Targeted Testing and Treatment of Latent TB Infection

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Diagnosing TB infection and disease is a primary care issue...
Tuberculosis is Global

Figure 1. Estimated Per Capita Incidence Rates of Tuberculosis (All Forms) by Country in 1997

No estimates are available for disputed territories Taiwan, Kashmir, and Western Sahara. Estimates for French Guyana and Guadeloupe are included with France, following their system of case notification. Circled arrows represent islands off the map. Left, top to bottom: Cook Islands, French Polynesia, Pitcairn Island, Niue. Right, Tokelau, Samoa, American Samoa, Wallis and Futuna, Tonga. Printed with permission from the World Health Organization.
Tuberculosis is Local
United States of America

- 10-20 million infected individuals
- Pool of infected individuals grows by 400,000 per year due to legal immigration
- 2004, 81% of 14,511 TB cases among racial and ethnic minorities
Goals of Screening

- Identify active cases
- Identify infected persons likely to benefit from treatment of latent TB infection (LTBI)
- Surveillance
  - evaluate efficacy of institutional control measures
  - surrogate marker of TB case rate
  - prevalence of TB infection in a population
Who Should Be Screened

**NOT** the general population. Screening should be **targeted** to those at higher risk of TB.

- Populations with increased rates of TB infection
- Persons with increased risk of progression to active TB if infected

Program prioritization should be made on the basis of local epidemiologic data and the number of risk factors present in a given population or individual (e.g., shelters with high HIV rate, etc.)
Tuberculosis Screening: Determining Risk by Your Assessment

- Risk of infection
  - prior exposure to TB
    - current/recent exposure to TB
    - ongoing/chronic exposure

- Risk of disease progression
  - medical risk factors
  - history of prior TB
Risk of Infection

- Contacts of infectious TB cases

  *Risk associated with disease burden and presence of cough of the source case*

- Foreign-born persons from TB endemic countries

- Healthcare workers

- Correctional facilities (inmates and staff)

- Nursing homes

- Long-term care facilities

- Renal dialysis units
Risk of Infection (2)

Medically underserved/low-income groups:

- Homeless
- Migrant workers
- Low-cost hotel dwellers or crowded impoverished living conditions
- Street drug users
- Racial and ethnic minorities
- Children with parents that have TB risk factors
Risk of Progression

- HIV infection and other medical conditions
- Individuals with abnormal chest x-ray compatible with past TB
- Infants and children <5 yrs of age (sentinels of transmission)
Risk of Progression (2)

Recent infection (contacts and converters):

- 4-5% risk of developing active disease within the first 1-2 years
- Risk may double if contact is <4 years old
- 40% progression to disease in infants younger than 12 months
- HIV co-infected progression much higher than 7-10 per year%!!!!
Risk of Progression (3)

Medical conditions:

- Immunosuppression
- Lymphoma, leukemia
- Head and neck cancer
- Injection drug use
- Diabetes
- Malnutrition
- Renal failure
- Silicosis
- Alcoholism
- Gastrectomy/Jejunoileal bypass
Risk of Progression (4)

Immunosuppressive agents

- Steroids
- Cancer chemotherapy
- Cyclosporine

**New:** TNFa blockade

- Etanercept (Enbrel®)
- Infliximab (Remicade®)
- Adalimumab (HumiraTM)
MMWR Article

- California surveillance results:
  - 12 cases Jan. 2002 – Sept. 2003
  - 11 infliximab; 1 etanercept

- Risk factors for LTBI in 11/12

- Other immunosuppressive agents in 9/12
Frequency of Screening

- Retesting: dependent on ongoing risk of TB exposure

**Frequency:** dependent on degree of chronic TB exposure (use local epidemiology)

- Annual testing*: HCWs, long term-care residents, shelter or homeless CBO or substance recovery program staff
- Q 6 month testing*: TB clinic frontline staff, ER workers, pulmonologists performing bronchoscopy
- Periodic testing*: extended travel to high risk area

*Need to correlate with local epidemiologic data
Screening of Immigrants Entering the U.S. with TB Notifications

CDC classification system for TB notification before immigration (as of 1990)

- **Class A**
  Active case of TB, contagious, not cleared for further travel

- **Class B-1**
  TB, clinically active, not infectious

- **Class B-2**
  TB, not clinically active, not infectious
Screening of Immigrants Entering the U.S. with TB Notifications (2)

- Class is determined by x-ray and sputum smears only, *not* cultures.

- A high rate of active TB is found in Class B patients (higher than contact investigation!)

- Class B immigrants are allowed to enter the country, but they must report to a state-designated health officer within 1 month of arrival in the U.S. (NOT MANDATORY)
The Tuberculosis Evaluation

- Assess patient for risk for disease progression and LTBI treatment criteria
- Symptom review
- TB test (Mantoux or new blood test)
- CXR (BEWARE of inappropriate radiologist diagnosis “no active disease or infiltrates”)
Diagnosis of Tuberculosis Infection

TB Skin Test (TST)  QuantiFERON® Blood Test (QFT)
The Mantoux Tuberculin Skin Test (TST)

- One of two available standardized method for identifying LTBI. NO tine and multi-puncture tests!
- Must be read by trained health professionals: NO self or parent reading!
- 0.1 ml PPD tuberculin “5 TU” injected intradermally into the volar surface of the forearm
- Read 48-72 hours after placement (can read up to 7 days if positive)
- Record size of induration in millimeters
Mantoux TST: Not a Perfect Test

- Assume sensitivity = specificity = 95%
- When the prevalence of infection is 90%, the positive predictive value is 99%
- When the prevalence of infection is 1%, the positive predictive value is 15% [85% false positives]
Tuberculin Skin Test Interpretation: CDC/ATS/AAP Cut Points

> 5 mm
- HIV co-infection
- Immune compromise
- Recent contact to TB
- Suspected disease

> 10 mm
- Foreign-born from a HR country
- Drug-users
- Living in HR congregate setting
- Specific HR groups
- Children < 4 yrs old (AAP)

> 15 mm
- All others (low risk groups). Why did you test?
Tuberculin Skin Test Interpretation: Tuberculin Skin Test Conversion

- Signifies new infection
- CDC definition: >10 mm increase within 2 year period
- Problems with interpretation: conversions may actually represent BOOSTED reactions in some individuals
Tuberculin Skin Test Interpretation: False-negative Results

**Host factors**
- HIV
- Recent TB infection (<3 months)
- Infections (viral, fungal, bacterial)
- Other illness affecting lymphoid organs
- Live virus vaccination
- Imunosuppressive drugs
- Overwhelming TB
- Age (newborn, elderly)

**Technical factors**
- The tuberculin used (i.e., improper storage, contamination)
- Improper method of administration, reading and/or recording of results
Tuberculin Skin Test Interpretation: False-positive Results (2)

Causes

- Cross-reactions and boosted reactions from atypical mycobacterial infections and BCG
- Recent (<1 yr) or multiple BCG vaccination
- Misinterpretation of immediate hypersensitivity to tuberculin
- Switching tuberculin products (Tubersol with Aplisol)
Tuberculin Skin Testing “Boosting”

<table>
<thead>
<tr>
<th>Years</th>
<th>TST</th>
<th>TST</th>
<th>TST</th>
<th>TST TST</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td>11 mm</td>
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<td>5</td>
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<td>14 mm</td>
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<tr>
<td>31</td>
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<td></td>
<td>12 mm</td>
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</table>

Induration (mm)

- Infection
- TST
Tuberculin Skin Test Interpretation: The Booster Phenomenon (2)

Who needs two-step testing for booster response?

- Individuals who will be tested on a regular basis (i.e., yearly)
- Elderly in high risk groups (>55 years)

The booster dose is usually administered 1-4 weeks after initial PPD and read in 48-72 hours
Screening Individuals Who Are Likely to Have False-negative TST Results (Young Infants, HIV+s, Immunosuppressed)

- Chest x-ray – look for evidence of TB infection (e.g., hilar calcification, upper lobe fibrosis, calcified granuloma)
- Symptom review
- Assess TB risk factors
- Decision to provide LTBI treatment in the absence of a positive TB test should be based on risk of true infection and public health implications
New Test for Tuberculosis Infection: QuantiFERON®-TB Gold Test (QFT)

- Whole blood IFN $\gamma$ release assay
- Measures immune reactivity to $M.tb$
- Approved for use by the FDA: QFT 1g-11/01, 2nd generation-12/04
- CDC guidelines 1/31/03 MMWR, 52(RR02);15-18
- Current CDC guidelines: MMWR. December 16, 2005 / Vol. 54/ No. 49
  - Recommends use of the test in situations where the skin test is used
  - However, limited data on children and HIV infected adults
How QuantiFERON® is Performed

**Stage 1 Blood Culture**

- 5 cc Heparinized whole blood
- Transfer undiluted whole blood into wells of a culture plate and add antigens
- Culture overnight at 37°C
- TB infected individuals respond by secreting IFN-γ

**Stage 2 IFN-gamma ELISA**

- Harvest plasma from above settled cells and incubate 60 min in ‘Sandwich’ ELISA
- Wash, add substrate, incubate 30 min then stop reaction
- Measure OD, determine IFN-γ levels and interpret test

IFN-γ IU/ml

Standard Curve

OD 450nm
QFT vs. TST

—in vitro
—specific antigens with controls
—No boosting
—1 patient visit
—Minimal inter-reader variability
—Results in 1 day
—Stimulate w/i 12 hrs

—in vivo
—Single antigen group
—Boosting
—2 patient visits
—Inter-reader variability
—Results in 2-3 days
—Read in 48-72 hrs
Clinical Trial Results: QFT-1g

- 1,226 patients at 5 sites
- QFT-1g vs. TST agreement = 83.6%
- Factors associated with discordance
  - Prior BCG
  - NTM immune reactivity
  - Site bias in reading TST
  - TB treatment
  - Risk group studied

Mazurek J, et al. JAMA 2001;286:1740-1747
At Last….FDA Approved

QuantiFERON® “Gold”

— Specific *M. tb* antigens ESAT-6 and CFP-10

— Improved specificity: able to distinguish between TB and NTM, BCG infection

— Studies in contacts, HIV infected and children underway
## Species Specificity of ESAT-6 and CFP-10

<table>
<thead>
<tr>
<th>Tuberculosis complex</th>
<th>Antigens</th>
<th>Environmental strains</th>
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<tr>
<td></td>
<td>ESAT</td>
<td>CFP</td>
<td>ESAT</td>
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<tr>
<td><em>M. tuberculosis</em></td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><em>M. africanum</em></td>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td><em>M. bovis</em></td>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>→ BCG substrain</td>
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<tr>
<td>gothenburg</td>
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<tr>
<td>montreal</td>
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<tr>
<td>pasteur</td>
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</tbody>
</table>

Species Specificity of ESAT-6 and CFP-10

| *M. tuberculosis*    | +        | +                      |
| *M. africanum*       | +        | +                      |
| *M. bovis*           | +        | +                      |
| → BCG substrain      |          |                        |
| gothenburg           | -        | -                      |
| moreau               | -        | -                      |
| tice                 | -        | -                      |
| tokyo                | -        | -                      |
| danish               | -        | -                      |
| glaxo                | -        | -                      |
| montreal             | -        | -                      |
| pasteur              | -        | -                      |

- *M. abcessus*  
- *M. avium*   
- *M. branderi* 
- *M. celatum* 
- *M. cheloneae*
- *M. fortuitum*
- *M. gordonii*
- *M. intracellulare*
- *M. kansasii*  
- *M. malmoense* 
- *M. marinum*   
- *M. oenavense* 
- *M. scrofulaceum*  
- *M. smegmatis* 
- *M. szulgai*  
- *M. terrae*  
- *M. vaccae*  
- *M. xenopi*  

- -
# QFT-gold Comparison with QFT-1g and TST

<table>
<thead>
<tr>
<th></th>
<th>QFT-gold</th>
<th>QFT-1g</th>
<th>TST</th>
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<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>89.0%*</td>
<td>82.1%</td>
<td>65.7%</td>
</tr>
<tr>
<td></td>
<td>105 / 118 +ve</td>
<td>92 / 112 +ve</td>
<td>50 / 76 ≥ 5mm</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>98.1%</td>
<td>56.0%</td>
<td>35.4%</td>
</tr>
<tr>
<td></td>
<td>213 / 216 –ve</td>
<td>108 / 192 –ve</td>
<td>40 / 113 &lt; 10mm</td>
</tr>
</tbody>
</table>

*Mori, et al. AJRCCM 2004; 170:59-64*
QuantiFERON®: Advantages Over TST

- Single patient visit, result every time
- Does not cause boosting…no more 2-step testing!
- Less subject to reader bias
- Can distinguish between true TB infection and prior BCG or atypical mycobacterial infection – reduce/eliminate unnecessary treatment and evaluation
- Automated lab reporting (decrease data entry errors, better analysis potential)
- Inexpensive: $12-15/test kit, $20-30 w/ lab fees
QuantiFERON®: Disadvantages

- Blood sample must be processed within 12 hours
- More cumbersome to use in the field?
- Current guidelines limit use to certain groups (because more evidence needed to expand the guidelines)
- No long-term studies to determine disease progression in humans
QuantiFERON®: Current CDC Guidelines Based on QFT-1 Test

QFT recommended for:
- Initial and serial testing of persons with increased risk of infection
- Initial and serial testing of HCWs and others who have required serial testing
- Low risk individuals who require screening (e.g., military, school-age children, food handlers)

Not advised (yet):
- TB suspects, contacts, HIV infected persons, children <17 years, pregnant women
- Should not be used to confirm a TST result
- Should not be used to diagnose *M. avium* disease
QFT-gold: Real Life Applications in San Francisco

- MDR newborn contact to smear+ mother. BCG given X2. TST at 4 months negative
  - Results at 6 months
    - QFT-1: conditionally positive
    - QFT-gold: negative

- Feisty 4 yr old Chinese adoptee with hx of 2 BCGs and 12mm TST result. (New mom does not want to unnecessarily give the child INH when she is struggling to bond with her)
  - QFT-1: conditionally positive
  - QFT-gold: negative
Flowchart: Evaluation to Treatment of LTBI

At-risk person

Tuberculin test + symptom review

- Negative
  - Treatment not indicated
- Positive
  - Chest x-ray
    - Normal
      - Candidate for Rx of latent TB
    - Abnormal
      - Evaluate for active TB
Clinical Trials of Isoniazid Treatment of LTBI

**Efficacy of INH Based on Duration of Treatment and Compliance**

<table>
<thead>
<tr>
<th>Duration of INH</th>
<th>Risk Reduction</th>
<th>Compliant if Compliant</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mos</td>
<td>21%</td>
<td>87%</td>
</tr>
<tr>
<td>6 mos</td>
<td>65%</td>
<td>78%</td>
</tr>
<tr>
<td>12 mos</td>
<td>75%</td>
<td>68%</td>
</tr>
</tbody>
</table>

_Bull WHO 1982; 60:555_
## Cost-effectiveness of Isoniazid Treatment of LTBI

<table>
<thead>
<tr>
<th>Treatment Duration, mos</th>
<th>3</th>
<th>6</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net costs, $</td>
<td>47,500</td>
<td>75,000</td>
<td>192,000</td>
</tr>
<tr>
<td>Cases prevented</td>
<td>3.28</td>
<td>10.54</td>
<td>11.99</td>
</tr>
<tr>
<td>Cost per case prevented</td>
<td>$14,488</td>
<td>7,112</td>
<td>26,024</td>
</tr>
</tbody>
</table>

Snider JAMA 1986; 255:1579
Current Guidelines for Tuberculosis Prevention: Changes from the Past

- DECISION TO TEST IS DECISION TO TREAT!
- No 35-year-old cut-off
- 9 months of INH preferred over 6 months
- Baseline laboratory monitoring not routinely indicated
Treatment of Latent TB Infection
How long is enough?

- Lower TB rates among those who took 0-9 mo
- No significant further decrease in rates among those who took >9 mo

New Tuberculosis Guidelines for INH
A Numbers Game

HIV Co-Infection

Children

Prior TB on CXR (TB-4)

Regular Folk
Current Options for Treatment of Latent TB Infection

- Isoniazid for 9 months – either daily or twice weekly (6 months acceptable for programmatic reasons)
- Rifampin for 4 months (+/- INH)

ATS/CDC AFRCCM 2000;161:s221

**NOTE:** Rifampin/pyrazinamide 2 months regimen is no longer recommended due to severe liver injury and deaths

(CDC revision 8/03)
Treatment of Latent TB Infection in Special Situations

- Intermittent dosing: always DOT

- Contacts of INH-resistant TB: 4-6 months of rifampin (longer for children and immunocompromised)

- Use rifabutin in HIV-infected patients on protease inhibitors

- For persons intolerant of INH, use 4 months of rifampin
Monitoring Patients

- Baseline laboratory testing **not** needed except for:
  1) HIV infection
  2) pregnancy
  3) hx of liver disease/heavy EtOH use

- Evaluate monthly for:
  1) adherence
  2) symptoms of hepatitis
INH Hepatotoxicity in the Modern Era

- 11,141 patients treated with INH from 1989-1995
- 11 had hepatitis (defined by symptoms, ? AST, resolution after stopping INH), no deaths
- Overall rate was 1 per 1,000!

Nolan JAMA 1999;281:1014
Window Prophylaxis: LTBI Treatment of TB Exposed Individuals with Negative TB Test Results

Who should get window prophylaxis?

- High risk TB contacts (young children and immunocompromised/HIV+) who have initial negative TB test results AND significant TB exposure

When can window treatment be discontinued?

- HIV-negative children: 8-10 weeks after contact is broken to untreated case and repeat TB test negative
- Immunocompromised/HIV: Repeat testing may not be helpful because of false negative results
- Use discretion of your TB program (some programs will treat for 9 months, while others may use CD-4 counts, hours of exposure, bacillary burden of index case and environmental factors)
Re-treatment of Latent TB Infection

- Re-infection can occur
- Serious issue for immunocompromised individuals
- Recommended for those who have HIV infection, other diseases causing chronic immune suppression, and <21 years old who have been in contact with a smear-positive case
Counseling a Patient with Latent TB Infection

**NEVER SAY:** You’ve been “exposed” so you need to be treated

**INSTEAD:** You have been exposed AND *infected* with the TB bacteria. But don’t worry…

**Good news:** You do not have the disease and you are not contagious to anyone

**Bad news:** It is sleeping in your body and can wake up later, make you very ill and contagious to others
Counseling a Patient with Latent TB Infection (2)

Why get treated? Treatment will prevent future disease and protect you and those close to you.

Warning:

— Taking medication for 6-9 months is a long time but it takes that long to kill all or most of the TB germs.
— “TOUGH bugs”… so take your medicine correctly and completely.
Summary

- TB will remain a primary care issue until better control is established outside of the U.S. and within our inner cities.
- Physicians caring for at risk populations need to “THINK TB” and “TB RISK” and always include TB in the DDX.
- The specificity of the new blood test for TB offers a significant advance in our ability to accurately diagnose LTBI.
- Final Pearl: Absence of PPD reaction or negative QFT DOES NOT EXCLUDE DISEASE.
Resources for Tuberculosis Medical Consultation

- Local TB program
- Your Regional Training and Medical Consultation Center
- For the Western Region:
  Francis J. Curry National TB Center,
  TB Warmline (415) 502-4700 or (877) 390-6682