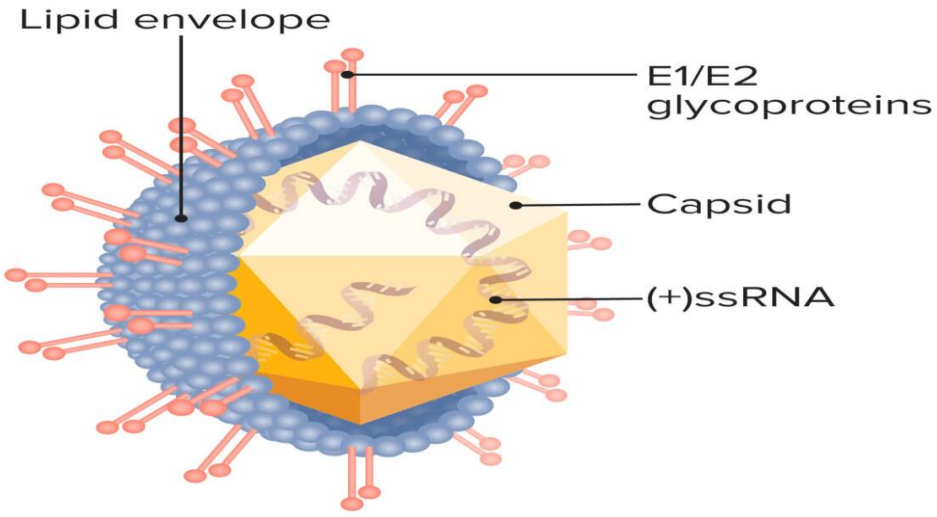
Hepatitis C Virus

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. The genetic variability is due to the high mutation rate in the envelope gene coupled with the absence of a proofreading function in the virion-encoded RNA polymerase. As a result, multiple subspecies (quasispecies) often occur in the blood of an infected individual at the same time.



Summary of Replicative Cycle;

The replication of HCV is uncertain because it has not been grown in cell culture. Other flaviviruses replicate in the cytoplasm and translate their genome RNA into large polyproteins, from which functional viral proteins are cleaved by a virion-encoded protease. It is likely that HCV replication follows this model.

The replication of HCV in the liver is enhanced by a liver-specific micro-RNA. This micro-RNA acts by increasing the synthesis of HCV mRNA. (Micro-RNAs are known to enhance cellular mRNA synthesis in many tissues.)

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. Unlike yellow fever virus, another flavivirus that infects the liver.

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.

Blood found to contain antibody is discarded—a procedure that has prevented virtually all cases of transfusion-acquired HCV infection since 1994, when screening began. There is no vaccine, and hyperimmune globulins are not available. Pooled immune serum globulins are not useful for postexposure prophylaxis. There is no effective regimen for prophylaxis following needle-stick injury; only monitoring is recommended.

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.

Patients coinfected with HCV and HIV should be prescribed "HAART" (highly active antiretroviral therapy) with caution because recovery of cell-mediated immunity (immune reconstitution) can result in an exacerbation of hepatitis. Consideration should be given to treat the HCV infection prior to starting HAART.

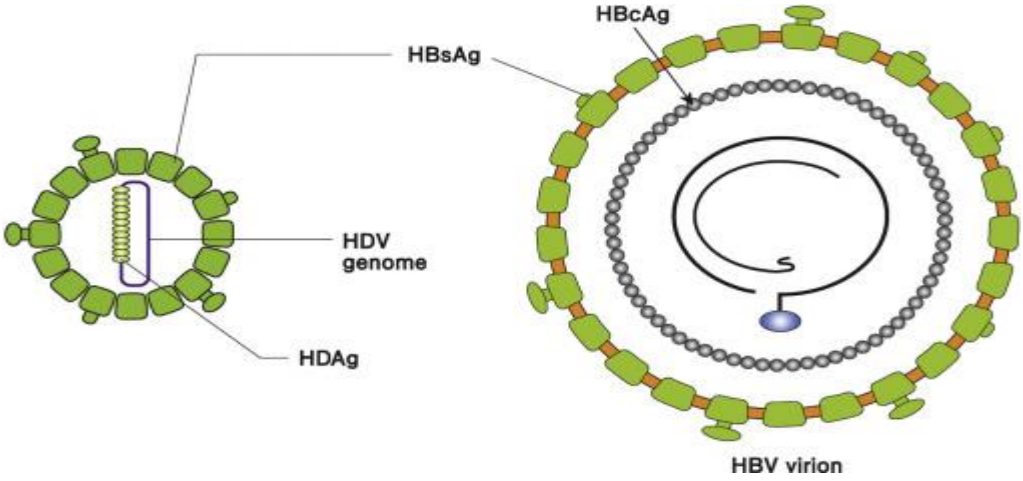
Hepatitis D Virus (Delta Virus)

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 genome RNA is a "ribozyme", i.e., it has the ability to self-cleave and self-ligate—properties that are employed during replication of the genome. HDV replicates in the nucleus, but the specifics of the replicative cycle are complex.

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.

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.