Management of Adverse Drug Reactions in Tuberculosis

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Introduction

• Management of patients with tuberculosis (TB) can be a difficult task in any patient

• Drug reactions commonly occur in the treatment of TB and should be anticipated

• Keep a vigilant eye for adverse events and anticipate them in the high risk patient
Introduction

• Symptoms may occur due to the medication itself, due to tuberculosis infection, or due to other medical conditions

• All attempts must be made to avoid discontinuation of treatment and remind patients that a break in treatment will result in prolonged duration of treatment
DRUGS

• First line drugs are:
  • Isoniazid, Rifampin, Pyrazinamide and Ethambutol

• Second line drugs are:
  • Cycloserine, Ethionamide, Streptomycin, Amikacin, Kanamycin, Capreomycin, P-Aminosalicyclic Acid (PAS), and Levofloxacin
Adverse Drug Reactions

- Adverse drug reactions may affect a variety of organ systems:
  - Gastrointestinal
  - Dermatological
  - Neurological
  - Ophthalmical
  - Musculoskeletal
Gastrointestinal

- Nausea and vomiting are the most common side effects noted
- Encourage patient to continue taking medications
- Treat the symptoms and continue anti-TB therapy
- Often times the symptoms of nausea and vomiting lessen with time
- Always consider drug induced hepatitis & monitor LFT’s
Hepatotoxicity

Hepatotoxicity is present if:

- AST greater than 3 times upper limit of normal with symptoms
- OR
- AST greater than 5 times upper limit of normal without symptoms
Hepatotoxicity

- LFT’s must be closely monitored in patients who:
  - Chronically consume alcohol
  - Take other hepatotoxic drugs
  - Have a hx of viral hepatitis or other liver disease
  - Are pregnant
  - Are <3 months post-partum
  - Have HIV infection

Asymptomatic patients with mild elevations in LFT’s can be seen & represents hepatic adaptation.
Hepatotoxicity

- ALT is more specific for hepatocellular injury than AST

- If AST > 2 times the ALT then this is suggestive of alcohol related liver injury

- Consider other causes of hepatotoxicity including viral hepatitis, gallstones, & other concomitant hepatotoxic medications
Management of Hepatotoxicity

- When hepatotoxicity is suspected hold all tuberculosis medications

- Monitor for signs of hepatotoxicity, i.e., jaundice, hepatomegaly, ascitis, edema, caput medusa, spider angioma

- Monitor LFT’s closely and resume medications when LFT’s return to <2 times upper limit of normal
Spider Angiomata & Jaundice
Management of Hepatotoxicity

• First drug to be re-instituted is Rifampin and monitor patient’s signs and symptoms & LFT’s for 3-7 days

• If no signs of hepatotoxicity then re-institute INH and monitor for 3-7 days

• PZA may be reinstituted if the initial reaction was not severe

• If symptoms recur or if the ALT increases then the last drug added should be stopped
Hepatotoxicity

• Patients should be cautioned regarding signs and symptoms of hepatotoxicity

• These patients should be closely monitored for the remainder of the treatment with monthly LFT’s

• Patients should contact health care workers if signs & symptoms of hepatotoxicity reoccur
Dermatologic Reactions

- Maculopapular rash and pruritis are common
- These may resolve after the first several weeks of treatment
- Encourage patients to continue medications as rash may resolve on its own
- For mild reaction treat the rash & pruritis symptomatically and continue the medications. May use antihistamines and topical corticosteroids
Dermatologic Reactions

- **Hives & urticaria** may occur related to all medications

- Stop all drugs immediately until the reactions resolve

- If the initial reaction was not severe and there was no anaphylaxis, angioedema, or airway compromise then restart medications one at a time
Severe Drug Reaction

- **Steven Johnson Syndrome**
  This is a systemic reaction associated with:
  - High fever
  - Widely distributed urticaria
  - Bullae
  - Mucous membrane erosions

- Steven Johnson Syndrome requires treatment with systemic corticosteroids and supportive care. Stop the offending medication and do not use again

- **Anaphylaxis** can rarely occur with TB medications
Steven Johnson Syndrome
Neurotoxicity

- **Peripheral neuropathy** presents with tingling and numbness of the hands and feet

- **Glove and stocking pattern**

- Risk factors for peripheral neuropathy include: diabetes, alcoholism, HIV, hypothyroidism, pregnancy, poor nutrition, inadequate dietary intake of pyridoxine
Peripheral Neuropathy

- Pyridoxine supplementation is given
  - INH – Pyridoxine 50mg daily
  - Cycloserine & Ethionamide 100-200mg daily
Ophthalmic Toxicity

- Prevention & Monitoring:
  - Conduct baseline & monthly visual assessment with acuity testing and testing of color discrimination
  - Educate patients to report changes in visual acuity or red-green color discrimination, scotomata, change in visual fields, erythema, or eye pain
  - Improve diabetic control
  - Avoid or adjust Ethambutol dose and dosing interval and monitor concentrations when creatinine clearance is <30 ml/minute
  - Correct nutritional deficiencies
Visual Acuity & Ishihara Test
Retrobulbar Neuritis

- Manifested as decreased visual acuity or decreased red-green color discrimination
- Stop Ethambutol (EMB)
- Refer patient to an ophthalmologist
- Higher risk with patients on higher doses and with renal insufficiency
Retrobulbar Neuritis

- Do not restart EMB unless another cause of the neuritis or vision problem is definitely identified.

- Gradual improvement in vision is noted in many patients after the offending medication is stopped.

- Whenever a question about visual toxicity exists, immediately discontinue the offending medication.
Retrobulbar Neuritis
Uveitis

- Rifabutin, especially in higher doses, can cause pan-uveitis that is reversible

- Patients typically present with erythematous, painful eyes, and blurring of vision

- Hold Rifabutin until symptoms have resolved and then reinstitute at lower dose

- Consult an ophthalmologist
Uveitis

- Consider other etiologies, especially in HIV-infected individuals (exclude bacterial & viral infection)

- Use topical steroid drops if ocular infection is ruled out
Musculoskeletal Adverse Effects

- **Myalgias & Arthralgias:**
  - Pain and tenderness of muscles and joints are relatively common side effects
  - Do not discontinue medications
  - NSAIDS are usually helpful
Musculoskeletal Adverse Effects

- If acute swelling, erythema, and warmth are present, evaluate for presence of inflammatory diseases

- Evaluate for hypothyroidism or hyperthyroidism

- Draw serum electrolytes, calcium, and magnesium; and correct deficiencies

- Monitor uric acid if on Pyrazinamide
Ototoxicity

• Seen with aminoglycosides (streptomycin, amikacin, kanamycin, capreomycin)

• Associated with older age, longer duration of treatment, and total dose given

• Results in disturbance in vestibular balance and hearing disturbance

• Monitor with audiogram and with Rhomberg’s

• Hearing loss may be permanent therefore stop the drug
Nephrotoxicity

- Aminoglycosides should be used in caution in patients with renal insufficiency.

- PAS is contraindicated in severe renal insufficiency. If PAS is given in patients on hemodialysis the drug is given after hemodialysis.

- Fluroquinolones dose should be adjusted to three times a week in patients with creatinine clearance <50ml/min.
Specific Drug Reactions

- **Rifampin** – orange discoloration of urine, tears, perspiration, & feces. Inform contact lens wearers.

- **PZA** – blocks renal tubular excretion of uric acid & results in elevation of uric acid. Hyperuricemia without gout is NOT a reason to discontinue PZA.
Specific Drug Reactions

- **Ethionamide** – endocrine abnormalities such as gynecomastia, alopecia, hypothyroidism, impotence, irregular menses

- **Capreomycin** – electrolytic depletion of magnesium, potassium, calcium & proteinuria
Specific Drug Reactions

- **Quinolones** – tendinitis and tendon rupture. Incidence more common in patients > 60 yrs, patients on corticosteroids, & transplant patients

- **PAS** – hypothyroidism & goiter can occur. It reverses when the drug is stopped
Importance of Monitoring

- Close monitoring of patients throughout treatment can:
  - Prevent serious complications
  - Promote continuity of care
  - Improve patient-health care provider relationship
  - Encourage adherence
  - Ensure successful completion of treatment
Summary

- Adverse reactions & toxicity accompany essentially all treatment courses for tuberculosis

- Close attention to toxicity & reports of discomfort are essential in maintaining patient’s cooperation with the regimen

- In many cases, some toxicity will have to be tolerated
Clinical Case

- **HPI:**
  - 46-year-old Filipino male comes to USA in 2006. Later he presents with cough, fever, chest pain

- **PMHx:**
  - None

- **Social Hx:**
  - Patient is a non-smoker, no ETOH, no recreational drug use
Clinical Case

- Labs:
  - WBC 6000, Hg 12.9gm/dl, HCT 39, PLT 244,
  - Electrolytes: nl
  - HIV: negative
  - AST (0-40): 46 u/l
  - ALT (0-35): 89 u/l
  - ALK (30-115): 121 u/l
  - TB (0-1.0): 0.4 mg/dl
Clinical Case

- **CXR:**
  - Reveals right upper lobe infiltrate

- **Sputum:**
  - Positive for AFB smear x 3
CXR
Clinical Case

- Clinical Course:
  - Patient was started on 4 drug therapy – RIPE
  - Patient has no abdominal pain, nausea, vomiting, What would be the appropriate next step?
Clinical Case

- Medication were continued with request to repeat liver function testing
- Results were further elevated but patient remained asymptomatic
- LFT repeated a week later and hepatitis profile ordered
- Medications were now held (6 weeks after initiation)
## Lab Results

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Clinical Case

- With drug induced liver injury when should drug re-challenge commence?
- Which drugs should be initiated first?
- How often would you repeat LFT’s on these patients?