VIRAL HEPATITIS

INTRODUCTION

The clinical diseases we now know as viral hepatitis have been recognized since ancient times as outbreaks of "infectious jaundice." It is important to realize that there are many infectious agents which manifest themselves as "hepatitis." It will be your job as a physician to be able to decipher, from patient history and laboratory results, the nature of the particular agent (or even agents!) which caused the disease. This is essential not only for immediate therapy, but also to predict the long term effect the infection will have on the individual.

There are at least five different viruses that cause hepatitis (see summary table). These viruses vary in their mode of transmission and mechanism of genome replication.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
<th>Hepatitis D</th>
<th>Hepatitis E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common name</td>
<td>&quot;Infectious&quot;</td>
<td>&quot;Serum&quot;</td>
<td>&quot;Non-A, non-B posttransfusion&quot;</td>
<td>&quot;Delta agent&quot;</td>
<td>&quot;Enteric non-A, non-B&quot;</td>
</tr>
<tr>
<td>Virus structure</td>
<td>Picornavirus; capsid, RNA</td>
<td>Hepadnavirus; envelope, DNA</td>
<td>Flavivirus; envelope, RNA</td>
<td>Viroid-like; envelope, circular RNA</td>
<td>Calicivirus-like capsid, RNA</td>
</tr>
<tr>
<td>Transmission</td>
<td>Fecal-oral</td>
<td>Parenteral, sexual</td>
<td>Parenteral, sexual</td>
<td>Parenteral, sexual</td>
<td>Fecal-oral</td>
</tr>
<tr>
<td>Onset</td>
<td>Abrupt</td>
<td>Insidious</td>
<td>Insidious</td>
<td>Abrupt</td>
<td>Abrupt</td>
</tr>
<tr>
<td>Incubation period (days)</td>
<td>15-50</td>
<td>45-160</td>
<td>14-180+</td>
<td>15-64</td>
<td>15-50</td>
</tr>
<tr>
<td>Severity</td>
<td>Mild</td>
<td>Occasionally severe</td>
<td>Usually subclinical; 70% chronicity</td>
<td>Co-infection with HBV occasionally severe; superinfection with HCV often severe</td>
<td>Normal patients, mild; pregnant women, severe</td>
</tr>
<tr>
<td>Mortality</td>
<td>≤0.5%</td>
<td>1%-2%</td>
<td>=4%</td>
<td>High to very high</td>
<td>Normal patients, 1%-2%; pregnant women, 20%</td>
</tr>
<tr>
<td>Chronicity/Carrier state</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Other disease associations</td>
<td>None</td>
<td>Primary hepatocellular carcinoma, cirrhosis</td>
<td>Primary hepatocellular carcinoma, cirrhosis</td>
<td>Cirrhosis, fulminant hepatitis</td>
<td>None</td>
</tr>
<tr>
<td>Laboratory diagnosis</td>
<td>Symptoms and anti-HAV IgM</td>
<td>Symptoms and serum levels of HBSAg, HBeAg, and anti-HBc IgM</td>
<td>Symptoms and anti-HCV ELISA</td>
<td>Anti-HCV ELISA</td>
<td>—</td>
</tr>
</tbody>
</table>

DNA, Deoxyribonucleic acid; ELISA, enzyme-linked immunosorbent assay; HAV, hepatitis A virus; HBc, hepatitis B core; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBC, hepatitis B virus; HCV, hepatitis C virus; HCV, hepatitis D virus; IgM, immunoglobulin M, RNA, ribonucleic acid.

HEPATITIS B VIRUS

Hepatitis B, previously known as "serum hepatitis"

- Is produced by a DNA virus
- Is spread parenterally by blood or needles, by sexual contact, and perinatally
- Has a median incubation time of approximately 3 months
- Is followed by chronic hepatitis in 5% - 10% of patients, and
- Is causally associated with primary hepatocellular carcinoma.

An estimated 300,000 cases of hepatitis B occur in the United States each year, with 4,000 fatalities caused by the agent.
Unique features of hepadnavirus

HBV is a small enveloped DNA virus with several unusual properties

- Enveloped virion contains a partial double-stranded circular DNA genome
- Replication involves a circular RNA genome intermediate
- Virus encodes and carries a reverse transcriptase
- Virus encodes several proteins (HBsAg; HBe/HBc) that share genetic sequences but with different mRNAs or in-frame start codons (AUGs)
- HBV has strict tissue tropism to the liver
- HBV infected cells produce and release large amounts of HBsAg particles lacking DNA
- The HBV genome can integrate into the host chromosome

STRUCTURE OF THE VIRIONS

![Diagram of HBV virions](image-url)
FIGURE 66-6. DNA, RNA, mRNA, and proteins of hepatitis B virus (HBV). The inner green circles represent the DNA genome with the nucleotide number at the center. DR1 and DR2 are direct repeat sequences of DNA and are important for replication and integration of the genome. The 3500-base transcript (outer black thin-line circle) is larger than the genome and is the template for replication of the genome. Bold arcs represent mRNA for viral proteins. Note that several proteins are translated from the same mRNA but from different AUG codons and that different mRNAs overlap. AAA, 3' Polya at end of mRNA; C, C mRNA (HBeAg); E, E mRNA (HBeAg); L, large glycoprotein; m, medium glycoprotein; P, polymerase-protein primer for replication; s, small glycoprotein; S, S mRNA (HbsAg); X, X mRNA. (Modified from Armstrong D, Cohen I: Infectious diseases, St Louis, 1999, Mosby.)
Hepadnavirus replication is unique in that it involves reverse transcription of a RNA into DNA and the partially double-strand DNA is the genetic information found in the virus particles.
Proposed pathway for replication of hepatitis B virus. Following entry into the hepatocyte and uncoating of the nucleocapsid core, the partially double-stranded DNA genome is completed by enzymes in the core and then delivered to the nucleus. Transcription of the genome produces four mRNA including a mRNA larger than the genome (3500 bases). The mRNA moves to the cytoplasm and is translated into protein. Core proteins assemble around the 3500 base mRNA and (-) sense DNA is synthesized from the mRNA template by the viral polymerase (reverse transcription). This step is sensitive to lamivudine. The polymerase then uses the (+) sense DNA as a template for the synthesis of the partial by a completion of the (+) DNA. Virus particles are then released by exocytosis.

**PATHOGENESIS**

HBV can cause acute or chronic, symptomatic or asymptomatic, hepatitis. Which of these occurs seems to be determined by the individual’s immune response to the infection.

Figure 4
Sequence of appearance of viral antigens and antibodies in acute self-limiting cases of hepatitis B. HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; anti-HBc, antibody to hepatitis B core antigen; anti-HBe, antibody to HBeAg; anti-HBs, antibody to HBsAg.
Figure 5

Sequence of appearance of viral antigens and antibodies in chronic active hepatitis B. HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; anti-HBc, antibody to hepatitis B core antigen. Antibodies to HBsAg and HBeAg not detected.
LABORATORY DIAGNOSIS OF HBV INFECTION

The laboratory diagnosis of acute hepatitis B is best made by demonstrating the IgM antibody to hepatitis B core antigen in serum. Almost all patients who develop jaundice will be anti HBC IgM positive at the time of clinical presentation. In patients with self-limiting anicteric disease, HBsAg detection is serum may also occur. Past infection with Hepatitis B is best determined by detecting anti-HBc, anti-HBs or both. Chronic infection with Hepatitis B is best detected by persistence of HBsAg in blood for more than 6 to 12 months.

ANTIVIRAL THERAPY FOR HBV INFECTION

Antiviral therapy for HBS has dramatically improved over the last 20 years. Lamivudine, a nucleoside analogue that inhibits reverse transcriptase activity, was shown to be effective in clearance of HBV DNA from the serum (virtually 100% clearance during treatment, but sustained remission in only 19% of patient). Drug resistance does arise, so alternative therapies were developed.

In 2002, the FDA approved Hepsera (adefovir dipivoxil) for treatment of HBV infection. Hepsera is an acyclic nucleotide analogue of adenosine monophosphate. It inhibits HBV RT by competing with the natural substrate deoxyadenosine triphosphate and by causing DNA chain termination after it’s corporation. Importantly, HBV strains that are resistant to lamivudine were shown to be susceptible to Hepsera. In addition, entecavir (2005), telbivudine (2006) and tenofovir DF (2008) (all RT inhibitors originally developed for HIV) have been shown to be effective for inhibition of HBV. Importantly, the development of drug resistance was found to be lower using the newer drugs (see table from NEJM 359:23-24, 2008)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Peglated Interferon</th>
<th>Lamivudine</th>
<th>Adefovir Dipivoxil</th>
<th>Entecavir</th>
<th>Telbivudine</th>
<th>Tenofovir DF</th>
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<tbody>
<tr>
<td>HBsAg-positive patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 yr</td>
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<td>36</td>
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<td>67</td>
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</tr>
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<td>42</td>
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<td>5 yr</td>
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<td>76</td>
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<td>HBsAg-negative patients</td>
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<tr>
<td>Undetectable HBV DNA by PCR†</td>
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<tr>
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<tr>
<td>Resistance</td>
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<td></td>
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</tr>
<tr>
<td>1 yr</td>
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<td>&lt;1</td>
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<tr>
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<td>29</td>
<td>1</td>
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</tbody>
</table>

* Data are from Yuen et al.,15 Marcellin et al.,12,14 Hadziyannis et al.,17 Tenney et al.,18 and Liaw et al.19 HBsAg denotes hepatitis B anti- gen. HBV hepatitis B virus. NA not available. and PCE polymerase chain reaction.
† The lower limit of detection varied from 40 to less than 200 IU per milliliter (200 to <1000 copies per milliliter).
VACCINE

HBV vaccine is safe and effective

- HBsAg manufactured by yeast via recombinant DNA technology
- Active immunization with recombinant HBsAg vaccine is recommended for healthcare workers and has been incorporated into childhood vaccine schedule.

HEPATITIS DELTA VIRUS

HDV is transmitted via blood, either as a co-infection with HBV or, a HBV carrier can be super-infected with HDV (although the contaminated blood probably also contains HBV).

HDV infection results in fulminant hepatitis with a high mortality rate (mortality rate varies depending on the study but estimates are 40-60% mortality). If the patient survives, they can also be persistently infected with HDV.

STRUCTURE

- 35 nm particle-HBsAg on the surface
- Capsid- delta antigen (the only protein encoded by the virus)
- Genome- circular RNA

REPLICATION

The single-stranded, circular RNA is thought to replicate via a "rolling circle" mechanism:

Fig. 6. As the RNA "rolls off" the circle, it cleaves itself. The delta virus RNA acts as a ribozyme to cleave itself. The linear RNA then ligates itself back together into a circle. This self-cleavage, self-ligation property is very unique, only HDV RNA and some plant viroid RNAs have this ability.

DIAGNOSIS OF HDV INFECTION

Diagnosis is made most commonly by detecting IgM or IgG to delta antigen in serum. IgM antibodies appear within 3 weeks of infection and persist for several weeks. IgG antibodies persist for years.
HEPATITIS C VIRUS

Previously, NonA-NonB Hepatitis was a diagnosis of exclusion. We now know that there is a specific virus that is responsible for the majority of non-HBV, post-transfusion hepatitis. The new virus is designated Hepatitis C Virus (HCV). Recombinant DNA technology was used to develop reagents for testing blood for HCV. HCV is a positive strand RNA virus classified in the Flaviviridae.
PATHOGENESIS
Hepatitis C is usually insidious in onset, mild and anicteric, but results in chronic liver disease in many patients. As most transmitters of the disease are asymptomatic, a chronic carrier state is presumed. Current estimates suggest that 1% of the U.S. population is HCV positive, and 3% of the world’s population is HCV positive.
DETECTION OF HCV

Infection with HCV is generally detected by demonstration of anti-HCV antibodies. Unfortunately, the antibody responses in acute disease may remain negative for 1 to 3 weeks after clinical onset. Reverse-transcription-polymerase chain reaction (RT-PCR) assay can also be performed to detect HCV RNA in the sera. Antibody assays are most helpful in chronic hepatitis, especially when multiple antigens are sought.

ANTI-VIRAL THERAPY

Previous anti-viral therapy for HCV was treatment with a combination of IFN and ribavirin, termed Rebetron. This treatment has significant side-effects and resulted in a sustained virologic response in about 50% of patients (genotype dependent).

Current treatment calls for the use of direct acting antivirals (DAAs). In general, 2 drugs that target different HCV proteins are used at once. This reduces the incidence of drug resistance and shortens the duration of treatment required to obtain a sustained virologic response (no detectable RNA by RT-PCR of serum sample).

Figure 1: Specific targets of the direct acting antiviral agents.

American Journal of Transplantation 2014; 14: 994–1002
Studies from 2016 provide evidence that a 12 week treatment with sofosbuvir (NS5B inhibitor) and velpatasvir (NS5A inhibitor) provides a sustained virologic response (SVR), with undetectable levels of HCV RNA at 12-24 weeks after stopping treatment (advertised as Epclusa on TV).

**VACCINE DEVELOPMENT**

Currently there are no effective vaccines for HCV.

**HEPATITIS E VIRUS**

HEV is transmitted by the fecal-oral route and results in a self-limiting illness similar to HAV.

HEV infection was seen in India and Southeast Asia and is not commonly seen in the U.S.A. (yet). Testing for HEV requires sending the blood sample to the CDC or Public Health Dept.

Killed virus vaccine is in development and undergoing testing in India and Nepal. Currently it is unclear if the HEV vaccine could be used for post-exposure prophylaxis similar to the HAV vaccine. Watch for future developments.
STUDY QUESTIONS

1. How do the acute viral hepatitides differ epidemiologically?

2. What are the distinguishing features of hepatitis C virus ... of D virus?

3. Discuss the prophylactic measures available for the viral hepatitides.

EXAMPLE OF TEST QUESTION

Chronic viral infection has been associated with all the following EXCEPT:

A. HAV
B. HBV
C. HCV
D. HDV
E. CMV

CORRECT ANSWER TO ABOVE QUESTION: A