Definitions

- Pediatric tuberculosis (TB):
  - TB disease in a person <15 years of age
  - Latent TB infection (LTBI) – infection with *M. tuberculosis* without evidence of active disease in a person <15 years of age

- Infectious TB:
  - TB disease in the lungs or larynx in a person who has the potential to transmit infection to other people

Epidemiology - Global

- Leading cause of infectious disease morbidity and mortality
  - Approximately 1/3 of the world’s population (>1.9 billion people) are infected with *M. tuberculosis*
    - In the 2000s:
      - 90 million new cases
      - 30 million deaths
    - Among children <15 years of age:
      - ~13 million cases
      - 14% of total cases
      - 5 million deaths
      - 17% of total mortality
      - Case fatality rate: 39%
    - 2012 Estimated: 8.6 million new cases
      - 530,000 in children (<15 yrs of age); 74,000 deaths

Epidemiology: United States

- TB in children and adolescents appears to be declining
  - Annual case notifications in persons <18 years of age decreased from 997 (2007) to 818 (2010)
  - Between 2008 and 2010 69% of children and adolescents with reported TB were born in the US
    - Of those 69% had at least one foreign-born parent
    - 4% of pediatric TB patients had parents who were both born in the US (international adoptees?)
    - Between 2008 and 2010 of the 2628 children and adolescents with TB with known race/ethnicity
      - 45% - Hispanic
      - 27% - Black
      - 20% - Asian
      - 7% - White
      - 1% - Native American (including Native Alaskan)

Transmission of *M. tuberculosis* to Children

- Children are most commonly exposed in the immediate household by a family member with active disease
- Casual extra-familial contact is less often the source of infection
- Children rarely infect other children or adults:
  - Tubercle bacilli are relatively sparse in secretions
    - Paucibacillary TB (smear negative, culture positive)
  - Children with pulmonary TB rarely cough
  - Cough, when present, lacks the tussive force needed to aerosolize bacilli
Risk of Tuberculosis Disease by Age

Increased Risk of Progression of LTBI to TB Disease

- **Age groups:**
  - Infants and young children
  - Post pubertal adolescents
- **Recent infection:**
  - Highest risk in first 6 months after infection
  - Remains high for 2 years
- **Recent immigration**
- **Immunodeficiency:**
  - HIV infection, Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, malnutrition
  - Immunosuppressive drugs: prolonged or high-dose corticosteroid therapy, chemotherapy, tumor necrosis factor (TNF-alpha) antagonists used to treat rheumatoid arthritis and Crohn disease

Clinical Manifestations

- Pulmonary disease and associated intrathoracic adenopathy: most common presentation of TB in children
  - Common symptoms are often nonspecific
    - Chronic, unremitting cough that is not improving and present for >3 weeks
    - Fever >38°C for at least 2 weeks, other common causes excluded
    - Weight loss or failure to thrive (based on growth chart)
  - Children, 5–10 years may present with clinically silent but radiographically apparent disease
  - Infants: more likely to present with signs of lung disease
  - Elucidating the epidemiologic risk factors for TB vital in evaluation for TB
  - Adolescents can present with features common in children or adults

Extrapulmonary tuberculosis

- In the context of exposure to TB, presence of any of the following signs should prompt evaluation for extrapulmonary TB
- **Superficial lymph nodes (scrofula):**
  - Fixed, painless, enlarged superficial nodes (usually cervical)
- **TB meningitis:**
  - Meningitis not responding to antibacterial medications, with a subacute onset, communicating hydrocephalus, stroke, and/or elevated intracranial pressure
- **Pleural TB:**
  - Pleural effusion
- **Pericardial TB:**
  - Pericardial effusion
- **Abdominal TB:**
  - Diseased abdomen with ascites, abdominal pain, jaundice, or unexplained chronic diarrhea

Extrapulmonary TB

- TB of the joint
  - Nontender joint effusion
- Vertebral TB (Pott’s disease)
  - Back pain, gibbus deformity (a form of structural kyphosis) especially of recent onset (uncommon)
- **Skin:**
  - Warty lesion(s), papulonecrotic lesions, lupus vulgaris, erythema nodosum may be a sign of tuberculin hypersensitivity
- **Renal:**
  - Sterile pyuria, hematuria
- **Eye:**
  - Iritis, optic neuritis, phlyctenular conjunctivitis

Pediatric TB Cases by Site of Disease, 1993–2012

<table>
<thead>
<tr>
<th>Site of Disease</th>
<th>Cases (totaling 29.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapulmonary</td>
<td>(%)</td>
</tr>
<tr>
<td>Lymphatic</td>
<td>18.8%</td>
</tr>
<tr>
<td>Meningeal</td>
<td>3.4%</td>
</tr>
<tr>
<td>Miliary</td>
<td>1.4%</td>
</tr>
<tr>
<td>Bone &amp; Joint</td>
<td>1.8%</td>
</tr>
<tr>
<td>Other</td>
<td>4.1%</td>
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</tbody>
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Tuberculosis in Adolescents

- Adolescents develop tuberculosis in one of two ways:
  - Reactivation of infection acquired during childhood
    - The closer to puberty at the time of infection the greater the risk of reactivation
    - Chronic pulmonary tuberculosis
  - Progression of infection acquired during adolescence to disease:
    - Classic primary disease
    - Progressive primary pulmonary tuberculosis
    - Chronic pulmonary tuberculosis

Adolescents: Reactivation Tuberculosis

- Constitutional symptoms often more prominent than respiratory symptoms
  - Weight loss and fever are very common
  - Cough, chest pain, hemoptysis
  - Drenching night sweats occur several times per week
- Cavitary lesions frequently seen

Significance of Tuberculosis in Children

- Public Health: Diagnosis of LTBI or tuberculosis disease in a child is considered a "sentinel public health event" usually representing recent transmission of TB within a community
- Personal Health: High rates of morbidity and mortality

Prevention of TB in Children: Potential Missed Opportunities

- Failure to find and appropriately manage adult source cases (case finding)
- Delay in reporting the initial diagnosis of TB
- Contact investigation interview failure
- Delay in evaluation of exposed children
- Failure to completely evaluate exposed children
- Failure to prescribe INH "window prophylaxis"
- LTBI diagnosed; treatment not prescribed
- Failure to complete treatment for LTBI

TB Control: Targeted TB Testing

- What is Targeted TB Testing?
  - Identifies persons at high risk of infection with M. tuberculosis
  - Identifies persons at high risk of progressing to disease should they be infected

Why Use Risk-Based Targeted TB Testing?

- Why not use routine, universal, administratively mandated TB testing? Why not use the Tuberculin Skin Test (TST) or Interferon Gamma Release Assay (IGRA) as a screening tool?
  - Daycare
  - Schools
  - Colleges
  - Summer camps
- Answer: Limitations of the TST/IGRA
  - Universal testing means that large numbers of low risk children will be tested: Inefficient use of healthcare resources
  - Even if the specificity of the test approaches 99%, testing of persons in low-prevalence groups would result in mostly false-positives
  - IGRA specificity reduces but does not eliminate false positives in low risk population
Targeted TB Testing
- Risk assessment:
  - Signs and symptoms consistent with TB disease
  - Contact and source-case investigations
  - >1 risk factor identified on screening risk-assessment questionnaire
    - General pediatric practice
    - School-based healthcare
  - High risk of progression due to underlying conditions:
    - HIV infection, Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, malnutrition, prolonged or high-dose corticosteroid therapy, chemotherapy, tumor necrosis factor (TNF-alpha) antagonists

Control of TB 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
  - Can be complex and may require lots of detective work
  
Targeted TB Testing Risk-Assessment Questionnaire
- Has a family member or contact had TB disease?
- Has a family member had a positive TB test?
- Was your child born in a high-risk country (i.e. outside US, Canada, Australia, New Zealand, or Western European countries)

Using the Risk Assessment Questionnaire
- At first contact with child and every 6 months until age 2 years
- After age 2 years, ask risk assessment questions every year if possible
- Anytime a risk factor is identified, a TST or IGRA should be performed

TST and IGRA
- TST preferred, IGRA acceptable
  - Children <5 years of age
    - Positive result of either test is considered significant
  - IGRA preferred, TST acceptable
    - Children ≥5 years of age who have received BCG vaccine
    - Children ≥5 years of age who are unlikely to return for TST reading

TST and IGRA
- TST and IGRA should be considered:
  - The initial and repeat IGRA are indeterminate
  - The initial test is negative (TST or IGRA) and:
    - Clinical suspicion for TB is moderate to high
    - Risk of progression and poor outcome is high
  - The initial TST is positive and:
    - ≥5 years of age and a history of BCG vaccination
    - Additional evidence needed to increase compliance
    - Nontuberculosis mycobacterial disease is suspected
Limitations

- TST and IGRA by themselves cannot distinguish between infection and disease
- In circumstances of moderate to high clinical suspicion for TB disease, negative results in either TST and IGRA do not exclude the diagnosis
- The IGRA should not be used in children <2 years of age unless TB disease is suspected
  - In children 2 through 4 years of age, there are limited data about its usefulness in determining TB infection, but can be performed if disease is suspected
- Children with a positive IGRA result should be considered infected with MTB complex
  - TST results may be confounded by previous BCG administration (age-dependent) and infection with nontuberculosis mycobacteria
- Indeterminate IGRA results do not exclude TB infection and may necessitate repeat testing
  - Should not be used to make clinical decisions

Red Book Online. Report of the Committee on Infectious Diseases, 29th Edition

Mycobacteriologic Diagnosis of Tuberculosis

- Adults: 70-90% have a sputum that is (+) for M. tuberculosis
- Children:
  - Tubercle bacilli are relatively few in number
  - Sputum generally cannot be obtained from children <10 yrs old
  - Gastric aspirates in children with PTB
    - 30-40% sensitive in children
    - 60-70% sensitive in infants
  - Bronchoalveolar lavage (BAL): Sensitivity may be less than gastric aspirates

Establishing a definitive diagnosis of TB disease in children is often associated with great difficulty!!

Treatment of Latent Tuberculosis Infection

- INH 10-15 mg/kg (max., 300 mg) PO daily for 270 doses
  - Efficacy approaches 100%
- Alternative: Twice weekly directly observed (DOT) INH 20-40 mg/kg (max., 900 mg) PO for 72 doses
- Monitor index case isolate sensitivities
- Hepatotoxicity from INH is rare in children:
  - Monthly assessment for clinical evidence of hepatotoxicity should be made: malaise, loss of appetite or weight, nausea, vomiting, abdominal pain, jaundice
  - Routine monitoring of LFTs is not indicated

Treatment of Late Latent Tuberculosis Infection

- Rifampin 10-15 mg/kg/day (max. 600 mg) po daily for 6 months is an alternative
  - INH not tolerated
  - Index patient isolate INH-resistant
- Rifapentine/INH
  - 12 week course
  - 900mg/900mg maximum taken once a week via Direct Observed Therapy (DOT)
- MDR-LTBI: TREAT???? NOT TREAT????
  - Treatment can reduce risk of disease by up to 2/3
  - Regimen based on susceptibilities of index patient isolate

Treatment of TB in Children & Adolescents

- If INH resistance rate >4% or if other risk for resistance include four drugs in initial regimen:
  - Isoniazid (10 mg/kg/day, range 10-20, max. 300)
  - Rifampin (15 mg/kg/day, range 10-20, max. 600)
  - Pyrazinamide (20-30 mg/kg/day)
  - Ethambutol (15-25 mg/kg/day)
- Treatment complicated by child unfriendly preparations of the medications
  - Directly observed therapy (DOT)
- Monitor liver transaminases? – Depends on severity of disease
- Follow susceptibility studies of Mtbc isolate (index and/or child isolate)
  - Important to be familiar with resistance patterns in the community