Diagnosis of Tuberculosis: A Practical Guide for Los Angeles County

Part I: Tuberculosis Infection

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Introduction

The diagnostic evaluation of tuberculosis (TB) infection and disease has undergone significant change in the last decade. For this reason, the Los Angeles County Tuberculosis Control Program (TBCP) is creating practical guidance and tools to assist clinicians with the assessment and diagnosis of tuberculosis. This article will summarize the recommended approach to diagnose TB infection in LA County and will be followed by a future article on the diagnosis of active TB disease. The recommendations are organized in four sections: Assess for TB Risk, Test for TB Infection, Diagnose TB Infection, and Be Prepared for a New IGRA. These recommendations are based on the 2017 American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention (ATS/IDSA/CDC) Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children as well as recent California Department of Public Health (CDPH) TB Control and LA County TBCP guidance.1-3

1. ASSESS FOR TB RISK

The initial step in screening for TB infection is an assessment of TB risk, NOT laboratory testing. TB testing is not recommended for asymptomatic patients at low risk for TB because both the tuberculin skin test (TST) and the interferon gamma release assay (IGRA) often yield false positive results and can lead to costly evaluations and unnecessary treatment in patients with a low probability of infection.1 The risks for TB infection in adults in LA County are shown below. TB infection risk assessment tools have been created and now replace TST/IGRA testing of low risk persons.2-5

Risks for TB Infection in Asymptomatic Adults in LA County

- Foreign-born person from country with elevated TB rate
  Includes countries other than the U.S., Canada, Australia, New Zealand, or Western or North European Countries

- Immunosuppression, current or planned
  HIV infection, organ transplant recipient, treated with TNF-alpha antagonist (e.g., infliximab, etanercept, others), steroids (equivalent of prednisone >15 mg/day for >1 month) or other immunosuppressive medication

- Close contact to someone with TB disease at any time

- History of homelessness

- History of incarceration

TB Infection Risk Assessment

TBCP has adapted a CDPH series of risk assessment questionnaires to determine if TB testing is
Diagnosis of Tuberculosis

If completed by a licensed clinical professional, a negative risk assessment, with some exceptions, fulfills most California institutional TB screening requirements. As shown in the algorithm below, a negative risk assessment completes the TB evaluation.

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**Assessment Algorithm for TB Infection**

**Risk Assessment + Symptom Review**

**Risk Factors for TB:**
- Foreign birth person from country with elevated TB rate
- Immunosuppression, current or planned
- Close contact to someone with TB disease at any time
- History of Homelessness
- History of incarceration

**TB Symptoms:**
- Cough > 2 – 3 weeks
- Fever
- Night Sweats
- Weight Loss
- Hemoptysis

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**Negative TB Risk Assessments Fulfill Many—but Not All—Institutional TB Clearance Requirements**

The majority of educational institutions in LA County can now accept a negative TB risk assessment, defined as a questionnaire administered by a licensed clinical professional, to fulfill the legal requirements for TB screening. This has been the case since 2012, for most children entering preschools, daycare settings, and K-12 educational institutions in LA County. More recently, California laws have been amended to expand the use of TB risk assessment questionnaires to employees and volunteers working in educational settings. Table 1 summarizes educational settings where negative TB risk assessments are accepted in lieu of testing.

Clinicians can provide their patients with a formal certificate and memo from TBCP that states that the patient has fulfilled their mandated TB screen and are negative for TB.

Clinicians should be aware that there remain very specialized institutional settings and programs that by health code still mandate TB testing for employees and volunteers and program participants (Table 2). Because these laws require more stringent criteria for TB clearance, they supersede the recently amended laws cited in Table 1. Public health professional associations are working to change requirements for the groups in Table 2, but until then, clinicians are required to order TB tests in low risk patients.

Providers who have questions about institutional TB testing requirements may contact the LA...
### Diagnosis of Tuberculosis

http://rx.ph.lacounty.gov/RxTB0118

County TBCP at 213-745-0800 or tbc@ph.lacounty.gov for assistance.

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Table 1. California Health Codes Allowing TB Risk Assessments for TB Clearance in for Educational and Childcare Settings

<table>
<thead>
<tr>
<th>Code</th>
<th>Affected Group</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDC 49406</td>
<td>K-12 teachers, staff, and volunteers</td>
<td></td>
</tr>
<tr>
<td>EDC 87408.6</td>
<td>Community college staff</td>
<td></td>
</tr>
<tr>
<td>HSC 121525</td>
<td>Employees of private or parochial elementary or secondary schools</td>
<td>Risk based screening every four years</td>
</tr>
<tr>
<td>HSC 121545</td>
<td>Volunteers at private or parochial elementary or secondary schools</td>
<td></td>
</tr>
<tr>
<td>HSC 1597.055</td>
<td>Day care workers</td>
<td></td>
</tr>
<tr>
<td>HSC 1597.54</td>
<td>Family day care home workers</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. California Health Codes Requiring TB Testing for TB Clearance in Specialized Educational and Community Program Settings

<table>
<thead>
<tr>
<th>Code</th>
<th>Affected Group</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRC 5163</td>
<td>Park and recreation employees</td>
<td>TB testing on hire and every four years</td>
</tr>
<tr>
<td>EDC 33195.6</td>
<td>Employees and volunteers at heritage schools (part time language/culture schools)</td>
<td>TB testing upon commencement</td>
</tr>
<tr>
<td>EDC 59150</td>
<td>Pupils at schools for the deaf and blind</td>
<td>TB testing every two years</td>
</tr>
<tr>
<td>FAM 8732</td>
<td>Foster parents</td>
<td>TB testing upon application</td>
</tr>
<tr>
<td>HSC 1526.8</td>
<td>Volunteers at crisis nurseries (24-hour nonmedical care and supervision for children &lt; 6 years old, for no more than 30 days)</td>
<td>TB testing upon commencement</td>
</tr>
</tbody>
</table>

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### 2. TEST FOR TB INFECTION

#### Diagnostic Test Selection for TB Infection in LA County: IGRA and/or TST

Once a risk for TB infection has been established, the choices for TB infection testing are either an IGRA blood test or a TST. The LA County TBCP Recommendations for Diagnostic Testing for TB infection, Table 3, incorporates the ATS/CDC/IDSA testing strategies with the updated TBCP recommended approach for diagnostic testing for TB infection in LA County. Key points from the recommendations are the following:

- In LA County, IGRA is the preferred testing strategy for adults and children ≥ 2 years of age, especially for populations that are BCG vaccinated. The TST remains an acceptable alternative, particularly in young children given challenges with phlebotomy. TBCP has created an IGRA FAQ, including information about how to approach indeterminate/borderline IGRA test results.
- Though the ATS/CDC/IDSA testing guidelines also recommend IGRA s for adults and children, the lower recommended age limit is 5 years of age. The TBCP rationale for extending the lower age range to ≥ 2 years old is based upon anticipated national guidance for pediatric TB testing, published experience with IGRA results in young children in California, and guidance from the California Department of Public Health.²,6,7
- It is now recommended that highly immunosuppressed patients be considered for testing with both IGRA and TST. This recommendation, new to the ATS/CDC/IDSA guidelines, is to...
maximize the sensitivity for the diagnosis of TB infection as these patients are at high risk of progression to active TB.

- Though diagnostic testing is not recommended for patients at low risk for TB, the ATD/CDC/IDSA guidelines now recommend an algorithm if testing occurred and was initially positive.
- A chest x-ray (CXR) is recommended for all positive TB tests (IGRA or TST) regardless of immune status. See the CXR section below for more details.

### Risk for TB Infection

<table>
<thead>
<tr>
<th>Risk for TB Infection</th>
<th>Testing Strategy</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At risk</strong></td>
<td>IGRA preferred (TST acceptable) in</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Adults</td>
<td>IGRA in particular is strongly preferred for individuals with history of BCG vaccination</td>
</tr>
<tr>
<td></td>
<td>- Children ≥ 2 years old</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider both IGRA and TST in severely immunosuppressed individuals</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Severely immunosuppressed groups include patients with:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- AIDS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Immunosuppressive therapy (anti-TNF, corticosteroids, organ transplant)</td>
<td></td>
</tr>
<tr>
<td><strong>Low risk</strong></td>
<td>No diagnostic testing indicated.</td>
<td>If low risk individual is tested and is found to be IGRA positive, do CXR.</td>
</tr>
<tr>
<td>(none of the above risk factors)</td>
<td>Risk assessment alone is acceptable.</td>
<td>- If CXR is positive, evaluate for active TB.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If CXR is negative, repeat TB risk assessment:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If risk found, offer treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- If no risk found, repeat TB test (IGRA or TST):</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- if TB test negative, accept negative test.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- if TB test positive, consider treatment.</td>
</tr>
</tbody>
</table>

### Indications for Chest X-Ray in Work-Up of TB Infection

The LA County TBCP makes the following recommendations regarding chest x-rays for the work-up of TB infection that differ from the ATS/CDC/IDSA guidelines:

- A chest x-ray (if none in the past 90 days) is recommended for all positive TB tests (IGRA or TST) regardless of immune status.
- Some experts and TBCP obtain a chest x-ray in addition to TB tests even if both tests are negative in severely immunocompromised patients to maximize sensitivity.
- A chest x-ray is recommended for all individuals with indeterminate TB infection test results.

**Note:** A chest-x-ray is recommended, regardless of IGRA or TST results, if a patient develops any symptoms of TB.

http://rx.lacounty.gov/RxTB0118 1/16/2018
symptoms of TB disease at any point in the evaluation for TB infection (Figure 1). A chest x-ray with any abnormalities consistent with TB should trigger an evaluation for active TB disease with sputum AFB smears, cultures and nucleic acid amplification testing. A negative TST or IGRA does not rule out active TB disease.1-3

Serial evaluations for TB Infection – When to Retest
A patient whose most recent TB infection test was negative should only be tested again if a new risk for TB infection has been identified (i.e. positive risk in the risk assessment tool)2,3 or when mandated for institutional clearance. Patients with ongoing risk, (e.g. homelessness) should be tested annually.8
A patient with a prior positive TB test with a new risk for TB infection should be evaluated with a TB symptom review and chest x ray. In most cases, this situation would arise when a person who has a previous diagnosis of TB infection is identified as a contact to a TB case.

3. DIAGNOSE TB INFECTION
The diagnosis of TB infection must meet both clinical and laboratory criteria (see box below).9 Medical consultation regarding the diagnosis of TB infection is available at the TBCP at 213-745-0800.

<table>
<thead>
<tr>
<th>Diagnostic Criteria of TB Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Laboratory Criteria</strong></td>
</tr>
<tr>
<td>• Positive TB test (IGRA or TST)</td>
</tr>
<tr>
<td>• <em>Mycobacterium tuberculosis</em> (Mtbc) not isolated from a clinical specimen, if a specimen was collected</td>
</tr>
<tr>
<td><strong>AND</strong></td>
</tr>
<tr>
<td><strong>Clinical Criteria</strong></td>
</tr>
<tr>
<td>• No signs or symptoms of TB disease</td>
</tr>
<tr>
<td>• Chest imaging without abnormalities consistent with TB disease –OR– abnormal chest imaging that could be consistent with TB disease with confirmed microbiologic testing that is negative for Mtbc</td>
</tr>
</tbody>
</table>

4. BE PREPARED FOR A NEW IGRA IN 2018
Replacement of Quantiferon (QFT) - In Tube Assay with QFT-Plus Assay in the United States
As of October, 2017, the newer generation QFT-Plus assay was launched in the U.S., after having been implemented in Europe in 2016 and adopted by countries in the Middle East, Africa, Asian, and Latin America. It is anticipated that most U.S. laboratories will transition to the new QFT-Plus assay in 2018, as the QFT-In Tube assay will not be available in the U.S. after June 2018. The QFT Plus assay is very similar to the QFT-In Tube assay which measures the interferon gamma production by CD4 cells after exposure to TB antigens. The QFT Plus assay includes an additional tube containing TB antigens that allows the measurement of interferon gamma release by CD8 cells after exposure to TB antigens. The information about CD8 cell activity may be helpful, as CD8 cells contribute to the immune response to active TB and new infection, and function in young children and individuals living with HIV. More information on the QFT Plus, including guidance on how to interpret the test may be accessed here. Questions regarding interpretation of the QFT Plus assay may be directed to the medical consultation at the TBCP at 213-745-0800.

Reminder: Testing for TB infection now a preventive care benefit under the Affordable Care Act in 2018
The USPSTF issued a recommendation that all adults at increased risk for TB be screened for TB infection. As mentioned in the May Rx for Prevention article, diagnostic testing for TB infection is now (effective January 2018) included as part of the preventive care benefit for adults and children as part of implementation of the Affordable Care Act. This means that Californians with health insurance who are at risk for TB infection will not have additional out of pocket costs for TB testing, thus eliminating one additional barrier to accessing diagnosis and treatment of TB infection.10 In LA County, uninsured patients at risk for TB infection can be referred to Public Health Centers and low cost clinics.
Summary

In LA County, clinicians are encouraged to incorporate an approach for diagnosing TB infection into their routine patient care. Key steps include:

- **Assess for TB infection.** Use an LA County TB Infection Risk Assessment to determine TB infection risks. Asymptomatic patients with a negative risk assessment are considered negative for TB infection and need no further evaluation.

- **Test for TB infection in patients at risk.** All asymptomatic patients with a positive TB infection risk assessment should be tested for TB. An IGRA is the preferred TB test in adults and children ≥ 2 years old who are at risk for TB infection. Obtain a chest x-ray for all asymptomatic persons with positive IGRA and/or TST results. Re-test for TB infection only if new risks occur. For serial evaluations of TB infection, only re-test if there is a new risk identified or California law mandating a TB test.

- **Diagnose TB infection.** Use the combined laboratory and clinical criteria to diagnose TB infection. Once a provider has made a diagnosis of TB infection, offer and provide treatment for TB infection.

- **Be prepared for a new IGRA.** A new version of the QFT called the QFT Plus is undergoing implementation in the U.S in 2018.

Clinicians are encouraged to read the three clinical scenarios to test their knowledge of TB infection testing recommendations.

National TB Conference/California Tuberculosis Controller’s Association Conference

**TB Elimination in the US: Mirage or Oasis?**

May 21-25, 2018 at the Omni Rancho Las Palmas in Palm Springs, California.


Community providers are welcome to attend and learn about TB disease and TB infection at this national meeting, which is a rare occurrence in Southern California. Specific days and sessions with CME and MOC will be targeted for a clinical audience.

References


2. California Tuberculosis Risk Assessment Pediatric Risk Assessment and User Guide


5. Personal communication, Phil Lobue, Director, Division of TB Elimination, Centers for Disease Control, June 21, 2017.

6. Personal communication, California TB Controller’s Association Fall Meeting, November 15, 2017.


8. Council of State and Territorial Epidemiologists Position Statement 17-ID-09
   [http://www.tbcontrollers.org/docs/noteworthy/2017-06_TB_Infection_Case_Definition_CTSE_Adopted.pdf](http://www.tbcontrollers.org/docs/noteworthy/2017-06_TB_Infection_Case_Definition_CTSE_Adopted.pdf)


Definition:

In LA County, the TB Control Program (TBCP) refers to "latent TB infection" as "TB infection" to encourage clinicians to take action once they diagnose TB infection in their patients.