Chapter 29

Hepatitis viruses

There are **five** medically important hepatitis viruses, **Hepatitis viruses A to E**.

There are viruses such as **Epstein-Barr virus, cytomegalovirus** and **yellow fever virus** which infect the liver but other organs as well.

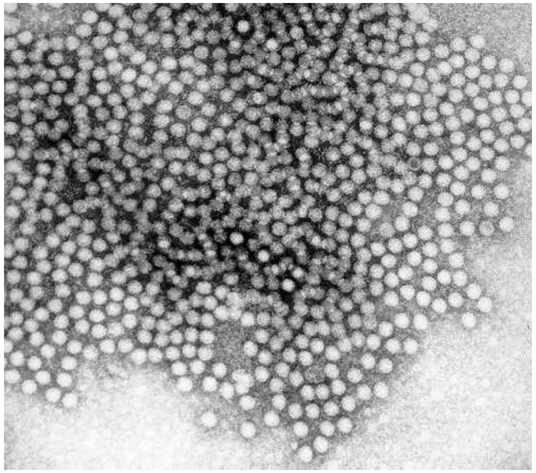
Hepatitis A virus

It causes **Hepatitis A**.

It is **atypical** **enterovirus** of **picornavirus** family.

It has **single stranded RNA genome** and a **nonenveloped icosahedral nucleocapsid** and replicates in the **cytoplasm** of cell.

It has **one** serotype.



It is **not related** to any other hepatitis virus.

Its replicative cycle is similar to poliovirus.

-- **Hepatitis A virus (HAV)** is spread by the **fecal-oral route** and continues to be **endemic throughout the world** and hyperendemic in areas with poor standards of sanitation and hygiene.

-- Relatively **large quantities of virus are shed in the feces** during the incubation period before the onset of clinical symptoms, and a brief viremia occurs.

-- **Children** are **most frequently infected** and outbreaks are usually in **crowded** living places.

-- **Polluted** water and food are the source.

-- It is **rarely transmitted through blood** due to **low numbers**.

Pathogenesis and Immunity

- Pathogenesis is **not clearly understood**.
- **The virus probably replicates in GIT and spreads to liver via the blood.**
- Mechanism of cell damage is not understood because there are **no CPE**.
- It is likely that **attack by cytotoxic T cells** cause the damage.
- The disease is overcome naturally and there is **no chronic infection**.

Clinical findings

-- **Clinical manifestations of hepatitis are *virtually the same* regardless of which hepatitis virus is the cause.**

-- ***Fever*, *anorexia*, *nausea*, *vomiting*, and *jaundice* are typical.**

-- **Dark urine**, **pale feces**, and **elevated transminase levels** are seen.

-- Most cases **resolve spontaneously** in 2-4 weeks.

-- Hepatitis A has a **short incubation period** (3-4 weeks) in contrast to that of hepatitis B which is 10-12 weeks.

-- **No chronic hepatitis** or **chronic carrier state** occurs, and there is no predisposition to hepatocellular carcinoma.

Laboratory Diagnosis

-- The **detection of IgM antibody is the most important test.**

-- A **four-fold rise** in **IgG** antibody titer is **diagnostic**.

-- Isolation of virus in cell culture is possible.

Treatment and Prevention

-- **No antiviral therapy** is available.

-- Active immunization with **formalin inactivated** **HAV** is available.

-- A **combination vaccine** against **HAV** and **HBV** called **Twinrix** is also available.

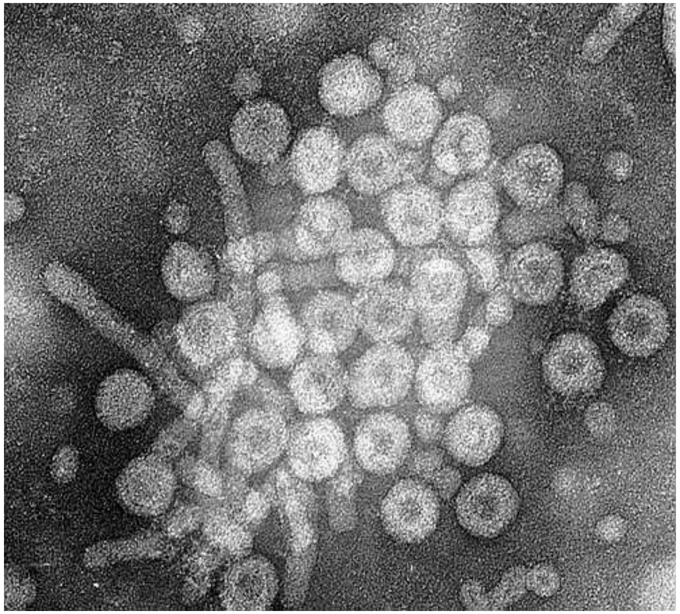
-- Observation of **proper hygiene** is of prime importance.

Hepatitis B virus

It causes **hepatitis B**.

Important Properties

The **hepatitis B virion** is a **42-nm** particle comprising a nucleocapsid (**27 nm** in diameter) surrounded by an **outer envelope of the surface protein (HBsAg)** embedded in **membranous lipid** derived from the host cell.



-- The **surface antigen is produced in excess** by the **infected hepatocytes** and is secreted in the form of **22-nm particles and tubular structures** of the same diameter (initially referred to as **Australia antigen**).

-- Within the core is a **DNA-dependent DNA polymerase**.

-- The genome contains **four genes** that **encode five proteins**.

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

-- **X protein** is an activator of **viral RNA transcription**.

-- **The DNA polymerase has both RNA-dependent (reverse transcriptase) and DNA-dependent activity.**

-- In addition to HBsAg, there are two other important antigens, the **core antigen (HBcAg)** and **e antigen (HBeAg).**

-- **HBcAg forms nucleocapsid** whereas **HBeAg is secreted from infected cells** into the blood.

-- **HBeAg** is an important indicator of **transmissibility**.

-- For **vaccine purposes**, **HBV** has **one serotype**.

-- For **epidemiological purposes**, it has **four subtypes of HBsAg** based on a **group specific antigen "a"** and two sets of **mutually exclusive** epitopes, **d** or **y** and **w** or **r.**

-- This leads to **four** serotypes **adw, adr, ayw**, and **ayr**.

-- The **specificity of HBV for liver cells** is based on **two** properties.

-- One is **virus specific receptors on hepatocytes cell membrane** and other is **transcription factors found only in hepatocytes** that enhance **viral mRNA synthesis**.

-- Humans are **only** natural host.

-- There is **no** animal reservoir.

Replicative cycle

-- First the virus **attaches to liver cell membrane**.

-- The virus is then **transported into the liver cell**.

-- The **core particle then releases its contents of DNA** and **DNA polymerase** into the **liver cell nucleus** where **double stranded circular DNA is formed**.

-- **DNA polymerase** causes the liver cell to **make copies of Hepatitis B DNA from messenger RNA**.

-- The **copies of the virus** and **excess surface antigen** are released **from the liver cell membrane** into the **blood stream** and from there can infect other liver cells and thus replicate effectively.

Transmission and Epidemiology

-- Although various body fluids (blood, saliva, menstrual and vaginal discharges, serous exudates, seminal fluid, and breast milk) have been implicated in the spread of infection, **infectivity appears to be especially related to blood.**

-- **Very little amount of blood is needed** as evident by needle-stick injuries.

-- **HBV** infection is **especially prevalent in addicts**.

-- Transfusion blood screening has greatly reduced the incidence.

-- **Main causes** include **infection by inadequately sterilized syringes and instruments**, transmission by **unscreened blood transfusion and blood products**, by **close contact**, and **mother to child**.

-- It has **global** distribution but is **particularly prevalent in Asia**.

-- Out of **300 million** chronically infected people, **75% are Asian**.

-- There is high incidence of **hepatocellular carcinoma (hepatoma)** in many Asian countries.

-- Immunization against **HBV** has significantly reduced the incidence of **hepatoma** in children.

Pathogenesis and immunity

-- Viral antigens are **displayed** on surface of infected cell which prompt **cytotoxic T cells** to attack.

-- It results in **inflammation** and **necrosis** which is related to pathogenesis.

-- HBV itself does not cause a CPE.

-- **Antigen-antibody complexes** cause some of the **early symptoms**, e.g., arthralgia, arthritis and urticaria.

-- They also cause **complications** in **chronic infections** such as **glomerulonephritis**, **cryoglobulinemia**, and **vasculitis**.

-- About **5% patients become chronic carriers** (HbsAg persisting in blood for at least 6 months) due to persistent infection of hepatocytes.

-- A **high rate of hepatoma** occurs in **these carriers** which is due to **persistent cellular regeneration** that attempts to **replace the dead hepatocytes**.

-- **Chronic carriage** is more likely to happen in **newborn (90%)** due to incompletely developed immune system.

-- These infants have **high risk of carcinoma** as well.

-- **Lifelong immunity** occurs after **natural infection** due to **antibody against HbsAg**.

-- The antibody **blocks HbsAg** and virus cannot attach to its receptor.

Clinical findings

-- Many infections are **asymptomatic**.

-- Incubation period is **10-12 weeks**.

-- Clinical picture is **similar to HAV infection** but with **more severity** which may become **life-threatening**.

-- Most chronic carriers are asymptomatic, but **some have chronic active hepatitis** which can lead to **cirrhosis** and **death**.

-- Patients **coinfected** with **HBV** and **HIV** may have **increased** hepatic damage if **HIV is treated first**, due to restored competent cytotoxic T cells.

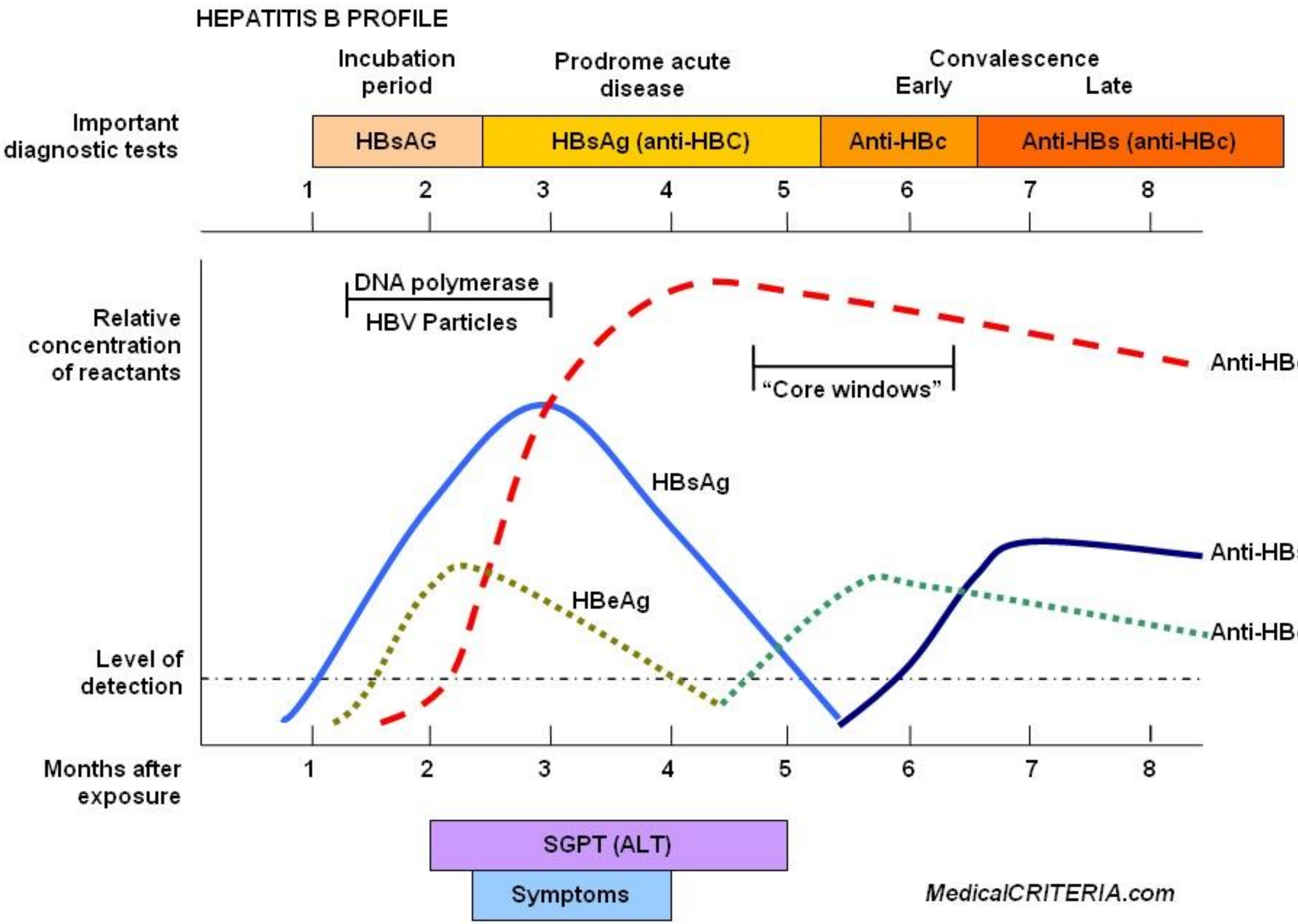
Laboratory Diagnosis

-- Most **important** for detection of **early infection** is **immunoassay for HbsAg** which appears during incubation period and is detectable during **prodrome** and **acute** phase.

-- Its **detection in convalescence phase indicate carrier state** and risk of chronic hepatitis and hepatic carcinoma.

-- **HbsAb is not detectable in chronic state.**

-- It is produced but **binds to excessive HbsAg** present in blood.


HEPATITIS B PROFILE
Incubation period
Prodrome acute disease
Convalescence
Early
Late
Important diagnostic tests
HBsAG
HBsAg (anti-HBC)
Anti-HBc
Anti-HBs (anti-HBc)
1 2 3 4 5 6 7 8
DNA polymerase
HBV Particles
Relative concentration of reactants
"Core windows"
Anti-HBc
HBsAg
Anti-HBs
HBeAg
Anti-HBe
Level of detection
Months after exposure
1 2 3 4 5 6 7 8
SGPT (ALT)
Symptoms
MedicalCRITERIA.com

-- 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 **HbcAg is always positive** and can be used for diagnosis.

-- **HbcAg** is present in **both acute and chronic** infections so it cannot differentiate between two.

-- The **IgM** form of **HbcAb** disappears app. 6 months after infection.

-- **HbeAg arises during incubation period** and is **present during prodrome and early acute disease** and in certain chronic carriers.

-- Its presence indicates a **high likelihood of transmissibility**.

-- Detection of viral load in the serum by **real time PCR** is helpful.

Treatment and prevention

- **No antiviral therapy is typically used in acute hepatitis B.**

- For **chronic** hepatitis B, peginterferon **alfa-2a** (**Pegasys**) or peginterferon **alfa-2b** (**Peg intron**) and/ or a nucleoside analogue (e.g., **limuvidine**) which inhibits the reverse transcriptase of **HBV**, can also be used.

- Nucleoside analogues are **preferred** over peginterferon because they are **better tolerated** and can be taken **orally**.

- These drugs **reduce haptic inflammation** and **lower the viral load** of **HBV** in patients with **chronic active hepatitis**.

-- **None of these drugs cure the HBV infection**.

-- In most patients when the drug is **stopped**, **HBV** replication **resumes**.

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

-- The **vaccine** contains **HBsAg** produced in **yeasts** by **recombinant DNA techniques**.

-- It is **highly effective** in preventing hepatitis B and has **few side effects**.

-- The **seroconversion rate** is app. **95% in healthy adults**.

Hepatitis C Virus

-**HCV** causes **Hepatitis C**.

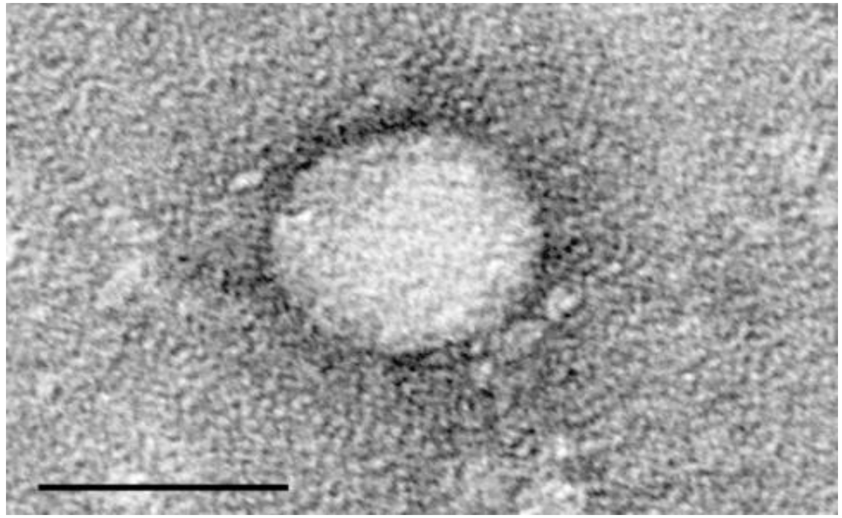
Important properties

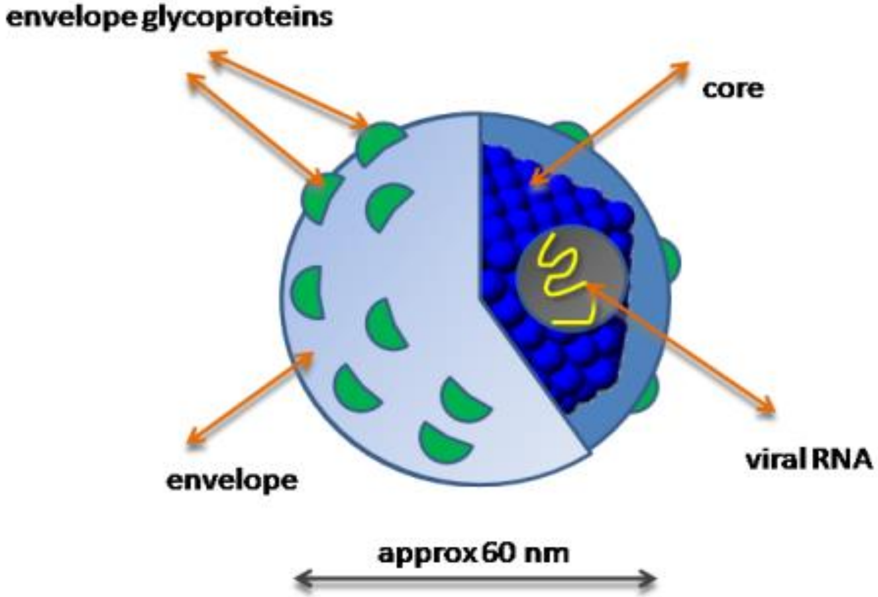
-- **HCV** is a member of the **flavivirus** family.

-- It is an **enveloped virion** containing a genome of **single-stranded, positive polarity RNA**.

-- It has **no virion polymerase**.

-- It is only about **50 nanometers** in diameter.





Structure of Hepatitis C Virus

-- It 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 proof reading** 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**.

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 into **large polyproteins**, from which functional viral proteins are cleaved by a **virion encoded protease**.

-- It is likely that **HCV** replication follows this model.

Transmission and Epidemiology

-- **Humans are the reservoirs for HCV.**

-- It is transmitted primarily via **blood**.

-- Worldwide, it is estimated that **180 million people** are infected with **HCV**.

-- People who **share needles** when taking intravenous drugs are very commonly infected.

Pathogenesis and Immunity

-- **HCV** infects hepatocytes primarily but **no CPE is induced**.

-- Like **HBV**, the **cell death** is probably **due to attack by cytotoxic C cells.**

-- **HCV infection** strongly predisposes to **hepatic carcinoma** but there is **no oncogene** in the virus.

-- **Nor there is evidence** of **insertion of viral genome in DNA** of infected cell.

-- Antibodies against **HCV** are produced but app. **75% of patients are chronically infected** and continue to produce virus for at least 1 year, a rate much higher than **HBV** infection.

-- **Chronic active hepatitis** and **cirrhosis** occurs in app. **10%** of these patients.

Clinical findings

-- **Clinically, acute infection is milder than that with HBV.**

-- **It resembles Hepatitis B in effecting liver chronically, cirrhosis and risk of hepatoma.**

-- **Cirrhosis** resulting from **chronic HCV infection** is the **most common indication for liver transplantation.**

-- **HCV infection** also leads to significant **autoimmune** reactions including **vasculitis, arthralgia, glomerulonephritis.**

Laboratory diagnosis

- **It is often diagnosed by ELISA.**

- **ELISA** can give **false positive results**. **RIBA** (recombinant immunoblot assay) may be used for confirmation.

- If RIBA is positive, **PCR** should be performed to **detect active disease**.

- Isolation of virus is **not done**.

- A **chronic infection** is characterized by **elevated transaminase levels**, a **positive ELISA/RIBA** and **detectable viral RNA** for at least 6 months.

Treatment and prevention

-- Treatment of **acute hepatitis C** with **alpha interferon** decreases the number of patients who become chronic carriers.

-- The treatment of choice for **chronic hepatitis C** is a combination of **peginterferon (Pegasys)** and **ribavirin.**

-- **Peginterferon** is **alpha interferon conjugated to polyethylene glycol** which significantly enhances it half life.

-- **Response** depends among other things, on the **genotype**.

-- **Type 2 and 3 are more responsive** than **Type 1** which may need a treatment of 1 year instead of 6 months.

-- Recently an oral medicine named **Sofosbuvir (Sovaldi)** has been introduced which has given very promising results.

-- It is a nucleotide **analog inhibitor** of hepatitis C virus **NS5B polymerase**—the key enzyme mediating HCV RNA replication.

-- There is **no vaccine and hyperimmune globulins** are **not available**.

-- Chronic **HCV** patient should stop alcohol consumption.

-- Liver should regularly be monitored with **alpha-fetoprotein tests** and **liver sonograms** to detect carcinoma at early stage.

-- **Liver transplant** in serious cases is an option but **infection of the graft** typically occurs.

-- Patients **coinfected** with **HCV** and **HIV** should be treated carefully to improve their immune response by **HAART** (highly active antiretroviral therapy) as it may exacerbate hepatitis due to activated cell mediated immunity.

-- If possible **HCV** should be treated before **HIV**.

Hepatitis D virus

It causes **Hepatitis D** (**hepatitis delta**).

Important properties

-- **HDV** is unusual in being a **defective virus**. It **requires a helper function of HBV** for its transmission.

-- **HDV** is **coated with HBsAg** which is needed for release from the host hepatocyte and for entry in the next round of infection.

-- The HDV particle is approximately **36 nm** in diameter and composed of an **RNA genome** associated with HDAg, surrounded by an envelope of HBsAg.

-- Genome is **very small** and codes only **one protein**, the core protein called **delta antigen**.

-- RNA has **no sequence homology** to **HBV** genome DNA.

-- **HDV** has **no virion polymerase**. The genome RNA is replicated and transcribed by the **host RNA polymerase**.

-- **HDV** genome is a **“ribozyme”.** It means that it has the **ability to self-cleave and self-ligate**, properties needed for replication of genome.

-- It replicates in **nucleus**.

-- It has **one serotype** because HBsAg has only one serotype.

-- No animal reservoir is known.

Transmission and Epidemiology

-- Transmission is **similar to HBV**.

-- It has **worldwide occurrence** with similar distribution as **HBV**.

Pathogenesis and immunity

-- Probably pathogenesis is also **similar to HBV**.

-- There is some evidence that delta antigen is **cytopathic for hepatocytes**.

-- It is **uncertain** whether long term IgG based immunity exists.

Clinical findings

-- Because **HDV cannot replicate without HBV**, it occurs **only in HBV infected persons**.

-- A person may be **coinfected** or an **HBV** infected person may be **superinfected** by **HDV**.

-- Acute disease is **more severe in coinfected persons** but **chronic disease is of same intensity** as with **HBV** alone infection.

-- 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

-- It is made by detecting either **delta antigen** or **IgM antibody to delta antigen** in the patient's serum.

Treatment and Prevention

-- **Alpha interferon** can **suppress** symptoms of chronic hepatitis but does **not eradicate carrier state**.

-- There is no **antiviral therapy or vaccine**.

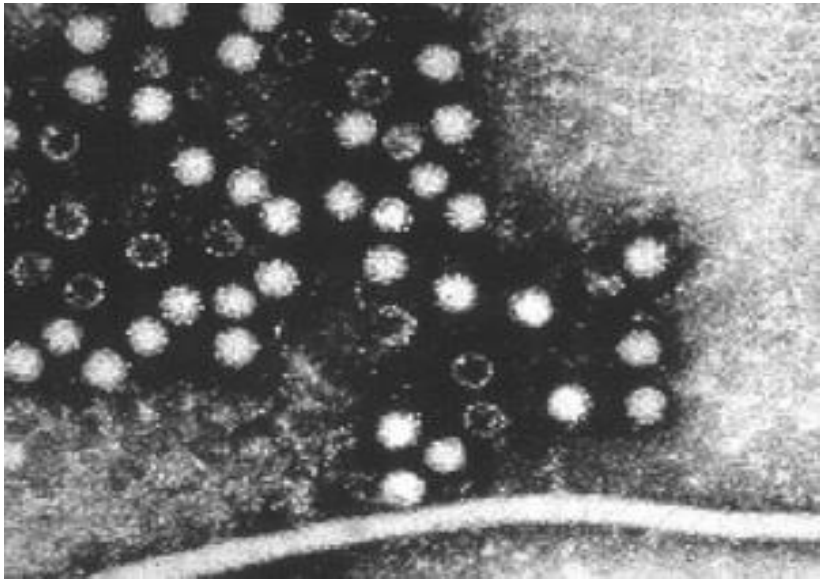
-- **A person immunized against HBV will not be infected by HDV.**

Hepatitis E virus

HEV is a **major cause** of hepatitis transmitted by **fecal-oral route**, second only to **HAV**.

It is a common cause of waterborne epidemics of hepatitis in Asia, Africa, India and Mexico.

It is a **nonenveloped, single stranded RNA** virus classified as a member of **hepeviruses**.



- -- Clinically the disease **resembles HAV infection** but mortality rate in pregnant women is higher.

- **--** **Chronic disease does not occur** and there is no prolonged carrier state.

- -- Diagnostic test is not readily available so diagnosis is usually made by **excluding HAV and other causes**.

- -- There is **no antiviral treatment or vaccine**.

Hepatitis G virus

-- **HGV** is a **flavivirus** but **unlike HCV**, it is not proven to cause hepatitis or cancer.

-- It is known that it **can cause chronic infection** lasting for decades.

-- Nearly 60-70% of those infected **clear the virus** and develops antibodies.

-- It is transmitted sexually or through blood and is carried in blood of **millions of people worldwide**.

-- Patients **coinfected with HIV and HGV have a lower mortality rate** and have l**ess HIV in their blood** than those infected with **HIV** alone.

-- It is also known as **GB virus C**.


Thank You!