Diagnosis and Treatment of Tuberculosis, 2011

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Diagnosis of TB

• Diagnosis follows “Suspicion”

• When should we “Think TB”? 
  – Who is at risk for TB? 
  – Is TB presenting differently than in the past? 
  – How do we make the diagnosis? 
  – And ... are there new ways to improve diagnostic capacity?

Define Groups at-Risk

• Epidemiology of recent cases 
  – Majority of cases are non-US born from high prevalence countries 
  – Community-specific (e.g., homeless, substance abusers, Haitians...) 
  – Children from high-prevalence groups 

• Medical risk factors (if infected) 
  – HIV 7-10% / yr 
  – Diabetes 4% / yr 
  – ESRD 10-20% / yr 
  – Immunosuppressive therapies (e.g., organ transplant recipients, anti-TNF-α agents, chronic steroids) 
  – Age 

• Recent transmission versus reactivation 
**Evaluation for TB**

- Medical history
- Physical examination
- Mantoux tuberculin skin test / IGRA
- Chest radiograph
- Bacteriologic or histologic exam

**TB Symptom Assessment**

Symptoms of pulmonary TB

- Persistent cough, productive or non-productive
- Chest pain, hemoptysis
  +/− Anorexia, weight loss
  +/− Fever, chills, night sweats

* 25% of people with active pulmonary TB are asymptomatic


**Medical History**

- Symptoms of disease
- History of prior TB exposure, infection, or disease
- Past TB treatment (TB regimen, completion status)
- Demographic risk factors for TB
- Medical conditions that increase risk for TB disease

**Tuberculin Skin Test and IGRA**

- TST can be used in the diagnosis of TB disease but is less sensitive during severe illness

- IGRA is approved for use in both diagnosis of latent or active TB
Abnormalities often seen in apical or posterior segments of upper lobe or superior segments of lower lobe

May have unusual appearance in HIV-positive persons

Cannot confirm diagnosis of TB
### Bacteriologic Exam

- **Smear examination and culture**
  - Follow infection control precautions during specimen collection
- **TB diagnosis confirmed by culture**

### Drug Susceptibility Testing

- **Drug susceptibility testing for initial *M.tuberculosis* isolate**
- **Repeat for patients who**
  - Do not respond to therapy
  - Have positive cultures despite 2 months of therapy
- **Communicate with lab for prompt reporting**

### Nucleic Acid Amplification Tests

- **PCR is a more sensitive assay that can be applied directly**
- **Detection of *M. tuberculosis* in laboratory specimen**
- **Detection of mycobacteria in clinical specimen**
  - Pulmonary TB: smear positive / negative (positive predictive value = 75%)
  - Extrapulmonary TB – meningitis, pericarditis, pleurisy

### Other Routine Examinations

- **Testing for HIV infection**
  - CD4+ T-lymphocyte count for HIV-positive persons
- **Hepatitis B and C serologic tests, if risks present**
- **Measurements of aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, alkaline phosphatase, serum creatinine, and platelet count**
- **Visual acuity and color vision tests (when EMB used)**
Treatment of Tuberculosis

Responsibility for Successful Treatment

- Goals for treatment of TB are to cure the individual patient and to minimize transmission of *M. tb*
- Successful treatment benefits the individual patient and the community
- Responsibility lies with health care provider, not only for prescribing appropriate regimen, but for ensuring successful completion of therapy

“A decision to start TB treatment is a decision and obligation to cure the patient.”

Management Strategies

- Circumstances surrounding each patient may affect their ability to complete treatment
- Case management, using a patient-centered approach
- Interventions using enablers to assist in completion of therapy (transportation, convenient clinic hours, bilingual staff)
- Interventions using incentives meaningful to the patient (movie passes, gift cards, meal vouchers, clothing)
- Individualized care plan for completion including directly observed therapy (DOT)

Factors Guiding Treatment Initiation

- Epidemiologic information
- Clinical, pathological, chest x-ray findings
- Microscopic examination of acid-fast bacilli (AFB) sputum smears and cultures
- Rapid diagnostic tests (nucleic acid amplification test)
**Treatment Initiation**

- Positive AFB smear
- Treatment should not be delayed because of negative AFB smears if high clinical suspicion:
  - History of cough and weight loss
  - Characteristic findings on chest x-ray
  - Emigration from a high-incidence country

**Antituberculosis Drugs Currently in Use**

<table>
<thead>
<tr>
<th>First-Line Drugs</th>
<th>Second-Line Drugs</th>
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</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Streptomycin</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Cycloserine</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>p-Aminosalicylic acid</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Ethionamide</td>
</tr>
<tr>
<td>Rifabutin*</td>
<td>Amikacin or kanamycin*</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>Capreomycin</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin*</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin*</td>
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</tbody>
</table>

* Not approved by the U.S. Food and Drug Administration for use in the treatment of TB.

**Treatment Regimens**

- Four regimens recommended for treatment of culture-positive TB, with different options for dosing intervals in continuation phase
- Initial phase: standard four drug regimens (INH, RIF, PZA, EMB), for 2 months
- Continuation phase: additional 4 months or (7 months for some patients)

**Why 4 drugs?**

- Combination of drugs needed over sufficient time
  - Kill the TB bacilli rapidly
  - Prevent the emergence of drug resistance
  - Eliminate persistent bacilli to prevent relapse or failure
- Drugs differ in their activity against TB
  - Bactericidal
  - Bacteriostatic
**Bactericidal**

- Ability of drug to rapidly kill multiplying *M. tb*
- Drugs that have early bactericidal activity reduce the chance of resistance developing
  - INH > EMB > RIF
  - PZA is poor in this regard

**Bacteriostatic**

- Ability of drug to kill bacilli, mainly in the subpopulations of *M.tb*, that persist beyond the early months of therapy
  - RIF and PZA have the greatest sterilizing activity followed by INH and SM
  - Sterilizing activity of RIF persists throughout the course of therapy but the same is not true for PZA

**Why DOT?**

- DOT enables early identification of non-adherence, adverse drug reactions, and clinical worsening of TB
- Can lead to reductions in relapse and acquired drug resistance

**DOT Impact on Completion Rates**

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Completion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-supervised therapy (n=9)</td>
<td>61%</td>
</tr>
<tr>
<td>Modified DOT (n=2)</td>
<td>79%</td>
</tr>
<tr>
<td>DOT (n=4)</td>
<td>86%</td>
</tr>
<tr>
<td>Enhanced DOT (n=12)</td>
<td>91%</td>
</tr>
</tbody>
</table>

DOT = Directly Observed Therapy
Modified DOT = DOT given only for a portion of the treatment period, often while the patient was hospitalized
Enhanced DOT = Individualized incentives & enablers were provided in addition to DOT
**Why Extend Continuation-Phase Treatment for 3 Months?**

- Cavitary disease and positive sputum culture at 2 months associated with increased relapse in clinical trials
- Extended continuation phase decreased relapses in silicotuberculosis (from 20% to 3%)

**When to Extend Continuation-Phase Treatment for 3 Months?**

- Cavitary pulmonary disease and positive sputum cultures at completion of initial phase
- Once-weekly INH and rifapentine started in continuation phase and sputum specimen collected at the end of initial phase is culture positive
- HIV-infected with positive 2-month sputum culture
- Initial phase excluded PZA

**Duration of Continuation-Phase Treatment for Culture (+) TB**

- High clinical suspicion for active TB
- Place patient on initial-phase regimen: INH, RIF, EMB, PZA for 2 months
- Specimen collected at end of initial phase (2 months) culture positive?
  - YES: Give continuation-phase treatment of INH/RIF daily or twice weekly for 7 months
  - NO: Go to next question
- Specimen collected at end of initial phase (2 months) culture positive?
  - YES: Give continuation-phase treatment of INH/RIF daily or twice weekly for 4 months
  - NO: Go to next question
- Is the patient HIV positive?
  - YES: Give continuation-phase treatment of INH/RIF daily for 7 months
  - NO: Give continuation-phase treatment of INH/RIF daily or twice weekly for 4 months

**Treatment of Culture (+) TB – 1**

(Rated: AI in HIV-negative, AII in HIV-positive patients)

**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 if initial chest x-ray shows cavitation and specimen collected at end of initial phase (2 months) is culture positive.
### Treatment Monitoring – 1

- Monthly sputum for AFB smear and culture (until 2 consecutive cultures negative)
- Serial sputum smears every 2 weeks to assess early response
- Additional drug-susceptibility tests if culture-positive after 3 months of treatment

### Treatment Monitoring – 2

- Periodic (minimum monthly) evaluation to assess adherence and identify adverse reactions
- **Repeat chest x-ray:**
  - At completion of initial treatment phase for patients with initial negative cultures
  - At end of treatment for patients with culture-negative TB
- Renal function, AST, ALT, bilirubin, and platelet count if abnormalities at baseline
- Visual acuity and color vision monthly if EMB used > 2 months or doses > 15-20 mg/kg

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### Treatment of Culture (+) TB – 2

**Regimens without Pyrazinamide**

(Rated: CI for HIV-negative, CII for HIV-positive patients)

<table>
<thead>
<tr>
<th>Initial Phase</th>
<th>Continuation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months - INH, RIF, EMB daily (56 doses, within 8 weeks)</td>
<td>Options:</td>
</tr>
<tr>
<td>1) 7 months - INH, RIF daily (217 doses, within 31 weeks)</td>
<td></td>
</tr>
<tr>
<td>2) 7 months - INH, RIF twice / week (62 doses, within 31 weeks)*</td>
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</tr>
</tbody>
</table>

* Twice weekly dosing is not recommended for persons with CD4+ T-lymphocytes cell count < 100/µl

### Treatment of Culture (–) TB*

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<tr>
<td>2 months - INH, RIF, EMB, PZA daily (56 doses, within 8 weeks)</td>
<td>Options:</td>
</tr>
<tr>
<td>1) 2 months - INH, RIF daily (56 doses, within 8 weeks)</td>
<td></td>
</tr>
<tr>
<td>2) 2 months - INH, RIF twice / week (16 doses, within 8 weeks)*</td>
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* All cultures are negative, but evaluation at 2 months reveals clinical and chest x-ray response to antituberculous drug therapy
**Special Treatment Situations**

**Extrapulmonary TB**

- Similar treatment regimen for pulmonary TB*
- 6 to 9 month regimens that include INH and RIF are effective
- Corticosteroids used as adjunctive therapy for patients with TB meningitis and pericarditis
- If PZA cannot be used in the initial phase, continuation phase must be increased to 7 months

*Except for central nervous system (CNS) TB, including meningitis; length of therapy is 9-12 months

**Pregnancy and Breastfeeding**

- Untreated TB represents greater hazard to a woman and her child than treatment of disease
- Treatment of pregnant woman with suspected TB should be started if probability of TB is moderate to high
- Initial phase treatment regimen should consist of INH, RIF, and EMB
  - SM should not be substituted for EMB because of possible teratogenic effects
  - PZA not generally recommended for pregnant women in the United States

**Renal Insufficiency & End-Stage Renal Disease**

- Renal insufficiency complicates management of TB because some anti-TB medications are cleared by the kidneys
- Dosage should not be decreased because peak serum concentrations may be too low; smaller doses may decrease drug efficacy
- Dosing interval of anti-TB drugs should be increased
- Most drugs can be given 3 times weekly after hemodialysis
  - Dose must be adjusted for some drugs

**Hepatic Disease (1)**

- Choose regimens with fewer hepatotoxic agents for patients with liver disease
- **Recommended regimens:**
  1) Treatment without PZA
     - Initial phase (2 months): INH, RIF, and EMB
     - Continuation phase (7 months): INH and RIF
  2) Treatment without INH
     - Initial phase (2 months): RIF, PZA, and EMB
     - Continuation phase (4 months): RIF, EMB, and PZA
Special Treatment Situations

Hepatic Disease (2)

- **Recommended regimens**: (continued)

  3) Regimens with only one potentially hepatotoxic drug
     - RIF should be retained
     - Duration of treatment is 12-18 months

  4) Regimens with no potentially hepatotoxic drugs
     - Duration of treatment is 18-24 months

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### Treatment Guidelines Available Online

- CDC’s Morbidity and Mortality Weekly Report:
  [http://www.cdc.gov/mmwr](http://www.cdc.gov/mmwr)

- American Thoracic Society:

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### Additional TB Resources

For additional information on tuberculosis, visit the Division of Tuberculosis Elimination Web site at: