Tuberculosis Intensive
San Antonio, Texas
April 3 – 6, 2012

Childhood Tuberculosis
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Kim Smith, MD, MPH has the following disclosures to make:

• No conflict of interests
• No relevant financial relationships with any commercial companies pertaining to this educational activity
Childhood Tuberculosis

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OUTLINE

• Stages of tuberculosis
• Differences of disease in children and adults
• Diagnostic challenges of pediatric TB
• Treatment of TB in children
• Clinical cases
Stages of Tuberculosis

Exposure to Contagious Adult with Pulmonary Disease

- Household contacts: 20-30%
- Latent TB Infection (LTBI)
  - Adult Active TB Disease: 5-10%
  - Child Active TB Disease: Risk varies by age 5-50%
### Percent Risk of Disease by Age

<table>
<thead>
<tr>
<th>Age at Infection</th>
<th>Risk of Active TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth – 1 year*</td>
<td>43%</td>
</tr>
<tr>
<td>1 – 5 years*</td>
<td>24%</td>
</tr>
<tr>
<td>6 – 10 years*</td>
<td>2%</td>
</tr>
<tr>
<td>11 – 15 years*</td>
<td>16%</td>
</tr>
<tr>
<td>Healthy Adults</td>
<td>5-10% lifetime risk</td>
</tr>
<tr>
<td>HIV Infected Adults+</td>
<td>30-50% lifetime</td>
</tr>
</tbody>
</table>

*Miller, Tuberculosis in Children
Little Brown, Boston, 1963

+WHO, 2004

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### Risk of Progression to TB Disease by Age

<table>
<thead>
<tr>
<th>Age @ primary infection</th>
<th>Risk of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth-12months</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>50%</td>
</tr>
<tr>
<td>Pulmonary Dis</td>
<td>30-40%</td>
</tr>
<tr>
<td>Miliary or TBM</td>
<td>10-20%</td>
</tr>
<tr>
<td>1-2 years</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>20-25%</td>
</tr>
<tr>
<td>Pulmonary Dis</td>
<td>75%</td>
</tr>
<tr>
<td>Miliary or TBM</td>
<td>2-5%</td>
</tr>
</tbody>
</table>

Marais BJ. *Int J Tuberc Lung Dis* 2004;8:392-402
### Pediatric Tuberculosis Treatment Table

<table>
<thead>
<tr>
<th>Stages of TB</th>
<th>Skin Test or IGRA</th>
<th>CXR</th>
<th>SXs</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| **Exposure** | Child < 4 years of age  
Household contact with adult with active pulmonary disease | Negative | Normal | None | Meds: INH  
Duration: 8-10 weeks  
Repeat skin test: 8-10 wks after exp if positive ≥ 5mm, see LTBI |
| **Latent TB infection (LTBI)** | Positive | Normal | None | Meds: INH  
Duration: INH 9 mo or for INH resistant LTBI, RIF 6 mo |
| **Disease** | Pulmonary and extrapulmonary (except disseminated disease and meningitis, see below)  
**Pulmonary and extrapulmonary (except disseminated disease and meningitis, see below)** | 90% positive | Abnormal | +/- | Meds: INH, RIF, PZA and an aminoglycoside  
Duration: 6 mo total  
Stop PZA after 2 mo for susceptible disease |
| **Disease** | Disseminated including miliary, bone/joint and multi-site disease  
TST may be negative early in disseminated TB, most positive by end of treatment | +/- | Yes | Meds: INH, RIF, PZA and EMB or an aminoglycoside  
Duration: 9-12 mo total  
Stop PZA and EMB or aminoglycoside after 2 mo for susceptible disease |
| **Disease** | Meningitis  
Often negative early in meningitis and miliary disease  
90% positive by end of tx | +/- | Yes | Meds: INH, RIF, PZA and an aminoglycoside or EMB or Ethionamide daily for 2 mo, then INH and RIF for 7-10 mo  
Duration: 9-12 mo total for drug susceptible disease  
Steroids recommended for first 1-2 mo for meningitis |
Daycare Exposure

- Index case, teacher assistant with AFB smear positive pulmonary disease and cough for 6 weeks
- 135 children < 4 years of age, plus adult staff members exposed

Daycare Exposure Management

- Who is at risk?
  - Children and staff

- Who needs TST?
  - Everyone with significant contact with source case

- Who needs CXR?
  - All children less than 4 years of age even if TST negative
  - Any contacts with positive TST (> 5mm)

- Who needs treatment?
  - LTBI (positive TST >5mm and normal CXR) INH for 9 months
  - Exposed children less than 4 years of age need INH window prophylaxis for 8-10 weeks

- Follow up?
  - Repeat TST 8-10 weeks after exposure
  - If negative and contact broken, stop INH prophylaxis
**Window Prophylaxis**

- **Exposure**
  - Household contact with contagious person
  - Usually > 4 hours of contact
  - Teen or adult with pulmonary TB disease
- **Initial TST negative**
  - Window period for TST conversion
    - (8-10 weeks)
- **CXR and physical exam normal**
- **INH prophylaxis recommended:**
  - For children <4 yrs of age
  - Prevention of disease during window period
- Repeat TST 8-10 wks after exposure
- May stop INH if 2nd TST negative <5mm and contact broken

**Preventable Case**
Pediatric TB Case a Missed Opportunity

15 mo old
- 10 days fussiness & decreased appetite
- 3 days inability to walk or sit up
- CSF: 96 WBC (NL <7), 72% Lymphs, 198 Protein (NL <45), Glucose 8
- Source case: mother of child
- Diagnosis: TB Meningitis

Family history
- Mom with pulmonary TB diagnosed 5 mo earlier on appropriate treatment
- Dad diagnosed with LTBI on INH
- Baby initial TST 0mm @ 10 months of age
  - no CXR
  - no treatment
  - lost to follow up

TB Meningitis
Treatment and Clinical Course

12 months RIPE therapy
- Steroids for 1-2 month with 2-3 week taper
  - decreases CNS inflammation
- Fever common for first month, symptoms may initially worsen followed by gradual improvement
- Possible complications
  - Seizures
  - Hydrocephalus
  - CNS tuberculoma, stroke, MR, CP
  - Mortality may be 100% if not diagnosed and treated
- This case was potentially preventable if treated with window prophylaxis when parent diagnosed
Differences In Adult and Pediatric TB

**Reactivation Disease**

- Occurs years after primary infection
- Typical of adult disease
- Occasionally seen in teens
- Often cavitary disease
- High numbers of organisms (AFB +)
- Usually symptomatic and contagious
Primary Disease

- Typical of childhood TB
- Usually not cavitary
- Classic x-ray:
  - **Hilar lymphadenopathy** with or without pulmonary infiltrates
  - Miliary infiltrates
- Low numbers of organisms
  - AFB smears negative in 95% of pedi cases
  - Culture negative in 60% of cases
- Most children <12 yrs not contagious
- Often asymptomatic (50%)
Pediatric Case
TB Disease

Father
- Cavitary pulmonary disease
- AFB smear positive
- Pansusceptible TB

9 year old son
- Contact investigation TST 5 mm
- Healthy kid with no symptoms
- Initial CXR with small pleural effusion
- No treatment started
- What was the diagnosis at this point?
Treatment and Follow up

- 6 weeks later
  - Fever
  - Respiratory difficulty
  - Worsening CXR

- What went wrong?
- What treatment recommended?
Adult TB Disease

- **Pulmonary**: 85%
- **Extrapulmonary**: 15%

Adult Extrapulmonary TB Disease (15%)

- **Lymphatic**: 25%
- **Pleural**: 23%
- **GU**: 16%
- **Other**: 13%
- **Bone/Joint**: 10%
- **Miliary**: 9%
- **Meningeal**: 4%
Pediatric TB Disease

- 75% Pulmonary
- 25% Extrapulmonary

Extrapulmonary TB Disease in Children (25%)

- 67% Lymphatic
- 14% Meningeal
- 5% Miliary
- 5% Other
- 4% Bone/Joint
- 6% Pleural

CDC
Symptoms of TB Disease in Children

- Cough and/or respiratory distress
- Pulmonary findings on examination
- Lymphadenopathy or lymphadenitis
- S/Sx of meningitis including seizures
- Persistent fever (FUO)
- Weight loss or failure to thrive
- Unlike adults, up to 50% of children with TB disease have no symptoms
Unique Challenges of TB in Children

- More difficult diagnosis
- Nonspecific signs and symptoms
- Fewer mycobacteria
- Fewer positive bacteriologic tests
- Increases risk of progression to disease
- Higher risk of extrapulmonary and TB meningitis

Diagnosis for TB in Children

- **Gold Standard** – Positive TB Culture
  OR, **Clinical Diagnosis**:  
  - Abnormal CXR, laboratory, or physical examination consistent with TB **AND**
  1 or more of the following:
  - Positive tuberculin skin test
  - Contagious adult source case identified
  - Clinical course consistent with TB disease, or
  - Improvement on TB therapy
Diagnostic Triad for TB Disease in Children

- Abnormal CXR and/or physical exam
- Positive TST or IGRA
- Infectious adult source case identified

AFB smears and Cultures in Children and Infants

- AFB smear usually negative
  - In 95% of patients <12 years of age
- Low yield on TB culture
  - Only 40% positive in children 1-12 yrs of age with pulm TB
- Obtaining cultures from children with pulmonary TB
  - Early morning gastric aspirates (x3)
  - Broncho alveolar lavage (BAL)
  - Induced sputum
- Infants with pulmonary TB
  - 60-70% cultures pos
### Gastric Aspirates

- Inpatient procedure
- Overnight fasting
- Lavage with NS
- Collected morning x3
- Inpatient costs substantial
- AFB smear yield: minimal
- AFB Culture yield: 20-50%

### Induced Sputum

- Outpatient procedure
- 2-3h fasting period
- Pretreatment:
  - Nebulized salmeterol and saline
  - Chest physiotherapy (CPT)
  - Nasopharynx suctioned
  - One specimen sufficient
- Minimal costs

Lancet. 2005;365:130
Lymphadenopathy

Clinical Case
Cervical Lymphadenopathy

- 8 yr old with cervical lymphadenopathy
- **History:**
  - LAN for 3 months
  - PMHx: Healthy
  - BCG vaccine at birth
  - TB skin test 10 mm
- **Physical Exam:**
  - 3 cm anterior cervical LAN
  - 1.5 cm supraclavicular LAN
- **CXR:**
  - Hilar LAN, no infiltrates
- Is this TB disease?
- What else could it be?
Hilar & Cervical Lymphadenopathy

**Differential Dx**
- Tuberculosis
- Non TB mycobacteria (NTM)
- Lymphoma/Leukemia
- HIV
- Other causes

**Diagnostic tests**
- Biopsy (FNA or surgical for culture and path)
- Interferon γ Blood test for TB infection

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**Results**

- **Fine needle aspirate of node:**
  - Pathology: lymphoma, no TB by culture or microscopy

- **Interferon γ Blood test for TB**
  - Positive
  - Diagnostic for latent TB infection or disease

- **Diagnoses:**
  - LTBI
  - Hodgkin’s Lymphoma

- **Treatment:**
  - Chemotherapy for lymphoma AND
  - INH daily for 9 months for LTBI
  - Consider prolonged treatment during immunosuppression
**IGRAs in Children**

- **Sensitivity**
  - Variable 60-90%
- **Highly specific**
  - Specificity 90-95%
  - Eliminates false positives from BCG or most other mycobacteria
- Single visit required
- Helpful (preferred) in BCG vaccinated patients
- Children <5 years of age
  - Not FDA approved in this age due to limited data
  - Consider either test (IGRA or TST) positive in high risk patients
- More expensive than TST but
  - Saves costs of unnecessary x-rays/medical visits and tx in patients with false positive TST
  - False positives reduced by 30% or more in BCG vaccinated populations

**QuantiFERON TB Meta Analysis in Children**

- Systematic review and meta analysis of QFT for diagnosing LTBI and TB disease in children – 20 of 68 studies used
- Conclusions:
  - LTBI: QFT has higher specificity compared to TST
  - Disease: Sensitivity of QFT was no different from the TST
  - Lower QFT sensitivity was found in high-burden settings (55%) compared with low burden settings (70%)

Machingaidze et al. *P&DJ* 2011; 30: epub
TABLE 2. Studies Comparing the Sensitivity of QFT With That of TST in the Diagnosis of Active TB Disease (All Cases) in Children

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Test Type</th>
<th>TB Burden</th>
<th>Age (yr)</th>
<th>Sample Size</th>
<th>No. TB Cases</th>
<th>TST Cutoff (mm)</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okada et al., 2008</td>
<td>QFT-G</td>
<td>High</td>
<td>&lt;5</td>
<td>105</td>
<td>19</td>
<td>10</td>
<td>79% 53%</td>
</tr>
<tr>
<td>Dogra et al., 2006</td>
<td>QFT-G IT</td>
<td>High</td>
<td>1–12</td>
<td>165</td>
<td>8</td>
<td>10</td>
<td>83% 63%</td>
</tr>
<tr>
<td>Bianchi et al., 2009</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>&lt;16</td>
<td>336</td>
<td>15</td>
<td>10</td>
<td>86% 94%</td>
</tr>
<tr>
<td>Haustein et al., 2009</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>&lt;16</td>
<td>337</td>
<td>27</td>
<td>6</td>
<td>73% 72%</td>
</tr>
<tr>
<td>Brdard et al., 2009</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>&lt;16</td>
<td>333</td>
<td>195</td>
<td>15</td>
<td>55% 52%</td>
</tr>
<tr>
<td>Kumpmann et al., 2009</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>&lt;16</td>
<td>300</td>
<td>63</td>
<td>15</td>
<td>69% 63%</td>
</tr>
</tbody>
</table>

*Year of publication.
QFT indicates QuantiFERON; TST, tuberculin skin test; TB, tuberculosis; QFT-G, QuantiFERON Gold; QFT-G IT, QuantiFERON Gold In-Tube.

Machingaidze et al. PIDJ 2011; 30: epub
Skin Test in Foreign Born

- 6 year old with positive TST for school entry
- Born in Asia
- BCG history
  - Vaccinated at birth
  - BCG scar present
- TST measures 12mm

CXR Normal

- How do you interpret the skin test?
- Is this BCG effect or LTBI?
- What tests may help?
**Algorithm for TB Testing in Children**

1. **TB Risk Questionnaire positive?**
   - Yes
   - No

2. **Age < 5 years?**
   - Yes
   - No

3. **BCG Vaccinated?**
   - Yes
   - No

4. **Initial TST Done?**
   - Yes
   - No

5. **TST Result?**
   - Positive
   - Negative
   - Indeterminate

6. **Concern for TB disease?**
   - Yes
   - No

7. **Likely to return for TST reading?**
   - Yes
   - No

8. **TST or IGRA Acceptable**

9. **IGRA Preferred**

10. **TST Preferred**

*If clinical suspicion of TB disease consider doing both tests and either positive TST or IGRA may be significant

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**TST Preferred, IGRA Acceptable**

- **Children < 5 years of age**
  
  Note: most experts would not use an IGRA to detect TB infection in a child < 2 years of age

**IGRA preferred, TST acceptable**

- **Children > 4 yrs of age who have had**
  
  BCG vaccine

- **Children > 4 years of age who are unlikely to return for TST reading**
What to do with Discordant IGRA and TST Results?

- Consider **either** test positive
  - If disease is suspected
  - If patient is at high risk for progression to disease (infants or immune compromised)

- For healthy patients without risk factors
  - Choose the more specific test (IGRA)

Monitoring Children on TB Treatment

- Risk of drug toxicity very low
- Monitor clinical signs
  - regular clinical visits (4-6 wks)
  - patient education
- Routine blood work not necessary unless
  - symptoms
  - risk factors for toxicity
- Monitor and reinforce adherence
- When to follow up CXR’s for pulmonary TB
  - Beginning and end of therapy
  - If clinical change
- Completion of therapy certificate
Management of TB Medication Reactions

- Hepatotoxicity
- Medication refusal in children
  - Crush tablets, medication sandwich
- Vitamin B6
  - Breastfed infants, teens & picky eaters
- Going back to school
  - Children <12 yrs of age are not contagious

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subcategory</th>
<th>All Patients</th>
<th>Completed</th>
<th>Defaulted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td>248</td>
<td>186 (76%)</td>
<td>62 (25%)</td>
</tr>
<tr>
<td>Age, y</td>
<td>Mean</td>
<td>7.4</td>
<td>7.2 (6.5-7.8)</td>
<td>8.2 (7-8.4)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>145 (59%)</td>
<td>108 (74%)</td>
<td>37 (26%)</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>68 (28%)</td>
<td>43 (74%)</td>
<td>15 (26%)</td>
</tr>
<tr>
<td></td>
<td>Non-Hispanic Black</td>
<td>38 (15%)</td>
<td>30 (79%)</td>
<td>8 (21%)</td>
</tr>
<tr>
<td></td>
<td>Non-Hispanic White</td>
<td>7 (3%)</td>
<td>5 (71%)</td>
<td>2 (29%)</td>
</tr>
<tr>
<td>Region of country of origin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>United States</td>
<td>61 (25%)</td>
<td>73 (89%)</td>
<td>38 (20%)</td>
</tr>
<tr>
<td></td>
<td>Latin America</td>
<td>48 (19%)</td>
<td>34 (71%)</td>
<td>24 (29%)</td>
</tr>
<tr>
<td></td>
<td>Asia</td>
<td>33 (13%)</td>
<td>24 (73%)</td>
<td>9 (27%)</td>
</tr>
<tr>
<td></td>
<td>Middle East</td>
<td>17 (7%)</td>
<td>10 (59%)</td>
<td>7 (41%)</td>
</tr>
<tr>
<td></td>
<td>N.D.</td>
<td>7 (3%)</td>
<td>3 (43%)</td>
<td>4 (57%)</td>
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<tr>
<td>No. medications used</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 drug</td>
<td>245 (99%)</td>
<td>184 (69%)</td>
<td>61 (25%)</td>
</tr>
<tr>
<td></td>
<td>2 drugs</td>
<td>3 (1%)</td>
<td>2 (67%)</td>
<td>1 (33%)</td>
</tr>
<tr>
<td></td>
<td>INH</td>
<td>242 (98%)</td>
<td>183 (76%)</td>
<td>59 (24%)</td>
</tr>
<tr>
<td></td>
<td>RIF</td>
<td>1 (0.4%)</td>
<td>1 (100%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>PZA + EMB</td>
<td>3 (1%)</td>
<td>2 (67%)</td>
<td>1 (33%)</td>
</tr>
<tr>
<td></td>
<td>Changed from INH to RIF</td>
<td>2 (0.8%)</td>
<td>0</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>How medications administered</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Self-medicated</td>
<td>59 (45%)</td>
<td>49 (69%)</td>
<td>10 (51%)</td>
</tr>
<tr>
<td></td>
<td>INH</td>
<td>20 (8%)</td>
<td>17 (85%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td></td>
<td>DOPT</td>
<td>129 (52%)</td>
<td>120 (96%)</td>
<td>9 (4%)</td>
</tr>
<tr>
<td></td>
<td>INH or DOPT</td>
<td>149 (60%)</td>
<td>137 (92%)</td>
<td>12 (8%)</td>
</tr>
</tbody>
</table>

Cruz and Stokle
The Pediatric Infectious Disease Journal • Volume 31, Number 2, February 2012
Prevention of TB Disease in Children

- Contact Investigation
- INH Window Prophylaxis
- Treatment of LTBI
Questions
Consider Both TST and IGRA

- The initial and repeat IGRA is indeterminate
- The initial test (TST or IGRA) is negative and
  - Clinical suspicion for TB disease
  - Risk of progression or poor outcome is higher
- The initial test TST is positive and:
  - > 5 yrs of age and history of BCG vaccination
  - Need additional evidence to increase compliance
  - NTM disease is suspected

Expected Clinical Course for TB Disease in Children

- **Pulmonary**
  - CXR takes months to improve
- **Hilar lymphadenopathy**
  - May take a year or more to regress on x-ray
- **Cervical lymphadenitis**
  - Gets worse before improvement over months to years
- **Meningitis**
  - Inflammation increases initially with treatment
  - Hospitalization recommended until clinically stable or improving
Comparison of Pediatric TB Infection and Disease

- MTB organism is present in both cases
- Infection and disease are on a continuum – when does "infection" turn into "disease"?
- Treatment
  - Infection - 1 drug
  - Disease - 3-4 drugs
  - The functional difference is the burden of organisms
- In low prevalence conditions such as the U.S.
  - Tests for infection need to be specific
  - Tests for disease need to be sensitive