**Pediatric TB**

- Defined by WHO and CDC
  - TB in children less than 15 years old historically
  - WHO only reports AFB smear positive cases by age
  - WHO will now report cases <5 yrs, 5-14 yrs, >/= 15 yrs

- In contrast to adults
  - Clinical manifestations are usually related to primary tuberculosis rather than reactivation tuberculosis

**Stages of Tuberculosis**

**Exposure**
- to contagious adult with pulmonary disease

- Household contacts 20-30%

- **Latent TB infection** (LTBI)
  - 5-10%
  - Disease
    - Active TB Adult
    - Disease
    - Active TB Child
  - 5-50%
Epidemiology of Childhood TB
Percent Positive PPD
Household contacts 0-14 yrs of age

England, 1954: 709 contacts
Smear+: 65%
Culture+: 27%

Canada, 1954: 1876 contacts
Smear+: 45%
Culture+: 26%

Pediatric TB

- Diagnostic and therapeutic challenges
  - Less specific signs and symptoms of disease
  - Paucibacillary resulting in fewer positive cultures
  - Increased risk of progression of disease once infected
  - Increased risk of dissemination

Age Related Risk for TB

- Risk of progression to active disease in first year after infection
  - <12 months: 43%
  - 1-5 years: 24%
  - 6-10 years: 2%
  - 11-15 years: 15%
  - Healthy adults: 5-10% lifetime risk
  - HIV infected adult: 30-50% lifetime risk
Age Related Risk for TB

Disease manifestations vary

- Immune competent, <2 yrs of age
  - Highest rate of disease of any age group
  - Experience most of the disseminated disease

- 2-5 yr olds
  - Disease rate is the same as those <2 yrs
  - Less risk for meningeal or disseminated disease

- School age children have the lowest disease rate of any age

Exposure

Household contact with contagious teen or adult
Usually > 4 hours of contact

Chest 2 view PA and Lat

TWO VIEW CHEST:

IMPRESSION: Airway disease. No infiltrate, adenopathy or evidence of active pulmonary tuberculosis

Pt: 2 week old infant

Adult index case: father, incarcerated during gestation, ill for several months prior to hospitalization

Cavitary, smear + pulmonary disease, pericarditis, osteomyelitis

MTB pansenstive isolated
**Pediatric Exposure Treatment**

- **Window prophylaxis**
  - Window period for TST conversion: 2-12 weeks
  - Indicated for those \( \leq 4 \) years
  - Baseline TST – / CXR normal
  - INH prophylaxis recommended
    - Children \( \leq 4 \) yrs
    - Immunosuppressed pts
    - Pts on TNF alpha blockers

- Follow up TST done 10-12 weeks after last exposure to infectious contact
  - Induration less than 5 mm stop prophylaxis,
  - Induration greater than 5 mm treat for LTBI

**TB diagnosis**

- Risk assessment important
- Diagnosis in children more often based on epidemiology and clinical findings than on smear or culture
TST and pediatric disease

- Positive TST with TB disease
  - Pediatrics 89%
  - Adults 54%
- Up to 20% of children with TB disease will have a negative TST at diagnosis
- Approximately 5% will be persistently negative

TST and BCG

- BCG prevents infection in approximately 50% of vaccine recipients
- BCG may prevent severe forms of TB disease in young children
- BCG influence on TST results depends on:
  - Age at immunization (less effect if at birth)
  - Time since immunization
  - Exposure to nontuberculous mycobacteria (false positives)
  - Prevalence of LTBI (if prevalence high then PPV better)
  - Type of vaccine used (higher # of bacilli= greater effect)
TST and BCG

- Study of children given BCG at birth:
  - <50% of infants will have a positive TST at 6-12 mos of age
  - Most children will have nonreactive TSTs by 5 years of age
  - Previous BCG is not a contraindication for TST
  - TST positivity in BCG vaccinated children from TB endemic countries is more likely related to LTBI than BCG
  - BCG vaccination status should be disregarded in interpreting TSTs

TB disease

Clinical and radiographic findings
(1993-2001 11,480 US cases)

- Pulmonary 76.9%
  - Primary
  - Progressive
  - Chronic/reactivation

- Extra-pulmonary 15.5%
  - Lymphatic 2.1%
  - Miliary 1.1%
  - Pleural 1.1%
  - Bone/joint 1.4%

TB in newborns
Pediatric TB disease
Laboratory diagnosis

• Adult source isolate can direct treatment
• Cultures need to be obtained from the child if:
  • source case is unknown
  • several possible source cases with different susceptibility patterns
  • if the likely source has drug resistant TB
  • extrapulmonary disease

• Childhood pulmonary disease
  • Inpatient early morning gastric aspirate x3 (cx + ~40%)
  • Induced sputum x 3 in cooperative older children-first morning best
  • Bronchoscopy: culture yield is lower than properly obtained gastric aspirate (cx + ~20%)
  • Newer testing modalities are not used for various reasons:
    • PCR sensitivity only slightly better than culture, specificity less, so not widely used in pediatrics
    • NAA and IGRAs not approved for use
• Extrapulmonary disease
  • Culture from affected body site (cx +~40%)
TB disease
Clinical and radiographic findings

- Pulmonary primary TB
  - Most common presenting symptoms:
    - cough, fever, wheeze, decreased appetite, and fatigue
  - 50% are asymptomatic
  - Usually not infectious
    - Lack cavities
    - Cough not strong enough to produce airborne bacilli

- Radiographic findings
  - Intrathoracic lymphadenopathy (hilar, mediastinal, subcarinal)
  - Parenchymal changes
    - Segmental hyperinflation and atelectasis due to bronchial obstruction
    - Alveolar consolidation
    - Interstitial densities
    - Bronchiectasis
13 yo asymptomatic, identified as part of contact investigation PPD 20mm

Chest CT: Multiple pulmonary nodules in the lung bases bilaterally, in the right lower lobe, one in the posterolateral right middle lobe and two in the left lower lobe. Also present is extensive adenopathy.
Primary Pulmonary
LLL infiltrate

TB disease
Clinical and radiographic findings

- Progressive pulmonary primary TB
  - Associated with weight loss or FTT, anorexia, fatigue, low grade temp, intermittent cough
  - May cause cavitation or endobronchial disease
### TB disease
#### Clinical and radiographic findings

- **Chronic pulmonary/ reactivation disease**
  - Most common in adolescents with primary infection after 7 years of age
  - Present with fever, weight loss, productive cough, hemoptysis, night sweats
  - Xray findings include cavitations, typically upper lobe

#### US data

<table>
<thead>
<tr>
<th></th>
<th>&lt;10 years of age</th>
<th>10-14 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavitary disease</td>
<td>3.5%</td>
<td>11.8% (p&lt;0.001)</td>
</tr>
<tr>
<td>Sputum smear positive</td>
<td>1.7%</td>
<td>10.3% (p&lt;0.001)</td>
</tr>
<tr>
<td>Sputum culture positive</td>
<td>4.2-5.0%</td>
<td>21.3% (p&lt;0.001)</td>
</tr>
</tbody>
</table>
TB disease
Clinical and radiographic findings

- Superficial lymphadenitis
  - Usually the anterior cervical and submandibular nodes
  - Usually presents within 6 months of infection
  - Affects children with median age 31-36 months
  - Nodes are firm, nontender or minimally so
  - No systemic symptoms
  - Chest radiographic findings may be present

- Pleural effusion
  - Most occur 3 months after primary infection
  - Usually affect older children (mean 13.5 years)
  - Present with fever, fatigue, respiratory distress, chest pain
  - CXR shows unilateral pleural effusion
    - Associated parenchymal abnormalities in about half of pts
  - Excellent prognosis
TB meningitis

SA, 8 month old East Indian girl
RUL pneumonia, possible abscess or Loculated pleural fluid

SA, 8 month old with pulmonary TB and TB meningitis.

Chest CT with RUL dense Consolidation with multiple Cavitations.

Superior mediastinum findings Consistent with abscess
Meningeal disease
- Most within 3-6 months of primary infection
- Often associated with miliary disease, esp in < 5 yr olds
- Median age affected 17-23 months
- Most severe form of disease

Meningeal disease
- Indolent with symptoms present 1-4 weeks before diagnosis
- Most common symptoms are fever, vomiting, lethargy, headache, seizure (esp in < 2 year olds)
- Hydrocephalus common on presentation
- Brain parenchymal disease (tuberculoma) in 20-37%
- CXR abnormal in 40-86%
TB disease
Clinical and radiographic findings

Meningeal disease
- Outcome depends on age and severity of symptoms at presentation
- Mortality <10% with effective therapy
- Long term sequelae are common
  - Mental retardation
  - Seizures
  - Hemiparesis

Miliary disease
- Similar to meningitis in pathogenesis, time of onset after infection, indolent presentation, and severity
- Median age affected is 6-11 months
- Often present with weeks of fever, cough, weight loss, anorexia, and malaise
TB disease
Clinical and radiographic findings

- **Miliary disease**
  - 50-70% have generalized lymphadenopathy and hepatosplenomegaly
  - 90% have diffuse micronodular pulmonary consolidations

YY 21 mo Hmong male
F/U CXR 3mos:
improving micronodular infiltrates and hilar fullness
TB disease
Clinical and radiographic findings

Bone/joint disease
- Onset 6-18 months after primary infection
- Median age of onset 6 years
- Affect vertebrae, knee, hip, and elbow most commonly
- Present with localized inflammation, pain, swelling, decreased range of motion, and fever
- Xrays may show spondylitis, arthritis, and osteomyelitis
- 50% will have abnormal CXR

LH 7 yo Hmong refugee
Pott’s disease spine MRI
Destruction and collapse of L3 and L4 along with inferior L2 and Superior L5.
Kyphosis and gibbus formation, mild Central stenosis
Pediatric TB disease
Treatment

- Well established adult regimens used (ATS/IDSA/CDC 2002)
- Emphasis on number of doses in given time period
- DOT DOT DOT DOT DOT DOT DOT DOT
- Empiric regimens require 4 drugs in initial phase in Minnesota

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary TB</td>
<td>6 mos</td>
</tr>
<tr>
<td>Isolated hilar adenopathy</td>
<td>6 mos INH+Rifampin</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td></td>
</tr>
<tr>
<td>TB adenitis</td>
<td>6 mos</td>
</tr>
<tr>
<td>Bone and joint TB</td>
<td>6-9 months</td>
</tr>
<tr>
<td>TB meningitis</td>
<td>12 months</td>
</tr>
<tr>
<td>Miliary/severe disseminated</td>
<td>9-12 months</td>
</tr>
</tbody>
</table>

Durations listed are for drug susceptible TB disease
Pediatric TB disease
Treatment

- First line drugs
  - INH
  - rifampin
  - pyrazinamide
  - ethambutol
  - streptomycin (im)
- Pills preferred over suspensions

<1% of children develop adverse effects (rash, N/V/D)
- Hypersensitivity reaction causing MP or morbiliform rash can occur and occasionally require D/C of INH

8% of 965 children: transient increase in LFTs (Palusci el al)
- 0.4% discontinued INH

Check LFTs and monitor in those with risk factors for hepatitis
Inhibits metabolism of some drugs resulting in increased levels (ie anticonvulsants)

Pediatric TB disease
Treatment

INH and peripheral neuropathy
- Caused by vitamin B6 deficiency
- Caused by increased excretion
- Manifests as tingling of fingers and toes
- Rare in children
- Predisposition in:
  - diabetes
  - uremia
  - milk/meat deficient diet
  - malnutrition
  - symptomatic HIV
  - ETOH use
  - pregnancy
  - breastfeeding

- Can result in orange discoloration of urine, tears, sweat
- Increases metabolism of many drugs (OCPs, HIV protease inhibitors and NNRTIs, corticosteroids, phenytoin)

- Adverse effects:
  - Rash, GI upset
  - Flu-like symptoms (intermittent therapy)
  - Hepatotoxicity
  - Severe immunologic reaction (rare)

### Adverse effects

- Fever
- GI upset
- Transient increase in uric acid
  - Hepatotoxicity rare
- Not recommended with underlying liver disease or INH induced hepatotoxicity


### Table 3. Pyrazinamide

<table>
<thead>
<tr>
<th>Child's weight</th>
<th>Daily pyrazinamide dose 20-40 mg/kg/dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>kg</td>
<td>mg/kg/day</td>
</tr>
<tr>
<td>5.0-6.25</td>
<td>120 mg</td>
</tr>
<tr>
<td>6.26-8.25</td>
<td>14-27 mg</td>
</tr>
<tr>
<td>8.26-12.5</td>
<td>27-44 mg</td>
</tr>
<tr>
<td>12.5-20</td>
<td>46-58 mg</td>
</tr>
<tr>
<td>20-27</td>
<td>59-77 mg</td>
</tr>
<tr>
<td>27-30</td>
<td>77-101 mg</td>
</tr>
<tr>
<td>30-35</td>
<td>102-139 mg</td>
</tr>
<tr>
<td>35-40</td>
<td>118-156 mg</td>
</tr>
<tr>
<td>40-45</td>
<td>1750 mg</td>
</tr>
<tr>
<td>45-54</td>
<td>2000 mg</td>
</tr>
</tbody>
</table>

Note: Doses above children on lean body weight.

Maximum daily pyrazinamide dose is 2 grams.

### Table 4. Ethambutol

<table>
<thead>
<tr>
<th>Child's weight</th>
<th>Daily ethambutol dose 15-20 mg/kg/dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>kg</td>
<td>mg/kg/day</td>
</tr>
<tr>
<td>4-6</td>
<td>100 mg</td>
</tr>
<tr>
<td>6-8</td>
<td>150 mg</td>
</tr>
<tr>
<td>8-12.5</td>
<td>200 mg</td>
</tr>
<tr>
<td>12.5-17.5</td>
<td>300 mg</td>
</tr>
<tr>
<td>17.6-22.5</td>
<td>400 mg</td>
</tr>
<tr>
<td>22.5-27.5</td>
<td>600 mg</td>
</tr>
<tr>
<td>27.5-32.5</td>
<td>800 mg</td>
</tr>
<tr>
<td>32.5-37.5</td>
<td>1200 mg</td>
</tr>
</tbody>
</table>

Note: Doses above children on lean body weight.

Maximum daily ethambutol dose is 2.5 grams.

- **Adverse effects**
  - GI, hypersensitivity, and visual
  - Retrobulbar neuritis
    - Reversible in most
    - Dose and renal function dependent
    - Manifests as decreased visual acuity or red-green color discrimination
    - Two reviews on use in children did not find evidence for visual toxicity
    - Monitor monthly

Medication delivery

- Expect resistance!
- Prepare the family for the challenge!
- Give medications all at once and at same time each day
- Incent the child
  - Rewards
  - Praise
  - Choices

INH
- Commercial suspension in sorbitol
- High osmotic load can cause GI upset and diarrhea
- Poorly tolerated in older children
- Other meds can be compounded into suspensions
- Recommend pill/capsules over suspensions
Medication delivery

- Pill and capsules taken intact or halves is easiest
- Tip head back to swallow pills, forward for capsules
- Place crushed tabs in empty capsule if capsules are easier
- Crushed pills can be given in soft food or liquid

Soft vehicle ideas
- Chocolate sauce, pudding, fudge sauce, ice cream
- Jelly or marmalade (texture can hide granularity)
- Apple sauce or berry sauce (can hide red rifampin color)
- Nutella or peanut butter
- Cream cheese or chili
- Oreo cookie cream
Case presentation

#1

- 20 mo old Somali refugee with 8 mo hx of fever, cough, chronic otitis media, constitutional symptoms
  - +PPD
  - Chest imaging with miliary opacities and extensive mediastinal and hilar adenopathy
  - CNS tuberculomas
  - Splenomegaly, retroperitoneal, and peri-portal adenopathy
  - Mildly increased aminotransferases and inflammatory markers

JO 20 months, Somali
Refugee from Kenya 2 m prior
8 m hx cough, fever, Poor appetite
No interest in play
11-15-06
Case presentation
#1

- Gastric washings X3
  - 1/3 + MTB pansensitive
- Induced sputum X3 all neg
- Left ear drainage cx +MTB
- Blood culture neg
- Urine culture neg

Case presentation
#1

- Started therapy
  - INH
  - Rifampin
  - PZA
  - EMB
  - B6
  - Steroids
  - Ranitidine
  - Dilantin
- NG feeds
Case presentation #1

- Rapid improvement in symptoms
  - Defervesced
  - More interactive and playful
  - Improved appetite
- Discharged home on directly observed therapy on hospital day 11
- Follow up CT one month after start of therapy

IMPRESSION: 12-27-06
1. Improved findings of miliary tuberculosis compared to 11-17-06.
2. Mild cylindrical bronchiectasis right upper and middle lobes.
3. Very slight improvement in extensive necrotic mediastinal and right hilar lymphadenopathy.
4. Improved aeration right upper lobe
Case presentation

#1

- Follow up chest CT: improvement in all findings except mediastinal and hilar adenopathy
- Head CT: marked improvement in tuberculomas
- Pt had been seen in clinic prior with verification that all meds were being given, TB meds by TB clinic staff, others by mom

On repeat questioning steroids were not being given, and had not been given after the pt was discharged from the hospital

Steroids are an important part of treatment in miliary disease
- Reduce adenopathy and potential for further airway compression and late pulmonary complications such as
  - collapse-consolidation
  - Bronchial erosion and endobronchial disease
- Reduce risk of broncho- or tracheo- esophageal fisutula
- Reduce CNS inflammation
Case presentation #1

- Steroids were started again, with one dose by DOT and the other verified each day
- Treatment for 4 weeks with 3 week taper
- Prolonged rx and taper reduce risk of rebound
- Pt did well thereafter

Pt had 6 sibs: 4 yrs-12 yrs
- 5/6 with +PPD
- 4/5 with pulmonary disease
- 1/4 had normal CXR on initial screen and presented 2 ½ weeks later with unilateral pleural effusion, not responsive to antibacterial therapy
- 1/6 –PPD and CXR (4 yr old), remains PPD neg
WO, 5 yo PPD +, CXR L hilar fullness, retrocardiac LLL infiltrate, medial RUL infil vs atelectasis; GW 1/3 + MTB; induced sputum + MTB pansensitive

IO, 11 yo Somali refugee
PPD 18 mm
11/18/06 CXR normal

12/10/06 admit with chest pain, fever
CXR unilateral effusion
IO
Chest CT on admit with unilateral pleural effusion

Persistent fever and rising CRP on parenteral antibiotics, BC neg, pleural fluid cx neg

CXR 3 months after starting antimycobacterial meds

LO 6 yo Somali refugee
PPD 16 mm, poor appetite

11/18/06 CXR bilat hilar prominence L>R
Interstitial prominence
Medial RUL infiltrate
Case Presentation

#2

Chest 2 view PA and Lat

FINDINGS: Normal cardiothymic silhouette. There is diffuse reticulonodular density of the lungs suspicious for possible disseminated miliary tuberculosis in patient with positive skin test. No focal air space opacity or effusion. Hilar shadows are mildly prominent and hilar adenopathy is not excluded.

IMPRESSION: Suspicious for disseminated miliary TB.

Miliary TB

Chest 2 view PA and Lat

FINDINGS: Normal cardiothymic silhouette. There is diffuse reticulonodular density of the lungs suspicious for possible disseminated miliary tuberculosis in patient with positive skin test. No focal air space opacity or effusion. Hilar shadows are mildly prominent and hilar adenopathy is not excluded.

IMPRESSION: Suspicious for disseminated miliary TB.
TCS 12 mo miliary TB
Pansensitive
Endobronchial lesion with collapse-consolidation 4 mos into therapy
Initial steroid therapy non-compliance

Neck CT showing large necrotic left cervical nodes
4 months into DOT therapy
Immune reconstitution phenomenon in 14 month old HIV negative with miliary TB
Case Presentation

#3

N.L., 15 mo Indian female FUO
presenting chest x-ray

TB disease

Left hilar fullness
Gastric washing cx
INH resistant MTB
TB disease

N.L. FUO Chest CT

Pulmonary TB

Necrotic perihilar adenopathy and peripheral nodular infiltrate