Tuberculosis in Children

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TB Intensive
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Kim Connelly 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
Differences in Adult and Pediatric TB
**REACTIVATION DISEASE**

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

**PRIMARY TB DISEASE**

- Typical of childhood TB
- Usually not cavitary
- Classic x-ray:
  - Hilar lymphadenopathy
  - Infiltrates or miliary pattern
- Low numbers of organisms
  - AFB smears negative (95%)
  - Cultures negative in 60%
- Most children <12 yrs not contagious
- Often asymptomatic (50%)
**RADIOPHAGIC FINDINGS IN PEDIATRIC TB DISEASE**

**Typical of TB**
- Hilar and interthoracic lymphadenopathy
- Miliary pattern
- Apical cavitary lesions in adults and teens
- Basilar enhancement on brain imaging

**Not specific but common**
- Lobar pneumonia
- Pleural effusion

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**RISK OF DISEASE WITH NO TREATMENT BY AGE INFECTED OR MEDICAL CONDITION**

| Age/Condition       | Risk of Disease
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Birth-12 months</td>
<td>50%</td>
</tr>
<tr>
<td>1-3 years</td>
<td>24%</td>
</tr>
<tr>
<td>4-11 years</td>
<td>5%</td>
</tr>
<tr>
<td>12-18 years</td>
<td>10%</td>
</tr>
<tr>
<td>Healthy Adults</td>
<td>7%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10%</td>
</tr>
<tr>
<td>HIV Infected</td>
<td>50%</td>
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</tbody>
</table>
TB Disease

Adult TB Disease

- Pulmonary: 85%
- Extrapulmonary: 15%

Pediatric TB Disease

- Pulmonary: 75%
- Extrapulmonary: 25%

Adult Extrapulmonary TB Disease (15%)

- Lymphatic: 25%
- Pleural: 23%
- GU: 16%
- Other: 13%
- Miliary: 9%
- Bone/Joint: 10%
- Meningeal: 4%
**Extrapulmonary TB Disease in Children (25%)**

- **Lymphatic** 65%
- **Meningeal** 14%
- **Pleural** 6%
- **Miliary** 5%
- **Other** 5%
- **Bone/Joint** 5%

**DIAGNOSIS OF TB IN CHILDREN**

- **Gold Standard** – Positive Culture (40%)
- OR, **Clinical Diagnosis**: Abnormal CXR, lab or exam consistent with TB **AND**
  - 1 or more of the following:
    - Positive TST or IGRA
    - Adult source case found
    - Clinical course consistent with TB disease, or
    - Improvement on TB therapy
**DIAGNOSTIC TRIAD**

**PEDI TB DISEASE**

1. Positive TST
2. Abnormal CXR
3. Infectious source case

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**GASTRIC ASPIRATES**

- Inpatient procedure
- Overnight fasting
- Lavage with normal saline
- Collected in morning x 3 days
- Inpatient costs substantial
- AFB smear yield: <5%
- Sensitivity of culture 20-50%
- Future: possible use of NAAT’s in children
TB CULTURES FROM CHILDREN

- Bronchoalveolar lavage (BAL)
  - Sensitivity 40% (20-50% range)
- Lymph nodes
  - Sensitivity 30-70%
- CSF in TB meningitis
  - High volume (> 6 ml) improves yield
  - Sensitivity 20% average (12-50% range)
- Nucleic acid amplification tests (NAAT) in children
  - Data limited
  - Sensitivity 60-85%
- Bottom line
  - Negative test does not rule out disease

PEDIATRIC CASE

- 6 month old
- 1-2 week history of fever, vomiting and sweating
- OSH with bilateral pneumonia on CXR
- Transferred with respiratory distress

Family history
- Father
  - History of incarceration and mental health issues
  - Hospitalized 2 months prior with cavitary pneumonia
  - Sputum AFB smear negative
  - Not reported, no TB treatment started
  - Sputum grew TB at 4 weeks
- Health Department unable to locate family
HOSPITAL COURSE

- Respiratory failure, seizures, intubation
- Altered mental status, abnormal neurologic exam
- Meningitis diagnosed
  - Abnormal spinal fluid
  - Abnormal MRI including hydrocephalus
- Long term complications
  - Hydrocephalus and VP shunt
  - Developmental delay

OUTCOME

- All family members tested positive for TB
- Mother was suspect
- Baby grew TB on sputum and tracheal aspirate
- Baby treated with RIPE (12 months) and steroids (2 months)

- How could this have been prevented?
TREATMENT OF TB IN CHILDREN

<table>
<thead>
<tr>
<th>Stages of TB</th>
<th>TST/IGRA</th>
<th>CXR/Lab Physical</th>
<th>Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure Child &lt;4yrs (adult source)</td>
<td>Negative</td>
<td>Normal</td>
<td>None</td>
<td>Window CPX INH or Rif 8-10 wks Repeat TST 8-10 wks after last contact</td>
</tr>
<tr>
<td>LTBI</td>
<td>Positive</td>
<td>Normal</td>
<td>None</td>
<td>• INH x 9 mo or • Rif x 4-6 mo or • 3HP wkly x 12 wks, DOT only</td>
</tr>
<tr>
<td>Disease</td>
<td>90% Positive</td>
<td>Abnormal CXR, PE or labs</td>
<td>50% of children have symptoms</td>
<td>RIPE x 6-12 months, duration depends on site</td>
</tr>
</tbody>
</table>
TB MENINGITIS

TREATMENT AND CLINICAL COURSE

- 9-12 months RIPE therapy
- Steroids for 6-8 weeks 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, mental disabilities, CP
  - Mortality high (>90%) if not diagnosed and treated
Skin Test in Foreign Born

BCG Vaccination Scars

SKIN TEST IN FOREIGN BORN

- 6 year old with positive TB skin test (TST)
- Born in Asia
- BCG on vaccine record and scar present
- TST measures 12mm
- No known TB exposure

- What would you do next?
  - Further testing?
  - Diagnosis?
  - Treatment?

QFT = 0.86
Borderline/Low Positive QFT
(0.35-2.0)

What now?
**IGRA Sensitivity in Children < 5 yrs of age Insufficient to Replace TST**

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity &lt;5 years (CI)</th>
<th>Sensitivity &gt;5 years (CI)</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>90% (79-100)</td>
<td>98% (93-100)</td>
<td>NA, ref standard</td>
</tr>
<tr>
<td>QFT-G-IT</td>
<td>73% (58-89)</td>
<td>93% (84-100)</td>
<td>93% (88-99)</td>
</tr>
<tr>
<td>T-SPOT.TB</td>
<td>63% (46-80)</td>
<td>83% (75-90)</td>
<td>92% (87-99)</td>
</tr>
</tbody>
</table>

338 children total, 210 not infected, 58 LTBI, 42 probable TB disease by clinical criteria, 28 culture confirmed disease.
SKIN TEST IN FOREIGN BORN

- 6 year old with 12 mm TST
- BCG history
- CXR and physical exam normal
- Borderline QFT (0.86)
- Repeat QFT positive > 3.5

TREATMENT OPTIONS FOR LTBI

Traditional
- INH for 9 months

Newer Options
- Rifampin daily for 4-6 months

3HP - Health Department Only
- INH-Rifapentine once weekly for 12 doses

What are the Pros and Cons of each regimen?
TREATMENT OPTIONS FOR LTBI

Traditional
- INH for 9 months
  - Dose: daily or twice weekly (DOT)
  - Inexpensive
  - Low completion rates for self administered treatment

Newer Options
- Rifampin daily for 4-6 months
  - Potential drug interactions (OCA's, protease inhibitors)
  - Cost higher than INH
  - Higher completion rates

3HP - Health Department Only
- INH-Rifapentine once weekly for 12 doses
  - Must be DOT
  - Not approved for children < 2 years
  - Expensive
  - Higher completion rates

Comparing LTBI Treatment Options

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Isoniazid x 9 months</th>
<th>Rifampin x 4 months</th>
<th>INH/Rifapentine x 3 months (3HP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completion Rates</td>
<td>62% (self admin)</td>
<td>93% (self admin)</td>
<td>90% (DOT)</td>
</tr>
<tr>
<td>Administration</td>
<td>Daily self meds BiW DOPT ESAT</td>
<td>Daily self meds Daily DOPT M-F ESAT</td>
<td>Weekly x 12 wks DOPT only Video DOPT</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>2-6%</td>
<td>3%</td>
<td>0.4-5%</td>
</tr>
<tr>
<td>Total Drug Cost</td>
<td>$40-100</td>
<td>$400</td>
<td>$120-350</td>
</tr>
<tr>
<td>Considerations</td>
<td>Long successful track record</td>
<td>Possible drug interactions Expensive</td>
<td>Newest regimen Age (≥12 or ≥2 yr)</td>
</tr>
</tbody>
</table>
MONITORING CHILDREN ON TB TREATMENT

- Risk of drug toxicity very low
  - Less than 1:1000
- Monitor clinical signs/symptoms
  - Clinic follow up every 4-8 weeks
  - Family or HD – call if symptoms
- Routine blood work not necessary in kids
  - Exceptions: Symptoms or Risk factors for toxicity
- Liquid INH causes diarrhea due to high sorbitol, crushed tablets preferred
- Going back to school
  - Children <12 yrs of age with TB disease are not contagious
  - LTBI is not contagious

BABY EXPOSED TO TB DISEASE

- 2 month old infant
- Mother with TB disease
- How do you determine risk to baby?
BABY EXPOSED TO TB DISEASE

- AFB positive
- Mom just starting treatment
- Mother’s CXR

BABY EXPOSED TO TB DISEASE

- Baby with cough
- TST 0 mm
- What would you do next?
BABY EXPOSED TO TB DISEASE

- What would you do next?
  - CXR
  - Diagnosis?
  - Treatment?

OUTCOME

- Diagnosis:
  - Miliary TB
  - TB meningitis (CSF: 27 WBC, 120 protein)
  - Normal brain MRI
- Treatment:
  - RIPE therapy x 12 months
  - Prednisone x 2 months
- Baby did well with normal exam and development after treatment
**TEEN CASE**

- 15 year old AA boy with 5 week history
  - Abdominal pain
  - Cough, fever, 20 lb weight loss
  - Denied high risk behavior
  - No foreign travel or known TB exposure
- Physical
  - 220 lb, football player
  - Cervical LAN
  - Abdominal exam normal, no HSM
  - Lungs clear
- TST: negative, 0 mm
- CXR normal
- Is this TB disease?

Abdominal CT shows multiple lymph nodes with low attenuation centers and prominent rim enhancement (arrow).
TEEN CASE OF LYMPHADENOPATHY CASE, CONT

- Differential diagnosis
  - Lymphoma, leukemia
  - HIV, EBV, other disseminated infections
  - Tuberculosis
- Laboratory
  - Peripheral smear negative for cancer
  - HIV – negative, x 2
  - Quantiferon (IGRA) - positive
  - Node biopsy:
    - AFB smear negative
    - TB culture positive at 5 weeks for MTB
    - Susceptible to all drugs
- Treatment RIPE, 9 months total for disseminated disease
**Pediatric Tuberculosis**

**Summary**

- Higher risk of progression to disease
- Children often have no symptoms
- IGRA is not as sensitive in kids < 5 years
- Pulmonary disease and lymphadenopathy common
- AFB smears and cultures are usually negative
- Diagnosis usually clinical
- Kids tolerate treatment well

**Prevention of TB Disease in Children**

- Identify high risk patients
  - Contact investigation
  - TB Questionnaire at well child visits
- TB skin test or IGRA for at risk patients
- Window prophylaxis for kids < 5 yrs with TB exposure
- Treat TB infection and disease
CENTRAL NERVOUS SYSTEM
TB DRUG PENETRATION

<table>
<thead>
<tr>
<th>Drug</th>
<th>CNS Penetration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Good</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Good</td>
</tr>
<tr>
<td>PZA</td>
<td>Good</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Infamed meninges only</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Good</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Infamed meninges only</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Good except Cipro poor</td>
</tr>
</tbody>
</table>

Good
ETHAMBUTOL IN CHILDREN

- Risk of optic neuritis:
  - Visual acuity
  - Color perception
  - Dose related
  - Usually reversible
  - Risk around 1-3% in adults
  - Risk in children about the same

- EMB safe in children with monitoring
  - Monitor vision on treatment
  - Infants – visual evoked potentials (VEP)

Ethambutol in Children

Table 2. Studies that have specifically sought optical toxicity in children treated with Ethambutol

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (n)</th>
<th>Age range</th>
<th>Method of evaluation</th>
<th>Length of follow up (months)</th>
<th>Number with toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>47</td>
<td>3-13 years</td>
<td>Visual evoked responses</td>
<td>15-18</td>
<td>0</td>
</tr>
<tr>
<td>25</td>
<td>36</td>
<td>3-13 years</td>
<td>Acuity/field/colour</td>
<td>24-48</td>
<td>0</td>
</tr>
<tr>
<td>Fox*</td>
<td>45</td>
<td>1-15 years</td>
<td>Acuity/field/colour</td>
<td>9-18</td>
<td>0</td>
</tr>
<tr>
<td>26</td>
<td>30</td>
<td>4-5 years</td>
<td>Acuity/field/colour</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>27</td>
<td>27</td>
<td>5-15 years</td>
<td>Acuity/field/colour</td>
<td>12-36</td>
<td>0</td>
</tr>
<tr>
<td>28</td>
<td>6</td>
<td>9-16 years</td>
<td>Computerized visual field examination</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>


FLUOROQUINOLONES IN CHILDREN

- Initial clinical trials in children not done
- Some children have been treated without problems:
  - CF, chronic UTI, shigellosis and TB

- Most consider safe in children:
  - Some case series and RCT with good results
  - Germany study: 2030 patients treated, 31 (1.5%) with self resolving arthralgia*

- Not indicated for routine infections in children
- Consider risks and benefits
- Monitor clinically for joint and tendon problems