Diagnosis and Treatment of Active TB Disease in Adults

Shu-Hua Wang, MD, MPH, TM
Assistant Professor of Medicine
The Ohio State University
Medical Director, Ben Franklin TB Control Program

Elderly patient with chronic cough and weight loss

HOPI
- 74 year-old, African American female
- Seen at OSU ER with complaints of shortness of breath and progressive weakness
- Increasing SOB over the last 4 days
- Associated with fevers, chills, cough, with purulent sputum
- Family noted history of cough and weight loss over last several months
74 YO Female

• Physical Exam
  – Temp 97.8°F; BP 136/77; Pulse 136; RR 22
  – O₂ Sat. 98% on 3L/min NC O₂
  – NAD
  – Chest: crackles R base

LAB:
WBC 9,700
  PMN 86.5%, Lymph 8.2%  Mono 5.2%
Hb 9.3 gm/dL; Platelets 570K;
BUN/Creat 12/0.84 mg/dL

CXR

Admission

8 months prior to admission
CT Scan: Extensive air-space disease left apical, post cavitary

Hospital Course

- Admitted to floor – Community Acquired Pneumonia
- Treated: ampicillin/sulbactam/azithromycin
- Respiratory failure → Intubated 24 hours later
- Blood and routine sputum cultures negative.
Hospital Course

- Admitted to floor – Community Acquired Pneumonia
- Treated: ampicillin/sulbactam/azithromycin
- Respiratory failure → Intubated 24 hours later
- Blood and routine sputum cultures negative.
- Bronchial alveolar lavage (BAL)
- 5/5 Sputa “Heavy acid fast bacilli (AFB)-Positive”

Estimated TB incidence rate

- 9 million new TB cases each year
- 2 million deaths
- One life every 20 seconds

# new cases per 100,000 population

WHO
The hidden Epidemic – Latent TB Infection

- Every one second someone is newly infected with TB
- Two billion people, 1/3 of the world’s total population, are infected with TB
- One in 10 people infected with TB bacilli will develop active TB

Slide courtesy of Ian Durrant, PhD

USA: 1953  84,304 cases of TB
Rate 52.6 Cases per 100,000

U.S. Public Health Campaign

CDC photo image and A public health campaign poster, lungchicago.org
Historical Collections and Services, The Claude Moore Health Sciences Library, University of Virginia
Reported TB Cases
United States, 1982–2010*

*Updated as of July 21, 2011

TB Case Rates,* United States, 2010
Ohio TB Cases by County for 2010
190 Total Cases

<table>
<thead>
<tr>
<th>Year</th>
<th>Rate</th>
<th>#</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>1.6</td>
<td>190</td>
</tr>
<tr>
<td>2009</td>
<td>1.6</td>
<td>180</td>
</tr>
<tr>
<td>2008</td>
<td>1.9</td>
<td>213</td>
</tr>
<tr>
<td>2007</td>
<td>2.2</td>
<td>252</td>
</tr>
<tr>
<td>2006</td>
<td>2.1</td>
<td>239</td>
</tr>
<tr>
<td>2005</td>
<td>2.3</td>
<td>260</td>
</tr>
<tr>
<td>2004</td>
<td>1.9</td>
<td>219</td>
</tr>
<tr>
<td>2003</td>
<td>2.0</td>
<td>229</td>
</tr>
</tbody>
</table>

Ohio Department of Health

Cases and Rates of Incident TB Disease in Franklin County, OH by Year

Number of Cases | Rate/100,000
--- | ---

- Franklin County: 5.8
- USA: 3.6
- Ohio: 1.6
### Clinical Case

**HOPI**
- 28 year old Chinese female, 32 week pregnant
- Presented to OSH ER with hemoptysis
- C/O cough X 2 days, associated with mild SOB
- No fever, chills, night sweat, appetite loss, fatigue, or weight loss
- Denies any history contact with known active tuberculosis
- History positive TST, no latent TB therapy
- Received BCG vaccine in China as a child

### Hospital course

**Laboratory**
- WBC 6.1, Hgb 10.1gm/dL, Platelets 192, Cr. 0.5, AST 41, ALT 51, HIV negative

**Radiology**
- CXR - Mild asymmetric patchy LUL opacity
- CT - No PE
  - Extensive diffuse nodular disease
### Hospital course

- Admitted for Community Acquired Pneumonia and
  - Azithromycin and ceftriaxone

- Rule out TB - in Negative Air Isolation
  - Sputum AFB and smear X 3
  - Tuberculin Skin Test
  - Interferon gamma release assay

### AFB SMEAR and CULTURE

<table>
<thead>
<tr>
<th>Ziehl-Neelsen</th>
<th>AFB smear</th>
<th>&lt; 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>X 1,125</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

X 1440
AFB SMEAR and CULTURE

<table>
<thead>
<tr>
<th>Ziehl-Neelsen</th>
<th>X 1,125</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFB smear</td>
<td>&lt; 24 hours</td>
</tr>
<tr>
<td>X 1440</td>
<td></td>
</tr>
</tbody>
</table>

Solid Culture
3 – 8 weeks

Liquid Culture
7 – 21 days

• PPD 17mm
• Interferon gamma release assay (QuantiFERON-TB Gold®)
  – Positive

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Smear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum day 1</td>
<td>Negative</td>
</tr>
<tr>
<td>Sputum day 2</td>
<td>Negative</td>
</tr>
<tr>
<td>Sputum day 3</td>
<td>Negative</td>
</tr>
<tr>
<td>BAL day 4</td>
<td>Negative</td>
</tr>
</tbody>
</table>
• PPD 17mm
• Interferon gamma release assay
  (QuantiFERON-TB Gold®)
  – Positive

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Smear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum day 1</td>
<td>Negative</td>
</tr>
<tr>
<td>Sputum day 2</td>
<td>Negative</td>
</tr>
<tr>
<td>Sputum day 3</td>
<td>Negative</td>
</tr>
<tr>
<td>BAL day 4</td>
<td>Negative</td>
</tr>
</tbody>
</table>

• Discharge home on INH for Latent TB Treatment
• Follow up at the Health Department

Is there another test you can order to help you make a diagnosis sooner?

Specimen collection and processing

- AFB Smear
- MGIT (Liquid medium, automated system)
- Agar Plate

  No Growth: Incubate for 6 weeks
  Positive Growth
  No Growth: Incubate for 4 weeks

NAAT: Nucleic acid amplification test
Mycobacterium tuberculosis Direct Test (MTD) or Amplicor
Is there another test you can order to help you make a diagnosis sooner?

Specimen collection and processing

- **AFB Smear**
- **MGIT** (Liquid medium, automated system)
- **Agar Plate**

   - **NAAT**
     - No Growth: Incubate for 6 weeks
     - Positive Growth
     - No Growth: Incubate for 4 weeks

NAAT: Nucleic acid amplification test
Mycobacterium tuberculosis Direct Test (MTD) or Amplicor

---

**Nucleic Acid Amplification Test (NAAT)**

- Direct, rapid, detection of *M. tb* complex (rRNA)
  - Patients suspected of TB
  - Takes about 4 to 5 hours
  - Approved for respiratory specimens only
    - Smear positive and smear negative
  - Non-respiratory specimen (validated by labs)
  - Can detect fewer than 10 organisms
  - Does not distinguish live vs dead organism

MMWR July 7, 2000
CDC Guidelines - 2009
Nucleic Acid Amplification Test

- Collect specimen for AFB, culture, & NAAT
- Interpret results with AFB smear.

<table>
<thead>
<tr>
<th>NAAT</th>
<th>AFB</th>
<th>Recommend</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>Start treatment. PPV &gt;95% NAAT in AFB+ cases</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>Repeat NAAT test. Presume TB if &gt;=2 NAA (+)</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>Presume nontuberculous mycobacteria (NTM)</td>
</tr>
</tbody>
</table>
| -    | -   | • Use clinical judgment.  
• NAAT sensitivity 50-80% in detection AFB (-)  
Culture (+) pulmonary TB |

- PPD 17mm
- Interferon gamma release assay (QuantiFERON-TB Gold®)
  - Positive
- Nucleic acid amplification test:
  - Positive
• PPD 17mm
• Interferon gamma release assay (QuantiFERON-TB Gold®)
  – Positive
• Nucleic acid amplification test:
  – Positive

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Smear</th>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum day 1</td>
<td>Negative</td>
<td><em>M. tb</em></td>
</tr>
<tr>
<td>Sputum day 2</td>
<td>Negative</td>
<td><em>M. tb</em></td>
</tr>
<tr>
<td>Sputum day 3</td>
<td>Negative</td>
<td><em>M. tb</em></td>
</tr>
<tr>
<td>BAL day 4</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Sputum day 9*</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*All subsequent sputum smear and culture negative

---

**Antimyobacterial Drugs**

**First-Line Drugs**
- Isoniazid (INH)
- Rifampin (RIF)
- Pyrazinamide (PZA)
- Ethambutol (EMB)

**Second-Line Drugs**
- Streptomycin
- Cycloserine
- p-Aminosalicylic acid
- Ethionamide
- Amikacin or kanamycin*
- Capreomycin
- Levofloxacin*
- Moxifloxacin*
- Linezolid*

* Not approved FDA for TB Treatment
Treatment of Culture-Positive TB

**Initial Phase**

2 months - INH, RIF, PZA, EMB daily (56 doses, within 8 weeks)

**Continuation Phase**

Options:

1) 4 months - INH, RIF daily (126 doses, within 18 weeks)
2) 4 months - INH, RIF twice/week (36 doses, within 18 weeks)
3) 7 months - INH, RIF daily (217 doses, within 31 weeks)*
4) 7 months - INH, RIF twice/week (62 doses, within 31 weeks)*

- Continuation phase increased to **7 months**
- Chest x-ray shows cavitation and CX positive at 2 months
- Or NO PZA in initial phase

Drug Susceptibility testing

MDR (Multi-drug resistant) TB
= Resistant to isoniazid and Rifampin

XDR (Extensive Drug Resistance) TB
MDR + Resistance fluoroquinolone +
Resistance injectable (amikacin, capreomycin)
Rapid Molecular Detection of Drug Resistance for *M. tuberculosis*


Common Adverse Reactions to Drug Treatment

<table>
<thead>
<tr>
<th>Caused by</th>
<th>Adverse Reaction</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any drug</td>
<td>Allergy</td>
<td>Skin rash</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Eye damage</td>
<td>Blurred or changed vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Changed color vision</td>
</tr>
<tr>
<td>Isoniazid, Pyrazinamide, or Rifampin</td>
<td>Hepatitis</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abnormal liver function test results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lack of appetite</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yellowish skin or eyes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dark urine</td>
</tr>
</tbody>
</table>
### Common Adverse Reactions to Drug Treatment

<table>
<thead>
<tr>
<th>Caused by</th>
<th>Adverse Reaction</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Peripheral neuropathy</td>
<td>Tingling sensation in hands and feet</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Gastrointestinal intolerance</td>
<td>Upset stomach, vomiting, lack of appetite</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>Joint aches</td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
<td>Gout (rare)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Ear damage</td>
<td>Balance problems</td>
</tr>
<tr>
<td></td>
<td>Kidney damage</td>
<td>Hearing loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ringing in the ears</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abnormal kidney function test results</td>
</tr>
</tbody>
</table>

### Common Adverse Reactions to Drug Treatment

<table>
<thead>
<tr>
<th>Caused by</th>
<th>Adverse Reaction</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifamycins</td>
<td>Thrombocytopenia</td>
<td>Easy bruising</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Gastrointestinal intolerance</td>
<td>Slow blood clotting</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>Drug interactions</td>
<td>Upset stomach</td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
<td>Interferes with certain medications, such as birth control pills, birth control implants, and methadone treatment</td>
</tr>
</tbody>
</table>
LTBI
• TST positive
• CXR Negative
• No symptoms or physical findings suggestive of TB disease

Pulmonary TB Disease
• TST and IGRA may be positive
• CXR may be abnormal
• Symptoms may include one or more of the following: fever, cough, night sweats, weight loss, fatigue, hemoptysis, decreased appetite
• Respiratory specimens may be smear or culture positive
• NAAT may be positive

LTBI = Latent TB Infection; TST = Tuberculin skin test, IGRA = interferon gamma release assay
NAAT= Nucleic acid amplification test

What to do if you suspect TB?
• Airborne Infection Isolation/precautions –
  – Negative airflow room and N-95 respirator mask
• CXR
• Respiratory AFB smear and culture
• Tuberculin skin test/ IGRA -TB blood test
• HIV Test
• Smear and culture from other sites
• Nucleic Acid amplification test on sputum smear
• Drug Susceptibility
• REPORT ALL TB SUSPECTS to TB Control Program
Pediatric Tuberculosis Update

W. Garrett Hunt, MD, FAAP
Associate Professor of Pediatrics
The OSU College of Medicine
Nationwide Children’s Hospital
# Objectives

- To become familiar with the epidemiology of infection and disease caused by *Mycobacterium tuberculosis* complex (TB) in children
- To understand current algorithms for the diagnosis of TB infection and disease in children
- To know the treatment regimens for latent TB infection (LTBI) in children

---

## Pediatric TB

- *Mycobacterium tuberculosis* complex* (TB)
  - *M. tuberculosis*
  - *M. africanum*
  - *M. bovis* and *M. bovis* bacillus Calmette-Guérin
  - *M. microti* and *M. pinnipedii*
  - *M. canettii*, oryx bacillus, and dassie bacillus (proposed)
- Pediatric TB
  - Infection or disease in children or adolescents < 15 years of age

*BMC Infectious Diseases 2010, 10:80*
### TB Case Definitions and Verification

- **Incident case of disease**

- **Case verification categories**
  - Laboratory confirmed cases – “Gold Standard”
    - Positive culture, DNA probe, or nucleic acid amplification test
    - Positive AFB smear when culture not attainable
  - Clinical case definition
    - Positive tuberculin skin test
    - Signs and symptoms of TB disease
    - Current treatment for TB disease

- **Provider diagnosis**
  - Diagnosed by health care provider
  - Does not fulfill all criteria necessary to meet laboratory or clinical case definitions
TB Case Rates* by Age Group
United States, 1993–2010

* Updated as of July 21, 2011

TB Case Rates by Pediatric Age Groups
1993–2008, N=17,502

Note: Rates presented on a logarithmic scale
~35% of household contacts are infected

LTBI” major focus for PPD screening

95%

Bacteremia and dissemination to multiple body organs

Small & Fujiwara. NEJM 345:189, 2001

Age-Specific Risk of TB Disease

<table>
<thead>
<tr>
<th>Age [years]</th>
<th>Disease</th>
<th>Risk of disease after primary infection [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>None</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Pulmonary</td>
<td>30–60</td>
</tr>
<tr>
<td></td>
<td>Meningitis or miliary</td>
<td>10–20</td>
</tr>
<tr>
<td>1–2</td>
<td>None</td>
<td>70–80</td>
</tr>
<tr>
<td></td>
<td>Pulmonary</td>
<td>10–20</td>
</tr>
<tr>
<td></td>
<td>Meningitis or miliary</td>
<td>2–5</td>
</tr>
<tr>
<td>2–5</td>
<td>None</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>Pulmonary</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Meningitis or miliary</td>
<td>0.5</td>
</tr>
<tr>
<td>5–10</td>
<td>None</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>Pulmonary</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Meningitis or miliary</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>&gt;10</td>
<td>None</td>
<td>80–90</td>
</tr>
<tr>
<td></td>
<td>Pulmonary</td>
<td>10–20</td>
</tr>
<tr>
<td></td>
<td>Meningitis or miliary</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>

Reproduced with permission from Marais et al. IJTLD 2004; 8:392-402
INCORRECT

CORRECT
### Definition of Positive Mantoux Tuberculin Skin Test (TST) Results in Children

- **Induration ≥ 5 mm**
  - Children in contact with known active TB
  - Children with clinical or radiographic illness consistent with TB
  - Children who are immunocompromised
- **Induration ≥ 10 mm**
  - Children at increased risk of disseminated disease
    - Age < 4 years of age or underlying medical illness
  - Children with increased exposure to TB
    - Born or parents born in high-prevalence countries
    - Frequent exposure to adults with high risk of TB
    - Travel to high-prevalence countries
- **Induration ≥ 15 mm**
  - Age ≥ 4 years of age without any risk factors

### BCG Scar after Vaccination at Birth

2 months after birth  
6 months after birth

Santiago EM et al. Pediatr 2003;112:e298
TST 6 Months after BCG at Birth in 69 Infants in Peru

Santiago EM et al. Pediatr 2003;112:e298

Updated CDC Guidelines 2010

Updated CDC Guidelines 2010

“An IGRA may be used in place of (but not in addition to) a TST in all situations in which CDC recommends tuberculin skin testing as an aid in diagnosing *M. tuberculosis* infection . . . .”


Updated CDC Guidelines 2010

“A TST is preferred for testing children aged <5 years. “
Updated CDC Guidelines 2010

“An IGRA may be used in place of (but not in addition to) a TST in all situations in which CDC recommends tuberculin skin testing as an aid in diagnosing *M. tuberculosis* infection . . . .”

“A TST is preferred for testing children aged <5 years. “

“Using both a TST and an IGRA . . . might be useful . . . when additional evidence of infection is required to encourage compliance.”

Interferon-γ Release Assay for Detection of TB Infection

Antigens used: ESAT-6, CFP-10, TB 7.7

QuantiFERON-Gold In-Tube

Positive when antigen (–) null elisa = ≥ 0.35 IU/ml
### IGRA vs TST

<table>
<thead>
<tr>
<th>IGRA</th>
<th>TST</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>in vitro test</em></td>
<td><em>in vivo test</em></td>
</tr>
<tr>
<td><strong>Specific antigens</strong></td>
<td><strong>Less specific PPD</strong></td>
</tr>
<tr>
<td>Not affected by prior BCG</td>
<td></td>
</tr>
<tr>
<td><strong>Does not cause boosting</strong></td>
<td>May cause boosting</td>
</tr>
<tr>
<td><strong>Single patient visit</strong></td>
<td>2 patient visits</td>
</tr>
<tr>
<td><strong>Results possible in 1 day</strong></td>
<td>Results in 2-3 days</td>
</tr>
<tr>
<td><strong>Requires phlebotomy</strong></td>
<td>TST placement skills</td>
</tr>
<tr>
<td><strong>Error in collecting, transporting, lab</strong></td>
<td>Inter-reader variability</td>
</tr>
</tbody>
</table>

### Species Specificity of ESAT-6 and CFP-10

<table>
<thead>
<tr>
<th>Tuberculosis Complex</th>
<th>ESAT</th>
<th>CFP 10</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. tuberculosis</em></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><em>M. africanum</em></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><em>M. bovis</em></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><em>BCG substrains</em></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
### Species Specificity of ESAT-6 and CFP-10

<table>
<thead>
<tr>
<th>Tuberculosis Complex</th>
<th>ESAT</th>
<th>CFP 10</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. tuberculosis</em></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><em>M. africanum</em></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><em>M. bovis</em></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><em>BCG substrains</em></td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-tuberculous Mycobacteria</th>
<th>ESAT</th>
<th>CFP 10</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. kansasii</em></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><em>M. marinum</em></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><em>M. szulgai</em></td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

### Tuberculosis Testing and Treatment

1. **Place TST**
2. **Interpret TST 48-72 hrs**
   - **< 10 mm** → **No infection**
   - **≥ 10 mm** → **Likely Infection**
3. **Likely Infection**
   - **CXR at NCH Radiology**
     - **No Active Air-Space Disease** → **NCH TB Clinic**
     - **Active Air-Space Disease**

Approach to Diagnosis of TB in Children

- Child ≥ 5 yrs old with known exposure to TB: IGRA and TST
- Child < 5 yrs old with known exposure to TB: use TST
- Child of any age with suspected TB: TST and IGRA,
  and aggressively seek TB isolate and epidemiology of exposure.
- Child < 5 yrs old immigrating from high risk country
  without known TB exposure: use TST as screen – follow Redbook guidelines for interpretation.
- Child ≥ 5 yrs old immigrating from high risk country
  without known TB exposure: use TST ≥ 15 mm, assume TB infection.
- If TST 10-14 mm, obtain IGRA to confirm or refute TB infection.

Powell DA. Pediatr Infect Dis J 2009;28:676
**Question**

Which of the regimen(s) would you prescribe for LTBI therapy in a child?

a. 2 months of pyrazinamide and rifampin  
b. 3 months of isoniazid and rifapentine (12 weekly doses)  
c. 4 months of rifampin  
d. 6 months of rifampin  
e. 9 months of Isoniazid

---

**Answers – b, d, or e**

- Recommend 9 months of INH  
- Acceptable alternatives  
  - 6 months of Rifampin  
  - 12 doses of INH and Rifapentine*  
    - Directly Observed Therapy (DOT) only  
    - Enrollment 6/01-2/08, follow-up ended 9/30/10  
    - 9H, 15/3745 (0.43%) – 69% completion, discontinuation 3.6%  
    - 3HP, 7/3986 (0.19%) – 82% completion, discontinuation 4.7%  
  - Otherwise healthy patients ≥ 12 years of age  
- PZA and RIF combination therapy is no longer recommended due to hepatotoxicity and deaths

---

*MMWR. Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection  
### Treatment of LTBI in Children

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration</th>
<th>Daily Dose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9</td>
<td>10-15 mg/kg</td>
<td>270 doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(max 300 mg)</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>6</td>
<td>10-20 mg/kg</td>
<td>180 doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(max 600 mg)</td>
<td>INH resistant TB</td>
</tr>
<tr>
<td>Isoniazid/Rifapentine</td>
<td>3 H – 15 mg/kg</td>
<td>12 weeks</td>
<td>≥ 12 years old</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(max 900 mg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>P - 10.0–14.0 kg</td>
<td>300 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14.1–25.0 kg</td>
<td>450 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25.1–32.0 kg</td>
<td>600 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32.1–49.9 kg</td>
<td>750 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥50.0 kg</td>
<td>900 mg max</td>
</tr>
</tbody>
</table>

### Progressive Primary Pulmonary TB in Children

4-month-old female with RLL consolidation and R hilar lymphadenopathy
Gastric lavage (GL) is better than bronchoaleolar lavage (BL) for isolation of *Mycobacterium tuberculosis* in childhood tuberculosis  Abadco and Steiner, PIDJ 1992;11:735-738

- 20 children, 4 mo – 7.5 y/o, admitted over 16 months for suspected pulmonary tuberculosis in Brooklyn, NY

- GL: 10 (50%) cx + and 0 smear +, BL: 2 (10%) cx + and 0 smear +
Diagnosis of Pulmonary TB

Gastric lavage (GL) is better than bronchoalveolar lavage (BL) for isolation of *Mycobacterium tuberculosis* in childhood tuberculosis  Abadco and Steiner, PIDJ 1992;11:735-738

- 20 children, 4 mo – 7.5 y/o, admitted over 16 months for suspected pulmonary tuberculosis in Brooklyn, NY

- GL: 10 (50%) cx + and 0 smear +, BL: 2 (10%) cx + and 0 smear +


- 250 children, 1 mo – 5 y/o, admitted 2000-2002 for suspected pulmonary tuberculosis in Cape Town, South Africa; 58 (23%) cx + and 29 (12%) smear +

Diagnosis of Pulmonary TB

Gastric lavage (GL) is better than bronchoalveolar lavage (BL) for isolation of *Mycobacterium tuberculosis* in childhood tuberculosis  Abadco and Steiner, PIDJ 1992;11:735-738

- 20 children, 4 mo – 7.5 y/o, admitted over 16 months for suspected pulmonary tuberculosis in Brooklyn, NY

- GL: 10 (50%) cx + and 0 smear +, BL: 2 (10%) cx + and 0 smear +


- 250 children, 1 mo – 5 y/o, admitted 2000-2002 for suspected pulmonary tuberculosis in Cape Town, South Africa; 58 (23%) cx + and 29 (12%) smear +

- 1 induced sputum, smear or cx + = 41/62 (66%)

- 3 gastric aspirates, smear or cx + = 40/62 (64%)
### Diagnosis of Pulmonary TB

Gastric lavage (GL) is better than bronchoaleolar lavage (BL) for isolation of *Mycobacterium tuberculosis* in childhood tuberculosis  

- 20 children, 4 mo – 7.5 y/o, admitted over 16 months for suspected pulmonary tuberculosis in Brooklyn, NY
  - GL: 10 (50%) cx + and 0 smear +, BL: 2 (10%) cx + and 0 smear +

**Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study**  

- 250 children, 1 mo – 5 y/o, admitted 2000-2002 for suspected pulmonary tuberculosis in Cape Town, South Africa; 58 (23%) cx + and 29 (12%) smear +
  - 1 induced sputum, smear or cx + = 41/62 (66%)
  - 3 gastric aspirates, smear or cx + = 40/62 (64%)
  - 3 induced sputa, smear or cx + = 54/62 (87%) yield, youngest 3 mo

---

### Pediatric TB Cases by Site of Disease, 1993–2008

- **Any extrapulmonary involvement** (totaling 29.1%)
  - Lymphatic 18.9%
  - Meningeal 3.1%
  - Miliary 1.5%
  - Bone & Joint 1.5%
  - Other 4.1%

*Any extrapulmonary involvement, with or without pulmonary involvement (patients may have > 1 disease site but are counted in mutually exclusive categories for surveillance purposes)*
Percent of Pediatric TB Cases with Extrapulmonary Involvement* by Age Group & Sites of Disease, 1993–2008 (N=17,502)

<table>
<thead>
<tr>
<th>Site of Disease</th>
<th>Age &lt; 1 (n=1,697)</th>
<th>Age 1-4 (n=8,616)</th>
<th>Age 5-9 (n=3,991)</th>
<th>Age 10-14 (n=3,198)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphatic</td>
<td>7.8</td>
<td>19.3</td>
<td>22.2</td>
<td>19.4</td>
</tr>
<tr>
<td>Meningeal</td>
<td>7.6</td>
<td>3.6</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Miliary</td>
<td>5.5</td>
<td>1.2</td>
<td>0.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Bone &amp; Joint</td>
<td>0.4</td>
<td>1.3</td>
<td>1.6</td>
<td>2.4</td>
</tr>
<tr>
<td>Other</td>
<td>3.5</td>
<td>2.7</td>
<td>4.2</td>
<td>8.4</td>
</tr>
<tr>
<td>Total</td>
<td>24.8</td>
<td>28.1</td>
<td>30.1</td>
<td>33.1</td>
</tr>
</tbody>
</table>

*Any extrapulmonary involvement includes extrapulmonary only and both

Percent of Pediatric TB Cases with Extrapulmonary Involvement* by Age Group & Sites of Disease, 1993–2008 (N=17,502)

<table>
<thead>
<tr>
<th>Site of Disease</th>
<th>Age &lt; 1 (n=1,697)</th>
<th>Age 1-4 (n=8,616)</th>
<th>Age 5-9 (n=3,991)</th>
<th>Age 10-14 (n=3,198)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphatic</td>
<td>7.8</td>
<td>19.3</td>
<td>22.2</td>
<td>19.4</td>
</tr>
<tr>
<td>Meningeal</td>
<td>7.6</td>
<td>3.6</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Miliary</td>
<td>5.5</td>
<td>1.2</td>
<td>0.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Bone &amp; Joint</td>
<td>0.4</td>
<td>1.3</td>
<td>1.6</td>
<td>2.4</td>
</tr>
<tr>
<td>Other</td>
<td>3.5</td>
<td>2.7</td>
<td>4.2</td>
<td>8.4</td>
</tr>
<tr>
<td>Total</td>
<td>24.8</td>
<td>28.1</td>
<td>30.1</td>
<td>33.1</td>
</tr>
</tbody>
</table>

*Any extrapulmonary involvement includes extrapulmonary only and both
## Symptoms in Children with Tuberculosis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency (%)</th>
<th>Study A*</th>
<th>Study B^</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(47 infants &lt; 1 Yr old)</td>
<td>(156 children &lt; 20 yrs)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>79</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>64</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Loss of Appetite</td>
<td>43</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Diarrhea/vomiting</td>
<td>17</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Weight Loss</td>
<td>15</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Night Sweats</td>
<td>NR</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>NR</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>11</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

Symptoms in Children with Tuberculosis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study A*</td>
</tr>
<tr>
<td></td>
<td>(47 infants &lt; 1 Yr old)</td>
</tr>
<tr>
<td>Cough</td>
<td>79</td>
</tr>
<tr>
<td>Fever</td>
<td>64</td>
</tr>
<tr>
<td>Loss of Appetite</td>
<td>43</td>
</tr>
<tr>
<td>Diarrhea/vomiting</td>
<td>17</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>15</td>
</tr>
<tr>
<td>Night Sweats</td>
<td>NR</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>NR</td>
</tr>
<tr>
<td>Seizures</td>
<td>11</td>
</tr>
</tbody>
</table>


Conclusions

- A major focus of TB eradication in the US has been to identify and treat patients with LTBI – treatment is prolonged and compliance is difficult
- Childhood TB is most often pulmonary and may appear like many other forms of pneumonia
- In the U.S., interferon-γ release assays have already replaced TSTs for targeted screening in adults, but their use in children, < 5 years of age in particular, continues to be defined
- Pediatric LTBI and TB disease treatment mirrors that in adults - a weekly 12-dose regimen of INH and rifapentine has been approved recently by the CDC for LTBI