Treatment of TB: Current Drugs in Use

Adrian Gardner MD, MPH
Assistant Professor of Medicine (Research)
Alpert Medical School of Brown University
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Primary Anti-TB Drug Resistance
United States, 1993–2009*

*Updated as of July 1, 2010.

Note: Based on initial isolates from persons with no prior history of TB. Multidrug resistant TB (MDR TB) is defined as resistance to at least isoniazid and rifampin.
Outline

• Principles
• First-line drugs
  – Fixed-dose combinations
• Commonly used Second-line drugs
• Other Second-line drugs
TB Drugs in Use

**First-line**
- Isoniazid
- Rifampin/Rifabutin
- Ethambutol
- Pyrazinamide

**Injectables**
- Streptomycin
- Kanamycin
- Amikacin
- Capreomycin

**Quinolones**
- Ofloxacin
- Levofloxacin
- Moxifloxacin

**Other 2nd-line**
- Ethionamide
- Cycloserine
- PAS
- Linezolid
- Amox-Clav
- Clofazamine
- Imipenem
- Clarithromycin
Principles

• Combination therapy
  – Eradicate TB infection
  – Protect against resistance
  – Prevent Relapse

• Weight-based dosing
  – All first-line TB drugs are dosed based on patient’s weight

• Directly Observed Therapy
Limitations

• Lack of good information on pediatric pharmacokinetics
  – Utility of serum drug levels
First Line Drugs
Isoniazid (INH)

- **Mechanism:** Affects cell wall synthesis (Bactericidal)
- **Dosing**
  - Adults: 5 mg/kg/d to max 300mg/d; “high dose”: 900-1500 mg twice/thrice weekly
  - Children: 10-15 mg/kg/d to max 300mg/d; 20-30 mg/kg/dose twice/thrice weekly
- **Route:** oral, IV, IM
- **Oral Preparations:** 50/100/300mg scored tablets; 50mg/5ml solution (sorbitol)
- **Metabolism:** Hepatic (cytochrome p450)
- **Adverse Reactions:**
  - Hepatitis (age-related), peripheral neuropathy, hypersensitivity
- **Common Drug Interactions:**
  - Seizure meds: ↑ phenytoin (dilantin); carbamazepine (tegretol) → hepatotoxicity
- **Special circumstances:**
  - Safe during pregnancy, breastfeeding
  - Vitamin B6 (pyridoxine) supplementation
Rifampin

- **Mechanism:** inhibits protein synthesis (Bactericidal)
- **Dosing**
  - Adults: 10 mg/kg/d to max 600mg/d
  - Children: 10-20 mg/kg/d to max 600mg/d
- **Route:** oral, IV
- **Oral Preparations:** 150/300mg capsules
- **Metabolism:** Hepatic (cytochrome p450)
- **Adverse Reactions:**
  - Rash, pruritis, orange body fluids, hepatotoxicity, hematologic, GI upset, flu-like syndrome
- **Common Drug Interactions:**
  - Many HIV medications (protease inhibitors), oral contraceptives, warfarin, methadone, corticosteroids
- **Special circumstances:**
  - Safe during pregnancy, breastfeeding

Other rifamycins

• Rifabutin
  – 5mg/kg (max 300mg/d)
  – Fewer problematic drug interactions

• Rifapentine
  – Drug interactions similar to rifampin
  – Once weekly regimen with INH for continuation phase for...
    • HIV neg adults, non-cavitary dz, cx neg at 2 months
Pyrazinamide (PZA)

- **Mechanism:** Unclear (Bactericidal inside cells (acidic pH))
- **Dosing**
  - Adults: 25 mg/kg/d to max 2 g/d
  - Children: 20-40 mg/kg/d
- **Route:** oral
- **Oral Preparation:** 500mg scored tablets
- **Metabolism:** Renal
- **Adverse Reactions:**
  - GI upset, hepatitis, gout (hyperuricemia), rash, photosensitivity
- **Common Drug Interactions:** none
- **Special circumstances:**
  - Dose not protect against resistance, allows for short-course therapy
  - Dose-adjust with renal failure
  - Dose based on lean body weight
  - ? Safety in pregnancy
Ethambutol

- **Mechanism:** Inhibits cell wall synthesis (mostly bacteriostatic)
- **Dosing**
  - Adults: 15-20 mg/kg/d
  - Children: 15-20 mg/kg/d
- **Route:** oral
- **Oral Preparations:** 100/400mg scored tablets
- **Metabolism:** Renal
- **Adverse Reactions:**
  - Optic neuritis (dose-related)
- **Common Drug Interactions:** none
- **Special circumstances:**
  - Baseline and monthly visual acuity, color-vision testing
  - Safe during pregnancy, breastfeeding
  - Dose adjust for renal disease
Streptomycin

- **Mechanism:** Inhibits protein synthesis (bactericidal)
- **Dosing**
  - Adults: 15 mg/kg/d 5-7x/wk, then 2-3x/wk
  - Children: 20-40 mg/kg/d
- **Route:** IV, IM
- **Oral Preparations:** none
- **Metabolism:** Renal
- **Adverse Reactions:**
  - Nephrotoxicity, Ototoxicity/Vestibular toxicity (increased with age, prolonged use), Electrolyte abnormalities (hypokalemia, hypomagnesemia), local pain
- **Common Drug Interactions:**
  - Careful with other nephrotoxins (diuretics, NSAIDs)
- **Special circumstances:**
  - Avoided during pregnancy (congenital deafness), can be used during breastfeeding
  - Monitor serum levels, renal function
  - Dose adjust for renal disease, obesity (ideal body weight + 40% excess weight)
Example Case

• 32 yo F with AFB smear+ pulmonary TB

Past Medical History: none
Current Medications: OCP
Weight: 130 lbs (59 kg)

TB med dosing:
R 59kg x 10mg/kg = 590 ~ 600 mg 600mg/59kg = 10.17 mg/kg
I 59 kg x 5 mg/kg = 295 ~ 300 mg 300mg/59kg = 5.08 mg/kg
Z 59kg x 25mg/kg = 1475 ~ 1500 mg 1500mg/59kg = 25.4 mg/kg
E 59kg x 15-20mg/kg = 885-1180 ~ 1200 mg 1200mg/59kg = 20.3 mg/kg

Barrier contraception!
Fixed Dose Combinations (FDC)

• USA
  – Rifamate (RH)
  – Rifater (RHZ)

• Worldwide
  – Many different combinations with different names
    • Rifafour (RHZE)
    • Rifater (RHZ)
    • Rifinah (RH)
    • Ethizide (HE)
## Treatment Regimens: LTBI

<table>
<thead>
<tr>
<th>Adults</th>
<th>Children</th>
<th>Max dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH 5mg/kg/d x 9 mo</td>
<td>INH 10mg/kg/d x 9 mo</td>
<td>Max 300 mg/d</td>
</tr>
<tr>
<td>INH 900 mg twice weekly* x 9 mo</td>
<td>INH 20-30 mg/kg twice weekly* x 9 mo</td>
<td>Max 900 mg/d</td>
</tr>
</tbody>
</table>

**ALTERNATIVE REGIMEN**

<table>
<thead>
<tr>
<th>Adults</th>
<th>Children</th>
<th>Max dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin 600 mg daily x 4 months</td>
<td>Rifampin 10-20 mg/kg/d x 6 months</td>
<td>Max 600 mg/d</td>
</tr>
</tbody>
</table>

*Twice weekly must be administered by DOT
## Treatment Regimens: Culture + Pulmonary TB Disease

<table>
<thead>
<tr>
<th>Initial phase (minimum # doses)</th>
<th>Continuation phase (minimum # doses)</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>RHZE 5-7 d/wk x 8 wks (40 – 56 doses)</td>
<td>RH 5-7 d/wk x 18 wks (90 – 126 doses)</td>
<td>97-99%</td>
</tr>
<tr>
<td></td>
<td>RH 2-3x/wk x 18 wks (36 - 54 doses)</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td>H/RPT weekly x 18 wks (18 doses)</td>
<td>97%</td>
</tr>
</tbody>
</table>

(HIV neg, non-cavitary, cx neg)

- Patients with cavitation on CXR, + culture at 2 months require 7 month continuation phase (total 9 months)
- 2x/wk regimens not recommended in resource-limited settings (smaller margin for safety if doses missed) or for advanced HIV+ patients
**Alternative Regimens**

<table>
<thead>
<tr>
<th>Initial phase (minimum # doses)</th>
<th>Continuation phase (minimum # doses)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RHZE 5 - 7 d/wk x 2 wks (10 - 14 doses), then 2x/wk x 12 wks (24 doses)</td>
<td>RH 2x/wk x 18 wks (36 doses)</td>
<td>2x/wk regimens not recommended in resource-limited settings (smaller margin for safety if doses missed) or for advanced HIV+ patients</td>
</tr>
<tr>
<td>RHZE 3x/wk x 8 wks (24 doses)</td>
<td>RH 3x/wk x 18 wks (54 doses)</td>
<td>Higher relapse rate in HIV+</td>
</tr>
</tbody>
</table>

- Patients with cavitation on CXR, + culture at 2 months require 7 month continuation phase (total 9 months)
Commonly Used 2\textsuperscript{nd} line Drugs
Fluoroquinolones

- **Mechanism:** Inhibit DNA gyrase (Bactericidal)
- **Dosing**
  - Adults: Levo: 500-1000 mg/day, Moxi: 400 mg/d
  - Children: Levo: 15-20 mg/kg divided bid, 10 mg/kg/d for older children
- **Route:** oral, IV
- **Oral Preparations:** 250/500/750mg tablets, oral solution (25mg/ml)
- **Metabolism:** Renal
- **Adverse Reactions:**
  - Nausea, headache, tremulousness, arthralgias, rare tendon rupture, prolonged QTc, rare hepatotoxicity
- **Common Drug Interactions:**
  - Avoid administration with milk, antacids, vitamins (iron, zinc, magnesium)
- **Special circumstances:**
  - Generally not used during pregnancy, breastfeeding
  - Dose adjust for renal disease
Injectables (Aminoglycosides)

- **Mechanism:** Inhibit protein synthesis (Bactericidal)
- **Dosing**
  - Adults: 15 mg/kg/d to max of 750-1g; 5-7x/wk, then 2-3x/wk
  - Children: 15-30 mg/kg to max 1g; 5-7x/wk, then 2-3x/wk
- **Route:** IV, IM, [inhalation]
- **Oral Preparations:** none
- **Metabolism:** Renal
- **Adverse Reactions:**
  - Nephrotoxicity, Ototoxicity/Vestibular toxicity (increased with age, prolonged use), Electrolyte abnormalities (hypokalemia, hypomagnesemia)
- **Common Drug Interactions:**
  - Careful with other nephrotoxins (diuretics, NSAIDS)
- **Special circumstances:**
  - Avoided during pregnancy (congenital deafness), can be used during breastfeeding
  - Monitor serum levels, renal function
  - Dose adjust for renal disease, obesity (ideal body weight + 40% excess weight)
Other 2\textsuperscript{nd} line Drugs
Cycloserine

- **Mechanism:** Inhibits cell wall synthesis (Bacteriostatic)
- **Dosing**
  - Adults: 10-15 mg/kg/d; usually 250mg bid- tid
  - Children: 10-20 mg/kg bid (max 1g daily)
- **Route:** Oral
- **Oral Preparations:** 250mg capsule
- **Metabolism:** Renal
- **Adverse Reactions:**
  - CNS toxicity (poor concentration, lethargy, seizures, psychosis, depression, suicidal ideation), rash, peripheral neuropathy
- **Common Drug Interactions:**
  - May have increased toxicity when ethionamide also used
- **Special circumstances:**
  - All patients should receive vitamin B6 supplementation
  - Best taken on empty stomach (antacids, juice OK)
  - Renal dosing required
Ethionamide

- **Mechanism:** Blocks mycolic acid synthesis (weakly bactericidal)
- **Dosing**
  - Adults: 10-15 mg/kg/d; usually 500-750 mg daily or divided (bid); (max 1g daily)
  - Children: 15-20 mg/kg bid usually divided bid-tid (max 1g daily)
  - Often dose must be ramped up gradually with symptomatic tx of nausea
- **Route:** Oral
- **Oral Preparations:** 250mg tablet
- **Metabolism:** Hepatic
- **Adverse Reactions:**
  - GI upset, anorexia, metallic taste, hepatotoxicity, endocrine effects (hair loss, hypothyroidism gynecomastia), neurotoxicity
- **Common Drug Interactions:**
  - May have increased toxicity when used with cycloserine
- **Special circumstances:**
  - All patients should receive high-dose vitamin B6 supplementation
  - Monitor TSH, LFTs
Para-aminosalicylate (PAS)

- **Mechanism:** Bacteriostatic
- **Dosing**
  - Adults: 8-12 g/d; usually divided bid- tid
  - Children: 200-300 mg/kg/d; usually divided 2-4 times per day
  - Sprinkle granules over applesauce/yogurt or mix in acidic juice
- **Route:** Oral
- **Oral Preparations:** 4g packet
- **Metabolism:** Renal/hepatic
- **Adverse Reactions:**
  - GI distress, reversible hypothyroidism, rare hepatotoxicity/coagulopathy
- **Common Drug Interactions:**
  - Increased risk of hypothyroidism when ethionamide also used
- **Special circumstances:**
  - Packets should be kept in refrigerator/freezer
  - Monitor TSH, electrolytes, blood counts, LFTs
  - Avoid with severe renal failure
  - Shells of the granules can be seen in the stool
Linezolid

- **Mechanism:** Inhibits protein synthesis (? Bacteriocidal)
- **Dosing**
  - Adults: 600mg daily
  - Children: 10 mg/kg tid
- **Route:** Oral, IV
- **Oral Preparations:** 400/600 mg tablet, oral powder for suspension (100mg/5ml)
- **Metabolism:** Renal
- **Adverse Reactions:**
  - Myelosuppression, diarrhea, nausea, optic and peripheral neuropathy, serotonin syndrome
- **Common Drug Interactions:**
  - Do not use with other drugs that increase serotonin levels (anti-depressants)
- **Special circumstances:**
  - All patients should receive vitamin B6 supplementation
  - Avoid in patients with symptoms of neuropathy
  - Monitor CBC
Amoxicillin-Clavulanate

- **Mechanism:** penicillin-beta-lactam inhibitor (? Early bacteriocidal)
- **Dosing**
  - Adults: 2000mg/125mg twice daily
  - Children: 80 mg/kg bid (amoxicillin component)

- **Route:** Oral
- **Oral Preparations:** 1000/62.5 mg tablet (Augmentin XR), 600mg/5ml solution
- **Metabolism:** Renal/hepatic
- **Adverse Reactions:**
  - Diarrhea/abdominal discomfort, nausea/vomiting, rash, hypersensitivity
- **Common Drug Interactions:**
  - Drugs that inhibit renal clearance can increase toxicity
- **Special circumstances:**
  - Use with caution in patients with liver disease
  - Renal dosing required
Clofazamine

- **Mechanism:** in vitro activity (limited in vivo data)
- **Dosing**
  - Adults: 100-200 mg daily
  - Children: 1 mg/kg/day
- **Route:** Oral
- **Oral Preparations:** 50/100 mg capsule
- **Metabolism:** Hepatic
- **Adverse Reactions:**
  - Red discoloration of skin, body fluids, GI intolerance, photosensitivity, retinopathy, pruritus, bleeding, bowel obstruction
- **Common Drug Interactions:**
  - May have increased toxicity when ethionamide also used
- **Special circumstances:**
  - Not commercially available in the US, obtain from FDA
  - Not recommended in pregnancy, breastfeeding
Imipenem-cilastatin

- **Mechanism:** beta-lactam, in vitro activity (very limited clinical experience)
- **Dosing**
  - Adults: 1000 mg every 12 hours
  - Children: 20-40 mg/kg IV every 8 hours (meropenem preferred)
- **Route:** IV, IM
- **Oral Preparations:** none
- **Metabolism:** Hepatic
- **Adverse Reactions:**
  - Diarrhea, nausea, vomiting, seizures, transaminitis
- **Common Drug Interactions:**
  - Estrogens
- **Special circumstances:**
  - Renal dosing required
# Cross-Resistance

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cross-Resistance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Ethionamide</td>
<td>Cross-resistance to ethionamide may occur when there is low-level resistance to isoniazid.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Rifamycins</td>
<td>Cross-resistance among the rifamycin class of drugs is typical. In a few strains that are resistant to rifampin, rifabutin may retain susceptibility <em>in vitro</em>.</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>Kanamycin</td>
<td>High likelihood of cross-resistance since it is associated with the same mutation.</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Amikacin</td>
<td>High likelihood of cross-resistance since it is associated with the same mutation.</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Amikacin/Kanamycin</td>
<td>Variable frequency of cross resistance has been reported.</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Other fluoroquinolones</td>
<td>In general, there is a complete class effect cross-resistance among fluoroquinolones <em>in vitro</em>. However, data suggest that moxifloxacin may continue to demonstrate some activity despite <em>in vitro</em> resistance to ofloxacin.</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>PAS</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Isoniazid</td>
<td>Cross-resistance to isoniazid may occur when there is low-level resistance to ethionamide.</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>
## Treatment of Drug Resistant TB

<table>
<thead>
<tr>
<th></th>
<th>Length of treatment</th>
<th>Regimen/ # of drugs</th>
<th>Cure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pansusceptible</td>
<td>6 months</td>
<td>H/R/Z x 2, H/R x 4</td>
<td>99%</td>
</tr>
<tr>
<td>INH resistance</td>
<td>12 months</td>
<td>2 (R/E)</td>
<td>95% Z throughout</td>
</tr>
<tr>
<td>Rifampin resistance</td>
<td>18 months</td>
<td>2 (H/E)</td>
<td>95% ? FQ, ? inject may</td>
</tr>
<tr>
<td>INH and Rifampin</td>
<td>18-24 months</td>
<td>4 to include injectable and a quinolone</td>
<td>70% Consider surgery</td>
</tr>
<tr>
<td>INH, Rifampin plus</td>
<td>24 months after sputum culture conversion</td>
<td>At least 5 to include an injectable</td>
<td>50-70% Consider surgery</td>
</tr>
</tbody>
</table>
Thank you for your attention