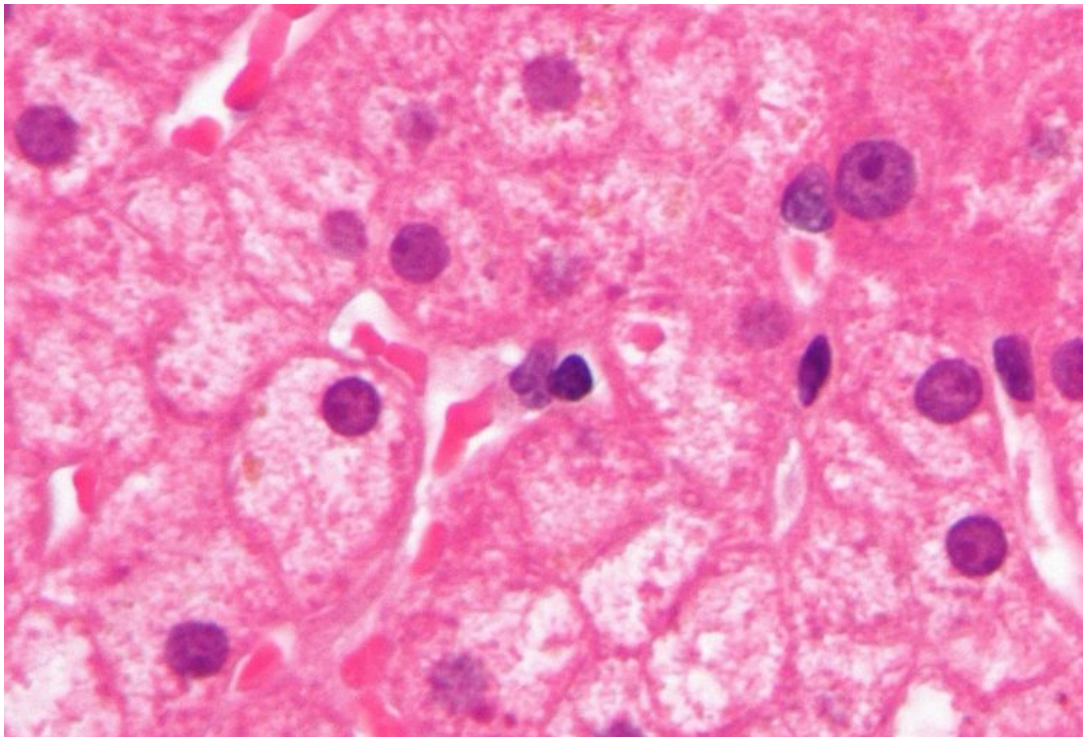


Viral Hepatitis — Epidemiology and Symptoms

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Viral hepatitis can be caused by different kinds of viruses which include hepatitis A, B, C, D, and E. These viruses cause targeted inflammation of the liver. In the acute stage, patients develop non-specific symptoms, such as nausea, vomiting, anorexia and abdominal pain. Later on, jaundice becomes evident. During this stage, supportive therapy is important. Antiviral therapy is indicated in the acute and chronic stages of hepatitis B and C.



Definition of Viral Hepatitis

The term 'hepatitis' means **inflammation of the liver**, which can be due to viral, immunologic, bacterial, or idiopathic pathology. Viral hepatitis is defined as the inflammation of the liver due to infection by one of the hepatitis viruses. **Hepatitis A, B, or C viruses** are the most common causes of viral hepatitis.

- **Hepatitis B** is closely linked with hepatocellular carcinoma, which is one of the top 10 cancers in the world. In some parts of the globe, this cancer is also associated with chronic hepatitis C
- **Hepatitis E** has a similar presentation to hepatitis A in that both have a fecal-oral mode of transmission
- **Hepatitis D virus** infection only occurs as a coinfection with the hepatitis B

virus

Adults infected with the hepatitis A or B virus commonly have **acute viral hepatitis**, while the hepatitis C virus more commonly results in a **subclinical acute stage**.

Another important definition related to hepatitis is **a poor hepatic synthetic function**, which is defined as a prothrombin time of > 16 seconds or an international normalized ratio of > 1.5.

Fulminant hepatic failure is a possible complication of acute hepatitis where the patient develops acute liver failure and hepatic encephalopathy within 8 weeks of the inciting event.

Epidemiology of Viral Hepatitis

Estimates suggest that there are approx. 25,000 new cases of **acute hepatitis A infection** annually. The mode of transmission for hepatitis A virus is fecal-oral and the infection is more common in places with poor sanitation. It is common both in developed and developing countries. Other transmission methods include contact with an infected person, as well as overcrowding. Food-borne hepatitis A is more common than water-borne hepatitis A. It has a low mortality rate since it is a self-limiting disease but incapacitates the patient for weeks, especially in fulminant presentations.

Hepatitis B infection is more common in the United States with about 43,000 new cases per year. Hepatitis B infection in children is not commonly reported because most cases are asymptomatic. Hepatitis B infection is more common among African Americans with an estimated incidence of 2.3 per 100,000. Chronic hepatitis B is more common in Asians.

Hepatitis B infection can result in **chronic hepatitis** and eventually **liver cirrhosis** in about 5% of the cases. This figure reaches about 90% in neonates affected by hepatitis B.

Hepatitis B transmission can occur during the **intrapartum period** or **in utero**. **Sexual transmission** with the hepatitis B virus is also common through vaginal, rectal, and oral-genital intercourse. Approx., 1/3 of the sexual partners of people affected with hepatitis B will also develop the condition. Hepatitis B transmission by **blood transfusion** is a very uncommon incident currently because of the routine screening of donor blood for hepatitis B-specific antibodies.

Hepatitis C infection rates are increasing and, in 2007, it was estimated that about 17,000 new persons were infected with the virus.

Hepatitis C virus transmission modes are similar to those of hepatitis B, but hepatitis C appears to be more prevalent in certain societies. Occupational exposure and intravenous drug abuse are possible risk factors for hepatitis C infection. Hepatitis C virus can also be transmitted sexually, but this is less likely to happen as only 5% of the sexual partners of people with the confirmed disease are known to acquire the infection.

Hepatitis D virus is a defective virus that requires the presence of hepatitis B in order to replicate. Hepatitis D virus can be **superimposed on chronic hepatitis B** or can be **co-transmitted with the hepatitis B** virus in the acute stage.

Finally, **the hepatitis E virus** remains a common cause of acute hepatitis that has a similar mode of transmission to hepatitis A.

Etiology of Viral Hepatitis

Various groups of viruses can cause acute viral hepatitis:

- **Hepatotropic viruses:** Which include hepatitis A, B, C, D, or E viruses.
- **Common non-hepatotropic viruses:** They include cytomegalovirus, varicella-zoster virus, and Epstein-Barr virus, among others.
- **Rare non-hepatotropic viruses:** These include herpes simplex viruses and yellow fever-causing viruses.

This discussion is focused on hepatotropic viruses because other viral pathogens can cause hepatitis as part of a more widespread phenomenon, rather than a specific targeting of the liver.

Hepatitis A and E viruses are usually transmitted via the **fecal-oral** route. Parenteral transmission via **blood transfusion**, shared use of **needles by drug users**, and **tattooing** are the common routes for hepatitis B, C, and D transmission.

Sexual activities can put people at risk of acquiring hepatitis B or D and, to a much lower extent, hepatitis C. Hepatitis B transmission during **delivery** or **in utero** is common. Finally, **sporadic cases** of hepatitis B and C are common but the most likely cause for these sporadic cases is the sexual transmission.

Hepatitis A, C, D, and E viruses are **RNA** viruses. However, the hepatitis B virus is unique because it is a **DNA** virus.

Pathophysiology of Viral Hepatitis

Hepatitis A virus has an **incubation period** of 2–4 weeks, during which it continually replicates itself in the liver. Viral transmission is possible in the first few weeks before the onset of symptoms. It is shed off in feces in huge quantities at this stage, thus, the fecal-oral transmission is possible. Hepatitis A virus infection is associated with **elevated alkaline phosphatase** levels. Patients infected with hepatitis A are at risk of developing **fulminant hepatic failure**.

Hepatitis B infection is classified into **acute and chronic stages**. The incubation period for the hepatitis B virus is usually 12 weeks and, once symptoms start in the acute stage, they are usually mild. Serum levels of hepatitis B viral DNA are usually elevated in the acute stage and patients are at first in the **immune-tolerant phase**. During this phase, **alanine aminotransferase** levels are usually normal, but **HBeAg**, a marker for viral replication, is usually positive.

In some cases, HBeAg becomes negative. These people enter the **inactive carrier state** in which viral replication and transmission are minimum. People in the inactive carrier state can still transmit the virus sexually or via blood transfusion. People who enter this state might develop chronic hepatitis, which is marked by **elevated liver enzymes** and **liver damage on biopsy**.

In the **chronic stage** of hepatitis B infection, people are usually **tired**. At this stage, **hepatic dysfunction** becomes evident by the presence of **extrahepatic manifestation** of liver disease. **Liver enzymes** are usually elevated, **HBeAg** is positive, indicating active viral replication, and liver biopsy show **inflammation** and **fibrosis**.

Extensive fibrosis of the liver eventually leads to **liver cirrhosis** and **hepatic failure**. It is clear from this pathophysiologic overview of hepatitis B that the immune response

plays an important role in repeated liver injury and repair. People who develop chronic hepatitis B are at risk of developing **hepatocellular carcinoma**.

Hepatitis C has an incubation period of 8 weeks. People in the acute stage usually have mild elevations of **hepatic aminotransferases**. The risk of chronic hepatitis from infection with the hepatitis C virus is markedly higher compared to that from other hepatitis viruses. If the patient enters the chronic stage, it usually takes 10 years until they develop **liver cirrhosis**.

Hepatitis D infection can be superimposed on a cirrhotic liver that is already infected with hepatitis B. If this happens, patients develop a **flare** of their disease and might develop **fulminant hepatic failure**.

Hepatitis E virus has an incubation period of 2-9 weeks. **Aminotransferases** might be elevated in hepatitis E in contrast to hepatitis A. **Pregnant women** infected with the hepatitis E virus are at a significant risk of **mortality** due to fulminant hepatic failure.

- Hepatitis A virus does NOT cause chronic hepatitis
- Prolonged hepatocellular necrosis and inflammation for > 6 months
 - Hepatitis B, C, E, and Hepatitis B-associated Hepatitis D
- Hepatitis E virus occurs only in immunosuppressed patients

Clinical Presentation of Viral Hepatitis

Regardless of the exact etiology of viral hepatitis, the symptoms of the disease can be classified into **4 main stages**:

- In **stage 1** of the disease, patients are **asymptomatic** but **viral replication** is ongoing. During this stage, laboratory investigations and liver chemistry can detect **subclinical hepatitis**
- In **stage 2** of the disease, patients enter the **prodromal phase**. During this phase, patients develop **non-specific symptoms** which include nausea, vomiting, [anorexia](#), fatigue, and pruritus
- **Stage 3** is characterized by jaundice, dark urine, and pale-colored stools. At this stage, patients might develop **upper gastrointestinal pain** that is more localized to the right side. Further, the physician usually makes a diagnosis of acute hepatitis
- In **stage 4**, patients enter the **convalescent phase**. During this stage, symptoms of acute illness resolve. Depending on the infecting viral pathogen, patients might enter an **inactive carrier stage**, develop **active chronic hepatitis**, or their condition might completely resolve

Diagnostic Workup for Viral Hepatitis

Based on the clinical picture and the most likely mode of transmission, one can suspect whether a patient is infected with hepatitis A, or B and C viruses. Accordingly, the different diagnostic workup modalities will differ depending on the most likely causative virus.



Image: Electron micrograph of Hepatitis E viruses (HEV). By Centers for Disease Control and Prevention's Public Health Image Library (PHIL), License: Public Domain

If hepatitis A is the most likely cause, patients can undergo **serum testing for IgM antibodies** against hepatitis A virus which happens in the acute stage. **IgG antibodies** are usually present in people who were previously infected by the hepatitis A virus, but testing for them is not useful in the acute stage. Possible serologic tests to identify hepatitis A include enzyme immunoassays, radioimmunoassay which has many convenient, specific, sensitive, and accurate methods, complement fixation, and immune adherence hemagglutination. Volunteers have been infected with the MS-1 strain of hepatitis and tissue culture used to isolate the virus but this method has not proven effective for making a diagnosis.

People infected with the hepatitis B virus first show a **positive HBsAg** (hepatitis B surface antigen). HBeAg can also be present in the acute stage and is a marker of viral replication. People can then enter the **inactive carrier stage** once HBeAg becomes negative and **anti-HBe antibodies** become positive.

In the acute stage, antibodies against the core antigen of the hepatitis B virus can be identified. These are usually **IgM antibodies** that can be used to diagnose acute hepatitis B infection. If the patient develops complete clearance of hepatitis B, **anti-HBs antibodies** become positive. This usually happens 4-6 months after acquiring the infection.

People infected with the hepatitis C virus benefit from **liver chemistry testing, hepatitis C virus RNA polymerase chain reaction (PCR) testing, and a liver biopsy.**

There are specific diagnostic tests for hepatitis E, such as PCR which helped identify hepatitis E virus RNA. The immunoabsorbent assay is an enzyme that can detect IgG and IgM hepatitis E virus antibodies. The latter applied HEV-glutathione-S-transferase fusion protein to detect antibodies that led to non-A and non-B hepatitis.

Patients with hepatitis B disease who suddenly develop a worsening of their symptoms might have **acquired hepatitis D. IgM anti-HDV antibodies** are useful in detecting acute superimposed infection with hepatitis D. The hepatitis E virus can be identified by **RNA testing** or by the detection of **IgM anti-HEV antibodies.**

Diagnostic interpretation	HBsAg	IgM Anti-HAV	IgM Anti-HBc	Anti-HCV
Acute HBV	+	-	+	-
Chronic HBV	+	-	-	-
Acute HAV on chronic HBV	+	+	-	-
Acute HAV and HBV	+	+	+	-

Acute HAV	-	+	-	-
Acute HAV and HBV (HBsAg below detection threshold)	-	+	+	-
Acute HBV (HBsAg below detection threshold)	-	-	+	-
Acute HCV	-	-	-	+

Treatment of Viral Hepatitis

Treatment of acute hepatitis A is mainly **symptomatic**. Patients are at risk of **dehydration**, and adequate **fluid replacement therapy** is indicated.

Patients with acute hepatitis B benefit from **supportive treatment**, but **specific antiviral therapy might** also be useful. **Lamivudine** and **adefovir dipivoxil** has been used in the acute stage and have been shown to lower the risk of developing the inactive carrier state or chronic hepatitis B.

Patients who develop chronic hepatitis B should receive **interferon therapy**. Interferon-alpha might be beneficial in the treatment of chronic hepatitis B. **Lamivudine** inhibits DNA polymerase-associated reverse transcriptase which is found in hepatitis B virus particles. Due to this effect, lamivudine can prevent or suppress hepatitis B virus replication.

Adefovir dipivoxil is another DNA polymerase inhibitor that has been used with excellent results in chronic hepatitis B. **Entecavir** is another antiviral approved for the treatment of hepatitis B with viral clearance rates of 60% in people who are HBeAg positive and 90% in patients who are HBeAg negative.

Patients with acute hepatitis C are rarely identified. If the patient is confirmed to have acute hepatitis C, **interferon-alpha therapy** should be initiated. People who develop chronic hepatitis C should receive **interferon-alpha-2b or 2a combined with ribavirin**. New drugs are being approved for the treatment of hepatitis C.

Treatment of superimposed hepatitis D is not yet well established. **Supportive treatment** of hepatitis E and the **close monitoring of pregnant women** is indicated to detect people who develop fulminant hepatic failure. **Liver transplantation** might be needed in patients with [fulminant hepatic failure](#).

Hepatitis A can be prevented by avoiding contact with infected persons and by getting vaccinated during travel to areas identified as high-risk areas for the disease. High-risk groups include sex workers, intravenous drug abusers, some health workers, such as those working in mental institutions, as well as daycare workers and members of the military. They should be immunized for protection. Treatment includes 100 IU/mL of anti-HAV at a recommended dose of 2 IU/kg of their body weight.

References

[Hepatitis Viruses](#) via nih.gov

Han SH, Saab S, Martin P. **Acute Viral Hepatitis**. Curr Treat Options Gastroenterol. 2000 Dec;3(6):481-486. PubMed PMID: 11096609.

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