HEPATITIS VIRUSES

• Hepatitis A (HAV)
• Hepatitis B (HBV)
• Hepatitis C (HCV)
• Hepatitis D (HDV)
• Hepatitis E (HEV)
• Hepatitis G (HGV)
Hepatitis-related mortality, 2013

1.45 million deaths from viral hepatitis per year

Global Impact of Viral Hepatitis

- Viral hepatitis accounted for 1.45 million deaths in 2013, a 63% increase compared with the 0.89 million deaths in 1990.
- Increased morbidity - Years lived with disability
  - From 0.65 million to 0.87 million
- Increased morbidity - adjusted life-years
  - From 31.7 million to 42.5 million
- Most of the morbidity and mortality is caused by hepatitis B and C infections

Chronic Hepatitis and its Sequelae

Fibrosis
Chronic HCV infection can lead to the development of fibrous scar tissue within the liver.

Cirrhosis
Over time, fibrosis can progress, causing severe scarring of the liver, restricted blood flow, impaired liver function, and eventually liver failure.

Hepatocellular Carcinoma (with cirrhosis)
Cancer of the liver can develop after years of chronic HCV infection.

Decompensated cirrhosis:
- Ascites
- Bleeding gastroesophageal varices
- Hepatic encephalopathy
- Jaundice
Talk Objectives

• Understand the basic facts about Hepatitis B
• Understand the basic facts about Hepatitis C
• Identify unique features of tuberculosis and viral hepatitis co-infections
• Review the management of tuberculosis and drug-induced hepatitis
240 million people are chronically infected with hepatitis B
More than 686,000 people die every year due to complications of hepatitis B

Adopted and modified from CDC website: http://www.cdc.gov/Features/dsHepatitisAwareness/
Hepatitis B Virus

- **Transmission**
  - Parental
  - Perinatal
  - Sexual

- **Chronic infection develops in**
  - 80-90% of those infected as infants
  - 30-50% of children <6 years
  - <10% of those infected as adults

- **Chronic infection can lead to chronic liver disease, cirrhosis, liver cancer or liver failure, usually over 20-30+ years**
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

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: Transmission

60% of HCV in the US is due to IV Drug Abuse
IVDU, Tattoos, Snorting cocaine, Sex, Peri-natal,
Blood transfusion before 1991

cdc.gov
HCV distribution across the world

130–170 million people worldwide are infected with HCV

Prevalence of HCV
- >10%
- 5–10%
- 2–5%
- 1–2%
- <1%
- No data

* Estimated number of chronically infected individuals (2010)

Hepatitis C in the US

150,000 new cases every year in the US
Annual costs of acute and chronic hepatitis C in the US is over $1 billion
Baby Boomers (Born in 1945–1965) Account for 76.5% of HCV in the US

An estimated 35% of undiagnosed baby boomers with HCV currently have advanced fibrosis (F3-F4; bridging fibrosis to cirrhosis)

Mortality associated with Hepatitis B, Hepatitis C, and HIV
United States, 1999 – 2008

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td>0.0</td>
</tr>
<tr>
<td>1970</td>
<td>0.0</td>
</tr>
<tr>
<td>1980</td>
<td>0.0</td>
</tr>
<tr>
<td>1990</td>
<td>2.0</td>
</tr>
<tr>
<td>2000</td>
<td>2.0</td>
</tr>
<tr>
<td>2010</td>
<td>1.0</td>
</tr>
<tr>
<td>2020</td>
<td>1.0</td>
</tr>
<tr>
<td>2030</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Davis GL. Rev Gastroenterol Disord 2004;4:7-17.
Evolution of Standard of Care in HCV Therapeutics

Webster DP, et al. The Lancet 2015 385, 1124-1135DOI: (10.1016/S0140-6736(14)62401-6)
Reported SVRs of IFN-free, Multi-DAA Rx

ION1, 12Weeks: 98%
ION1, 24Weeks: 99%
ION2, 12Weeks: 95%
ION2, 24Weeks: 99%
ION3, 8Weeks: 94%
ION3, 12Weeks: 95%
SAPP1, 12Weeks: 97%
SAPP2, 12Weeks: 97%
TURQ2, 12Weeks: 92%
TURQ2, 24Weeks: 96%
HALLD, GT1b, Cirrhosis, TN: 91%
HALLD, GT1b, Cirrhosis, TE: 85%
BMS3DAA, Mixed: 93%
CWOR, 12Weeks, Cirrhosis, TN: 94%
CWOR, 18Weeks, Cirrhosis, TN: 97%
CWOR, GT1a, Cirrhosis, Null: 94%
CWOR, GT1b, Cirrhosis, Null: 100%
Impact of Treatment on Liver Failure

Impact of Treatment on HCC

Treatment Reduces All-Cause Mortality in Patients With Advanced Fibrosis

HCV Screening Guidelines

- Anyone born between 1945 and 1965
- HIV-infected
- History of illicit injection drug use or intranasal cocaine use, even if only used once
- Received clotting factors made before 1987
- Ever on chronic hemodialysis
- Persistently elevated ALT level
- Informed that they received blood from a donor who later tested positive for HCV
- Received blood/organs before July 1992
- Children born to HCV-infected mothers.
- Needle stick injury or mucosal exposure to HCV+ blood

Tuberculosis and Viral Hepatitis

When the Lung needs the Liver
## 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, INH, Ethambutol (EMB), Cycloserine, Ethionamide</td>
</tr>
<tr>
<td>Skin problems</td>
<td>Clofazimine, INH, Rifabutin, PAS, Ethionamide, 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, Rifabutin, 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>Cycloserine, Fluoroquinolones, Aminoglycosides / capreomycin (as manifestation of vestibular toxicity)</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 Lung 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%)
Tuberculosis and Hepatitis

Factors that exacerbate hepatitis during treatment:

- Advanced age
- Female sex
- Alcohol use
- Malnutrition
- HIV co-infection
- Underlying Liver disease
- HBV co-infection
- HCV co-infection

(Int J Tuberc Lung Dis 2004;8:1499)
**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 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

Int J Tuberc Lung Dis 2010;14:616
Managing Hepatitis During TB Treatment

- Resuming Treatment
- Educating patients
- Prevention
- Early Identification
- Systematic Evaluation
- Isolation Cause
- Managing Reaction

Managing Reaction
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 implicate 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 LFTs¹ / Negative Hepatitis Screen: whether symptoms improve or not related to anti-TB drugs
  - Restart same regimen

- Abnormal LFTs¹ / Negative hepatitis screen
  - Is treatment absolutely essential?
    - Yes
      - Give EMB, SMN, FQ
      - Follow LFTs weekly
    - No
      - Discontinue treatment
      - Follow LFTs weekly

- 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, PZA² (assume RIF-induced hepatitis)
        - Consider trial of RBT³
      - Follow LFTs, if LFTs stable 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 week¹
    - Repeat LFTs
    - If LFTs worsen, discontinue RIF (and EMB) for 1 week
    - When LFTs stable, rechallenge with EMB and INH for 1 week
    - Repeat LFTs
    - If LFTs stable, add INH for 1 week
    - If LFTs stable, add PZA for 1 week
        - When LFTs stable, treat with INH, RIF, EMB (assume PZA-induced hepatitis)
        - Repeat LFTs
        - If LFTs stable, add PZA for 1 week
        - If LFTs stable, add PZA for 1 week
            - When LFTs stable, treat with EMB, RIF, PZA, ± FQ if extensive disease (assume INH-induced hepatitis)
            - Follow LFTs monthly for remainder of treatment

- If LFTs stable
  - Treat with INH, EMB, PZA² (assume RIF-induced hepatitis)
  - Consider trial of Rifabutin²
  - Repeat LFTs, if LFTs stable
  - 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!
Questions & Discussion