Treatment of TB Disease
“The Basics”

Jennifer Whitaker, MD, MS
Tuberculosis Clinical Intensive Program, Mayo Clinic, Rochester
November 19, 2013
Disclosures

• Pfizer Educational Grant for Learning and Change
Objectives

• Describe the current guidelines for the treatment of TB disease

• Describe the common adverse reactions to TB treatment regimens

• Explain how to manage adverse reactions to TB treatment regimens
Treatment Before Antimicrobial therapy

First (Modern) Sanitarium: Poland 1854, Hermann Brehmer

Abiding Principles:
- Isolation of those with active disease in infection control
- Further investigation into role of vitamin D in treatment
Timeline of TB Antimicrobials

- Robert Koch discovers *M. tuberculosis*
- "Collapse theory" of artificial pneumothorax as therapy
- Streptomycin discovered
- PAS discovered
- Isoniazid found to treat TB
- Cycloserine discovered; Triple therapy: SM, PAS, INH x 2 yr
- Rifampin discovered; RIF & INH x 9 mo
- Ethambutol discovered
- Pyrazinamide for TB therapy
- 1882
- 1920
- 1944
- 1946
- 1952
- 1955
- 1959
- 1961
- 1962
- 1992
- 2012
- Rifabutin
- Bedaquiline

©2013 MFMER | slide-5
Evolution of TB Drug Treatment

• Single Drug Treatment
  • Rapid development of resistance; High relapse rates

• Dual therapy
  • Prevents resistance; Prolonged treatment required

• 1952 Triple therapy: Isoniazid + Streptomycin + PAS
  • Duration 24 months; Cure rates ~ 95%

• 1960s Triple therapy: Ethambutol replaces PAS
  • Duration 18 months; Cure rates ~95%

• INH, SM, EMB and RIF x 9 mo shown to be as effective as without RIF; Cure rates ~95%

• PZA was found to accelerate the time required to achieve culture negativity and overall course to 6 mo with 95% cure rates when combined with INH/RIF

Iseman MD. Eur Respir J 2002; 20: Suppl. 36, 87s–94s
Evolution of TB Drug Treatment

• 6 mo therapy with 2 mo intensive “bactericidal phase” of INH, RIF, PZA, and either SM or EMB, followed by a 4 mo “continuation phase” of INH and RIF as effective as 9 mo therapy

• Established that “continuation phase” drugs could be administered twice or thrice weekly, facilitating DOT

• Neither SM nor EMB improved results over a three-drug regimen (INH, RIF, and PZA) during the first 2 months of intensive therapy when the isolate was fully susceptible

Iseman MD. Eur Respir J 2002; 20: Suppl. 36, 87s–94s
Noncompliance or Abandonment of Therapy is Major Impediment of TB Treatment

• Directly observed therapy (DOT) has been shown to:
  • Facilitate treatment completion rates and bacteriologic evidence of cure
  • Decrease acquired and primary drug resistance
  • Decrease relapse rates

• CDC and American Thoracic Society (ATS) recommend consideration of DOT for all and
  • Especially for those with drug resistant organisms, cavitary disease, or HIV infection

Current Preferred Regimens for Drug-Susceptible TB disease:

• Isoniazid, Rifampin, Pyrazinamide, Ethambutol

• *Isoniazid and Rifampin are the cornerstone of therapy*
  • Both are bactericidal against rapidly dividing mycobacteria
  • Rifampin also exhibits excellent late sterilizing effect on semi-dormant organisms
  • Non-INH based regimen = usually 9 months
  • Non-Rifampin regimen = 12-18 months (variable)

• Pyrazinamide
  • Potent sterilizing ability within acidic environment of areas of acute inflammation, suppuration
Standard TB Therapy for Drug-Susceptible Disease

- **Initiation Phase:**
  - 4 drugs for 2 months (8 weeks)
  - Rifampin, isoniazid, pyrazinamide, ethambutol
  - Okay to stop ethambutol once it is known that isolate is susceptible to rifampin, isoniazid, and pyrazinamide

Question 1:

In what cases should the continuation phase of TB therapy be prolonged from 4 months to 7 months?

A. HIV co-infection

B. Cavitary disease with positive cultures at end of initiation phase

C. Initiation regimens of Isoniazid, Rifampin, and Ethambutol, without use of PZA

D. B and C

E. All cases of extrapulmonary disease
Standard TB Disease Continuation Therapy

• **Continuation Phase:**
  - Rifampin & Isoniazid for 4 months (18 weeks)
  - Six months total course of therapy
  - If PZA not used in initiation, then 7 months continuation

• **Continuation Phase (cavitary disease AND positive cultures after initiation phase)**
  - Rifampin & Isoniazid x 7 months (31 weeks) if cavitary disease at diagnosis and positive cultures after initiation phase at 2 months
  - Same therapy first 8 weeks + RIF/INH x 31 wks; Rifapentine should not be used
  - Nine months total course of therapy
First Line TB Drugs

• Isoniazid (INH, H)

• Rifamycins:
  • Rifampin (Rifampicin, RIF, R)
  • Rifabutin (RFB)
  • Rifapentine (RPT)

• Pyrazinamide (PZA, Z)

• Ethambutol (EMB, E)

• Streptomycin (SM, S)
Second Line TB Drugs

- Fluoroquinolones
  - Moxifloxacin, Levofloxacin
- Aminoglycosides
  - Amikacin & Kanamycin
- Capreomycin
- Ethionamide
- Cycloserine
- Para-Aminosalicylic Acid (PAS)
Third Line TB Drugs

- Linezolid
- Amoxicillin/clavulanate
- Clofazimine
- Imipenem
- Bedaquiline (FDA approved Dec 2012; first active agent for TB to be registered since 1963)
Recommended Treatment Regimens for Drug-Susceptible Organisms

### TABLE 2. Drug regimens for culture-positive pulmonary tuberculosis caused by drug-susceptible organisms

<table>
<thead>
<tr>
<th>Initial phase</th>
<th>Continuation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen</td>
<td>Drugs</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>1</td>
<td>INH</td>
</tr>
<tr>
<td></td>
<td>RIF</td>
</tr>
<tr>
<td></td>
<td>PZA</td>
</tr>
<tr>
<td></td>
<td>EMB</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>INH</td>
</tr>
<tr>
<td></td>
<td>RIF</td>
</tr>
<tr>
<td></td>
<td>PZA</td>
</tr>
<tr>
<td></td>
<td>EMB</td>
</tr>
</tbody>
</table>

**Evidence Ratings:**
- A=preferred
- B=acceptable alternative
- C= when A&B cannot be given
- E=never
- I=randomized controlled trial
- II=Clinical trials, not randomized or done in other populations

ATS/CDC/IDSA. Treatment of Tuberculosis. MMWR 2003.
Question 2:

Which standard treatment regimens are not recommended for patients co-infected with HIV?

• A. Any regimen that is not a daily or 5 times a week dosing regimen
• B. Regimens containing rifapentine
• C. A & B
• D. None of the above
Regimen 1: Initiation with INH, RIF, PZA, EMB for 5 or 7 days/week x 8 weeks

Initiation Phase: Preferred, RCT data in HIV (-)
If 7 days/week = 56 doses
If 5 days/week (DOT) = 40 doses

Continuation Phase x 18 weeks
1a: INH/RIF: 7 days/wk = 126 or 5 days/wk (DOT) = 90 doses
1b: INH/RIF: twice weekly = 36 doses
*1c: INH/RPT: once weekly = 18 doses
* Alternative for HIV(-), DO NOT use in HIV+
Regimen 2: Initiation with INH, RIF, PZA, EMB x 8 wk (daily dosing with change to intermittent after 2 wk)

**Level of Evidence:**

2a: pref, non-RCT

2b: alternative, RCT

**Initiation Phase:**

- 7d/wk x 2 wk, then twice weekly x 6 wk or
- 5d/wk x 2 wk (DOT), then twice weekly x 6 wk

**Continuation Phase x 18 weeks**

2a: INH/RIF: twice weekly = 36 doses

*2b: INH/RPT: once weekly = 18 doses

* Alternative for HIV(-); DO NOT use in HIV+ patients
Regimen 3: Initiation with INH, RIF, PZA, EMB *three times per week* x 8 weeks

**Initiation Phase:** Alternative regimen; RCT data in HIV (-)

INH, RIF, PZA, EMB three times/week x 8 weeks = 24 doses

**Continuation Phase** x 18 weeks

3a: INH/RIF: twice weekly = 36 doses
Regimen 4: Initiation with INH, RIF, EMB x 8 weeks (NO PZA)

Initiation Phase: Use only when other regimens cannot be used, RCT data in HIV (-)
   If 7 days/week = 56 doses
   If 5 days/week (DOT) = 40 doses

Continuation Phase: INH/RIF x 31 wks (7 mo)
Summary: Standard Therapy for TB Susceptible to First Line Drugs

• RIF/INH/PZA/EMB until susceptibilities confirmed
  • Can stop EMB if susceptible to RIF/INH/PZA
• RIF/INH/PZA for 8 weeks
• RIF/INH for 18 weeks
  • (If PZA not used in initiation, then 31 wk)
  • Directly observed therapy (DOT)
  • Usually intermittent
• Six months total (9 mo if no PZA)
  • Missed doses added to end of therapy
Therapy for Cavitary Disease and Positive Culture at 8 weeks (end of initiation period)

- Same therapy first 8 weeks (2 months)
- RIF + INH for 31 weeks (7 months)
- 9 months total therapy administered
- Rifapentine should not be used
Summary: Intermittent Therapy with DOT

- Daily therapy = 5 days/week
- Multiple options for once, twice, or three times weekly therapy
- Individual doses increased for less frequent dosing
- Rifapentine used in once weekly regimens
  - Not for HIV patients
Treatment of Culture-negative Pulmonary TB

• Abnormal CXR + positive TST/IGRA; suspicion for TB disease
  • Start standard treatment: INH/RIF/PZA/EMB
  • Attempt to collect appropriate specimen
  • If no specimen or culture negative, then look at CXR and clinical outcome

• Clinical/CXR improvement
  • Clinical diagnosis of TB
  • Complete 2 more months of INH/RIF

• Radiograph unchanged after 2 months
  • Discontinue treatment
  • Completed therapy for LTBI
Question 3:

A 55 year old HIV-negative male is diagnosed with TB meningitis. What is your treatment recommendation?

A. Same treatment as for pulmonary TB (INH/RIF/PZA/EMB x 2 mo, then INH/RIF x 4 mo)

B. A + corticosteroid treatment for first 8 wk

C. INH/RIF/PZA/EMB x 2 mo, then INH/RIF x 7-10 months (if drug susceptible)

D. C + corticosteroid treatment for first 8 wk
Treatment of Extrapulmonary TB Disease

• Generally the same treatment as for pulmonary TB
• Addition of corticosteroids for:
  • TB pericarditis
  • TB meningitis
• Recommended that duration of therapy extended to 9-12 mo for TB meningitis
Sputum Culture Monitoring During Pulmonary TB Treatment

• Serial sputum smears every 2 weeks to assess early response

• Monthly sputum for AFB smear and culture (until 2 consecutive cultures negative)

• Repeat drug-susceptibility tests if culture-positive after 3 months of treatment
Clinical Monitoring During Pulmonary TB Treatment

• Periodic (minimum monthly) evaluation to review adherence and identify adverse reactions

• Repeat chest x-ray:
  • After 2 months treatment for patients with negative cultures
  • As clinically indicated for worsening
  • At end of treatment
Diagnostic Monitoring During Pulmonary TB Treatment

- Liver enzymes at least monthly
- Renal function and CBC if abnormalities at baseline
- Visual acuity and color vision monthly
  - If EMB used > 2 months or
  - EMB dose > 15-20 mg/kg or
  - EMB with renal failure
Special Scenarios
When Standard TB “RIPE” Therapy Cannot Be Used

• Intolerance/toxicity of first line medications
• Suspected or confirmed drug resistance
• Special Circumstances
  • Retreatment in patient who relapses after self-administered therapy or inappropriate therapy
  • Liver disease with $\text{AST} \geq 3$ times normal
  • Pregnancy; may consider avoiding PZA
When Standard “RIPE” Therapy Cannot Be Used

• TB medication pharmacology discussed in other lectures
  • Approaches to TB drug intolerance

• TB medication resistance discussed in other lectures
Treatment Interruptions

ATS. Am J Respir Crit Care Med 2003;167:603–662
Adverse Outcomes

• Treatment failure: positive cultures after 4 months of treatment
  • After 3 mo of regimen containing INH+RIF for pulmonary TB with drug-susceptible organisms, 90-95% of patients have negative cultures and demonstrate clinical improvement

• Relapse: recurrent TB disease at any time after completion of treatment with apparent cure
Treatment Failure

- A single drug should never be added to a failing regimen

- Reasons for treatment failure in patients receiving appropriate regimens:
  - Nonadherence to the drug regimen
  - Drug resistance
  - Malabsorption of drugs
  - Extreme biological variation

- If treatment failure occurs, early consultation with a specialty center is strongly advised.
Relapse

• Most relapses occur within the first 6–12 months after completion of therapy.
  • In nearly all patients with tuberculosis caused by drug-susceptible organisms and who were treated with rifamycin containing regimens using DOT, relapses occur with susceptible organisms.

• Suspect drug resistance in those who had:
  • Self-administered therapy
  • Non-rifamycin regimen
  • If initial drug susceptibility testing was not performed and the patient fails or relapses with a rifamycin-containing regimen given by DOT
Treatment in Relapse

• If suspected drug resistance:
  • Expanded regimen with INH, RIF and PZA + 2-3 new drugs, to minimize the probability of developing further resistance.

• If exogenous reinfection as the cause of apparent relapse:
  • Susceptibility profile of the source case may be used to guide, pending susceptibility results of the patient's own isolate.

• Drug susceptible disease treated with DOT, initiation of the standard four drug regimen may be appropriate until drug susceptibility test results are available.
  • Caveat is life threatening forms of tuberculosis (eg, meningitis or miliary disease)
    • 3 additional drugs from different drug classes to which the patient has not been exposed should be included in the empiric treatment regimen.
TB Treatment in Pregnancy

- INH considered safe in pregnancy
  - Risk of hepatitis increased in peripartum period
  - Pyridoxine (25 mg/day) recommended if INH is administered during pregnancy

- RIF considered safe in pregnancy

- EMB considered safe in pregnancy

- PZA - little information in pregnancy
  - Benefits of PZA may outweigh the risk
  - WHO & IUATLD recommend this drug for use in pregnant women with tuberculosis

- Avoid Streptomycin - may cause congenital deafness
TB Treatment in Breastfeeding

• Breastfeeding should not be discouraged for women being first-line TB agents
  • Small concentrations of these drugs in breast milk do not produce toxicity in the nursing newborn.
  • Drugs in breast milk should not be considered to serve as effective treatment for TB in LTBI in nursing infant
TB Treatment in Liver Disease

• INH, RIF, PZA all may cause liver damage, but because of their effectiveness, they should be used if possible.

• If AST ≥ 3 times upper limit of normal before starting treatment & liver disease is not due to TB, can consider:
  
  • RIF/EMB/PZA for 6 months (avoiding INH)
  
  • INH/RIF for 9 mo, supplemented by EMB until INH and RIF susceptibility (avoiding PZA)
  
  • In severe liver disease a regimen with only 1 hepatotoxic agent, generally RIF plus EMB, could be given for 12 months + another agent, such as a fluoroquinolone, for the first 2 months (no evidence)
Questions & Discussion
Question 1:

In what cases should the continuation phase of TB therapy be prolonged from 4 months to 7 months?

A. HIV co-infection

B. Cavitary disease with positive cultures at end of initiation phase

C. Initiation regimens of Isoniazid, Rifampin, and Ethambutol, without use of PZA

D. B and C

E. All cases of extrapulmonary disease
Question 2:

- Which standard treatment regimens are not recommended for patients co-infected with HIV?

- A. Any regimen that is not a daily or 5 times a week dosing regimen

- B. **Regimens containing rifapentine**

- C. A & B

- D. None of the above
Question 3:

A 55 year old HIV-negative male is diagnosed with TB meningitis. What is your treatment recommendation?

A. Same treatment as for pulmonary TB (INH/RIF/PZA/EMB x 2 mo, then INH/RIF x 4 mo)

B. A + corticosteroid treatment for first 8 wk

C. INH/RIF/PZA/EMB x 2 mo, then INH/RIF x 7-10 months (if drug susceptible)

D. C + corticosteroid treatment for first 8 wk