Hepatitis B Virus

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Disclosures

- Dr. Chastain has received grant/research support paid to his institution from Gilead Sciences, Inc.:
  - Site investigator for HIV/HCV SWITCH Registry Study
  - Key faculty personnel for Gilead FOCUS HCV Screening Program through Vanderbilt University Medical Center Emergency Department
Objectives

At the end of this lecture, the learner will be able to:

- Review trends in the epidemiology of hepatitis B virus (HBV)
- Understand the indications for screening and/or immunization for HBV
- Identify the clinical manifestations of HBV
- Discuss the principles of and indications for treatment of HBV
Outline

- Epidemiology
- Screening and Immunization
- Clinical Manifestations and Natural History
- Interpreting Serologies
- Clinical Management
Outline

- Epidemiology
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Figure. Annual age-adjusted mortality rates from hepatitis B and hepatitis C virus and HIV infections listed as causes of death in the United States between 1999 and 2007.

Because a decedent can have multiple causes of death, a record listing more than 1 type of infection was counted for each type of infection.
HBV: A Global Problem

- 2 billion people worldwide have been infected with HBV\textsuperscript{[1]}
- ~350 million chronic carriers\textsuperscript{[2]}
- Leading cause of cirrhosis and HCC worldwide\textsuperscript{[2]}
- Causes 80% of all HCC in Asian Americans\textsuperscript{[3]}
- 30% to 50% of HCC associated with HBV in the absence of cirrhosis\textsuperscript{[4]}
- Second only to tobacco in causing the most cancer deaths\textsuperscript{[5]}
- HBV is 50-100 times more infectious than HIV\textsuperscript{[1]}

Worldwide Rates of Chronic Hepatitis B

620,000 deaths worldwide each year
Figure 3.1. Reported number of acute hepatitis B cases—United States, 2001–2016

Source: National Notifiable Diseases Surveillance System (NNDSS)
A total of 3,218 case-reports of acute hepatitis B were received in 2016. More than one risk exposure/behavior may be indicated on each case-report. No risk data reported.

A total of 1,957 acute hepatitis B cases were reported among males in 2016. Source: National Notifiable Diseases Surveillance System (NNDSS)

<table>
<thead>
<tr>
<th>Risk Exposure/Behavior</th>
<th>Yes</th>
<th>No</th>
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<tr>
<td>Injection-drug user</td>
<td>472</td>
<td>899</td>
<td>1,847</td>
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<tr>
<td>Sexual contact</td>
<td>28</td>
<td>635</td>
<td>2,555</td>
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<tr>
<td>Men who have sex with men</td>
<td>9</td>
<td>95</td>
<td>1,853</td>
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<tr>
<td>Multiple sex partners</td>
<td>143</td>
<td>339</td>
<td>2,736</td>
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<tr>
<td>Household contact</td>
<td>4</td>
<td>659</td>
<td>2,555</td>
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</tbody>
</table>

*Figures include all cases reported during the year in which the case-patient was first seen for hepatitis B.
†More than one risk exposure/behavior may be indicated on each case-report.
§No risk data reported.
¶A total of 1,957 acute hepatitis B cases were reported among males in 2016.

Source: National Notifiable Diseases Surveillance System (NNDSS)
A total of 3,218 case reports of hepatitis B were received in 2016. More than one risk exposure/behavior may be indicated on each case-report. No risk data reported.

Source: National Notifiable Diseases Surveillance System (NNDSS)
Outline

- Epidemiology
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HBV Screening

- Transmitted by blood and body fluids
- ~10% of HIV patients are co-infected with HBV

Who is at risk?
Although anyone can get Hepatitis B, some people are at greater risk, such as those who:
- Have sexual contact with an infected person
- Have multiple sex partners
- Have a sexually transmitted disease
- Are men who have sexual encounters with other men
- Inject drugs or share needles, syringes, or other injection equipment
- Live with a person who has Hepatitis B
- Are on hemodialysis
- Are exposed to blood on the job
- Are infants born to infected mothers
HBV Immunization

- **Recommended for:**
  - Infants/children
  - Travelers
  - People with multiple sex partners
  - Household contacts of persons with HBV
  - Men who have sex with men
  - Injection drug use
  - Healthcare workers
  - Hemodialysis patients
  - Patients with HIV
  - Chronic liver disease

- **Inactivated vaccine**

- **Administered as:**
  - Two shot series (0 and 1 month)
  - Three shot series (0, 1, and 6 months)
  - In three shot combination series with HAV vaccine (0, 1, and 6 months).

www.cdc.gov/hepatitis
Outline

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Hepatitis B Disease Progression

1. CDC. HBV FAQs for health professionals.

- Acute Infection
  - > 90% of infected infants progress to chronic disease[1]
  - < 5% of infected immunocompetent adults progress to chronic disease[1]
- Chronic Infection
- Cirrhosis
  - 30% of chronically infected individuals[2]
  - 23% of patients decompensate within 5 yrs of developing cirrhosis[3]
- Liver Failure
  - Chronic hepatitis B is the 6th leading cause of liver transplantation in the US[4]
- Liver Cancer (HCC)
- Liver Transplantation
- Death

Liver Cancer (HCC)
**FIGURE 1. Typical serologic course of acute hepatitis B virus infection with recovery**

- Symptoms
  - HBeAg
  - anti-HBe

- Titer:
  - Total anti-HBc
  - HBsAg
  - IgM anti-HBC
  - anti-HBs

- Postexposure (wks):
  - 0 4 8 12 16 20 24 28 32 36 52 100

* Hepatitis B e antigen.
† Antibody to HBeAg.
§ Antibody to hepatitis B core antigen.
¶ Hepatitis B surface antigen.
** Immunoglobulin M.
†† Antibody to HBsAg.

**FIGURE 2. Typical serologic course of acute hepatitis B virus (HBV) infection with progression to chronic HBV infection**

- Acute (6 mos) to Chronic (yrs)
  - HBeAg
  - anti-HBe

- Titer:
  - Total anti-HBc
  - HBsAg
  - IgM anti-HBC

- Postexposure (wks):
  - 0 4 8 12 16 20 24 28 32 36 52 Yrs

* Hepatitis B e antigen.
† Antibody to HBsAg.
§ Antibody to hepatitis B core antigen.
¶ Hepatitis B surface antigen.
** Immunoglobulin M.
Phases of Chronic HBV Infection

- Immune tolerant
- Immune clearance HBeAg-positive chronic hepatitis
- Inactive carrier state
- Reactivation HBeAg-negative chronic hepatitis


Slide courtesy of clinicaloptions.com/hepatitis
Outline

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## Interpretation of Hepatitis B Serologic Test Results

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<tr>
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<th>Interpretation</th>
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<tr>
<td>HBsAg (-)</td>
<td>Susceptible</td>
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<tr>
<td>Total anti-HBc (-)</td>
<td></td>
</tr>
<tr>
<td>anti-HBs (-)</td>
<td></td>
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<tr>
<td>HBsAg (-)</td>
<td>Immune due to natural infection</td>
</tr>
<tr>
<td>Total anti-HBc (+)</td>
<td></td>
</tr>
<tr>
<td>anti-HBs (+)</td>
<td></td>
</tr>
<tr>
<td>HBsAg (-)</td>
<td>Immune due to hepatitis B immunization</td>
</tr>
<tr>
<td>Total anti-HBc (-)</td>
<td></td>
</tr>
<tr>
<td>anti-HBs (+)</td>
<td></td>
</tr>
<tr>
<td>HBsAg (+)</td>
<td>Acutely self-limited infection</td>
</tr>
<tr>
<td>Total anti-HBc (+)</td>
<td>or Chronic infection with hepatitis flare (less common)</td>
</tr>
<tr>
<td>IgM anti-HBc (+)</td>
<td></td>
</tr>
<tr>
<td>anti-HB (-)</td>
<td></td>
</tr>
<tr>
<td>HBsAg (+)</td>
<td>Chronically infected</td>
</tr>
<tr>
<td>Total anti-HBc (+)</td>
<td></td>
</tr>
<tr>
<td>IgM anti-HBc (-)</td>
<td></td>
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<tr>
<td>anti-HBs (-)</td>
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### Interpretation unclear; four possibilities:
1. Resolved infection (most common)
2. False-positive anti-HBc, thus susceptible
3. "Low level" chronic infection
4. Resolving acute infection

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**Figure 2 - Interpretation of Serologic Markers in HBV Infection**

## HBV Diagnosis

<table>
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<tr>
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Case Version #1

- Mrs. R is a 65 y/o woman with a PMH of HTN and rheumatoid arthritis referred for primary care.
- She has been previously treated with NSAIDs, prednisone, and methotrexate with poor response.
- Adalimumab is being considered for therapy.
- Additional history notes pRBC transfusion after childbirth 40 years ago.
- LFTs are within normal limits.
- HBV serology reveals:
  - Anti-HBs sAb positive
  - Total Anti-HBc negative
  - HBsAg negative
What is your interpretation of her HBV serology?

A. Susceptible
B. Immune due to natural infection
C. Immune due to immunization
D. Acute infection
E. Chronic infection
F. Other
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Additional history notes pRBC transfusion after childbirth 40 years ago.

LFTs are within normal limits.

HBV serology reveals:
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# HBV Diagnosis

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Case Version #3

- Mrs. R is a 65 y/o woman with a PMH of HTN and rheumatoid arthritis referred for primary care.
- She has been previously treated with NSAIDs, prednisone, and methotrexate with poor response.
- Adalimumab is being considered for therapy.
- Additional history notes pRBC transfusion after childbirth 40 years ago.
- AST is 65 and ALT is 80 (upper limit of normal 40).
- HBV serology reveals:
  - Anti-HBs sAb negative
  - Total Anti-HBc positive
  - HBsAg positive
What is your interpretation of her HBV serology?

A. Susceptible
B. Immune due to natural infection
C. Immune due to immunization
D. Acute infection
E. Chronic infection
F. Other
### HBV Diagnosis

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Outline

- Epidemiology
- Screening and Immunization
- Clinical Manifestations and Natural History
- Interpreting Serologies
- Clinical Management
HBV Treatment

- Acute adult infection is not usually treated as most clear infection
- Chronic infection MAY require suppressive therapy.
- *There is no cure.*
- Available Agents:
  - Interferon alfa-2b (Intron A®)
  - Telbivudine (Tyzeka®)
  - Lamivudine (Epivir®)
  - Emtricitabine (Emtriva®)
  - Adefovir (Hepsera®)
  - Entecavir (Baraclude®)
  - Tenofovir (Viread® and Vemlidy®)
Chronic HBV Management Pearls

- Patients with other chronic viral infections (i.e. HCV and HIV) should receive HBV treatment.
- Patients with cirrhosis should receive HBV treatment.
- Patients with severe hepatic inflammation and/or elevated HBV DNA should receive HBV treatment.

- All patients with chronic HBV should be screened for hepatocellular carcinoma regardless of fibrosis status.
WHAT ABOUT THE BLACK BOX WARNING RE: HBV FOR HCV TREATMENT?
WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV

See full prescribing information for complete boxed warning.

Hepatitis B virus (HBV) reactivation has been reported, in some cases resulting in fulminant hepatitis, hepatic failure, and death. (5.1)
Hepatitis B Virus Reactivation Associated With Direct-Acting Antiviral Therapy for Chronic Hepatitis C Virus: A Review of Cases Reported to the U.S. Food and Drug Administration Adverse Event Reporting System

Susan J. Bersoff-Matcha, MD; Kelly Cao, PharmD; Mihaela Jason, PharmD; Adebola Ajao, PhD; S. Christopher Jones, PharmD, MS, MPH; Tamra Meyer, PhD, MPH; and Allen Brinker, MD, MS

Published June 6, 2017
Case Series

- 29 cases reported from 11/2013 – 10/2016
  - 13 occurred in patients with positive sAg
  - 4 occurred in patients with negative sAg
  - 12 occurred with unknown baseline sAg status
- 2 deaths and 1 liver transplant
- Resulted in boxed warning with all DAA therapies
Hepatitis B virus reactivation during direct-acting antiviral therapy for hepatitis C: a systematic review and meta-analysis

Marcus M Mücke, MD, Lisa I Backus, MD, Victoria T Mücke, MD, Nicola Coppola, MD, Carmen M Preda, MD, Ming-Lun Yeh, MD, Lydia S Y Tang, MBChB, Pamela S Belperio, PharmD, Eleanor M Wilson, MD, Prof Ming-Lung Yu, MD, Prof Stefan Zeuzem, MD, Prof Eva Herrmann, PhD, Johannes Vermehren, MD

Published: 19 January 2018
Meta-Analysis

- 17 observational trials
- 1621 patients treated with DAAs for HCV
  - 242 with chronic HBV (i.e. sAg positive)
  - 1379 with resolved HBV (i.e. cAb positive)
- HBV reactivation rates variable
  - 24% among patients with chronic HBV
  - 1.4% among patients with resolved HBV
- Clinically significant events variable
  - 9% of chronic HBV patients with HBV-reactivation-related hepatitis
    - More common among those with measureable HBV DNA at baseline
    - 1 liver decompensation, 2 with liver failure (one requiring liver transplant)
  - No clinically significant events among those with resolved HBV infection
Approaching HCV In Setting of HBV

- Treat chronic HBV based on guideline recommendations
- Do not withhold HCV therapy if HBV not treated but monitor closely
- Consider treatment of chronic HBV prior to or during HCV therapy, particularly among those with measurable HBV DNA
- Consider closer monitoring of HBV and associated liver disease in those with resolved HBV infection while on DAA therapy
Summary

- Screen
- Immunize
- Interpret serology (with tools if needed)
- Recognize indications for treatment
- Consider HBV when treating HCV
QUESTIONS?