Standard TB Treatment

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Objectives

• Describe the recommended treatment regimen and first-line medications for TB disease
• Identify the common side effects of first-line tuberculosis medications and recommended monitoring
General Principles, pan-susceptible

• Initial Phase (initial 2 months of treatment)
  • Prevents drug resistance until drug susceptibility testing (DST) is known
  • Bacillary burden is the highest during this phase

• Continuation Phase (subsequent 4-7 months of treatment)
The Drugs (first-line)

- Rifampin (RIF, “R”), 10 mg/kg/d
- Isoniazid (INH, “H”), 5 mg/kg/d
- Pyrazinamide (PZA, “Z”), 25 mg/kg/d
- Ethambutol (EMB, “E”), 15-25 mg/kg/d
Rifamycins

- Includes: rifampin, rifabutin
- **Mechanism of action:** Inhibits bacterial RNA synthesis by binding to DNA-dependent RNA polymerase
- **Adverse reactions / Side effects:**
  - Orange discoloration of body fluids (e.g. urine) (nearly 100%, non-toxic)
  - Increased liver enzymes or bilirubin (10-14%)
  - Rash (1-5%)
  - Gastrointestinal (1-2%)
  - Serious (but rare): hypersensitivity (0.07-0.3%), hematologic (thrombocytopenia, leukopenia, anemia)
- **Cytochrome P450 Inducer = MANY drug-drug interactions**
  - Examples include: OCP, methadone, ART, 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
INH

- **Mechanism of action:** Inhibits mycolic acid (i.e. cell wall) synthesis
- **Adverse reactions / Side effects:**
  - Peripheral neuropathy - co-administer pyridoxine in at-risk patients (diabetes, HIV, renal failure, advanced age, nutritional deficiency, alcoholism)
  - Mild/transient elevation in AST/ALT (10-20%)
  - Hepatitis (black-box warning)
  - Fatal hepatitis
  - Rare: Lupus-like syndrome, fever, rash
  - Increases carbamazepine / phenytoin levels
PZA

• **Mechanism of action:** Exact mechanism unknown, conversion to pyrazinoic acid results in pH lowering, disruption of cell membrane

• **Adverse reactions / Side effects:**
  - Hepatotoxicity
  - Hyperuricemia, predisposition to gout (avoid in patients with pre-existing gout)
  - Arthralgias / myalgias
  - Gastrointestinal (1-10%)

• One of the required drugs for shortening duration to 6 months

• Used in the first 2 months of treatment (initial phase)
EMB

• **Mechanism of action:** inhibits cell wall synthesis by inhibiting arabinosyl transferase

• **Adverse reactions / Side effects:**
  • Optic neuritis- baseline and monthly visual acuity and color discrimination should be monitored
  • Rare: hypersensitivity, gastrointestinal, rash
# First-line medications

<table>
<thead>
<tr>
<th>Drug / dose</th>
<th>Hepatotoxicity</th>
<th>Specific adverse</th>
<th>Additional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin, 10mg/kg</td>
<td>+</td>
<td>Rash, pruritus, hypersensitivity, GI upset, Thrombocytopenia, Hemolytic anemia</td>
<td></td>
</tr>
<tr>
<td>(max: 600 mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH, 5 mg/kg</td>
<td>++</td>
<td>Peripheral neuropathy, Drug-induced lupus, CNS symptoms, Optic neuritis</td>
<td>Co-administer with B6</td>
</tr>
<tr>
<td>(max: 300 mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PZA, 25 mg/kg</td>
<td>++</td>
<td>Gout, Hyperuricemia, Arthralgias, Photosensitivity</td>
<td>Dose adjustment to TIW in CrCl&lt;30, Dose after HD</td>
</tr>
<tr>
<td>EMB, 15-25 mg/kg</td>
<td></td>
<td>Retrobulbar neuritis (dose-related, exacerbated by CKD)</td>
<td>Use higher dose only during initial months. Dose adjustment to TIW in CrCl&lt;30, Dose after HD</td>
</tr>
</tbody>
</table>
### Second-line (commonly used)

<table>
<thead>
<tr>
<th>Drug / dose</th>
<th>Hepatotoxicity</th>
<th>Specific adverse</th>
<th>Additional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifabutin, 5 mg/kg (max: 300 mg)</td>
<td>+</td>
<td>Anterior uveitis</td>
<td>&lt;20% of rifampin-resistant strains will have in vitro susceptibility to RFB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leukopenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arthralgias</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin, 400mg qday</td>
<td>Rare</td>
<td>QTC prolongation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tendon rupture</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GI upset</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C diff risk</td>
<td></td>
</tr>
<tr>
<td>Levaquin, 750mg qday (typically)</td>
<td>QTC prolongation</td>
<td>Tendon rupture</td>
<td>Dose adjustment to TIW in CrCl&lt;30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GI upset</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C diff risk</td>
<td></td>
</tr>
<tr>
<td>Injectable (e.g. streptomycin, capreomycin, amikacin)</td>
<td></td>
<td>Nephrotoxicity</td>
<td>Adjust to BIW-TIW depending on renal function and phase of treatment (i.e. continuation phase)</td>
</tr>
<tr>
<td>10-15 mg/kg/day with max 750-1000 mg / day based on age</td>
<td></td>
<td>Ototoxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Electrolyte abnormalities</td>
<td></td>
</tr>
</tbody>
</table>
### Drug Regimens for Pan-Susceptible Disease

<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, RIF, PZA, EMB</td>
<td>7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)</td>
<td>INH, RIF</td>
</tr>
<tr>
<td>2</td>
<td>INH, RIF, PZA, EMB</td>
<td>7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)</td>
<td>INH, RIF</td>
</tr>
<tr>
<td>3</td>
<td>INH, RIF, PZA, EMB</td>
<td>3 times weekly for 24 doses (8 wk)</td>
<td>INH, RIF</td>
</tr>
<tr>
<td>4</td>
<td>INH, RIF, PZA, EMB</td>
<td>7 d/wk for 14 doses then twice weekly for 12 doses*</td>
<td>INH, RIF</td>
</tr>
</tbody>
</table>

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## Alternate regimens (in order of preference)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
<th>Pattern of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIF/PZA/EMB</td>
<td>6-9 months</td>
<td>INH</td>
</tr>
<tr>
<td>+/- FQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIF/EMB</td>
<td>9-12 months (preferably with PZA during first 2 months)</td>
<td>INH</td>
</tr>
<tr>
<td>+/- FQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH/EMB/FQ</td>
<td>12-18 months (preferably with PZA during first 2-3 months for extensive disease or to shorten duration to 12 mo)</td>
<td>RIF</td>
</tr>
<tr>
<td>RIF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH/EMB/PZA</td>
<td>18 months (consider injectable in first 2-3 months for extensive disease or to shorten duration to 12 mo)</td>
<td>RIF</td>
</tr>
<tr>
<td>INH/PZA/SM</td>
<td>9 months</td>
<td>RIF</td>
</tr>
</tbody>
</table>
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 intensive phase
• HIV not on ART
• If Cavitary disease on CXR OR delayed culture conversion, consider extending if suggestions of poor response: e.g. immunosuppression, extensive disease, delayed clinical/radiographic response, silicosis, poorly controlled diabetes, smoker, >10% below ideal body weight

* TBTC. Lancet. 2002 Aug17;360(9332):528-34.
HIV infection

• Daily regimen recommended
  • High rates of relapse seen in once weekly, BIW, TIW regimens
  • Emergence of rifamycin resistance in intermittent therapy

• Duration of treatment (for pan-suscept)
  • On ART- 6 mo (2HRZE, 4HR)
  • Off ART- 9 mo (2HRZE, 7HR)
HIV infection

• Drug-drug interactions must be carefully reviewed, in particular with antiretroviral therapy and rifamycins (see DHHS HIV guidelines). Work closely with HIV provider as newer agents have DDI (TAF, dolutegravir)

• ART start
  • CD4<50: within 2 weeks of TB tx start
  • CD4≥50: by 8-12 weeks of TB tx start
  • TB meningitis: should not be initiated in 1st 8 weeks

• Paradoxic reactions (IRIS) 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
    • Initial phase of 2 months within 3 months +
    • Continuation phase of 4 months within 6 months
<table>
<thead>
<tr>
<th>Location</th>
<th>Duration</th>
<th>Special Considerations</th>
</tr>
</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>Consider steroids</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 6-8 weeks</td>
</tr>
</tbody>
</table>
Scenario

A patient with pan-susceptible pulmonary TB is started on standard therapy, but has a worsening CXR 2 months into treatment. What do you do?
Treatment failure

• Red flags-
  • Delayed culture conversion (i.e. after 2 months); may need to use smears as surrogate while awaiting cultures
  • Worsening imaging at 2 months
  • Worsening or persistent symptoms at 2 months

• At risk- large burden of disease, cavitary, diabetic

• Recommendations-
  • Determine if development of resistance has occurred (repeat DST, molecular testing) and if regimen needs to be expanded
  • Assess if malabsorption present
  • Assess adherence
  • Check drug levels (TDM)
Case

96 yo South Asian F diagnosed with pulmonary TB
96 yo F with pulmonary TB

- Numerous smear positive disease
- CXR- RUL cavity
- Weight 85 lbs
- Creatinine 1.0
- How do you proceed?
Advanced Age

• Risk of DILI (drug-induced liver injury) increases with age
• Some experts avoid PZA in pts >75 yo
• Risk / benefit decisions on HRZE vs HRE vs HRE + FQ
  • Consider severity of disease and bacillary load
  • Consider risk for drug resistance
  • Consider risk for DILI
• Close medication review due to drug-drug interactions needed

Advanced Age

- Low BMI / malnutrition is often an issue:
  - Close monitoring of weight and dose adjustments
  - May need nutritional supplementation
- Creatinine may not accurately reflect actual CrCl/GFR due to low muscle mass. Calculation recommended.
- Close medication review needed due to drug-drug interactions and an ever-changing polypharmaceutical list (often includes anti-HTN, thyroid replacement, antidepressants, and blood thinners)
- Associated with higher mortality and poor outcomes.

96 yo F with pulmonary TB- back to the case

• Calculated CrCl~19.9
• How do you proceed?
## Renal Disease

<table>
<thead>
<tr>
<th>Requires dose / frequency adjustment</th>
<th>No adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrazinamide- 25-35 mg/kg TIW</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Ethambutol- 20-25 mg/kg TIW</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>Levofloxacin- 750-1000 mg TIW</td>
<td>Moxifloxacin</td>
</tr>
</tbody>
</table>

- Patients with CKD have worse clinical outcomes.
- Interval should be decreased with CrCl<30 mL/min
- All TB medications should be ideally given after HD on HD days.
- Consider monitoring therapeutic drug monitoring
- PD- no data available

Helpful resources

• **Treatment Guidelines:**
  • ATS/CDC/IDSA, Treatment of Drug-Susceptible Tuberculosis, 2016
  • Regional Training and Medical Consultation Centers (RTMCC), http://www.cdc.gov/tb/education/rtmc/
  • Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, Curry Center

• **Med side effects:**
  • Drug-Induced Liver Injury, http://www.currytbcenter.ucsf.edu/trainings/tuberculosis-drug-induced-liver-injury
  • Tuberculosis Drug Information Guide, Curry Center
  • ART-TB DDI: Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, https://aidsinfo.nih.gov
thank you!

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