Evaluation and Management of Pediatric Patients in Contact Investigations

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Objectives

• Evaluation of the preschool-aged child exposed to tuberculosis

• Role of IGRAs in contact investigations

• Guidance for families whose children are receiving antituberculous therapy

• Optimizing the relationship between the clinician and the health department
### Definitions we use for TB

<table>
<thead>
<tr>
<th>Category</th>
<th>Age</th>
<th>Exam</th>
<th>PPD/IGRA</th>
<th>CXR</th>
<th>Contagious</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure</td>
<td>&lt; 5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Never</td>
<td>1 drug, usually for 2-3 months (given by health department)</td>
</tr>
<tr>
<td>Infection</td>
<td>All</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Never</td>
<td>Usually 1 drug, given 6-9 months (given by family or health department)</td>
</tr>
<tr>
<td>Disease</td>
<td>All</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>Rarely</td>
<td>Multiple drugs (3-4), given 6-12 months (always given by health department)</td>
</tr>
</tbody>
</table>

No patient with nontuberculous mycobacteria is contagious.
Evaluation of the preschool-aged child

• Why do we care?
  - Risk of rapid disease progression while we are waiting on the definitive TST

• What do we do with these children?
  - History and physical, chest Xray, TST
  - After ruling out disease, start chemoprophylaxis – usually INH

• What time frame?
  - As soon as possible; we often overbook these children so we can get them on therapy ASAP
Risk of Progression to Disease, Stratified by Patient Age

<table>
<thead>
<tr>
<th>Age at Primary Infection (yr)</th>
<th>No Disease (%)</th>
<th>Pulmonary Disease (%)</th>
<th>Miliary or Central Nervous System TB (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>50</td>
<td>30 to 40</td>
<td>10 to 20</td>
</tr>
<tr>
<td>1 to 2</td>
<td>75 to 80</td>
<td>10 to 20</td>
<td>2.5</td>
</tr>
<tr>
<td>2 to 5</td>
<td>95</td>
<td>5</td>
<td>0.5</td>
</tr>
<tr>
<td>5 to 10</td>
<td>98</td>
<td>2</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>&gt;10</td>
<td>80 to 90</td>
<td>10 to 20</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>


Risk of disease progression in adults: 1-13% lifetime risk
Why Do We Do This?
To Prevent This:
## Childhood TB Disease Sites, US: 1993-2001

<table>
<thead>
<tr>
<th>Site*</th>
<th>% of cases</th>
<th>Median Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>76.9</td>
<td>6</td>
</tr>
<tr>
<td>Lymphatic</td>
<td>15.5</td>
<td>5</td>
</tr>
<tr>
<td>Meningeal</td>
<td>2.1</td>
<td>2</td>
</tr>
<tr>
<td>Bone/joint</td>
<td>1.4</td>
<td>8</td>
</tr>
<tr>
<td>Pleural</td>
<td>1.1</td>
<td>16</td>
</tr>
<tr>
<td>Miliary</td>
<td>1.1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1.9</td>
<td>Variable</td>
</tr>
</tbody>
</table>

*: United States (almost all are normal hosts)
## Signs and Symptoms of Pulmonary TB

<table>
<thead>
<tr>
<th>Clinical Feature or Disease Type</th>
<th>Infants</th>
<th>Children</th>
<th>Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>Common</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Night sweats</td>
<td>Rare</td>
<td>Rare</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Cough</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Productive cough</td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>Never</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Common</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Sign</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rales</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
</tr>
<tr>
<td>Wheezing</td>
<td>Common</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Decreased breath sounds</td>
<td>Common</td>
<td>Rare</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Location of Disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Pulmonary + Extrapulmonary</td>
<td>Common</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

Very young children can look good and have very abnormal chest radiographs!!
Why the chest x-ray?

• Young children identified via active surveillance may be asymptomatic (this is a good thing!)

• The TST may be anergic in the young child

• You are going to want to start this child on therapy, and need to rule out disease before doing so
CXR Findings in Pediatric TB

• Hilar or mediastinal adenopathy
• Segmental/lobar infiltrates
• Calcifications (seen in 75-80% of children with pulmonary TB)
• Miliary disease
• Pleural effusions

15% of children with TB disease will have normal CXRs
Why are we so conservative? Because young children should not be trusted!

• 9mo M presents to TB clinic with 23mm PPD done after grandfather diagnosed with smear-positive pulmonary TB. Baby is asymptomatic, normal vital signs, growing well.
Mild fever, no tachypnea
What if a child is diagnosed without a source case?

• TB disease in a child = evidence of recent community transmission

• Should prompt an emergent source case investigation – while our kids are rarely contagious, same is not true for the adults around them

• Cultures should be attempted for the child
TB Infection Control

• In the mid-1990s, Texas Children’s Hospital began to require that adults and adolescents accompanying inpatient children with suspected tuberculosis undergo chest radiography to rule-out infectious pulmonary TB.

• A previous report from TCH [Muñoz et al. Infect Control Hosp Epidemiol 2002;23:568-572.] demonstrated that 15% of the adults accompanying hospitalized children with suspected tuberculosis had previously undiagnosed pulmonary TB.

• Results from this study also showed that no healthcare worker who cared for a child with tuberculosis became infected.
When do we worry about children being contagious?

- Older adolescents
- Children with certain findings on CXR
- Producing sputum
- Any draining skin lesions

Children with tuberculosis are rarely contagious, but their caregivers may be. Only 7 (12%) of 59 children were potentially contagious, and 10 (17%) were accompanied by contagious adults. Screening caregivers was more cost-effective than performing employee contact investigations, with one-sixteenth the cost ($5,470 vs $88,323) and requiring screening of 35 times fewer persons.

_Infect Control Hosp Epidemiol 2011;32(2):188-190_
TST in the preschool-aged child

- There is never too young an age to place a TST. However, need to know TST limitations in young babies.
  - Often, we do the definitive TST in exposed newborns when they hit 6 months of age.

- If initial TST is $\geq 5$ mm, can give family a duration of therapy.

- If initial TST $< 5$ mm, I tell families child will be on medication for at least a few months.
  - Depends on break in contact (physical or microbiological).
Therapy: Exposure

• INH (or RIF for INH-monoresistance) until definitive TST is done

• If 2nd (or definitive) TST is < 5mm, stop therapy if child is old enough for you to rely on the TST (e.g., at least 6 months)

• If definitive TST is positive (converted from exposure to LTBI), continue INH to complete 9 months or RIF to complete 6 months
  - the time they already received counts toward the total
How do I convince parents?

• Data: INH works to prevent disease

• Safety: INH is safe (their kids generally don’t drink)

• Cost: we will provide the medication to you

• Guilt: how horrible would you feel if your child developed a preventable disease that could cause neurologic devastation
What about older children?

- If initial TST < 5mm and asymptomatic, they require a definitive TST, but do not need to be on prophylaxis in the meantime.

- If initial TST ≥ 5 mm, evaluate for disease and if negative, treat for LTBI:
  - 9 months INH
  - 6 months RIF
  - Rifapentine data for children < 13 years of age not yet available
IGRAs: The Good and Bad News!

Machingaidze et al. PIDJ 2011; 30: epub ahead of print

• A systematic review and meta analysis of studies of the utility of IGRAs for diagnosing LBTI and TB disease in children – 20 of 68 studies used

• Conclusions:

1. IGRAs have increased specificity for the diagnosis of LTBI compared with the TST [The Good!]

2. The sensitivity of IGRAs for TB disease was no different from the TST, and a significantly reduced IGRA sensitivity was found in high-burden settings compared with low burden settings [The Bad!]
IGRA: Limitations

• Indeterminate results: decrease the utility of a screening tool
• One cut-off: is this appropriate across risk strata?
• Unknown dynamics of when assays become positive
• Discordance: interpretation if TST and IGRA provide different results
• Limited pediatric data: especially for the most vulnerable risk groups
• Need for blood draw
IGRA in Children with TB Disease

• *Cannot distinguish infection and disease*
• IGRA are positive in most but not all cases
• TSPOT may be positive more often than TST in young age, HIV infection, malnutrition
• QFT and TSPOT seem to be equivalent in diagnosing TB
• Take-home message: we don’t have an abundance of tools to diagnose TB disease in children; if you suspect it, place a TST and send both IGRA
Diagnosis of LTBI in School Contact Investigations

• 349 15-16 y/o boys, all BCG vaccinated (Japan)

• Tested with TST: 95 of 349 (27%) positive

• 88/95 TST positive tested with QFT-TB Gold: 4 of 88 positive

• 3 of 4 in high exposure group – received INH

• Remaining TST positive students – no INH and no disease with 3+ years follow-up
Diagnosis of LTBI/school contacts: T-SPOT

Guidance to Families

• Explain rationale and importance of therapy
  - If you don’t sell them on it, they will never take it

• Medication safety
  - Warn against Googling INH!

• What do the meds do?
  - Kill *M. tb*; important to explain spectrum of coverage

• Other: flu shot annually, opportunity to catch up on other immunizations
Anticipatory Guidance

• When to call:
  - Questions/concerns about side effects: immediately
  - Other: business hours

• What to do:
  - Side effects: stop medications, then call

• Give instructions in verbal and written format

• Give good contact information to families
What do families & kids get out of it?

Families:
• Prevention for their kids
• Parking tokens
• Catch-up immunizations
• A (transient) medical home

Kids:
• Prevention
• Stickers
• Books
• Excused school absences…
INCREASING ADHERENCE FOR LATENT TUBERCULOSIS INFECTION THERAPY WITH HEALTH DEPARTMENT–ADMINISTERED THERAPY

Andrea T. Cruz, MD, MPH,*† and Jeffrey R. Starke, MD*

Abstract: Therapy is almost universally recommended for children with latent tuberculosis infection, but long courses of therapy can decrease adherence to drug therapy. The only variable positively associated with adherence to latent tuberculosis infection therapy in our population was health department–assisted administration of drugs (odds ratio, 7.2; 95% confidence interval, 3.8–13.8).
Treatment

• TB exposure

• TB infection

• TB disease
TB Exposure

• Children < 5 years of age with a negative PPD, normal CXR and examination exposed to contact with suspected TB

• Provide chemoprophylaxis in the window period (8-10 weeks) pending repeat skin testing

• Children > 4 yrs of age also need sequential skin testing, but no window chemoprophylaxis
Red Book Statement on TB Infection

“All infants, children, and adolescents who have a positive PPD result but no evidence of TB disease and who have never received antituberculosis therapy should be considered for INH unless resistance to INH is suspected or a specific contraindication exists”

Red Book 2009, p691
TB Prevention

• Isoniazid (INH) = mainstay of therapy
  - 10-15 mg/kg single daily dose if given by family
  - 20-30 mg/kg twice weekly if given by health department
  - Duration: 9 months

• Alternative: rifampin x 6 months
  - If person around child with TB is known to have INH-resistant disease or if child is INH-intolerant
LTBI Treatment Pearls

• Use INH suspension only in children < 5 kg
  - Otherwise, give tablets that can be crushed & mixed with food

• Compliance with 9 months of INH averages a bit over 50%; be skeptical

• Use health department to administer medications to high-risk patients: infants, immunocompromised children, recent contacts

• When children aren’t tolerating INH, the problem is more often with the parent than the child

• Routine LFTs not indicated unless: concomitant administration of other hepatotoxic drugs; pre-existing liver disease; or signs/symptoms of hepatitis
Therapy for TB Disease

• Start **4-drug** therapy
  - INH, rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB); INH/RIF are the backbone of therapy

• Use PZA only during 1\textsuperscript{st} 2 months for susceptible TB
  - This is your ‘shortening agent’: consolidate from 9 to 6 months of therapy

• Stop EMB once culture results known, if have pan-susceptible TB
  - This is your insurance in case you have drug-resistant TB

• Anticipate minimum 6 month therapy, and we often extend it to longer periods, especially for extrapulmonary disease

• **Always** administered by directly observed therapy (DOT)
Ethambutol

• Metabolized faster by children than adults
  - Same mg/kg dose results in lower serum levels in children

• Consequently, risk of optic neuritis is very low

• You can feel very comfortable using ethambutol even in the pre-verbal child in whom visual acuity screening is challenging!

• Remember, however, that it crosses the blood-brain barrier poorly and should not be used for meningitis
Medication Administration

• INH suspension only to child not taking any solid/pureed foods

• Warn parents about rifampin and urine color

• Make sure child can tolerate all medication doses prior to discharge (for some young babies, doses may need to be divided in the course of the day)

• Routine liver function tests not needed in the otherwise healthy, asymptomatic child
Medication Tolerance

• **Pediatrics:**
  - 5% risk of side effects in children
    - **Most minor – abdominal pain without elevation in LFTs**
    - 3.3% incidence of elevated LFTs in 1970s with INH and Rifampin (often asymptomatic)
  - Peripheral neuropathy quite rare before adolescence

• **Adults:**
  - Hepatotoxicity:
    - 3-4% with INH alone
    - Up to 5% with INH and Rifampin
  - Peripheral neuropathy: 4%
  - Bone marrow suppression: 2%
# Notes on TB Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side Effects</th>
<th>Other notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>Peripheral neuropathy; seizures in overdose</td>
<td>B6 helps prevent neuropathy and is only treatment for INH seizures, but doesn’t prevent hepatotoxicity</td>
</tr>
<tr>
<td>RIF</td>
<td>Orange discoloration of secretions; inactivates oral contraceptives; many drug interactions</td>
<td>Please warn of Longhorn-orange urine!</td>
</tr>
<tr>
<td>PZA</td>
<td>Can increase uric acid ‡ gout symptoms; rash</td>
<td>Of 1st-line drugs, greatest association with hepatotoxicity</td>
</tr>
<tr>
<td>EMB</td>
<td>Optic neuritis, red-green color blindness</td>
<td>Despite side effects, has very poor CNS penetrance and not used for meningitis</td>
</tr>
</tbody>
</table>

*All primarily hepatically metabolized, except EMB, which is also renally excreted*
Optimizing Relationships Between Clinicians and Health Departments

• Who do I call?

• What information do I need and must I convey?

• How do I prioritize patients?

• The key is to understand that there’s no way we can adequately take care of the kids on our own.
Who do I call?

• Exchange contact information: office, cell, pager, email

• Suggest what routes of communication you want for urgent versus non-urgent requests

• Let people know when you will be unavailable
What information do I need?

• Discuss what information you need for every child:
  - From H.D. to MD: TST result, source case information
  - From MD to H.D.: CXR read, plan, orders, +/- notes/labs

• What time frame works?
  - X # of days before clinic visit

• What information must accompany DOT/DOPT forms?

• What information should we convey to families?
  - Clinic-specific information, time frame to start medications, etc
How do I prioritize patients?

• Strategize about this up front:
  - Suspected cases
  - Young children with exposure (especially if smear + source)

• How to get this to happen:
  - Have H.D. be able to overbook appointments and make appointments for patients
  - See if they can have access to clinic schedule

• What to do if there are questions:
  - Gets back to communication
How are kids different?

<table>
<thead>
<tr>
<th>Differences</th>
<th>Ramifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less contagious</td>
<td>But.. Beware the family</td>
</tr>
<tr>
<td>Higher risk of progression to disease</td>
<td>Need for window prophylaxis</td>
</tr>
<tr>
<td>Frequency of asymptomatic disease</td>
<td>CXR irrespective of TST result</td>
</tr>
<tr>
<td>Frequency of extrapulmonary TB</td>
<td>Need urgent referral &amp; evaluation</td>
</tr>
<tr>
<td>Duration of LTBI therapy with RIF</td>
<td>4m for adults, 6 for children</td>
</tr>
</tbody>
</table>

- It is impossible to effectively manage childhood TB without close cooperation with an effective public health infrastructure
Acknowledgments

• Thank you to our friends and colleagues at our local and state health departments for helping us take care of our kids.