Tuberculosis in Children

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• I have **NO** financial relationships with the manufacturers of any commercial products and/or provider of commercial services discussed in this CME activity.

• **I may discuss** unapproved/investigative use of a commercial product/device in my presentation.

• I acknowledge that today’s activity may be certified for CME credit and thus cannot be promotional. I will give a balanced presentation using the best available evidence to support my conclusions and recommendations.
Pediatric tuberculosis: Objectives

• Describe the epidemiology of pediatric TB in the US.
• Describe the clinical presentation of TB in children.
• Describe treatment regimens for pediatric LTBI and active TB.
Pediatric tuberculosis: epidemiology

- ~9 million annual cases globally. **9557 cases occur in US in 2015.**
- 2008-2010: 2660 children and adolescents <18 years of age. **440 [4.6%] in 2015.**
- ~31% born in other countries.
- Among US-born pediatric patients: ~2/3 had at least 1 foreign-born parent.
- 75% of all pediatric patients: some type of international connection, family or residency history

Starke JR, COID. Pediatrics 2014;134:e1763
TB Cases, All Ages, by Age Group, 1993–2015

Number of TB Cases

< 15 yrs  15–24 yrs  25–44 yrs  45–64 yrs  65+ yrs

CDC
Pediatric tuberculosis: epidemiology

- ~52% of cases: 13-17 years of age
- High rate of progression: infection >> disease [weeks to months].
- Risk of progression, <12 months of age: 40%. 1-2 years: 25%. Older children: 10-15%.
- Immigrants, refugees: frequently lack testing for latent infections. Untreated.
- International “connection”: highest risk of infection. Targeted group for testing.

Starke JR, COID. Pediatrics 2014;134:e1763
Tuberculosis and children, US

- Tuberculosis: foreign born [~30%], US born + foreign-born parent [66%], international “contact” [75%].
- ~50% of cases in children ages 13-17 years.
- Infants and young children: higher rate of TB infection progressing to TB disease.
- Initial infections lead to latency. Reactivate later.
- Identify and treatment of latent TB infection.

Starke JR, COID. Pediatrics 2014;134:e1763-ee1773

*Rates are per 100,000 persons
Note: Rate presented on a logarithmic scale. Case data totals beginning in 1994

CDC
Pediatric TB Cases by Race/Ethnicity, 1993–2015

N=21,223

Note: Unknown, multiple race/ethnicity, and Native Hawaiian and Other Pacific Islander not shown
Recognizing tuberculosis: children as the “mine canary”

- In countries with poor TB control: ~15-20% of disease burden, children <15 years of age.
- Advanced disease frequent <5 years of age
- Developed countries: <5%
- Frequently, diagnosis of TB in a young child: sentinel markers for TB in family members [social circle].
- Unrecognized adult or adolescent with cavitary disease.
Question: Can you always tell if someone has tuberculosis based on clinical features?

Clinical features are frequently non-specific.

Pulmonary infiltrates mostly resemble common bacterial pneumonias.

Miliary pattern: while not pathogenomomonic, highly indicative of severe TB infection.

Epidemiologic history: a major determinant for considering TB as etiology.

Therapy will have to be started before [without] microbiologic confirmation.
Infant with failure to thrive

Infant with failure to thrive, cough

- History: key to diagnosis
- Ex-husband of mother: history of incarceration; with cough. Mother with history of bronchitis.
- TST, father and mother: >15 mm
- TST, infant: 8 mm
- Bronchoscopy: *Mycobacterium tuberculosis*
Clinical manifestations, children and adolescents

- Silent pulmonary infection is common [low grade fever and cough, ~1-2 weeks]
- Localized non-specific infiltrate; regional lymphadenopathy
- Large lymph nodes; compression; segmental lesions [usually <2 years of age]; erosion
- Progressive primary TB: enlarging caseous cavity
- “Reactivation” TB: infection acquired >7 yrs of age: upper lobes
Infant with asthma + influenza

6 month old infant with a 4 day history of coughing, tachypnea and fever. She was diagnosed with asthma at 4 months of age. Worsening respiratory condition; hospitalized in PICU. Found to have influenza B. Failure to thrive.
Miliary tuberculosis; children

- Early complication of infection [usually within ~2-6 months]
- Usually involves lungs, spleen, liver and bone marrow
- Explosive or gradual onset
- Malaise, anorexia, listlessness, weight loss, failure to thrive, fever
- Fever, hepatosplenomegaly, lymphadenopathy [~50%]
- Positive TST: 30%
Infant with swollen neck

- 4 ½ month-old previously-healthy infant with right-sided neck and ear swelling of 1 day duration. Fevers at home for ~2 weeks; as high as 103°F.

- Treated with broad-spectrum antibiotics with no improvement.
Infant with swollen neck

- History: key to diagnosis
- Maternal grandfather with lung cancer, tuberculosis [no treatment, no DOT]. Close contact with infant.
- TST: > 10 mm
- Gastric aspirate: *Mycobacterium tuberculosis*
TB meningitis; children

• Positive tuberculin skin test: ~40%
• Normal chest radiograph: ~50%
• CSF cell count: 10-500 WBC/mm$^3$
• CSF glucose: ~20-40 mg/dL
• CSF protein: elevated
• CSF AFB stain: ~30% [with 10 mL]
Child with pleural effusion

- TST: negative
- QuantiFERON assay: negative
- Key to diagnosis: history
- Maternal uncle, paternal aunt with history of tuberculosis
- Pleural fluid: *Mycobacterium tuberculosis*
- TST, 6 months later: positive
Which one is most important?

- History and physical examination
- Radiographic studies
- Cultures
- Tuberculin skin testing
- Interferon-γ release assays
How do we confirm TB in a child?

- Sputum culture: “good luck with young children.”
- Gastric aspirates: ~50% positivity
- Bronchoscopy: invasive, expensive
- Clinicians rely on “diagnostic-triad”
  - Contact history
  - Clinical history, signs of TB on CXR/CT [with expert interpretation]
  - Positive TST and/or IGRA
Diagnosis of latent tuberculosis infection

• History of exposure is not always helpful.

• Is there a gold-standard test?

• **Tuberculin skin test**: technique-dependent, false-positives [BCG, non-TB mycobacteria]. False-negatives [old infection, malnutrition, anergy, parasitic infections]. Some require two tests. Requires 2-4 visits for completion.

• **IGRAs**: False-negatives [young age, old infection, malnutrition, anergy, parasitic infections]. **False-positives.**
Truths about tuberculin skin testing in children

- False-negative tests do not exclude TB; initially in refugees, immigrants, adoptees, immunocompromised; poor technique

- False-positives: non-tuberculous mycobacterial infections. BCG [≈50% newborns]; ≈80-90% lose reactivity within 2-3 years of vaccination

- BCG: not a contraindication for testing
Interferon-γ release assays

- *Ex vivo* tests that measure release of IFN-γ from patient’s CD4+ T lymphocytes after stimulation by antigens found in *M. tuberculosis* complex [*M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*, *M. canetti*].

- QuantiFERON®-TB Gold In-Tube, T-SPOT.TB® [ELISPOT]
Interferon-γ release assays

• Antigens encoded in *M. tuberculosis* complex [not *M. bovis*-BCG strains, nor *M. avium* complex].

• Antigens found in *M. marinum*, *M. kansasii*, *M. szulgai*, *M. flavescens*.

• Do not distinguish between TB infection [LTBI] and TB disease.
Question: 15 month old with pneumonia + hilar adenopathy

Primary care physician calls to ask if he can order an IGRA [interferon-gamma release assay] on this patient.

There are family members with chronic coughs and weight loss.

Family and child have traveled to Mexico.

Guidelines recommend that not performing IGRAs in children <5 years of age?
IFN-γ release assays, TB; children

• QuantiFERON®-TB Gold In-Tube

• Retrospective, tertiary care center, UK

• 237 children; 25% immunocompromised

• Indeterminate: 35%

• ↑ indeterminate with ↓ in age; impaired immunity
  
  < 1 yr: 40%  
  10-13 yrs: 7%

• Positive TST, positive QFT-IT: 89%

• 12/16 with proven TB: positive QFT-IT

IFN-γ release assays, children

- 73 children; median age, 39 months
- 28 culture-proven TB, 23 culture-proven nontuberculous mycobacteria, 22 other respiratory infections.
- Specificity:

<table>
<thead>
<tr>
<th>Test</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>QFT-IT</td>
<td>100%</td>
</tr>
<tr>
<td>T-SPOT</td>
<td>98%</td>
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<tr>
<td>Tuberculin skin test</td>
<td>58%</td>
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</table>

IFN-γ release assays, children

**Sensitivity:**

- **QFT-IT:** 93%
- **T-SPOT:** 93%
- **TST:** 100%

Quantiferon-TB Gold In-Tube, children

• Retrospective analysis, 517 children 0-14 years of age, Italy. 336 tested with TST.

• Overall agreement: 89.9%

• Sensitivity, detecting symptomatic TB: 93.3% [86.5%, TST]. High specificity: 99.3%.

• Indeterminate rate: 3.9%
• Active tuberculosis, 45 [8.7%].
• Latent TB infection, 38 [7.4%]
• Exposed, 245 [47.4%]
• 19/22, discordant results: QFT-/TST+, 18 were BCG vaccinated.
<table>
<thead>
<tr>
<th>Age Group [yr]</th>
<th>QFT-IT Results +</th>
<th>TST Results +</th>
<th>% Agreement</th>
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<tbody>
<tr>
<td><strong>Active TB</strong></td>
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<tr>
<td>0-1.9</td>
<td>8 [100]</td>
<td>4 [57.1]</td>
<td>57.1</td>
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<tr>
<td>2-4.9</td>
<td>12 [92.3]</td>
<td>11 [91.7]</td>
<td>100</td>
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<td>5-9.9</td>
<td>11 [91.7]</td>
<td>10 [90.9]</td>
<td>81.8</td>
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<td>10-14</td>
<td>11 [91.7]</td>
<td>7 [100]</td>
<td>100</td>
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<tr>
<td><strong>Latent TB</strong></td>
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<tr>
<td>0-1.9</td>
<td>3 [75]</td>
<td>1 [33.3]</td>
<td>33.3</td>
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<td>2-4.9</td>
<td>8 [88.9]</td>
<td>4 [66.7]</td>
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<td>5-9.9</td>
<td>15 [93.7]</td>
<td>12 [80]</td>
<td>73.3</td>
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<tr>
<td>10-14</td>
<td>8 [88.9]</td>
<td>7 [77.8]</td>
<td>66.7</td>
</tr>
</tbody>
</table>
Interferon-γ release assay: caution

- T-cell assays, measure interferon-γ released after stimulation by MTB antigens.
- T-SPOT. _TB_, QuantiFERON-TB Gold In-Tube
- More specific than TST; potentially more sensitive
- Useful in children with BCG

- Results of studies in young children: inconsistent
- A negative IGRA ≠ absence of infection
- Should not be used in children < 5 years of age
- Immunocompromised host, malnutrition, parasitic infections: false-negative IGRAs
International adoptions: why is repeat TB screen testing needed?

- International Adoption Center, Cincinnati Children’s Hospital Medical Center.
- 527 international adoptees.
- Tuberculin skin testing positivity: 111 (21%).
- Repeat testing of 191 IAs with negative initial TST (46.9% of those initially testing negative).
- Repeat TST group: 20% were positive.
Question: Patient with pulmonary tuberculosis needs to be treated.

**Three** drug therapy: isoniazid, rifampin, and pyrazinamide?

**Four**-drug therapy: isoniazid, rifampin, and pyrazinamide + ethambutol?

I am worried about optic neuritis due to ethambutol.
Treatment of tuberculosis in children\textsuperscript{2}

• Meningitis:

2 months, INH + RIF + PZA + ETH or aminoglycoside, ethionamide. All daily, DOT.

Followed by 7-10 months of INH + RIF. Daily or twice weekly, DOT.

[If drug-susceptible \textit{M. tuberculosis}]
I am be worried about ethambutol: ocular toxicity

- Ethambutol, recommended dose: 20 mg/kg/day [15-25 mg/kg/day]
- Prevention of ocular toxicity. Use 3-drug regimen [isoniazid, rifampin, and pyrazinamide] instead, 2 months followed by INH + rifampin?

- How can you predict resistance in children with tuberculosis?
Question: Since isoniazid and rifampin are potentially hepatotoxic, do I need to monitor for elevated liver enzymes?

I have treated many patients with isoniazid for latent TB infection [LTBI], they tolerate the patient well with no jaundice. One of my partners ordered ALT/AST on one of his patients. It was 89 and 120, respectively.

Patient is asymptomatic.

Does he need to continue with weekly LFTs?
Hepatotoxicity with isoniazid: a pediatric problem?

• Retrospective review, INH hepatotoxicity, 1582 patients <18 years of age.

• 13 patients with LTBI developed hepatotoxicity [0.8% who started INH, 1.1% who completed 9 months of INH. Most within 6 months of starting.

• Symptoms: abdominal pain, anorexia, vomiting and nausea.

• Reversible

Adults: ~20%

Latent tuberculosis infection

- Isoniazid: 94% reduction in TB 1 year after treatment, ~70% reduction over 9 years.

- Infants: develop TB ~40% if untreated LTBI.

- More dissemination, complications during childhood.
Treatment of tuberculosis in children

- Latent tuberculosis infection [LTBI]: 9 months, isoniazid. Once daily or twice weekly DOT.
- Isoniazid-resistant: 4-6 months, rifampin, once daily or twice weekly DOT.
- Pulmonary, extrapulmonary [no meningitis]: 2 months INH + RIF + PZA + ETH, all daily. Followed by 4 months of INH + RIF.

[If drug-susceptible *M. tuberculosis*]
Dosage for a combination regimen of **isoniazid** and **rifapentine** in 12 once-weekly doses under direct observation for treating latent *Mycobacterium tuberculosis* infection.

**Isoniazid**

- 15 mg/kg rounded up to the nearest 50 or 100 mg;
- 900 mg maximum

**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

Isoniazid (INH) is formulated as 100 mg and 300 mg tablets. Rifapentine (RPT) is formulated as 150 mg tablets packed in blister packs that should be kept sealed until usage.

MMWR 2011;60:1650-1653
Mycobacterium avium-intracellulare
Pediatric tuberculosis in a single slide

- Frequently asymptomatic or non-specific.
- Foreign-born, foreign-born parent, international connection
- Disseminated disease in the very young.
- Less cavitation
- Less bacilli
- Rarely contagious
- Few microbiologic confirmations
- History key for making diagnosis
- Medications are generally tolerated well.