LECTURE-7
Hepatitis virus

Hepatitis Viruses:

Hepatitis is a clinical syndrome caused by many pathogens including viruses. There are **six medically** important viruses that are called hepatitis viruses because their main site of infection is liver. These viruses are hepatitis **A** virus (**HAV**), hepatitis **B** virus (**HBV**), hepatitis **C** virus (**HCV**), hepatitis **D** virus (**HDV**), hepatitis **E** virus (**HEV**), and newly described **G** virus (**HGV**). Although these viruses infect the liver as common target organ, they however, differ greatly in their morphology, replication pattern, and course of infection. Hepatocytes are the primary target of true.

The characteristics of the five known hepatitis viruses are shown in Table 35-1

TABLE 35-1 Characteristics of Hepatitis Viruses

Virus	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Family	Picornaviridae	Hepadnaviridae	Flaviviridae	Unclassified	Hepeviridae
Genus	*Hepatovirus*	*Orthohepadnavirus*	*Hepacivirus*	*Deltavirus*	*Hepevirus*
Virion	27 nm, icosahedral	42 nm, spherical	60 nm, spherical	35 nm, spherical	30–32 nm, icosahedral
Envelope	No	Yes (HBsAg)	Yes	Yes (HBsAg)	No
Genome	ssRNA	dsDNA	ssRNA	ssRNA	ssRNA
Genome size (kb)	7.5	3.2	9.4	1.7	7.2
Stability	Heat and acid stable	Acid sensitive	Ether sensitive, acid sensitive	Acid sensitive	Heat stable
Transmission	Fecal–oral	Parenteral	Parenteral	Parenteral	Fecal–oral
Prevalence	High	High	Moderate	Low, regional	Regional
Fulminant disease	Rare	Rare	Rare	Frequent	In pregnancy
Chronic disease	Never	Often	Often	Often	Never
Oncogenic	No	Yes	Yes	?	No

ds, double stranded; HBsAg, hepatitis B surface antigen; ss, single stranded.

These viruses infect the liver and cause distinct clinical pathology by producing characteristic symptoms of **jaundice** and **production and release of liver enzymes in the serum.** Most of these diseases spread very fast because infected individuals are contagious **not only** during stage of manifestation of the disease but also during the phase of incubation. Human infections associated with hepatitis viruses are summarized in Table 66-2.

TABLE 66-2 Diseases associated with hepatitis viruses

Virus	Diseases
HAV	Acute hepatitis
HBV	Acute and chronic hepatitis
HCV	Acute HCV infection, chronic HCV infection, and cirrhosis and other complications
HDV	Acute self-limited infection to acute fulminant liver failure
HEV	Serious infection in pregnant women
HGV	Coinfection in chronic HBV and HCV infection

Most cases of acute viral hepatitis in children and adults are caused by one of the following five agents:

1- Hepatitis A virus (HAV): the etiologic agent of viral hepatitis type A (infectious hepatitis)

2- Hepatitis B virus (HBV): which is associated with viral hepatitis B (serum hepatitis)

3- Hepatitis C virus (HCV): the agent of hepatitis C (common cause of posttransfusion hepatitis)

4- Hepatitis D (HDV): a defective virus dependent on coinfection with HBV

5- Hepatitis E virus (HEV): the agent of enterically transmitted hepatitis

Hepatitis viruses produce acute inflammation of the liver, resulting in a clinical illness characterized by fever, gastrointestinal symptoms such as nausea and vomiting, and jaundice.

Hepatitis Type A and E

Viral classification

Hepatitis A Virus

HAV is an **Enterovirus** belonging to the **Picornaviridae** family in the genus **Hepatovirus**. HAV is a non- enveloped virus that has evolved a unique strategy by which it hijacks cellular membranes, exiting the host cells fully cloaked in a lipid membrane.

The viral particle is an **icosahedral** capsid and the genome is a **single-stranded, positive-polarity RNA**.

Hepatitis E Virus

HEV belongs to the family **Hepeviridae** in the genus **Hepevirus**.

HEV is **non**- enveloped RNA virus with an **icosahedral** capsid. The genome is a **positive**-sense single-stranded RNA.

Transmission

Both HAV and HEV transmitted to humans fecal-orally, usually through fecally contaminated food and water.

Clinical Significance

HAV

Acute HAV infection is presented as an acute illness causing jaundice or elevated serum **aminotransferases**. Incubation period 2-6 weeks. HAV infection may manifest as fatigue, malaise, vomiting, anorexia, fever, and abdominal pain.

HAV is not a serious virus and has a vaccine

HEV

The incubation period for hepatitis E ranges from 15 to 40 days. Acute HEV infection is presented as an acute illness causing jaundice or elevated serum **aminotransferases**. Gastrointestinal symptoms include diarrhea, nausea, hepatomegaly, splenomegaly, and vomiting.

Detection of HAV and HEV

Serologic testing is required for adequate diagnosis for both HAV and HEV.

Both could be diagnosed by PCR

Hepatitis B virus

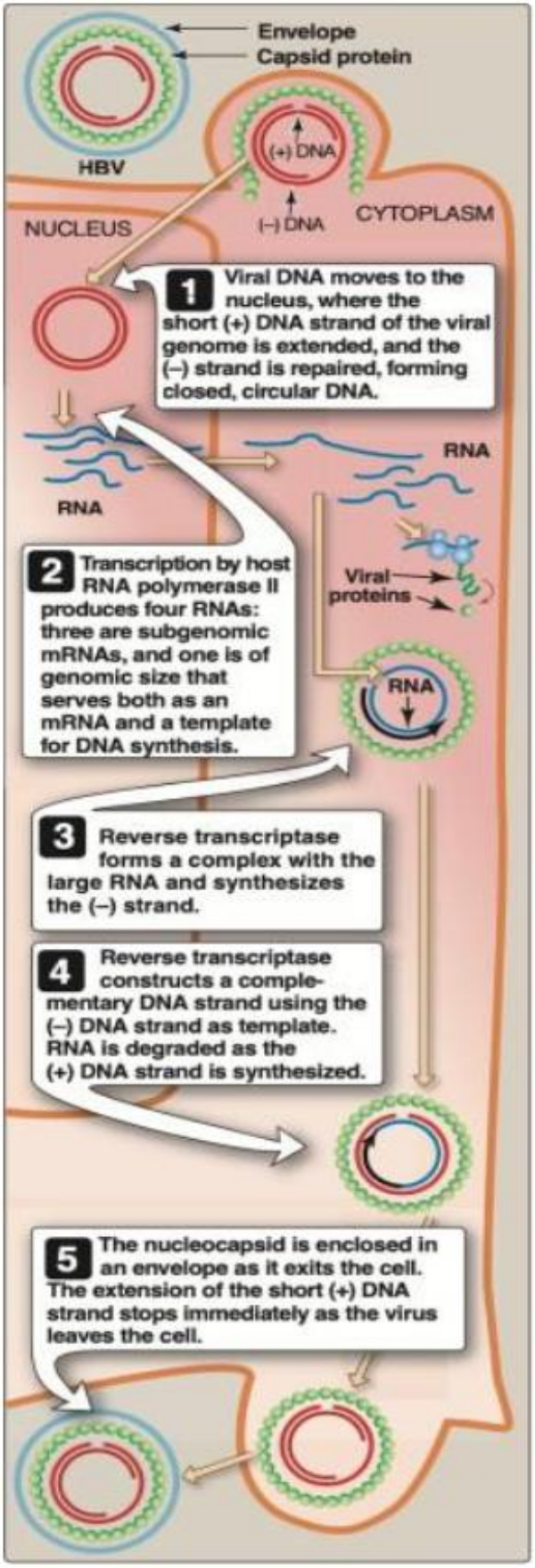
HBV is classified as a genus of **hepadnavirus**, **Hepadnaviridae** family. HBV establishes chronic infections, especially in those infected as infants; it is a major factor in the eventual development of liver disease and hepatocellular carcinoma in those individuals.

Structure and replication of hepatitis B virus

The HBV virion, historically referred to as the "Dane particle," consists of an **icosahedral** nucleocapsid enclosed in an **envelope**.

- **Organization of the hepatitis B virus genome:** HBV DNA genome is a partly doublestranded, circular DNA molecule (that is, one strand is **longer** than the other) as shown in Figure 26.4. The short "plus" strand is only 50 to 80 percent as long as its complementary strand, the "minus" strand.
- **Viral proteins:** The **four** proteins encoded by viral DNA are:

1) the **core protein** [hepatitis B nucleocapsid core antigen (HBcAg)];
2) envelope protein [a glycoprotein referred to as hepatitis B surface antigen (**HBsAg**)];
3) multifunctional reverse transcriptase/DNA polymerase, which is complexed with the DNA genome within the capsid; and
4) a **nonstructural regulatory protein** designated the "**X protein B**.



igure 26.4 Replication of hepatitis B virus (HBV)

Transmission Infectious

HBV is present in all body fluids of an infected individual. Therefore, blood, semen, saliva, and breastmilk, for example, serve as sources of infection. Individuals infected at an early age have an increased risk of developing hepatocellular carcinoma later in life. Hepatitis B is primarily a disease of infants in developing nations, and, in Western countries, it is mostly confined to adults who usually contract HBV infection through sexual intercourse or blood exposure from shared needles during injecting drug use.

Pathogenesis

Hepatocytes are the primary cell type infected by HBV. The primary cause of hepatic cell destruction appears to be the **cell-mediated immune response**, which results in **inflammation** and **necrosis**. The cells involved are **cytotoxic T cells**, which react specifically with the fragments of nucleocapsid proteins (**HBcAg and HBeAg**), expressed on the surface of infected hepatocytes.

Clinical significance

Acute disease Chronically infected people serve as the reservoir of transmissible virus in the population. In most individuals, the primary infection is asymptomatic and resolves as a result of an effective cellmediated immune response Phases in acute hepatitis B virus infections: Following infection, HBV has incubation period of **between 45 and 120 days**. Following this period, a **pre-jaundice phase** occurs. The acute, icteric (jaundice) phase then follows. During this phase, **dark urine**, due to bilirubinuria, and jaundice (a yellowish coloration of mucous membranes, conjunctivae, and skin) are evident.

Laboratory identification

The purpose of diagnostic laboratory studies of patients with clinical hepatitis is to, first, determine which hepatitis virus is the cause of the illness and, second (for HBV), to distinguish **acute from chronic** infections. Elevations of aminotransferases, bilirubin, and prothrombin time all contribute to the initial evaluation of hepatitis. Commonly known as ELISA, enzymelinked immunosorbent assay and other immunologic techniques for detection of viral antigens and antibodies are the primary means to distinguish among HAV, HBV, HCV, and HDV. In addition, identification of the presence or absence of specific antiviral antibodies and viral antigens permits differentiating between acute and chronic HBV infections.

Prevention

The use of a highly effective **vaccine** has led protection of adults from infection as well as newborns from infection by transmission from HBV- positive mothers.

1. Active immunization: The use of a highly effective vaccine has led protection of adults from infection as well as newborns from infection by transmission from HBV- positive mothers.

2. Passive immunization: Hepatitis B immunoglobulin (HBIG) is prepared from the blood of donors is recommended as the initial step in preventing infection of individuals accidentally exposed to HBV-contaminated blood by needlestick or other means and of those exposed to infection by sexual contact with an HBV-positive partner.

It is also strongly recommended that pregnant women should be screened for HBsAg. Infants born to mothers who are HBV positive are given HBIG plus hepatitis B vaccine at birth, followed by additional doses of vaccine at 1 and 6 months.

Hepatitis D virus (Delta Agent)

HDV is found in nature only as a **coinfection with HBV**. It is significant because its presence results in more severe acute disease, with a greater risk of fulminant hepatitis and, in chronically infected patients, a greater risk of cirrhosis and liver cancer.

Structure and replication

HDV does not fall into any known group of animal viruses. It has a circular, single-stranded RNA genome with negative polarity. HBV-coded HBsAg. Thus, HDV requires HBV to serve as a helper virus for infectious HDV production. The HDV RNA genome is replicated and transcribed in the nucleus by cellular enzymes.

Transmission and pathogenesis

Because HDV exists only in association with HBV, it can be transmitted by the same routes. However, it does not appear to be transmitted sexually as frequently as HBV or HIV.

Pathologically, liver damage is essentially the same as in other viral hepatitides, but the presence of HDV usually results in more extensive and severe damage.

Laboratory identification

The immunologically based methods used to diagnosis HBV are also applied to HDV. The delta (D) antigen and immunoglobulin M antibodies against it can be detected in serum. The presence of HDV RNA in serum or liver tissue, as detected by hybridization with or without the use of reverse transcriptase and polymerase chain reaction amplification, is an indicator of active infection.

Hepatitis C virus

HCV is a **positive-stranded RNA virus**, classified as family **Flaviviridae**, genus **Hepacivirus**.

Hepatitis C virus genera

Hepatitis C virus (HCV) was discovered in 1988 in the course of searching for the cause of non-A, non-B, transfusion-associated hepatitis. At that time, HCV accounted for 90 percent of the cases of non-A, non-B hepatitis.
Transmission and pathogenesis:

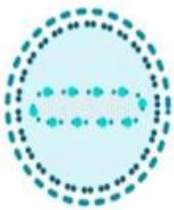
Although HCV was initially identified as a major cause of **posttransfusion hepatitis**, intravenous drug users and patients on hemodialysis are also at high risk for infection with HCV. Tattooing is also a leading cause of HCV infection. In addition, there is evidence for sexual transmission of HCV as well as for transmission from mother to infant.

In the infected individual, viral replication occurs in the hepatocyte and, probably, also in mononuclear cells (lymphocytes and macrophages). Destruction of liver cells may result both from a direct effect of the activities of viral gene products and from the host immune response, including cytotoxic T cells. HCV have been associated with hepatocellular carcinoma development.
Chronic Hepatitis

The risk of chronic HCV infection is high. - Patients with chronic infection are asymptomatic or have only mild nonspecific symptoms since cirrhosis is not present. The most frequent complaint is fatigue. Less common manifestations are nausea, weakness, myalgia, arthralgia, and weight lose.
Viral coinfection:

HCV progression is more rapid inHIV-infected patients. Acute hepatitis B in a patient with chronic hepatitis C may be more severe. Liver damage is usually worse and progression faster in patients with dual HBV/HCV infections.
Laboratory identification:

A specific diagnosis can be made by demonstration of antibodies that react with a combination of recombinant viral proteins. Sensitive tests are also now available for detection of the viral nucleic acid by RT-PCR.

	Hepatitis A virus (HAV)	Hepatitis B virus (HBV)	Hepatitis C virus (HCV)	Hepatitis D virus (HDV)	Hepatitis E virus (HEV)
					
Viral family	*picornavirus*	*hepadnavirus*	*flavivirus*	*deltavirus*	*hepevirus*
Chronic	no	yes	yes	yes	no
Vaccine	yes	yes	**NO**	yes	yes

Questions

1.The transmission of HCV will be via
a- Contaminated needle. b- Contaminated food. c- Aerosols d- Contaminated water
2.HBV genome is
a- ssRNA b- dsRNA c- Gaped dsDNA d- ssDNA
3.The transmission of HAV will be via
a- Contaminated needle. b- Contaminated food. c- Aerosols d- Sexual transmission
4.Which virus belongs to Flaviviridae
family? a- HAV b- HBV c- HCV d- HDV
5.Which virus belongs to hepadnaviridae
family? a- HAV b- HBV c- HCV d- HDV