MEDICAL MANAGEMENT OF TB

OBJECTIVES

Upon completion of this session, participants will be able to:

1. Describe the recommended treatment regimens and first-line medications for TB disease
2. Identify the common side effects of first-line tuberculosis medications and recommended monitoring
3. Describe evaluation and treatment of side effects of first-line tuberculosis medications
4. Define and describe appropriate completion of treatment for TB disease

INDEX OF MATERIALS

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1. Medical Management of TB – slide outline
   Presented by: Chris Keh, MD

SUPPLEMENTAL READING MATERIALS

none
ADDITIONAL REFERENCES


- American Thoracic Society/ Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. MMWR June 20, 2003; 52(RR11):1-77. URL: [http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm)


**Medical Management of TB**

**Objectives**

- Describe the recommended treatment regimens and first-line medications for TB disease
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- Describe evaluation and treatment of side effects of first-line tuberculosis medications
- Define and describe appropriate completion of treatment for TB disease

**General Principles**

- Never add a single drug to a failing regimen
- Completion of treatment is based on number of doses taken, not duration alone
- Duration of therapy (or number of doses needed) is dependent on:
  - drugs used
  - extent of disease
  - response to treatment
  - Co-morbidities (e.g. HIV, immune-compromise)
Directly observed therapy (DOT)

- DOT should be considered for all patients with active TB.
- If resources do not allow for DOT, prioritize DOT for those with highest consequences for individual or public:
  - Individual (pediatric, HIV, clinical worsening while on treatment)
  - Public (sputum smear positive, correctional facility, drug resistance, dialysis, congregate living setting, marginally housed, prior TB treatment, or relapsed disease, slow response to treatment)
  - Potential for non-adherence (psychiatric disease, pediatric, adverse reactions to meds, etoh/drug use, too ill to self manage / elderly / cognitive impairment)

The Drugs (first-line)

- Rifamycin (rifampin 10 mg/kg/d, rifabutin, rifapentine)
- Isoniazid (INH), 5 mg/kg/d
- Pyrazinamide (PZA), 25 mg/kg/d
- Ethambutol (EMB), 15-25 mg/kg/d

Rifamycins

- Includes: rifampin, rifabutin, rifapentine
- Active against rapidly dividing organisms (bactericidal) and against semidormant bacteria
- Inhibits protein synthesis
- Cytochrome P450 Inducer = MANY drug-drug interactions
  - Examples include: OCP, methadone, ART, anti-seizure medications, coumadin
  - Complete medication review is needed and any new additions should be noted during treatment.
- Rifabutin: alternative for drug-drug interaction (has lesser degree of induction) or intolerance to rifampin
- Rifapetine: alternative for use in continuation phase, once weekly

Medical Management of TB
INH

- ++ Activity against rapidly dividing organisms (early bactericidal)
- Inhibits mycolic acid (cell wall) synthesis
- Use Vitamin B6 in specific populations (uremia, HIV, diabetes, malnutrition) to prevent peripheral neuropathy
- Increases carbamazepine / phenytoin levels

PZA

- Largest activity against dormant / semidormant bacteria within macrophages / acidic environment of caseous granulomas (bactericidal).
- One of the required drugs for shortening duration to 6 months
- Used in the first 2 months of treatment (initial phase)

EMB

- Bacteriostatic at typical doses
- Inhibitor of cell wall synthesis
- Used to in initial treatment to prevent emergence of resistance
Treatment Regimens

General Principles

- Initial Phase (initial 2 months of treatment)
  - Prevents drug resistance until drug susceptibility testing (DST) is known

- Continuation Phase (subsequent 4-7 months of treatment)

<table>
<thead>
<tr>
<th>Initial Phase</th>
<th>Continuation Phase</th>
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<tbody>
<tr>
<td>7 days/wk</td>
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<tr>
<td>8 wk (56 doses)</td>
<td>18 wk (126 doses)</td>
</tr>
<tr>
<td>5 days/wk</td>
<td>5 days/wk</td>
</tr>
<tr>
<td>8 wk (40 doses)</td>
<td>18 wk (90 doses)</td>
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<tr>
<td>INH/RIF</td>
<td>INH/RIF</td>
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<td>PZA</td>
</tr>
<tr>
<td>EMB</td>
<td>EMB</td>
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<tr>
<td>INH/RIF</td>
<td>INH/RIF</td>
</tr>
<tr>
<td>BIW</td>
<td>BIW</td>
</tr>
<tr>
<td>18 wk (36 doses)</td>
<td>18 wk (90 doses)</td>
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<tr>
<td>Qweek</td>
<td>Qweek</td>
</tr>
<tr>
<td>18 wk (18 doses)</td>
<td>18 wk (58 doses)</td>
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CDC/MMWR, Treatment of Tuberculosis, 2003

Medical Management of TB
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Regimen 2

<table>
<thead>
<tr>
<th>Initial Phase</th>
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<th>Total</th>
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<td>Drugs</td>
<td>Interval and Doses</td>
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</tr>
<tr>
<td>INH</td>
<td>7 days/wk</td>
<td></td>
</tr>
<tr>
<td>RIF</td>
<td>2 wk (14 doses)</td>
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</tr>
<tr>
<td>PZA</td>
<td>6 wk (12 doses)</td>
<td></td>
</tr>
<tr>
<td>EMB</td>
<td>5 days/wk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 wk (10 doses)</td>
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</tr>
<tr>
<td></td>
<td>6 wk (12 doses)</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH/RIF</td>
<td>BIW (18 wk, 36 doses)</td>
<td>26 wk (62-58 doses)</td>
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<tr>
<td>INH/RPT</td>
<td>Qweek (18 wk, 18 doses)</td>
<td>26 wk (44-40 doses)</td>
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CDC/MMWR, Treatment of Tuberculosis, 2003

Regimen 3, 4

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<td>INH</td>
<td>TIW (8 wk, 24 doses)</td>
<td>26 wk (78 doses)</td>
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<tr>
<td>RIF</td>
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<tr>
<td>PZA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMB</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 days/wk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 wk (56 doses)</td>
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</tr>
<tr>
<td></td>
<td>5 days/wk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 wk (40 doses)</td>
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</tr>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>INH/RIF</td>
<td>TIW (18 wk, 54 doses)</td>
<td>39 wk (273 doses)</td>
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</tr>
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<td>7 days/wk</td>
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<td>31 wk (217 doses)</td>
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<td>5 days/wk</td>
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</tr>
<tr>
<td></td>
<td>31 wk (155 doses)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH/RIF</td>
<td>BIW (31 wk, 62 doses)</td>
<td>39 wk (118-102 doses)</td>
</tr>
</tbody>
</table>

CDC/MMWR, Treatment of Tuberculosis, 2003

Baseline evaluation

- CBC
- Renal profile
- Liver function testing, uric acid
- HIV screening
- Hepatitis B/C screening (for IVDU, foreign-born Asia/Africa, HIV)
- Weight
- Visual acuity, red-green color discrimination
- History and Physical
- Imaging (CXR for pulmonary, may be other imaging for extra-pulm)
## Monitoring

- **Monthly:**
  - Face-to-face symptom review
  - Adherence
  - Visual acuity, color discrimination (if on EMB)
  - Weight: re-dose medications as needed
- **CXR (for pulmonary TB) or other imaging:** every 3-6 months, end of treatment
- **Sputum:**
  - Smear positive: at least q2 weeks until smear conversion then monthly until culture conversion
  - Smear negative: monthly until culture conversion

## Lab Monitoring

- Routine lab monitoring is not typically recommended except for those at high-risk or symptomatic.
- **Regardless, clinical monitoring is a MUST!**
  - **LFT:**
    - Underlying hepatic disease
    - Pregnancy or post-partum
    - HIV
    - IVDU or ETOH abuse
    - Consider: Age >50 yo, concomitant hepatotoxic medications
  - Creatinine
    - Underlying renal disease
    - PZA, EMB require renal dosing if creatinine clearance <30
  - **CBC**
    - Underlying hematologic abnormality
    - Rifabutin (can cause leukopenia, thrombocytopenia)

## Who should receive extended therapy (i.e. at least 9 mo)?

- Identify those at risk of treatment failure / relapse
- **Cavitary disease on CXR, delayed culture conversion*:**
  - Cavitary disease on CXR: 5-6% relapse
  - Delayed culture conversion (culture positive after 2 months of treatment): 5-6% relapse
  - Cavitary disease on CXR + delayed culture conversion: 21% relapse
- PZA < 2 months during initiation phase
- Consideration: HIV, cancer/chemotherapy, extensive disease, delayed clinical/radiographic response, silicosis, poorly controlled diabetes

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*TBTC Study 22*
HIV infection

- Daily regimen should be used, based on expert opinion
  - Once weekly regimens should NOT be used; twice weekly considered in CD4>100; TIW could be considered (CDC)
- Drug-drug interactions must be carefully reviewed, in particular with antiretroviral therapy and rifamycins (see DHHS HIV guidelines)
- Paradoxic reactions can occur during treatment

Treatment Completion

- Determined by the total number of doses ingested over a period of time, not by the duration of treatment
  - E.g. “6 month” daily regimen: patient should complete 182 doses (6 months worth of doses) within 9 months

Extrapulmonary TB

<table>
<thead>
<tr>
<th>Location</th>
<th>Duration</th>
<th>Special Considerations</th>
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</thead>
<tbody>
<tr>
<td>Pleural</td>
<td>6 mo</td>
<td>Drainage if possible recommended. Empyema: surgery, optimal duration unknown</td>
</tr>
<tr>
<td>Lymphadenitis</td>
<td>6 mo</td>
<td>LN’s may enlarge or develop new LN’s during and after Rx</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>6 mo</td>
<td>Recommend steroids during first 11 weeks</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>6 mo</td>
<td>May need stent / nephrostomy w/ urology</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>6 mo</td>
<td></td>
</tr>
<tr>
<td>Disseminated</td>
<td>6-9 mo</td>
<td>Longer course for immune compromised / children</td>
</tr>
<tr>
<td>Bone / Joint</td>
<td>6-9 mo</td>
<td>Longer course typically recommended</td>
</tr>
<tr>
<td>CNS / meningitis</td>
<td>9-12 mo</td>
<td>Recommend steroids during first 6 weeks</td>
</tr>
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</table>
Alternate regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
<th>Pattern of resistance</th>
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</thead>
<tbody>
<tr>
<td>RIF/PZA/EMB</td>
<td>6 months</td>
<td>INH</td>
</tr>
<tr>
<td>RIF/EMB</td>
<td>12 months (preferably with PZA during first 2 months)</td>
<td>INH</td>
</tr>
<tr>
<td>INH/EMB</td>
<td>12-18 months (preferably with PZA during first 2 months; consider injectable in first 2-3 months for extensive disease or to shorten duration to 12)</td>
<td>RIF</td>
</tr>
<tr>
<td>INH/PZA/SM</td>
<td>9 months</td>
<td>RIF</td>
</tr>
</tbody>
</table>

Adverse Reactions (common)

- Hepatotoxicity
- Rash
- GI intolerance
- Arthralgias / Gout
- Peripheral neuropathy
- Optic neuritis

Adverse Reactions

- Hepatotoxicity
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Medical Management of TB
Hepatotoxicity

- Causative:
  - PZA (1%)
  - INH
    - Asymptomatic elevation <5x ULN in 10-20%
    - Clinical hepatitis, 0.1-2.7% depending on combo
    - Fatal hepatitis <0.023%
  - RIF
    - rare except in combination with other drugs
    - Asymptomatic hyperbilirubinemia (0.6%)
    - Cholestatic pattern of hepatitis

Hepatotoxicity (management)

- HOLD medications for the following or any GI complaint: abdominal pain, diarrhea, fatigue, nausea/vomiting, anorexia, malaise, jaundice, dark urine.
- Check LFT’s
  - If LFT <5x upper limit of normal (ULN) and asymptomatic, okay to restart but may need closer monitoring.
  - If LFT <3x ULN and symptomatic, okay to restart with supportive measures, e.g. treatment of gastritis or nausea. May need closer monitoring.

- STOP medications for the following:
  - Asymptomatic + LFT >5x upper limit of normal (ULN)
  - Symptomatic + LFT >3x ULN
  - Screen for hepatitis (A, B, C) or other underlying causes of liver disease (alcohol use, other hepatotoxic medications). Check INR.
  - Determine if urgent evaluation or admission is needed (e.g. >10x ULN or any evidence of liver failure- asterixis, confusion, dehydration, coagulopathy)
Hepatotoxicity (re-challenge)

- Monitor LFTs weekly until 2x ULN (some programs completely normal), before re-challenging with medications. If severe TB disease, may need to start liver-sparing regimen.
- Seek consultation in re-introduction of medications.
- Choice in med re-challenge depends on co-morbidities (cirrhosis), degree of hepatitis (mild vs severe), susceptibilities (pan-susceptible or pending), phase (initial or continuation), and most likely suspect (PZA>INH>RIF).
- Typically, start least suspect agent first (along w/ non-hepatotoxic meds), monitor LFTs in 3-7 days, and if remain normal then re-challenge with next agent.

Gastrointestinal (GI) Intolerance

- Symptoms: nausea, vomiting, diarrhea
- Causes: any
- Rule out hepatotoxicity first
- Treatment:
  - Anti-emetics: Reglan, phenergan, zofran. Consider pre-medication, 30-60 minutes prior to TB meds.
  - Probiotics / loperamide for diarrhea
  - Light snack prior to medications
  - Consider bedtime dosing (if on video-DOT or on SAT)
  - Treat gastritis with H2 blocker or proton pump inhibitor
  - Evaluate for other causes: ulcer, pancreatitis, C diff, kidney injury, biliary causes (gallstones)

Rash (mild)

- Causative: any drugs, esp RIF, PZA
- Symptoms: maculopapular rash, flushing, pruritus
- Treatment:
  - Antihistamines (e.g. claritin, hydroxyzine, benadryl)
  - Triamcinolone cream / steroid cream
  - Low dose steroids (10-20mg/day) if above unsuccessful
  - For flushing: Avoid tyramine-containing foods with INH (wine, salami, cheese) and certain fish (tuna)
  - Avoid sun / use sunblock (PZA/FQ)
Rash (mod-severe)

- Drugs should NOT be continued if: systemic symptoms, fever, urticaria, angioedema, blisters, SOB, anaphylaxis
- Symptoms: any drugs, esp RIF, PZA
- Treatment:
  - If serious (e.g. Stevens-Johnson, anaphylaxis, TEN) do NOT re-challenge. May need hospitalization / urgent derm consult.
  - If moderate symptoms and no anaphylaxis, HOLD meds, then re-challenge once rash improves. Antihistamines / steroids as needed. Consider derm referral.
  - May need desensitization for those meds deemed to be necessary.

Arthralgias / Gout

- Arthralgias (up to 40%):
  - Causative: PZA>>EMB, INH, RIF
  - Treatment: NSAIDs or ASA
- Gout (rare):
  - Causative: PZA>>EMB
  - Elevated uric acid
  - Prevention: consider allopurinol or optimization of gout at time of TB med start
  - Treatment: NSAIDs, allopurinol, colchicine

Peripheral neuropathy

- Causative: INH>>EMB
- Occurs <0.2% with INH at conventional dosing (10mg/kg/d)
- Prevention: pyridoxine 25-50 mg daily in diabetes, pregnancy, HIV, kidney disease, alcoholism, breastfeeding women
- Treatment: consider either discontinuation of INH or increasing pyridoxine dosing (100-200 mg/d)
- Ddx: consider other causes including thyroid disease, vitamin deficiency, other medications
Optic neuritis

- **Causative:** EMB>>INH
- **Screening:** monthly visual acuity, red-green color discrimination (Ishihara plates)
- **Symptoms:** blurry vision, vision loss, spots, red-green color issues, eye pain
- **Treatment:** hold medications, urgent ophthalmology evaluation to determine etiology

Helpful resources

- **Treatment Guidelines:**
  - Local/State specific guidelines (e.g. CDHS/CTCA Joint Guidelines for the Treatment of Active Tuberculosis Disease)
  - Regional Training and Medical Consultation Centers (RTMCC), [http://www.cdc.gov/tb/education/rtmcc/](http://www.cdc.gov/tb/education/rtmcc/)
- **Med side effects:**

Additional pearls…

- **Typically avoid EMB in children whose visual acuity cannot be monitored, unless concerns for drug resistance or upper lobe/cavitary disease.**
- **Situations where you might avoid PZA:**
  - Pregnancy, severe liver disease, gout
- **Use fixed dose combinations when possible. Avoid splitting doses if possible.**
Frequency of Random Naturally Occurring Resistance Mutations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>1 in $10^6$</td>
</tr>
<tr>
<td>RIF</td>
<td>1 in $10^4$</td>
</tr>
<tr>
<td>EMB</td>
<td>1 in $10^6$</td>
</tr>
<tr>
<td>Strep</td>
<td>1 in $10^6$</td>
</tr>
<tr>
<td>INH+RIF</td>
<td>1 in $10^{14}$</td>
</tr>
</tbody>
</table>

(Approximately $10^8$ organisms per cavity)

Random drug-resistant mutants in large (> $10^6$) bacterial population

Multidrug therapy works: No bacteria resistant to all 3 drugs

Monotherapy: INH-resistant bacteria grow

When treated with just one drug, resistant bacteria begin to grow

Spontaneous mutations to other drugs (RIF) develop as bacilli grow to $>10^8$ organisms

INH monoresist. mutants killed by adding RIF, but RIF-resist. mutants proliferate → MDR TB