

TB Drugs: Common Side Effects and Interactions

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First-line Drugs

- Isoniazid (INH)
- Rifampin (RIF)
- Ethambutol (EMB)
- Pyrazinamide (PZA)

- Moxifloxacin
- Rifapentine (RPT)
- Rifabutin (RBT)

Adverse Events of First-line TB Drugs

- Side Effects
- Toxicities



Side Effects

- Unpleasant reaction
- Not damaging to health
- Does not usually require changes in therapy:
 - gas
 - bloating
 - discoloration of body fluids
 - photosensitivity
 - irritability



"Listen, when the side effects of this medication kick in, you'll forget what was wrong in the first place!"

TB Drug Toxicities

- More severe than side effects
- May be life threatening
- May require changes in dosage or discontinuation of the drug(s)
- May require additional treatment or hospitalization



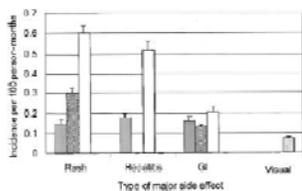
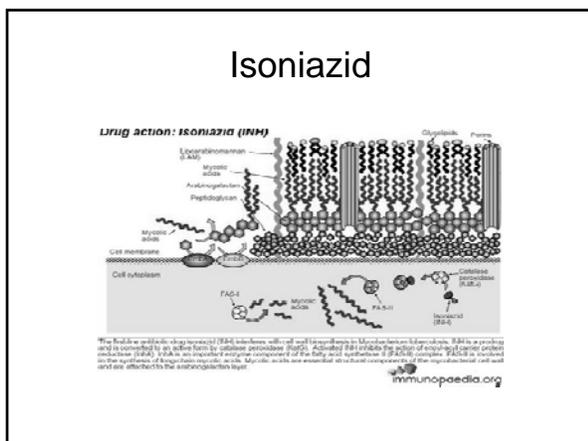


Figure 1. Incidence of serious side effects by type and drug. Shaded columns, Isoniazid; cross-hatched columns, rifampin; open columns, pyrazinamide; dotted columns, ethambutol.



- ### Isoniazid—Side Effects
- GI Intolerance:
 - Nausea, abdominal pain common
 - Vomiting less common
 - Steps to ameliorate:
 - Co-administer with food (small snack)
 - Pre-medicate with anti-nausea medications (promethazine, pepcid)
 - Reassurance

- ### Isoniazid—Side Effects
- Peripheral neuropathy:
 - dose-related
 - <0.2% of patients will have
 - symptoms include burning, tingling, numbness of fingers/toes (usually toes first)
 - usually occurs in "stocking glove" distribution
 - can be managed by starting/increasing B6 dose
-

Isoniazid—Side Effects

- Rash:
 - Mild rash or itching →pre-medicate with Benadryl
 - Erythematous rash with fever and/or mucous membrane involvement
 - stop all medications
 - rule out anaphylaxis
 - rule out Steven-Johnson Syndrome
- If rash improves, can restart medications sequentially

Isoniazid—Side Effects

- Hepatitis
 - 10-20% of persons who take isoniazid will develop asymptomatic LFT increase
 - In most cases these will resolve with continued treatment
 - Not dose-related
 - Clinically significant hepatitis occurs in 0.1-1% of patients
 - Risk increased with age, ETOH, HIV, concurrent viral hepatitis

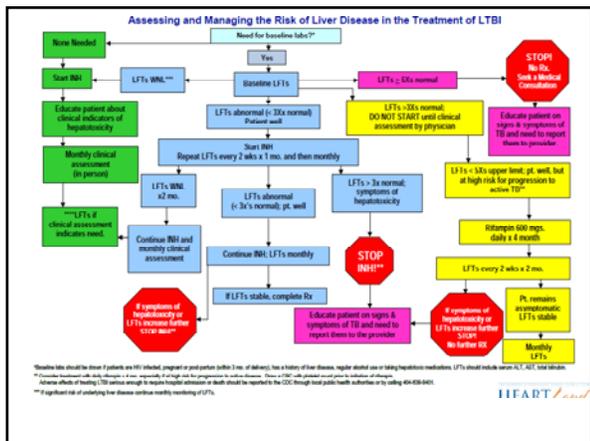
Isoniazid-associated Hepatitis

- Patients can be asymptomatic
- Fatigue, nausea, abdominal pain, vomiting common
- Jaundice



Management of INH Hepatitis

- ALT < 3x ULN, no symptoms → monitor
- ALT 3-5x ULN, no symptoms → monitor
- ALT > 3x ULN + symptoms or ALT > 5x ULN without symptoms → stop drugs



Isoniazid—Side Effects

- Tyramine poisoning—may cause flushing, palpitations when taken with foods high in tyramine (red wine, aged cheese)
- CNS toxicity—confusion, psychosis, insomnia, headache
- Fatigue
- Lupus-like syndrome: fever, joint pain, fatigue, weight loss

INH Drug Interactions

- ↑ Dilantin toxicity
- ↑ Anticoagulant effect
- ↑ Valium toxicity
- ↑ Tylenol hepatotoxicity
- Antacids decrease INH absorption

Rifampin—Side Effects



- GI side effects
- Orange urine/body fluids (sweat)
 - harmless but may stain contact lenses, clothing
 - need to let patients know beforehand



Rifampin—Side Effects



- Hepatitis:
 - occurs in about 0.6% of patients with rifampin alone
 - Not dose-related
 - More frequent in setting of other TB drugs
 - Isolated cholestasis (increased bilirubin) can also be seen
 - Managed similarly to isoniazid

Rifampin—Side Effects

- Flu-like syndrome:
 - Fever, myalgias, arthralgias, headache
 - Onset of symptoms usually 1-2 hours after dose, usually resolves within 12 hours of dose
 - More common with intermittent administration, higher dose of medications
 - Happens in 0.4-1.5% of patients

Rifampin—Side Effects

- Flu-like syndrome:
 - May also have thrombocytopenia
 - To manage, first change to daily therapy
 - If that doesn't work, may also try rifabutin

Rifampin—Side Effects

- Interstitial nephritis (rare):
 - Kidney failure due to hypersensitivity reaction to rifampin
 - May be accompanied by rash, fever, eosinophilia in blood
 - Urine for eosinophilia may be helpful
 - Stop drug and do not rechallenge



Rifampin



- Increases the metabolism of medications, particularly those metabolized by cytochrome P450 3A:
- birth control
- coumadin
- methadone
- glipizide, glimepiride, glyburide
- levothyroxine
- protease inhibitors

Rifampin and Anti-Diabetic Agents: Drug-Drug Interactions

Drug	Interaction	Severity	Management
Birth control pills	Decreased efficacy due to increased metabolism	Major	Use alternative method of birth control
Coumadin	Decreased efficacy due to increased metabolism	Major	Monitor INR closely; adjust dose as needed
Methadone	Decreased efficacy due to increased metabolism	Major	Monitor for withdrawal symptoms; adjust dose as needed
Glipizide, glimepiride, glyburide	Decreased efficacy due to increased metabolism	Major	Monitor blood glucose levels; adjust dose as needed
Levothyroxine	Decreased efficacy due to increased metabolism	Major	Monitor thyroid function tests; adjust dose as needed
Protease inhibitors	Decreased efficacy due to increased metabolism	Major	Monitor for resistance; adjust dose as needed

Pyrazinamide—Side Effects



- GI symptoms
- Arthralgias (joint pain)
- Rash
- Hyperuricemia (elevated uric acid)
 - usually asymptomatic
 - may precipitate gout, kidney stones
 - TB medications do not usually require discontinuation

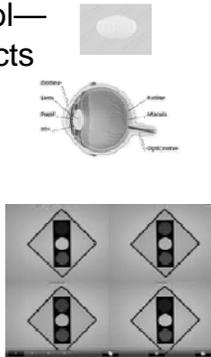


Pyrazinamide—Side Effects

- Hepatitis
 - dose-related
 - risk factors for hepatitis include: prior liver disease, advanced age (>60), concomitant use of isoniazid and rifampin
- Need to adjust dose in renal insufficiency
- Not usually used in pregnancy in the US
- Major drug interactions: rifampin

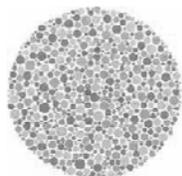
Ethambutol—Side Effects

- Optic neuritis:
 - blurred vision
 - "spots" in patient's field of vision
 - red/green color blindness
- Dose-related
- Uncommon with intermittent tx
- Drug should be discontinued
- Usually reversible if stopped right away
- Risk increased when used in renal failure



Prevention of Optic Neuritis

- Monitor vision
- Improve diabetic control
- Multivitamin (B complex, Folate)



Rifapentine (1)

- Longer half-life than rifampin
- Lower minimum inhibitory concentration (MIC)
- Induces cytochrome P450 metabolizing enzyme



Rifapentine (2)

- Longer half life than rifampin
- Orange discoloration of secretions, urine, tears
- Can stain contact lenses
- Rare adverse effects:
 - elevated liver function tests
 - thrombocytopenia
 - headache and dizziness

<http://www.fda.gov/medwatch>.

Rifabutin



- May be used in HIV + patients due to less drug interactions with HAART
- May also be less hepatotoxic than rifampin
- Other side effects:
 - Anterior uveitis: Painful, red eye
 - dose dependent

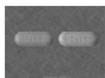


Moxifloxacin (Avelox)

- Potent bactericidal activity against *M. tuberculosis*
- Additive sterilizing effect when used in combination with isoniazid, rifampin and pyrazinamide



Moxifloxacin (1)



- Nausea/GI side effects
- CNS: headache, insomnia, confusion
- Tendonitis:
 - stop exercise, consider NSAIDS
- Tendon rupture
 - stop drug
- Not used in children due to concern for joint pain, damage to cartilage

Moxifloxacin (2)



- Drug interactions:
 - Any divalent or trivalent cations (antacids, multivitamins, zinc, calcium, iron)
 - moxifloxacin should be taken 2-4 hours before or 8 hours after
 - sevelamer (renagel)
 - anti-arrhythmics: amiodarone, procainamide



Sorting it all out

- For common significant side effects, multiple drugs may be responsible
 - Rash→INH, RIF, PZA, EMB
 - Hepatitis→INH, RIF, PZA
 - GI→INH, RIF, PZA
- Remember: It may not be the TB drugs!
 - ETOH, other drugs, other conditions

Managing Drug-Induced Hepatitis

- Assess severity:
 - elevated bilirubin/jaundice, abnormal bruising/bleeding, new edema are all markers of severe hepatitis
- Look for other causes
 - Check for Hep A/B/C
 - Assess alcohol intake
 - Assess use of other hepatotoxic drugs

Managing Drug-Induced Hepatitis

- Determine if TB treatment can be held entirely
- If not (severe, infectious), change to liver-sparing regimen:
 - ethambutol, avelox, streptomycin

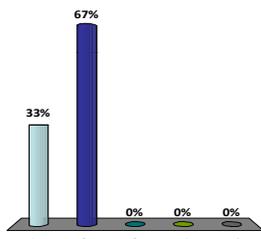
Managing Drug-Induced Hepatitis

- Wait until the liver cools down (usually <100)
- Reintroduce medications one at a time:
 - ETH
 - RIF
 - INH
 - PZA
- New drug every week

Case 1

A 24-yr nurse presents to clinic with a positive TST, negative CXR, and negative symptom screen. She has heard about the “new” LTBI regimen of INH/RPT. You advise her on which of the following:

1. Symptoms of hepatitis
2. Discoloration (orange) of body fluids
3. Avoidance of ETOH
4. Need for barrier birth control methods
5. All of the above



The 12-Dose Regimen for Latent Tuberculosis (TB) Infection

Taking Your Pills
If your stomach is upset after taking your medicine, try eating right before your next dose.

Alcohol
Daily alcohol use is associated with an increased risk of liver damage when taking isoniazid. You should discuss your alcohol use with your doctor before starting isoniazid and rifampin.

Women
• This medication may interfere with hormone-based birth control (including birth control pills, rings, and shots). During treatment, barrier forms of birth control (condoms or diaphragms) should be used to avoid pregnancy.
• If you become pregnant or think you might be pregnant, tell the doctor or nurse right away.

Normal Side Effects
Rifampin may cause your urine (pee), saliva, tears, or sweat to appear an orange red color. This is normal.

NOTE: If your saliva and tears have an orange red color, contact lenses or dentures worn during treatment may become permanently stained.

To avoid staining during treatment:

- Stop wearing your contact lenses, and wear glasses.
- If you use dentures, take your dentures out whenever possible.

Possible Problems

Most people can take their TB medicines without any problems. But any medicine you take may cause problems.

The most common side effects and symptoms that your body may not tolerate this treatment.

If you have any of these problems, your doctor or nurse will need to make decisions about the medicine and other treatment options.

Please talk to your doctor or nurse if you have any questions or concerns about treatment for latent TB infection.

<http://www.cdc.gov/tb/publications/pamphlets/12DoseLTBITreatmentbrochure8.5x11.pdf>

Case 2

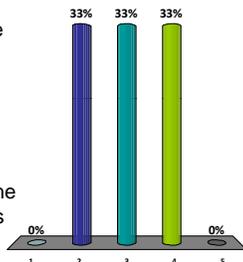
- A 76 yo Vietnamese gentleman is started on INH/RIF/PZA/ETH for pulmonary TB. He presents to clinic 5 days later for follow-up. His exam is as follows:



Case 2 continued

You:

1. Prescribe benadryl, continue all medications
2. Stop pyrazinamide as this is the most likely cause of the rash.
3. Stop all medications
4. Stop all medications, examine mucous membranes, assess for fever



Stevens-Johnson Syndrome



Case 3

41 yo lady with pulmonary TB started on 4 drugs. Soon after twice-weekly therapy is started she begins to have fatigue, low-grade fever and myalgias. You:

- 1. Check LFTs
- 2. Change back to daily therapy
- 3. Stop rifampin
- 4. A and B
- 5. All of the above

