Classification System for TB

<table>
<thead>
<tr>
<th>Class</th>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No TB exposure</td>
<td>No history of exposure, negative reaction to tuberculin skin test</td>
</tr>
<tr>
<td>1</td>
<td>TB exposure</td>
<td>History of exposure, negative reaction to tuberculin skin test</td>
</tr>
<tr>
<td>2</td>
<td>TB infection, no disease</td>
<td>Positive reaction to tuberculin skin test, negative bacteriologic studies (if done), no clinical, bacteriologic, or radiographic evidence of active TB</td>
</tr>
<tr>
<td>3</td>
<td>TB, clinically active</td>
<td>History of exposure, positive reaction to tuberculin skin test, clinical, bacteriologic, or radiographic evidence of current disease</td>
</tr>
<tr>
<td>4</td>
<td>TB, not clinically active</td>
<td>History of exposure, positive reaction to tuberculin skin test, and abnormal but stable radiographic findings</td>
</tr>
<tr>
<td>5</td>
<td>TB suspected</td>
<td>Diagnosis pending</td>
</tr>
</tbody>
</table>

Epidemiology

- Tuberculosis remains the leading infectious disease in the world
  - Approximately 1/3 of the world's population (>1.9 billion people) is infected with *M. tuberculosis*
  - In the 1990s:
    - 90 million new cases
    - 30 million deaths
  - Among children <15 years of age:
    - Approximately 13 million cases
    - 5 million deaths

**Reported TB Cases* United States, 1982–2009**

*Updated as of March 19, 2010.


*Updated as of March 19, 2010.

**Number and Percent Foreign-born Pediatric TB Cases, 1993–2006**

**Epidemiology: United States**

- Case rates for all ages are higher in urban, low-income areas, and in nonwhite racial and ethnic minorities
- Specific groups with high LTBI and TB disease rates:
  - Immigrants and refugees from high-prevalence regions (Asia, Africa, Latin America, countries of the former Soviet Union)
  - International adoptees
  - Travelers to countries with high-prevalence
  - Homeless people
  - Residents of correctional facilities
Transmission of *M. tuberculosis* to Children

- Children are usually infected by an adult or adolescent in the immediate household.
- 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.
  - Children with pulmonary TB rarely cough.
  - Cough, when present, lacks the force needed to aerosolize bacilli.

### AFB smear

AFB (shown in red) are tubercle bacilli.
Increased Risk of Progression of LTBI to Tuberculosis 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 arthritis, Crohn’s disease: Infliximab, etanercept, adalimumab, golimumab

---

Risk of Progression to TB Disease

- Immunocompetent adults: 5-10% lifetime risk of developing disease after infection
- Adults with TB infection and HIV infection: 5-10% annual risk of developing disease
- Children and the risk of TB disease:

Risk of Tuberculosis Disease by Age

<table>
<thead>
<tr>
<th>Risk of disease following primary infection</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disseminated tuberculosis</td>
<td>Tuberculosis meningitis</td>
</tr>
<tr>
<td>5-10 years</td>
<td>&lt;5 years</td>
</tr>
<tr>
<td>16-20%</td>
<td>50%</td>
</tr>
<tr>
<td>5-19%</td>
<td>5%</td>
</tr>
<tr>
<td>10-20%</td>
<td>5%</td>
</tr>
<tr>
<td>5-19%</td>
<td>5%</td>
</tr>
<tr>
<td>80-99%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Adapted from reference 36.

**Significance of Tuberculosis in Children**

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

*Red Book 2009
American Academy of Pediatrics*

**Control of Tuberculosis in the United States**

- Case finding and treatment
- 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 testing with tuberculin skin test or IGRA.

*Red Book 2009
American Academy of Pediatrics*

**Concentric-Circle Approach to Contact Investigations or Tracing**

- Home Environment
- Leisure Environment
- Work/School Environment
- Close
- Casual
- Index
- Case


**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”
- Failure to maintain a contact under surveillance
- LTBI diagnosed; treatment not prescribed
- Failure to complete treatment for LTBI
**Tuberculosis Exposure in Children**

- **History, PE, TST, CXR are done**
  - CXR is done regardless of TST result

- **IF the child is:**
  - Asymptomatic and physical examination is normal
  - TST is negative (<5 mm)
  - Chest X-ray is normal

- **AND IF <4 years of age START:** Isoniazid (INH) 10 mg/kg (max., 300 mg) PO once daily

- **Why is INH given as “Window Prophylaxis” even if there is no evidence of TB infection or disease at the initial visit?**
  - May already be infected
  - Infection more likely to progress to disease
  - Infants and younger children are more likely to have disseminated disease or meningitis

- **TST repeated 8-10 weeks after contact broken with infectious adult:**
  - If TST (-), discontinue INH
  - If TST (+), re-evaluate child and treat accordingly

---

**Timetable of Tuberculosis in Children after Walgren**

- Bacilli: 1st week
- Glandular: 30% of cases
- Pleural effusion
- Reticular infiltration
- Larynx or trachea
- Initial fever

---

**4 yr old**

TST: 0.0 mm
Case #1. Nightmare in Daycare: Opportunities we almost missed but didn’t....

Contact Investigation

• Maintaining confidentiality, TB controller calls asst. dir. of DCC who volunteers that index pt. is her aunt (“I know who this is…”):
  – Secretarial volunteer 1-2 hrs/week
  – Works at desk doing paperwork, filing
  – Little or no contact with children in the daycare

• Simultaneously, first of 4 interviews of index pt. by 3 different interviewers is held in hospital
  – Spent more time in daycare (2-3 hrs/day) than originally described by niece
  – Not much contact with children

Daycare Contact Investigation

• On-site assessment of DCC conducted by TB controller:
  – High priority contacts: 35
    • 30 children attend: All ≤4 years of age
    • 5 staff members: Adults and adolescents
  – Daycare is in a church basement and the index case’s desk is in the middle of the play area

• Social contacts
  – High priority contacts: 9
  – 4 are children: 2 are ≤1 year of age
Summary: Daycare Contact Investigation

Investigation Totals

Children <4 yrs old
(+) TST 13/32 (40%) 7 with disease
(-) TST 19/32 (60%) 2 with disease
TB disease 9/32 (28%)

Observations on Pediatrician Involvement in Contact Investigations

• 6 of 30 (20%) of the exposed children were initially evaluated in conjunction with their pediatricians:
  – TSTs read by pediatricians were reported in at least one case as negative, i.e.: Not in millimeters
  – TSTs 0.0 (zero) mm: (3)
    • H & PE, CXR done: None
  – TSTs 0.0 (zero) mm + CXR (-): (2)
    • H & PE done: None
  – INH prescribed for prophylaxis for 6 contacts <4 yrs of age: None

• In each case telephone calls made to pediatricians to assure proper evaluation were followed by a referral to the TB Center for the evaluation

Case #2. Three generations, two families and a pediatrician....

Or, Source cases, index cases, and contact investigations.... you never know what you'll get if you keep your eyes open....and keep asking the right questions....THE IMPORTANCE OF EPIDEMIOLOGY, i.e., is this TB? If we could only find an adult source case?
Potential Missed Opportunities in TB Control

- Two children with LTBI from one family see their private pediatrician for evaluation and management after mother insists to health department that she would like them seen by the pediatrician:
  - Receive prescriptions for INH plus 8 refills
    - No follow-up appointments are given
    - Social history: Homeless, 5 children, mother with her own serious health problems, holding down a full-time job
  - Set-up for another missed opportunity? Strong probability
    - Will therapy for LTBI be completed?
    - Was it? Yes, why? DOT for LTBI (DOTI)

Potential Missed Opportunities in TB Control

- Initially, 5/18 children are diagnosed as TB-exposed
  - Two (Ages 6 & 28 months) identified in the contact investigation have 0.0 mm TSTs and normal CXRS at the health department
  - Mother (same family as above) insists to health department that she would like them to be seen by their private pediatrician
    - No PE done
    - No INH “window prophylaxis” given
Case History: Final Numbers

- Eighteen children were exposed to a 26-year old woman with bilateral cavitary pulmonary tuberculosis:
  - 15/18 (83%) children are infected
    - 9/15 (60%) develop TB disease
      - Two after initial negative TST (Missed opportunity)
      - 1 TB meningitis, 2 miliary
    - 6/15 (40%) have LTBI
  - 3/18 (17%) are TB-exposed but not infected

- Through 3 generations: All 2nd and 3rd generation cases preventable
  - TB-infected child of today may become the index pt. of tomorrow without treatment for LTBI

Case #3. The six year-old boy who was not a household contact but was....so says Dr. Kreiswirth....and a memory of LTBI treatment long ago....
The six year old boy…. The six year old boy…. The six year old boy…. The six year old boy…. The six year old boy…. The six year old boy….

• A 16 year old male was referred to oncology for evaluation of a lump in the neck
  – There was history of decreased appetite, 20 lb weight loss, and intermittent, nonproductive cough
  – A CXR was done:

• A 22-year-old aunt remembered being treated for LTBI about 10 yrs ago
  – An uncle who had a cough and may have had TB but was not sure of the diagnosis

• Using the name provided, the TB controller was able to find the uncle’s medical record
  – Was a highly infectious case 9 years earlier
  – Review of the contact investigation showed 5 household contacts including the niece and 4 work contacts
  • The 6-yr-old boy who spent several hours in the uncle’s apartment each day after school was not mentioned
The six year old boy....

- RFLP analysis was a match between the uncle and the 16 year-old (Dr. Kreiswirth)
- The contact investigation of the now 16 year-old (now a computer whiz) involved evaluation of his H.S. (1600 students) and targeted testing of 50 high priority classmates and teachers

The High Cost of Missed Opportunities

- Missed opportunities documented:
  - Failure to find and appropriately manage adult source cases (Case finding)
  - Contact investigation interview failure
  - Delay in evaluation of exposed children
  - Failure to completely evaluate exposed children
  - Failure to prescribe prophylactic INH
  - Failure to complete treatment for LTBI (Adherence)

- Resulted in: 20 cases of TB in children (23 total cases):
  - 3 miliary
  - 1 TBM, 1 GI TB
  - Extended hospitalizations (acute and rehab), CIs, DOT

AAP Recommendations: Targeted TB Testing

- What is Targeted TB Testing?
  - Identifies persons at high risk for TB who would benefit by treatment of LTBI

- Risk of exposure to TB should be assessed at routine healthcare evaluations:
  - Risk Assessment Questionnaire
  - Only children with an increased risk of TB infection or disease (a positive response to a question on the questionnaire) should be considered for tuberculin skin testing

Why Use Risk-Assessment-Based Targeted TB Testing?

- Why not use routine, universal, administratively mandated TB testing? Why not use the TST or IGRA as the screening tool?
  - Daycare
  - Schools
  - Colleges
  - Summer camps

- Answer: Limitations of the TST (Mantoux Skin Test)
  - Universal testing means that large numbers of low risk children will be tested
  - Even if the specificity of the TST approaches 99%, testing of persons in low-prevalence groups would result in mostly false-positives
  - IGRA specificity reduces but does not eliminate all 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

Targeted TB Testing

Risk-Assessment Questionnaire

• Has a family member or contact had TB disease?
• Has a family member had a positive TB skin test?
• Was your child born in a high-risk country (i.e. outside US, Canada, Australia, New Zealand, or Western European countries)
• Has your child traveled to a high-risk country and spent >1 week with the resident population?

Red Book 2009

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

Red Book 2009

BCG Vaccine and Tuberculin Skin Testing

• History of a BCG is never a contraindication to tuberculin skin testing
• Interpretation of TST results in BCG recipients is the same as for people who have not received the vaccine
• Difficult to distinguish between (+) TSTs caused by infection with *M. tuberculosis* and those caused by BCG
  – Reactivity does not occur in some children after receipt of BCG
  – If BCG does cause a positive TST, the reaction is generally negative by 5 years of age
  – If child is from a high-burden country, (+) TST is almost always due to LTBI
• Therefore, management of children with a history of BCG and a (+) TST includes:
  – Diagnostic evaluation including a chest radiograph
  – Appropriate treatment
IGRA: Use in children

- Published experience less in children
- Can be used in children >5 yrs of age
- May be useful in children who received BCG vaccine
- Do not distinguish between LTBI and TB disease
  - Negative IGRA does not rule out either in child with suspicious findings
- Interpretation of negative IGRA in child with (+) TST is not clear
  - No longitudinal studies to establish negative predictive value

AAP Red Book 2009

Evaluation of the Child with a positive TB test (TST, IGRA)

- Evaluation of all children with a positive TB test should include:
  - A careful history for symptoms of disease
  - Physical examination
  - Chest radiographs (PA & lateral)
  - Household investigation

Evaluation of the Child with a positive TB test (TST, IGRA)

- A careful history for symptoms of disease
- Physical examination
- Chest radiographs (PA & lateral)
- Household investigation

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:
  - A 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

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

MDR-LTBI: TREAT??? NOT TREAT????
  - Treatment can reduce risk of disease by up to 2/3
  - Regimen based on susceptibilities of index patient isolate

Child from a country with “a lot of resistance” shouldn’t treat with more than just INH? No.
How Children with Tuberculosis are Identified

- Presentation with a symptomatic illness
- Discovery of a child with pulmonary tuberculosis during contact investigation of an adult with tuberculosis
  - Few or no symptoms
  - Evaluation: (+) TST and abnormal CXR
  - In some areas of U.S up to 50% of children with PTB are discovered in this manner
    - Before significant symptoms have developed

Pediatric TB Cases by Site of Disease, 1993–2006

<table>
<thead>
<tr>
<th>Site of Disease</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>71.0</td>
</tr>
<tr>
<td>Extra pulmonary</td>
<td>21.9</td>
</tr>
<tr>
<td>Lymphatic</td>
<td>18.9</td>
</tr>
<tr>
<td>Meningeal</td>
<td>3.1</td>
</tr>
<tr>
<td>Miliary</td>
<td>1.5</td>
</tr>
<tr>
<td>Bone &amp; Joint</td>
<td>1.5</td>
</tr>
<tr>
<td>Other</td>
<td>3.9</td>
</tr>
</tbody>
</table>

*Any extrapulmonary involvement which includes cases that are extrapulmonary only and both
Patients may have more than one disease site but are counted in mutually exclusive category for
surveillance purposes.

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
  - CDC: 15,946 pediatric cases, 1993-2006: 24% lab (+), 51% clinical criteria, 24% provider diagnosis

Difficulties in the Diagnosis of Tuberculosis in Children

- Children are often asymptomatic or symptoms are nonspecific: Fever, poor appetite, poor weight gain or weight loss
  - Approximately 25-30% of disease is extrapulmonary
  - Meningitis and miliary disease tend to develop soon after infection
    - 70-80% occur in children 0-4 years of age
- Epidemiologic link (The adult source case)
  - Crucial to identify the adult source case for the child
    - Provides strong evidence that the child suspected of having TB disease actually has TB
    - May be the only isolate available for susceptibility testing
Difficulties in the Diagnosis of Tuberculosis in Children

- Physical examination may be normal
- TST may be negative (10%)
- Chest radiograph: Any lobe of the lung may be involved
  - Good technique/Experience with children
  - Two views
  - Careful interpretation
Tuberculosis in Adolescents

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

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
Treatment of Tuberculosis in Children and 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 LFTs – 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

Difficulties in Treatment

- Lack of symptoms initially
- Lack of observable improvement
- Lack of culture “proof”
- Education of the caregiver
- Multiple caregivers
- Chronic dosing
- Language/cultural differences
- Child unfriendly dosing forms
- Communication with the child

Assessing Adherence Barriers

- Parents: Adherence can be influenced by:
  - Parenting skills
  - Motivation
  - Personal health beliefs, stigma
  - Other competing life circumstances
- In children and adolescents adherence can be influenced by:
  - Developmental level
  - Behavioral characteristics

Summary

- Reported cases of tuberculosis in the U.S.:
  - More than 2/3 occurs in nonwhite racial and ethnic groups
  - More than 50% occur in foreign born persons
  - Among children case rates are highest in infants and postpubertal adolescents
- Children are usually:
  - Infected by adult or adolescent household contacts
  - Not infectious (contagious)
- Contact investigations and targeted TB testing are mainstays of TB control in the U.S.
  - Evaluation of TB-exposed child: PA, CXR, window prophylaxis
  - Risk assessment questionnaires are the most effective screening tool to detect children at risk for LTBI
- TB diagnosis in young children requires a high index of suspicion
- DOT is key to successful treatment