American College Health Association (ACHA)

TB Screening and Targeted Testing Recommendations

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Objectives for ACHA TB Recommendations (Part 1)

- Review the American College Health Association’s recommendations for TB screening of university students.
- Discuss ACHA’s recommendations for targeted testing of selected “at risk” students and what makes them at risk.
- Distinguish between latent TB vs. active TB disease
- Discuss the effect BCG vaccine has on TB skin testing
- Compare the new Interferon Gamma Release Assay (IGRA) testing options with Mantoux (PPD) testing to see how they may be best utilized
ACHA Recommendations

- Screen all incoming students with a questionnaire to identify TB risk
- Targeted testing of “at risk” students (mostly internationals) with PPD or IGRA
- Distinguish between latent and active disease in students with a positive test
- Offer follow-up care for both latent and active cases
TB screening similar to TSA screening

- We know highest risk groups on campus (mostly international students from countries with > 20 TB cases per 100,000)
- We need an evidence-based approach to accomplish goal in the most fair way
- So everybody needs to be screened but everybody doesn’t need to be tested (U.S. is a low incidence country)
- Goals: protect campus health and reduce TB burden in U.S.
Who To Test?
Sample TB Screening Questionnaire

Tool for Institutional Use to be Completed by Incoming Students (ACHA)
Tuberculosis (TB) Screening Questionnaire (short version)

Have you ever had a positive TB skin test? Yes  No
Have you ever had close contact with anyone who was sick with TB? Yes  No
Were you born in one of the countries listed below and arrived in the U.S. within the past 5 years? (If yes, which country) Yes  No
Have you ever traveled to/in one or more of the countries listed below? (If yes, please CHECK the country/ies)
Yes  No
Have you ever been vaccinated with BCG? Yes  No

If the answer is YES to any of the above questions, [insert your college/university name] requires that a health care provider complete a tuberculosis risk assessment (to be completed within 6 months prior to the start of classes).
If the answer to all of the above questions is NO, no further testing or further action is required.
Tuberculosis (TB) Risk Assessment (who needs to be tested?)

Persons with any of the following are candidates for either Mantoux tuberculin skin test (TST) or Interferon Gamma Release Assay (IGRA), unless a previous positive test has been documented:

**Risk Factors - including both population and medical risks**

- Recent close contact with someone with infectious TB disease  
  - Yes  
  - No
- Foreign-born from (or travel to/in) a high-prevalence area (e.g., Africa, Asia, Eastern Europe, or Central or South America)  
  - Yes  
  - No
- Fibrotic changes on a prior chest x-ray suggesting inactive or past TB disease  
  - Yes  
  - No
- HIV/AIDS  
  - Yes  
  - No
- Organ transplant recipient  
  - Yes  
  - No
- Immunosuppressed (equivalent of > 15 mg/day of prednisone for >1 month or TNF-α antagonist)  
  - Yes  
  - No
- History of illicit drug use  
  - Yes  
  - No
- Resident, employee, or volunteer in a high-risk congregate setting (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities)  
  - Yes  
  - No
- Medical condition associated with increased risk of progressing to TB disease if infected [e.g., diabetes mellitus, silicosis, head, neck, or lung cancer, hematologic or reticuloendothelial disease such as Hodgkin’s disease or leukemia, end stage renal disease, intestinal bypass or gastrectomy, chronic malabsorption syndrome, low body weight (i.e., 10% or more below ideal for the given population)]  
  - Yes  
  - No
Population Risks vs. Medical Risks

- Population risk: belonging to a group with higher risk of acquiring TB
- Medical risk: factors that place an individual at higher risk from progressing from latent TB infection to active disease.
Population Risks for TB

- **Foreign-born persons** who have immigrated within the last 5 years from countries with high incidence of TB disease (see Appendix A)
- Persons with a **history of travel** to/in areas with a high incidence of TB disease
- **Persons with signs and symptoms of active TB disease**
- **Close contacts** of a person known or suspected to have TB disease
- Employees, residents, and volunteers of **high-risk congregate settings** (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other healthcare facilities)
- Some **medically underserved, low income** populations as defined locally
- **High-risk racial or ethnic minority populations** having an increased prevalence of TB disease
- Persons who **inject illicit drugs** or other groups of high risk substance users (e.g., crack cocaine)
World TB Incidence 2008

High incidence countries: annual incidence > 20 cases TB disease/100,000 population. Includes most countries in Africa, Asia, C. and S. America, E. Europe and Russia (ACHA Recommendations Appendix A)
United States TB Disease Rates in different racial and ethnic populations

- American Indians or Alaska Natives: 6.0 cases per 100,000 persons
- Asians: 25.6 cases per 100,000 persons
- Blacks: 8.8 cases per 100,000 persons
- Native Hawaiians and other Pacific Islanders: 15.9 cases per 100,000 persons
- Hispanics or Latinos: 8.1 cases per 100,000 persons
- Whites: 1.1 cases per 100,000 persons
Medical Risks for TB

- Persons with HIV/AIDS
- Persons whose TB skin tests (TSTs) have converted to positive (with >10mm increase) within the past 2 years
- Persons with a history of inadequately treated TB, including persons with chest radiographic findings consistent with previous TB disease
- Persons who use illicit drugs or other groups of high-risk substance users
- Persons with the following medical conditions that place them at risk for disease if infection occurs: silicosis, diabetes mellitus, end stage renal disease/chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other malignancies (e.g., carcinoma of head, neck, or lung), low body weight ( >10% below ideal body weight), prolonged corticosteroid use (e.g., prednisone 15 mg/d for 1 month), use of other immunosuppressive treatments (e.g., tumor necrosis factor-alpha [TNF-α] antagonists), organ transplantation, gastrectomy or jejunoileal bypass, chronic malabsorption syndromes
What is Latent TB Infection?

- *Mycobacterium tuberculosis* infects one third of the world’s population.
- Tuberculosis organisms usually become dormant (latent) after infecting a healthy host.
- Infected individuals have no symptoms but develop a positive skin test about 6-8 weeks post infection; they are non-infectious themselves.
- Active disease may develop months or decades later—or not at all in most cases.
Latent TB Infection (LTBI)

- Dormant infection may persist for decades or life (PPD usually remains + ever after)
- 5-10% risk of progressing to active disease (increasing to 50% if HIV+) old data
- Half of this risk is w/in the first 2 yrs after infection
- Thus 1st 12-24 m after TST conversion (infection) is the most hazardous period for the patient
- Disease may be activated by illness (HIV), malnutrition, stress, injury, steroids or other immunosuppressant drugs
How can you tell if someone has LTBI?

- Positive Mantoux tuberculin skin test (PPD or TST) or positive Interferon Gamma Release Assay (IGRA) blood test
- Asymptomatic (lack 5 classic TB disease symptoms: persistent cough > 3w, hemoptysis, weight loss, fever or night sweats)
- CXR negative for active disease
- Sputum negative for acid fast bacilli (AFB) smears and culture
**LTBI vs. Active TB Disease**

<table>
<thead>
<tr>
<th>Latent TB</th>
<th>TB Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>Sick</td>
</tr>
<tr>
<td>Non-infectious</td>
<td>Potentially infectious</td>
</tr>
<tr>
<td>Negative sputum</td>
<td>Positive sputum</td>
</tr>
<tr>
<td>Positive skin test</td>
<td>Positive skin test</td>
</tr>
<tr>
<td>Positive IGRA</td>
<td>Positive IGRA</td>
</tr>
<tr>
<td>Normal CXR</td>
<td>Abnormal CXR</td>
</tr>
<tr>
<td>Consider treatment with INH x 6-9m to prevent active TB disease</td>
<td>Needs treated for active TB w/ 4 drug therapy x 2 m then 2 drugs x 4m</td>
</tr>
</tbody>
</table>
Diagnostic Testing for TB

- **Chest radiographs**: infiltrative lesions, cavities, eventual fibrosis often in upper segments; miliary form represents diffuse disease.
- **Chest CT** (when indicated by abnormal CXR)
- **Sputum smears x3** + acid fast bacilli (AFB) correlated w/ infectivity
- **Sputum culture** (if available)
- **Positive PPD or IGRA (e.g. T-SPOT) testing**
- **Don’t use IGRA/PPD by itself to R/O active TB disease**
Testing Record

1. Does the student have signs or symptoms of active tuberculosis disease?
   Yes _____ No _____
   If No, proceed to 2 or 3. If Yes, proceed with additional evaluation to exclude active tuberculosis disease including tuberculin skin testing, chest x-ray, and sputum evaluation as indicated.

2. Tuberculin Skin Test (TST)
   (TST result should be recorded as actual millimeters (mm) of induration, transverse diameter; if no induration, write “0”. The TST interpretation should be based on mm of induration as well as risk factors.)**
   Date Given: ____/____/____ Date Read: ____/____/____
   Result: ________ mm of induration **Interpretation: positive____ negative____
   Date Given: ____/____/____ Date Read: ____/____/____
   Result: ________ mm of induration **Interpretation: positive____ negative____

3. IGRA test (if performed) Type of Test _______ Date given______ Result_________

4. Chest x-ray: (Required if TST or IGRA is positive)
   Date of chest x-ray: ____/____/____ Result: normal____ abnormal
BCG Vaccine: does it affect PPD results? Well, yes but...

- Bacille Calmette Guerin (BCG) is a live attenuated *M. bovis* strain used for immunization of infants in higher risk countries
- Strains vary widely in effectiveness
- Protective against TB meningitis and disseminated disease in infancy (< 5y) but immunity later wanes as does skin reactivity
- PPD should be interpreted “WITHOUT REGARD for BCG status” per past CDC recommendations...BUT...
- It can increase reactivity of skin test in child or recently vaccinated adult (in 1/2 those vaccinated) but less likely to cause a strongly positive > 20mm reaction in adults vaccinated as infants
- BCG vaccine not recommended in developed countries

BCG Vaccine Adverse Reactions

Local BCG reaction

Axillary LN infection

Dactylitis
International Student Perspective

- TB testing viewed as a real nuisance—some even have a “chip” on their shoulder.
- “Of course, my skin test is positive, I’ve had BCG.” (maybe true)
- “Everyone in my country tests positive.” (not true)
- “Why should I risk INH? No one takes it in my country unless they are sick.” (often true)
- IGRA tests are a huge step forward since they deal with the BCG issue—when possible, bypass the PPD for international students and start w/IGRA test
Interferon Gamma Release Assays (IGRAS) as TST alternative/supplement

- QuantiFERON-TB 2001 (now obsolete)
- QuantiFERON-Gold 2005
- QuantiFERON-Gold In Tube (GIT) 2007
- T-SPOT (ELISAspot) 2008 easiest to process

Advantages: no return visit for reading, objective results (no observer bias), not affected by BCG
## Differences in Available IGRAS

<table>
<thead>
<tr>
<th>Format</th>
<th>QFT-G</th>
<th>QFT-GIT</th>
<th>T-Spot</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Process whole blood within <strong>12 hours</strong>.</td>
<td>Process whole blood within <strong>16 hours</strong></td>
<td>Process peripheral blood mononuclear cells (PBMCs) within <strong>30 hours</strong>.</td>
</tr>
</tbody>
</table>

### M. tuberculosis Antigen

<table>
<thead>
<tr>
<th></th>
<th>QFT-G</th>
<th>QFT-GIT</th>
<th>T-Spot</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Separate mixtures of synthetic peptides representing ESAT-6 &amp; CFP-10</strong></td>
<td><strong>Single mixture</strong> of synthetic peptides representing ESAT-6, CFP-10 &amp; TB7.7.</td>
<td>Separate mixtures of synthetic peptides representing ESAT-6 &amp; CFP-10</td>
<td></td>
</tr>
</tbody>
</table>

### Measurement

<table>
<thead>
<tr>
<th></th>
<th>QFT-G</th>
<th>QFT-GIT</th>
<th>T-Spot</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IFN-g concentration</strong></td>
<td><strong>IFN-g concentration</strong></td>
<td>Number of IFN-g producing cells (spots)</td>
<td></td>
</tr>
</tbody>
</table>

### Possible Results

<table>
<thead>
<tr>
<th></th>
<th>QFT-G</th>
<th>QFT-GIT</th>
<th>T-Spot</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive, negative, indeterminate</strong></td>
<td><strong>Positive, negative, indeterminate</strong></td>
<td>Positive, negative, indeterminate, borderline</td>
<td></td>
</tr>
</tbody>
</table>
Newest IGRA: T-Spot  (2008)

- T-SPOT-TB Test (T-spot) = ELI-spot
- Process whole blood **within 30 hours**
- Blood mononuclear cells incubated separately with ESAT-6 and CFP-10 and controls
- Enzyme-linked immunospot assay (ELI-spot) used to detect cells that secrete INF-gamma
- Less blood processing than QFT-GIT and more time to do so—current IGRA used in WV.
IGRA Test Limitations

- Blood must be processed while WBCs are still viable—QFT Gold test previously unavailable here due to 12h processing time limit.
- Additional delay in processing may result in false negative tests
- **Less reliable in children < 5** (prefer PPD), immune compromised (false negatives) and recently infected individuals
- Avoid using IGRA test within 6 weeks of giving live vaccines (like PPD—but less well studied)
**Indications for IGRA Tests**

- **Recent immigrants** w/ history of BCG vaccination—better to start w/ IGRA test rather than get PPD first
- **Recent contacts** of active TB cases
- **Equivocal/borderline + PPD reactions**
- Health care workers serving high-risk population
- Medically underserved patients/ pts unlikely to return
- Incidental positive PPD in low risk group
- Special populations (HIV+, IV drug abuse, abnormal CXR, malabsorption or LBW, bariatric surgery, diabetics)
- Unable or unlikely to return for reading in 48-72h
New Gamma Interferon Release Assays: 
CDC Recommendations 2010

- **Situations in Which an IGRA Is Preferred But a TST Is Acceptable**
  - An IGRA is preferred for testing persons from groups that historically have low rates of returning to have TSTs read. For example, use of an IGRA might increase test completion rates for homeless persons and drug-users. The use of IGRAs for such persons can increase test completion rates, so control efforts can focus on those most likely to benefit from further evaluation and treatment.

- **Situations in Which a TST Is Preferred But an IGRA Is Acceptable**
  - A TST is preferred for testing children aged <5 years. Use of an IGRA in conjunction with TST has been advocated by some experts to increase diagnostic sensitivity in this age group. Recommendations regarding use of IGRAs in children have also been published by the American Academy of Pediatrics.

Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection — United States, 2010 *MMWR* 2010; 59 (No. RR-5);1-25
CDC 2010 Recommendations

Currently, the CDC supports the use of IGRAs as an acceptable alternative to TSTs, but does not advocate using it as a confirmatory test for persons with a positive TST. It should be noted that some other countries are utilizing the IGRAs as confirmatory tests for positive TSTs.
Pros and cons of using IGRA to confirm positive PPD— Gerald Mazurek (CDC)

- This CDC recommendation is based on lack of sufficient data about ultimate outcomes in pts with discordant TST and IGRA results who have identified risks of TB infection.

- Currently it’s too soon to know which test is better at detecting LTBI or at predicting subsequent TB (however some very recent studies suggest that IGRAs might be better).

- Requiring a +IGRA may lead to LTBI under treatment while treating all +TST likely leads to over treatment (past U.S. policy).

- Should it be assumed that the IGRA test is always correct?

- "Guidelines are not regulations. A program is free to implement a sequential testing strategy if that works best for them."
CDC recommendations on discordant testing – Gerald Mazurek, IGRA expert

Our recommendation is as follows: “In persons with discordant test results (i.e., one positive and the other negative), decisions about medical or public health management require individualized judgment in assessing the quality and magnitude of each test result (e.g., size of induration and presence of blistering for a TST; and the TB Response for an IGRA), the probability of infection, the risk for disease if infected, and the risk for a poor outcome if disease occurs.”
What About Those w/ Discordant Results: +PPD, -IGRA?

At many health departments, no longer considered to truly have LTBI (+ skin test considered a false positive)

PPD likely to remain positive however (repeat PPD on a trial basis only if it was borderline or atypical)

Annual screening with symptom questionnaire and annual IGRA test preferable to annual CXR
**U.S. vs. U.K. Recommendations**

- Until recently, U.S. (CDC) recommended PPD screening s/p BCG and that >10mm induration in higher risk individuals be treated with INH x 6-9 months REGARDLESS of BCG status (IGRA test alone now ok for BCG pts in 2010)
- U.K. recommends only gamma interferon testing for individuals with BCG vaccine history
- Recommendations result in larger number of people being falsely diagnosed with LTBI in the U.S., while the UK approach probably misses patients with LTBI who should be treated
- CDC 2010 Recommendations now gradually approaching U.K’s
Should we change how we do things?

- We have been over treating many of our +PPD patients with INH—increased cost, side effects, hassle

- 3 Possible Models: Old: TST only, Current: TST/confirmation if questionable w/ IGRA, Future: IGRAs for all? Cost is major factor: QFT-GIT currently costs $194 at UML!

- Use IGRA testing in place of TST for those patients s/p BCG vaccination (as per UK and very recent CDC recommendations)

- Many starting to use IGRA as confirmatory test for those +PPD cases without BCG however this is still not current CDC policy.

- QFT-GIT should be not be used until 8-12 weeks after contact w/ TB case and it should not be used by itself to r/o TB

- Soon newer, better, cheaper IGRA tests may replace both the T-SPOT and Mantoux TST/PPD
Monongalia County Health Department
QuantiFERON Gold in Tube Test Results 2010

<table>
<thead>
<tr>
<th># QFT</th>
<th># Male</th>
<th># Female</th>
<th>Hx BCG</th>
<th># +</th>
<th>PPD ≥10 mm</th>
<th># +</th>
<th>PPD ≥15 mm</th>
<th># +</th>
<th>Hx + PPD</th>
<th># +</th>
<th>Symptoms</th>
<th># +</th>
<th>Contact</th>
<th># +</th>
<th>Total # +</th>
</tr>
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<tbody>
<tr>
<td>55</td>
<td>25</td>
<td>30</td>
<td>20</td>
<td>7</td>
<td>11</td>
<td>3</td>
<td>17</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>14</td>
</tr>
</tbody>
</table>

Only 7/20 **BCG + QFT** = 35% positive
Only 14/55 **Total** QFT tests were positive = 25% positive

Charleen Morgan, RN
Mon Co. Health Dept., Morgantown, WV
MCHD T-spot results from Fall 2011

- 9/2011 - 14 patients tested, 3 positive (all foreign born)
- 10/2011 – 13 patients tested, 0 positive
- 11/2011 – 5 patients tested, 1 positive (foreign born)
- **So only 4 out of 32 patients (12.5%) had positive T-spots, all foreign-born.**

- Of the 32 tested, 27 had BCG and the other 5 a history of + PPD

Charleen Morgan Kaczmarek, RN
Monongalia County Health Department
**LTBI References**

- Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection — United States, 2010 *MMWR* 2010; 59 (No. RR-5);1-25
- Tuberculosis Screening and Targeted Testing of College and University Students American College Health Assoc. (ACHA) Guidelines [http://www.acha.org/Publications/docs/Tuberculosis](http://www.acha.org/Publications/docs/Tuberculosis)
- Decrease in Reported Tuberculosis Cases *MMWR* 2010; 59 (No.10); 289-294
- Muzurak, Gerald (CDC): Phone interview and e-mail correspondence 2010
LTBI References


- International Union Against Tuberculosis Committee on Prophylaxis: efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of followup in the IUAT trial. *Bull WHO* 1982; 60: 555-64.


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Dheda K et al. Infect Dis Clin N Am 2010;24:705-725 Extensively drug-resistant tuberculosis: Epidemiology and management challenges

Diagnostic References

- Boehme CC et al. NEJM 2010;363:1005-15 Rapid molecular detection of tuberculosis and rifampin resistance
Clinical Management References


