Focus on LTBI October 17, 2017

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
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Case

- 34 yo female born in India
- Came to the US at age 15 on a student visa
- Healthy with no other medical problems
- Starting a new job and is required to get TB clearance
- What test would you do?
Testing for LTBI
Low, intermediate and high risk adults

- **IGRA preferred** over TST for individuals who
  - Have a history of BCG vaccination
  - Are unlikely to return to have their TST read

- TST if IGRA is not available, too costly, or too burdensome

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**Tuberculin Skin Test (TST)**
aka PPD
Tuberculin Skin Test (TST)

- How to read:
  - Measure induration (not erythema) at 48-72 hours
  - Record millimeters
- Often detectable 2-8 weeks after infection
Interpreting the TST

- ≥ 5mm for immunosuppressed including HIV, recent contacts
- ≥ 10mm for all others with TB risk

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></th>
<th>Specificity</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<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>
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**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

- Initial TST negative. Subsequent skin testing positive or
  - Response to TST gradually wanes
  - Due to immunologic recall from the initial test

- May incorrectly be interpreted as a “conversion”

- Two-step for initial test if serial screening or if >55 years age in high risk groups
Case

- 34 yo female born in India
- Came to the US at age 15 on a student visa
  - No screening on immigration
  - Required to get TB screening for new job

- TST 10 mm
- What do you do now?
Case

- 34 yo female born in India
- Came to the US at age 15 on a student visa
  - No screening on immigration
  - Required to get screening for new job
- TST 10 mm
- According to BCG Atlas, likely vaccinated
Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children

Unlikely to be infected but testing **required**.

A **second** test if the initial is **positive**
- Person is considered infected if **both** tests are positive.
- 2010 recommendations: if **either** test is positive, individual is infected

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**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
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IGRA

![Diagram of IGRA process]

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

### QuantiFERON®-TB Gold Test

#### Report of Results

<table>
<thead>
<tr>
<th>QFT-G Result</th>
<th>Report/Interpretation</th>
</tr>
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<tbody>
<tr>
<td>Positive</td>
<td>TB infection <strong>likely</strong></td>
</tr>
<tr>
<td>Negative</td>
<td>TB infection <strong>unlikely, BUT</strong> 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**

<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>Any</td>
<td>≥0.35 IU/ml and ≥50% of Nil</td>
<td>Any</td>
</tr>
<tr>
<td>Negative‡</td>
<td>≤0.7</td>
<td>&lt;0.35 IU/ml</td>
<td>≥0.5</td>
</tr>
<tr>
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<td></td>
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### T-SPOT Interpretation

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<tr>
<td>T Spot TB</td>
<td>≥ 8 spots*</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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* (TB Ag - Nil) and assumes appropriate control responses

#### T-Spot Test

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<td>1. Repeat T-Spot</td>
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<td>2. Administer a TST</td>
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TST and QFT Specificity

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Testing Foreign-Born Patients

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

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<th>Test</th>
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<th>False-positive rate</th>
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<td>94 – 98</td>
<td>12%</td>
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<td>TST</td>
<td>46 – 73</td>
<td>73%</td>
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BCG vaccinated population

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

- 34 yo female born in India
- Came to the US at age 15 on a student visa
  - No screening on immigration
  - Screening required for new job
- TST 10 mm
  - According to BCG Atlas, likely vaccinated
- IGRA indeterminate

Sources of Variability for QFT-GIT

Pai, Clin Micro Rev, 2014
High risk adults

- Conduct second test if initial negative for individuals at high risk of progression
  - Not based upon empirical evidence but clinical rationale.
  - Increases sensitivity in situation where missing LTBI has serious consequences
- Person is considered infected if either test is positive.

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

- TSTs and IGRAs 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

- IGRAs have advantages over TST in certain situations
The findings and conclusions in this presentation are those of the presenter and do not necessarily represent the views of CDC.