Tuberculosis in Children and Adolescents

Vandana L. Madhavan, MD, MPH
Pediatric Infectious Disease, MassGeneral Hospital for Children
New England TB Intensive Workshop
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- I have no relevant disclosures
## Classification System for TB

<table>
<thead>
<tr>
<th>Class</th>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No TB exposure</td>
<td>No history of exposure. Negative reaction to tuberculin skin test or IGRA.</td>
</tr>
<tr>
<td></td>
<td>Not infected</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>TB exposure</td>
<td>History of exposure. Negative tuberculin skin test or IGRA.</td>
</tr>
<tr>
<td></td>
<td>No evidence of infection</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>TB infection</td>
<td>Positive reaction to tuberculin skin test or IGRA. No clinical, bacteriological, or radiographic evidence of active TB.</td>
</tr>
<tr>
<td></td>
<td>No disease</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>TB, clinically active</td>
<td>M. tuberculosis cultured (if done). Clinical, bacteriological, or radiographic evidence of current disease.</td>
</tr>
<tr>
<td>4</td>
<td>TB</td>
<td>History of episode(s) of TB or Abnormal but stable radiographic findings. Positive reaction to a TST or IGRA. Negative bacteriologic studies (if done). and No clinical or radiographic evidence of current disease</td>
</tr>
<tr>
<td></td>
<td>Not clinically active</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>TB suspected</td>
<td>Diagnosis pending</td>
</tr>
</tbody>
</table>

**EPIDEMIOLOGY**
Brief Background

- From the CDC’s *Reported Tuberculosis in the United States, 2015*:
  - 9,557 TB cases (1.6% increase from 2014) – **first annual increase in 23 years**
  - 3 cases per 100,000 – stable annual incidence
  - Greatest burden in people born outside US - reactivation of latent TB infection from country of origin
  - Need for
    - More comprehensive public health approaches in TB prevention and control
    - Expanded approach to test and treat latent TB infection
    - Strengthened existing systems to stop TB transmission

Pediatric Tuberculosis in the U.S.

- Definition: TB disease (i.e., not latent TB) in a patient <15yo
- In 2015:
  - 9,557 TB cases were reported among all age groups
    - 440 (4.6%) were pediatric

<table>
<thead>
<tr>
<th>Age group</th>
<th>N</th>
<th>Percent out of all age groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 years</td>
<td>244</td>
<td>2.55%</td>
</tr>
<tr>
<td>5-14 years</td>
<td>196</td>
<td>2.05%</td>
</tr>
</tbody>
</table>
Pediatric Tuberculosis in the U.S.

- TB case rates for all ages are higher in
  - Urban, low-income areas
  - Non-white racial and ethnic minorities

- Specific groups with high LTBI and TB disease rates:
  - Immigrants and refugees from high-prevalence regions (Asia, Africa, Latin America, countries of the former Soviet Union)
  - International adoptees
  - Travelers to countries with high-prevalence
  - Homeless people
  - Residents of correctional facilities

Number and Percentage of Pediatric TB Cases by U.S. and Foreign Birth, 1993–2015
Percentage of Pediatric TB Cases with Foreign Birth by Birth Country, 1993 and 2015

1993 N=1,660
- Mexico 45%
- Vietnam 8%
- Haiti 4%
- Philippines 10%
- Other 29%

2015 N=440
- Myanmar 11%
- Mexico 10%
- Ethiopia 6%
- Philippines 6%
- Honduras 5%
- Other 57%

Tuberculosis Cases in Massachusetts, 2015

<table>
<thead>
<tr>
<th>Characteristics of TB Cases 2015 (N=192)</th>
<th># (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>100 (52%)</td>
</tr>
<tr>
<td>Female</td>
<td>92 (48%)</td>
</tr>
<tr>
<td>Race Ethnicity</td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>24 (13%)</td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>46 (24%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>36 (19%)</td>
</tr>
<tr>
<td>Asian</td>
<td>82 (43%)</td>
</tr>
<tr>
<td>Other, non-Hispanic</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Origin of Birth</td>
<td></td>
</tr>
<tr>
<td>U.S. born</td>
<td>25 (13%)</td>
</tr>
<tr>
<td>Non-U.S. born</td>
<td>167 (87%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>5-14</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>15-19</td>
<td>5 (3%)</td>
</tr>
<tr>
<td>20-24</td>
<td>9 (5%)</td>
</tr>
<tr>
<td>25-44</td>
<td>61 (32%)</td>
</tr>
<tr>
<td>45-64</td>
<td>59 (31%)</td>
</tr>
<tr>
<td>65+</td>
<td>51 (27%)</td>
</tr>
</tbody>
</table>

**Clinical Presentation**
- Primary Site of Disease
  - Pulmonary: 114 (69%)
  - Extra-pulmonary: 48 (25%)
  - Both: 30 (16%)

**Chest Radiography**
- Cavitary disease only: 28 (15%)
- Military disease only: 2 (1%)
- Cavitory and miliary: 1 (<1%)
- Non-cavitary disease only: 126 (66%)
- Normal findings: 33 (17%)
- Not reported: 2 (1%)

**Higher Risk Groups**
- Non-U.S. born: 167 (87%)
- Children <15 years of age: 7 (4%)
- Incarcerated in prison/jail: 1 (<1%)
- Homeless: 7 (4%)
- Substance use*: 12 (6%)
- HIV co-infection: 12 (6%)

**Drug Resistance (N=141)**
- Resistance to at least 1 drug: 30 (21%)
- Resistance to at least INH: 22 (16%)
- Resistance to at least INH and RIF (MDR-TB): 7 (5%)

* Not mutually exclusive groups
* Alcohol abuse, injecting and/or non-injecting drug use
Tuberculosis Cases in MA, 2015

Number of Persons with TB by Place of Birth and Year in Massachusetts, 2005-2015 *

Number of Non-US Born** 141 Number of US-Born Cases 245 Percentage of Non-US Born** 31% Percentage of US-Born Cases 69%

*Non-US Birth defined as outside the United States and its territories

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of TB Cases</th>
<th>Percent of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vietnam</td>
<td>17</td>
<td>10%</td>
</tr>
<tr>
<td>China</td>
<td>16</td>
<td>10%</td>
</tr>
<tr>
<td>India</td>
<td>14</td>
<td>8%</td>
</tr>
<tr>
<td>Haiti</td>
<td>13</td>
<td>8%</td>
</tr>
<tr>
<td>Cambodia</td>
<td>8</td>
<td>5%</td>
</tr>
<tr>
<td>Dominican Republic</td>
<td>8</td>
<td>5%</td>
</tr>
<tr>
<td>Nepal</td>
<td>7</td>
<td>4%</td>
</tr>
<tr>
<td>Philippines</td>
<td>7</td>
<td>4%</td>
</tr>
<tr>
<td>Brazil</td>
<td>5</td>
<td>3%</td>
</tr>
<tr>
<td>Ecuador</td>
<td>5</td>
<td>3%</td>
</tr>
<tr>
<td>34 Other Countries</td>
<td>67</td>
<td>40%</td>
</tr>
</tbody>
</table>

*Birth outside the United States and its territories

Tuberculosis Cases in MA, 2015

TB Drug Resistance, Massachusetts, 2015

<table>
<thead>
<tr>
<th>Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteriologically** confirmed cases*</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
</tbody>
</table>

* *Bacteriologically substantiated TB case rate of 2.2 per 100,000 population
**TB cases with either a positive sputum culture or a positive culture of tissue/other body fluids

Drug Resistant TB Cases by Place of Birth Massachusetts, 2015 (N=30)

- North America: 5 (17%)
- South America: 5 (17%)
- Asia: 5 (17%)
- Africa: 5 (17%)
- Caribbean: 5 (17%)

*Regions defined using UN classification

Tuberculosis Cases in MA, 2015

TB Cases by Site of Disease, Massachusetts 2015 (N=192)

Sites of Extra-Pulmonary Disease Only
Massachusetts, 2015 (n=48)

<table>
<thead>
<tr>
<th>Extra-Pulmonary Site of Disease</th>
<th># TB Cases</th>
<th>Percentage of Total Extra-Pulmonary Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphatic-Cervical</td>
<td>9</td>
<td>19%</td>
</tr>
<tr>
<td>Pleural</td>
<td>7</td>
<td>15%</td>
</tr>
<tr>
<td>Ocular</td>
<td>7</td>
<td>15%</td>
</tr>
<tr>
<td>Lymphatic-Other</td>
<td>6</td>
<td>13%</td>
</tr>
<tr>
<td>Other</td>
<td>19</td>
<td>40%</td>
</tr>
</tbody>
</table>

For additional information, please visit our web page: http://www.mass.gov/dph/cdctb

SPECIAL CONSIDERATIONS IN PEDIATRICS
Significance of Tuberculosis in Children

- **Personal Health**: High rates of morbidity and mortality compared to adults
- **Public Health**: Diagnosis of LTBI or tuberculosis disease in a child is considered a “sentinel public health event” usually representing recent transmission of TB

Risk of Progression to TB Disease

- **Immunocompetent adults**
  - 5-10% **lifetime** risk of developing disease after infection
- **Adults with TB infection and untreated HIV infection**
  - 5-10% **annual** risk of developing disease
- **Children and the risk of TB disease**…
### Risk of Progression to TB Disease by Age

<table>
<thead>
<tr>
<th>Risk of disease following primary infection</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated tuberculosis/tuberculosis meningitis</td>
<td>Pulmonary tuberculosis</td>
</tr>
<tr>
<td><strong>&lt;1 years</strong></td>
<td>10-20%</td>
</tr>
<tr>
<td><strong>1-2 years</strong></td>
<td>2-5%</td>
</tr>
<tr>
<td><strong>2-5 years</strong></td>
<td>0.5%</td>
</tr>
<tr>
<td><strong>5-10 years</strong></td>
<td>&lt;0.5%</td>
</tr>
<tr>
<td><strong>&gt;10 years</strong></td>
<td>&lt;0.5%</td>
</tr>
</tbody>
</table>

High rates of morbidity and mortality
High rates of morbidity and mortality
...
“Safe school years”
Effusions or adult-type pulmonary disease

Adapted from reference 30.

Table 1: Risk of pulmonary and extrapulmonary disease in children following infection with *Mycobacterium tuberculosis*.


### High-Risk Groups

- **Age groups:**
  - Infants and young children
  - Post-pubertal adolescents

- **Recent infection:**
  - Highest risk in first 6 months after infection
  - Remains high for 2 years

- **Recent immigration**

- **Immunodeficiency:**
  - HIV infection, Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, malnutrition
  - Immunosuppressive drugs: prolonged or high-dose corticosteroid therapy, chemotherapy, tumor necrosis factor (TNF-alpha) antagonists
Transmission of *M. tuberculosis* to/from children

- Children are usually infected by an adult or adolescent in the immediate household
- Extra-household contact is less common
- Children rarely infect other children or adults
  - Children with pulmonary TB rarely cough
  - *M. tb* are relatively sparse in secretions
  - If coughing, rarely forceful enough to aerosolize bacilli
- Airborne/negative pressure precautions in hospital are less about patient than about untested family members

TB PREVENTION STRATEGIES
Prevention and Treatment of TB in the United States

- Targeted testing of persons at increased risk
- Case finding and treatment
- Contact investigations

Targeted TB Testing

- What is Targeted TB Testing?
  - Identifies persons at high risk of infection with *M. tuberculosis*
  - Identifies persons at high risk of progressing to disease should they be infected
  - Reduces unnecessary testing, evaluations and treatment
Why Use Targeted TB Testing?

- Why not routine/universal/mandated TB testing?
  - Daycare
  - Schools
  - Colleges
  - Summer camps
  - Hospitals
- Limitations of TST/IGRA
  - Inefficient use of healthcare resources – large numbers of low-risk children tested
  - Testing in low-prevalence groups would result in mostly false-positives, even if specificity ~99%
  - IGRA > TST specificity but still does not eliminate false positives in low-risk population

MMWR 2010;59(No. RR-5)

Targeted TB Testing

- Risk assessment
  - >1 risk factor identified on screening risk-assessment questionnaire
    - General pediatric practice
    - School-based healthcare
  - Contact and source-case investigations
  - Signs and symptoms consistent with TB disease
  - High risk of progression due to underlying conditions:
    - HIV infection, Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, malnutrition, prolonged or high-dose corticosteroid therapy, chemotherapy, tumor necrosis factor (TNF-alpha) antagonists
Targeted TB Risk Assessment

• Has a family member or contact had TB disease?
• Has a family member had a positive TB test?
• Was your child born in a high-risk country (i.e., outside US, Canada, Japan, Australia, New Zealand, or Western Europe)
• Has your child traveled to a high-risk country and spent >1 week with the resident population?
• Does your child have an underlying immunodeficiency or take immunosuppressive medications?

Using Risk Assessment

• At first contact with child and every 6 months until age 2 years
• After age 2 years, ask risk assessment questions every year if possible
• Anytime a true risk factor is identified, a TST or IGRA should be performed**
  **Decision re: screening should include provider input, subspecialist consultation
When should you worry about TB?

- Short answer: ALWAYS
- Long(er) answer:
  - Age: <1y, 1-4y, 5-15y
  - Underlying issues: immunodeficiency, chronic illness, medications, pregnancy
  - Social history: country of birth, countries of residence or travel (>=1 mo), refugee camps, immigration (detention) centers, work/volunteer experience (hospitals, nursing homes, homeless shelters, prisons)
  - Other demographic considerations: suspected contact to active case(s), risk of spread to others (student, athlete, HCW, etc.)
TB Screening in Children

- Tuberculin skin test (TST) a.k.a. “PPD” = purified protein derivative
- Interferon-γ release assays (IGRA)
  - T-SPOT®. TB
  - Quanti-FERON® TB Gold In-Tube

Tuberculin skin test (TST)

- Mantoux test
  - 5 TU of purified protein derivative (PPD) or 2 TU of PPD-RT23
  - PPD tuberculin solution contains dozens of TB antigens, exact composition varies from batch to batch
TST

• Pros:
  – More widely available
  – Cheap

• Cons:
  – Difficulty with placement - intradermal injection by an experienced provider
  – Requires second visit for interpretation (48-72 hours)
  – Careful measurement of induration (not erythema) at site of injection by an experienced provider
  – Delayed screening if recent live vaccines
  – Negative in early disease
BCG Vaccine and Tuberculin Skin Testing

- History of BCG is never a contraindication to TST
- Interpretation of TST results in BCG recipients is the same as for people who have not received the vaccine
  - Difficult to distinguish between (+) TST caused by *M. tuberculosis* infection vs. other causes
    - Reactivity does not occur in some children after BCG vaccination
    - If BCG does cause a (+) TST, the reaction is generally negative by 5 years of age
    - If child is from a high-burden country, (+) TST is almost always due to LTBI
- Therefore, management of children with a history of BCG and a (+) TST includes:
  - IGRA if ≥5 years of age*
  - Diagnostic evaluation including a chest radiograph
  - Appropriate treatment

IGRAs

Table 1: Differences in Currently Available IGRAs

<table>
<thead>
<tr>
<th></th>
<th>QFT–GIT</th>
<th>T–Spot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Process</td>
<td>Process whole blood within 16 hours</td>
<td>Process peripheral blood mononuclear cells (PBMCs) within 8 hours, or if T-Cell Xtend® is used, within 30 hours.</td>
</tr>
<tr>
<td><em>M. tuberculosis</em> Antigen</td>
<td>Single mixture of synthetic peptides representing ESAT-6, CFP-10 and TB7.7</td>
<td>Separate mixtures of synthetic peptides representing ESAT-6 and CFP-10</td>
</tr>
<tr>
<td>Measurement</td>
<td>IFN-γ concentration</td>
<td>Number of IFN-γ producing cells (spots)</td>
</tr>
<tr>
<td>Possible Results</td>
<td>Positive, negative, indeterminate</td>
<td>Positive, negative, indeterminate, borderline</td>
</tr>
</tbody>
</table>

* Similar to the TST, IGRAs do not distinguish between TB infection and TB disease
* Negative IGRA does not rule out either infection or disease in child with concerning findings
Interferon gamma release assays: Use in children

- **Pros:**
  - Single visit
  - Results w/in 24 hours (sometimes)
  - No cross reactivity with *M. bovis* (BCG vaccine) nor with *M. avium* complex (MAC)
  - No “boosting” response

- **Cons:**
  - Expensive
  - Not as widely available
  - Specimen collection/transportation issues
  - Limited utility data under 5 (2?)
  - Negative in early disease


Interferon gamma release assays (IGRA): Use in children

- **Children <5**
  - TST preferred
  - IGRA acceptable BUT
    - Positive IGRA likely indicates infection with *M. tuberculosis* but negative IGRA does not rule out infection
    - Increasing evidence that IGRAs are reliable down to 2
      → again, trust a positive and do not rely solely on a negative

- **Children >5**
  - IGRA preferred*, TST acceptable
    *Children >5 years of age who have received BCG
    *Children >5 years of age unlikely to return for TST reading

Interferon gamma release assays: Dual testing in children

- Both TST & IGRA should be considered when
  - Initial and repeat IGRA are indeterminate
  - Initial test (TST or IGRA) is negative and
    - Clinical suspicion for TB disease is moderate to high
    - Risk of progression to TB disease/poor outcome is high
  - **Initial TST is positive and**
    - Child healthy and at low risk
    - Additional evidence needed to increase adherence
    - Nontuberculous mycobacterial infection suspected

- Interpretation of (-) IGRA in child with (+) TST:
  - Child unlikely to have LTBI → not universal, depends on clinical situation

Red Book 2015

AAP Technical Report 2014 (Starke)
Evaluation of Child with TST or IGRA positivity

- Evaluation of all children with a positive TB test should include:
  - Symptom assessment
    - Remember infants/young children may not have “classic” symptoms
  - Physical examination
  - Chest radiographs (PA & lateral preferred, not portable AP)
  - Household investigation
QUIZ – WHICH CHEST X-RAYS SHOW TB?

17yo
Imaging Pearls

- PA/lateral CXR
  - Children <5
  - Symptomatic
  - Household contact
  - Previously concerning portable or single-view
  - Any other concerns
- Low threshold for low-dose chest CT
  - Need contrast for lymphadenopathy
  - Better for subtle findings
  - Younger children without microbiology data – imaging may be only concrete information to follow

TREATMENT – TB INFECTION
Treatment of Tuberculosis Infection

- INH 10-20 mg/kg (max. 300 mg) PO daily for 270 doses
  - Efficacy approaches 100%
  - Alternative: Twice-weekly directly observed (DOT) INH 20-40 mg/kg (max. 900 mg) PO for 72 doses
- Counseling re: avoidance of acetaminophen and alcohol, side effects/toxicity (mostly minor)
- Pyridoxine supplementation for breastfeeding infants, those with malnutrition
- Crushed tablets (mixed with small amount of breast milk, formula, food) better tolerated than suspension (sorbitol-induced diarrhea)

Treatment of Tuberculosis Infection

- Monitoring while on Isoniazid:
  - Isolate sensitivities from contact (if available)
  - Monthly assessment for clinical evidence of hepatotoxicity malaise, loss of appetite/weight, nausea, vomiting, abdominal pain, jaundice
  - No baseline/routine LFTs unless:
    - Concurrent liver disease
    - Concurrent use of hepatotoxic medications
    - Clinical evidence of hepatotoxicity
    - Pregnancy or first 12 weeks postpartum
Treatment of TB Infection

- Rifampin 10-15 mg/kg (max. 600 mg) PO daily for 4-6 months
  - INH not tolerated
  - Index patient isolate INH-resistant
  - 4-month course ~ 9-month course of INH (Cruz & Starke, IJTLID 2014)
    - Counseling re: tears/urine, increased/decreased metabolism of other medications (esp. OCP)

- 12 weeks of Isoniazid (15 mg/kg, max. 900mg) + rifapentine
  - 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
  - Currently recommended as option for ≥ 12 years
    - Pros: Done in 12 weeks, no home Rx
    - Cons: Need to adhere to weekly visits w/in 24-hour window, increased side effects
  - Children 2-11 years of age
    - Emerging CDC safety and efficacy data to recommend universal use in this age group (forthcoming)
  - Children <2 years of age
    - Not recommended - lack of safety and pharmacokinetic data
Summary of TB Infection Recommendations

<table>
<thead>
<tr>
<th>Name</th>
<th>Medication(s)</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>9H</td>
<td>Isoniazid QD x 9 month</td>
<td>May need B6</td>
</tr>
<tr>
<td>4R</td>
<td>Rifampin QD x 4 months</td>
<td>Counseling re: other Rx</td>
</tr>
<tr>
<td>3HP</td>
<td>Isoniazid/Rifapentine QW x 3 months (12 weeks)</td>
<td>Weekly DOT, higher doses</td>
</tr>
</tbody>
</table>

- Isoniazid has historically been first-line medication choice in children
- Rifampin increasingly used given equivalent efficacy
- 2018 Red Book will list recommendations for pediatric TB infection
  - 3HP
  - 4R
  - 9H
- Alternative regimens are recommended by AAP/CDC for patients who are not able to tolerate above regimens

OTHER CONSIDERATIONS
**TB Prevention in the United States**

- **Contact investigations**
  - The most reliable TB program is based upon aggressive and expedient investigations of potentially exposed contacts, rather than routine screening of large populations.

  ![Diagram](image)

  **High priority contact:**
  - Household
  - Age <5 yrs
  - Med risk condition
  - Procedure
  - Congregate, Time

  Red Book 2009

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**How are Children with Tuberculosis Identified?**

- Presentation with a symptomatic illness
- Discovery of a child with pulmonary tuberculosis during contact evaluation of an adult
  - Typically few or no symptoms
  - Evaluation: (+) TST/IGRA and abnormal CXR
  - In some areas of the U.S. up to 50% of children with TB are discovered in this manner
    - **Before** significant symptoms have developed
The High Cost of Missed Opportunities

- Missed opportunities documented:
  - Failure to find and appropriately manage adult source cases (Case finding)
  - Contact investigation interview failure
  - Delay in evaluation of exposed children
  - Failure to completely evaluate exposed children
  - Failure to prescribe prophylactic INH
  - Failure to complete treatment for LTBI (Adherence)

“Window Prophylaxis”

- Children who are household/close contacts of known/suspected TB cases
  - Symptom analysis, PE, TST (or IGRA)
  - PLUS CXR (2 views) regardless of TST/IGRA result
- If <4 years of age, asymptomatic, NL PE, negative TST (<5mm), and NL CXR
  - START Isoniazid 10-15 mg/kg (max. 300 mg) PO once daily
  - Child may already be infected
  - Infection more likely to progress to disease
  - Infants and younger children are more likely to develop disseminated disease or meningitis
“Window Prophylaxis”

- TST repeated 8-10 weeks after last known/suspected contact with index case
  - If TST (-), discontinue INH
  - If TST (+), re-evaluate child and treat accordingly
  - Exceptions: neonates - TST likely not reliable until 4-6 months, could continue for full 9 months if concerned enough

TB DISEASE/ACTIVE TB – PEDIATRIC CONSIDERATIONS
Pediatric TB Cases by Site of Disease, 1993–2015

Any extrapulmonary involvement* (totaling 29.5%)

<table>
<thead>
<tr>
<th>Extrapulmonary site</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphatic</td>
<td>(18.8)</td>
</tr>
<tr>
<td>Meningeal</td>
<td>(3.6)</td>
</tr>
<tr>
<td>Miliary</td>
<td>(1.3)</td>
</tr>
<tr>
<td>Bone &amp; Joint</td>
<td>(1.5)</td>
</tr>
<tr>
<td>Other</td>
<td>(4.3)</td>
</tr>
</tbody>
</table>

*Any extrapulmonary involvement which includes cases that are extrapulmonary only and both. Patients may have more than one disease site but are counted in mutually exclusive categories for surveillance purposes.

Timetable of TB in Children

Tuberculosis. Starke JR, in Feigin, Cherry, Demmler, Kaplan, ed: Textbook of Pediatric ID 2009
Mycobacteriologic Diagnosis of TB

- Adults: 70-90% have a sputum that is (+) for *M. tuberculosis*
- Children:
  - Paucibacillary disease
  - Sputum difficult/impossible to obtain from younger children (but beneficial with respect to contagiousness)
  - Gastric aspirates in children with pulmonary TB
    - 30-40 % sensitive in children
    - 60-70% sensitive in infants
  - Bronchoalveolar lavage (BAL): Sensitivity may be less than gastric aspirates

Pediatric TB Cases by Case Verification Criteria* 1993–2015

- Clinical Case 52%
- Lab Confirmed 26%
- Provider Diagnosis 22%

N= 21,223

*Based on the public health surveillance definition for TB [MMWR 1997;46(No. RR-10):40-41]
Pediatric TB: Diagnostic Challenges

- Asymptomatic or non-specific symptoms
  - Fever, poor appetite, poor weight gain or weight loss
- Approximately 22-30% of disease is extrapulmonary
  - Meningitis and miliary disease tend to develop soon after infection - 70-80% occur in children 0-4 years of age
  - Low threshold for LP, ophthalmologic evaluation, other imaging
- Physical examination may be normal

- TST negative early in disease
- CXR challenges (remember quiz)
- Index case - crucial to identify the adult source case for the child
  - Provides strong evidence that the child suspected of having TB disease actually has TB
  - May be the only isolate available for susceptibility testing
Pediatric TB: Other Considerations

- Need for admission (gastric aspirates) vs. home isolation (induced sputum in clinic setting)
- Availability of negative pressure rooms
- Need for family screening (esp. re: visitation)
- HIV testing

Tuberculosis in Adolescents

- Reactivation of infection acquired during childhood
  - Greater risk of reactivation if initial infection closer to puberty
  - Chronic pulmonary tuberculosis
- Progression of new infection to disease
  - Classic primary disease
  - Progressive primary pulmonary tuberculosis
  - Chronic pulmonary tuberculosis
Adolescents: Reactivation Tuberculosis

- Constitutional symptoms
  > respiratory symptoms
  - Weight loss and fever very common
  - Drenching night sweats
  - Cough, chest pain, hemoptysis
- Cavitary lesions frequently seen

Treatment of TB in Children & Adolescents

- If INH resistance rate >4% or if other risk for resistance:
  - Isoniazid (10 mg/kg/day, range 10-20, max. 300)
  - Rifampin (15 mg/kg/day, range 10-20, max. 600)
  - Pyrazinamide (20-30 mg/kg/day)
  - Ethambutol (15-25 mg/kg/day)
  - Pyridoxine
- Medication considerations
  - Toxicity monitoring: clinical side effects, LFTs, uric acid (PZA), ophthalmologic exams (if patient too young for color/vision screening)
  - Formulations: INH crushed tablets, RIF open capsules
- Monthly MD visits
Treatment of TB in Children & Adolescents

- Directly observed therapy (DOT)
  - 5 days/week + self-administered on weekends
  - BOH RN in house vs. school RN – remember to think about holidays/vacations

- Typical course (pan-susceptible isolate):
  - RIF/INH/PZA/ETH + B6 as initial regimen
  - Discontinue ETH once susceptibility data available
  - Discontinue PZA after 2 months (60 doses)
  - Continue RIF/INH + B6 to complete 6-month course

- Follow laboratory and radiographic data
- Sensitivities very important, if none available, decisions regarding therapy made on combination of clinical and radiographic improvement

Other treatment challenges

- Case #1: 33moF with pulmonary TB and development of hepatitis on initial therapy
- Case #2: 17yoM with cavitary pulmonary TB, initial persistently positive smears and later poor compliance with appointments
Case #1: 33moF

- 33moF moved to US from El Salvador in December 2016
- PMH: BCG, no other issues
- Older brother (7) screened prior to school entry: IGRA+/CXR negative → started on isoniazid
- Patient recognized as being at risk:
  - TST >15mm w/ ulceration in March 2016
  - Positive CXR
  - IGRA also positive
  - Asymptomatic
- Admitted for serial gastric aspirates, initiation of 4-drug regimen (RIF/INH/PZA/ETH + B6) on 3/22 – no LP, no concern for disseminated disease; baseline and pre-discharge labs WNL, Ophtho exam WNL
Case #1 (cont’d)

- 4/11: AST ~6x upper limit of normal
  - RIF/INH/PZA stopped – potentially hepatotoxic
  - ETH continued with addition of moxifloxacin
    - <1mo into therapy, high potential for dissemination BUT no current concern for disseminated disease so no IV med started
- 4/25: LFTs WNL – RIF restarted
- 5/9: LFTs stable – INH + B6 restarted
- 5/17: LFTs stable and CXR improved – ETH/moxi discontinued, RIF/INH + B6 continued

Case #2: 17yoM
Case #2 (cont’d)

- 17yoM from Liberia presenting to Pulmonary clinic in September 2016
  - Chronic dry cough since prior winter
  - Increased SOB for 1 week, exertional dyspnea
  - CXR at PCP’s office: cystic abnormalities
  - No negative pressure room or mask use
- Additional history:
  - 2006: TST 12mm, CXR negative

Case #2 (cont’d)

- Additional ID history:
  - Born in Liberia, also spent time in Ghana and Cote d’Ivoire, refugee camps (in prior records but patient only recalls Liberia and Ghana)
  - 12mm TST reaction in December 2006 with negative CXR. Referred to NSMC TB clinic in January 2007:
    - 1/17/2007 MD eval positive TST and normal CXR
    - 1/24/2007 #1 INH 300 mg started with teaching nsg visit
    - 2/21/2007 no show (letter sent)
    - 3/5/2007 #2 INH 300 mg given nsg visit
    - 4/2/2007 no show (letter sent)
    - 4/18/2007 #3 INH 300 mg given nsg visit
    - 5/16/2007 no show (letters sent)
    - 7/9/2007 #4 INH 300 mg given nsg visit
    - 8/6/2007 no show (letters sent)
    - 9/10/2007 #5&6 INH given nsg visit
    - 11/14/2007 no show (letters sent)
    - 4/10/2008 no response to multiple letters program terminated noncompliant needs restart
Case #2 (cont’d)

- 9/30 Induced sputum M. tb PCR positive, smear - abundant 3-4+ AFB Cx M. tb complex
- 10/1 Induced sputum smear - abundant 3-4+AFB, Cx NGTD
- BAL RUL 1 GS mod polys, no org, Cx NURF; fungal prep neg, cx NGTD; smear abundant 3-4+ AFB, Cx AFB
- BAL RUL 2 GS mod polys, no org, Cx NGTD; fungal prep neg, cx NGTD; smear abundant 3-4+ AFB, Cx AFB
- BAL LUL GS abundant polys, no org, Cx NGTD; fungal prep neg, cx NGTD; smear abundant 3-4+ AFB, Cx

  - Mycobacterium tuberculosis - pan-susceptible (INH, RIF, ETH, PZA, streptomycin)
  - 10/10 Induced sputum Smear rare (1+) AFB, no modified AFB, Cx AFB
  - 10/11 Induced sputum Smear abundant 3-4+ AFB, Cx AFB
  - 10/12 Induced sputum Smear abundant 3-4+ AFB, Cx AFB
  - 10/19 Induced sputum Smear negative, Cx negative
  - 10/19 Induced sputum Smear negative, Cx negative
  - 10/20 Induced sputum Smear negative, Cx AFB
  - 11/16 Induced sputum Smear negative, Cx negative
  - 11/16 Induced sputum Smear negative, Cx negative
  - 11/17 Induced sputum Smear negative, Cx negative
  - 12/7 Induced sputum Smear negative, Cx negative

Case #2 (cont’d)

- Infection control considerations:
  - Initial clinic visit (waiting room, exam room, CT suite)
  - Discharge criteria (2 weeks of therapy given concern for family members)
  - Follow-up clinic visits (availability of negative pressure rooms)
- Isolate pan-susceptible, easily narrowed from 4-drug to 2-drug therapy with clinical and radiographic improvement, no toxicity
- Difficulties with appointment no-shows, setting up DOT during school vacations
Take-home points

- TB cases are rising in the US
  - Pediatric TB case rates highest in infants and post-pubertal adolescents
- Children are usually:
  - Infected by adult/adolescent household contacts
  - Not infectious (contagious)
- Tuberculosis or LTBI in a child is a sentinel public health event
- TB control in the United States:
  - Targeted testing – TST vs. IGRA
  - Contact investigations
  - Evaluation of TB-exposed child - TST/IGRA, CXR, "window prophylaxis"
  - Importance of LTBI identification and treatment
- Always have a high index of suspicion for TB in children – diagnostic challenges
- Medication challenges in children and importance of DOT

HAVE A HEALTHY ANXIETY RE: PEDIATRIC TB
• Be a detective
• Always feel free to call an expert

• Never treat patient in isolation...
  – Always think about families and other contacts
• ….But use isolation when indicated
THANK YOU – QUESTIONS?
VMADHAVAN@MGH.HARVARD.EDU