Mayo Clinic Center for Tuberculosis

DIAGNOSIS AND TREATMENT OF TUBERCULOSIS

James Sunstrum, M.D.
Beaumont Health
Disclosure and Objectives

• Disclosure: No conflicts of interest

• Objectives
  • Review 3 regimens to treat LTBI
  • Discuss key points for diagnosis of active TB
  • Review latest CDC guidelines for treatment of active TB, with emphasis on DOT
LTBI Case Studies
Case Study A (1)

Patient History

- 47-year-old Hispanic male
- Moved to U.S. from Bolivia 4 years ago
- Known contact of infectious TB case
- TST = 5 mm of induration
- 3 months later TST = 23 mm of induration
- No symptoms of TB disease
- Normal CXR, CBC, AST, and bilirubin
Case Study A (2)

Questions

1. What are this patient’s risk factors for TB infection or disease?

2. Has the management of this patient to date been appropriate?
Case Study A (3)

Discussion of risk factors

- Patient is a contact of an infectious TB case
- Recent immigrant to the US from a country with a high prevalence of TB
- If the patient had not been a contact, his immigration history would have made him a candidate for TB testing, but the 5-mm reaction would not be considered positive
Case Study A (4)

Discussion of risk factors

- Persons who immigrate from TB-endemic countries have increased rates of TB
- Rates of TB approach those of their countries of origin for 5 years after arrival in the U.S.
- These increased rates most likely result from recent *M. tuberculosis* infection in their native country
Case Study A (5)

Discussion of management

- As a contact of an active TB case, 5 mm of induration is considered positive
- This patient should have been treated for LTBI immediately after the first TST
Case Study C (1)

Patient History

- 28-year-old Asian male
- Moved to U.S. from China < 5 years ago
- Received BCG vaccine in China as a child
- QFT-GIT result = Positive
- CXR normal
- No symptoms of TB disease
- Known contact with a TB patient
Case Study C (2)

Questions

1. What are this patient’s risk factors for TB infection or disease?
2. What is the appropriate management for this patient?
Case Study C (3)

Discussion of risk factors

- Positive QFT-GIT result suggests that *M. tuberculosis* infection is likely (result is not affected by prior BCG vaccination)
- Recent immigrant to the US from a country with a high prevalence of TB
- Foreign-born status is a risk factor, i.e., he immigrated < 5 years ago
- Known contact with a TB patient
Case Study C (4)

Discussion of management

- Patient recently immigrated from a TB endemic country, positive QFT-GIT result may be indicative of LTBI
- Contact with a TB patient could have been source of infection
- Should be treated for LTBI
LTBI Treatment Regimens
Initiating Treatment

Before initiating treatment for LTBI

- Rule out TB disease by history, physical examination, chest radiography and, when indicated, bacteriologic studies
- Determine prior history of treatment for LTBI or TB disease
- Assess risks and benefits of treatment
- Determine current and previous drug therapy
### Treatment Regimens for Latent TB Infection

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Duration</th>
<th>Interval</th>
<th>Minimum Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9 months</td>
<td>Daily</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>Daily</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>52</td>
</tr>
<tr>
<td>Isoniazid &amp; Rifapentine</td>
<td>3 months</td>
<td>Once weekly</td>
<td>12</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4 months</td>
<td>Daily</td>
<td>120</td>
</tr>
</tbody>
</table>
Latent TB Infection Treatment Regimens – Isoniazid (INH) - 1

- 9-month regimen of isoniazid (INH) is one of the preferred regimens
  - 6-month regimen is less effective but may be used if unable to complete 9 months
- May be given daily or intermittently (twice weekly)
- Use directly observed therapy (DOT) for intermittent regimen
- Preferred regimen for children 2-11 years of age
Latent TB Infection Treatment Regimens – 3HP
Isoniazid (INH) and Rifapentine (RPT) - 1

- 3-month regimen of INH and RPT is an option equal to 9-month INH regimen for treating LTBI in certain groups, such as otherwise healthy people, 12 years of age and older, who were recently in contact with infectious TB or who had tuberculin skin test conversions or positive blood test for TB*

- Must use directly observed therapy (DOT)

*MMWR. Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w

Mayo Clinic Center for Tuberculosis
Latent TB Infection Treatment Regimens –
Isoniazid (INH) and Rifapentine (RPT) - 2

- Not recommended for children younger than 12 years of age, HIV-infected people taking antiretroviral therapy, pregnant women, or women expecting to be pregnant within the 12-week regimen
- INH and RPT once a week for 3 months - 12 doses within 4 months
Latent TB Infection Treatment Regimens – Rifampin

- Rifampin (RIF) given daily for 4 months is an acceptable alternative when treatment with INH is not feasible.
- In situations where RIF cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted.
- RIF daily for 4 months - 120 doses within 6 months
- Check for drug interactions
Latent TB Infection Treatment Regimens for Specific Situations – Fibrotic Lesions

Persons with Fibrotic Lesions Suggesting Previous TB

- Should be treated for LTBI if they have
  - A positive TST reaction (at least 5 mm) or IGRA result
  - No symptoms of infectious TB disease
  - No history of treatment for TB disease

- Treat only after active disease excluded with sputum testing

- Acceptable regimens include
  - 9 months of INH
  - 4 months of RIF (with or without INH)
  - 3 months of INH and RPT (12-dose regimen)
Latent TB Infection Treatment Regimens for Specific Situations - Pregnancy

Pregnancy and Breast-Feeding

- 9 months of INH daily or twice weekly; give with vitamin B6
- If cannot take INH, consult with TB expert
- Women at high risk for progression to TB disease should not delay LTBI treatment; monitor carefully
- Breast-feeding not contraindicated
Completion of Therapy

Completion of therapy is based on the total number of doses administered, not on duration alone.
Monitoring Drug Treatment
Clinical Monitoring - 1

Instruct patient to report signs and symptoms of adverse drug reactions:

- Fever
- Headache
- Rash
- Anorexia, nausea, vomiting, or abdominal pain in right upper quadrant
- Fatigue or weakness
- Dark urine
- Persistent numbness in hands or feet
Clinical Monitoring - 2

Monthly visits should include a brief physical exam and a review of:

- Rationale for treatment
- Adherence with therapy
- Symptoms of adverse drug reactions
- Plans to continue treatment
Laboratory Monitoring - 1

Baseline liver function tests (e.g., AST, ALT, and bilirubin) are not necessary except for patients with risk factors:

- HIV infection
- History of liver disease
- Regular alcohol use
- Pregnancy or in early postpartum period
Repeat laboratory monitoring if patient has:

- Abnormal baseline results
- Current or recent pregnancy
- High risk for adverse reactions
- Symptoms of adverse reaction
- Liver enlargement or tenderness during examination
Laboratory Monitoring - 3

- Asymptomatic elevation of hepatic enzymes seen in 10%-20% of people taking INH
  - Levels usually return to normal after completion of therapy
- Discontinue treatment if transaminase level exceeds 3 times the upper limit of normal if patient has symptoms of hepatotoxicity, and 5 times the upper limit of normal if patient is asymptomatic
ACTIVE TUBERCULOSIS DISEASE
Case #1

From: Current Approaches to Tuberculosis in the United States


Figure Legend:

Admission chest radiograph showing bilateral lung infiltrates with prominence in the right upper lobe and lingula of the left lung.
Active TB or not?

Smear negative

- PCR negative
- CXR negative
- PPD negative
Active TB or not?

- Smear positive
  - PCR +
  - CXR abnormal
  - PPD or IGRA +
Directly Observed Therapy (DOT)

- Health care worker watches patient swallow each dose
- DOT is preferred management strategy for all patients
- Can reduce acquired drug resistance, treatment failure, and relapse
- Nearly all regimens can be intermittent if given as DOT
- DOT reduces total number of doses and encounters
- For drug-resistant TB, use daily regimen and DOT
Treatment of TB Disease (3)

- Initial regimen should contain the following four drugs:
  - Isoniazid (INH)
  - Rifampin (RIF)
  - Pyrazinamide (PZA)
  - Ethambutol (EMB)
## Drug Abbreviations

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ABBREVIATION</th>
<th>USA INITIAL</th>
<th>WHO INITIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISONIAZID</td>
<td>INH</td>
<td>I</td>
<td>H</td>
</tr>
<tr>
<td>RIFAMPIN</td>
<td>RIF</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>PYRAZINAMIDE</td>
<td>PZA</td>
<td>P</td>
<td>Z</td>
</tr>
<tr>
<td>ETHAMBUTOL</td>
<td>EMB</td>
<td>E</td>
<td>E</td>
</tr>
<tr>
<td>RIFAPENTINE</td>
<td>RPT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Treatment of TB Disease

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Initial Phase** | • First 8 weeks of treatment  
• Most bacilli killed during this phase  
• 4 drugs used                                                                                           |
| **Continuation Phase** | • After first 8 weeks of TB disease treatment  
• Bacilli remaining after initial phase are treated with at least 2 drugs |
| **Relapse**   | • Occurs when treatment is not continued for long enough  
• Surviving bacilli may cause TB disease at a later time |
Basic TB Treatment Regimen

- **Isoniazid**
- **Rifampin**
- **Pyrazinamide**
- **Ethambutol**

**INITIAL (INTENSIVE) PHASE**
- 4 drugs
- 8 weeks

**CONTINUATION PHASE**
- Isoniazid + Rifampin
- 18 weeks

Mayo Clinic Center for Tuberculosis
CDC Guidelines 2016
Intensive Phase 8 weeks

• Daily dosing, rather than intermittent dosing, is preferred.
• If intermittent therapy is needed, use treatment three times per week for patients with:
  • Low risk of relapse (i.e. drug-susceptible TB organisms, non-cavitary and/or smear negative) and
  • Negative HIV-infection test result
CDC Guidelines 2016
Continuation Phase 18 weeks

• Daily dosing or treatment three times per week is recommended.
• If intermittent therapy is needed, treatment three times per week is preferred.
2 month sputum very important

INITIAL (INTENSIVE) PHASE

4 drugs × 8 weeks

CONTINUATION PHASE

• Isoniazid + Rifampin
• 18 weeks

Isoniazid
Rifampin
Pyrazinamide
Ethambutol
Why Extend Continuation-Phase Treatment for 3 more Months?

• Cavitary disease and positive sputum culture at 2 months of treatment, is associated with increased relapse in clinical trials

• Extended continuation phase decreased relapses in silicotuberculosis (from 20% to 3%)
Resources

- Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection *MMWR* 2000; 49 (No. RR-6) http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm

- Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?z_cid=mm6048a3_w

- CDC TB Website http://www.cdc.gov/tb

Additional TB Resources Available Online

- CDC’s Morbidity and Mortality Weekly Report
  http://www.cdc.gov/tb/publications/reportsarticles/mmwr/default.htm

- American Thoracic Society
  http://www.thoracic.org/statements/

- U.S. Preventive Services Task Force

- Bright Futures Recommendations for Pediatric Preventive Health Care