

MANAGEMENT OF COMMON SIDE EFFECTS of INH (Isoniazid), RIF (Rifampin), PZA (Pyrazinamide), and EMB (Ethambutol)

1. Hepatotoxicity: In Active TB Disease

a. Background:

1. Among the 4 standard anti-TB drugs, Isoniazid (INH) is the most likely to cause drug induced liver toxicity. The incidences of hepatotoxicity are ranged as the following (from high to low): INH>PZA>RIF. Ethambutol (EMB) can be used safely in patients with hepatic disease.
2. Nearly 20% of patients treated with the standard four- drug regimen show asymptomatic increase in AST concentration. It usually occurs during the first 3 months of treatment.
3. Symptoms: unexplained anorexia, nausea, vomiting, dark urine, yellow skin or eyes, fever, persistent fatigue, abdominal tenderness especially right upper quadrant discomfort.
4. Patients at high risk for hepatotoxicity:
 - a. HIV.
 - b. Pregnant or postpartum (3 months of delivery).
 - c. History or at risk of chronic liver disease (daily use of alcohol, IV drug users, hepatitis, liver cirrhosis).
 - d. Patients who are taking liver toxicity inducing drugs for chronic medical conditions.
 - e. Incidence of liver toxicity increases with age (>35 years old).
5. Routine baseline liver function test (LFT) is **recommended** prior to starting the standard four-drug therapy for suspect or active TB disease. If the tests are normal, no further tests are required unless symptoms develop.
6. If the tests are abnormal, monthly LFT are required. .
7. If results less than 2X upper limits and no side effects repeat in one month. Consult with physician when greater than 2X upper limit. If any of LFT > 3X upper limit of normal (ULN) at any time, consider stopping therapy and following protocol.
8. Drug induced hepatotoxicity is defined as AST/ALT \geq 3x ULN with the presence of symptoms; or AST/ALT >5x ULN in the absence of symptoms; or disproportional increase in alkaline phosphatase (ALP) and total bilirubin.

9. INH is contraindicated in patient with active hepatitis and end stage liver disease.

b. How to manage liver toxicity:

1. If LFT (AST/ALT) <5x ULN and no symptoms, continue with the regimen and increase monitoring frequency.
2. If alkaline phosphatase and bilirubin are disproportionately increased, this pattern is more consistent with Rifampin hepatotoxicity. Rifampin may be stopped. Recheck LFTs.
3. If LFT ≥ 3x upper limit of normal PLUS symptoms; or LFT ≥ 5x ULN with or without symptoms:
 - a. STOP immediately all antituberculosis drugs.
 - b. Consult with an expert who is familiar with the management of hepatotoxicity.
 - c. Perform serologic testing for Hepatitis A, B, and C on patients who are high risk for hepatitis.
 - d. Rule out other causes (hepatotoxic medications, alcohol consumption, etc.) and treat accordingly.
 - e. In acutely ill and acid-fast stain positive patients, three “liver friendly” drugs such as Levofloxacin, Ethambutol (EMB), and Streptomycin should be started until diagnosis of liver toxicity causes are identified.
 - f. How to rechallenge anti-tuberculosis drugs?
 - Continue checking LFT. If LFT <2x ULN, rechallenge first with Rifampin because of its efficacy and is least likely to cause hepatotoxicity. Also, EMB should be added to the regimen.
 - If LFT does not increase after 1 week, then INH should be added to the regimen.
 - Pyrazinamide (PZA) can be added next (1 week after INH) if LFT does not increase.
 - Important point: if at any time of rechallenged period, symptoms recur or AST increases, the last drug added should be stopped.

2. Gastrointestinal intolerance

- a. Symptoms: nausea, vomiting, poor appetite, abdominal pain.
- b. GI upset symptoms are very common and usually occur in the first few weeks of therapy.
- c. Any anti-TB drugs can cause GI upset.
- d. How to manage GI upset:

1. Recommend changing hour of drug administration, preferably closer to meal time. If patient is not on directly observed therapy (DOT), medication can be taken at bedtime.
2. Take medication with a light snack. However, since aluminum salt-containing antacid reduces INH bioavailability, antacid should be avoided 1 hour before and 2 hours after INH administration.
3. Ask patients if they are taking NSAIDs, alcohol, or have a history of gastritis, acid reflux GERD, pancreatitis, etc.
4. If GI symptoms persist or worsen,
 - a. Rule out other possible causes of hepatotoxicity, drugs induced GI upset, history of GI disease.
 - b. Perform LFTs. If ALT/AST $\geq 3 \times$ ULN, assume it is liver toxicity. Stop antituberculosis drugs.
5. HYDRATION! Important to encourage patients to increase fluid intake.

3. Rash

- a. All anti-TB drugs can cause rash. Rash can be managed depending on its severity:
 1. Mild rash or itching: pre-medicate with antihistamine (Benadryl) 30 minutes before anti-TB drugs are administered. Recommend to continue anti-TB drugs.
 2. Prednisone can be given at 40mg/day and when rash clears gradually taper the dose down to 0 mg.
 3. Petechial rash (pinpoint sized red dots under the surface of the skin caused by leakages of capillaries); Rifampin (RIF) hypersensitivity is suspected. A platelet count (CBC without differential) should be ordered. If the platelet count is below normal (normal range: 150,000-450,000 platelets per microliter), stop RIF and never restart it again. Monitor the platelet count until it returns to baseline.
 4. Erythematous rash with fever, and/or mucous membrane involvement.
 - a. STOP ALL drugs immediately
 - b. Rule out anaphylaxis reactions (angioedema, swollen tongue and throat, flushed face, airway constriction, wheezing, difficulty breathing, hypotension).
 - c. Rule out Stevens-Johnson Syndrome: systemic shedding of mucous membrane and fever. It can be life threatening. Immediate urgent care is required.
 - d. If treatment of TB can not be interrupted (severely ill with tuberculosis), try three new drugs (different class of drugs). Second-line anti-TB drugs such as

injectable aminoglycosides (streptomycin, amikacin) and 2 oral agents can be used.

- e. If rash has improved substantially, anti-TB drugs can be restarted one by one every 2-3 days.
 - First, start with RIF because of its efficacy and is the least likely to cause rash.
 - Second, INH can be added after 3 days.
 - Third, PZA or EMB can be added after 3 days of INH.
 - Monitor signs and symptoms of rash. If rash recurs at any point; the last agent added should be removed.

4. Peripheral neuropathy:

- a. The primary agent that causes peripheral neuropathy is INH.
- b. It is more common in the malnourished (vitamin B6 deficiency), diabetes, HIV, renal failure, alcoholism, pregnant and breastfeeding women.
- c. The side effect is dose related. It is uncommon at conventional INH dosage. Vitamin B6 can also cause peripheral neuropathy.
- d. Signs and Symptoms: numbness, tingling feet and hands, sensitive to touch, and stabbing pain.
- e. Management:
 1. Prevention is the key! Pyridoxine (vitamin B6) prophylaxis 10 mg Pyridoxine for every 100 mg INH (usually about 25-50 mg vitamin B6) is recommended in high risk patients.

5. Ophthalmic toxicity (Optic neuritis):

- a. The main agent that causes a decrease in visual acuity and may lead to irreversible blindness is Ethambutol (EMB). It is a dose related side effect (EMB > 15 mg/kg/day) and it also gets more intense if therapy is continued.
- b. Signs and symptoms: difficulty reading road signs, decreased red-green color discrimination, blurred vision, color blindness. These side effects can happen to one or both eyes.
- c. Management:
 1. Snellen eye charts (testing visual acuity) and Ishihara color blindness test are recommended at baseline and monthly while on EMB. If there is a defined fluctuation of 1 or 2 lines of the Snellen chart, patients should not receive EMB.
 2. Stop the EMB immediately and permanently if decrease in visual acuity is confirmed. More than 10% visual loss is considered significant.
 3. EMB is not recommended in children under 5 years old since visual changes are difficult to monitor.

6. Hepatotoxicity in Latent TB Infection

a. Background:

1. Isoniazid (INH) is the most likely TB drug to cause drug induced liver toxicity. Of people taking INH 0.1% to 0.15% develop clinical hepatitis.
2. Nearly 20% of patients treated with the standard four-drug regimen show asymptomatic increase in AST concentration. It usually occurs during the first 3 months of treatment.
3. Symptoms: unexplained anorexia, nausea, vomiting, dark urine, yellow skin or eyes, fever, persistent fatigue, abdominal tenderness, especially right upper quadrant discomfort.
4. Patients at high risk for hepatotoxicity:
 - a. HIV
 - b. Pregnant or postpartum (3 months of delivery)
 - c. History or at risk of chronic liver disease (daily use of alcohol, IV drug users, hepatitis, liver cirrhosis)
 - d. Patients who are taking liver toxicity inducing drugs for chronic medical conditions.
 - e. Incidence of liver toxicity increases with age (>35 years old)
5. Routine baseline liver function test (LFT) is not recommended. However, LFT (AST/ALT and total bilirubin) are indicated for high risk patients.
6. If the tests are normal, no further tests are required unless symptoms develop.
7. If the tests are abnormal, monthly LFT are required. If results less than 2X upper limits and no side effects repeat in one month. Consult with physician when greater than 2X upper limit. If any of LFT > 3X upper limit of normal (ULN) at any time, consider stopping therapy.
8. Drug induced hepatotoxicity is defined as AST/ALT \geq 3x ULN with the presence of symptoms; or AST/ALT >5x ULN in the absence of symptoms; or disproportional increase in alkaline phosphatase (ALP) and total bilirubin.

7. Rash

- a. All anti-TB drugs can cause rash. Rash can be managed depending on its severity:
 1. Mild rash or itching: pre-medicate with antihistamine (Benadryl) 30 minutes before INH is administered. Recommend to continue anti-TB drugs.
 2. Stop INH, wait for rash to clear and then restart at 10mg using pediatric liquid and gradually increase until the dose is back to 300 mg.

3. Prednisone can be given at 40mg/day and when rash clears gradually taper the dose down to 0 mg.
4. Petechial rash (pinpoint sized red dots under the surface of the skin caused by leakages of capillaries); Rifampin (RIF) hypersensitivity is suspected. A platelet count (CBC without differential) should be ordered. If the platelet count is below normal (normal range: 150,000-450,000 platelets per microliter), stop RIF and never restart it again. Monitor the platelet count until it returns to baseline.

8. Peripheral neuropathy:

- a. The primary agent that causes peripheral neuropathy is INH.
- b. It is more common in the malnourished (vitamin B6 deficiency), diabetes, HIV, renal failure, alcoholism, pregnant and breastfeeding women.
- c. The side effect is dose related. It is uncommon at conventional INH dosage. Vitamin b6 can also cause peripheral neuropathy.

9. Other Side Effects:

- a. **Fatigue** Usually due to INH. Take medicine about 2 hours before bedtime so can sleep through the symptoms. If continues evaluate to assure not due to hepatotoxicity.
- b. Joint pains/flu like symptoms usually due to Rifampin.
- c. Lupus syndrome due to INH. May evaluate with blood tests to discriminate between SLE and drug induced lupus. Treat with prednisone while still on INH.

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