-40</th>
<th>&gt;40</th>
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<tbody>
<tr>
<td>Non-converters</td>
<td></td>
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<td>5.5 mm</td>
<td>0.64</td>
<td>0.64</td>
<td>0.13</td>
<td>0.07</td>
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<tr>
<td>10-14 mm</td>
<td>0.19</td>
<td>0.18</td>
<td>0.15</td>
<td>0.16</td>
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<tr>
<td>&gt;25 mm</td>
<td>0.06</td>
<td>0.06</td>
<td>0.14</td>
<td>0.12</td>
<td>0.12</td>
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<tr>
<td>New converters or TB contacts</td>
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<tr>
<td>5.5 mm</td>
<td>0.29</td>
<td>0.66</td>
<td>0.36</td>
<td>0.21</td>
<td>0.12</td>
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<tr>
<td>10-14 mm</td>
<td>0.17</td>
<td>0.13</td>
<td>0.17</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>&gt;25 mm</td>
<td>0.14</td>
<td>0.12</td>
<td>0.34</td>
<td>0.47</td>
<td>0.47</td>
</tr>
</tbody>
</table>
Prior BCG Vaccination Does Affect the TST Result

- Many countries give BCG at birth
- Some give BCG a 2nd and even a 3rd time
- BCG has the greatest effect on TST when given at birth and again as a teenager
- Unfortunately, no one can remember the BCG policies of every other country
- Wouldn’t it be great if there was a website…

www.bcgatlas.org
New Idea: Framework for a TB Spectrum

Active TB disease → Clinical Disease → Disease (Treat LTBI)
LTBI: High Risk for TB → Replication maintained at a subclinical level by the immune system → Active Infection (Treat LTBI)
LTBI: Low Risk for TB → Infection controlled with some bacteria persisting in non-replicating form → Quiescent Infection (Maybe don’t Treat)
LTBI: Zero Risk for TB → Infection eliminated in association with T cell priming → Acquired Immune Response
We can’t find these → Infection eliminated without priming antigen-specific T cells → Innate Immune Response

Old LTBI Pearls

• A decision to test is a decision to treat
• No new diagnostic tests in over a hundred years
• 10% lifetime risk of progression to TB disease
• Prior BCG vaccination does not affect subsequent TST results

New LTBI Pearls

• Test only people you would treat
• IGRAs help with false positive TSTs but still require sophisticated interpretation
• Risk of progression to TB disease should be estimated using clinical risk factors and remaining years of life
• Prior BCG vaccination does affect subsequent TST results <www.bcgatlas.org>
• Need better tools to recognize LTBI patients with high, low, and zero risk for progression to active TB disease
Questions?