SHEET NO.

# MICROBIOLOGY (Virology)

## DOCTOR 2019 | MEDICINE | JU


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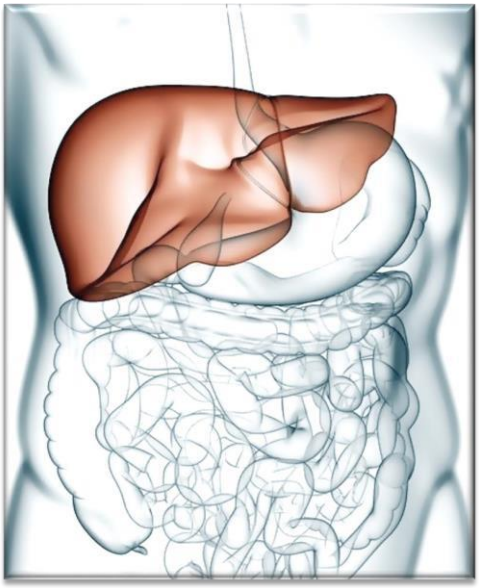


*UNDERLINED IS COPIED DIRECTLY FROM SLIDES* في اضافات شوي عن الكلامم لكن بالغالب زي تلخيص

لشرح الدكتور حطيته قبل او بعد الشرح
في كلام مكرر، لا يخوفكم طول الشيت

- Viral hepatitis is a systemic disease primarily involving the liver.
- Most cases of acute viral hepatitis are caused by one of the following agents: HAV, HBV, HCV, or HEV.
- Hepatitis viruses produce acute inflammation of the liver, resulting in a clinical illness characterized by fever, nausea, vomiting, and jaundice.
- Regardless of the virus type, **identical histopathologic lesions are observed in the liver during acute disease**.

| Virus | Hepatitis A | Hepatitis B | Hepatitis C | Hepatitis D | Hepatitis E |
|---|---|---|---|---|---|
| Family | Picornaviridae | Hepadnaviridae | Flaviviridae | Unclassified | Hepeviridae |
| Genus | *Hepatovirus* | *Orthohepadnavirus* | *Hepacivirus* | *Deltavirus* | *Hepevirus* |
| Virion | 27 nm, icosahedral | 42 nm, spherical | 60 nm, spherical | 35 nm, spherical | 30–32 nm, icosahedral |
| Envelope | No | Yes (HBsAg) | Yes | Yes (HBsAg) | No |
| Genome | ssRNA | dsDNA | ssRNA | ssRNA | ssRNA |
| Genome size (kb) | 7.5 | 3.2 | 9.4 | 1.7 | 7.2 |
| Stability | Heat and acid stable | Acid sensitive | Ether sensitive, acid sensitive | Acid sensitive | Heat stable |
| Transmission | Fecal–oral | Parenteral | Parenteral | Parenteral | Fecal–oral |
| Prevalence | High | High | Moderate | Low, regional | Regional |
| Fulminant disease | Rare | Rare | Rare | Frequent | In pregnancy |
| Chronic disease | Never | Often | Often | Often | Never |
| Oncogenic | No | Yes | Yes | ? | No |

They share common features, like the ability to cause acute infections and tropism for hepatocytes while differing in other features like the ability or potential to cause chronic infections, modes and routes of transmission, oncogenic potential. You have to know that different virus belong to different families.

(Hepatitis A and E were either skipped or delayed till the next lecture)

# Hepatitis B:

It was well known before its discovery that there's a difference between two types of hepatitis: First type caused by hepatitis A virus, named infectious hepatitis, another caused by hepatitis B virus called serum hepatitis. The two terms were no longer used after 1973, after WHO introduced these two terms to distinguish between these two types of viruses; which was achieved after the discovery of these "Australian antigens" in the serum by Bloomberg and colleagues by chance after investigating genetic diseases of different populations, finding the antigens in the serum of an Australian patient, thus calling them "Australian antigens". After this discovery in 1965, and discoveries in the early 70's of the complete viral particle the antigens became known as the 'hepatitis B surface antigen" while the Dane particle as the complete virion.

The virus is a partially double-stranded DNA enveloped virus. Genome is made of: a partial + sense strand and a complete –ve sense strand.
After the entry of the virus into the hepatocyte, completion of the partial +ve sense strand takes place turning the genome into a complete closed circular DS DNA.

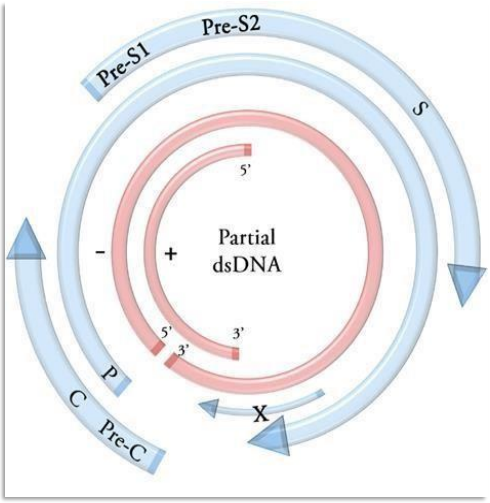
## HBV is the only human virus that belongs to the family *Hepadnaviridae* that can infect humans, classified in group 7 of the Baltimore classification system thus it's a DNA virus with a reverse transcriptase and a reverse transcription step in its cycle, as the only humanvirus virus to do so.

## HBV is a DNA virus with a peculiar genome that is a circular partially double-stranded DNA of about 3.3 kb.

Peculiar: overlapping reading frames, causing a sort of genetic economy. Ie within a small sized genome multiple genes can be expressed that are overlapping. (4 overlapping reading frame in the complete –ve strand <outside the cell>)

# HBV Genome

*because of the presence of different initiation codons, different proteins can be translated. Starting from "C" on the arrow translates to the core protein, while starting upstream will give the E antigen that is soluble which isn't present in the capsid unlike the core protein. The same applies for the S gene(arrow), starting from S produces the small surface protein, while starting from pre-S2 produces the medium sized and starting from pre-S1 produces the large surface antigen protein.




The genome encodes for:

- the structural proteins, which are the HBV surface antigens on the envelope, and the hepatitis B core antigens of the capsid.
- the replicating proteins: the polymerase, X-protein regulator of transcription, and regulatory elements.

The genomic structure of HBV with the blue arrows indicating the four open reading frames (S: surface, X: trans-activator of transcription, C: core and P: polymerase). The genomic DNA is shown in pink

*most of the genomic sequences are important to induce an infection. *this compact organization restricts fixation of mutation within HBV population, but also the presence of a reverse transcriptase lacking proofreading activity makes the virus more susceptible to occurrence of mutations compared to other DNA viruses. (it is in the middle between RNA and DNA viruses <he probably refers to rate of occurrence of mutations>. **(so it has an intermediate rate of occurrence of mutations)**

*the presence of genetic differences within different genotypes and subgenotypes of the HBV may impact the response to treatment and ability to cause more sever disease, or ability to cause faster progression towards cirrhosis And hepatocellular carcinoma.

- HBV is characterized by the circulation of three EM morphologically recognized structures: The 42-nm virion particles, the 22-nm spherical particles and the 22-nm tubular particles that are up to 200 nm in length.

- The 22-nm particles, that are non-infectious, are produced in excess compared to the virions which might be a viral decoy mechanism to trick the immune system.

If we examine the serum of a patient with HBV infection, this examination with show 3 morphologic structure in different concentrations. The most common form is noninfectious; this is an important point.

It is used as a decoy mechanism to trick the immune system.
These 22 nm particles are bimorphic (meaning that the average is 22nm, but 17 to 25 nm), they are more common that other forms by a factor of 10k to 1M. For about **100,000** noninfectious 22nm particles, there is only 1 infectious virion, the Dane particle.
They have a count of more than 10B particle per ml in the serum of patients infected with HBV.
The other form is the filamentous particle, which vary in length but may reach up tp 200nm in length.

The other form is the HBV virion particles, known as Dane particles.

It is able to infect hepatocytes but within the huge population of the spherical and the tubular particles by hiding from the immune system.

The complete virion has an outer envelope wit HBV surface antigen surrounding the core, the capsid, which contains the genome of the particles.

The other particles, contain only the HBV surface antigens without the ability to cause infection.
For the 42 nm particle the genome length varies between 3.33k >>> depending on the genotype.

*Hepatitis B virus binds to hepatocytes through the Sodium taurocholate cotransporting polypeptide as its receptor. After the virus is taken up its uncoated, and then the partially double stranded **relaxed** DNA is converted into a covalently closed circular DNA, called a triple C DNA template that will take a supercoiled form. It is the template for the transcription of the pregenomic RNA ( the virus replicates through an RNA intermediate).
It also gives rise to messenger RNAs.

After about 24 hrs from infection, DNA can be detected in the liver but the time for the time response to make manifestations makes the incubation period very long.

Then the pregenomic RNA through the action of reverse transcriptase will give rise to the DNA genome of the virus.
After the synthesis of the structural proteins (surface and core antigens) the assembly of the virion will take place.
*Hepatitis B antigen is expressed in excess giving rise to the spherical and tubular/filamentous particles.

HBV replication is unique in the way that its replication occurs through an RNA intermediate (the pregenomic RNA) from the minus DNA strand.

- **The polymerase of HBV has the following activities in four domains: terminal protein at the amino end that has a role in initiation of DNA synthesis, a spacer domain that is not critical in function, RT and RNase H.**
- **The core protein (HBcAg) form the capsid and exists as a dimer.**
- **Translation of the preCore region results in the production of the soluble form of core protein (HBeAg) with its presence in serum marking higher transmissibility.**
  *The presence of HB antigen in sera of patients indicates a higher likelihood of transmission and correlates to a higher viral load thus higher probability of transmission.

- **The surface proteins embedded in the envelope are small (S), medium (M) and large (L). The most abundant is the S protein that is the product of S while translation of both PreS2 and S results in the production of M protein and translation of PreS1, PreS2 and S all together results in L protein production.**
- **The pre-S1 domain of the L protein binds to the hepatic receptor of HBV namely sodium taurocholate co-transporting polypeptide (NTCP).**
- **HBV is currently classified into at least eight genotypes designated with capital letters (A-H).**

(IMPORTANT: HBV is currently classified into at least eight genotypes designated with capital letters (A-H), which are further classified into sub genotypes designated by Arabic numerals (regular letters used in English text..1.2.3 etc) e.g. A1, A2 etc.

**Genotypes differ by 8% by nucleotide/genome comparisons. If the difference is higher than 8% they're classified into genotypes.**
*if the difference is between 4% -8 % they're classified into sub genotypes.
*two recently identified genotypes are I (i in lowercase) and J genotypes. So the recent classification divides Hepatitis B virus into 10 genotypes (A-J)

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**The percutaneous transmission is the major route for HBV infection.**

- **Other major routes of transmission include sexual spread and MTCT.**
- **In areas with high endemicity (sero-prevalence ≥8%, e.g. Southeast Asia), MTCT represents a frequent mode of spread with its subsequent high prevalence of chronicity.**

- An area with sero-prevelance between 2% and 8% is classified as intermediate endemicity region>
- And an area with less than 2% sero-prevelance is classified as a low endemicity area. E.g. japan, US, Western Europe. (Dr.Malik thinks Jordan is classified as a low endemicity area.

  * In South Asia, an area of high endemicity vertical transmission is the most common mode of transmission, which is associated with higher probability of development of chronic infection, because age is an important factor to determine whether an infection with HB will turn into chronic hepatitis or not. Age is an important factor beside genetics, polymorphism, certain interleukin receptors, etc.

  *Those are also important factors in potential development of chronic infections in hepatitis C virus infection.

## Transmission can also be:

*parenteral
* vertically whether perinatally or by breast feeding.
* sexually, (whether homo or heterosexually)
*By injection and drug use (especially in certain European countries) (HBV is common among drug users)
*Physical contact with infected body fluids (especially for healthcare workers {occupational exposure, especially by needle stick injuries})
*Horizontal transmission among siblings.
*(Blood) Transfusion. {Not common due to screening of blood and its products}

Incubation period for acute hepatitis ranges from 6 weeks to 6 months, a bit long compared to hepatitis A and Hepatitis E viruses; but comparable to hepatitis C incubation period.

(Again, HBV enters through the Sodium taurocholate co-transporting polypeptide (**NTCP**), which is the same receptors used by Hepatitis D virus, will be discussed later)

**Symptoms**:

* Of Acute infection depends on the age of the patient, but generally there are flu like symptoms.
*patients developing active hepatitis will experience sign similar to Jaundice (Dark urine, clay colored stools, hepatomegaly,

## Prodromal phase:

*prolonged compared to hepatitis (A and E) In some patients it might last 2 weeks.
-Manifestations (in prodromal period): {fever (usually low-grade), malaise, fatigue, nausea and vomiting, anorexia, (sometimes right upper quadrant pain but can be associated with hepatomegaly)}

After the prodromal phase, the icteric phase occurs:
*Accompanied by jaundice, dark urine (usually precedes the presence of jaundice)
*lasts about 1month
*some patients might experience extra hepatic manifestations. Most likely due to immune system response (the disease is classified as an immune complex disease, and will give manifestations of serum sickness,

{which are the prototype of immune complex disease hypersensitivity reaction (type 3)}

- **HBV can cause both acute and chronic infections, with age as one of determinants of chronicity. Fulminant hepatitis can follow acute infection.**
- **In adults, the majority clear the infection and a minority develops chronic infection during which, hepatocyte damage occurs as a result of T cell mediated immune attack on hepatocytes expressing HBV antigens on the context of their HLA molecules.**

## Chronic Hepatitis B:

-Presence of hepatitis B surface antigen for more than 6 months - majority will have hepatitis B surface antigen positivity for the rest of their lives (unless there's some sort of a treatment)
-Majority, unless on treatment, will have a presence of nucleic acid in their blood, indicated by positive results in PCR.
- Age, again, is a very important factor and determinant of chronicity.
* For some of those who acquired chronic infection, there will be spontaneous resolution, especially in the elderly after the age of 40 years.
*If the infection is acquired before the age of **three**, large proportion will develop chronic infection. In contrast, the infection among the elderly will give rise to more severe acute manifestations but will be associated will a much lower likelihood of developing chronic infection.

### Pathogenesis:

*It seems that the virus does not inflict direct cytopathic injury into the cells and that the manifestations are mainly immune mediated.

**Resolution** depends on the presence of antibodies against multiple epitopes of the surface antigens
***Cytotoxic T lymphocytes** response is important in the clearance of infection.

## *Important point:

There is an association between chronic HBV infection and hepatocellular carcinoma.

*Multiple factors are proposed to link between the infection and the development of hepatocellular carcinoma.

*cause is still under investigation, but the strong association is linked to the integration of HBV DNA to hepatocytes', which are proposed to activate protooncogenes, or suppress certain growth regulation genes inside hepatocytes.

*Take home message: HBV is an oncovirus and is associated to hepatocellular carcinoma. (Just like the HCV is associated to hepatocellular carcinoma

## Diagnosis of HBV:

HB: Hepatitis B s: Surface e: Is a soluble antigen (indicates viral replication) c: Core
Ag: Antigen
Ab: Antibody

Clinical diagnosis of HBV cannot be achieved because acute hepatitis b share familiar features with all hepatitis viruses, it is almost impossible to diagnose the type of hepatitis base on the clinical features solely, usually there is a huge dependence on the lab markers such as: ○ Presence of nucleic acid by PCR (or NAT nucleic acid amplification test for blood screening/blood products)

○ Serological Markers and antigens (HBsAg / HBeAg / HBcAb / HBsAb/ HBeAb)

- After HBV infection, the first markers of the disease is viral DNA in the liver and plasma together with circulating HBsAg. High levels of viremia is followed by rise in the level of markers of hepatocyte damage (mainly
- ALT) and the appearance of clinical features (fever, malaise and jaundice).
- HBsAg becomes undetectable 1–2 months after the appearance of jaundice.
- The persistence of HBsAg beyond 6 months marks HBV chronicity.
- HBcAb appears within the first two weeks after the appearance of HBsAg and preceding HBsAb.

The first markers of the disease is the viral DNA in the liver and plasma Followed by HBsAg (after 3-4 weeks), these markers are especially important in recognizing a patient with Chronic HB infection, as Chronic HB infection is defined as continuance of having **evidence** of viral replication beyond 6 months from onset of infection. The most important factor connected to chronicity is **Age,** in younger individuals (children) there is a higher probability of developing chronic HB infection and a less probability of developing a strong acute infection, the **opposite is observed** in adults.

Serological Markers and antigens of the HB infection can help in identifying (and can be used in exam case questions) to differentiate between if the patient has an acute, chronic, previous infection, and can show if the patient was previously vaccinated (immunized).

Let's start with the HBsAg, this antigen can be detected in the serum of a patient with an acute or chronic infection, in acute the detection is viable after a short period of time from getting infected, the vaccine for HBV uses the recombinant HBsAg which will give the vaccinated patient antibodies to the HB surface antigen ONLY. HBsAg are detected 2-4 weeks before abnormalities that occur in the liver enzymes (like rise in the ALT 'Alanine amino transferase'), and 3-5 weeks before symptoms arise.

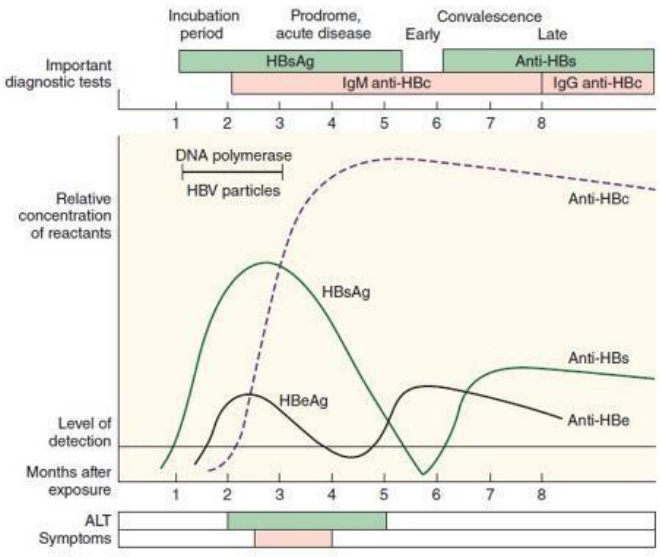
Moving on towards our second antigen HBeAg, it is a marker for active viral infectivity meaning the virus is active in replication and the patient has a higher load of virus, and the patient who is positive has an increased probability of transmitting the infection than those who are negative.

Coming after the first markers (viral DNA and HBsAg), we get our first serological marker (antibodies) anti HBcAb of the IgM class, that are present simultaneously with high levels of viremia which are followed by rise in the level of hepatocyte damage markers (Mainly ALT), and appearance of clinical features (fever malaise and jaundice). HBcAb (IgG) in addition to HBsAb are used to know if the patient was infected previously (Since the vaccine only presents the immune system with the HBsAg so if a patient had both **HBsAb AND HBcAb** this means he was infected in the past)

While HBcAb levels increase the HBsAg levels decrease and the second antibody HBsAb increase (until they are almost the same they cancel each other out) here we have a window period where serological testing (which uses an essay for total IgM and IgG) will only show HBcAb, this is extremely important in blood donations (where the donor is within the window period), blood screening is done for HIV 1 (M, N, O groups), HIV 2, Hepatitis C and Hepatitis B for two markers (HBsAg and anti HBcAb). Testing for HBcAb in the window period is also important for decreasing false negatives (when only testing for HBsAg and presuming that the patient doesn't have an infection while he is in the window period).

The second antibody anti HBsAb is important for the differentiation of acute and chronic infections, if HBsAb increases and HBsAg decreases (after the window period) the acute infection would have resolved without transforming to a chronic one, however if HBsAb doesn't appear and HBsAg continues this determines that the infection has transformed to a chronic infection.

The third Antibody anti HBeAb is developed in a group of people which will slowly decrease the amount of HBeAg and likewise decrease the infectivity of the patient.




The figure is a combination of serological and clinical events occurring in a patient with a Hepatitis B virus infection.
In green we see the concentration of HBsAg which increases with the onset of the disease and then decreases because of the increase of HBsAb and around at month 6 we have the window period.

- The window between the decline of HBsAg and rise of HBsAb is associated with HBcAB as the only serologic evidence of infection.

The lines below show how hepatocyte damage markers such as ALT and clinical symptoms arrive around the same time we detect HBcAb (which at first is IgM then according to the graph after 6 months we get IgG.

Finally in black we see the HBeAg which determines how infective the patient is then followed by the antibody HBeAb

- **Clearance is associated with the appearance of HBsAb.**
- **NAT is also available for screening blood/blood products**

**TABLE 35-8 Interpretation of Hepatitis B Virus Serologic Markers in Patients With Hepatitis[a]**

| Assay Results | | | |
|---|---|---|---|
| HBsAg | Anti-HBs | Anti-HBc | Interpretation |
| Positive | Negative | Negative | Early acute HBV infection. Confirmation is required to exclude nonspecific reactivity. |
| Positive | (±) | Positive | HBV infection, either acute or chronic. Differentiate with IgM anti-HBc. Determine level of replicative activity (infectivity) with HBeAg or HBV DNA. |
| Negative | Positive | Positive | Indicates previous HBV infection and immunity to hepatitis B. |
| Negative | Negative | Positive | Possibilities include HBV infection in remote past; "low-level" HBV carrier; "window" between disappearance of HBsAg and appearance of anti-HBs; or false-positive or nonspecific reaction. Investigate with IgM anti-HBc and HBV DNA. When present, anti-HBe helps validate the anti-HBc reactivity. |
| Negative | Negative | Negative | Never infected with HBV. Possibilities for liver injury include another infectious agent, toxic injury to the liver, disorder of immunity, hereditary disease of the liver, or disease of the biliary tract. |
| Negative | Positive | Negative | Successful vaccine response to HBV immunization. |

Anti-HBc, antibody to hepatitis B core antigen; anti-HBe, antibody to hepatitis B e antigen; anti-HBs, antibody to hepatitis B surface antigen (HBsAg); HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; IgM, immunoglobulin M.

[a]Modified and reproduced with permission from Hollinger FB: Hepatitis B virus. In Fields BN, Knipe DM, Howley PM (editors-in-chief). *Fields Virology*, 3rd ed. Lippincott-Raven, 1996.

This Table from Jawetz gives us a simpler way to deal with serological testing and case questions (hope it makes your life a tiny bit easier).

## Treatment of HBV:

- **Multiple options are available for treatment of chronic hepatitis B including IFNs and several nucleotide and nucleoside analogs with the goal of reducing the viral load to an undetectable level and to reach HBsAg clearance**

There is **no curative treatment** for the HBV infection, but it has a control associated with clearance of HBsAg but it doesn't remove the HBV from the

hepatocyte, regarding the acute infection usually the patients need supportive and symptomatic care.

As for chronic infection we give a group drugs, interferons and several nucleotide (adefovir, tenofovir) and nucleoside (lamivudine, entecavir) analogs, we usually get wanted response but we sometimes get **resistance** especially in lamivudine therapy, this resistance is caused by a mutation in the reverse transcriptase which will give the virus resistance (mutations in the HBV have a good chance in producing defective viruses (overlap in genome) so mutation levels in HBV is lower than RNA viruses but is higher than other DNA viruses).

These Drugs work to **suppress the viral replication** to stop progression of liver damage, cirrhosis and hepatocellular carcinoma, and to effectively reduce viral load to an undetectable level and to reach HBsAg clearance.

## Prevention of HBV:

**For prevention of HBV infection we have an effective vaccine (Recombinant HBsAg) that has been available from mid-1980s, with many countries worldwide implementing universal vaccination of infants** and also to health, it is given in 3 doses (at birth then after a month then 6 months after birth), if a skip has happened in one of the doses we stay on schedule the asses the amount of HBsAb (titer test) if higher than 10 then the patient is immune. The efficacy of the drug is about 90-95% and is effected by the immune make up to the vaccine.

Some HBV vaccine escape mutants were found to not be **neutralized** by HBsAb and were found to cause ill infection, and might not be screened by current essays (Since the mutation occurred to the HBsAg) this can be devastating if no improvements to our screening methods occur. (Thankfully they are rare but they have a surviving advantage).

# Hepatitis D (delta agent) Virus (HDV):

## Genome:

- HDV is known to be defective and require a helper function from 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.
- HDV is unique among human viruses, having an internal nucleocapsid comprising the genome surrounded by the delta antigen and enveloped by an outer protein coat of HBsAg.
- The genome consists of a single-stranded, circular RNA of around 1700 nucleotides, the delta antigen being encoded by antigenomic RNA

HDV is closely related to HBV, since HDV is a defective virus (needs a helper virus), that helper virus is HBV, HDV isn't from the same family as HBV and the differ in the type of genome (HDV is a RNA virus), the genome is a single stranded circular RNA of around 1700 nucleotides it is encoded by an antigenomic RNA (so it is a negative sense RNA).

## Structure and transmission:

It is an **enveloped virus** the envelope has HBsAg that it **uses to gain entry** to the hepatocytes by interaction by the same receptor (in HBV) which is the sodium taurocholate co-transporting polypeptide. If HDV entered a hepatocyte that isn't infected by HBV it won't be able to leave (it needs signals from the HBV and needs its HBsAg), even if it was able to leave it won't be able to reenter hepatocytes (it won't be able to cause infection since it doesn't have the HBsAg).

### Two Types of infection are described:

- **Co-infection:** Where a person who is susceptible to HBV is exposed to someone who is co-infected with HBV and delta virus, this results in acute coinfection with both the viruses at the same time.
- **Super-infection:** When an HBV carrier is exposed to infected blood from coinfected patients then the exposure results in super-infection of the existing HBV infection with delta virus; this may result in development of acute hepatitis (due to delta virus) in an HBV chronic carrier.

HDV needs either a cell already infected by HBV (on top of HBV) we call this **superinfection** which may result in acute hepatitis in a HBV chronic infected

patient, and can cause chronic HDV in up to 80% * of patients (super infection has a shorter incubation period).

*I was not exactly sure whether he said 80% OR 8%, but **trustworthy websites** (nih.gov, Cleveland clinic, etc) mentioned it AS **80%**. You can check yourself at almost 49:55

Or both HDV and HBV infect the cell together which we call **co-infection** which can cause an increase of probability of fulminant hepatitis causing severe liver damage and rapid liver failure, leading to hepatic encephalopathy, it also has a high mortality rate (in fulminant) 5% in coinfection). Both ways HDV needs HBV to be involved to provide it with HBsAg.

In general we see in HDV an increases in the risk, rate (can be as fast as two years in chronic hepatitis D), severity and progression of cirrhosis and hepatocellular carcinoma than that of HBV alone. (Also increase in fulminant hepatitis mortality can reach up to 80% # ). Thus it increases severity of symptoms, rate of progression, mortality rates etc.

# The doctor will be asked about the difference (5% and 80%), but I think he meant 80% in superinfection OR **chronic infection**

We find a resemblance between HBV and HBD in mode of transmission and risk factors (which is mainly the blood), so the risk is through sharing contaminated needles (**drug users**), and also **hemophiliacs**.

These diseases have been discovered lately (such as HCV which was discovered in 1989), so during the duration before being able to screen them as efficiently as today it was easy for the hepatitis infections (C, B, D) to spread.

## Epidemiology:

- Infection with HDV has a worldwide distribution, but two epidemiologic patterns exist.
- In Mediterranean countries (northern Africa, southern Europe, the Middle East), HDV infection is endemic among those with hepatitis B, and the disease is transmitted predominantly by non-percutaneous means, especially close personal contact.
- In non-endemic areas, such as the United States and northern Europe, HDV infection is confined to persons exposed frequently to blood and blood products, primarily injection drug users and hemophiliacs.
- The presence of HDV infection can be identified by demonstrating intrahepatic HDV antigen or anti-HDV Ab. Circulating HDV antigen, also diagnostic of acute infection, is detectable only briefly, if at all.

- Tests for the presence of HDV RNA are useful for determining the presence of ongoing HDV replication and relative infectivity.
- HDV prevalence is less than HBV, it has a worldwide distribution but two epidemiologic patterns exist:

**Endemic areas**: certain places in the world mainly concentrated in central Asia which has high injection drug use, also concentrated in some places in the Mediterranean countries (northern Africa, southern Europe, the Middle East) where it is endemic among those with HBV and transmitted mainly by nonpercutaneous means (not through the skin), and especially personal contact.

**Non-Endemic areas**: such as the United States and Northern Europe HDV infection is confined to persons exposed frequently to blood and blood products, primarily injection drug users and hemophiliacs.

## Diagnosis:

Usually by antigen detection wither by **enzyme immune essay** (ELISA) or **western blot** (for detection of proteins which is more sensitive than ELISA), we can also use nucleic acid detection using **RT-PCR** (Reverse transcriptase PCR) which is more precise to detecting the HDV virus

## Treatment:

**Lamivudine** is used to control the HB as treatment (since controlling HBV will inevitably control HDV).

## Prevention:

- **Delta hepatitis can be prevented by vaccinating HBVsusceptible persons with hepatitis B vaccine**

HDV **doesn't have a vaccine per se**, but using the HBV vaccine can prevent the infection with HDV

**Here are some review questions I was able to pile up, Good luck.**

1. HDV (delta agent) is found only in patients who have either acute or chronic infection with HBV. Which of the following is most correct?

(A) HDV is a defective mutant of HBV.

(B) HDV depends on HBV surface antigen for virion formation.

(C) HDV induces an immune response indistinguishable from that induced by HBV.

(D) HDV is related to HCV.

(E) HDV contains a circular DNA genome.

2. 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 HBsAgpositive carriers.

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

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

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

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

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

4. A 35-year-old man addicted to intravenous drugs has been a carrier of HBsAg for 10 years. He suddenly develops acute fulminant hepatitis and dies within 10 days. Which of the following laboratory tests would contribute most to diagnosis?

(A) Anti-HBs antibody

(B) HBeAg

(C) Anti-HBc antibody

(D) Anti-delta virus antibody

Answers
1. B
2. A
3. C
4. D

This is another table just in case

| | HBsAg HBeAg* HBV-DNA | HBcAb IgM | HBcAb IgG | HBeAb | HBsAb |
|---|---|---|---|---|---|
| Acute infection | + | + | – | – | – |
| Window period | – | +/– | + | + | – |
| Prior infection | – | – | + | + | + |
| Immunization | – | – | – | – | + |
| Chronic infection | + | – | + | +/– | – |