Diagnosis Latent Tuberculosis

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Disclosures

- No affiliation or financial relationship with any of the tests or companies mentioned in this presentation
- This presentation does not necessarily represent the official position of the US Centers for Disease Control and Prevention

Case

- 34 yo female born in India
- Came to the US at age 15 on a student visa
  - No screening on immigration
    - Per self report, history TST negative
- Healthy with no other medical problems
- Starting a new job and changing visa to employment visa for lawful permanent residence
- What test would you do?
Tuberculin Skin Test (TST)

**aka PPD**

- Often detectable 2-8 weeks after infection
- **How to read:**
  - Measure induration (not erythema) at 48-72 hours
  - Record millimeters
- Safe and reliable during pregnancy
- Co-administer on same day as live-virus vaccine OR 4-6 weeks after vaccine
Interpreting the TST

<table>
<thead>
<tr>
<th>Induration of &gt;5 mm is considered positive for:</th>
<th>Induration of &gt;10 mm is considered positive for:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induration of &gt;10 mm is considered positive for:</td>
<td></td>
</tr>
<tr>
<td>HIV-infected persons</td>
<td>Recent arrivals (&lt;5 yrs) from high-prevalence areas (Asia, Africa, Russia, Eastern Europe, and Latin America)</td>
</tr>
<tr>
<td>Recent contacts of persons with infectious TB</td>
<td>Injection drug users</td>
</tr>
<tr>
<td>Persons with fibrotic changes on chest radiograph consistent with prior TB</td>
<td>Residents and employees of high-risk congregate settings</td>
</tr>
<tr>
<td>Patients with organ transplants and other immunosuppressed patients (&gt;15 mg/day prednisone)</td>
<td>Persons with conditions that increase risk for progression to TB disease</td>
</tr>
<tr>
<td>Abnormal CXR/TB4</td>
<td>Children</td>
</tr>
</tbody>
</table>

Tuberculin skin test interpretation: False-negative results

- **Host factors**
  - Immunosuppression
  - Recent TB infection (<3 months)
  - Age (newborn, elderly)
  - Infections (viral, fungal, bacterial)
  - Live virus vaccination
  - Overwhelming tuberculosis
  - ESRD
  - Other illness affecting lymphoid organs

- **Technical factors**
  - Tuberculin product (improper storage, contamination)
  - Improper method of administration, reading and/or recording of results


TST Specificity

<table>
<thead>
<tr>
<th>Frequency</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST without BCG</td>
<td>97</td>
</tr>
<tr>
<td>TST with BCG</td>
<td>59</td>
</tr>
<tr>
<td>QFT</td>
<td>96</td>
</tr>
</tbody>
</table>

*Menaeve, Ann Intern Med. 2007

Tuberculin skin test interpretation: False-positive results

- Cross-reactions from atypical mycobacterial infections
- Recent or multiple BCG vaccination
- Misinterpretation of immediate hypersensitivity to tuberculin
- Switching tuberculin products (aplisol > tubersol)

Booster phenomenon

- Response to TST gradually wanes (especially older adults, >55 years)
- Initial TST falsely negative. Subsequent skin testing will be “boosted” due to immunologic recall from the initial test
- May incorrectly be interpreted as a “conversion”
- Consider two-step for initial test of individuals who will be tested on a regular basis or if >55 years age in high risk groups
Case

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- Came to the US at age 15 on a student visa
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- TST 10 mm
- What do you do now?

BCG and TST reactivity

| Reference | Survey location | Year of survey | Age when vaccinated | Interval from vaccination to TST | % of subjects with a TST reaction 

| vaccine | No. 1 | 1965 | Newborn | 1.4 | 3
| vaccine | [8] | No. 16 | 1985 | Newborn | 5 | --
| vaccine | [9] | Person | 1987 | Newborn | 11.20 | --
| vaccine | [10] | New. | 1994 | Newborn | 1 | --
| vaccine | [12] | Southern USA | 1973 | 4-10 | 16 | 52

Menzies D. CID 2000;31:71-74

BCG and TST

- Greater duration between BCG and TST less likely false positive
  - True positive >2 years post-vaccination

- TST reaction ≥20 mm assume true TB infection

- CDC recommendations: Ignore BCG history
  - IGRA recommendations: If either test is positive, individual is infected
Case

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- Came to the US at age 15 on a student visa
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  - Per self report, history TST negative
    - TST 10 mm
- According to BCG Atlas, likely vaccinated
Interferon-Gamma Release Assays (IGRAs)

- QuantiFERON®-TB Gold (QFT)
  - Reported as positive, negative, or indeterminate
- T-SPOT.TB (T-Spot)
  - Reported as positive, borderline, negative, or indeterminate

**QuantiFERON®-TB Gold Test Report of Results**

<table>
<thead>
<tr>
<th>QFT-G Result</th>
<th>Report/Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>TB infection <strong>likely</strong></td>
</tr>
<tr>
<td>Negative</td>
<td>TB infection <strong>unlikely</strong>, BUT cannot be excluded especially if patient has TB signs and symptoms</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Test inconclusive about the likelihood of TB infection. Either: 1. Repeat QFT-G 2. Administer a TST 3. Evaluate quantitative QFT result</td>
</tr>
</tbody>
</table>
Reading QFT-GIT Results

**NIL: 0**  
TB Antigen-NIL: 7.03

**Mitogen-NIL: >10.00**

**TB Antigen-NIL**

<table>
<thead>
<tr>
<th>Interpretation</th>
<th>nil</th>
<th>TB Response</th>
<th>Mitogen Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>nil</td>
<td>&gt;50% nil</td>
<td>nil</td>
</tr>
<tr>
<td>Positive*</td>
<td>nil</td>
<td>30–50% nil</td>
<td>nil</td>
</tr>
<tr>
<td>Indeterminate*</td>
<td>0.7</td>
<td>&lt;30% nil</td>
<td>nil</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>0.7</td>
<td>&lt;50% nil</td>
<td>nil</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>0.7</td>
<td>&lt;80% nil</td>
<td>nil</td>
</tr>
</tbody>
</table>

* (TB Ag - Nil) and assumes appropriate control responses

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T-SPOT Interpretation

<table>
<thead>
<tr>
<th>T Spot TB</th>
<th>Positive</th>
<th>Negative</th>
<th>Borderline</th>
<th>Indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 8 spots*</td>
<td></td>
<td>≤ 4 spots*</td>
<td>5-7 spots*</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>Poor Mitogen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>response</td>
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TST and QFT Specificity

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<tr>
<td>TST without BCG</td>
<td>97</td>
<td>95–99</td>
</tr>
<tr>
<td>TST with BCG</td>
<td>59</td>
<td>46–73</td>
</tr>
<tr>
<td>QFT</td>
<td>96</td>
<td>94–98</td>
</tr>
</tbody>
</table>

Testing Foreign-Born Patients

- Using a test with poor specificity will result in many false-positive results

<table>
<thead>
<tr>
<th>Test</th>
<th>Specificity</th>
<th>False-positive rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>QFT</td>
<td>94 – 98</td>
<td>12%</td>
</tr>
<tr>
<td>TST</td>
<td>46 – 73</td>
<td>73%</td>
</tr>
</tbody>
</table>

BCG vaccinated population

- Pai, Clin Micro Rev, 2014
- Miramontes, PLOS One, 2015

Sources of Variability for QFT-GIT

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  - No screening on immigration
  - Per self report, history TST negative
- TST 10 mm
  - According to BCG Atlas, likely vaccinated
- IGRA indeterminant
IGRA vs. TST

- **Advantages** over TST:
  - Not affected by BCG vaccination
  - Not affected by most non-tuberculous mycobacteria
  - Interpretation is more objective
  - No return visit needed for interpretation of test
  - Patients and providers may lack confidence in TST results

- **Disadvantages** over TST:
  - Blood draw

CDC Guidelines for Selecting a TB Screening Test

- IGRA preferred for:
  - People with poor rates of return for TST reading
  - BCG vaccinated individuals

- TST preferred for children under the age of 5 years

What about doing both tests?

- If the initial test is negative and:
  - High risk of infection, progression, or poor outcomes (HIV positive, <5 years of age, immunocompromised)
  - High clinical suspicion of active TB

- If the initial test is positive and:
  - Need for additional evidence to encourage compliance
  - Healthy person with low risk of both infection and progression

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- TST 10 mm
  - According to BCG Atlas, likely vaccinated
- IGRA indeterminant
- Repeat IGRA positive (TB antigen – NIL = 3.45)

Diagnosing Latent TB Infection

- TSTs and IGRA cannot distinguish between latent TB infection and active TB disease
- Active TB disease must always be ruled out

Summary

- Either IGRA or TST can aid in the diagnosis of latent TB infection
- Neither test can distinguish between latent TB infection and active TB disease
- IGRA have advantages over TST in certain situations
Questions
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The findings and conclusions in this presentation are those of the presenter and do not necessarily represent the views of CDC.