Pediatric Tuberculosis: Pearls, Pitfalls and Progress

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Disclosures

- I have no relationships with commercial interests related to this presentation
- I will be discussing off-label use therapeutic agents
Pediatric TB: Overview

- Epidemiology
- Natural history
- Clinical presentation
- Evaluation
  - Screening, contact investigation
  - Latent TB infection (LTBI)
  - Evaluation for disease
- Evaluation of an infant born to a mother with TB
- Treatment
Pediatric Tuberculosis: Why Children Are Not Little Adults

- Natural history
  - Increased risk of progression to disease
  - Paucibacillary disease
- Clinical presentation
  - Nonspecific symptoms
- Diagnosis of LTBI/TB
  - Immune system- TST and IGRA less reliable
  - Sputum collection difficult
  - Paucibacillary disease- microbiological confirmation difficult
- Treatment of LTBI/TB
  - Recommendations based on adult treatment trials
Tuberculosis in the United States

- ~ 11,000 cases/year
- ~ 5% of cases in children < 15 years of age
- ~ 10-15 million cases of LTBI

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th>US Born, No. (%)</th>
<th>Foreign Born, No. (%)</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Male)</td>
<td>(Female)</td>
<td>(Male)</td>
</tr>
<tr>
<td><strong>Children and Adolescents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6435 (50)</td>
<td>2947 (51)</td>
<td>81 189 (67)</td>
</tr>
<tr>
<td>Median age, y</td>
<td>3</td>
<td>11</td>
<td>50</td>
</tr>
<tr>
<td><strong>Hispanic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>4952 (39)</td>
<td>2 664 (46)</td>
<td>14 355 (12)</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>1 491 (12)</td>
<td>377 (6)</td>
<td>45 600 (37)</td>
</tr>
<tr>
<td>Non-Hispanic Black or African American</td>
<td>4865 (38)</td>
<td>1 211 (21)</td>
<td>56 195 (46)</td>
</tr>
<tr>
<td>Non-Hispanic American Indian or Native Alaskan</td>
<td>300 (2)</td>
<td>3 (&lt;1)</td>
<td>2 751 (2)</td>
</tr>
<tr>
<td>Non-Hispanic Asian or Pacific Islander</td>
<td>1 049 (8)</td>
<td>1 494 (26)</td>
<td>2 321 (2)</td>
</tr>
</tbody>
</table>

Am J Public Health 2010; 100: 1724-1729
FIGURE 1—Tuberculosis cases among foreign-born persons who were younger than 18 years at time of US entry, by age at US arrival and number of years in the United States prior to TB diagnosis: 1994-2007.
Pearls and Pitfalls: Epidemiology

- TB or LTBI in a child is a sentinel event representing ongoing transmission of TB within a community.
- Children at risk include the foreign-born and those with foreign-born guardians.
Natural History of Pediatric TB

- Exposure → Infection → Disease
  - Disease usually a rapidly evolving complication of the primary infection as opposed to reactivation type disease in adults

- Incubation period for disease may be 6-8 weeks, before delayed type hypersensitivity (DTH) develops

- Timely identification of children exposed to TB is critical in preventing disease
## Risk of Disease Following Primary Infection

<table>
<thead>
<tr>
<th>Age</th>
<th>Disseminated TB/TB meningitis</th>
<th>Pulmonary TB</th>
<th>No Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>10-20%</td>
<td>30-40%</td>
<td>50%</td>
</tr>
<tr>
<td>1-2 years</td>
<td>2-5 %</td>
<td>10-20%</td>
<td>75-80%</td>
</tr>
<tr>
<td>2-5 years</td>
<td>0-5%</td>
<td>5%</td>
<td>95%</td>
</tr>
<tr>
<td>5-10 years</td>
<td>&lt; 0-5%</td>
<td>2%</td>
<td>98%</td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>&lt; 0-5%</td>
<td>10-20%</td>
<td>80-90%</td>
</tr>
</tbody>
</table>

Lancet Infect Dis 2008; 8: 498-510
Pearls: Pediatric versus Adult TB

- Rate of progression to disease is faster
  - Disease may be a rapid consequence of infection

- Risk of progression to disease is higher
  - Adults: 5-15%
  - Children 1-5 y: 25-30%
  - Infants <1 y: 40%

- Severe disease is more common
  - Adults: 15% extrapulmonary
  - Children: 25% extrapulmonary
Clinical Presentation of Pediatric TB

- Pulmonary TB
  - Typically asymptomatic
  - Most cases identified by contact investigation

- Extrapulmonary
  - Lymphatic, meningitis, miliary, osteomyelitis
  - Typically symptomatic
### Presentation of Childhood Tuberculosis

<table>
<thead>
<tr>
<th></th>
<th>Cases 1984-87</th>
<th>Cases 1985-92</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. cases</td>
<td>110</td>
<td>47</td>
</tr>
<tr>
<td>Median age</td>
<td>24 mo</td>
<td>8 mo</td>
</tr>
<tr>
<td>Initial visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>48 (44%)</td>
<td>37 (79%)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>62 (56%)</td>
<td>10 (21%)</td>
</tr>
<tr>
<td>Asymptomatic-Referral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contact investigation</td>
<td>55 (89%)</td>
<td>9 (90%)</td>
</tr>
<tr>
<td>Screening</td>
<td>7 (11%)</td>
<td>1 (10%)</td>
</tr>
</tbody>
</table>
Pulmonary TB in Children

- The majority of children have no or few signs or symptoms of disease
  - Identified through contact investigation

- Infants / adolescents more likely symptomatic
  - Fever, cough, weight loss or FTT

- Physical findings are limited
  - Cough, wheezing
  - Hemoptysis, night sweats in adolescents
Extrapulmonary TB: Lymphadenitis

- Localized adenopathy
  - Supraclavicular, cervical, submandibular
  - Systemic symptoms minimal

- Generalized adenopathy
  - Cervical, supraclavicular
  - Systemic symptoms present

- Abnormal CXR only in 30-70% cases
Extrapulmonary TB : Meningitis

- Occurs in 2-5% of untreated children
  - Highest attack rate in those < 4 years
  - Occurs within 8 weeks of infection

- Progression of disease
  - Stage I- nonspecific symptoms, fever
  - Stage II- vomiting, CN palsies, seizures
  - Stage III- coma
TB of the Central Nervous System

- Cerebrospinal fluid
  - Mild pleocytosis (10-500 WBC/mm$^3$)
  - Glucose low / protein elevated (up to 400 mg/dl)
  - MTB isolation in 20-50% of cases

- Radiography (CT, MRI)
  - Basilar meningitis, hydrocephalus, infarcts, tuberculomas
Pearls and Pitfalls: Clinical Presentation

- **Pulmonary TB**
  - Nonspecific signs and symptoms - high index of suspicion required to prevent progression of disease

- **Extrapulmonary TB**
  - CXR not always abnormal in EP TB
  - TB meningitis/tuberculoma may present with nonspecific symptoms in early disease
  - Aseptic meningitis with hydrocephalus or basilar meningitis should be assumed to be TB until proven otherwise
Evaluation of Children for TB

- **Screening as part of general pediatric care**

- **Exposure**
  - Evaluation of a child who is a contact to an adult with potentially contagious TB
  - Evaluate for LTBI and TB

- **Infection - evaluation of child diagnosed with reactive TST**
  - Evaluate for LTBI and TB

- **Disease (symptomatic or asymptomatic)**
  - Confirm TB
  - Evaluate for extent of disease and extrapulmonary TB
Screening : Targeted TB Skin Testing

- Immediate TST
  - Contacts of confirmed or suspected TB
  - Radiographic or clinical suggestion of TB
  - Travel to/ immigration from endemic countries (including international adoptees)

- Annual TST
  - HIV-infected
  - Incarcerated adolescents

Report of Committee on Infect Dis, 2009
Diagnostic Tools for LTBI

- **Tuberculin skin test (TST)**
  - Purified protein derivative (PPD)
  - Reactivity is the hallmark of primary infection
    - DTH may take 2-12 weeks
  - Sensitivity and specificity 90%
    - Negative TST does not definitively exclude TB

- **IFN $\gamma$ assays (IGRAs)**
  - Blood tests measuring lymphocyte IFN $\gamma$ release
Interpretation of Reactive TST

- ≥ 5 mm  Contact of infectious case
-  Suspected disease
-  Immunosuppressed

- ≥ 10 mm  Age ≤ 4 years
-  Medical risk factors
-  Birth/travel to high prevalence area
-  Contact with high-risk adult

- ≥ 15 mm  Age > 4 years and no risk factors

Report of Committee on Infect Dis, 2012
What about BCG?

- Administered routinely in most areas of the world

- < 50% of infants given BCG at birth have a reactive TST at 9-12 months of age
  - 80-90% have nonreactive test by 5 years

- Interpretation of reactivity should be independent of BCG history, as with adults
## Pearls and Pitfalls: TST Confounders

<table>
<thead>
<tr>
<th>False Positives</th>
<th>False Negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nontuberculous mycobacteria</td>
<td>Immunodeficiency</td>
</tr>
<tr>
<td>Receipt of the BCG vaccine</td>
<td>Young age</td>
</tr>
<tr>
<td>Inexperienced reader</td>
<td>Receipt of live viral vaccines</td>
</tr>
<tr>
<td></td>
<td>Overwhelming disease</td>
</tr>
<tr>
<td></td>
<td>Inexperienced reader</td>
</tr>
</tbody>
</table>

- PPV depends on prevalence
  - 90% prevalence, PPV is 99%
  - 1% prevalence, PPV is 8%
Progress (?) in Diagnosis of LTBI: Interferon $\gamma$ Release Assays (IGRAs)

- Release of IFN $\gamma$ from white blood cells in response to stimulation by MTB antigens

- Proteins coded by a unique region of MTB
  - ESAT-6, CFP-10, TB7.7
  - No cross reactivity with BCG or most NTM

- Two assays
  - Quantiferon Gold® In Tube (QFT IT)
  - ELISPOT, T-SPOT
TST versus IGRAs

Crude mixture of proteins

Highly specific antigens

Lancet 2000; 356: 1099-1104
# TST versus IGRAs

<table>
<thead>
<tr>
<th>TST</th>
<th>IGRAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheap</td>
<td>Not so much</td>
</tr>
<tr>
<td>Requires no laboratory support</td>
<td>Requires equipped laboratory</td>
</tr>
<tr>
<td>Requires 2 visits</td>
<td>Completed in 1 visit</td>
</tr>
<tr>
<td>Reliability variable</td>
<td>Reliable</td>
</tr>
<tr>
<td>Results delayed 48-72 h</td>
<td>Rapid results</td>
</tr>
<tr>
<td>Cross reactivity with NTM</td>
<td>Limited cross reactivity with NTM</td>
</tr>
<tr>
<td>Cross reactivity with BCG</td>
<td>No cross reactivity with BCG</td>
</tr>
<tr>
<td>Cannot distinguish between LTBI and TB</td>
<td>Cannot distinguish between LTBI and TB</td>
</tr>
</tbody>
</table>
Progress: Should IGRAs Replace TSTs?

- Multiple studies comparing IGRA to TST
  - Interpretation of results confounded by lack of gold standard and heterogenous study designs

- Confounders
  - Young age - lower mitogen and antigen response
    - May be unreliable in young children
  - Indeterminate results

Ann Intern Med 2008; 149: 177-84
Performance of IGRAs: Estimates

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity ( %)</th>
<th>Specificity ( %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult and Pediatric Studies</strong></td>
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<td></td>
</tr>
<tr>
<td>TST</td>
<td>89 (63-100)</td>
<td>85 (22-100)</td>
</tr>
<tr>
<td>QFT</td>
<td>83 (56-93)</td>
<td>99 (99-100)</td>
</tr>
<tr>
<td>T-Spot</td>
<td>90 (50-100)</td>
<td>88 (85-100)</td>
</tr>
<tr>
<td><strong>Pediatric Studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TST</td>
<td>80 (70-90)</td>
<td>85 (63-100)</td>
</tr>
<tr>
<td>QFT</td>
<td>83 (75-92)</td>
<td>91 (78-100)</td>
</tr>
<tr>
<td>T-Spot</td>
<td>84 (63-100)</td>
<td>94 (87-100)</td>
</tr>
</tbody>
</table>
How do we use IGRAs in children?

- Not routinely recommended to replace TST
  - Consider for older children, children who are unlikely to return for a TST reading, and as part of dual testing for high risk situations
- Discourage use for:
  - Diagnosis or exclusion of disease
  - Young children (< 5 years of age)
    - More indeterminate results
    - Less agreement between TST and IGRA
    - Higher risk for development of disease
  - Immunocompromised
Out of Africa

- 3 year old adopted from Ethiopia
  - BCG scar present
- TST placed - 15 mm
- Mother has read about a new blood test that can tell BCG reaction from true LTBI
- What do you do?
Learning is Contagious

- 14 year old exposed to a teacher with tuberculosis
- TST reactive
- CXR normal
- The mother does not believe the TST

- Mother wants TST repeated
- Should you offer Quantiferon Gold IT?
- Mother wants them both—she’ll take the best 2 out of 3!
Pearls, Pitfalls and Progress: Screening for TB

- Screening for TB should be targeted towards those at risk for LTBI or progression to TB
  - Immigrants (adoptees, refugees)
  - International travel

- Beware of limitations of TSTs and IGRAs
  - Sequential or dual testing in limited circumstances
  - Consider IGRAs in older children
Evaluation of Children for TB

- Screening as part of general pediatric care

- Exposure
  - Evaluation of a child who is a contact to an adult with potentially contagious TB
  - Evaluate for LTBI and TB

- Infection - evaluation of child diagnosed with reactive TST
  - Evaluate for LTBI and TB

- Disease (symptomatic or asymptomatic)
  - Confirm TB
  - Evaluate for extent of disease and extrapulmonary TB
Contact Investigation

- CI of children exposed to *confirmed* or *suspected* TB is a critical role of the HD
  - History, physical examination
  - TST
  - CXR (PA and lateral films)
    - To evaluate for disease if TST reactive
    - Before initiating INH if TST nonreactive
Contact Investigation in Adults and Children ≥ 5 Years of Age

- TST nonreactive
  - Repeat TST in 8 weeks

- TST reactive
  - CXR normal
    - Treatment for LTBI
  - CXR abnormal- evaluate further for disease
    - Treatment for TB
Contact Investigation in Children < 5 Years of Age

- Initial TST nonreactive
  - CXR normal → INH for 8 weeks
    - Repeat TST nonreactive → stop INH
    - Repeat TST ≥ 5 mm → repeat CXR
      - If CXR normal, INH for 9 mo
      - For infants < 6 months, consider INH for 9 mo
    - CXR abnormal → Consult physician

- Initial TST ≥ 5 mm
  - CXR normal → INH for 9 mo
  - CXR abnormal → Consult physician

NC TB Manual: http://www.epi.state.nc.us
Tia with TB

- 4 month old exposed to an aunt with suspected pulmonary TB
- PE normal
- TST nonreactive
- How do you proceed?
- Repeat TST in 8 weeks is reactive - now what?
Latent Tuberculosis Infection

- Hallmark of LTBI is reactive TST in the absence of clinical or radiographic evidence of disease

- Identified either through
  - Contact investigation
  - Targeted tuberculin skin testing (risk-based)

- Further evaluation for disease
  - Physical exam
  - CXR
We all have positive TSTs...It’s cultural

- 10 year old born in India; BCG vaccinated
- Returned home last year for 2 months
- Screened – has reactive TST

How do you proceed with evaluation?
Imported TB

- 9 month old adopted from Guatemala
  - BCG vaccinated
- TST reactive at 15 mm
- Asymptomatic except for a cold with cough
- Now what?
Imported TB

- Patient admitted
  - GA, BAL
  - Induced sputum
  - HIV testing, LP

- Treatment with IRPE started

- MTB isolated
  - Fully susceptible
  - IRP for 2 months, IR continued for 4 months

Picture reprinted with permission from parents.
Pearls and Pitfalls: Exposure and LTBI

- Preventable cases of childhood TB occur when timely contact investigation is not performed
  - For young children, “window prophylaxis” indicated
    - Sometimes window prophylaxis fails...
- Evaluate any child with a reactive TST for disease
- The placement and reading of TSTs is a lost art
  - Consider repeating or IGRA if false positive likely
Evaluation of Children for TB

- Screening as part of general pediatric care

- Exposure
  - Evaluation of a child who is a contact to an adult with potentially contagious TB
  - Evaluate for LTBI and TB

- Infection - evaluation of child diagnosed with reactive TST
  - Evaluate for LTBI and TB

- Disease (symptomatic or asymptomatic)
  - Confirm TB
  - Evaluate for extent of disease and extrapulmonary TB
Suspected Tuberculosis

- **Pulmonary**
  - Pneumonia unresponsive to antibacterials
  - Hilar adenopathy on CXR
  - Cavitary pneumonia (adolescents)
  - Pneumonia or hilar adenopathy after exposure

- **Extrapulmonary**
  - Lymphadenitis (subacute, granulomatous)
  - “Aseptic” meningitis
  - Miliary pattern on CXR
Diagnostic Tools: Disease

- TST
- Radiography
  - CXR- PA and lateral
  - CT (chest), MRI (brain)
- Mycobacteriology
  - Gastric aspirate (GA)
  - Bronchoalveolar lavage (BAL)
  - Induced sputum, tissue
  - CSF
- MTB PCR
- Source identification
Radiographic Findings in Pediatric TB

- Hilar adenopathy is the most common abnormality
  - PA and lateral films recommended
  - Segmental collapse, hyperinflation

- Lobar infiltrate noted occasionally
  - Cavitary lesions uncommon
Mycobacteriology

- Bacteriologic confirmation is difficult in children
  - Sputum difficult to obtain in children < 10 y
  - GA collection requires hospitalization
  - Tubercle bacilli sparse

- Isolation of MTB important if:
  - Source case unknown or more than one source
  - Isolate not available
  - Resistance suspected
Specimens for Mycobacteriology

- **Pulmonary**
  - GA is specimen of choice
    - Isolation of MTB in 50-70% specimens can be higher!
  - Bronchoalveolar lavage (BAL) - yield lower but helpful
  - Induced sputum

- **Extrapulmonary**
  - Tissue - yield > 50%
  - CSF - yield < 50%

- AFB smears positive in < 10% of all specimens

- **Negative smear or negative culture does not exclude TB in children**
Collection of Gastric Aspirate

- Hospitalize patient; notify laboratory

- 3 consecutive early morning specimens after overnight fasts

- NG tube placed the night before collection
  - Gastric contents aspirated
  - Lavage with 10-20 ml sterile water if no aspirate

- Timely transport to the lab for immediate neutralization

NC TB Manual: http://www.epi.state.nc.us
Management of Pulmonary Disease Identified by Contact Investigation

- A child contact of an adult with TB with an abnormal CXR is presumed to have TB until proven otherwise
  - An abnormal CXR is not always TB - review with a pediatric radiologist if possible

- Attempt bacteriologic confirmation if CXR suggestive of TB and isolate not available or resistance suspected
If at first you don’t succeed...

- 19 month old with a mother hospitalized with suspected TB
- TST reactive
- CXR sent for review
- Physical examination normal per PCP

How would you manage this patient?

Do we need to obtain gastric aspirates?

If she has pulmonary TB, what further evaluation is recommended?
Further Evaluation of TB

- Mycobacteriological confirmation not needed
  - Source case known and isolate available

- Evaluate for dissemination of disease
  - Physical examination, LFTs, HIV test

- LP recommended in children \( \leq 2 \) years of age even if asymptomatic
Why the Lumbar Puncture?

- Meningitis is an early complication of infection
  - May occur before DTH develops
  - Children $\leq 4$ y of age primarily affected
  - Insidious process occurring over 3-6 weeks

- Management of disease affected by meningitis
  - Duration of therapy prolonged
  - Adjunctive use of corticosteroids

- Recommended in children $\leq 2$ years of age with TB disease, even in the absence of neurological symptoms
Back to the patient...

- Asymptomatic except perhaps irritable
  - To ED for LP (and repeat CXR)
    - CXR done but not checked
    - LP required sedation but patient ate Tootsie Pop

- Return to ED the next day for LP
  - No staff for LP- admitted for LP

- LP done- CSF reported normal; patient discharged
  - WBC 30, RBC 113,000, glucose 52, protein 466
Management of Clinically Suspected TB

- Bacteriologic confirmation if source case unknown
  - GA, BAL, sputum
  - Yield from 3 GA is higher than from BAL

- Source case investigation
  - Identification of adult source of infection
  - Critical to diagnostic evaluation
  - Likelihood of identifying source case (and isolating MTB) is higher than isolating MTB from patient
It’s a Family Affair

- 5 month old Hispanic female evaluated in ED with a cough
- CXR - hilar adenopathy
- Admitted for evaluation

- How would you manage this patient?
  - TST?
  - Gastric aspirates?
  - LP?

- How would you treat this patient?
Diagnosis: Source Identification

- Identification of (adult) source of infection
- Critical to diagnostic evaluation of the child with suspected TB disease
- Source case is likely an adult from whom MTB more likely to be isolated
Back to the patient...

- GA X 3, induced sputum X 1
  - CSF: 0 WBC, 0 RBC, protein 30, glucose 55
  - 4 drug regimen initiated

- Source case hunt
  - 4 siblings with LTBI
  - Parents with LTBI

- Isolation of MTB from GA specimen- matched source’s
Pearls and Pitfalls: Symptomatic Disease

- Children get TB from adults around them
  - Rapid progression to disease
  - The younger the child, the higher the risk

- Most children with pulmonary TB are asymptomatic

- Evaluation of suspected pulmonary TB
  - Bacterial isolation necessary if unknown source
  - Bacterial isolation not necessary if source is known
  - Source case identification is helpful for diagnosis
  - LP is recommended in young children (< 2 y) with pulmonary TB
TUBERCULOSIS

DON'T KISS ME!

YOUR KISS OF AFFECTION
THE GERM OF INFECTION
Pregnancy and Tuberculosis

- Rates of LTBI mimic those of the general population
  - Pregnant and postpartum women may have a higher risk of TB disease

- Controversies in treatment of LTBI

- Risk to fetus and newborn infant
  - Congenital TB, perinatal TB
Congenital Tuberculosis

- Rare - true incidence unknown
  - Most cases reported in foreign-born women living in nonendemic areas
  - May be due to infertility due to genital TB
- Pathogenesis
  - Hematogenous spread from placenta to umbilical vein
  - In utero ingestion/aspiration of infected amniotic fluid
  - Intrapartum ingestion of amniotic fluid or infected genital secretions
### Reviews of Cases of Congenital Tuberculosis Cases Reported in the English-Language Literature in the Era of Chemotherapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Years Cases Reported</th>
<th>No. of Cases</th>
<th>Age at Clinical Presentation (d)</th>
<th>No. of Infants With Reactive TST</th>
<th>Common Symptoms</th>
<th>Mortality (%) (With Treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cantwell et al, 1994</td>
<td>1980-1994</td>
<td>31</td>
<td>Median 24 (range 1 to 84)</td>
<td>0 of 9</td>
<td>Hepatosplenomegaly, Respiratory distress, Fever</td>
<td>38 (22)</td>
</tr>
<tr>
<td>Laartz et al, 2002</td>
<td>1994-2002</td>
<td>16</td>
<td>Mean 17.4 (range 1 to 60)</td>
<td>1 of 4</td>
<td>Respiratory distress, Hepatomegaly, Fever</td>
<td>20</td>
</tr>
</tbody>
</table>

Avery’s Dis of the Newborn, 9th Ed.
Congenital Tuberculosis

- Presentation typically at 2-4 weeks of age
  - Nonspecific - mimics bacterial sepsis
  - Fever, respiratory distress
  - Hepatomegaly, OM/drainage, rash
  - CXR may be abnormal
- Criteria for diagnosis
  - Evidence of TB in the first week of age
  - Infection of the placenta or genital tract
  - Exclusion of postnatal transmission
Clinical Signs of Congenital Tuberculosis in 58 Infants

<table>
<thead>
<tr>
<th>Sign</th>
<th>No. of Patients</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory distress</td>
<td>44</td>
<td>76</td>
</tr>
<tr>
<td>Hepatomegaly with or without splenomegaly</td>
<td>38</td>
<td>65</td>
</tr>
<tr>
<td>Fever</td>
<td>33</td>
<td>57</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>19</td>
<td>33</td>
</tr>
<tr>
<td>Poor feeding</td>
<td>18</td>
<td>31</td>
</tr>
<tr>
<td>Lethargy, irritability</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>15</td>
<td>26</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Ear discharge</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Rash</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Abnormal fundoscopic findings</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Jaundice</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Seizure</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Bloody diarrhea</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Ascites</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>
Evaluation for Congenital TB

- TST
  - Unreliable but helpful to have baseline
- CXR (PA, lateral)
- Mycobacterial confirmation
  - GAs, tracheal secretions, CSF, otorrhea, tissue
  - Yield higher than for older children
- Examination of mother
  - PE including genital/uterine examination
  - Placenta biopsy, culture
Management of the Newborn Whose Mother has LTBI

- Mother has reactive TST and normal CXR
  - If mother is asymptomatic, no separation
    - Mother should be treated for LTBI

- Newborn needs no further evaluation

- Household members should be evaluated for TB infection or disease
Management of the Newborn whose Mother has Suspected TB

- Mother has clinical signs/symptoms or abnormal CXR
  - Evaluation of mother (e.g. sputum, HIV serology)
  - Evaluate infant for congenital TB
    - If excluded, begin INH
  - Separation of mother and infant until evaluation complete and, if TB suspected, until mother receiving appropriate therapy

- Once INH started for infant, separation no longer necessary unless mother has DR TB

- Isolation of newborn only if intubated or undergoing procedures involving airway
Management of the Newborn whose Mother has Suspected TB

- Mother has reactive TST and abnormal findings on CXR but no evidence of TB
  - Mother should receive LTBI treatment

- Separation not necessary
  - Household should be investigated for TB
Management of Infants Born to Mothers with a Positive TST

Mother: Tuberculin Skin Test Positive

Asymptomatic Infant

Maternal chest x-ray normal; no active disease

Maternal chest x-ray abnormal

Mother with clinical or radiographic evidence of contagious TB

Symptomatic Infant

• TST, chest x-ray
• Lumbar puncture
• AFB culture: gastric aspirate, endotracheal aspirate, CSF
• Head CT scan or MRI
• Multi-drug treatment (see text)
• Airborne isolation
• Consult infectious disease specialist

Maternal evaluation consistent with TB?

No

Maternal treatment for TB ≥ 2 wks, sputum AFB negative, and strain not multi-drug resistant

Yes

Maternal treatment none or ≤ 2 wks, sputum AFB positive, or strain is multi-drug resistant

No infant evaluation or therapy required

Evaluation consistent with congenital tuberculosis?

No

• INH for 3-4 months
• If maternal TB strain is multi-drug resistant, consider BCG vaccine
• Follow-up TST at 3-4 months:
  • Negative test: stop INH.
  • Positive test:
    • Reassess for TB as in symptomatic infant.
    • If no other evidence of TB, INH for 9 months.

Yes

• Lumbar puncture if not previously done
• Consider head CT or MRI
• Multi-drug treatment (see text)

• Separate infant from mother until she is non-contagious (treatment ≥ 2 wks) or infant on appropriate TB drug(s).

• Evaluate infant for congenital tuberculosis
  • TST; chest x-ray
  • AFB culture: gastric aspirate, endotracheal aspirate
  • Consider lumbar puncture and AFB culture of CSF
  • Consult infectious disease specialist; notify local health department

Avery’s Dis of the Newborn, 9th Ed.
Tuberculosis Robs You

Public Health Protects You

Christmas Seals finance the campaign against tuberculosis
Treatment of LTBI and TB

- LTBI
  - Self-administered
  - For children < 5 years of age, directly observed preventive therapy (DOPT) twice weekly

- TB
  - Directly observed therapy (DOT)
Progress: Treatment of LTBI

- **Standard**
  - INH for 9 months (daily or DOPT twice weekly)
    - 90% effective in reducing risk of TB in children

- **Alternatives**
  - Rifampin for 6 months
  - INH and rifapentine weekly by DOT for 12 weeks
    - Option for children $\geq 12$ years of age

- **Alternatives to come..**
  - INH and rifapentine for children $\geq 2$ years of age
  - Rifampin for 4 months
  - INH and rifampin daily for 3 months

MMWR 2011; 60 (48): 1650-53
### TABLE 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subcategory</th>
<th>All Patients N (%)</th>
<th>Completed N (%)</th>
<th>Defaulted N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td>248</td>
<td>166 (75%)</td>
<td>62 (25%)</td>
</tr>
<tr>
<td>Age, y</td>
<td>Mean</td>
<td>7.4</td>
<td>7.2 (6.5–7.8)</td>
<td>8.2 (7–9.4)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>Hispanic</td>
<td>145 (58%)</td>
<td>108 (74%)</td>
<td>37 (26%)</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>58 (23%)</td>
<td>43 (74%)</td>
<td>15 (26%)</td>
</tr>
<tr>
<td></td>
<td>Non-Hispanic Black</td>
<td>38 (15%)</td>
<td>30 (79%)</td>
<td>8 (21%)</td>
</tr>
<tr>
<td></td>
<td>Non-Hispanic White</td>
<td>7 (3%)</td>
<td>5 (71%)</td>
<td>2 (29%)</td>
</tr>
<tr>
<td>Region of country of origin</td>
<td>United States</td>
<td>91 (37%)</td>
<td>73 (80%)</td>
<td>18 (20%)</td>
</tr>
<tr>
<td></td>
<td>Latin America</td>
<td>48 (19%)</td>
<td>34 (71%)</td>
<td>14 (29%)</td>
</tr>
<tr>
<td></td>
<td>Asia</td>
<td>23 (13%)</td>
<td>24 (73%)</td>
<td>9 (27%)</td>
</tr>
<tr>
<td></td>
<td>Africa</td>
<td>17 (7%)</td>
<td>10 (59%)</td>
<td>7 (41%)</td>
</tr>
<tr>
<td></td>
<td>Middle East</td>
<td>7 (3%)</td>
<td>3 (43%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td></td>
<td>N.D.</td>
<td>47 (19%)</td>
<td>37 (79%)</td>
<td>10 (21%)</td>
</tr>
<tr>
<td>No. medications used</td>
<td>1 drug</td>
<td>245 (99%)</td>
<td>184 (65%)</td>
<td>61 (25%)</td>
</tr>
<tr>
<td></td>
<td>2 drugs</td>
<td>3 (1%)</td>
<td>2 (67%)</td>
<td>1 (33%)</td>
</tr>
<tr>
<td></td>
<td>INH</td>
<td>242 (98%)</td>
<td>183 (76%)</td>
<td>59 (24%)</td>
</tr>
<tr>
<td></td>
<td>RIF</td>
<td>1 (0.4%)</td>
<td>1 (100%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>PZA + FQ</td>
<td>3 (1%)</td>
<td>2 (67%)</td>
<td>1 (33%)</td>
</tr>
<tr>
<td></td>
<td>Changed from INH to RIF</td>
<td>2 (0.8%)</td>
<td>0</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>How medications administered</td>
<td>Self-medicated</td>
<td>99 (40%)</td>
<td>49 (49%)</td>
<td>50 (51%)</td>
</tr>
<tr>
<td></td>
<td>ESAT</td>
<td>20 (8%)</td>
<td>17 (85%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td></td>
<td>DOPT</td>
<td>129 (52%)</td>
<td>120 (93%)</td>
<td>9 (7%)</td>
</tr>
<tr>
<td></td>
<td>ESAT or DOPT</td>
<td>149 (60%)</td>
<td>137 (92%)</td>
<td>12 (8%)</td>
</tr>
<tr>
<td>How identified</td>
<td>Contact investigation</td>
<td>82 (33%)</td>
<td>75 (91%)</td>
<td>7 (9%)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>166 (67%)</td>
<td>111 (67%)</td>
<td>57 (34%)</td>
</tr>
</tbody>
</table>

Pediatr Infect Dis J 2012;31:193
Progress: PREVENT TB Trial

- 3 months of INH and rifapentine administered weekly by DOPT compared with 9 months of daily INH
  - TB in 7/3986 subjects in the combination-therapy group (0.19%) and in 15/3745 subjects in the INH group (0.43%)

- Rates of completion
  - 82% in the combination group vs 69% in the INH group

- Rates of discontinuation and hepatotoxicity
  - Significantly lower in the combination group

Progress: PREVENT TB Pediatric Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>INH/RPT</th>
<th>INH</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>539</td>
<td>493</td>
<td>-</td>
</tr>
<tr>
<td>Completion</td>
<td>88%</td>
<td>80%</td>
<td>0.0006</td>
</tr>
<tr>
<td>Permanent discontinuation due to adverse event</td>
<td>1.3%</td>
<td>0.8%</td>
<td>0.65</td>
</tr>
<tr>
<td>Drug-related hepatotoxicity</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

- 1032 children 2-17 yrs old
- 7 cases of possible hypersensitivity in INH/RPT group, 0 in INH group

Villarino et al. IDSA Abstract, 2012
Treatment of Pulmonary TB

- Drug-susceptible disease
  - Initial
    - INH, RIF, PZA +/- EMB daily for 2 weeks, then daily or 2x/week for 6 weeks
  - Continuation
    - INH and RIF daily or 2x/week for 4 months

- Children or adolescents with adult-type disease or children in whom drug-resistance suspected
  - Initial: four drugs (INH, RIF, PZA, and EMB)

2009 Committee on Infectious Disease, American Academy of Pediatrics (Red Book)
Treatment of Extrapulmonary TB

- As for pulmonary TB except for meningitis, miliary and bone/joint disease

- Meningitis
  - Initial: 4 drugs (INH, RIF, PZA, and EMB)
  - Continuation: INH and RIF for 7-10 months

- Miliary disease and bone/joint disease
  - Total of 9-12 months of therapy

2009 Committee on Infectious Disease, American Academy of Pediatrics (Red Book)
Administration of Therapy

- Children with low bacillary load and low likelihood of resistance
  - Patient may not have pathogen isolated – confirm susceptibility from source

- Daily therapy in first 2 weeks is 5 or 7 days/week

- Continuation phase daily or 2x/week
Monitoring of Therapy: Adherence

- Children often receive little medication in the first few weeks due to vomiting and difficulty with administration.

- Convey to family that incomplete compliance to be expected early in treatment.

- Health department ultimately responsible for ensuring that appropriate treatment is delivered.
Monitoring of Therapy: Adverse Effects

- Rates of adverse effects are low

- Monthly clinical monitoring for signs/symptoms
  - Monitoring of transaminases not recommended except for
    - CNS or disseminated TB
    - Underlying liver disease
    - Symptoms of liver dysfunction

- EMB- visual acuity and color vision should be monitored
Monitoring of Therapy: Outcome

- Clinical
  - Symptoms typically mild at initiation of therapy

- Microbiological efficacy often not possible in children

- Radiological resolution
  - Hilar adenopathy may not resolve for 1-3 years
  - CXR should be repeated 1-2 months into regimen; if improving, repeat at the end of therapy
  - Normal CXR not necessary to stop therapy
Are we going to see

THE END OF TB

in our lifetimes?

A call from the millennium children of the Eastern Mediterranean Region