Tuberculosis in Children and Adolescents

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Objectives

• Explain criteria used to establish a diagnosis of Diabetes Mellitus.
• Identify interactions between Tuberculosis and Diabetes Mellitus that pose concern for positive outcomes.
Disclosures

• None financial

• Also - I’m not a pediatrician
  • Thank you to Dr. Ritu Banerjee (who indeed is a Pediatrician!)
The pediatric age group (< 15) can be divided into four groups that reflect age-dependent differences in TB pathophysiology.

Age < 1: Infancy
- Cases in this age group represent the most recent transmission and also are slightly more likely to be the severe forms of disease that were uniformly fatal before the discovery of chemotherapy.

Age 1–4: Toddler/preschool.
- Primary pulmonary TB is the most common form, and self-resolution of recent infection is a greater possibility.

Age 5–9: School age
- Primary pulmonary TB is the expected form of disease, but rare instances of contagious adult form/reactivation disease are reported.

Age 10–14: Early adolescence
- Disease patterns more similar to adult forms.
Pearls of Pediatric TB

1. **Age of child** important to define risk of developing active TB (once infected)

2. **Primary TB disease** more common in young children compared to adults

3. Clinical presentation of TB in children can **vary by age**

4. Children with pulmonary TB generally **less infectious** compared to adults

5. **Relative similar approaches** for treating LTBI and TB in children compared to adults
Pearls of Pediatric TB

6. Diagnosing TB in children can be very challenging

7. Diagnosing TB in a child necessitates a comprehensive contact investigation for the source / index case

8. Children usually tend to tolerate TB medications well (better than adults)
Pearl #1: Age of child important to define risk of developing active TB 
(once infected with MTB)

- Children < 4 years age (esp. infants < 12 mo) have **highest risk** for developing of TB disease after infection
  - Immature / blunted T-cell and mononuclear phagocyte immunologic responses
  - Lack of MTB local containment after initial infection
  - MTB infection frequently progresses to active TB disease within first 12 months
- Similar situation with **immunosuppressed Adults** (HIV, transplantation, etc)

[Int J Tuber Lung Dis 2004;8:636-647]
[Int J Tuber Lung Dis 2004;8:392-402]
Age of child important to define risk of developing active TB
(once infected with MTB)

• Risk of infection progression to active TB declines by age 5-10 yrs

• Mild rise in risk during adolescence

• Thereafter – similar risks as with adults *(immunocompetent)*

Int J Tuber Lung Dis 2004;8:636-647
Int J Tuber Lung Dis 2004;8:392-402
Varying Incubation Periods of select Pediatric TB disease syndromes

- **2 - 6 months**: miliary or disseminated disease
- **4 - 12 months**: pulmonary and lymphatic disease
- **1 - 2 years**: skeletal TB
- **5 years**: renal TB

- *Most clinical TB disease in children develops within 1-2 years of initial infection*
## Risk of progression to disease by age

<table>
<thead>
<tr>
<th>Age at infxn (yrs)</th>
<th>No disease (%)</th>
<th>Pulmonary TB (%)</th>
<th>Miliary/CNS TB (%)</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>75-80</td>
<td>10-20</td>
<td>2.5</td>
</tr>
<tr>
<td>2-5</td>
<td>95</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>5-10</td>
<td>98</td>
<td>2</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>&gt;10</td>
<td>80-90</td>
<td>10-20</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>

*Am J Resp Crit Care Med. 2006;173:1078-1090*  
*Pediatrics in Review 2010; 31:13-26*
Pearl # 2: Primary TB disease more common in young children compared to adults

- Lack of initial immunologic containment enables progression:
  - Infection → Disease
    - Primary pulmonary disease
    - Extrapulmonary disease
      - With or without pulmonary disease
    - Miliary / disseminated disease
Primary pulmonary disease

- **Children**
- Immunosuppressed adults

Includes:

- **Intrathoracic lymphadenopathy**
  - Often hilar / mediastinal enlarged LNs only
  - Radiologic clue for active TB
  - Enlarging LNs may compress adjacent bronchi, collapse lobes, etc

- **Parenchymal disease**
  - Progressive lung tissue damage
  - Cavities less common (than in adults); but can develop
Primary complex
Hilar Lymphadenopathy
# Radiographic patterns: pulmonary TB

<table>
<thead>
<tr>
<th>TB pattern</th>
<th>Reactivation</th>
<th>Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrate</td>
<td>85% upper</td>
<td>Upper:lower 60:40 (can be anywhere)</td>
</tr>
<tr>
<td>Cavitation</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>Rare</td>
<td>Common in children</td>
</tr>
<tr>
<td>Effusion</td>
<td>May be present</td>
<td>May be present</td>
</tr>
</tbody>
</table>
Pearl # 3: Clinical presentation of TB in children can vary by age & different compared to adults

- Infants & toddlers – more likely to:
  - Develop active TB / disease progression after initial infection
  - Primary pulmonary disease
  - Extrapulmonary disease

- Teenagers – higher rates of ‘reactivation’ pulmonary TB disease
## Signs & Symptoms of Pediatric Pulmonary TB – by patient age

<table>
<thead>
<tr>
<th>Clinical Feature or Disease Type</th>
<th>Infants</th>
<th>Children</th>
<th>Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>Common</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Night sweats</td>
<td>Rare</td>
<td>Rare</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Cough</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Productive cough</td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>Never</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Common</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Sign</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rales</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
</tr>
<tr>
<td>Wheezing</td>
<td>Common</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Decreased breath sounds</td>
<td>Common</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Location of Disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Pulmonary + Extrapulmonary</td>
<td>Common</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
Pediatric TB Cases by Site of Disease, 1993–2014

Any extrapulmonary involvement* (totaling 29.4%)

<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>3.5%</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.
Pediatric Pulmonary TB

• Infants and adolescents more likely to become *symptomatic* than 5-10 year old children

• Pulmonary “reactivation” disease more common in adolescents
  • Not as commonly seen in apices (as in adults)
  • Disease may be anywhere in lungs
    • High overlap with primary TB disease
Pediatric Extrapulmonary Disease

• Highest risk among infants, immunosuppressed children (e.g. HIV+); adolescents

• Most common extrapulm. TB sites include:

  • Lymphadenopathy (e.g. head/neck) → 67%
  • Meningitis → 3%
    • most often in infants & toddlers
  • Pleural TB → 6%
  • Miliary TB → 5%
  • Skeletal TB → 4%
Lymphadenitis (Scrofula)
Pleural TB
Miliary TB
Miliary TB

- Most common in infants or IC
- Occurs shortly after infxn
- Usually insidious
- CXR normal early on
- Associated with hepatosplenomegaly, lymphadenopathy, cutaneous lesions
- TST negative in up to 50%
- Gastric aspirate, bronchoscopy, biopsy of lung, liver, bone marrow, urine cx, bld cx, LP
Cavitary, pulmonary TB in adolescent
Skeletal TB
**Pearl # 4:** Children with pulmonary TB generally **less infectious** compared to adults
Young children with TB disease are rarely contagious

- CXR findings are typically the immune response
- Rarely do young children have cavitary disease
- Children harbor few MTB organisms (*Paucibacillary*)
- Young children do typically do not generate forceful cough
Pearl # 5: Diagnosing TB in children can be very challenging

• Only 30-40% of children with pulmonary TB have positive cultures
  • Generally more ‘paucibacillary’ compared to adults

• Up to 15% of children with TB disease have negative TST

• Therefore, need to consider:
  1. Positive TST (or IGRA)
  2. Epidemiologic factors of the child & assoc. contacts
  3. The clinical and radiographic findings

Pediatr Respir Rev. 2007(8);107-117
Int J Tuberc Lung Dis 2001(5);594-603
Variable MTB culture results in children

Yield of Mycobacterium tuberculosis in Culture Using Various Specimen Collection Methods

<table>
<thead>
<tr>
<th>Type of specimen</th>
<th>Yield of M. tuberculosis in culture, %</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric lavage</td>
<td>40-92</td>
<td>Difficult, invasive procedure; increased yield in infants and patients with extensive disease; 3 consecutive specimens required after overnight fasting; can be done by trained nurses</td>
</tr>
<tr>
<td>Bronchoalveolar lavage</td>
<td>4-43</td>
<td>Extremely invasive; requires tertiary care facilities; useful if performed with diagnostic bronchoscopy</td>
</tr>
<tr>
<td>Nasopharyngeal aspiration</td>
<td>24-30</td>
<td>Less invasive; appropriate for low-income countries with limited facilities</td>
</tr>
<tr>
<td>Laryngeal swab</td>
<td>27-63</td>
<td>Useful in older children who are unable to expectorate</td>
</tr>
<tr>
<td>Induced sputum</td>
<td>20-30</td>
<td>Yield comparable to gastric lavage and nasopharyngeal aspiration; requires training; can be done by nurses; useful in hospital setting; infection-control procedures needed</td>
</tr>
<tr>
<td>String test</td>
<td>Not determined</td>
<td>Patients as young as 4 years of age tolerated the procedure well; peak discomfort at the time of swallowing and mild during string retrieval; additional studies required</td>
</tr>
</tbody>
</table>

Clin Infect Dis. 2010;50(Supplement_3):S184-S194

- **Contrasting data:** culture yield from gastric aspirates ranges from 10 - 30% in children in whom there exists a clinical suspicion for tuberculosis
  - Lancet 2005. 365:130–4

- **GA sensitivity** largely depends upon both technique (hospitalization, early morning collectioning) and serial samples
Laboratory-confirmed pediatric TB cases

- < 1 y: 50%
- 1-4 y: 20%
- 5-9 y: 10%
- 10-14 y: 30%

Pediatric TB Cases by Case Verification Criteria*, 1993–2014
N=20,789

Provider Diagnosis 23%
Laboratory Confirmed 26%
Clinical Case 51%

*Based on the public health surveillance definition for TB [MMWR 1997:46(No. RR-10):40-41]
Role of IGRAs in children

• IGRAS cannot distinguish LTBI from TB disease

• IGRAs preferred in BCG-vaccinated, asymptomatic children ≥ 5 Y of age

• In young children, performance of IGRAs is variable and utility is unclear
  • TST preferred/IGRA acceptable in children <5 Y

• Both TST and IGRA can be used sometimes

BCG vaccinated? No

Age <5 yrs? Yes

Likely to return for TST reading?

Either TST or IGRA acceptable

Negative TST - Testing complete unless criteria A* met, then IGRA

Positive TST - Testing complete unless criteria B** are met, then IGRA

IGRA preferred

Negative result – testing complete

Positive result – testing complete

Repeat IGRA

Indeterminate

TST preferred

Negative result - Testing complete unless criteria A* met, then IGRA

Positive result - Testing complete unless criteria B** are met, then IGRA

*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

Red Book AAP (2015)
Evaluation of child with suspected TB

• Evaluate contacts/caregivers*
• TST or IGRA
• Radiographs / CXR
• Sputum AFB stain, culture
• Other / invasive options:
  • 3 early morning gastric aspirates
  • Consider CSF evaluation if child is < 1 year
  • Bronchoscopy (if available)
• Notify public health – eval of contacts/family

*Cruz et al, ICHE 2011, 32: 188
Pediatric TB Cases by HIV Status, 1993–2012*
N=19,842

Information on HIV results are not available for **75%** of pediatric TB cases

<table>
<thead>
<tr>
<th>Pediatric TB cases with HIV-positive test results, minimum estimate**</th>
<th>0.9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric cases with HIV-positive test results of those patients with known results</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

*California HIV data missing from 2005 - 2010; Vermont HIV data through 2006 only.

**Pediatric TB cases with positive HIV test results divided by all pediatric TB cases.

Note: Through 2004, California only reported positive HIV test results based on TB and AIDS registry matching; all other California TB cases were classified as “Unknown.”

http://www.cdc.gov/tb/publications/slidesets/pediatrictb/d_link_text.htm
Pearl # 6: Relative similar approaches for treating LTBI and TB in children compared to adults

- Exceptions
  - Drug dosing and formulations (e.g. infants)
  - Ocular evaluations can be problematic in young children (EMB usage)
  - *“Window prophylaxis”* after exposure for Children < 5 years age
    - (contacts with active case)
Treatment of young children exposed to TB

• Window prophylaxis (INH) indications:
  • Exposed to TB
  • Neg. TST/CXR
  • < 4 years of age
  • Immunocompromised

• If second TST negative, stop medication
Treatment of children with LTBI

- Drug-susceptible strain
  - INH x 9 months (or 2x/week by DOT)
  - Rifampin x 4 months (or 2x/week by DOT)
  - INH plus RIF x 3 months (UK)
  - INH/Rifapentine weekly x 12 weeks (>2 yo)

- MDR strain
  - No data
    - PZA plus EMB
    - Fluoroquinolone
    - Fluoroquinolone plus EMB or PZA
    - 9-12 months
## Treatment of drug-susceptible TB disease in children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg/day)</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>10-15</td>
<td>Hepatitis, neuropathy</td>
</tr>
<tr>
<td>Rifampin</td>
<td>10-20</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>20</td>
<td>Optic neuritis</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>30-40</td>
<td>Gout, rash</td>
</tr>
</tbody>
</table>

* Baseline labs not necessary unless underlying liver disease
## Treatment of MDR TB disease in children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg/day)</th>
<th>Toxicity</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>15-30</td>
<td>Nephrotoxicity, ototoxicity</td>
<td>Baseline, monthly Cr, drug conc, hearing</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>10-15</td>
<td>Arthropathy</td>
<td></td>
</tr>
<tr>
<td>Ethionamide</td>
<td>15-20</td>
<td>Hepatotoxicity, GI, hypersens., hypothyroidism, neuropathy, optic neuritis</td>
<td>Baseline ALT, TSH</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>10-20</td>
<td>Rash, seizures, psychosis</td>
<td>neuropsych eval monthly</td>
</tr>
<tr>
<td>PAS</td>
<td>200-300</td>
<td>Hepatotoxicity, GI, hypersens., hypothyroidism</td>
<td>Baseline ALT, TSH</td>
</tr>
</tbody>
</table>
Pearl # 7: Diagnosing TB in a child necessitates a *comprehensive contact investigation for the source / index case

- Pediatric TB most often reflects recent MTB infection/disease progression
  - Into primary TB disease

- Time-delayed reactivation TB (common in adults) not typical in young children
TB disease in a young child marks recent acquisition and ongoing TB transmission within the community

• Need to evaluation child’s immediate / close contacts for index TB case identification:
  • **Parents
  • **Grandparents
  • Siblings
  • Aunt’s & Uncles

• Especially paramount in larger families living together:

• U.S. examples:
  • Somali & Hmong families (WI, MN)
  • Native Amer Families
    • Sioux Nation – SD
    • Navajo Nation - AZ
Pearl # 8: Children usually tend to tolerate TB medications well (better than adults)

- Generally fewer side effects
- Hepatoxicity and neuropathy quite uncommon (without underlying hepatic disease)
Summary Take Home Points

• Children with TB (vs. adults with TB)
  • Fewer symptoms
  • More culture-negative and extrapulmonary TB
  • Rapid progression infection → disease
  • Different CXR findings
  • Less contagious

• TST conversion and TB disease in a child signify recent infection and ongoing transmission

• Children with TB should be offered HIV testing

• Consult your RTMCC or make friends with a pediatrician!
Part II

Tuberculosis and Diabetes
Diabetes is a risk factor to develop TB and is on the rise

- People with diabetes are 3x more likely to develop active TB than those without DB
- Currently there are more people with active TB and concurrent DB than people with TB – HIV coinfection
DB associated with Poorer TB outcomes

• Diabetes is associated with increased TB treatment failure, relapse and death
  • Unclear, however, if optimal optimum glucose control reduces these effects is unclear

• Patients with TB and diabetes were more likely to remain sputum smear positive at 2–3 months after starting treatment for tuberculosis
DB associated with Poorer TB outcomes

- Potential causes of TB treatment failure in DB pts include:
  - More extensive tuberculosis disease
  - Altered immune response in people with DB
  - Possible reduced concentrations of TB drugs in patients with diabetes
    - Reports of lower RIF concentrations (although body weight may factor in)
Additional challenges with Diabetes

• How to achieve optimum glucose control can be challenging as both TB disease and TB drugs (e.g. rifampin) can reduce efficacy of oral DB drugs (sulfonurea agents)

  *Trop Med Int Health* 2010; 15: 1289–99

• The International Diabetes Federation (IDF) predicts that the number of people with diabetes globally will ↑ 55% in the next 20 years
  • In Africa (↑↑ endemic TB) the rise in DB cases expected to be far greater
    • around 110%

  *Lancet, Diabetes & Endocrinology* 2014;Vol 2, Issue 9:677-677
Diabetes is on the Rise

- Either type 1 and type 2 diabetes can increase tuberculosis risk
  - Type 2 diabetes accounts for 85–95% of global cases of diabetes
  - Burden of comorbid disease from type 2 diabetes is much greater
- Diabetes prevalence is increasing substantially
  - Estim ~ 151 million adults in 2000
  - 382 million in 2013
  - predicted to increase to 592 million in 2035.
Clinical considerations for managing patients with concurrent TB and DB

• **Tuberculosis treatment** – considerations:
  - Increased duration of treatment
  - Weight-adjusted doses of TB drugs

• **Drug–drug interactions**
  - Rifampin increases metabolism of antidiabetes drugs, except insulin and metformin

• **Treatment adherence**
  - Disease symptoms, high pill load, and side-effects could compromise treatment adherence
Clinical considerations for managing patients with concurrent TB and DB

- **Monitoring**
  - Higher risks of neuropathy & nephropathy
  - DB ocular changes may confound EMB use

- **Counselling and education**
  - Needs to address both TB and diabetes
  - Counselling needed for patients starting insulin therapy

- **Lifestyle and smoking**
  - Diet, exercise, smoking cessation
The End

- Questions?