GIS 9

MICROBIOLOGY

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Hepatitis (part I)

Hepatitis is an inflammation of the hepatocytes (liver cells).

- Acute hepatitis is an acute inflammation of the liver characterized by hepatocyte damage and elevations in serum AST and ALT. It can be infectious and non-infectious.

1. Infectious hepatitis:
   A. Viral hepatitis:
      The most common causes of viral hepatitis are the five viruses; hepatitis A, B, C, D, and E (HAV, HBC, HCV, HDV, HEV). Other viruses can also cause liver inflammation, including cytomegalovirus (CMV), Epstein-Barr virus (EBV), Herpes Simplex virus (HSV),Varicella Zoster virus (VZV), Measles, Rubella, Adenovirus, Coxsackie, and yellow fever.
   B. Non-viral hepatitis:
      Liver inflammation (hepatitis) is frequently seen in Leptospirosis, Q fever (Coxiella burnetti), Legionella, TB, Brucellosis, plague (Yersinia pestis), brucellosis…etc.
2. Non-infectious hepatitis:
   A. Toxic hepatitis; caused by toxins and drugs.
   B. Alcoholic hepatitis; caused by drinking too much alcohol, which harms the liver.
   C. Autoimmune hepatitis is caused by the immune system attacking the liver.
   D. Ischemic hepatitis; caused by insufficient blood flow to the liver.
   E. HELLP syndrome; characterized by Hemolysis, Elevated Liver enzymes, and a Low Platelet count.

- Please study this table and memorize it perfectly before we keep on truckin'...

VIRUS	HAV	HBV	HCV	HDV	HEV
FAMILY	PICORNA	HEPADNA	FLAVIVIRUS	DELTAVIRUS	HEPVIRUS
GENOME	RNA single stranded	DNA*	RNA single stranded	RNA single stranded	RNA single stranded
TRANSMISSION	FECO-ORAL	BLOOD, SEX	MAINLY BLOOD	BLOOD, SEX	FECO-ORAL
PROGNOSIS	GOOD	MOSTLY GOOD (NOT FOR NEONATES)	MAY PROGRESS TO HCC, CIRRHOSIS		MOSTLY GOOD (NOT FOR PREGNANTS)
HCC RISK Hepato-Cellular-Carcinoma	NO	YES	YES	YES	NO
CARRIER STATE	NO	YES	YES	*YES	NO

- Note: HDV (delta virus) can propagate only in the presence of the hepatitis B virus (HBV); either via simultaneous$_1$ infection with HBV (co-infection) or superimposed$_2$ on chronic hepatitis B or hepatitis B carrier state (super-infection).

➢ **Hepatitis A** virus (HAV) is an enterically (feco-orally) transmitted picornavirus. Outbreaks of infectious hepatitis have been recognized for centuries, but it was first demonstrated in the stool of infected volunteers in 1973. (Why stool? It's a feco-orally transmitted virus).

- HAV is a 27–28nm spherical, non-enveloped virus (it's resistant to gastric acidity).
- Upon purification, three distinct types of HAV are demonstrated:
  1. Mature virions: complete viruses consisting of an outer shell and an inner core of nucleic acid.
  2. Empty capsids: protein capsids with no genomic material.
  3. Partial genome particles: protein capsids which are partially loaded with the viral nucleic acid. These particles are less stable with a more open structure.

Some viruses (e.g. HAV, HBV…) replicate by forming protein capsid shells first and then package their genomes into these capsids.

Therefore, the final copies vary according to the mode of packaging; some capsids are completely or partially loaded giving mature or partial genome particles, respectively, while others may be missed and remain empty.

- The HAV genome is a ssRNA of 7474 nucleotides. As with other picornaviruses, the coding region is divided into three parts: P1 (encoding the four capsid proteins VP1–4), P2, and P3 (encoding seven non-structural proteins (both P2 and P3)).
- Four genotypes have been identified; all belong to the same serotype (then it's the same immune response against the four genotypes).
- Viral infection of hepatocytes is not cytopathic (it doesn't kill cells), but the cytotoxic T-cell response results in cell death (that's why children show less severe forms of the disease; their immunity is not completely developed).

Epidemiology:

- HAV has a worldwide distribution and is associated with overcrowding and poor sanitation (since it's feco-orally transmitted), and is endemic in the developing world where it is an infection of childhood.
- Improved hygiene caused reduction in the incidence in children but causes greater susceptibility in adults.
- Main risk groups: occur among homosexuals$_1$, IV abusers$_2$, and homeless people$_3$.
- Other risk groups: children$_1$ and staff in childcare facilities$_2$, patients$_3$ and staff in mental health institutions$_4$, and travelers$_5$ to endemic areas (Indian subcontinent, Far East, Eastern Europe).
- Transmission occurs feco–orally thus community outbreaks have occurred as a result of water or food contamination.

Clinical features:

- Its incubation period is 4 weeks.
- Subclinical infection is common in children because their immune systems are still developing (>90% if <5 years of age).
- The classical picture of acute hepatitis occurs more frequently with increasing age.
- An abrupt prodrome of fever, headache, malaise, anorexia, and vomiting (+/- Right upper quadrant pain) is followed after <7 days by dark urine, pruritus, and pale stools. Occasionally, diarrhea, cough, coryzal symptoms (inflammation of the mucous membrane of the nasal cavities), or arthralgia may occur (more common in children).

Arthralgia → children

- Physical findings: jaundice, hepatomegaly, splenomegaly (5–15%).
- People feel better once jaundice appears (it appears when the virus is undetectable), which peaks within 14 days.
- Complications include prolonged cholestasis, relapsing disease, fulminant hepatitis (rare, commoner in older patients), extrahepatic disease, and triggering of autoimmune chronic active hepatitis.

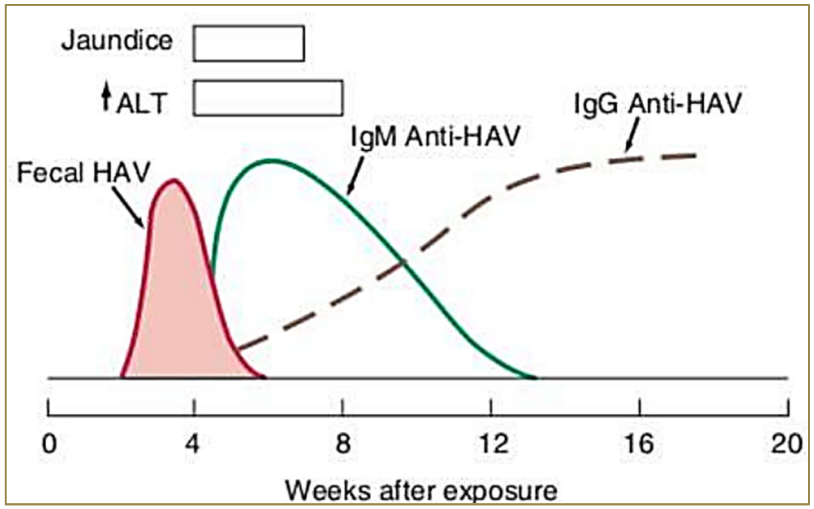
Fulminant hepatitis → elderlies

- Recall: (doesn't mean it's extra)
  Jaundice results from high levels of bilirubin in the blood. Bilirubin is the normal breakdown product from the catabolism of hemoglobin, and thus is formed from the destruction of red blood cells.
  Under normal circumstances, bilirubin undergoes conjugation within the liver, making it water-soluble. It is then excreted via the bile into the GI tract, the majority of which is passed in the stool giving it its normal brown color. Around 10% is reabsorbed into the bloodstream and excreted through the kidneys, which gives the urine its normal color. Jaundice occurs when this pathway is disrupted.

Diagnosis

- It has only one serotype.
- Its replication is limited to hepatocytes, but it's present in the liver, bile, STOOL, BLOOD during pre-icteric (prodromal) phase and incubation period.
- Once jaundice is apparent infectivity in stool and blood is diminished, so the patient starts shedding before the jaundice appears and this helps in the dissemination of the disease.
  So keep in mind that shedding diminishes once jaundice appears

- Anti HAV (IgM) antibodies can be detected during acute illness while stool shedding is still present and ALT is high.
- These antibodies (IgM) can persist for several months, after convalescence, IgG becomes predominant (to provide lifelong immunity).
- LFTs (liver function tests) are elevated, with very high aspartate transaminase (AST) and alanine transaminase (ALT) levels.
- Bilirubin and alkaline phosphatase (ALP) are usually only mildly elevated.
- Serology detection of anti-HAV (IgM) confirms the diagnosis (acute illness) and remains positive for (3–6) months, so it is present at the onset of symptoms (since symptoms appear early at the 2nd month).
- Anti-HAV (IgG) becomes positive at 2–3 months and persists for life.



Treatment

- In symptomatic acute hepatitis patients should avoid paracetamol and alcohol.
- 85% have full clinical/biochemical recovery by 3 months, and nearly all by 6 months (v. good prognosis).
- Cholestasis and fulminant hepatitis patients should be treated with supportive therapy and referred for consideration of liver transplantation.
- Fatalities are more common with advancing age and in those with hepatitis C co-infection.

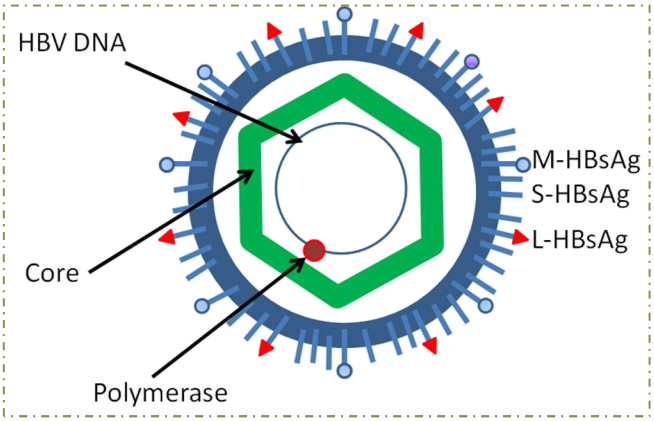
prevention

- It can be inactivated by boiling for 1 minute, UV light (by damaging its RNA), chlorine, and formaldehyde.
- Pre-exposure prophylaxis: By vaccination (several inactivated HAV vaccines exist) and these have largely superseded the use of immunoglobulin. Two doses of HAV vaccine are given, at 0 and 6–12 months, and provide protection for at least 10 years.
- Indications for immunization include people at risk; travelers to endemic areas, homosexuals, IV drug users, chronic liver disease, regular recipients of blood products, people that work in high risk institutions (childcare, mental health and military personnel).

Hepatitis A √

- **Hepatitis B** virus is a DNA virus that causes acute and chronic viral hepatitis in humans.
  - It replicates in the liver but it can exist extra-hepatically (e.g. pancreas, lung, kidneys…).
  - It has a diameter of 42nm, the outer envelope that contains HBsAg (**H**epatitis **B** **S**urface **A**nti**g**en) proteins$_1$, glycoproteins$_2$, and cellular lipid$_3$.

  - These HBsAg proteins may be released from infected cells as small spherical$_1$ or filamentous particles$_2$ during the life cycle of the virus.
  - Beneath the envelope is the internal core or nucleocapsid, which contains hepatitis B core antigen (HBcAg).
- The third antigen (HBeAg) is a truncated form of the major core antigen (HBcAg). It is released from infected liver cells in which HBV is replicating.

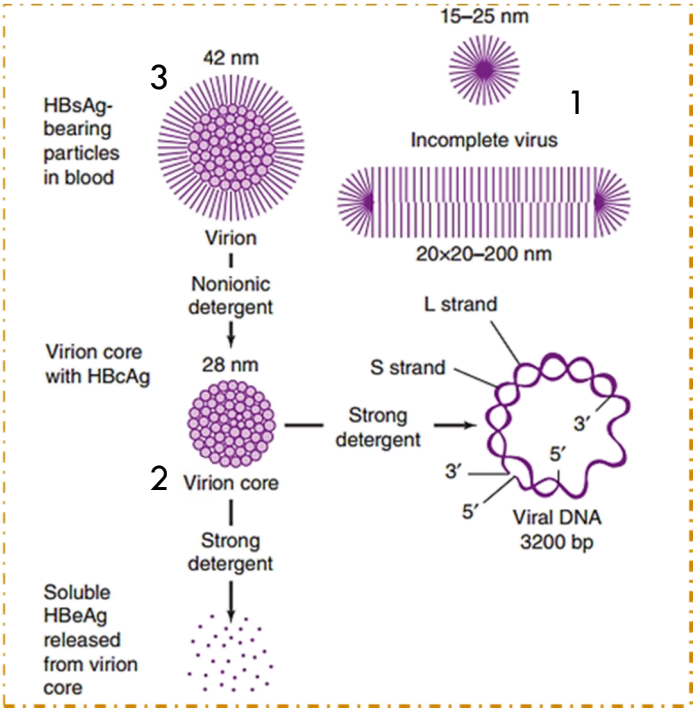


- Hepatitis B can be found in three morphologic forms:

  1. Small spherical$_1$ or filamentous$_2$ particles which are made up exclusively of HBsAg.

  2. 27-nm inner nucleocapsid cores which contain hepatitis B core antigens (HBcAg). Note: HBcAgs are found in hepatocytes; they don't circulate.

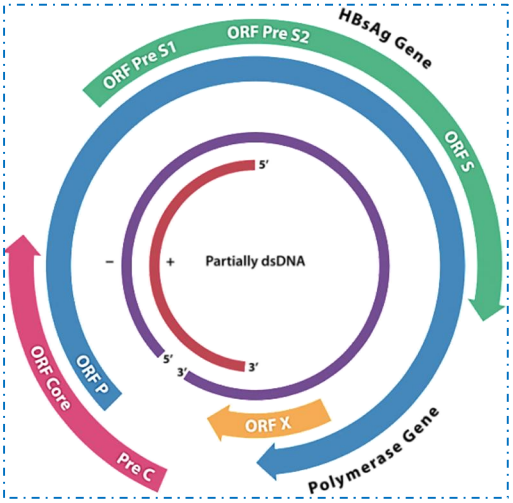
  3. Spherical complete virions. The outer surface, or envelope, contains HBsAg$_1$ and surrounds an inner nucleocapsid core that contains hepatitis B core antigen (HBcAg)$_2$.



- HBV has small compact circular DNA genome (considered dsDNA and partially ssDNA (from the slides)) with eight genotypes (A–H) and four long open reading frames (ORFs):

ORF: DNA sequence that has the ability to be translated.

1. C (core/nucleocapsid) gene, encodes HBcAg and HBeAg (since it is a truncated form of HBcAg).



- HBcAg (major core antigen) is coded for by gene C, and its coding regionis preceded by an upstream in-frame (within the gene) signal sequence from which the secretory core protein is produced HBeAg.
- Note: to express HBeAg secretory protein both HBcAg coding region and the signal sequence should be read.

(I.e. there are two regions within the C gene; one is for HBcAg expression, and the other comprises the first one and is for the secretory core protein HBeAg expression).

- Therefore, mutations in the pre-core region result in HBV mutants that lack HBeAg.

Recall that RNA polymerase synthesizes a messenger RNA (mRNA) transcript complementary to the DNA template strand in the 5′ to 3′ direction. Therefore, it moves along the template strand in the 3′ to 5′ direction.

2. S (surface/envelope) gene, which includes the pre-S1, pre-S2, and S regions; encodes HBsAg.

- The same idea is applied here; the HBsAg gene is one long open reading frame but contains three in-frame start codons that divide the gene into three sections, pre-S1, pre-S2, and S. Because of the multiple start codons, polypeptides of three different sizes called large$_1$ (when pre-S1, pre-S2, and S regions are expressed), middle$_2$ (when pre-S2, and S regions are expressed), and small$_3$ (when only S region is expressed) are produced.

3. P (polymerase) gene which encompasses 3/4 of the viral genome. It encodes a polypeptide (DNA polymerase (works as a reverse transcriptase) with ribonuclease H (catalyzes the degradation of RNA) activity).

4. X gene, encodes a polypeptide, with several functions which help in viral replication.

- The presence of HBeAg in a host's serum is associated with high rates of viral replication and enhanced infectivity, since the polymerase needs to read the entire genome in order to reach the HBeAg coding sequence and thus the virus should be super-active.

To clarify: (according to the figure in the previous page)

Read the negative sense strand (the purple strand) in the 3′- 5′ direction; at first, you will read the X region (it's not antigenic and does not help in diagnosis; ignore it), then the S region which produces the small surface antigen, then the PreS2 region → PreS1 → polymerase gene → → →and lastly the Pre C region.

Epidemiology

- HBV is a global public health problem ~400 million chronically infected and ~1 million deaths per year.
- Prevalence ranges from 0.1–2% in low-prevalence countries (USA, West EU),10–20% in parts of China (east Asia) and sub-Saharan Africa.
- Variation reflects differences of age which infection occurs (risk of chronicity is greatest in the very young) (90% for peri-natal infections), compared to adults (5% become chronic).
- HBV may be transmitted vertically/perinatally (in high-prevalence areas), sexually, blood, by IV drug use, by needle stick injury, and horizontally (especially between children in intermediate prevalence areas). (horizontally: among individuals of the same generation)
- Perinatal transmission rates reach 90% in HBeAg-positive mothers the majority occur at or after birth (neonatal vaccination is 95% protective). However, if the –infected- mother is HBeAg negative (the virus is not highly replicative), then the perinatal transmission rate reaches ~10%.

Clinical features

- Acute hepatitis B incubation period is 1–4 months.
- 70% of cases are asymptomatic; 30% develop acute hepatitis.
- Symptoms include malaise$_1$, nausea$_2$, abdominal pain$_3$, and jaundice$_4$. They subside over 1–3 months, but fatigue may persist.
- Fulminant hepatic failure occurs in 0.1–0.5% of acute infections and is thought to be immunologically mediated, rather than directly due to the virus.
- Severe cases of acute disease should be considered for antiviral therapy

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Chronic hepatitis

- 5–10% of adult acute infections progress to chronic hepatitis. It may be asymptomatic for many years.
- Exacerbations of infection may occur, mimicking acute hepatitis$_1$ or presenting as liver failure$_2$.
- Extra-hepatic manifestations (immune complex-mediated) include serum sickness$_1$, poly-arteritis nodosa$_2$, and membranous glomerulonephritis$_3$, with most cases seen in children (presents as nephrotic syndrome).
- Three phases of chronic hepatitis B infection have been identified: the replicative immune-tolerant phase, the replicative immune clearance phase, and the inactive hepatitis B phase ("inactive carrier"). Let's discuss them in details.

1. The replicative immune-tolerant phase is seen almost exclusively in children infected at birth by mothers (perinatal infections only).
   HBV is nonpathogenic in the immune-tolerant person (normal liver ALT levels, and no hepatitis (normal liver)) and these individuals (children) are positive for HBeAg (since it's a "replicative" phase).

2. These individuals then go into the replicative immune-clearance phase. During this phase, the immune system recognizes HBV as foreign and tries to "clear" the virus.
   This phase is often associated with biochemical exacerbations (due to an increase in immune lysis of infected hepatocytes) which may be misinterpreted as acute hepatitis B.
   HBeAg seroconversion (loss of HBeAg and development of antibodies to HBeAg (anti-HBeAg)) may occur, and by this, patients go into the following phase "the inactive hepatitis".

3. Persons eventually develop inactive hepatitis (inactive carrier) phase begins in which liver disease is in remission and patients are HBeAg negative$_1$ (that's why it's not a "replicative" phase), anti-HBeAg positive$_2$, ALT usually normal$_3$, and HBV DNA loads are low to undetectable$_4$, although some cases may still have histologically active liver disease.

- Several normal ALT$_1$ levels and low HBV viral loads$_2$ over 12 months are required to confirm someone is inactive due to the fluctuating nature of disease.
- Some patients have moderate HBV replication and active liver disease but remain HBeAg negative, since some variants cannot produce HBeAg due to pre-core or core promoter mutations. Such patients tend to be older$_1$ with more advanced$_2$ liver disease and fluctuations$_3$ in HBV DNA and ALT.
- A few patients with chronic HBV infection may show delayed clearance of HBsAg (around 0.5–2% patients per year) (i.e. they remain HBV DNA-positive).
- Complications of chronic HBV: end-stage liver disease (15-40 % of cases)$_1$ and hepatocellular carcinoma (HCC)$_2$.
- Disease progression is associated with HBeAg positivity, high DNA levels, those with prolonged replicative phase, alcohol, and co-infection with HCV or hepatitis D virus (HDV).

Diagnosis (serology)

Things might appear a bit complicated at first, no worries, everything will be clarified insha'allah.

1) HBsAg appears 1–10 weeks after acute infection, prior to symptoms.

- Those who clear acute infection become negative after 4–6 months, while positivity beyond this time (6 months) indicates chronic HBV.
- Its disappearance is followed by the development of anti-HBs antibody.
- A few patients may be positive for HBsAg and anti-HBs, suggesting that the antibody cannot neutralize the virus and patients are therefore carriers.

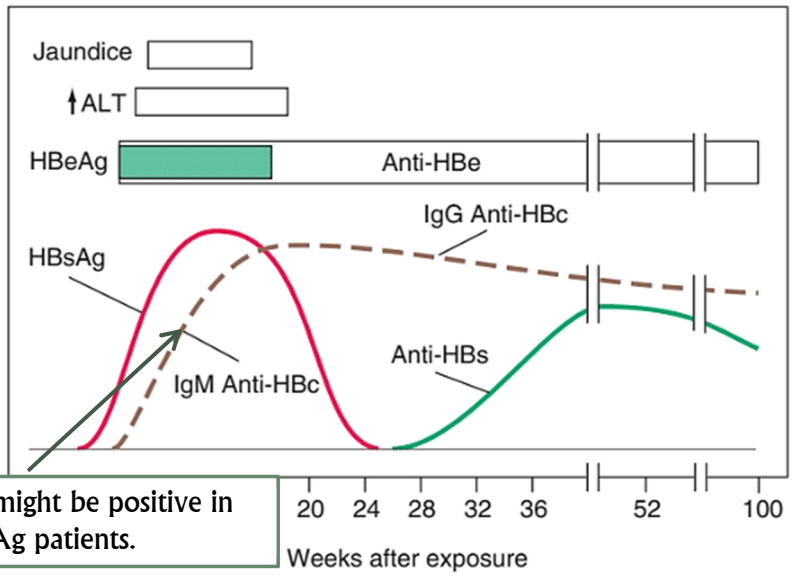
2) HBcAg is an intracellular antigen and not detectable in serum.

- Anti-HBc is predominantly IgM in early infection and may be the only indicator of infection in the window between HBsAg loss and anti-HBs production.
- When individuals clear the acute infection, eventually the HBsAg↘ will become undetectable and will be followed by IgG↗ antibodies to the hepatitis B surface$_1$ (anti-HBs IgG) antigen and core antigen$_2$ (anti-HBs and anti-HBc IgG).
- Anti-HBc may remain for a couple of years, and titers can rise during flares, which may lead to the mistaken diagnosis of acute infection.
- Isolated anti-HBc (IgG type) may be seen in two situations:
    1. Many years after recovery from acute HBV (anti-HBs fallen to undetectable levels).
    2. Many years after chronic HBV (HBsAg fallen to undetectable levels (present in low concentrations).
       HBV DNA may be detected in the liver of these patients, since it is an indicative of active disease, specifically in highly infective chronic hepatitis.

3) HBeAg is a secretory protein and a qualitative marker of HBV replication and infectivity.

- Associated with high levels of HBV DNA (a quantitative marker of HBV).
- HBeAg seroconversion to anti-HBe may be delayed for years in patients with chronic HBV. Therefore, HBV chronic carriers are those in whom HBsAg persists for more than 6 months in the presence of HBeAg or anti-HBe.
- When seroconversion occurs, it is usually associated with a decrease in DNA and reduction in liver inflammation. (Inactive hepatitis)
- After a person is infected with HBV, the first marker detectable in serum within 1–12 weeks is HBsAg.
- Circulating HBsAg precedes elevations of serum ALT and clinical symptoms by 2–6 weeks and remains detectable during the entire symptomatic phase of acute hepatitis B and beyond.

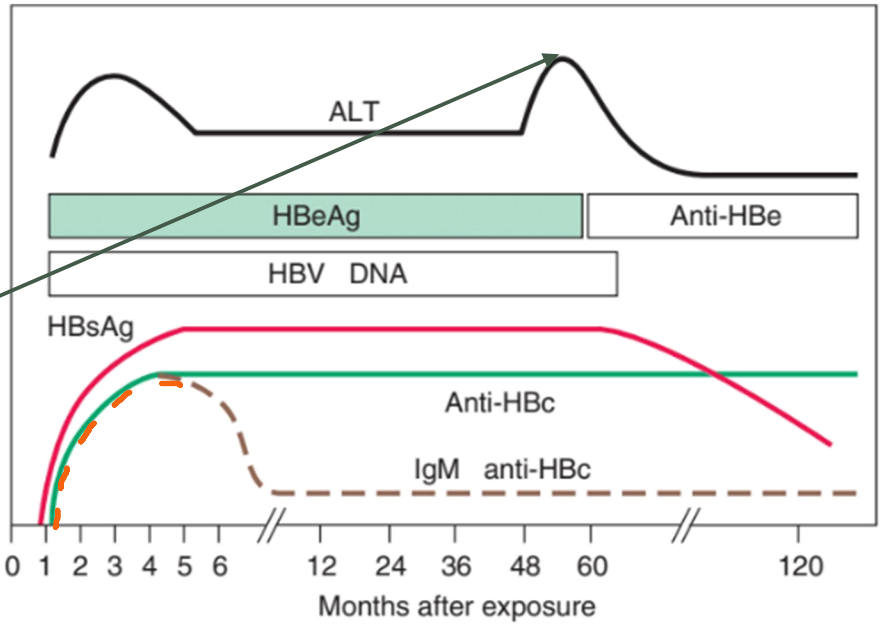
- In typical cases, HBsAg becomes undetectable 1–2 months after the onset of jaundice and rarely persists beyond 6 months (chronicity).
- After HBsAg disappears, antibody to HBsAg (anti-HBs) becomes detectable in serum and remains detectable forever.
- Because HBcAg is intracellular and when in the serum, sequestered within an HBsAg coat, naked core particles do not circulate in serum and, therefore, HBcAg is not detectable routinely in the serum of patients with HBV infection.



Anti-HBc might be positive in some HBsAg patients.

- However, anti-HBc is readily demonstrable in serum, beginning within the first 1–2 weeks after the appearance of HBsAg and preceding detectable levels of anti-HBs. A gap of several weeks or longer may separate the disappearance of HBsAg and the appearance of anti-HBs. During this "gap" or "window" period, IgM anti-HBc may represent the only serologic evidence of current or recent HBV infection, and blood containing IgM anti-HBc in the absence of HBsAg and anti-HBs has been implicated in the development of transfusion-associated hepatitis B.
- Recent and past HBV infections can be distinguished by determination of the immunoglobulin class of anti-HBc.
  - Anti-HBc of the IgM class (IgM anti-HBc) predominates during the first 6 months after acute infection, whereas IgG anti-HBc is the predominant class of anti-HBc beyond 6 months. Therefore, patients with current or recent acute hepatitis B, including those in the anti-HBc window, have IgM anti-HBc in their serum.
  - In patients who have recovered from hepatitis B in the remote past as well as those with chronic HBV infection, anti-HBc is predominantly of the IgG class.
- Generally, in patients who have recovered from hepatitis B; anti-HBs and anti-HBc persist forever.
- HBeAg, appears concurrently with or shortly after HBsAg. Its appearance coincides temporally with high levels of virus replication and reflects the presence of circulating intact virions and detectable HBV DNA (with the notable exception of patients with pre core-mutations who cannot synthesize HBeAg.
- In self-limited HBV infections, HBeAg becomes undetectable before the disappearance of HBsAg, and anti-HBe then becomes detectable, coinciding with a period of relatively lower infectivity. Because markers of HBV replication appear transiently during acute infection, testing for such markers is of little clinical utility in typical cases of acute HBV infection.

- In chronic HBV infection, HBsAg remains detectable beyond 6 months, anti-HBc is primarily of the IgG class, and anti-HBs is either undetectable or detectable at low levels.
- During early chronic (replicative immune clearance phase) HBV infection, HBV DNA can be detected both in serum[1] and in hepatocyte nuclei[2].This replicative stage of HBV infection is the time of maximal infectivity and liver injury; HBeAg is a qualitative marker and HBV DNA a quantitative marker of this replicative phase, during which all three forms of HBV circulate, including intact virions.
- Over time, the replicative phase of chronic HBV infection gives way to a relatively non-replicative phase. This occurs at a rate of ~10% per year (i.e. the likelihood of a patient with HBeAg-reactive chronic hepatitis B of converting from relatively replicative to non-replicative infection is approximately 10% per year), and is accompanied by seroconversion from HBeAg-positive to anti-HBe-positive.
- In most cases, this seroconversion coincides with a transient, elevation in aminotransferase activity.
- In the non-replicative phase of chronic infection, only spherical and tubular forms of HBV, not intact virions, circulate, and liver injury tends to subside. Most such patients would be characterized as inactive HBV carriers.



General points regarding HBV serology:

- HBsAg and HBeAg positive serum is highly infectious, thus it's expected to detect HBV DNA in such a serum (rather than HBeAg negative and HBeABs positive serum).
  - That's why, an infected mother with HBsAg and HBeAg positive serum will >90% transmit HBV to her child, while HBeAg negative mothers have 10-15% chance only to transmit the disease to their children.
- Resolution of HBeAg antigens predict resolution of disease, having it positive for more than three months indicates chronicity (highly infective chronic hepatitis).
- Anti-HBs are deemed the protective antibody, as it seems to protect from reinfection, thus susceptible people are given anti-HBs for protection.
- The outer HBsAg (the envelope protein on the virion) has eight genotypes; genotypes B and C are dominant in Asia, A and D in the US.
  - Subtype does not correlate to clinical picture; however genotype B is associated with less rapid progressive liver disease and lower chance of hepatocellular carcinoma (HCC) than genotype C. Genotype A in patients is likely to be cleared (viremia) and patients achieve HBsAg seroconversion (with or without therapy).

👌 Let's gather the information:

- ✓ Anti-HBs presence indicates past infection$_1$ with HBV or immune response from HBV vaccine$_2$ (appears in the resolution of the disease).
- ✓ HBeAg presence in serum of HBV carrier suggests replicative hepatitis.
- ✓ IgG anti-HBc presence Indicates past infection$_1$ with HBV (appears in the resolution of the disease).
- ✓ IgM anti-HBc presence indicates recent acute infection with HBV. High levels are frequently detected at the onset of clinical illness.
- ✓ HBsAg is usually detectable before clinical evidence of hepatitis and persists throughout the active course of the disease.
- ✓ Antibody to HBsAg is first detected after the disappearance of HBsAg. Before it disappears, HBeAg is replaced by anti-HBe, signaling the start of resolution of the disease.
- ✓ HBV chronic carriers are those in whom HBsAg persists for more than 6 months in the presence of HBeAg (highly infective chronic hepatitis) or anti-HBe (low infectivity).
  - However, some patients can develop HBeAg negative chronic hepatitis with pre-core HBV mutants, that results in absent HBeAg production but with continued viral progression (although it's infective).

🖒 Well now it's easy to memorize the following tables, learn them by heartttt (they're very important).

Table 1: features of hepatitis B virus

HEPATITIS TYPE	VIRUS PARTICLE, nm	MORPHOLOGY	GENOME[a]	CLASSIFICATION	ANTIGEN(S)	ANTIBODIES	REMARKS
HAV	27	Icosahedral nonenveloped	7.5-kb RNA, linear, ss, +	Hepatovirus	HAV	Anti-HAV	Early fecal shedding Diagnosis: IgM anti-HAV Previous infection: IgG anti-HAV
HBV	42	Double-shelled virion (surface and core), spherical	3.2-kb DNA, circular, ss/ds	Hepadnavirus	HBsAg HBcAg HBeAg	Anti-HBs Anti-HBc Anti-HBe	Bloodborne virus; carrier state Acute diagnosis: HBsAg, IgM anti-HBc Chronic diagnosis: IgG anti-HBc, HBsAg Markers of replication: HBeAg, HBV DNA
	27	Nucleocapsid core			HBcAg HBeAg	Anti-HBc Anti-HBe	Liver, lymphocytes, other organs Nucleocapsid contains DNA and DNA polymerase; present in hepatocyte nucleus; HBcAg does not circulate; HBeAg (soluble, nonparticulate) and HBV DNA circulate—correlate with infectivity and complete virions
	22	Spherical and filamentous; represents excess virus coat material			HBsAg	Anti-HBs	HBsAg detectable in >95% of patients with acute hepatitis B; found in serum, body fluids, hepatocyte cytoplasm; anti-HBs appears following infection—protective antibody

Table 2: diagnosis of HBV

	HBsAg	Anti-HBs	HBeAg	Anti-HBe	Anti-HBc IgM	Anti-HBc IgG	HBV DNA
Acute infection	✓		✓				+++
Window					✓		+
Prior infection		✓		✓		✓	
Vaccinated		✓					
Chronic (high infectivity)	✓		✓			✓	+++
Chronic (low infectivity)	✓			✓		✓	±
Pre-core mutant	✓			✓		✓	++

HBV DNA assays (from here till the end of the sheet; the doctor only read the slides and didn't add any point)

I) Real-time PCR techniques allow quantification of HBV DNA.

Note: a normal ALT does not predict mild findings in someone with active viral replication.

- This is useful in determining whether a patient will benefit from therapy, as high levels are associated with cirrhosis and its complications.
- DNA may remain detectable in the serum after recovery from acute infection, suggesting "clearance" is more about "control" by the immune system. This contrasts with patients who become HBeAg negative during nucleoside/nucleotide therapy who generally have undetectable DNA by PCR.
- Rare cases of occult HBV infection OBI (DNA is detectable in HBsAg-negative patients even in the absence of anti-HBc) have been described; this may be due to mutations leading to altered expression or structure of HBsAg (not mentioned).

II) Other investigations include: LFTs, gamma-glutamyl transferase (GGT), clotting, screening for other blood -borne viruses and haemochromatosis, liver biopsy (disease severity).

III) Liver biopsy is especially important in those who do not meet treatment criteria but have high HBV DNA, as they may benefit from treatment if the disease is histologically active.

Treatment

- Generally: avoid alcohol, practice safe sex, hepatitis A vaccination (low-prevalence areas), avoid occupations with high risk of transmission such as surgery, dentistry; HBV immunization of household members, monitor for HCC and varices.
- Treatment to prevent hepatitis B infection after exposure (exposure with no previous vaccination history) → immunoglobulin (AntiHBs) within 12 hours + vaccine.
- Treatment for acute hepatitis B infection (after infection) → Supportive care unless severe cases or patients with underlying illness. In these cases, antiviral drugs or a hospital stay is needed to prevent complications.
- Treatment for chronic hepatitis B infection which may require lifelong treatment to reduce risk of complications (HCC, liver failure) and to prevent disease transmission.

  - Antiviral medications include entecavir (Baraclude), tenofovir (Viread), lamivudine (Epivir), adefovir (Hepsera) and telbivudine (Tyzeka). They all help reduce amount of virus (viral load) and thus reduce liver damage.
  - Interferon injections (Interferon alfa-2b (Intron A)) are mainly used for younger hepatitis B patients who wish to avoid long-term treatment$_1$ or women who might want to get pregnant$_2$ (to consider discontinuing therapy since it shouldn't be used during pregnancy) within a few years, usually given after a course of antiviral therapy.
  - Liver transplant is used in the event of severe liver damage.

Prevention

1) Education.
2) Screening of blood products.
3) Immunization (e.g. health care workers, MSM (men who have sex with men), close family contacts of an infected individual, those regularly receiving blood products, haemodialysis recipients).
4) Post- exposure vaccination (sexual contacts, needlestick recipients, neonates born to infected mothers).
5) Hepatitis B immunoglobulin should be given to neonates born to HBsAg-positive mothers (unless anti-HBe positive) and unvaccinated needlestick recipients from HBsAg -positive donors.

Hepatitis B √

Practice questions:

1. A 30-year-old student goes to the emergency room because of fever and anorexia for the past 3 days. She appears jaundiced. Her liver is enlarged and tender. A laboratory test shows elevated aminotransferases. She reports a history of having received hepatitis B vaccine 2 years ago but has not had hepatitis A vaccine. The results of her hepatitis serologic tests are as follows: HAV IgM-negative, HAV IgG-positive, HBsAg-negative, HBsAb-positive, HBcAb-negative, HCV Ab-positive.

The most accurate conclusion is that she probably

(A) Has hepatitis A now, has not been infected with HBV, and had hepatitis C in the past.

(B) Has hepatitis A now and has been infected with both HBV and HCV in the past.

(C) Has been infected with HAV and HCV in the past and has hepatitis B now.

(D) Has been infected with HAV in the past, has not been infected with HBV, and has hepatitis C now.

(E) Has been infected with HAV and HCV in the past, has not been infected with HBV, and has hepatitis E now.

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2. A 39-year-old African-American man comes to the physician because of anorexia, malaise, dark urine and upper abdominal discomfort. His temperature is 37.9°C (100.2°F). Physical examination shows scleral icterus and moderate right upper quadrant tenderness. The liver is palpable below the right costal margin. Laboratory studies show:

HBsAg: positive

HBsAb: negative

Anti-HBc IgM: positive

HBeAg: positive

Which of the following will most likely change in his serologic findings when this patient enters the window period?

(A) He will become HBcAg-positive

(B) He will become HBc IgG-positive

(C) He will become HBeAg-negative

(D) He will become HBsAb-positive

(E) He will become HBsAg-negative

3. A 36-year-old nurse is found to be both HBsAg positive and HBeAg positive. The nurse most likely

(A) Has acute hepatitis and is infectious.

(B) Has both HBV and HEV infections.

(C) Has a chronic HBV infection.

(D) Has cleared a past HBV infection.

(E) Was previously immunized with HBV vaccine prepared from healthy HBsAg-positive carriers.

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4. Which of the following persons are not recommended to receive hepatitis B vaccine because they have a risk factor for HBV infection?

(A) Sexually active persons who are not in long-term, mutually monogamous relationships

(B) Injection drug users

(C) Pregnant women

(D) Persons who live in a household with a person who is HBsAg positive

(E) Persons seeking treatment for a sexually transmitted disease

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5. Which of the following serologic patterns is suggestive of a patient with chronic hepatitis B with a pre-core mutation?

(A) HBsAg positive, HBsAb negative, anti-HBc positive, HBeAg positive, HBV DNA positive

(B) HBsAg positive, HBsAb negative, anti-HBc positive, HBeAg positive, HBV DNA positive

(C) HBsAg positive, HBsAb positive, anti-HBc positive, HBeAg negative, HBV DNA positive

(D) HBsAg negative, HBsAb positive, anti-HBc positive, HBeAg negative, HBV DNA negative

6. A 38 year old Caucasian female who works as a nurse at a large community hospital has the following readings of serologic markers for viral hepatitis:

Anti-HAV IgM (negative)

Anti-HAV IgG (positive)

HBsAg (negative)

HBeAg (negative)

Anti-HBsAg (positive)

Anti-HBcAg IgM (negative)

Anti-HBcAg IgG (negative)

This patient is most likely:

(A) Is actively shedding HAV

(B) Is infected with HDV

(C) Is an asymptomatic carrier of HBV

(D) Has recovered from HBV infection recently

(E) Has been vaccinated against HBV

(F) Has a chronic hepatitis but is non-contagious

Good luck