Treatment of Active Tuberculosis

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Disclosures

• No relevant financial relationships
• No conflicts of interest
Objectives

• Identify the basic principles of treatment of active tuberculosis

• Describe the current guidelines for the treatment of TB disease
A Case

- 39 yo woman recently immigrated to the US from the Philippines, found to have abnormal chest imaging
- No symptoms
- No personal history of diagnosis or treatment of tuberculosis
- No known TB contacts
Case Imaging
Case Management

• Bronchoalveolar lavage grows out Mycobacterium tuberculosis
• No evidence of TB disease outside of the lung
• Now what?
  • What drugs?
  • What dosing schedule?
  • What duration of treatment?
  • What special considerations?
Treatment of TB Disease – The Big Picture

• Only about 30% of individuals with advanced TB disease heal spontaneously, despite supportive measures

• With effective therapies, treatment of drug-susceptible TB disease is usually successful

• There remain major barriers to adequate treatment of TB disease:
  • Drug resistance
  • Requirement for multidrug therapies
  • Need for prolonged therapeutic courses
Objectives of TB Disease Therapy

• Rapidly reduce the number of actively growing bacilli in the patient
  • Decreases disease severity
  • Reduces patient infectivity
  • Requires **bactericidal** effect

• Eradicate populations of persisting bacilli
  • Necessary to achieve durable cure
  • Requires **sterilizing** effect

• Prevent development of drug resistance
  • Requires **multidrug regimens**
Current ATS/CDC/IDSA Guidelines


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Deciding to Initiate Therapy for TB Disease

• Consider the likelihood of TB disease based on clinical, radiographic, and microbiologic grounds

• Balance the risk/benefit to the patient of initiating or deferring, based on clinical status

• Weigh the public health risk with respect to transmission risk and concern for potential loss to follow-up
Deciding to Initiate Therapy for TB Disease

Figure 1. Factors to be considered in deciding to initiate treatment empirically for active tuberculosis (TB) (prior to microbiologic confirmation). Abbreviations: AFB, acid-fast bacilli; HIV, human immunodeficiency virus; IGRA, interferon-γ release assay; Mtb, Mycobacterium tuberculosis; TNF, tumor necrosis factor; TST, tuberculin skin test.

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First-Line Antituberculosis Drugs

- Rifamycins
  - Rifampin
  - Rifabutin
  - Rifapentine
- Isoniazid
- Pyrazinamide
- Ethambutol
Rifampin (RIF)

- **Mechanism of action:**
  - Inhibits bacterial DNA-dependent RNA polymerase

- **Effect:**
  - Bactericidal and sterilizing

- **Resistance:**
  - Missense mutations in the *rpoB* gene

- **Adverse Effects:**
  - Hepatotoxicity, GI effects, hematologic effects (thrombocytopenia, neutropenia, acute hemolytic anemia), orange discoloration of body fluids
Isoniazid (INH)

• Mechanism of action:
  • Inhibits mycolic acid synthesis in the mycobacterial cell wall

• Effect:
  • Bactericidal

• Resistance:
  • Loss of the katG-encoded catalase peroxidase
  • Overexpression or alterations in the INH target InhA
  • Loss of NADH dehydrogenase II activity (ndh)
  • Alterations and overexpression of KasA

• Adverse Effects:
  • Hepatotoxicity, neuropathy
Pyrazinamide (PZA)

• Mechanism of action:
  • Converted by PZase to active pyrazinoic acid, which likely exerts effect on cell membrane and cytoplasmic targets

• Effect:
  • Accelerates sterilizing effect of INH and RIF

• Resistance:
  • Mutations to the \( pncA \) gene, which encodes PZase

• Adverse Effects:
  • Hepatotoxicity, hyperuricemia, arthralgia, GI effects
Ethambutol (EMB)

- **Mechanism of action:**
  - Disrupts the mycobacterial cell wall synthesis by inhibiting arabinosyl transferase

- **Effect:**
  - Bacteriostatic companion drug, prevents resistance

- **Resistance:**
  - Mutations increase production of the arabinosyl transferase, overcoming inhibitory effect

- **Adverse Effects:**
  - Hepatotoxicity, optic neuritis
Phases of First-Line Therapy

- **Intensive phase**
  - Two months of 3-4 drug therapy
  - Goal is to realize symptomatic improvement and microbiologic conversion, as a consequence of reduced bacillary burden

- **Continuation phase**
  - At least four months of 2 drug therapy
  - Goal is bacillary eradication for sustained TB cure
Intensive Phase: First-Line Therapy

- Begin with four-drug therapy with RIF, INH, PZA, EMB
- EMB can be discontinued if drug susceptibility studies demonstrate that an isolate is susceptible to RIF & INH
- Current ATS/CDC/IDSA guidelines strongly recommend use of daily rather than intermittent dosing in the intensive phase
Continuation Phase: First-Line Therapy

• After the two-month intensive phase, narrow therapy to RIF & INH

• During the continuation phase, daily and thrice-weekly dosing schedules are both acceptable

• The duration of the continuation phase is usually 4-7 months, depending on disease characteristics and response to treatment

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Alternative Dosing Regimens

• Thrice-weekly dosing throughout intensive and continuation phases
  • May be considered when daily treatment is not feasible or is poorly tolerated

• Twice-weekly dosing during continuation phase
  • Not generally recommended, due to concerns regarding missed doses

• Once-weekly INH/RPT during continuation phase
  • Generally recommended against, with rare exceptions
### Summary of Recommendations: First-Line Therapy for Drug-Susceptible TB

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#### Table 2. Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Intensive Phase</th>
<th>Continuation Phase</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>INH 7 d/wk for 56 doses (8 wk), or RIF 7 d/wk for 126 doses (18 wk), or PZA 5 d/wk for 40 doses (8 wk), or EMB 5 d/wk for 90 doses (18 wk)</td>
<td>INH 7 d/wk for 126 doses (18 wk), or RIF 5 d/wk for 90 doses (18 wk)</td>
<td>This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.</td>
</tr>
<tr>
<td>2</td>
<td>INH 7 d/wk for 56 doses (8 wk), or RIF 3 times weekly for 54 doses (18 wk)</td>
<td>INH 3 times weekly for 54 doses (18 wk)</td>
<td>Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.</td>
</tr>
<tr>
<td>3</td>
<td>INH 3 times weekly for 24 doses (8 wk), or RIF 3 times weekly for 54 doses (18 wk)</td>
<td>INH 3 times weekly for 54 doses (18 wk)</td>
<td>Use regimen with caution in patients with HIV and/or cavitory disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.</td>
</tr>
<tr>
<td>4</td>
<td>INH 7 d/wk for 14 doses then twice weekly for 12 doses</td>
<td>INH Twice weekly for 36 doses (18 wk)</td>
<td>Do not use twice-weekly regimens in HIV-infected patients or patients with smear-positive and/or cavitory disease. If doses are missed, therapy is equivalent to once weekly, which is inferior.</td>
</tr>
</tbody>
</table>

*Abbreviations: DOT, directly observed therapy; EMB, ethambutol; HIV, human immunodeficiency virus; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin.*

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Special Considerations

• INH resistance or intolerance
• Pregnancy
• Pulmonary TB with cavitation or persistently positive sputum after intensive phase
• Culture-negative pulmonary TB
• Extrapulmonary TB
• HIV
• Rifampin or multi-drug resistance
INH Resistance or Intolerance

Tuberculosis Cases by Drug Susceptibility Patterns and Year, Minnesota, 2011-2015

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases With Susceptibility Results*</th>
<th>Any Drug Resistance† No. (%)</th>
<th>INH-Resistant** No. (%)</th>
<th>MDR-TB‡ No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>101</td>
<td>22 (22)</td>
<td>12 (12)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>2012</td>
<td>124</td>
<td>23 (19)</td>
<td>12 (10)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>2013</td>
<td>113</td>
<td>26 (23)</td>
<td>13 (12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2014</td>
<td>105</td>
<td>25 (24)</td>
<td>19 (18)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>2015</td>
<td>115</td>
<td>23 (20)</td>
<td>9 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>558</td>
<td>119 (21)</td>
<td>65 (12)</td>
<td>5 (0.9)</td>
</tr>
</tbody>
</table>
INH Resistance or Intolerance

• (1) Daily RIF/EMB/PZA +/- fluoroquinolone for 6-9 months
  • Generally preferred

• (2) Daily RIF/EMB + fluoroquinolone for 9-12 months
  • Reserved for those intolerant to PZA

• (3) Daily RIF/EMB/PZA + moxifloxacin for 2 months, followed by weekly rifapentine/moxifloxacin for 4 months
  • Least evidence
Pregnancy

- Whether to include PZA in the treatment of pregnant women is controversial in the United States
- In high-burden countries, PZA has been used extensively for treatment of pregnant women, without clear fetal impact
- Current ATS/CDC/IDSA guidelines recommend:
  - Individualized, shared decision regarding PZA use in low-risk women who are pregnant
  - Favor inclusion of PZA for women with HIV or severe or extrapulmonary TB
PZA Avoidance or Intolerance

- PZA is not necessary for successful treatment of pan-sensitive, low-risk, pulmonary TB
- Intensive phase:
  - RIF, INH, EMB daily for 2 months
- Continuation phase:
  - RIF, INH daily or TIW for 7 months
- Total duration of therapy: 9 months
Pulmonary TB – Special Circumstances

• Increased risk of TB disease relapse after 6 months of standard therapy in patients with:
  • Cavitary pulmonary disease
  • Persistently positive sputum cultures following completion of the intensive phase

• In those with both features above:
  • Risk of relapse is ~20%
  • Expert opinion is to extend continuation phase to 7 months (9 months total duration)

• Consideration also given to extended continuation phase in those with one of the features listed
Culture-Negative Pulmonary TB in Adults: Diagnosis

- Speculative diagnosis when:
  - Clinical and radiographic features suggest pulmonary TB disease
  - Cultures are AFB smear and culture negative

- Presumptive diagnosis when:
  - Patient has radiographic and/or clinical improvement following two months of intensive phase therapy
Culture-Negative Pulmonary TB in Adults: Treatment

• Optimum treatment regimens and duration are not well established

• Consensus is to treat with RIF/INH/PZA/EMB daily through the two-month intensive phase

• Details of the continuation phase in HIV-negative patients are controversial
  • Daily or TIW RIF/INH for 2 months is given a conditional recommendation in current guidelines (very low certainty of evidence)
  • Some recommend daily or TIW RIF/INH/PZA/EMB for 4 months

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Treatment of Extrapulmonary TB Disease: General Principles

- Same overall strategy that guides treatment of pulmonary TB
- Still utilize 2-month intensive phase, followed by continuation phase
- Stronger consideration may be given to utilizing a daily dosing regimen in the continuation phase
- Duration of continuation phase may need to be extended

*Clin Infect Dis* 2016;63:e147-e195
Treatment of Extrapulmonary TB Disease: Specific Site Involvement

• Lymph Node Tuberculosis
  • Standard 6 month regimen
  • Therapeutic lymph node excision is not typically indicated
  • Incision and drainage often harmful

• Pleural Tuberculosis
  • Standard 6 month regimen

• Pericardial Tuberculosis
  • Standard 6 month regimen
  • Routine adjunctive corticosteroids not recommended

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Treatment of Extrapulmonary TB Disease: Specific Site Involvement

• Bone, Joint, and Spinal Tuberculosis
  • Optimal duration of therapy not established
  • Reasonable to extend treatment to 9 months for routine cases
  • If there is hardware present, may extend treatment to 12 months
  • Surgical debridement may be considered, but is not routinely required

• Abdominal and Genitourinary Tuberculosis
  • Standard 6 month regimen

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Treatment of Extrapulmonary TB Disease: Specific Site Involvement

• Tuberculous Meningitis
  • Given high morbidity and mortality, treatment is generally more aggressive
  • Intensive phase: RIF/INH/PZA/EMB through the full 2 months
  • Continuation phase: RIF/INH for 10 months
  • Adjunctive corticosteroids tapered over 6-8 weeks strongly recommended

• Disseminated Tuberculosis
  • Standard 6 month regimen
  • Consider corticosteroids for respiratory failure

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Treatment of TB Disease in the Setting of HIV Infection

• Routine HIV testing is recommended for individuals diagnosed with TB disease

• Antiretroviral therapy should be started during anti-TB therapy
  • CD4 < 50 cells/µl: within 2 weeks
  • CD4 ≥ 50 cells/µl: within 8-12 weeks

• Adjustments in continuation phase:
  • Dosing should be **daily** (not TIW)
  • If ART not started, extend duration to 7 months (i.e., 9 months total therapy)
Rifampin Resistance

• Makes treatment of TB disease much more difficult

• Even rifampin mono-resistance requires expanded medication regimens for prolonged durations
Resistance Categories

• Rifampin-Resistant TB
  • Resistance to RIF, but not other first line agents

• Multidrug-Resistant TB (MDR-TB)
  • Resistance to both RIF & INH

• Extensively drug-resistant TB (XDR-TB)
  • Resistance to INH, RIF, a fluoroquinolone, and a second-line injectable (i.e., amikacin, kanamycin, or capreomycin)
The Scope of the Problem - 2015

• Estimate of burden:
  • Of all new TB cases worldwide, 4% harbor MDR-TB and 1% rifampicin-resistant TB

• Estimate of morbidity:
  • When treated in a programmatic setting, cure achieved in just 62% of patients with MDR-TB (and only 40% of those with XDR-TB)

1. WHO Global Tuberculosis Report 2015
2. Eur Respir J. 2013;42:156–68
Rifampin-Resistant TB Treatment

- Preferred Regimen:
  - INH/EMB/fluoroquinolone for 12-18 months
  - + PZA for at least first 2 months
  - +/- injectable agent for at least first 2 months

- Other Regimens:
  - INH/EMB/PZA daily for 18 months +/- injectable agent for at least the first 2 months
  - INH/PZA/streptomycin daily for 9 months (generally not preferred)
Principles of MDR-TB Treatment

- Consultation with an expert should be obtained in all cases of MDR-TB
- MDR-TB regimens should contain at least 4-6 likely effective drugs
- Drug choice depends on susceptibility testing, prior treatment history, overlapping toxicities, and other factors
- Duration is usually very prolonged
### Classification of Anti-TB Drugs

#### Comparison between standard U.S.-based classification and the WHO classification system for anti-tuberculosis drugs

<table>
<thead>
<tr>
<th>U.S. First-line Drugs</th>
<th>U.S. Second-line Drugs</th>
<th>U.S. Third-line Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Amikacin</td>
<td>Bedaquiline</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Capreomycin</td>
<td>Delamanic²</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Kanamycin²</td>
<td>(Linezolid¹)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Streptomycin</td>
<td>Clofazimine</td>
</tr>
<tr>
<td>Rifabutin</td>
<td></td>
<td>Imipenem/clastin³</td>
</tr>
<tr>
<td>Rifampetine</td>
<td>Levofloxacin</td>
<td>Meropenem³</td>
</tr>
</tbody>
</table>

**WHO Group 1**

**WHO Group 2**

**WHO Group 3**

**WHO Group 4**

**WHO Group 5**

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1. Linezolid: Traditionally classified as third-line drug, but now often used as a second-line agent in the United States (but considered WHO Group 5).
2. Kanamycin, prothionamide, terizone, and delamanid: Not currently available in the United States.
3. Clavulanate (available as amoxicillin/clavulanate): Recommended as an adjunctive agent to imipenem/clastatin and meropenem.

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**Curry International TB Center**  

Mayo Clinic Center for Tuberculosis
When to Suspect MDR-TB (Or: When to Consider and Expanded Regimen)

- Individual has previously been treated for TB
- Patient is failing TB treatment
- Contact to established MDR-TB case
- Person born in country or residing in setting where drug-resistant TB is prevalent
Expanded Empiric Treatment Regimen

• Usual elements:
  • All four first-line agents (RIF/INH/PZA/EMB)
  • **Two or more** additional drugs:
    • Fluoroquinolone
    • Injectable agent (amikacin or capreomycin, not streptomycin)
    • Linezolid, ethionamide, cycloserine, PAS

• Drug choice based on:
  • Personal treatment history, drug resistant pattern of source case or region of origin
Individualized Regimen for MDR-TB

**STEP 1**

Use any available **First-line drugs**
- Pyrazinamide
- Ethambutol

Plus one of these **Fluoroquinolones**
- Levofloxacin
- Moxifloxacin

Plus one of these **Injectable agents**
- Amikacin
- Capreomycin
- Kanamycin
- Streptomycin

**STEP 2**

Pick one or more of these **Oral second-line drugs**
- Cycloserine
- Ethionamide
- PAS
- Linezolid

**STEP 3**

Consider use of these **Third-line drugs**
- Bedaquiline
- Delamanid
- Clofazimine
- Imipenem
- Meropenem/Cilavulanate
- Amoxicillin/Cilavulanate
- Clarithromycin
- High-dose INH

Curry International TB Center
Duration of MDR-TB Therapy

• Optimal duration not established

• Current U.S. expert opinion and practice:
  • Intensive phase (includes injectable): at least 6 months beyond culture conversion
  • Total duration: at least 18 months beyond culture conversion

• Current WHO treatment recommendation:
  • Intensive phase: at least 8 months
  • Total duration: at least 20-24 months, longer if previously treated for MDR-TB

1. Curry International TB Center  
2. WHO Treatment Guidelines for Drug-Resistant Tuberculosis: 2016 Update

Mayo Clinic Center for Tuberculosis
Short-Course Treatment for MDR-TB

- Observational studies have reported 84-89% treatment success with 9-12 month regimens for MDR-TB
- Promising, but requires confirmation before becoming the standard of care
- In certain populations, WHO supports use of short-course standardized regimens for MDR TB (conditional recommendation, very low certainty in the evidence)
Finally…Treatment Setting – DOT

- No matter the TB resistance profile, the treatment regimen, or the duration of therapy, **direct observed therapy** is the standard of care.

- Practical considerations regarding DOT for daily dosing regimens – an acceptable weekly schedule may include:
  - 5 days of direct observed therapy
  - 2 days of self administered therapy
Summary

• Treatment of TB disease requires multiple drugs dosed for extended periods

• Successful treatment depends on achieving both bactericidal and sterilizing effects

• Several factors can affect treatment duration and dosing schedules

• Rifamycins are the cornerstone of shorter course regimens – with rifamycin resistance, additional drugs and longer durations required
Thank you!
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