What to do with TB adverse drug reactions?

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Objectives

• Identify the potential adverse events that are associated with medications (first line and second line) used to treat tuberculosis disease to ensure optimum outcomes in patients with TB.
• Understand the appropriate evaluation and monitoring of patients being treated for tuberculosis to enable rapid identification and appropriate management of potential side effects.
• Recognize common and uncommon clinical manifestations of adverse effects to TB drugs in order to mitigate these in a timely manner and improve outcomes in patients with TB.
• Describe the risk of hepatotoxicity during treatment for tuberculosis and how to manage this complication to safely enable completion of treatment using an effective regimen.
Adverse Reactions to TB Medications

• TB medications have been in use since 1940’s
• Relatively safe but known adverse effects have been associated and well studied over this time though few studies recently
• Major adverse reactions (eg causing change in therapy and/or hospitalization) can cause significant morbidity and compromise treatment regimens for tuberculosis
  - “Virtual MDR”-stopping rifampin and or other first line medications causes prolonged therapy more often in US than actual X/MDR
• Knowing how to monitor and detect adverse reactions and proper interventions can improve treatment

Adverse Reactions to TB Medications

• Adverse reactions causing a change in treatment has been estimated to occur in 5-15% of patients prescribed Anti-TB medications (Omerand Tubercle 1996)
Serious Adverse Reactions in Canada

- Associated with:
  - Female Sex
  - Age over 60
  - Asian
  - HIV (+)
- PZA seemed to be associated with more adverse reactions than the other medications
Patient Tolerance Issues

• Besides Adverse reactions to TB medications, other tolerance issues arise that often make administering TB medications difficult

Common Problems in TB Treatment and Approach to Management

• Can’t swallow pills
• GI intolerance
• Adverse drug reactions
• Allergies

• Peripheral Neuropathy
• CNS Changes
• Drug interactions
• Renal failure
• 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
  - Quinolones
  - 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 or Zofran (for N/V)
  - Zyprexia/Ativan for psychological component of nausea/vomiting
- Divide doses

Allergies / Pruritis/Severe Dermatologic Reactions

- Pruritus very common
- Antihistamines/Topical Corticosteroids when localized
- Severe rash-desensitization (Steven-Johnson, Toxic Epidermal Necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome
  - Stop all meds as soon as diffuse, severe reaction noted especially if involves mucous membranes
  - Low doses given frequently and in gradually increasing doses
  - Do only where emergency treatment is available
Re-administration Protocol

<table>
<thead>
<tr>
<th>Solution</th>
<th>Volume</th>
<th>Concentration</th>
<th>Volume</th>
<th>Concentration</th>
<th>Volume</th>
<th>Concentration</th>
<th>Volume</th>
<th>Concentration</th>
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<tbody>
<tr>
<td>solution A</td>
<td>1 mL</td>
<td>7.5 mg/mL</td>
<td>solution C</td>
<td>1 mL</td>
<td>10 mg/mL</td>
<td>0.5 mL</td>
<td>10 mg/mL</td>
<td>0.5 mL</td>
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<td>10 mg/mL</td>
<td>0.5 mL</td>
<td>10 mg/mL</td>
<td>0.5 mL</td>
</tr>
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* A suspension was prepared by adding 5 tablets of isoniazid (300 mg) to a volume of 10 mL of 0.9% NaCl to a final concentration of 15 mg/mL.
* A suspension was prepared by mixing 1 capsule of rifampicin (600 mg) into a volume of 10 mL of 0.9% NaCl to a final concentration of 60 mg/mL.
* A suspension was prepared by mixing 1 capsule of ethambutol (500 mg) into a volume of 10 mL of 0.9% NaCl to a final concentration of 50 mg/mL.
* A suspension was prepared by mixing 1 capsule of streptomycin (600 mg) into a volume of 10 mL of 0.9% NaCl to a final concentration of 60 mg/mL.
Peripheral Neuropathy

- Symmetric polyneuropathy Early: paresthesias
- Late: sensory loss, ↓ reflexes, ↓ proprioception
- Predisposed in patients with: Alcoholism, diabetes, HIV infection, malnutrition
- TB drugs implicated: Isoniazid, ethionamide, cycloserine, linezolid (not B6 responsive), aminoglycosides
  - Note: overly high Vit. B6 doses (> 200 mg/d) can occasionally produce neuropathy
- Treatment Start Vit. B6 if not already done so (typically 100-150 mg/d)
- Stop/change TB drug therapy (if possible)
- Low dose TCAs or gabapentin (if refractory)

CNS Changes

- Depression/Change in Moods: INH, Cycloserine
  - Can cause sleepiness (best to give at night / before bedtime for LTBI therapy)
- Agitation: Fluoroquinolones, INH
- Psychosis: Cycloserine, INH
- Seizures: INH, ethionamide
- Remember: Pyridoxine (Vit B6) required with Cycloserine and Ethionamide; used with INH in pts with select risk factors
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
• Poncet’s Syndrome-reactive Arthritis associated with TB

Drug Interactions

• Phenytoin-? Neurontin
• Warfarin-? LMWH (New oral anticoagulants (NOACs) are affected by rifampin and not recommended to be used concomitantly at this time)
• 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
  - INH, rifampin, Moxifloxacin
- Give lower doses of drugs renally excreted as active agents
- Give after dialysis TIW
- Monitor-TDM

**TB Medication Associated Interstitial Nephritis (IN)**

- Usually associated rifampin but may be seen with INH
- Usually see bump in Cr while on therapy without any other apparent cause
- Can see Eosinophils on UA but diagnosis made on renal biopsy with eosinophils in interstitium
- Stop “offending” medication and start steroids
  - Usually rapid response to therapy
  - Recommended not to re-start offending medication
- No reports of IN associated with rifabutin
  - Anecdotally using steroids with Rbt with good results
Hepatic Issues and TB therapy

“A Situation Where Beer and TB Mixed Well”
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.

### 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.
“LFTs-Liver Function Test”-NOT!!!!

- 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.

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 1

• 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 1

• 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

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

• Hepatitis C Ab positive, HIV negative

• Hep C ribosomal RNA @ high levels
CASE 1

• 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 1

- 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


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### TABLE 2

<table>
<thead>
<tr>
<th>Age as a Risk Factor</th>
<th>DIH (%)</th>
<th>No DIH (%)</th>
<th>HCV (+) (%)</th>
<th>HCV (-) (%)</th>
<th>HIV (+) (%)</th>
<th>HIV (-) (%)</th>
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</thead>
<tbody>
<tr>
<td>Age &lt; 35</td>
<td>7</td>
<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>
<td>15</td>
<td>83</td>
<td>63</td>
<td>36</td>
<td>62</td>
<td>28</td>
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<td>p = NS</td>
<td>p &lt; 0.02</td>
<td>p &lt; 0.02</td>
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</table>

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

### TABLE 4

<table>
<thead>
<tr>
<th>Relative Risks for Developing Drug-Induced Hepatitis</th>
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<tr>
<td>Viral Serologies</td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>HCV (-) HIV (-)</td>
</tr>
<tr>
<td>HCV (+) HIV (-)</td>
</tr>
<tr>
<td>HIV (+) HCV (-)</td>
</tr>
<tr>
<td>HIV (-) HCV (+)</td>
</tr>
</tbody>
</table>

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Alpha IFN in ATDIH

- 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.

New HCV Therapies

- New therapies for HCV very effective at eradicating HCV
- Unfortunately, for now Harvoni (ledipasvir/sofosbuvir) and Rifampin is not recommended due to decreased serum levels and effectiveness of the anti-viral agents (Co-administration of LDV and SOF with rifampin resulted in a reduced $C_{max}$ and AUC by 77% and 72%)
CASE 2

• 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 2

• 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 2

• 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 2

• All meds held but Liver parameters remained elevated AST 3351, ALT 3274 and T. Bili 0.5
• MRI of Abd performed
Case 2

- 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 2

- 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
Approach to TB of Liver

- 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 INH/RPT weekly for 12 weeks or RIF/rifabutin for 4 mths after active disease ruled out

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### Three months of weekly rifapentine plus isoniazid is less hepatotoxic than nine months of daily isoniazid for LTBI

**Table 1**

<table>
<thead>
<tr>
<th>Demographic factors</th>
<th>RR (95%CI)</th>
<th>P value</th>
<th>Attributable risk %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per year increase</td>
<td>1.03 (1.02-1.05)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Female sex</td>
<td>2.70 (1.65-4.42)</td>
<td>0.0001</td>
<td>52</td>
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<tr>
<td>Race</td>
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<tr>
<td>White</td>
<td>1.00 (reference)</td>
<td>&lt;0.0001</td>
<td>38</td>
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<tr>
<td>Black</td>
<td>0.32 (0.17-0.62)</td>
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<tr>
<td>Asian</td>
<td>0.13 (0.04-0.43)</td>
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<tr>
<td>Other</td>
<td>1.32 (0.60-3.22)</td>
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<td>Ethnicity</td>
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<td>Non-Hispanic</td>
<td>2.22 (1.28-3.85)</td>
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<td>Not applicable (not US or Canada)</td>
<td>0.87 (0.11-6.76)</td>
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<td>Health factors</td>
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<tr>
<td>BMI, per km² increase</td>
<td>0.94 (0.91-0.99)</td>
<td>0.008</td>
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<tr>
<td>Elevated baseline AST</td>
<td>5.57 (3.31-9.37)</td>
<td>&lt;0.0001</td>
<td>80</td>
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<td>Anti-tuberculosis treatment factors</td>
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<tr>
<td>Treatment with 9H</td>
<td>4.55 (2.53-8.18)</td>
<td>&lt;0.0001</td>
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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

- 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
- 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.

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 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
Alcohol and Tuberculosis Treatment

- 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 ATDIH
  - 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 sparing regimen)
Southeast National TB Center
Hotline
1-800-4TB-INFO