PA25.6
VIRAL HEPATITIS SEROLOGY PANEL

DR. SANJEEV KUMAR
SENIOR RESIDENT,
PATHOLOGY
ESICMC&H, BIHTA
PATNA

- The term viral Hepatitis is used for the histologic patterns of hepatic injury, both acute and chronic (depending upon the specific virus), that are seen in liver infected by hepatotropic viruses.

- The term hepatitis is also used to name the specific hepatotropic viruses (hepatitis A, B,C, D, and E).

- Apart from hepatotropic viruses, other causes of hepatitis are- autoimmune, drugs or toxin induced, other systemic viruses (EBV, CMV, herpes, adenovirus, yellow fever virus), and parasites.

HEPATITIS A

- HAV is a small, non-enveloped, positive-strand RNA picornavirus of the genus Hepatovirus.

- It has an icosahedral capsid with 27nm diameter having single stranded RNA.
- The receptor for HAV is HAVcr-1 (HAV cellular receptor-1) located primarily on T-cells.

- Hepatitis A is a usually benign, self limited disease with an incubation period of 2 to 6 weeks. It does not cause chronic hepatitis or a carrier state and only uncommonly causes acute hepatic failure. The fatality rate is about 0.1-0.3%. It is endemic in countries with poor hygiene and sanitation.

- Hepatitis A virus is spread by ingestion of contaminated water and foods and is shed in the stool for 2 to 3 weeks before and 1 week after the onset of jaundice. So most cases occur among close personal contacts, overcrowded unsanitary conditions, and institutional settings.

- HAV can also be detected in serum and saliva. HAV viremia is transient, so blood-borne transmission occurs rarely.

- HAV itself does not seem to be cytopathic. Cellular immunity, particularly CD8+ T cells plays a key role in hepatocellular injury during HAV infection.

- The most common signs and symptoms include fatigue, nausea, vomiting, fever, hepatomegaly, jaundice, dark urine, anorexia, and rash.

- HAV infection usually occurs as a mild self-limited disease and confers lifelong immunity to the virus. Chronic HAV infection does not occur.

- Specific IgM antibody against HAV appears with the onset of symptoms. Fecal shedding of the virus ends as the IgM titer rises.

- The IgM response begins to decline in a few moths with gradually increasing IgG anti-HAV. It persists for years providing almost lifelong immunity against all strains of HAV..

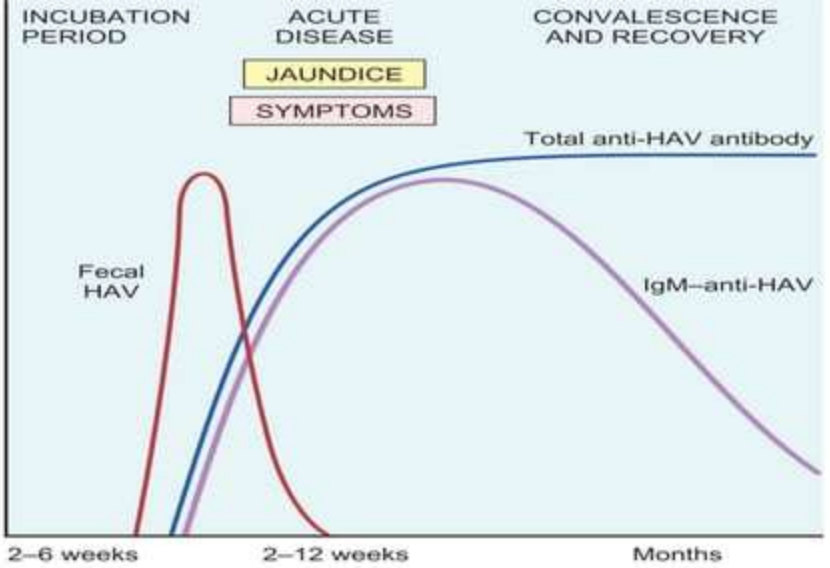


Figure 18-10 Temporal changes in serologic markers in acute hepatitis A infection. HAV, Hepatitis A virus.

- Since there is no routinely available tests for IgG anti-HAV, the presence of IgG anti-HAV is inferred from the difference between total and IgM anti-HAV.

HEPATITIS B

- Hepatitis B virus (HBV) can cause:

1. Acute hepatitis followed by recovery and clearance of the virus
2. Non-progressive chronic hepatitis
3. Progressive chronic disease ending in hepatic cirrhosis
4. Acute hepatic failure with massive liver necrosis
5. An asymptomatic healthy carrier state

HBV-induced chronic liver disease is also an important precursor for the development of hepatocellular carcinoma even in absence of cirrhosis.

- HBV has a prolonged incubation period (2-6 weeks). HBV remains in the blood during active and chronic hepatitis.
- Approximately 65% of adults with newly acquired infection have mild or no symptoms and do not develop jaundice. 25% have non-specific constitutional symptoms such as anorexia, fever, jaundice and right upper quadrant pain.
- 5-10% individuals develop chronic hepatitis
- Fulminant hepatitis (acute hepatic failure) is rare, in 0.5-1% cases of acute hepatitis.

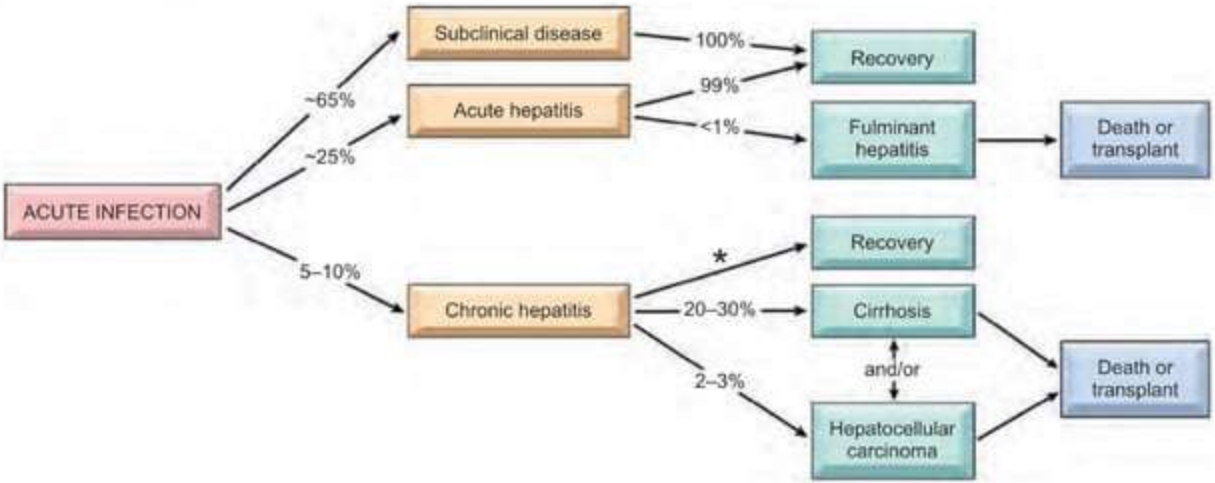


Figure 18-11 Potential outcomes of hepatitis B infection in adults, with their approximate frequencies in the United States. *Spontaneous HBsAg clearance occurs during chronic HBV infection at an estimated annual incidence of 1 to 2% in Western countries. As mentioned in the text, fulminant hepatitis and acute hepatic failure are used interchangeably

- Epidemiology:

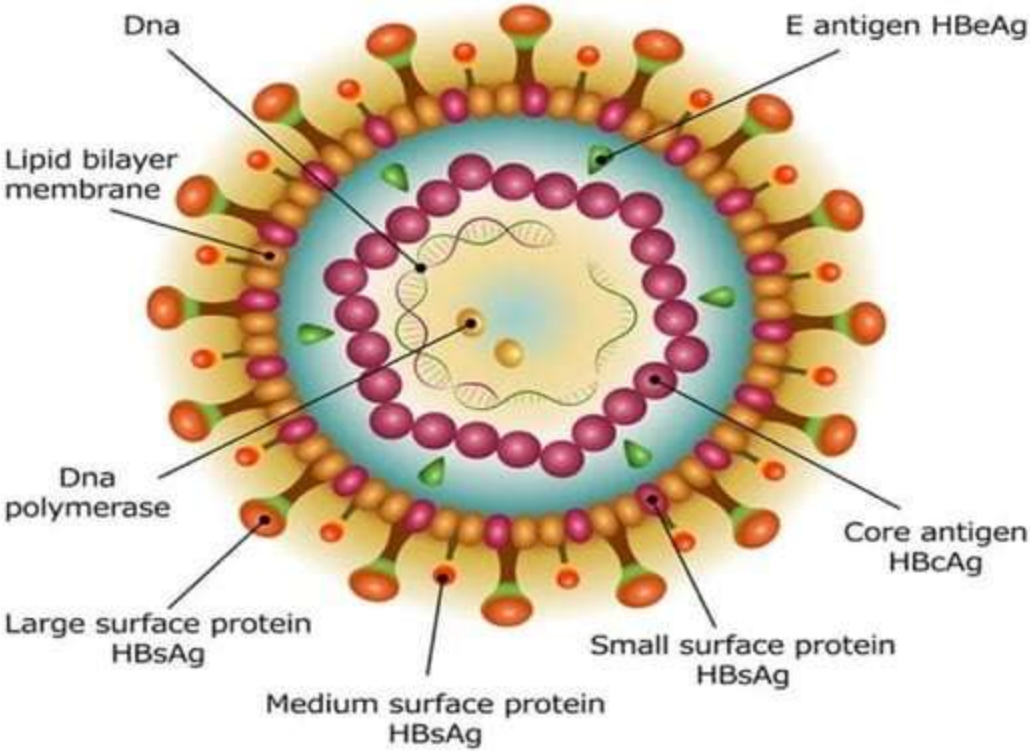
- One third (2 billion) of the global population have been infected with HBV and 400 million having chronic infection.
- 75% of all chronic carriers live in Asia and western pacific area.
- The carrier rate is largely dictated by the age at infection with highest in children and lowest when adults are infected.

- Transmission:
- In high prevalence regions, transmission during childbirth accounts for 90% of cases.
- Horizontal mode of transmission is seen during early childhood in intermediate prevalence areas through minor breaks in the skin and mucous membrane among children with close body contacts.
- In low prevalent areas, unprotected sex and intravenous drug abuse with sharing of needles and syringes are the chief modes of spread.

- Morphology:
- HBV is a member of Hepadnaviridae family with eight genotypes globally.
- The mature virus is a 42-nm, spherical double-layered "Dane particle" having outer envelop made up of protein, lipid and carbohydrate enclosing an electron dense, 28-nm slightly hexagonal core.
- The genome is partially double stranded circular DNA molecule having 3200 nucleotides.

Hepatitis B Virus

Baltimore Group VII (dsDNA-RT)



- The HBV DNA has four open reading frames (ORFs) which codes for:

➢ A nucleocapsid core protein HBcAg, and a longer polypeptide for core and precore region, HBeAg. HBcAg remains in the hepatocytes where it participates in the assembly of complete virions while part of HBeAg is secreted in the plasma.

➢ Envelope glycoproteins (HBsAg)- consists of three related proteins: large, middle, and small HBsAg. Infected hepatocytes are capable of synthesizing and secreting large amount of HBsAg, particularly small HBsAg.

- A polymerase (Pol) that exhibits both DNA polymerase and reverse transcriptase activity. Replication of viral genome occurs through a unique DNA-RNA-DNA cycle.
- HBx protein, necessary for viral replication and may act as transcriptional transactivator for both viral and a subset of host genome. It has been implicated in the pathogenesis of hepatocellular carcinoma in HBV infection.

- The natural course of the disease can be followed by serum markers:

➢ HBsAg- appears before the onset of symptoms, peaks during overt disease, and then often declines to undetectable level in 12-24 weeks.

➢ Anti-HBs antibody rise after acute disease is over, with gradual disappearance of HBsAg. Sometimes appearance of Anti-HBs is delayed. During this window period, serological diagnosis is made by detection of anti-HBc antibody.

➢ Anti-HBs may persist for life, conferring protection.

➢ Current vaccination strategies use non-infectious HBsAg.

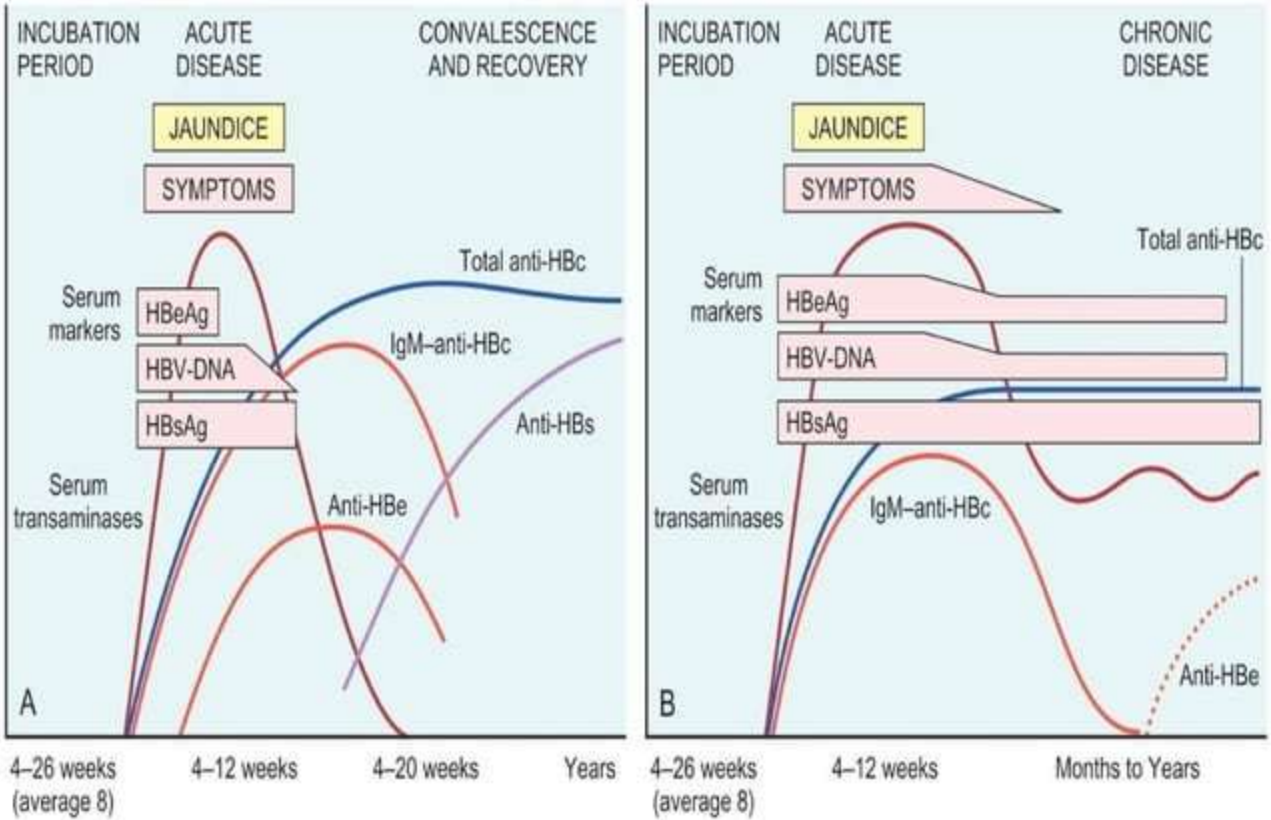


Figure 18-12 Temporal changes in serologic markers in hepatitis B viral infection. **A,** Acute infection with resolution. **B,** progression to chronic infection. Note in some cases of chronic HBV, serum transaminases may become normal.

- HBeAg, HBV-DNA, and DNA polymerase appear in serum soon after HBsAg, and all signify active viral replication.
- Persistent HBeAg is an important indicator of continued viral replication, infectivity, and probable progression to chronic hepatitis.
- The appearance of anti-HBeAb indicates the terminal phase of acute infection.

- IgM anti HBc-Ab becomes detectable in serum shortly before the onset of symptoms, along with elevated liver enzymes (indicative of hepatocyte destruction). Over the time IgM anti-HBc is replaced by IgG anti-HBc Ab.

- The host immune response to the virus is the most important determinant of the outcome of the infection. Innate immune response protect the host during initial phases of the infection and virus-specific CD4+ and CD8+ interferon-γ-producing cells are associated with resolution of acute infection.
- HBV generally does not cause direct hepatic injury. Instead the injury is caused by CD8+ T cells attacking infected hepatocytes.

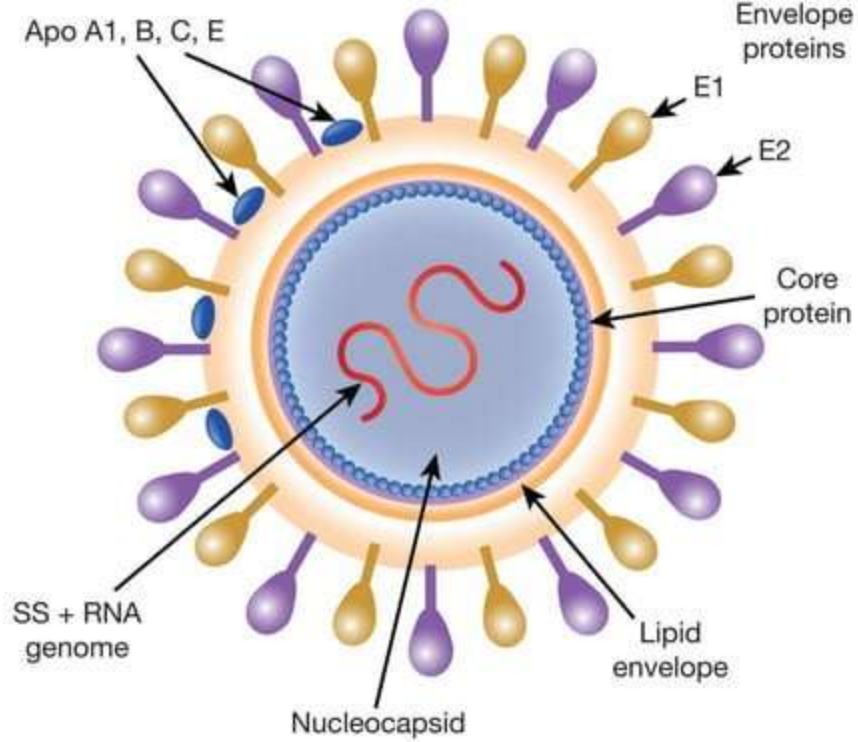
- Age at the time of infection is the best predictor of chronicity. Complete cure is extremely difficult despite using highly effective antiviral agents. The virus inserts itself in the host DNA, thus limiting the development of effective immune response, and allows the virus to persist despite treatment.
- The goal of the treatment of chronic hepatitis B is to slow disease progression, reduce liver damage, and prevent liver cirrhosis and liver cancer.

- Hepatitis B can be prevented by vaccination, screening of donor blood, organs and tissues. Vaccination induces a protective anti-HBsAb response in 95% cases.

HEPATITIS C

- Hepatitis C is a major cause of liver disease worldwide with approximately 170 million people affected.
- The most common risk factors for HCV infection are:
  - IV drug abuse
  - Multiple sex partners
  - Having had surgery within last 6 months
  - Needle stick injury
  - Multiple contact with HCV infected parsons
  - Heath care workers
  - Unknown
- For children the most common route of infection is perinatal (6%, compared to 20% in case of HBV infection)

- HCV, discovered in 1989, is a member of Flaviviridae family. It is a small, enveloped, ss-RNA virus with 9.6-kb genome having only one ORF.
- Due to low fidelity of RNA-polymerase, any individual can have multiple closely related variants of HCV, known as quasispecies.


Apo A1, B, C, E
Envelope proteins
E1
E2
Core protein
SS + RNA genome
Nucleocapsid
Lipid envelope
50–60 μm viron
70–80 μm lipoviral particle

- The E2 protein of the envelop is the target of many anti-HCV antibodies, but is also the most variable region, enabling emerging virus strains to escape from neutralizing antibodies.

- Even the elevated titer of anti-HCV IgG do not confer effective immunity due to genomic instability. So, repeated bouts of hepatic damage, either due to reactivation of preexisting infection or emergence of endogenous, newly mutated strains.

- The incubation period of HCV ranges from 4 to 26 weeks (mean 9 weeks).
- It is asymptomatic in approximately 85% cases.
- Following the incubation period, HCV RNA is detectable in serum for 1-3 weeks, along with elevated hepatic enzymes, followed by appearance of anti-HCVAb in 50-70% cases. Remaining cases take longer time to show anti-HCVAb (3-6weeks).

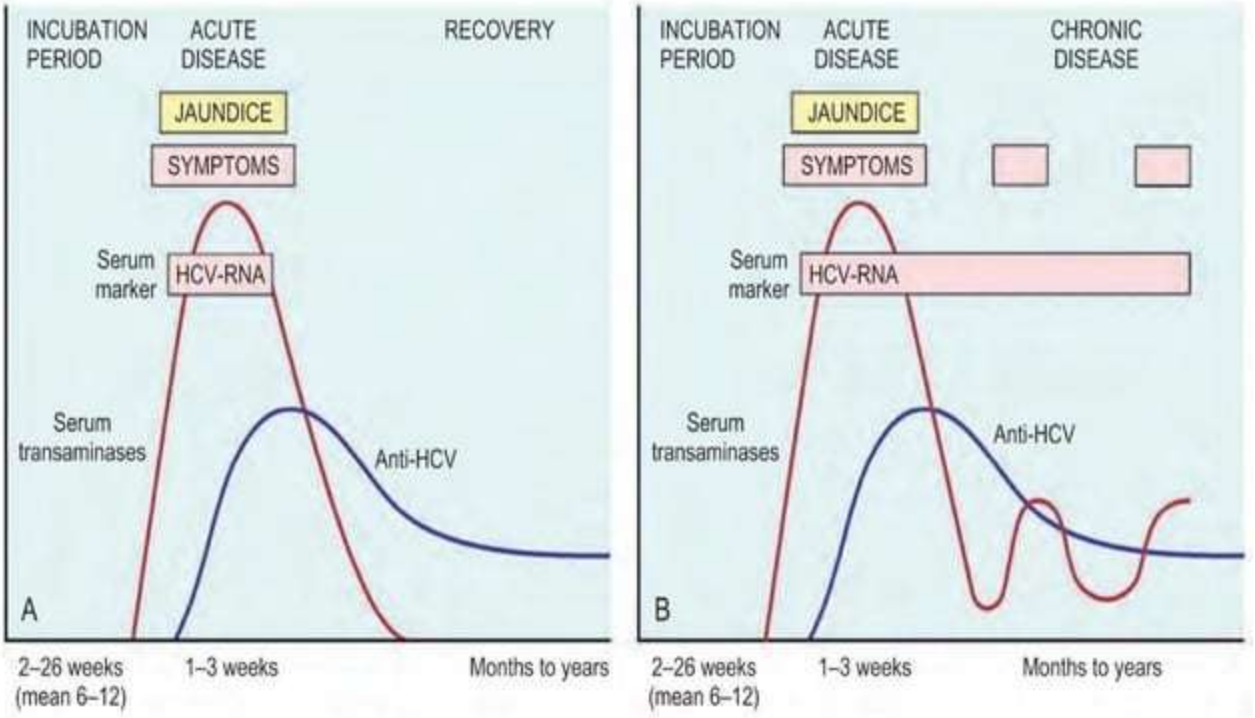


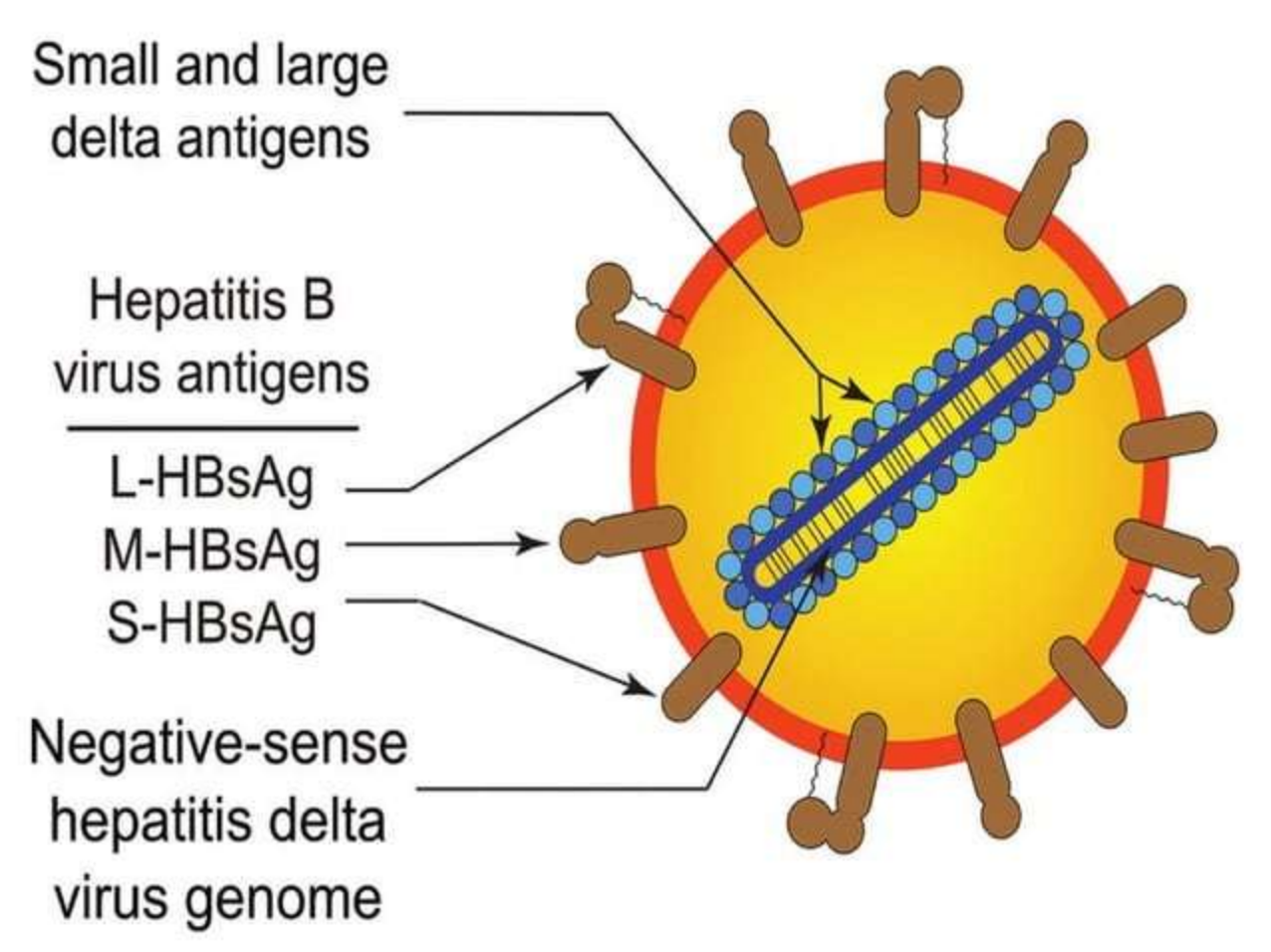
Figure 18-13 Temporal changes in serologic markers in hepatitis C viral infection. **A,** Acute infection with resolution. **B,** progression to chronic infection.

- Though, the clinical course of HCV hepatitis is milder than HBV, persistent infection and chronic hepatitis are the hallmarks of HCV infected individuals (80-90% cases). Hepatic cirrhosis develops in about 20% of individuals with chronic hepatitis C infection.

- In more than 90% individuals with chronic HCV, HCV RNA and anti-HCV Ab persist simultaneously with variable, but elevated level of serum aminotransferases. So, viral RNA testing must be performed to assess viral replication. Any individual with detectable level of HCV RNA in serum needs close follow up.
- HCV can also give rise to insulin resistance and fatty liver disease.

HEPATITIS D

- Also called "the delta agent"
- It is a unique RNA virus that is dependent for it's life cycle on HBV.
- HDV is a 35-nm, double-shelled particle.
- The external coat antigen of HBsAg surrounds an internal polypeptide structure, known s delta antigen HDAg, the only protein produced by the virus.


Small and large delta antigens
Hepatitis B virus antigens
L-HBsAg
M-HBsAg
S-HBsAg
Negative-sense hepatitis delta virus genome

- HDAg surrounds a small circular single negative-stranded RNA (smallest animal virus genome, having approx. 1700 nucleotides)
- Replication of the virus occurs through RNA synthesis by host RNA polymerase.

- Epidemiology: worldwide 15million people are estimated to have HDV infection (about 5% of HBV infected persons). It is uncommon in a large population with HBV in southeast Asia and China.

- Infection of HDV occurs in following two settings:

I. Co-infection with HBV- the HBV infection must occur first to provide HBsAg necessary for development of complete HDV virion. It results in acute hepatitis indistinguishable from acute hepatitis B. it is usually self limited followed by clearance of both viruses, however, there is higher rate of acute hepatic failure.

II. Superinfection in a chronic carrier of hepatitis B- it results in severe acute hepatitis in a previously unrecognized or asymptomatic hepatitis B carrier, usually after 30-50 days after HDV infection.

The superinfection may have two phases:

- An acute phase with active HDV replication with suppression of HBV and elevated serum transaminase level.
- A chronic phase with increased HBV and decreased HDV replication and fluctuating transaminase level, gradually progressing to hepatic cirrhosis and sometimes, hepatocellular carcinoma.

HEPATITIS E

- HEV is an enterically transmitted water-borne infection that occurs primarily in young and middle-aged adults.
- HEV is a zoonotic disease having animal reservoirs such as monkeys, cats, pigs, and dogs.
- HEV infection accounts for 30 to 60% cases of sporadic acute hepatitis in India, exceeding the frequency of hepatitis A.
- The average incubation period following exposure is 4 to 5 weeks.

- HEV is an unenveloped, positive-stranded RNA virus of genus Hepevirus.
- The viral particles are 32-34 nm is diameter, and the genome is approx.7.3 kb in size.
- Virus is shed in stool during acute illness. HEV virion and viral RNA can be detected in stool by PCR before the onset of clinical illness.

- The onset of clinical illness, elevated serum aminotransferases, and elevated IgM anti-HEV occurs virtually simultaneously.
- Symptoms usually resolves in 2 to 4 weeks with gradual replacement of IgM anti-HEV by IgG antibodies.

- A characteristic feature of HEV infection is the high mortality rate among pregnant women, approaching 20%.
- In most cases the disease is self-limited without chronic liver disease or viremia in immunocompetent individuals. However it can cause chronic infection in immunosuppressed patients such as in case of AIDS or post organ transplant.


Thank you.