Management of TB Treatment Complications and Adverse Effects

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Problems in Treatment

- Can’t swallow pills
- GI intolerance
- Adverse drug reactions
- Allergies
- Drug interactions
- Renal failure
- TB meningitis
- Hepatitis
Can’t Swallow Pills

- Use oral liquids
  - INH syrup
  - RIF
    - Simple syrup
    - Jam, honey, applesauce, etc
    - Stability?
  - PZA, EMB
    - No stability data
    - Crush in jelly, apple juice
Can’t Swallow

- Gastrostomy Tubes
- Injectables
  - INH
  - RIF
  - Aminoglycosides
  - Quinilones
  - EMB
GI Intolerance

- Very common
- Start with low dose and increase over several days
- Give at bedtime
- Give after meals
  - Lin et al (IJTLD 2010 Jul;14(7):806-18) meta-analysis showed antacids (without aluminum better choice than food to avoid lower than expected TB drug levels)
- Proton pump inhibitors and/or Reglan
- Divide doses
Allergies / Pruritis

- Pruritis very common
- Antihistamines
- Severe rash-desensitization
  - Low doses given frequently and in gradually increasing doses
  - Do only where emergency treatment is available
Joint Pains

- Arthralgia vs. joint involvement
- Arthralgia TX symptoms
  - NSAIDS
- Gout like-increased uric acid from EMB and/or PZA
  - Allopurinol, colchicine, probenecid
  - NSAIDS
  - Rifampin decreases febuxostat (Uloric) level
- Switch to a different drug
Drug Interactions

- Phenytoin-? Neurontin
- Warfarin-? LMWH
- Efavirenz-adjust doses, TDM
- HIV protease inhibitors-adjust doses, TDM
- Transplant medications (rifampin lowers the transplant medications in the calcineurin inhibitor family (cyclosporine and tacrolimus), as well as rapamycin and corticosteroids)-adjust doses, TDM or rifampin sparing regimens
Renal Failure

- Use drugs metabolized by liver
  - Cipro vs. floxin
- Give lower doses of drugs renally excreted as active agents
- Give after dialysis
- Monitor-TDM
# TB Meningitis

<table>
<thead>
<tr>
<th>CNS Penetration</th>
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<tbody>
<tr>
<td>INH</td>
<td>90 - 100%</td>
</tr>
<tr>
<td>RIF</td>
<td>10 - 25%</td>
</tr>
<tr>
<td>PZA</td>
<td>75%</td>
</tr>
<tr>
<td>EMB</td>
<td>10 - 50%</td>
</tr>
<tr>
<td>STM</td>
<td>Low</td>
</tr>
<tr>
<td>Quinilones</td>
<td>10%</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>50 - 80%</td>
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Hepatic Issues and TB therapy
“A Situation Where Beer and TB Mixed Well”

Antituberculosis Drug-induced Hepatotoxicity
The Role of Hepatitis C Virus and the Human Immunodeficiency Virus

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Until recently it was thought that age greater than 50 yr was the main risk factor for the development of drug-induced hepatitis (DIH) in patients receiving antituberculosis therapy. We conducted a study to determine whether infection with either the hepatitis C virus or the human immunodeficiency virus (HIV) were significant risk factors for the development of DIH in patients receiving antituberculosis therapy. Our study consisted of two parts. In the first part, 334 consecutive patients admitted for the treatment of tuberculosis (TB) were followed for the development of DIH. All of these patients were also screened for the presence of hepatitis C and HIV. In the second part of the study, three patients who were hepatitis C positive and who developed DIH on repeated reintroduction of the anti-TB drugs were offered a liver biopsy. A tissue inflammatory, which may be suggestive of hepatitis C infection, was present on the biopsy specimen. Treatment with alpha-interferon was begun and the anti-TB drugs were subsequently reintroduced. During the 18 mo of the study, 22 patients developed DIH. The relative risk of developing DIH in the patient was hepatitis C or HIV positive was threefold and fourfold, respectively (p < 0.005). If a patient was coinfected with both hepatitis C and HIV the relative risk of developing DIH was increased 14.4-fold (p < 0.0002). In the treatment part, four patients were treated with alpha-interferon, and all were able to undergo the reintroduction of anti-TB therapy without recurrence of DIH. Patients with hepatitis C and HIV are more likely to develop active TB (1). Similarly, these same groups have also been shown to have an increased incidence of infection with the hepatitis C virus (HCV) (6, 10).

Recently, alpha-interferon has been recommended as a first-line treatment for patients with hepatitis C infection who show pathologic evidence of active inflammation (11). In patients infected with hepatitis C, there has been evidence of pathological healing and resolution of active inflammation, and the return to normal liver function during treatment with interferon (12). The use of interferon in patients with chronic active hepatitis is controversial. The use of interferon in patients with chronic active hepatitis is a complex and controversial issue. The use of interferon in patients with chronic active hepatitis is a complex and controversial issue. The use of interferon in patients with chronic active hepatitis is a complex and controversial issue. The use of interferon in patients with chronic active hepatitis is a complex and controversial issue. The use of interferon in patients with chronic active hepatitis is a complex and controversial issue. The use of interferon in patients with chronic active hepatitis is a complex and controversial issue. The use of interferon in patients with chronic active hepatitis is a complex and controversial issue. The use of interferon in patients with chronic active hepatitis is a complex and controversial issue. The use of interferon in patients with chronic active hepatitis is a complex and controversial issue. The use of interferon in patients with chronic active hepatitis is a complex and controversial issue.
Antituberculosis Drug-Induced Hepatotoxicity (ATDIH) or Drug-induced Liver Injury (DILI)

- The most frequent adverse effects of antituberculosis treatment are hepatotoxicity, skin reactions, gastrointestinal and neurological disorders.

- Hepatotoxicity is potentially the most serious of the above
  - Isoniazid hepatotoxicity is the most commonly implicated agent leading to drug-induced acute liver failure in the United States and the most common reason that adults require emergency Liver Transplant for idiosyncratic drug hepatotoxicity.
Case 1

- 54 yo h male with no PMH developed right cervical LN enlargement over 2 months associated with fevers, cough and 10 pound weight loss.
- CXR showed bilateral upper lobe infiltrates
- Sputum AFB (+), MTD (+), and sputum and R cervical LN aspirate were culture (+) for TB, pansusceptible.
- The patient was started on 4 drugs (RIPE) but after 1 week of therapy developed itching and a macular-papular rash that was thought by the treating clinicians to be due to “flea bites” -unrelieved by hydroxyzine
Case 1

- The patient was clinically responding and feeling stronger.
- Approx 3 weeks after starting the TB meds the patient started c/o anorexia, abd pain, nausea/vomiting and weight loss.
- Labs drawn and returned 3 days later revealed a sodium of 125, Alb 3.1, T. Bili 2.6, Alk Phos 381, AST 337, ALT 580.
- The patient was asked to come into the clinic immediately (3 days after the above labs drawn) and patient found to have scleral icterus, 6 pound weight loss and maculopapular rash on arms and legs.
WHAT WOULD YOU DO NOW?

1. Hold all meds
2. Abd Sonogram
3. Hepatitis Viral Serology
4. Start EMB/Levofloxacin/SM
5. All of the above
6. Choices 1-3
Case 1

- Labs drawn, meds held and patient sent home
- 2 days later, patient found by roommate to be very weak, unable to eat or drink due to N/V and unable to stand up
- Patient taken to ER by roommate
- Labs from 2 days earlier returned and showed Alk Phos 332, AST 302, ALT 441, T Bili 11.9, D Bili 9.0
Case 1

In the ER the patient was found to be in hepatorenal failure, with thrombocytopenia, leukocytosis, anemia, and hyponatremia with a total bilirubin of 17.3, SGOT of 360, SGPT of 500, and an ammonia level of 38. His Na 125, BUN was 20; his creatinine was 1.25 (in April it had been 0.5), albumin of 1.4, WBC 28,000 with a hemoglobin of 9.9, a platelet count of 63,000, and an INR of 2.

He was described as having a non-erythematous vesicular rash.
What Would You Do Now?

1. Start EMB/Moxifloxacin
2. Supportive care including aggressive hydration
Case 1

- The patient was admitted to the hospital
- Abd Sono (-) for liver masses, evidence of biliary obstruction or gallstones
Case 1

- The patient was started on ethambutol and moxifloxacin
- ID suggested stopping EMB and starting Vancomycin for the rash
- Hepatology suggested holding all TB medications until liver enzymes normalized-the patient's hepatorenal failure was generally felt to be secondary to the TB medications.
- The patient was seen by ID after 5 days and started on rifampin, ethambutol, levofloxacin and prednisone-his total bilirubin and creatinine at that time remained significantly elevated.
- His T. Bili remained elevated after 1 week so the rifampin was stopped and cycloserine added, but the rifampin was restarted two days later.
- Chemistries at that time were significant for an SGOT of 28, SGPT of 13, and total bilirubin of 2.4. BUN and creatinine was 46 and 1.9. The creatinine had been as high as 2.42.
- CBC from June 2, 2011, showed a white count of 8.8, 30% eosinophils, and a hemoglobin and hematocrit of 10.6 and 31.4 with a platelet count of 109,000.
Case 1

The infection control nurse “suggested” to the MDs that the patient should be transferred to AGH.
CASE 1

- The patient’s meds were held until his T. Bili was 1.3
- The patient was then started on rifabutin for four days without incidence.
Do You Agree With Starting RBT First?

1. No, his enzyme elevation was probably due to rifamycins
2. No, you shouldn’t use rifamycins in this case because of the severe hepatorenal reaction
3. Yes-I LIKE RIFABUTIN
CASE 1

1. Next PZA was started
Do You Agree With Starting PZA Next?

- No-PZA tends to be very hepatotoxic-Don’t you remember what happened with Rif/PZA for LTBI Jerkhead!!!!!!

- Yes-I LIKE PZA!!!!
CASE 1

- Within eight hours of starting PZA, he developed fever and elevation of his liver parameters and creatinine with a drop in his hematocrit, similar to his previous reaction.
- All medications were stopped and the reaction subsided over the next 72 hours.
- The patient was kept off his medications until his chemistries returned to normal.
- He was started on rifabutin again without a problem.
- The next day he was started on INH.
Do You Agree With Starting INH Now?

1. No-INH is hepatotoxic

2. Yes-I **LIKE INH!!!** (also INH/Rbt is a good regimen and could cure this individual in 9 months)

3. I Don’t Know What I Would Start Now
CASE 1

- Within an hour of getting the INH he developed abdominal discomfort but his labs at that time were within normal limits.
- The medications were held.
- The repeat labs the following day showed that his LFTs had increased and his creatinine increased to 2.1 and he developed a generalized rash with facial swelling with periorbital and perioral edema, which was sparing the lips. He had no mucous membrane involvement.
- His LFTs decreased, but his creatinine remained elevated but he had an elevated eosinophil count of 24%.
WHAT WOULD YOU DO NOW?

1. PANACEA (Do you remember this mnemonic?)
2. I DON’T CARE
CASE 1

- Cortisol level baseline was 6.5 and post ACTH stimulation was 15.7
- Urine for eosinophils (-)
- Stool for O&P was negative
- TFTs WNL
- CT of Abd negative for any adrenal lesions
- The patient was started on hydrocortisone 50mg BID
- The patient was started on Rbt and then Levoquin without problems
- Most recent labs show his white count is 2.8, hematocrit 47, and platelet count 168,000 with eosinophils being 2%. BUN of 26, creatinine 0.6, albumin 4.1, AST 16, ALT 23, and total bilirubin 0.2
- The patient was treated for 12 mths total and remains disease free 1 yr later
An Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy

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American Thoracic Society Documents

An Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy

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Antituberculosis Drug-Induced Hepatotoxicity (ATDIH)

- Asymptomatic transaminase elevations occur in 20% of patients treated with standard antituberculosis regimens; prior to treatment or immediately after the start of treatment. Usually these elevations resolve spontaneously.
- Toxic drug reactions usually occur in the first 3 months (60% of DIH) of treatment but may happen at any moment during the treatment period (80% of DIH occur at 6 mths).
- The signs and symptoms of liver injury are jaundice, abdominal pain, nausea, vomiting and anorexia. They are not specific enough to ascertain a liver disorder. Therefore, confirmation by laboratory liver testing is required.
- Complaints of ATDIH are mostly relieved when treatment is interrupted.
- When treatment is not interrupted in time, ATDIH can be fatal.
Antituberculosis Drug-Induced Hepatotoxicity (ATDIH)

- The incidence of ATDIH during standard multidrug TB treatment has been variably reported as between 2% and 28% (depending on definition used).

- A common definition of ATDIH is a treatment-emergent increase in serum alanine aminotransaminase greater than three or five times the upper limit of normal, with or without symptoms of hepatitis, respectively.
We do not routinely measure “Liver Function Tests”
- PT, PTT, Albumin, and ammonia are more indicative of Liver Function

AST and ALT are transaminases-increased with inflammation of the hepatocytes
- AST non specific and produced in other tissue-muscle, brain, organs, heart, blood cells
- ALT more specific for liver

With inflammation of liver should see a rise in both AST/ALT approx evenly

Conditions that affect other organs will cause difference in AST/ALT ratio
- Rhabdomyolysis, Acute Coronary Syndrome, Stroke, Hemolysis, ETOH abuse (through muscle breakdown), organ perforation
  - If AST (ALT is now the recommended transaminase to follow) is elevated always get an AST, ALT and T. Bili

T. Bili, Alk Phos and GGT are representative of the biliary tract and elevations seen in obstructive pictures (eg gallstone and TB and NTM of liver)
“Don’t Always Blame the Drugs”

Drug-induced liver injury (DILI) is ultimately a clinical diagnosis of exclusion.

- “Rechallenge with the suspected offending agent with more than twofold serum alanine aminotransferase (ALT) elevation, and discontinuation leading to a fall in ALT, is the strongest confirmation of the diagnosis. Rechallenge may, in some instances, endanger the patient and is usually confined to essential drugs or used when multiple potentially hepatotoxic drugs have been administered concomitantly”

Abnormal liver parameters not always associated with TB meds (tendency to always blame the TB meds and then end up treating with weaker meds for longer)

Need to rule out other causes—not always the medications

- Other conditions such as gallstones, masses, cirrhosis
  - Sonogram
  - Gilberts Syndrome—affects 5-10% of the population Asymptomatic elevation of T. Bili, almost exclusively indirect Bili, one way to test for this syndrome is by administering rifampin 900mg.

- ETOH and other meds (eg Tylenol, HMG-CoA inhibitors)
  - History
  - Ratio of AST/ALT
  - Drug Screen

- Viral Serologies
  - Hep A IgM Ab, HBV SAg and Ab, HCV Ab

- Rarely other medical conditions including autoimmune and pregnancy
  - Suspect based on other history/clinical factors
Antituberculosis Drug-Induced Hepatotoxicity (ATDIH)

- The exact mechanism of ATDIH is unknown.
- Isoniazid-induced hepatotoxicity is considered idiosyncratic (Unpredictable or idiosyncratic reactions are adverse drug reactions that are not related to the pharmacological properties of the drug).
- For INH it has been suggested that reactive metabolites, (?hydrazine) rather than the parent drug, are responsible for the idiosyncratic reactions.
- For rifampin, it is thought to be due to interference with bilirubin excretion
Liver Parameter Patterns from TB Medications

- INH, PZA more likely to cause increased transaminases
- Rifamycin more likely to cause obstructive picture
  - Rifabutin just as effective against TB but less P450 system and hepatic interactions and in our experience better tolerated in patient with evidence of liver disease
- EMB, CS, Aminoglycosides mainly renally excreted. Ofloxacin and Levofloxacin mainly renally excreted-Moxifloxacin has more hepatic metabolism
Recommended Monitoring of Liver Parameters During Treatment for Active TB Disease

- Face-to-face monthly assessments and patient education for adverse drug events are essential.
  - If symptomatic, hold meds pending labs/further evaluation
  - Rash and elevated liver enzymes very ominous

- Baseline measurements of serum transaminases, bilirubin, alkaline phosphatase, and creatinine, and a blood platelet count are recommended for all adults beginning treatment for TB disease.

- Routine measurements during treatment are recommended when baseline abnormalities are present and for patients who chronically consume alcohol, take other potentially hepatotoxic medications, or who have viral hepatitis or history of liver disease, HIV infection, or prior TB DILI (ALT q2-4 weeks).

- Some providers prefer to monitor ALT in women or older adults being treated for TB disease.
Figure 3. Monitoring for hepatotoxicity during treatment of TB disease. Dotted lines signify management according to physician’s discretion. ALT = alanine aminotransferase; AST = aspartate aminotransferase; HCV = hepatitis C virus; HepBsAg = hepatitis B surface antigen.
Figure 2. Flow chart monitoring the liver function prior to and during tuberculosis (ITBI) treatment, and the management of antituberculosis drug-induced hepatotoxicity (ATDH), based on the American Thoracic Society guidelines. ALT, alanine aminotransferase; INH, isoniazid; LF, liver function; PZA, pyrazinamide; RIF, rifampicin; ULN, upper limit of normal. *In patients with baseline serum ALT of more than three times ULN, several regimens without PZA and, if necessary, with a fluoroquinolone or cyclosporine are recommended. *Risk groups in which screening for viral hepatitis is recommended include intravenous drug users, patients from endemic areas (Asia, Africa, the Pacific Islands, Eastern Europe, or the Amazon region), sexual or household contacts of infected individuals, HIV-infected patients. If the patient is very sick or still smear-positive, some form of TB treatment should be given until liver function is normal.
Our Approach

- Always ask for symptoms
- Stop meds if symptomatic or if more than 3-5x normal (May continue meds in a closely observed environment-more likely to continue meds when increased transaminases vs. T. Bili and asymptomatic)
  - Markedly increased transaminase concentrations followed by jaundice imply severe liver disease with a 10% possibility of fulminant failure, a maxim known as “Hy’s Law,” after the late hepatologist and DILI expert Hyman Zimmerman
Our Approach

- Rule out other causes
  - Consider drug levels to assure not toxic (rare)
- Determine if need to be treated **for TB immediately** (Liver Sparing vs. No meds)
- Allow transaminases to return to “normal” or “baseline”
Re-challenge Approach

- MUST BE DONE WITH CLOSE SUPERVISION/MONITORING AND UNDERSTANDING OF PATIENT TO NOTIFY OF ANY SYMPTOMS

- Try to determine if elevation was felt to be cholestatic versus transaminase
  - Determine first if can try to adjust meds if not too ill
  - If elevated transaminases:
    - Does the patient still need PZA (have they gotten more than 2 months of meds) and if susceptibilities have not come back also assure (consider HAINS or MDST test) that they are not resistant to one of the meds being used and no longer need it
    - try to stop INH and continue with rifabutin (we like using Rbt in patients with increased LFTs) and EMB/PZA-remember still can cure someone with R/E/Z for 6 mths-try not to stop PZA early as this would prolong treatment-this is somewhat contrary to ATS approach that favors stopping PZA somewhat more conservatively
    - Consider BIW (some studies suggest less toxicity) therapy if patient has gotten more than two weeks of meds and is not HIV (+)
Re-challenge Approach

- If elevated due to cholestasis:
  - Rule out other causes:
    - Sonogram
      - If gallstones consider ursoldiol
    - Viral Serologies
      - See this pattern with HCV commonly (see later case)
      - Remember Gilbert’s Syndrome-affects 5-10% of the population
        Asymptomatic elevation of T. Bili, almost exclusively indirect Bili, one
        way to test for this syndrome is by administering Rifampin 900mg.
      - Try switching to rifabutin and BIW
      - If this does not work and patient is HCV/HBV positive consider therapy
        for HCV/HBV (see later case)
  - Consider drug levels to assure TB meds are in expected range
  - If all else fails consider Liver Sparing regimen of EMB/FQN and/or CS
    or SM for 18 mth regimen
CASE 2

- W.Z., 45 Y.O., HX OF ALCOHOL ABUSE
- DIAGNOSED WITH ACTIVE TB
- BASELINE LFT’S NORMAL
- STARTED ON INH, RIFAMPIN, ETHAMBUTOL AND PYRAZINAMIDE
CASE 2

- AFTER 1 MONTH OF THERAPY, AST, ALT AND TOTAL BILIRUBIN WERE 6X, 3X, AND 2X NORMAL RESPECTIVELY
- HE WAS ICTERIC, FEBRILE AND HAD AN ENLARGED, TENDER LIVER
CASE 2

- Abdominal sonogram: Enlarged liver, normal gallbladder, duct and pancreas

- Hepatitis C Ab positive, HIV negative

- Hep C ribosomal RNA @ high levels
CASE 2

- Every time Rifampin/Rbt was re-introduced, transaminases and bilirubin rose again
What Would You Do Now?

1. Restart INH/Rbt and continue treating despite the elevated liver parameters and symptoms
2. Use a liver sparing regimen
3. Try treating the HCV and reintroducing Rbt/EMB
CASE 2

- Liver biopsy showed active inflammation, cirrhosis, consistent with hepatitis C and alcohol-induced damage
- α-interferon was started, with normalization of liver function tests
- INH and Rifabutin restarted uneventfully
Anti-TB Drug Induced Hepatotoxicity (ATDIH): The Role of Hepatitis C Virus (HCV) and HIV

- Traditionally alcohol use, increasing age and presence of liver disease was associated with developing ATDIH.

- Those at risk for HIV, the elderly, substance abusers and immigrants from countries with high incidence of TB are more likely to develop active TB.

- These same groups at increased incidence of infection with HCV.

### TABLE 2
AGE AS A RISK FACTOR

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<tr>
<th></th>
<th>DIH</th>
<th>No DIH</th>
<th>HCV (+)</th>
<th>HCV (-)</th>
<th>HIV (+)</th>
<th>HIV (-)</th>
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<tbody>
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<td>23</td>
<td>4</td>
<td>26</td>
<td>16</td>
<td>14</td>
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<tr>
<td>Age &gt; 35</td>
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<td>83</td>
<td>36</td>
<td>62</td>
<td>28</td>
<td>70</td>
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*p = NS p < 0.02 p < 0.02*

Definition of abbreviations: DIH = drug-induced hepatitis; HCV = hepatitis C virus.

### TABLE 4
RELATIVE RISKS FOR DEVELOPING DRUG-INDUCED HEPATITIS

<table>
<thead>
<tr>
<th>Viral Serologies</th>
<th>Patients (n, %)</th>
<th>DIH (n, %)</th>
<th>Relative Risk</th>
<th>95% Confidence Limits</th>
<th>p Value</th>
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<tbody>
<tr>
<td>HCV (-) HIV (-)</td>
<td>55 (43)</td>
<td>3 (5)</td>
<td>1</td>
<td>—</td>
<td>—</td>
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<tr>
<td>HCV (+) HIV (-)</td>
<td>29 (23)</td>
<td>7 (24)</td>
<td>5</td>
<td>1.305–23.311</td>
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<tr>
<td>HIV (+) HCV (-)</td>
<td>33 (26)</td>
<td>7 (21)</td>
<td>4</td>
<td>1.114–19.541</td>
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<td>HIV (+) HCV (+)</td>
<td>11 (9)</td>
<td>5 (45)</td>
<td>14.44</td>
<td>2.740–76.135</td>
<td>0.002</td>
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* Significant when confidence interval does not include 1.
† Fisher's exact test. Significant when compared with patients without risk factors.
Four patients with HCV and HIV(-), developed recurrent ATDIH, unable to tolerate RIF/RBT and/or INH.

All underwent liver biopsy which revealed changes consistent with HCV.

All given α-IFN with resultant improvement in liver chemistries and able to tolerate RBT, and completed short course therapy.

Viral Hepatitis and ATDIH

- Other studies have confirmed increased risk of ATDIH with therapy for active TB disease
- Not clear if HCV associated with an increased risk for LTBI therapy (see later)
- Difficult to tell how much of liver parameter abnormalities due to virus versus drugs (“salt in wound effect”) due to “sine wave” pattern of liver parameters in patients with chronic active/persistent hepatitis due to HBV and HCV
- Most cases you can successfully treat with modifications of drug regimens as previously described
- Rarely, may need to treat underlying viral pathogen
Recommended Screening for Viral Hepatitis in TB patients

- Screening for viral hepatitis should be considered for individuals who inject drugs; were born in endemic areas of Asia, Africa, the Pacific Islands, Eastern Europe, or the Amazon Basin;
- HIV infected;
- may have had sexual or household contact with chronically infected individuals;
- may have had occupational exposure to infected blood;
- are chronic hemodialysis patients;
- are recipients of clotting factors before 1987;
- have undiagnosed liver disease;
- Are recipients of blood or solid organ transplants before 1992
- Infants born to infected mothers should also be considered for screening.
CASE 3

- 43 yo AA female with a history of HIV for 11 years presented to a hospital with a 2 month history of cough, fevers, and weight loss of 50 pounds over 1 year
- CXR showed right perihilar lymphadenopathy
Case 3

- Sputum was AFB smear (+), HAINS (+) rpoB mutation and subsequently culture positive for TB and confirmed rifampin resistance on DST
- The patient was sent home on RIPE with SM and FQ pending DST results
- Patient had not been on HIV meds for 2 years due to non adherence and not started on HIV meds at this time due to starting TB meds first
Case 3

- Patient was clinically improving but ~2 months after starting TB therapy the patient started developing N/V and abdominal pain.
- Patient went to the Emergency Room and was found to have an Alk Phos 479, AST 2527, ALT 1216 and Tot Bili of 1.1
- The patient admitted to be drinking ETOH 6-12 beers/day
- HAV IgM (-), HBV SAg (-), HCV Ab (-)
- CD4 123 (up from 17 at time of TB diagnosis)
Case 3

- All meds held but Liver parameters remained elevated; AST 3351, ALT 3274 and T. Bili 0.5
- MRI of Abd performed
Case 3

Liver Biopsy showed mild inflammation with periportal fibrosis with ballooning degeneration with acidophilic bodies seen. No granulomas are seen. AFB and gram stains were negative.

The patient continued to have high liver function tests which remained elevated despite being off the TB meds and the patient was transferred to A. G. Holley Hospital for further care.
Case 3

- On admission, patient’s meds were held until AST/ALT decreased.
- Patient found to be HSV IgM (+) and treated with acyclovir.
- After acyclovir and off meds AST/ALT ~500 range with normal T.
  Bili
- Patient started on EMB/Levoquin/SM with continued decrease of LFTs which eventually normalized.
- INH added without incident.
- Patient started on ARV (atripla) with slight increase in LFTs, but patient asymptomatic and drugs continued and LFTs normalized.
- Patient completing 18 mths of TB therapy.
When patients are acutely ill from TB or have TB of Liver may have to continue to treat and not stop drugs but may need to use liver sparing agents, IV agents, decompression procedures, steroids.

Especially seen in HIV or immunosuppressed individuals:
- May not see lesions on Sono/CT or even biopsy
- Can be seen in IRIS usually with increased alk phos out of proportion to rest of enzymes
- Gets better with continued therapy
- Voluntary HIV counseling and testing are recommended for all patients with TB disease.

APPROACH-try to continue meds-if really bad first with liver sparing and then try to get on rifabutin to shorten therapy and reintroduce meds as tolerated.
Special Situations
LTBI Therapy in Patients at Risk For ATDIH

- LTBI Therapy and elevated transaminases-INH DIH occurs ~0.5% overall (ATS Hepatotoxicity of ATT Official Statement 2006) but higher in individuals with pre-existing conditions
  - There does not clearly seem to be an increase risk of ATDIH in pts with HCV and LTBI Rx

- **Must weigh risks of treatment vs. risk of developing TB** (Lower Benefit/Risk Ratio for LTBI as opposed to TB Disease)

- Can try alternative therapy such as RIF/rifabutin for 4 mths after active disease ruled out
Figure 1. Latent tuberculosis infection (LTBI) pretreatment clinical evaluation and counseling. Dotted lines signify management according to physician’s discretion. ALT = alanine aminotransferase; DILI = drug-induced liver injury; INR = international normalized ratio; PTT = partial thromboplastin time; ULN = upper limit of normal.
Liver Monitoring During LTBI

- Face-to-face clinical assessments are the cornerstone of clinical monitoring for treatment adherence and adverse effects.
- Provider checklists for questioning patients should include adverse effects of anti-TB drugs and use of alcohol and other potentially hepatotoxic drugs.
Liver Monitoring During LTBI

1. Baseline blood tests are generally not recommended for healthy patients treated with isoniazid or rifampin.
   - Baseline laboratory testing should be considered individually for patients receiving other medications and for those with chronic medical conditions.

2. Baseline and follow-up serum ALT and bilirubin are recommended for patients with:
   - a possible liver disorder;
   - those with a history of chronic liver disease (e.g., chronic hepatitis B and C, alcoholic hepatitis, and cirrhosis),
   - patients with chronic use of alcohol,
   - those with HIV infection and/or treated with HAART,
   - pregnant women, and those who are up to 3 months postpartum.
Liver Monitoring During LTBI

Some experts recommend that healthy individuals older than 35 years treated with isoniazid or isoniazid with rifampin have baseline and scheduled monitoring of ALT.

- Monitoring schedules in such cases may be monthly; every other month; or at 1, 3, and 6 months in those taking a 9-month regimen, depending on the perceived hepatotoxicity risk, effectiveness of patient education, and the stability of ALT.
Figure 2. Monitoring for hepatotoxicity during LTBI treatment. Dotted lines signify management according to physician's discretion. ALT = alanine aminotransferase; AST = aspartate aminotransferase; HAV = hepatitis B virus; HCV = hepatitis C virus; HepBsAg = hepatitis B surface antigen; ULN = upper limit of normal.

Pregnancy, LTBI Treatment and Hepatitis

- No increased risk of teratogenicity with INH and Rif

- However, pregnant women in the third trimester and in the first 3 months of the postpartum period may be at higher risk for the development of hepatitis
  
  - Usually wait 3 mths after delivery due to increased risk of hepatitis
  
  - If immunosuppressed or recent contact treat during pregnancy but close monitoring recommended of LFTs
LTBI therapy in patients awaiting/recently received a Liver Transplant (LT)

- In a recent systemic review (Holty et al Liver Transpl 2009;15:894-906), isoniazid treatment was associated with a significant reduction in MTB reactivation in LT patients versus no treatment (0.0% versus 8.2%, P = 0.02), and isoniazid hepatotoxicity occurred in only 6% of treated patients, with no reported deaths.

- May use INH and monitor closely (Significant incidence of discontinuation for “adverse effects”)

- Many like Rbt for 4 mths but rule out active TB (esp extrapulmonary TB in these immunosuppressed individuals)
  - If use Rbt and patient on immunosuppressant Rx to prevent rejection may consider levels on both Rbt and anti-rejection meds.
Several studies have indicated that alcohol use was a significant predictor of TB DILI. Increased metabolism may interfere with the effectiveness of therapy:
- Try to get pt to stop drinking (not easy)
- ? legal intervention
- Monitor closely
TB Disease and Cirrhosis

- Similar approach as ATDlH
  - Try to use Rbt and if possible PZA to shorten therapy
  - Consider Urosodiol (Actigall)
  - Liver Sparing Regimens

- Many times patient’s lifespan less than TB therapy and treat with regimen which treats patient and makes them not contagious (eg to protect others in congregate setting such as hospice) but not necessarily cure them (eg liver sparring regimen)
THANK YOU!!

1-800-4TB-INFO
Southeast National TB Center/
A.G. Holley Hospital/ FL DOH
TB HOTLINE
Hepatic Dysfunction

- Use renally excreted drugs (EMB, quinolones, aminoglycosides, CS)
- Allow liver to cool off
- Give twice weekly doses
- Rifabutin vs. Rifampin

- Adjunct agents
  - Actigall
  - Interferon Alfa

- Monitor