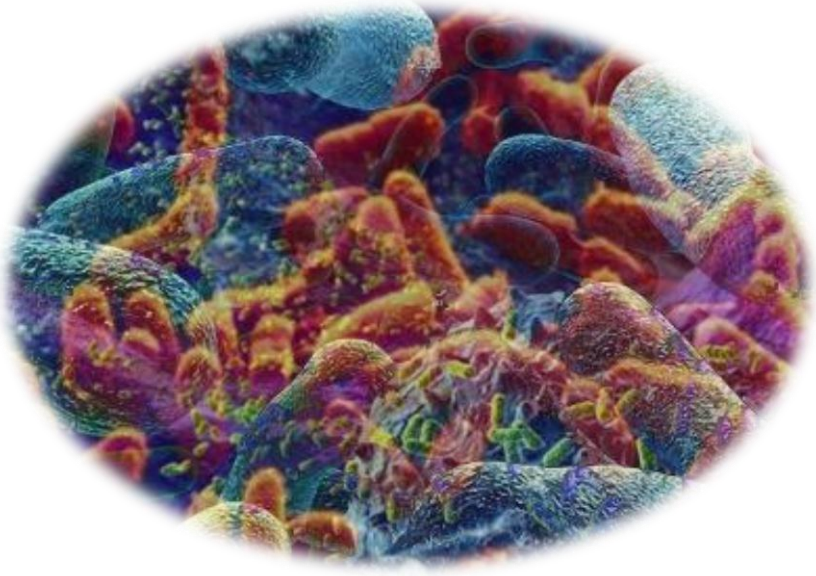
431 Microbiology Team

Blood Borne Hepatitis

GIT & HAEMATOLOGY BLOCK



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Blood Borne Hepatitis

- Hepatitis feature of many diseases usually as a part of a generalized infection e.g. cytomegalovirus, yellow fever, Epstein-Barr virus.
- **However, some viruses primarily target the liver to cause viral hepatitis**.
- Viral Hepatitis presents more or less **similar clinical picture** whatever the causative viruses.
- Laboratory tests can differentiate between different viruses.
- We have to determine the causative virus to know how **to treat** and what the **prognosis.**

Viral Hepatitis:

- **Enterically transmitted viral Hepatitis***(Fecal-oral route)***:** Hepatitis A & Hepatitis E
- **Parenterally Transmitted** *(Blood Borne)* **viral Hepatitis:** Hepatitis B, Hepatitis D (Defective), Hepatitis C and Hepatitis G

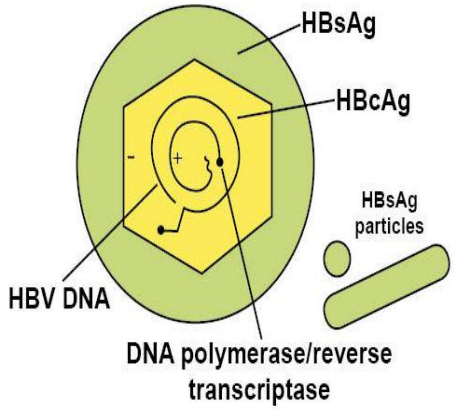
Hepatitis B Virus:

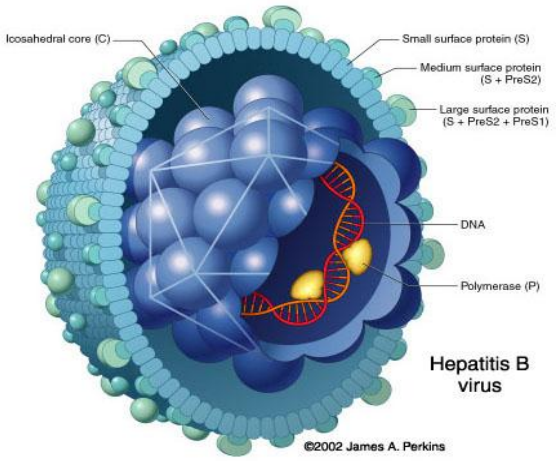
- **Infection with** HEPATITIS B VIRUS (HBV)
- **Can result in:**
  - Acute hepatitis
  - Acute fulminant hepatitis *(massive destruction NECROSIS of all liver cells and death occurrence is 100%)*
  - Chronic asymptomatic carrier *(carrying the virus without the symptoms)*
  - Chronic persistent hepatitis
  - Chronic active hepatitis → cirrhosis → hepatocellular carcinoma.
- HBV replicates in **HEPATOCYTES** and possibly the entire genome can be integrated into the host genome.

HBV Classification & Structure:

- ***Family****:* hepadnaviridae.
- The complete virus particle is 42-nm in diameter
- It consists of an outer envelope containing **hepatitis B surface antigen (HBsAg)** *(This is detected in the patient serum* **'Marker'***)*
- And internal core (nucleocapsid) composed of hepatitis B core antigen **(HBcAg)**
- The viral genome is small partially circular **ds-DNA**
- There are eight known genotypes (A – H)
- **Genotype D is the dominant in Saudi patients**
- The virus contains the **reverse transcriptase** and **polymerase** enzymes

Numbers are not included

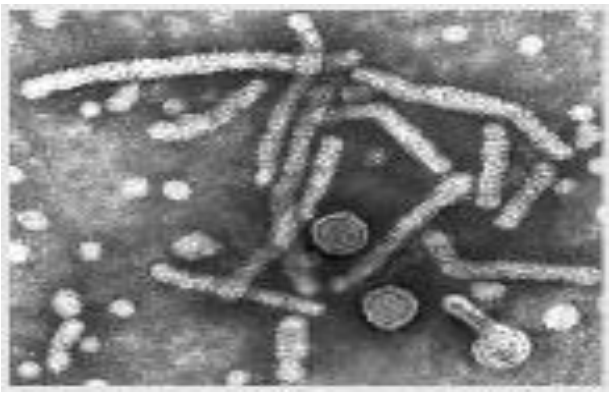




Types of HBV particles:

- *The serum of infected individual contains three types of hepatitis B particles:*
- Large number of small spherical free HBsAg particles.
- Some of these HBsAg particles are linked together to take the form of filaments
- In addition to the complete HBV-particles (Dane particles)
- There are 8 known genotypes (A-H), Genotype D is the dominant in Saudi patients

Electron Micrograph Of Particles In The Blood Of A Patient Infected With HBV:



This Picture Might Come In The Practical:

- Identify it: DNA Virus e.g. Hepatitis B Virus
- Small circles: HBsAg (detection)
- Cylindrical shapes: HBsAg linked together
- Big Circles "Dane particles": complete HBV-particles

<u>Stability of HBV</u>

- Heating up to 60c for **<u>10 hours inactivates</u>** the virus.
- Treatment with hypochlorite (10 000ppm available chlorine) or 2% glutaraldehyde for **<u>10 min</u>** will inactivate virus.
- **HBV** resist treatment with ether, low pH, Freezing and moderate heating.

HBV is very stable resistant to atmosphere

e.g. infected person could bleed and the Virus in his blood will be activated even after several hours and infect other people

Transmission of HBV:

1- Infected blood (parenteral:

- Direct exposure to infected blood. *(Blood transfusion, accidents..etc.)*
- Using contaminated needles, syringes, dental and surgical instruments
- Using contaminated instruments in the practice of tattooing, body piercing, cupping, etc.
- Sharing contaminated toothbrushes, razors, cuticle scissors and nail clippers.

2- Sexually

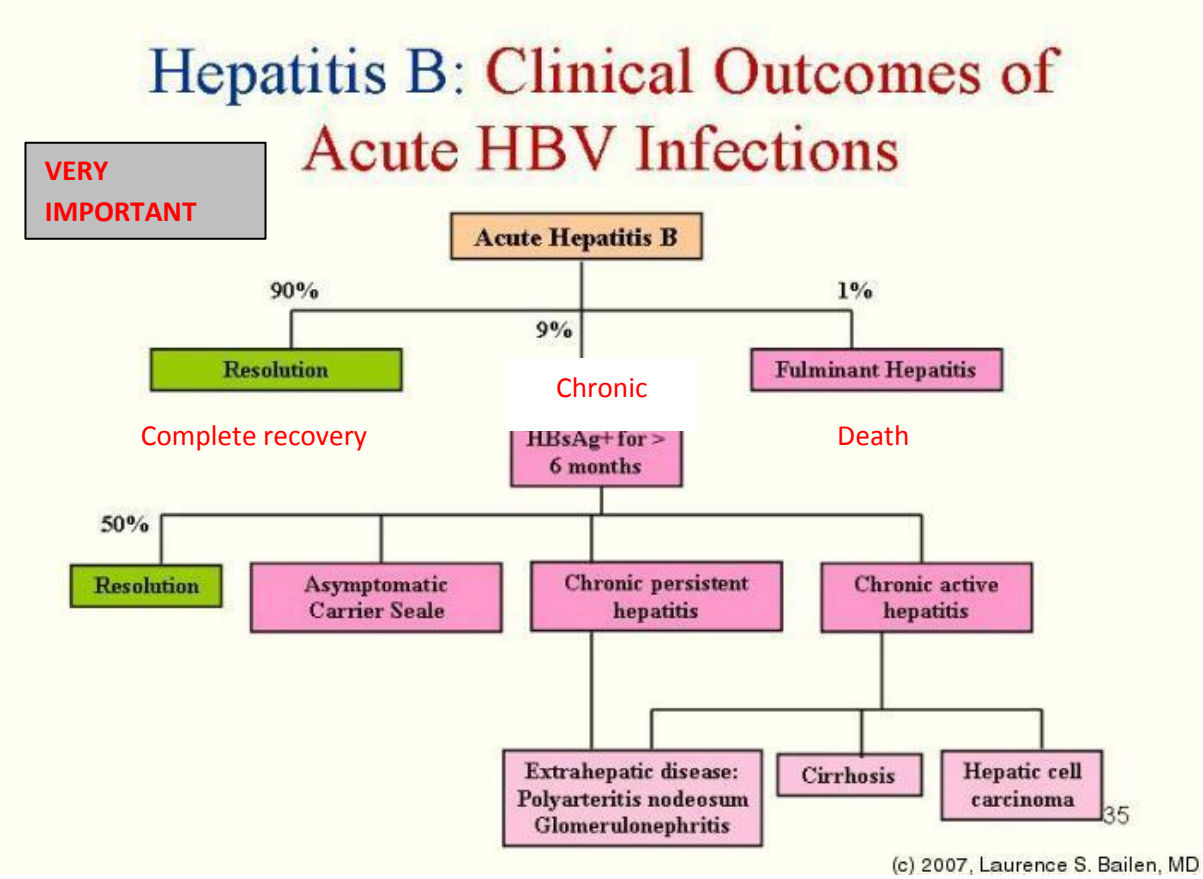
- By having sexual contacts with infected person, virus is present in semen and vaginal secretion.

3- from mother to child

- Mostly (**prenatally** *[during labor or after]*) during delivery, nursing, breast feeding and less likely through placenta **(vertical transmission)**

The following groups are at high risk of acquiring hepatitis B

- Intravenously drug users.
- Hemodialysis patients.
- Patients receiving clotting factors. *(Hemophilic patients because they take factor 8 from another person similar to blood transfusiun)*
- Individuals with multiple sexual partners.
- Recipient of blood transfusion, before **1992.**
- Health care workers with frequent blood contact.
- Individuals exposed to risk factors such as tattooing, body piercing and cupping



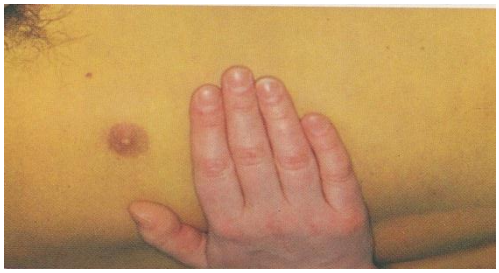
The clinical outcome of HBV infection

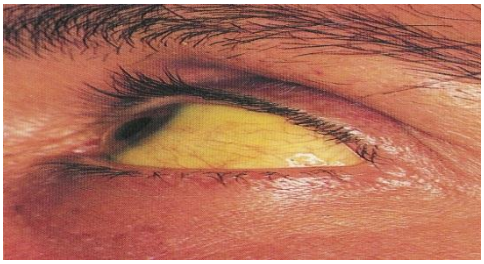
- About **90%**f infected individuals will develop acute hepatitis B infection and recover completely *(to know if the patient has recovered completely check in serum for)* →**(Anti- HB sAg)**

- About **9%** of the infected adult will become chronic hepatitis, **90% of infected infants** born to mother who are **(HBeAg +ve)** will progress to chronic hepatitis, and 20% of infected children will progress to chronic hepatitis
- Less than 1% will develop fulminant hepatitis with massive liver necrosis, liver failure and death.

Clinical Picture Of Acute Hepatitis B Infection

- Incubation period varies from 1→6 months
- 70% of infected patient will be asymptomatic *(no symptoms)* or having subclinical symptoms *(not specific)* prodromal phase as:
  - **An-icteric** *(no jaundice)* **hepatitis:** *fever*, malaise, anorexia, rash, nausea, vomiting and high upper quadrant abdominal pain with raised liver enzyme.
  - **Icteric hepatitis:** about 25% of the patient becomes icteric (Jaundice) with raised bilirubin, **dark urine** containing bile and **pale stools**.





- 90% acute hepatitis B infection last for several weeks to maximally 6 months.

Hepatitis B markers

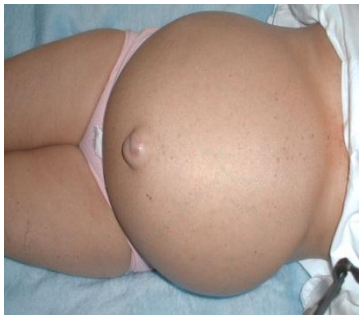
Types	Description
HBV DNA	Marker of infection *(First Marker that appear in serum after infection) Need PCR to detect*
Hepatitis B surface antigen (HBsAg)	Marker of infection (ELISA)
Hepatitis B e antigen (HBeAg)	Marker of active virus replication, the patient is highly infectious, the virus is present in all body fluids.
Antibody to hepatitis B e antigen (Anti-HBe)	Marker of low infectivity, the patient is less infectious *(Patient is recovering)*
Antibody to hepatitis B core (Anti-HBc)	Marker of exposure to hepatitis B infection
Antibody to hepatitis B surface antigen (Anti-HBs)	Marker of immunity *(patient is immune)*

Chronic asymptomatic hepatitis B infection (9%)

- **Chronic hepatitis B** is defined by the presence of **HBsAg** or **HBV-DNA** in the blood for more than> 6 months.
- The majority of patients with chronic hepatitis B are **asymptomatic** may only be detected by elevated liver enzyme on a routine blood chemistry profile, some have mild fatigue, Right upper quadrant abdominal pain or enlarged liver &spleen

Chronic active hepatitis

The major long-term risk of chronic HBV infection is **cirrhosis** with **hepatic failure** and **hepatocellular carcinoma**

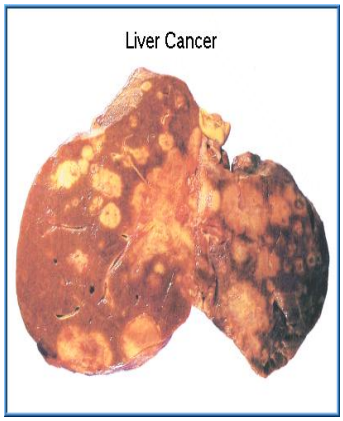


Cirrhosis

- A chronic diffuse liver disease.
- Characterized by fibrosis and nodular formation.
- Results from liver cell necrosis and the collapse of hepatic lobules.

Symptoms include: ascites, coagulopathy (bleeding disorder), portal hypertension, and hepatic encephalopathy, vomiting blood, weakness, and weight loss.

Hepatocellular carcinoma (HCC)

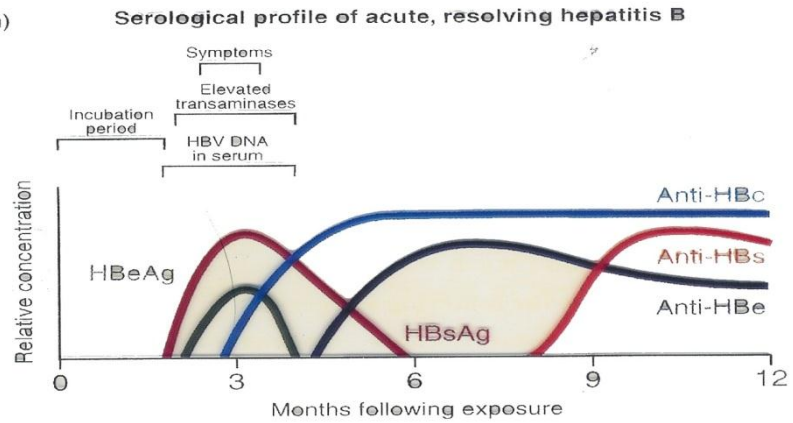


- One of the most common cancers in the world. Also, one of the most deadly cancers if not treated.
- Hepatitis B and C viruses are the leading cause of chronic liver diseases.
- Symptoms include: abdominal pain, abdominal swelling, weights loss, anorexia, vomiting, and jaundice.
- Physical examination reveals hepatomegaly, splenomegaly and ascites.

I won't ask you about it (Cirrhosis and HCC) it's just for you information – Dr. Mona

Serological profile of acute HBV infection

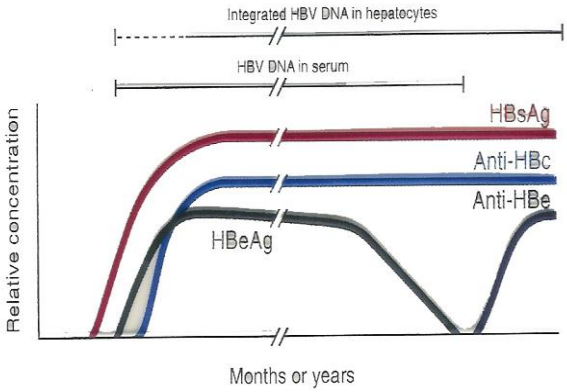
- **Hepatitis B- DNA** is the **first marker** that appears in circulation, 3-4 weeks after infection **(PCR)**
- **Hepatitis B surface antigen (HBsAg)** is the second marker that appears in the blood and persists for less than 6 months, then disappears.
- **Hepatitis B e-antigen (HBeAg)** is the third maker that appears in circulation and disappears before HBsAg
- **Anti-HBcore Ag IgM** is the first antibody that appears in the blood and Followed by Anti-HB coreAg **IgG** which persists for several years
- **Anti HBeAg:**
  With the disappearance of HBeAg, anti-HBeAg appears and usually persists for several weeks to several months
- **Anti HBsAg**
  Anti-HBs is the last marker that appears in the blood, **marker of immunity.**



Serological profile of chronic HBV infection

- Chronic hepatitis B infection is defined by the presence of HBV-DNA or HBsAg in the blood for > 6 months.
- **HBsAg** may <u>persist in the blood for life.</u>
- After disappearance of HBsAg, anti-HBs Ab appear and persist for several years.

b) Serological profile of chronic hepatitis B with seroconversion



Lab diagnosis of hepatitis B infection

<u>Hepatitis B infection is diagnosed by</u> detection of
HBsAg in the blood (ELISA)

- Positive results must be **repeated in <u>duplicate</u>**
- Repeatedly reactive results must be confirmed by neutralization test

Additional lab investigations:
1- Liver function tests (LFT)
2- Ultrasound of the liver
3- Liver biopsy, to determine the severity of the diseases

Prevention and Control of HBV:

- Proper screening of blood donor and use of plastic syringe.
- **<u>Pre-exposure prophylaxis:</u>**
  Active vaccination given to all newborn, children or adult
- **<u>Post exposure prophylaxis</u>**.
  Persons exposed to needle prick or infant born to **HBsAg +ve** mother should immediately receive → **Active Vaccine & Hepatitis B specific immunoglobulin**

Hepatitis B Vaccine

- It contains highly purified preparation of HBsAg particles, produced by <u>genetic engineering in yeast</u> (it's not attenuated nor killed vaccine)
- The vaccine is administered by IM injection in three dosages at 0, 1 & 6 months then booster dose after 5 years; the vaccine is safe and protective.

HBV treatment

<u>Criteria for treatment:</u>

- Treatment is limited to patients having chronic hepatitis B, based on liver biopsy.
- Positive for HBsAg
- Positive for HBV-DNA, > 20,000 IU/ml
- **ALT** (Alanine aminotransferase) > twice the upper normal limit.
- Moderate liver damage
- Age > 18 years

Treatment:

- The hepatitis B infection does not usually require treatment because most adults <u>clear the infection</u> spontaneously.
- On the other hand, treatment of chronic infection may be necessary to **reduce the risk of cirrhosis** and liver cancer. Chronically infected individuals with persistently elevated serum alanine aminotransferase, a marker of liver damage, and HBV DNA levels are

candidates for therapy. **Treatment lasts from six months** to a year, depending on medication and genotype.

- Antiviral drugs as Lamivudine or Adefovir and Iinterferon are used.

- ***There are several approved anti-viral drugs.***

  1- pegylated alpha interferon, one injection per week, for 6- 12 months

  2- Lamivudine, nucleoside analogue

  3- Adefovir, nucleoside analogue

Won't be asking about the drugs – Dr. Mona

Hepatitis D virus (delta virus)

- It is a defective virus *(why?),* that cannot replicates by its own it requires HBV to replicate
- It transfers in the same way as HBV
- HDV is small ss-RNAgenome
- Diagnosis by detection of Anti-HDV antibodies

Types of HDV infections:

- ***1- Co-infection:***
  - The patient is infected with HBV and HDV at the same time leading to severe acute hepatitis
  - Prognosis: recovery is usual.
- ***2- Super infection:***

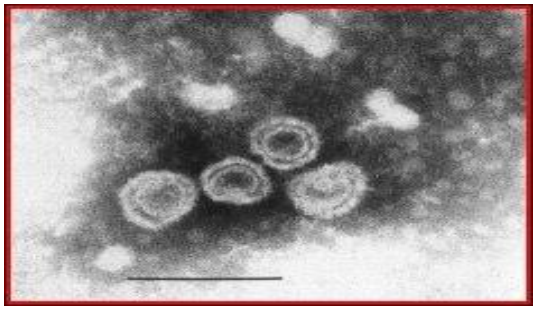
In this case, delta virus infects those who are already having chronic hepatitis B leading to severe chronic hepatitis

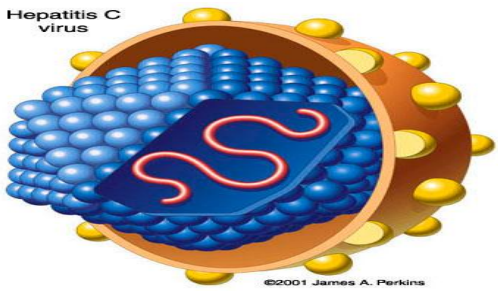
Hepatitis C virus

Classification & structure:

- Family: *Flaviviridae.*
- Genus: *hepacivirus.*
- The virus is small, 60 – 80 nm in diameter.
- Consists of an outer envelope, icosahedral core and linear positive polarity ss-RNA gemone.
- There are 6 major genotypes (1 – 6), genotype 4 is the dominant in Saudi patients.
- **HCV is extremely heterogeneous and has a high mutation rate**

HCV was previously named as Non-A Non-B for 30 years





Transmission of HCV

1- Parenterally:

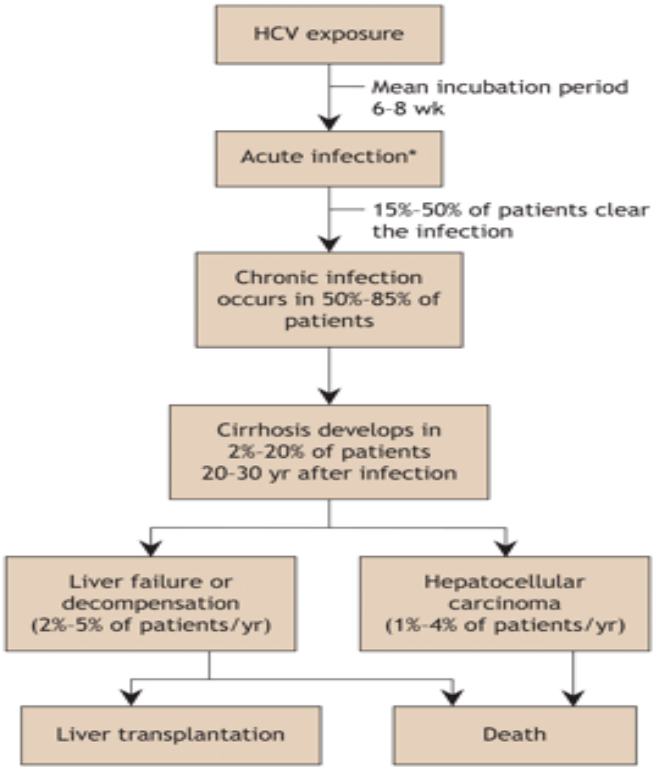
- Direct exposure to infected blood.
- Using contaminate needles, surgical instruments.
- Using contaminate instruments in the practice of tattooing, ear piercing & cupping.
- Sharing contaminated razors 7 tooth brushes.

2-Sexually.

3- From mother to child perinatally

The clinical outcome of HCV infection

- About 20 % of the infected individuals will develop self-limiting acute hepatitis C and recover completely.
- About 80 % of the infected will progress to chronic hepatitis C
- < 1 % will develop fulminant hepatitis C, liver failure and death.



Hepatitis C markers:

1- Hepatitis C Virus RNA

- Is the 1st marker that appears in circulation, it appears as early as 2-3 weeks after exposure the (incubation period 4- 6 weeks), It is a *marker of infection.*

2- Hepatitis C Core Antigen

- The 2nd marker that appears in the blood, usually 3-4 weeks after exposure. Marker of infection

3- IgG Antibody To Hepatitis C.

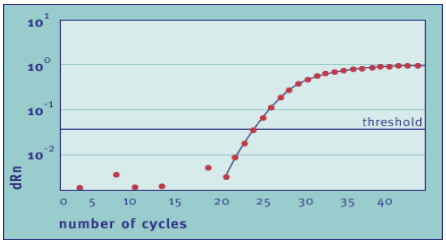
- Antibodies to hepatitis C virus is the last marker that appears in the blood, usually appear 50 days after exposure (long window period)

Lab Diagnosis of HCV infection:

- **By detection of both:**

1- Antibody to HCV in the blood by ELISA, if positive the result must be confirmed by RIBA or PCR

2- HCV-RNA in the blood using PCR



Treatment of HCV and Vaccination:

- The currently used treatment is the combined therapy using: Pegylated alpha interferon and ribavirin. **NO VACCINE AVAILABLE TO HEPATITIS C**
- **Criteria for treatment:**
  - Positive for HCV-RNA.
  - Positive for anti-HCV.
  - Known HCV genotype.
  - ALT > twice the upper normal limit.
  - Moderate liver damage based on liver biopsy.

Hepatitis G virus

- Hepatitis G virus or GB-virus was discovered in 1995.
- Share about 80% sequence homology with HCV.
- Family: *Flaviviridae*, genus: *Hepacivirus.*
- Enveloped, ss-RNA with positive polarity.
- Parenterally, sexual and from mother to child transmission have been reported.
- Causes mild acute and chronic hepatitis infection.
- Usually occurs as co-infection with HCV, HBV and HIV.

Summary (MOST IMPORTANT POINTS)

- All (C, D and G) viruses have the same genome (ss-RNA) EXCEPT B virus which is (ds-DNA).
- All of them have the same route of transmission which are:
  1- Parentally = blood borne.
  2- Sexually.
  3- From mother to child: Mostly during delivery or breast feeding.

(HBV)

- HBV has envelop consist of Hepatitis B surface Antigen (HBsAg); It's a marker of infection.
- In B virus: The genotype D is dominant in Saudi patients.
- When we identify the marker of Hepatitis B by Electron microscope (EM), we'll find 3 shapes:
  1- Dane particles (Complete virus).
  2- Small spherical HBsAg particles.
  3- HBsAg particles linked together forming filaments.

- HB virus is very stable resistant to atmosphere (Highly infectious).
- The clinical outcomes of Hepatitis B virus:
  1- Resolution (complete recovery) : 90%
  2- OR Fulminant hepatitis → Death
  3- If HBsAg become positive (+) for > 6 months → Chronic hepatitis.

- The incubation period of Acute hepatitis B infection is **1 – 6 months**.
- First marker appears in the serum of HBV patient is (HB-DNA).
- Antibody – HBsAg = Marker of IMMUNITY.
- Antibody – Hb core Ag = Marker of EXPOSURE.
- HBeAg = Marker of highly infectious patient and exist in all body fluids.
- Chronic hepatitis B infection is defined by the presence of HBV-DNA or HBsAg in the blood for > 6 months.

- To know the patient is completely recovered we have to find (Anti – HbsAg) in the serum.
- 90 % of infected infants born to mothers who are POSITIVE to (HBeAg) and (HBsAg) together, they will progress to chronic hepatitis.

- Prevention and Control of HBV:

➢ Proper screening of blood donor and use of plastic syringe.
➢ Pre-exposure prophylaxis:
Active vaccination given to all newborn, children or adult
➢ Post exposure prophylaxis.
Persons exposed to needle prick or infant born to HBsAg +ve mother should immediately receive → Active Vaccine & Hepatitis B specific immunoglobulin.

(HDV)

- It's a DEFECTIVE virus because it'll not produce any infection by itself, so it must be co-infection with HBV or super-infection.
- Diagnosis by detection of Anti-HDV antibodies through (ELISA).

(HCV)

- HCV is extremely heterogeneous and has a high mutation rate.
- There are 6 genotypes; Genotype 4 is the most dominant in saudi Arabia.
- Clinical outcomes of HCV:
  1- About 20 % will recover completely.
  2- About 80 % will progress to chronic hepatitis C.
  3- < 1 % → Fulminant hepatitis C which is FATAL.
- Incubation period = 6 – 8 weeks (Less than IP for HBV).
- **Hepatitis C virus RNA**: 1st marker appears in serum (MARKER OF INFECTION).
- **IgG Antibody to Hepatitis C**: Last marker appears in serum after exposure.
- Hepatitis C core Antigen: (MARKER OF INFECTION).
- Lab Diagnosis of HCV infection:
  - **By detection of both:**

1- Antibody to HCV in the blood by ELISA, if positive the result must be confirmed by RIBA or PCR
2- HCV-RNA in the blood using PCR

- The currently used treatment is the combined therapy using: Pegylated alpha interferon and ribavirin
- NO VACCINE.

Questions

1- A patient diagnosed with hepatitis B virus infection, the first marker that appears in the serum is…….:
   A- HBsAg.
   B- HB-DNA.
   C- HB core Ag.
   D- HBeAg.

2- A dentist exposed to blood of a patient while he treated him, the patient has HBV infection. The symptoms of infection will appear on dentist after about:
   A- (1 – 6 days).
   B- (1 – 6 weeks).
   C- (3 – 4 months).
   D- (1 – 6 months).

3- An infant born to mother who is positive to "HBeAg" and "HBsAg", we'll expect the infant to have:
   A- Hepatocellular carcinoma.
   B- Liver cirrhosis.
   C- Chronic hepatitis B.
   D- Acute hepatitis B.

4- The virus that always comes with HBV, also it's a defective virus:
   A- HBV.
   B- HCV.
   C- HDV.
   D- HGV.

5- The last marker appears after exposure to HCV is:
   A- Hepatitis C virus RNA.
   B- Hepatitis C core Antigen.
   C- HBsAg.
   D- IgG Antibody to hepatitis C.

Answers:
1 → B 2 → D
3 → C 4 → C
5 → D