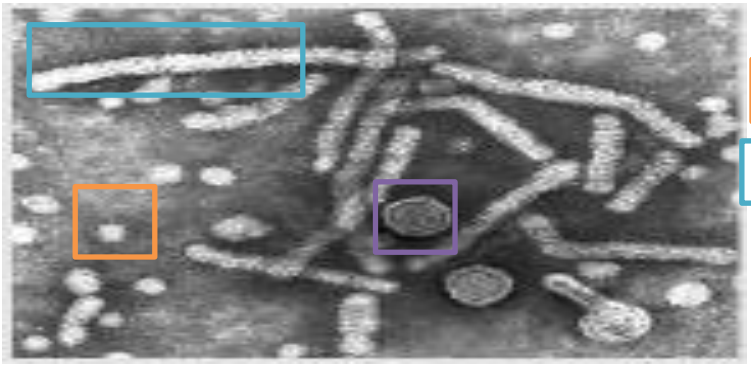
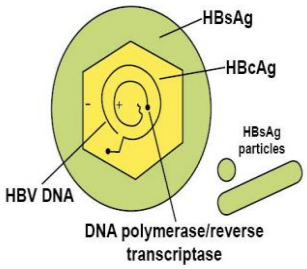
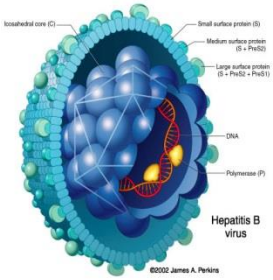
Hepatitis
B – C – D - G

microBiology
434

Viral Hepatitis : Hepatitis = inflammation of liver cells

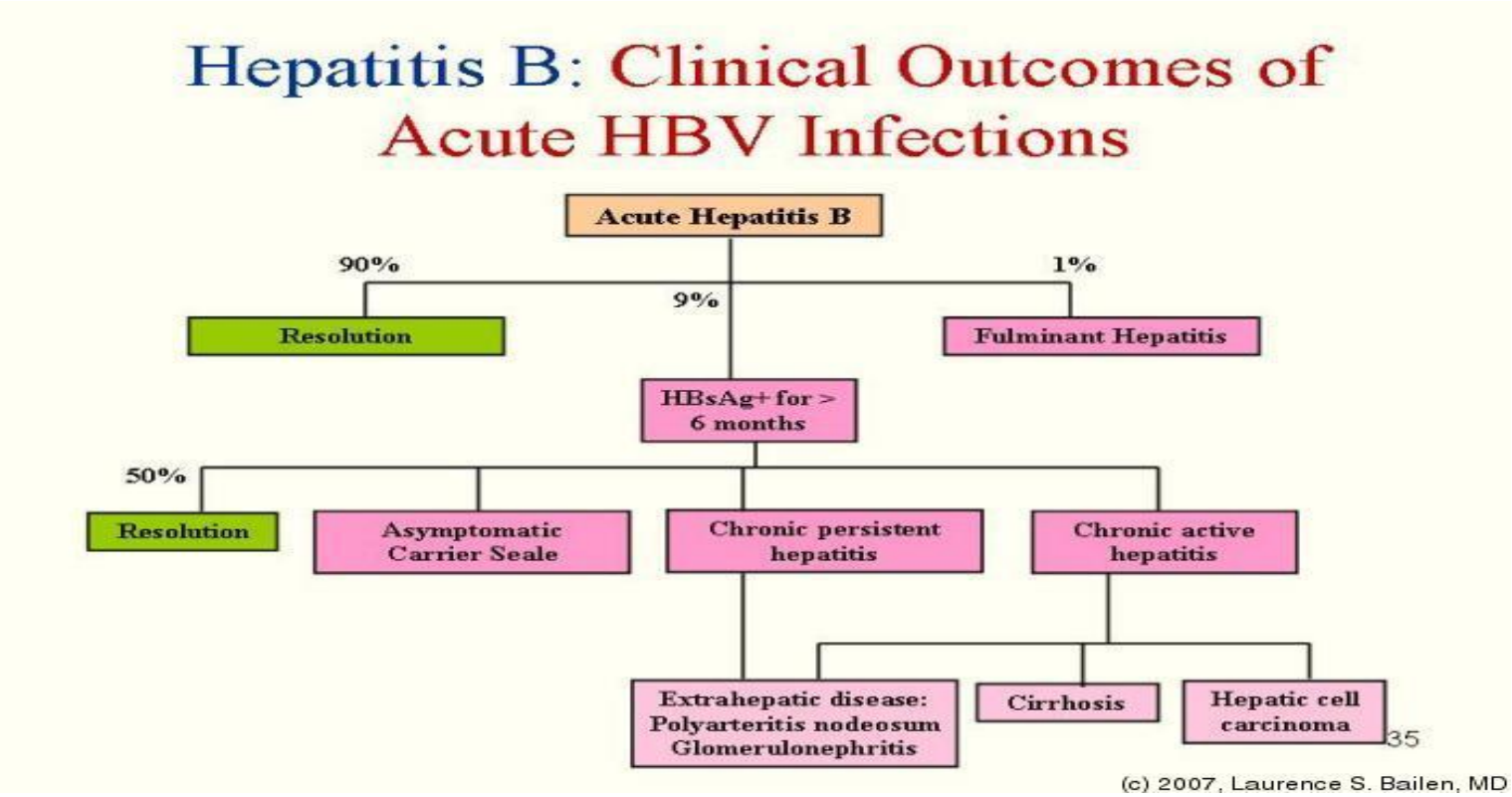
- Hepatitis feature of many diseases usually as a part of a **generalized infection** e.g. **CMV – YFV - EBV**
- However, some viruses primarily targeting the liver to cause viral Hepatitis, viral hepatitis presents more or less **similar clinical picture** whatever the causative viruses.
- **Laboratory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

- **Viral hepatitis is divided into two large groups, based on the mode of transmission:**
  a) **Enterically or water born hepatiti (fecal- oral route) :** HAV & HEV
  b) **Parenteral (blood-to-blood)** : HBV - HCV was known as non-A non-B hepatitis - HDV(**Defective virus**) & HGV

	HBV [hepadnaviridae]
Constitutes of the VIRION	• **Outer envelope** [containing hepatitis B surface antigen] → **(HBsAg).** • **Internal core** (nucleocapsid)[composed of hepatitis B core antigen]→ **(HBcAg**). • The viral genome which is **small** partially circular **ds-DNA.** • There are **8** genotype (A-H)- [genotype **D** is dominant in Saudi Arabia] • The virus contains the **2 enzymes reverse transcriptase & protease enzyme**. • **The serum of infected individual contains three types of hepatitis B particles**: 1. Large number of small spherical free **HBsAg** particles. 2. Some of these **HBsAg** particles are linked together to form **filaments**. 3. The **complete** HBV particles → (**Dane particles**).  Electron micrograph of particles in the blood of a patient infected with HBV  
Transmittion	**1-Parentally:** • Direct exposure to infected **blood or body fluids** (e.g. receiving blood from infected donor). • Using contaminated or not adequately sterilized tools in **surgical or cosmetic practice** (dental, tattooing, body piercing). • Sharing contaminated needles, razors, or tooth brushes. **2- Sexually (unprotected sex):** • The virus is present in **blood and body fluids**. By having sexual contacts with infected person ,virus is present in **semen and vaginal secretion.** **3- From mother to the fetus :** • Mostly(**perinatally**) during **delivery ,nursing ,breast feeding** and less likely through **placenta (vertical transmission) .**
Risk factors	Intravenously drug users - Hemodialysis patients - Patients receiving clotting factors - 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 %** of infected adults will develop **acute hepatitis B infection** and **recover completely**.
- **<9 %of** the infected **adult**, **90%** of infected **infants** and **20%** of infected **children** may progress to **chronic hepatitis B**.
- **< 1 %** may develop **fulminant hepatitis B**, characterized by massive liver necrosis, liver failure and death



Hepatitis B markers and serelogical profile

Types	Description	Serological profile
HBV DNA	Marker of infection, contiguous.	1st marker that appears in circulation, 3-4 weeks after infection.
Hepatitis B surface antigen **(HBsAg)**	Marker of infection, contagious .	the 2nd marker that appears in the blood and persists up to 6 months, then disappears.
Hepatitis B e antigen **(HBeAg)**	Marker of active virus replication, the patient is highly infectious, the virus is present in all body fluids, highly contiguous.	the 3rd maker that appears in circulation and disappears before the disappearance of HBsAg.
Antibody to hepatitis B e antigen **(Anti-HBe)**	Marker of low infectivity, the patient is less infectious, contiguous.	appears with the disappearance of HBeAg, and usually persists for several weeks to several months.
Antibody to hepatitis B core **(Anti-HBc)**	Marker of exposure to hepatitis B infection,contigous.	the 1st antibody that appears in the blood and usually persists for several years.
Antibody to hepatitis B surface antigen **(Anti-HBs)**	Marker of immunity.NOT CONTIGOUS.	is the last marker that appears in the blood, It appears few weeks after disappearance of HBsAg and persists for several years, It indicates immunity to hepatitis B infection.

Acute hepatitis B infection:

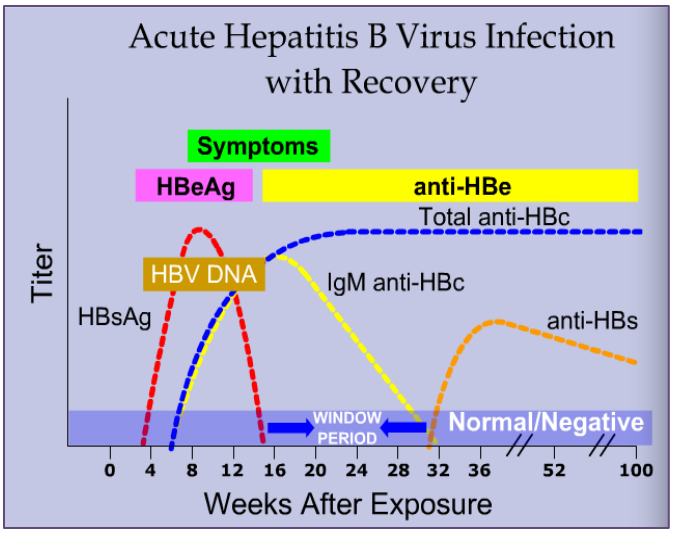
- Incubation period varies from [2m - up to 4m]
- Most acute hepatitis B & C are **asymptomatic or anicteric.**

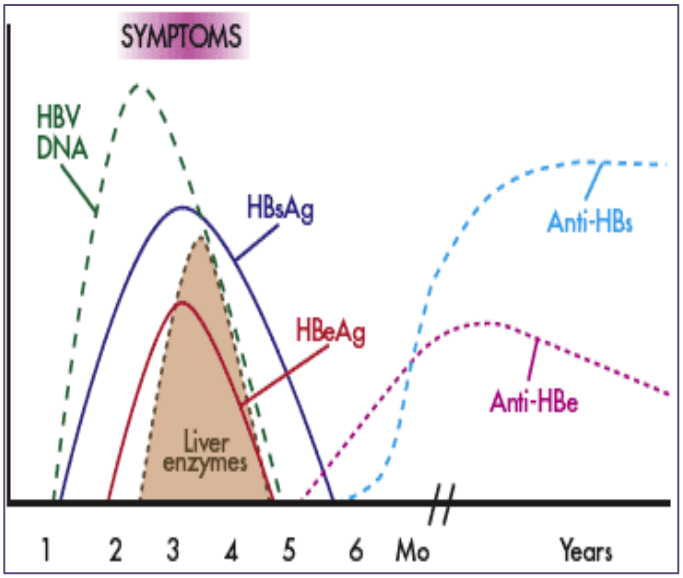
Clinical presentation:

1- Anicteric phase: **Low grade fever** – anorexia – malaise – nausea - vomiting - pain at the **right upper** quadrant of the abdomen - **raised liver enzyme.**

2- Icteric phase (25%): which is characterized by jaundice - **raised** bilirubin leading - **dark** urine and pale stool.

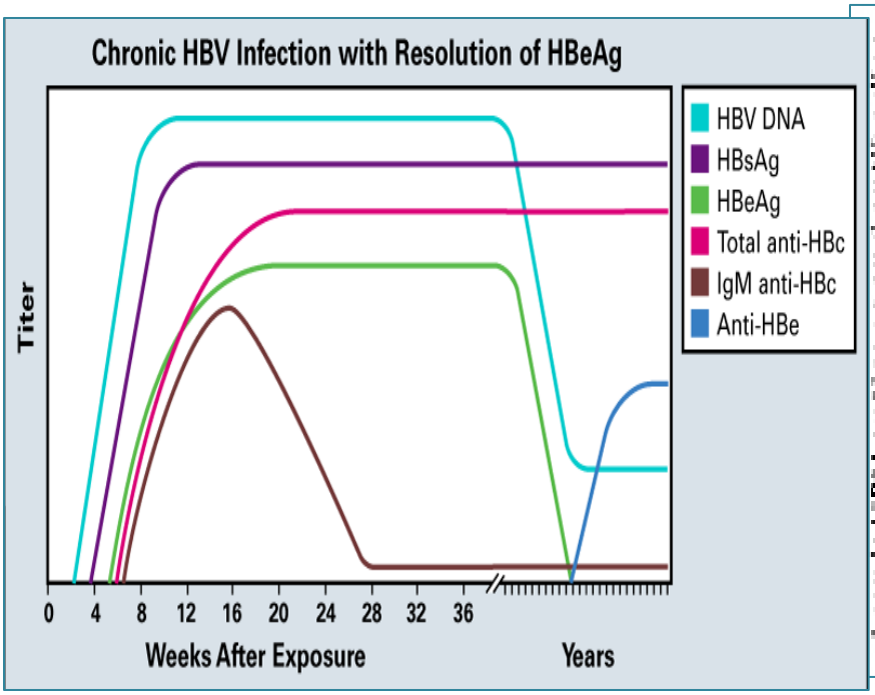
- Hepatitis **B DNA** is the **1st** marker that appears in circulation, 3-4 weeks after infection.
- **HBsAg** is the 2nd marker that appears in the blood and persists up to 6 months, then disappears.
- **HBeAg** is the 3rd maker that appears in circulation and disappears before the disappearance of **HBsAg**.
- **Anti-HBc Ab** is the 1st antibody that appears in the blood and usually persists for several years.
- with the disappearance of HBeAg, anti-HBe appears and usually persists for several weeks to several months.
- **Anti-HBsAg (Anti-HBs) is the last marker that appears in the blood, It appears few weeks after disappearance of HBsAg and persists for several years, It indicates immunity to hepatitis B infection.**

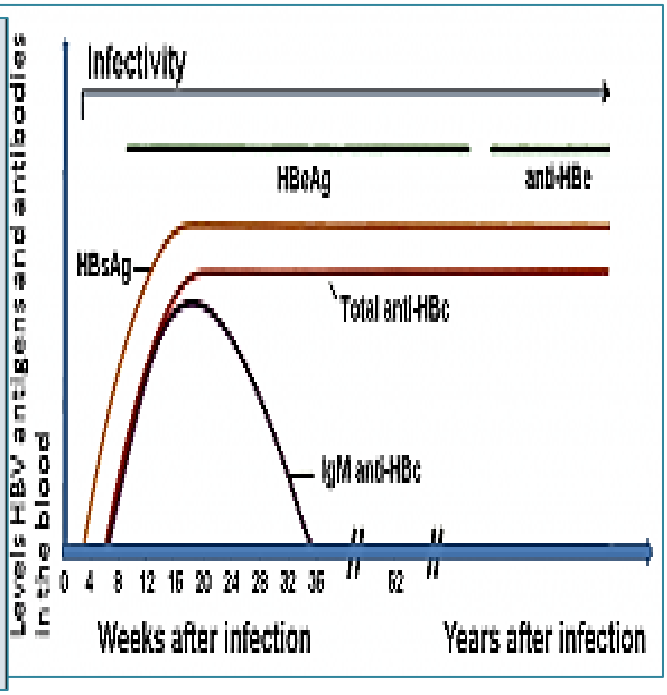




Chronic hepatitis infection:

- **Chronic** hepatitis is limited to hepatitis **B, C , D and may be G** viruses.
- The majority of patients with chronic hepatitis B are **asymptomatic** may only be detected by **elevated liver enzymes** on a routine blood chemistry profile , some have mild fatigue, right upper quadrant abdominal pain or enlarged liver &spleen. Jaundice may or may not developed.
- Chronic hepatitis B is defined by **the presence of HBsAg or HBV-DNA in the blood for > 6 months.**





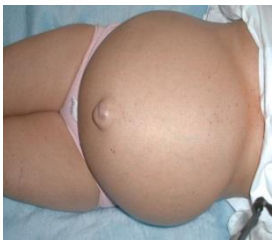
* **Chronic** hepatitis B infection is defined by the presence of **HBsAg** in the blood for more than 6-momths .

***HBsAg** may persists in the blood for life

*Some patients may clear HBsAg after the 6 monthes and develop anti hepatitis surface antigen **(Anti-HBs)** ,they become immune. [cured]

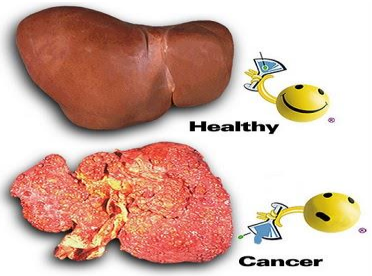
The major long term risk of chronic HBV infection are **cirrhosis with hepatic failure** and **hepatocellular carcinoma**, when HBV genome integrates into hepatocytes DNA.

Cirrhosis: [for reading]

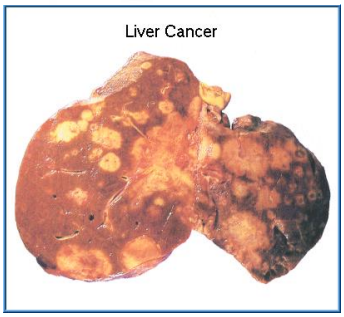


- **Is a chronic diffuse liver disease.**
- Characterized by fibrosis and nodular formation.
- Results from liver cell necrosis and the collapse of hepatic lobules.
- Symptoms includes: ascites, coagulopathy (bleeding disorder), portal hypertension, hepatic encephalopathy, vomiting blood, weakness, weight loss.

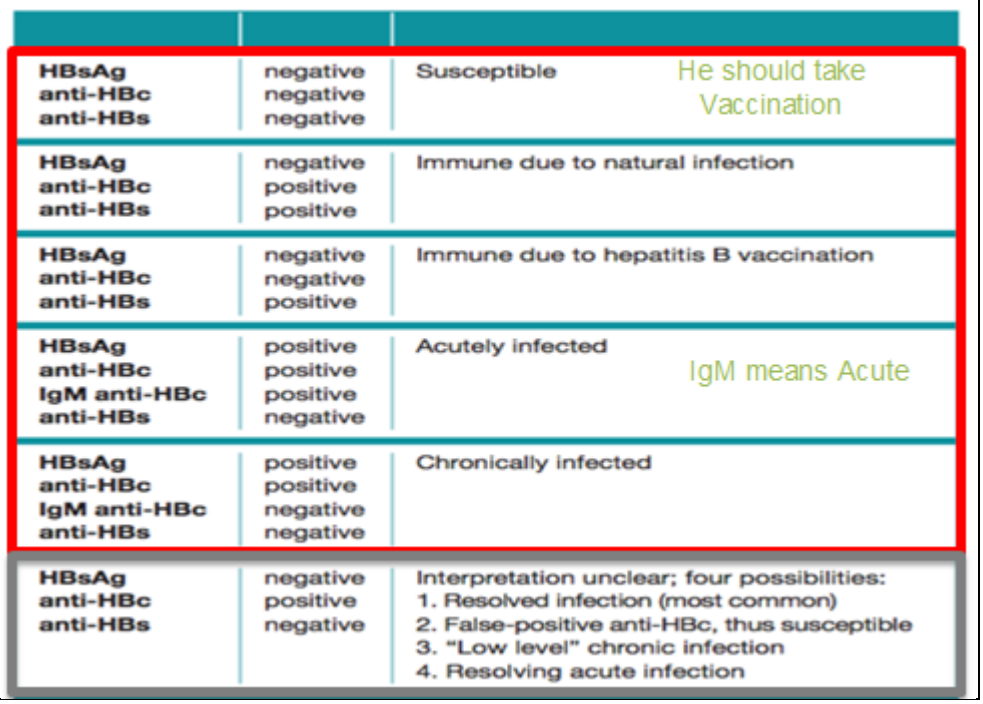
Hepatocellular carcinoma (HCC) [for reading]



- 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, weight loss, anorexia, vomiting, and jaundice.
- Physical examination reveals hepatomegaly, splenomegaly and ascites.
- Prognosis: without liver transplantation, the prognosis is poor and one year survival is rare.
- Diagnosis: alpha-fetoprotein measurement with multiple CT-abdominal scan are the most sensitive method for diagnosis of HCC.
- Treatment: surgical resection and liver transplant.

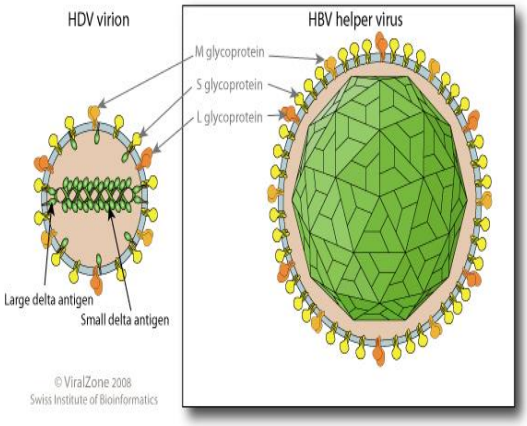


	HBV [hepadnaviridae]
Lab diagnosis	-Hepatitis B infection is diagnosed by detection of HBsAg in the blood. -**Positive results must be repeated in duplicate**. -Repeatedly reactive results must be **confirmed by neutralization test.** **Additional lab investigations:** 1-Liver function tests (LFT). 2-Ultrasound of the liver. 3-Liver biopsy to determine the severity of the diseases.
HBV vaccine	-It contains highly purified preparation of **HBsAg** particles, produced **genetic engineering in yeast.** -It is **not live attenuated nor killed vaccine**. The vaccine is administered in three **doses IM injection at 0 [today] &1 & 6 ms**. Booster doses may be reacquired after 3-5 years. **-It is safe and give excellent protection**
Prevention and control	-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 both Hep B **Active Vaccine & specific immunoglobulin.**
Treatment	**There are several approved antiviral drugs:** - **Pegylated alpha interferon (B, C),** one injection per week, for 6- 12 months. - **Lamivudine (B),** antiviral drug, nucleoside analogue. One tablet a day for at least one year. - Adefovir, antiviral drug, nucleoside analogue. One tablet a day for at least one year. Treatment is limited to patients having chronic hepatitis B based on **liver biopsy.** **Criteria for treatment:** -Positive for HBsAg -Positive for HBV-DNA > 20,000 IU/ml. -ALT > twice the upper normal limit. -Moderate liver damage. -Age > 18 years.



Hepatitis D virus (delta virus): Structure

- It is a **defective virus** that cannot replicates by its own**.**
- It requires a helper virus.
- The helper virus is **HBV**.
- HBV provides the free **HBsAg** particles to be used as an envelope.
- HDV is small 30-40 nm in diameter
- Composed of small **ss-RNA** genome, surrounded by **delta** antigen, that form the nucleocapsid.



[ALL Hepatitis Viruses RNA EXCEPT B is DNA.]

Types of HDV infections

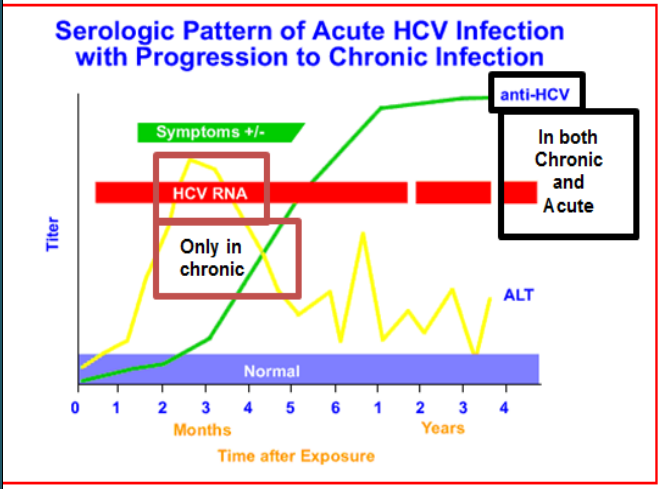
1- Co-infection:

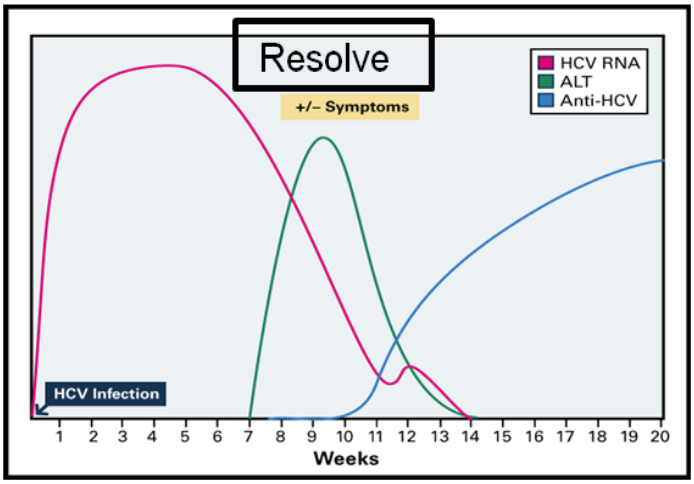
- The patient is infected with **HBV and HDV** at the same time leading to **severe acute hepatitis.**
- **Prognosis:** recovery is usual.

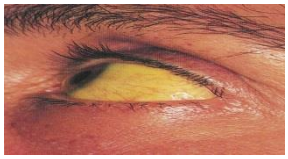
2- Super infection:

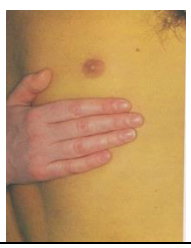
- In this case, delta virus infects those who are already have chronic hepatitis B leading to severe chronic hepatitis.

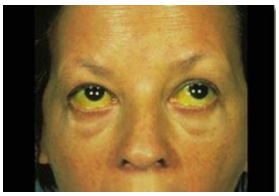
	HCV
transmition	**Similar to HBV:** 1- **Parenterally:** - Direct exposure to infected blood. - Using contaminate needles, surgical instruments. - Using contaminate instruments in the practice of tattooing, ear piercing & cupping. - Sharing contaminated razors 7 tooth brushes. 2- **Sexually.** 3- **From mother to child perinatally.**
Clinical picture	• Incubation period from **2 to 7** weeks. • Clinically, the acute infection with **HCV is milder** than infection with HBV. • Fever, anorexia, nausea, vomiting, and jaundice **are common**. • Dark urine, pale feces, and elevated **liver enzyme (transaminase**) are seen.









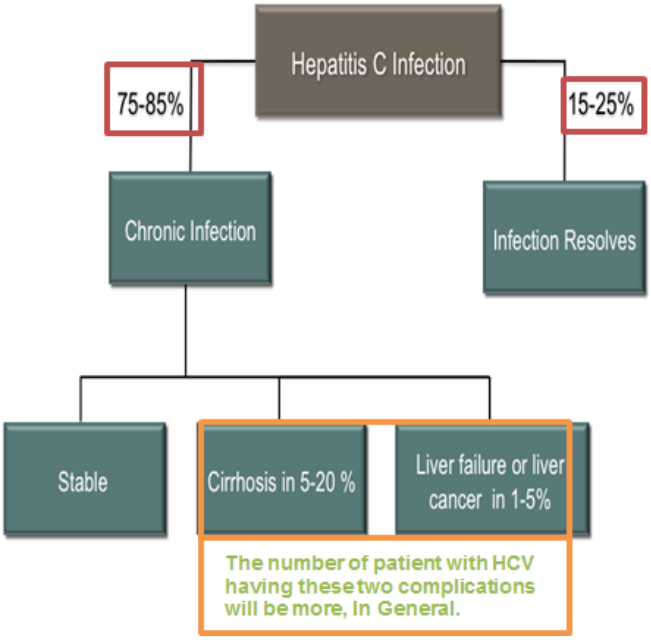


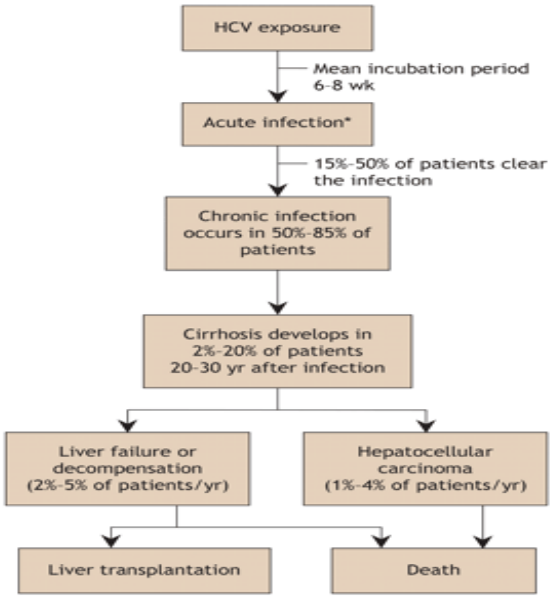
Jaundice

HCV

Clinical outcome

-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.





HCV Markers

Hepatitis C virus RNA

- Is **the 1st** marker that appears in circulation
- weeks after 3-2 it appears as early as .exposure
- **It is** a marker of infection.

Hepatitis C Ab [antibody]

- .**second marker** Antibodies to hepatitis C virus is the
- **blood** appears in the
- usually appear **50 days after exposure** (long window period)
- marker of immunity **not** it is
- and **red patientrecove** can be detected in completely .chronic and acute

Lab Diagnosis

By detection of both:

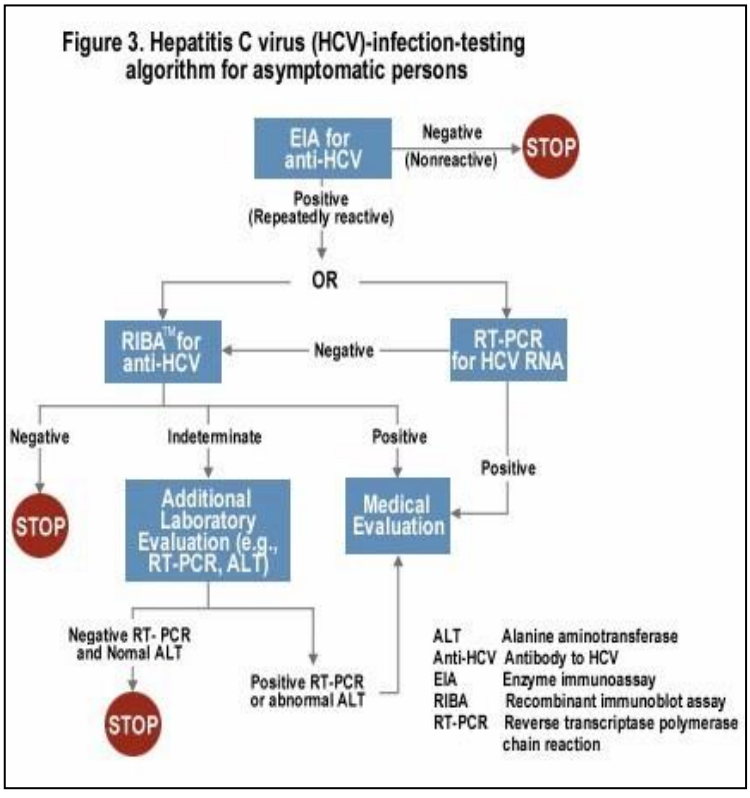
- Antibody to HCV in the blood **by ELISA,** if positive we have to repeat it in duplicate ,then, the result must be confirmed by **RIBA & PCR.**
- **HCV-RNA** in the blood using **PCR**

Serology:

- **Positive anti-HCV EIA** [enzyme immunoassay] needs confirmation
- **HCV RIBA** [recombinant immunoblot assay] confirms + EIA. It doesn't distinguish between past/present infection. Being replaced by HCV-RNA.
- **Liver Biopsy**

Molecular:

- **Qualitative:** +ve in ongoing infection and chronic hepatitis and –ve after recovery **[most specific]**
- **Quantitative:** It gives indirect assessment of viral load by measuring the concentration or level of virus in serum. **Methods include quantitative PCR & branched DNA test**



Treatment	***Vaccination in H(A&B)V only*** ▪ The currently used treatment is the combined therapy using: **Pegylated alpha interferon** and **ribavirin**. ▪ The dose: for **pegylated alpha interferon (B,C)**, one injection per week. ▪ For **Ribavirine** two capsules a day. ▪ New treatment for hepatitis C name **SOVALDI (sofosbuvir).** ▪ Treatment is limited to those positive for **HCV-RNA, HCV-Ab, elevated ALT and moderate liver injury** based on liver biopsy. **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. ✓ **No vaccine available to hepatitis C.** **New Drugs** * **Promising and good** - The goal of HCV treatment is to cure the virus, which can be done with a combination of drugs. The specific medication to be used and the duration depend on: HCV genotype, viral load, past treatment experience, degree of liver damage, ability to tolerate the treatment and whether the patient is waiting for liver transplant or is a transplant recipient. - There are number of approved therapies as **SOVALDI** and OLYSIO may be given together with or without RIBAVIRIN & PEGINTERFERON, or each may be given alone with RIBAVIRIN and peginterferon. - When hepatitis C treatment is working , the virus will become undetectable within 4 to 12 weeks and will remain that way throughout treatment .patients consider cured when virus remain undetectable for 12 to 24 weeks after completing therapy.

HDV Family: Flaviviridae, genus: Hepacivirus.

- Hepatitis G virus or GB-virus was discovered in 1995.
- Share about 80% sequence homology with HCV.
- **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

[if someone has cronic hepatitis then they are always contagious]

HBV:

If someone gets infected then :the markers that appear are:

1- HBV DNA

2-ab to HBc and it will stay positive for the rest of their life (if it was negative then this means that they never had HBV)

3- HBsAg positive

4- if the disease was severe then they will have HBeAg positive and that means that they highly contagious

5- if the surface antigen persisted for more than 6 months then this person has chronic hepatitis

If they are cured of hepatitis B then :the serum will show:

1-antibody against Hbc positive

2-antibody aginst Hbe

3- antibody against Hbs AG and it will dissapear in a couple of years not like c will stay forever

HCV:

It has two markers only:

- **HCV RNA**
- **Anti-HCV :** present when the patient is cured and also when the patient develops chronic hepatitis . So to know if the patient became better or not we look for the RNA , if RNA is present then he is chronic
- also look for the **ALT** enzyme if it was present then he has chronic disease

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Questions:

1-The most common natural mode of transmission of infection with hepatitis B virus is via:

A-Contaminated water supply. B-Body fluids, such as urine and semen.

C-Respiratory droplets. D-Direct contact.

Answer: B

2-Delta hepatitis virus only occurs in patients who also have either acute or chronic infection with hepatitis B virus. The delta agent is:

A-An incomplete hepatitis B virus B-Related to hepatitis A virus

C-A hepatitis B mutant D-An incomplete RNA virus

Answer: D

3-A nurse develops clinical symptoms consistent with hepatitis. She recalls sticking herself with a needle approximately 4 months ago after drawing blood from a patient. Serologic tests for HBsAG, antibodies to HBsAG, and hepatitis A virus (HAV) are all negative; however, she is positive for IgM core antibody. The nurse

A-Does not have hepatitis B B-Has hepatitis A C-Is in the late stages of hepatitis B infection D-Has hepatitis C

E-Is in the "window" (after the disappearance of HBsAG and before the appearance of anti-HBsAG)

Answer: E

4-Infection with hepatitis D virus (HDV; delta agent) can occur simultaneously with infection with hepatitis B virus (HBV) or in a carrier of hepatitis B virus because HDV is a defective virus that requires HBV for its replicative function. What serologic test can be used to determine if a patient with HDV is an HBV carrier?

A-HBsAg B-HBc IgM C-HBeAg D-HBs IgM

Answer: B

5-A hospital worker is found to have hepatitis B surface antigen. Subsequent tests reveal the presence of e antigen as well. The worker most likely:

A-Is infective and has active hepatitis
B-Is infective but does not have active hepatitis
C-Is not infective
D-Is evincing a biologic false positive test for hepatitis
E-Has both hepatitis B and C

Answer: A

6-Hepatitis C (HCV) is usually a clinically mild disease, with only minimal elevation of liver enzymes. Hospitalization is unusual. All the following statements regarding HCV are true except:

A-30 to 50 percent of cases progress to chronic liver disease
B-It often occurs in post transfusion patients
C-Many HCV infections occur in IV drug abusers
D-It is a DNA virus
E-Blood products can now be tested for antibody to HCV

Answer: D

7-The antigens and antibody below are associated with hepatitis. For each, choose the description with which it is most likely to be associated:

A-is usually the first viral marker detected in blood after HBV infection.	1-HBeAg
B-May be the only detectable serologic marker during the early convalescent phase of an HBV infection ("window phase")	2-HBsAg
C-Appears in the blood soon after infection, rises to very high concentrations, and falls rapidly with the onset of hepatic disease	3-HBcAg
D-Found within the nuclei of infected hepatocytes and not generally in the peripheral circulation	4-Anti-HBc
E-Closely associated with hepatitis B infectively and DNA polymerase activity	

Answers:
1:e 2:a 3:d 4:b

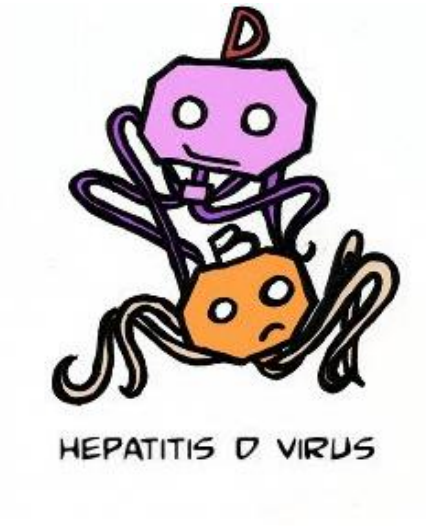
8-killing of liver cells infected with hepatitis B virus is primarily caused by:

A-shut-off of cellular protein synthesis
B-Intracytoplasmic accumulation of HBV antigen aggregates
C-Degradation of cellular mRNA
D-Attack by cytotoxic T lymphocytes directed against HBV antigens
E-Virus-induced aberrant chromosome rearrangements and deletions

Answer: D

Hey, *Hepatitis B Virus* here.
I'm from the *Hepadnaviridae* family.

I visit many babies through their mums.
I'm often sexually transitted.
I get into your liver.
There I get to work, giving you pain, nausea, fever and jaundice.
I can hang around for years.
I make you more likely to get liver cancer.



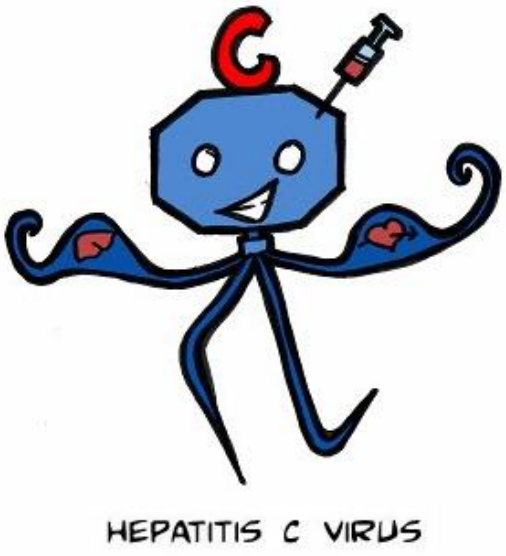
Hey folks.
My name is *Hepatitis D virus*.
I'm also called Hepatitis Delta.

I can't get you on my own, I need my friend HBV.
We have a "co-infection".
I can get into you at the same time as my cousin.
Or I can visit people who already have him.

My job is to make your liver even worse.

Hiho!
I am *Hepatitis C Virus*.
I'm from the family *Flaviviridae*.

I get to you in blood.
I use needles, piercings, tattoos and blood transfusions.
I often hang around for years and can give you cirrhosis.



There are vaccines for my cousins Hep A and Hep B, but not for me.

حنان محمد عبدالمنعم

ملاك الخثلان

رنا البراك

رشا بصاص

حنان خشيم