

Objectives

TB Drugs: Side Effects, Adverse Events and Their Management

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- Describe the difference between side effects and adverse events associated with medications
- Identify the main side effects associated with common TB medications and review their basic management
- Describe management of hepatotoxicity associated with TB medications

First-line Tuberculosis Medications

- Isoniazid (INH)
- Rifampin (RIF)
- Ethambutol (EMB)
- Pyrazinamide (PZA)
- Moxifloxacin
- Rifapentine (RPT)
- Rifabutin (RBT)

Adverse Events of First-line TB Drugs: Side Effects

- Unpleasant reaction
- Not damaging to health
- Commonly includes:
 - gas/bloating
 - discoloration of body fluids
 - photosensitivity
 - irritability
- DOES NOT usually require change in therapy



Adverse Events of First-line TB Drugs: Toxicities

- More severe than side effects
- May be life threatening
- May require change in dosage of drug
- May require discontinuation of drug
- May require additional treatment or hospitalization



Adverse Drug Events

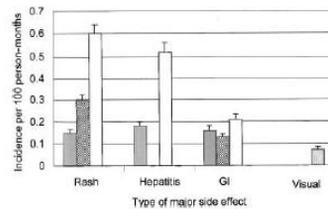


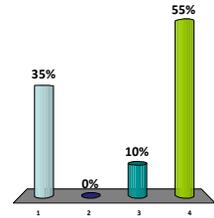
Figure 1. Incidence of serious side effects by type and drug. Shaded columns, Isoniazid; cross-hatched columns, rifampin; open columns, pyrazinamide; dotted columns, ethambutol.

Mrs. P

- 63 yo lady presents for evaluation of an 18 mm TST. She recently immigrated from the Philippines to live with her daughter, who accompanies her to today's appointment.
- They have read the information packet that was provided to them about LTBI treatment and they express interest in taking isoniazid (INH) for 9 months.
- But, first, they have a lot of questions....

Mrs. P has heard that INH can cause "upset stomach." Is there anything she can do to help prevent this?

1. Take INH with food
2. Pre-medicate with anti-nausea meds
3. Reassurance-symptoms usually resolve after the first few days of treatment
4. All of the above

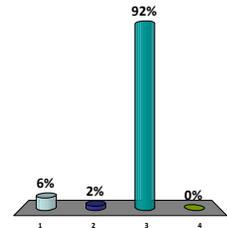


Isoniazid—GI Intolerance

- Nausea, abdominal pain common
- Vomiting less common
- Steps to ameliorate:
 - Co-administer with food such as a small snack
 - Pre-medicate with anti-nausea medications (promethazine, ranitidine, ondansetron, omeprazole)
 - Reassurance

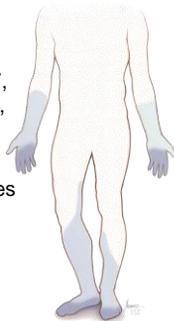
You ask Mrs. P about her other medical conditions and learn that she is a diabetic. What other side effect of INH is she particularly at risk for?

1. Tyramine poisoning
2. Insomnia
3. Peripheral neuropathy
4. Lupus-like syndrome



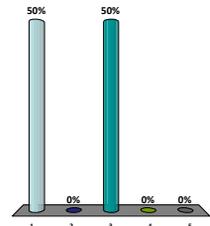
Peripheral Neuropathy

- Dose-related
- Will affect 2% of patients
- More common: malnourished, HIV, diabetics, renal failure, alcoholism, pregnant, breastfeeding
- Symptoms include: burning, tingling, numbness of fingers & toes (usually toes first)
- Occurs in "stocking glove" distribution
- Prevent by prescribing Vitamin B6



On review of Mrs. P's home medications, you notice she is on atorvastatin (Lipitor). You:

1. Discuss with her that INH can cause hepatitis.
2. Advise her of the signs and symptoms of hepatitis.
3. Discuss with her that the risk of INH hepatotoxicity is increased when other hepatotoxic medications are taken.
4. Draw baseline LFTS prior to starting INH
5. All of the above



Isoniazid--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

Isoniazid-associated Hepatitis

- Common symptoms:
 - fatigue
 - nausea
 - abdominal pain
 - vomiting
- Jaundice



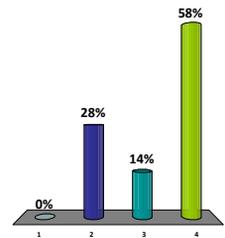
Increased Risk of INH Hepatotoxicity

- HIV-positive
- Underlying liver disease (Hep B, Hep C)
- Average alcohol use of ≥ 3 drinks per day or binge drinking (≥ 5 drinks in one day, intermittently)
- Pregnant women
- Women up to three months post-partum
- Those currently taking other potentially hepatotoxic drugs such as:
 - "Statins": atorvastatin, pravastatin, simvastatin, rosuvastatin
 - Anticonvulsant drugs: carbamazepine, phenytoin, valproic acid
 - Methotrexate
 - Pioglitazone, rosiglitazone

BASELINE HEPATIC FUNCTION PANEL SHOULD BE OBTAINED ON THESE PATIENTS PRIOR TO STARTING INH

Mrs. P's baseline LFTs are normal and she is ready to start INH. When will you check LFTs again?

1. Never-she is low risk for developing INH-associated hepatitis
2. Only if she develops signs or symptoms of hepatitis
3. Once a month for the next 3 months
4. Monthly while she is taking INH



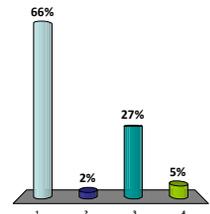
Check Hepatic Function Panel Monthly in the Following:

- Those with abnormal baseline LFTS
- Pregnant women
- Women up to three months postpartum
- HIV-positive
- Those taking potentially hepatotoxic drugs
- Those with symptoms of adverse reactions
- Chronic active hepatitis B or hepatitis C
- Chronic or binge use of alcohol

Baseline and monthly LFTS should also be obtained in these patients if they are offered rifampin or INH/RPT for LTBI therapy

Mrs. P presents a month later to pick up INH. Her symptom screen and clinical assessment is negative. Her LFTS are: AST 30 (5-20) ALT 78 (5-40). You:

1. Re-educate on s/s of hepatitis & continue INH at current dose, check LFTs again in a month
2. Cut the dose of INH in half to prevent further LFT elevation
3. Stop INH, re-check LFTs in a week, if normal, restart INH
4. Stop INH, start Rifampin



Management of INH Hepatitis

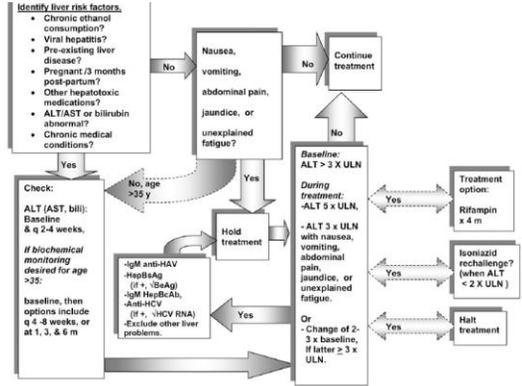
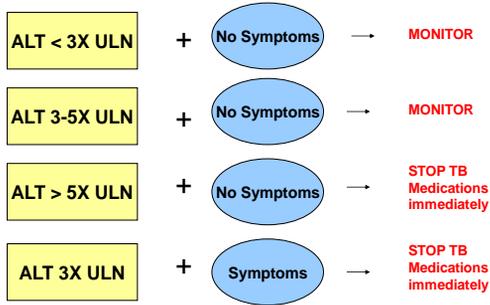


Figure 2. Monitoring for hepatotoxicity during TB treatment. Dotted lines signify management according to physician's discretion. ALT = alanine aminotransferase; AST = aspartate aminotransferase; HAV = hepatitis B virus; HCV = hepatitis C virus; HepB sAg = hepatitis B surface antigen; ULN = upper limit of normal.

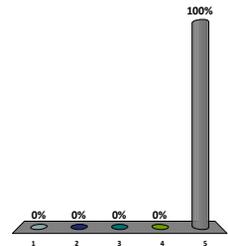
Rifampin—Hepatitis



- 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

Ms T, a 24 yo nurse with a positive TST, negative CXR and negative symptom screen. She is interested in taking 3HP. You advise her on which of the following....

- Symptoms of hepatitis
- Discoloration of body fluids (orange)
- Avoidance of ETOH
- Need for barrier birth control method
- All of the above



Rifapentine

- Longer half-life than rifampin
- Induces cytochrome P450 metabolizing enzyme
- Orange discoloration of secretions, urine, tears

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 rifapentine.

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
Rifapentine may cause your urine (pee), saliva, tears, or sweat to appear an orange-red color. This is normal.
NOTE: If your urine and tears turn an orange-red color, contact your doctor or dentist when during treatment may become permanently stained.

To avoid staining during treatment:
• Sleep 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 next page lists signs 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.

<http://www.cdc.gov/tb/publications/pamphlets/12DoseLTBTreatmentbrochure8.5x11.pdf>

Call your doctor or nurse right away if you have ANY of these signs or symptoms:

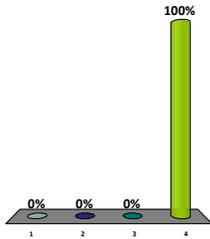
- Dizzy or lightheaded when sitting, standing, or lying down
- Less appetite, or no appetite for food
- Stomach upset, nausea, or vomiting
- Stomach pain or stomach cramps
- Pain in your lower chest or heartburn
- Flu-like symptoms with or without fever
- Severe tiredness or weakness
- Fevers or chills
- Severe diarrhea or light colored stools (poop)
- Brown, tea-colored, or cola-colored urine
- Skin or whites of your eyes appear yellow
- Skin rash or itching
- Bruises, or red and purple spots on your skin that you cannot explain
- Nosebleeds, or bleeding from your gums or around your teeth
- Shortness of breath
- Pain or tingling in your hands, arms, or legs

NOTE: People react differently to medicines. If you think you are having any reaction to your treatment, call the doctor right away.

<http://www.cdc.gov/tb/publications/pamphlets/12DoseLTBTreatmentbrochure8.5x11.pdf>

Mr. A, a 53 yo US-born man referred for treatment of active pulmonary TB. The plan: start standard 4-drug TB therapy (RIPE), At the first visit you..

1. Educate him about s/s of hepatotoxicity
2. Obtain baseline CBC, LFTs, creatinine, uric acid and test for HIV
3. Do baseline testing for visual acuity and red/green color discrimination
4. All of the above



Pyrazinamide—Hepatitis

- Dose-related
- Risk factors 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



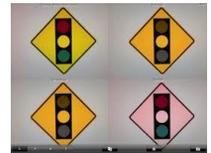
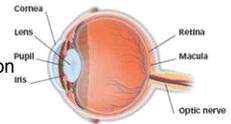
Pyrazinamide—Elevated Uric Acid

- Hyperuricemia (elevated uric acid)
- Usually asymptomatic
- May precipitate gout, kidney stones
- TB medications do not usually require discontinuation
- Other side effects: GI intolerance, rash, muscle aches



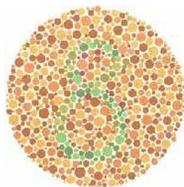
Ethambutol—Optic Neuritis

- Symptoms include:
 - 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



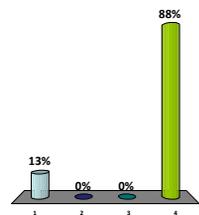
Prevention of Optic Neuritis

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



About one week after starting medications, Mr. A complains that he has developed an 'itchy' rash. You..

1. Recommend benadryl over the phone, continue medications
2. Over the phone, tell him to stop PZA since this is the likely cause of the rash
3. Over the phone tell him to stop all medication
4. Stop all medications, arrange for a visual assessment for mucous membrane involvement and fever



Adverse Events—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

Mr. A comes in clinic so you can assess his rash:

- Fortunately, he does not have any mucous membrane involvement (no lesions in his mouth)
- Afebrile
- No symptoms of shortness of breath, swelling
- TB medications held until rash has improved

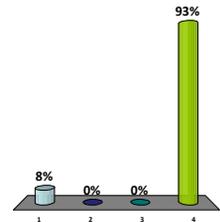


After rash resolved:

- Meds re-introduced sequentially at increasing doses: INH, Rifampin, Ethambutol, PZA
- Rash recurred after PZA restarted
- PZA held
- Mr. A continued on Rifampin, INH, Ethambutol with plans to complete 9 months of therapy

Mr. A completes the initial phase of therapy, he has pan-sensitive TB. His regimen is changed to BIW INH/RIF. He now complains of "flu-like" symptoms including fever, headache. You...

1. Arrange for a clinical evaluation
2. Check LFTs, CBC
3. Consider changing back to daily regimen
4. **All of the above**



Rifampin—Flu-like Syndrome:

- Fevers, myalgias, arthralgias, headache, thrombocytopenia
- Onset of symptoms usually 1-2 hours after dose, usually resolves within 12 hours of dose
- More common with intermittent administration
- Happens in 0.4-1.5% of patients
- To manage, first change to daily therapy
- If that doesn't work, may also try rifabutin



Mr. N

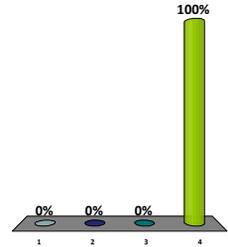
- Mr. N is a 76 yo Vietnamese gentleman, recently diagnosed with pulmonary TB
- He has extensive cavitory disease and remains smear positive
- He spent the past 3 weeks in the local hospital and was started on 4-drug therapy with RIPE during this time period
- He was discharged on a Friday afternoon and the health department was not notified.

Mr. N

- Fortunately, you are able to track Mr. N down.
- He is complaining of nausea, and vomited that morning.
- No LFTs have been done since starting RIPE so you perform this test..

Mr. N's lab results are:
AST: 340, ALT: 600. You....

1. Hold all medication
2. Check Hep B/C serologies
3. Check other home medications for potential hepatotoxic drugs
4. All of the above

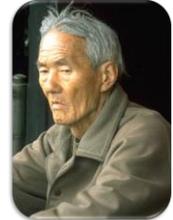


Management of Drug-Induced Hepatitis

ALT < 3X ULN	+	No Symptoms	→	MONITOR
ALT 3-5X ULN	+	No Symptoms	→	MONITOR
ALT > 5X ULN	+	No Symptoms	→	STOP TB Medications immediately
ALT 3X ULN	+	Symptoms	→	STOP TB Medications immediately

Managing Drug-Induced Hepatitis

- Assess severity:
 - elevated bilirubin/jaundice
 - abnormal bruising/bleeding
 - new edema
- 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, moxifloxacin, streptomycin

Mr. N

- Mr. N's TB medications are held and due to ongoing symptoms and severity of disease, he is admitted to local hospital
- Started on ethambutol/moxifloxacin/streptomycin (liver-sparing regimen)
- Hep A/B/C negative
- Had been on simvastatin and pioglitazone; these are discontinued

Moxifloxacin



- Nausea/GI side effects
- CNS: headache, insomnia, confusion
- Tendonitis:
 - stop exercise, consider NSAIDS
- Tendon rupture
 - stop drug
- Can cause QT prolongation when used with certain antiarrhythmics: amiodarone

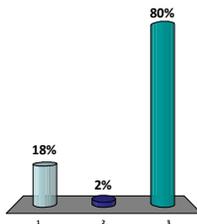


Mr. N

- Symptoms improve and after 5 days he is discharged home
- Continues on streptomycin/ethambutol/moxifloxacin
- LFTs monitored weekly
- After three weeks off original medications, AST/ALT are <100

Mr. N is doing generally well on current medication regimen but does not 'enjoy' IM streptomycin. You..

1. Continue current regimen, there are no other options due to prior hepatitis
2. Add RIF/INH/PZA back all at once and check LFTs in one week (past hepatotoxicity was likely due to other hepatotoxic drugs that have been stopped)
3. Add RIF back, check LFTs in one week, if okay, add INH, check LFT's a week later. If okay, add PZA check LFT's in a week.



Managing Drug-Induced Hepatitis

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

Suggested Flow Chart for Reintroducing TB Medications (daily administration)

Week #1:	
Dose #1	EMB, RIF 600 mg
Dose #2	EMB, RIF 600 mg
Dose #3	EMB, RIF 600 mg
Dose #4	EMB, RIF 600 mg
Dose #5	EMB, RIF 600 mg
Draw hepatic function panel	
Week #2:	
Dose #6	EMB, RIF 600 mg, INH 300 mg
Dose #7	EMB, RIF 600 mg, INH 300 mg
Dose #8	EMB, RIF 600 mg, INH 300 mg
Dose #9	EMB, RIF 600 mg, INH 300 mg
Dose #10	EMB, RIF 600 mg, INH 300 mg
Draw hepatic function panel	
Week #3:	
Dose #11	EMB, RIF 600 mg, INH 300 mg, PZA 500 mg
Dose #12	EMB, RIF 600 mg, INH 300 m, PZA 1000mg
Dose #13	EMB, RIF 600 mg, INH 300mg, PZA 1500 mg
Dose #14	EMB, RIF 600 mg, INH 300mg, PZA full dose
Dose #15	EMB, RIF 600 mg, INH 300mg, PZA full dose
Draw hepatic function panel	

http://epi.publichealth.nc.gov/cd/hhds/manuals/tb/Chapter_IV.pdf

Mr. N

- Mr. N tolerates addition of rifampin and INH to regimen
- Now streptomycin and moxifloxacin discontinued
- It is decided not to re-introduce PZA
- Continues on INH/RIF/EMB successfully to complete 9 months of therapy

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