Microbiology

Doctor 2017 | Medicine | JU

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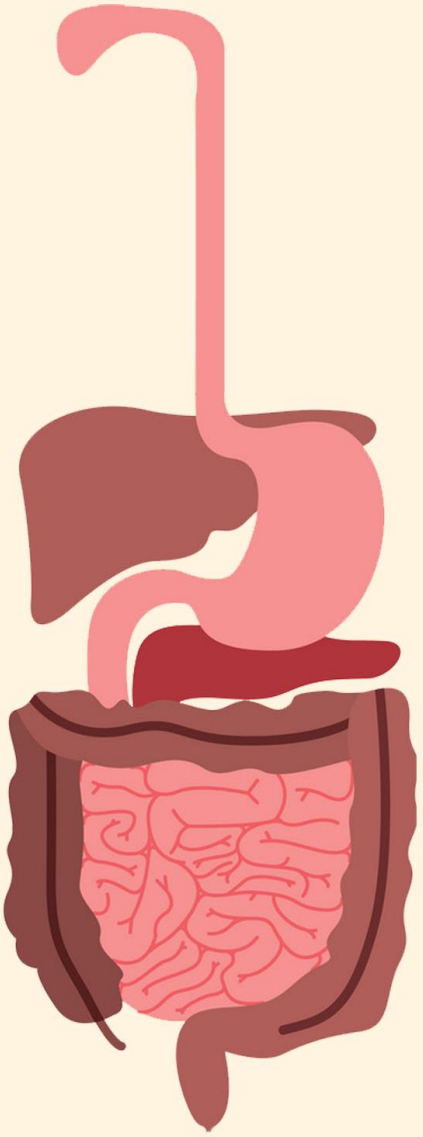


2nd system - GI

Acute Hepatitis

- It is an acute inflammation of the liver characterized by **hepatocyte damage** and elevations in serum **ALT** and **AST** levels.
- Can be caused by a variety of **infectious** and **non-infectious** agents, such as:
  - **a- Viral hepatitis**: Hepatitis viruses (A, B, C, D, and E) and other viruses *(EBV, CMV, HSV, VZV, Measles, Rubella, Adenovirus, Coxsackie, yellow fever).*
  - **b- Non viral infectious diseases**:
    - *1- Leptospirosis, Q fever (coxiella burnetti), sepsis, legionella, TB, Brucellosis, plague (Yersinia pestis).*
    - *2- Drug-induced, toxins, alcohol, ischemia, autoimmune, HELLP (hemolysis, elevated liver, low platelet syndrome)*

1- Hepatitis A Virus

- HAV is an **enterically** transmitted **picornavirus**; **feco-orally**.
- Outbreaks of infectious hepatitis have been recognized for centuries, but it was first demonstrated in the **stool** of infected volunteers in 1973.
- HAV is a 27–28nm spherical, **non-enveloped virus**, it has **3** types:
  - **a- Mature virions**
  - **b- Empty capsids**; without a genome.
  - **c- Partial genome particles**; less stable particles with a more open structure.
- The HAV genome is very **small**, it is an **ssRNA** of 7474 nucleotides.
- As with other picornaviruses, the coding region is divided into three parts:
  - **a- P1** (encoding the four capsid proteins VP1–4),
  - **b- P2**, and **P3** (encoding seven non-structural proteins).
- HAV has one serotype with 4 different genotypes.
- Viral infection of hepatocytes is **not** cytopathic, but the **cytotoxic T-cell** (immune) response results in **cell death.**
- The virus can be **inactivated** by boiling for 1 minute, UV light, **chlorine**, formaldehyde.

Epidemiology:

- HAV has a **worldwide** distribution and is associated with **overcrowding** and **poor sanitation** and is endemic in the developing world where it is an infection of **childhood**.
- Improved **hygiene** caused a **reduction** in the incidence in children but causes **greater** susceptibility in **adults**. Also, **adults** show **more severe** forms of the disease compared to **children** where it is **mild**; children tend to **tolerate** hepatitis A **more** than adults.

- Main risk groups for **all** hepatitis viruses: among **homosexuals, IV abusers, and homeless** people.
- Other risk groups: children and staff in childcare facilities, patients and staff in mental health institutions, and travelers to endemic areas *(Indian subcontinent, Far East, Eastern Europe).*
- Transmission is **feco–orally**, thus community outbreaks have occurred as a result of **water** or **food contamination**.

Clinical Features:

- An incubation period of 4 weeks.
- **Subclinical infection** *(symptoms are unnoticed)*: common in children less than 5 years of age (>90%).
- As age increases, patients show more symptoms of acute hepatitis:
  - ⇨ An abrupt prodrome of **fever**, headache, malaise, anorexia, vomiting, and **right upper quadrant** pain is followed <7 days after by **dark urine**, **pruritus**, and **pale stools**. Occasionally, diarrhea, cough, coryzal symptoms, or arthralgia may occur (commoner in children).
- **Physical findings**: **jaundice**, hepatomegaly, splenomegaly (5–15%). People **feel better** once jaundice appears, which peaks within 14 days.
- **Complications**: prolonged cholestasis, relapsing disease, **fulminant hepatitis** (rare, commoner in older patients), extrahepatic disease, and triggering of autoimmune chronic active hepatitis predisposing to **carcinoma**.

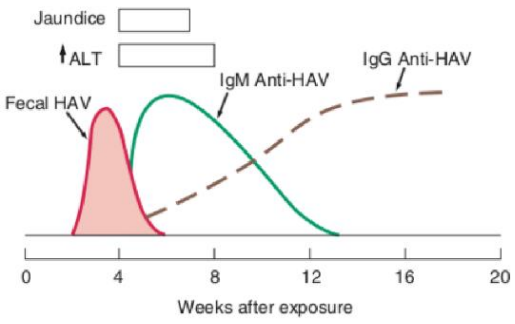
Diagnosis:

- It has only **one serotype**, as mentioned before.
- **Replication** limited to **liver**, but it's present in the liver, bile, **stool, and blood** during preicteric phase *(period prior to the appearance of jaundice)* and incubation period.
- Once **jaundice** is apparent infectivity in **stool** and **blood**, as well as symptoms, are **diminished**.
- **AST** and **ALT** levels are **very high**, while **bilirubin** and **ALP** are usually only **mildly** elevated.

1- **Early** fecal shedding reaches its **peak before** symptoms of **jaundice** and **elevated ALT** levels appear.

2- Once symptoms appear, **IgM** can be detected aiding in early diagnosis during **acute illness**. Here the virus is **still shedding** but it is not at the peak, i.e. IgM **can** be detected during shedding.

3- After recovery, **IgG** becomes **predominant** providing **life-long immunity**.



⇨ Detection of **anti-HAV IgM confirms** the diagnosis and remains **positive** for several months (3-6), they are present **once** symptoms appear. **Anti-HAV IgG** is **protective** and becomes positive at 2-3 months after exposure **predominating** after recovery persisting for life.

Treatment:

- **Acute hepatitis symptoms** → Avoid **paracetamol** and **alcohol**. 85% have full clinical/biochemical recovery by 3 months, and nearly all by 6 months.
- **Fulminant hepatitis** → Patients should be treated with **supportive** therapy and referred for consideration of **liver transplantation**.
- **Fatalities** are commoner with **advancing age** and in those with **hepatitis C co-infection**.

Prevention:

- Pre-exposure prophylaxis through **vaccination** where several inactivated HAV vaccines exist, these vaccinations replaced the use of **immunoglobulins**.
- 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).*

2- Hepatitis B Virus:

- HBV is a DNA virus that causes both **acute** and **chronic** viral hepatitis in humans.
- It has a diameter of 42nm, the **outer envelope** contains **HBsAg** (HB surface antigen) proteins, **glycoproteins**, and **cellular lipid**.
- It has 3 morphological forms, as seen in the table on the last page.
- **Replicates** in **liver** but **exists extrahepatically**.
- **Antigens**:
  1- **HBsAg** → present on the **surface/envelope** and may be released from infected cells as small spherical or filamentous particles. 8 genotypes are identified according to this antigen *(genotypes B and C are dominant in Asia, while A and D in the US)*
  2- **HBcAg** → beneath the envelope is the **internal core** or nucleocapsid, which contains hepatitis B core antigen (HBcAg). It is never found in the serum.
  3- **HBeAg** → a **condensed** form of the major **core** polypeptide. It is released from infected liver cells when HBV is **replicating**; it is a **marker** for **replication**.

Genome:

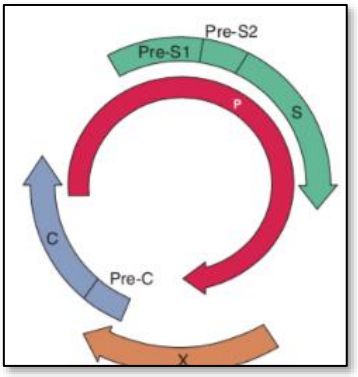
- HBV has a **small** circular DNA with an unusual genome, as it has both a **dsDNA** with partial **ssDNA**.
- There are **eight** genotypes (A–H) and **four** long known genes (ORFs):

1- **C (core/nucleocapsid) gene**: encodes both **HBcAg** and **HBeAg**. Mutations in the pre-core region result in HBV mutants that **lack HBeAg**.

2- **S (surface/envelope) gene**: which includes the pre-S1, pre-S2, and s regions encoding **HBsAg**.

3- **P (polymerase) gene**: encompasses 3/4 of the viral genome, encodes the **DNA polymerase** with ribonuclease H activity.

4- **X gene:** encodes a **polypeptide**, with several functions.



Epidemiology:

- HBV is a global public health problem where ~400 million are chronically infected with ~1 million deaths per year.
- **Low** prevalence ranges from 0.1–2% in (USA, West EU), but **high** 10–20% in parts of China and sub-Saharan Africa.
- Variation due to **age** in which the risk of chronicity is **greatest** in the **very young** *(90% for perinatal infections)*, compared to **adults** *(5% become chronic).*
- HBV may be transmitted **vertically/perinatally** *(mostly in high-prevalence areas)*, **sexually**, by **blood**, by **IV drug** use, by needlestick injury, and **horizontally** *(especially between children in intermediate-prevalence areas).*
- Perinatal transmission rates reach 90% in **HBeAg-positive**; replication is active and is highly contagious. Luckily, neonatal vaccination is 95% protective.

Clinical Features:

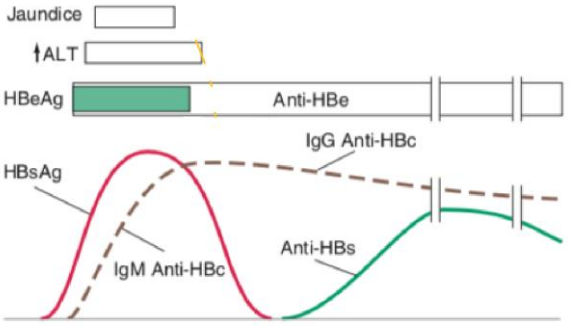
- The incubation period is **long**; 1–4 months.
- 70% are **asymptomatic**, while 30% develop **acute hepatitis** with symptoms including malaise, nausea, abdominal pain, and jaundice.
- Symptoms **subside** over 1–3 months, but **fatigue** may **persist**.
- **Fulminant hepatic failure** occurs in 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.

- Subtype does not correlate to the clinical picture, however **genotype B** is associated with **less** rapid progressive **liver disease** and **lower** chance of **HCC** than **genotype C**.
- **Genotype A** in patients is likely to be **cleared** (viremia) and patients achieve **HBsAg seroconversion** (with or without therapy).

Diagnosis: *"Try to understand then memorize. Contact me upon having any difficulties"*

> ***Note:*** *The **window period** starts once **HBeAg** is converted into **Anti-HBe**, it is dependent on the **time taken** for **seroconversion** from **HBsAg into Anti-HBs**.*

Briefly, in this diagram, during the **active phase** of hepatitis **HBeAg** is present denoting the **replication** of the virus with **HBsAg +ve**. HBsAg can be detected **before** the symptoms. In the **window** period, **HBeAg** becomes **absent** and thus **reducing** the levels of **HBsAg** where **seroconversion** into **Anti-HBs** then occurs. **Anti-HBs** indicates recovery. With the presence of **IgG Anti-HBc**, this indicates that the patients had a **prior infection**.



1- **HBsAg** appears 1–10 weeks after **acute** infection, **prior to symptoms** of **jaundice** and high **ALT** when the virion fully matures, thus it's the **main marker** in diagnosis.
   - Those who clear infection become **negative** after **4–6 months**.
   - Positivity **beyond** 6 months indicates **chronic** HBV.
   - Its disappearance is followed by the development of **anti-HBs** antibody 'seroconversion' indicating **recovery**.
   - If the patient is positive for both **HBsAg** and **anti-HBs**, this means that the antibody couldn't neutralize the virus and the patient is, therefore, an active **carrier**.

2- **HBcAg** is an **intracellular** antigen that **doesn't** leave the virus and thus **cannot** be detectable in the serum.
   - **Anti-HBc IgM** is predominant in **early** infection and may be the **only** indicator of infection in the **window period**; between HBsAg loss and anti-HBs production.
   - **Anti-HBc IgM** may remain for a couple of years, and titers (concentration) can rise during chronic flares, which may lead to the **mistaken** diagnosis of **acute infection**.

3- **HBeAg** is a secretory protein and **marker** of HBV **replication and infectivity**.

- Associated with **high levels** of **HBV DNA** denoting **active replication**, it appears with **HBsAg**.
- HBeAg **seroconversion** to anti-HBe may be **delayed** for years in patients with **chronic** HBV especially if it remains beyond **3** months. When seroconversion into **anti-HBe** occurs, it is usually associated with a **decrease in DNA** and a reduction in **liver inflammation**.

> ***Note:*** *Nucleocapsid core genes (C) forms **HBcAg** (not a marker, not secreted) or **HBeAg** (marker, secreted). Thus, there is no **HBcAg** in the serum (only inside hepatocytes), while the secreted part, HBeAg, gives a good prediction on replication activity.*
>
> ***Pre-core mutants** (cannot encode HBeAg) may have **active liver disease** in the absence of **HBeAg**. Such patients tend to be **older** with more advanced liver disease and fluctuations in HBV DNA load and ALT.*

- **In serum:**

1- **HBsAg +ve, and HBeAg +ve** → Patient is **highly infectious** with **active** replication, complete virion, and HBV DNA is detectable.

2- **HBsAg +ve and, HBeAg –ve / with HBeABs** → Patient **isn't as infectious** as in the first scenario.

⇨ So a mother with **HBsAg +ve and HBeAg +ve**, will >**90%** transmit HBV to the child, while **HBeAg -ve** mothers have **10-15%** chance only

- **Anti-HBs** are deemed the **protective** antibody, as it seems to protect from reinfection, thus susceptible people are given Anti-HBs for protection.
- **ALT** levels **increase** following **HBsAg** in the acute phase. *'refer to the diagram'*
- In predicting chronicity of the disease:

1- Having **HBeAg +ve** for more than **3** months indicates a chronic state.

2- Having **HBsAg +ve** for more than **6** months indicates a chronic state.

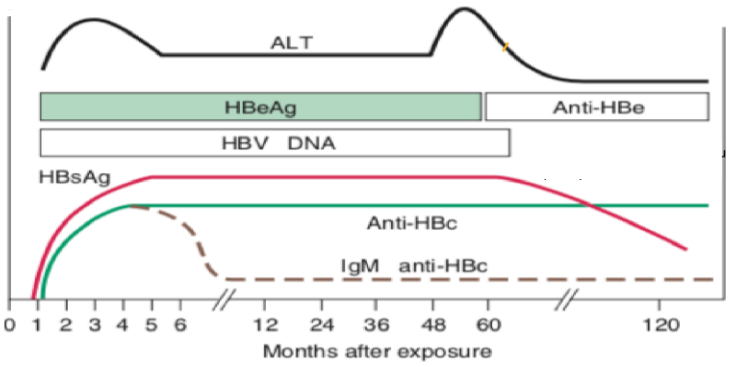
3- **No** or very low **Anti-HBs levels**; as they are markers of recovery.

Chronic Hepatitis:

- Chronic hepatitis develops in 5–10% of adult acute infections. It may be **asymptomatic** for many years. Exacerbations (active chronic) of infection may occur, mimicking **acute hepatitis** or presenting as **liver failure. Serology** is important to confirm the patient is a carrier to treat; where IgG is present unlike acute hepatitis.

- **Extrahepatic manifestations** are **immune-mediated** including serum sickness, polyarteritis nodosa, and membranous glomerulonephritis, with most cases seen in children (presents as nephrotic syndrome).

Briefly, in this diagram, during the **first 6 months** is the **acute** phase of hepatitis. Since **HBsAg** remained **beyond** 6 months this indicates **chronicity** where **HBsAg** is present with **Anti-HBc IgG**.



Phases of chronic hepatitis:

1- **Replicative phase**: **HBeAg** is **active** with **high** HBV DNA loads and **normal ALT**.

2- **Immune-active phase**: HBeAg **seroconversion** into Anti-HBe at the end.

3- **Low replicative phase**: HBeAg becomes **absent** with **low DNA** loads and **normal ALT** levels. In 10% of patient, a peak of ALT level may occur as shown.

Now we will discuss it in detail:

Chronic Infection Include 3 Phases: *Anti-HBc IgG is always present. Refer to the diagram above*

1- **Replicative immune-tolerant phase** (perinatal infections only) → **Active** viral **replication** and **minimal** liver damage. The patient is said to be **infectious chronic**.

HBeAg +ve, anti-HBe -ve, HBV DNA load is high, normal ALT, and a normal liver.

2- **Replicative immune-clearance / immune-active phase** → **Seroconversion** may occur, often associated with **biochemical exacerbations**; due to an increase in **immune-lysis** of infected hepatocytes which may be misinterpreted as **acute hepatitis B**.

HBeAg +ve, HBsAg +ve, HBeAg +ve, anti-HBe -ve, but HBV DNA load is lower.
Having IgM -ve confirms that it is not acute hepatitis.
Seroconversion into Anti-HBe may start at the end of this phase.

3- **Non (low) replicative phase / Inactive carrier state** → What most patients are, in which liver disease is in **remission** although some cases may still have histologically **active liver disease**.

HBeAg -ve, anti-HBe +ve, anti-HBc +ve, HBV DNA load is very low, and ALT usually normal.

Several **normal ALTs and HBV viral loads** over **12 months** are required to **confirm** someone is an **inactive carrier** due to the fluctuating nature of the disease.

➔ Resolution is when we have **HBsAg -ve** and **Anti-HBs +ve**.

- **Complications of chronic HBV:**

  1- **End-stage liver disease** (15-40 % of cases) and hepatocellular carcinoma (HCC).

  2- **Disease progression** in patients with **prolonged** replicative phase, **alcoholic**, and **co-infection** with **HCV** or **HDV**. It is associated with **high DNA** levels and **HBeAg +ve**.

HBV DNA Assays and special cases:

- **Real-time PCR techniques** allow quantification of **HBV DNA**. This is useful in determining whether a patient will **benefit** from therapy, **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 patients who generally have **undetectable DNA** by PCR who become **HBeAg negative** after nucleoside/nucleotide therapy.
- **Rare cases of occult HBV** *(detectable DNA, but negative HBsAg, and even absent anti-HBc)* have been described. This may be due to **mutations** leading to **altered** expression or structure of **HBsAg**.
- A few patients with **chronic HBV** infection may show **delayed clearance** of **HBsAg** (around 0.5– 2% patients per year) even after years. Some even remain **HBV DNA-positive**.
- In **inactive carrier patients** (non/low replicative phase), 10% per year, coincides with another **peak in ALT** levels. Unlike the replicative phase, where virions are in their spherical and tubular forms, there are no intact virions and **liver injury is very low**.
- **Isolated anti-HBc** may be seen in **two** situations, **HBV DNA** may be detected in the liver of these patients:

  1- Many years after **recovery from acute HBV** where **anti-HBs** fallen to undetectable levels.
  2- Many years after **chronic HBV** where **HBsAg** fallen to undetectable levels.

Other Investigations: *"the doctor didn't focus on it"*

- LFTs, gamma-glutamyl transferase (GGT), clotting, screening for other blood-borne viruses and hemochromatosis, liver biopsy (disease severity).
- 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.
- A **normal ALT** does not predict **mild findings** in someone with **active viral** replication, recall the first phase in chronic hepatitis.

Treatment: *"the doctor didn't focus on it and said to know the treatment briefly"*

- **General**: avoid alcohol, practice safe sex, hepatitis A vaccination (in low-prevalence areas), avoid occupations with a high risk of transmission such as surgery and dentistry, HBV immunization of household members and monitor for HCC.
- **Exposure with no previous vaccination history** → Immunoglobulin (Anti-HBs) within 12 hours + vaccine.
- **Treatment for acute hepatitis B infection** → Supportive care unless severe cases or patients with an underlying illness are present we use antivirals or a hospital stay is needed to prevent complications.
- **Treatment for chronic hepatitis B infection** → It may require lifelong treatment to reduce the risk of complications (HCC, liver failure) also to reduce the risk of transmission.
- **Antiviral medications**: Entecavir (Baraclude), Tenofovir (Viread), Lamivudine (Epivir), Adefovir (Hepsera) and Telbivudine (Tyzeka), all help reduce the amount of virus and thus reduce liver damage.
- **Interferon injections:** Interferon α-2b (Intron A) mainly used for **younger patients** hepatitis B who wish to avoid long-term treatment or women who might **want to get pregnant** within a few years (not used in pregnancy). Usually given **after a course of antiviral therapy.**
- **Liver transplant**, in the event of severe liver damage.

Prevention:

- Education and screening of blood products.
- Immunization, e.g. HCWs, MSM, close family contacts of an infected individual, those regularly receiving blood products, hemodialysis recipients.
- **Post-exposure vaccination**, after sexual contacts, needlestick recipients and neonates born to infected mothers.
- **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.

The rest of the lecture is in this link, up until 12:50 is a revision of this sheet:

https://www.youtube.com/watch?v=fIcS9yc9N8g

Quick Notes:

HBsAg and Anti-HBc IgM +ve → *Acute*
HBsAg and Anti-HBc IgG +ve → *Chronic*
HBeAg / HBV DNA → *Replication*
HBeAg +ve for > 3months / HBsAg +ve for > 6months → *Chronic*
HBsAg +ve → *Main marker; active carrier state.*
HBeAg -ve and anti-HBe +ve → *Inactive carrier state*
Anti-HBs → *Recovery / immunity (vaccination).*
Anti-HBs and Anti-HBc IgG → *Past resolved infection.*
Anti-HBc IgM → *Window period "in acute phase".*

A useful short video discussing HBV diagnosis markers:
https://drive.google.com/open?id=1OjGZAk91IGZKfQOTLpeVLkEVglfOZQ1F

Important Tables to understand:

NOMENCLATURE AND FEATURES OF HEPATITIS VIRUSES

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 Liver, lymphocytes, other organs
	27	Nucleocapsid core			HBcAg HBeAg	Anti-HBc Anti-HBe	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 8.3 Diagnosis of hepatitis B virus

	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	✓			✓		✓	++

Good Luck ♥