Tuberculosis in Children and Adolescents 2017

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Rutgers Global Tuberculosis Institute
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Objectives

• Utilize a risk assessment tool to identify children and adolescents for targeted testing and evaluation for TB infection
• Apply current recommendations for management of TB infection and TB disease in children and adolescents
• Understand the difficulties in the diagnosis of TB disease in children and adolescents
Tuberculosis in Children and Adolescents

- Classification system for tuberculosis
- Epidemiology: Global, national, state
- Transmission of tuberculosis to children and its significance
- Public Health Aspects of Tuberculosis Control
  - Targeted Tuberculosis Testing: Why and how to
    - Use of a Risk Assessment Questionnaire
    - Contact Investigations
      - Management of the TB-exposed child
      - Missed opportunities and their effects
- Latent TB Infection: Diagnosis and treatment
  - The tests
  - BCG vaccine and the TST
- Difficulties in the diagnosis and treatment of tuberculosis disease in children
  - Clinical presentation and radiographic appearances
  - Mycobacteriology and culture confirmation
  - Barriers to adherence and the importance of DOT
  - Medication: dosages, preparations, administration, Monitoring
## 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><em>M. tuberculosis</em> 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>

**Class Type Description**

- **Class 0**: No TB exposure. Not infected. No history of exposure. Negative reaction to tuberculin skin test or IGRA.
- **Class 1**: TB exposure. No evidence of infection. History of exposure. Negative tuberculin skin test or IGRA.
- **Class 2**: TB infection. No disease. Positive reaction to tuberculin skin test or IGRA. No clinical, bacteriological, or radiographic evidence of active TB.
- **Class 3**: TB, clinically active. M. tuberculosis cultured (if done). Clinical, bacteriological, or radiographic evidence of current disease.
- **Class 4**: TB. Not clinically active. 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.
- **Class 5**: TB suspected. Diagnosis pending.
Epidemiology

• Tuberculosis remains the leading infectious disease in the world
  – Approximately 1/3 of the world’s population (>1.9 billion people) is infected with *M. tuberculosis*
  – In the 2000s:
    • 90 million new cases
    • 30 million deaths
  – Among children <15 years of age:
    • Approximately 13 million cases
    • 5 million deaths
• 10.4 million of new TB cases in 2015 globally
  – 1 million of these were in children (approx. 10% of total cases)
  – Approx. 3% of these cases likely have MDR-TB and 40,000 are HIV-infected
  – 136,000 children <15 years old died in 2014 from TB
    • Account for 25-40% of severe morbidity, mortality, and sequelae
Background: Pediatric Tuberculosis

- **Definition of pediatric tuberculosis (TB):**
  - TB disease in a person < 15 years old

- **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>
Pennsylvania TB Cases 2015

- All ages: 200
  - 5-15 years of age: 3
  - <5 years of age: 1
  - 15-24 years of age: 12
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

- Ethiopia 2%
- Somalia 2%
- Haiti 4%
- Vietnam 8%
- Philippines 10%
- Other 29%

2015
N=440

- Mexico 45%
- Ethiopia 6%
- Philippines 10%
- Myanmar 11%
- Mexico 10%
- Honduras 6%
- Kenya 5%
- Other 57%
Epidemiology: United States

• TB case rates for all ages are higher in urban, low-income areas, and in nonwhite 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
Transmission of *M. tuberculosis* to Children

- Children are usually infected by an adult or adolescent in the immediate household.
- Casual extra-familial contact is less often the source of infection.
- Children rarely infect other children or adults:
  - Tubercle bacilli are relatively sparse in secretions.
  - Children with pulmonary TB rarely cough.
  - Cough, when present, lacks the tussive force needed to aerosolize bacilli.
CT chest, cavitary TB adult

CT chest, primary TB child
Significance of Tuberculosis in Children

Public Health: Diagnosis of LTBI or tuberculosis disease in a child is considered a “sentinel public health event” usually representing recent transmission of TB within a community.

Personal Health: High rates of morbidity and mortality

Red Book 2009
American Academy of Pediatrics
Risk of Progression to TB Disease

• Immunocompetent adults: 5-10% lifetime risk of developing disease after infection
• Adults with TB infection and HIV infection: 5-10% annual risk of developing disease
• Children and the risk of TB disease:
## Risk of Tuberculosis Disease by Age

<table>
<thead>
<tr>
<th>Risk of disease following primary infection</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated tuberculosis/</td>
<td></td>
</tr>
<tr>
<td>tuberculosis meningitis</td>
<td></td>
</tr>
<tr>
<td>&lt;1 years &lt;10-20%</td>
<td>High rates of morbidity and mortality</td>
</tr>
<tr>
<td>1-2 years 2-5%</td>
<td>High rates of morbidity and mortality</td>
</tr>
<tr>
<td>2-5 years 0.5%</td>
<td></td>
</tr>
<tr>
<td>5-10 years &lt;0.5%</td>
<td>“Safe school years”</td>
</tr>
<tr>
<td>&gt;10 years &lt;0.5%</td>
<td>Effusions or adult-type pulmonary disease</td>
</tr>
<tr>
<td>10-20%</td>
<td>80-90%</td>
</tr>
<tr>
<td>30-40%</td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>75-80%</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from reference 30.

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

Increased Risk of Progression of LTBI to TB Disease

- **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 used to treat rheumatoid arthritis and Crohn disease
Control of Tuberculosis in the United States

- Targeted testing of persons with risk
- Case finding and treatment
- Contact investigations
TB Control: 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

CDC, AAP
Why Use Risk-Based Targeted TB Testing?

- Why not use routine, universal, administratively mandated TB testing? Why not use the TST or IGRA as a screening tool?
  - Daycare
  - Schools
  - Colleges
  - Summer camps

- Answer: Limitations of the TST/IGRA
  - Universal testing means that large numbers of low risk children will be tested: Inefficient use of healthcare resources
  - Even if the specificity of the test approaches 99%, testing of persons in low-prevalence groups would result in mostly false-positives
  - IGRA specificity reduces but 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 Testing Risk-Assessment Questionnaire

• 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, Australia, New Zealand, or Western European countries)
• Has your child traveled to a high-risk country and spent >1 week with the resident population?

Red Book 2012
Using the Risk Assessment Questionnaire

• 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 risk factor is identified, a TST or IGRA should be performed

Red Book 2009
Diagnosis of TB infection in children

- Tuberculin skin test (TST)
- Interferon-γ release assays (IGRAs)
Tuberculin skin tests (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

• Can be difficult to place and interpret properly:
  – Intradermal injection by an experienced provider
  – Requires second visit for interpretation
  – Interpretation requires careful measurement of induration at the site of injection by a provider experienced in this measurement
Tuberculin skin tests (TST)

• False negative results:
  – Improper handling of PPD solution
  – Improper placement of the test
  – Incorrect interpretation of results
  – Immunosuppression:
    • Disease: HIV, early or advanced TB disease, cancer, malnutrition, viral illness (measles, varicella, influenza)
    • Medications:
      – Corticosteroids
      – Cancer chemotherapy
      – Immunomodulating biologic agents (tumor necrosis factor-α inhibitors)
      – Live viral vaccines (measles, perhaps varicella)

• Positive test can be due to:
  – Infection with *M. tuberculosis*
  – Infection with nontuberculous mycobacteria (NTM)
  – Receipt of bacille Calmette-Guerin (BCG) vaccine

• Cannot distinguish LTBI from TB disease
Summary: Tuberculin skin tests (TST)

• There are limitations to both the sensitivity and specificity of the TST
• PPV is much greater when patients with risk factors for LTBI are tested
• When used in patients without risk factors, most positive results are false positives
  – This is accentuated among children who have received the BCG vaccine
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 and those caused by BCG
  - 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, perhaps down to age 2 years, lower if you call me
  - If IGRA positive: Diagnostic evaluation including a chest radiograph and appropriate treatment
Interferon-γ Release Assays (IGRAs)

- Detect interferon-γ release ex vivo from CD4+ lymphocytes stimulated by antigens found on the *M. tuberculosis* complex

- Two assays are available:
  - QuantiFERON-TB Gold In-Tube assay (QFT)
  - T-SPOT.*TB* assay (T-SPOT)
  - Both assays use ESAT-6 and CFP-10
  - QFT uses a third antigen TB7.7
  - These antigens are not encoded in the genomes of *M. bovis*-BCG or *Mycobacterium avium* intracellulare

- Similar to the TST, IGRAs do not distinguish between TB infection and TB disease
  - Negative IGRA does not rule out either in child with suspicious findings

- No cross reactivity with *M. bovis* (BCG vaccine) nor with *M. avium* complex (MAC)
  - Specificity >TST
  - May cross react with *M. kansasi*, *M. fortuitum*, *M. marinum*
Interferon gamma release assays (IGRA): Use in children

• TST preferred, IGRA acceptable
  – Children <5 years of age
    • Positive IGRA likely indicates infection with *M. tuberculosis*
    • Negative IGRA does not rule infection with *M. tuberculosis*
    • Increasing evidence that IGRAs are reliable down to 2 years of age and below

• IGRA preferred, TST acceptable
  – Children ≥5 years of age who have received BCG vaccine
  – Children ≥5 years of age unlikely to return for TST reading

Interferon gamma release assays: Use in children

• Both TST and 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 and 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)
**TB Screening: IGRA**

**QuantiFERON Gold in-tube**
- **Company:** Cellestis, Australia
- **US FDA approved**
- **Method:**
  - Enzyme linked immunosorbant assay (EIA)
  - Whole blood
  - Incubated with MTB antigens (ESAT-6, CFP-10, TB7.7)
  - T-Cells produce INF-γ
  - Supernatant removed
  - INF-γ measured by ELISA reader

**T-Spot.TB**
- **Company:** Oxford Immunotec, UK
- **US FDA approved**
- **Method:**
  - Enzyme linked immunospot test (Elispot)
    - PBMC/T-cells
    - Incubated with MTB antigens (ESAT-6 & CFP-10)
    - T-Cells produce INF-γ
    - IFN-γ binds to antibody in wells
    - Spots develop and are counted manually or by reader
### QuantiFERON®-TB Gold IT: ELISA
Interpretation of test result

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>≤ 8.0</td>
<td>&lt; 0.35</td>
<td>≥ 0.5</td>
<td>Negative</td>
<td><em>M. tuberculosis</em> infection NOT likely</td>
</tr>
<tr>
<td></td>
<td>≥ 0.35 and &lt; 25% of Nil value</td>
<td>≥ 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 0.35 and ≥ 25% of Nil value</td>
<td>Any</td>
<td>Positive</td>
<td><em>M. tuberculosis</em> infection likely</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.35</td>
<td>&lt; 0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 8.0</td>
<td>Any</td>
<td>Any</td>
<td>Indeterminate</td>
<td>Results are indeterminate for TB-Antigen responsiveness</td>
</tr>
</tbody>
</table>

*From: QuantiFERON®-TB Gold IT product insert*
**Indeterminate results: Test vs. host failure**

High background gamma interferon (abnormal negative control)
- Concurrent illness
- Mitogen put in the wrong well (nil)
- Defective tubes

Low mitogen (abnormal positive control)
- Transient or chronic immune suppression
- QFT-G or T-spot: no mitogen in control well
- QFT-GIT: defective tubes, overfilling, or inadequate shaking
Interferon-γ Release Assays (IGRAs)

- Standard instructions are provided for performing IGRAs but concerns have been raised about the reproducibility of results on serial performance
  - Serial testing of healthcare workers at low risk of TB infection has shown unexplained conversion of IGRA to positive and then reversion to negative
  - 79/405 Ugandan children tested at age 5 years had positive T-SPOT but only 38 (30%) remained positive when tested 3 weeks later
- IGRA results are susceptible to variability due to a number of factors:
  - Manufacturing issues, inconsistencies in specimen collection, inadequate blood volume, time of collection, delays in isolation and incubation of cells, inadequate mixing of QFT blood, laboratory error

Nkurunungi PLoS One 2012
New York City Experience

• Enhanced LTBI treatment outcomes
• IGRAs reliable tests for TB infection (risk factors)
• Contact investigations:
  – One stop testing
  – Fewer false positives (BCG)
    • No need for evaluation and treatment
• Costs
• Training of staff
• Logistics
• Phlebotomy in infants
**AAP Technical Report 2014 (Starke)**

- **BCG vaccinated?**
  - No
  - Yes: Age < 5 y?
    - No
      - Likely to return for TST reading?
        - Yes
          - Either TST or IGRA acceptable
        - No
          - TST preferred
    - Yes: TST preferred
      - Negative result: Testing complete unless criteria A are met, then IGRA
      - Positive result: Testing complete unless criteria B are met, then IGRA

- **IGRA preferred**
  - Negative result: testing complete
  - Indeterminate
  - Positive result: testing complete

**Criteria A**
1. High clinical suspicion for TB disease and/or
2. High risk for infection, progression, or poor outcome

**Criteria B**
1. Additional evidence needed to ensure adherence and/or
2. Child healthy and at low risk and/or
3. NTM suspected
Evaluation of the child with a positive TB test (TST, IGRA)

- Evaluation of all children with a positive TB test should include:
  - A careful history for symptoms of disease
  - Physical examination
  - Chest radiographs (PA & lateral)
  - Household investigation
Control of TB in the United States

• Contact investigations
  – The most reliable TB control program is based upon aggressive and expedient contact investigations, rather than routine screening of large populations

  Can be complex and may require lots of detective work

High priority contact:
  Household
  Age <5 yrs
  Med risk condition
  Procedure
  Congregate, Time
Prevention of TB in Children: Potential Missed Opportunities

• Failure to find and appropriately manage adult source cases (case finding)
• Delay in reporting the initial diagnosis of TB
• Contact investigation interview failure
• Delay in evaluation of exposed children
• Failure to completely evaluate exposed children
• Failure to prescribe INH “window prophylaxis”
• Failure to maintain a contact under surveillance
• LTBI diagnosed; treatment not prescribed
• Failure to complete treatment for LTBI
Tuberculosis Exposure in Children <4 years of age and “Window Prophylaxis”

- History, PE, TST, CXR are done
  - CXR is done regardless of TST result

- IF the child is:
  - Asymptomatic and physical examination is normal
  - TST is negative (<5 mm)
  - Chest X-ray is normal

- AND IF <4 years of age START: Isoniazid (INH) 10 mg/kg (max., 300 mg) PO once daily
Tuberculosis Exposure in Children

Why is INH given as “Window Prophylaxis” even if there is no evidence of TB infection or disease at the initial visit?

- 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

TST repeated 8-10 weeks after contact broken with infectious adult:

- If TST (-), discontinue INH
- If TST (+), re-evaluate child and treat accordingly
Timetable of TB in Children after Walgren

Tuberculosis. Starke JR, in Feigin, Cherry, Demmler, Kaplan, ed: Textbook of Pediatric ID 2009
Case #2: Three generations, two families and a pediatrician…

Or, source cases, index cases, and contact investigations… you never know what you’ll get if you keep your eyes open… and keep asking questions….

Clinicians were asking “Could this child have TB?”
THE IMPORTANCE OF EPIDEMIOLOGY in childhood TB… If we could only find an adult source case…
Potential Missed Opportunities in TB Control

• Initially, 5/18 children are diagnosed as TB-exposed
  – Two (Ages 6 & 28 months) identified in the contact investigation have 0.0 mm TSTs and normal CXRS at the health department
  – Mother says at the health department that she would like to have them seen by their private pediatrician
    • No PE done
    • No INH “window prophylaxis” given
Potential Missed Opportunities in TB Control

- Two other children from the same family who have LTBI are referred to the same pediatrician for evaluation and management at mother’s request:
  - Receive prescriptions for INH plus 8 refills
    - No follow-up appointments are given
    - Social history: Homeless, 5 children, mother with her own serious health problems, holding down a full-time job
  - Set-up for another missed opportunity? Strong probability
    - Will therapy for LTBI be completed?
    - Was it? Yes, why? DOT of infection (DOTI)
Case History: Final Numbers

- Eighteen children were exposed to a 26-year old woman with bilateral cavitary pulmonary tuberculosis:
  - 15/18 (83%) children are infected
    - 9/15 (60%) develop TB disease
      - Two after initial negative TST (Missed opportunity)
      - 1 TB meningitis, 2 miliary
    - 6/15 (40%) have LTBI
      - 3/18 (17%) are TB-exposed but not infected
- Through 3 generations: All 2nd and 3rd generation cases preventable
  - TB-infected child of today may become the index pt. of tomorrow without treatment for LTBI
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)
Evaluation of the Child with a positive TST or IGRA

• Evaluation of all children with a positive TB test should include:
  – A careful history for symptoms of disease
  – Physical examination
  – Chest radiographs (PA & lateral)
  – Household investigation
Treatment of Latent Tuberculosis Infection

- INH 10-15 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
- Monitor index case isolate sensitivities
- Hepatotoxicity from INH is rare in children:
  - Monthly assessment for clinical evidence of hepatotoxicity should be made: malaise, loss of appetite or weight, nausea, vomiting, abdominal pain, jaundice
  - Routine monitoring of LFTs is not indicated, except:
    - Concurrent liver disease
    - Pregnancy or first 12 weeks postpartum
    - Concurrently on other hepatotoxic medications
    - Clinical evidence of hepatoxic effects
Treatment of Latent Tuberculosis Infection

- Rifampin 10-15 mg/kg/day (max. 600 mg) po daily for 6 months is an alternative
  - INH not tolerated
  - Index patient isolate INH-resistant

- Cruz & Starke, (IJTLD 2014): Rifampin 10-15 mg/kg/day (max. 600 mg) po daily for 4 months: Safe, completion rates similar to 9INH by DOPT

- Additional regimens for LTBI treatment:
  - 3 months of INH + rifampin
  - 2 months of rifampin + PZA (When given as part of regimen: H, R, Z, E to treat TB disease and child subsequently found to have LTBI only)
What about the 12-dose, intermittent INH-RPT regimen for children?

• Children ≥12 years of age: Recommended as equal alternative to 9 months of INH
• Children 2-11 years of age: INH for 9 months recommended
  – INH-RPT: Insufficient safety and efficacy data to recommend universal use in this age group
  – INH-RPT: An option if completion of 9H unlikely and likelihood or hazard of TB is great
• Children <2 years of age: INH for 9 months recommended
  – INH-RPT: Not recommended: Lack of safety and pharmacokinetic data in this age group
How Children with Tuberculosis are Identified

- Presentation with a symptomatic illness
- Discovery of a child with pulmonary tuberculosis during contact investigation of an adult with tuberculosis
  - Few or no symptoms
  - Evaluation: (+) TST/IGRA and abnormal CXR
  - In some areas of U.S. up to 50% of children with TB are discovered in this manner
    - Before significant symptoms have developed
Mycobacteriologic Diagnosis of Tuberculosis

• Adults: 70-90% have a sputum that is (+) for \textit{M. tuberculosis}

• Children:
  – Tubercle bacilli are relatively few in number
  – Sputum generally cannot be obtained from children <10 yrs old
  – Gastric aspirates in children with PTB
    • 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
N= 21,223

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

*Based on the public health surveillance definition for TB [MMWR 1997:46(No. RR-10):40-41]
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.
Difficulties in the Diagnosis of Tuberculosis in Children

• Children are often asymptomatic or symptoms are nonspecific: 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

• Epidemiologic link (the adult source 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
Difficulties in the Diagnosis of Tuberculosis in Children

- Physical examination may be normal
- TST may be negative (10-40%). IGRA?
- Chest radiograph: Any lobe of the lung may be involved
  - Good technique/experience with children
  - Two views
  - Careful interpretation
Tuberculosis in Adolescents

- Adolescents develop tuberculosis in one of two ways:
  - Reactivation of infection acquired during childhood
    - The closer to puberty at the time of infection the greater the risk of reactivation
    - Chronic pulmonary tuberculosis
  - Progression of infection acquired during adolescence to disease:
    - Classic primary disease
    - Progressive primary pulmonary tuberculosis
    - Chronic pulmonary tuberculosis
Adolescents: Reactivation Tuberculosis

• Constitutional symptoms often more prominent than respiratory symptoms
  – Weight loss and fever are very common
  – Drenching night sweats occur several times per week
  – Cough, chest pain, hemoptysis

• Cavitary lesions frequently seen
Case #7: Another missed opportunity:

Just how bad can this get?

OR

Can you die from TB if you are a teenager?

AND

Why LTBI is important!
Case #21

- 8-year old girl, recently arrived from Haiti was evaluated at the DOH for a 12 mm TST reaction
- There were no symptoms of TB disease and PE was normal
- A chest radiograph was done:
- INH 200 mg po once daily; #30 tabs dispensed
- 6 months later the chart reads: “Overdue for medication refill.”
- There were no further notes ....until 5 years later.
Hospital Admission

- The patient, now 13-years of age, was admitted to a local hospital with a 3 week history of fever, cough, increasing dyspnea, and weakness
  - She had been sent home by the school nurse on 4 occasions over the previous 2 months for the fever and cough and then for weight loss and weakness
- She was seen on 2 occasions by her PCP and was given antibiotics (azithromycin) and twice in EDs of local hospitals:
  - The last ED visit was 9 days PTA when chest radiographs were done and amoxicillin-clavulanate (Augmentin) was given
  - There was no improvement with antibiotic
  - A chest x-ray was done in the last ED:
Case

• PE: Cachetic, weak appearing female with flat affect in mild respiratory distress
• T – 103.2°F  HR – 160’  RR – 22’  O₂ sat = 92%
• Wt: 78.7 lbs  UBWt.: 96.7 lbs
• Treatment IV ceftriaxone and oral azithromycin
• Infectious Diseases consultation:
  – Sputa: AFB smear: (+), few AFB; culture (+): pansensitive MTB
• Anti-TB medications started:
  – INH 300 mg po daily
  – RIF 600 mg po daily
  – PZA 500 mg po, three times a day (?)
  – Emb 400 mg po, twice daily (?)
102°F

Vital Sign Graphic Sheets
Case

- **7/12: At hospital discharge**
  - Remains febrile
  - Came directly to Hudson County Chest Clinic with driven by her brother and sister with “TB escort”
    - Cachetic, weak with unsteady gate
    - Continued treatment added supplement, ibuprofen
    - DOT by RN
    - Home visit by CRNP (PED)
      - Weak, tires easily, bed ridden, bed-bathroom, bedroom had no windows, home was very warm (no AC)
      - Poor oral intake
      - Tachypneic, tachycardic
• Hospitalized 7/24-8/17: Weaker, hypoxemic, cachectic with weight down to 66 lbs
• RR - 40’ 0₂ sat 90%
• Continued TB meds; oxygen
• NGT placed for continuous nutritional supplementation
Case

- Gradually regained strength and began to walk
- Discharge: 8/17  RR – 20’ on 1L oxygen; Wt 76 lbs
  - TB meds and supplement
  - AC purchased and placed in home
- 8/23: Wt. 88 lbs; RR = 18’
  O₂ sat 97% on RA
- 9/20: Wt. 97 lbs; RR = 18”
- 11/1: Wt. 99 lbs
- 12/13: Wt 102 lbs
- 12/13 CXR:
Treatment of TB in Children & Adolescents

• If INH resistance rate >4% or if other risk for resistance include four drugs in initial regimen:
  – 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)

• Treatment complicated by child unfriendly preparations of the medications

• Directly observed therapy (DOT)

• Monitor liver transaminases? – Depends on severity of disease

• Follow susceptibility studies of Mtbc isolate (index and/or child isolate)
  – Important to be familiar with resistance patterns in the community
Summary

• Reported cases of tuberculosis in the U.S.:
  – More than 2/3 occurs in nonwhite racial and ethnic groups
  – More than 50% occur in foreign born persons
  – Among children case rates are highest in infants and postpubertal adolescents

• Children are usually:
  – Infected by adult or adolescent household contacts
  – Not infectious (contagious)

• Tuberculosis or LTBI in a child is a sentinel public health event

• Contact investigations and targeted TB testing are mainstays of TB control in the U.S.
  – Risk assessment questionnaires are the most effective screening tool to detect children at risk for LTBI

• TB diagnosis in young children requires a high index of suspicion

• DOT is key to successful treatment