Hepatitis B & C

Richard Braun, MD
Medical Director
Hepatitis Cases

Case 1 – A 37 year old woman applies for life insurance. She moved from Taiwan to the US 15 years prior to application. Her OB/Gyn noticed an elevated ALT of 60 IU/L and referred her to a GI specialist. She does not smoke or drink alcohol; family history revealed that her mother has chronic Hepatitis B and her father died of liver cancer at age 57. A brother also has Hepatitis B. Testing reveals she is HBsAg positive, HBeAg positive, and a Hep B DNA count of 350,000 IU/L. The last note says They are considering treatment options.

Case 2 – a 49 year old man applied for life insurance. 2 years ago he had an ALT of 66 IU/L. Reflex testing revealed a positive Hepatitis C antibody. He followed up with his AP and had a positive PCR for HCV RNA at 450,000 IU/L. He was treated with Peg IFN and Ribivarin for 48 weeks and RNA has been undetectable for 6 months after that. His next exam is planned in 6 months.
Hepatitis B

- Etiology
- Epidemiology
- Natural History
- Diagnosis
- Treatment
- Prognosis
Hepatitis B Virus (HBV)

Member of the Hepadna virus family
42 nm diameter

Can survive for 6 months
At room temperature
HBV infects Hepatocyte
Hepatitis B

- Transmission by bodily fluids
- Varies by region
  - Low Prevalence areas – sexual and percutaneous
  - Intermediate areas (3-5%) sexual, percutaneous, and perinatal
  - High Prevalence (10-20%) predominately perinatal
Hepatitis B

**Worldwide**
- Estimated 1/3 of the world’s population is infected
- ~350 million are lifelong carriers
- Estimated 620,000 worldwide die of Hepatitis B each year

Transmission predominately
- Perinatal
- Taiwan – Prevalence
  - Before vaccination = 10%
  - After vaccination = 1%
Hepatitis B - USA

- Estimated 800K to 1.25 million have chronic Hepatitis B in the USA
- Chronic HBV accounts for 5-10% of chronic End-stage liver disease & 10-15% of Hepatocellular Carcinoma (HCC)
- 5000 deaths per year

Vaccination
-infants 1992
-adolescents 1995

www.cdc.gov/hepatitis/statistics/index.htm
## Prevalence of Hepatitis B in Selected US Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>HBV Marker (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%Prevalence HBsAg⁺</td>
<td>Any Marker</td>
</tr>
<tr>
<td>Residents in endemic areas</td>
<td>10-20</td>
<td>70-85</td>
</tr>
<tr>
<td>Alaskan natives</td>
<td>5-15</td>
<td>40-70</td>
</tr>
<tr>
<td>Residents of institutions for mentally disabled</td>
<td>10-20</td>
<td>35-38</td>
</tr>
<tr>
<td>Parenteral drug users</td>
<td>5-10</td>
<td>60-80</td>
</tr>
<tr>
<td>Men who have sex with men</td>
<td>4-8</td>
<td>35-80</td>
</tr>
<tr>
<td>Household contacts of HBsAg⁺</td>
<td>3-6</td>
<td>30-60</td>
</tr>
<tr>
<td>Hemodialysis patients</td>
<td>3-10</td>
<td>20-80</td>
</tr>
<tr>
<td>Prison inmates</td>
<td>1-8</td>
<td>10-80</td>
</tr>
<tr>
<td>Heterosexuals with multiple sex partners</td>
<td>0.5</td>
<td>5-20</td>
</tr>
<tr>
<td>Health care workers</td>
<td>0.5</td>
<td>3-10</td>
</tr>
<tr>
<td>General U.S. population</td>
<td>0.2</td>
<td>4.8</td>
</tr>
<tr>
<td>Blacks</td>
<td>0.85</td>
<td>13</td>
</tr>
<tr>
<td>Whites</td>
<td>0.19</td>
<td>3</td>
</tr>
</tbody>
</table>

Mandell: Mandell, Douglas, and Bennett’s Principles and Practice of Infectious Diseases, 7th Edition, 2009, Elsevier
# HBV Immune Response – Based on age at infection

<table>
<thead>
<tr>
<th>Mode of Transmission</th>
<th>Age at Infection</th>
<th>Risk of Chronic HBV</th>
<th>Lifetime Risk of HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal – Mother HBeAg positive</td>
<td>Birth</td>
<td>90%</td>
<td>15%-40%</td>
</tr>
<tr>
<td>Perinatal – Mother HBeAg negative</td>
<td>Birth</td>
<td>&lt;15%</td>
<td>15%-40%</td>
</tr>
<tr>
<td>Horizontal</td>
<td>Birth – 2 years</td>
<td>50%</td>
<td>15%-40%</td>
</tr>
<tr>
<td>Horizontal</td>
<td>2-5 years</td>
<td>30%</td>
<td>15%-25%</td>
</tr>
<tr>
<td>Horizontal</td>
<td>5-10 years</td>
<td>16%</td>
<td>15%-25%</td>
</tr>
<tr>
<td>Horizontal</td>
<td>&gt; 10 years</td>
<td>7-14%</td>
<td>Unknown</td>
</tr>
<tr>
<td>Horizontal</td>
<td>Adults</td>
<td>&lt;5%</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Screening for Hepatitis B

- Hepatitis B surface antigen – HBsAg is the screening test of choice in immunocompetent individuals. Antigens are parts of the virus found in blood or in the liver.
- Antibodies develop from the host’s immune system in response to the virus.

<table>
<thead>
<tr>
<th>Viral particle</th>
<th>Antigen</th>
<th>Antibody</th>
<th>Anti Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface</td>
<td>HBsAg</td>
<td>Anti-HBs</td>
<td>Immunity (vaccine)</td>
</tr>
<tr>
<td>Core</td>
<td>HBcAg</td>
<td>Anti-HBc</td>
<td>Developing immunity</td>
</tr>
<tr>
<td>e antigen also core</td>
<td>HBeAg</td>
<td>Anti-HBe</td>
<td>Infectivity &amp; reproduction</td>
</tr>
</tbody>
</table>
HBV infection in an adult

Acute Hepatitis B Virus Infection with Recovery

Typical Serologic Course

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>HBeAg</th>
<th>anti-HBe</th>
</tr>
</thead>
</table>

Titer

- HBsAg
- IgM anti-HBc
- Total anti-HBc
- Anti-HBs

Weeks after exposure

Progression to chronic HBV

Titer

- IgM anti-HBc
- Total anti-HBc
- HBeAg
- anti-HBe

Weeks After Exposure

Acute (6 months)  Chronic (Years)
Clinical Definitions HBV

- **Chronic hepatitis B** — Chronic necroinflammatory disease of the liver caused by persistent infection with hepatitis B virus. Chronic hepatitis B can be subdivided into HBeAg positive and HBeAg negative chronic hepatitis B.
  - 1. HBsAg-positive 6 months
  - 2. Serum HBV DNA >20,000 IU/mL (105 copies/mL), lower values 2,000-20,000 IU/mL (104-105 copies/mL) are often seen in HBeAg-negative chronic hepatitis B
  - 3. Persistent or intermittent elevation in ALT/AST levels
  - 4. Liver biopsy showing chronic hepatitis with moderate or severe necroinflammation
Clinical Definitions HBV

- Inactive HBsAg carrier state — Persistent HBV infection of the liver without significant, ongoing necroinflammatory disease.
  - 1. HBsAg-positive 6 + months
  - 2. HBeAg−, anti-HBe +
  - 3. Serum HBV DNA <2,000 IU/mL
  - 4. Persistently normal ALT/AST levels
  - 5. Liver biopsy confirms absence of significant hepatitis

HEPATOLOGY, Vol. 50, No. 3, 2009
Clinical Definitions HBV

Resolved hepatitis B — Previous HBV infection without further virologic, biochemical or histological evidence of active virus infection or disease.

1. Previous known history of acute or chronic hepatitis B or the presence of anti-HBc +- anti-HBs
2. HBsAg negative
3. Undetectable serum HBV DNA*
4. Normal ALT levels
Acute exacerbation or flare of hepatitis B — Intermittent elevations of aminotransferase activity to more than 10 times the upper limit of normal and more than twice the baseline value.

Reactivation of hepatitis B — Reappearance of active necroinflammatory disease of the liver in a person known to have the inactive HBsAg carrier state or resolved hepatitis B.

HBeAg clearance — Loss of HBeAg in a person who was previously HBeAg positive.

HBeAg seroconversion — Loss of HBeAg and detection of anti-HBe in a person who was previously HBeAg positive and anti-HBe negative.

HBeAg reversion — Reappearance of HBeAg in a person who was previously HBeAg negative, anti-HBe positive.
Neonatal or early childhood HBV

Viral production & Immune reaction

Up to 90%

Immune Tolerant
Normal ALT
High HBV DNA

With genotype C
May last into the 40’s in women

Chronic Hepatitis B
8-12% per year
10-20%

Inactive HBsAg Carrier State
Neg HBeAg, NI ALT, DNA<2000

Resolved hepatitis B

Immune “bump” at adolescence

Cirrhosis
Survival:
84% 5 yr
68% 10 yr

Hepatocellular Carcinoma (HCC)
30-50% of HCC develops Without cirrhosis

0.5-3% Per year
Poor Prognostic Factors HBV (Cirrhosis or HCC)

- Male gender
- Older Age – longer duration of infection
- HBV Genotype C
- Concurrent infection with hepatitis C (HCV), hepatitis D (HDV), or HIV
- Heavy Alcohol use
- Smoking
- Exposures to carcinogens (e.g. aflatoxins)
- Family history of HCC
- Presence of HBeAg
- High levels of HBV DNA
Demographic and social factors increasing HCC & Cirrhosis risk

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Increased Risk of HCC</th>
<th>Increased Risk of Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>3+</td>
<td>+</td>
</tr>
<tr>
<td>Increasing Age &gt; 40</td>
<td>3+</td>
<td>3+</td>
</tr>
<tr>
<td>Family History of HCC</td>
<td>3+</td>
<td>+</td>
</tr>
<tr>
<td>Social and Environmental</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Aflatoxin</td>
<td>3+</td>
<td>Unknown</td>
</tr>
<tr>
<td>Smoking</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Steatosis, metabolic syndrome, DM</td>
<td>No association</td>
<td>No association</td>
</tr>
<tr>
<td>Coffee</td>
<td>Decreased Risk</td>
<td>Slower Progression</td>
</tr>
</tbody>
</table>
## HBV factors with increased risk

<table>
<thead>
<tr>
<th></th>
<th>Increased Risk of HCC</th>
<th>Increased Risk Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBV Genotype</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype C (east Asia, Pacific Islands)</td>
<td>3+</td>
<td>2+</td>
</tr>
<tr>
<td>Genotype F (Alaska, Central and South Amer)</td>
<td>2+</td>
<td>No evidence</td>
</tr>
<tr>
<td>DNA &gt; 20,000 IU in persons &gt; 40 years</td>
<td>3+</td>
<td>3+</td>
</tr>
<tr>
<td>Basal Core Promoter mutation</td>
<td>3+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Co-infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV/HIV</td>
<td>+</td>
<td>2+</td>
</tr>
<tr>
<td>HBV/HCV</td>
<td>3+</td>
<td>2+</td>
</tr>
<tr>
<td>HBV/HDV</td>
<td>+</td>
<td>3+</td>
</tr>
</tbody>
</table>
HBV and Risk of HCC

Hepatocellular Carcinoma (HCC) Screening

- **Recommendations for HCC Screening:**
- HBV carriers at high risk for HCC such as Asian men over 40 years and Asian women over 50 years of age, persons with cirrhosis, persons with a family history of HCC, Africans over 20 years of age, and any carrier over 40 years with persistent or intermittent ALT elevation and/or high HBV DNA level >2,000 IU/mL should be screened with *Ultrasound (US) examination every 6-12 months.*
- For HBV carriers at high risk for HCC who are living in areas where US is not readily available, periodic screening with Alpha-fetoprotein (AFP) should be considered.

**HEPATOLOGY, Vol. 50, No. 3, 2009**
A

Management of Chronic HBV Infection*

HBsAg +

HBeAg

Positive

ALT < 1 X ULN
Q 3-6 mo ALT
Q 6-12 mo HBeAg

ALT 1-2 X ULN
Q 3 mo ALT
Q 6 mo HBeAg
Consider biopsy if persistent or age > 40,
Rx as needed

ALT >2 X ULN
Q 1-3 mo ALT, HBeAg
Treat if persistent
Liver bx optional
Immediate Rx if jaundice or decompensated

* HCC surveillance if indicated

B

Management of Chronic HBV Infection*

HBsAg +

HBeAg

Negative

ALT > 2X ULN
HBV DNA ≥ 20,000 IU/mL
Treat if persistent,
Liver biopsy optional

ALT 1-2X ULN
HBV DNA 2,000-20,000 IU/mL
Q 3 mo ALT & HBV DNA
Consider biopsy if persistent
Rx as needed

ALT < 1X ULN
HBV DNA < 2,000 IU/mL
Q 3 mo ALT X 3,
Then Q 6-12 mo
if ALT still <1x ULN

* HCC surveillance if indicated
Liver Biopsy – Grade of Inflammation & Stage of fibrosis

Fibrosis Staging Systems

Feldman: Sleisenger and Fordtran's Gastrointestinal and Liver Disease, 9th ed. 2010
Elsevier.
Rx for HBV

Therapy:
- Interferon (IFN)-A: 16 weeks
- Pegylated Interferon (PegIFN-A): 48 weeks
- Lamivudine, Adefovir, Entecavir, telbivudine, tenofovir: minimum 1 year, continue for at least 6 months after HBeAg – seroconversion
- If starting with the oral anti-retrovirals, end point is not defined
Hepatitis B Mortality

A  Cirrhosis Mortality

Deaths per 100,000 HBsAg-positive persons

Age (years)

B  Hepatocellular Carcinoma Mortality

Deaths per 100,000 HBsAg-positive persons

Age (years)

Hepatology 2009;49:S45–S55;
Long-term follow-up of alpha-interferon treatment of patients with chronic hepatitis B

Hepatology
Hepatitis C

- Etiology
- Epidemiology
- Natural History
- Diagnosis
- Treatment
- Prognosis
HCV

RNA virus of the Flaviviridae family
50 nm diameter
Worldwide infection HCV

- 170 million infected
  - .01-.02% UK
  - 1-1.5% Southern Europe
  - 6.5% Equatorial Africa
  - 15% in Egypt
USA infection with HCV

- HCV test for Antibody to HCV developed in 1990.
- This protected the blood supply from contamination.
  - 30,000 new infections per year
  - 8,000-10,000 deaths per year
  - Prevalence of anti-HCV antibodies is ~ 1.8%
  - ~ 74% have HCV RNA
  - ~ 2.7 million in the US have chronic infection
  - Genotype 1a in 57%; 1b in 17%
  - 65% infected are aged 30-49
  - Males 2.1%; Females 1.1%
  - Rare in age 20 and younger
  - Incarcerated persons 12-35%
Prevent Transmission HCV

- HCV-infected persons should be counseled to avoid sharing toothbrushes and dental or shaving equipment, and be cautioned to cover any bleeding wound in order to prevent contact of their blood with others.
- Stop using illicit drugs. Avoid reusing or sharing syringes, or other paraphernalia; and to dispose of syringes and needles after one use.
- HCV-infected persons should be advised to not donate blood, body organs, other tissue or semen.
- HCV-infected persons should be counseled that the risk of sexual transmission is low (i.e., those in long-term relationships need not start using barrier precautions and others should always practice “safer” sex).

Natural HX HCV 2

Natural History of HCV Infection

- **Exposure (Acute Phase)**
  - 15% (15) Resolved

- **Chronic**
  - 85% (85) Chronic
    - 80% (68) Stable
    - 20% (17) Cirrhosis
    - 75% (13) Slowly Progressive

- **HIV and Alcohol**
  - 25% (4) HCC Transplant Death

www.medscape.com
Natural History HCV

RX Varies by Genotype
- GT 1 – Liver biopsy suggested and Rx if more than portal fibrosis
- GT 2 & 3 – Liver biopsy optional; Begin Treatment

Diagram:
- Acute Infection
  - 55-89%
  - Peg IFN & Ribavirin
  - 60% response rate
- Chronic HCV Infection
- Cirrhosis
  - 2-24% over 20 years
  - 1-4% per year
- Liver Decompensation
  - 3% per year
- HCC
  - Factors for Sustained Viral Response (SVR)
    - Genotype 2, 3, 4, & 1 (in order)
    - Lower initial viral load < 400,000 IU/mL
    - age < 40 years
    - absence of bridging fibrosis or cirrhosis
    - absence of obesity, hepatic steatosis, or glucose intolerance
    - no HIV co-infection
    - Female
    - single-nucleotide polymorphism (SNP) rs12979860, located near the IL28B gene

Testing for HCV

- Screening – Detects HCV Antibody
  - EIA ~ 97% Specific for Anti-HCV
  - Confirmatory - Recombinant Immunoblot Assay (RIBA)
    - 2 antibodies detected – positive
    - 1 antibody - Indeterminant

- Gold Standard
  - Polymerase Chain Reaction (PCR) for HCV RNA, also gives a viral load
Treatment for HCV

- ALT is not as big a factor in Rx decisions for HCV
  - Those with normal ALT have significantly less fibrosis
  - But there are reports of liver Bx showing 5-30% with marked fibrosis & 1.3% with cirrhosis in the absence of ALT elevation
Criteria for Rx widely accepted

- Age 18 years or older, and HCV RNA positive in serum, and *Liver biopsy showing chronic hepatitis with significant fibrosis* (bridging fibrosis or higher), and compensated liver disease (total serum bilirubin 1.5 g/dL; INR <1.5; serum albumin 3.4+, platelet count 75,000+ mm and no evidence of hepatic decompensation (hepatic encephalopathy or ascites), and acceptable hematological and biochemical indices (Hemoglobin 13 g/dL for men and 12 g/dL for women; neutrophil count 1500 /mm3 + and serum creatinine <1.6 mg/dL, and

- Willing to be treated and to adhere to treatment requirements, and

- No contraindications
Contraindications for Rx HCV

- Major uncontrolled depressive illness
- Solid organ transplant (renal, heart, or lung)
- Autoimmune hepatitis or other autoimmune condition known to be exacerbated by peginterferon and ribavirin
- Untreated thyroid disease
- Pregnant or unwilling to comply with adequate contraception
- Severe concurrent medical disease such as severe hypertension, heart failure, significant coronary heart disease, poorly controlled diabetes, chronic obstructive pulmonary disease
- Age less than 2 years
- Known hypersensitivity to drugs used to treat HCV

Response to Therapy Predicts Sustained Response

Nonresponders <5% Respond to a second Rx

EVR - Early Virological Response
RVR – Rapid Virological Response
ETR – End of Treatment Response

SVR Sustained, ND 24 weeks
After Rx stopped
Late relapse after 48 weeks is Very uncommon
HCV response to treatment by Genotype

Peg-interferon Alfa-2b + Ribavirin
Virologic Response by Genotype

$RBV \text{ Dose} > 10.6 \text{ mg/kg}$

![Graph showing virologic response by genotype with different treatment regimens.]

www.medscape.com
Survival with chronic HCV

Number of patients under observation
838  799  708  566  420  274  164  106  71   35   7   0

Age-specific survival by hepatitis C virus (HCV) status, all causes of death, United States, 1991–2003.

Hepatitis Cases

Case 1 – A 37 year old woman applies for life insurance. She moved from
- Taiwan to the US 15 years prior to application. Her OB/Gyn noticed an
  elevated ALT of 60 IU/L and referred her to a GI specialist. She does not
- smoke or drink alcohol; family history revealed that her mother has chronic
- Hepatitis B and her father died of hepatocellular carcinoma at age 57.
- A brother also has Hepatitis B. Testing reveals she is HBsAg positive,
- HBeAg positive, and a Hep B DNA count of 350,000 IU/L. The last note says
  They are considering treatment options.

  Chronic Hepatitis B

Case 2 – a 49 year old man applied for life insurance. 2 years ago he
- had an ALT of 66 IU/L. Reflex testing revealed a positive Hepatitis C antibody.
- He followed up with his AP and had a positive PCR for HCV RNA at 350,000
- IU/L. He was treated with Peg IFN and Ribivarin for 48 weeks and RNA has
  been undetectable for 6 months after that. His next exam is planned
  for 6 months.
Thank you for attending our webinar

Questions?
- Send questions later to rbraun@scor.com
- Or call (913) 901-4749.