Diagnosis and Prevention of Viral Hepatitis

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“Nearly all men can stand adversity, but if you want to test a man's character, give him power and destination”

— Abraham Lincoln, American Ex-President
Viral Hepatitis Introduction
Hepatitis
Inflammation of the Liver

- Hepatitis can have many causes at its roots, including but not limiting to, factors such as:
  - Drugs and medications
  - Toxins (poisoning)
  - Alcohol (intoxication)
  - Viral infections (A, B, C, D, E)
  - Other microbial infections (e.g., parasites, bacteria)
  - Physical insults, hepatic injury and damage
Where is My, Your Liver? The Anatomic Liver
Histology of the Liver

Figure 24.15ab Tortora - PAP 12/e
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Liver Physiology

- Several of the physiologic functions of the liver are well established:
  - Stores sugar needed for energy and metabolism
  - Absorbs minerals and nutrients
  - Breaks down poisons (toxins) and drugs
  - Makes molecular proteins that help build new tissue and repair broken tissue
  - Produces bile, which helps with digestion and removal of waste from the body
Liver Functions at a Glance:

- **Metabolism** – Carbohydrate, fat and protein
- **Secretory** – Bile acids, salts and pigments
- **Excretory** – Bilirubin, drugs, toxins
- **Synthesis** – Albumin, coagulation factors
- **Storage** – Vitamins, carbohydrates
- **Detoxification** – Toxins, ammonia
Hepatitis Terminology

- **Acute Hepatitis**: Short-term hepatitis
  - Body’s immune system clears the virus from the body within 6 months – *negligent to low viremia*

- **Chronic Hepatitis**: Long-term hepatitis
  - Infection lasts longer than 6 months, because the body’s immune system, due to certain causes, cannot efficiently clear the virus from the body – *moderate to high viremia*
Hepatic Injury

- The liver is vulnerable to a variety of toxic, metabolic, infectious, circulatory, and neoplastic insults, both primary and secondary

- The liver has a limited number of responses to an infinite number of insults:
  - Inflammation
  - Degeneration
  - Necrosis
  - Fibrosis
  - Cirrhosis
Hepatic Injury, *cont’d*

- Hepatitis – Inflammation of liver
- Hepatocyte Necrosis – liver function jeopardized – e.g., jaundice
- Viral, Alcohol, Immune, Drugs & Toxins
- Biliary obstruction – gall stones
- Acute, Chronic & Fulminant – clinical types
- Viral Hepatitis –
  - Specific – Hepatitis A, B, C, D, E, & other
  - Systemic – CMV (cytomegalovirus), EBV (epstein-barr virus), other
Patterns of Viral Hepatitis:

- Carrier state / Asymptomatic phase
- Acute hepatitis
- Chronic hepatitis
  - Chronic persistent hepatitis (CPH)
  - Chronic active hepatitis (CAH)
- Fulminant hepatitis
- Cirrhosis
- Hepatocellular carcinoma (HCC)
# Categories of Conditions Causing Hepatic Encephalopathy (Cirrhosis)

<table>
<thead>
<tr>
<th>Type</th>
<th>Description (Cause)</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Acute liver failure</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Portosystemic bypass (shunt)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Cirrhosis</td>
<td>Episodic Persistent Minimal</td>
</tr>
</tbody>
</table>
## West Haven Criteria of Severity of Hepatic Encephalopathy (Cirrhosis)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>Normal standard clinical exam; abnormal responses to detailed psychometric tests</td>
</tr>
<tr>
<td>1</td>
<td>Euphoria or anxiety; shortened attention span; mild lack of awareness</td>
</tr>
<tr>
<td>2</td>
<td>Lethargy or apathy; mild distortion of place or time; mild personality changes; impaired performance on addition/subtraction</td>
</tr>
<tr>
<td>3</td>
<td>Confusion, disorientation, or somnolence to semistupor but responsive to verbal stimuli</td>
</tr>
<tr>
<td>4</td>
<td>Coma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Item</th>
<th>Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does the patient know which month it is (e.g., January, February)?</td>
<td></td>
</tr>
<tr>
<td>2. Does the patient know the day of the week (e.g., Monday, Tuesday)?</td>
<td></td>
</tr>
<tr>
<td>3. Can the patient count backward from 10 to 1 without making mistakes or stopping?</td>
<td></td>
</tr>
<tr>
<td>4. If asked to do so, does the patient raise arms?</td>
<td></td>
</tr>
<tr>
<td>5. Does the patient understand what you are saying? (Based on answers to questions 1-4)</td>
<td></td>
</tr>
<tr>
<td>6. Is the patient awake and alert?</td>
<td></td>
</tr>
<tr>
<td>7. Is the patient fast asleep and difficult to awake/arouse?</td>
<td></td>
</tr>
<tr>
<td>8. Can the patient talk?</td>
<td></td>
</tr>
<tr>
<td>9. Can the patient speak correctly? (i.e., can you understand what they say, and do they speak without stammering)</td>
<td></td>
</tr>
</tbody>
</table>

*Clinical hepatic encephalopathy staging scale score is the sum of scores for all 9 questions. Range is from 0 (no hepatic encephalopathy) to 9.

Utility of Liver Biopsy

Confirm presence of chronic hepatitis

Assess severity of necroinflammation

Role of Liver Biopsy

Evaluate possible concomitant disease processes

Assess fibrosis

Assess therapeutic intervention

Progression of Fibrosis on Liver Biopsy

**No Fibrosis**

**Stage 1: Fibrous expansion of some portal areas**

**Stage 3: Fibrous expansion of most portal areas with occasional portal to portal bridging**

**Stage 4: Fibrous expansion of portal areas with marked bridging (portal to portal and portal to central)**

**Stage 5, 6: Cirrhosis, probable or defined**

**Cirrhotic liver: Gross anatomy of cadaver**
Elements of Hepatitis Management and Strategizing

Phase I: Screening and diagnosis
Phase II: Counseling and health care maintenance
Phase III: Evaluation for prevention and treatment
Phase IV: Monitoring treatment
Phase V: Managing progressive liver disease
Hepatitis Screening is the First Step on the Long Road to a Prevention and Cure

- Screening
- Testing
- Counseling
- Assessment
- Treatment
- Cure
Viral Hepatitis A-E at a Glance

An Overview
Viral Hepatitis - Historical Perspectives

- "Infectious"
- "Serum"
- Viral hepatitis
- Enterically transmitted
- Parenterally transmitted
- NANB
- F, G, TTV
- ? other
# Type of Hepatitis

<table>
<thead>
<tr>
<th>Source of virus</th>
<th>Feces</th>
<th>Blood/blood-derived body fluids</th>
<th>Blood/blood-derived body fluids</th>
<th>Blood/blood-derived body fluids</th>
<th>Feces</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of transmission</td>
<td>Fecal-oral</td>
<td>Percutaneous permucosal</td>
<td>Percutaneous permucosal</td>
<td>Percutaneous permucosal</td>
<td>Fecal-oral</td>
</tr>
<tr>
<td>Chronic infection</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Prevention</td>
<td>Pre/post-exposure immunization</td>
<td>Pre/post-exposure immunization</td>
<td>Blood donor screening; risk behavior modification</td>
<td>Pre/post-exposure immunization; risk behavior modification</td>
<td>Ensure safe drinking water</td>
</tr>
</tbody>
</table>
Transmission of Viral Hepatitis

<table>
<thead>
<tr>
<th>Transmission Route</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>Food - Borne</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Fecal - Oral</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Water - Borne</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Raw Shellfish</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Intra-Institutional</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>I.V. Drug Use</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Transfusion</td>
<td>▲</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Sexual</td>
<td>▲</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Anal - Oral Contact</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Oral - Oral Contact</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Household</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Mother to Newborn</td>
<td>▲</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

- **Common**: ●
- **Infrequent**: ▲
- **Never**: ●
- **Suspected**: ●

Legend:
- ●: Common
- ▲: Infrequent
- ■: Never
- ●: Suspected
### ABCs of Hepatitis

**HEPATITIS A** is caused by the Hepatitis A virus (HAV).

<table>
<thead>
<tr>
<th>U.S. Statistics</th>
<th>Routes of Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated 25,000 new infections in 2007</td>
<td>Ingestion of fecal matter, even in microscopic amounts, from:</td>
</tr>
<tr>
<td></td>
<td>Close person-to-person contact with an infected person</td>
</tr>
<tr>
<td></td>
<td>Sexual contact with an infected person</td>
</tr>
<tr>
<td></td>
<td>Ingestion of contaminated food or drinks</td>
</tr>
</tbody>
</table>

**HEPATITIS B** is caused by the Hepatitis B virus (HBV).

<table>
<thead>
<tr>
<th>U.S. Statistics</th>
<th>Routes of Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated 43,000 new infections in 2007</td>
<td>Infection of blood, semen, or other body fluids, primarily through:</td>
</tr>
<tr>
<td>Estimated 1.2 million people with chronic HBV infection</td>
<td>Contact with infected blood, semen, or other body fluids</td>
</tr>
<tr>
<td></td>
<td>Birth to an infected mother</td>
</tr>
<tr>
<td></td>
<td>Sexual contact with an infected person</td>
</tr>
<tr>
<td></td>
<td>Sharing of contaminated needles, syringes, or other injection equipment</td>
</tr>
<tr>
<td></td>
<td>Needlestick or other sharp instrument injuries</td>
</tr>
</tbody>
</table>

**HEPATITIS C** is caused by the Hepatitis C virus (HCV).

<table>
<thead>
<tr>
<th>Screening Recommendations for Chronic Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testing is recommended for:</td>
</tr>
<tr>
<td>All pregnant women</td>
</tr>
<tr>
<td>Persons born in regions with intermediate or high rates of Hepatitis B (HBsAg prevalence ≥ 5%)</td>
</tr>
<tr>
<td>U.S.-born persons not vaccinated as infants whose parents were born in regions with high rates of Hepatitis B (HBsAg prevalence &gt; 5%)</td>
</tr>
<tr>
<td>Infants born to HBsAg-positive mothers</td>
</tr>
<tr>
<td>Household, needle-sharing, or sex contacts of HBsAg-positive persons</td>
</tr>
<tr>
<td>Men who have sex with men</td>
</tr>
<tr>
<td>Injection drug users</td>
</tr>
<tr>
<td>Patients with elevated liver enzymes (ALT/AST) of unknown etiology</td>
</tr>
<tr>
<td>Hemodialysis patients</td>
</tr>
<tr>
<td>Persons needing immunosuppressive or cytotoxic therapy</td>
</tr>
<tr>
<td>HCV-infected persons</td>
</tr>
<tr>
<td>Donors of blood, plasma, organs, tissues, or semen</td>
</tr>
</tbody>
</table>

**Persons at Risk** |

| Travellers to regions with intermediate or high rates of Hepatitis A |
| Sex contacts of infected persons |
| Persons with multiple sex partners |
| Persons with a sexually transmitted disease (STD) |
| Men who have sex with men |
| Injection drug users |
| Patients with elevated liver enzymes (ALT/AST) of unknown etiology |
| Hemodialysis patients |
| Residents and staff of facilities for developmentally disabled persons |
| Travellers to regions with intermediate or high rates of Hepatitis B (HBsAg prevalence ≥ 2%) |

**Incubation Period** 15 to 50 days (average: 28 days) 45 to 160 days (average: 120 days) 14 to 42 days

**Symptoms of Acute Infection**

<table>
<thead>
<tr>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of appetite</td>
<td>Vomiting</td>
<td>Screening assay (EIA or CIA) for anti-HCV</td>
</tr>
<tr>
<td>Nausea</td>
<td>Abdominal pain</td>
<td>Verification by an additional, more specific assay (e.g., nucleic acid testing (NAT) for HCV RNA)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Fatigue</td>
<td>Testing is recommended for:</td>
</tr>
</tbody>
</table>

**Likelihood of Symptomatic Acute Infection**

<table>
<thead>
<tr>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10% of children &lt; 6 years have jaundice</td>
<td>&lt; 1% of infants &lt; 1 year develop symptoms</td>
<td>Screening assay (EIA or CIA) for anti-HCV</td>
</tr>
<tr>
<td>40%–50% of children age 6–14 years have jaundice</td>
<td>5%–15% of children 1–5 years develop symptoms</td>
<td>Testing is recommended for:</td>
</tr>
<tr>
<td>70%–80% of persons &gt; 14 years have jaundice</td>
<td>30%–50% of persons &gt; 5 years develop symptoms</td>
<td>Persons who currently inject drugs or who have injected drugs in the past, even if once or many years ago</td>
</tr>
</tbody>
</table>

**Potential for Chronic Infection**

<table>
<thead>
<tr>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>No medication available</td>
<td>Acute: No medication available; best addressed through supportive treatment</td>
</tr>
</tbody>
</table>

**Severity**

<table>
<thead>
<tr>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most persons with acute disease recover with no lasting liver damage; rarely fatal</td>
<td>Most persons with acute disease recover with no lasting liver damage; acute illness is rarely fatal</td>
<td>Most persons with chronic liver disease, including HCV-infected persons with chronic liver disease</td>
</tr>
<tr>
<td>Most persons with acute disease recover with no lasting liver damage; acute illness is rarely fatal</td>
<td>Most persons with chronic liver disease, including HCV-infected persons with chronic liver disease</td>
<td></td>
</tr>
<tr>
<td>15%–25% of chronically infected persons develop chronic liver disease, including cirrhosis, liver failure, or liver cancer</td>
<td>Acute: No medication available; best addressed through supportive treatment</td>
<td></td>
</tr>
<tr>
<td>Estimated 3,000 persons in the United States die from HBV-related illness per year</td>
<td>Most persons with chronic liver disease, including HCV-infected persons with chronic liver disease</td>
<td></td>
</tr>
</tbody>
</table>

**SeroLogic Tests for Acute Infection**

<table>
<thead>
<tr>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM anti-HAV</td>
<td>HBsAg</td>
<td>Screening assay (EIA or CIA) for anti-HCV</td>
</tr>
<tr>
<td>HBsAg in acute and chronic infection</td>
<td>Additional markers as needed</td>
<td>Testing is recommended for:</td>
</tr>
<tr>
<td>IgM anti-Hbc is positive in acute infection only</td>
<td>No vaccine available</td>
<td>Persons who currently inject drugs or who have injected drugs in the past, even if once or many years ago</td>
</tr>
</tbody>
</table>

**Vaccination Recommendations**

**Hepatitis A vaccine is recommended for:**

- All infants at birth
- Older children who have not previously been vaccinated
- Susceptible sex partners of infected persons
- Persons with multiple sex partners
- Persons seeking evaluation or treatment for an STD
- Women who have sex with men
- Injection drug users
- HIV-infected persons
- Persons with end-stage renal disease, including predialysis, hemodialysis, peritoneal dialysis, and home dialysis patients
- Residents and staff of facilities for developmentally disabled persons
- Travellers to regions with intermediate or high rates of Hepatitis B ( HBsAg prevalence ≥ 25%)
- Anyone else seeking long-term protection

**Hepatitis B vaccine is recommended for:**

- All infants at birth
- Older children who have not previously been vaccinated
- Susceptible sex partners of infected persons
- Persons with multiple sex partners
- Persons seeking evaluation or treatment for an STD
- Women who have sex with men
- Injection drug users
- HIV-infected persons
- Persons with end-stage renal disease, including predialysis, hemodialysis, peritoneal dialysis, and home dialysis patients
- Residents and staff of facilities for developmentally disabled persons
- Travellers to regions with intermediate or high rates of Hepatitis B ( HBsAg prevalence ≥ 25%)
- Anyone else seeking long-term protection

**Vaccination Schedule**

- Infants and children: 3 to 4 doses given over a 6–18-month period depending on vaccine type and schedule
- Adults: 3 doses given over a 6–month period

No vaccine available

**Treatment**

- Acute: No medication available; best addressed through supportive treatment
- Chronic: Regular monitoring for signs of liver disease progression; some patients are treated with antiviral drugs

**Vaccination**

- Hepatitis A vaccine is recommended for:
- All children at age 1 year
- Travellers to regions with intermediate or high rates of Hepatitis A
- Men who have sex with men
- Users of certain illegal drugs (injection and non-injection)
- Persons with clotting-factor disorders
- Persons who work with HIV-infected primates or with HAV in a research laboratory
- Persons with chronic liver disease, including HBV- and HCV-infected persons with chronic liver disease
- Anyone else seeking long-term protection

- Hepatitis B vaccine is recommended for:
- All infants at birth
- Older children who have not previously been vaccinated
- Susceptible sex partners of infected persons
- Persons with multiple sex partners
- Persons seeking evaluation or treatment for an STD
- Women who have sex with men
- Injection drug users
- HIV-infected persons
- Persons with end-stage renal disease, including predialysis, hemodialysis, peritoneal dialysis, and home dialysis patients
- Residents and staff of facilities for developmentally disabled persons
- Travellers to regions with intermediate or high rates of Hepatitis B ( HBsAg prevalence ≥ 25%)
- Anyone else seeking long-term protection

- There is no Hepatitis C vaccine.
Viral Hepatitis A
HEPATITIS A

General Information

What is hepatitis?
“Hepatitis” means inflammation of the liver, which is the organ that processes nutrients, filters the blood, and removes waste products. When the liver is inflamed or damaged, its function can be impaired.

Hepatitis is most often caused by a virus. The most common types of viral hepatitis are hepatitis A, B, and C. Heavy alcohol use, toxins, smoking, and some medical conditions can also cause hepatitis.

What is Hepatitis A?
Hepatitis A is a contagious liver disease that is caused by the Hepatitis A virus. It can range in severity from a few weeks to a severe illness lasting several months.

How common is Hepatitis A?
Hepatitis A still occurs in the United States, and the number of cases has increased in recent years. New cases are reported in the United States each year. Many experts believe these numbers are underestimated, but it is estimated that 90% of cases go unreported. New cases are particularly common in adults, and the number of cases may increase as a result of the vaccination of children and other groups.

Who is at risk?
Although anyone can get Hepatitis A, some people are at greater risk, such as those who:
- Travel to or live in countries where Hepatitis A is common
- Have sexual contact with someone who has Hepatitis A
- Are men who have sexual encounters with other men
- Use recreational drugs, whether injected or not
- Have clotting-factor disorders, such as hemophilia
- Are household members or caregivers of a person infected with Hepatitis A

How is Hepatitis A spread?
Hepatitis A is usually spread when a person ingests the virus in microscopic amounts—from contact with an infected person, food, or water contaminated by feces or stool from an infected person. Hepatitis A can be spread when:
- An infected person does not wash his or her hands after using the bathroom and then touches food
- A caregiver does not properly wash his or her hands after changing diapers or cleaning the stool of an infected person
- Someone engages in certain sexual activities, such as anal-oral contact with an infected person

Hepatitis A can also spread through contaminated food or water. This most often occurs in countries where Hepatitis A is common, especially if personal hygiene or sanitary conditions are poor. Contamination of food can happen at any point: growing, harvesting, processing, handling, and even after cooking.

Who should get vaccinated against Hepatitis A?
Vaccination is recommended for certain groups, including:
- Men who have sexual encounters with other men
- Users of recreational drugs, whether injected or not
- People with chronic or long-term liver disease, including Hepatitis B or Hepatitis C
- Travelers to countries where Hepatitis A is common
- People with clotting-factor disorders
- Family and caregivers of adoptees from countries where Hepatitis A is common
- All children at age 1 year

What are the symptoms of Hepatitis A?
Not everyone has symptoms. If symptoms develop, they usually appear 2 to 6 weeks after exposure and can include:
- Fever
- Fatigue
- Loss of appetite
- Nausea
- Vomiting
- Abdominal pain
- Joint pain
- Grey-colored stools
- Jaundice
- Dark urine

Symptoms are more likely to occur in adults than in children. They usually last less than 2 months, although some people can be ill for as long as 6 months.

How is Hepatitis A diagnosed and treated?
A doctor can determine if a person has Hepatitis A by discussing his or her symptoms and taking a blood sample. To treat Hepatitis A, doctors usually recommend rest, adequate nutrition, fluids, and medical monitoring. Some people will need to be hospitalized. It can take a few months before people begin to feel better.

How serious is Hepatitis A?
Most people who get Hepatitis A feel sick for several months, but they usually recover completely and do not have lasting liver damage. Sometimes Hepatitis A can cause liver failure and death, although this is rare and occurs more commonly in people older than 50 and people with other liver diseases.

Can Hepatitis A be prevented?
Yes. The best way to prevent Hepatitis A is by getting vaccinated. Experts recommend the vaccine for all children, some international travelers, and people with certain risk factors and medical conditions. The Hepatitis A vaccine is safe and effective and given as 2 shots, 6 months apart. Both shots are needed for long-term protection. Frequent handwashing with soap and water—particularly after using the bathroom, changing a diaper, or before preparing or eating food—also helps prevent the spread of Hepatitis A.

For more information
Talk to your health professional, call your health department, or visit www.cdc.gov/hepatitis or www.cdc.gov/travel.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Disease Control and Prevention
Division of Viral Hepatitis

www.cdc.gov/hepatitis
June 2010
Hepatitis A Virus
Basics of Hepatitis A Virus

- Naked RNA virus
- Related to enteroviruses, formerly known as enterovirus 72, currently put in its own family: *heptovirus* (heptoviridae)
- One stable *serotype* only
- Difficult to grow in cell culture: primary marmoset cell culture and also *in vivo* in chimpanzees and marmosets
- Four (4) genotypes exist, but in practice most of them are group 1
Basics of Hepatitis A Infection

- Major cause by RNA Picornavirus
  - Single serotype worldwide
  - Acute disease and asymptomatic infection

- Technically, no chronic infection
  - Protective antibodies develop in response to infection – confers lifelong immunity
Epidemiology and Geographic Distribution (Prevalence) of Hepatitis A Virus (HAV) Infection
Hepatitis A - Clinical Features

Incubation period:
- Average: 30 days
- Range: 15-50 days

Jaundice by age group:
- <6 yrs: <10%
- 6-14 yrs: 40%-50%
- >14 yrs: 70%-80%

Complications:
- Fulminant hepatitis
- Cholestatic hepatitis
- Relapsing hepatitis

Chronic sequelae:
- None
Acute Hepatitis A Case
Definition For Surveillance

- **Clinical criteria of an acute illness with:**
  - Discrete onset of symptoms (e.g. fatigue, abdominal pain, loss of appetite, intermittent nausea, vomiting)
  - Jaundice or elevated serum amino-transferase levels

- **Laboratory criteria**
  - IgM antibody to hepatitis A virus (anti-HAV) positive (AHAV+)

- **Case Classification**
  - Confirmed. A case that meets the clinical case definition and is laboratory confirmed or a case that meets the clinical case definition and occurs in a person who has an epidemiologic link with a person who has laboratory-confirmed hepatitis A during the 15-50 days before the onset of symptoms.
Hepatitis A Infection
Typical Serological Course

ALT (Alanine aminotransferase)

Total anti-HAV

Fecal HAV

IgM anti-HAV

Symptoms

Titer

Months after exposure

0  1  2  3  4  5  6  12  24
Typical Events in Hepatitis A Virus Infection

- Infection
- Viremia
- HAV in stool
- ALT
- IgM
- IgG

Weeks 0-13:

0. Infection
1. Viremia
2. HAV in stool
3. ALT peak
4. IgM rise
5. IgG rise

Clinical illness timeline:
0-8 weeks

Response timeline:
0-13 weeks
Concentration of Hepatitis A Virus in Various Body Fluids

- Feces: $10^8$ infective doses per mL
- Serum: $10^4$ infective doses per mL
- Saliva: $10^2$ infective doses per mL
- Urine: $10^0$ infective doses per mL

Source: Viral Hepatitis and Liver Disease 1984;9-22
J Infect Dis 1989;160:887-890
Hepatitis A Virus Transmission

Close personal contact
  (e.g., household contact, sex contact, child day care centers)

Contaminated food, water
  (e.g., infected food handlers, raw shellfish)

Blood exposure (albeit rare)
  (e.g., injecting drug use, transfusion)
# Global Patterns of Hepatitis A Virus Transmission

<table>
<thead>
<tr>
<th>Endemicity</th>
<th>Disease Rate</th>
<th>Peak Age of Infection</th>
<th>Transmission Patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Low to High High</td>
<td>Early childhood</td>
<td>Person to person; outbreaks uncommon</td>
</tr>
<tr>
<td>Moderate</td>
<td>High</td>
<td>Late childhood/young adults</td>
<td>Person to person; food and waterborne outbreaks</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>Young adults</td>
<td>Person to person; food and waterborne outbreaks</td>
</tr>
<tr>
<td>Very low</td>
<td>Very low</td>
<td>Adults</td>
<td>Travelers; outbreaks uncommon</td>
</tr>
</tbody>
</table>
Risk Factors Associated with Reported Hepatitis A

- Unknown: 46%
- Other Contact: 8%
- Contact of day-care child/employee: 6%
- Sexual or Household Contact: 14%
- International travel: 5%
- Men who have sex with men: 10%
- Injection drug use: 6%
- Child/employee in day-care: 2%
- Food- or waterborne outbreak: 4%

Source: NNDSS/VHSP (CDC)
Serology and Laboratory Diagnosis

- Acute infection is diagnosed by the detection of HAV-IgM in serum by EIA (ELISA) – short-term immunity

- Past Infection i.e. immunity is determined by the detection of HAV-IgG by EIA – long-term immunity

- Cell culture – difficult and take up to 4 weeks, not routinely performed

- Direct Detection – EM, RT-PCR of feces. Can detect illness earlier than serology, but rarely performed
Prevention of Hepatitis A

- **Vaccination (pre-exposure)**
  - Cell culture adapted virus grown in human fibroblasts
  - Purified product inactivated with formalin (fixative)
  - Adsorbed to aluminum hydroxide (Alum) adjuvant

- **Immune globulin therapy**
  - IGT – confers immediate, yet transient, protection (passive immunity)
Prevention of Hepatitis A

- Good hygiene and health style (behavioral)

- Clean water systems (sanitation); avoidance of food contamination and congestion of contaminated food
HEPATITIS A VACCINES

## Recommended Dosages of Hepatitis A Vaccines

<table>
<thead>
<tr>
<th>Schedule Vaccine</th>
<th>Age (yrs)</th>
<th>Dose (mL)</th>
<th>Volume (mL)</th>
<th>2-Dose (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAVRIX ® #</td>
<td>1-18</td>
<td>720 (EL.U.*)</td>
<td>0.5</td>
<td>0, 6-12</td>
</tr>
<tr>
<td></td>
<td>&gt;18</td>
<td>1,440</td>
<td>1.0</td>
<td>0, 6-12</td>
</tr>
<tr>
<td>VAQTA ® ##</td>
<td>1-18</td>
<td>25 (U**)</td>
<td>0.5</td>
<td>0, 6-18</td>
</tr>
<tr>
<td></td>
<td>&gt;18</td>
<td>50</td>
<td>1.0</td>
<td>0, 6-18</td>
</tr>
</tbody>
</table>

* EL.U. – Enzyme-linked immunosorbent assay (ELISA) units

** Units

# has 2-phenoxyethanol as a preservative

## has no preservative
Most common side effects
- Soreness/tenderness at injection site - 50%
- Headache - 15%
- Malaise - 7%

No severe adverse reactions attributed to vaccine
Safety in pregnancy not determined – risk likely low
Contraindications - severe adverse reaction to previous dose or allergy to a vaccine component
No special precautions for immunocompromised persons
Many cases occur in community-wide outbreaks

- No risk factor identified for most cases
- Highest attack rates in 5-14 year olds
- Children serve as reservoir of infection

Persons at increased risk of infection

- Travelers
- Homosexual men
- Injecting drug users
HEPATITIS A VAC
WHAT YOU NEED TO

1 What is hepatitis A?

Hepatitis A is a serious liver disease caused by the hepatitis A virus (HAV). HAV is found in the stool of persons with hepatitis A. It is usually spread by close personal contact and sometimes by eating food or drinking water containing HAV.

Hepatitis A can cause:
- mild "flu-like" illness
- jaundice (yellow skin or eyes)
- severe stomach pains and diarrhea

People with hepatitis A often have to be hospitalized (up to about 1 person in 5).

Sometimes, people die as a result of hepatitis A (about 3-5 deaths per 1,000 cases).

A person who has hepatitis A can easily pass the disease to others within the same household.

Hepatitis A vaccine can prevent hepatitis A.

2 Who should get hepatitis A vaccine and when?

WHO?

Some people should be routinely vaccinated with hepatitis A vaccine:
- All children 1 year (12 through 23 months) of age.
- Persons 1 year of age and older traveling to or working in countries with high or intermediate prevalence of hepatitis A, such as those located in Central or South America, Mexico, Asia (except Japan), Africa, and eastern Europe. For more information see www.cdc.gov/travel.
- Children and adolescents through 18 years of age who live in states or communities where routine vaccination has been successful in eliminating hepatitis A from the community.
- People who have sex with men who have sex with men.
- Persons who use street drugs.
- Persons with chronic liver disease.
- People who are treated concentrates.
- Persons who work with who work with HAV in

Other people might get special situations:
- Hepatitis A vaccine might children or adolescents outbreaks of hepatitis A

Hepatitis A vaccine is not lic than 1 year of age.

WHEN?

For children, the first dose months of age. Children w years of age can be vaccinate

For travelers, the vaccine should be given at least one month before travel.

Persons who get the vaccine 1 month before travel:
- Men who have sex with men.
- Persons who use street drugs.
- Persons with chronic liver disease.
- People who are treated concentrates.
- Persons who work with who work with HAV in

Some people should not get hepatitis A vaccine or should wait

- Anyone who has ever had a severe (life-threatening) allergic reaction to a previous dose of hepatitis A vaccine should not get another dose.
- Anyone who has a severe (life-threatening) allergy to any vaccine component should not get the vaccine. Tell your doctor if you have any severe allergies. All hepatitis A vaccines contain alum and some hepatitis A vaccines contain 2-phenoxethanol.
- Anyone who is moderately or severely ill at the time a shot is scheduled should probably wait until they recover. Ask your doctor or nurse. People with a mild illness can usually get the vaccine.
- Tell your doctor if you are pregnant. The safety of hepatitis A vaccine for pregnant women has not been determined. But there is no evidence that it is harmful to either pregnant women or their unborn babies. The risk of harm is thought to be low.

3 What are the risks from hepatitis A vaccine?

A vaccine, like any medicine, could possibly cause serious problems, such as severe allergic reactions. The risk of hepatitis A vaccine causing serious harm, or death, is extremely small.

Getting hepatitis A vaccine is much safer than getting the disease.

Mild problems
- soreness where the shot was given (about 1 out of 2 adults, and up to 1 out of 6 children)
- headache (about 1 out of 6 adults and 1 out of 25 children)
- loss of appetite (about 1 out of 12 children)
- tiredness (about 1 out of 14 adults)

If these problems occur, they usually last 1 or 2 days.

Severe problems
- serious allergic reaction, within a few minutes to a few hours of the shot (very rare)

4 What if there is a moderate or severe reaction?

What should I look for?
- Any unusual condition, such as a high fever or behavior changes. Signs of a serious allergic reaction can include difficulty breathing, hoarseness or wheezing, hives, paleness, weakness, a fast heart beat or dizziness.

What should I do?
- Call a doctor, or get the person to a doctor right away.
- Tell your doctor what happened, the date and time it happened, and when the vaccination was given.
- Ask your doctor, nurse, or health department to report the reaction by filling a Vaccine Averse Event Reporting System (VAERS) form.
- You can file this report through the VAERS website at www.vaers.hhs.gov or by calling 1-800-822-7967.

VAERS does not provide medical advice.

5 The National Vaccine Injury Compensation Program

In the event that you or your child has a serious reaction to a vaccine, a federal program has been created to help pay for the care of those who have been harmed.

For details about the National Vaccine Injury Compensation Program, call 1-800-338-2382 or visit their website at www.hrsa.gov/vaccinecompensation.

6 How can I learn more?

- Ask your doctor or nurse. They can give you the vaccine package insert or suggest other sources of information.
- Call your local or state health department.
- Contact the Centers for Disease Control and Prevention (CDC):
  - Call 1-800-232-4636 (1-800-CDC-INFO)
  - Visit CDC websites at: www.cdc.gov/hepatitis or www.cdc.gov/vaccines

7 How can I learn more?

- Visit the CDC website at: www.cdc.gov/hepatitis or www.cdc.gov/vaccines


DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention

CDC
The diagram contains information about vaccine safety and availability. It includes text in Arabic and English, highlighting the importance of vaccinating against diseases such as hepatitis A and others. The text emphasizes the need to consider travel history and vaccination status before traveling to areas with higher risk of disease. It also mentions the availability of online resources for more information. The diagram is designed to educate the public on how to protect themselves from preventable diseases while traveling.
Viral Hepatitis B
What is hepatitis?
“Hepatitis” means inflammation of the liver that processes nutrients, filters the blood, and stores energy. The liver is inflamed or damaged, its function is affected, and the body becomes ill.

Hepatitis is most often caused by a virus. The most common types of viral hepatitis are Hepatitis A, Hepatitis B, and Hepatitis C. Heavy alcohol use, toxins, some medications, and other medical conditions can also cause hepatitis.

What is Hepatitis B?
Hepatitis B is a contagious liver disease that occurs when the Hepatitis B virus gets into the body. When first infected, an “acute” infection, which can range in severity from mild illness with few or no symptoms to a serious hospitalization. Acute Hepatitis B refers to the period when someone is exposed to the Hepatitis B virus and is fighting to clear the virus. For some people, the virus may lead to a “chronic,” or lifelong, illness, the illness that occurs when the Hepatitis B virus remains in the body. Over time, the infection can cause serious liver problems, including cirrhosis and liver cancer.

The best way to prevent

to get vaccinated.

Is Hepatitis B common?
Yes. In the United States, approximately 1.2 million people have Hepatitis B. Unfortunately, many people are infected. The number of new cases of more than 80% over the last 20 years. An estimated 200,000 people now become infected each year. Many experts believe that widespread vaccination of children and adults will be needed to reduce the number of cases of Hepatitis B.

How is Hepatitis B spread?
Hepatitis B is usually spread when blood, semen, other body fluids from a person infected with the Hepatitis B virus enter the body of someone who is not infected. This can happen through contact with an infected person or sharing needles, syringes, or other injection drug equipment. Hepatitis B can also be passed from an infected mother to her baby at birth.

Hepatitis B is not spread through breastfeeding. Sharing eating utensils, hugging, kissing, touching, hands, coughing, or sneezing. Unlike some other viruses, Hepatitis B is also not spread by contaminated food or water.

Can Hepatitis B be spread through

Yes. In the United States, Hepatitis B is not spread through sexual contact. The Hepatitis B virus is less infectious than HIV and can be passed through fluids, such as semen, vaginal fluids, and

Who should get vaccinated against Hepatitis B?
Vaccination is recommended for certain groups, including:

- Anyone having sex with an infected partner
- People with multiple sex partners
- Anyone with a sexually transmitted disease
- Men who have sexual encounters with other men
- People who inject drugs
- People who live with someone with Hepatitis B
- People with chronic liver disease, end stage renal disease, or HIV infection
- Healthcare and public safety workers exposed to blood
- Travelers to certain countries
- All infants at birth

What are the symptoms of acute Hepatitis B?
Not everyone has symptoms with acute Hepatitis B, especially young children. Most adults have symptoms that appear within 3 months of exposure. Symptoms can last from a few weeks to several months and include:

- Fever
- Fatigue
- Loss of appetite
- Nausea
- Vomiting
- Abdominal pain
- Dark urine
- Joint pain
- Jaundice

What are the symptoms of chronic Hepatitis B?
Many people with chronic Hepatitis B do not have symptoms and do not know they are infected. Even though a person has no symptoms, the virus can still be detected in the blood. Symptoms of chronic Hepatitis B can take up to 30 years to develop. Damage to the liver can silently occur during this time. When symptoms do appear, they are similar to acute infection and can be a sign of advanced liver disease.

How serious is Hepatitis B?
Over time, approximately 15%–25% of people with chronic Hepatitis B develop serious liver problems, including liver damage, cirrhosis, liver failure, and liver cancer. Every year, approximately 3,000 people in the United States and more than 600,000 people worldwide die from Hepatitis B-related liver disease.

How is Hepatitis B diagnosed and treated?
Hepatitis B is diagnosed with specific blood tests that are not part of blood work typically done during regular physical exams. For acute Hepatitis B, doctors usually recommend rest, adequate nutrition, fluids, and close medical monitoring. Some people may need to be hospitalized. Those living with chronic Hepatitis B should be evaluated for liver problems and monitored on a regular basis. Even though a person may have no symptoms or feel sick, damage to the liver can still occur. Several new treatments are available that can significantly improve health and delay or reverse the effects of liver disease.

Can Hepatitis B be prevented?
Yes. The best way to prevent Hepatitis B is by getting vaccinated. For adults, the Hepatitis B vaccine is given as a series of 3 shots over a period of 6 months. The entire series is needed for long-term protection. Booster doses are not currently recommended.

For more information
Talk to your health professional, call your health department, or visit www.cdc.gov/hepatitis.

Publication No. 21-1073

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Disease Control and Prevention
Division of Viral Hepatitis

www.cdc.gov/hepatitis

June 2010
Hepatitis B Virus
Hepatitis B Virus - Virology

- Double stranded DNA virus, the + strand not complete
- Replication involves a reverse transcriptase (RT) enzyme
- Complete Dane particle 42 nm, 28 nm electron dense core, containing HBcAg and HBeAg. The coat and the 22 nm free particles contain HBsAg
- At least 4 phenotypes of HBsAg are recognized; adw, adr, ayw and ayr
- The HBcAg is of a single serotype
- Hepatitis B virus (HBV) has been classified into 8 genotypes (A-H)
  - Genotypes A and C predominate in the US. However, genotypes B and D are also present in the US. Genotype F predominates in South America and in Alaska, while A, D and E predominate in Africa. Genotype D predominates in Russia and in all its prior dominions, while in Asia, genotypes B and C predominate
  - Available data suggests that genotype produces a milder disease, respond better to IFN therapy, and is less likely to develop hepatocellular carcinoma
- It has not yet been possible to propagate the virus in cell culture
Hepatitis B Virus Genome

- Four (4) overlapping open reading frames
- Reverse transcriptase/DNA polymerase domain overlaps with surface gene
- 100 times more infective than HIV
- Found in blood and body fluids

Life Cycle of HBV in the Hepatocyte

Viral polymerase converts pregenomic RNA to partially dsDNA

Infectious HBV virion

Partially dsDNA

Cytoplasm

Minus strand DNA

Encapsulated pregenomic mRNA

cccDNA

mRNA

Nucleus

Hepatocyte

HBeAg

HBSAg

HBcAg

Precore/core

ER

Subviral particles

HBV-Trigged Immune Response

MHC class II
CD4+ T cell

Antigen Presenting Cell (APC)

HBV antigens
HBV peptides

CD8+ T cell
MHC class I

TNF-α Interferon-γ
Down-regulations of viral replication

Infected hepatocyte
HBV DNA
HBV RNA
HBV cores
HBsAg

Hepatitis B Virus – Replication

Viral entry

Uncoating

Assembly & budding

ER

Nuclear import

Repair

cccDNA

Transcription

Translation

HBsAg

Encapsidation

Positive strand synthesis

Removal of pregenome

Negative strand synthesis

Export

Viral accessory proteins: HBeAg and HBX

5'-3.5 kb RNA

2.4/2.1 kb RNA

5'-3'
### Hepatitis B - Clinical Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incubation period:</strong></td>
<td>Average 60-90 days</td>
</tr>
<tr>
<td></td>
<td>Range 45-180 days</td>
</tr>
<tr>
<td><strong>Clinical illness (jaundice):</strong></td>
<td>&lt;5 yrs, &lt;10%</td>
</tr>
<tr>
<td></td>
<td>5 yrs, 30%-50%</td>
</tr>
<tr>
<td><strong>Acute case-fatality rate:</strong></td>
<td>0.5%-1%</td>
</tr>
<tr>
<td><strong>Chronic infection:</strong></td>
<td>&lt;5 yrs, 30%-90%</td>
</tr>
<tr>
<td></td>
<td>5 yrs, 2%-10%</td>
</tr>
<tr>
<td><strong>Premature mortality from chronic liver disease:</strong></td>
<td>15%-25%</td>
</tr>
</tbody>
</table>
Spectrum of Chronic Hepatitis B Diseases

1. Chronic persistent hepatitis – asymptomatic
2. Chronic active hepatitis – symptomatic exacerbations of hepatitis
3. Cirrhosis of liver (liver encephalopathy)
4. Hepatocellular carcinoma (HCC)
Outcome of HBV Infection

Asymptomatic
- Resolved Immune
  - Asymptomatic
- Chronic infection
  - Cirrhosis Liver cancer

Symptomatic acute hepatitis B
- Resolved Immune
  - Asymptomatic
- Chronic infection
  - Cirrhosis Liver cancer
Acute Hepatitis B Virus Infection with Recovery
Typical Serologic Course

Titer

Symptoms

HBeAg

Anti-HBe

Total anti-HBc

HBsAg

IgM anti-HBc

Anti-HBs

Weeks after Exposure

0 4 8 12 16 20 24 28 32 36 52 100

HBe = Be antigen
HBc = Core antigen
HBs = Surface antigen
Progression to Chronic Hepatitis B Virus Infection

Typical Serologic Course

- **Acute** (6 months)
  - HBeAg
  - Anti-HBe
  - HBsAg
  - Total anti-HBc
  - IgM anti-HBc

- **Chronic** (Years)
  - HBeAg
  - Anti-HBe
  - HBsAg
  - Total anti-HBc

Weeks after Exposure vs. Years
# Phases of Chronic HBV Infection

<table>
<thead>
<tr>
<th>Immune Tolerance</th>
<th>Immune Clearance</th>
<th>Low Replicative Phase</th>
<th>Reactivation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg+</td>
<td></td>
<td>HBeAg-/-anti-HBe+ (precore/core promoter variants)</td>
<td></td>
</tr>
<tr>
<td>HBV DNA 2 x 10^8 - 2 x 10^{11} IU/mL</td>
<td>200,000 - 2 x 10^9 IU/mL</td>
<td>&lt; 2000 IU/mL</td>
<td>&gt; 2000 IU/mL</td>
</tr>
</tbody>
</table>

- **HBeAg+**
- **HBeAg-/-anti-HBe+ (precore/core promoter variants)**

**HBV DNA Levels**

- **Immune Tolerance**
  - 2 x 10^8 - 2 x 10^{11} IU/mL

- **Immune Clearance**
  - 200,000 - 2 x 10^9 IU/mL

- **Low Replicative Phase**
  - < 2000 IU/mL

- **Reactivation Phase**
  - > 2000 IU/mL
### Phases of Chronic HBV Infection

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**ALT**

- **< 2000 IU/mL**
- **> 2000 IU/mL**
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<td>&gt; 2000 IU/mL</td>
</tr>
<tr>
<td>HBV DNA</td>
<td></td>
<td>2 x 10⁸ - 2 x 10¹¹ IU/mL</td>
<td></td>
</tr>
<tr>
<td>Normal/mild CH</td>
<td>Moderate/severe CH</td>
<td>Normal/mild CH</td>
<td>Moderate/severe CH</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td></td>
<td>Inactive cirrhosis</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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**ALT**

- Normal/mild CH
- Moderate/severe CH
- Cirrhosis
- Inactive cirrhosis
- Cirrhosis

**HBV DNA Levels**

- 2 x 10⁸ - 2 x 10¹¹ IU/mL
- 200,000 - 2 x 10⁹ IU/mL
- < 2000 IU/mL
- > 2000 IU/mL
# Phases of Chronic HBV Infection

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<td>ALT</td>
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<td>Normal/mild CH</td>
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<td>Normal/mild CH</td>
<td>Moderate/severe CH Cirrhosis</td>
<td></td>
</tr>
<tr>
<td>HBeAg+ chronic hepatitis</td>
<td>Inactive-carrier state</td>
<td>HBeAg-chronic hepatitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Natural History of HBV Infection

- Early Childhood: > 95% Immune Tolerance
- HBeAg+ Chronic Hepatitis B
- Cirrhosis
- Inactive Carrier
- Adulthood: < 5% Immune Tolerance
- HBeAg- Chronic Hepatitis B
Inactive Carrier < 5% Immune Tolerance > 95% Early Childhood Adulthood HBeAg- Chronic Hepatitis B HCC HBeAg+ Chronic Hepatitis B Natural History of HBV Infection

Interpretation of Hepatitis B Serologic Test Results

Hepatitis B serologic testing involves measurement of several hepatitis B virus (HBV)-specific antigens and antibodies. Different serologic “markers” or combinations of markers are used to identify different phases of HBV infection and to determine whether a patient has acute or chronic HBV infection, is immune to HBV as a result of prior infection or vaccination, or is susceptible to infection.

- **Hepatitis B surface antigen (HBsAg):** A protein on the surface of hepatitis B virus; it can be detected in high levels in serum during acute or chronic hepatitis B virus infection. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part of the normal immune response to infection. HBsAg is the antigen used to make hepatitis B vaccine.

- **Hepatitis B surface antibody (anti-HBs):** The presence of anti-HBs is generally interpreted as indicating recovery and immunity from hepatitis B virus infection. Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B.

- **Total hepatitis B core antibody (anti-HBc):** Appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with hepatitis B virus in an undefined time frame.

- **IgM antibody to hepatitis B core antigen (IgM anti-HBc):** Positivity indicates recent infection with hepatitis B virus (<3 mos). Its presence indicates acute infection.

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>anti-HBc</th>
<th>anti-HBs</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>negative</td>
<td>anti-HBc</td>
<td>negative</td>
<td>Susceptible</td>
</tr>
<tr>
<td>HBsAg</td>
<td>negative</td>
<td>anti-HBs</td>
<td>Immune due to natural infection</td>
</tr>
<tr>
<td>HBsAg</td>
<td>positive</td>
<td>positive</td>
<td>Immune due to hepatitis B vaccination</td>
</tr>
<tr>
<td>HBsAg</td>
<td>positive</td>
<td>positive</td>
<td>Acutely infected</td>
</tr>
<tr>
<td>HBsAg</td>
<td>positive</td>
<td>negative</td>
<td>Chronically infected</td>
</tr>
<tr>
<td>HBsAg</td>
<td>positive</td>
<td>negative</td>
<td>Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. &quot;Low level&quot; chronic infection 4. Resolving acute infection</td>
</tr>
</tbody>
</table>

Outcome of Hepatitis B Virus Infection by Age at Infection

Chronic Infection (%)

Symptomatic Infection (%)

Age at Infection:
- Birth
- 1-6 months
- 7-12 months
- 1-4 years
- Older Children and Adults

Chronic Infection:
- Birth: 90%
- 1-6 months: 80%
- 7-12 months: 70%
- 1-4 years: 60%
- Older Children and Adults: 50%

Symptomatic Infection:
- Birth: 0%
- 1-6 months: 10%
- 7-12 months: 15%
- 1-4 years: 20%
- Older Children and Adults: 25%
Global Patterns of Chronic HBV Infection

High (≥8%): 45% of global population
- Lifetime risk of infection >60%
- Early childhood infections common

Intermediate (2%-7%): 43% of global population
- Lifetime risk of infection 20%-60%
- Infections occur in all age groups

Low (<2%): 12% of global population
- Lifetime risk of infection <20%
- Most infections occur in adult risk groups
HBsAg Prevalence

- High: ≥8%
- Intermediate: 2-7%
- Low: <2%

Geographic Distribution of Chronic HBV Infection
<table>
<thead>
<tr>
<th></th>
<th>High</th>
<th>Moderate</th>
<th>Low/Not Detectable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>blood</td>
<td>semen</td>
<td>urine</td>
</tr>
<tr>
<td></td>
<td>serum</td>
<td>vaginal fluid</td>
<td>feces</td>
</tr>
<tr>
<td></td>
<td>wound exudates</td>
<td>saliva</td>
<td>sweat</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>tears</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>breast milk</td>
</tr>
</tbody>
</table>
Risk Factors Associated with Reported Hepatitis B

- Blood transfusion: 0%
- Unknown: 32%
- Multiple sex partners: 17%
- Injection drug use: 14%
- Sexual contact with hepatitis B patient: 13%
- Men who have sex with men: 6%
- Household contact of hepatitis B patient: 2%
- Medical Employee: 1%
- Hemodialysis: 0%
- Other*: 15%

* Other: Surgery, dental surgery, acupuncture, tattoo, other percutaneous injury
Sexual – sex workers and homosexuals (MSM) are particular at risk.

Parenteral – IVDA (intravenous drug abusers) and health coworkers are at increased risk.

Perinatal – Mothers who are HBeAg positive are much more likely to transmit to their offspring than those who are not.

- Perinatal transmission is the main means of transmission in high prevalence populations.
HBV Diagnosis

A battery of serological tests are used for the diagnosis of acute and chronic hepatitis B infection

- **HBsAg** → Used as a general marker of infection
- **HBsAb** → Used to document recovery and/or immunity to HBV infection
- **Anti-HBc IgM** → Considered a marker of acute infection
- **Anti-HBc IgG** → Indicator of past or chronic infection
- **HBeAg** → Indicates active replication of virus and therefore infectiveness
- **Anti-HBe** → Virus no longer replicating. However, the patient can still be positive for HBsAg which is made by integrated HBV
- **HBV-DNA** → Indicates active replication of virus, more accurate than HBeAg especially in cases of escape mutants. Used mainly for monitoring response to therapy
<table>
<thead>
<tr>
<th>Marker</th>
<th>Acute HBV</th>
<th>Acute HBV Recovery</th>
<th>Chronic HBV Disease</th>
<th>Inactive HBeAgCarrier State</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HBeAg Positive</td>
<td>HBeAg Negative</td>
</tr>
<tr>
<td>HBsAg</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>(may clear)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HBs</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HBe IgM</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HBc</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>HBeAg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HBe (in some cases)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
HBV Treatment

- **Interferon** – for HBeAg +ve carriers with chronic active hepatitis. Response rate is 30 to 40%.
  - alpha-interferon 2b (original)
  - alpha-interferon 2a (newer, claims to be more efficacious and efficient)

- **Lamivudine** – a nucleoside analogue reverse transcriptase inhibitor. Well tolerated, most patients will respond favorably. However, tendency to relapse on cessation of treatment. Another problem is the rapid emergence of drug resistance.

- **Adefovir** – less likely to develop resistance than Lamivudine and may be used to treat Lamivudine resistance HBV. However more expensive and toxic

- **Entecavir** – most powerful antiviral known, similar to Adefovir

Successful response to treatment will result in the disappearance of HBsAg, HBV-DNA, and seroconversion to HBeAg.
### NIH Guidelines: Indications for HBV Treatment

<table>
<thead>
<tr>
<th>Patients for Whom Therapy Is Indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who have</td>
</tr>
<tr>
<td>- Acute liver failure</td>
</tr>
<tr>
<td>- Cirrhosis and clinical complications</td>
</tr>
<tr>
<td>- Cirrhosis or advanced fibrosis and HBV DNA in serum</td>
</tr>
<tr>
<td>- Patients who will be receiving cancer chemotherapy or immunosuppressive therapy</td>
</tr>
</tbody>
</table>

### NIH Guidelines: Indications for HBV Treatment, cont’d

<table>
<thead>
<tr>
<th>Patients for Whom Therapy May Be Indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with active liver disease who do not have advanced fibrosis or cirrhosis, i.e., patients with HBeAg-positive or HBeAg-negative chronic hepatitis B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients for Whom Immediate Therapy Is Not Routinely Indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients in the immune-tolerant phase (HBeAg positive, high levels of serum HBV DNA but normal ALT or little activity on liver biopsy)</td>
</tr>
<tr>
<td>Patients in the inactive carrier phase (HBeAg negative, low or undetectable levels of serum HBV DNA, and persistently normal ALT)</td>
</tr>
<tr>
<td>Patients who have latent HBV infection (HBV DNA without HBsAg)</td>
</tr>
</tbody>
</table>

HBV Prevention

- **Vaccination** – highly effective recombinant vaccines are now available. Vaccine can be given to those who are at increased risk of HBV infection such as health care workers. It is also given routinely to neonates as universal vaccination in many countries.

- **Hepatitis B Immunoglobulin** – HBIG may be used to protect persons who are exposed to hepatitis B. It is particularly efficacious within 48 hours of the incident. It may also be given to neonates who are at increased risk of contracting hepatitis B i.e. whose mothers are HBsAg and HBeAg positive.

- **Other measures** – screening of blood donors, blood and body fluid precautions.
Primary Goal of Hepatitis B Therapy: Preventing Cirrhosis, Hepatocellular Carcinoma (HCC), and Death

Durable Suppression of HBV Replication

Impact of viral suppression on liver disease outcomes

- Prolonged viral suppression is associated with
  - Reduction in necroinflammation, fibrosis, and cirrhosis
  - Reduction in decompensation
  - Reduction in rates of HCC
  - Reduction in mortality rate
HBV: Who Should Be Treated?

- **Benefits**
  - Likelihood of adverse clinical outcome without treatment
  - Activity and stage of liver disease at presentation
  - Risk of cirrhosis/HCC in the next 10-20 yrs
  - Likelihood of long-term benefit with treatment

- **Risks**
  - Adverse effects
  - Drug resistance

- **Patient’s age and preference, costs**
  - Adverse outcome
  - Long-lasting response
Elimination of HBV Transmission

**Strategy**

- Prevent perinatal HBV transmission
- Routine vaccination of all infants
- Vaccination of children in high-risk groups
- Vaccination of adolescents
  - all children up through age 18
- Vaccination of adults in high-risk groups
Korean Mummy Found With HBV

- Virus discovered in the liver of the South Korean Handong mummy
  - 500-year-old child
- First time HBV ever been found in a mummified body
- Study of the genome of the 500-year-old virus under way
  - To see if there have been any significant changes to HBV over time

Source: Seoul National University
HEPATITIS B VAC
WHAT YOU NEED TO KNOW

1 What is hepatitis B?
Hepatitis B is a serious disease that affects the liver. It is caused by the hepatitis B virus (HBV). HBV can cause:

Acute (short-term) illness. This can lead to:
- loss of appetite
- diarrhea and vomiting
- tiredness
- jaundice (yellow skin or eyes)
- pain in muscles, joints, and stomach

Acute illness is more common among adults. Children who become infected usually do not have acute illness.

Chronic (long-term) infection. Some people go on to develop chronic HBV infection. This can be very serious, and often leads to:
- liver damage (cirrhosis)
- liver cancer
- death

Chronic infection is more common among infants and children than among adults. People who are infected can spread HBV to others, even if they don’t appear sick.

- In 2005, about 51,000 people became infected with hepatitis B.
- About 1.25 million people in the United States have chronic HBV infection.
- Each year about 3,000 to 5,000 people die from cirrhosis or liver cancer caused by HBV.

2 Hepatitis B vac mounted?
Hepatitis B vaccine can prevent the serious consequences of liver cancer and cirrhosis.

Routine hepatitis B vaccine began in 1991. Since then, hepatitis B among children has dropped by more than 95%.

Hepatitis B vaccine is made by a virus. It cannot cause HBV.

Hepatitis B vaccine is usually given as 3 shots. This vaccine provides protection from HBV infection.

3 Who should get vaccine and when?

Children and Adolescents
- All children should get B vaccine at birth and and vaccine series by 6-18 months.
- Children and adolescents who did not get the younger should also be vaccinated.

Adults
- All unvaccinated adults should be vaccinated:
  - sex partners of people who have sex with people who inject drugs
  - people with more than one sex partner
  - people with chronic liver disease
  - people with jobs that involve blood exposure
  - household contacts of residents and staff in developmentally disordered
  - kidney dialysis patients

- people who travel to countries where hepatitis B is common.
- people with HIV infection.

Anyone else who wants to be protected from HBV infection may be vaccinated.

4 Who should NOT get hepatitis B vaccine?
- Anyone with a life-threatening allergy to yeast or any other component of the vaccine should not get hepatitis B vaccine. Tell your provider if you have any severe allergies.
- Anyone who has had a life-threatening allergic reaction to a previous dose of hepatitis B vaccine should not get another dose.
- Anyone who is moderately or severely ill when a dose of vaccine is scheduled should probably wait until they recover before getting the vaccine.

Your provider can give you more information about these precautions.

Pregnant women who need protection from HBV infection may be vaccinated.

5 Hepatitis B vaccine risks
Hepatitis B is a very safe vaccine. Most people do not have any problems with it.

The following mild problems have been reported:
- Soreness where the shot was given (up to about 1 person in 4).
- Temperature of 99.9°F or higher (up to about 1 person in 15).
- Severe problems are extremely rare. Severe allergic reactions are believed to occur about once in 1 million doses.

A vaccine is any medicine, could cause a serious reaction. The risk of a vaccine causing serious harm, or death, is extremely small. More than 100 million people have gotten hepatitis B vaccine in the United States.

6 What if there is a moderate or severe reaction?

What should I look for?
- Any unusual condition, such as a high fever or behavior changes. Signs of a serious allergic reaction can include difficulty breathing, hoarseness or wheezing, hives, paleness, weakness, a fast heart beat or dizziness.

What should I do?
- Call a doctor, or get the person to a doctor right away.
- Tell your doctor what happened, the date and time it happened, and when the vaccination was given.
- Ask your doctor, nurse, or health department to report the reaction by filing a Vaccine Adverse Event Reporting System (VAERS) form.
- Or you can file this report through the VAERS website at www.vaers.hhs.gov or by calling 1-800-822-7967.

VAERS does not provide medical advice.

7 The National Vaccine Injury Compensation Program
In the event that you or your child has a serious reaction to a vaccine, a federal program has been created to help pay for the care of those who have been harmed.

For details about the National Vaccine Injury Compensation Program, call 1-800-338-2382 or visit their website at www.hrsa.gov/vaccinecompensation.

8 How can I learn more?
- Ask your doctor or nurse. They can give you the vaccine package insert or suggest other sources of information.
- Call your local or state health department.
- Contact the Centers for Disease Control and Prevention (CDC):
  - Call 1-800-232-4636 (1-800-CDC-INFO)
  - Visit CDC websites at:
    - www.cdc.gov/nchid/Pages/diseases/hepatitis.aspx
    - www.cdc.gov/vaccines
    - www.cdc.gov/travel

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
Vaccine Information Statement (Hepatitis B) 2007
Hepatitis B 2007
42 U.S.C. 300a-26

CDC
هل التعرض لللقاحات أثناء الحمل إذا كنت محاربة؟

هذا.moveLINEA

<table>
<thead>
<tr>
<th>الوقت</th>
<th>الشكل</th>
<th>باللغة العربية</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 أشهر</td>
<td>نص</td>
<td>شرح التعرض لللقاحات أثناء الحمل إذا كنت محاربة</td>
</tr>
</tbody>
</table>


**ما هو الضرر الذي يمكن أن يسببه التعرض لللقاحات أثناء الحمل؟**

- التعرض لللقاحات أثناء الحمل يمكن أن يسبب ضرراً جراحيًا أو خلقيًا.
- المحتمل أن يكون التعرض لللقاحات أثناء الحمل يسبب ضرراً جراحيًا أو خلقيًا.
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- المحتمل أن يكون التعرض لللقاحات أثناء الحمل يسبب ضرراً جراحيًا أو خلقيًا.

**ما هي القضايا المتعلقة باللقاحات أثناء الحمل؟**

- القضايا المتعلقة باللقاحات أثناء الحمل يمكن أن تشمل:
- الاستجابات السلبية ضد اللقاحات أثناء الحمل.
- الاستجابات السلبية ضد اللقاحات أثناء الحمل.
- الاستجابات السلبية ضد اللقاحات أثناء الحمل.
- الاستجابات السلبية ضد اللقاحات أثناء الحمل.
- الاستجابات السلبية ضد اللقاحات أثناء الحمل.

**ما هو اللقاح المُنْتَجِ المُتَّخَطِم؟**

- اللقاح المُنْتَجِ المُتَّخَطِم يمكن أن يكون من:
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- اللقاح المُتَّخَطِم يمكن أن يكون من:

**ما هو اللقاح المُتَّخَطِم؟**

- اللقاح المُتَّخَطِم يمكن أن يكون من:
- اللقاح المُتَّخَطِم يمكن أن يكون من:
- اللقاح المُتَّخَطِم يمكن أن يكون من:
- اللقاح المُتَّخَطِم يمكن أن يكون من:
- اللقاح المُتَّخَطِم يمكن أن يكون من:
Viral Hepatitis C
HEPATITIS C

General Information

What is hepatitis?
"Hepatitis" means inflammation of the liver that processes nutrients, filters the blood, the liver is inflamed or damaged, its function is impaired. Hepatitis most often caused by a virus. Most common types of viral hepatitis are Hepatitis A, B, and C. Heavy alcohol use, toxins, or medical conditions can also cause hepatitis.

What is Hepatitis C?
Hepatitis C is a contagious liver disease that results from infection with the Hepatitis C virus. When first infected, a person can develop an "acute" infection, which can range in severity from a very mild illness with few symptoms to a serious condition requiring hospitalization.

Acute: Hepatitis C is a short-term illness that occurs within the first 6 months after someone is exposed to the Hepatitis C virus. For reasons that are not known, 15%–25% of people "clear" the virus without treatment. Approximately 75%–85% of people who become infected with the Hepatitis C virus develop "chronic," or lifelong, infection.

Chronic: Hepatitis C is a long-term illness that occurs when the Hepatitis C virus remains in the person's body. Over time, it can lead to serious liver problems, including liver cirrhosis, liver failure, or liver cancer (see chronic hepatitis)

How is Hepatitis C spread?
Hepatitis C is usually spread when blood with the Hepatitis C virus enters the body. Today, most people become infected by sharing needles or other equipment to inject drugs, or by others in the household. This is most commonly spread through sexual contact or through blood transfusions. Although uncommon, outbreaks of Hepatitis C have been reported in medical settings.

Can Hepatitis C be spread through sexual contact?
Yes, although scientists do not know how. Sexually transmitted diseases can cause life-threatening diseases. However, cases of Hepatitis C in gay men and people who have sex with women have been reported. The risk of Hepatitis C increases with the number of sex partners and the length of time a person is sexually active.

Can a person get Hepatitis C from a transfusion?
There is no evidence that Hepatitis C is transmitted through blood transfusions. However, Hepatitis C can be transmitted through blood transfusions if the blood is contaminated with Hepatitis C. All blood used for transfusions is tested for Hepatitis C, so the chance of getting Hepatitis C from a transfusion is very small.

Can a person get Hepatitis C from tattooing or piercing?
There is no evidence that Hepatitis C is transmitted through tattooing or piercing. However, tattooing and piercing can cause bleeding, which can increase the risk of Hepatitis C. The risk of Hepatitis C from tattooing or piercing is very small.

Can a person get Hepatitis C from sharing personal items?
Yes, although scientists do not know how. Sharing personal items such as razors, nail clippers, toothbrushes, or other items can increase the risk of Hepatitis C. However, the risk of Hepatitis C from sharing personal items is very small.

Is there a vaccine for Hepatitis C?
Although there is currently no vaccine to prevent Hepatitis C, research is being conducted to develop one.

How common is Hepatitis C?
An estimated 3.2 million people in the United States have chronic Hepatitis C. Most are unaware of their infection. Each year, about 17,000 Americans become infected with Hepatitis C.

How serious is Hepatitis C?
Chronic Hepatitis C is a serious disease that can result in long-term health problems, including liver damage, liver failure, and liver cancer. Approximately 12,000 people die every year from Hepatitis C-related liver disease.

What are the symptoms of Hepatitis C?
Many people with Hepatitis C do not have symptoms and do not know they are infected. Even though a person has no symptoms, the virus can still be detected in the blood.

If symptoms occur with acute infection, they can appear anytime from 2 weeks to 6 months after exposure. Symptoms of chronic Hepatitis C can take up to 30 years to develop. Damage to the liver can silently occur during this time. When symptoms do appear, they are often a sign of advanced liver disease. Symptoms for both acute and chronic Hepatitis C include fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, dark urine, grey-colored stools, joint pain, and jaundice.

How is Hepatitis C diagnosed?
Doctors can diagnose Hepatitis C using specific blood tests that are not part of blood work typically done during regular physical exams. Typically, a person first gets a screening test that looks for "antibodies" to the Hepatitis C virus. Antibodies are chemicals released into the bloodstream when a person becomes infected. The antibodies remain in the bloodstream, even if the person clears the virus. If the screening test is positive for Hepatitis C antibodies, different blood tests are needed to determine whether the infection has been cleared or has become a chronic infection.

Who should get tested for Hepatitis C?
Testing for Hepatitis C is recommended for certain groups, including people who:
- Currently inject drugs
- Injected drugs in the past, even if it was just once or occurred many years ago
- Have HIV infection
- Have abnormal liver tests or liver disease
- Received donated blood or organs before 1992
- Have been exposed to blood on the job through a needlestick or injury with a sharp object
- Are on hemodialysis

For more information
Talk to your health professional, call your health department, or visit www.cdc.gov/hepatitis/
The Hepatitis C Virus
HCV Lifecycle and STAT-C (Specifically Targeted Antiviral Therapy for HCV) Targets

Hepatitis C Virus Genome

capsid

envelope

protein

c22

protease/helicase

33c

c-100

RNA-dependent

RNA polymerase

core

E1

E2

NS 2

NS 3

NS 4

NS 5

hypervariable

region

5' 3'
HCV NS3/4A Serine Protease: The “Master Switch” for Replication

Hepatitis C Virus

- Genome resembled that of a flavivirus positive stranded RNA genome of around 10,000 bases
- One single reading frame, structural genes at the 5' end, the non-structural genes at the 3' end. Enveloped virus, virion thought to be 30-60 nm in diameter
- Morphological structure remains unknown
- HCV has been classified into a total of six genotypes (type 1 to 6) on the basis of phylogenetic analysis
- Genotype 1 and 4 has a poorer prognosis and response to interferon therapy
- In Hong Kong, genotype 1 accounts for around 67% of cases and genotype 6 around 25%
## Terminology

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>% Nucleotide Similarity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>Genetic heterogeneity among different HCV isolates</td>
<td>65.7-68.9</td>
</tr>
<tr>
<td>Subtype</td>
<td>Closely related isolates within each of the major genotypes</td>
<td>76.9-80.1</td>
</tr>
<tr>
<td>Quasispecies</td>
<td>Complex of genetic variants within individual isolates</td>
<td>90.8-99</td>
</tr>
</tbody>
</table>

Family $\rightarrow$ Genus $\rightarrow$ Species $\rightarrow$ Genotype $\rightarrow$ Subtype $\rightarrow$ Quasispecies
Hepatitis C - Clinical Features

Incubation period: Average 6-7 wks
                Range 2-26 wks

Clinical illness (jaundice): 30-40% (20-30%)

Chronic hepatitis: 70%

Persistent infection: 85-100%

Immunity: No protective antibody response identified
Prevalence of HCV Infection by Age, Race, and Gender

![Graph showing prevalence of HCV infection by age, race, and gender.](image)

Source: NHANES III
Chronic Hepatitis C Infection

- The spectrum of chronic hepatitis C infection is essentially the same as chronic hepatitis B infection.

- All the manifestations of chronic hepatitis B infection may be seen, albeit with a lower frequency i.e. chronic persistent hepatitis, chronic active hepatitis, cirrhosis, and hepatocellular carcinoma.
Serologic Pattern of Acute HCV Infection With Progression to Chronic Infection

Time after Exposure

HCV RNA

Symptoms +/-

Ant-HCV

ALT

Normal
Pattern of Acute HCV Infection with Recovery

- **HCV RNA**
- **Symptoms +/-**
- **Anti-HCV**
- **ALT Normal**

**Titer**

**Time after Exposure**

0 1 2 3 4 5 6

1 2 3 4

Years

Months

Normal
Risk Factors Associated with Transmission of HCV

- Transfusion or transplant from infected donor
- Injecting drug use
- Hemodialysis (yrs on treatment)
- Accidental injuries with needles/sharps
- Sexual/household exposure to anti-HCV-positive contact
- Multiple sex partners
- Birth to HCV-infected mother
Natural History of HCV Infection

100 People

- 15% Resolve (15)
- 80% Stable (68)
- 75% Stable (13)
- 85% Chronic (85)
- 20% Cirrhosis (17)
- 25% Mortality (4)

Leading Indication for Liver Transplant

Time
Sentinel Counties Study of Acute Viral Hepatitis
Reported Risk Factors for Acute Hepatitis C

- Illegal Drug Use: 60%
- Sexual: 21%
- No Identified Risks: 10%
- Household: 3%
- Occupational: 3%
- Transfusions *: 3%

*None since 1994
Prevalence of HCV Infection Among Blood Donors*

Anti-HCV Prevalence

- >5% - High
- 1.1%-5% - Intermediate
- 0.2%-1% - Low
- ≤0.1% - Very Low
- Unknown

* Anti-HCV prevalence by EIA-1 or EIA-2 with supplemental testing; based on data available in January, 1995.
Laboratory Diagnosis

- **HCV antibody** – generally used to diagnose hepatitis C infection. Not useful in the acute phase as it takes at least 4 weeks after infection before antibody appears.

- **HCV-RNA** – various techniques are available e.g. PCR and branched DNA. May be used to diagnose HCV infection in the acute phase. However, its main use is in monitoring the response to antiviral therapy.

- **HCV-antigen** – an EIA for HCV antigen is available. It is used in the same capacity as HCV-RNA tests but is much easier to carry out.
Prognostic Tests

- **Genotyping** – genotype 1 and 4 have a worse prognosis overall and respond poorly to interferon therapy. A number of commercial and in-house assays are available.
  - Genotypic methods – DNA sequencing, PCR-hybridization, e.g. INNO-LIPA.
  - Serotyping – particularly useful when the patient does not have detectable RNA.

- **Viral Load** – patients with high viral load are thought to have a poorer prognosis. Viral load is also used for monitoring response to IFN therapy. A number of commercial and in-house tests are available.
Treatment

- **Interferon** – may be considered for patients with chronic active hepatitis. The response rate is around 50% but 50% of responders will relapse upon withdrawal of treatment.

- **Ribavirin** – there is less experience with ribavirin than interferon. However, recent studies suggest that a combination of interferon and ribavirin is more effective than interferon alone.
Prevention of Hepatitis C

- Screening of blood, organ, tissue donors
- High-risk behavior modification
- Blood and body fluid precautions
**Hepatitis C Virus (HCV) Infection Testing for Diagnosis**

- **Anti-HCV**
  - **NEGATIVE**
    - **STOP**
  - **POSITIVE**
    - High signal-to-cut-off ratio* or RIBA1 positive or HCV RNA positive
      - **Confirmed**
    - and no other test done
      - **Unconfirmed**
    - and HCV RNA negative
      - **Unconfirmed**

- **Nucleic Acid Testing (NAT) for HCV RNA**
- **RIBA1 for Anti-HCV**
- **Medical Evaluation for active infection and liver disease**
- **Indeterminate**
- **Repeat Anti-HCV ≥ 1 month**

---

*Samples with high s/co ratios usually (>95%) confirm positive, but supplemental serologic testing was not performed. Less than 5 of every 100 might represent false-positives; more specific testing should be requested, if indicated.

1Recombinant immunoblot assay

**RIBA** = Recombinant immunoblot assay; **NAT** = Nucleic acid test
HCV Infection Testing Algorithm for Diagnosis of Asymptomatic Persons

EIA for Anti-HCV
- Negative (non-reactive) → STOP
- Positive (repeat reactive) OR
  - RIBA for Anti-HCV
    - Negative → STOP
    - Indeterminate
    - Positive
      - RT-PCR for HCV RNA
        - Negative
          - Additional Laboratory Evaluation (e.g. PCR, ALT)
            - Negative PCR, Normal ALT → STOP
            - Positive PCR, Abnormal ALT
          - Medical Evaluation

Source: MMWR 1998;47 (No. RR 19)
HCV Screening is the First Step on the Road to a Cure
Viral Hepatitis D
Hepatitis D (Delta) Virus

δ antigen

HBsAg

RNA

RNA
Hepatitis D Virus

- The delta agent is a defective virus which shows similarities with the viroids in plants.
- The agent consists of a particle 35 nm in diameter consisting of the delta antigen surrounded by an outer coat of HBsAg.
- The genome of the virus is very small and consists of a single-stranded RNA
Hepatitis D - Clinical Features

Coinfection

severe acute disease.

low risk of chronic infection.

Superinfection

usually develop chronic HDV infection.

high risk of severe chronic liver disease.

may present as an acute hepatitis.
Hepatitis D Virus Modes of Transmission

Percutanous exposures
  • Injecting drug use

Permucosal exposures
  • Sex contact
HBV – HDV Coinfection

Typical Serological Course

- Symptoms
- ALT Elevated
- Anti-HBs
- Total anti-HDV
- IgM anti-HDV
- HDV RNA
- HBsAg

Time after Exposure

Titer
HBV – HDV Super-infection

Typical Serological Course

- **Jaundice**
- **Symptoms**
- **Total anti-HDV**
- **ALT**
- **HDV RNA**
- **HBsAg**
- **IgM anti-HDV**

Time after Exposure

Titer
Geographic Distribution of HDV Infection

HDV Prevalence
- High
- Intermediate
- Low
- Very Low
- No Data
Hepatitis D - Prevention

HBV-HDV Coinfection

Pre or post-exposure prophylaxis to prevent HBV infection.

HBV-HDV Superinfection

Education to reduce risk behaviors among persons with chronic HBV infection.
Viral Hepatitis E
Hepatitis E Virus
Hepatitis E Virus

- Calicivirus-like viruses
- Unenveloped RNA virus, 32-34nm in diameter
- +ve stranded RNA genome, 7.6 kb in size.
- Very labile and sensitive
- Can only be cultured recently
### Hepatitis E - Clinical Features

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Incubation period:</strong></td>
<td>Average 40 days</td>
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<tr>
<td></td>
<td>Range 15-60 days</td>
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<tr>
<td><strong>Case-fatality rate:</strong></td>
<td>Overall, 1%-3%</td>
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<tr>
<td></td>
<td>Pregnant women,</td>
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<tr>
<td></td>
<td>15%-25%</td>
</tr>
<tr>
<td><strong>Illness severity:</strong></td>
<td>Increased with age</td>
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<tr>
<td><strong>Chronic sequelae:</strong></td>
<td>None identified</td>
</tr>
</tbody>
</table>
Hepatitis E Virus Infection
Typical Serologic Course

Symptoms

Virus in stool

ALT

IgG anti-HEV

IgM anti-HEV

Weeks after Exposure

Titer

0 1 2 3 4 5 6 7 8 9

0 1 1 1 1 1 3
Most outbreaks associated with fecally contaminated drinking water.

Several other large epidemics have occurred since in the Indian subcontinent and the USSR, China, Africa and Mexico.

In the United States and other non-endemic areas, where outbreaks of hepatitis E have not been documented to occur, a low prevalence of anti-HEV (<2%) has been found in healthy populations. The source of infection for these persons is unknown.

Minimal person-to-person transmission.
Geographic Distribution of Hepatitis E

Outbreaks or Confirmed Infection in >25% of Sporadic Non-ABC Hepatitis
Avoid drinking water (and beverages with ice) of unknown purity, uncooked shellfish, and uncooked fruit/vegetables not peeled or prepared by traveler.

IG prepared from donors in Western countries does not prevent infection.

Unknown efficacy of IG prepared from donors in endemic areas.

Future vaccine?
Acknowledgments

The author thankfully refers to the following educational resources in creating this series of lectures on viral hepatitis:

- Centers for Disease Control and Prevention – CDC
- Clinical Care Options – CCO
- World Health Organization – WHO

This is my website

http://johnjhaddad.weebly.com/