IGRA Use in a Local Public Health Setting

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Disclaimer

- We have done no research for companies
- We have not received funding from companies
- Use QuantiFERON®-Gold In Tube; only available IGRA without shipping samples out of state
Objectives

- Describe the difference between tuberculosis skin tests and IGRAs (Interferon-Gamma Release Assays)
- List three benefits of using IGRAs in contact investigations and for certain populations
Meeting the Challenge of Tuberculosis

- Diagnosis TB infection and disease is a primary care issue....
- Preventing TB is a primary care issue....
- Know the TB status of your *at risk* patients
  - Not just medical/social history
  - Black box warning on current medications
- Ensure evaluation and appropriate treatment
  - Decision to test is a decision to treat
Meeting the Challenge of LTBI

- Latent TB Infection should be treated as a condition in itself which is a precursor to a serious and potentially fatal disease.

- Much the same way we treat hypertension as a condition in itself because it significantly heightens risk of heart disease, renal failure, and stroke or place infants in car seats because of the significant risk of injury without them, so should we approach latent TB infection.

- While the condition in itself is asymptomatic, the risks assumed by ignoring it are substantial.

Source: Carey Jackson, MD. Internal Medicine. International Clinic, Harborview Medical Center, Seattle, Washington
Methods for detecting *M. tb* infection

- Mantoux tuberculin skin test (TST)
- IGRAs
  - QuantiFERON-TB Gold In-Tube (QFT-GIT)® (2007)

- These tests do not exclude LTBI or TB disease
- Decisions about medical management should include other information, and not rely solely on TST/TGRA results
TB Screening with TST & IGRA

- Tests should not be mixed
  - If baseline/annual is TST then TST should be done for post-exposure screening
- Negative reaction to either test does not exclude active disease
  - Some data suggests IGRAs may not be a good predictor of active disease
  - If suspected, CXR and consider sputum
441A.192 “Tuberculosis screening test”
Means any tuberculosis screening test that has been
- Approved by the Food and Drug Administration; and
- Endorsed by the Centers for Disease Control and Prevention

441A.350 Health care provider to report certain cases and suspected cases within 24 hours of discovery.
- Active or suspected active disease
- Not solely positive TST or IGRA results
TST Considerations

- 100+ years old
- Staff must be trained in correct placement and measurement
  - Wheal must form upon injection of PPD solution
  - Measure induration only, not redness
  - Cutoff depends on individual risk factors
  - Must be recorded in millimeters
- Boosting
- Concerns abound about lack of sensitivity and specificity resulting in false positive and false negative results
## Factors Affecting TST Reaction

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Possible Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>False-positive</td>
<td>• Nontuberculous mycobacteria</td>
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<tr>
<td></td>
<td>• BCG vaccination</td>
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<tr>
<td></td>
<td>• Problems with TST administration</td>
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<tr>
<td>False-negative</td>
<td>• Anergy</td>
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<td>• Viral, bacterial, fungal coinfection</td>
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<td></td>
<td>• Recent TB infection</td>
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<td></td>
<td>• Very young age; advanced age</td>
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<td></td>
<td>• Live-virus vaccination</td>
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<td></td>
<td>• Overwhelming TB disease</td>
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<td>• Renal failure/disease</td>
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<td>• Lymphoid disease</td>
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<td>• Low protein states</td>
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<td>• Immunosuppressive drugs</td>
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<td>• Problems with TST administration</td>
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</table>
Interferon Gamma Release Assays (IGRAs)

- Detect *M. tb* infection by measuring immune response in blood
- Cannot differentiate between TB and LTBI
- Use in place of, not in addition to, TST
- Especially preferred when testing persons
  - Who might not return for TST reading
  - Who have received BCG vaccination
- Generally not used in children <5 years
IGRAs

- Specific antigens: ESAT6 and CFP10
  - Found in all *M. tb* complex organisms
  - Not present in BCG
  - Not present in most non-TB mycobacteria (including MAI)
- If individual has been TB infected, memory CD4 cells should react to ESAT 6 and CFP10
- ESAT 6/CFP10 release interferon gamma that can be measured
  - Serum level or by staining cells
- Magnitude of the measured INF-γ cannot be correlated to stage or degree of infection
<table>
<thead>
<tr>
<th>Tuberculosis complex</th>
<th>Antigens</th>
<th>Environmental strains</th>
<th>Antigens</th>
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<tbody>
<tr>
<td></td>
<td>ESAT-6</td>
<td>CFP-10</td>
<td>ESAT-6</td>
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<td></td>
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<td>CFP-10</td>
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<tr>
<td><strong>M tuberculosis</strong></td>
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<td>M abcessus</td>
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<td><strong>M africanum</strong></td>
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<td>M avium</td>
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<td><strong>M bovis</strong></td>
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<td>M branderi</td>
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<td>BCG Substrain</td>
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<td>M celatum</td>
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<td>pasteur</td>
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<td><strong>M szulgai</strong></td>
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<td><strong>M terrae</strong></td>
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QuantiFERON®-Gold In Tube

### Stage 1 – Blood collection and harvesting

- **Option 1:** Shipment of the blood collection tubes within 16 hours to a laboratory prior to incubation
- **Option 2:** Shipment of blood collection within 3 days after incubation to the laboratory
- Possibility to batch samples

3x1mL blood collection

Incubation at 37°C for 16-24 hours

Centrifuge tubes for 5 min

IFN-γ stable refrigerated for at least 8 weeks.
QuantiFERON®-Gold In Tube

- Stage 2 – Interferon-γ ELISA

  - Add plasma and conjugate
  - Incubate for 120min at room temperature
  - Wash and add substrate
  - Add stop-solution and read absorbance
  - Software calculates and prints results

- Easy “Standard”-Elisa
- Software supplied free-of-charge from Cellestis
- No need for new equipment
# QuantiFERON®-Gold In Tube

<table>
<thead>
<tr>
<th>Nil (IU/mL)</th>
<th>TB Antigen minus Nil (IU/mL)</th>
<th>Mitogen minus Nil (IU/mL)</th>
<th>RESULT</th>
<th>REPORT/INTERPRETATION</th>
</tr>
</thead>
</table>
| ≤ 8.0       | ≥ 0.35 and ≥ 25% of Nil value | Any                      | POSITIVE | *M. tuberculosis* infection likely
|             | < 0.35 OR ≥ 0.35 and < 25% of Nil value | ≥ 0.5 | NEGATIVE | *M. tuberculosis* infection unlikely
|             |                                           | < 0.5 |          | No ESAT-6 or CFP-10 responsiveness detected |
| > 8.0       | Any                                       | Any | INDETERMINATE | MTB infection status cannot be determined as a result of impaired immunity and/or incorrect performance of the test |

- ≥ 0.35 and ≥ 25% of Nil value
- < 0.35 OR ≥ 0.35 and < 25% of Nil value
- ≥ 0.5
- < 0.5
- > 8.0

*Nil value* refers to the baseline level of immunological response observed in the absence of stimulation with specific antigens.
T-Spot® TB

- **Step 1 – Preparation of cells**
  - Blood collected into Vacutainer CPT™ tube
  - Tube centrifuged
  - Lymphocyte band removed
  - Cells washed & counted
  - Cells added to 96-well plate
  - Antigens added to wells
  - Incubate overnight
T-Spot®.TB

- Step 2 – Forming spots
  - Plate washed
  - Add detection reagent for 60 minutes
  - Plate washed
  - Add substrate
    - Spots in 7 minutes
  - Plate washed and dried
T-Spot®. TB

• Step 3 – Counting spots
  ○ Count spots by “eye” using a magnifying glass or dissecting microscope
  ○ Alternatively use an automated elispot reader
    ▶ Plate placed in reader and read automatically
    ▶ Computer stores all images, a tamperproof audit log, and calculates the number of spots in each well
    ▶ Camera and analysis settings set automatically

Above: Automated T-SPOT plate reader
T-Spot®. TB

Nil Control Count

≤ 10 spots

Positive (Mitogen) Control

> 10 spots

Invalid Result (Repeat test)

≥ 20 spots

Either (Panel A-Nil) or (Panel B-Nil) ≥ 8 spots

Positive Result

The highest of (Panel A-Nil) or (Panel B-Nil) is 5, 6, or 7 spots

Borderline (equivocal) Result (Repeat test)

Both (Panel A-Nil) and (Panel B-Nil) ≤ 4 spots

Negative Result

< 20 spots

Either (Panel A-Nil) or (Panel B-Nil) ≥ 8 spots

Positive Result

The highest of (Panel A-Nil) or (Panel B-Nil) is 5, 6, or 7 spots

Borderline (equivocal) Result (Repeat test)

Both (Panel A-Nil) and (Panel B-Nil) ≤ 4 spots

Invalid Result (Repeat Test)
General Recommendations for IGRA Use

May be used in place of TST to test recent contacts of infectious TB

- Detect *M. tb* infection with greater specificity than TST
- Data are limited on ability to predict subsequent TB
- In contact investigations, confirm negative via retest 8-10 weeks post exposure
- Use same test for repeat testing to reduce misclassification errors
General Recommendations for IGRA Use

- May be used for periodic screening (health care workers)
- IGRAs do not boost subsequent test results
- Administered with one patient visit
- Results from both IGRA and TST may be useful when initial test is
  - Negative, and patient has high risk of TB infection or disease
  - Unclear or indeterminate
Immigration Screening

Estimated TB incidence rates, 2010

Immigration Screening

- HHS/CDC regulations require all immigrants/refugees coming to USA be screened for TB (also adoptees)
- Specific testing requirements are based on age and country of origin
- Prior receipt of BCG does not change screening requirements or required actions
SNHD Immigration Screening

- Applicants require medical history, physical examination, TST or IGRA, and CXR. If suggestive of TB 3 sputum specimens should be collected.
- Release for travel dependent on sputum results
- If active TB, treatment initiated prior to travel release & must be non-communicable to travel
- Re-evaluated upon arrival in USA (SNHD)
- Adults receive IGRA, CXR, 3 sputum specimens
- Children receive IGRA (PPD if <5) and CXR
# Immigration Screening

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immigrants completing evaluation process</td>
<td>307</td>
<td>353</td>
</tr>
<tr>
<td>Latent TB Infection</td>
<td>253 (82.4%)</td>
<td>249 (70.5%)</td>
</tr>
<tr>
<td>Active Disease</td>
<td>4 (1.3%)</td>
<td>4 (1.1%)</td>
</tr>
<tr>
<td>No treatment needed (not infected or active)</td>
<td>50 (16.3%)</td>
<td>100 (28.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTBI started treatment</td>
<td>253 (100%)</td>
<td>249 (100%)</td>
</tr>
<tr>
<td>LTBI completed treatment</td>
<td>89* (35.2%)</td>
<td>100 (40.2%)</td>
</tr>
<tr>
<td>Not completed (Reasons)</td>
<td>20* (7.9%)</td>
<td>12 (4.8%)</td>
</tr>
<tr>
<td>Death</td>
<td>1* (0.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>5* (2.0%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Moved: follow-up unknown</td>
<td>14* (5.5%)</td>
<td>11 (4.4%)</td>
</tr>
</tbody>
</table>

*Completion data is year to date comparison, not total number complete*
Immigration Screening

- Fewer QFT positives
- Similar LTBI treatment acceptance rate
- Higher rate of completion
  - Greater believability of blood test vs. TST
  - Intensified follow-up efforts on those that are late for refills
IGRA Use in SNHD Contact Investigations

- Research shows exposure characteristics associated with increased risk of infection correlate better with IGRAs than TST
- High percentage of foreign born active cases = high percentage of contacts with history of BCG vaccination
- Many contacts see blood tests as more reliable
  - "My arm always does that when I go to jail."
- When clients have more faith in the test they are more likely to accept LTBI treatment
IGRA Use in SNHD Contact Investigations

- One step test eliminates need for return reading
  - If needing 8-10 week follow-up, cuts total number of visits from 4 to 2
- Reduces time DIIS spends locating those that do not return for reading
  - Allows more time for further contact identification and LTBI treatment follow-up
Conclusions

- IGRAs are highly specific resulting in a lower number of positive results compared to TST
  - No evidence to date that cases are being missed
- Blood-based TB testing is a superior surveillance tool with more believable results
- IGRAs are most useful in nonadherent and BCG-vaccinated populations
- IGRAs may remain positive even after appropriate treatment of active or latent TB
- NEVER use an IGRA to rule out active disease…it’s another tool from the toolbox
References

- Centers for Disease Control and Prevention. Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Settings, 2005. MMWR 2005;54(No. RR-17)
- Centers for Disease Control and Prevention. Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis; Recommendations from the National Tuberculosis Controllers Association and CDC, and Guidelines for using the QuantiFERON®-TB Gold test for Detecting *Mycobacterium tuberculosis* infection, United States. MMWR 2005;54 (No. RR-15)
- World Health Organization. Global Tuberculosis Control 2011