TB DISEASE IN CHILDREN AND PREGNANT WOMEN

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Objectives

- Discuss the unique aspects of TB disease in children
- Highlight the clinical presentation and laboratory findings
- Review the diagnosis and treatment of TB disease in children and pregnant women
- Go over the new short-course therapies for tuberculosis in children

Disclosure: I have no conflicts of interest
RISK OF DISEASE WITH NO TREATMENT
BY AGE INFECTED OR MEDICAL CONDITION

- Birth-12 months: 50%
- 1-3 years: 24%
- 4-11 years: 5%
- 12-18 years: 15%
- Healthy Adults: 7%
- Diabetes: 30%
- HIV Infected: 50%
## Risk of Progression to TB Disease by Age

<table>
<thead>
<tr>
<th>Age @ primary infection</th>
<th>Risk of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth-12months</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>50%</td>
</tr>
<tr>
<td>Pulmonary Dis</td>
<td>30-40%</td>
</tr>
<tr>
<td>Miliary or TBM</td>
<td>10-20%</td>
</tr>
<tr>
<td>1-2 years</td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>20-25%</td>
</tr>
<tr>
<td>Pulmonary Dis</td>
<td>75%</td>
</tr>
<tr>
<td>Miliary or TBM</td>
<td>2-5%</td>
</tr>
</tbody>
</table>

Marais BJ. Int J Tuberc Lung Dis 2004;8:392-402
FIGURE 101-5 The timetable of tuberculosis.
TB Disease

Adult TB Disease

- Pulmonary: 85%
- Extrapulmonary: 15%

Pediatric TB Disease

- Pulmonary: 75%
- Extrapulmonary: 25%

Source: U.S. Cases CDC
TB Extrapulmonary Disease

Adult Extrapulmonary Disease 15%
- Lymphatic 25%
- Pleural 23%
- GU 16%
- Bone/Joint 10%
- Meningeal 4%
- Miliary 9%
- Other 13%

Pedi Extrapulmonary Disease 25%
- Lymphatic 65%
- Pleural 6%
- Meningeal 14%
- GU 16%
- Bone/Joint 5%
- Miliary 5%
- Other 5%

Source: U.S. Cases CDC
**Reactivation Disease**

- Occurs *years* after primary infection
- Typical of adult disease
- Also seen in teens
- Often cavitary disease
- High numbers of organisms (AFB +)
- Usually symptomatic and contagious
PRIMARY TB DISEASE

- Typical of childhood TB
- May be seen in adults
- Usually not cavitary

- Classic x-ray:
  - Hilar lymphadenopathy
  - Infiltrates or
  - Miliary pattern

- Low numbers of organisms
  - AFB smears negative in 95%
  - Cultures negative in 60%

- Most children <10 years are not contagious
- Half asymptomatic (50%)
COMMON SYMPTOMS OF TB DISEASE IN CHILDREN

- Cough and/or other respiratory symptoms
- Wheezing, crackles or decreased breath sounds on lung examination
- Lymphadenopathy / lymphadenitis
- Persistent fever (FUO)
- Weight loss or failure to thrive
- Signs and symptoms of meningitis
  - Headache, vomiting, irritability, lethargy or seizures
- Unlike adults, half of children with TB disease have no symptoms
Diagnosis of TB in Children

- **Gold Standard** –
  
  Positive TB Culture, OR

**Clinical Diagnosis** (most common):

- Abnormal CXR or laboratory or physical examination consistent with TB **AND**

1 or more of the following:

- Positive tuberculin skin test or IGRA
- Contagious adult contact identified
- Clinical course consistent with TB disease
- Improvement on TB therapy
International Panel
Case Definition of
TB in Children

Diagnostic Triad
Pediatric TB Disease

❖ Positive TB skin test or IGRA
❖ Abnormal CXR
❖ Infectious contact
Radiographic Findings in Pediatric TB Disease

**Classic in TB disease**
- Hilar and interthoracic lymphadenopathy
- Miliary pattern
- Apical cavitary lesions in adults and teens
- Basilar meningitis

**Not specific but seen in TB**
- Lobar pneumonia in any lobe
- Pleural effusion more common in teens and adults
Hilar Lymphadenopathy

Hallmark of Pediatric TB Disease
Six week old with respiratory failure
Miliary Tuberculosis
Peripheral Lymphadenopathy

Central hypodensity
Peripheral enhancement on contrast CT
Cavitary Disease

- Common in adults and teens
- Occasionally in infants with severe TB disease
Source of Infection

- Contact Investigation may support diagnosis and guide treatment of a child with negative cultures

- Source: Adult or teen with contagious TB
  - Usually symptomatic with cough
  - AFB smear positive pulmonary TB
  - NAAT, Xpert, cultures and susceptibilities
    - Should help guide treatment of pediatric contacts
PERIPHERAL LYMPHADENOPATHY

- Physical exam, carefully check for:
  - Cervical, supraclavicular, axillary and inguinal nodes
- TB disease of lymph nodes usually measure > 1 cm
- Diagnosis: Fine needle aspirate or excisional biopsy for pathology and culture recommended
- May progress to necrosis, caseation or chronic drainage
- Node may become more inflamed with TB treatment
TEEN WITH NECK MASS

- 15-year-old African American boy with 5 week history of:
  - Neck mass
  - Fever, 20 lb weight loss
  - No foreign travel or known TB exposure

- Physical
  - 100 kg, football player
  - 5 cm cervical lymphadenopathy
  - Lungs clear

- PPD negative, 0 mm
- CXR normal
NECK CT

Lymphadenopathy
**Teen Case of Lymphadenopathy**

- **Differential diagnosis**
  - Lymphoma, leukemia
  - HIV, EBV, Cat scratch disease
  - Tuberculosis
  - Mycobacterium avium (MAC) or other NTM

- **Laboratory**
  - CBC with peripheral smear - negative
  - HIV – negative
  - Node biopsy:
    - Negative for cancer
    - AFB smear negative
    - Granulomas seen on path
    - TB culture positive at 5 weeks for MTB
    - Susceptible to all drugs
  - Quantiferon (IGRA) positive at 5 days

- **All symptoms resolved on RIPE therapy**
Collecting Specimens from Children
Gastric Aspirates

- Usually inpatient but can be collected outpatient
- Overnight fasting
- Lavage with normal saline
- Collected in morning x 3 days
- AFB smear yield: minimal <5%
- TB Culture yield: 40% average (20-50% range)

 Protocol: Curry International TB Center
**Induced Sputum**

- Outpatient procedure
- 2-3h fasting period
- Pretreatment:
  - Nebulized bronchodilator and hypertonic saline
  - Chest physiotherapy (CPT)
- Nasopharynx suctioned
- One specimen sufficient
- Culture yield 40%
- May be successful in children 3 years and over

Lancet. 2005;365:130
TB Cultures from Children

- Bronchoalveolar lavage (BAL) or induced sputum
  - Single specimen with similar yield to 3 GA’s
- Lymph nodes
  - Biopsy or FNA for path and culture
  - Sensitivity 30-70% yield on culture
- For TB meningitis
  - LP recommended for ≤ 12 months with TB disease
  - Sensitivity 20% average (12-50% range)
  - High volume (>6 ml) CSF sample improves culture yield but still low
- Bottom Line
  - Negative AFB smear, NAAT or culture does not rule out disease
- Culture and sensitivities from adult may guide treatment for child
Molecular Tests including Nucleic Acid Amplification Tests NAAT

- **Gen-Probe, Xpert MTB/RIF and Xpert Ultra**
  - Highly specific, rapid results, Xpert detects rifampin resistance
  - Not FDA approved in U.S. for smear negative samples

- **Adults with AFB smear negative, culture positive pulmonary disease**
  - Xpert on sputum samples: Sensitivity 66-79% Specificity 99%

- **Cochrane Review of Xpert & Xpert Ultra in Children with culture positive TB**
  - Sputum samples: Sensitivity 65-73% Specificity 98-99%
  - Pulmonary TB: Gastric Aspirates > Sputum > Stool > Nasopharyngeal (lowest)
  - Lymph node TB: Sensitivity 90% Specificity 90%
  - TB Meningitis CSF: Sensitivity 54% Specificity 94%

**Baby Exposed to TB Disease**

- 6 month old infant
- Mother with TB disease
- How do you determine the risk to the baby?

- Mother’s
- Chest x-ray
- AFB smears
- Treatment duration
- Contact with baby
BABY EXPOSED TO TB DISEASE

- Mother AFB positive
- Mom just starting treatment
- Mother’s CXR with severe cavitary disease
EVALUATION OF INFANT

- History, baby with
  - Cough and fever for 2 weeks
  - Seen at clinic and urgent care x 2
    - Diagnosed as viral illness

- Physical exam 2 weeks later
  - Alert infant with tachypnea and wheezing
  - Eye deviation and left sided weakness

- Laboratory and imaging
  - CXR
  - Lumbar puncture
  - Brain MRI
DIFFUSE MILIARY DISEASE
OUTCOME

Diagnosis:
- Miliary TB and TB meningitis
  - CSF: 27 WBC (80% L), 120 protein
- Brain MRI: multiple tuberculomas and stroke

Treatment:
- RIPE therapy x 12 months
- Prednisone x 2 months

Baby did well with normal exam and development after treatment
## TB vs Bacterial Meningitis

Table 2
Multivariate logistic regression analysis, at various levels of the predictor variables, for TBM cases

<table>
<thead>
<tr>
<th>Predictor variables</th>
<th>( P )</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of illness &gt; 5 days</td>
<td>0.000</td>
<td>6.1</td>
<td>2.5 – 14.8</td>
</tr>
<tr>
<td>WBC count &lt; 1000/mm(^3)</td>
<td>0.009</td>
<td>2.9</td>
<td>1.3 – 6.4</td>
</tr>
<tr>
<td>Lymphocytes &gt; 30%</td>
<td>0.000</td>
<td>10.1</td>
<td>4.5 – 22.6</td>
</tr>
<tr>
<td>Protein content &gt; 100 mg/dL</td>
<td>0.002</td>
<td>2.5</td>
<td>1.2 – 6.1</td>
</tr>
<tr>
<td>Headache</td>
<td>0.001</td>
<td>5.4</td>
<td>2.0 – 14.2</td>
</tr>
<tr>
<td>CSF appearance (clear)</td>
<td>0.002</td>
<td>2.4</td>
<td>1.2 – 5.9</td>
</tr>
</tbody>
</table>

CI = confidence interval.

TB MENINGITIS
TREATMENT AND CLINICAL COURSE

- Rule out TBM in children ≤ 12 months with TB disease and patients with miliary TB
- 9-12 months RIPE therapy
- Steroids for 6-8 weeks with 2-3 week taper
  - decreases CNS inflammation
- Symptoms initially worsen then gradually improve over 2-4 weeks
  - Fever common for first month
- Possible complications
  - Seizures
  - Hydrocephalus
  - SIADH
  - CNS tuberculoma, stroke, intellectual disabilities, CP
  - Mortality high (>90%) if not diagnosed and treated
TB Disease in Pregnant Women
POTENTIAL MODES OF INOCULATION AND PATHOGENESIS OF TUBERCULOSIS IN THE NEWBORN INFANT

FOCUS

POSTNATAL

Pneumonitis

PRENATAL

Placentitis

PERINATAL

Cervicitis or Vaginitis

MODE OF SPREAD

Airborne Inoculation

Hematogenous Spread

Aspiration of Infected Amniotic Fluid

OUTSIDE CONTACT

A. Nursery Personnel

B. Household or Family Contacts

Treatment for TB disease in Pregnant Women

• Women diagnosed or suspected of having TB disease
  – Should start TB treatment without delay

• All first line drugs are considered safe in pregnancy

• Treatment regimen
  – PZA or not?
  – If PZA is not included, treat for 9 months with Rifampin, INH and EMB

Source: Dr. Lisa Armitige HNTC
PZA in Pregnant Women

• The WHO and IUATLD recommend
  – Include PZA in the treatment of TB in pregnant women

• The CDC 2003 treatment guidelines
  – Did not recommend PZA in pregnancy
  – Due to lack of safety data

• Current (2016) CDC/IDSA/ATS treatment guidelines state
  – Evaluate risk/benefit of PZA
  – Benefits may outweigh risk
  – Women with HIV, extrapulmonary or severe disease should receive PZA in their treatment regimen
After-Delivery Concerns

• Should mother and infant be separated?
  – Yes if mother is suspected of having MDR-TB
  – But if mother is infectious but not MDR disease:
    • Start baby on INH or Rifampin window prophylaxis
    • Minimize exposure
      – Mother can wear a mask while holding the baby
      – Sleep in separate rooms until mother is no longer infectious

• Can mother breastfeed?
  – Yes
  – TB drugs cross the placenta and breast milk in low but safe levels
Take Home Points

• Treating a pregnant mother also protects her baby, her family and her community

• If a CXR is warranted, it should be performed

• Pregnant women can be safely treated for TB infection and TB disease

• PZA, though controversial, in most cases will add more benefit than harm to the treatment of pregnant women
Treatment of TB in Children
TREATMENT OPTIONS FOR PEDIATRIC TB DISEASE

- 6-9-month old standard RIPE therapy

NEWER
- 4-month RIP +/- E therapy for uncomplicated pediatric disease (SHINE study)
  - WHO endorsed
  - CDC expected to endorse

- 4-month Rifapentine, Moxifloxacin, INH and PZA
  - Adults and children ≥ 12 ys of age
  - For uncomplicated, mostly pulmonary TB, including cavitary disease
  - CDC and WHO endorsed
SHINE STUDY
4- vs 6-month treatment in children with TB disease

Criteria:
- Smear-negative disease in children < 16 years of age, symptomatic, nonsevere, drug-susceptible TB

Nonsevere TB defined as:
- No cavities, no miliary TB
- Pulm disease confined to 1 lobe, non-complex pleural effusions, no significant airway obstruction
- No drug resistant disease or drug resistant exposure

Randomized to 4 or 6 months first-line WHO fixed-dose regimens
- Daily, self administered, used check lists and pill counts with 94% adherence
- 95% study retention at 72 weeks

SHINE STUDY
4-MONTH TREATMENT IN CHILDREN

Population:
- 1204 children from Africa (88%) and India (12%)
- Median age 3.5 years (range 2 month – 15 years)
- 11% with HIV
- 14% were culture or Xpert confirmed, 86% clinical diagnosis
  - 67% pulmonary TB
  - 29% mixed resp/lymph node TB
  - 3% peripheral lymph-node TB

Outcome:
- Noninferiority of the shorter regimen with favorable outcome in 98% in 4-month and 97% in 6-month regimen
- Study Power 90%

Death from any cause: 7;12 patients
Tx failure requiring extension: 9;5
Recurrence of TB: 6;4

Pneumonia and/or Liver events 47;48 patients of 1204 total patients
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**Fixed-Dose Combinations for Children**

- **Intensive phase of TB treatment:**
  - Rifampicin 75 mg + Isoniazid 50 mg + Pyrazinamide 150mg

- **Continuation phase of TB treatment:**
  - Rifampicin 75mg + Isoniazid 50 mg

- Ethambutol should be added in the intensive phase for:
  - Children with extensive disease or in areas with high prevalence of HIV or isoniazid resistance

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<table>
<thead>
<tr>
<th>Weight</th>
<th>Intensive phase RHZ 75/50/150*</th>
<th>Continuation phase RH 75/50</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-7 kg</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>8-11 kg</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>12-15 kg</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>16-24 kg</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>≥25 kg</td>
<td>Adult dose recommended</td>
<td>Adult dose recommended</td>
</tr>
</tbody>
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TB Alliance [www.tballiance.org/children](http://www.tballiance.org/children)

4 MONTH REGIMEN FOR ADULTS AND CHILDREN ≥ 12-YRS

Rifapentine, Moxifloxacin, Isoniazid and Pyrazinamide daily
- Intensive phase daily 8 weeks of 4 drugs daily
- Continuation phase 9 weeks of daily RPT, MOX and INH
- Endorsed by WHO and CDC

Eligible
- Ages ≥ 12 years and weight ≥ 40 kg
- Drug susceptible pulmonary TB disease

NOT eligible
- < 12 years of age
- Pregnant women
- Most extrapulmonary TB
- Prolonged QT-syndrome
- History of partial TB treatment in preceding 6 months
- Drug resistant TB

MONITORING CHILDREN ON TB TREATMENT

- Risk of drug toxicity very low
- Monitor clinical signs
  - Regular clinical visits (4-6 wks)
  - Patient education
- Routine blood work not necessary unless
  - Signs or symptoms of toxicity
  - Risk factors for toxicity (obesity, other hepatotoxic medications)
- Follow up to monitor symptoms and reinforce adherence
- When to follow up x-rays
  - Pulmonary TB: beginning and end of therapy or anytime if clinical change
  - For TB meningitis: MRI at beginning, 1-2 mo into tx and at end
- Document completion of therapy
PEDIATRIC TB DISEASE SUMMARY

- Higher risk for
  - Progression to disease
    - Especially infants and children ≤ 2 years
  - Extrapulmonary and disseminated disease including TB meningitis
- Most common TB disease sites in children
  - Pulmonary and lymph nodes
- Symptoms may be subtle or absent in children

- Children ≤ 10 years
  - Have low bacterial load (paucibacillary disease)
  - Usually are not contagious
    - Unless cavitary or AFB smear positive disease
- AFB smears and TB cultures
  - Often negative in children
  - Clinical diagnosis most common
References

- Marais BJ. Int J Tuberc Lung Dis 2004;8:392-402
- Global TB Programme, WHO http://www.who.int/tb/areas-of-work/children/
- TB Alliance www.tballiance.org/children