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 caused by viral, immunologic, bacterial, or idiopathic pathology. Viral hepatitis is defined as the inflammation of the liver as a consequence of infection by one of the viral hepatitis viruses. Hepatitis A, B, or C viruses are the most common causes of viral hepatitis.

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

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

Another important definition related to hepatitis is **poor hepatic synthetic function**, which is defined as a prothrombin time longer than 16 seconds or an international normalized ratio more than 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 since the onset of the inciting event.

**Epidemiology of Viral Hepatitis**

**Acute hepatitis A infection** is estimated to affect approximately 25,000 new cases annually. The mode of transmission for the hepatitis A virus is fecal-oral and the infection is more common in places with poor sanitation. It is an endemic that 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 presentation states.

**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 goes significantly higher to about 90% of neonates affected by hepatitis B.

Hepatitis B transmission can happen during the **intrapartum period** or in utero. **Sexual transmission** with the hepatitis B virus is also common which is through vaginal, rectal and oral-genital intercourse. Approximately, one-third of sexual partners of people affected with hepatitis B will also develop the condition. Hepatitis B transmission by **blood transfusion** is a very uncommon incident nowadays 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 cases were infected with the virus.

Hepatitis C virus transmission modes are similar to hepatitis B but hepatitis C appears to more prevalent in certain societies. Occupational exposure and intravenous drug abuse are possible risk factors for the hepatitis C infection. The 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 for it to replicate. The hepatitis D virus can be **superimposed on chronic hepatitis B** or can be **co-transmitted with hepatitis B** 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 bar virus (EBV) among others.
- **Rare non-hepatotropic viruses**: They include herpes simplex viruses and yellow fever causing viruses.

This discussion is focused on the hepatotropic viruses because other viral pathogens can cause hepatitis as part of a more wide-spread phenomenon, rather than 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*, or *tattooing* is the common route 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, in fact, sexual transmission.

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

Pathophysiology of Viral Hepatitis

The hepatitis A virus has an **incubation period** of two to four weeks, during which it is continually replicating 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 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**.

The hepatitis B infection is classified into **acute and chronic stages**. The incubation period for the hepatitis B virus is usually 12 weeks and, once the 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 within 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 shows inflammation and fibrosis.

**Extensive fibrosis** of the liver eventually leads to **liver cirrhosis** and hepatic failure. It is clear from this pathophysiologic overview of the hepatitis B disease 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 other hepatitis viruses. If the patient enters the chronic stage, it usually takes 10 years until they develop liver cirrhosis.

The hepatitis D virus 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.

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

- HAV does NOT cause chronic hepatitis.
- Prolonged hepatocellular necrosis and inflammation for >6 months.
  - HBV, HCV, HBV-associated HDV, HEV.
- HEV 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 **four main stages**:

- **In phase 1** of the disease, patients are asymptomatic but viral replication is happening. During this stage, laboratory investigations and liver chemistry can detect subclinical hepatitis.
- **In phase 2** of the disease, patients enter the prodromal phase. During this phase, patients develop non-specific symptoms that include nausea, vomiting, **anorexia**, fatigue, and pruritus.
- **Phase 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. At this stage, the physician usually makes the diagnosis of acute hepatitis.
- **In phase 4**, patients enter the convalescent phase. During this stage, symptoms of acute illness resolve. Depending on the infecting viral pathogen, patients might develop 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 the 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.

If hepatitis A is the most likely cause, patients can undergo serum testing of IgM antibodies against the hepatitis A virus which happens in the acute stage. IgG antibodies are usually present in people who were previously infected by hepatitis A virus but are 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 to make a diagnosis.

People infected with the hepatitis B virus first show a positive HBsAg, which is defined as 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 to 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 testing and a liver biopsy.

There are specific diagnostic tests for hepatitis E, such as the polymerase chain reaction (PCR) which helped identify HEV RNA. The immunoabsorbent assay is an enzyme that can detect IgG and IgM anti-HEV. 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.
Treatment of Viral Hepatitis

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

Patients with the acute hepatitis B virus benefit from **supportive treatment**, but **specific antiviral therapy might also be useful**. Lamivudine and adenofovir dipivoxil have been used in the acute stage and 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 hepatitis B chronic state. **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 with HBeAg negative state.

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 well established yet. **Supportive treatment** of hepatitis E and **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, as well as getting vaccinated when one is traveling to areas identified as high-risk areas for this disease. High-risk groups include sex workers, homosexuals, drug abusers who are intravenous, some health workers, such as those working in mental institutions, as well as daycare workers. They should be immunized for protection. 100 IU/ml of anti-HAV can be administered at a recommended dose of 2 IU/kg of their body weight.

References

**Hepatitis Viruses** via nih.gov


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