Beyond HCV: An Update on Hepatitis B, D, and E Viruses

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Learning Objectives
After attending this presentation, learners will be able to:

- Describe the natural history of HBV infection
- Identify who should be treated for HBV infection and which antiviral agents to choose
- Describe the clinical presentation and management of HDV infection
- Understand the epidemiology of HEV in the United States

Epidemiology of HBV

- 350 million chronically infected & leading cause of cirrhosis worldwide
- 1.25 million chronically infected in the United States
Serologic Markers in HBV Infection

- **HBeAg**
  - Indicates ongoing viral replication
  - Levels correlate with replication and infectivity

- **Anti-HBc**
  - Antibody to the HBV core antigen can be used as a marker of infection

- **HBsAg**
  - Marker of immunity to HBV

- **Anti-HBs**
  - Indicates ongoing viral replication
  - Levels correlate with replication and infectivity

Complications of HBV Infection

- Chronic Hepatitis B is the 6th leading cause of liver transplantation in the US

CHB Treatment Guidelines

<table>
<thead>
<tr>
<th>Guidelines/Algorithm</th>
<th>HBsAg+</th>
<th>HBsAg-</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBV DNA (IU/mL)</td>
<td>ALT (IU/L)</td>
</tr>
<tr>
<td>AASLD 2009p</td>
<td>&gt;20,000</td>
<td>&gt;2x ULN or (+) biopsy</td>
</tr>
<tr>
<td>US Treatment Algorithm 2008p</td>
<td>≥200,000</td>
<td>&gt;ULN or (+) biopsy</td>
</tr>
<tr>
<td>EASL 2009p</td>
<td>≥2000</td>
<td>&gt;ULN or (+) biopsy</td>
</tr>
<tr>
<td>APASL 2008p</td>
<td>≥200,000</td>
<td>&gt;2x ULN or (+) biopsy</td>
</tr>
</tbody>
</table>

AASLD, American Association for the Study of Liver Diseases; APASL, Asian Pacific Association for the Study of the Liver; EASL, European Association for the Study of the Liver; ULN, upper limit of normal.
HBV Treatment Regimens

<table>
<thead>
<tr>
<th>PegIFN α-2a*</th>
<th>Lamivudine</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Telbivudine</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>Subcutaneous</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Dose</td>
<td>180 μg/wk</td>
<td>100mg/day</td>
<td>10 mg/day</td>
<td>0.5mg/day</td>
<td>600 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>600 mg/day</td>
<td>300 mg/day</td>
</tr>
<tr>
<td>Duration</td>
<td>48 wks</td>
<td>Indefinite</td>
<td>Indefinite</td>
<td>Indefinite</td>
<td>Indefinite</td>
</tr>
<tr>
<td>Resistance</td>
<td>None</td>
<td>High</td>
<td>Moderate</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Anti-HIV</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>1st line?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*Standard IFNα is also approved for CHB

- Renal dosing necessary; Dose entecavir higher in lam-resistant disease

When to Consider PegIFN

- Favorable predictors of response[^1-2]
  - Low HBV DNA*
  - High ALT*
  - Genotype A or B > C or D[^3-5]
  - Not advanced disease

- Patient demographics[^1,2]
  - Generally young people
  - Young women wanting pregnancy in near future
  - Absence of comorbidities
  - Patient preference[^2]
  - Concomitant HCV infection


5-Yr Resistance Rates, Treatment Naïve Patients

<table>
<thead>
<tr>
<th>Cumulative Resistance Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>70</td>
</tr>
</tbody>
</table>

High barrier to resistance; preferred 1st line therapy

[^1]: Tenofovir rate determined at Yr 2.

[^2]: Telbivudine rate determined at Yr 2.

Virologic Breakthrough and Rebound


HBV DNA (log10 IU/mL)
ALT (U/L)

Virologic breakthrough
Hepatitis flare
Biochemical breakthrough
ULN

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HBV Primary Resistance Mutations


rtM204V/I LAM resistance
rtA181T/V ADV/TDF resistance*
rtM204I LDT resistance
rtN236T ETV resistance
rtA181T/V ADV/TDF resistance
rtL180M ETV resistance
rtA181T/V ADV/TDF resistance
rt184S/A/I/L/G/M ETV resistance
rtM204V ADV/TDF resistance
rtS202G/C/I
rtM250I/V

*Based on in vitro data and therapy switch following emergence of genotypic ADV resistance.

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Hepatitis D (Delta) Virus

- Small, defective RNA virus
- Requires HBsAg for transmission and packaging
- HBV DNA usually negative or low due to suppression by HDV
Geographic Distribution of HDV
- 350 million chronic HBV infected worldwide: 15 million with evidence of HDV exposure
- In general, highest rates of HDV in HBV endemic areas

Forms of HDV Infection
- Coinfection of HBV and HDV:
  - More severe acute hepatitis and higher mortality compared to acute HBV monoinfection
  - Fate of HDV determined by host response to HBV
- HDV superinfection of a HBV carrier:
  - Can manifest as an acute hepatitis in HBV carrier
  - Usually results in chronic HDV infection
- Consequences of chronic HBV/HDV:
  - Higher risk of cirrhosis, liver decompensation, and possibly HCC

Diagnostic Markers in HDV

<table>
<thead>
<tr>
<th>Marker</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HDV IgM</td>
<td>+ in acute HDV; Can persist in chronic infection; Used as surrogate for HDV replication</td>
</tr>
<tr>
<td>Anti-HDV IgG</td>
<td>Indicates HDV exposure; May persist with viral clearance</td>
</tr>
<tr>
<td>HDV RNA qualitative</td>
<td>Marker of HDV replication; + in chronic infection</td>
</tr>
<tr>
<td>HDV RNA quantitative</td>
<td>Useful to monitor treatment response</td>
</tr>
<tr>
<td>HBsAg quantitative</td>
<td>May be useful to monitor treatment response; ↓ may heralds HBsAg loss and HDV clearance</td>
</tr>
<tr>
<td>HBV DNA quantitative</td>
<td>Usually negative or low because suppressed by HDV</td>
</tr>
<tr>
<td>ALT</td>
<td>Usually ↑; Correlates poorly with histology</td>
</tr>
</tbody>
</table>

Adapted from Hughes S. Lancet 2011; 378: 73-8.
Treatment of HDV

- PegIFNα for 48 weeks+

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>N</th>
<th>Follow-up</th>
<th>Virologic Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castelnau, 2006</td>
<td>PEG-IFNα2a 1.5 μg/kg/wk x 12 months</td>
<td>14</td>
<td>16 months (median)</td>
<td>43%</td>
</tr>
<tr>
<td>Erbank, 2006</td>
<td>PEG-IFNα2a 1.5 μg/kg/wk x 12 months</td>
<td>12</td>
<td>6 months</td>
<td>17%</td>
</tr>
<tr>
<td>Niro, 2006</td>
<td>PEG-IFNα2a 1.5 μg/kg/wk x 12 months</td>
<td>16</td>
<td>6 months</td>
<td>29%</td>
</tr>
<tr>
<td>Wedemeyer, 2011</td>
<td>PEG-IFNα2b 180 μg/wk + adefovir</td>
<td>29</td>
<td>6 months</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>10 mg/day x 48 wks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PEG-IFNα2b 180 μg/kg x 48 wks</td>
<td>31</td>
<td>30%</td>
<td></td>
</tr>
</tbody>
</table>

* Trial of 120 pts receiving PEG-IFNα2b 180 μg/kg x 48 wks +/− adefovir x 2 years is ongoing:
  * Week 48 HDV RNA undetectable: 42% PEG + TDF, 34% PEG + placebo
  * Phase 2 trial of prenylation inhibitor (Lonafarnib) currently enrolling at NIH

Management of HDV

- HBsAg
- Anti-HDV IgG Ab
- Treat per HBV guidelines
- HBV DNA >2,000 IU/mL
- Add Ribavirin
- Consider PEG-IFNα for at least 48 wks
- Liver biopsy
- HCV RNA +
- Consider adding potent nucleos(t)ide analog
- Reactivation of HBV
- Add potent nucleos(t)ide analog
- Adapted from Hughes S. Lancet 2011; 378: 73–8.

Hepatitis E Virus

- Single-stranded, nonenveloped RNA virus of the Hepeviridae family
- Unknown mode of hepatocyte entry
- 5 genotypes identified: genotypes 1–4 infect humans
**Epidemiology of HEV**

- Endemic in multiple Asian and African countries

**Epidemiology of HEV**

- Genotype 1: Asia
- Genotype 2: Central America, Africa
- Genotype 3: US, Japan
- Genotype 4: Eastern Asia

**Classic Epidemic HEV**

- Genotypes 1, 2
- Most common cause of acute hepatitis in endemic areas
- No known animal reservoir
- Fecal-oral transmission; large water-borne outbreaks
- Typically occurs in adolescents/young adults
- High rate of jaundice, cholestasis
- High fatality rate among pregnant women
- Consider if acute hepatitis and recent travel to endemic area
Autochthonous HEV

- Genotypes 3, 4
- Typically transient, anicteric, and asymptomatic
- Fatality rate is not increased in pregnant women
- Can become chronic in immunosuppressed patients
- Consider in patients with:
  - Unexplained hepatitis, particularly if older, solid organ transplant recipient, or HIV+
  - Acute decompensation of chronic liver disease

Individual cases and small outbreaks linked to zoonotic spread

- Case reports from undercooked deer, undercooked pig liver, shellfish
- HEV RNA has been isolated in commercially available pig liver and sausage
- Cases reports have linked HEV to blood transfusions, donated organs
- Most patients have no specific risk factors

Diagnosis of Acute HEV

- +Anti-HEV IgM
  - Commercially available
  - Not formally approved by the FDA
  - Sensitivity/Specificity of assays vary widely
- Confirmatory test: HEV RNA
  - Not commercially available
  - Contact NIH
Acute HEV and HIV

Chronic HEV and HIV

Chronic Infection
Treatment of Chronic HEV

- Solid organ transplantation
  - Reduction of immune suppression → 1/3 spontaneously clear
  - Antiviral therapy: RBV x 3 months → RBV x 6 months or pegIFN x 3 months → RBV + pegIFN x 3-6 months
- HIV
  - Unlikely to spontaneously clear despite immune reconstitution with ART
  - Case reports (5 patients) treated with pegIFN +/- RBV or RBV monotherapy
- No established guidelines or approved regimens


Summary

- HBV is the leading cause of cirrhosis worldwide
- HDV causes accelerated liver disease progression
- Chronic HEV infection leads to rapid development of cirrhosis
- Reliable antibody assays and molecular tests for HDV and HEV are needed
- PEG-IFN continues to have a role in viral hepatitis beyond HCV