Hepatitis B: An Update 2005

Donald M Jensen, MD, FACP
Professor of Medicine
Director, Center for Liver Diseases
University of Chicago

Viral Hepatitis

- What is “viral hepatitis”?
  - What is “hepatitis”?  
  - How many hepatitis viruses are there?

- Hepatitis B
  - Who is at risk?
  - What can happen if you have it?
  - What treatment is available?
  - Are there new treatments on the horizon?

Hepatitis

- “Hepatitis” simply means liver inflammation (hepar = liver; -itis = inflammation)
- Many causes of “hepatitis”
  - Viruses (A, B, C, D, E, CMV, EBV...)
  - Alcohol
  - Drugs and medications
  - Autoimmunity
  - Metabolic and genetic diseases
  - Others

Hepatitis

- Typically, “hepatitis” is suggested by laboratory signs of damage to liver cells.
- AST (SGOT) and ALT (SGPT) are enzymes that are abundant within liver cells and leak into the bloodstream when the liver cell membrane is damaged.
  - These are non-specific
  - The height of the enzyme level in the blood correlates with amount of damage, but not with the overall liver function or outcome.
If there is evidence of liver damage, we first try to determine the cause (etiologic):
- An accurate history is essential
- A good physical examination can offer additional clues
- Confirm or exclude options with laboratory testing
- Scans and X-rays are not very helpful

Laboratory testing:
- Viral hepatitis: IgM HAV, HBsAg, HCV Ab
- Autoimmune: ANA, ASMA, LKM, P-ANCA
- Alcohol: no specific lab test; AST>>ALT
- Drugs / medications: history

Viral hepatitis:
Five major hepatitis viruses: A, B, C, D, E
Three clinical patterns and outcomes:
- Acute hepatitis with resolution and immunity
  - Less than 3-6 months duration
  - Immunity specific to the type of virus
- Chronic hepatitis w/ or w/o progression to cirrhosis (B, C, D)
  - Typically, greater than 6 months duration
- Chronic carrier state without liver damage
  - AST, ALT normal; liver biopsy may be normal

1st hepatitis virus discovered (late 60’s)
- Nobel prize
- 350,000,000 chronically infected worldwide
- 1.25 million chronically infected in the USA
- 100,000 new infections annually in USA
- 8,000 - 32,000 chronic infections/year
- 5,000 - 6,000 deaths/year
**Hepatitis B**

- Why is it so common in Asia and Africa?

- To understand this, we need to first understand 3 things:
  - What type of virus is hepatitis B (HBV)?
  - How does it cause liver damage?
  - What happens if you are infected at birth?

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**Risk Factors for Acute HBV Infection in U.S.**

- Injection drug use
- Men having sex with men
- Multiple sex partners
- Sexual contact with HBV carriers
- Contact with HBV carriers
- Blood transfusion
- Occupational / hemodialysis

**Unknown**

CDC

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**Global Distribution of Chronic HBV Infection**

- 350 million chronic carriers worldwide
- Ninth leading cause of death
- Nearly 75% of HBV chronic carriers are Asian

**HBsAg Prevalence (%)**

- >8: High
- 2-7: Intermediate
- <2: Low

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**Hepatitis B Virus: Characteristics**

- Nucleic Acid: 3.2 kb DNA
- Classification: **Hepadnaviridae**
- Multiple serotypes and genotypes A-F
- Enveloped

- 22 nm
- 42 nm
Hepatitis B Virus - Replication

Viral entry

Nucleus

Uncoating

Nuclear import

Repair

Transcription

cccDNA

5' 3.5 kb RNA

3' 2.4/2.1 kb RNA

Positive strand synthesis

Removal of pregenome

Negative strand synthesis

Encapsidation

Export

Viral entry

Uncoating

Nuclear import

cccDNA

5' 3.5 kb RNA

3' 2.4/2.1 kb RNA

Positive strand synthesis

Removal of pregenome

Negative strand synthesis

Encapsidation

HBsAg

Assembly & budding

ER

Positive strand synthesis

Removal of pregenome

Negative strand synthesis

Encapsidation
The outcome following an exposure to hepatitis B depends upon the immune response to the virus...

- **Vigorous response**: => immune clearance of infected liver cells (acute hepatitis, but recover)
- **Partial response**: => immune clearance of some, but not all, infected liver cells => allows virus infection to persist by reinfecting new cells (chronic hepatitis)
- **No response**: => virus replicates and persists but no liver damage (chronic inactive carrier; no symptoms)

### Inactive Carriers
- Will often have very high levels of HBV in blood and liver
  - No symptoms and liver tests are normal
- Carrier mothers can infect their children at the time of birth...
- Newborns will often not recognize the virus as “foreign”, so they also become carriers, and......
- Infect their children at birth, and so on, and so on.
- After 30-40 years, they may develop chronic hepatitis, cirrhosis or even liver cancer
Prevention of Mother to Infant Transmission
► In the USA, all pregnant women are tested for HBV
  ▪ If they have HBsAg, and thus capable of transmitting the virus, their infants receive HBV-specific antibodies AND vaccine at birth
  ▪ Even if they don’t have HBV, all infants are now offered HBV vaccine at birth (since 1991)
  ▪ If children were not vaccinated at birth, they are vaccinated in middle school (since 1995)

Vaccine Indications
• HBIG and HB vaccine to infants of HBsAg+ mothers
• Routine vaccination of infants and adolescents
• Catch-up vaccination of children
• Vaccination of adults at risk of infection

Hepatitis B Immune Globulin for Neonates Born to HBsAg+ Mothers
Vaccine
HBIG

Vaccination of Selected High-Risk Groups in Adults
• Sexual and household contacts of carriers
• Sexually active individuals with multiple sex partners and men who have sex with men
• Injection drug users
• Hemodialysis patients
• Recipients of clotting factor concentrates
• Families of adoptees from endemic areas

CDC and WHO
Vaccination Of Selected High-risk Groups In Adults

- Health care and public safety workers with occupational risks
- Persons in institutions for the developmentally disabled or in long-term correctional facilities
- Travelers to countries endemic for hepatitis B who plan to stay > 6 months
- Transplant candidates before transplantation
- Patients with chronic liver disease

Declining Incidence of Acute Hepatitis B in the U.S.

Clinical Outcome of Acute Hepatitis B

Clinical Outcome of Chronic Hepatitis B
Hepatitis B Treatment

► Who should be treated?
  ▪ Acute hepatitis B? Probably not
  ▪ Chronic hepatitis B? Probably yes
  ▪ Inactive carrier? Controversial

► Does treatment “cure” HBV?
  ▪ No, but is able to suppress viral replication and minimize liver damage
  ▪ May prevent cirrhosis and liver cancer

Therapeutic Agents for Chronic Hepatitis B

<table>
<thead>
<tr>
<th>Immune Modulators</th>
<th>Nucleo(s) tide analog</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon</td>
<td>Lamivudine</td>
</tr>
<tr>
<td>Peginterferon</td>
<td>Adefovir dipivoxil</td>
</tr>
<tr>
<td>Therapeutic vaccines</td>
<td>Entecavir</td>
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<tr>
<td></td>
<td>Tenofovir</td>
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<tr>
<td></td>
<td>Emtricitabine</td>
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<tr>
<td></td>
<td>L-dT/ L-dC</td>
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<tr>
<td></td>
<td>Clevudine</td>
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<td></td>
<td>Famciclovir</td>
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</tbody>
</table>

Goals of Treatment of Chronic Hepatitis B

- Sustained suppression of HBV replication
  - HBV DNA undetectable in serum
  - HBeAg to anti-HBe seroconversion
  - HBsAg to anti-HBs seroconversion

- Remission of liver disease
  - Normalization of serum ALT levels
  - Improvement in liver biopsy

- Improvement in clinical outcome
  - Prevention of liver failure and cancer
  - Increased survival

Indications for Treatment of Chronic Hepatitis B

- Chronic HBV infection: HBsAg+ > 6 months
- Evidence of virus replication: serum HBV DNA >10⁵ copies/ml
- Evidence of liver damage: elevated ALT and/or chronic hepatitis on liver biopsy
Comparisons: HBeAg Loss and Seroconversion

Loss of HBeAg and Seroconversion Results at Week 48

<table>
<thead>
<tr>
<th>Drug</th>
<th>Entecavir 0.5 mg n=354</th>
<th>Lamivudine 100 mg n=355</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of HBeAg*</td>
<td>22%</td>
<td>20%</td>
</tr>
<tr>
<td>Seroconversion*</td>
<td>21%</td>
<td>18%</td>
</tr>
</tbody>
</table>

*P=NS
Non-completer = Failure Analysis


Please see Indication and Important Safety Information for BARACLUDE (entecavir) on pages 3-6 and pages 74-77. Please see speaker for Full Prescribing Information, including boxed WARNINGS.

Drug Resistance

Table 2: Relative Potency and Drug Resistance Observed with Current Drug Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Loga Decline in Serum HBV DNA at Week 48</th>
<th>Drug Resistance¹ (% of Patients)</th>
<th>Years on Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>PEG-IFN</td>
<td></td>
<td></td>
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<tr>
<td>Lamivudine</td>
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<tr>
<td>Adefovir</td>
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<tr>
<td>Telbivudine</td>
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*Based on results with lamivudine.

Effects May Last After Drug is Stopped
Different Therapeutic Options

Summary

► Hepatitis B is an important cause of liver disease worldwide.
► An effective vaccine is available and safe and is highly effective in preventing infection.
► Current treatments are effective in approximately 30% of patients with chronic infection.

### Table 2: Advantages and Disadvantages of Currently Available Antiviral Agents

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finite duration of treatment</td>
<td>Interferon</td>
</tr>
<tr>
<td>Durable off treatment response</td>
<td>Shown by injection</td>
</tr>
<tr>
<td>Loss of HBeAg (9-16%)</td>
<td>Frequent side effects</td>
</tr>
<tr>
<td>Immunomodulatory</td>
<td>Expensive</td>
</tr>
<tr>
<td>No drug resistance</td>
<td>Unpredictable immunologic effects</td>
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<td></td>
<td>Lower response rate with high level of viremia</td>
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<td></td>
<td>Viralologic response depends on genotype</td>
</tr>
</tbody>
</table>

**Nucleoside Analogues**

- Oral delivery
- Drug resistance
- Negligible side effects
- Long or indefinite treatment duration
- Patent inhibition of viral replication
- Low rate of HBeAg disappearance
- Less expensive than interferon
- Expensive relapse from long-term

*Average cost per pill is approximately $200-300 USD per month, depending on drug, vs. more than $1000 USD per month for peginterferon.

HBeAg, Hepatitis B e antigen.