Primary Care Management of Latent Tuberculosis Infection in the Foreign-Born

Investigators

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- Stacey Bryant RN, Research Coordinator
Definitions
Active TB Disease

- Tubercle bacilli in the body
- Usually positive skin test
- Infectious (before treatment)
- Symptoms of TB
- Chest x-ray usually abnormal
- Sputum smears and cultures usually positive
- An active “case” of TB

Granuloma breaks down and tubercle escape and multiply
## Symptoms of Active TB Disease

<table>
<thead>
<tr>
<th>Systemic Symptoms</th>
<th>Pulmonary Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>Coughing (duration of ≥ 3 weeks)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Chest pain (when breathing or coughing)</td>
</tr>
<tr>
<td>Fever</td>
<td>Hemoptysis</td>
</tr>
<tr>
<td>Night sweats</td>
<td></td>
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<tr>
<td>Chills</td>
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</tbody>
</table>
Latent TB Infection (LTBI)

LTBI is the presence of *M. tuberculosis* organisms (tubercle bacilli) without symptoms or radiographic evidence of active TB disease.
Latent TB Infection (LTBI)

- Tubercle bacilli in the body
- Usually positive skin test
- NOT infectious
- No symptoms
- Normal chest X-ray
- Sputum smears and cultures are negative
- Not a “case” of TB
Epidemiology
Active TB Incidence Worldwide, 2005

2 billion infected with LTBI!

(Active TB all forms [per 100,000 population per year])
Source: WHO Stop TB Department,
website: http://www.who.int/globalatlas/interactiveMapping/MainFrame2.asp
TB Case Rates,* United States, 2006

15 million infected with LTBI!

*Cases per 100,000.
Trends in TB Cases in Foreign-born Persons, United States, 1986–2006*

57% of cases in 2006 were foreign-born

*Updated as of April 6, 2007.
Percentage of TB Cases Among Foreign-born Persons, United States*

*Updated as of April 6, 2007.
TB Rates in Countries of Birth 2005

Source: World Health Organization
TB Case Rates by Age Group and Sex, United States, 2006

Highest Incidence is in 65+
Percent of Foreign-born with TB by Time of Residence in U.S. Prior to Diagnosis,* 2006

Over HALF of active TB cases in the Foreign-Born have been in the US more than 5 years!

*Data exclude foreign-born TB patients for when length of residence in the U.S. prior to diagnosis was unknown.
Countries of Birth of Foreign-born Persons Reported with TB
United States, 2006

- Mexico (25%)
- Philippines (11%)
- Viet Nam (8%)
- India (7%)
- China (5%)
- Haiti (3%)
- Guatemala (3%)
- Other Countries (38%)
Latent TB Infection Testing
Flow Chart for Latent TB Infection (LTBI) in Primary Care

Patient with risk factors for LTBI

TST (PPD)

Negative
No treatment; Document status in medical record

Positive
History/HIV risk, physical exam, chest x-ray

Normal
Candidate for LTBI Treatment

Abnormal
Refer to TB clinic for evaluation of active TB

Positive
Treatment of active TB by TB clinic

Negative

Note: Evaluate patient for LTBI testing and treatment regardless of BCG status
Rule out active TB disease before treatment for LTBI is started
Who Should Be Tested

Know the TB status of your *at risk* patients.

<table>
<thead>
<tr>
<th>Who is considered at risk?</th>
<th>What countries are considered TB endemic?</th>
</tr>
</thead>
</table>
| Foreign born patients from **TB endemic** countries, where prior TB exposure is almost certain | • **All** of Asia except Japan  
• **All** of Central and South America  
• **All** of Africa  
• **All** of Eastern Europe  
   (Yes, that is practically the whole world) |
Other Groups At High Risk for TB

<table>
<thead>
<tr>
<th>Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Close contacts of Active TB cases</td>
</tr>
<tr>
<td>• Usually taken care of by TB clinic</td>
</tr>
<tr>
<td>• Healthcare workers who serve high risk clients</td>
</tr>
<tr>
<td>• Residents &amp; employees of congregate settings</td>
</tr>
<tr>
<td>• Medically underserved/low-income groups:</td>
</tr>
<tr>
<td>• Homeless</td>
</tr>
<tr>
<td>• Migrant workers</td>
</tr>
<tr>
<td>• Street drug users</td>
</tr>
<tr>
<td>• Children with parents who have risk factors</td>
</tr>
</tbody>
</table>
Medical Conditions that Put People at High Risk for TB

<table>
<thead>
<tr>
<th>Medical Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV +</td>
</tr>
<tr>
<td>Renal dialysis</td>
</tr>
<tr>
<td>Immunocompromised</td>
</tr>
<tr>
<td>(&gt;15 mg prednisone qd for 1 month or more)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Silicosis</td>
</tr>
<tr>
<td>Cancer of the head and neck</td>
</tr>
<tr>
<td>Hematologic and reticuloendothelial diseases</td>
</tr>
<tr>
<td>Intestinal bypass or gastrectomy</td>
</tr>
<tr>
<td>Chronic malabsorption syndromes</td>
</tr>
<tr>
<td>Low body weight</td>
</tr>
<tr>
<td>Organ Transplant</td>
</tr>
</tbody>
</table>
Who needs repeat LTBI testing?

1) Healthcare workers
2) Close contacts to infectious TB cases
3) Frequent travelers to abroad
   - If baseline TST is negative, consider retesting your patients that have extended travel to high risk areas.
   - Do symptom review upon return and possibly retesting 8-10 week after return.
Reading the Tuberculin Skin Test (TST)

- Measure reaction in 48 to 72 hours
- Measure induration, not erythema (redness)
- Record reaction in millimeters, not “negative” or “positive”
- Ensure trained health care professional measures and interprets the TST (PPD)
Interpreting the TST (PPD)

A positive TST (PPD) is determined by

• The size of the induration
• The patient’s risk factors
Interpreting Tuberculin Skin Test Reactions

<table>
<thead>
<tr>
<th>5 mm or greater</th>
<th>10 mm or greater</th>
<th>15 mm or greater</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV positive persons</td>
<td>Immigrants from high-prevalence areas</td>
<td>No known risk factors</td>
</tr>
<tr>
<td>Recent contacts of persons with active tuberculosis</td>
<td>Injection drug users</td>
<td></td>
</tr>
<tr>
<td>Fibrotic changes on chest radiograph, consistent with tuberculosis</td>
<td>Residents and employees* of high-risk congregate settings</td>
<td></td>
</tr>
<tr>
<td>Patients with organ transplants and other immunosuppressed patients</td>
<td>Personnel in mycobacteriology laboratories</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Persons with clinical conditions that place them at high risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Children: &lt;4 years of age; all exposed to adults at high-risk</td>
<td></td>
</tr>
</tbody>
</table>

(Note: the CDC discourages testing of people at low risk for infection.)
TB screening for those coming to US

1) Refugees and Immigrants
   In Country of Origin
   • Evaluated for active TB ONLY
   In the US
   • Those applying for an adjustment of status are evaluated for LTBI but treatment is NOT mandated

2) Visitors, students, temporary workers, undocumented
   • Not evaluated

The Immigration Process does not take care of Latent TB Infection (LTBI) for you!
BCG

Should persons who have been vaccinated with BCG (Bacille Calmette-Guerin) be tested for LTBI

- According to CDC guidelines, persons who have received BCG should be tested for LTBI as otherwise indicated

How should the results be interpreted?

- Positive TST should be assumed to be due to TB infection, not BCG, and treatment should be recommended, unless contraindicated

Source: CDC TB Fact Sheet “BCG Vaccine” 2006.
Literature Review on BCG 2006

- 1500 papers reviewed from 1980-2005
- Data demonstrate that the TST (PPD) performs well on BCG vaccinated adult (15+) patients and on patients from high and intermediate incidence countries
- The effect of the BCG vaccine on TST (PPD) reaction decreases with increasing time since vaccination.
Conclusion:

• “Adults (15+) from intermediate and high-incidence countries are at high risk for LTBI and the results of tuberculin testing can be interpreted in the same manner, regardless of vaccination status.”

Treatment for Latent Tuberculosis Infection (LTBI)
Who Should be Treated for Latent TB Infection (LTBI)?

Anyone who has been diagnosed with latent TB infection is a candidate for treatment, if they also fulfill the following criteria:

• Willing and able to complete a full course of therapy
• Available to be monitored during the full course of treatment
• No medical contraindications such as active liver disease

(Note: careful assessment to rule out the possibility of active TB disease is always necessary before treatment for LTBI is started.)
Risk Factors for Progression from Latent TB Infection (LTBI) to Active TB Disease

Medical Conditions

Your patient’s TB infection may be latent now, but many factors could increase the risk of progression

- Immunosuppression
- Lymphoma, leukemia
- Diabetes
- Renal dialysis
- Malnutrition
- Silicosis
- Gastrectomy/jejunoileal bypass
- Head and neck cancer
- HIV +
Risk Factors for Progression from Latent TB Infection (LTBI) to Active TB Disease (cont.)

Drugs

Immunosuppressive agents

• Steroids (not inhaled) (prednisone >15 mg/day for 1 month or more)
• Cancer chemotherapy
• Cyclosporine
• Anti-Rheumatics*
  • Etanercept (Enbrel)
  • Infliximab (Remicade)
  • Adalimumab (Humira TM)
  • Anakinra (Kineret)

Case Example of Progression from LTBI to Active TB

Case #1:

- 68 yo Chinese man with latent TB untreated
- Hx of Hepatitis B with low level activity
- Family history of colon cancer
- Developed adenocarcinoma of the colon and was receiving chemotherapy
- Developed hemoptysis and was thought to have a lung metastasis
- Bronchoscopy aspirate grew TB
Case Example of Progression from LTBI to Active TB

Case #2

- 66 yo Vietnamese female with latent TB (untreated), diabetes inflammatory arthritis, and depression/PTSD
- Developed idiopathic thrombocytopenic purpura and began to have bleeding
- Treated with systemic high dose steroids in the hospital and developed milliary TB
- Died of complications

Source: from practice of PI, Carey Jackson, MD. Internal Medicine. International Clinic, Harborview Medical Center, Seattle, Washington.
# Current Treatment for LTBI

## Preferred Regimen

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Frequency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>300 mg</td>
<td>Daily</td>
<td>9 months</td>
</tr>
</tbody>
</table>

A minimum of 270 doses must be administered within 12 months.
# Alternative Regimens for LTBI

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Frequency</th>
<th>Duration</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>900 mg</td>
<td>Twice weekly</td>
<td>9 months</td>
<td>DOT</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>300 mg</td>
<td>Daily</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>900 mg</td>
<td>Twice weekly</td>
<td>6 months</td>
<td>DOT</td>
</tr>
<tr>
<td>Rifampin</td>
<td>600 mg</td>
<td>Daily</td>
<td>4 months</td>
<td></td>
</tr>
</tbody>
</table>
No Longer Recommended
Regimen for LTBI

Rifampin plus pyrazinamide x 2 months

This regimen has been associated with increased risk of severe hepatic injury and death

Monitoring of Patients on Treatment for LTBI

- Baseline and monthly laboratory testing *not needed* except for patients with:
  - HIV infection
  - Pregnancy or within 3 months post-partum
  - History of liver disease/heavy alcohol use
  - Patient on chemotherapy

- Evaluate patients monthly for:
  - Adherence to treatment
  - Symptoms of hepatitis (fatigue, weight loss, nausea, vomiting, jaundice)
Treatment of Patients
35 Years of Age and Older

• The CDC changed its guideline in 2000 and now encourages treatment of LTBI in all age groups
• Use clinical judgment in treating older patients

Hepatic Adverse Drug Effects of Isoniazid (INH)

- **Frequent** (~5%): Liver Enzyme Elevations
- **Infrequent** (~0.1%): Hepatitis

**Large Scale Study:**
- 11,141 treated with INH from 1989-1995
- 11 had hepatitis, no deaths
- **Overall rate was 1 per 1000 (or 0.1%)**

(Nolan CM, Goldberg SV, Buskin SE. JAMA. 1999 Mar 17;281(11):1014-8.)
Patients with Chronic Hepatitis B But No Active Liver Disease

Yes, they can receive treatment for LTBI

- Baseline liver function tests and at 1 month
- If the tests are normal at 1 month, no further testing is necessary unless symptoms develop
- If the tests are elevated at 1 month, continue monthly testing as long as levels are abnormal
- If any one of the liver function tests exceeds 3-5 times the upper limit of normal at any time, strongly consider stopping therapy
Counseling a Patient with LTBI

Don’t Say:

• “You’ve been exposed” to TB so you need to be treated.”

Say Instead:

• “You have been exposed AND infected with the TB bacteria. But don’t worry…”
Counseling a Patient with LTBI (cont.)

Good news:
• “You do not have the disease and you are not contagious to anyone.”

Bad news:
• “However, it is sleeping in your body and if you don’t treat it now it can wake up later and make you very ill and contagious to others.”
Counseling a Patient with LTBI (cont.)

Why get treated?

• “Treatment will prevent future disease and protect you and those close to you.”

Warning

• “Taking medication for 9 months is a long time but it takes that long to kill all the TB germs.”
• “TB germs are ‘TOUGH bugs’ … so take your medicine correctly and completely.”
Summary
Meeting the Challenge of LTBI

For every patient

• Assess TB risk factors
• If risk is present, perform TST (PPD)
• If TST (PPD) is positive, rule out active TB disease
• If active TB disease is ruled out, evaluate as candidate for LTBI treatment
• If good candidate, initiate treatment for LTBI
• If treatment is initiated, ensure completion
Latent TB Infection should be treated as a condition in itself which is a precursor to a serious and potentially fatal disease.

Much the same way we treat hypertension as a condition in itself because it significantly heightens risk of heart disease, renal failure, and stroke or place infants in car seats because of the significant risk of injury without them, so should we approach latent TB infection.

While the condition in itself is asymptomatic, the risks assumed by ignoring it are substantial.
Physicians Caring for At Risk Populations

- Always include TB in the DDX
- “THINK TB” and “TB RISK”
The following individuals provided consultation and review of this presentation:

- Masa Narita MD, TB Controller for Seattle-King County Public Health
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References


References (cont.)
