Disclosure

- Dr. Ahmed’s institution receives funding for CDC Tuberculosis Epidemiology Studies Consortium (TBESC) for research on latent tuberculosis infection.

- Dr. Ahmed’s institution receives funding from the North Carolina DHHS for consultation on pediatric tuberculosis.
Advanced Concepts in Pediatric Tuberculosis (TB)

1. Mycobacteriology, Pathogenesis and Epidemiology
2. Latent TB Infection
3. Diagnosis: Old and New Diagnostic Tools and Challenges
4. Clinical Manifestations and Evaluation
5. TB and HIV
6. Pharmacotherapeutics of TB drugs
7. Treatment of TB, including MDR
8. Infection Control, Source Case and Contact Investigation

Objectives

At the end of this session, participants will be able to:

- Recognize the clinical and radiographic manifestations of pulmonary TB.
- Recognize the clinical manifestations of extra-pulmonary TB, including
  - Tuberculous meningitis
  - Miliary tuberculosis
  - Tuberculosis lymphadenitis.
- Discuss the appropriate work up for the diagnosis of pediatric TB
  - Active case finding (screening, contact investigation)
  - Passive case finding (symptomatic disease)
**Terminology**

- **Exposure**

- **Latent tuberculosis infection (LTBI)**
  - Tuberculin skin test (TST) reactive or interferon γ release assay (IGRA) positive
  - Asymptomatic, chest radiograph (CXR) normal

- **Disease (TB)**
  - Signs/symptoms and/or radiographic changes
  - TST / IGRA positive or negative

**Transmission and Pathogenesis**

- Inhalation of droplet nuclei → alveolus
- Ingestion by alveolar macrophages
  - Multiplication → lymphohematogenous dissemination
- Macrophage and lymphocyte activation
- Development of DTH within 3-12 weeks of exposure
Pathophysiology of Pediatric TB

- Exposure → Infection → Disease
  - Disease usually a rapidly evolving complication of primary infection in children

- Incubation period for disease may be 6-8 weeks, before delayed type hypersensitivity develops

- Timely identification of children exposed to TB is critical in preventing disease

<table>
<thead>
<tr>
<th>Age</th>
<th>Disseminated TB/ TB meningitis</th>
<th>Pulmonary TB</th>
<th>No Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>10-20%</td>
<td>30-40%</td>
<td>50%</td>
</tr>
<tr>
<td>1-2 years</td>
<td>2-5%</td>
<td>10-20%</td>
<td>75-80%</td>
</tr>
<tr>
<td>2-5 years</td>
<td>0-5%</td>
<td>5%</td>
<td>95%</td>
</tr>
<tr>
<td>5-10 years</td>
<td>&lt; 0-5%</td>
<td>2%</td>
<td>98%</td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>&lt; 0-5%</td>
<td>10-20%</td>
<td>80-90%</td>
</tr>
</tbody>
</table>

Lancet Infect Dis 2008; 8: 498-510
Pediatric TB Disease

- **Pulmonary (70-80%)**
  - Intrathoracic lymphadenopathy
  - Progressive primary disease
  - Pleural effusion

- **Extrapulmonary TB (20-30%)**
  - Lymphadenitis
  - Tuberculous meningitis/ tuberculoma
  - Miliary TB
  - Osteoarticular, abdominal, genitourinary TB
  - Congenital TB

---

Characteristics of Pediatric TB Cases, United States, 1993-2001

<table>
<thead>
<tr>
<th>Major site of disease</th>
<th>Total†</th>
<th>%</th>
<th>US-Born</th>
<th>%</th>
<th>Foreign-Born</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td></td>
<td>n</td>
<td></td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>11,480</td>
<td>100.0</td>
<td>8,603</td>
<td>100.0</td>
<td>2,877</td>
<td>100.0</td>
</tr>
<tr>
<td>Pleural</td>
<td>8924</td>
<td>76.9</td>
<td>6,629</td>
<td>77.2</td>
<td>2,295</td>
<td>75.9</td>
</tr>
<tr>
<td>Lymphatic</td>
<td>1778</td>
<td>15.5</td>
<td>1,313</td>
<td>15.3</td>
<td>465</td>
<td>16.2</td>
</tr>
<tr>
<td>Bone or joint</td>
<td>156</td>
<td>1.4</td>
<td>96</td>
<td>1.1</td>
<td>60</td>
<td>2.1</td>
</tr>
<tr>
<td>Miliary</td>
<td>125</td>
<td>1.1</td>
<td>104</td>
<td>1.2</td>
<td>21</td>
<td>0.8</td>
</tr>
<tr>
<td>Meningeal</td>
<td>242</td>
<td>2.1</td>
<td>204</td>
<td>2.4</td>
<td>38</td>
<td>1.4</td>
</tr>
<tr>
<td>Other</td>
<td>217</td>
<td>1.9</td>
<td>149</td>
<td>1.7</td>
<td>66</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Pediatrics 2004; 114: 333-341
## Clinical Syndromes Associated with Pediatric TB

<table>
<thead>
<tr>
<th>Disease Stage</th>
<th>Group at Risk</th>
<th>Condition</th>
<th>Age Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-6 mo</td>
<td>Uncomplicated lymph node disease</td>
<td>&lt; 10 y</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Progressive Ghon focus</td>
<td>&lt; 1 y or severely compromised</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Miliary TB, TB meningitis or both</td>
<td>&lt; 3 y or severely compromised</td>
<td></td>
</tr>
<tr>
<td>4-12 mo</td>
<td>Complicated lymph node disease</td>
<td>&gt; 1 y</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pleural disease</td>
<td>&gt; 3 y</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral lymphadenitis</td>
<td>1-10 Y</td>
<td></td>
</tr>
<tr>
<td>Late disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-24 mo</td>
<td>Adult-type pulmonary disease</td>
<td>&gt; 10 y</td>
<td></td>
</tr>
<tr>
<td>1-3 y</td>
<td>Osteoarticular disease</td>
<td>&gt; 1 y</td>
<td></td>
</tr>
<tr>
<td>&gt; 3 y</td>
<td>Urinary tract disease</td>
<td>&gt; 5 y</td>
<td></td>
</tr>
</tbody>
</table>


### Pulmonary TB

- **Lung parenchyma**
  - Ghon focus
    - Primary parenchymal process
  - Ghon complex
    - Ghon focus, local lymphangitis, regional lymph node involvement
    - Adult-type disease
- **Lymph node (LN) disease**
  - Uncomplicated
  - With hyperinflation, airway obstruction, bronchopneumonia
- **Progressive primary**
  - Primary focus develops caseous center
  - Resembles bacterial pneumonia
Pulmonary TB: Clinical Presentation

- Most children have no or few signs or symptoms of disease
- Infants / adolescents more likely symptomatic
- Physical findings are limited
  - Most children will have a normal chest exam
  - Infants- wheezing, respiratory distress
  - Adolescents- rales/crackles, diminished breath sounds

Pulmonary TB: Clinical Presentation

- Signs and symptoms vary based on airway irritation and obstruction
  - Uncomplicated LN disease
    - Asymptomatic; physical examination unremarkable
  - LN disease with obstruction or hyperinflation (e.g. infants)
    - Fever, persistent cough, dyspnea
    - Respiratory distress, wheezing on examination
  - Adult-type cavitary disease (e.g. adolescents)
    - Fever, cough, weight loss, hemoptysis, night sweats
    - Diminished breath sounds, rales/crackles
Pulmonary TB: Diagnosis

- Diagnosis relies on:
  - Epidemiology
  - Clinical findings
  - Immunologic tests - TST, IGRAs
  - Radiography
  - Microbiological/molecular confirmation
  - Identification of a source case

- Definitive diagnosis requires detection of *Mycobacterium tuberculosis* (MTB) in respiratory specimen by culture or NAAT
  - Microbiologic confirmation difficult due to paucibacillary nature of disease

Pulmonary TB: Radiography

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*Note: Diagram shows various radiographic findings associated with pulmonary tuberculosis.*

*Source: N Engl J Med 2011; 367: 348-361*
Uncomplicated LN Disease

- 2 y old male of Hmong descent
- Presents with cervical adenopathy
- CXR with hilar adenopathy
  - Hospitalized
  - MTB isolated from GA

- 3 y old “aunt” of Hmong male
- Evaluated as part of CI
  - TST reactive
  - CXR abnormal
- Treatment based on nephew’s isolate
Uncomplicated LN Disease: Hilar Lymphadenopathy

- 3 year old girl exposed to uncle with pulmonary TB
- Contact investigation (CI)
  - PE normal except for gastrostomy tube
  - TST nonreactive
  - CXR done prior to window prophylaxis
- Disease identified by CI

Hilar Adenopathy: Value of Lateral CXR
LN Disease with Airway Compression

LN Disease with Hyperinflation
LN Disease with Bronchopneumonia

- 9 mo old Hispanic girl with FUO
- CXR demonstrates pneumonia
  - Fullness in hilar area
  - CT confirms adenopathy
- TST reactive at 12 mm
- Gastric aspirates, bronchoalveolar lavage
- Source case identified

Ghon Focus with Cavitation and Bronchopneumonia

Pediatr Radiol 2004; 34: 886-894
Pleural TB

- Occurs within 6-9 months of initial infection
  - Uncommon in < 5 y of age

- Hypersensitivity response bacilli discharged from subpleural focus into pleural space
  - Unilateral, not associated with segmental pulmonary lesions

- Clinical presentation
  - Fever, pleuritic chest pain
  - Diminished breath sounds on affected side

---

Pleural Effusion

Pediatr Radiol 2004; 34: 886-894
**Pleural TB: Diagnosis**

- **Pleural fluid**
  - Yellow, blood-tinged
  - Protein 2-4 g/dL; glucose 20-40 mg/dL
  - WBC 100-1000 cells/mm³
- **Definitive diagnosis requires detection of MTB by culture or NAAT in pleural fluid sample or pleural tissue**
  - AFB stain usually negative
  - MTB isolated in 30-50% of cases
  - Biopsy- granuloma in 90% of cases
  - MTB isolated in up to 70% of cases

**Tuberculous Lymphadenitis**

- **Most common form of extrapulmonary disease**
  - “Scrofula”
- **Epidemiology differs from pulmonary TB**
  - Predilection for immigrants from Southeast Asia
  - Women> men; peak age 30-40 y
  - May be associated with ingestion of unpasteurized dairy products (*Mycobacterium bovis* disease)
**TB Lymphadenitis: Clinical Presentation**

- Typically occurs 6-9 months after infection

- Typically unilateral, involving 1-3 nodes
  - Cervical, submandibular, supraclavicular LN
  - Firm, painless; slightly discolored
  - Slow progression over 1-2 months
  - Draining sinus in < 10% cases

- Pulmonary disease may be absent

**TB Lymphadenitis: Diagnosis**

- **Diagnostic tests**
  - TST typically reactive
  - CXR abnormal in 10-40% of cases

- **Definitive diagnosis by detection of MTB by culture or NAAT**
  - Excisional biopsy offers highest yield
  - Fine needle aspiration (FNA) lower yield

- **Histology**
  - Granulomas, Langerhans giant cells, caseous necrosis
**Diagnostic Tests in TB Lymphadenitis**

<table>
<thead>
<tr>
<th>Location (Year)</th>
<th>Culture (+)</th>
<th>AFB (+)</th>
<th>GI (+)</th>
<th>Culture + GI (+)</th>
<th>NAAT (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>California (1992) [28]</td>
<td>28/30 (93%)</td>
<td>11/30 (37%)</td>
<td>23/30 (77%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Excisional Biopsy</td>
<td>18/29 (62%)</td>
<td>10/29 (35%)</td>
<td>16/29 (55%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>FNA</td>
<td>12/39 (31%)</td>
<td>2/39 (5%)</td>
<td>32/39 (82%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>France (1999) [9]</td>
<td>8/26 (31%)</td>
<td>2/26 (8%)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>California (1999) [28]</td>
<td>44/238 (18%)</td>
<td>5/238 (24%)</td>
<td>84/238 (35%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Ind.(2000) [30]</td>
<td>4/22 (18%)</td>
<td>5/22 (23%)</td>
<td>13/22 (59%)</td>
<td>17/22 (77%)</td>
<td>15/22 (68%)</td>
</tr>
<tr>
<td>Excisional Biopsy</td>
<td>2/22 (10%)</td>
<td>4/22 (15%)</td>
<td>7/22 (32%)</td>
<td>9/22 (41%)</td>
<td>12/22 (55%)</td>
</tr>
<tr>
<td>FNA</td>
<td>2/24 (8%)</td>
<td>15/20 (75%)</td>
<td>36/31 (88%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>UK (2010) [12]</td>
<td>48/77 (61%)</td>
<td>5/19 (26%)</td>
<td>47/76 (62%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>FNA</td>
<td>65/97 (67%)</td>
<td>22/97 (23%)</td>
<td>77/97 (79%)</td>
<td>88/97 (91%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Clin Infect Dis 2011; 53: 555-564

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**Case: Like mother, like daughter**

- 16 year old Vietnamese girl with cervical adenitis
- Referred to pulmonologist → TST placed → referred to surgeon
  - TST 21 mm
- CXR normal
Advanced Concepts in Pediatric TB

Clinical Manifestations and Work Up
Case: TB or not TB?

- 2 year with subacute cervical lymphadenitis
  - Afebrile
  - After 10 days of amoxicillin-clavulanate, the lymphadenitis is unchanged

- TST is reactive at 8 mm
  - CXR normal.

- Mother has a history of LTBI, untreated

MTB versus NTM Lymphadenitis

<table>
<thead>
<tr>
<th></th>
<th>MTB</th>
<th>NTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range (years)</td>
<td>20-40</td>
<td>1-6</td>
</tr>
<tr>
<td>Sex distribution</td>
<td>F&gt;M</td>
<td>F&gt;M</td>
</tr>
<tr>
<td>Birth country</td>
<td>TB-endemic</td>
<td>Non-TB-endemic</td>
</tr>
<tr>
<td>HIV infection</td>
<td>Common in HIV-endemic</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Uncommon in developed</td>
<td></td>
</tr>
<tr>
<td>Clinical features</td>
<td>Indolent painless swelling</td>
<td>Indolent painless swelling</td>
</tr>
<tr>
<td></td>
<td>Systemic symptoms:</td>
<td>Systemic symptoms:</td>
</tr>
<tr>
<td></td>
<td>uncommon in HIV-negative,</td>
<td>uncommon in HIV-positive</td>
</tr>
<tr>
<td></td>
<td>common in HIV-positive</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>Cervical</td>
<td>Cervicofacial</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>Common</td>
<td>Absent</td>
</tr>
<tr>
<td>Tuberculin skin test</td>
<td>Positive</td>
<td>Occasionally positive</td>
</tr>
<tr>
<td>IGRA</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Histology</td>
<td>Reactive adenitis</td>
<td>Caseating granuloma</td>
</tr>
<tr>
<td>Treatment</td>
<td>Antibiotics +/- excision</td>
<td>Excision +/- antibiotics</td>
</tr>
<tr>
<td>Paradoxical reactions</td>
<td>Common</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Clin Infect Dis 2011; 53: 555-562
**TB versus NTM Lymphadenitis**

- **Mycobacterium tuberculosis complex**
  - *M. tuberculosis* (scrofula), *M. bovis*

- **Nontuberculous mycobacteria (NTM)**
  - Most commonly due to *M. avium* complex
  - NTM lymphadenitis more common than TB lymphadenitis

- **NTM versus *M. tuberculosis***
  - Not distinguishable clinically or histologically
  - TST may be reactive in either; CXR may be normal in TB
  - Differentiation requires isolation of pathogen in tissue

---

**Tuberculous Meningitis**

- Occurs within 2-6 months after initial infection

- Reactivation of caseous lesion in meninges or cerebral cortex from early occult lymphohematogenous dissemination or from direct invasion during uncontrolled dissemination
  - Exudative discharge of bacilli into subarachnoid space
  - Infiltration of cortical and meningeal blood vessels
  - Inflammation, obstruction and infarction of cerebral cortex
  - Exudate interferes with flow of CSF at basilar cisterns, leading to communicating hydrocephalus
TB Meningitis: Clinical Presentation

- **Stage I (1-2 weeks)**
  - Nonspecific symptoms: fever, HA, irritability
  - No focal neurologic signs (GCS 15)
- **Stage II (2-4 weeks)**
  - Lethargy, nuchal rigidity
  - Seizures, CN palsies (GCS 11-14)
- **Stage III**
  - Coma, hemiplegia or paraplegia
  - Decerebrate or decorticate posturing (GCS < 11)

Presenting Symptoms and Signs in > 500 Children with Central Nervous System TB, South Africa, 1985-2005

<table>
<thead>
<tr>
<th>Symptoms / Signs</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased consciousness</td>
<td>356 (70)</td>
</tr>
<tr>
<td>Fever</td>
<td>339 (67)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>269 (53)</td>
</tr>
<tr>
<td>Malaise</td>
<td>263 (52)</td>
</tr>
<tr>
<td>Seizures</td>
<td>240 (47)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>236 (46)</td>
</tr>
<tr>
<td>Cough</td>
<td>164 (32)</td>
</tr>
<tr>
<td>Weakness</td>
<td>157 (31)</td>
</tr>
<tr>
<td>Headache</td>
<td>128 (25)</td>
</tr>
<tr>
<td>Meningeal irritation</td>
<td>445 (98)</td>
</tr>
<tr>
<td>Cranial nerve palsies</td>
<td>145 (27)</td>
</tr>
</tbody>
</table>

Pediatrics 2009; 123: e1
TB Meningitis: Diagnosis

- Ancillary criteria
  - TST nonreactive in up to 40% of cases
  - CXR normal in up to 50% of cases
- CSF
  - Pleocytosis (10-500 WBC/mm³)
  - Glucose low/normal (20-40 mg/dL)
  - Protein elevated (up to > 400 mg/dL)
  - MTB isolation in 20-50% of cases
    - With 10 ml CSF, AFB smear positive in up to 30%, MTB culture positive in up to 70%

TB Meningitis: CNS Imaging

- Computed tomography (CT)
  - Hydrocephalus (90%)
  - Basal meningeal enhancement
  - Infarcts, tuberculoma
- MRI - more sensitive than CT
  - Hydrocephalus
  - Basal meningeal enhancement
  - Infarcts, tuberculoma (especially of brainstem)
# Advanced Concepts in Pediatric TB

## Clinical Manifestations and Work Up

### Diagnostic Findings in > 500 Children with Central Nervous System TB, South Africa, 1985-2005

<table>
<thead>
<tr>
<th>Symptoms / Signs</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST, reactive</td>
<td>304 (61)</td>
</tr>
<tr>
<td>Chest radiograph, abnormal</td>
<td>249 (46)</td>
</tr>
<tr>
<td>Chest radiograph, miliary</td>
<td>66 (12)</td>
</tr>
<tr>
<td>CT, abnormal</td>
<td>165 (70)</td>
</tr>
<tr>
<td>CT, basal meningeal enhancement</td>
<td>387 (75)</td>
</tr>
<tr>
<td>CT, infarction</td>
<td>164 (32)</td>
</tr>
<tr>
<td>CT, tuberculoma</td>
<td>66 (13)</td>
</tr>
<tr>
<td>Culture positive, CSF</td>
<td>64 (12)</td>
</tr>
<tr>
<td>Culture positive, other specimen</td>
<td>104 (19)</td>
</tr>
</tbody>
</table>

*Pediatrics 2009; 123: e1*

### TB Meningitis: Diagnosis

- **Definitive diagnosis**
  - Identification of MTB in CSF by culture or by NAAT

- **Presumptive diagnosis**
  - Identification of MTB from specimen other than CSF
  - Clinical findings consistent with TB meningitis

- **Consensus statement on diagnostic criteria for meningitis**
Case: Missed Opportunity

- 16 mo old Vietnamese girl, obtunded
  - CSF: 56 WBC/mm³, glucose 11 g/dL, protein 129 mg/dL
- MRI: basilar meningitis, infarcts
  - TST nonreactive
  - CXR with RUL infiltrate
  - CSF AFB smear negative
  - Sputum smear negative
    - MTB isolated by culture
- Source investigation
  - Mother with pulmonary TB

TB Meningitis: Diagnosis

- Aseptic meningitis in the setting of hydrocephalus or basilar meningitis should be suspected to be TB.

- Antituberculosis treatment should be instituted empirically in any child with basilar meningitis, hydrocephalus, infarction or CN involvement that has no other apparent cause

- Source case identification is often the key to diagnosis
**Tuberculoma**

- Another manifestation of CNS TB disease
  - May not be distinct from TB meningitis
  - Most often occurs in children < 10 y of age

- Lesion that is typically singular and infratentorial

- Symptoms
  - Headache, fever
  - Seizures

**Case : If at first you don’t succeed...**

- 19 month old with a mother hospitalized with suspected TB

- Contact investigation (Health Department)
  - Physical examination notable for irritability
  - TST reactive
  - CXR abnormal

- Physical examination normal per PCP
Case: If at first you don’t succeed...

- Patient to ED for repeat CXR and lumbar puncture (LP)
  - CXR done but not reviewed
  - LP required sedation but patient ate Tootsie Pop

- Return to ED the next day for LP

- LP done- CSF reported normal; patient discharged
  - WBC 30 cells/mm³, RBC 113,000 cells/mm³
  - Glucose 52 mg/dL, protein 466 mg/dL
Miliary TB

- **Occult hematogenous spread with primary infection**
  - Bacilli enter bloodstream via pulmonary lymphatic drainage
  - Form tubercles in capillaries - typical (< 2mm) miliary lesions
  - Insidious presentation with fever, lymphadenopathy and hepatosplenomegaly before radiographic abnormalities
  - Disseminated disease in very young or immunocompromised

- **Second type (rare)**
  - Caseous focus eroding into blood or lymph vessel
  - Frequently progresses to disseminated disease irrespective of age or immune status
**Symptoms and Signs of Miliary TB**

<table>
<thead>
<tr>
<th>Symptoms / Signs</th>
<th>Percent (%) Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatomegaly</td>
<td>82</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>54</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>46</td>
</tr>
<tr>
<td>Fever</td>
<td>39</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>34</td>
</tr>
<tr>
<td>Meningitis</td>
<td>19</td>
</tr>
</tbody>
</table>

*Ped Infect Dis J 1991; 10:832-6*

**Miliary TB in Young Infant**
Miliary TB in Immunocompromised Host

Miliary TB: Diagnosis

- Definitive diagnosis requires detection of MTB by culture or NAAT in respiratory or other appropriate specimen

- Presumptive diagnosis based on clinical and radiographic findings and/or evidence of dissemination

- Further evaluation
  - LP and/or CNS imaging to exclude dissemination to CNS
  - US or CT to evaluate for HSM
Evaluation and Diagnosis of Pediatric TB

- Evaluation and diagnosis relies on:
  - Epidemiologic factors
  - Immunologic findings
  - Clinical presentation
  - Radiographic findings
  - Microbiologic /molecular confirmation

- Source investigation is often the key to diagnosis

Approach to Diagnosis of Pediatric TB

- Active case finding
  - More common in industrialized countries
  - Most children asymptomatic/mildly symptomatic
  - Identified by contact investigation or screening

- Passive case finding
  - Children present with symptoms- need to confirm disease
    - In low and middle-income countries, limited resources for microbiological confirmation
    - In industrialized countries, microbiological confirmation not always attempted
Primary Reason Evaluated Among Children and Adolescents with TB, United States, 2009-2010

<table>
<thead>
<tr>
<th>Reason</th>
<th>US-born With Linked TB Case, 188 (100), N (%)</th>
<th>All US-born, 1182 (100), N (%)</th>
<th>Foreign-born With Linked TB Case, 13 (100), N (%)</th>
<th>All Foreign-born, 518 (100), N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact investigation</td>
<td>131 (70)</td>
<td>367 (32)</td>
<td>13 (100)</td>
<td>39 (8)</td>
</tr>
<tr>
<td>TB symptoms</td>
<td>31 (18)</td>
<td>334 (29)</td>
<td>—</td>
<td>186 (33)</td>
</tr>
<tr>
<td>Abnormal radiograph</td>
<td>17 (9)</td>
<td>170 (15)</td>
<td>—</td>
<td>112 (22)</td>
</tr>
<tr>
<td>Targeted testing</td>
<td>5 (3)</td>
<td>40 (3)</td>
<td>—</td>
<td>32 (6)</td>
</tr>
<tr>
<td>Immigration examination</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>—</td>
<td>43 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1)</td>
<td>36 (3)</td>
<td>—</td>
<td>18 (5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1)</td>
<td>215 (18)</td>
<td>—</td>
<td>105 (20)</td>
</tr>
</tbody>
</table>

Diagnostic Tools

- Clinical
  - Diagnostic scores
- Immunologic
  - TST, IGRA
- Radiological
  - CXR
  - US, CT, MRI
- Microbiological / molecular
  - Microscopy, culture
  - NAAT, Xpert MTB/RIF
- Source investigation
Advanced Concepts in Pediatric TB

Clinical Manifestations and Work Up

Immunological Tests

- **TST**
  - Delayed hypersensitivity to PPD
  - Limitations of sensitivity and specificity

- **IGRAs**
  - Immune-based tests that measure ex-vivo IFN-γ production by lymphocytes incubated with highly specific antigens

TST and IGRA in Diagnosis of TB

- **Neither distinguishes between infection and TB disease**

- **Variable sensitivity in TB disease**
  - Young age
  - Overwhelming infection
  - Immunocompromised state (e.g. HIV+)

- **Neither test excludes TB disease if negative**
  - Consider dual testing to increase sensitivity
Immunologic Tests in TB Disease

<table>
<thead>
<tr>
<th>Test</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Positive tuberculin skin test (%)</th>
<th>Positive interferon-gamma release assay (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatients (n=183)</td>
<td>64 (35)</td>
<td>119 (65)</td>
<td>15 (8.1)</td>
<td>21 (11.4)</td>
</tr>
<tr>
<td>Culture-positive tuberculosis (n=127)</td>
<td>6 (5)</td>
<td>121 (95)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Highly probable tuberculosis (n=37)</td>
<td>6 (16)</td>
<td>31 (84)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Probable tuberculosis (n=42)</td>
<td>5 (12)</td>
<td>37 (88)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Tuberculosis (n=63)</td>
<td>5 (8)</td>
<td>58 (92)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Indeterminate (n=33)</td>
<td>5 (15)</td>
<td>28 (85)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

- **Pulmonary TB**
  - Chest radiograph (CXR)
  - Computed tomography (CT)

- **Extrapulmonary TB**
  - Lymphadenitis- US, CT
  - Meningitis- CT, MRI
  - Osteoarticular disease- MRI

**Radiography**

- **Pulmonary TB**
  - Chest radiograph (CXR)
  - Computed tomography (CT)

- **Extrapulmonary TB**
  - Lymphadenitis- US, CT
  - Meningitis- CT, MRI
  - Osteoarticular disease- MRI
Proposed Radiological Classification of Pediatric TB

- Lymph node disease
  - Uncomplicated
  - With airway compression
  - With hyperinflation
  - With infiltration
- Lung parenchymal disease
  - Ghon complex
  - Adult-type cavitary disease
- Disseminated (miliary)
- Pleural effusion
- Pericardial effusion

Chest Radiograph

- Diagnostic value limited by lack of radiologist or inexperienced radiologist

- Features suggestive of childhood TB
  - Hilar adenopathy- most common manifestation
    - Frontal and lateral films recommended
Microbiological Confirmation

- **Definitive diagnosis of pediatric TB is difficult**
  - Specimens difficult to obtain
  - Microbiology limited by *paucibacillary disease*

- **Most pediatric TB is not culture-confirmed**
  - AFB smear positive in <10-15% of children
    - **Negative AFB smear does not exclude TB**
  - MTB isolated in < 30-60% of children
    - **Negative culture does not exclude TB**

---

**Characteristics of Pediatric and Adult TB Cases, United States, 1993-2001**

<table>
<thead>
<tr>
<th>Major site of disease</th>
<th>Pediatric Total</th>
<th>Pediatric US-Born</th>
<th>Pediatric Foreign-Born</th>
<th>Adult Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>n</em></td>
<td>%</td>
<td><em>n</em></td>
<td>%</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>11480</td>
<td>100.0</td>
<td>6603</td>
<td>100.0</td>
</tr>
<tr>
<td>Pleural</td>
<td>132</td>
<td>1.1</td>
<td>63</td>
<td>1.1</td>
</tr>
<tr>
<td>Lymphatic</td>
<td>1779</td>
<td>15.5</td>
<td>1313</td>
<td>15.3</td>
</tr>
<tr>
<td>Bone of joint</td>
<td>156</td>
<td>1.4</td>
<td>96</td>
<td>1.1</td>
</tr>
<tr>
<td>Miliary</td>
<td>125</td>
<td>1.1</td>
<td>104</td>
<td>1.4</td>
</tr>
<tr>
<td>Meningeal</td>
<td>242</td>
<td>2.1</td>
<td>234</td>
<td>2.4</td>
</tr>
<tr>
<td>Other</td>
<td>217</td>
<td>1.9</td>
<td>149</td>
<td>1.7</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>0.5</td>
<td>2</td>
<td>0.3</td>
</tr>
<tr>
<td>Phone-confirmed</td>
<td>11480</td>
<td>100.0</td>
<td>6603</td>
<td>100.0</td>
</tr>
<tr>
<td>Culture positive</td>
<td>2712</td>
<td>23.6</td>
<td>1386</td>
<td>21.3</td>
</tr>
<tr>
<td>Smear positive</td>
<td>92</td>
<td>0.8</td>
<td>6</td>
<td>0.1</td>
</tr>
<tr>
<td>Clinical diagnosis</td>
<td>6000</td>
<td>52.4</td>
<td>4370</td>
<td>50.8</td>
</tr>
<tr>
<td>Spinal fluid for acid fast bacilli</td>
<td>11480</td>
<td>100.0</td>
<td>6603</td>
<td>100.0</td>
</tr>
<tr>
<td>Positive</td>
<td>362</td>
<td>3.2</td>
<td>244</td>
<td>3.7</td>
</tr>
<tr>
<td>Negative</td>
<td>2584</td>
<td>22.5</td>
<td>1638</td>
<td>24.9</td>
</tr>
<tr>
<td>Not done</td>
<td>8373</td>
<td>72.3</td>
<td>6571</td>
<td>99.9</td>
</tr>
</tbody>
</table>
When is Confirmation of TB Important?

- Bacteriologic confirmation often not attempted in children
  - Specimens difficult to obtain
  - Low yield from culture (30-60%)

- Attempt at microbiologic isolation especially important if:
  - Source case unknown or > 1 source case
  - Isolate not available
  - Resistance suspected in source case
  - Patient has extrapulmonary disease

Specimens for Diagnosis of Pediatric TB

- Sputum
  - Expectorated sputum (ES)
  - Induced sputum (IS)
- Gastric aspirates/ lavages (GA)
- Bronchoalveolar lavage (BAL)
- Nasopharyngeal aspirates (NPA)
- Stool
Gastric Aspirates/Lavage

- For children < 10 y of age who cannot produce sputum
  - Requires hospitalization
  - Requires overnight fast
  - Generally unpleasant for patient and HCW

- Yield depends on reproducibility and number of specimens
  - Yield is 40-70% depending on age and presentation
  - 3 consecutive GAs optimal
  - Yield with protocol higher than if no protocol

Bronchoscopy and BAL

- Not available in resource-limited areas

- Yield traditionally lower than GA
  - 1 specimen versus 3
  - Bronchoscopy may induce cough and increase yield of GA collected after BAL

- Increased yield of culture using both specimens
Gastric Aspirate and BAL

- Turkey, 2008-2012

- 157 children with suspected TB
  - BAL and 3 GAs
    - MTB isolated in 54 (33%) GAs
    - MTB isolated in 48 (29%) BAL

- Overall yield in 70 (42%) from both BAL and GAs

Induced Sputum (IS)

- Can be used in young infants and children
  - Yield higher than GAs if done correctly

- Requires training, equipment, consumables, staffing and infection control
  - Pretreatment with β-agonist to prevent bronchospasm
  - Nebulized hypertonic saline
  - Chest physiotherapy
  - Expectoration or catheter suctioning
Induced Sputum versus GA

- 250 children with suspected TB (South Africa)
  - 1 month- 5 years of age
- IS (3 samples) compared with GA (3 samples)
  - 58 (23%) with MTB isolated
    - IS 54/58 (87%) versus GA 40/58 (64%)
    - Yield from 1 IS equal to that from 3 GA
- IS safe and useful for microbiologic confirmation; preferable to GA for diagnosis of pulmonary TB in HIV infected and noninfected children

Induced Sputum versus Gastric Aspirate

<table>
<thead>
<tr>
<th>Specimens</th>
<th>GA Smear Positive</th>
<th>IS Smear Positive</th>
<th>GA Culture Positive</th>
<th>IS Culture Positive</th>
<th>GA Cumulative Yield</th>
<th>IS Cumulative Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>3%</td>
<td>8%</td>
<td>7%</td>
<td>15%</td>
<td>32%</td>
<td>66%</td>
</tr>
<tr>
<td>Second</td>
<td>5%</td>
<td>5%</td>
<td>9%</td>
<td>11%</td>
<td>56%</td>
<td>79%</td>
</tr>
<tr>
<td>Third</td>
<td>4%</td>
<td>5%</td>
<td>8%</td>
<td>13%</td>
<td>64%</td>
<td>87%</td>
</tr>
<tr>
<td>Total</td>
<td>7%</td>
<td>10%</td>
<td>15%</td>
<td>20%</td>
<td>64%</td>
<td>87%</td>
</tr>
</tbody>
</table>

Lancet 2005; 365:130-34
Approach to Evaluation of Pediatric TB

- **Active case finding**
  - Screening for LTBI or TB
  - Contact investigation
    - Microbiologic confirmation not necessary if isolate available from source case

- **Passive case finding**
  - Children present with symptoms or with radiological findings suggestive of TB
    - Attempt at microbiologic confirmation is important
    - Source case investigation important

Screening : Source Case Unknown

- 9 month old adopted from Guatemala
- TST reactive at 14 mm
  - CXR abnormal
- Hospitalized for evaluation
  - GA X 3
  - Lumbar puncture
Evaluation of the Child with Pulmonary TB Identified by Screening with Source Case Unknown

- Microbiologic confirmation important - no known source case
  - MTB isolated from GA
  - Treatment tailored based on susceptibility

- Further evaluation
  - PE to evaluate for dissemination
  - LP to evaluated for dissemination to CNS
    - Patient’s CSF normal
  - Testing for HIV
    - Patient HIV negative

Why the lumbar puncture?

- Meningitis is an early complication of infection
  - May occur before DTH develops
  - Children ≤ 4 y of age primarily affected
  - Insidious process occurring over 3-6 weeks

- Management of disease affected by meningitis
  - Duration of therapy, adjunctive use of corticosteroids

- LP recommended in children ≤ 1-2 y diagnosed with TB disease even in the absence of symptoms
Contact Investigation: Source Case Known

- 7 month old exposed to aunt with TB
- Contact investigation
  - PE normal
  - TST 20 mm
  - CXR abnormal

Evaluation of the Child with Pulmonary TB Identified by Contact Investigation with Source Case Known

- Microbiologic confirmation not necessary if source case known and clinical and radiological findings consistent with TB
  - Patient was afebrile, asymptomatic
  - CXR consistent with TB

- Further evaluation
  - CSF normal
  - HIV- negative

- Treatment initiated based on source case’s isolate
Symptomatic Presentation: Source Case Unknown

- 5 month old Hispanic female evaluated in ED with a cough
- CXR - hilar adenopathy
- Admitted for evaluation
  - GA X 3
  - LP
  - Source investigation

Evaluation of the Symptomatic Child with Suspected Pulmonary TB with Source Case Unknown

- Bacteriologic confirmation if source case unknown
  - GA, sputum, BAL, CSF, tissue, etc
  - Negative culture does not exclude TB
- Source case investigation
  - Identification of adult source of infection
  - Critical to diagnostic evaluation
  - Likelihood of identifying source case (and isolating MTB) is often higher than isolating MTB from the patient
- Further evaluation
  - HIV testing, LP if indicated
Symptomatic Presentation: Source Case Unknown

- GA X 3, induced sputum X 1
  - MTB ultimately isolated from GA
- CSF normal, HIV negative

- Source case investigation
  - Parents with LTBI
  - Uncle with abnormal CXR

- Isolation of MTB from GA specimen- matched source’s

Symptomatic Presentation: Source Case Known

- 9 month old exposed to MDR TB
  - Initial TST nonreactive
    - CXR normal
    - No window prophylaxis
  - Repeat TST nonreactive but patient symptomatic
    - CXR- ? Abnormal
    - CT confirmed adenopathy

- Hospitalized for PICC
  - 3 GAs, BAL
  - MDR MTB isolated from GA
Evaluation of the Symptomatic Child with Suspected Pulmonary TB with Source Case Known

- **Microbiologic confirmation important if:**
  - Source case unknown or > 1 source case
  - Isolate not available
  - Resistance suspected in source case
  - Patient has extrapulmonary disease

- **Further evaluation**
  - Lumbar puncture- CSF normal
  - Testing for HIV- negative

- **Treatment initiated based on source case's isolate but important to verify in child given toxicity of therapy**

Symptomatic Presentation: Meningitis

- **7 month old male with lethargy**
  - Afebrile, 4 days of URI
  - Receiving amoxicillin

- **Apneic and hypoperfused in ED**
  - Intubated

- **CSF- 143 WBC/mm³, glucose 21 mg/dL, protein 424 mg/dL**
Symptomatic Presentation: Meningitis

- Antibiotics initiated for partially treated meningitis
- CT demonstrated infarcts
- Infectious disease consultation
  - TST nonreactive
  - CXR with infiltrate
  - Sputum and CSF - AFB culture
  - Source investigation
- MTB isolated from GA
  - Isolated from source first

Evaluation of the Symptomatic Child with Suspected CNS TB with Source Case Unknown

- **Bacteriologic confirmation if source case unknown**
  - GA, sputum, BAL, CSF, tissue, etc.
  - Negative culture does not exclude TB
- **Source case investigation**
  - Identification of adult source of infection
  - Critical to diagnostic evaluation
  - Likelihood of identifying source case (and isolating MTB) is often higher than isolating MTB from the patient
- **Further evaluation**
  - HIV testing, LP if indicated (already done in this case)
**Symptomatic Presentation: Lymphadenitis**

- 2 year old Hispanic female with subacute adenitis
  - Amoxicillin for 2 weeks without improvement
- Enlargement noted
  - Referred to a surgeon
- TST reactive at 12 mm
  - CXR normal

- Excisional biopsy recommended
  - Granulomata, necrosis
  - AFB smear positive
  - MTB complex isolated

- Empiric treatment initiated
  - PZA resistance
  - *M. bovis* confirmed

- Father sells Mexican cheese in store, and patient eats it
Evaluation of the Symptomatic Child with Suspected TB Lymphadenitis with Source Case Unknown

- Bacteriologic confirmation if source case unknown
  - GA, sputum, BAL, CSF, tissue, etc.
  - Negative culture does not exclude TB

- Source case investigation
  - Sometimes the source is cheese

- Further evaluation
  - HIV testing, LP if indicated (not done in this case)

Summary

- Epidemiology
  - Young children at highest risk for TB disease

- Pathogenesis
  - Young children at higher risk of progressing to primary disease

- Clinical manifestations
  - Most disease in children is pulmonary
  - EP disease plays more significant role in children

- Evaluation of disease
  - Approach to evaluation depends on whether identified through screening, contact investigation, or symptomatic presentation
  - Microbiologic confirmation is important in pediatric TB and should always be attempted unless an isolate is available from the source
Are we going to see
THE END OF TB
in our lifetimes?

A call from the children of the Eastern Mediterranean Region

World Health Organization

http://www.who.int/tuberculosis/schools iniciatives/en