

# Recognizing and Managing Side Effects of TB Treatment

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## Objectives

Be able to:

1. List the common side effects associated with first-line TB medications
2. Describe monitoring for and diagnosis of adverse drug reactions during TB therapy
3. Discuss approaches for managing adverse drug effects of TB drugs to minimize toxicity and ensure treatment completion

## 73 year old (1)

- Patient with rheumatoid arthritis who develops pulmonary TB while on a TNF-alpha inhibitor
- Chronic difficulty with nausea and dysphagia
- Baseline liver function tests are normal

## 73 year old (2)

- Starts on isoniazid, rifampin, pyrazinamide and ethambutol
- Cultures grow pan-susceptible TB
- Chronic nausea is worsened on 4 drug therapy with occasional vomiting
- After 2 weeks, repeat ALT is 57 (upper limit of normal = 40)

## Definitions

### Gastrointestinal (GI) Symptoms

- Nausea
- Vomiting
- Loss of appetite
- Abdominal pain

### Hepatotoxicity

- Drug induced liver injury manifest as changes in the liver function tests
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or bilirubin

## Common Risk Factors for Hepatotoxicity

- Older age
  - > 35 yrs has traditionally been used as a cutoff for determining increased risk
- Alcohol consumption
- Chronic viral hepatitis
- Pregnancy or within 3 months post-partum
- Concomitant hepatotoxic medications
- Prior abnormal ALT or bilirubin

## Diagnosing Hepatotoxicity

- Alanine aminotransferase (ALT) is the preferred test for diagnosing hepatotoxicity
- Baseline testing is recommended for:
  - All patients starting treatment for TB disease
  - Patients with risk factors for hepatotoxicity who are starting treatment for latent TB infection
- Any new or worsening GI symptom should prompt an ALT +/- holding treatment

## GI Symptoms without Hepatotoxicity

- Common complaints during TB treatment
- Relative frequency for different drugs:  
pyrazinamide > isoniazid > rifampin & fluoroquinolones > ethambutol & aminoglycosides
- Symptom monitoring should occur continuously (every directly observed dose and at monthly visits)

## Management of GI Symptoms <sup>(1)</sup>

Initial options after excluding hepatotoxicity:

- Change the timing of the dose
- Give the meds with food
- Daily dosing with fewer pills rather than intermittent therapy
- Antacids 2hr before or after
- Anxiolytic if the nausea occurs prior to swallowing the pills
- Antiemetics

## Antiemetic Options

- Ondansetron (Zofran<sup>®</sup>)  
4 to 8 mg PO twice daily prn
- Promethazine (Phenergan<sup>®</sup>)  
12.5 to 2mg every 6 hours prn
- Prochlorperazine (Compazine<sup>®</sup>)  
5 to 10 mg every 6 hours prn
- Hydroxyzine (Vistaril<sup>®</sup> or Atarax<sup>®</sup>)  
25 to 50 mg every 6 hours prn

## Management of GI Symptoms (2)

### Other considerations:

- Stop ethambutol if the organism is pansusceptible
- Discontinue pyrazinamide
- Hold meds except ethambutol and add a fluoroquinolone

## 40 year old (1)

- Alcoholic diagnosed with smear (+) pulmonary TB

### Baseline labs:

AST **78**, ALT **88** (nl for both 0-40), Alk Phos 127, TBili 0.9, platelets **105** (nl 140-415)

- Starts on isoniazid, rifampin, pyrazinamide and ethambutol

## Diagnosing and Managing Hepatotoxicity

- Routine laboratory monitoring is not recommended
- Repeat an ALT in 2 to 4 weeks if:
  1. Baseline abnormal liver function testsOr
  2. Risk factors for hepatotoxicity
- All patients with GI symptoms should be checked

## Diagnosing and Managing Hepatotoxicity

- Hold medications as needed for symptoms
- STOP Medications if :
  1. ALT  $\geq$  3 times normal with symptomsor
  2. ALT  $\geq$  5 times normal without symptoms
- Consider changing to liver “friendly” medications – fluoroquinolones, ethambutol and aminoglycosides

## 43 year old

- Non-alcoholic cirrhosis
- TB diagnosed during a transplant work-up
- Starts on rifampin and ethambutol

What else would you add?

- A. Isoniazid
- B. Levofloxacin
- C. Pyrazinamide
- D. Moxifloxacin

## Fluoroquinolones

Potential side effects:

- GI symptoms
- CNS – headache, dizziness, insomnia
- Tendinopathy or tendon rupture
- QT prolongation

Levofloxacin – cleared by the kidneys

Moxifloxacin – cleared by the liver



## 85 year old <sup>(1)</sup>

- Born in Laos, diagnosed with smear (+) pulmonary TB
- Starts on isoniazid, rifampin, pyrazinamide and ethambutol
- Baseline labs delayed by 1 week
  - AST 357 ALT 150 Alk Phos 48 Tbili 0.8
- Isoniazid and pyrazinamide discontinued

## Transaminitis

- \* Don't be too quick to give up on first-line drugs

### Remember

- Disseminated TB can cause abnormal liver function tests
- 20% of patients on treatment will have a transient, asymptomatic increase in AST
- Always consider alternative or confounding factors such as alcohol or viral hepatitis
  - Complete history important

## 85 year old (3)

- Tolerated restarting isoniazid
- After 2 months - complains of a pruritic, erythematous maculopapular rash
- No other symptoms (fever, nausea, vomiting, anorexia, etc.)
- Rash has been stable for > 1 month by the time he reports it

What would you do?

## Rash (1)

- All TB drugs can cause rash
- Management depends on the type and severity
- Consider other causes
  - Other medications including over the counter and herbals
  - New chemicals, soaps or detergents at home or work
  - Insect bites, bed bugs

## Rash (2)

### 1. Minor rash / itching

- Often maculopapular
- Acute flushing after a dose can be associated with pyrazinamide
- Manage symptomatically with antihistamines or topical steroids
- Continue meds
- Consider other causes

## Rash (3)

### 2. Petechial rash

- Suggests thrombocytopenia, possibly rifampin induced
- Check platelets and hold meds if abnormal

### 3. Generalized erythematous rash

- Suggestive of a hypersensitivity reaction (particularly when assoc w/ fever or mucus membrane involvement)
- Stop all drugs until symptoms resolve, then restart meds one at a time

## Hypersensitivity (1)

- Best described with Rifampin
- Wide range of manifestations described:
  - Rash
  - Flu-like symptoms
  - Thrombocytopenia and / or hemolytic anemia
  - Acute renal failure
  - Hypotension and shock
- More common with intermittent dosing

## Hypersensitivity (2)

- No definitive diagnostic test
- Minor reactions such as rash or flu-like symptoms can be managed by giving daily rifampin or a change to rifabutin
- For more severe symptoms, rifampin should be discontinued and avoid all rifamycins

## 69 year old <sup>(1)</sup>

- Newly diagnosed with pleural TB
- Starts standard 4 drug therapy
- 1 week into therapy he complains of acute worsening of his chronic knee pain
- Hydrocodone/ acetaminophen (Vicodin) is not working

## Acute Gout

- Pyrazinamide causes increased uric acid levels but new onset gout is rare
- A past history of gout is usually a contraindication to pyrazinamide
- Colchicine should be avoided
  - Levels are unpredictable (increased by isoniazid and decreased by rifamycins)
- Steroids and NSAIDs are safe to give during TB treatment

## Rifamycin Drug Interactions

- Rifamycins cause an increase of hepatic enzymes involved in drug metabolism
- Rifampin is a more potent inducer than rifabutin (rifapentine is likely in between)
- Many medications will be ineffective:
  - Oral contraceptives
  - HIV protease inhibitors
  - Warfarin
  - Narcotics (e.g. methadone)

## 45 year old <sup>(1)</sup>

- Type II Diabetes x 15 years
- Smear (+) pulmonary TB
- Started on standard 4 drug therapy
  
- At 1 month, patient complains of decreased vision in her left eye

Is this related to the TB treatment?

## Ocular Toxicity (1)

- Optic neuritis is a rare side effect of ethambutol >> isoniazid
- Presentation:
  - Usually bilateral
  - Blurred vision
  - Decreased color vision
  - Asymptomatic
- Fundoscopic exam is typically normal

## Ocular Toxicity (2)

### Monitoring:

- Instruct patients on the importance of reporting visual changes immediately
- Baseline visual acuity and color vision using a Snellen Chart and Ishihara test
- Repeat assessment at monthly visits

## Ocular Toxicity (2)

### Management:

- Stop ethambutol immediately
- If severe vision changes occur, stop both ethambutol and isoniazid
- Refer to an ophthalmologist
- If an alternative etiology is found, restart ethambutol as needed

## 45 year old (1)

- Type II Diabetes x 15 years
- Ocular disease due to diabetes
- Smear (+) pulmonary TB
  
- At 2 months, patient complains of tingling in the hands and feet



## Peripheral neurotoxicity

- Dose related toxicity associated with isoniazid
- Risk is increased in patients with other conditions causing neuropathy
- Isoniazid can cause a functional pyridoxine (vitamin B<sub>6</sub>) deficiency
- Rarely requires isoniazid discontinuation
- Treat with pyridoxine supplementation

## Summary <sup>(1)</sup>

### Isoniazid

- GI symptoms
- Transient elevation of hepatic enzymes
- Drug-induced hepatitis
- Peripheral neurotoxicity
- Decreased seizure threshold
- Rash

## Summary (2)

### Rifampin

- GI symptoms
- Drug-induced hepatitis
- Rash
- Hypersensitivity
- Flu-like syndrome
- Hepatic enzyme induction

## Summary (3)

### Pyrazinamide

- GI symptoms
- Drug-induced hepatitis
- Rash – acute flushing with pruritus
- Elevated uric acid +/- gouty arthritis
- Nongouty polyarthralgia

## Summary (4)

### Ethambutol

- Optic neuritis – typically retrobulbar
- Peripheral neuropathy
- Rash

## Summary (5)

- Patient education
- Face-to-face assessments and monitoring
- Address and relieve symptoms
- Avoid unnecessary breaks in therapy
- Emphasize importance of treatment completion

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