TUBERCULOSIS SCREENING AND TREATMENT IN PREGNANCY

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Epidemiology of TB

- 9.6 million new cases in 2014
- 12% of them are in HIV positive patients
- 1.5 million deaths in 2014
- ~646 million women are infected worldwide
- Kills more women than any other infectious disease
- Can be vertically or horizontally transferred
- Spread through the air by droplets
- Pregnancy does not alter course

MAP 3-13. ESTIMATED TUBERCULOSIS INCIDENCE RATES

TB in the United States

Figure 1  Reported TB cases in the USA for 1982–2008\textsuperscript{9}
Who is at risk?

• HIV positive patients
• Close contact with persons known or suspected to have tuberculosis
• Medical risk factors known to increase risk for disease if infected
  • E.g. Immunocompromised, on TNF blockers
• Recent immigrants from TB endemic areas
• Low income
• IV Drug Use
• Alcohol addiction
• Residency in a long-term care facility (e.g. correctional institution, mental institution, nursing home)
• Health professionals working in high-risk health care facilities
Signs/Symptoms of Active TB

- Cough (74%)
- Weight loss (41%)
- Fever (30%)
- Malaise and fatigue (30%)
- Hemoptysis (19%)
- Abnormal CXR
  - Adenopathy
  - Multinodular infiltrates
  - Cavitation
  - Loss of volume in upper lobes
  - Upper medial retraction of hilar markings
- HIV infected patients can have normal CXR
Extrapulmonary TB

- Occurs in 16% of cases
- Occurs in up to 60 to 70% of AIDS patients with TB
- Can affect
  - Lymph nodes
  - Bone
  - Kidneys
  - Intestine
  - Meninges
  - Breasts
  - Endometrium
- Rare in pregnancy
Latent TB

- Positive PPD or blood test
- Asymptomatic
- Not infectious
- Negative CXR
- Negative Sputum Cultures
- Without treatment only 5 to 10% of HIV negative patients will progress to active disease (most likely to occur within 2 years of infection)
- 50% of HIV positive patients develop active disease within 2 years of infection
- 5-10% of patients with TB who acquire HIV will develop active disease each year
Screening Tests

- PPD (Mantoux Tuberculin Skin test)
- Interferon-Gamma Release Assays (IGRAs)
  - QuantiFERON® – TB Gold In-Tube test (QFT–GIT)
  - SPOT® TB test (T–Spot)
PPD (Tuberculin Skin Test)

- Tuberculin injected subcutaneously
- Delayed hypersensitivity reaction
- Must be read 48 to 72 hours later
- Requires two visits
- Measure induration (not erythema)
- Positive test is induration >5 to 15 mm depending on population
## Cutoffs for Positive PPD

<table>
<thead>
<tr>
<th>≥ 5mm</th>
<th>≥ 10 mm</th>
<th>≥ 15 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV positive individuals</td>
<td>Recent immigrants (&lt; 5 years) from high-prevalence countries</td>
<td>Considered positive in anyone</td>
</tr>
<tr>
<td>Recent contact of a person with active TB</td>
<td>Injection drug users</td>
<td></td>
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<tr>
<td>Fibrotic changes on CXR consistent with prior TB</td>
<td>Residents and employees of high-risk congregate settings</td>
<td></td>
</tr>
<tr>
<td>Patients with organ transplants</td>
<td>Mycobacteriology laboratory personnel</td>
<td></td>
</tr>
<tr>
<td>Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of &gt;15 mg/day of prednisone for 1 month or longer, taking TNF-α antagonists)</td>
<td>Persons with clinical conditions that place them at high risk</td>
<td></td>
</tr>
<tr>
<td>Children &lt; 4 years of age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infants, children, and adolescents exposed to adults in high-risk categories</td>
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</tbody>
</table>
# Causes of False Positive or Negative PPD

<table>
<thead>
<tr>
<th></th>
<th>False Positive</th>
<th>False Negative</th>
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</thead>
<tbody>
<tr>
<td>False Positive</td>
<td><strong>Infection with non tuberculosis mycobacterium</strong></td>
<td><strong>Weakened immune system and impaired cellular reactivity</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Previous BCG Vaccination</strong></td>
<td><strong>Recent TB infection within 8 to 10 weeks of exposure</strong></td>
</tr>
<tr>
<td>Technical Factors</td>
<td>• Improper Storage</td>
<td><strong>Very old TB infection</strong></td>
</tr>
<tr>
<td></td>
<td>• Improper placement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Improper Interpretation</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Technical Factors</strong></td>
<td><strong>Very young age &lt; 6 months</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Recent live virus immunization</strong></td>
<td><strong>Recent live virus immunization</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Overwhelming TB disease</strong></td>
<td><strong>Overwhelming TB disease</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Some Viral illnesses</strong></td>
<td><strong>Some Viral illnesses</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Technical Factors</strong></td>
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</tr>
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</table>

Modified from: http://www.mayomedicallaboratories.com/articles/communique/2010/01.html
Interferon Gamma Release Assays

- QuantiFERON® – TB Gold In-Tube test (QFT–GIT)
- SPOT® TB test (T–Spot)
- Measure immune reactivity to *M. tuberculosis*
- Interferon gamma released from white blood cells in patients with *M. Tuberculosis* infection when mixed with *M. tuberculosis* antigens

**Advantages**
- Single blood draw
- Does not require second visit for interpretation
- Results available in 24 hours
- Prior BCG does not affect results

**Disadvantages**
- Expensive
- Blood samples must be processed within 8-30 hours after collection while white blood cells are still viable
- Errors in collecting or transporting blood specimens or in running and interpreting the assay can decrease the accuracy of IGRA
<table>
<thead>
<tr>
<th></th>
<th>Specificity (%)</th>
<th>Sensitivity(%)</th>
<th>Affected by BCG Vaccine</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPD</td>
<td>97*</td>
<td>77**</td>
<td>Yes</td>
<td>Measures amount of skin induration based on cutaneous delayed-type hypersensitivity response to purified protein derivative</td>
</tr>
<tr>
<td>T-SPot</td>
<td>93†</td>
<td>90†</td>
<td>No</td>
<td>Measures the number of IFNγ producing T cells in reaction to the antigens ESAT-6 and CFP-10 produced by MTB and not in the BCG vaccine</td>
</tr>
<tr>
<td>QFT–GIT</td>
<td>96†</td>
<td>70†</td>
<td>No</td>
<td>Measures the IFNγ produced by T cells in reaction to the antigens ESAT-6 and CFP-10 produced by MTB, and not in the BCG vaccine</td>
</tr>
</tbody>
</table>

BCG, Bacille Calmette-Guerin; ESAT-6, early secretory antigen target-6; CFP-10, culture filtrate protein 10; MTB, *Mycobacterium tuberculosis*; IFN, interferon

* in non-BCG vaccinated individuals **From Pai et al. †From Lalvani et al
Which Test to Choose

• PPD
  • Children < 5 years old

• IGRA
  • Prior BCG Vaccine
  • Patient who is unlikely to return for PPD reading
Diagnostic Tests

- Culture for M. Tuberculosis
  - Sputum
  - Bronchoaveolar lavage
  - Gastric lavage
  - CSF
  - Urine
- Tissue biopsy
- Must be performed by experienced lab
- Negative test does not rule out infection
- Can take up to 6 to 8 weeks to get results
BCG Vaccine

- Bacille Calmette-Guerin
- Vaccine for TB
- Live vaccine made from mycobacterium bovis
- Used to prevent childhood tuberculous meningitis and miliary disease
- Has variable effectiveness against pulmonary TB
- Recommended for children in endemic areas
- Recommended for children exposed to active TB
BCG Vaccine and Screening Tests

• CAN still screen with PPD
  • Can cause false positive, most likely in those recently immunized
  • If >10 years since BCG vaccine assume infected with TB if positive PPD
• QuantiFERON® – TB Gold In-Tube test (QFT–GIT)
  • Not affected by BCG vaccine
• SPOT® TB test (T–Spot)
  • Not affected by BCG vaccine
Who to Screen (ACOG)

- **ONLY screen women at high risk of tuberculosis**
  - Known HIV infection
  - Close contact with individuals known or suspected to have TB
  - Medical risk factors known to increase risk of disease if infected
    - Diabetes
    - Lupus
    - Cancer
    - Alcoholism
    - Drug Addiction
  - Birth in or emigration from high-prevalence countries
  - Medically underserved
  - Homelessness
  - Living or working in long term care facilities such as correctional institutions, mental health institutions and nursing homes
Positive Result—Now what?

• Suspect active TB
  • Chest X-ray
  • Sputum culture x3
  • If evidence of active TB treat during pregnancy

• Suspect latent TB
  • Chest X-Ray
  • Consider treatment during pregnancy in those at high risk for conversion
  • When to treat controversial in those not at high risk for conversion
PPD Positive (Without prior treatment)

- **CXR Normal**
  - No respiratory symptoms
    - “High risk” or conversion within 2 years
      - Antepartum INH/B6
    - Old conversion >2 years or 1st positive PPD
      - If ≤ 35 years old Postpartum INH/B6
  - “High risk” or conversion within 2 years

- **CXR Abnormal OR other evidence of active disease**
  - Three morning sputum samples For smear/culture
    - Negative for AFB
      - If ≤ 35 years old Postpartum INH/B6
    - Positive for AFB
      - Immediate antepartum 3 drug therapy

Modified from Creasy & Resnik
Standard Treatment Active TB

- **CDC**
  - Isoniazid (10mg/kg daily, up to 300mg)*
  - Rifampin (10mg/kg daily, up to 600 mg)
  - Ethambutol (15mg/kg daily, up to 2.5 grams)
  - 3 Drug regimen x 2 months followed by INH and Rifampin x 7 months

- **WHO**
  - Isoniazid (10mg/kg daily, up to 300mg)*
  - Rifampin (10mg/kg daily, up to 600 mg)
  - Pyrazinamide (15-30mg/kg, up to 2 grams)
  - Ethambutol (15mg/kg daily, up to 2.5 grams)
  - 4 Drug regimen x 2 months followed by INH and Rifampin x 4 months

*Pyridoxine 25 to 50mg daily should be given with INH*
## Treatment for Latent TB

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosing</th>
</tr>
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<tbody>
<tr>
<td>Isoniazid (INH) + B6</td>
<td>300mg INH Daily + 50 mg B6 x 9 months (Preferred)</td>
</tr>
<tr>
<td></td>
<td>300mg INH Daily + 50mg B6 x 6 months</td>
</tr>
<tr>
<td></td>
<td>900mg INH Twice weekly + 50mg B6 x 9 months*</td>
</tr>
<tr>
<td></td>
<td>900mg INH Twice weekly + 50mg B6 x 6 months*</td>
</tr>
<tr>
<td>Rifampin</td>
<td>600mg daily x 4 months</td>
</tr>
</tbody>
</table>

*Twice weekly therapy should be given as directly observed therapy
B6 (25mg to 50mg daily) given to prevent peripheral neuropathy, should be given to infants of breastfeeding mothers
Modified from UptoDate
Drug Toxicity

• Isoniazid
  • Hepatitis
  • LFT’s should be checked prior to starting therapy
  • Monitor LFT’s during treatment
  • Pregnancy increases risk of hepatotoxicity
  • Screen for other Hep B, C and HIV
  • Stop treatment if asymptomatic and LFT’s 5x normal
  • Stop treatment if symptomatic and LFT’s 3 x normal
  • Other side effects include rash and neuropsychiatric symptoms
  • Peripheral neuropathy (Supplement with B6)

• Rifampin
  • Orange discoloration of secretions and urine
  • Hepatitis, Nausea, vomiting
Drug Toxicity (Continued)

- Ethambutol
  - Optic neuritis
  - Rash
- Pyrazinamide
  - Hepatotoxicity
  - Hyperuricemia
  - Arthralgias
  - Rash
Contraindicated Drugs in Pregnancy

- **Streptomycin**
  - Causes ototoxicity

- **Kanamycin**
  - Auditory, vestibular and nephrotoxicity

- **Amikacin**
  - Concern for ototoxicity and nephrotoxicity

- **Capreomycin**
  - Teratogenic in animals
  - No human data

- **Fluoroquinolones**
  - Affects cartilage development
Multidrug Resistant TB (MDR TB) 
Extensively Drug Resistant TB (XDR TB)

- **MDR TB**
  - Resistant to INH
  - Resistant to Rifampin

- **XDR TB**
  - Resistant to INH
  - Resistant to Rifampin
  - Resistant to a fluoroquinolone
  - Resistant to amikacin, kanamycin or capreomycin
Breastfeeding

• Not contraindicated if mother is being treated
• Infant of mother receiving INH should receive B6 supplementation
• Breastfeeding not recommended if on Rifabutin or fluoroquinolones
QUESTIONS?
References

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