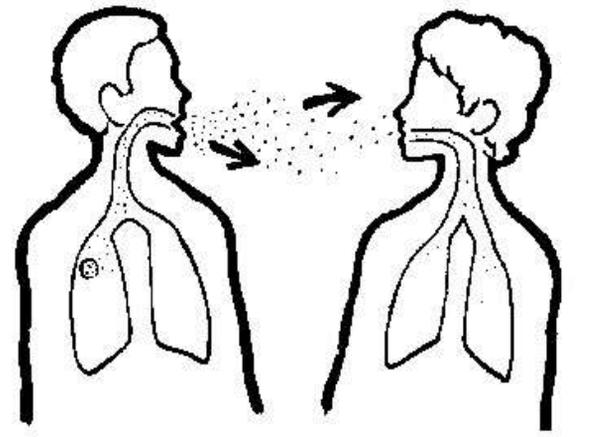
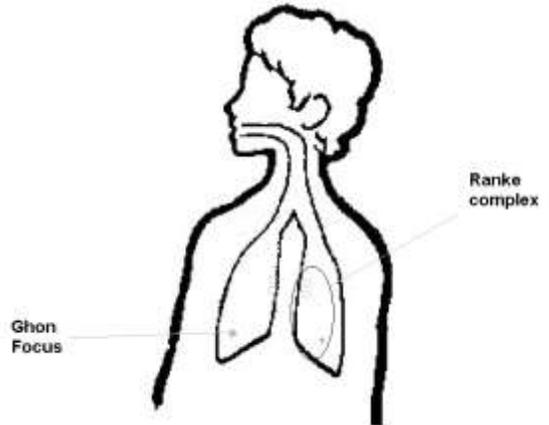
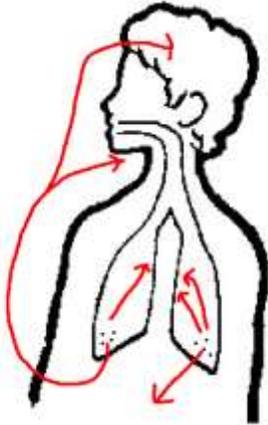


Latent TB Infection: An Update on Diagnosis and Treatment

Beth Gadkowski MD MPH MS
Assistant Professor
Eastern Virginia Medical School
Norfolk, VA





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

Person with latent TB infection (LTBI)
Usually has a skin test or blood test result indicating TB infection
Has a normal chest x-ray and a negative sputum test
Has TB bacteria in his/her body that are alive, but inactive
Does not feel sick
Cannot spread TB bacteria to others
Needs treatment for latent TB infection to prevent TB disease, however, if exposed and infected by a person with multidrug resistant TB (MDR TB) or extensively drug-resistant TB (XDR TB), preventive treatment may not be an option

<http://www.cdc.gov/tb/publications/factsheets/general/LTBIandActiveTB.pdf>

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 $\geq 10\%$ 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



Picture from: www.info.gov.hk/dh/diseases/CD/TB.htm

Interpreting a Tuberculin Skin Test

Classification of the Tuberculin Skin Test Reaction		
<p>An induration of 5 or more millimeters is considered positive in:</p> <ul style="list-style-type: none"> • HIV-infected persons • A recent contact of a person with TB disease • Persons with fibrotic changes on chest radiograph consistent with prior TB • Patients with organ transplant • Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer; taking TNF-alpha antagonists) 	<p>An induration of 10 or more millimeters is considered positive in:</p> <ul style="list-style-type: none"> • Recent immigrants (< 5 years) from high-prevalence countries • Injection drug users • Residents and employees of high-risk congregate settings • Mycobacteriology laboratory personnel • Persons with clinical conditions that place them at high risk • Children < 4 years of age • Infants, children, and adolescents exposed to adults in high-risk categories 	<p>An induration of 15 or more millimeters is considered positive in any person, including persons with no known risk factors for TB. However, targeted skin testing programs should only be conducted among high-risk groups.</p>

<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

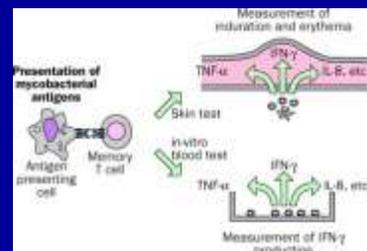
HIV and Tuberculosis

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



Blood Tests for TB (1)

- Also known as interferon gamma release assays (IGRA)



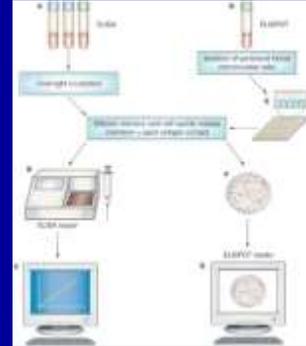
Lancet 358: 1099 2000

Types of IGRAs

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

	QFT-GIT	T-Spot
Format	Process whole blood within 18 hours	Process peripheral blood mononuclear cells (PBMCs) within 8 hours, as IFT-Git Xpert® is used, within 30 hours
IF. isobacterin Antigen	Single mixture of synthetic peptides representing ESAT-6, CFP-10 & TB7.7	Separate mixtures of synthetic peptides representing ESAT-6 & CFP-10
Measurement	IFN-γ concentration	Number of IFN-γ-producing cells (spots)
Possible Results	Positive, negative, indeterminate	Positive, negative, indeterminate, borderline

May 2011 www.cdc.gov



Lange C et al. (2007) Rapid immunodiagnosis of tuberculosis in a woman receiving anti-TNF therapy *Nat Clin Pract Rheumatol* 3: 528–534 doi:10.1038/ncprheum0571

IGRAs

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

The image shows the cover of the Morbidity and Mortality Weekly Report (MMWR) from June 25, 2010, Volume 59, Number 25. The cover features the CDC logo at the top, followed by the MMWR logo and the text 'Morbidity and Mortality Weekly Report'. Below this, it says 'Recommendations and Reports' and 'June 25, 2010 / Vol. 59 / No. 25'. The main title of the report is 'Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection – United States, 2010'. At the bottom, there is a URL: <http://www.cdc.gov/mmwr/pdf/rrrr5905>.

Interpreting IGRAs

TABLE 2. Interpretation criteria for the QuantiFERON-TB Gold In-Tube Test (QFT-GIT)

Interpretation	SI*	TB Response†	Mitogen Response‡
Positive†	>5.0	>0.20 IU/ml or >0% of TB	Any
Negative**	≤5.0	≤0.20 IU/ml or ≤0% of TB	≤5.0
Indeterminate†	≤5.0	≤0.20 IU/ml or ≤0% of TB	>5.0

Source: Based on Centers for Disease Control and Prevention (CDC) QuantiFERON-TB Gold In-Tube (Package Insert), available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm54a01a.htm> (accessed 10/20/10).

* The interferon gamma (IFN-γ) concentration in plasma from blood collected without anticoagulant.

† The IFN-γ concentration in plasma from blood stimulated with a single cocktail of peptides representing early secretory antigens (ESAT-6), culture filtrate protein 10 (CFP-10), and some of TB23A and TB23B.

‡ The IFN-γ concentration in plasma from blood stimulated with mitogen is used for this purpose.

§ Interpretation indicating that Mycobacterium tuberculosis infection is likely.

** Interpretation indicating that M. tuberculosis infection is not likely.

†† Interpretation indicating an uncertain likelihood of M. tuberculosis infection.

TABLE 3. Interpretation criteria for the T-SPOT.TB Test (T-SPOT)

Interpretation	SI*	TB Response†	Mitogen‡
Positive†	≥70 spots	≥4 spots	Any
Indeterminate†	≤70 spots	≤ 6, 6, or 7 spots	Any
Negative**	≤70 spots	≤4 spots	Any
Indeterminate††	≤70 spots	Any	Any

Source: Based on Centers for Disease Control and Prevention (CDC) T-SPOT.TB (Package Insert), available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm54a01a.htm> (accessed 10/20/10).

* The number of spots resulting from incubation of PBMCs in culture media without antigen.

† The greater number of spots resulting from stimulation of peripheral blood mononuclear cells (PBMCs) with two separate cocktails of peptides representing early secretory antigens (ESAT-6/CFP-10) or culture filtrate protein 10 (CFP-10) versus TB.

‡ The number of spots resulting from stimulation of PBMCs with mitogen without adjustment for the number of spots resulting from incubation of PBMCs without antigen.

§ Interpretation indicating that Mycobacterium tuberculosis infection is likely.

** Interpretation indicating an uncertain likelihood of M. tuberculosis infection.

†† Interpretation indicating that M. tuberculosis infection is not likely.

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



<http://www.tbtesting.com/TB%20Testing>

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)

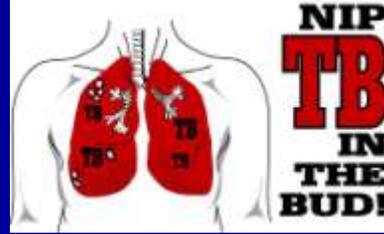
- When the initial test is **positive**:
 - 1) When additional evidence of infection is required to encourage compliance
 - 2) In healthy persons who have a low risk for both infection and progression

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



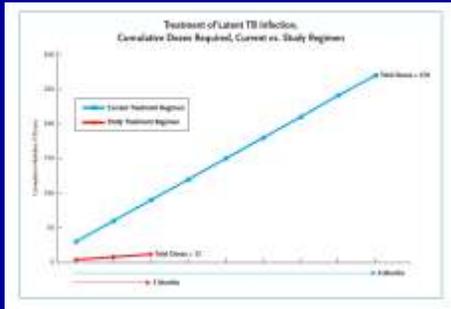
Neither an IGRA nor TST can distinguish LTBI from active tuberculosis!

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