Overview to Diagnosis and Treatment of TB Infection and Disease

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TB INFECTION

TB EXPOSURE

You have been sharing the air you breathe with someone who has active TB
CHARACTERIZING THE EXPOSURE

- Frequency and duration of exposure
- Dilution effect (volume of air)
- Ventilation
- Exposure to ultraviolet light

RISK OF TB TRANSMISSION

Figure 2: Percentage of persons infected with Mycobacterium tuberculosis, by bacteriologic status of sputum and proximity to the source case—British Columbia and Saskatchewan, 1966–1971. Source: Reference 57.

TB INFECTION

- The TB organism has breached the barriers and caused infection

- Outcome of TB Infection
  - Latent TB Infection (LTBI) (90%)
    - No Active TB Disease
  - Active TB Disease (10%)
    - 50% Primary Progression in first 2 years
    - 50% Reactivation later in life
Clinical Presentation of LTBI

- No symptoms or signs of infection
- Positive tuberculin skin test or IGRA
- Chest x-ray may be normal, or show granulomata, pleural or parenchymal scarring
- NOT infectious

LTBI → ACTIVE TB DISEASE

- Recent infection
- HIV infection
- Chest x-ray abnormality
- Underweight by >10%
- Intravenous drug use
- Immunosuppression

LTBI → ACTIVE TB DISEASE

- Immunosuppression
  - HIV
  - Hematologic cancers
  - Medical Co-morbidities
  - Medications
    - TNF-α inhibitors
    - Prednisone >15 mg, > 4 weeks
    - Chemotherapy
    - Other immunosuppressive drugs
LATENT TB INFECTION
What’s really happening?

• Bacteria are dormant (metabolically inactive). They later start to divide for reasons that are not clear.

• Bacteria are metabolically active and dividing, but infection is controlled by the immune system.
  – Disease develops when immunity is compromised

Latent Tuberculosis Infection (LTBI)

Latent Tuberculosis Infection (LTBI)
TB Infection Diagnosis

Who Should be Tested for TB Infection?
Targeted Testing for TB Infection

- Contacts of persons with active TB
- HIV positive individuals
- Recent immigrants (<5 yrs) from high prevalence countries
- Injection Drug Users
- Residents and Employees of high risk congregate settings:
  - Correctional facilities and Homeless Shelters
  - Hospitals, Clinics, Nursing Homes, Substance Abuse Facilities
- Newest Category:
  - Patients considering treatment with TNF-α Antagonists

Contacts of Active TB Case

- Among close contacts to a TB Case:
  - 30% have TB Infection
  - 1-3% have active TB disease

- Without TB Infection treatment:
  - 10% with TB Infection with develop Active TB
  - Approximately 5% of contacts with newly acquired TB Infection progress to TB disease within 2 years
  - The other 5% activate >2 years after acquisition

- Examination of contacts is one of the most effective strategies for TB Infection diagnosis and TB control!
Number of TB Cases in U.S.-born vs. Foreign-born Persons, United States, 1993–2014*

<table>
<thead>
<tr>
<th>Year</th>
<th>U.S.-born</th>
<th>Foreign-born</th>
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<tbody>
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<td>1993</td>
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<td>2012</td>
<td></td>
<td></td>
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<tr>
<td>2013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014</td>
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</tbody>
</table>

*Updated as of June 5, 2015.

Who Should be Tested for TB Infection?
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  - Patients considering treatment with TNF-α Antagonists

Percent of Foreign-born with TB by Time of Residence in U.S. Prior to Diagnosis, 2014

- Mexico
- Philippines
- Vietnam
- All Other Foreign-born

*Foreign-born TB patients for whom information on length of residence in the U.S. prior to diagnosis is unknown or missing.
Tests for Diagnosis of TB Infection

TB Infection Diagnostics

• TB Skin Test (TST)
• Interferon Gamma Release Assays (IGRA)

TB Skin Test (TST)

• Uses Purified Protein Derivative (PPD)
• PPD is given via intradermal injection
• Read induration, not erythema, at 48-72 hrs
TB Skin Test (TST)

- **Pros:**
  - Inexpensive
  - Simple to perform
  - (If you know what you are doing....)

- **Cons:**
  - Must return in 48-72 hrs
  - Interpretation is somewhat subjective
  - False Negatives:
    - Elderly
    - Immunosuppressed
  - False Positives:
    - Low risk populations
    - Non-tuberculous mycobacteria
    - BCG vaccination

Reading the TB Skin Test

Measure induration, not erythema!!!

Induration of ≥ 5mm
Considered a Positive TST

- HIV positive persons
- Recent contacts of TB cases
- Fibrotic Changes on CXR c/w prior TB
- Patients with organ transplants or other immunosuppression
  - Prednisone therapy 15 mg/day > 1 month

CDC. June 2000
Induration of ≥10mm
Considered a Positive TST

- Recent arrivals (<5 yrs?) high prevalence countries
- IVDU
- Residents/employees - high-risk congregate facilities (health care, prisons, shelters, etc.)
- TB lab personnel
- Children <4 yrs or exposed to adults at risk
- Persons with “high-risk” medical conditions

CDC. June 2000

Induration of ≥10mm
Considered a Positive TST

- Persons with “high-risk” medical conditions
  - Silicosis
  - Diabetes
  - Chronic renal failure
  - Hematologic disorders/leukemia/lymphoma
  - Cancers, particularly head/neck and lung
  - Low body weight less than 10% below ideal body weight
  - Gastrectomy
  - Jejunal bypass

CDC. June 2000

Induration of ≥15mm
Considered a Positive TST

- Persons with no risk factors
  (Why was a TST placed?)

CDC. June 2000
Interferon Gamma Release Assays (IGRAs)

TST vs In-vitro Assays

Antigens Specific to M. tuberculosis
Genetic Region of Difference 1 (RD-1)

- Not found in BCG or most NTM
  - NTM exceptions: M. kansasi, M. szulgi, M. marinum
- Codes for 9 proteins
- Two found to produce strong immunologic responses in persons infected with *M. tuberculosis*
  - 10-kDa culture filtrate protein (CFP-10)
  - 6-kDa early-secreted target antigen (ESAT-6)

Antigens for Newer Generation IGRAs

- Negative control or nil (e.g., saline, heparin)
- Positive control or mitogen: non-specific immune response stimulator (e.g., phytohemagglutinin)
- *M. tuberculosis*-specific antigens
  - Unlike PPD used in TST, do not cross-react with BCG or NTM (some exceptions)
  - ESAT-6, CFP-10, TB 7.7 (actually simulated using overlapping peptides)
**FDA-Approved IGRAs**

**QuantiFERON®-TB Gold-In-Tube (QFT-GIT)**

Stage 1: Whole Blood Culture in special blood collection tubes

Stage 2: Measure [IFN-γ] & Interpret

*Mtb = ESAT-6 + CFP-10 + TB 7.7*

**T-Spot.TB (T-Spot)**

- Collect blood in CFT tube
- Recover, wash, & count PBMCs
- Aliquot 250,000 PBMCs to 4 wells with anti-IFN-γ
- Add saline, PHA, ESAT-6 or CFP-10 & incubate
- Wash away cells
- Develop & count spots where cells produced IFN-γ
What Result is Considered Positive?

- Depends on the test
- Based on calculation of IFN-\(\gamma\) response to TB antigens relative to IFN-\(\gamma\) response to nil
- Unlike TST, not risk stratified (i.e., there are not multiple cutoffs for different risk groups)
- Still somewhat complicated
  - Software performs calculations

### Interpretation Criteria for the QFT-GIT Test

<table>
<thead>
<tr>
<th>Nil (IU/mL)</th>
<th>TB Antigen minus Nil (IU/mL)</th>
<th>QFT-GIT (IU/mL)</th>
<th>Mitogen</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 8.0</td>
<td>≤ 0.35 or &lt; 25% of Nil value</td>
<td>Negative</td>
<td>≥ 5.0</td>
<td>(M.) tuberculosis infection unlikely</td>
</tr>
<tr>
<td>≤ 8.0</td>
<td>≥ 0.35 and ≥ 25% of Nil value</td>
<td>Positive</td>
<td>ANY</td>
<td>(M.) tuberculosis infection likely</td>
</tr>
<tr>
<td>≥ 8.0</td>
<td>ANY</td>
<td>Indeterminate</td>
<td>ANY</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>≤ 8.0</td>
<td>≤ 0.35 and or &lt; 25% of Nil value</td>
<td>Indeterminate</td>
<td>&lt; 5.0</td>
<td>Indeterminate</td>
</tr>
</tbody>
</table>

### QuantiFERON-TB Gold

TABLE 2: TEST SENSITIVITY AND SPECIFICITY FOR CFP-10 AND ESAT-6 AT VARIOUS CUTOFFS IN WHOLE-BLOOD MANToux

<table>
<thead>
<tr>
<th>CFP-10</th>
<th>ESAT-6</th>
<th>CFP-10 and ESAT-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
<td>Sensitivity (%)</td>
</tr>
<tr>
<td>0.05</td>
<td>90.3</td>
<td>81.4</td>
</tr>
<tr>
<td>0.10</td>
<td>95.4</td>
<td>77.5</td>
</tr>
<tr>
<td>0.15</td>
<td>97.7</td>
<td>71.6</td>
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<tr>
<td>0.20</td>
<td>97.2</td>
<td>67.8</td>
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<tr>
<td>0.25</td>
<td>99.7</td>
<td>63.8</td>
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<tr>
<td>0.30</td>
<td>99.7</td>
<td>63.8</td>
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<td>0.35</td>
<td>99.7</td>
<td>63.8</td>
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<td>0.40</td>
<td>99.7</td>
<td>63.8</td>
</tr>
<tr>
<td>0.45</td>
<td>99.7</td>
<td>63.8</td>
</tr>
</tbody>
</table>

Sensitivity was determined in the blood of culture-negative patients with culture-positive tuberculosis, and specificity was determined on the basis of data from 118 low-risk subjects. The chosen cut-offs (IU/L) are in italics.
### Interpretation Criteria for the T-Spot.TB

<table>
<thead>
<tr>
<th>Result</th>
<th>Nil* Response</th>
<th>Mitogen++ Interpretation+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>≤ 10 spots</td>
<td>≥ 8 spots</td>
</tr>
<tr>
<td>Borderline</td>
<td>≤ 10 spots</td>
<td>5, 6, or 7 spots</td>
</tr>
<tr>
<td>Negative</td>
<td>≤ 10 spots</td>
<td>≤ 4 spots</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>&gt; 10 ≤ 10 spots</td>
<td>Any</td>
</tr>
</tbody>
</table>

### T-Spot.TB

- **Negative Result**
- **Positive Result**

### Indeterminate and Borderline Results

- **Indeterminate**
  - Negative control result is too high
    - High background production of IFN-γ
  - Positive control result is too low
    - Immunocompromised patients may not respond to mitogen

- **Borderline (T-Spot only)**
  - Falls within borderline zone close to negative/positive cut point
CDC Guidelines

MMWR
Morbidity and Mortality Weekly Report

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

Recommendations
CDC Recommendations

• TST or IGRAs should be used as aids in diagnosing infection with M. tuberculosis
  • Both the standard qualitative test interpretation and the quantitative assay measurements should be reported
  • As with the TST, IGRAs generally should not be used for testing persons who have a low risk of infection and a low risk of disease due to M. tuberculosis

CDC Recommendations

• Populations/situations in which IGRAs are preferred
  – testing persons from groups that historically have poor rates of return for TST reading
  – testing persons who have received BCG (as a vaccine or for cancer therapy)

CDC Recommendations

• Populations/situations in which TST is preferred
  – testing children younger than 5 years old
CDC Recommendations

• Populations/situations in which there is no preference between IGRAs and TST
  — testing recent contacts of persons with infectious tuberculosis
  — periodic screening that addresses occupational exposure to TB (e.g., surveillance programs for healthcare workers)

CDC Recommendations

• Routine testing with both TST and an IGRA is not recommended

• Results from both tests may be useful when the initial test is negative if increased sensitivity is desired (considered infected if either test is positive)
  — risk of infection, the risk of progression, and the risk of a poor outcome are increased
  — clinical suspicion of active tuberculosis and confirmation of M. tuberculosis infection is desired

• Results from both tests may be useful when the initial test is positive if increased specificity is desired (considered infected only if both tests are positive)
  — additional evidence of infection is required to encourage compliance (such as in foreign-born healthcare workers who believe their positive TST is due to BCG)
  — in healthy persons who have a low risk of both infection and progression

CDC Recommendations

• Repeating an IGRA or performing a TST may be useful when the initial IGRA result is indeterminate, borderline, or invalid, and a reason for testing persists
CDC Recommendations

- A diagnosis of *M. tuberculosis* infection, and the decisions about medical or public health management should include epidemiological, historical, and other clinical information when using IGRA or TST results
  - Decisions should not be based on IGRA or TST results alone
- Particularly relevant for managing discordant test results (e.g., TST+/QFT-)

Sources of variability for QFT-GIT

Pearls for TST vs. IGRA

- Discordance between the TST and IGRA has been measured up to 20% in patients known to be infected with *Mtb*. Don’t order both tests, pick the right test to start with!
- IGRA shine when used in BCG-vaccinated populations (increased specificity)
- No study has shown the IGRA to be ‘better’ in US-born (or non-BCG-vaccinated) individuals. The TST can be used AND trusted in this population
- No test (TST or IGRA) overrides clinical, epidemiologic or historical data
Treating TB Infection

First!

The single most important thing prior to starting treatment for TB Infection is to

RULE OUT ACTIVE DISEASE!!

Active TB Disease or TB Infection?
The Clinical Evaluation
Standard Components of TB disease/TB Infection Evaluation

• If the TST or IGRA is Positive
  – Patient History
  – Physical examination
  – Radiologic evaluation
  – ?Collect sputum or other specimens

Patient History

• Symptoms
  – Fever
  – Chills
  – Night Sweats
  – Weight Loss
  – Cough
  – Productive Cough
  – Hemoptysis

• PMH:
  – Diabetes
  – HIV
  – Other Immunosuppression
  – Silicosis
  – Drug/alcohol/tobacco
  – TB exposures or Risk?

Physical Exam

• Lung exam
• Check for lymph nodes
• Palpate liver
• Look for anything that will complicate therapy!
Radiologic Exam

• CXR must be done
• Must be normal
  Or
• IF abnormal:
  – Not consistent with Active TB
  – Stable abnormality confirmed over a 3 month period

Laboratory Exam

• Sputum AFB smear and culture
  – Collect if you suspect active disease
  – If you order, and AFB smear is negative, don’t start TBI treatment until cultures are negative – 6 weeks!!!!!

TB Infection Treatment
Who should be treated for TB Infection?

• 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

TB Infection Treatment Options

• CDC Recommended Treatment regimens:
  - INH x 9 months
    - Daily (5 mg/kg: 300 mg max) or BIW (15 mg/kg: 900 mg max)
  - Rifampin x 4 months
    - Daily (10 mg/kg: 600 mg max)
  - INH/Rifapentine x 3 months (3HP)
    - Once weekly DOT x 12 weeks
  - INH x 6 months (only if.....)
    - Daily or BIW

3HP

• Must be administered by DOT
• Approved for individuals >12 y/o
  - Published data shows safety down to age 2
• Dosing:
  INH:
    15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum
  RPT:
    10.0–14.0 kg 300 mg
    14.1–25.0 kg 450 mg
    25.1–32.0 kg 600 mg
    32.1–49.9 kg 750 mg
    ≥50.0 kg 900 mg maximum
Duration of Therapy

- INH 9
- Rifampin
- INH +RPT

9 months (270 doses)
4 months (120 doses)
12 weeks (12 doses)

The longer the duration/more doses, the less likely your patient is to complete Rx!
Fewer than 60% complete 9 months of INH!

INH TB Infection Therapy

INH Side Effects

- Hepatotoxicity
- Migraine Headaches
- Gastrointestinal
  - Nausea, Diarrhea, Constipation
- Rash
- Peripheral Neuropathy
  - Pyridoxine 50mg daily can help prevent this
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).


- "Medical providers should emphasize to patients that INH treatment should be stopped immediately upon the earliest onset of symptoms (e.g. excess fatigue, nausea, vomiting, abdominal pain, or jaundice), even before a clinical evaluation has been conducted, and that initial symptoms might be subtle and might not include jaundice."

Rifampin TB Infection Therapy
4 Months Rifampin vs 9 Months INH for Treatment of TB Infection

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

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

  - Significantly higher rate of treatment completion with fewer serious adverse events

Rifampin Treatment of TB Infection

- Pros:
  - Higher Completion Rates
  - Fewer Side Effects
  - Less Hepatotoxicity

- Cons:
  - Drug Interactions
    - Hormone Contraceptives
    - Warfarin
    - Prednisone
    - HIV Antiretrovirals
    - And many more... must look up all drugs for interactions!!
  - Orange Body Fluids
  - Other Potential Side Effects:
    - Rash
    - Thrombocytopenia
    - Anemia
    - Leukopenia
    - Allergic interstitial nephritis

INH/Rifapentine TB Infection Treatment
INH/Rifapentine TB Infection Therapy

• It is another effective regimen option for otherwise healthy patients aged ≥ 2 years who have a predictive factor for greater likelihood of TB developing including:
  – Recent TB contacts
  – TST/IGRA Converters
  – Radiographic findings of healed pulmonary TB

CDC. November 2011.

INH + RPT is NOT recommended for:

• Children under 2 y/o
• HIV infected persons on Antiretroviral Therapy
• Presumed INH or Rifampin Resistance in the source case
• Pregnant women

Pearls of Wisdom for Treating TB Infection

• Consider the shortest regimen possible to increase the odds of completion
• Be vigilant….and suspicious
• Be supportive….and forgiving
Management of TB Disease

Treatment Regimens for TB Disease

- **Initiation phase** of therapy
  - 8 weeks
  - INH, Rifampin and PZA +/- EMB

- **Continuation phase** of therapy
  - 16 weeks
  - INH and Rifampin

Treatment of Culture-Positive Drug Susceptible Pulmonary TB

- **General conclusions from the literature**
  - 6 mo (26 wk) is the **MINIMUM** duration of RX
  - 6 mo regimens require rifampin (and INH) throughout and PZA for the first 2 months
  - 6 – 9 mo regimens are effective without INH if PZA given throughout
  - Intermittent regimens (2-3x/wk): DOT ONLY!
    * Drug susceptible isolate
Treatment of Culture-Positive Drug Susceptible Pulmonary TB

• General conclusions from the literature:
  – Without PZA - minimum duration is 9 months
  – Without rifampin - minimum duration is 12 months (up to 18 months)

Questions?
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