Latent TB Infection: An Update on Diagnosis and Treatment

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Latent TB Infection (LTBI)

- Approximately 9-14 million people in U.S. have LTBI
- Risk of developing active TB disease in individuals with LTBI is 5-10% over their lifetime


Targeted Testing for LTBI

- Identifies persons at high risk for developing TB disease
- De-emphasizes testing of groups that are not at high risk for TB
- Can help reduce the waste of resources and prevent inappropriate treatment

CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 2000; 49 (No. RR-6).
Who should be tested for LTBI?

- Close contacts of a person with active TB
- Non-U.S. born, lived or traveled for more than a month in a TB endemic country (i.e. Africa, India)
- Lived or worked in a prison, nursing home, homeless shelter, HIV residential home or hospital
- Injection drug users
- Use of prednisone, TNF-alpha, immunosuppressive agents
- HIV infection
- Persons with conditions that increase risk of progression to disease once infected

High Risk Clinical Conditions

- Diabetes mellitus
- Chronic renal failure
- Chronic malabsorption syndrome
- Leukemia, lymphomas, Hodgkin's disease
- Cancer of the head or neck
- Silicosis
- Weight loss of >10% ideal body weight
- Gastrectomy or intestinal bypass
- Crack cocaine use

Tuberculin Skin Testing

- Inject 0.1 ml of standardized mix of TB proteins (purified protein derivative)
- Given intradermally on volar forearm
- Measure induration 48-72 hrs after placement
- Measure in millimeters, not “positive” or “negative”
- Should be interpreted by well-trained health care professional

Interpreting a Tuberculin Skin Test

[Image from: www.info.gov.hk/dh/diseases/CD/TB.htm]

[Interpreting a Tuberculin Skin Test from CDC website: http://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm]
TB Risk in Foreign-born Individuals

- **High TB prevalence countries include:** Asia, Africa, Caribbean, Latin America, Mexico, South America, Pacific Islands or Eastern Europe
- **Low TB prevalence countries include:** USA, Canada, Japan, Australia, Western Europe, and New Zealand

BCG Vaccine

- Bacille Calmette-Guerin vaccine is given in many countries with a high prevalence of TB
- Used primarily to prevent TB meningitis or miliary disease in children
- May cause a false-positive reaction to a TST
- Evaluation of TST reaction in a BCG-vaccinated individual should be interpreted using the same criteria for those who are not BCG-vaccinated

HIV and Tuberculosis

- HIV increases the risk of TB reactivation enormously.
- PPD+, HIV- ⇒ lifetime risk ~10%
- PPD+, HIV+ ⇒ YEARLY risk ~10%
- A deadly duo

Blood Tests for TB (1)

- Also known as interferon gamma release assays (IGRA)
Types of IGRAs

• Two commercially available IGRAs: QuantiFERON TB Gold In-Tube, T-Spot

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<thead>
<tr>
<th>Format</th>
<th>QFT-GIT</th>
<th>T-Spot</th>
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<tbody>
<tr>
<td>Process whole blood within 18 hours/ Process peripheral blood mononuclear cells (PBMCs) within 6 hours, as of T-Cell Xpress it is used, within 18 hours</td>
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<tr>
<td>M. tuberculosis Antigen</td>
<td>Single mixture of recombinant antigens representing SLA-1, SLA-2, a6, 7, TCP-10, TBF7</td>
<td>Separate mixture of recombinant antigens representing SLA-1, SLA-2, a6, 7, TCP-10, TBF7</td>
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<tr>
<td>Measurement</td>
<td>IFN-γ concentration</td>
<td>Number of IFN-γ producing cells (spots)</td>
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<tr>
<td>Possible Results</td>
<td>Positive, negative, indeterminate</td>
<td>Positive, negative, indeterminate, borderline</td>
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PROS:
• Requires single patient visit “One and done”
• Results can be available within 24 hours
• Does not boost responses measured by subsequent tests
• Prior BCG vaccination does not cause a false-positive result

CONS:
• Blood samples must be processed 8-30 hours after collection
• Errors in collecting or transporting blood specimens or in running and interpreting the assay can decrease accuracy
• Limited data to predict who will progress to TB disease in the future
• Limited data on the use of IGRAs for: children<5, persons recently exposed to MTB, immunocompromised persons, serial testing

May 2011 www.cdc.gov

http://www.cdc.gov/mmwr/pdf/rr/rr5905.pdf

Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection—United States, 2010

Interpreting IGRAs


Screening for LTBI with either TST or IGRA

- TST and IGRAs should be used as aids in diagnosing infection with *M. tuberculosis*
- Test recent contacts of individuals with or suspected to have TB disease
- Periodic screening of persons who might have occupational exposure to *M. tuberculosis*

TST preferred LTBI screening test

- Testing children<5 years old
IGRA preferred LTBI screening test

- Groups that historically have low rates of returning to have a TST read (i.e. homeless persons, drug users)
- Individuals who have received BCG (as a vaccine or as cancer therapy)

Use of both tests for LTBI screening (1)

- Routine testing with both a TST and IGRA is not generally recommended
- However, when the initial test (either TST or IGRA), is negative, performing the other test may be helpful in the following situations:
  1) when risk for infection, risk for progression to active disease and risk for poor outcomes are increased (i.e. HIV+, children< 5)
  2) When clinical suspicion exists for TB disease, may increase detection sensitivity

Use of both tests for LTBI screening (2)

- When the initial test is positive:
  1) When additional evidence of infection is required to encourage compliance
  2) In healthy persons who have a low risk for both infection and progression

Use of both tests for LTBI screening (3)

- Repeating IGRA or performing a TST if initial IGRA result is indeterminate, borderline or invalid and a reason for testing persists
- If the IGRA is repeated, a new blood sample must be obtained
Discordant results

- Taking a positive result from either test as evidence of infection is reasonable when:
  1) clinical evidence exists for active TB
  2) risks of infection, progression, poor outcomes are increased
- For health persons with low risk for infection and progression, reasonable to discount positive test as false positive
- For otherwise healthy persons who have received BCG, okay to discount positive TST when IGRA clearly negative

Neither an IGRA nor TST can distinguish LTBI from active tuberculosis!

The decision to test is the decision to treat

- Accepted treatment regimens for LTBI:
  - Isoniazid for 9 months
  - Rifampin for 4 months—recommended use only in Isoniazid intolerance
  - Isoniazid/Rifapentine once weekly for 3 months

PREVENT TB Trial

- Enrolled 8,053 patients
- Most participants were from the US and Canada, some from Spain and Brazil
- Participants either received 9 months of INH or a once-weekly dose of rifapentine and isoniazid for 3 months given via DOT
- Trial lasted for 10 years and participants were followed for approximately 33 months to evaluate for development of TB disease
12-Weeks of once weekly INH/Rifapentine (1)

Pros:
- Shorter duration of treatment (270 doses vs. 12 doses)
- Individuals more likely to complete therapy (82% vs 69%)
- 7 cases of TB in INH/Rifapentine group vs. 15 cases in INH group
- Similar amount of adverse drug events in each group

12-Weeks of once weekly INH/Rifapentine (2)

Cons:
- More Expensive: $503 vs $237
- May have difficulty getting Rifapentine
- Trial results are applicable only in low-to-medium TB incidence countries
- Not clear how to use this regimen in special populations:
  - HIV positive
  - Children under 5

Rifapentine

- Side effects:
  - similar to those seen with Rifampin
- Drug interactions:
  - decreases drug levels of glipizide, coumadin, digoxin, some antibiotics, antiretrovirals
Monitoring of LTBI Therapy

- Prior to starting INH therapy, obtain baseline liver function tests on the following individuals:
  - ETOH use > 3 drinks daily
  - HIV-positive
  - underlying liver disease (Chronic Hepatitis B or C)
  - pregnant women
  - those on potentially hepatotoxic drugs such as:
    1) “statins”
    2) anticonvulsants (phenytoin, valproic acid)
    3) methotrexate
    4) pioglitazone, rosiglitazone

TNF-α inhibitors

- Patients with negative TST or IGRA but epidemiological link, evidence of remote TB on CXR, should be treated
- Certain TNF-α inhibitors have higher risk of TB reactivation than others
- Many patients cannot wait to complete 9 months of LTBI therapy prior to starting TNF-α inhibitors so most experts recommend completing at least one month INH then starting TNF-α inhibitor to complete 9 months of therapy

LTBI in Pregnant Women

- Asymptomatic TST positive pregnant women with a negative CXR should start INH therapy as soon as possible if they have one of the following factors:
  - HIV infection
  - close contact to infectious TB disease
  - TST conversion
  - high-risk medical condition
- Asymptomatic TST positive pregnant women with negative CXR and no risk factors may elect to delay therapy

LTBI in HIV

- High risk group
- Situations in which patients with HIV should be treated for LTBI regardless of TST status once active disease is excluded:
  - recent contact to a case
  - history of prior untreated or partially treated active TB
  - CD4<200 with fibrotic lesions consistent with TB on a chest x-ray and no prior history of TB treatment