## Slide 1: Medical Update Webinar: Treatment of TB: Managing Adverse Reactions

* August 30, 2011
* Provided by New Jersey Medical School Global Tuberculosis Institute, University of Medicine & Dentistry of New Jersey (UMDNJ)

## Slide 2: Faculty

List of faculty members

## *Robert Belknap, MD*

## Assistant Professor, University of Colorado; Infectious Disease Specialist, Denver Public Health

## *Henry Fraimow, MD*

## Associate Professor Medicine, UMDNJ-Robert Wood Johnson Medical School; Infectious Disease Specialist, Cooper University Hospital (Camden, NJ)

## Slide 3:Recognizing and Managing Side Effects of TB Treatment

* Presented by Bob Belknap MD
* Infectious Disease Specialist, Denver Public Health

## Slide 4: Objectives

## Upon completion of this presentation, participants will be able to:

## List the common side effects associated with first-line tuberculosis (TB) medications

## Describe monitoring for and diagnosis of adverse drug reactions during TB therapy

## Discuss approaches for managing adverse drug effects of TB drugs to minimize toxicity and ensure treatment completion

## Slide 5: 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

## Slide 6: 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 Alanine transaminase (ALT) is 57 (upper limit of normal is 40)

## Slide 7: What would you do now?

1. Continue current treatment and repeat the ALT in 1 week
2. Stop all drugs
3. Stop isoniazid and pyrazinamide
4. Continue treatment but add an anti-emetic

## Slide 8: 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 (Tbili)

## Slide 9: 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

## Slide 10: 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

## Slide 11: 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)

## Slide 12: 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

## Slide 13: 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

## Slide 14: Management of GI Symptoms (2)

Other considerations:

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

## Slide 15: 40 year old (1)

* Alcoholic diagnosed with smear (+) pulmonary TB
* Baseline labs:
* AST 78
* ALT 88 (nl for both 0-40)
* Alkaline phosphatase (Alk Phos) 127
* TBili 0.9
* platelets 105 (nl 140-415)
* Starts on isoniazid, rifampin, pyrazinamide and ethambutol

## Slide 16: 40 year old (2)

* 2 weeks later
* AST 546, ALT 328, Alk Phos 223, TBili 0.6
* What would you do?

1. Stop isoniazid and pyrazinamide
2. Hold all medications
3. Switch to levofloxacin and ethambutol
4. Continue meds and refer for alcohol treatment

## Slide 17: Diagnosing and Managing Hepatotoxicity

* Routine laboratory monitoring is not recommended
* Repeat an ALT in 2 to 4 weeks if:

1. Baseline abnormal liver function tests OR
2. Risk factors for hepatotoxicity

* All patients with GI symptoms should be checked

## Slide 18: Diagnosing and Managing Hepatotoxicity

* Hold medications as needed for symptoms
* STOP Medications if :
* ALT > 3 times normal with symptoms OR
* ALT > 5 times normal without symptoms
* Consider changing to liver “friendly” medications – fluoroquinolones, ethambutol and aminoglycosides

## Slide 19: 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

1. Pyrazinamide
2. Moxifloxacin

## Slide 20: 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

## Slide 21: Questions

## Slide 22: 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

## Slide 23: 85 year old (2)

* What would you do?

## Slide 24: 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

## Slide 25: 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

## Slide 26: 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

## Slide 27: 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

## Slide 28: Rash (3)

1. Petechial rash

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

1. 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

## Slide 29: 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

## Slide 30: 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

## Slide 31: 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

## Slide 32: 69 year old (1)

What medication is the cause of the knee pain?

## Slide 33: 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

## Slide 34: Rifamycin Drug Interactions

1. Rifamycins cause an increase of hepatic enzymes involved in drug metabolism
2. Rifampin is a more potent inducer than rifabutin (rifapentine is likely in between)
3. Many medications will be ineffective:

* Oral contraceptives
* HIV protease inhibitors
* Warfarin
* Narcotics (e.g. methadone)

## Slide 35: 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?

## Slide 36: 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

## Slide 37: 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

## Slide 38: 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

## Slide 39: 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

## Slide 40: 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

## Slide 41: Summary (1)

Isoniazid

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

## Slide 42: Summary (2)

Rifampin

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

## Slide 43: Summary (3)

Pyrazinamide

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

## Slide 44: Summary (4)

Ethambutol

* Optic neuritis – typically retrobulbar
* Peripheral neuropathy
* Rash

## Slide 45: Summary (5)

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

## Slide 46: References

1. MMWR 2003; 52 No. RR-11

* ATS/CDC/IDSA TB Treatment Guidelines

1. AJRCCM 2006; 174: 935

* ATS Statement on Hepatotoxicity

1. Curry International TB Center (http://www.currytbcenter.ucsf.edu)

* Tuberculosis Drug Information Guide

1. Hong Kong Med J 2006; 12(1): 56

* Review of ethambutol ocular toxicity

## Slide 47: Questions

## Slide 48: Case Discussions: Managing Toxicities of Anti-TB Medications

* Henry Fraimow, MD
* Division of Infectious Diseases,
* Cooper University Hospital, Camden, NJ
* Medical Consultant, Southern New Jersey Regional Chest Clinic

## Slide 49: Case 1: Increasing LFTs while on therapy for Central Nervous System tuberculosis

## Slide 50: History of Present Illness

* 62 year old (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

## Slide 51: 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-hydrochlorthiazide
* Ursodiol
* Tramadol
* Insulin

## Slid 52: 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

## Slide 53: 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
* The images show repeat MRI images of her head. These MRI scans show enlargement of white nodules scattered throughout the brain and were getting larger. The patient had about 20 of these white nodules in various places.

## Slide 54: 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

## Slide 55: 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

## Slide 56: 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

## Slide 57: Trend of Liver Enzymes:

## Table 1-1: TB Meds Started 12/31

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Date | | | | | |
|  | 12/5 | 12/25 | 1/1 | 1/4 | 1/7 | 1/11 |
| AST | 22 | 30 | 35 | 23 | 87 | 226 |
| ALT | 22 | 47 | 24 | 24 | 69 | 341 |
| Bilirubin Total | 0.4 | 0.4 | 0.5 | 0.5 | 0.4 | 0.7 |
| Alk Phos | 53 | 90 | 61 | 57 | 64 | 94 |

* This table shows the trend in her liver enzymes, looking particularly at the transaminases, the ALT and the AST. Her anti-tuberculosis medications were started on December 31st. She was discharged on January 7th. The high AST and ALT values on January 7 and 11 prompted her readmission.

## Slide 58: Trend of Liver Enzymes: TB Meds Started 12/31

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

## Slide 59: 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

## Slide 60: Trend of Liver Enzymes: INH Stopped 1/11

## Table 1-2: INH Stopped 1/11

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Date | | | | | |
|  | 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 |
| Bilirubin Total | 0.4 | 0.7 | 0.5 | 0.4 | 0.4 | 0.5 |
| Alk Phos | 64 | 94 | 68 | 81 | 91 | 75 |

* This table shows the trend in lab values during the hospital. Both of her transaminase levels are slowly decreasing.

## Slide 61: Trend of Liver Enzymes: INH Stopped 1/11

* What would you do now?

## Slide 62: 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

## Slide 63: Trend of Liver Enzymes: After Reintroduction of INH

## Table 1-3: After Reintroduction of INH

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Date | | | | | |  |
|  | 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 |
| Bilirubin Total | 0.3 | 0.4 | 0.3 | 0.3 | 0.3 | 0.4 | 0.3 |
| Alk Phos | 83 | 76 | 66 | 76 | 76 | 90 | 65 |

* This table shows her trend in liver enzymes from the time that these manipulations were made. There are transient blips in her transaminases, particularly the AST at different times

## Slide 64: Questions

## Slide 65: Case 2

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

## Slide 66: 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

## Slide 67: 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

## Slide 68: Treatment Course

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

## Slide 69: Treatment Course

What should we do with her regimen at this point?

## Slide 70: 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

## Slide 71: 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

## Slide 72: 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

## Slide 73: Treatment Course

What would you do at this point?

## Slide 74: Case 2: Important Points!

* There may be differences in patterns of enzyme elevations with hepatic injury from INH or RIF
* When an anti-TB agent is discontinued due to adverse effects, re-evaluate the entire regimen
* Neurotoxicity from INH can occur late in the course of treatment, even on vitamin B6
* Assessing patient perceptions of their adverse drug reactions and providing education is critical

## Slide 75: Questions

* Verbal questions by phone
* Un-mute your phone by pressing #6
* After your question, re-mute your phone by pressing \*6
* Introduce yourself and say from where you are calling
* Type your questions by clicking on the Q&A icon, priority will be given to verbal questions

## Slide 76: Medical Consultation

## Slide 77: Thank you for your participation!