Hepatitis B Virus (serum hepatitis)

Disease; HBV causes hepatitis B.

Important Properties; HBV is a member of the hepadnavirus family. It is a 42-nm **enveloped** virion,[1] with an icosahedral nucleocapsid core containing a **partially double-stranded circular** DNA genome.

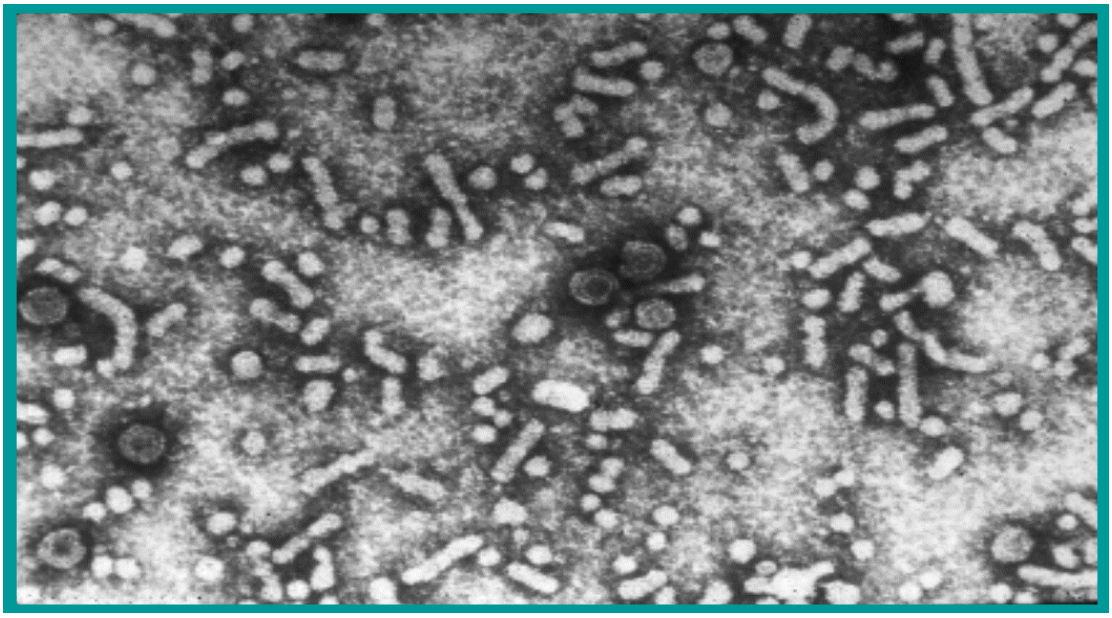
The envelope contains a protein called the **surface antigen** (HBsAg), which is important for laboratory diagnosis and immunization.[2]

Within the core is a **DNA-dependent DNA polymerase.** The genome contains **four genes** (four open reading frames) that encode five proteins, namely,

the **S gene** encodes the surface antigen, the **C gene** encodes the core antigen and the **e antigen** encodes the polymerase, and the **X gene** encodes the X protein.

The X protein is an activator of viral RNA transcription. The DNA polymerase has both RNA-dependent (reverse transcriptase) and DNA-dependent activity.

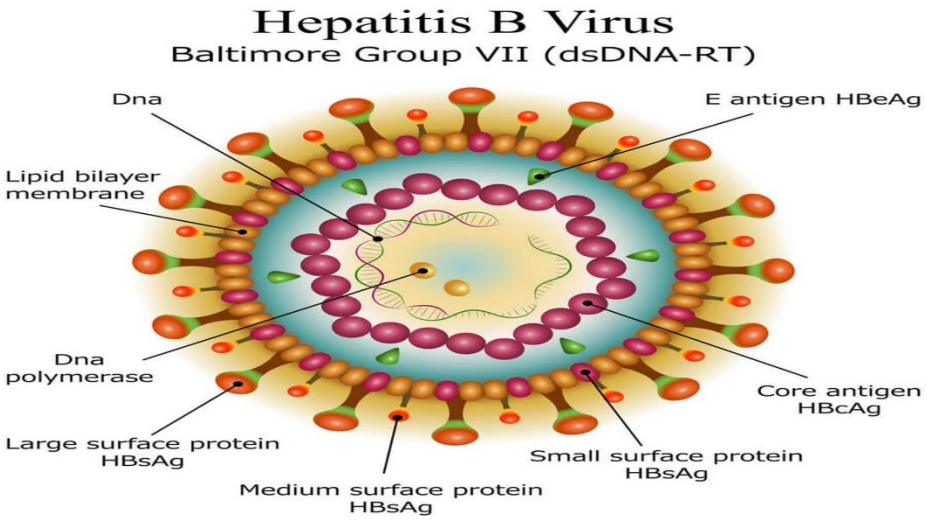
Electron microscopy of a patient's serum reveals three different types of particles: a few 42-nm virions and many 22-nm **spheres** and long **filaments** 22-nm wide, which are composed of surface antigen. HBV is the only human virus that produces these spheres and filaments in such large numbers in the patient's blood. The ratio of filaments and small spheres to virions is 1000:1.



In addition to HBsAg, there are two other important antigens: the **core antigen** (HBcAg) and the **e antigen** (HBeAg). The core antigen, as the name implies, forms the nucleocapsid core of the virion, whereas the e antigen is secreted from infected cells into the blood. The e antigen is an important indicator of **transmissibility.**

The specificity of HBV for liver cells is based on two properties: virus-specific receptors located on the hepatocyte cell membrane (facilitate entry) and transcription factors found only in the hepatocyte that enhances viral mRNA synthesis (act post entry).

Humans are the only natural hosts of HBV. There is no animal reservoir.



Transmission & Epidemiology; The three main modes of transmission are via *blood*, during sexual intercourse, and perinatally from mother to newborn. The observation that needle-stick injuries can transmit the virus indicates that only very small amounts of blood are necessary. HBV infection is especially prevalent in addicts who use intravenous drugs. Screening of blood for the presence of HBsAg has greatly decreased the number of transfusion-associated cases of hepatitis B.

However, because blood transfusion is a modern procedure, there must be another, natural route of transmission. It is likely that **sexual** transmission and transmission from **mother to child** during birth or breast feeding are the natural routes. Note that enveloped viruses, such as HBV, are more sensitive to the environment than nonenveloped viruses and hence are more efficiently transmitted by intimate contact, e.g., sexual contact.

Hepatitis B is found worldwide but is particularly prevalent in Asia. Globally, more than 300 million people are chronically infected with HBV and about 75% of them are Asian. There is a high incidence of **hepatocellular carcinoma (hepatoma)** in many Asian countries—a finding that indicates that HBV may be a human tumor virus .Immunization against HBV has significantly reduced the incidence of hepatoma in children. It appears that the HBV vaccine is the **first vaccine to prevent a human cancer.**

Pathogenesis & Immunity; After entering the blood, the virus infects hepatocytes, and viral antigens are displayed on the surface of the cells. Cytotoxic T cells mediate an immune attack against the viral antigens, and inflammation and necrosis occur. **Immune attack** against viral antigens on infected hepatocytes is mediated by cytotoxic T cells. The pathogenesis of hepatitis B is probably the result of this cell-mediated immune injury, because HBV itself does not cause a cytopathic effect. Antigen–antibody complexes cause some of the early symptoms, e.g., arthralgias, arthritis, and urticaria, and some of the complications in chronic hepatitis, e.g., glomerulonephritis, cryoglobulinemia, and vasculitis.

About 5% of patients with HBV infection become chronic carriers;. A chronic carrier is someone who has **HBsAg persisting in their blood for at least 6 months.** The chronic carrier state is attributed to a persistent infection of the hepatocytes, which results in the prolonged presence of HBV and HBsAg in the blood. The main determinant of whether a person clears the infection or becomes a chronic carrier is the adequacy of the cytotoxic T-cell response. HBV DNA exists primarily as an episome in the cytoplasm of persistently infected cells; a small number of copies of HBV DNA are integrated into cell DNA.

A high rate of **hepatocellular carcinoma occurs in chronic carriers.** The HBV X protein genome is an oncogene, or hepatocellular carcinoma appears to be the result of persistent cellular regeneration that attempts to replace the dead hepatocytes. Alternatively, malignant transformation could be the result of insertional mutagenesis, which could occur when the HBV genome integrates into the hepatocyte DNA. Integration of the HBV DNA could activate a cellular oncogene, leading to a loss of growth control.

Chronic carriage is more likely to occur when infection occurs in a newborn than in an adult, probably because a newborn's immune system is less competent than that of an adult's. Approximately 90% of infected neonates become chronic carriers. Chronic carriage resulting from neonatal infection is associated with a high risk of hepatocellular carcinoma.

Clinical Findings

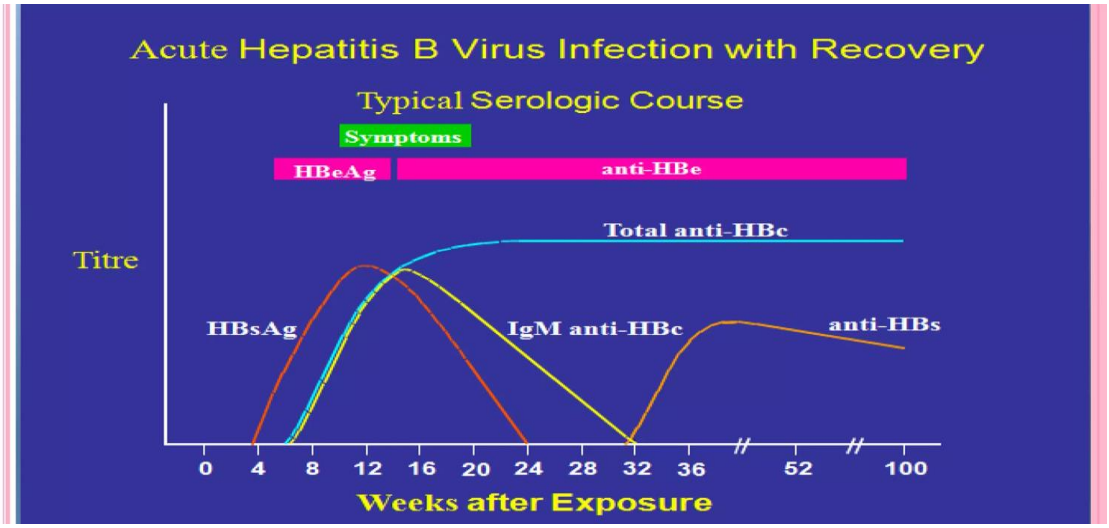
Many HBV infections are asymptomatic and are detected only by the presence of antibody to HBsAg. The mean incubation period for hepatitis B is 10 to 12 weeks, The clinical appearance of acute hepatitis B is similar to that of hepatitis A. However, with hepatitis B, symptoms tend to be more severe, and life-threatening hepatitis can occur. Most chronic carriers are asymptomatic, but some have chronic active hepatitis, which can lead to cirrhosis and death. SIGNS & SYMPTOMS :fatigue • abdominal pain • loss of appetite • nausea, vomiting • joint pain

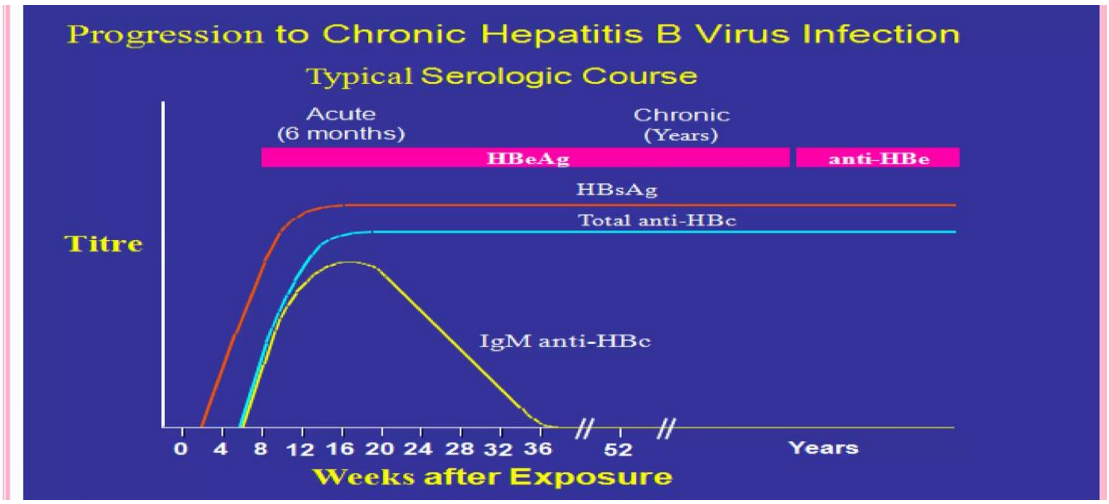
Laboratory Diagnosis; The most important laboratory test for the detection of early HBV infection is the immunoassay for **HBsAg.** HBsAg appears during the incubation period and is detectable in most patients during the prodrome and acute disease .It falls to undetectable levels during convalescence in most cases; its **prolonged presence** (at least 6 months) indicates the carrier state and the risk of chronic hepatitis and hepatic carcinoma. As described in Table –4, HBsAb is not detectable in the chronic carrier state. Note that HBsAb is, in fact, being made but is not detectable in

the laboratory tests because it is bound to the large amount of HBsAg present in the blood. HBsAb is also being made during the acute disease but is similarly undetectable because it is bound in antigen–antibody complexes.

Note that there is a period of several weeks when HBsAg has disappeared but HBsAb is not yet detectable. This is the **window phase.** At this time, the HBcAb is always positive and can be used to make the diagnosis. HBcAb is present in those with acute infection and chronic infection, as well as in those who have recovered from acute infection. Therefore, it cannot be used to distinguish between acute and chronic infection. The IgM form of HBcAb is present during acute infection and disappears approximately 6 months after infection. The test for HBcAg is not readily available.

HBeAg arises during the incubation period and is present during the prodrome and early acute disease and in certain chronic carriers. Its presence indicates a **high likelihood of transmissibility,** and, conversely, the finding of HBeAb indicates a lower likelihood, but transmission can still occur. DNA polymerase activity is detectable during the incubation period and early in the disease, but the assay is not available in most clinical laboratories. The detection of viral DNA in the serum is strong evidence that infectious virions are present.





HBsAg anti-HBc anti-HBs	negative negative negative	Susceptible
HBsAg anti-HBc anti-HBs	negative positive positive	Immune due to natural infection
HBsAg anti-HBc anti-HBs	negative negative positive	Immune due to hepatitis B vaccination
HBsAg anti-HBc IgM anti-HBc anti-HBs	positive positive positive negative	Acutely infected
HBsAg anti-HBc IgM anti-HBc anti-HBs	positive positive negative negative	Chronically infected
HBsAg anti-HBc anti-HBs	negative positive negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection

Treatment & Prevention; Alpha interferon in the form of long-acting pegylated interferon (Pegasys) is clinically useful for the treatment of chronic hepatitis B infections. Some nucleoside analogues, such as lamivudine (Epivir-HBV), that inhibit the reverse transcriptase of HIV also are effective against the DNA polymerase of HBV. Adefovir (Hepsera) is a nucleotide analogue of adenosine monophosphate that also inhibits the DNA polymerase of HBV. • **These drugs should not be used by pregnant women.**

Prevention involves the use of either the **vaccine** or **hyperimmune globulin** or both.

1. The vaccine, e.g., Recombivax, contains HBsAg produced in yeasts by recombinant DNA techniques. The vaccine is highly effective in preventing hepatitis B and has few side effects. It is indicated for people who are frequently exposed to blood or blood products, such as certain health care personnel (e.g., medical students, surgeons, and dentists), patients receiving multiple transfusions or dialysis, patients with frequent sexually transmitted disease, and abusers of illicit intravenous drugs. Travelers who plan a long stay in areas of endemic infection, such as many countries in Asia and Africa, should receive the vaccine. The U.S. Public Health Service recommends that all newborns and adolescents receive the vaccine.

   At present, booster doses after the initial three-dose regimen are not recommended. However, if antibody titers have declined in immunized

patients who are at high risk, such as dialysis patients, then a booster dose should be considered.

Widespread immunization with the HBV vaccine has significantly reduced the incidence of hepatocellular carcinoma in children. A vaccine called Twinrix that contains both HBsAg and inactivated HAV provides protection against both hepatitis B and hepatitis A.

2. Hepatitis B immune globulin (HBIG) contains a high titer of HBsAb because it is prepared from sera of patients who have recovered from hepatitis B. It is used to provide immediate, passive protection to individuals known to be exposed to HBsAg-positive blood, e.g., after an accidental needle-stick injury.

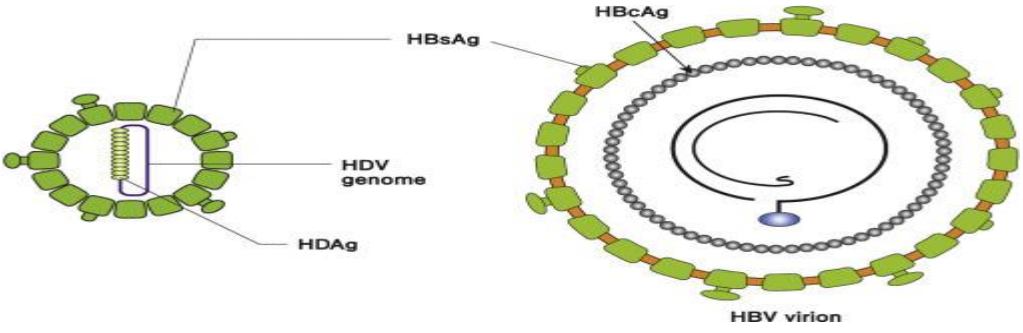
However, the recommendation regarding one common concern of medical students, the needle-stick injury from a patient with HBsAg-positive blood, is that both the vaccine and HBIG be given (at separate sites). This is true even if the patient's blood is HBeAb positive. Both the vaccine and HBIG should also be given to a newborn whose mother is HBsAg-positive. These are good examples of **passive–active** immunization, in which both immediate and long-term protection are provided.

Hepatitis D Virus (Delta Virus)

Disease; Hepatitis D virus (HDV) causes hepatitis D (hepatitis delta).

Important Properties & Replicative Cycle; HDV is unusual in that it is a **defective** virus, i.e., it cannot replicate by itself because it does not have the genes for its envelope protein. HDV can replicate only in cells also infected with HBV because HDV uses the surface antigen of HBV (HBsAg) as its envelope protein. HBV is therefore the helper virus for HDV.

HDV is an enveloped virus with an RNA genome that is a single-stranded, negative-polarity, covalently closed circle. The RNA genome of HDV is very small and encodes only one protein, the internal core protein called **delta antigen.** HDV genome RNA has no sequence homology to HBV genome DNA. HDV has no virion polymerase; the genome RNA is replicated and transcribed by the host cell RNA polymerase. HDV has one serotype because HBsAg has only one serotype. There is no evidence for the existence of an animal reservoir for HDV.



Transmission & Epidemiology; HDV is transmitted by the same means as is HBV, i.e., sexually, by blood, and perinatally. In the United States, most HDV infections occur in intravenous drug users who share needles. HDV infections occur worldwide with a similar distribution to that of HBV infections.

Pathogenesis & Immunity; It seems likely that the pathogenesis of hepatitis caused by HDV and HBV is the same, i.e., the virus-infected hepatocytes are damaged by cytotoxic T cells. There is some evidence that delta antigen is cytopathic for hepatocytes.

IgG antibody against delta antigen is not detected for long periods after infection; it is therefore uncertain whether long-term immunity to HDV exists.

Clinical Findings; Because HDV can replicate only in cells also infected with HBV, hepatitis delta can occur only in a person infected with HBV. A person can either be infected with both HDV and HBV at the same time, i.e., be "coinfected," or be previously infected with HBV and then "superinfected" with HDV.

Hepatitis in patients coinfected with HDV and HBV is more severe than in those infected with HBV alone, but the incidence of chronic hepatitis is about the same in patients infected with HBV alone. However, hepatitis in chronic carriers of HBV who become superinfected with HDV is much more severe, and the incidence of fulminant, life-threatening hepatitis, chronic hepatitis, and liver failure is significantly higher.

- Co-infection: acquire infection at same time as Hep B- usually Hepatitis is more severe than those infected by HBV alone.
  - low risk of chronic infection.
- Superinfection: infection of HDV in chronic Hep B. Hepatitis in chronic carriers of HBV who become superinfected with HDV is much more severe ,and the incidence of fulminant ,life threatening hepatitis, chronic hepatitis and liver failure is higher.

Laboratory Diagnosis; The diagnosis of HDV infection in the laboratory is made by detecting either delta antigen or IgM antibody to delta antigen in the patient's serum.

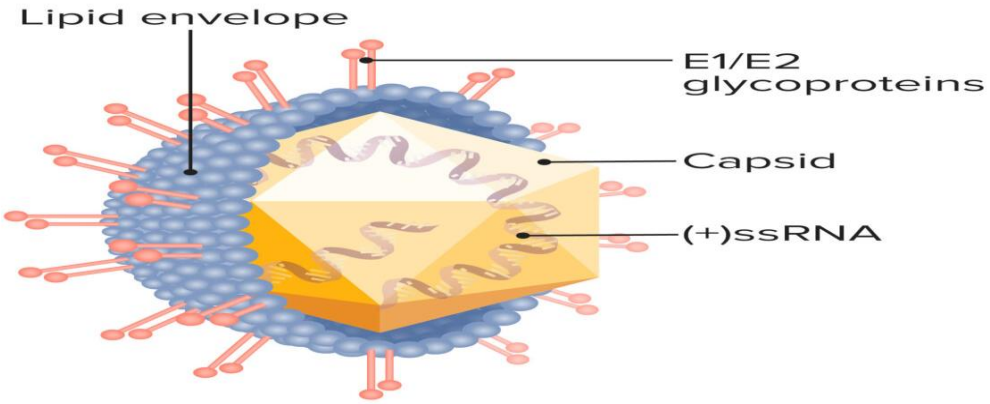
Treatment & Prevention; Alpha interferon can mitigate some of the effects of the chronic hepatitis caused by HDV but does not eradicate the chronic carrier state. There is no specific antiviral therapy against HDV. There is no vaccine against HDV, but a person immunized against HBV will not be infected by HDV because HDV cannot replicate unless HBV infection also occurs.

Hepatitis C Virus (non-A non -B hepatitis)/ transfusion hepatitis.

Disease; HCV causes hepatitis C.

Important Properties; HCV is a member of the flavivirus family. It is an enveloped virion containing a genome of single-stranded, positive-polarity RNA. It has no virion polymerase.

HCV has at least six genotypes and multiple subgenotypes based on differences in the genes that encode one of its two envelope glycoproteins. This genetic variation results in a "hypervariable" region in the envelope glycoprotein.



Transmission & Epidemiology;

Humans are the reservoir for HCV. It is transmitted primarily via **blood.** At present, injection drug use accounts for almost all new HCV infections. Transmission via blood transfusion rarely occurs because donated blood containing antibody to HCV is discarded. Transmission via needle-stick injury occurs, but the risk is lower than for HBV. Sexual transmission and transmission from mother to child occur but are inefficient modes.

HCV is the **most prevalent blood-borne pathogen** in the United States. (In the nationally reported incidence data, HCV ranks below HIV and HBV as a blood-borne pathogen, but it is estimated that HCV is more prevalent.) Approximately 4 million people in the United States (1%–2% of the population) are chronically infected with HCV.

In the United States, about 1% of blood donors have antibody to HCV. People who share needles when taking intravenous drugs are very commonly infected. Commercially prepared immune globulin preparations are generally very safe, but

several instances of the transmission of HCV have occurred. This is the only example of an infectious disease transmitted by immune globulins.

Pathogenesis & Immunity;

HCV infects hepatocytes primarily, but there is no evidence for a virus-induced cytopathic effect on the liver cells. Rather, death of the hepatocytes is probably caused by immune attack by cytotoxic T cells. HCV infection strongly predisposes to hepatocellular carcinoma, but there is no evidence for an oncogene in the viral genome or for insertion of a copy of the viral genome into the DNA of the cancer cells.

Alcoholism greatly enhances the rate of hepatocellular carcinoma in HCV-infected individuals. This supports the idea that the cancer is caused by prolonged liver damage and the consequent rapid growth rate of hepatocytes as the cells attempt to regenerate rather than by a direct oncogenic effect of HCV. Added support for this idea is the observation that patients with cirrhosis of any origin, not just alcoholic cirrhosis, have an increased risk of hepatocellular carcinoma. (A report in 1998 that the core protein of HCV causes hepatocellular carcinoma in mice may lead to a greater understanding of oncogenesis by HCV.)

Antibodies against HCV are made, but approximately 75% of patients are chronically infected and continue to produce virus for at least 1 year. (Note that the rate of **chronic carriage of HCV is much higher** than the rate of chronic carriage of HBV.) Chronic active hepatitis and cirrhosis occur in approximately 10% of these patients. For patients who clear the infection, it is not known whether reinfection can occur or whether there is lifelong immunity.

Clinical Findings;

Clinically, the acute infection with HCV is milder than infection with HBV. Fever, anorexia, nausea, vomiting, and jaundice are common. Dark urine, pale feces, and elevated transaminase levels are seen.

Hepatitis C resembles hepatitis B as far as the ensuing chronic liver disease, cirrhosis, and the predisposition to hepatocellular carcinoma are concerned. Note that a chronic carrier state occurs more often with HCV infection than with HBV. Liver biopsy is often done in patients with chronic infection to evaluate the extent of liver damage and to guide treatment decisions. Many infections with HCV, including both acute and chronic infections, are asymptomatic and are detected only by the presence of antibody. The mean incubation period is 8 weeks. Cirrhosis resulting from chronic HCV infection is the most common indication for liver transplantation.

HCV infection also leads to significant autoimmune reactions, including vasculitis, arthralgias, purpura, and membranoproliferative glomerulonephritis. HCV is the main cause of essential mixed cryoglobulinemia. The cryoprecipitates often are composed of HCV antigens and antibodies.

Laboratory Diagnosis;

HCV infection is diagnosed by detecting antibodies to HCV in an ELISA. The antigen in the assay is a recombinant protein formed from three immunologically stable HCV proteins and does not include the highly variable envelope proteins. The test does not distinguish between IgM and IgG and does not distinguish between an acute, chronic, or resolved infection.

Because false-positive results can occur in the **ELISA, a RIBA** (recombinant immunoblot assay) should be performed as a confirmatory test. If the results of RIBA are positive, a PCR-based test that detects the presence of viral RNA in the serum should be performed to determine whether active disease exists. Isolation of the virus from patient specimens is not done. A chronic infection is characterized by elevated transaminase levels, a positive RIBA, and detectable viral RNA for at least 6 months.

Treatment & Prevention

Treatment of **acute** hepatitis C with

1. Alpha interferon significantly decreases the number of patients that become chronic carriers.

2. Combination of peginterferon (Pegasys) and ribavirin. Peginterferon is alpha interferon conjugated to polyethylene glycol. Polyethylene glycol significantly enhances the half-life of alpha interferon. In some patients, treatment significantly reduces viral replication and viral RNA becomes undetectable. HCV genotype 1 is less responsive to interferon and ribavirin than are genotypes 2 and 3. As a result, patients infected with genotype 1 are treated for 12 months, whereas those infected with genotypes 2 and 3 are usually treated for 6 months.

3. Direct-acting antivirals (DAA) are drugs used to treat hepatitis C infections. They are a combination of antiviral drugs that target stages of the hepatitis C virus reproductive cycle. They are more effective than older treatments such as ribavirin and interferon. The DAA drugs are taken orally, as tablets, for 8 to 12 weeks.

Patients with chronic HCV infection should be advised to reduce or eliminate their consumption of alcoholic beverages to reduce the risk of hepatocellular carcinoma and cirrhosis. Patients with chronic HCV infection and cirrhosis should be monitored with alpha-fetoprotein tests and liver sonograms to detect carcinoma at an early stage. Patients with liver failure due to HCV infection can receive a liver transplant, but infection of the graft with HCV typically occurs.

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