Tuberculosis in children
“They are not small adults”

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Objectives

• Discuss clinical manifestations of children with tuberculosis

• Diagnostic “struggles” in children: family history, TST, interferon assays

• Providing medications to children with tuberculosis

• Formula for success
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. Receiving albuterol and Pulmocort. Worsening respiratory condition; hospitalized in PICU. Found to have influenza B. Failure to thrive. Workup negative. Abnormal CXR.
Infant with asthma + influenza

- Key to diagnosis: CXR findings; miliary pattern
- TST: 15 mm
- Gastric aspirates: *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 failure to thrive

Infant with failure to thrive, cough²

- 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*
• Isoniazid [INH]
• Rifampin [RIF]
• Ethambutol [ETH]
• Pyrazinamide [PZA]
• Corticosteroids [tracheal compression]
Dissemination, miliary TB; children\(^3\)

- Usually infants and HIV-infected children
- Intermittent release, bacilli from a foci; protracted bacteremia; dissemination
- Hepatosplenomegaly, meningitis, lymphadenitis, papulonecrotic tuberculids; miliary disease
Miliary TB; 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

- 4½ 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.
- MRI: lymphadenitis or lymphangangioma.
- Treatment: ticarcillin-clavulanic acid + clindamycin; vancomycin and ampicillin-sulbactam
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 lymphadenitis; children

- Most common form of extrapulmonary disease in children, scrofula
- Superficial lymph nodes
- Usually within ~6-9 months of infection
- Supraclavicular, anterior cervical, tonsillar, submandibular
• 15 month old child born in Iowa; now living in Indiana, Vincennes area
• Transferred from Deaconess, Evansville on March 7, 2008
• January 2008: fever, pneumonia; antibiotics; hospitalized 2 days; improved
• Did well for ~1 month
• Late January-early February: fevers of unknown source; diagnosed with otitis media R >> L [or L >> R]
• 4 visits to EDs; 2 visits to primary care MD
• ~20 days with fevers; intermittent vomiting
• No diarrhea, no respiratory symptoms, no coughing, no rashes, no arthritis, no mucocutaneous changes
• Got amoxicillin; another antibiotic: no improvement
• Intermittent periods of moaning, lethargy, “not very responsive”

• 1 week prior to admission: diagnosed with pneumonia

• ~March 5, 2008: admitted to PICU Deaconess: spasticity, grunting, cyanotic

• CT/MRI: ventriculomegaly, infarctions [3], meningitis
Laboratory data

- **Deaconess, CSF**: WBC: 130; RBC: 20,000; 91% monocytes; 5% segs; **protein, 185**; glucose, 37

- **Riley, CSF [ventricular]**: WBC: 31; RBC: 325; segs, 11%; lymphs, 71%; monocytes, 18%; glucose 57; **protein 45**
Exposure history

- November-December 2007: friend of father lived with family in Indiana for 1½ months: ill coughing, weight loss, fevers
- He progressively worsened
- Was asked to leave the home: too ill
- Went to Kentucky: diagnosed with tuberculosis [UL] in December; "very ill"
- [20s; diagnosed with suspected TB, 2004-2005; took therapy for ~6 weeks. In January 2008, refused to provide names in Indiana. At UL, susceptible MTB]
TB meningitis; children

- Most common age: 6 months-4 years of age
- Within ~2-6 months of infection
- Onset is rapid or gradual
- Clues to diagnosis: basilar enhancement with communicating hydrocephalus, focal ischemia; cranial nerve involvement [III, VI, VII]
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Stage I</td>
<td>[1-2 weeks] Fever, headache, irritability, drowsiness. Recognition, retrospective</td>
</tr>
<tr>
<td>Stage II</td>
<td>Abrupt, lethargy, nuchal rigidity, Kerning/Brudzinski signs, seizures, hypertonia, vomiting, cranial nerve abnormalities, focal neurologic signs</td>
</tr>
<tr>
<td>Stage III</td>
<td>Coma, hemiplegia, paraplegia, hypertension, decerebrate or decorticate posturing, abnormalities of vital signs, death</td>
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</table>
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

11 year old female with history of left-sided chest pain; onset \( \sim 6 \) months ago. Left pleural effusion + “patchy” opacities and calcifications [old granulomatous disease]. Persistent pleural effusion. Two weeks ago, pleurocentesis performed. Fluid reaccumulated. Occasional low-grade fevers.
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
Pleural tuberculosis

- Hypersensitivity response to bacilli in pleural space [from subpleural foci]
- Usually within ~6-9 months of initial infection
- Disease uncommon < 6 yrs of age; rare < 2 yrs
- Abrupt onset: fever, chest pain, shortness of breath; high fevers
- Pleural fluid, AFB stain: usually negative
- Pleural fluid culture: positive, 30-50%
- Biopsy, pleural membrane: granulomas ~90%; positive culture, 70%
• Osteoarticular disease, including Pott disease
• Tuberculous enteritis [jejunum, ileum]
• Tuberculous peritonitis
• Renal involvement [sterile pyuria]
• Cutaneous disease: erythema nodosum, papulonecrotic tuberculids
• Congenital infection
Erythema nodosum
How do you find children infected [or at risk] with tuberculosis?

• Contact investigations of adults with contagious tuberculosis

• Adults with HIV: at risk for tuberculosis
Definitions of positive tuberculin skin test results

Induration \( \geq 5 \) mm

- Children with close contact with known or suspected contagious people with TB disease.
- Children suspected to have TB disease.
- Immunocompromised children [also HIV]
Definitions of positive tuberculin skin test results

Induration $\geq$ 10 mm

- Children < 4 years of age
- Children with medical conditions, including lymphoma, diabetes mellitus, chronic renal failure, or malnutrition
- Children with increased exposure to TB disease [born in high-prevalence regions of world; exposed to high-risk groups]
- Children who travel to high-prevalence regions of the world
Definitions of positive tuberculin skin test results

Induration ≥ 15 mm

• Children 4 years of age or older without risk factors

2009 RedBook®, pages 680-701
Diagnostic laboratory tests, tuberculosis

- Acid fast stains
- Cultures
- DNA probes
- Polymerase chain reaction
- Interferon-γ release assays
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-gamma release assays

• QuantiFERON®-TB Gold; In-Tube
  Measure production of IFN-γ by T-cells

• T-SPOT.TB® [ELISPOT]
  Number of mononuclear cells that release IFN-γ
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:
  - QFT-IT: 100%
  - T-SPOT: 98%
  - TST: 58%

IFN-γ release assays, children²

• Sensitivity:
  QFT-IT: 93%
  T-SPOT: 93%
  TST: 100%

IFN-γ release assays, LTBI; children

- Retrospective analysis, 496 children [0-19 yrs]
- QFT-TB Gold, QFT-TB IT, T-SPOT
- More indeterminate results: QFT assays, children < 4 years of age 21.5-35.9% vs 0.4-5.6% [children > 4 yrs]
- Less indeterminate with T-SPOT [1.7-2%]

Treatment of tuberculosis in children

- Latent tuberculosis infection [LTBI]: 9 months; isoniazid; once daily; twice weekly DOT
- Isoniazid-resistant: 6 months; rifampin, once daily; 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*]

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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 latent tuberculosis infection

• Isoniazid?
• Rifampin?
• Ethambutol
• Other agent?

Finnell SME, Christenson JC, Downs SM. Pediatrics 2009;123:816-822
Treatment of tuberculosis in children

• 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 *M. tuberculosis*]

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Side-effects of antituberculous agents, children

- Routine laboratory testing not necessary
- Side effects: mild, if any. All agents cause GI discomfort
- Rifampin: orange discoloration; vomiting, hepatitis, influenza-like illness, pruritis; careful with BCP and contact lens
- Isoniazid: hepatitis, peripheral neuritis

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- Ethambutol: optic neuritis? 15-25 mg/kg safe

## Treatment of tuberculosis, dosages

<table>
<thead>
<tr>
<th>Agent</th>
<th>Daily†</th>
<th>Twice-weekly†</th>
<th>Max. dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethambutol</td>
<td>20-25</td>
<td>50</td>
<td>2.5 g</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>10-15</td>
<td>20-30</td>
<td>300 mg [daily]</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>30-40</td>
<td>50</td>
<td>2 g</td>
</tr>
<tr>
<td>Rifampin</td>
<td>10-20</td>
<td>10-20</td>
<td>600 mg</td>
</tr>
</tbody>
</table>

† mg/kg
Recipe for success: treatment of tuberculosis in children

- Directly-observed-therapy
- Health care workers comfortable with children
- Health care workers knowledgeable in TB care
- Availability of reliable interpreters
- Improved communication
- Prompt screening [and treatment when indicated] of refugees and immigrants
“Mommy, can I also have a mask?”
How come children are less contagious?

- Sparse bacilli in endobronchial secretions
- Children do not cough as much
- Diminished force of cough
Contagiousness? Careful with the parent and adult visitors-relatives
Can we do more to prevent TB infections in children?²

- San Diego patients, 32.4% of patients had *M. bovis*
- Foreign born: children, 32.5%; parents, 33.3%
- Travel ≥ 7 days, past 1 year: 38.8%
- TB suspected: symptoms, 46.3%; contact investigations, 21.1%

Can we do more to prevent TB infections in children?³

- 63.5% source patients were foreign-born
- No documented TB evaluation prior to immigration
- 21/59 [35.6%] US-born children had sources born outside US
- Many risk factors: no interventions
- 30.2% source patients, LTBI: never treated

Barriers to proper investigations\(^4\)

- Language barrier
- Incomplete information
- Translators needed, not used
- Unable to find contacts
- Unwilling to name contacts
- Contacts refused evaluation
