



Medical Update Webinar

Treatment of TB: Managing Adverse Drug Effects

August 30, 2011

**Sponsored by the New Jersey Medical School Global
Tuberculosis Institute**



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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)

What would you do now?

- A. Continue current treatment and repeat the ALT in 1 week
- B. Stop all drugs
- C. Stop isoniazid and pyrazinamide
- D. Continue treatment but add an anti-emetic

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 ⁽¹⁾

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®)
4 to 8 mg PO twice daily prn
- Promethazine (Phenergan®)
12.5 to 2mg every 6 hours prn
- Prochlorperazine (Compazine®)
5 to 10 mg every 6 hours prn
- Hydroxyzine (Vistaril® or Atarax®)
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

40 year old ⁽²⁾

2 weeks later

AST **546**, ALT **328**, Alk Phos **223**, TBili 0.6

What would you do?

- A. Stop isoniazid and pyrazinamide
- B. Hold all medications
- C. Switch to levofloxacin and ethambutol
- D. Continue meds and refer for alcohol treatment

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

Questions & Discussion

85 year old ⁽¹⁾

- 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

85 year old (2)

What would you do?

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

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 ⁽¹⁾

- 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

69 year old ⁽¹⁾

What medication is the cause of the knee pain?

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 ⁽¹⁾

- 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 B₆) deficiency
- Rarely requires isoniazid discontinuation
- Treat with pyridoxine supplementation

Summary (1)

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

References

1. MMWR 2003; 52 No. RR-11
ATS/CDC/IDSA TB Treatment Guidelines
2. AJRCCM 2006; 174: 935
ATS Statement on Hepatotoxicity
3. Curry International TB Center
(<http://www.currytbcenter.ucsf.edu>)
Tuberculosis Drug Information Guide
4. Hong Kong Med J 2006; 12(1): 56
Review of ethambutol ocular toxicity

Questions & Discussion

Case Discussions: Managing Toxicities of Anti-TB Medications

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Case 1

Increasing LFTs while on therapy
for Central Nervous System
tuberculosis

History of Present Illness

- 62 y.o. African-American woman with Sjogren's syndrome and autoimmune hepatitis on chronic immunosuppressive medications
- 12/5/10: Admitted to local hospital with 6 month history of intermittent fevers, SOB and new onset of increasing lethargy, headaches, and neck pain

Past Medical History

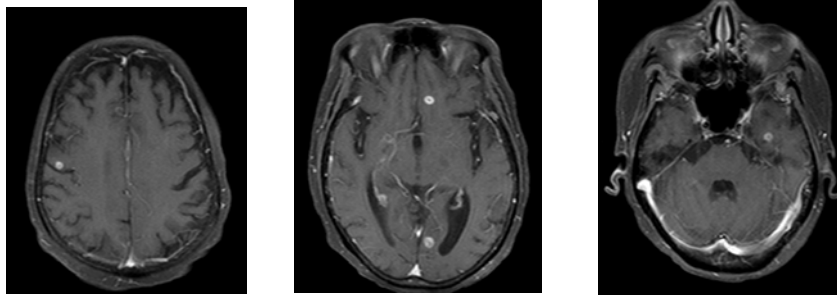
- Additional past medical history
 - Diabetes Mellitus
 - Breast cancer, S/P chemotherapy and radiation 2009
 - Hypertension
 - (Positive TST, not treated)
- Medications
 - Mycophenolate and prednisone 15 mg daily for autoimmune hepatitis
 - Irbesartan-hydrochlorothiazide
 - Ursodiol
 - Tramadol
 - Insulin

Admission Exam and Labs

- On admission, febrile, lethargic, oriented x 2, stiff neck
- CAT scan of head: Normal
- LP:
 - 151 WBC (90% PMNs)
 - Protein: 77
 - Glucose: 83
 - All micro stains including AFB negative, bacterial cultures negative

Hospital Course

- Remained febrile over next 2 weeks
- Repeat serial LPs with increasing WBC lymphocyte counts and decreasing glucose
- Serial head MRI's with enlarging nodular lesions



Brain Biopsy

- Well circumscribed lesions with necrotic material
- AFB stain positive, pathology showing neutrophils, macrophages, granuloma and AFB
- Cultures ultimately grew *M.tb* from both initial spinal fluid and brain biopsy specimen
- **Diagnosis: Central nervous system (CNS) tuberculosis**

Treatment Course

- 12/31/11: Initiated on RIPE post procedure
 - INH 300, RIF 600, PZA 1500, EMB 1200 plus B6
- Mycophenolate discontinued
- Prednisone increased to 80 mg daily
- 1/7/11: Discharged to rehab facility
- Also started on seizure medication, levetiracetam

Treatment Course

- 1/11/11: Readmitted to hospital for elevated liver enzymes
- Family reported persistent poor appetite but denied any new symptoms including vomiting, abdominal pain
- Neurologic symptoms and fevers slowly improving on TB medications

Trend of Liver Enzymes TB Meds Started 12/31

	12/5	12/25	1/1	1/4	1/7	1/11
AST	22	30	25	23	87	226
ALT	22	47	24	24	69	341
Bili Total	0.4	0.4	0.5	0.5	0.4	0.7
Alk Phos	53	90	61	57	64	94

Trend of Liver Enzymes TB Meds Started 12/31

What is the most likely cause of the patient's liver enzymes?

Treatment Course

- Admitted to hospital 1/11/11
- INH discontinued and all other TB medications continued
- LFT's began to improve
- 1/15/11: Patient discharged on regimen of RIF, EMB, and PZA with plan for follow up in TB Clinic
- Steroids to be slowly tapered

Trend of Liver Enzymes INH Stopped 1/11

	1/7	1/11	1/12	1/13	1/14	1/15
AST	87	226	196	78	64	59
ALT	69	341	278	234	222	176
Bili Total	0.4	0.7	0.5	0.4	0.4	0.5
Alk Phos	64	94	68	81	91	75

Trend of Liver Enzymes INH Stopped 1/11

What would you do now?

Treatment Course

- 1/25/11: Levofloxacin added to regimen
- 2/7/11: INH reintroduced with frequent monitoring of LFTs
 - 100 mg daily x 1 week
 - Increased to 300 mg daily
- 2/7/11: PZA discontinued
- LFTs remained stable on this regimen
- New Regimen: INH, RIF, EMB and LEVO

Trend of Liver Enzymes After Reintroduction of INH

	1/25	2/7	2/14	2/24	3/8	3/31	4/25
AST	43	34	50	44	159	42	76
ALT	101	52	43	35	79	35	54
Bili Total	0.3	0.4	0.3	0.3	0.3	0.4	0.3
Alk Phos	83	76	66	59	76	90	65

Case 2

Cholestatic hepatitis and possible
peripheral neuropathy on a
pulmonary TB treatment regimen

History of Present Illness

- 55 y.o. Liberian woman in the US since 2002; works as a nurse
- History of interstitial lung disease and intermittent steroids
- July 2010: Went on trip to Ghana; became febrile there and on return, with increasing cough and SOB
- 8/21 – 9/3: Hospitalized in California
 - Negative smears but bronchoscopic NAAT positive for *M.tb*
 - Positive cultures from sputum and bronchoscopy specimens

Treatment Course

- 9/10: Treatment initiated with RIPE
 - INH 300, RIF 600, EMB 1200, PZA 1500 plus B₆ 50
- Complaints of decreased appetite and malaise
- 10/5: LFTs noted to be elevated
 - Bili 5.2, AST 99, ALT 134, Alk Phos 165
 - All TB medications discontinued
- 10/11: LFT's improved
 - Bili 1.5, AST 51, ALT 75

Treatment Course

What is the most likely cause of her elevated liver enzymes?

Treatment Course

What should we do with her regimen at this point?

Treatment Course

- Isolate found to be pan-susceptible
- 10/16: After consultation with California TB program, patient restarted on INH, PZA, EMB and B₆, RIF was discontinued
- PZA discontinued after 40 doses (?why), INH, EMB and B₆ continued
 - LFTs remained stable on this regimen
- January 2011: Patient moved to NJ and TB care transitioned to Regional Chest Clinic

Treatment Course

- 1/19/11: Initial evaluation in New Jersey
 - LFTs: AST 26, ALT 14, Bili 0.3
 - Sputum smears and cultures negative
- INH, EMB and B₆ continued, Moxifloxacin added to regimen
- Plan to continue her regimen for 12-18 months

Treatment Course

- 7/20/11: Presented to TB Clinic with c/o several weeks of worsening paresthesias and numbness in both feet, left greater than right. No other findings other than very mild sensory deficits on exam
- Neurology evaluation including EMGs consistent with mild lower extremity distal neuropathy

Treatment Course

What would you do at this point?

