Can the Interferon Gamma Release Assays Replace the Tuberculin Skin Test: Updates and Challenges?

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Disclosures

• No financial conflicts
• Current CDC funding to conduct laboratory quality control and assessment for the CDC-funded TB Epidemiologic Studies Consortium (TBESC)
• Multiple CDC and collaborative studies in which Qiagen (Celestis) and Oxford Immunotec (OI) provided discounted kits to investigate PI initiated projects.
• Director of a CLIA/CAP certified clinical lab at Houston Methodist Hospital which runs the QuantiFERON and/or T-SPOT. TB assays per client request.
• Non-paid IGRA consultant for the Heartland National TB Center
• Two children enrolled in ACHA affiliated colleges
Objectives

- Overview
  - TB epidemiology and spectrum
  - ACHA targeted testing 2014 guidelines and their assessment in the light of TB epidemiology
  - CDC Interferon Gamma Release Assays (IGRA) guidelines
- Comparison of platforms
- Variability
- Conclusions

TB Epidemiology and Spectrum of Disease
Tuberculosis (TB) in the World and U.S.

- **Worldwide, World Health Organization (WHO) estimates**: 1.
  - 2012 - 8.6 million cases, (530,000 <15 years) 1.3 million deaths (25% HIV)
  - ≈ 450,000 multidrug (MDR)-TB cases
  - ≈ 2 billion TB infected individuals

- **Active TB surveillance began in the U.S. by the Public Health Service (PHS/CDC) in 1953**: 2.
  - 1953 - 84,304 cases, incidence 52.6/100,000.
  - 2013 - 9,588 cases, incidence 3.0/100,000.

- **In the U.S., burden of disease is in stigmatized sub-populations**: 1.
  - Foreign-born (FB): 64.6% of U.S. TB cases, 15.6/100,000 population
  - 54% of cases - Mexico, Philippines, India, Vietnam, and China

- **Ethnic inequalities**
  - Asians: (90% FB), Blacks (40% FB) and Hispanics (75% FB)
  - Homeless - 5.7/100,000
  - HIV - 6.8% TB cases co-infected

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Natural History (Spectrum) of TB Infection

4-6 Weeks
- Elimination of Bacteria
- Dendritic Cell (Innate Response)
- T Cell (Adaptive Response)
- Inability to Control Bacteria

Years-Decades
- Elimination of Bacteria
- Initial Immune Control of Bacteria
- Granuloma
- Reactivation
- Latent TB
- Active TB
- Active TB
- Containment
- Life-long Containment

Control of TB through Identification and Treatment of Infected Individuals

TB
- US - 9,588

LTBI
- US - 11 million
- 4% population

Modified from Oxford Immunotec, 2009
ACHA 2014 Guidelines
(Are we all on the same page?)

ACHA Guidelines

Tuberculosis Screening and Targeted Testing of College and University Students

Purpose
Screening and targeted testing for tuberculosis (TB) is a key strategy for controlling and preventing TB infection on college and university campuses. The American College Health Association (ACHA) recommends that institutions of higher education establish a TB screening program for students and employees. The primary objective of TB screening and targeted testing is to identify infected students who are contagious or require treatment. TB screening has been shown to reduce the potential spread of TB to others.

The ACHA Tuberculosis Screening and Targeted Testing of College and University Students Guidelines provide recommendations for TB screening and targeted testing programs.

Screening through questionnaire
Testing through LTBI diagnosis
- Tuberculin Skin Test (TST) or
- Interferon Gamma Release Assay (IGRA)
ACHA 2014 Guidelines – Screening Questions

Contact with person known or suspected of having TB?

Where you born in a high (and middle) incidence country?

Frequent or prolonged visits to high (and middle) incidence countries?

Resident or employee of a high-risk congregational setting (correctional, extended care facility, homeless shelter)?

Volunteer or HCW serving high risk populations

Member of a group having an increased incidence of LTBI or active TB disease (underserved, low income, and alcohol or drug abuse)

Estimated TB Incidence, 2012

Estimated TB incidence rates, 2012

(Global Tuberculosis Report 2013. WHO. 2013)
ACHA 2014 Guidelines – Screening Questions

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TABLE 1

**Persons at Higher Risk for Exposure to and/or Infection with *M. tuberculosis***

- Close contacts of persons known or suspected to have active TB disease
- Foreign-born persons from areas that have a high incidence of active TB disease (e.g., Africa, Asia, Eastern Europe, Latin America, and Russia)
- Persons who visit areas with a high prevalence of TB disease, especially if visits are frequent or prolonged
- Residents and employees of high-risk congregational settings (e.g., correctional facilities, long-term care facilities, and homeless shelters)
- Health-care workers who serve clients who are at increased risk for active TB disease
- Populations defined locally as having an increased incidence of latent *M. tuberculosis* infection or active TB disease, possibly including medically underserved, low-income populations, or persons who abuse drugs or alcohol
- Infants, children, and adolescents exposed to adults who are at increased risk for latent tuberculosis infection or active TB disease
Harris County TB Cases 1995-2004


Source: Houston Tuberculosis Initiative & United States 2000 Census

Average Incidence/Kernel Density Overlay

Feske, ML. Tuberculosis (Edinb), 2011; 91:S24-S33.
### TABLE 1

**Persons at Higher Risk for Exposure to and/or Infection with *M. tuberculosis*\(^2\)**

- Close contacts of persons known or suspected to have active TB disease
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- Infants, children, and adolescents exposed to adults who are at increased risk for latent tuberculosis infection or active TB disease

### TABLE 2

**Persons at Increased Risk for Progression of LTBI to TB Disease\(^3\)**

- Persons infected with HIV;
- *Children younger than 5 years of age*;
- Persons who were recently infected with *M. tuberculosis* (within the past 2 years);
- Persons with a history of untreated or inadequately treated TB disease, including persons with fibrotic changes on chest radiograph consistent with prior TB disease;
- Persons who are receiving immunosuppressive therapy such as tumor necrosis factor-alpha (TNF) antagonists, systemic corticosteroids equivalent to greater than 15 mg of prednisone per day, or immunosuppressive drug therapy following organ transplantation;
- Persons with silicosis, diabetes mellitus, chronic renal failure, leukemia, or cancer of the head, neck, or lung;
- Persons who have had a gastrectomy or jejunoileal bypass;
- Persons who weigh less than 90% of their ideal body weight;
- Cigarette smokers and persons who abuse drugs and/or alcohol; and
- Populations defined locally as having an increased incidence of disease due to *M. tuberculosis*, including medically underserved, low-income populations.
Pediatric TB Exposure – Foreign Born Connection

• Pediatric TB is the “litmus paper” of TB transmission in a community

• Two-thirds of all children and adolescents with TB in the U.S. had at least 1 foreign-born parent, and only ¼ of children with TB lacked an international connection

• CDC population-based project of children <5 years of age, in 22 jurisdictions in the U.S.
  • U.S.-born (TB = 0.75/100,000)
  • Foreign-born (TB = 24.03/100,000)
  • U.S.-born with 1 FB parent (TB = 4.81/100,000)

1 Marquez, L et al. PJID.2012. 31:e1144-7

ACHA 2012 Guidelines
http://www.acha.org/Publications/docs/ACHA_Tuberculosis_Screening_April2014.pdf

<table>
<thead>
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HOUSTON Methodist
LEADING MEDICINE
CDC 2010 IGRA Guidelines
(IGRAs – Here we go ready or not)

Historical Perspective - FDA and CDC IGRA Statements

2001: QFT (1st generation) – FDA approved
   Confirmation of QFT with TST prior to LTBI treatment
2005: QFT –Gold (2nd generation) – FDA approved
2005: CDC Guidelines – MMWR 2005:54(RR-15); 49-55
   QFT-G can be used in all circumstances where TST used
2007: QFT – Gold In-tube (3rd generation) – FDA approved
2008: T-SPOT. TB FDA approved
2008: CDC convenes expert panel (n = 27) to review scientific
evidence, provide findings and opinions for guidelines
2010: CDC Guidelines – MMWR 2010:59(RR-5); 1-26
2010: T-SPOT. TB Xtend FDA approved
Updated guidelines regarding the use of Interferon Gamma Release Assays (IGRAs)

- TST or IGRAs should not be used for testing persons who have a low likelihood of *Mtb* infection and of progression to TB disease if infected
- IGRAs may be used in place of tuberculin skin test (TST) in all situations, including contact investigation
- In certain situations IGRAs are the preferred test

*MMWR 2010; 59 - RR5: 1-26

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Updated guidelines regarding the use of Interferon Gamma Release Assays (IGRAs)

- Selection of the most suitable test should be based on the reasons and the context for testing and the assay availability and cost
  - IGRA is preferred for testing persons who seem unlikely to return for TST reading
  - IGRA is preferred for testing BCG vaccinated
  - IGRA is preferred for testing persons with a low likelihood of both *Mtb* infection and of progression to TB disease if infected

*MMWR 2010; 59 - RR5: 1-26
Updated guidelines regarding the use of Interferon Gamma Release Assays (IGRAs)

- IGRA should be used in place of (and not in addition to) TST. **Dual testing not recommended**
- Both the qualitative and quantitative assay measurements should be reported, together with the criteria for test interpretation
- TST is preferred when testing children younger than 5 years of age

Comparison: TST vs. IGRAs
(What’s best for my patients and practice)
### TST and IGRA Comparison
**Advantages / Benefits**

<table>
<thead>
<tr>
<th>TST</th>
<th>IGRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple, low-tech assay; No lab and no major equipment needed</td>
<td>Require fewer visits than TST for test completion (1 vs. 2)</td>
</tr>
<tr>
<td>PPD shortage over the last 9 months; Manufactureres R&amp;D</td>
<td>No potential boosting response, results with in 24/48 hours</td>
</tr>
<tr>
<td>Administered by trained HCW. Effect of BCG minimal if vaccine given at birth and not repeated</td>
<td>No cross-reactivity with BCG</td>
</tr>
<tr>
<td>Cohort studies and systematic reviews show INH prevention therapy (IPT) is effective in TST+</td>
<td>Limited data (developed countries), less cross-reactivity than TST with NTM</td>
</tr>
</tbody>
</table>

**TST and IGRA Comparison**
**Risks or undesired effects**

<table>
<thead>
<tr>
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<th>IGRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>False negative reactions due to infections, live virus vaccines and other factors</td>
<td>Require phlebotomy - challenging in certain subpopulations (e.g. children)</td>
</tr>
<tr>
<td>False positive reactions – BCG vaccination and NTMs; rare adverse reactions</td>
<td>Blood-borne pathogen exposure risk, no BCG cross-reactivity</td>
</tr>
<tr>
<td>Interpretation of serial TSTs complicated by boosting, conversions and reversion</td>
<td>Interpretation of serial IGRAAs complicated by frequent conversions and reversion</td>
</tr>
<tr>
<td>Inter- and intra-reader variation; 48-72 hours needed for read</td>
<td></td>
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</tbody>
</table>
### TST and IGRA Comparison

#### Client preferences

<table>
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<th>TST</th>
<th>IGRA</th>
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</thead>
<tbody>
<tr>
<td>Pt. may prefer to avoid visible TST skin reaction</td>
<td>Pt. may prefer to avoid blood draw (culture /technical reasons)</td>
</tr>
<tr>
<td>Pt. may prefer not to come back for 2nd visit (reading / test results)</td>
<td>Pt. with prior BCG may not trust TST results and prefer IGRA</td>
</tr>
<tr>
<td>Pt. with prior BCG may not trust TST results and may be reluctant to accept IPT</td>
<td></td>
</tr>
<tr>
<td>Pt. may self-read TST results erroneously.</td>
<td></td>
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</tbody>
</table>

#### Resource Implications

<table>
<thead>
<tr>
<th>TST</th>
<th>IGRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct costs are cheaper; indirect costs – more expensive compared to IGRA</td>
<td>Well-equipped lab that performs either IGRA needed. Lab quality control and assurance critical</td>
</tr>
<tr>
<td>No lab required, but established program to train staff to place and read TST results</td>
<td>Staff blood-borne pathogens training necessary</td>
</tr>
<tr>
<td>Staff training need to minimize reading errors and variability (within/between reader variability)</td>
<td>Well trained staff needed, possible false positive conversions during serial testing</td>
</tr>
<tr>
<td>Refrigerated PPD storage needed, standardized PPD is used</td>
<td>Cold transport chain and careful handling and processing of blood.</td>
</tr>
</tbody>
</table>
Published data – 15 studies consisting of 6615 HCWs (more to come)

Variability:
- Conversions (22.1 – 71.4%)
- Reversions (0.7 – 14.4)

Most variability occurs around assay cut points

Ringshausen FC. J Occ Med Tox 2012:7:6

(PLoSone 2009; 4(12): e8517)
Serial Testing – HCW Study

Screened 2767

Enrolled 2563

Baseline testing complete 2495

Main analysis group 2418

18-month completion 2122

No TB cases Reported

204 Not Enrolled (86 ineligible, 118 declined)

68 Baseline testing Not complete

77 Prior h/o LTBI treatment

296 did not have 18m visit

Baseline testing complete 2495 (83% of enrolled, 88% of main analysis group)

77 Prior h/o LTBI treatment

296 did not have 18m visit

Structured Interview, then Blood drawn for IGRA’s, then Placement of TST (read 48-72 hours later)

all participants

Baseline 6 months 12 18

A B C

Sub-studies
A, impact of TST on IGRA’s
B, repeatability
C, reproducibility

Blood drawn for IGRA’s

* Time point A was 7 to 21 days after baseline.
For repeatability (B), two sets of tubes were drawn two weeks apart.
For reproducibility (C), two sets of tubes were drawn during a single blood draw.

AJRCCM. 2014; 189:77-87
Summary Points: Conversions (1)

- Proportion of participants who underwent a “conversion” from Neg to Pos was higher when assessed by either IGRA than by the TST
- Approximately 75% of IGRA conversions were transient (after 6 months and no treatment)
- Compared with transient T-SPOT converters, stable T-SPOT converters had higher median (Ag-nil) values at conversion (10 vs 13)
- Conversions (by any test method) were not associated with TB exposure variables assessed

Summary Points: Conversions (2)

- The likelihood of IGRA conversion increased as the baseline quantitative result increased toward the positivity cut-point, but proportionately few conversions were accounted for by individuals with baseline quantitative results just below the cut point.
- Test variability explained only a small proportion of apparent IGRA conversion (QFT: 5.2% – 7.5%; T-SPOT: 6.0% - 8.1%)
- In a sub-study in which QFT plasma were rerun immediately, half of the apparent conversions were not conversions on the re-runs
- Similar proportions of participants had IGRA “conversions” over intervals of 0 days, 2 weeks, and 6 months
Conclusion

- For BCG-vaccinated individuals, use of an IGRA at the time of initial LTBI testing will reduce the number of LTBI diagnoses compared with using TST alone (the assumption is that IGRA will correctly label as LTBI-negative those with a TST that is positive due to BCG sensitization, although there is no data available to support or refute this assumption).

- In this group of HCWs undergoing periodic LTBI screening, a large % of apparent IGRA conversions did not represent a true change in biological status with respect to MTB infection.

- Strategies for discerning “true” vs “false” IGRA conversions are required; until then caution should be used in interpreting a single newly positive test in an individual with one or more prior negative tests.
  - For QFT, doing repeat ELISA on the existing stimulated plasmas may be helpful.
  - Repeating the IGRA should be considered, although we did not formally assess this as a strategy.

Serial Testing HCWs – QFT Algorithm

- The expected false reversion rates is dependent on the test sensitivity, while the conversion rate is more dependent on specificity.

- Lower prevalence of infection and higher test sensitivity increase reversion rates, while higher specificity and higher infection prevalence increased conversion rates.


Ringhausen J Occ Med Tox 2012
QFT Quality Control Procedures in the Graviss Lab (1)

- Assay results with the following conditions are repeated to ensure accurate results are reported:
  - Any negative test where the Nil value is >.15 IU/mL AND the test would be positive if the Nil was lower
  - Any test that is indeterminate due to a high Nil value or a low Mitogen value
  - Any test that is positive
- Negative tests are not repeated

QFT Quality Control Procedures in the Graviss Lab (1)

- If the repeat results and the original results match, the results are reported.
- If the repeat results and the original results do not match
  - The test is repeated in duplicate.
  - If the test results are still inconclusive, the submitter is notified and a redraw is recommended.
Normal Expected Variability of Borderline TB Response
Take home message

- TST can be used in U.S. – born students, if return can be guaranteed. Availability, standardization?
- IGRA preferred in foreign-born populations or immunocompromised
- Choice of IGRA depends on multiple factors.
  - Lab and their relationship with you, proximity, communication, QC, and results provided (qualitative and quantitative)
  - $$$$$$ (weigh direct vs indirect costs)

Questions?

HMRI Lab

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Justin Lew, BS
Ngan Ha, BS
Sophie Im, BS
Kim Truong, BS