TB Nurse Case Management
San Antonio, TX
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Pediatric Tuberculosis

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Lisa Armitige, MD, PhD has the following disclosures to make:

• No conflict of interests

• No relevant financial relationships with any commercial companies pertaining to this educational activity
Epidemiology of Pediatric TB

Reported TB Cases
United States, 1982–2010*

*Updated as of July 21, 2011
TUBERCULOSIS CASES IN THE UNITED STATES: CHILDREN 0-14 YEARS OLD

Stages of Tuberculosis

Exposure to Contagious Adult with Pulmonary Disease

- Household contacts 20-30%
- Latent TB Infection LTBI 5-10%
- Risk varies by age 5-50%

Adult Active TB Disease
Child Active TB Disease
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

Risk of Progression to TB Disease by Age

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

| 1-2 years               | Disease                  |
|                        | 20-25%                   |
|                        | Pulmonary Dis            |
|                        | 75%                      |
|                        | Miliary or TBM           |
|                        | 2-5%                     |

Marais B J. Int J Tuberc Lung Dis 2004;8:392-402
### Risk of Progression from TB Infection to Disease by Age

<table>
<thead>
<tr>
<th>Age at Primary Infection (yr)</th>
<th>No Disease (%)</th>
<th>Pulmonary Disease (%)</th>
<th>Nervous System TB (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>50</td>
<td>30 to 40</td>
<td>10 to 20</td>
</tr>
<tr>
<td>1 to 2</td>
<td>75 to 80</td>
<td>10 to 20</td>
<td>2.5</td>
</tr>
<tr>
<td>2 to 5</td>
<td>95</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>5 to 10</td>
<td>98</td>
<td>2</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>&gt;10</td>
<td>80 to 90</td>
<td>10 to 20</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>


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### 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:
  - Lobar pulmonary infiltrates
  - Hilar lymphadenopathy or
  - 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%)
Adult TB Disease

- Pulmonary: 78%
- Extrapulmonary: 22%

Adult Extrapulmonary TB Disease

- Lymphatic: 40%
- Pleural: 16%
- GU: 18%
- Bone/Joint: 10%
- Miliary: 9%
- Other: 5%
- Meningeal: 5%

CDC 2010
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
Diagnosing Tuberculosis in Children

How is tuberculosis diagnosed?

Adults – Mycobacterial-based diagnosis
• positive sputum AFB smear - 60% - 75%
• positive sputum culture - 90%
• positive tuberculin skin test - 80% [HIV < 50%]

Children
• positive sputum or gastric AFB smear - 10%
• positive sputum or gastric culture - 10% - 40%
• positive tuberculin skin test - 50% - 80%
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 ages 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
  - Teens similar to adults

Gastric Aspirates

- Inpatient procedure
- Overnight fasting
- Lavage with NS if volume < 20cc

- Generally done qAM x3
- Inpatient costs
- AFB smear yield: minimal
- AFB Culture yield: 20-30%
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 TST/IGRA
  - Contagious adult source case identified
  - Clinical course consistent with TB disease, or
  - Improvement on TB therapy

Interferon $\gamma$ Release Assays (IGRAs)

• MTB specific antigens:
  - Genes in region of difference (RD1) on MTB genome
  - Culture filtrate protein 10 (CFP-10)
  - Early secretory antigen target 6 (ESAT-6)
  - TB7.7(p4) in QuantiFERON Gold In-Tube

• Identifies LTBI &/or disease
• Does not cross react with BGC vaccine or most other mycobacteria

• Requires:
  - single medical visit [for LTBI, not for exposure]
  - blood collection
  - laboratory equipment and personnel

• Results in 24-48 hrs
TST preferred, IGRA acceptable

- Children < 5 years of age

IGRA preferred, TST acceptable

- BCG recipients
- Groups with historically low rates of return for TST reading

T-cell assays for tuberculosis in children

- More data available for Elispot technique
- Appear to be more specific for tuberculosis infection, especially in low prevalence conditions
- Correlate better with degree of exposure in contact investigations than does the TST: likely many false-positive TSTs in BCG-vaccinated children
- Dynamics of tests are largely unknown
- Results have been highly variable, and indeterminate results are common with QuantiFERON-TB Gold
IGRAs and the 2009 AAP “RED BOOK”

- Can use IGRAs in immunocompetent children > 4 years of age in all situations when a TST would be used
- Particularly useful/preferred for children who have received a BCG vaccination
- Use with caution in children < 5 years of age, immunocompromised children
- Neither IGRAs nor the TST are perfect; always need clinical judgment!

IGRA Tests in Kids

- **Good sensitivity**
  - Variable 70-90%

- **Highly specific**
  - Does not cross react with BCG vaccine or most other mycobacteria
  - Specificity is 90-95%

- Single visit required

- Helpful (preferred) in BCG vaccinated patients

- Children <5 yrs
  - Not FDA approved in this age, limited data
  - Consider either test (IGRA or TST) positive in this vulnerable age

- More expensive than TST but
  - May prevent unnecessary x-rays/medical visits and bx in patients with BCG history and false pos TST
  - Adult studies estimate false positives reduced by 30% or more in BCG vaccinated populations
Clinical Presentation of TB in children

Common 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
### Signs and Symptoms of Pulmonary TB

<table>
<thead>
<tr>
<th>Clinical Feature or Disease Type</th>
<th>Infants</th>
<th>Children</th>
<th>Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Common</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Night sweats</td>
<td>Rare</td>
<td>Rare</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Cough</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Productive cough</td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>Never</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Common</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>CXR Findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hilar or mediastinal adenopathy</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>• Segmental/lobar infiltrates</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>• Calcifications (seen in 75-80% of children with pulmonary TB)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Miliary disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pleural effusions</td>
<td></td>
<td></td>
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</tbody>
</table>

15% of patients with TB disease will have normal CXRs
Intrathoracic Lymphadenopathy
Uncommon in children, but if see cavities, treat the child as contagious and take appropriate infection control precautions.
Cavitary Lesions

Calcifications

Usually indicates disease present for 2-6 months

W.C. 2005
Miliary Disease

Tuberculomas

At initiation of therapy

After 2 months of therapy
Unique Diagnostic 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

Treating Tuberculosis in Children
Why treat exposed children?

- Very high rate of infection
- Takes up to 3 months for the skin test to turn positive
- U.S. studies – 10% to 20% of childhood TB cases can be prevented if children exposed in a household receive isoniazid
- WHO standards – children <5 years old in a TB household should be treated

TB Prevention After Exposure

- Household contact with contagious person
  - Teen or adult with pulmonary TB disease
  - Usually ≥ 4 hours of contact
- 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
  - Immunosuppressed patients
  - Patients on tumor necrosis factor-alpha blockers
  - May prevent progression to disease during window period
- Repeat TST 8-10 wks after exposure
- May stop INH if 2nd TST negative <5mm in immunocompetent patients
TB Prevention

- Isoniazid (INH) = mainstay of therapy
  - 10-15 mg/kg single daily dose if given by family
  - 20-30 mg/kg twice weekly if given by health department
  - Duration: 9 months

- Alternative: rifampin x 6 months
  - If person around child with TB is known to have INH-resistant disease or if child is INH-intolerant

3HP in children

- Approved for children >12 y/o
- Children 2-12 y/o on a case by case basis
- 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
Pearls of wisdom for treating LTBI in children

- Use INH suspension only in children ≤ 5 kg
- Compliance with 9 months of INH averages 50% - be vigilant and skeptical
- Use DOPT for: recent contacts, infants, immune compromised
- When children aren’t tolerating INH, the problem is more often with the parent than the child
- Routine LFTs only for: other liver toxic drugs, liver disease, signs or symptoms of hepatitis

Directly observed therapy for tuberculosis

- means a dispassionate 3rd party is actually present when medications are taken with every dose
- “standard of care” in U.S. for treating tuberculosis disease
- desirable for high risk infections - newborns and infants, household contacts, HIV - infected or immune compromised
Therapy for TB Disease

- Start 4-drug therapy (a change from 2006 Red Book)
  - INH, rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB); INH/RIF are the backbone of therapy
- Use PZA only during 1st 2 months for susceptible TB
  - This is your ‘shortening agent’: consolidate from 9 to 6 months of therapy
- Stop EMB once culture results known, if have pan-susceptible TB
  - This is your insurance in case you have drug-resistant TB
- Anticipate minimum 6 month therapy, may need to extend it to longer periods, especially for extrapulmonary disease
- Always administered by directly observed therapy (DOT)
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 usually 100% if not diagnosed and treated
- This case was potentially preventable if treated with window prophylaxis when parent diagnosed

Monitoring Children on TB Treatment

- Risk of drug toxicity very low
- Monitor clinical signs
  - regular clinical visits (4-6 wks)
  - patient education
  - Weigh at least monthly and increase dose as needed
- Routine blood work not necessary unless
  - symptoms
  - risk factors for toxicity
- Monitor and reinforce adherence
Monitoring Children on TB Treatment

- When to follow up CXR’s for pulmonary TB
  - Beginning and end of therapy
  - If clinical change
- Completion of therapy certificate
- Adequate nutrition
- Routine vitamin B₆ not necessary except breastfeeding, pregnant adolescents, poor diet
  - Breastfed babies can be given Poly-vi-sol
  - Vitamin B₆ doses 1-2 mg/kg

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
  - Steroids crucial for 1st month
  - Hospitalization recommended until clinically stable or improving
When do we worry about contagiousness?

- Older adolescents
- Children with certain findings on CXR
- Producing sputum
- Any draining skin lesions

Children with tuberculosis are rarely contagious, but their caregivers may be. Only 7 (12%) of 59 children were potentially contagious, and 10 (17%) were accompanied by contagious adults. Screening caregivers was more cost-effective than performing employee contact investigations, with one-sixteenth the cost ($5,470 vs $88,323) and requiring screening of 35 times fewer persons.

Infect Control Hosp Epidemiol 2011;32(2):188-190

Questions?
Case studies

Clinical Disease Examples

3 Year Old
- Contact to AFB smear + source case (parent)
- TST 0 mm
- No symptoms
- Normal physical exam
- CXR hilar LAN

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
Clinical Disease Examples

5 Year Old
- Cervical LAN
- TST 15 mm
- Hx BCG vaccine
- QFT positive
- CXR normal
- TB cultures negative

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

Clinical Disease Examples

8 Month Old
- Mother with cavitary TB
- Baby TST 0 mm
- CXR normal
- Exam: Fever & irritability
- Meningitis on CSF
- Brain MRI consistent with TB meningitis

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
Clinical Disease Examples

2 Year Old
• Normal physical
• TST 10 mm
• CXR hilar adenopathy
• TB cultures negative

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

More questions?