Hepatitis

Prof. Faten M. Rabie

Learning objectives:

- Identify hepatitis viruses regarding their structure , epidemiology and pathogenesis of the disease and prevention methods.
- Recognize the important serological makers during various stages of Hepatitis B.

Viral hepatitis

- "**Hepatitis viruses**" the main site of infection is the liver. These are hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV, delta virus), and hepatitis E virus (HEV).

- Other viruses, such as Epstein–Barr virus (the cause of infectious mononucleosis), cytomegalovirus, and yellow fever virus, infect the liver but also **infect other sites** in the body and therefore are **not exclusively** hepatitis viruses.

HEPATITIS A VIRUS (HAV)

- HAV is a typical **enterovirus** classified in the picornavirus family.
- It has a ssRNA genome
- non enveloped with icosahedral nucleocapsid.
- It has one serotype,

Transmission & Epidemiology

- HAV is transmitted by the **fecal–oral** route.
- Humans are the reservoir for HAV.
- Virus appears in the feces roughly 2 weeks before the appearance of symptoms, so quarantine of patients is ineffective.
- **Children are the most frequently infected.**
- Unlike HBV, HAV is **rarely transmitted via the blood,** because the level of viremia is low and chronic infection does not occur.

Pathogenesis & Immunity

- The virus probably replicates in the gastrointestinal tract and spreads to the liver via the blood.
- Hepatocytes are infected, no cytopathic effect is seen . It is likely that attack by cytotoxic T cells causes the damage to the hepatocytes.
- The infection is cleared, the damage is repaired, and no chronic infection ensues.
- Hepatitis caused by the different viruses cannot be distinguished pathologically.

.

Clinical Findings

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

- Fever, anorexia, nausea, vomiting, and jaundice are typical. Dark urine, pale feces, and elevated transaminase levels.
- Most cases resolve spontaneously in 2 to 4 weeks.

- Most HAV infections are **asymptomatic** and are detected solely by the presence of IgG antibody.
- **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.

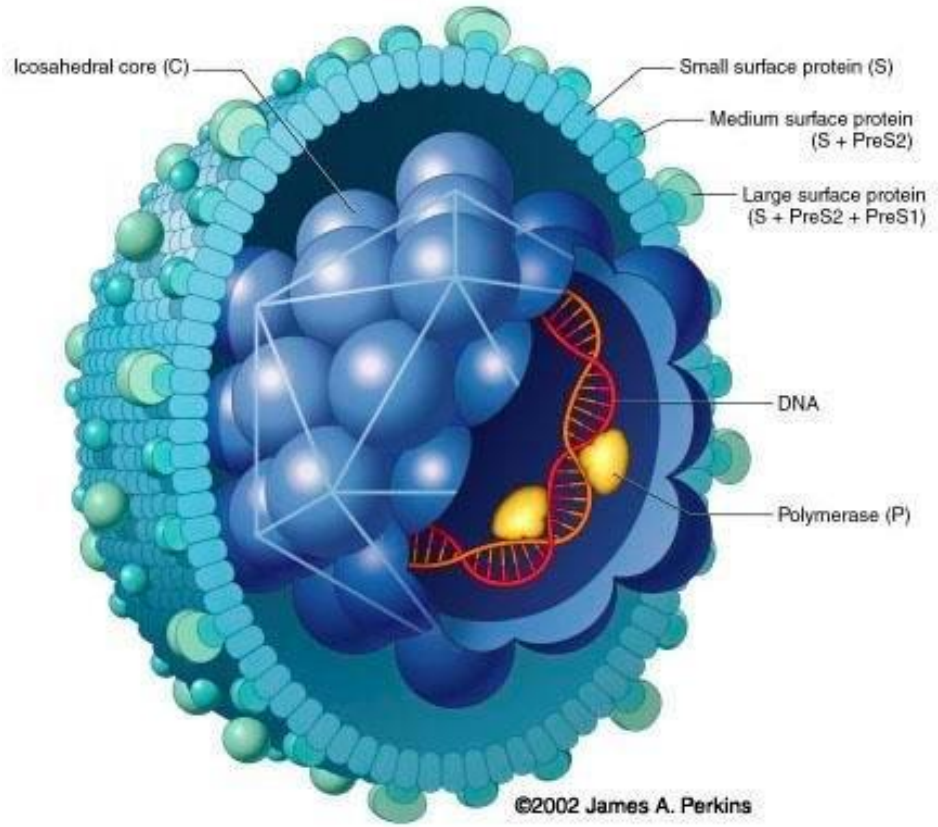
  A fourfold rise in IgG antibody titer can also be used..

- Isolation of the virus in cell culture is possible but not available in the clinical laboratory.

Treatment & Prevention

- Symptomatic treatment
- **Active immunization by inactivated HAV**.
  - The vaccine is also effective in post exposure prophylaxis if given within 2 weeks of exposure.
  - A combination vaccine that immunizes against both HAV and HBV called **Twinrix** is available.
- **Passive immunization** with immune serum globulin prior to infection or within 14 days after exposure can prevent the disease.
- Proper hygiene is of prime importance.

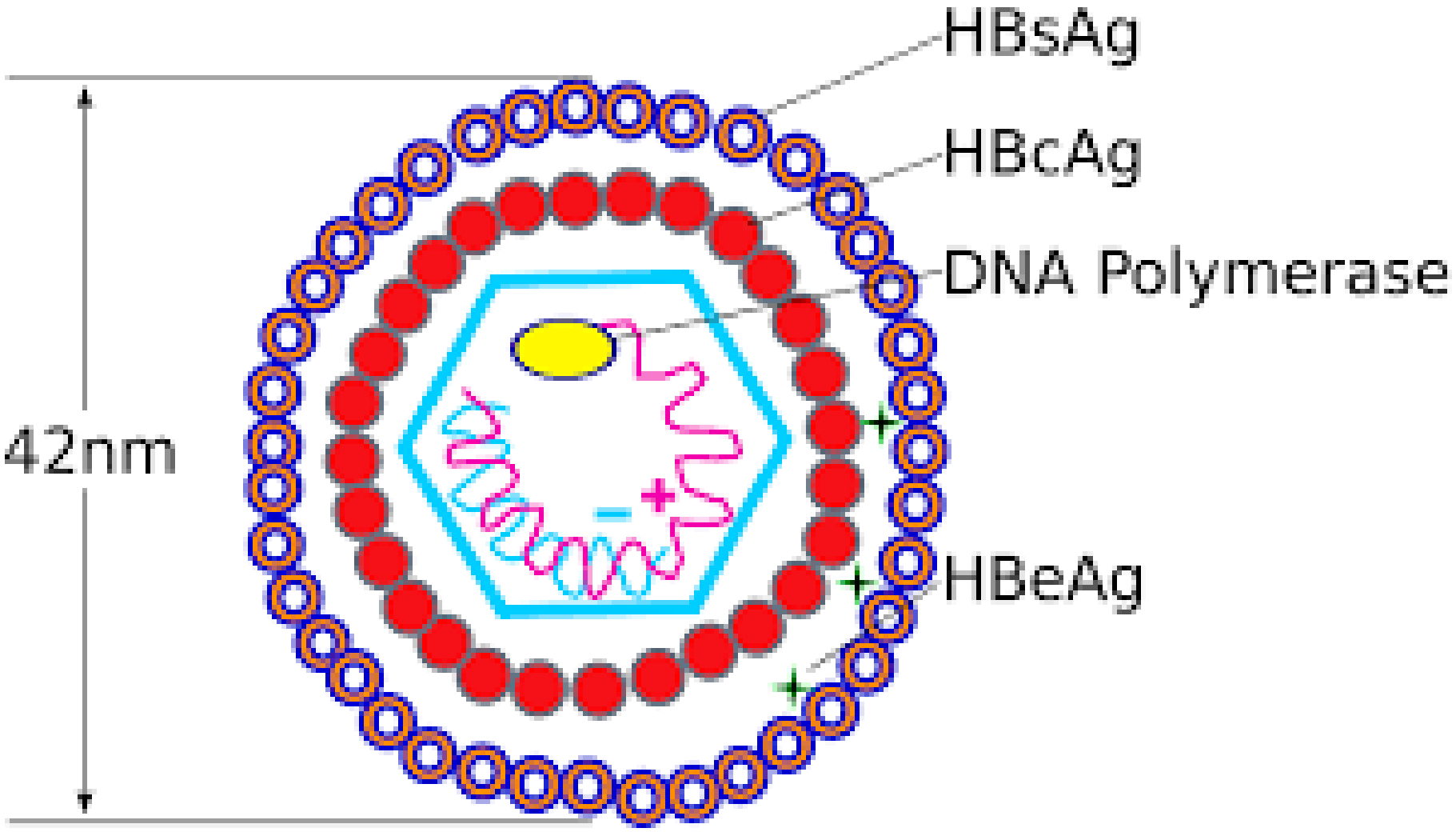
HEPATITIS B VIRUS (HBV)
Serum hepatitis



HEPATITIS B VIRUS (HBV)

Important Properties

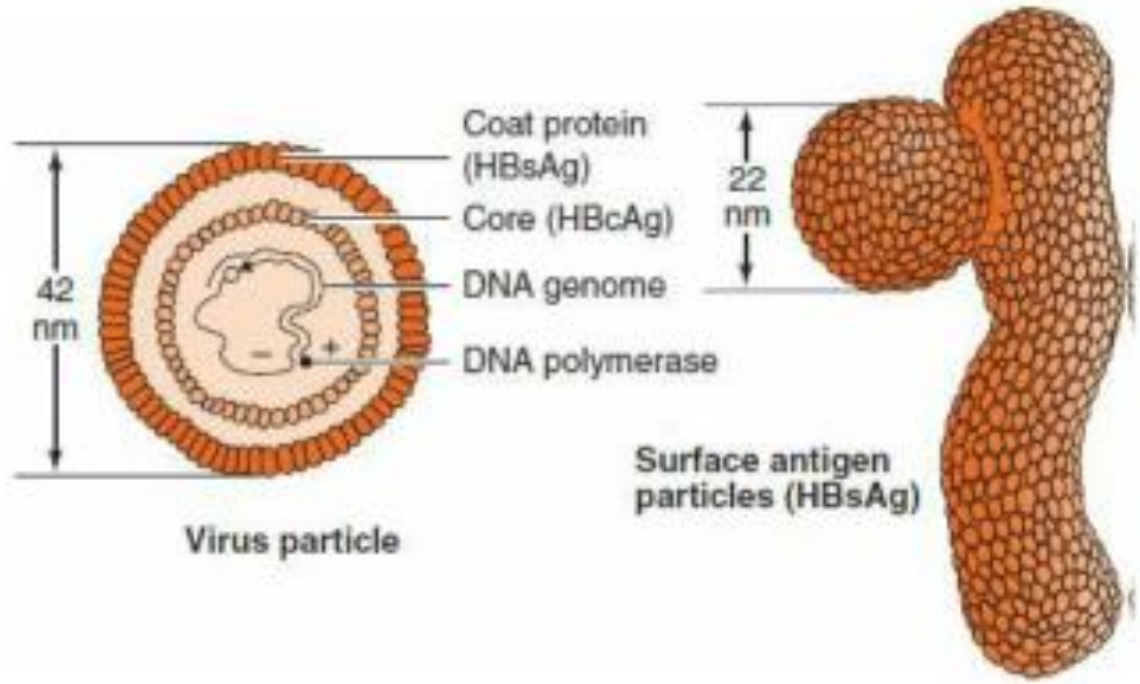
- HBV is a member of the hepadnavirus family.
- It is a 42-nm **enveloped** virion,
- The envelope contains a protein called the **surface antigen** (HBsAg),
- an icosahedral nucleocapsid **core** containing a **partially double-stranded circular** DNA genome
- Within the core is a **DNA-dependent DNA polymerase**. has both RNA-dependent (reverse transcriptase) and DNA dependent activity.


HBsAg
HBcAg
DNA Polymerase
HBeAg
42nm

Three different types of HBV particles seen by Electron microscopy of a patient's serum

- 42-nm virions (**dane particle**).
- 22-nm **spheres.**
- long **filaments** 22 nm wide.

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

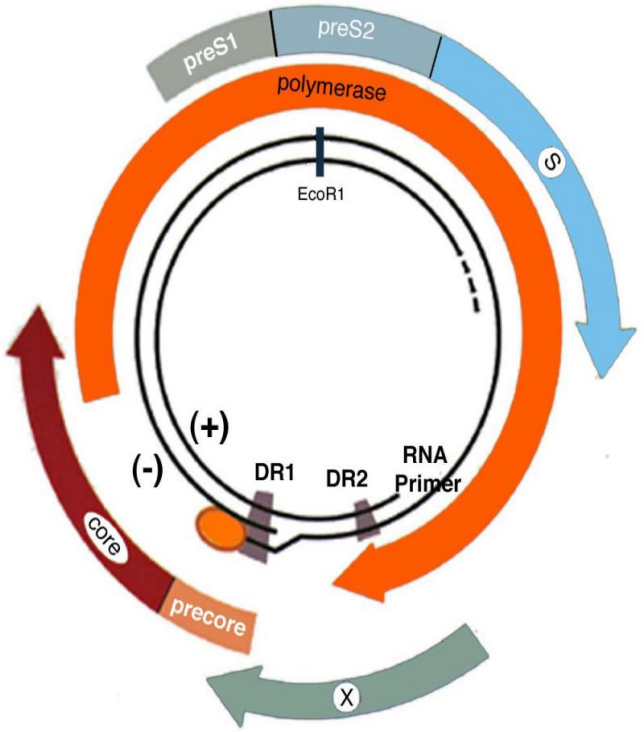

Coat protein
(HBsAg)
Core (HBcAg)
DNA genome
DNA polymerase
42
nm
22
nm
Surface antigen
particles (HBsAg)
Virus particle

Hepatitis B virus genome

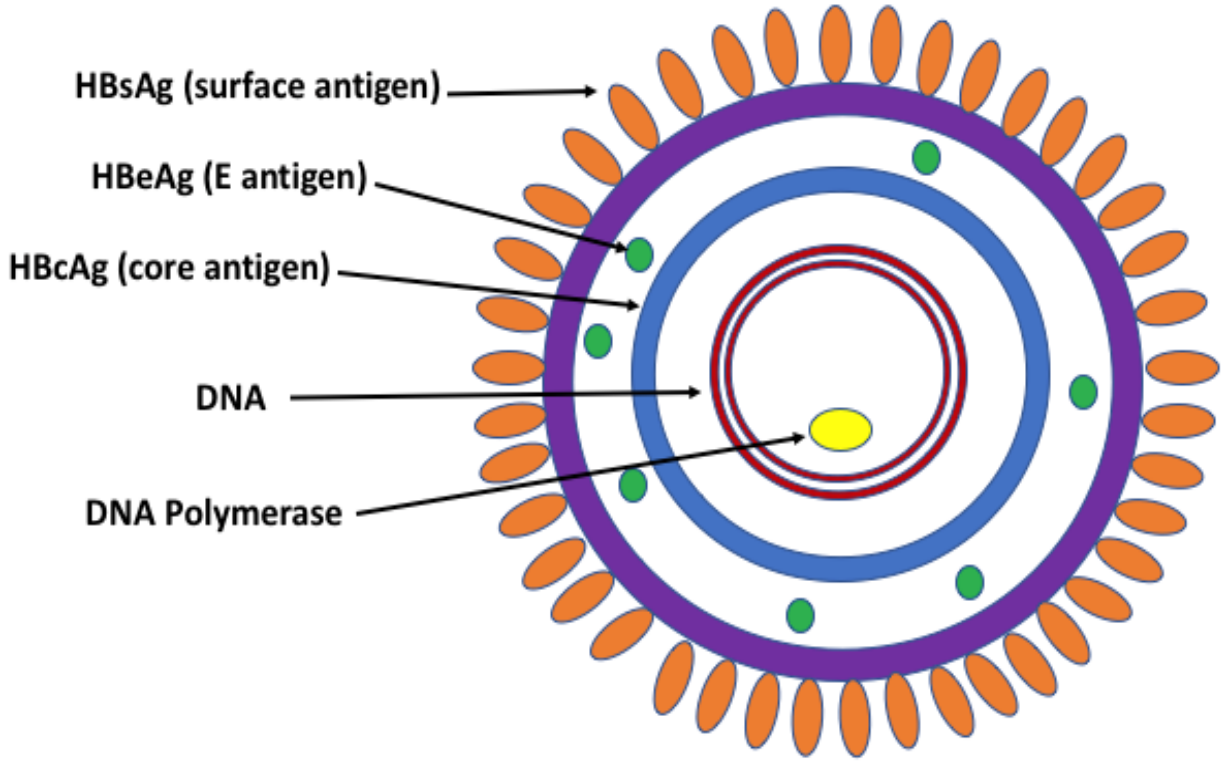
Genome contains **four orf** encode five proteins;

- S gene encodes HBsAg.
- C gene encodes HBcAg and HBeAg
- P gene encodes polymerase,
- X gene encodes X protein (HBx).

HBx is an activator of viral RNA transcription and
be involved in oncogenesis.



HBV antigens



- **HBsAg**
- **HBcAg** located on the nucleocapsid
- **HBeAg** soluble & released from infected cells into the blood and indicate **transmissibility**.

Transmission & Epidemiology

The three main modes of transmission are:

- Blood including needle stick injury.
- Sexual contact.
- Perinatally from mother to newborn.

Pathogenesis

- HBV is not directly cytopathic instead liver injury is immune mediated especially T-lymphocyte mediated cell injury
- Antigen–antibody complexes cause some of the early symptoms (e.g., arthralgias, arthritis, and urticaria)
- About 5% of adult patients with HBV infection become **chronic** carriers**.** **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.

Laboratory Diagnosis

The **two most important serologic tests** for the diagnosis of early hepatitis B are **HBsAg** and for **IgM antibody to the core antigen**. Both appear in the serum early in the disease.

- **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.

Serological markers of hepatitis(cont.)

- **HBsAb** neutralizes the infectivity of HBV **and l**ifelong immunity occurs.
- **HBcAb** is ***not*** protective because the core antigen is inside the virion and the antibody cannot interact with it.

Serological markers of hepatitis(cont.)

- The **window phase** a period of several weeks when HBsAg has disappeared but HBsAb is not yet detectable. 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.

Serological markers of hepatitis(cont.)

- **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..

Serological markers of HBV (cont.)

Viral marker	significance
HBsAg	Acute infection , chronic infection: if persist more than 6 months
HBsAb	Protection
HBcAb	IgM: acute infection IgG: past or chronic infection
HBeAg	High transmissibility
HBeAb	disease recovering
HBV –DNA	Active viral replication

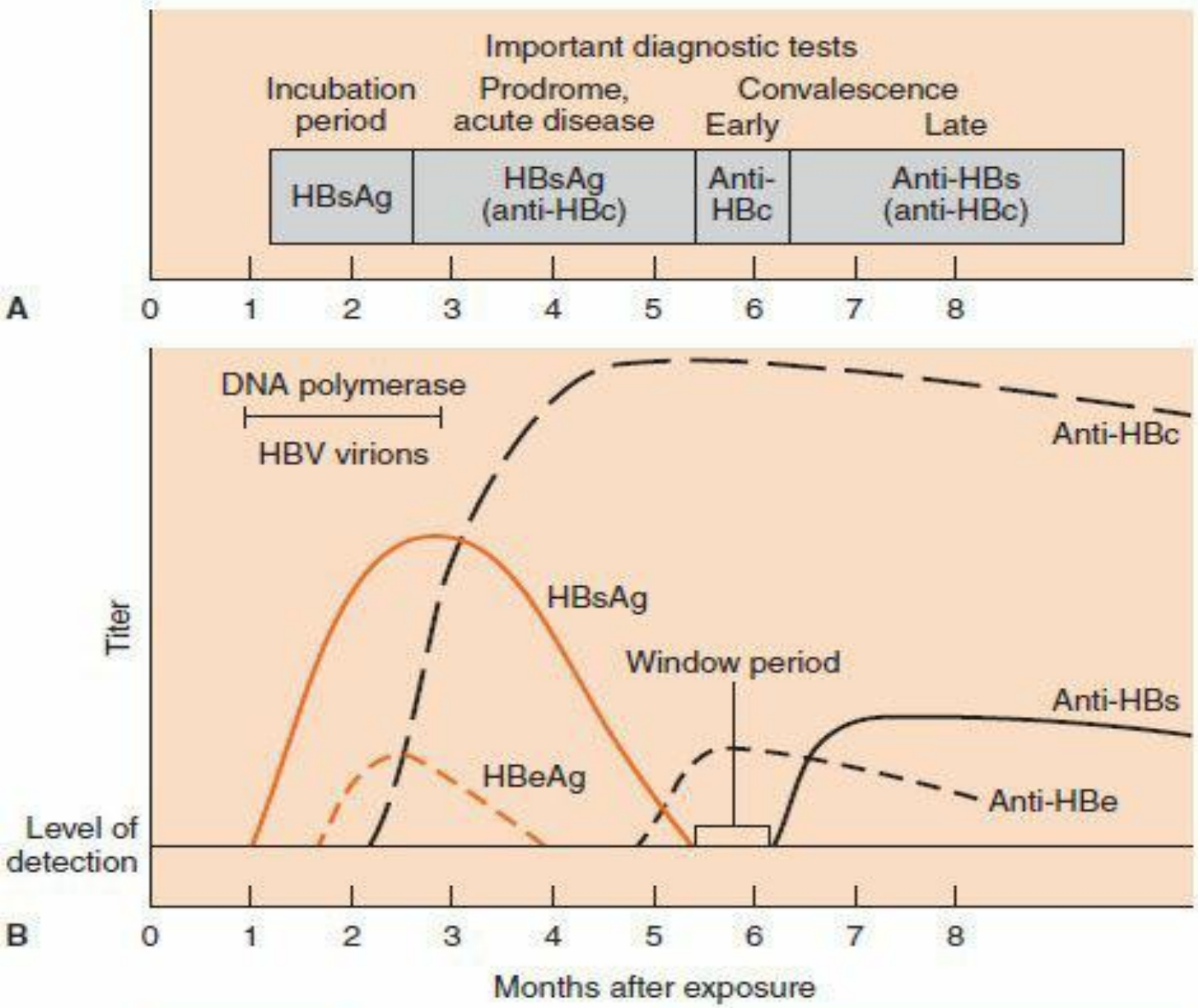
Serological markers of HBV

Test	Acute Disease	Window Phase	Complete Recovery	Chronic Carrier State
HBsAg	Positive	Negative	Negative	Positive
HBsAb	Negative	Negative	Positive	Negative[1]
HBcAb	Positive[2]	Positive	Positive	Positive

[1]Chronic carriers have negative antibody tests, but HBsAb is being made by these individuals. It is undetected in the tests because it is bound to the large amount of HBsAg present in the plasma. They are not tolerant to HbsAg.

[2]IgM is found in the acute stage; IgG is found in subsequent stages.

Note: People immunized with HBV vaccine have HBsAb but not HBcAb because the immunogen in the vaccine is purified HBsAg.


Important diagnostic tests
Incubation period
Prodrome, acute disease
Convalescence
Early
Late
HBsAg
HBsAg (anti-HBc)
Anti-HBc
Anti-HBs (anti-HBc)
A
0 1 2 3 4 5 6 7 8
DNA polymerase
HBV virions
Anti-HBc
HBsAg
Window period
Anti-HBs
HBeAg
Anti-HBe
Titer
Level of detection
B
0 1 2 3 4 5 6 7 8
Months after exposure

Treatment

- No antiviral therapy is typically used in acute hepatitis B.
- For chronic hepatitis B
  - nucleoside analogues that inhibit the reverse transcriptase of HBV are used.
  - Interferon is also used.

Prevention

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

- **Recombivax** contains HBsAg produced by recombinant DNA techniques.
  - 3 dose series 0,1 and 6 months , no booster
  - The vaccine is highly effective .
  - It is indicated for people who are frequently exposed to blood or blood products.
- A vaccine called **Twinrix** that contains both HBsAg and inactivated HAV provides protection against both hepatitis B and hepatitis A.

- **Hepatitis B immune globulin (HBIG**) contains a high titer of HBsAb.

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).

- Both the vaccine and HBIG should also be given to a newborn whose mother is HBsAg-positive (**passive–active)** immunization, in which both immediate protection and long-term protection are provided.

Thanks