الجهاز الهضمي

علم الأحياء الدقيقة

رقم المحاضرة :

الكتّاب : عمر الصمادي ، حلا البطوش

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الدكتور : نادر العرايضة

دلالات الألوان :

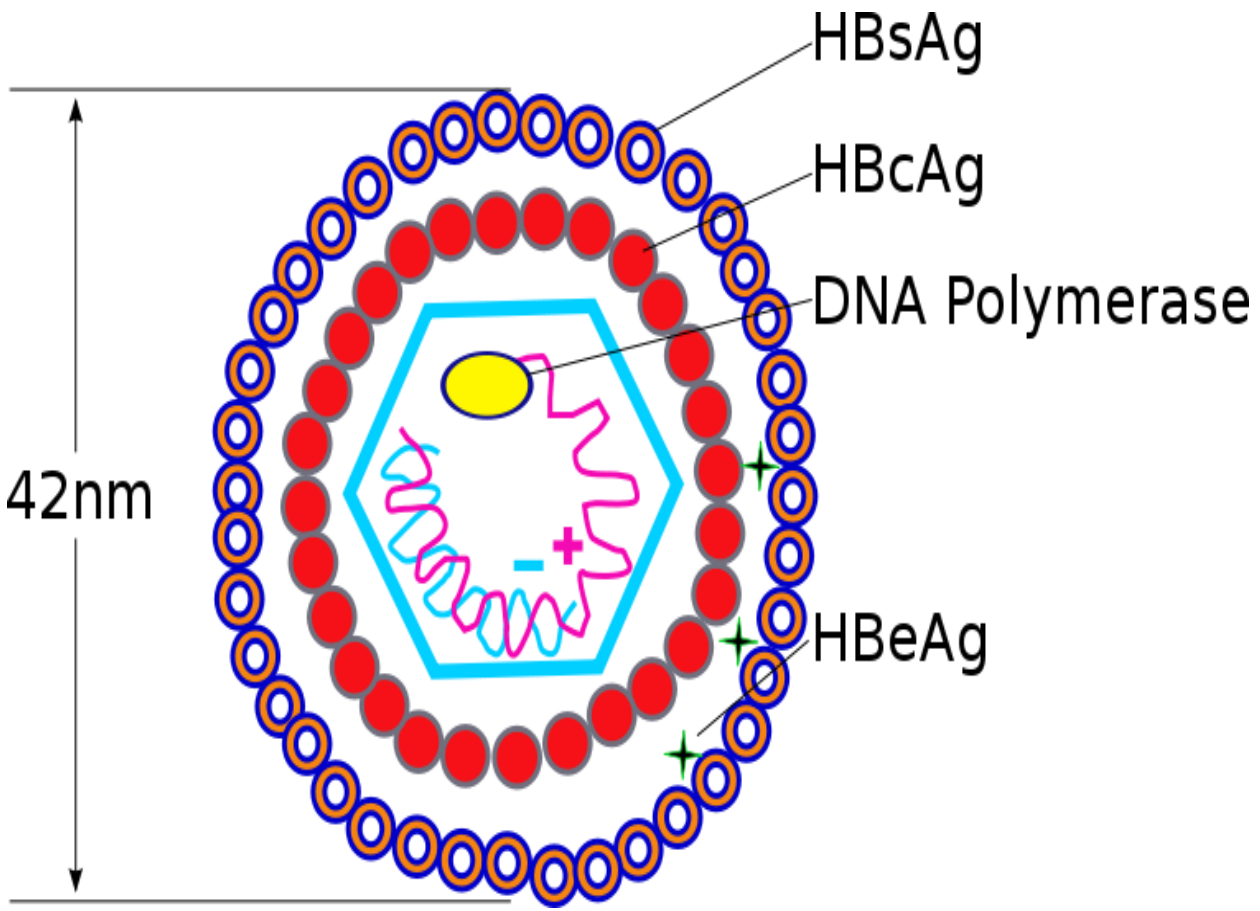
- شرح الدكتور باللون الأحمر .
- كلام الدكتور من السلايدات تحته خط
- مهم من شرح الدكتور باللون البنفسجي
- المعلومات الخارجية باللون الأزرق

Hepatitis Viruses

By Nader Alaridah MD, PhD

Hepatitis B virus

- Hepadnavirus , Partially –Double stranded circular DNA genome.
- Enveloped
- Icosahedral nucleocapsid
- Antigens:
- The main components of the virus include the core - hepatitis B core antigen (HBcAg) and the pre-core hepatitis B e antigen (HBeAg), and the envelope of the virus contains the hepatitis B surface antigen (HBsAg)



- It’s partially double stranded DNA ,usually with a short and a single stranded piece.
- It’s also the smallest DNA virus known with 3200 nucleotides.
- It has 3 main antigens :1) HBcAg 2) HBeAg ,that indicate infectivity and replication . 3)and the envelope of the virus contains HBsAg.
- It’s asymptomatic or limited illness in 90% of patients, showing jaundice and fever for few days to weeks.
- It becomes chronic in up to 10% of patients which might develop to liver cirhhosis or hepatocellular carcinoma .
- It has its own DNA polymerase(DNA dependent polymerase) with only one serotype .
- There is a vaccine for hepatitis B virus
- It has 3 different types of particles : virions, spheres, and filaments.
- For epidemiological and medicolegal purposes, Hepatitis B virus (HBV) is classified into four strains based on the serologic subtypes of the surface antigen (HBsAg): group-specific, usually given abbreviation A, and two sets of mutually exclusive sets of epitopes, either D or Y, as well as W or R.

Hepatitis B virus

➢ Transmission:

- Parenteral via blood or plasma, needle stick injury
- Vertically: mother to baby
- Body fluids

Semen and saliva

Hepatitis B virus (HBV) is distributed globally, with an estimated 2 billion people having markers of HBV infection. Among these individuals, approximately 400 million have a chronic infection with HBV. This means there are 400 million carriers of the virus worldwide. The incidence of death attributable to HBV-related complications is approximately 1 million per year

➢ Risk groups:

- Health care workers
- Drug abusers
- Recipients of blood or its products (blood should be ideally screened)
- Dialysis patients, Homosexual men…

- ✓ **The spread of the hepatitis B virus (HBV), known as serum hepatitis, occurs through intravenous routes such as transfusions of infected blood or through contaminated needles used by drug addicts, as well as through practices like tattoos and acupuncture. It can also be transmitted through close personal contact, including sexual intercourse, particularly among male homosexuals.**

- ✓ **HBV can be found in semen and saliva, and vertical transmission during childbirth or shortly after birth has been documented. Needlestick injuries pose a higher risk of HBV transmission, especially among medical personnel**

Hepatitis B virus

- Pathogenesis:
- Blood borne > liver cells > hepatocytes injury and necrosis (piecemeal necrosis) ---Largely cell mediated.
- Clinically :
- Incubation period: 1-4 months (infectious dose)

✓Asymptomatic: 90% of children and 50% of adults (increased liver enzymes)

✓Symptomatic:

- Preicteric phase: flu like symptoms nausea, anorexia, malaise
- Icteric phase: Jaundice, pale stool, dark- coloured urine, increased liver enzymes and billirubin

- Piecemeal necrosis (also called interface hepatitis) : is a common form of necrosis seen in hepatitis, it's characterized by inflammation extending from the portal tract to the periportal zone (the zone around the portal veins) with necrosis in the periportal hepatocytes.
- The incubation period is from 7 days to 160 days (mean : 10 weeks or 70 days).
- The patient could be symptomatic or asymptomatic based on the immune response.
- In acute hepatitis B infection, patients typically experience a gradual onset of symptoms including fatigue, loss of appetite, nausea, and pain or fullness in the right upper quadrant of the abdomen. In the early stages of the disease, patients may also experience pain and swelling of the joints, as well as occasional transient arthritis. These symptoms are often mediated by antigen-antibody complexes. Additionally, some patients may develop a rash as a manifestation of the immune response to the virus.
- Hepatitis causes cholestasis which makes light colored stool and dark colored urine and jaundice.

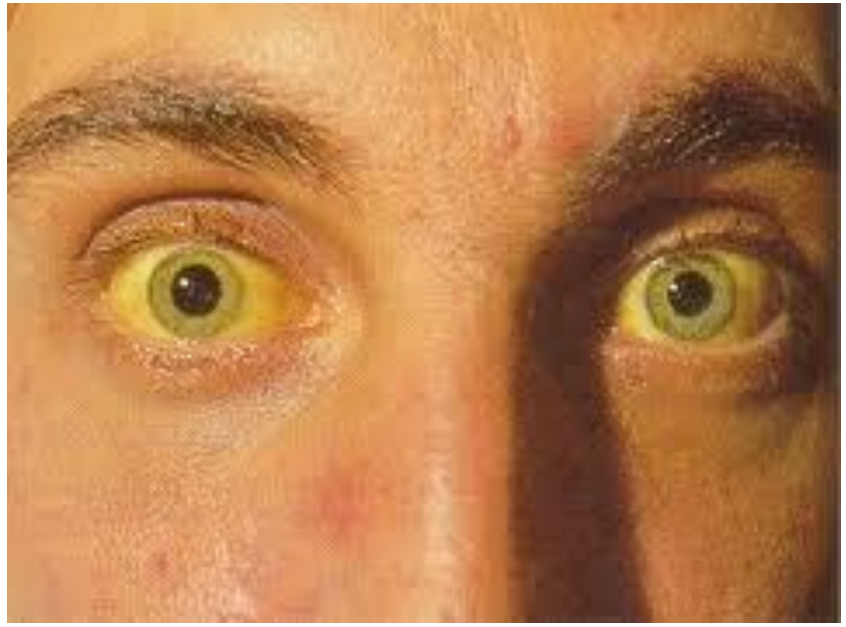
- Fulminant hepatitis, characterized by extensive liver necrosis , is a rare complication of hepatitis B infection, occurring in less than 1% of affected individuals and can lead to death.
- chronic hepatitis occurs in 10% of patients. Younger patients are more likey to develop chronic hepatitis, mostly neonates.
- 20% of chronic patients get hepatocellular carcinoma.
- Hepatocellular carcinoma is caused by the integration of the viral DNA with the DNA of the hepatocyte.
- Approximately 90% of affected neonates become chronic carriers of HB infection; progression to chronic disease is inversely related to the age of infection
- Having antibodies to the Hep B surface antigen (HBsAg) gives lifelong immunity.

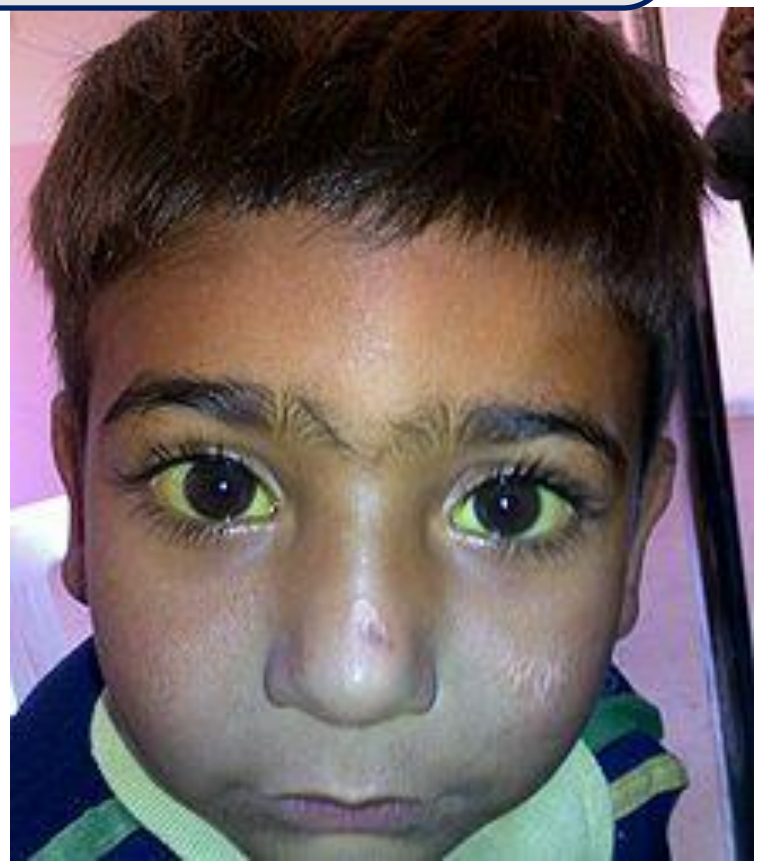
Very important :

Hepatocellular injury is caused by the immune response, particularly CD8+ cytotoxic T cells.
Antigen-antibody complex cause the arthritis and vasculitis.

Hepatitis B

HB patients in their Icteric phase :Jaundice, caused by cholestasis .





Hepatitis B virus

- Outcome:

- 90-95% recovery
- 5-10% chronic carriers (sAg > 6 months):

- chronic active hepatitis (more fatal)

- 1% fatality

- 1% of HBV chronic carriers develop hepatocellular carcinoma

The clinical presentation of HBV in children is generally less severe than in adults, and it may even be asymptomatic. However, clinically apparent illness occurs in as many as 20% of those infected, with the majority (80%) recovering. Recovery is typically marked by declining fever and renewed appetite.Chronic hepatitis develops in 5-10% of patients, usually after mild or asymptomatic initial disease. Approximately one third of these individuals progress to chronic active hepatitis, characterized by ongoing liver destruction, leading to scarring (cirrhosis), liver failure, or primary hepatocellular carcinoma. The remaining two thirds may have chronic passive hepatitis, which is less likely to cause problems. Chronic hepatitis may be incidentally detected when elevated liver enzymes are found on routine blood chemistry profiles.Chronically infected individuals are the main source of virus transmission and are at risk of developing fulminant disease, especially if co-infected with HDV. Fulminant hepatitis occurs in approximately 1% of icteric patients and can be fatal in some cases.

- Diagnosis of HBV :

1. Clinical picture

Patients with jaundice show antibodies to Hep B core antigen (HBcAG), and sometimes (HBsAg).

2. Liver, kidney function tests, other tests to role out other causes e.g: CMV, EBV infection

3. Serology:

- We rely on:

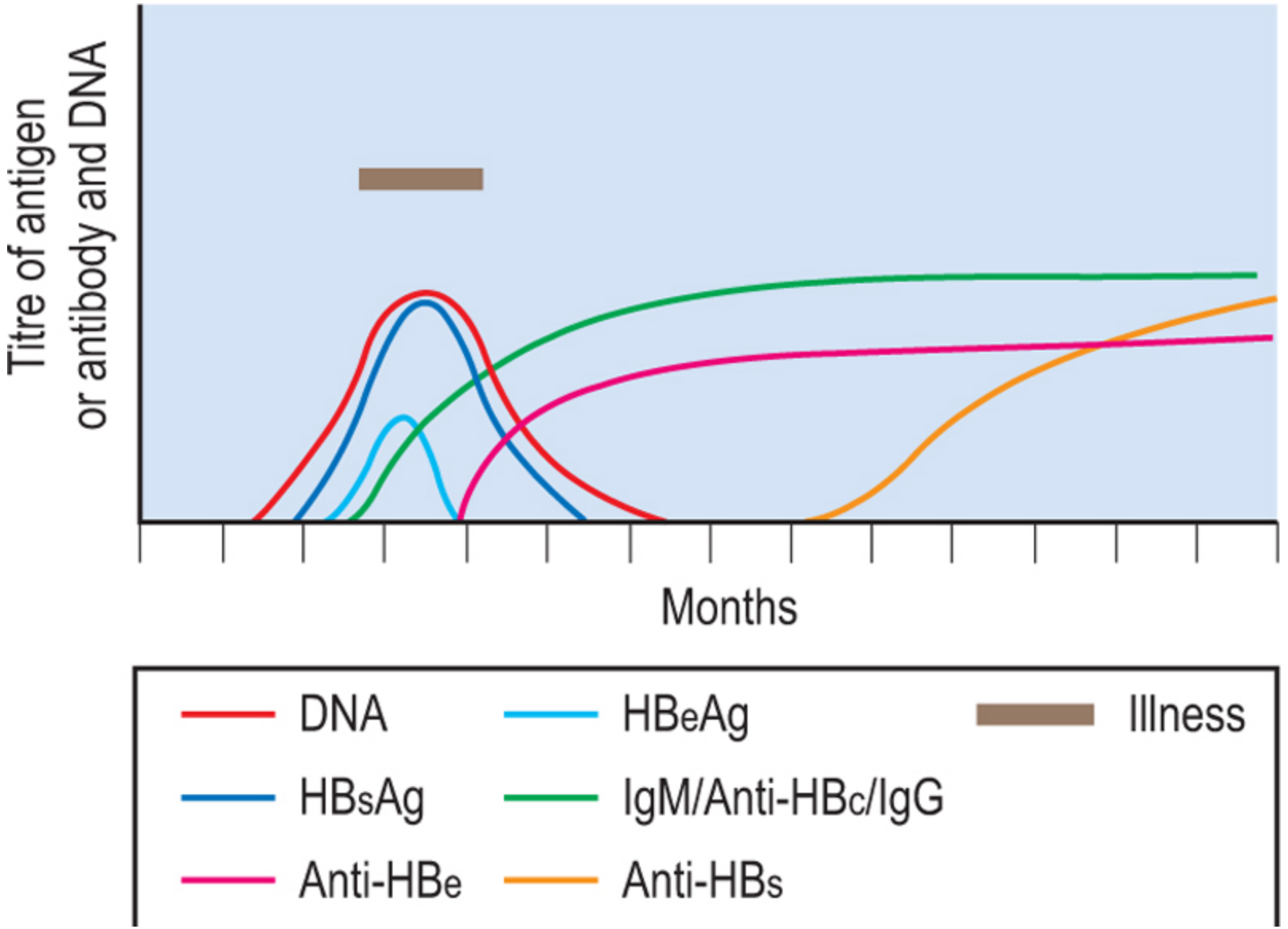
Past infections show anti core or surface (or both) antibodies in the form of IgG

PCR for Hep B DNA is the most accurate marker.

- S, e antigens and antibodies
- Anti core antibodies
- DNA detection

Liver biopsy is needed to determine the stage of the disease.

Important to understand the graph



In general:

- IgM antibody to HBcAg show acute case of Hep B.
- IgG show past infection or chronicity.
- E antigen show active replication of the virus, therefore infectivity, the antibodies of e antigen(antibodies of HBeAg) means it stopped replicating, however patients Wii still be positive for HBsAg .
- The DNA in PCR is a more accurate indicator of active replication than the HBeAg .
- Hepatitis B Surface antigen is a general marker for infection despite the stage of the disease, persisting for more than 6 months indicates chronicity.
- The antibody for the surface antigen means the immune system has successfully killed the virus and indicates recovery.
- Notice there is a difference between finding the antigen itself or finding its antibody.

In the window phase, the virus is active, but the surface antigen is not apparent.

TABLE 41–4 Serologic Test Results in Four Stages of HBV Infection

Test	Acute Disease	Window Phase	Complete Recovery	Chronic Carrier State
HBsAg	Positive	Negative	Negative	Positive
HBsAb	Negative	Negative	Positive	Negative[1]
HBcAb	Positive[2]	Positive	Positive	Positive

Notice that the surface antigen and its antibody never appear simultaneously.

Note that past infection gives antibodies to all types of antigens, while immunization (vaccination) gives antibodies only to the surface antigen.

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

Hepatitis B virus

-There is no specific treatment for acute hepatitis B
-A high calorie diet is desirable
-Corticosteroid therapy has no value in uncomplicated acute viral hepatitis

Treatment:

1. ***Peg Interferon alpha***

-For chronic hepatitis use , as they provide the long-term benefit usually in 1/3 of patients

2. ***Lamivudine,***

-A potent inhibitor of HIV
-Active versus Hepatitis B (both in vitro &initial clinical trials)
-Resistance to this agent develops in about 1/4 of the patients after 12 months of therapy

That leaves us with :

3. ***Tenofovir, entecavir***

-these are nucleotide analog adenosine monophosphate
-They are newly approved for the treatment of chronic hepatitis B

Hepatitis B virus

Prevention:

1. Immunoglobulin / passive

Accidental exposure in non-vaccinated

Newborns of infected mothers

More explanation in next slide

-vaccination is highly effective against HBV infection

-The safe practices and avoidance of needle stick injuries especially for:

- **medical personnel**

Or

- **injection drug abusers**

(they are the approaches that can be used to diminish the risk of hepatitis B infection)

2. Vaccine (Recombinant HBsAg) 3 I.M doses at 0, 1, 2 OR 6 months

- *Fridge storage*
- *Check response by measuring anti HBsAg (anti hepatitis B surface antigen) antibodies 2 months after last dose (>10mIU/ml is protective)*
- *Part of ministry of health vaccination program (2, 3, 4 months)*

More than 10 million international unit /ml---->protective

- **The vaccine can be given to those who are at increased risk of Hepatitis virus infection such as:**
- **Healthcare workers**

-Also given routinely to neonate in many countries

*Hepatitis B immunoglobulin may be used to:
-protect persons who are exposed to hepatitis B
(it is officious within 48 hours of the incidence post prophylaxis post exposure)
ALSO, may be given to:
-Neonates who are at increased risk of contracting hepatitis

**Other measures include:

- Screening of blood donors as well as the blood itself and other body fluids.

**Here in Jordan, we have the hepatitis B virus as part of the Hexaxim vaccine (المطعوم السداسي) and it's given as 3 doses, Typically at the second, third, and fourth month of the infant's life

Hepatitis D virus will cause-->(Delta hepatitis/ Hepatitis D)

Explanation in next slide
Note: for this part read the doctor's notes first (it's simple, don't worry)

- *It needs HBV to replicate (provide the envelop)*
- *Route of transmission:*

✓ *As HBV*

✓ *conditions:*

✓ *Co- infection with HBv*

✓ *Super infection of HBV chronically infected patients (High risk of liver failure)*

- *Diagnosis: serology*
- *Rx: as HBV*

****HDV is a small single stranded RNA virus that requires the presence of hepatitis B surface antigen for its transmission ----> thus found only in presence of chronic or acute hepatitis B infection**

- **Delta hepatitis is most prevalent in group at high risk of hepatitis B injection drug users (as many as 50% of such individuals may have IgG antibody to the delta virus antigen.**
- **Other risks include dialysis**

**Two major types of delta infection have been noted :

- Simultaneously infected with both (delta + hepatitis B) as a co-infection.

--> results in clinical hepatitis that is indistinguishable from acute hepatitis A or B.

--> fulminant hepatitis is much more common than with the hepatitis B virus infection alone

- Delta super infection (in those with chronic hepatitis B who acquire infection with hepatitis D) :

-suffer relapse of Jaundice

&

-have high likelihood of developing chronic cirrhosis.

**Diagnosis:

Most commonly by demonstrating IgM or IgG antibodies or both (delta antigen in the serum)

-IgM : appear within 3 weeks of infection

Persist-> for several weeks

-IgG: Persist-> for years!!

**Response to treatment (infection delta + HBV << HBV alone)

-recommended doses for (delta + HBV) are :

- Higher
- May produce sustained improvement only in ¼ of the patients(because the capsid of delta hepatitis is hepatitis B surface antigen measured end at limiting the transmission of hepatitis B
- **to prevent the transmission of delta hepatitis:
- individual with hepatitis B or D should not donate (blood, organ tissue or Semen)
- Methods to reduce transmission: decrease the use of contaminated needles and syringes by injection drug users (will reduce the transmission)
- Use of needle safety devices by healthcare workers

Hepatitis C virus

- Flavivirus **(family name)**, Enveloped , single stranded , positive sense RNA virus

-It has a very simple genome consisting just (3 structural & 5 non-structural genes)

- No polymerase in the virion

Hyper variable regions in the envelope glycol protein and it's called quasi species

- 6 genotypes**(and multiple subtype)**: needed for Rx and medicolegal
- Spread**(transmission)** via:

Transmission is less well understood than hepatitis A,B and D

- infected blood**(well documented indeed until screening blood for transfusions was introduced it caused the great majority of cases of post-transfusion hepatitis)**

- sexual contact**(maybe transmitted but to a much lesser degree than HBV)**

-Needle sharing (accounts for up to 40% of the cases

- 6 - 8 week incubation period / most infections are sub-clinical
- Clinical infections are generally less severe than HBV, damage due to cell mediated immune response
- HCV has *a higher incidence of chronic liver disease than HBV* (70-80% of patients remain viremic for more than 1 year)
- 170 million cases globally

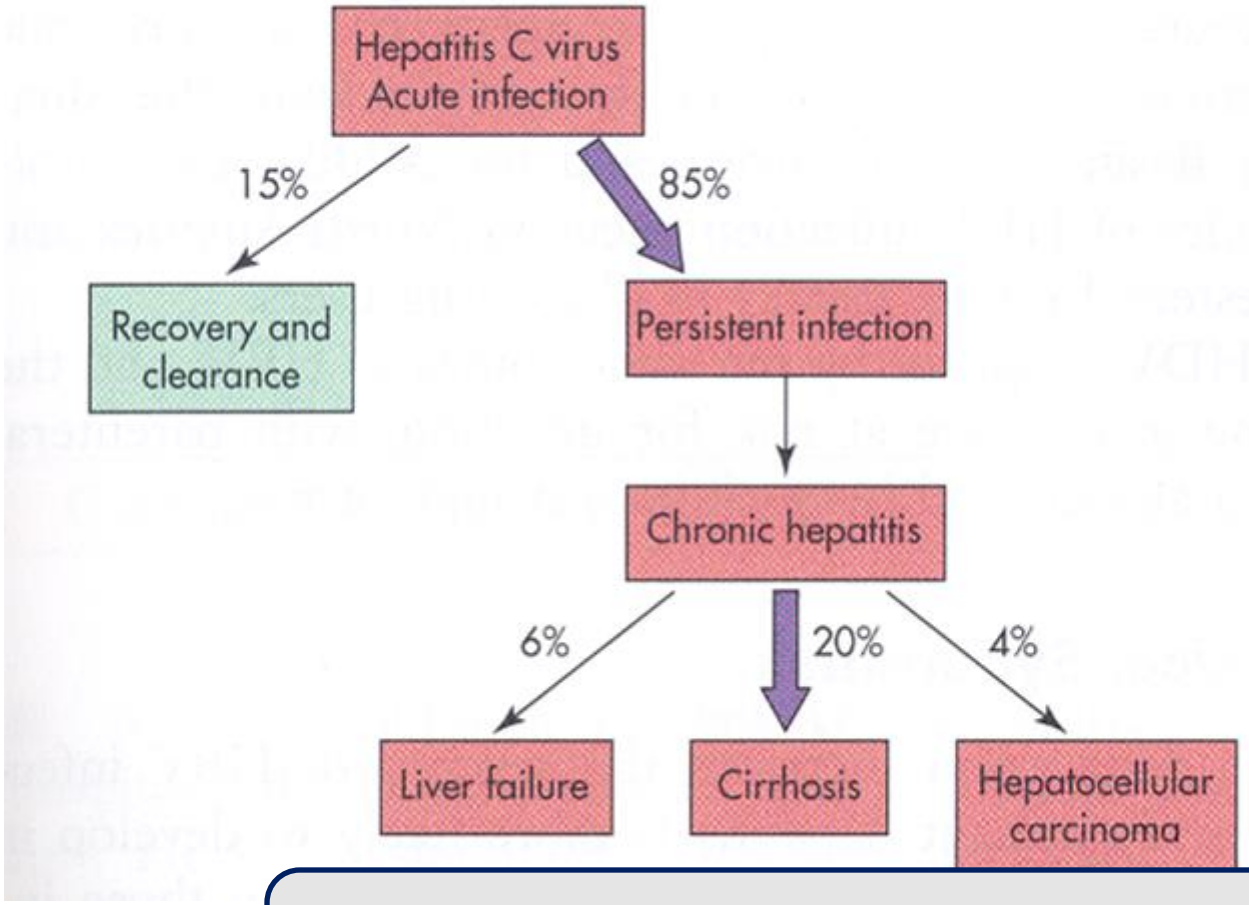
Hepatitis C was the major cause of post-transfusion hepatitis until a serologic test for screening blood donors was developed

-Hepatitis C is an Insidious disease : does not usually cause a clinically evident acute illness ~ instead-> its first manifestation in about ¼ of those infected may be the presence of mold during chronic hepatitis that may ultimately lead to --> Liver failure

- ✓ In the United States, approximately 3.5 million people have antibodies to hepatitis C virus (HCV).
- ✓ Screening donor blood for hepatitis C antibodies has led to a significant reduction in the incidence of post-transfusion hepatitis C cases. Specifically, this screening process has resulted in an 80 to 90% reduction in the transmission of hepatitis C through blood transfusions.
- ✓ Other individuals considered to be at risk of hepatitis C infection include chronic hemodialysis patients and spouses of individuals infected with hepatitis C.

Hepatitis C virus

This slide shows the outcome of hepatitis C virus infection



**Incubation period of hepatitis C average between 6 to 12 weeks

**The infection is usually

- asymptomatic

OR

- mild and anicteric (but result in chronic carrier state in up to 85% of adults of the patients)

- the average time from infection to the development of chronic hepatitis is years (10-18 years)

Cirrhosis and hepatocellular carcinoma are the Late sequelae of chronic hepatitis

Hepatitis C virus

Diagnosis:

1. *Anti HCV IgM*
2. *RNA detection*

(the quantitative assays of hepatitis C RNA) may be used for diagnosis, estimating prognosis predicting interferent responsiveness, and monitoring therapy, but there is not a very good correlation between the viral load and the histology

3. *Treatment:*

antivirals

-combination therapy with (interferon alpha + ribavirin) is the current treatment of choice
****Corticosteroids-> are not beneficial in hepatitis C infection**

Immunoblotting (IB) also known as Western Blotting, is a technique used most to confirm the presence of autoantibodies.

Antigens of hepatitis C are not detectable in blood --> so diagnostic tests attempt to demonstrate antibody in HCV infection
-Unfortunately, antibody response in acute disease remains negative for 1 to 3 weeks after clinical onsets and may never become positive in up to 20% of patients with acute resolving disease
-current test measure antibodies to multiple hepatitis C antigen by either :

- **Enzyme immune essay**

Or

- **Immunoblot**

-even with newer assays IgG antibody to Hepatitis C may not develop for up to 4 months --> making the serodiagnosis of acute hepatitis C very difficult.

Hepatitis C virus / prevention

-Not clear whether prophylactic immune serum globulins protect against Hepatitis C.

- No vaccine
- Blood screening ,important and preventive.

Public Health Service Guidelines for Counseling Anti-HCV-Positive Persons

Anti-HCV-positive persons should:

- Be considered potentially infectious
- Keep cuts and skin lesions covered
- Be informed of the potential for sexual transmission
- Be informed of the potential for perinatal transmission
  - no evidence to advise against pregnancy or breastfeeding

Anti-HCV-positive persons should not:

- Donate blood, organs, tissue, or semen
- Share household articles (e.g., toothbrushes, razors)

CDC

**Important preventive measures:

- Avoidance of injection drug use
- Screening the blood products

Post exposure prophylaxis

This table explain post-exposure prophylaxis of different scenarios

جدول رقم (9) الاجراءات الفورية بعد اصابة عمل

المريض مصدر الاصابة	الوضع التطعيمي للموظف	الاجراء
التهاب الكبد (B) موجب HBsAg (positive)	- لم يتم تطعيمه - غير مكتمل الجرعات - ثلاث جرعات من التطعيم	-اعطاء التطعيم فورا + جرعة جليوبيولين مناعي* - إكمال كل الجرعات و اعطاء جليوبيولين مناعي* - فحص الاجسام المناعية (اذا كان أكثر أو يساوي 10 وحدة دولية لا شيء) **
التهاب الكبد (B) سالب HBsAg (negative)	- لم يتم تطعيمه - تم تطعيمه	- يتم تطعيمه - لا شئ
غير معروف اصابته بالتهاب الكبد ب	- لم يتم تطعيمه - غير مكتمل الجرعات - ثلاث جرعات من التطعيم	- -يعامل كما لو كان مصدر الاصابة ايجابيا - يعامل كما لو كان مصدر الاصابة ايجابيا - يعامل كما لو كان مصدر الاصابة ايجابيا
حامل لمضاد فيروس التهاب الكبد (C)	لا يوجد لقاح للالتهاب الكبد (C)	فحص الموظف بعد الاصابة مباشرة ثم بعد اسبوعين و بعد شهر ثم بعد 3 اشهر بطريقة HCV-Abو PCR و اذا ظهرت بوادر اصابته يحول الى أخصائي جهاز هضمي
غير معروف اصابته بالتهاب الكبد (C)	لا يوجد لقاح للالتهاب الكبد (C)	فحص الموظف بعد الاصابة مباشرة ثم بعد اسبوعين و بعد شهر ثم بعد 3 اشهر بطريقة HCV-Abو PCR و اذا ظهرت بوادر اصابته يحول الى أخصائي جهاز هضمي
حامل لفيروس العوز المناعي البشري HIV	لا يوجد لقاح لفيروس العوز المناعي البشري HIV	- مدة اربعة اسابيع يتم فيه تناول ثلاثة ادوية مضادة للفيروسات (مثل زيدوفودين ولاميفودين) ويجب الرجوع الى البرنامج الوطني لمكافحة الايدز*** - يبدأ العلاج فوراً(خلال ساعات)

* يتم ذلك خلال 24 ساعة من التعرض للعدوى

* *تقاس الاستجابة المناعية لمطعوم الكبد (B) بفحص الاجسام المضادة (Hbs Ab) وتعتبر ايجابية اذا كانت أكبر أو يساوي 10 وحدة دولية

Table 1 summary

Comparison of A, B, D (Delta), C, and E Hepatitis

Feature	A	B	D	C[a]	E
Virus type	Single-stranded RNA	Double-stranded DNA	Single-stranded RNA	RNA	RNA
Percent of viral hepatitis	50	41	<1	5	<1
Incubation period (days)	15–45 (mean, 25)	7–160 (mean, 60–90)	28–45	15–160 (mean, 50)	?
Onset	Usually sudden	Usually slow	Variable	Insidious	?
Age preference	Children, young adults	All ages	All ages	All ages	Young adult
Transmission					
Fecal–oral	+++	±	±	–	+++
Sexual	+	++	++	+	+?
Transfusion	–	++	+++	+++	–
Severity	Usually mild	Moderate	Often severe	Mild	Variable
Chronicity (%)	None	10	50–70	>50%	None
Carrier state	None	Yes	Yes	Yes	?
Immune serum globulin protective	Yes	Yes[b]	Yes[c]	Uncertain	?

Abbreviation: Plus and minus signs indicate relative frequencies.

[a] Many individuals with hepatitis C virus are also infected with the hepatitis G virus, which is similar to hepatitis C.

[b] Hyperimmune globulin more protective.

[c] Prevention of hepatitis B prevents hepatitis D.

The end ✅

الحَقُّ يُرْجِعُهُ سَـيْفٌ وَرَشّــاشُ
وَفَارِسٌ ضَارِبٌ في الحَرْبِ جَيَّاشُ

فَاسْتَوْحِ مِنْ كُتُبِ التَّارِيْخِ عِـبْرَتَها
هَلْ أَرْجَعَ الحَقَّ خَوَّافٌ وَرَعَّاشُ؟

فَيَا (صَـلاحُ) وَيَا (بِيْبَرْسُ) يا (قُطُزٌ)
إِنَّا عَلَى إِرْثِـكُمْ لِلْيَوْمِ نَعْتَاشُ

أَحْفَادُكُمْ هَا هُمُ: (القَسَّـامُ) مُنْتَفِضَاً
ضَمَّتْهُ في (يَعْبِدِ) الأَبْطَالِ أَحْرَاشُ

-أيمن العتوم .