DIAGNOSIS AND MANAGEMENT OF LATENT TUBERCULOSIS

R. Bryan Rock, M.D.
Division of Infectious Diseases and International Medicine, University of Minnesota
Hennepin County Public Health Clinic
What is the Difference Between Tuberculosis Disease and Infection?

- **Tuberculosis Infection**
  - Latent tuberculosis infection (LTBI)
  - Identified as a positive tuberculin skin test (TST) in the absence of focal disease
  - Estimated 2 billion with LTBI

- **Tuberculosis Disease**
  - Active disease in an organ
  - 9 million cases annually world-wide

Why should we care about LTBI

- **LTBI**
  - Dormant state following primary infection
  - Persists for life
  - Estimated 5-10 million cases in the US

- Prevent progression of infection to disease

- Interrupt transmission of disease
  - The next step that must be taken to move toward TB elimination in the US
**LTBI vs. Pulmonary TB Disease**

**Latent Tuberculosis Infection**
- TST or IGRA positive
- Negative chest radiograph
- No symptoms or physical findings suggestive of TB disease

**Pulmonary Tuberculosis Disease**
- TST or IGRA usually positive
- Chest radiograph may be abnormal
- Symptoms may include one or more of the following: fever, cough, night sweats, weight loss, fatigue, hemoptysis, decreased appetite
- Respiratory specimens may be smear or culture positive

Division of Tuberculosis Elimination
Centers for Disease Control and Prevention, 2005
• Persons with recent close contact with persons known to have active tuberculosis
• Health care workers who work at facilities where patients with tuberculosis are treated

• Foreign-born persons from countries with a high prevalence of tuberculosis
• Homeless persons
• Persons living or working in facilities providing long-term care

• HIV-infected persons
• Persons with recent tuberculosis infection†
• Injection-drug users
• Patients with end-stage renal disease
• Patients with silicosis
• Patients with diabetes mellitus
• Patients receiving immunosuppressive therapy
• Patients with hematologic cancers
• Malnourished persons or those with a recent weight loss of more than 10% of their ideal body weight
• Persons who have undergone gastrectomy or jejunoileal bypass

**High Risk of Exposure**

**High Risk of Infection**

**High Risk of Conversion from Infection to Active Disease**

---

**Number of TB Cases in U.S.-born vs. Foreign-born Persons United States, 1993–2008***

*Updated as of May 20, 2009.*
Substance abuse is the most commonly reported behavioral risk factor among patients with TB in the U.S.

Patients who abuse substances are more contagious and remain contagious longer because treatment failure extends periods of infectiousness.

Contacts of Active TB Case

- Among close contacts approximately 30% have LTBI and 1-3% have active TB disease.

- Without treatment, approximately 5% of contacts with newly acquired LTBI progress to TB disease within 2 years.

- Examination of contacts is one of the most important activities for identifying persons with disease and with LTBI.
Specific Medical Conditions Which Increase Risk for Progression to Active Tuberculosis

- HIV infection
- Chronic renal failure
- Diabetes mellitus
- Malignancy
- Silicosis

- Immunosuppressive Rx
- TNF Alpha blocker therapy
- > 15 mg Prednisone/day
- Transplant recipients

Adapted from David Griffith

Diagnosis of Latent Tuberculosis

- No gold standard exists
- Tuberculin Skin Test (TST)
- Interferon-gamma release assays (IGRAs)
  - Quantiferon TB-Gold In-Tube (Cellestis)
  - T-SPOT TB (Oxford Immunotec)
Tuberculin Skin Test (TST)

- Tuberculin is a broth culture filtrate of tubercule bacilli developed in 1891
- Specificity is a major shortcoming
- Anergy in patients with high risk of disease
- Inter- and intra-reader variability

Robert Koch injects one of his patients with tuberculin. He hoped that it would be a cure to tuberculosis.

Correct Measurement
### Tuberculin Skin Testing

**Reaction ≥5 mm of induration**
- Human immunodeficiency virus (HIV)-positive persons
- Recent contacts of tuberculosis (TB) case patients
- Fibrotic changes on chest radiograph consistent with prior TB
- Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of \( \geq 15 \text{ mg/d of prednisone for 1 mo or more} \))

**Reaction ≥10 mm of induration**
- Recent immigrants (i.e., within the last 5 yr) from high-prevalence countries
- Injection drug users
- Residents and employees of the following high-risk congregate settings: prisons and jails, nursing homes, and other long-term facilities for the elderly, hospitals, and other health care facilities, residential facilities for patients with AIDS, and homeless shelters
- Mycobacteriology laboratory personnel
- Persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head or neck and lung), weight loss of \( \geq 10\% \) of ideal body weight, gastrectomy, and jejunileal bypass
- Children younger than 4 yr of age or infants, children, and adolescents exposed to adults at high-risk

**Reaction ≥15 mm of induration**
- Persons with no risk factors for TB

**Unique to:**
- **M. tuberculosis**
- **Pathogenic M. bovis**
- **M. kansasii**
- **M. szulgai**
- **M. flavescens**
- **M. marinum**

**Antigens:**
- ESAT-6
- CFP-10
- TB7.7

![Tuberculin Skin Testing Diagram](image)
Blood Test for LTBI

- Quantiferon (Cellestis)
- Quantiferon TB-GOLD (Cellestis)
- T-SPOT TB (Oxford Immunotec)
- Quantiferon TB-Gold In-Tube (Cellestis)

**QuantiFERON® TB Gold In-Tube Test**

- **Heparinized Whole Blood (1mL)**
- **T-lymphocytes**
- **Phytohemagglutinin**
- **Saline**
- **TB7.7**, **CFP-10**, **ESAT-6**

16-24 h Incubation

Centrifuged

Interferon $\gamma$ by ELISA
Interpretation of QuantiFERON® TB Gold In-Tube Test

<table>
<thead>
<tr>
<th>TB Antigen minus Nil (IU/mL)</th>
<th>Nil (IU/mL)</th>
<th>Mitogen minus Nil (IU/mL)</th>
<th>QFN-G Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.35 &amp; ≥25% of Nil</td>
<td>≤8.0</td>
<td>Any</td>
<td>Pos</td>
<td>M. tuberculosis likely</td>
</tr>
<tr>
<td>&lt;0.35 OR ≥0.35 &amp; &lt;25% of Nil</td>
<td>≤8.0</td>
<td>≥0.5</td>
<td>Neg</td>
<td>M. tuberculosis unlikely, but cannot rule-out</td>
</tr>
<tr>
<td>&lt;0.35 OR ≥0.35 &amp; &lt;25% of Nil</td>
<td>≤8.0</td>
<td>&lt;0.5</td>
<td>Indet</td>
<td>Cannot be interpreted due to low mitogen response</td>
</tr>
<tr>
<td>Any</td>
<td>&gt;8.0</td>
<td>Any</td>
<td>Indet</td>
<td>Cannot be interpreted due to high background response</td>
</tr>
</tbody>
</table>

**QuantiFERON® TB Gold In-Tube Test**

- **Good performance**
  - Active TB: 89% pos
  - No known exposure: 98% neg

- **83% agreement with TST**

- **Discordant with TST in BCG vaccinated**
  - 41% agreement vs. 80% in non-vaccinated
  - 332 HCW (BCG-vaccinated, Japan)
    - TST: 93.1% pos
    - QFN: 9.9% pos

References:

- Mori et al., Am J Resp Crit Care Med 2004;170:59-64
- Mazurek et al., JAMA 2001;286:1740-7
- Harada et al., Infect Control Epi 2006;27:442-8
Guidelines for Using the QuantiFERON-Gold® Test for Detecting *Mycobacterium tuberculosis* Infection, United States

- CDC recommends that QFN-G may be used in all circumstances in which the TST is currently used

Cautions and Limitations

- Cannot distinguish LTBI from TB disease
- There is an 8-10 week incubation period after exposure
**T-SPOT.TB**

Add cells to wells coated with anti-IFN-gamma antibodies

IFN-gamma binds to antibodies

Add second antibody and substrate, which gives color change

Each spot represents one IFN-gamma-producing cell

Nil

Ag 1

Ag 2

Mitogen

---

**Interpretation of Results**

- Results are interpreted by subtracting the spot count in the NIL control well from the spot count in each of the antigens, according to the following algorithm:

  - The test result is **Positive** if (ESAT-6 minus NIL) and/or (CFP-10 minus NIL) \( \geq 8 \) spots

  - The test result is **Borderline** (equivocal) where the highest of (ESAT-6 minus NIL) or (CFP-10 minus NIL) spot count is 5, 6 or 7 and retesting by collecting another sample is recommended

  - The test result is **Negative** if (ESAT-6 minus NIL) and/or (CFP-10 minus NIL) \( \leq 4 \) spots. This includes values less than zero.
T-SPOT.TB®

- Requires washing in triplicate
- $2.5 \times 10^5$ cells per well
- Cells may settle
- Pipette can damage membrane
- Incubation time must be exact
- >5 spots is positive

T-SPOT.TB® compared with QuantiFERON®

- Immune deficiency
  - Corrects T-cell number
  - T > Q
- Under age 5
  - T > Q
- Contacts
  - T > Q
- Indeterminate
  - T > Q
  - (11% vs. 3%)
- BCG
  - T = Q
- Ease of use
  - Simpler lab test
  - Can freeze after incubation
  - Q > T

Lee et al., Eur Respir J 2006;28:24-30
Ferrara et al., Lancet 2006;367:1328-34
IGRA Caveats

- Short-term variability commonly occurs with both T-SPOT.TB® and QuantiFERON®

- A significant increase in mean QFT-Gold IFN-γ responses was noted by day 7 post-TST that persisted for up to 3 months after the TST
  - Results can be boosted by TST (between 3 days and 3 months)
  - QFT-Gold testing should not be done more than 3 days after TST

- Results of IFNγ based tests change with treatment (sometimes without treatment)
  - Do these tests offer clues to pathophysiology, treatment course and response?

"Until information is available to define IGRA conversion, results of serial IGRA testing will be largely uninterpretable." Ann Intern Med 2007; 146: 340

Evidence-based comparison of commercial interferon-gamma release assays for detecting active TB-a meta-analysis

- Pooled sensitivity
  - TST 70%
  - QFT-IT 81% - 84% (developed countries)
  - T-Spot.TB 88% - 90% (developed countries)

- Pooled specificity
  - QFT-IT 99%
  - T-Spot.TB 88%

- Pooled indeterminate results
  - QFT-IT 2.1% - 4.4% (immune compromised)
  - T-Spot.TB 3.8 – 6.1% (immune compromised)

- Newest IGRAs are superior to TST for detecting confirmed active TB disease

Adapted from David Griffith
Patient acceptance of a positive IGRA test may be higher

- Cleveland Clinic: 2500 HCWs hired annually
- 80% are foreign born
- Only 11% with a positive TST agreed to take INH
- 53% who later had positive QFT assay agreed to take INH


Who Should be Treated for LTBI?

- A decision to test is a decision to treat!
  - Tests should only be placed on persons who would benefit from treatment
  - Occasional tests placed for administrative reasons and these individuals should be evaluated on a case by case basis regarding initiation of treatment

Adapted from David Griffith
Standard Components of TB/TLBI Evaluation

- **Patient History**
  - Symptoms
  - History, co-morbidities, demographics, family history

- **Physical examination**

- **Radiologic evaluation**
  - CXR, CT, MRI

- **Laboratory testing**
  - Tuberculin Skin Test (TST),
  - Interferon Gamma Release Assays (IGRA):
    - QFT Gold In Tube, TSpot TB
  - If available: CBC, LFTs, sputum smears/cultures, Tissue histology

Clinical Evaluation: CXR

- Obtain CXR if new TST positive or symptoms of TB

- May be indicated in some asymptomatic, TST negative contacts at increased risk
  - Children 4 years and younger
  - HIV infected
  - Immunosuppressed

Adapted from David Griffith
Treatment of LTBI

- INH x 9 months
- Rifampin 600mg daily x 4 months for adults,
- Rifampin daily for 6 months for children
- Possible alternate:
  - INH & Rifampin x 3 to 4 months
  - INH, Rifampin, EMB & PZA x 2 months
- REVOKED: Rifampin/PZA x 2 months
- Rifapentine & INH weekly x 12 months??

Division of Tuberculosis Elimination
Centers for Disease Control and Prevention, 2005

Duration of INH Therapy for LTBI

- IUAT study of INH 3, 6 or 9 months
- Reduction in culture positive TB at 5 years:

<table>
<thead>
<tr>
<th>All participants</th>
<th>Completers</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months therapy</td>
<td>6 months therapy</td>
</tr>
<tr>
<td>65%</td>
<td>69%</td>
</tr>
<tr>
<td>12 months therapy</td>
<td>12 months therapy</td>
</tr>
<tr>
<td>75%</td>
<td>93%</td>
</tr>
</tbody>
</table>

Bulletin WHO, 1982
LTBI Treatment Acceptance and Completion in the U.S. and Canada  
Horsburgh et al Chest 2010, 137; 401

- Employees at health care clinics more likely to decline therapy

- Risk factors for failing to complete treatment:
  - 9 month INH regimen
  - Residence in a congregate setting
  - Injection drug use
  - Age \(\geq 15\) years
  - Employment at health care facility

- Overall, fewer than half of the people starting LTBI therapy completed treatment

Compliance

- Only 30-60% of patients who start tx complete at least 6 months

- Adherence decreases with time while efficacy increases with time!

- Refer to public health department for management

INH Hepatotoxicity

- Asymptomatic elevation of aminotransferases
  - 20% of patients

- Clinical hepatitis
  - 0.6% of patients

- Fulminant hepatitis (hepatic failure):
  - Approximately 4/100,000 persons completing therapy
    (continued INH with symptoms of hepatitis, prior INH hepatotoxicity, malnutrition)

Severe INH Liver Injuries Among Persons Being Treated for LTBI, U.S., 2004-2008 MMWR 2010 59(08); 224-229

- CDC project to monitor SAEs with treatment of LTBI 2004-2008

- 17 patients with SAEs, all hepatotoxicity
  - 2 children < 15 yrs of age
  - Adults median age 39
  - Diagnosed between 2nd and 9th month
  - One patient HIV seropositive for Hep C, HIV
  - 5/17 liver transplant (one child), 5/17 died (one transplant)

Adapted from David Griffith
Severe INH Liver Injuries Among Persons Being Treated for LTBI, U.S., 2004-2008  MMWR 2010 59(08); 224-229

- 10 patients with CDC on-site investigation
- All patients had indications for LTBI treatment, were prescribed INH within recommended dosage range, took the medication as prescribed
- Prescribers followed ATS/CDC guidelines for monthly clinical monitoring
- Baseline ALT WNL for 5 patients, 2 patients with monthly ALT monitoring

Evaluation of the 10 patients with CDC on-site investigation
- Symptoms 1-7 months after INH started
- Fatigue, nausea, abdominal pain in 7 patients who waited for jaundice to seek medical attention
- 3/10 with possible predispositions
- 7/10 patients diagnosed by provider other than the prescriber of INH
- 2 patients INH discontinued within 3 days of symptoms, 8 stopped at least one week after symptom onset, all after medical instruction

Adapted from David Griffith

- Death and liver transplantation approximately 1/150,000 - 1/220,000 patients receiving LTBI treatment
- All patients monitored according to current guidelines
- SAEs idiosyncratic reaction, independent of dosing, possible anytime during treatment, can occur in children

INH Toxicity Monitoring

- The critical element for INH toxicity monitoring is CLINICAL MONITORING
Four Months Rifampin vs Nine Months INH for Treatment of LTBI

- **Menzies et al AJRCCM 2004, 170; 445**
  - Completion of therapy significantly better with rifampin with fewer side effect than INH

- **Lardizabal et al Chest 2006, 130; 1712**
  - Patients receiving rifampin were significantly more likely to complete therapy than those receiving INH

- **Menzies et al Ann Int Med 2008, 149; 689**
  - Significantly higher rate of treatment completion with fewer serious adverse events

Management of Close Contacts Who Have an Initial Negative TST

- **Asymptomatic with a negative CXR**
  - **Treatment with INH should be started for:**
    - HIV Infected
    - Children < 5
    - Significant Immunosuppressant
    - Repeat TST in 8 – 12 weeks

- **Symptomatic**
  - Evaluate for active tuberculosis
  - CXR, smears and culture
  - If a TB suspect, treat for TB disease

Adapted from David Griffith
Management of LTBI in Pregnancy in HIV negative women

- Evaluate patients at risk of progression during pregnancy with TST
- Asymptomatic TST positive women should have CXR after first trimester
- Symptomatic women should have immediate CXR to exclude active disease even in first trimester
- Increased risk of hepatotoxicity first 3 months postpartum

"Women should be counseled that x-ray exposure from a single diagnostic procedure does not result in harmful fetal effects. Specifically, exposure to less than 5 rad has not been associated with an increase in fetal anomalies or pregnancy loss."


Management of LTBI in Pregnancy in HIV positive women

- Increased morbidity and mortality in HIV TB in pregnant women noted in US and developing world
- HIV infected women with LTBI at risk of rapid progression to active disease
- Treatment of both LTBI and Disease should be aggressive and instituted when diagnosis is made.

Adapted from David Griffith.
Management of TST Positive Persons With an Abnormal CXR

- Isolated CXR with nodules and/or fibrotic lesions:
  - Collect sputum culture
  - Evaluate for symptoms
    - If no symptoms - wait
  - Repeat CXR

- If CXR stable at 2 – 3 months and cultures negative, treat LTBI

- Isolated CXR with nodules and/or fibrotic lesions:
  - If patient has any signs or symptoms of TB disease: the patient is a TB Suspect
    - Start 4 drugs
  - Never start a single drug in a patient with possible active TB

Management of Contacts of INH Resistant Tuberculosis

- Adults
  - Four months daily Rifampin

- HIV-infected
  - Six months daily Rifampin

- Children
  - Six months daily Rifampin

Adapted from David Griffith
Guidelines Available on the Diagnosis and Treatment of Latent TB Infection (LTBI)

- ATS/CDC. Treatment of Latent TB April 2000
- ATS/CDC/IDSA. Controlling Tuberculosis in the U.S. November 2005
- NTCA/CDC. Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis. December 2005
- CDC. Guidelines for Using the QuantiFERON-TB Gold Test for Detecting Mycobacterium tuberculosis Infection, United States. December 2005

Questions