Anti-Tuberculosis Drugs

Objectives

- Describe the anti-tb medications used to treat drug-susceptible TB infection and disease and their role in the treatment of each

- Describe how acquired drug-resistance develops and principles of TB treatment to prevent acquired resistance

- Identify resources available to guide nursing management of common side-effects of anti-TB medications
The Drugs for TB

TB Chemotherapy Fun Fact Match

- What is the origin of the discovery of rifamycins?
- What is the origin of the discovery of streptomycin?
- What is the origin of the discovery of isoniazid?

A. A soil sample from a pine forest in the French Riviera
B. Chemical variation of PAS and thioacetazone’s molecular structure
C. A soil actinomycete isolated from the throat of a sick chicken in New Jersey
Introduction of Anti-TB Drugs

**First-line**
- 1946: Ethambutol
- 1952: Isoniazid and Pyrazinamide
- 1955: Cycloserine
- 1957: Kanamycin/Amikacin
- 1962: Ethambutol
- 1966: Ethionamide
- 1967: Rifampin
- 1970: Pyrazinamide
- 1972: Ethionamide
- 1980: Rifapentine
- 1998: Rifapentine

**Second-line**
- 1940-1950: Streptomycin
- 1945: Streptomycin
- 1950: Thiacetazone
- 1955: Thiacetazone
- 1960: Para-aminosalicylic acid (PAS)
- 1962: Thiacetazone
- 1966: Capreomycin
- 1970: Pyrazinamide
- 1980: Pyrazinamide
- 2000: Linezolid


The “First-line” Anti-TB Drugs

- **Rifamycins**
  - Rifampin (RIF, “R”)
  - Rifabutin (RFB)
  - Rifapentine (RPT, “P”)

- **Isoniazid** (INH, “H” or “I”)
- **Pyrazinamide** (PZA, “Z”)
- **Ethambutol** (EMB, “E”)

Anti-TB Drugs: What Nurses Need to Know
Rifamycins

- **Includes:** rifampin (150mg, 300mg caps), rifabutin (150mg caps), and rifapentine (150mg tab)
- Bactericidal; inhibits protein synthesis
- **Rifampin** is a powerful inducer of hepatic cytochrome P450 enzymes increases metabolism of MANY drugs
  - **Examples:** hormonal contraception, methadone, anti-seizure medications, anti-coagulants, anti-retrovirals
  - Complete medication review is needed and any new additions should be noted during treatment

### Drug-Drug Interactions - Rifampin

<table>
<thead>
<tr>
<th>Rifampin</th>
<th>Hypoglycemic (sulfonylureas)</th>
<th>Anticoagulants</th>
<th>Antidepressants</th>
<th>Beta-Blockers</th>
<th>Contraceptives</th>
<th>Corticosteroids</th>
<th>Cyclosporine</th>
<th>Protease Inhibitors</th>
<th>Delavirdine</th>
<th>Efavirenz</th>
<th>Digoxin</th>
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<tbody>
<tr>
<td></td>
<td>↓ efficacy of antidiabetics, RIF also ↑ intestinal glucose absorption ~ monitor glucose</td>
<td>↓ anticoagulant effect</td>
<td>↓ antidepressants effect</td>
<td>↓ beta blockade</td>
<td>↓ OCP effect</td>
<td>↓ steroid effect</td>
<td>↓ CsA effect, ↑ RIF</td>
<td>↓ PI effect, ↑ RIF</td>
<td>↓ effect DLV</td>
<td>Slightly ↓ effect EFV, ↓ RIF</td>
<td>↓ DIG levels</td>
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<tr>
<td></td>
<td></td>
<td>Diltiazem</td>
<td>Fluconazole</td>
<td>Itraconazole</td>
<td>Haloperidol</td>
<td>Methadone</td>
<td>Phenytoin</td>
<td>Verapamil</td>
<td>Tetracyclines</td>
<td>TMP-SMX</td>
<td>Chloramphenicol</td>
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RIF Side Effects and Monitoring

Side Effects
- Pruritus +/- rash ~ 6%
- Hepatotoxicity ~ <1%-2.7% (↑ w/INH, PZA)
- Orange discoloration of body fluids (expected)

Less common:
- Hyperbilirubinemia ~ 0.6%
- GI upset, flu-like syndrome (more common with intermittent dosing)
- Hypersensitivity ~ 0.3%
- Hemolytic anemia, acute renal failure, and TTP ~ <0.1%

Monitoring
- Baseline LFTs, bilirubin, alkaline phosphatase, and platelet count (CBC)
- No routine monitoring
- Therapeutic drug monitoring (TDM) when indicated:
  - Situations of slow response to therapy
  - Those at risk for malabsorption
  - When concern of drug-drug interactions

Isoniazid (INH)

- Discovered anti-TB properties ~ 1945
- Causes the greatest early reduction in colony forming units found in the sputum

Mechanism of Action:
- INH is a prodrug activated by mycobacterial KatG catalase-peroxidase
- INH also blocks InhA, a key enzyme involved in fatty and mycolic acid synthesis (cell wall)

Used in treatment of TB infection and active disease

Anti-TB Drugs: What Nurses Need to Know
### Drug-Drug Interactions - INH

<table>
<thead>
<tr>
<th>INH</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemics</td>
<td>Monitor glucose, may ↑ BG</td>
</tr>
<tr>
<td>APAP</td>
<td>↑ hepatotoxicity</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>↑ anticoagulant effect</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>↑ toxicity</td>
</tr>
<tr>
<td>Anti-epileptics</td>
<td>↑ toxicity of carbamazepine and phenytoin</td>
</tr>
<tr>
<td>Disulfiram (Antabuse)</td>
<td>Psychotic episodes</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>↑ toxicity antipsychotics</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>↓ efficacy of ketoconazole</td>
</tr>
<tr>
<td>Dilantin</td>
<td>↑ toxicity antiepileptic</td>
</tr>
<tr>
<td>Theophylline</td>
<td>↑ toxicity theophylline; monitor levels</td>
</tr>
<tr>
<td>Valproate</td>
<td>↑ hepatic and CNS toxicity</td>
</tr>
</tbody>
</table>

### INH Side Effects and Monitoring

#### Side Effects
- Asymptomatic ↑ ALT ~12-15%
- Rash ~ 2%
- Fever ~ 1.2%
- Overt hepatotoxicity ~ 1% - 2.7% (↑ w/RIF, PZA)
- Neuropathy ~ <0.2% (B₆ supplement 25-50mg/day)
- CNS ~ restlessness, insomnia,
- Dysarthria, seizures
- Lupus-like syndrome

#### Monitoring
- LFTs ~ baseline and monthly if symptoms of hepatotoxicity
  - Discontinue if transaminases ↑ > 3 × ULN with symptoms
  - OR
  - ↑ > 5 × ULN
Pyrazinamide (PZA)

- Generally used during intensive phase of treatment for active TB disease (first 2 months)
  - One of the required drugs for shortening duration of active treatment to 6 months
- Mechanism of Action:
  - Synthetic prodrug; converts to form pyrazinoic acid (POA)
  - Bactericidal; accumulates in bacteria, causing lethal membrane damage
  - Active against dormant / semidormant bacteria within macrophage/acidic environment of caseous granulomas

PZA Side Effects and Monitoring

**Side Effects**
- Hepatotoxicity
- GI: anorexia and nausea
- Nongouty polyarthralgia
  - ~ 40% receiving daily doses
- Asymptomatic hyperuricemia
- Rash, photosensitive dermatitis

**Monitoring**
- Baseline LFTs, serum creatinine and uric acid
- Follow-up LFTs in patients with underlying liver disease
- Follow-up renal function in renal impairment
Ethambutol (EMB)

- Discovered ~ 1961
- Bacteriostatic at typical doses (bactericidal at higher end of dose range)
  - Least potent first-line drug
  - Included in regimen primarily to prevent emergence of Rifampin (RIF) resistance, when primary INH resistance is suspected
  - Discontinue once drug susceptibility test results confirm fully drug-susceptible

Mechanism of Action:
- Inhibits cell wall synthesis

EMB Side Effects and Monitoring

Side Effects
- Retrobulbar neuritis ~ 1%-5%, dose-dependent and increased with renal impairment
- Blurred vision
- Red-green color blindness

Monitoring
- Baseline serum creatinine
- Follow-up renal function in impairment
- Baseline visual acuity test and color discrimination
- Question patients at monthly visit about visual changes
**Rifabutin (RFB)**

- Alternative for drug-drug interaction (has lesser degree of induction) or intolerance to rifampin
- Sometimes used in place of RIF
  - HIV co-infected patients on PIs, some NNRTIs (etravirine, rilpivirine), solid organ transplant recipients, patients on methadone maintenance therapy
- Mechanism of action ~ same as RIF
- Concentration dependent, bactericidal activity
- Supplied:
  - Capsules (150mg)

**Rifabutin (RFB) (2)**

- Doses must be adjusted when administered with antiretroviral therapy (ARVs)
- Renal dose adjustment NOT required, but some sources recommend renal dose adjustment
  - T ½ ~ 45 hours (much longer than RIF)
- Penetrates CNS
- Cross-resistance often seen when resistant to RIF
### RFB Side Effects and Monitoring

#### Side Effects
- Leukopenia (dose dependent); thrombocytopenia
- Rash and skin discoloration (bronzing or pseudojaundice)
- Anterior uveitis
- Hepatotoxicity $\sim <1\%$
- Arthralgias $\sim 1-2\%$

#### Monitoring
- Baseline CBC
- Baseline LFTs and follow-up as indicated
- Question patients at monthly visit about visual changes (vision screening)
- Drug-drug interactions similar to RIF, but lesser degree ($\sim 40\%$ that of RIF)
- Adherence to treatment

### Rifapentine (RPT)
- Bactericidal activity
- Concentration dependent killing
- Mechanism of action $\sim$ same as RIF
- Induces CYP enzymes $\sim 85\%$ of RIF
- Drug-drug interactions similar to RIF
- Absorption:
  - Food ↑ AUC 40-50% (but ↓ INH $C_{max}$)
Rifapentine (RPT) (2)

- Approved for LTBI when dosed once weekly with INH for 3 months
- Prolonged t½ (~ 13-14 hours) permits weekly dosing
- 25-O-desacetyl metabolite is active t½ (~ 13-24 hours)
- Highly protein bound ~ 98%

RPT Side Effects and Monitoring

**Side Effects**
- Rash and pruritus
- Hypersensitivity
- Hepatotoxicity
- Hematologic abnormalities
- Red-orange discoloration of body fluids (expected)

**Monitoring**
- LFT monitoring as appropriate
- Baseline CBC
- When indicated, monitor drug concentrations of interacting medications
### Rationale for Multiple Drugs for Treating Active Tuberculosis

- Past observation of treatment failure with individual drugs
- Mutation conferring resistance to any one first-line drug occurs at a predictable rate
- Likelihood of bacilli developing resistance to 2 or more anti-TB drugs is the product of the individual mutation rates

<table>
<thead>
<tr>
<th>EMB</th>
<th>SM</th>
<th>INH</th>
<th>RIF</th>
<th>Combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1 \times 10^7$</td>
<td>$2.3 \times 10^8$</td>
<td>$2.6 \times 10^8$</td>
<td>$3.3 \times 10^9$</td>
<td>$\sim 1 \times 10^{17}$ (HR)</td>
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<td></td>
<td>$\sim 1 \times 10^{24}$ (HRE)</td>
</tr>
</tbody>
</table>

Selection for Drug Resistance

1 = INH resistant, R = RIF resistant, P = PZA resistant

Selection for Drug Resistance (2)

1 = INH resistant, R = RIF resistant, P = PZA resistant
Four Drug Combination

- Rifampin (RIF, R) or Rifabutin
- Isoniazid (INH, H)
- Pyrazinamide (PZA, Z)
- Ethambutol (EMB, E)

(Referred to as “RIPE” or HRZE outside the U.S.)

- Designed to prevent secondary development of resistance to RIF in populations with a high rate of primary resistance to INH (≥ 4%)


TB Treatment Side Effects
Resources for Nursing Care
Nursing Guide for Managing SE’s

Designed as a reference guide so nurses can quickly:
- Identify symptoms that may indicate a drug-related side effect
- Assess for severity as well as potential contributors
- Intervene appropriately in order to:
  - minimize patient discomfort,
  - reduce side effect progression, and
  - ultimately support successful treatment completion

Structure: Presenting Symptoms

HEPATOTOXICITY

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>POSSIBLE OFFENDING DRUG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, vomiting PLUS abdominal pain, fatigue, and loss of appetite. Later stage symptoms may include: fever, rash and jaundice (yellowing of the eyes and skin)</td>
<td>Anti-TB: Inh, Rif, Pza, Eto/pto, Bdq, PAS. Rarely, Emb and Mfx ARVs: NVP, EFV, PIs (TPV/tr others) most NRTIs (d4T, ddI, AZT)</td>
</tr>
</tbody>
</table>

- Presents symptoms that a patient may express during treatment
- Indicates the potential toxicity: diagnosis associated with these presenting symptoms
- Lists possible TB and/or anti-retroviral (ARV) drugs associated with the symptom(s)/toxicity
Structure: Nursing Assessment

**NURSING ASSESSMENT**

Same observations and questions for assessing nausea and vomiting PLUS:

- Observe for signs of jaundice (yellowing of the skin and whites of the eyes)
- Use PQRST pain assessment approach when patient c/o pain (see Appendix A)

Ask the patient:
- Do you drink alcohol? If yes, how much, how often and when was your last drink?

Check:
- Latest liver function test (LFT), total bilirubin, serum albumin and electrolytes
- Viral hepatitis panel results
- Urine and stool color
- Patient’s nutritional status (weight and BMI) and nutritional intake

- What to observe for?
- What questions to ask the patient?
- What tests or evaluations should the nurse check for?

Structure: Nursing Interventions

**NURSING INTERVENTIONS**

- Urgent action to take when indicated (criteria provided)
- Information to cover in counseling the patient
- When to bring to the doctor’s attention and what questions to raise with the doctor regarding potential medical interventions

- Seek urgent medical evaluation when these symptoms are present together and/or if liver enzymes are ≥ 5 times the upper limit of normal.
- Stop all anti-TB drugs and other hepatotoxic medications
- Evaluate and treat other potential causes

Counsel the patient:
- Comfort measures to minimize pain
- Limited activity to conserve energy
- Frequent small meals to maintain optimal energy metabolism
- Avoid alcohol

Discuss with the doctor:
- Whether oral or IV rehydration needed if patient shows signs of dehydration
- Nutrition consult if available
- Whether blood tests should be obtained/ repeated (LFT, T. bilirubin, albumin, viral serology)
- Plans for re-introduction of TB medications and whether to discontinue likely offending drug(s)
Structure: Comments

- Provides additional information on potential causes of the symptom(s)
- May provide location for additional resources
- May provide information on related considerations for management

**COMMENTS**

Abdominal pain may be an early symptom of severe side effects, such as pancreatitis, hepatitis or lactic acidosis.

HIV coinfection may increase risk of hepatitis.

Other medications may also contribute (e.g., TPM/SMX, ibuprofen, acetaminophen).

Viral causes of hepatitis (hepatitis A, B, C, and Cytomegalovirus) should be evaluated.

EFV, NVP and TPV/r are not recommended in patients with HIV and hepatic insufficiency.

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TB Drug-related Resources

[https://www.heartlandntbc.org/products/](https://www.heartlandntbc.org/products/)

- **Rifamycins and Anti-Diabetic Agents - Drug Drug Interactions**
  
  A 2-sided diagram for clinicians and healthcare providers that describes drug-drug interactions of Rifamycins and Anti-Diabetic Agents.

- **Rifamycins and Cardiovascular Agents - Drug Drug Interactions**
  
  This drug guide is to provide the clinician with a quick reference tool for use with their TB patient who is on cardiovascular drugs highlighting common interactions and cautions between TB medications and the most common cardiovascular drugs. It also provides recommendations for optimal outcomes.

- **Rifamycins and Psychotropic Drugs - Drug Drug Interactions**
  
  This drug guide is to provide the clinician with a quick reference tool for use with their TB patient who is on psychotropic drugs highlighting common interactions and cautions between TB medications and the most common psychotropic drugs. It also provides recommendations for optimal outcomes.
Anti-TB Drugs: What Nurses Need to Know
Summary

- Anti-TB drugs have associated adverse effects that require monitoring and management
- A combination of drugs active against *M. tuberculosis* is required for patients with active TB disease
  - Synergistic effect when used in combination
  - Target different aspects of the TB organism
  - EMB is on board until TB organism is known to be fully drug sensitive (Pan Sensitive)
- Drug interactions are numerous for RIF and many for INH; careful medication history is important prior to TB treatment start
- TB Consultation Warmline = (877) 390-6682

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References


