Pediatric Tuberculosis
Myths & Truths
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Significance of Tuberculosis in Children
A case of tuberculosis in a child is considered a “sentinel healthcare event” representing recent transmission of TB within the community.

Mycobacterium: OVERVIEW
- There are > 100 species of mycobacteria
- Of these, three are major pathogens:
  - *Mycobacterium tuberculosis* (Koch, 1882)
  - *Mycobacterium bovis*
  - *Mycobacterium leprae* (Hansen, 1874)
- The remaining are environmental organisms collectively known as MOTT (Mycobacteria Other Than Tubercular)
- MOTT organisms are responsible for opportunistic infections, especially in people with AIDS

Mycobacterium tuberculosis
Ziehl-Neelsen stain

Mycobacterium
Staining characteristics
- Mycobacteria are classical acid-fast organisms. Stains used in evaluation of specimens include
  - Ziehl-Neelsen stain
  - Auramine-Rhodamine Stain
- Mycobacteria appear phenotypically most closely related to members of
  - *Nocardia*
  - *Rhodococcus*
  - *Corynecleberium*

Auramine-Rhodamine Staining
### Pigmentation

- **Photochromogens (Group I)**
  - Produce nonpigmented colonies when grown in the dark and pigmented colonies only after exposure to light and reincubation.
  - *M. kansasii, M. marinum, M. simiae.*

- **Scotochromogens (Group II)**
  - Produce deep yellow to orange colonies when grown in either the light or dark.
  - *M. scrofulaceum, M. gordonae, M. xenopi, M. szulgai.*

- **Non-chromogens (Groups III & IV)**
  - Nonpigmented in the light and dark or have only a pale yellow, buff or tan pigment that does not intensify after light exposure.
  - *M. tuberculosis, M. avium-intracellulare, M. bovis, M. ulcerans, M. fortuitum, M. chelonae.*

### Tuberculosis Terms

- **Exposed.**
  - Contact with a patient with active Tuberculosis
  - Negative PPD, CXR & Physical Exam are Normal

- **LTBI (Latent Tuberculosis Infection)**
  - PPD +
  - Organism is dormant
  - Physical exam & radiograph are normal

- **Tuberculosis (Active Disease)**
  - Metabolically active M-TB in some part of the body
  - Children may be asymptomatic at the time of diagnosis

### Pediatric TB—Background

- **Definition of pediatric tuberculosis (TB):**
  - TB disease in a person <15 years old

- **In 2006,**
  - 13,779 TB cases were reported among all age groups
  - 807 (5.9%) were pediatric

### Global Epidemiology of TB

- **TB remains the leading infectious disease in the world**
  - More than 40% of the world’s population (>2 billion people) are infected with *M. tuberculosis*

- **In the 1990s:**
  - 90 million new cases
  - 30 million deaths

- **Among children <15 years of age:**
  - Approximately 13 million cases

### Summary of Epidemiology of TB

- Cases and case rates are on the decline
- Foreign born account for > 50% of U.S. cases
  - Highest risk for disease:
    - < 5 years of age
    - Foreign born children
      - 60% of cases develop within 18 months of arrival
      - Most common countries of birth: Mexico, Philippines, Vietnam

### TB Control In the United States

- **Identification of new cases of TB**
  - Initiation of appropriate treatment
  - Directly observed therapy

- **Contact Investigations**
  - Identify persons at risk for infection

- **Targeted tuberculin testing**
  - Identifies persons at high risk for TB who would benefit by treatment of LTBI
  - Treatment of latent TB infection (LTBI)
LESIONS ASSOCIATED WITH PRIMARY TUBERCULOSIS

- **Ghon focus.** Initial infection in an immunocompetent individual usually occurs in an upper region of the lung producing a sub-pleural lesion.
- **Peribronchial and/or hilar lymph nodes involvement** is frequent in primary tuberculosis due to lymphangitic spread from the Ghon focus.
- **Ghon complex.** The early Ghon focus together with the lymph node lesion.

These lesions undergo healing and over time usually evolve to fibrocalcific nodules.

**Ranke complex.** The combination of late fibrocalcific lesions of the lung and lymph node which evolved from the Ghon complex.

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**Ghon complex**

Healed Ghon Focus

Heavily calcified, healed focus of primary infection

Subpleural fibrocalcific nodule (white arrows)

&

thickened, scarred lymphatic vessel (red)
**TUBERCULOMA:**

- A well-circumscribed tuberculopulmonary lesion usually presenting as a "coin lesion" on chest X-ray.
- Usually a single nodule but may be more than one.
- These lesions are usually larger than the Ranke lesions and probably also represent a late phase of a primary tuberculopulmonary infection.

**Sub-pleural fibrocalcific Tuberculoma**

**Miliary Tuberculosis**

- Miliary tuberculosis (or disseminated TB) is characterized by:
  1. a wide dissemination into the human body
  2. by the tiny size of the lesions (1-5 mm)
    - a distinctive pattern seen on a chest X-ray of many tiny spots distributed throughout the lung fields with the appearance similar to millet seeds, thus the term "miliary" tuberculosis.
- Miliary TB may infect any number of organs including the lungs, liver, and spleen.
- It is a complication of 1-3% of all TB cases.

**Miliary Tuberculosis with positive acid-fast bacilli pediatric patient**
**Pediatric TB Cases by Site of Disease, 1993–2006**

- **Pulmonary**: 71.1%
- **Extrapulmonary**: 28.9%

- **Lymphatic**: 18.9%
- **Meningeal**: 3.1%
- **Miliary**: 1.5%
- **Bone & Joint**: 1.5%
- **Other**: 3.9%

*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.*

**Children <15 years with TB: Extrapulmonary Disease**

- **Miliary**: 63 cases
- **Lymphatic**: 12 cases
- **Pleura**: 5 cases
- **Meningeal**: 6 cases
- **Bone/Joint**: 6 cases
- **Other**: 6 cases

*Images showing miliary TB of lung with accompanying chest X-ray, miliary TB - kidney, miliary TB - liver, and miliary TB - spleen.*
TUBERCULOUS LYMPHADENITIS

DIAPHRAGM - PLEURAL SURFACE

Meninges - Brain
Basilar leptomeningitis

Bone - Joints

Tuberculous Pericarditis

PERITONEUM
**Tuberculosis Control in the United States**

- **Contact Investigations**
  
  “The most reliable TB control program is based upon aggressive and expedient contact investigations, rather than routine screening of large populations with low risk.”

  Can be complex, require experience and often a lot of detective work.

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**TB Case Definition and Verification**

1) **Laboratory confirmed cases** "Gold Standard"
   - Positive culture, DNA probe, or nucleic acid amplification
   - Positive AFB smear when culture not attainable

2) **Clinical case definition**
   - Positive tuberculin skin test
   - Signs and symptoms of TB disease
   - Current treatment for TB disease

3) **Provider diagnosis**
   - Diagnosed by health care provider
   - Does not fulfill all criteria necessary to meet laboratory or clinical case definitions

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**Pediatric TB Cases by Case Verification Criterion*, 1993–2006**

- **N = 15,946**

- Provider Diagnosis: 24%
- Laboratory confirmed: 25%
- Clinical Case Definition: 51%

*Based on the public health surveillance definition for TB [MMWR 1997;46(RR-10):40-41]*

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**TB Cases, All Ages, by Age Group, 1993–2006**

- Trend over time with age groups from 1993 to 2006

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Deaths Occurring Among Pediatric TB Cases, by Age Group, 1993–2004

N = 14,282

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cases</th>
<th>Deaths**</th>
<th>% of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 1</td>
<td>1298</td>
<td>26</td>
<td>2.0</td>
</tr>
<tr>
<td>Age 1–4</td>
<td>7094</td>
<td>46</td>
<td>0.6</td>
</tr>
<tr>
<td>Age 5–9</td>
<td>3334</td>
<td>20</td>
<td>0.6</td>
</tr>
<tr>
<td>Age 10–14</td>
<td>2556</td>
<td>20</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Note: Cause of death not recorded in TB case reports.
**Death includes died during therapy or died at TB diagnosis.

TST basics

- Store PPD in the bottle, clearly labeled in refrigerator; discard open bottles after 1 month
- Providers who administer TST should be trained and evaluated on TST technique
- Inject 0.1 ml of PPD material intradermally into volar aspect of forearm
  - Correct placement yields pale, distinct wheal, raised for several minutes

PPD = purified protein derivative

Reading TST results

- A trained professional should read TST results 48 to 72 hours after placement
- A positive test has distinct induration, not just erythema:
  - Bend arm at elbow, look with indirect light
  - Feel gently with your non-dominant hand or pen across the induration
  - Measure and record result in millimeters of induration perpendicular to long axis of arm
TST interpretation

- ≥5 mm is (+) only if child is:
  - Immunocompromised
  - A contact to a known or suspected case of TB
  - Has clinical or radiographic evidence of TB or old TB
- ≥10 mm is (+) for child with intermediate risk:
  - Age <4 years
  - Medical conditions predisposing them to TB or increased risk of TB exposure
- ≥15 mm is (+) if child has no risk (should not be skin tested!)

Myths about TST

- **Myth # 1**
  - A positive TST confirms the diagnosis of TB

- **Myth # 2**
  - A negative TST excludes the diagnosis of TB

False Positive TST

- Infection with Nontuberculous Mycobacteria
- BCG Vaccination
- Booster Phenomenon
- Bottom line, a positive tuberculin skin test is not sufficient to diagnose TB
- Falsely interpreted as positive.

TST results are not definitive

- A positive TST does not confirm the diagnosis of TB
- A negative TST does not exclude TB
- TST results are merely one factor in the equation

Evaluation of the Child with a Positive TST

- Evaluation of all children with a positive TST should include:
  - A careful history
  - Household investigation
  - Physical examination
  - Chest radiographs (PA & lateral)
Clinical suspicion, negative TST

- A negative TST never rules out TB
- 20% of culture-proven pediatric TB cases are TST (-) when initially evaluated
- Pursue diagnosis and treatment of TB:
  - Known source case
  - Radiographic abnormalities most consistent with TB
  - Clinical findings are subtle or more modest than radiographic findings
  - Intrathoracic lymphadenopathy

What about BCG?

- BCG vaccine is routinely given to newborns/infants in most areas of the world
- Ignore history of BCG when placing or interpreting TST
- Increased risk of positive TST results being caused by BCG
  - BCG received as an older infant or child (>1 month of age)
  - Multiple BCG doses
  - BCG in recent past
- Treat LTBI or TB based on breakpoints from last slide

BCG – Myths & Truths

<table>
<thead>
<tr>
<th>MYTHS</th>
<th>TRUTHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG protects against getting TB infection</td>
<td>BCG will not protect against becoming infected with TB.</td>
</tr>
<tr>
<td>BCG provides lifetime protection against developing active TB</td>
<td>BCG protects against severe complications of TB disease in young children, provides little or no protection in adolescents and adults</td>
</tr>
<tr>
<td>BCG causes the tuberculin skin test (TST) to be positive for life</td>
<td>BCG causes the TST to be positive for a few years, then the TST reaction becomes much weaker. Generally, no reaction is present after 5 yrs.</td>
</tr>
</tbody>
</table>

BCG – Myths & Truths

- In a BCG-vaccinated person, a positive TST is most likely due to BCG
- A positive TST in a person of any age from any country is most likely due to BCG, not TB
- There is no way to tell whether a positive TST is due to BCG or to TB infection
- A positive TST in an adolescent or adult from a TB high-burden country is almost always due to TB infection, not BCG

LTBI (latent TB infection)

- Normal chest radiograph and physical exam, (+) TST = diagnosis of LTBI
- Why treat all children who have LTBI?
  - LTBI treatment is less toxic in children than in adults
  - Young children are more likely to develop TB once infected than are adults
  - Young children were infected recently, increasing risk of progression to TB

M-TB Immune Response

- The immune response to infection $M\text{-}TB$ is mediated predominantly through T cell activation.
- T cells are sensitized to $M\text{-}TB$ antigens and the activated effector T cells, both CD4+ and CD8+, produce the cytokine interferon gamma (IFN-y) when stimulated by these antigens
**The QFT-G (QuantiFERON® - TB Gold Test)**

- Approved by FDA December 2004
- Relatively new blood test that can be used as an alternative or follow-up to the TB skin test to help diagnose a LTBI.
- It is not affected by previous QFT-G, TST or by BCG.
- It does not require the patient to return in 48 to 72 hours.
- However, the blood sample must be collected and processed for testing within 12 hours.
- A positive QFT-G must be followed up in a similar fashion to a positive TB skin test.

**QuantiFERON®-TB Gold test**

- New option for clarifying dx of TB infection
- Aliquots of whole blood are exposed to TB-specific proteins and controls
- Plasma is tested for levels of gamma-interferon
- Test is (+) if the lymphocytes have recognized TB proteins and produced gamma-interferon well above the level in control tube
- QFT-G can distinguish true TB infections from those caused by NTM or BCG exposure

**QuantiFERON-TB Gold in Tube**

- Approved by FDA October 12, 2007
- Next generation QuantiFERON
- Blood is collected in tubes coated with stimulated proteins
- No need to transport the blood within 12 hours
- Good correlation with TST

**T-SPOT®. TB - P070006**

- Approved by FDA July 30, 2008
- T-SPOT.TB uses the enzyme-linked immunospot (ELISpot) methodology to enumerate *M TB*-sensitized T cells by capturing interferon-gamma (IFN-y) in the immediate vicinity of the T cell from which it was secreted.

**T-SPOT.®TB**

- Quite promising for children
- Gamma-interferon release assay
- Requires separation of peripheral blood mononuclear cells from whole blood
- Technically more challenging than QFT-G tests

**Culture collection**

- Sputum: Older children can collect sputum by induction or in shower
- Gastric aspirate
  - Highest yield specimen for infants
  - ~50% yield in children with TB
- Other specimens: Cerebrospinal fluid, lymph node tissue, blood, urine, bone biopsy, synovial fluid
- Submit large volume specimens in sterile container without formalin
**Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis**

- NAA tests can reliably detect \(M\)-TB bacteria in specimens 1 or more weeks earlier than culture.
- Earlier laboratory confirmation of TB can lead to:
  - Earlier treatment initiation,
  - Improved patient outcomes,
  - Earlier identification of contacts of cases.

**CDC recommends that NAA testing be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities, such as contact investigations.**

**Treatment of LTBI**

- All children with LTBI should be treated
- 270 doses of isoniazid (INH)
- Minimum 9 months
- Goal is to finish 270 doses within 12 months

**Liver toxicity**

- Liver function testing (LFT) is no longer standard
- Most children tolerate therapy well
- LFT's only for children with:
  - Underlying liver disease
  - Taking other hepatotoxic meds
  - Symptoms of hepatotoxicity
- Watch for anorexia, malaise, abdominal pain
- Make sure family stops treatment and returns for evaluation if symptoms develop

**INH: Peripheral Neuritis**

- Peripheral Neuritis or Seizures caused by the inhibition of pyridoxine metabolism are rare
- Most do not need Pyridoxine supplement
- Exceptions:
  - Exclusively breast fed infants
  - Children on meat and milk deficient diets
  - Nutritional deficiencies
  - All HIV infected children
  - Pregnant adolescents & women
Treatment of TB

- Send child to TB clinic with pediatric expertise
- Confer with local health department and pediatric TB consultant
- Four-drug empiric therapy using directly observed therapy (DOT)
  - DOT: Non-family member observes patient taking medication
  - DOT can increase completion rates to 90% range
  - Can take place at home, work, school, clinic, or street corner

Four-drug treatment table

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DAILY dose in mg/kg/dose (maximum dose)</th>
<th>TWICE-WEEKLY dose in mg/kg/dose (maximum dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>10-15 (300 mg)*</td>
<td>20-30 (900 mg)</td>
</tr>
<tr>
<td>Rifampin</td>
<td>10-20 (600 mg)*</td>
<td>10-20 (600 mg)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>20-40 (2 grams)</td>
<td>50 (2 grams)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15-30 (2.5 grams)</td>
<td>50 (2.5 grams)</td>
</tr>
</tbody>
</table>

* When using both INH and Rifampin DAILY, dose INH at 15mg/kg dose and Rifampin to no more than 15 mg/kg.

Consider risks and benefits of Ethambutol in children whose visual acuity cannot be monitored.

Course of treatment

<table>
<thead>
<tr>
<th>Isoniazid</th>
<th>Rifampin</th>
<th>Pyrazinamide</th>
<th>Ethambutol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuation Phase</td>
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</tr>
</tbody>
</table>

- Ethambutol can be stopped if the patient or source case isolate is INH/RIF susceptible.

Assess the course of treatment

- At two months:
  - Repeat chest radiograph and assess the situation.
  - If adherence and response are good and no particular concern for resistance, treat with INH and RIF for remainder of course
  - Total duration of therapy is six months, measured by number of doses observed
  - Patients receiving a typical regimen receive 40 daily doses and 30 twice-weekly doses

Challenges of treating children

- Microbiologic confirmation is less common
- Monitoring success by serial sputum is nearly impossible
- Monitoring for toxicity is more difficult
- Children tolerate regimens better than adults
- INH liquid is poorly tolerated
- Need to open capsules, crush tablets, hide drug into soft foods or liquids

Circumstances for prolonged therapy

- If disease is extensive or slow to respond
- If patient has TB meningitis or osteomyelitis (treated for 12 mo)
- If TB isolate is drug-resistant
  - Includes treatment of M. bovis (inherently resistant to PZA and often sluggishly responsive to therapy)
- If patient has been poorly adherent
Conclusion

- Pediatric TB is relatively uncommon in U.S. and sometimes missed
- Screen healthy children with risk factor questionnaires and reserve TST for those at risk of exposure
- Evaluate children exposed to active cases of TB promptly and thoroughly; they are at highest risk of infection and disease
- Not all children with TB have (+) TST and not all children with (+) TSTs and radiographic abnormalities have TB