Pediatric Tuberculosis: Clinical Disease and Evaluation

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Overview

- Pathophysiology of pediatric TB
- Clinical manifestations of TB
  - Pulmonary, extrapulmonary (EP)
- Diagnosis of pediatric TB
- Evaluation 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 \( \gamma \) 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

1. Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to the alveoli.

2. Tubercle bacilli multiply in the alveoli.
A small number of tubercle bacilli enter the bloodstream and spread throughout the body. The tubercle bacilli may reach any part of the body, including areas where TB disease is more likely to develop (such as the brain, larynx, lymph node, lung, spine, bone, or kidney).

Within 2 to 8 weeks, special immune cells called macrophages ingest and surround the tubercle bacilli. The cells form a barrier shell, called a granuloma, that keeps the bacilli contained and under control (LTBI).

If the immune system cannot keep the tubercle bacilli under control, the bacilli begin to multiply rapidly (TB disease). This process can occur in different areas in the body, such as the lungs, kidneys, brain, or bone (see diagram in box 3).
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
## Risk of Disease Following Primary Infection

<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>
Pediatric versus Adult TB

- **Rate** of progression to disease is faster
  - Primary disease versus reactivation disease

- **Risk** of progression to disease is higher
  - Adults: 5-10%
  - Children: 5-40%

- **Severe disease** is more common
  - Adults: 15% is extrapulmonary (EP)
  - Children: 25% is EP
# Pediatric TB Disease

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

## Extrapulmonary
- Lymphadenitis
- Tuberculous meningitis/tuberculoma
- Miliary TB
- Osteoarticular, abdominal, genitourinary TB
## Characteristics of Pediatric TB Cases, United States, 1993-2001

<table>
<thead>
<tr>
<th>Major site of disease</th>
<th>Total†</th>
<th>US-Born</th>
<th>Foreign-Born</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>8824</td>
<td>76.9</td>
<td>6639</td>
</tr>
<tr>
<td>Pleural</td>
<td>132</td>
<td>1.1</td>
<td>92</td>
</tr>
<tr>
<td>Lymphatic</td>
<td>1778</td>
<td>15.5</td>
<td>1313</td>
</tr>
<tr>
<td>Bone or joint</td>
<td>156</td>
<td>1.4</td>
<td>96</td>
</tr>
<tr>
<td>Miliary</td>
<td>125</td>
<td>1.1</td>
<td>104</td>
</tr>
<tr>
<td>Meningeal</td>
<td>242</td>
<td>2.1</td>
<td>204</td>
</tr>
<tr>
<td>Other</td>
<td>217</td>
<td>1.9</td>
<td>149</td>
</tr>
</tbody>
</table>

† Includes data from states that reported at least 5 cases in any year of the study period.
# Clinical Syndromes Associated with Pediatric TB

<table>
<thead>
<tr>
<th>Group at Risk</th>
<th>Early disease</th>
<th>Late disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 y</td>
<td>Uncomplicated lymph node disease</td>
<td>Adult-type pulmonary disease</td>
</tr>
<tr>
<td>&lt; 3 y or severely compromised</td>
<td>Miliary TB, TB meningitis or both</td>
<td>&gt; 10 y</td>
</tr>
<tr>
<td>&gt; 1 y</td>
<td>Complicated lymph node disease</td>
<td>1-10 Y</td>
</tr>
<tr>
<td>&gt; 3 y</td>
<td>Pleural disease</td>
<td>&gt; 1 y</td>
</tr>
<tr>
<td>1-10 Y</td>
<td>Peripheral lymphadenitis</td>
<td>&gt; 5 y</td>
</tr>
<tr>
<td>&gt; 3 years</td>
<td>Urinary tract disease</td>
<td></td>
</tr>
</tbody>
</table>

Pulmonary TB

- Lung parenchyma
  - Ghon focus - primary parenchymal process
  - Ghon complex
    - Ghon focus, local lymphangitis, regional lymph node
  - 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 few or no signs or symptoms of disease

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

- Definitive diagnosis requires detection of *Mycobacterium tuberculosis* in respiratory specimen by culture or NAAT
  - Difficult due to paucibacillary nature of disease

- Presumptive diagnosis based
  - Epidemiology (e.g. risk factors, exposure)
  - Clinical findings
  - Immunologic tests - TST, IGRAs
  - Radiography
  - Source case identification (if unknown exposure)
Pulmonary TB: Radiography
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
  - 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 girl with FUO
- CXR - pneumonia
  - Fullness in hilar area
  - CT confirms adenopathy
- TST - 12 mm
- Gastric aspirates, bronchoalveolar lavage
- Source case identified
Ghon Focus with Cavitation and Bronchopneumonia
Adult-Type Cavitary Disease
Adult-Type Disease

- 15 year old girl from Liberia
- TST during pregnancy
  - 15 mm
  - No CXR
- 3 months postpartum developed fever, cough, weight loss
  - Treated as atypical pneumonia
  - Symptoms persisted
  - CXR repeated
Adult-Type Cavitary Disease
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 of tissue
  - 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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France (1999) [9]</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>Excisional Biopsy</td>
<td>8/26 (31%)</td>
<td>2/26 (8%)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>FNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>California (1999) [29]</td>
<td>44/238 (18%)</td>
<td>58/238 (24%)</td>
<td>84/238 (35%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>FNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India (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 (18%)</td>
<td>7/22 (32%)</td>
<td>9/22 (41%)</td>
<td>12/22 (55%)</td>
</tr>
<tr>
<td>FNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>California (2005) [5]</td>
<td>24/34 (71%)</td>
<td>15/39 (38%)</td>
<td>36/31 (88%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Excisional Biopsy</td>
<td>48/77 (62%)</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></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK (2010) [12]</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>
Case: Like mother, like daughter

- 16 year old Vietnamese with cervical adenitis
- Referred to pulmonologist → TST → referred to surgeon
  - TST 21 mm
- CXR normal
TB Lymphadenitis: Differential Diagnosis

- Infectious
  - Nontuberculous mycobacterial (NTM) adenitis
  - Cat-scratch disease (*Bartonella henselae*)
  - Toxoplasmosis
  - Tularemia
  - Plague
- Noninfectious
  - Malignancy
  - Autoimmune disease
Case: TB or not TB?

- 2 year with subacute lymphadenitis
  - Afebrile
  - No change after 10 days of amoxicillin-clavulanate
  - TST is reactive at 8 mm
  - CXR normal.

- Mother has a history of LTBI, untreated
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
  - 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, 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>
TB Meningitis: Diagnosis

- 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
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)
## 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>
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 and radiological findings consistent with TB meningitis

- Consensus statement on diagnostic criteria
Case: Missed Opportunity

- 16 month old Vietnamese girl
  - 2 week history of malaise
  - Fever, obtunded

- Nuchal rigidity noted
  - CSF: 56 WBC/mm³, glucose 11 g/dL, protein 129 mg/dL

- Diagnosed with partially treated meningitis (aseptic)
Case: Missed Opportunity

- MRI: basilar meningitis, infarcts
- Infectious disease consultation
  - TST nonreactive
  - CXR with RUL infiltrate
  - CSF AFB smear negative
  - Sputum smear negative
    - MTB isolated by culture
- Source investigation
  - Mother with TB disease identified by CXR
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 with no other apparent cause.

- Source case identification is often the key to diagnosis in children with symptomatic TB.
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 checked
  - LP required sedation but patient ate Tootsie Pop

- Return to ED the next day for LP
  - No staff for LP - admitted for LP

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

- 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
  - Progresses to disseminated disease irrespective of age or immune status
## Symptoms and Signs of Miliary TB

<table>
<thead>
<tr>
<th>Symptoms / Signs</th>
<th>% 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
  - Detection of MTB by culture or NAAT in respiratory or other appropriate specimen

- Presumptive diagnosis
  - 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
Diagnosis of Pediatric TB

- Diagnosis relies on:
  - Epidemiologic factors
  - Immunologic findings
  - Clinical presentation
  - Radiographic findings
  - Microbiologic /molecular confirmation

- Source investigation is often the key to diagnosis
Diagnosis of Pediatric TB

- **Active case finding**
  - *Identified by contact investigation or screening*
    - Most children asymptomatic/mildly symptomatic
    - Microbiologic confirmation not necessary if source case known
- **Passive case finding**
  - *Children presenting with symptoms*
    - 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></th>
<th>US-born With Linked TB Case, 188 (100), N (%)</th>
<th>All US-born, 1162 (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 (16)</td>
<td>334 (29)</td>
<td>—</td>
<td>169 (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 (3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1)</td>
<td>215 (19)</td>
<td>—</td>
<td>105 (20)</td>
</tr>
</tbody>
</table>
Diagnostic Tools

- Clinical
  - Diagnostic scores
- Immunologic
  - TST, IGRAs
- Radiological
  - CXR
  - US, CT, MRI
- Microbiological / molecular
  - Microscopy, culture
  - NAAT, Xpert MTB/RIF
- Source investigation
Immunological Tests

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

- IGRAs
  - Measure IFN-\(\gamma\) production by lymphocytes incubated with highly specific antigens
## Comparison of TST and IGRAs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TST</th>
<th>IGRAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigens</td>
<td>Many -PPD</td>
<td>ESAT-6, CFP-10, (TB-7.7)</td>
</tr>
<tr>
<td>Cross-reactivity with BCG</td>
<td>Yes</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Cross-reactivity with NTM</td>
<td>Yes</td>
<td>Less Likely</td>
</tr>
<tr>
<td>Distinguish between TB infection and TB disease</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Patient visits required</td>
<td>Two</td>
<td>One</td>
</tr>
<tr>
<td>Inexpensive</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
## TST versus IGRAs: Estimates of Performance

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity ( %)</th>
<th>Specificity ( %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult and Pediatric Studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TST</td>
<td>89 (63-100)</td>
<td>85 (22-100)</td>
</tr>
<tr>
<td>QFT</td>
<td>83 (56-93)</td>
<td>99 (99-100)</td>
</tr>
<tr>
<td>T-Spot</td>
<td>90 (50-100)</td>
<td>88 (85-100)</td>
</tr>
<tr>
<td><strong>Pediatric Studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TST</td>
<td>80 (70-90)</td>
<td>85 (63-100)</td>
</tr>
<tr>
<td>QFT</td>
<td>83 (75-92)</td>
<td>91 (78-100)</td>
</tr>
<tr>
<td>T-Spot</td>
<td>84 (63-100)</td>
<td>94 (87-100)</td>
</tr>
</tbody>
</table>
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
# Immunologic Tests in TB Disease

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=113)</th>
<th>Culture-confirmed tuberculosis (n=18)</th>
<th>Highly probable tuberculosis (n=8)</th>
<th>Probable tuberculosis (n=12)</th>
<th>Not tuberculosis (n=63)</th>
<th>Indeterminate (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>6.1 (2.1-10.3)</td>
<td>4.6 (1.5-12.7)</td>
<td>8.1 (5.2-11.9)</td>
<td>6.1 (1.8-10.5)</td>
<td>6.1 (2.0-9.8)</td>
<td>5.4 (2.2-10.5)</td>
</tr>
<tr>
<td><strong>Female sex</strong></td>
<td>52 (46%)</td>
<td>8 (44%)</td>
<td>5 (63%)</td>
<td>6 (50%)</td>
<td>27 (43%)</td>
<td>6 (50%)</td>
</tr>
<tr>
<td><strong>Symptoms at enrolment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>108 (96%)</td>
<td>16 (89%)</td>
<td>6 (75%)</td>
<td>12 (100%)</td>
<td>62 (98%)</td>
<td>12 (100%)</td>
</tr>
<tr>
<td>Fatigue or lethargy</td>
<td>28 (25%)</td>
<td>8 (44%)</td>
<td>2 (25%)</td>
<td>2 (17%)</td>
<td>16 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>Wheezing</td>
<td>16 (14%)</td>
<td>1 (6%)</td>
<td>1 (13%)</td>
<td>3 (25%)</td>
<td>9 (14%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Breathing difficulties</td>
<td>47 (42%)</td>
<td>10 (56%)</td>
<td>4 (50%)</td>
<td>8 (67%)</td>
<td>22 (35%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Fever</td>
<td>82 (73%)</td>
<td>16 (89%)</td>
<td>6 (75%)</td>
<td>9 (75%)</td>
<td>45 (71%)</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>23 (20%)</td>
<td>1 (6%)</td>
<td>0</td>
<td>1 (8%)</td>
<td>18 (29%)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>4 (4%)</td>
<td>1 (6%)</td>
<td>0</td>
<td>1 (8%)</td>
<td>1 (2%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Enlarged lymph nodes</td>
<td>12 (11%)</td>
<td>5 (28%)</td>
<td>1 (13%)</td>
<td>1 (8%)</td>
<td>5 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Weight loss</td>
<td>55 (49%)</td>
<td>13 (72%)</td>
<td>3 (38%)</td>
<td>5 (42%)</td>
<td>32 (51%)</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>Abdominal pains</td>
<td>20 (18%)</td>
<td>5 (28%)</td>
<td>2 (25%)</td>
<td>3 (25%)</td>
<td>9 (14%)</td>
<td>1 (8%)</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>60 (53%)</td>
<td>12 (67%)</td>
<td>4 (50%)</td>
<td>5 (42%)</td>
<td>24 (38%)</td>
<td>5 (42%)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>33 (29%)</td>
<td>4 (22%)</td>
<td>3 (38%)</td>
<td>7 (58%)*</td>
<td>15 (24%)</td>
<td>4 (33%)</td>
</tr>
<tr>
<td>WHO immunological staging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not clinically significant</td>
<td>7/33 (21%)</td>
<td>0/4 (0%)</td>
<td>0/3 (0%)</td>
<td>2/7 (29%)</td>
<td>4/15 (27%)</td>
<td>1/4 (25%)</td>
</tr>
<tr>
<td>Mild</td>
<td>6/33 (18%)</td>
<td>1/4 (25%)</td>
<td>1/3 (33%)</td>
<td>2/7 (29%)</td>
<td>2/15 (13%)</td>
<td>0/4 (0%)</td>
</tr>
<tr>
<td>Advanced</td>
<td>1/33 (3%)</td>
<td>1/4 (25%)</td>
<td>0/3 (0%)</td>
<td>0/7 (0%)</td>
<td>0/15 (0%)</td>
<td>0/4 (0%)</td>
</tr>
<tr>
<td>Severe</td>
<td>19/33 (58%)</td>
<td>2/4 (50%)</td>
<td>2/3 (67%)</td>
<td>3/7 (43%)</td>
<td>9/15 (60%)</td>
<td>3/4 (75%)</td>
</tr>
<tr>
<td>On antitubercial therapy at enrolment</td>
<td>13/32 (29%)</td>
<td>3/4 (50%)</td>
<td>1/3 (33%)</td>
<td>2/7 (29%)</td>
<td>7/15 (47%)</td>
<td>1/4 (25%)</td>
</tr>
<tr>
<td>Positive tuberculin skin test</td>
<td>31/103 (30%)</td>
<td>13/17 (76%)</td>
<td>3/8 (38%)</td>
<td>2/11 (18%)</td>
<td>9/57 (16%)</td>
<td>4/10 (40%)</td>
</tr>
<tr>
<td>Positive interferon-γ release assay</td>
<td>27/110 (25%)</td>
<td>13/18 (72%)</td>
<td>1/7 (14%)</td>
<td>3/12 (25%)</td>
<td>8/61 (13%)</td>
<td>4/12 (33%)</td>
</tr>
<tr>
<td>Positive tuberculin skin test or interferon-γ release assay</td>
<td>47/112 (42%)</td>
<td>17/18 (94%)</td>
<td>3/8 (38%)</td>
<td>4/12 (33%)</td>
<td>15/63 (24%)</td>
<td>4/11 (36%)</td>
</tr>
</tbody>
</table>

Data are median (IQR), number (%), or n/N (%). *p=0.033 compared with not tuberculosis distribution (Fisher's exact test).
Radiography

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

- Extrapulmonary TB
  - Lymphadenitis- US, CT
  - Meningitis- CT, MRI
  - Osteoarticular disease- MRI
Chest Radiograph

- Diagnostic value limited by lack of radiologist or inexperienced radiologist

- Features suggestive of childhood TB
  - Hilar adenopathy - most common manifestation
    - Segmental collapse, hyperinflation may occur
    - Frontal and lateral films recommended
  - Lobar infiltrate/ Ghon complex may be noted
  - Adult-type cavitation
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 Children and Adolescents with TB, United States, 2008-2010

<table>
<thead>
<tr>
<th></th>
<th>US-born</th>
<th>Foreign-born</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boy</strong></td>
<td>945 (52)</td>
<td>447 (54)</td>
<td>.21</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>268 (15)</td>
<td>17 (2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>1–4</td>
<td>839 (46)</td>
<td>135 (16)</td>
<td></td>
</tr>
<tr>
<td>5–12</td>
<td>369 (20)</td>
<td>240 (29)</td>
<td></td>
</tr>
<tr>
<td>13–17</td>
<td>350 (19)</td>
<td>430 (52)</td>
<td></td>
</tr>
<tr>
<td><strong>Race/ethnicity(^a)</strong></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hispanic</td>
<td>947 (52)</td>
<td>242 (30)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>139 (8)</td>
<td>38 (5)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>454 (25)</td>
<td>244 (30)</td>
<td></td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>240 (13)</td>
<td>291 (36)</td>
<td></td>
</tr>
<tr>
<td>American Indian or Native Alaskan</td>
<td>32 (2)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Site of disease</strong></td>
<td></td>
<td></td>
<td>.002</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1225 (67)</td>
<td>593 (72)</td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>439 (24)</td>
<td>184 (22)</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>161 (9)</td>
<td>42 (5)</td>
<td></td>
</tr>
<tr>
<td><strong>TB case verification</strong></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Positive culture</td>
<td>592 (32)</td>
<td>353 (43)</td>
<td></td>
</tr>
<tr>
<td>Nucleic acid amplification test</td>
<td>18 (1)</td>
<td>9 (1)</td>
<td></td>
</tr>
<tr>
<td>Positive smear absent culture</td>
<td>14 (0.8)</td>
<td>2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Clinical case</td>
<td>804 (44)</td>
<td>332 (40)</td>
<td></td>
</tr>
<tr>
<td>Provider diagnosis</td>
<td>398 (22)</td>
<td>126 (15)</td>
<td></td>
</tr>
</tbody>
</table>
### Bacteriologic Yield in Children with Intrathoracic TB, South Africa

<table>
<thead>
<tr>
<th>Disease manifestation</th>
<th>No. (%) of children</th>
<th>Proportion (%) with bacteriologic confirmation&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghon focus</td>
<td>4 (1.3)</td>
<td>4/4 (100)</td>
</tr>
<tr>
<td>Primary (Ghon) complex</td>
<td>15 (3.6)</td>
<td>5/9 (55.6)</td>
</tr>
<tr>
<td>Lymph node disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncomplicated</td>
<td>147 (47.9)</td>
<td>24/69 (34.7)</td>
</tr>
<tr>
<td>Complicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Airway compression</td>
<td>25 (8.1)</td>
<td>10/18 (55.6)</td>
</tr>
<tr>
<td>Parenchymal consolidation</td>
<td>62 (20.6)</td>
<td>40/49 (81.6)</td>
</tr>
<tr>
<td>Pleurisy</td>
<td>24 (7.8)</td>
<td>10/17 (58.8)</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>1 (0.3)</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>Disseminated (miliary) disease</td>
<td>15 (4.9)</td>
<td>14/15 (93.3)</td>
</tr>
<tr>
<td>Adult-type disease</td>
<td>14 (4.6)</td>
<td>14/14 (100)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>All</td>
<td>307 (100)</td>
<td>122/196 (62.2)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes subtypes.

<sup>b</sup> No confirmation for pleurisy cases.
When is Microbiological Confirmation 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 in place 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 vs 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 $\beta$-agonist to prevent bronchospasm
  - Nebulized hypertonic saline
  - Chest physiotherapy
  - Expectoration or catheter suctioning
## 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>

Total Patients = 250  
Culture positive = 58 (23%)  
GA = Gastric Aspirate  
IS = Induced Sputum

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

- Active case finding
  - Screening for LTBI or TB
  - Contact investigation

- Passive case finding
  - Symptoms or signs of TB
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 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 evaluate 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 $\leq 4$ 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 $\leq 1$- 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 Identified by Contact Investigation with Source Case Known

- Microbiologic confirmation not necessary if source case known and clinical/radiological findings consistent with TB
  - Patient 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 Source Case Unknown

- Bacteriologic confirmation if source case unknown
  - GA, sputum, BAL, CSF, tissue, etc
  - Negative cultures do not exclude TB

- Source case investigation
  - Critical to diagnostic evaluation
  - Likelihood of identifying adult source case and isolating MTB from source is often higher than of 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 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 Source Case Unknown

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

- Source case investigation
  - Critical to diagnostic evaluation

- 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
Symptomatic Presentation: Lymphadenitis

- 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 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 are 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 millennium children of the Eastern Mediterranean Region

World Health Organization
Regional Office for the Eastern Mediterranean