9 month old with stridor, cough, low-grade fever, mild hypoxia
3 months of age – CXR normal
Scenarios:

- Pregnant woman with + PPD
  - Next steps?
  - CXR negative, asymptomatic: treat for LTBI after delivery (INH x 9 mos). May wish to confirm with T-Spot (IGRA)
Tuberculosis

Stephen J Swanson, MD
HCMC Dept of Pediatrics
2013
6 year returning traveler with mild cough (Ethiopia x 3 mos)
6 year returning traveler with mild cough
PPD+ 18mm
MYCOBACTERIOLOGY

- Non-motile, nonspore-forming, weakly Gram-positive rods; often appear bent or beaded
- Obligate aerobes
- MTB vs NTM, *M. uclerans*, *M. leprae*
Nontuberculous Mycobacteria

- Termed: Mycobacterium other than tuberculosis (MOTT), Atypical mycobacterium, Environmental mycobacterium
- No evidence for person-to-person transmission
- Environmental sources: soil, water, dust, animals
- MAI, M. fortuitum, M. kansasii, M. scrofulaceum, M. marinum
NTM - II

- Most common sites: adults – lungs, children – lymph nodes, skin
- Granulomas often absent, AFB stains usually negative
- Reaction to PPD variable, usually < 10mm, wanes after months
Appearance over weeks to months...
Tuberculosis Epidemiology

- 1/3 of world’s population infected (~2 billion)

- WHO estimate – worldwide:
  - ~10 million annual new cases
  - 1.3 – 3 million annual deaths from TB

- Poor countries bear most of global TB burden (majority TB cases in Asia/Africa)

- ~15% of TB cases = HIV+
Worldwide Burden of Pediatric TB

- Incidence ???
- Prevalence ???
- Death Rate ???
- Rate of Infection ???
- ~ 11% of TB disease occurs in children < 15y, with 400,000 annual pediatric TB deaths
Challenges of *M. tuberculosis* Diagnosis

- Slow growing mycobacteria
  - Replicates every 12-24 hours
  - Delay in culture results
  - AFB smears not specific for MTB (suggestive)

- Requires specialized media & labs for growth

- TB drug susceptibility testing (not available overseas)

- Pulmonary TB may be AFB smear and culture negative (USA = 10-15% of PTB)

- Chronic respiratory conditions common overseas
Treatment Challenges with MTB

- Combination Therapy Required
- Prolonged Treatment
- 2\textsuperscript{nd} line TB drugs
  - Expensive
  - Poorly tolerated
  - Less effective
Transitions in Tuberculosis

Susceptible
Exposed
Infected
Diseased
Sick
Diagnosed
Treated
Cured
Stages of Tuberculosis

Exposure

- Defined by contact investigation – recent (< 3 months) contact with infectious case
- Negative ST, physical exam, CXR
- Period during which skin test may be negative in infected person
- Children < 5 years old usually treated because disease may develop rapidly
- Older children, adults often not treat, but repeat skin test after exposure over
Stages of Tuberculosis

Infection

- Hallmark is “positive” PPD
- “Germs in the body”
- CXR is often normal
- No symptoms, physical exam normal
- Anyone with infection should be treated when risk of dz outweighs adverse reaction to medication
Stages of Tuberculosis

Disease

- Clinical and/or radiographic manifestations
- Primary: complication of initial infection
- Reactivation (Postprimary): disease after period of dormancy
- TST negative in 10 – 20% of all disease cases (50% of miliary or meningeal diseases)
Pathogenesis of Tuberculosis

- Lungs are portal of entry in > 95% of cases
- Organisms in droplet land in alveoli
- Infectious dose is unknown
- Organisms are ingested by non-sensitized macrophages; intracellular replication occurs
- Organisms travel to regional lymph nodes via cells; lympho-hematogenous dissemination occurs
- CMI and delayed-type hypersensitivity generally develop in 4–12 weeks; if effective, replication is halted and infection remains subclinical
Lymphogenic spread of TB from Primary Pulmonary Focus (LUL)
Age-specific Risk for TB Disease Development following Primary Infection

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Risk of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>Pulmonary* 30 – 40%, TBM or miliary 10–20%</td>
</tr>
<tr>
<td>1 – 2</td>
<td>Pulmonary* 10 – 20%, TBM or miliary 2 – 5 %</td>
</tr>
<tr>
<td>2 – 5</td>
<td>Pulmonary* 5%, TBM or miliary 0.5 %</td>
</tr>
<tr>
<td>5 – 10</td>
<td>Pulmonary*† 2%, TBM or miliary &lt; 0.5 %</td>
</tr>
<tr>
<td>10 – 15</td>
<td>Pulmonary 10 – 20%, TBM or miliary &lt; 0.5%</td>
</tr>
</tbody>
</table>

*Ghon focus and/or lymph node  †pleural effusion or adult type  
TBM, tuberculous meningitis

Adapted from Marais BJ, Gie RP, Schaaf HS. et al. The natural history of childhood intra-thoracic TB – a critical review of the literature from the pre-chemotherapy era. Int J Tuberc Lung Dis 2004;8:392-402
Skin – Testing, Infection, and Disease

- TST takes 3 weeks to 3 months to turn positive after infection

- Risk of disease after untreated infection
  - Normal adults: 5 – 10 % in lifetime; (half of risk in first 2 – 3 years)
  - HIV – infected adults: 5 – 10% per year
  - Infants: 40-50% in initial 1 – 2 years
  - Older children (5 – 15 years): 2 – 10%
TST (PPD)

- False Negative?
- False Positive
TST (PPD)

**False Negative?**
- Window Period
- Extremes of age (neonate, elderly)
- Steroids
- Co-occurring viral infections (i.e., influenza)
- Recent live vaccines
- HIV
- Malnourished
- Extrapulmonary/miliary TB
- Improper Technique
- Inexperienced reader
- Reader Bias
- And for no explanation!

**False Positive**
- BCG
- Environmental NTB
- Allergic reaction to components (peaks at 24 – 48h)
Induration Size = Positive TST

- **≥ 5 mm**
  - HIV coinfection
  - Immune compromise
  - Recent contact to infectious TB case
  - Abnormal CXR, suspected dz

- **≥ 10 mm**
  - Foreign borne, high-risk country
  - Drug user
  - HR congregate setting
  - Children < 4 years

**No risk factors: ≥ 15mm**
BCG Vaccines

- Negligible effect on TB epidemiology
  - Does not prevent infection
  - Little effect on reactivation disease
- Major use is to prevent life-threatening forms of TB in infants and children
- Most studies, 80-90% of PPD reactivity lost within 5 years after newborn BCG vaccination
Interferon-\(\gamma\)Release Assays

- Detects IFN-\(\gamma\) after lymphocyte stimulation with MTB proteins
- More specific than TST, equal sensitivity
  - Not influenced by NTM, BCG
- Lower IGRA sensitivity in immunocompromised
- May be more sensitive in recent infection
- Not well studied in young kids (< 4 years)
- Preferred test in older kids, refugees/immigrants
Clinical and Radiographic Manifestations of Childhood Pulmonary TB

- Paucity of signs and symptoms relative to CXR findings
  - In U.S., up to 50% children with pulmonary TB have few or no symptoms

- Infants more symptomatic: fever, cough, focal wheezing, respiratory distress

- Predominance of hilar and/or mediastinal adenopathy (not always seen on plain film)

- Any lobe of lung involved; 25% multilobar

- Local pleural reaction/effusion is common

- Collapse – consolidation or segmental pattern most common

- Obstructive signs/symptoms with endobronchial lesions

- Not contagious
8-month-old girl with obstructive hyperaeration of the right lower lobe, large hilar nodes compressing RLL bronchi

TB should be considered in patients with hyperaeration of unknown etiology
9 month old
2 months later – on 4 drug therapy
RUL pulmonary TB,
Subcarinal node, bronchial obstruction
Fever and Cough in 12 year old
Widened mediastinum

Hilar adenopathy

Compression of L mainstem bronchus
Aorticopulmonary Node
Subcarinal Node
L Mainstem compression
RML Syndrome
RML Syndrome - TB
14 yo with PTB: 2 findings
Right pleural effusion and R pulmonary bleb
1 year old with pulmonary TB
Pulmonary TB
School age boy CXR
Cambodian 4 year old
When to suspect TB in kids

- CXR much worse than clinical picture
- Wheeze, cough not responsive to albuterol
- Failure to thrive, reduced playfulness
  - Don’t expect fevers, night-time sweats, significant cough, upper lobe (reactivated) disease, or +PPD in pediatric TB cases
Diagnosis of TB in children

- Clinical/epi: gold standard
- AFB stains: positive < 10% of cases
- AFB culture: 3 early a.m. gastric aspirates
  - All children: 20 – 40% of cases
  - Infants: up to 75% of cases
  - CSF, pleural fluid: ~25% of cases
- PCR: ? Sensitivity, specificity 80-90%
Diagnosis of TB adults

- Proper sputum collections
  - Best collected in early AM
  - $2^{nd}$ sputum smear increases AFB smear yield by 13%
  - $3^{rd}$ sputum smear – 4%
  - At least 2 quality sputum samples recommended (3 in settings where TB culture not readily available)
Complications of Primary Childhood Pulmonary TB

- Progressive local disease – cavitation
- Obstructive emphysema
- Pericardial or esophageal perforation from subcarinal nodes
- Sudden death – asphyxia, bleed
- Bronchiectasis
- Calcification – takes at least 6 months
TB Pleural Effusion in Pediatrics

- Primarily adolescents
  - uncommon before age 5, rare before age 2
- Usually unilateral, can be bilateral
- Rare in miliary disease
- Usually abrupt onset: fever, chest pain, SOB
- Thoracentesis: several hundred WBCs, high protein, glucose < 39, AFB negative, culture positive 30-60%
5-year-old boy with massive left pleural effusion caused by tuberculosis.

B: Patient 6 years later with a normal chest film and no physical complaint
Extrapulmonary Tuberculosis
Extrapulmonary disease by site in adults and children

Extrapulmonary cases in adults

- Miliary: 9%
- GU: 16%
- Bone/Joint: 10%
- Other: 13%
- Meningeal: 4%
- Lymphatic: 25%

Extrapulmonary cases in children <15 years of age

- Meningeal: 13%
- Miliary: 5%
- Other: 5%
- Bone/Joint: 4%
- Pleural: 6%
- Lymphatic: 67%
Miliary (Disseminated) TB in childhood

- Early complication of primary infection
- 1-2 mm opacities, aggregates of macrophages, lymphs w/ necrosis
- Most common in infants, recent after infection
- Protean manifestations – FUO common, rapid breathing, wt loss
- Insidious or explosive presentation
- CXR usually normal initially, then classic. LUNGS CTA!
- TST negative 50%
- Other findings: HSM, LAD, cutaneous
- Dx: gastric aspirate, bronchoscopy, bone marrow, urine cx
Miliary TB = extrapulmonary TB!
Miliary TB:
1-2 mm rounded opacities throughout all
Miliary TB
Miliary TB
Miliary TB – Up close
Multiple Bullae, Pleural Thickening
Lymphadenitis Caused by MTB

- Most often unilateral; may be bilateral
- CXR usually normal
- Usually indolent onset of enlarged, fixed, matted nodes in anterior chains, submandibular
- Submental, occipital, axillary, supraclavicular nodes less often
- Absence of systemic findings, minimal tenderness
- Often progress, “break down” with sinus tracts
- Major Ddx: NTM, malignancy
Weeks to months...
# NTM vs TB Lymphadenitis

<table>
<thead>
<tr>
<th></th>
<th>NTM</th>
<th>TB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age:</strong></td>
<td>1 – 5</td>
<td>any</td>
</tr>
<tr>
<td><strong>Residence:</strong></td>
<td>rural</td>
<td>urban</td>
</tr>
<tr>
<td><strong>TB risk factors:</strong></td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td><strong>CXR:</strong></td>
<td>negative</td>
<td>10% positive</td>
</tr>
<tr>
<td><strong>TST (mm)</strong></td>
<td>0 – 15mm</td>
<td>&gt;10 – 15mm</td>
</tr>
</tbody>
</table>

**NEVER** do incision & drainage

**Surgical excision diagnostic & curative for NTM**
(if complete excision)
7 year old male with a 2-month history of increasing lumbar pain and 5 day history of difficulty walking, vomiting, and progressive somnolence.
Pott’s Disease
Skeletal TB

- Lymphohematogenous spread or direct extension from paravertebral node
- WBC normal
- Skeletal TB: young > old children (intense blood flow)
  - Adults: 6mos – 3 years after primary TB
- Vertebrae (~50%) > knee > hip
- S/sxs: “night cries”, restless sleep, gait changes, low-grade fever, gibbus deformity, reflex changes, clonus
L3 – L5
76 yo presenting with abdominal TB presenting as GI bleed. Miliary TB.
76 yo - Miliary
Miliary – 76 yo
44yo – 20 kg wt loss. HIV-negative
Erythema Induratum
Primary Cutaneous TB
TB verucosa
cutis
Treatment of TB Disease in Children

- **Pulmonary**
  - INH, RIF x 6 mos + PZA for first 2 mos
  - Add ETH initially if risk of INH resistance
  - DOT
  - INH – resistant: RIF + PZA+ETH for 9 mos
  - MDR – depends on susceptibility; at least 18mos

- **CNS, Disseminated**
  - Usually start with 4 drugs
  - Usual length 9 – 12 months
  - Once daily initially, may use twice weekly later

- Steroids: meningitis, endobronchial, miliary with alveolar block, pericardial with construction, vertebral with spinal root involvement
Practical Aspects of TB Management

- Pregnancy: INH, Rif, EMB. PZA avoided.
- DOT from beginning!
- 1st line drugs administered together
  - Do not “split dosing” – lower efficacy
- GI upset common early in treatment (r/o hepatitis). Administer with food rather than split dosing.
- Asymptomatic ALT increase (<3x normal) okay with INH/RIF
- Never add single drug to failing regimen.
- Pyridoxine (B6) supplementation to prevent INH-associated peripheral sensorimotor neuropathy
  - (small children, malnourished, pregnant, alcoholics, diabetes, renal dz)
Scenarios:

- 2 month infant, mother has active pulmonary TB. Infant is breastfed... next steps?

Contagious vs noncontagious diseases?
- Hilar adenopathy only?
- Smear positive? Any treatment?
- Household members?

Infant: examine carefully
- TST/CXR at 3 mos & possibly 6 mos time
- ALWAYS start INH x 3 mos [window period]
- If TST, CXR, exam all normal at 3 mos, can stop INH
- Continues breastfeeding?
Mom has active disease, suspected contagious

- Contact-household tracing

- Mother – infant separated until mother confirmed non-contagious (~2 weeks of tx, smear neg)

- Infant careful physical exam

- Started on INH (high risk of disseminated TB)

- TST/CXR 3 mos and possibly 6 mos

- INH stopped at 3 months of well
Congenital TB