Treatment of Tuberculosis

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Objectives

• Determine the treatment differences for patients with LTBI versus those with active disease to ensure optimum health outcomes.

• Discuss the importance of treatment completion for 6 months vs 9 months of medication therapy for active disease to reduce the risk of reactivation in TB patients.
General Principles of Chemotherapy for TB Disease

- Existence of mutant bacilli with *innate resistance* to antibiotic action that occur at constant low rates
- Slow or intermittent growth of mycobacterium permits the persistence of viable organisms despite prolonged antibiotic treatment, because only actively replicating organisms are killed by antibiotics
- Combination therapy required for “durable” cure

1. Reduce the bacillary population rapidly, thereby decreasing severity of disease, preventing death and halting transmission of MTB
2. Eradicate persisting bacilli in order to prevent relapse after completion of therapy
3. Prevent acquisition of drug resistance during therapy through use of multidrug therapy
Treatment of Active Tuberculosis

• Initial treatment aimed at
  - Extracellular organisms
  - Sterilize sputum
  - Reduce infectivity

• Secondary treatment aimed at
  - Eradicating persisting organism from
    • Macrophage
    • Granulomas

Site of activity of TB drugs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>EXTRACELLULAR</th>
<th>MACROPHAGE</th>
<th>GRANULOCYTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>RIF</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>PZA</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>EMB</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>STM</td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Major Goals of Tuberculosis Treatment

• Provide safest, most effective therapy in the shortest period of time
• Minimize drug toxicity
• Maximize the likelihood of treatment completion

Safely cure the patient and Prevent TB transmission in the community

Factors Influencing TB Treatment Outcomes

• Patient: age, comorbid conditions, immune status, nutritional status, ETOH use
• Radiographic features: extent of disease, cavities on CXR
• Microbiology: baseline colony count, culture positivity at 2-3 months
• Pharmacokinetic: drug absorption
• Regimen: number of active drugs, duration of therapy
• Programmatic: case management, adherence support, DOT
Patient-Centered Care

“Providing care that is respectful of and responsive to individual patient preferences, needs and values, and ensuring that patient values guide all clinical decisions.”

---The Institute of Medicine, 2001
Case Management

1. Educate patients about TB, its treatment, including possible side effects
2. Discuss expected outcomes, specifically the ability to cure the patient of the disease
3. Review methods of supervision and assessing response to therapy
4. Discuss infectiousness and infection control measures using terminology appropriate to age, culture, language, reading level of the patient

Develop Treatment and Monitoring Plan

Plan should include:
- Description of treatment regimen
- Methods for assessing/ensuring adherence
- Monitoring methods for treatment response and adverse events
Enablers/Incentives for Adherence

| Table 4. Possible Components of a Multilocalized, Patient-Centered Treatment Strategy |
|------------------------------------------|------------------------------------------|
| **Enablers**                             | **Incentives**                           |
| Interventions to assist the patient in completing therapy [120] | Interventions to motivate the patient, tailored to individual patient wishes and needs and, thus, meaningful to the patient [130] |
| Transportation vouchers [30]             | Food stamps or snacks and meals [30]     |
| Clinic personnel who speak the languages of the populations served [47-8] | Assistance in finding or securing housing [47-8] |
| Reminder systems and followup of missed appointments [38] | Clothing or personal products [30] |
| Social service assistance [for substance abuse treatment and counseling, housing, and other services] [47-8] | Books [47-8] |
| Outreach workers bilingual/monolingual as needed; can provide many services related to maintaining patient adherence, including provision of directly observed therapy, followup on missed appointments, monthly monitoring, transportation, spu mcolot, social service assistance, and educational reinforcement [42-9] | Stipends [45-9] |
| Integration of care for tuberculosis with care for other conditions [42-9] | Patient contract [30] |

Directly Observed Therapy (DOT)

- Preferred management strategy for all patients
  - Health-care worker watches patient swallow each dose
  - Can reduce acquired drug resistance, treatment failure, and relapse
  - Allows for early recognition of adverse drug reactions, treatment complications
Deciding to Initiate Treatment

- Decision to start TB therapy based on clinical, radiographic, laboratory, patient and public health factors
- Clinical judgement and index of suspicion play a critical role
- Empiric therapy with a 4-drug regimen is initiated:
  - In patients with high likelihood of having TB
  - In seriously-ill patients with a clinical presentation suspicious for TB
### Case 1—Mr. P

- February: 36 yo Peruvian male presents to ER with cough, fever and hemoptysis
- Former smoker
- No ETOH use
- HIV negative
- Treated for pneumonia with levofloxacin with initial improvement in symptoms
Case 1—Mr. P

- April: Continues to complain of “chest tightness,” cough, sore throat
- Seen in Urgent Care
- Given Z-pak (azithromycin)
- Symptoms improved initially

Case 1—Mr. P

- May: Presents to ER c/o
  - Hemoptysis
  - Cough
  - Fever
- CXR worsening upper lobe infiltrate, now with cavitary lesion
- Placed in isolation
- Sputum smear AFB+
- TST+

**Would you start on TB treatment? Why or why not?**
Deciding to Initiate Treatment

- Decision to start TB therapy based on clinical, radiographic, laboratory, patient and public health factors
- Clinical judgement and index of suspicion play a critical role
- Empiric therapy with a 4-drug regimen is initiated:
  - In patients with high likelihood of having TB
  - In seriously ill patients with a disorder suspicious for TB


Case 2—Mr. T

- 63 yo African-American gentleman
- Presents with 4 months of feeling poorly, 25-30 lb weight loss, failure to thrive, cough, increasing dyspnea on exertion
- BMI: 18
- Recently complaining of nausea/vomiting
- Daily ETOH use: 2 x 40 oz
- Long-term smoker
Case 2—Mr. T

Heterogeneous consolidation in posterior and anterior segments of both UL as well superior segment of the LLL. Lateral aspect of consolidation in LUL is confluent with a full area of cavitation. Several other smaller probable cavities are noted more medially in LUL. This pattern may represent pneumonia although malignancy should be considered most highly. There are calcifications in the mediastinum at the level of the left paraspinal region and the azygos node. These probably represent calcifications in lymph nodes. There is no pleural effusion.

Case 2—Mr. T

- Placed in airborne precautions
- Sputum smear positive for AFB
- TST 0 mm induration
- Quantiferon negative
- HIV negative
- **Would you start TB treatment?**
- Why or why not?
### Case 3—Mr. W

- 28 yo African-American gentleman presents with 2 weeks of cough, fever
- Treated for pneumonia with azithromycin
- Without a stable living situation
Case 3—Mr. W

- Presents to ER two months later with similar complaints: cough, right flank pain, 10 lbs. weight loss
- History of incarceration for 30 days—3 years ago
- Undocumented history of positive TST while incarcerated, untreated for LTBI

Case 3—Mr. W

- Placed in isolation
- AFB smear x 3 negative
- Undergoes bronchoscopy; AFB smear negative
- HIV negative
- Would you order additional tests?
- Would you start on TB treatment?
- Why or why not?
Case 3—Mr. W

Pathology from bronchoscopy:

- Granulomatous pneumonitis accompanied by necrotic cellular debris (caseation)
- Acid Fast Bacterial Stain: Positive AFB

AFB cultures became positive for AFB at three weeks

- Identified as TB one week later
- (NAAT not done....could have made diagnosis sooner)
Case 4—Mrs. S

- 54 yo lady with diabetes, presents with 2-day history of fever, cough, worsening shortness of breath
- Placed in airborne isolation due to remote history of positive TST

Case 4—Mrs. S

- She is improving on antibiotics
- One AFB sputum smear is negative and the TB PCR (NAAT) on that specimen is also negative
If Clinical Suspicion for Active TB is Low:

Defer treatment until additional data obtained

**OR in a patient with a positive TST or IGRA**

Consider starting 4- drug combination chemotherapy and if after two months of therapy:

- cultures remain negative
- no clinical improvement
- no change/improvement in x-ray

**THEN**

Stop therapy and treatment for LTBI has been completed

“**No Loose Solution**”
TB Treatment: Drugs and Regimens

Current Anti-TB Drugs

**11 drugs FDA-approved for treatment of TB**

- Isoniazid (INH)
- Rifampin (RIF)
- Pyrazinamide (PZA)
- Ethambutol (EMB)
- Rifapentine (RPT)
- Streptomycin (SM)
- Cycloserine
- Capreomycin
- \( \rho \)-Aminosalicylic acid
- Ethionamide
- Bedaquiline
Current Anti-TB Drugs (cont.)

• Four first-line drugs considered standard treatment:
  - Isoniazid (INH)
  - Rifampin (RIF)
  - Pyrazinamide (PZA)
  - Ethambutol (EMB)

• Rifabutin and rifapentine also considered first-line drugs in some circumstances

• Streptomycin (SM) formerly first-line drug, but now less useful owing to increased SM resistance

• Fluoroquinolones (levofloxacin, moxifloxacin) can be substituted for first-line in the US if resistance, toxicity

Isoniazid (INH)

• Daily dose: 5 mg/kg → typically 300 mg
• Intermittent dose: 15 mg/kg → 900 mg
• INH absorption decreases when combined with glucose or lactose
Isoniazid (INH)

- Side effects: GI intolerance, hepatitis, peripheral neuropathy;
- To prevent peripheral neuropathy, give vitamin B6 25 mg daily to:
  - HIV +
  - ETOH Abuse
  - Malnutrition
  - Pregnant Women
- Give 100 mg B6 to patients to treat neuropathy

Rifampin (RIF)

- Daily dose: 10 mg/kg → typically 600 mg
- Intermittent dose: 10 mg/kg → 600 mg
- Side effects: red-orange urine, GI intolerance, hepatitis, flu-like syndrome
Ethambutol (EMB)

- Dosing based on weight

Table 11: Suggested Ethambutol Dosages, Using Whole Tablets, for Adults Weighing 40-90 kg

<table>
<thead>
<tr>
<th>Regimen</th>
<th>40-55</th>
<th>56-75</th>
<th>76-90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily (mg/kg)</td>
<td>800 mg (14.5-20.0)</td>
<td>1200 mg (16.0-21.4)</td>
<td>1600 mg (17.8-21.1)</td>
</tr>
<tr>
<td>Three weekly (mg/kg)</td>
<td>1000 mg (21.9-26.8)</td>
<td>2000 mg (26.7-21.6)</td>
<td>2400 mg (26.7-21.6)</td>
</tr>
</tbody>
</table>

- Side effects: optic neuritis

Pyrazinamide (PZA)

- Dosing based on weight:

Table 10: Suggested Pyrazinamide Dosages, Using Whole Tablets, for Adults Weighing 40-90 kg

<table>
<thead>
<tr>
<th>Regimen</th>
<th>40-55</th>
<th>56-75</th>
<th>76-90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily (mg/kg)</td>
<td>1000 mg (19.2-25.0)</td>
<td>1500 mg (20.0-26.0)</td>
<td>2000 mg (22.2-26.0)</td>
</tr>
<tr>
<td>Twice weekly (mg/kg)</td>
<td>1500 mg (27.3-32.5)</td>
<td>2500 mg (33.2-41.6)</td>
<td>3000 mg (33.3-39.9)</td>
</tr>
</tbody>
</table>

- Side effects: mild anorexia and nausea, dose-related hepatitis, polyarthralgias, hyperuricemia
- May be taken with food
Fluoroquinolones

- Daily dose: 400 mg moxifloxacin (MFX) or 500-1000 mg levofloxacin (LFX)
- Side effects:
  - GI upset
  - Tendonitis, tendon rupture
    - Mild-stop exercise, consider NSAIDS; rupture-stop drug
  - QT prolongation with other QTc prolonging drugs
  - CNS: headache, insomnia, confusion
- Take 2 hours before or after aluminum, magnesium or calcium containing antacids, iron, sucralfate, milk containing products and food supplements

TB Disease Treatment Regimens

- Four regimens recommended for treatment of drug-susceptible TB, with different options for number of doses and for length of continuation phase
- Initial phase: standard four drugs (INH, RIF, PZA, EMB) for 2 months
- Continuation phase: typically INH/RIF for an additional 4 months; 7 months for some patients
TB Disease Treatment Regimens (cont.)

• When to use 7-month continuation phase:
  - Disease is cavitary and sputum culture is positive at end of initial phase;
  - Initial phase excluded PZA

• Treatment also extended for:
  - Bone and joint TB (6-9 months total)
  - CNS TB (12 months)
  - Multi-drug resistant TB
  - HIV patients NOT taking ART
  - Some patients with significant burden of disease, slow to respond (decisions on a case by case basis)

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

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drug(s)</th>
<th>Intensive Phase</th>
<th>Continuation Phase</th>
<th>Range of Total Doses</th>
<th>Regimen Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>INH, RIF, PZA (EMB)</td>
<td>7 days for 66 doses (8 wk), or 5 days for 40 doses (8 wk)</td>
<td>7 days for 128 doses (16 wk), or 5 days for 90 doses (16 wk)</td>
<td>182-120</td>
<td>Greater</td>
</tr>
<tr>
<td>2</td>
<td>INH, RIF, PZA (EMB)</td>
<td>7 days for 56 doses (8 wk), or 5 days for 40 doses (8 wk)</td>
<td>3 times weekly for 54 doses (18 wk)</td>
<td>110-94</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, RIF, PZA (EMB)</td>
<td>3 times weekly for 24 doses (8 wk)</td>
<td>3 times weekly for 54 doses (18 wk)</td>
<td>78</td>
<td>User 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, RIF, PZA (EMB)</td>
<td>7 days for 14 doses when twice weekly for 12 doses</td>
<td>Twice weekly for 52 doses (18 wk)</td>
<td>62</td>
<td>Do not use twice-weekly regimens in HIV-infected patients or patients with smear-positive pulmonary disease. If doses are missed, therapy is equivalent to once weekly, which is inferior.</td>
</tr>
</tbody>
</table>

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

* Other combinations may be appropriate in certain circumstances; additional details are provided in the section “Recommended Treatment Regimen.”

** When DOT is used, drugs may be given 5 days per week plus the necessary number of doses of streptomycin. Although there are no studies that compare 7-month (DOT) continuation phase with the 9-month (RIF) continuation phase, the 9-month (RIF) continuation phase has been used in clinical practice for many years and is considered an effective practice. DOT should be used when drugs are administered 7 days per week.

*** Based on expert opinion, patients with cavitary disease, high ratings, and positive culture at completion of 6 months of therapy should receive a 7-month (DOT) continuation phase.

**** Post-sterile intrathoracic TB: Patients with INH or rifampin at risk of reactivation may start treatment without prior RIF or PZA. If RIF or PZA become positive, continue 6 months of INH and rifampin. For patients with positive INH, continue 4 months. If RIF or PZA are positive, continue 6 months of INH and rifampin.

***** A shorter initial phase of 4-6 months is sometimes used in the elderly, in patients with diffuse disease, and in HIV-infected patients.

****** See (59). Alternatively, some US tuberculosis control programs have administered intensive phase regimen 5 days per week for 15 days (2 weeks), then twice weekly for 12 doses.
Alternative regimens preferred by the KY TB Program

From the 2003 CDC/ATS TB Treatment Guidelines

Alternative Regimens from 2003 Treatment Guidelines

<table>
<thead>
<tr>
<th>Initial phase</th>
<th>Continuation phase</th>
<th>Range of total doses (minimal duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs</strong></td>
<td><strong>Interval and doses</strong> (minimal duration)</td>
<td><strong>Regimen</strong></td>
</tr>
<tr>
<td>INH, RIF, PZA, EMB</td>
<td>Seven days per week for 56 doses (8 wk) or 5 doses/week for 40 doses</td>
<td>1a</td>
</tr>
<tr>
<td></td>
<td>1b</td>
<td>INH, RIF</td>
</tr>
</tbody>
</table>

Definition of abbreviations: EMB = Ethambutol; INH = Isoniazid; PZA = Pyrazinamide; RIF = Rifampin; RFT = Rifapentine.

Regimen 2 for Treatment of Pulmonary, Drug-Susceptible TB
6-Month Standard Regimen for Most Patients

Initial phase
INH, RIF, PZA, EMB daily (7 or 5 days/week) for 8 weeks

4-month continuation phase
INH, RIF three times weekly for 18 weeks

*Only consider when more frequent DOT during continuation phase is difficult to achieve

Regimen 3 for Treatment of Pulmonary, Drug-Susceptible TB
6-Month Intermittent Dosing Options

Initial phase
INH, RIF, PZA, EMB intermittently (3 days/week) for 8 weeks

4-month continuation phase
INH, RIF intermittently (3 days/week) for 18 weeks

*Only consider in HIV-negative patients and also those at low risk of relapse i.e. noncavitary, pansusceptible, smear negative when daily DOT unavailable or unable to tolerate daily medications
Regimen 4 for Treatment of Pulmonary, Drug-Susceptible TB
6-Month Daily + Intermittent Dosing Options

Initial phase
INH, RIF, PZA, EMB daily (7 or 5 days/week) for 2 weeks, then 2 days/week for 6 weeks

4-month continuation phase options
INH, RIF intermittently (2 days/week) for 18 weeks

*The Denver Regimen: only consider in HIV-negative, and those also at low risk of relapse i.e. noncavitary, pansusceptible, smear negative

Other regimens

Once weekly continuation phase with INH 900 mg plus Rifapentine 600 mg:
• Less active than standard RIF-base treatment
• Relapse seen in: cavitation, underweight, sputum culture positivity at end of intensive phase
• ONLY recommended in the uncommon situation where more than once-weekly DOT is difficult to achieve in HIV-negative without cavitation on x-ray
Other regimens

If PZA cannot be used either due to intolerance, pregnancy, or resistance (M. bovis):
• Initial phase: INH, RIF, EMB for two months
• Continuation phase: INH, RIF given daily or thrice weekly for 7 months

Fluoroquinolones

Occasionally used:
• In place of INH throughout treatment when it cannot be used due to intolerance or resistance
• In place of EMB in intensive phase when it cannot be used
• No data to support substituting fluoroquinolone for RIF or PZA and still maintaining 6-month treatment duration
• Duration: 6 months or longer
TB Treatment: Monitoring Therapy

Evaluating Response to Treatment
Assess patient’s response to treatment using three methods:
- Clinical evaluation, bacteriological examination, chest x-ray
Evaluating Response to Treatment

Conduct clinical evaluations at least monthly

- Monitor adherence and improvement in TB symptoms
- Monitor weight monthly
- After 2 months of therapy, if symptoms do not resolve, reevaluate for: potential drug-resistance, non adherence to drug regimen, malabsorption

Evaluating Response to Treatment

Bacteriological examination
- If cultures do not convert to negative after 3 months of therapy, evaluate patient for drug resistance or adherence issues; after 4 months, consider treatment failed

Chest radiograph
- Patients with initially negative cultures should have CXR after 2 months of treatment and at completion of therapy
Evaluating Response to Treatment

- Patients with cavitation on CXR and positive cultures at two months are more likely to relapse so the continuation phase is extended to 7 months (9 months total)
- Extension of treatment to 9 months in pulmonary TB can be considered:
  - Cavitation on CXR
  - Positive cultures at two months
  - Diabetic
  - HIV +
  - Malnourished
  - Smoker
  - Having extensive disease on CXR

Patient Monitoring

Establish rapport with patient and emphasize:
- Benefits of treatment
- Importance of adherence to treatment regimen
- Possible adverse side effects of regimen
- Establishment of optimal follow-up plan
### Patient Monitoring—Baseline

<table>
<thead>
<tr>
<th>Patient</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>AST, ALT, bilirubin, alkaline phosphatase Platelet count Creatinine HIV</td>
</tr>
<tr>
<td>Patients at risk for hepatitis B or C (e.g., injection drug user, born in Asia or Africa, HIV infected)</td>
<td>Conduct serologic tests</td>
</tr>
<tr>
<td>Patients at risk for diabetes (age&gt;45 yo, BMI&gt;25, first-degree relative with DM, race/ethnicity of African American, Asian, Hispanic, American Indian/Alaska Native, or Hawaiian Native/Pacific Islander)</td>
<td>Fasting glucose or HbA1c</td>
</tr>
<tr>
<td>Patients who are taking EMB</td>
<td>Test visual acuity (Snellen chart) and color vision (Ishihara)</td>
</tr>
<tr>
<td>HIV-infected patients</td>
<td>Obtain CD4+ lymphocyte count</td>
</tr>
</tbody>
</table>

### Patient Monitoring—During Treatment

<table>
<thead>
<tr>
<th>Patient</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Repeat at least monthly clinical evaluations to • Identify possible adverse reactions to medications • Assess adherence</td>
</tr>
<tr>
<td>Those with: abnormal baseline LFTS, symptoms of hepatotoxicity, ETOH consumption, other hepatotoxic drugs, viral hepatitis or history of liver disease, HIV</td>
<td>Monthly AST, ALT, Bilirubin, Alkaline phosphatase</td>
</tr>
<tr>
<td>Patients who are taking EMB</td>
<td>• Question monthly regarding visual disturbances • Repeat monthly testing for visual acuity (Snellen chart) and color vision (Ishihara)</td>
</tr>
<tr>
<td>Extrapulmonary TB</td>
<td>• Depends on site and ease with which specimens can be obtained</td>
</tr>
</tbody>
</table>
Treatment Interruptions

- Treatment interruptions are common
- Restart or continue therapy based on when interruption occurred and duration of interruption
- Bacteriologic status of patient (i.e. smear/culture positive) prior to and after the interruption are also important considerations

### Table 6. Management of Treatment Interruptions

<table>
<thead>
<tr>
<th>Time Point of Interruption</th>
<th>Details of Interruption</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>During Intensive phase</td>
<td>Lapse is ≤14 d in duration</td>
<td>Continue therapy.</td>
</tr>
<tr>
<td></td>
<td>Lapse is &gt;14 d in duration</td>
<td>Restart therapy from the beginning if treatment is interrupted.</td>
</tr>
<tr>
<td>During continuation phase</td>
<td>Received ≥50% of doses and sputum was AFB smear negative on initial testing</td>
<td>Further therapy may not be necessary.</td>
</tr>
<tr>
<td></td>
<td>Received ≥50% of doses and sputum was AFB smear positive on initial testing</td>
<td>Continue therapy until all doses are completed.</td>
</tr>
<tr>
<td></td>
<td>Received &lt;50% of doses and sputum was AFB smear negative on initial testing</td>
<td>Continue therapy until all doses are completed and bacterial smear/culture is positive.</td>
</tr>
<tr>
<td></td>
<td>Received &lt;50% of doses and sputum was AFB smear positive on initial testing</td>
<td>Restart therapy from the beginning if treatment is interrupted.</td>
</tr>
<tr>
<td></td>
<td>Received &lt;50% of doses and sputum was AFB smear positive on initial testing</td>
<td>Restart therapy from the beginning, new intensive and continuation phases</td>
</tr>
<tr>
<td></td>
<td>Received &lt;50% of doses and sputum was AFB smear positive on initial testing</td>
<td>(i.e., restart intensive phase, to be followed by continuation phase).</td>
</tr>
</tbody>
</table>

* Abbreviations: AFB, acid-fast bacilli.
  * According to expert opinion, patients who are lost to follow-up (on treatment) and brought back to therapy, with interim treatment interruption, should have sputum exam for AFB smear, culture, and drug susceptibility testing.

* The recommended timeframe for regimens in tuberculosis control programs in the United States and in several European countries, is to administer all of the specified number of doses for the intensive phase within 2 months and those for the 4-month continuation phase within 6 months, so that the 8-month regimen is completed within 8 months.
Treatment Interruption During Initial Phase

The earlier the break and the longer the duration, the greater the need to start from the beginning:

• If lapse $\geq$ 14 days, restart treatment
• If lapse < 14 days, continue treatment to completion as long as all doses are completed within 3 months

Treatment Interruption During Continuation Phase

• If patient received $\geq$ 80% of doses and:
  - Sputum smear was negative on initial testing, further therapy may not be needed
  - Sputum smear was positive on initial test, continue therapy until all doses are completed
Treatment Interruption During Continuation Phase

• Obtain sputum smear and culture
• If patient received <80% of doses, and lapse is:
  - <3 months long, continue therapy, to complete in 6 months
  - >3 months long, restart therapy from beginning of initial phase

Treatment Interruption During Continuation Phase

• If culture is positive, restart treatment from the beginning
• If culture is negative, could treat as having culture-negative TB with 4 months of INH/RIF, as long as had drug susceptible organism and was treated originally with RIF/INH/PZA
Treatment Completion

• Defined as ingesting prescribed number of doses within specified time:
  - Initial phase: completed in 3 months
  - Continuation phase: completed in 6 months
• Duration depends on drugs used, isolate’s susceptibility, and patient’s response to drugs
• Most patients can be treated with 6-mo or 9-mo therapy; 6 mo is used for most patients

TB Treatment: Culture-negative TB
Case 5—Mr. F

• 60 yo gentleman, a recent immigrant from the Philippines presents for evaluation
• Denies cough, fever, chills, sweats
• Positive TST at 10 mm
• HIV negative

Case 5—Mr. F

• Sputum smears negative x 3
• 4 drug therapy started
• Due to concern for being a clinical case, patient kept on home isolation until he had received 5 days of therapy
Case 5—Mr. F

• Cultures finalized as negative at 8 weeks
• Repeat CXR performed after 2 months of therapy and found to be improved
• TB medications continued to complete 4 months of total therapy

Culture-Negative Pulmonary TB

• Failure to isolate TB bacilli from person with clinical evidence does not exclude TB
• Up to 15% of cases in US are culture negative
• At minimum, TB suspects should have 3 specimens for smear and culture
Treating Culture-Negative Pulmonary TB

• Start patient on four-drug TB therapy if high clinical suspicion for TB
• If cultures are negative, clinical and radiographic follow-up after two months of therapy is indicated

Treating Culture-Negative Pulmonary TB

If patients exhibit either a clinical response or significant improvement in their CXR, and no other etiology has been identified, continue therapy for 4-6 months:
• RIF/INH/EMB/PZA x 2 mos, then RIF/INH x 2 mos or
• RIF/INH/EMB/PZA x 4 months
  - If concern for drug resistance
If negative cultures, TST or IGRA+ and no clinical or radiographic changes after 2 months of treatment:

Treat for latent TB infection (LTBI):
1. Complete 2-months of 4 drugs
2. Continue treatment with rifampin for 4 months
3. Continue isoniazid for 9 months
4. Give 12 weekly doses of INH/RPT by DOT

TB Treatment: Special Situations
Case 6—Mrs. R

- 29 yo female originally from El Salvador
- Presents for obstetrics care around 20 weeks into her pregnancy
- Asymptomatic, IGRA positive
- CXR: a 1.9 cm nodule in the right mid lung with adjacent fibrotic linear density
- Sputum smears AFB negative x 3
- Sputum cultures AFB positive for TB
- What is the next step?

Pregnant and Breastfeeding Women

- TB drugs cross the placenta but do not appear to be teratogenic
- Initial regimen should consist of INH, RIF, and EMB
  - PZA not contraindicated, but detailed data on teratogenicity not available
  - If PZA not used, duration of therapy is 9 months
- Breast-feeding not contraindicated for women being treated for TB disease
- Vitamin B₆ supplementation (25-50 mg/day) is recommended if taking INH and breastfeeding
  - Baby may need INH if exposed to infectious mom
  - Baby should receive B6 supplement if mom taking INH
Case 7—Mr. V

- 58 yo Filipino gentleman with ESRD, on dialysis MWF
- As part of kidney transplant evaluation, he has a TST which is positive
- CXR is abnormal
- Sputum smears x 3 negative
- What is the next step?

Renal Insufficiency

- Patients with renal insufficiency or ESRD are immunocompromised
- They have worse clinical outcomes than those without renal failure
- In general, the doses of the anti-TB medications should not be reduced but rather the interval should be increased
Dosing of TB Medications in Renal Failure

- INH and Rifampin are metabolized by the liver so conventional dosing is used
- PZA is also metabolized by the liver but active metabolites are excreted by the kidney and requires interval modification
- EMB is 80% metabolized by the kidney and also needs an increase in the dosing interval

### Table 12. Dosing Recommendations for Adult Patients With Reduced Renal Function*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in Frequency?</th>
<th>Recommended Dose and Frequency for Patients With Creatinine Clearance &lt;30 mL/min, or Patients Receiving Hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>No</td>
<td>300 mg once daily, or 900 mg 3 times/wk</td>
</tr>
<tr>
<td>Rifampin</td>
<td>No</td>
<td>600 mg once daily, or 600 mg 3 times/wk</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Yes</td>
<td>25-35 mg/kg/dose 3 times/wk (not daily)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Yes</td>
<td>20-25 mg/kg/dose 3 times/wk (not daily)</td>
</tr>
<tr>
<td>Levoflaxone</td>
<td>Yes</td>
<td>750-1000 mg/dose 3 times/wk (not daily)</td>
</tr>
<tr>
<td>Mothroxacin</td>
<td>No</td>
<td>400 mg once daily</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Yes</td>
<td>250 mg once daily, or 500 mg/dose 3 times/wk*</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>No</td>
<td>250-500 mg/dose daily</td>
</tr>
<tr>
<td>Pyrazinoic acid</td>
<td>No</td>
<td>4 g/dose twice daily</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Yes</td>
<td>10-15 mg/kg dose 2-3 times/wk (not daily)</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Yes</td>
<td>15 mg/kg/2-3 times/wk (not daily)</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Yes</td>
<td>15 mg/kg/2-3 times/wk (not daily)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Yes</td>
<td>15 mg/kg/2-3 times/wk (not daily)</td>
</tr>
</tbody>
</table>

- Standard doses are given unless there is intolerance.
- The medications should be given after hemodialysis on the day of hemodialysis.
- Monitoring of serum drug concentrations should be considered to ensure adequate drug absorption, without excessive accumulation, and to assist in avoiding toxicity.
- Data currently are not available for patients receiving peritoneal dialysis. UNH data become available, begin with doses recommended for patients receiving hemodialysis and verify adequacy of dosing using serum concentration monitoring.
- In patients with 20-44 ml/min creatinine clearance, standard doses are used by experts, but measurement of serum concentrations 2 and 6 hours after timed administration can be used to assist with optimizing drug dosages.

* Including adult patients receiving hemodialysis.

** The appropriate use of 240-mg daily doses has not been established. There should be careful monitoring for evidence of necrotizing.
TB Treatment in Renal Failure

• Administer all medications post dialysis
• For patients with 30-50 ml/min CrCl use standard doses of medications
• May need to consider checking drug levels in these patients

Case 8—Mrs. P

• 54 yo African-American female presents with 3 months of cough
• CXR obtained
• Sputum smears 4+ AFB positive
• TB PCR positive
Case 8—Mrs. P

• On methadone
• Current ETOH use/abuse
• Active Hepatitis C with baseline elevated LFTS:
  AST: 65
  ALT: 48
• What therapy to start?

TB Treatment in Hepatic Disease

Drug-induced hepatitis increased in patients with:
• Prior advance liver disease, liver transplant, hepatitis C infection, abnormal baseline LFTS
• Consider treatment regimens with fewer hepatotoxic agents:
  ➢ In patients with advanced liver disease
  ➢ Those with ALT > 3 times ULN at baseline
• Try to retain INH/RIF
Alternative Regimens in Hepatic Disease

Treatment without PZA:
• INH/RIF/EMB for two months, followed by 7 months INH/RIF

Treatment without INH:
• RIF/PZA/EMB with or without a fluoroquinolone for 6 months

Treatment without INH/PZA:
• RIF/EMB with a fluoroquinolone, injectable agent or cycloserine for 12-18 months

Alternative Regimens in Hepatic Disease

For patients with severe, unstable liver disease:
• EMB, fluoroquinolone, cycloserine and second-line injectable for 18-24 months
Monitoring of Treatment in Hepatic Disease

• Consider checking LFTS/bilirubin every few weeks for the first 2-3 months of treatment
• Consider stopping medications if ALT 3X ULN in asymptomatic patients with severe liver disease (cirrhosis, encephalopathy)

Case 9—Mr. A

• 94 yo Filipino gentleman presents to local ER with the following: “generalized malaise, weakness, fatigue, decreased appetite, abdominal pain, and intermittent back pain”
• Abdominal pain started approximately two weeks earlier after a “fall”
• Denies fever, chills
• Son accompanies patient in ER, helps with translation
• Patient described as “cachectic” in appearance
Case 9—Mr. A

- Past Medical History: Stroke, Diabetes, HTN
- Diagnosed with: pneumonia

Case 9—Mr. A

- Treated for pneumonia with antibiotics
- Discharged to follow-up with his primary care doctor
- Unfortunately, started to feel poorly again
- Findings on chest x-ray were unchanged
- Finally referred to see a pulmonologist
Case 9—Mr. A

- Unable to produce sputum
- 5/10/13: underwent bronchoscopy
- AFB smear negative
- 6/18/13: 1 of 3 specimens became AFB positive (grew one colony)
- 8/13: Started on TB therapy
The Challenge of Diagnosing TB in an Older Adult

• Often complain about nonspecific symptoms:
  - Chronic fatigue/weakness
  - Cognitive impairment
  - Anorexia/weight loss
  - Persistent low-grade fever
  - Changes in activities of daily living

• Symptom duration may be greater in the elderly

• May be confused with age-related illnesses:
  - Malignancy
  - Diabetes mellitus
  - Malnutrition

Adverse Drug Effects

### TABLE 3. ADJUSTED HAZARD OF ALL, OR SPECIFIC, SIDE EFFECTS IN ASSOCIATION WITH CLINICAL CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Any Serious*</th>
<th>Rash/Fever*</th>
<th>Hepatitis*</th>
<th>GI Upset*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>Female sex (versus male)</td>
<td>2.5 1.3 to 4.7</td>
<td>2.2 0.7 to 6.9</td>
<td>3.6 0.6 to 11.8</td>
<td></td>
</tr>
<tr>
<td>Age, yr (versus &lt; 35)</td>
<td>1.7 0.8 to 3.1</td>
<td>4.8 0.9 to 25.2</td>
<td>2.1 0.3 to 14.9</td>
<td></td>
</tr>
<tr>
<td>From Asia (versus all others)</td>
<td>2.5 1.3 to 5.0</td>
<td>2.2 0.7 to 6.9</td>
<td>3.6 0.6 to 11.8</td>
<td></td>
</tr>
<tr>
<td>Method of detection passive (versus active)</td>
<td>2.5 0.9 to 6.6</td>
<td>2.3 0.6 to 8.2</td>
<td>2.6 0.6 to 11.7</td>
<td></td>
</tr>
<tr>
<td>Smear positive (versus smear negative)</td>
<td>1.3 0.7 to 2.6</td>
<td>1.8 0.6 to 5.7</td>
<td>0.5 0.1 to 2.4</td>
<td></td>
</tr>
<tr>
<td>Drug resistant (versus sensitive)</td>
<td>1.8 0.8 to 4.3</td>
<td>2.7 0.7 to 10.5</td>
<td>0.9 0.1 to 7.3</td>
<td></td>
</tr>
<tr>
<td>Abnormal baseline LFTs (versus normal)</td>
<td>1.6 0.6 to 4.2</td>
<td>3.9 0.8 to 19.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A-positive (versus negative or NA)</td>
<td>3.8 1.05 to 14.4</td>
<td>4.3 0.5 to 38.0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Definition of abbreviations: CI = confidence interval; GI = gastrointestinal; HIV = human immunodeficiency virus; HR = hazard ratio; LFT = liver function test; NA = not available.

Boldface entries indicate statistically significant associations.

Hazard ratio and 95% confidence interval estimated from Cox multivariate proportional hazards modeling.

* Any serious side effects.

† Occurrence of rash or drug fever.

‡ Hepatitis defined as transaminases greater than three times the upper limit of normal with symptoms, or five times the upper limit of normal in the absence of symptoms.

§ Severe GI intolerance sufficient to cause discontinuation of some or all medications and/or hospitalization.

¶ Insufficient numbers, so estimates unstable.

‖ Before anti-TB therapy the liver transaminases were above the upper limit of normal.
Hepatotoxicity

• Incidence of INH-associated hepatotoxicity increases with age:
  - risk of liver damage at age < 35: 0.3%
  - risk of liver damage at age > 50: 2.3%
• Severity of hepatitis also increases with age, higher mortality in patients older than 50
• Consider avoiding PZA in patients >75 years old
• Need to monitor for drug interactions

Case 9—Mr. A

• 8/14 Started on RIPE
• Four weeks into therapy:
  - AST 400
  - ALT 580
• All medications held until LFTS normalized
  • Isolate fully drug susceptible
  • Restarted sequentially on: rifampin/ethambutol, INH
• Tolerated remainder of therapy
  • Passed-away in mid-July due to “natural causes”
TB Treatment:
Extrapulmonary TB
Lymphatic TB

• Lymphatic TB in non-immunosuppressed patients is associated with female sex, foreign-birth, and Asian/Pacific Islanders
• Unlike pulmonary disease with 20-25% false negative PPD, PPD is positive in over 90%
Lymphatic TB Treatment

• A 6-month regimen is recommended:
  - 2 months of INH/RIF/EMB/PZA followed by
  - 4 months of INH/RIF
• Although the disease is pauci-bacillary, the development of nodes during therapy or at the end of therapy is common
• Usually there is no evidence of bacteriological relapse
• No role for steroids except perhaps in unusual circumstances of IRIS with HIV co-infection
Clinical Manifestations of TB Pleuritis

- Usually presents as an acute illness
- Associated with non-productive cough and pleuritis chest pain
- Effusion is usually unilateral and can be of any size
- 20% will have concomitant parenchymal disease on CXR
- Up to 80% may have concomitant parenchymal disease on CT
- Rarely, pleural TB can present with pleural-based nodules and thickening

Treatment of TB Pleuritis

- A 6-month regimen is recommended:
  - 2 months of INH/RIF/EMB/PZA followed by
  - 4 months of INH/RIF
- No evidence to support routine use of steroids
Bone and Joint TB

• Bone and joint disease due to TB affects all ages but the greatest risk appears to be in those > age 65y
• Prior to the HIV era, bone and joint disease accounted for about 9% of all extra-pulmonary disease in the US
• Spinal TB or Pott’s is the most common followed by hip and then knee

Bone and Joint TB

• Diagnosis is ideally made with isolation of the organism from the affected area
• The diagnosis is supported by
  - Monoarticular disease
  - Cold abscesses
  - Positive PPD
  - Epidemiological risks
  - Chest x-ray with findings consistent with TB
Treatment of Bone and Joint Disease

• Same therapy as for other forms
• Several studies have shown that six to nine month regimens containing RIF are as effective as 18 month regimens without RIF
• 9 months is favored because it is hard to assess response
• Myelopathy with or without functional impairment responds medically
Role of Surgery

• The role of surgery comes up most often with the treatment of Pott’s disease (spine)
• A randomized trial of the Medical Research Council comparing surgical debridement with multi-drug regimens found no benefit to surgery
• Instances where surgery should be considered:
  - poor response to chemotherapy
  - relief of cord compression when persistent neurologic deficit
  - instability of the spine

TB Pericarditis

• Very rare in the US
• Most common cause of pericarditis in Africa, Asia
• Typical signs/symptoms of pericarditis
• Treatment: 6 months of therapy
TB Pericarditis

- Corticosteroids previously universally recommended
- Recent data does not find statistically significant benefit in terms of mortality or constrictive pericarditis
- Adjunctive steroids no longer routinely recommended in treatment of pericarditis
- Selective use of steroids may be considered in patients at highest risk for inflammatory complications
TB Meningitis

• Historically, it has been a disease of mostly young children, however, HIV and other forms of immune suppression have led to an increase in older age groups
• Without therapy, thought to be uniformly fatal

Treatment for TB Meningitis

• Initial phase: INH/RIF/PZA/EMB for 2 months
• Continuation phase: INH/RIF for 7-10 months
• Optimal duration not defined
• Adjunctive corticosteroid therapy conveys mortality benefit:
  - dexamethasone taper over 6-8 weeks
Miliary TB

• Disseminated TB
• 1-2 mm nodules
• TST likely to be false negative

Miliary TB Treatment

• Standard daily 6-month regimen
Treatment Response

• Among patients with drug-susceptible pulmonary TB, even with extensive lung cavitation, 90-9% will be culture negative after three months with a RIF/INH containing regimen
• Clinical improvement: reduced fever, reduced cough and weight gain
• Paradoxical reaction

Resources

• 2016 : Treatment of Drug-Susceptible TB. Clinical Infect Dis http://cid.oxfordjournals.org/content/early/2016/07/20/cid.ciw376.full
• CDC Core Curriculum, https://www.cdc.gov/tb/education/corecurr/
• Self Study Modules on Tuberculosis (CDC), http://www.cdc.gov/tb/education/ssmodules/default.htm
• Medical Management of Tuberculosis: An Online Presentation http://www.currytbcenter.ucsf.edu/products/view/medical-management-tuberculosis-online-presentation
• Tuberculosis medication drug and food interactions pocket card, http://www.heartlandntbc.org/assets/products/tuberculosis_medication_drug_and_food_interactions.pdf
Resources

• TNF alpha antagonists and the risk of TB, [http://www.heartlandntbc.org/assets/products/tumor_necrosis_factor.pdf](http://www.heartlandntbc.org/assets/products/tumor_necrosis_factor.pdf)


• Tuberculosis adverse drug events pocket cards [http://www.heartlandntbc.org/assets/products/tuberculosis_adverse_drug_events.pdf](http://www.heartlandntbc.org/assets/products/tuberculosis_adverse_drug_events.pdf)


Resources


• Client/Patient Management Algorithms and Short Clinical Guides, [http://www.heartlandntbc.org/products/](http://www.heartlandntbc.org/products/)
Resources

- Fact sheets:
  - TB 101 for Health Care Workers
  - Diagnosis of Tuberculosis Disease
    http://www.cdc.gov/tb/publications/factsheets/testing/diagnosis.htm
  - General Considerations for Treatment of TB Disease
  - TB can be treated
  - TB in pregnancy
  - Bovine Tuberculosis in Humans,