Tuberculosis and Viral Hepatitis

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Disclosure

• None
Case 1

• 25 year old woman living in Minneapolis, MN working as a nursing assistant in a large public hospital.

• Presents with worsening cough for 3 months, occasional fevers and sweats.

• Mildly tachypneic, crackles in RUL, 3 tattoos, otherwise normal exam

• TST 1 year prior for work screen was neg. IGRA during evaluation is positive. CXR shows a RUL infiltrate

• Induced sputum cultures grow pan-sensitive TB
Case 1

• **HIV neg.** **WBC** = 5.6, serum **Creatinine** = 0.9, **ALT** = 25, **AST** = 26, **Bili** = 0.4, **Alk Phos** = 30

• Patient begins INH, Rif, Ethambutol, PZA with the public health department

• 2 weeks later, she reports, nausea, upset stomach and “not feeling well”

• **ALT** = 250, **AST** = 289, **Bili** = 1.4, **Alk Phos** = 60

• She takes no other medications or supplements, does not drink alcohol
Case 1

• What is the most likely culprit of the hepatitis?

1. She is drinking alcohol
2. She has a Gall Stone
3. Hepatitis C co-infection
4. Hepatitis B co-infection
5. Bad luck
Case 1

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Tuberculosis and Viral Hepatitis

When the Lung needs the Liver
Talk Objectives

• Describe the basic facts about Hepatitis B and Hepatitis C infections

• Identify unique features of tuberculosis and viral hepatitis co-infections

• Review the management of tuberculosis and drug-induced hepatitis
Tuberculosis

- Tuberculosis remains a world-wide health problem
- 8.6 million people ill with TB and 1.3 million died (2012).
- After HIV, second highest killer by a single infectious agent in the world
- Although the rate of TB infection is declining world-wide, it is slow and requires (1) strong public health measures, (2) accurate diagnosis and (3) aggressive treatment of active cases.
### Treating Tuberculosis

#### Common Side-effects of TB drugs

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI side effects</td>
<td>Ethionamide • Fluoroquinolones • Para-aminosalicylate (PAS) • Clofazimine • Rifabutin • Aminoglycosides</td>
</tr>
<tr>
<td>Headache</td>
<td>Fluoroquinolones • Ethambutol (EMB) • INH • Cycloserine • Ethionamide</td>
</tr>
<tr>
<td>Skin problems</td>
<td>Clofazimine • Cycloserine • Ethionamide • Rifabutin • PAS • EMB</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Clofazimine • Fluoroquinolones</td>
</tr>
<tr>
<td>Hepatotoxicity (early symptoms are anorexia and malaise, then abdominal pain, vomiting, jaundice)</td>
<td>INH • Rifabutin • Ethionamide • PZA • PAS • Fluoroquinolones • Rifampin (RIF)</td>
</tr>
<tr>
<td>Behavioral changes</td>
<td>INH • Cycloserine • Ethionamide • Fluoroquinolones</td>
</tr>
<tr>
<td>Musculoskeletal / joint / tendons</td>
<td>Fluoroquinolones • PZA • Rifabutin • INH (positive antinuclear antibody (ANA))</td>
</tr>
<tr>
<td>Visual changes, eye pain, change in color vision</td>
<td>EMB • Rifabutin • Clofazimine</td>
</tr>
<tr>
<td>Hearing loss, ringing in the ears, vestibular toxicity</td>
<td>Aminoglycosides • Capreomycin</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Aminoglycosides • Capreomycin / Fluoroquinolones</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>INH • Ethionamide • Cycloserine • Linezolid</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Ethionamide • PAS</td>
</tr>
<tr>
<td>Hypokalemia / hypomagnesemia</td>
<td>Aminoglycosides • Capreomycin</td>
</tr>
</tbody>
</table>
Tuberculosis and Hepatitis

• Reported incidence of hepatitis with first line anti-TB medications (INH, Rif, PZA) varies widely: **2.5-35%**

• The mechanism of drug induced hepatotoxicity is not fully understood

• Can be symptomatic or asymptomatic

Int J Tuberc Lund Dis 2004;8:1499
Am J Ther 2010 Jan-Feb;17(1):17
Liverfoundation.org
Tuberculosis and Hepatitis

- Causes symptoms
- Risks treatment interruption
  - Loss to follow up
  - Inducing drug resistance
  - Continued infectivity
- Death (3% vs. 13%)

Betterhealth.com

Am J Ther 2010 (1):17

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Tuberculosis and Hepatitis

• Factors that exacerbate hepatitis during treatment:
  • Advanced age
  • Female sex
  • Alcohol use
  • Malnutrition
  • HIV co-infection
  • Underlying Liver disease
  • HCV co-infection
  • HBV co-infection

Int J Tuberc Lung Dis 2004;8:1499
Talk Objectives

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Hepatitis C

• Positive single stranded RNA virus with an open reading frame

• Small, enveloped virus which is a member of the *Flaviviridae* family

• 1989 by Michael Houghton
HCV: Epidemiology

Hepatitis C, 2007

Prevalence of infection:
- >10%
- 2.5 - 10%
- 1 - 2.5%

Source: WHO, 2008. All rights reserved.
Hepatitis C in the US

1.3-1.9% Ever Infected with HCV

2.7-3.9 million in US Living with Chronic HCV

12,000 Annual Deaths Associated with chronic liver disease and HCV
Disease Burden of Patients Infected 20 Years or More is Peaking Now

Complications from chronic hepatitis C develop slowly over a period of 20–30 years

- Patients infected
- Infected > 20 y
HCV Infection

• 3.9 million Americans infected with HCV

• Over 170 million people worldwide are infected with HCV

• Leading cause for Liver transplantation in the US

CID 2001;32:492
www.CDC.gov
WHO.int
HCV Infection

• 150,000 new cases every year in the US
• 3% of the world’s population has been infected with HCV
• Annual costs of acute and chronic hepatitis C in the US is over $1 billion
• No Vaccine available
60% of HCV in the US is due to IV Drug Abuse
IVDU, Tattoos, Snorting cocaine, Sex, Peri-natal, Blood transfusion before 1991
Hepatitis C Virus
Natural History

40%

60%

HIV

Stage 1

Male
Smoking
Alcohol
HIV
Obesity

20%

Liver failure
HCC

Stage 4
Most Patients with Chronic Hepatitis C in the US Are Not Aware that They Are Infected

• ~3,300,000 individuals are infected with the hepatitis C virus in the United States

• Universal HCV Screening 1945-1965

Hepatitis C Treatment
NEUTRINO: SVR by Genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>SVR12 (%)</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>90</td>
<td>295/327</td>
</tr>
<tr>
<td>1</td>
<td>89</td>
<td>261/292</td>
</tr>
<tr>
<td>4</td>
<td>96</td>
<td>27/28</td>
</tr>
<tr>
<td>5, 6</td>
<td>100</td>
<td>7/7</td>
</tr>
</tbody>
</table>

Tuberculosis and HCV

• Limited data on the impact of viral hepatitis during TB treatment

• High incidence Country (Georgia)
  • 326 pt pulmonary pan-sensitive TB
  • Treated with INH, Rif, Ethambutol, PZA
  • 21% HCV co-infected

PLoS One 2013:8:12
• HCV co-infection was an independent risk factor for anti-TB drug hepatotoxicity
• 43% HCV+ vs. 18% HCV-
• HCV + developed toxicity faster than HCV -
• No medication discontinuation was required
Tuberculosis and HCV

• What about people with normal liver tests?
• 295 patients with pulmonary TB, normal liver tests at baseline (Hong Kong)
• 10% HCV positive
• On first line anti-TB therapy

Int J Tuberc Lung Dis 2010;14:616
HCV was a significant risk factor for drug induced hepatotoxicity

Onset of HCV hepatotoxicity was early

Hepatotoxicity was more prolonged

Hepatitis had an increased mortality, but not associated with viral hepatitis co-infection
Hepatitis B Virus

- 400 million
- 10% HIV + have HBV
- 20% in SE Asia
- 5% in N. America
Hepatitis B Structure

Health on the Net Foundation

2 positive HBsAg 6 months apart
Hepatitis B Virus

- Mostly dsDNA virus Hepadnaviriae
- Transmission
  - Parental
  - Perinatal
  - Sexual
- Asymptomatic $\Rightarrow$ fulminant hepatitis (2%)
- Integrates into host genome
Hepatitis B Treatment

• Goal of treatment = reduce liver damage, by decreasing viral replication
  
• Suppress viral replication as much as possible for as long as possible

• Prevent liver disease and HCC

Tuberculosis and HBV

• Many high incidence TB countries are also high incidence for HBV
  • Asia- 10% of population are HBV infected

• Active, replicating HBV can predict hepatotoxicity, but with low precision
  • Int J Tuberc Lung Dis 2010;14:332

• HBV infection resulted in a higher proportion of people developing drug-induced hepatotoxicity (34% vs 9%)
  • Hepatology 2003;31:200
Tuberculosis and HBV

- HBV infected individuals had more drug-induced hepatotoxicity than non-infected individuals
- Hepatotoxicity correlated with HBV DNA levels

Hepatology 2003;31:200
HBV and Tuberculosis

- 8% were HBV co-infected
- HBV + had a similar rate of hepatitis than HBV-
- Of those who developed hepatitis with HBV
  - Higher peak ALT
  - Occurred later in the course

Int J Tuberc Lung Dis 2010;14:616
Tuberculosis and Viral Hepatitis

Conclusions

• **Hepatitis C co-infection**
  - More likely to develop drug induced hepatitis
  - Occurs earlier in the course of treatment

• **Hepatitis B co-infection**
  - Mixed data on increasing risk of drug-induced hepatitis
  - When hepatitis occurs, there are higher markers of inflammation (ALT)
  - Occurs later in the course of treatment
Talk Objectives

• Understand the basic facts about Hepatitis B and Hepatitis C infections

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Managing Hepatitis During TB Treatment

General Principles

• Not unusual for patients just starting combination TB therapy to experience upset stomach
  • Pts need counseling that this is *NOT uncommon*
  • INH, Rifampin, PZA all can produce gastritis
    • Symptoms can be similar to hepatitis, but LFTs *remain normal*

• Patients who develop anorexia, nausea, vomiting, abdominal pain, jaundice – more concerning
  • Stop all medications promptly, examine patient and check LFTs
Managing Hepatitis During TB Treatment

General Principles

• ALT is more specific for hepatocellular injury
  • AST can also be produced from muscle, heart, etc.
• If AST > ALT, assess for excessive alcohol intake
• 10-20% of patients on INH will have asymptomatic rise in transaminases
  • Tends to occur during 1st few months on INH
  • Not a toxicity and does not require cessation of therapy
  • Improves with continuation of therapy
Managing Hepatitis During TB Treatment
Follow Up Assessments

• Stop meds with any abnormal LFTs and the presence of adverse symptoms
  • Some guidelines state adverse symptoms and transaminases ≥ 3 x upper limits of normal range

• If LFTs abnormal (AST or ALT > 5x upper limit of normal) or if bilirubin is elevated, with or without symptoms, all TB drugs should be promptly stopped

• Patient should have LFTs checked 1x – 2x weekly
  • If symptoms persist > 2 weeks off TB medications or if LFTs continue to worsen, then should suspect progressive hepatitis or an unrelated cause of hepatitis – may need hospitalization
    • E.g. HCV, HBV, HAV, other medications (non-TB); alcoholism, etc

• As soon as hepatitis is identified, viral hepatitis should be ruled out
Managing Hepatitis During TB Treatment

Important Notes

• If the patient has extensive pulmonary, meningeal or disseminated TB – then may not be able to temporarily observe off therapy:
  • Start a new combination drug regimen that is non-liver metabolized (i.e. EMB, FQ, AMK), while awaiting LFTs to improve:
    • Minimizing risk of further hepatotoxicity
    • May be started even before LFTs return to normal.

• Pattern of LFT abnormalities – clues to offending agent
  • Rifampin- **cholestatic pattern** (bilirubin & Alk phos. out of proportions to AST/ALT)
  • INH, RFP, PZA - **hepatocellular pattern** (AST/ALT elevated out of proportion to bilirubin or Alk phos)
Managing Hepatitis During TB Treatment

Restarting Drugs after LT improve

**Hepatocellular pattern:**
- Start with Ethambutol and Rifampin x 1 week
  - Recheck LFTs – if stable/improved:
- Add INH or PZA (either – which drug to add is debated)
  - Recheck LFTs – if they remain stable:
  - Continue with EMB / Rifampin / INH or EMB / Rifampin / PZA for the duration of therapy
    - At least monthly LFTs (more frequently early on)

**Notes:**
- INH and PZA are most commonly associated with hepatotoxicity
  - Some reports implication PZA more frequently
  - Combination using PZA may be more problematic
  - PZA less important in combination TB drug regimen

AJRCCM 2003 167:1472-77
Managing Hepatitis During TB Treatment Restarting Drugs after LT improve

**Cholestatic pattern:**
- Start with INH and ethambutol x 1 week
  - Recheck LFTs – if stable/improved:
- Add PZA
  - Recheck LFTs – if they remain stable:
  - Continue with INH/EMB/PZA – consider adding FQ
    - At least monthly LFTs (more frequently early on)

If symptoms are not related to TB drugs, then restart entire drug regimen promptly and observe
Restarting Anti-TB Medications in Patients with Drug-Induced Hepatitis

**Patient taking anti-TB drugs has symptoms consistent with hepatitis**

- **Discontinue medications**
  - Check LFTs and Hepatitis Screen
  - **Normal LFTs**/
  - Negative Hepatitis Screen whether symptoms improve or not related to anti-TB drugs
  - **Restart same regimen**
  - **Cholestatic LFT pattern initially**
  - **Rechallenge with INH, EMB for 1 week**
    - **Repeat LFTs**
    - If LFTs stable, add PZA
    - **Repeat LFTs**
    - If LFTs stable, treat with INH, EMB, PZA (assume Rif-induced hepatitis)
     - **Consider trial of RBT**
     - **Follow LFTs monthly for remainder of treatment**

- **Abnormal LFTs**/
  - Negative hepatitis screen
  - **Yes**
    - Is treatment absolutely essential?
    - **No**
      - **Give EMB, SMN, FQ** Follow LFTs weekly
    - When LFTs stable, rechallenge with EMB and INH for 1 week
    - **Repeat LFTs**
    - If LFTs stable, add PZA
    - **Repeat LFTs**
    - If LFTs stable, treat with INH, Rif, EMB, (assume PZA-induced hepatitis)
     - **Consider trial of Rifabutin**
     - **Follow LFTs monthly for remainder of treatment**

  - LFTs plateau or return to baseline
  - **Hepatocellular LFT pattern initially**
  - **Rechallenge with Rif and EMB (if not on it already) for 1 week**
    - **Repeat LFTs**
    - If LFTs worsen, discontinue Rif (and EMB) for 1 week
    - **Repeat LFTs**
    - If LFTs stable, add INH for 1 week
    - **Repeat LFTs**
    - If LFTs stable, add PZA for 1 week
    - **Repeat LFTs**
    - If LFTs stable, treat with EMB, Rif, PZA, ± FQ if extensive disease (assume INH-induced hepatitis)
     - **Follow LFTs monthly for remainder of treatment**
TB Eradication needs treatment
Treatment needs medications
Medications need the liver

Look for HBV and HCV co-infection!
Mayo Clinic Locations

- Rochester, Minnesota
- Mayo Clinic Health System
- Scottsdale and Phoenix, Arizona
- Jacksonville, Florida
Questions & Discussion