Disclosures

• No financial disclosures or conflicts of interest
Objectives

- To highlight important distinctions between pediatric and adult tuberculosis disease in:
  - Natural history of infection and clinical presentations
  - Epidemiology
  - Diagnostic tools and approaches
  - Treatment characteristics
  - Relevance of BCG vaccination to protection from disease
Pediatric TB: Clinical Pearls
Case 1: Rapid Progression

- 2 month-old male
- Exposure to father with active TB
Case 1

• 2 month-old male
• Exposure to father with active TB
• Asymptomatic at initial review
• Initial CXR:
Case 1

- 2 month-old male
- Exposure to father with smear positive cavitary TB
- Asymptomatic at initial review
- Initial CXR: Normal
- TST negative
- Treatment for window prophylaxis delayed
Case 1

- Six weeks after initial presentation, one month of rifampin
- Child taken to the ED with labored breathing, lethargic
- Mother failed to disclose evolving symptoms and ED visits
Case 1

- Hospital admission
- Gastric Aspirates: smear +
- 4 drug treatment started (Levofloxacin, INH, Ethambutol, PZA)
- Worsened respiratory distress
Age dependent progression from initial infection to TB disease

<table>
<thead>
<tr>
<th>Age at primary infection (years)</th>
<th>TB disease (%)</th>
<th>Pulmonary disease (%)</th>
<th>Miliary TB or TB of the central nervous system (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>50</td>
<td>30–40</td>
<td>10–20</td>
</tr>
<tr>
<td>1–2</td>
<td>20–25</td>
<td>10–20</td>
<td>2.5</td>
</tr>
<tr>
<td>2–5</td>
<td>5</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>5–10</td>
<td>2</td>
<td>2</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>&gt;10</td>
<td>10–20</td>
<td>10–20</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>

Adapted from Cruz et al, 2007
Case 2: Challenges of Pediatric Radiologic Dx

- 11 month-old male
- 2 month travel to Bangladesh
- Daily fevers to 105 since return
- Initial CXR read as normal
- PPD 10-15 mm?
- Empiric treatment for typhoid fever
Case 3: Subtle Presentation

• 13 month old adoptee (at 9 months) from China with negative screening
• 5\textsuperscript{th} centile for weight
• No respiratory symptoms
• Refractory otitis media
• BCG vaccinated at birth
• 18 mm TST by PCP
Case 4: Extrapulmonary Disease

- 14 year-old female
- Born in Kenya; lived between Kenya and Ethiopia until age 5 → USA
- 1 month hx of back pain
- Night sweats but no fever, weight loss (8#), weakness
- Lytic lesion on back XR—concern for metastatic cancer
Case 3, continued

• Pathology: caseating granulomas
• TST 27 mm; QFT positive
• CXR normal
• Sputum cultures and bone cultures negative
• Presumptive TB treatment (4 drugs)
• Clinical and radiographic improvement
Clinical Pearls of Pediatric Tuberculosis

- Limited Contagiousness
Clinical Pearls of Pediatric Tuberculosis

• Age-dependent risk of progression and disease severity

• Disease spectrum
  • More extra-pulmonary disease (25-40%)
  • Paucibacillary pulmonary disease
  • Lymph node
  • Severe forms (meningitis, miliary TB)

• Subtle presentation
  • Fever of unknown origin
  • Failure to thrive

• Limited Contagiousness

Cruz and Stark, 2013
Pediatric TB Epidemiology
Percentage of TB Cases Among Foreign-born Persons, United States*

2004

2014

- ≥50%
- 25%–49%
- <25%
- <25%
- No cases

*Updated as of June 5, 2015.

Source: CDC 2015
Colorado TB Epidemiology: 2015

• 73 Cases in 2015; Incidence 1.3/100,000
• 7 pediatric (<15), 5 adolescent/young adult (15-25)
  • 4 US born
  • 3 Foreign born
• 75% Denver Metro Area
• 21% US born
• 19% Mexico-born
• 60% Other countries
• 1 case in residents of correctional facilities
TB Case Rates by Race/Ethnicity: Colorado, 2006 - 2015

Source: Colorado State Department of Health and Environment, 2016

Fuente: Plataforma Única de Información/SUIVE/DGE/SS. Cierre 2012 *Tasa por 100 mil habitantes. Población CONAPO Proyección 2010-2050

Source: SECRETARÍA DE SALUD DE MÉXICO, 2013
Pediatric TB: Diagnostic Considerations
LTBI Testing in Pediatrics

• TST vs IGRA?
<table>
<thead>
<tr>
<th>Exposure Risk</th>
<th>Exposure and Test Results</th>
<th>N</th>
<th>Proportion With Positive QFT Results, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>No known risk, TST-negative</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>No known risk, TST-positive</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Low/moderate</td>
<td>Risk factors, TST-negative</td>
<td>62</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Risk factors, TST-positive</td>
<td>99</td>
<td>19</td>
</tr>
<tr>
<td>High</td>
<td>Known direct contact with tuberculosis index case, TST-negative</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Known direct contact with tuberculosis index case, TST-positive</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>Definite tuberculosis</td>
<td>Active tuberculosis, TST-negative</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Active tuberculosis, TST-positive</td>
<td>2</td>
<td>100</td>
</tr>
</tbody>
</table>
TST vs. QFT: How to choose?

• Either
  • Most situations
• TST only
  • Young children?
  • Difficult phlebotomy
• IGRA only
  • Poor follow-up
  • BCG?
  • Inexperience of staff (placement and interpretation)
• Both
  • High suspicion of disease
  • Motivation
<table>
<thead>
<tr>
<th>Location</th>
<th>Number of Tests</th>
<th>% Positive</th>
<th>% Negative</th>
<th>% Indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td>All testing</td>
<td>167</td>
<td>3</td>
<td>65</td>
<td>32</td>
</tr>
<tr>
<td>Lab Outpatient</td>
<td>22</td>
<td>5</td>
<td>86</td>
<td>9</td>
</tr>
<tr>
<td>Specialty Outpatient</td>
<td>36</td>
<td>0</td>
<td>94</td>
<td>6</td>
</tr>
<tr>
<td>Emergency</td>
<td>20</td>
<td>0</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>ICUs</td>
<td>12</td>
<td>0</td>
<td>42</td>
<td>58</td>
</tr>
<tr>
<td>HemeOnc Wards</td>
<td>7</td>
<td>0</td>
<td>57</td>
<td>43</td>
</tr>
<tr>
<td>Inpatient Wards</td>
<td>64</td>
<td>6</td>
<td>44</td>
<td>50</td>
</tr>
</tbody>
</table>

IGRA Results by Location, Children’s Hospital Colorado 3/1/14 to 2/23/15
## QFT Testing for LTBI, Denver Health Clinics

<table>
<thead>
<tr>
<th>Age</th>
<th>% positive</th>
<th>% negative</th>
<th>% indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 5</td>
<td>1.6</td>
<td>97.4</td>
<td>1.0</td>
</tr>
<tr>
<td>6 to 12</td>
<td>6.0</td>
<td>93.5</td>
<td>0.5</td>
</tr>
<tr>
<td>13 to 18</td>
<td>13.6</td>
<td>86.1</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Source: Mary O’Connor, MD, personal communication
Microbiologic Diagnosis

• Paucibacillary disease/Poor aerosolization: Sputum samples low yield
• Alternate options:
  • Bronchoscopy
  • Induced sputum
  • Gastric aspirates
  • Biopsy
• Molecular testing less well established on non-sputum samples
Gastric Aspiration Protocol: Denver Health

- Upon admission, nurse to place NG tube
  - Infant: 8 French
  - Child: 10 French
- Confirm placement of NG tube using standard ward methods; if uncertain, order 1-view XR.
- NPO after 8 PM (if infant unable to tolerate NPO, discuss with ID).
- Inform mycobacteria lab of admission and planned sample timing and collect appropriate tube.
- Nurse or Pediatric Resident to obtain gastric aspirate at 0600 or immediately if patient awakens earlier.
  - The patient should remain resting, lying down and NPO until after the procedure (should not get out of bed at all)
- Aspirate stomach contents (typically 5-10 ml) and place immediately in prepared buffered tube.
- If no fluid returns, 20 ml of sterile (but not homeostatic) saline should be infused, and then aspiration attempted again immediately.
- If still no significant yield, advance and withdraw the tube slightly while aspirating.
- If yield is less than 5–10 ml, roll the child on the left side, advance the tube, aspirating continuously to find the pool of mucous in the stomach.
- If still no yield, any collected mucous should be placed in the sample tube.
- Sample sent directly to mycobacterial lab for AFB stain and culture.
- Call mycobacterial lab to assure sample receipt and immediate buffering.
- Patient may eat/move ad lib until next NPO.
- NG tube should remain in place until all three aspirates are obtained.
Pediatric TB: Treatment Considerations
Pediatric latent TB infection: Current Guidelines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9 months*</td>
<td>Daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly**</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>6 months</td>
<td>Daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly**</td>
</tr>
<tr>
<td>Isoniazid and Rifapentine</td>
<td>3 months</td>
<td>Once weekly**</td>
</tr>
<tr>
<td>Rifampin***</td>
<td>4 months</td>
<td>Daily</td>
</tr>
</tbody>
</table>

*9 months preferred for children under 12 and HIV-infected

**Must use Directly Observed Therapy (DOT)

***Use rifampin if known to be IHN resistant, less data for this regimen

Source: CDC, 2015
TB drug dosing: pediatric vs. adult

<table>
<thead>
<tr>
<th>Drug</th>
<th>PEDIATRIC</th>
<th>ADULT (daily dosing)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose (mg/k)</td>
<td>Max dose (mg)</td>
</tr>
<tr>
<td>INH</td>
<td>10 (7-15)</td>
<td>300</td>
</tr>
<tr>
<td>RMP</td>
<td>15 (10-20)</td>
<td>600</td>
</tr>
<tr>
<td>PZA</td>
<td>35 (30-40)</td>
<td></td>
</tr>
<tr>
<td>EMB</td>
<td>20 (15-25)</td>
<td></td>
</tr>
</tbody>
</table>

Source: WHO 2010
Pediatric TB Treatment

• Tolerance of medications:
  • Low rates of hepatitis
    • Monitoring of LFT’s not needed for LTBI treatment
  • Low rates of INH-related neurotoxicity
    • Do not require pyridoxine unless malnourished, breast-fed, HIV infected

• Different compliance challenges in toddlers
Pediatric TB Vaccination/BCG
Bacille Calmette-Guérin (BCG)

- *M. bovis* strain: 13 years serial passage led to diminished virulence
- First BCG vaccination in 1921
- 1920-1940s’: Dissemination of BCG strains to multiple labs
  - Wide variation between BCG strains used for current vaccine manufacture
  - Certain strains may be more effective
- Most efficacious against invasive/severe TB infection
- Unlikely to block primary infection
- Lack of clear correlate of immunity
- Difficult to test in clinical trials
Thank you

Questions?
References/Sources


References/Sources, continued


