Hepatitis B

The virus and the disease
This material was prepared by the Viral Hepatitis Prevention Board
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The disease

- Infectious inflammatory illness of the liver caused by the hepatitis B virus (HBV)
- HBV can cause both acute and chronic infection
- People with chronic hepatitis B infection are at high risk of developing serious liver diseases (cirrhosis and liver cancer)
The hepatitis B virus (HBV)

- Hepadnavirus (Hepa from hepatotropic + DNA virus)
- First identification of Hep B surface antigen by Prof Blumberg in 1965
- Circular genome of partially double-stranded DNA
- Infection restricted to humans and some apes (chimpanzees)

HBsAg (spheric & filamentous) with complete virions (Dane particles)
Morphology

- Virion (Dane particle) consist of a surface and a core.
- Four major genes (DNA):
  - S (surface)
  - C (core)
  - P (polymerase)
  - X (transcriptional transactivating)
- S gene consists of 3 regions: S, pre-S1, pre-S2
  - encode the envelop protein HBsAg
- C gene consists of 2 regions: pre-core and core
  - encode 2 proteins, the core antigen (HBcAg) and the e antigen (HBeAg)
Replication in the liver through an RNA intermediate form by reverse transcription
Genotypes

- 8 genotypes: A to H
- 2 additional genotypes I and J described more recently in Asia, but still controversial
- Characteristic geographical distribution
- Genotype affects transmission, disease severity and response to treatment
Major distribution of genotypes

Updated January 2014

Adapted from Lin & Kao, J Gastroenterol Hepatol 2011
Transmission

- Transmitted by percutaneous or mucosal exposure to infectious blood or body fluids (such as semen and vaginal fluids) of an infected person
  - perinatal transmission
  - close contact in early childhood
  - sexual contact
  - blood transfusions
  - contaminated needles/syringes (health care setting, IDU, tattooing...)
- Same mode of transmission as HIV, but 50 to 100 times more infectious

Concentration of hepatitis B virus in various body fluids:

<table>
<thead>
<tr>
<th>High</th>
<th>Moderate</th>
<th>Low/Not detectable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>Semen</td>
<td>Urine</td>
</tr>
<tr>
<td>Serum</td>
<td>Vaginal fluid</td>
<td>Feces</td>
</tr>
<tr>
<td>Wound exudate</td>
<td>Saliva</td>
<td>Sweat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tears</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breastmilk</td>
</tr>
</tbody>
</table>
## Transmission by endemicity level

<table>
<thead>
<tr>
<th>Age at infection</th>
<th>High endemicity (≥8% HBsAg prevalence)</th>
<th>Intermediate endemicity (2-&lt;8% prevalence)</th>
<th>Low endemicity (&lt;2% prevalence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns and early childhood</td>
<td>All age groups, but primarily in infants and children</td>
<td>Adults (risk groups)</td>
<td></td>
</tr>
</tbody>
</table>

- **Transmission**
  - Perinatal, close contact (in early childhood)
  - Perinatal, early childhood exposure, sexual, percutaneous exposure
  - Sexual contact, percutaneous exposure (IDU)

*Update January 2014*
Pathogenesis

- Long incubation period (45-180 days, average of 60-90 days)
- Interference with liver functions by replicating in the hepatocytes
- Immune response causes both hepatocellular damage (via cytotoxic T-lymphocyte lysis of infected hepatocytes) and viral clearance
Natural course

Age of infection is determining factor for clinical expression and development of chronic infection:

- Acute infection symptomatic in 10% of children and 30-40% of adults
- Risk for chronic infection inversely related to age at infection: 90% for children < 1 year, 30% if infection at 1-4 years and <10% for adults

Clinical outcome

- Recovery: 10-70%
- Childhood infection: 30-90%
- Fulminant hepatitis: <1%
- Chronic infection: 10-20%*
- Compensated cirrhosis: 20-30%*
- Transplant or Death: 15%*
- Decompensation
- HCC: 10-15%*
- Inactive carrier: <1-2% per year
- Recovery: 95%

* Estimated 5 year cumulative incidence

Clinical features

Update January 2014

Acute hepatitis B

- Wide range of clinical manifestations, from subclinical to fulminant hepatitis
- Possible symptoms: insidious onset with anorexia, nausea, vomiting, body aches, mild fever and dark urine, often progressing to jaundice
- Icteric hepatitis in < 30% of acute infections
- Symptoms generally last for a few weeks, but can persist several months
- Case fatality rate: 0.5 to 1%

Clinical features

Update January 2014
Chronic hepatitis B

- Wide range of clinical manifestations, from asymptomatic carrier to cirrhosis and/or HCC
- Factors affecting progression: age, gender (male), viral load, genotype, host genetic factors, alcohol consumption, obesity, concomitant infection with other hepatitis virus(es) or HIV
- Premature mortality from chronic liver disease 15-25%\(^1\)
- Outcome depends on severity of liver damage at moment HBV replication is controlled

Clinical features

Update January 2014

Laboratory diagnosis

- Based on hepatitis B serologic testing, involving measurement of different hepatitis B virus (HBV)-specific antigens and antibodies:
  - Hepatitis B surface antigen (HBsAg): general marker of infection
  - Hepatitis B surface antibody (anti-HBs): documents recovery or immunity
  - Total hepatitis B core antibody (anti-HBc): documents present or past infection
  - IgM antibody to hepatitis B core antigen (IgM anti-HBc): marker of acute infection
  - Hepatitis B e antigen (HBeAg): presence associated with higher rates of viral replication. However, not all the HBV produce HBeAg
- HBV-DNA: indicates active replication of virus. Used for monitoring of response to therapy and transmission risk
## Interpretation of serologic tests results

<table>
<thead>
<tr>
<th>Marker</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg, anti-HBc, anti-HBs</td>
<td>-</td>
<td>Never infected or exposed</td>
</tr>
<tr>
<td>HBsAg, anti-HBc, anti-HBs</td>
<td>- +</td>
<td>Immune due to natural infection</td>
</tr>
<tr>
<td>HBsAg, anti-HBc, anti-HBs</td>
<td>+ +</td>
<td>Immune due to hepatitis B vaccination</td>
</tr>
<tr>
<td>HBsAg, anti-HBc, IgM anti-HBc, anti-HBs</td>
<td>+ + -</td>
<td>Acute infection</td>
</tr>
<tr>
<td>HBsAg, anti-HBc, IgM anti-HBc, anti-HBs</td>
<td>+ + -</td>
<td>Chronic infection</td>
</tr>
</tbody>
</table>
### Interpretation of serologic tests results (2)

<table>
<thead>
<tr>
<th>Marker</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg anti-HBc</td>
<td>-</td>
<td>Unclear, 4 possibilities:</td>
</tr>
<tr>
<td>anti-HBs</td>
<td>+</td>
<td>1) resolved infection</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>2) false positive anti-HBc, susceptible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3) low level chronic infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4) resolving acute infection</td>
</tr>
<tr>
<td>HBeAg anti-HBe</td>
<td>+</td>
<td>High viremic infection with active replication (in acute or chronic)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>Low viremic infection (in acute or chronic)</td>
</tr>
<tr>
<td>HBsAg anti-HBc</td>
<td>+</td>
<td>HBV precore mutant</td>
</tr>
<tr>
<td>HBeAg anti-HBe</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>HBV-DNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from. Recommendations of the Advisory Committee on Immunization Practices. MMWR 2005;54(No RR-16):4-5.
HBV serum markers in acute resolving infection

Serologic markers

Update January 2014

Source: CDC, MMWR September 28, 2008
Progression to chronic HBV infection

Serologic markers

Update January 2014

Source: CDC, MMWR September 28, 2008
Serological profiles of chronic infection

**Chronic hepatitis B**
**HBsAg positive > 6 months**

- **Inactive carrier**
  - HBsAg positive
  - HBeAg negative
  - Anti-HBe positive
  - Low or no detectable DNA
  - Normal ALT

- **Moderate viral replication**
  - HBsAg positive
  - HBeAg negative
  - Anti-HBe positive
  - Moderate levels DNA
  - Elevated/fluxuating ALT

- **Active liver disease**
  - HBsAg positive
  - HBeAg positive
  - Anti-HBe negative
  - High levels DNA
  - Persistently elevated ALT

Adapted from Fattovich et al. J Hepatol 2008 Feb;48(2):335-52