Hepatitis B Update

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Disclosures

• **Research Grants**
  – BMS, Gilead, Merck

• **Advisory Board**
  – BMS, Gilead, Merck, Roche

• **DSMB**
  – GSK
Hepatitis B Update

• How common is hepatitis B in the US?
• Who should be screened for HBV, which tests to order and how to interpret those test results?
• Which patients are most likely to develop cirrhosis or hepatocellular carcinoma?
• How can hepatitis B be prevented?
• How effective is HBV treatment?
• Who should be considered for treatment?
# HBV Infection - Disease Burden

<table>
<thead>
<tr>
<th></th>
<th>HBV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Worldwide</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic infection</td>
<td>350 million</td>
</tr>
<tr>
<td>New infection/yr</td>
<td>21 million</td>
</tr>
<tr>
<td>Mortality/yr</td>
<td>600,000</td>
</tr>
<tr>
<td><strong>U.S.</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic infection</td>
<td>0.8-1.4 million</td>
</tr>
<tr>
<td>(65% unaware of infection)</td>
<td></td>
</tr>
<tr>
<td>New infection/yr</td>
<td>43,000</td>
</tr>
<tr>
<td>Mortality/yr</td>
<td>3,000</td>
</tr>
</tbody>
</table>

IOM, 2010
Age Adjusted Prevalence of Chronic HBV Infection in the US, NHANES

Wasley A, J Infect Dis 2010; 202: 192
Age Adjusted Prevalence of Chronic HBV Infection in the US, NHANES 1999-2006

Wasley A, J Infect Dis 2010; 202: 192
Changing Epidemiology of HBV Infection in the US

- Incidence of acute HBV infection decreased
- Prevalence of chronic HBV infection decreased overall but remains high in some groups
- 95% of new cases of chronic HBV infection are imported
- Approximately 2/3 of those chronically infected are not aware of the infection
- Efforts to improve awareness and diagnosis are needed
Hepatitis B Update

- How common is hepatitis B in the US?
- Who should be screened for HBV, which tests to order and how to interpret those test results?
- Which patients are most likely to develop cirrhosis or hepatocellular carcinoma?
- How can hepatitis B be prevented?
- How effective is HBV treatment?
- Who should be considered for treatment?
Who Should be Screened for HBV?

- Persons born in geographical regions with HBsAg prevalence rate ≥ 2%
- Infants born to infected mothers
- Household contact / sexual partners of infected persons
- Persons with risk behaviors: IDU, MSM, multiple sex partners
- Hemodialysis patients
- Persons with HIV infection
- Persons who have chronic liver disease
- Persons who require long-term immunosuppressive therapy

Weinbaum C, MMWR 2008; 57: 1-20
Geographic Distribution of Chronic HBV Infection

HBsAg Prevalence

- ≥8% - High
- 2-7% - Intermediate
- <2% - Low
How can hepatitis B be diagnosed?

- The only way to know is to have a blood test
- Most people with hepatitis B have no symptoms until late stages of liver disease
- Tests for hepatitis B or liver enzymes are not included in most routine check-ups
- Hepatitis B may be present even if liver enzymes were tested and were normal
### Serological Markers of HBV Infection

<table>
<thead>
<tr>
<th>Marker</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>Acute/Chronic infection</td>
</tr>
<tr>
<td>Anti-HBc IgM</td>
<td>Recent infection</td>
</tr>
<tr>
<td>HBeAg</td>
<td>High infectivity</td>
</tr>
<tr>
<td>Anti-HBe</td>
<td>Low infectivity</td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>Immunity</td>
</tr>
<tr>
<td>Anti-HBc IgG + HBsAg</td>
<td>Chronic infection</td>
</tr>
<tr>
<td>Anti-HBc IgG + anti-HBs</td>
<td>Resolved infection</td>
</tr>
</tbody>
</table>
**Interpretation of HBV Serology**

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>Total anti-HBc</th>
<th>IgM anti-HBc</th>
<th>Anti-HBs</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td><strong>Not been exposed</strong></td>
</tr>
</tbody>
</table>


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<tbody>
<tr>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td><strong>Not been exposed</strong></td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td><strong>Chronic infection</strong></td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Not been exposed</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Chronic infection</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Acute Infection</td>
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<td>–</td>
<td>–</td>
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</tr>
<tr>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Chronic infection</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Acute Infection</td>
</tr>
<tr>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>Immunity from past infection</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>Not been exposed</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Chronic infection</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>Acute Infection</td>
</tr>
<tr>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>Immunity from past infection</td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>Immunity after vaccination</td>
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<tbody>
<tr>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td><strong>E - Not been exposed</strong></td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td><strong>B - Chronic infection</strong></td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td><strong>A - Acute Infection</strong></td>
</tr>
<tr>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td><strong>D - Immunity from past infection</strong></td>
</tr>
<tr>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td><strong>C - Immunity after vaccination</strong></td>
</tr>
<tr>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>?</td>
</tr>
</tbody>
</table>
Isolated Anti-HBc+: What does that mean? HBsAg-, anti-HBc+, anti-HBs-

- **Previous chronic HBV infection with loss of HBsAg**
  - Most common, particularly in patients from HBV endemic areas or in patients with risk factors for HBV
  - HBV persists in liver, reactivation may occur during immunosuppressive therapy
- **Recovery from transient HBV infection with loss of anti-HBs**
- **Window phase of acute HBV infection**
- **False positive anti-HBc test result**
Evaluation of Patients with Isolated Anti-HBc

- **Confirmation of test results**
  - Repeat test for HBsAg, IgG anti-HBc, anti-HBs
    - Confirm isolated anti-HBc
  - Consider testing for anti-HBe
    - Confirm exposure to HBV, true positive anti-HBc
  - Consider testing for HBV DNA
    - Undetectable in most cases, worthwhile in patients who will be starting immunosuppressive therapy

- **HBV vaccination**
  - Unnecessary in most cases

- **Educate patient of risk of HBV reactivation during immunosuppressive therapy**
Importance of Monitoring Serum HBV DNA Levels

- Direct measurement of HBV replication
- Determine phase of chronic HBV infection, indications for treatment and treatment response
- Fluctuating levels, serial tests important for clinical assessment
- HBV DNA levels do not always correlate with ALT levels or histologic activity of liver disease
- Persistently high serum HBV DNA levels are associated with increased risk of cirrhosis and HCC
Initial Evaluation of Patients with Hepatitis B

• Clinical evaluation
• Lab tests
  – HBeAg, anti-HBe, HBV DNA
  – Tests to r/o HCV, HDV, HIV, other causes of liver disease if indicated
  – Tests to assess liver disease severity – liver chemistry, CBC+P, PT
• +/- Abdominal ultrasound – assess cirrhosis, surveillance for liver cancer
• +/- Liver biopsy
Initial Evaluation of Patients with Hepatitis B

- Vaccination against hepatitis A
- Counseling on precautions to prevent transmission of infection, limit alcohol use, and healthy lifestyle
- Emphasize importance of long-term follow-up
- Screening of household and sexual contacts for HBV and vaccination of those who test negative for both HBsAg and anti-HBs
Hepatitis B Update

• How common is hepatitis B in the US?
• Who should be screened for HBV, which tests to order and how to interpret those test results?
• Which patients are most likely to develop cirrhosis or hepatocellular carcinoma?
• How can hepatitis B be prevented?
• How effective is HBV treatment?
• Who should be considered for treatment?
Outcome of Chronic HBV Infection

- Chronic HBV Infection
  - Inactive Carrier State
  - Chronic Hepatitis
    - Cirrhosis
    - HCC
Natural Course of Chronic HBV Infection

- **HBeAg**
- **Anti-HBe**

**HBV DNA**

**ALT**

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

**Years**

0  20  40  60
Hepatitis B
Factors affecting disease activity and progression

VIRUS
- Genotype
- Molecular Variants
- Viral load

HOST
- Gender
- Age
- Immune Response
- Genetics

ENVIRONMENT
- Alcohol
- HCV, HDV, HIV
- Carcinogens
REVEAL-HBV Study
Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer

- Community based cohort study in Taiwan
- 3,653 HBsAg+, anti-HCV-, mean age 43 (range 30-65)
- At enrollment, 38% women, 15% HBeAg+, 94% normal ALT, 2% cirrhosis
- Prospective follow-up q 6-12 months until June 2004

Chen CJ, JAMA 2006; 295: 65
High Viral Load is Associated with Increased Incidence of HCC

REVEAL Study (n=3,653)

Baseline HBV DNA level, copies/mL
- $\geq 10^6$ (n=627)
- $10^5$–$<10^6$ (n=349)
- $10^4$–$<10^5$ (n=643)
- $300$–$<10^4$ (n=1,161)
- $<300$ (n=873)

Log rank test of trend
p<0.001

Cumulative incidence of HCC (% subjects)

## Nomogram for Predicting Risks of HCC

<table>
<thead>
<tr>
<th></th>
<th>Model</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>0/2</td>
<td>F (0)</td>
<td>M (2)</td>
<td>M (2)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>0-6</td>
<td>29 (0)</td>
<td>62 (6)</td>
<td>46 (3)</td>
</tr>
<tr>
<td><strong>ALT</strong></td>
<td>0-2</td>
<td>22 (1)</td>
<td>40 (1)</td>
<td>36 (1)</td>
</tr>
<tr>
<td><strong>HBeAg</strong></td>
<td>0/2</td>
<td>Pos (2)</td>
<td>Neg (0)</td>
<td>Pos (2)</td>
</tr>
<tr>
<td><strong>HBV DNA (c/mL)</strong></td>
<td>0-5</td>
<td>9.2 log (4)</td>
<td>2.7 log (0)</td>
<td>5.3 (5)</td>
</tr>
<tr>
<td><strong>Total score</strong></td>
<td>0-17</td>
<td>7</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td><strong>10 year risk of HCC</strong></td>
<td></td>
<td>1.2%</td>
<td>3.2%</td>
<td>21%</td>
</tr>
</tbody>
</table>

Initial model developed with data from REVEAL study, validated with data from 3 cohorts of patients seen in liver centers in Hong Kong and Korea

Yang HI, Lancet Oncol 2011; 12: 568
Hepatitis B Update

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• Which patients are most likely to develop cirrhosis or hepatocellular carcinoma?
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• How effective is HBV treatment?
• Who should be considered for treatment?
**Prevention of Hepatitis B**

- **HBV vaccination**: universal vaccination of all newborns and at risk adults
- **Universal precaution**
- **Counseling of infected patients on precautions to prevent transmission, screening and vaccinating household and sexual contacts**
- **Education of health care providers**
- **Education of the public**
Hepatitis B Vaccines

- Genetically engineered hepatitis B surface antigen alone or in combination with hepatitis A vaccine
- 3 doses: month 0, 1, 6
- Immune response: 50% after 1 dose
  95% after 3 doses
- Duration of protection: >15 years, dependent on initial antibody response
- Factors associated with poor response: older age, chronic medical illness (cirrhosis, kidney failure, diabetes), decreased immune response, smoking, obesity, genetics
Indications for HBV Vaccines

- All infants (+HBIG for infants of HBsAg+ mothers)
- All children and adolescents who were not vaccinated at birth
- Vaccination of adults at risk of infection
  - Occupational
  - Sexual / household contacts
  - Persons with high risk behaviors, e.g. injection drug users, men who have sex with men, persons with multiple sexual partners
  - Persons born in endemic areas or persons born to parents from endemic areas
  - Dialysis patients
  - Patients with chronic liver disease
Impact of HBV Vaccination on Prevalence of HBsAg in Taiwanese Children and Young Adults

Ni YH, Gastroenterol 2007; 132: 1287
HBV Vaccine Prevents HCC

20 yr follow-up, adjusted RR of HCC among those vaccinated at birth: 0.31

Chang MH, NEJM 1997; 336: 1855; JNCI 2009; 101: 1348
Hepatitis B Update

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• How effective is HBV treatment?
• Who should be considered for treatment?
Goals of HBV Treatment

• Suppress HBV replication
• Decrease necroinflammation
• Reverse fibrosis
• Prevent progression to cirrhosis, liver failure, and hepatocellular carcinoma
Responses to HBV Treatment

• Virologic Response
  – Decrease in serum HBV DNA: preferably to undetectable by PCR
  – HBeAg loss / seroconversion: applicable to HBeAg+ patients only
  – HBsAg loss: Ultimate goal

• Biochemical Response
  – ALT normalization

• Histological Response

• Clinical Response
Decrease in Serum HBV DNA after 1 Year of Treatment

LAM=lamivudine, ADV=adefovir, ETV=entecavir, TBV=telbivudine, TDF=tenofovir, PEG-IFN=peginterferon
Reversal of Fibrosis and Cirrhosis
Tenofovir Phase III Trial: Biopsies at Year 0, 1 & 5

- 348/641 (54%) had liver biopsy at baseline and Year 5
- 71/96 (74%) with cirrhosis (Ishak Score ≥ 5) at baseline no longer had cirrhosis at Year 5
- 3/252 (1%) with no cirrhosis at baseline progressed to cirrhosis at Year 5

Marcellin, P, Lancet 2013
Antiviral Therapy Prevents Disease Progression

Bridging fibrosis or cirrhosis, HBeAg+ / HBV DNA >700,000 GEq/ml

% with disease progression

Increase CTP score, liver failure or HCC

Time to disease progression (months)

Placebo (n=215)   ITT population
Lamivudine (n=436)   p=0.001

Liaw YF, NEJM 2004; 351:1521
How Efficacious is Currently Available HBV Therapies?

- Potent viral suppression
- Low rate of HBeAg and HBsAg loss
  - HBeAg loss ~20% after 1 year and 40-50% after 5 years of nucleos(t)ide analogues
  - HBsAg loss ~1-5% after 5 years of nucleos(t)ide analogues
  - Higher rate of HBeAg and HBsAg loss after interferon therapy
- Reverse hepatic fibrosis and cirrhosis
- Prevent progression to liver failure (and HCC)
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When to Initiate Treatment in Non-Cirrhotics?
When to Initiate Treatment in Non-Cirrhotics?

- Active liver disease and high level HBV DNA
- HBeAg+/HBeAg-
  - ALT >2x ULN and HBV DNA >20,000 IU/mL
  - Lower threshold in patients >40, liver histology showing moderate-severe inflammation / fibrosis
  - HBeAg+ patients: can observe for 3-6 months to allow time for spontaneous seroconversion

Lok & McMahon, AASLD guidelines 2009, www.aasld.org
Which Is the Best Initial Treatment?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Interferon</th>
<th>Nucleos(t)ide Analogue Analogues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>Parenteral</td>
<td>Oral</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>Finite duration ~ 12 mos</td>
<td>Long duration, yrs to life long</td>
</tr>
<tr>
<td>Antiviral activity</td>
<td>Modest, additional immunomodulatory effects</td>
<td>Stronger antiviral activity</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>1-3% after 1 yr</td>
<td>Rare, 0-1% after 1 yr</td>
</tr>
<tr>
<td>Resistance mutations</td>
<td>None</td>
<td>0-25% after 1 yr</td>
</tr>
<tr>
<td>Side effects</td>
<td>Frequent</td>
<td>Rare</td>
</tr>
</tbody>
</table>
**Which Should be the Initial Oral Drug?**

<table>
<thead>
<tr>
<th></th>
<th>LAM</th>
<th>ADV</th>
<th>ETV</th>
<th>LdT</th>
<th>TDF</th>
</tr>
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<tbody>
<tr>
<td><strong>Antiviral activity</strong></td>
<td>+++</td>
<td>+</td>
<td>++++</td>
<td>+++</td>
<td>+++++</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Risk of drug resistance</strong></td>
<td>++++</td>
<td>++</td>
<td>1% after 5 yr</td>
<td>+++</td>
<td>0% after 5 yr</td>
</tr>
</tbody>
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LAM = lamivudine, ADV = adefovir, ETV = entecavir, LdT = telbivudine, TDF = tenofovir
Treatment

• When to start?
  – Life-threatening liver disease
  – High risk of cirrhosis or HCC
  – High levels of HBV DNA and ALT
  – Lower threshold in older patients, cirrhosis

• Which drug?
  – First line treatment: Peg-IFN, Entecavir or Tenofovir

• When to stop?