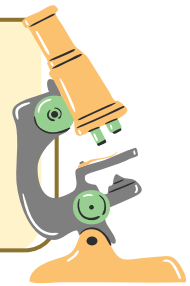
بسم الله الرحمن الرحيم

MICROBIOLOGY

Final | Lecture 3

Viral Hepatitis

Done by: Mahmoud Aljunaidi



﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

Hepatitis Viruses

By Nader Alaridah MD, PhD

Introduction

- Hepatitis: inflammation of liver; presence of inflammatory cells in organ tissue, that is the liver.
- The causes of hepatitis are varied and include infectious agents, such as viruses, bacteria, and protozoa, as well as non-infectious agents, such as drugs and toxins (eg, isoniazid, carbon tetrachloride, and ethanol).
- Acute hepatitis: symptoms last less than 6 months.
- Viral Hepatitis: is inflammation of the liver induced by viral infections.
- The clinical symptoms and course of acute viral hepatitis caused by hepatitis viruses can be similar, regardless of etiology, therefore they can't be distinguished clinically, and determination of a specific cause depends on laboratory tests, **Liver enzymes test** – go 3 slides forward for explanation.

Infectious Liver Pathologies: **Virus-Induced.**

- Among infectious liver diseases, viruses are the leading (major) cause.

- **Hepatitis viruses** are well characterized viruses, **exclusively** causing sporadic cases of hepatitis. While **other viruses** (e.g. Cytomegalovirus (CMV), Ebstein Barr virus (EBV), Yellow fever virus, Herpes simplex virus (HSV), Rubella virus and other enteroviruses) can still cause hepatitis, but **not as exclusive,** because they can cause infections in other sites in the body.

Infectious Liver Pathologies: **Viral hepatitis.**

- Although the target organ (liver) and basic symptoms of hepatitis viruses are similar, they **differ** in their structure, mode of replication, mode of transmission, time course, and sequelae of the disease they cause.

Viral Hepatitis – Liver Function Test (LFT).

- LFT: blood tests that assess enzyme and protein levels to help diagnose and monitor liver disease or damage.
- In case of liver damage caused by hepatitis, the following serum enzymes levels increase:
  - ASpartate aminoTransferase (**AST**).
  - ALanine aminoTransferase (**ALT**).

➢ Testing the pattern of the increase in these enzymes, allows the differentiation between different causes of hepatitis.

- **General rule**: serum ALT/AST ratio more than 1 **((ALT/AST) >1)** suggests viral hepatitis, reflecting cytoplasmic liver cell damage.

Viral hepatitis *types:*

- Most cases of acute viral hepatitis in both children and adults are caused by one of the following agents:
- ***A:*** **Picornavirus: +ssRNA, Non enveloped.**
  - HAV, causes hepatitis A, previously named infectious hepatitis.
- **B: Hepadnavirus Ds DNA, Partial, has enzyme, enveloped.**
  - HBV, causes hepatitis B, known as serum hepatitis.
- **C: Flavivirus, +ssRNA genome, enveloped.**
  - HCV, common cause of **post-transfusion** hepatitis.
- ***D: Deltaviruses, a Defective virus –ssRNA virus.***
  - HDV, always dependent on the **co-infection** with hepatitis B virus, as it's defective.
- **E: Hepevirus, +ssRNA non enveloped.**
  - HEV is an agent of enterically transmitted hepatitis, similar to the hepatitis A virus.

Viral hepatitis *types:*

Regardless of the virus type, **identical histopathological lesions** are observed in the liver during the acute disease. These viruses are not cytopathic; rather, it is mainly an immunological response that leads to those lesions.

Hepatitis A

Rememeber;
Viridae = family

- A typical Enterovirus, and a distinct member of the Picornaviridae, also known as entervirus 72.
- Naked Icosahedral nucleocapsid virus, non enveloped with a single stranded positive polarity RNA.
- No virion polymerase.
- One serotype, while there're seven genotypes of HAV.
- **Humans** appear to be the major **natural hosts** of HAV.
- Enterically transmitted (fecal/oral route):
- There are always outbreaks associated with contaminated food and water.

  Ingestion > Multiplies in oropharynx and intestinal epithelial cells > blood > Liver > Periportal necrosis + mononuclear infiltrates.
- Virus is not cytopathic, but the CMI causes cell necrosis.

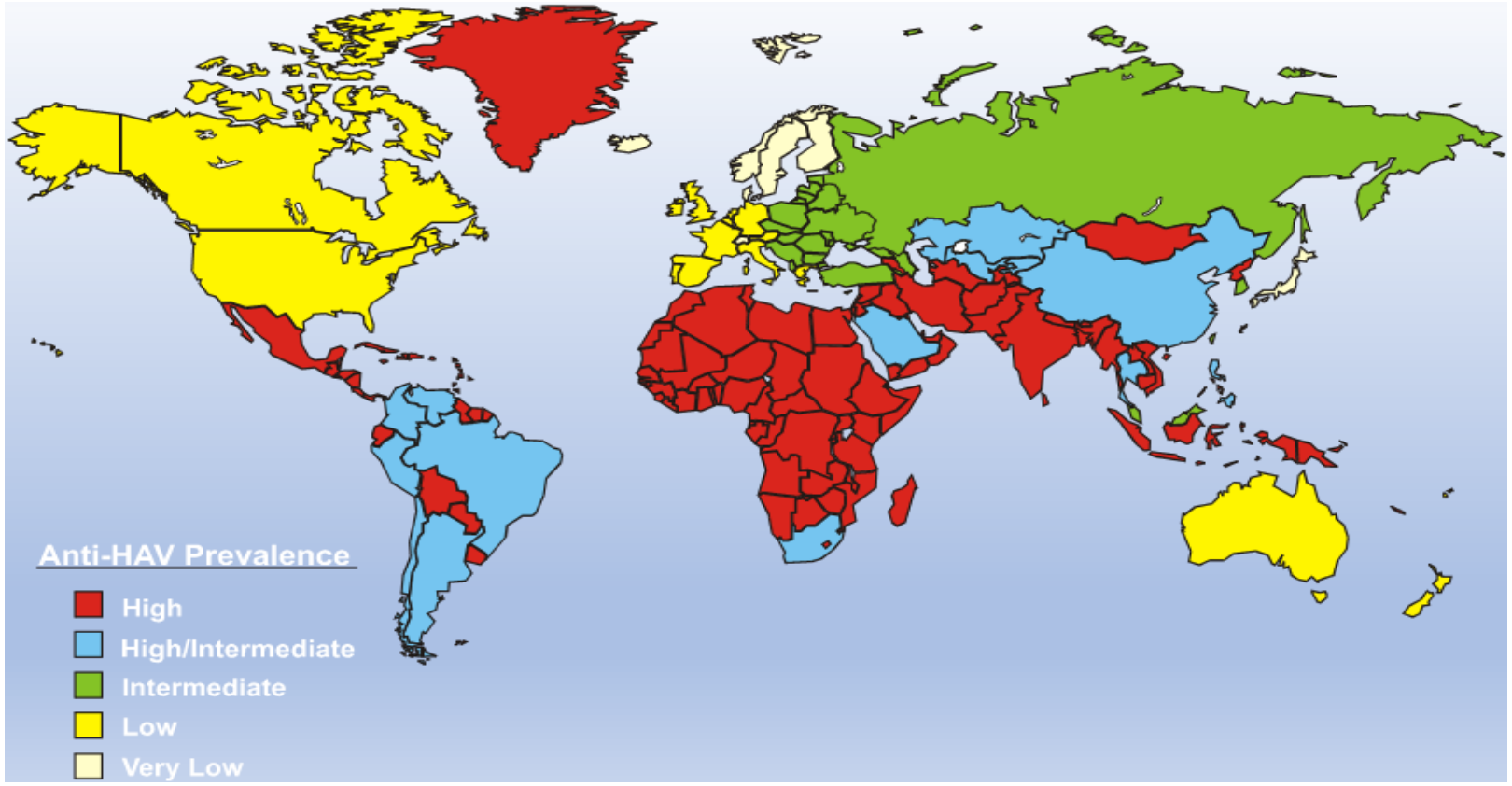
Hepatitis A – Transmission and Pathogenesis

1. After ingestion and reaching the liver by hematogenous spread, HAV replicates in liver.
2. Then it's excreted in the bile.
3. After that it gets excreted in feces of those infected persons for about two weeks **before** the onset of clinical illness and up to one week post symptoms in those affected patients.
   - Asymptomatic persons still transmit the virus to others by typical feco-oral transmission.
   - Viral particles can be detected in feces using **electron microscopy**.

- Hepatitis A is the most common cause of viral hepatitis, more than 40–50%.
- **HAV can never cause chronic hepatitis**; initially **IgM** antibody response then followed by **IgG** antibody response, which usually give a **lifelong immunity** post-infection with HAV. Also, there're **no carriers**.
  - This also applies to **HEV**.

Epidemiology of *Hepatitis A*

- Countries in **red** show **high** prevalence in **Anti-HAV**.
- Jordan has a **high** prevalence of HAV infection, thus **Anti-HAV**.



Epidemiology of *Hepatitis A – Pt.1*

- The most common type viral hepatitis that occur worldwide, most often outbreaks or epidemics.
  - Remember fecal-oral route → mass transmission.
- Commonly seen in children mainly and in young adults, 90% of infected children and up to (25-50%) of infected adults have **inapparent** but **productive** infection with HAV.
  - Remember, HAV is excreted in feces before the start and after the end of clinical manifestations, thus spread.
- **Spread of HAV infection**: mainly by **fecal-oral** route and arise from the ingestion of contaminated food and water, so overcrowding and **poor sanitation** facilitate the spread.

Epidemiology of *Hepatitis A – Pt.2*

- HAV causes **infectious hepatitis**, which is an acute disease that is clinically milder or asymptomatic in young children.
- There is no carrier or chronic state with HAV.
- More than **90%** of adults in many developing countries show evidence of **past hepatitis A infection**. Travelers from developed countries are particularly susceptible when visiting these endemic areas.
- Patients are **most contagious** during the two weeks **prior** to the onset of clinical symptoms, which are primarily characterized by **jaundice**.

Clinical Manifestations

- **Infectious dose**: less than 100 viral particles, which are sufficient to establish infection.
- Again, contagiousness and communicability typically begin about two weeks before the onset of clinical symptoms, which are usually marked by the appearance of **jaundice**.
  - Jaundice is observed in almost 70–80% of adults with hepatitis A, but in only about 10% of children, particularly those under 6 years of age.
- Incubation period: 2-6 WEEKS.
- Most HAV infections are asymptomatic, while in adults are symptomatic.
- fever; anorexia; nausea, vomiting and jaundice.
- Abdominal pain, hepatomegally, spenomegally, Dark urine and clay-colored stools and elevated transaminase levels.
- Resolve spontaneously in 2-4 weeks, recovery occur after days or weeks.

Clinical presentation – Adults and children[1].

- The most common presentation of HAV infection is **asymptomatic**, especially in children. In contrast, adults are more likely to develop **symptomatic** disease, which typically progresses through two distinct phases:

1. **Pre-icteric** (prodromal) **phase**:
   - Characterized by the abrupt onset of a **flu-like illness** accompanied by nausea, vomiting, and anorexia.
2. **Icteric phase**:
   - Characterized by jaundice, abdominal pain, hepatosplenomegaly, pale stools, and dark-colored urine, which is often noticed 1–5 days **before** the appearance of clinical jaundice.
   - A sudden onset of fever, anorexia, and pain, particularly in the **right upper quadrant** of the abdomen, may occur within a short timeframe and represents a classic presentation of symptomatic hepatitis A infection.
   - On physical examination, the liver is typically enlarged and tender.

Clinical presentation – Adults and children[2].

- **Many** individuals with hepatitis A are **asymptomatic** or experience only **mild** illness **without jaundice**.
- "**Resolve spontaneously in 2-4 weeks**"
  - Approximately 99% of HAV cases are self-limiting, with no progression to chronic hepatitis or carrier state. However, in fewer than 1% of cases, patients may develop **fulminant hepatitis**, these cases carry a mortality rate of 0.1–0.2%.
- Comparing HBV and HAV:

HAV	HBV
No chronic cases or carriers	Can be chronic
Not associated with hepatic cancer (hepatocellular carcinoma).	Associated with hepatic cancer (hepatocellular carcinoma).

Hepatitis A Diagnosis[1]:

- **Clinically**: diagnosis begins with a thorough history and physical examination.
- Liver biochemistry typically reveals elevated ***liver enzymes***: so, if tests were done and results are revealing *High AST and ALT, mild elevation of bilirubin,* indicate hepatic inflammation or injury.
- ***Serology or viral markers****: IgM, IgG (lifelong immunity)*

➢ *IgM: indicates Acute infection and remains high for 3-6 months*, which is followed by the production of IgG.

➢ *IgG: indicates Past infection or vaccine.*

  - Anti-HAV IgG becomes predominant later in life and is commonly found in the general population over the age of 50.

Hepatitis A Diagnosis[2]:

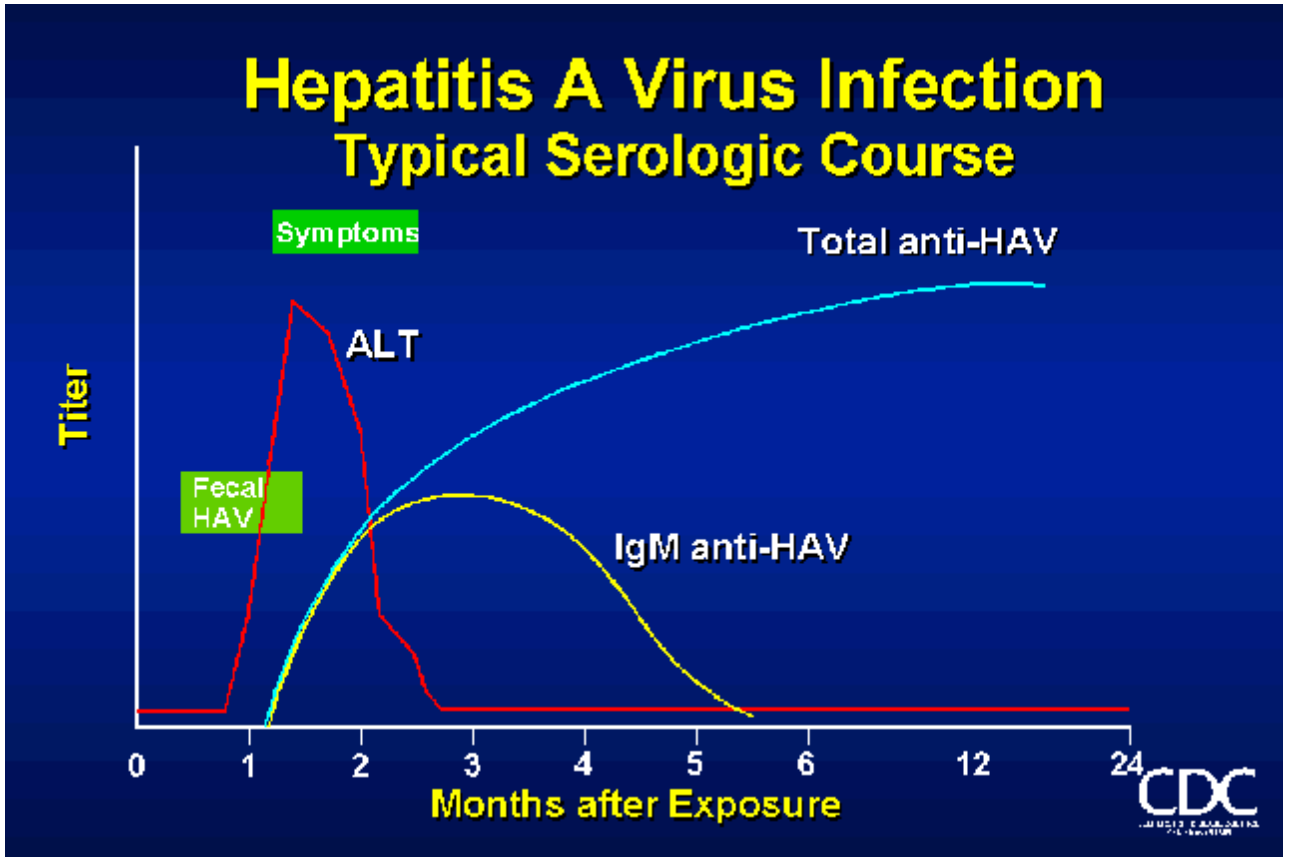
- **Hematological tests** in affected patients: often reveal **leukopenia** with **relative lymphocytosis**. Additionally, the erythrocyte sedimentation rate (ESR) may be elevated.
- Again, using immune electron **microscopy**, HAV particles can be identified in **fecal** specimens.
  - However, isolation of the virus in cell culture is used for research purposes (research tool) and is not routine in clinical practice.

Hepatitis A

- This graph shows the typical serological course in patients infected HAV.
- As previously mentioned, the virus can be initially detected in stool samples, and liver function tests, particularly ALT and AST are **elevated** early in the course.

❖ **Process of Antibodies production:**

- Anti-HAV **IgM** antibodies begin to rise about one month post-exposure, peak around the third month, and are eventually replaced by anti-HAV **IgG** antibodies, which indicate recovery and long-term immunity.
- Both previous infection and vaccination confer lifelong protection against HAV.



Summarizing, first elevated are the liver enzymes along fecally excreted HAV (even before symptoms), followed by IgM Anti-HAV which is later replaced by IgG, resulting in long lived immunity.

Treatment of Hepatitis A

- *Rx: Usually full recovery in 90% of patients in 3-6m.*

➢ *Acute:*

  - There is no specific antiviral treatment for acute hepatitis A.
  - *Mainly Supportive:* includes adequate nutrition, hydration, and bed rest. *Do not give Paracetamol and Alcohol.*
  - *Immunoglobulins; next slide.*

➢ *Fulminant hepatitis:*

  - *Supportive, but may need liver transplantation.*

- *Prevention:*

  - *Hygiene, Vaccine: killed, IM 2 doses separated by 3- 6 months.*
  - Preventive measures, such as avoiding contaminated food and water, are essential to reduce the risk of HAV infection.

Treatment of Hepatitis A

- In regard to immunization, **two** important terms are discussed:

1. **Passive immunization** involves the administration of immune serum globulin, which is most effective when given before or within 2 weeks of exposure to HAV. It provides short-term protection and is approximately 80–90% effective in preventing clinical illness.
2. **Active immunization** is achieved with the hepatitis A vaccine, which contains a formalin-inactivated/killed virus. It induces the production of anti-HAV antibodies like those produced after natural infection and offers nearly 100% protection with long-term immunity.

Prevention of Hepatitis A

- Remember, HAV is spread by the feco-oral route, so to prevent it's spread, the focus should be on how it's transmitted.
- Therefore, as a preventive measure, the spread of hepatitis A is reduced by interrupting the fecal-oral transmission route.
- This is typically achieved through:
  1. The **avoidance** of potentially **contaminated** food and water, especially undercooked shellfish, and through proper hand hygiene, particularly in high-risk settings such as childcare centers and mental health institutions.
  2. **Chlorination** of drinking water is also highly effective, as it is generally sufficient to **inactivate the HAV**.

Hepatitis E Virus

- Hepatitis E virus is a non-enveloped, single stranded RNA virus, similar but distinct from calicivirus.
- The viral particles in stool are spherical, 27 to 34 nm in size (Avg of 30nm), and unenveloped and exhibit spikes on their surface.

- Similar to HAV in transmission: Feco-oral transmission.
- Waterborne epidemics of hepatitis.
- High mortality rate in pregnant women.
- No chronicity, No carrier state.
- HEV resembles HAV.

Hepatitis E virus (HEV)

❖ **Clinical course:**

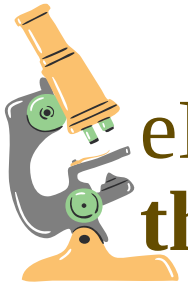
- Like HAV, HEV infection is often **subclinical** in children.
  - However, when symptomatic, HEV typically causes only acute disease, which may rarely progress to fulminant hepatitis.
- Clinically, acute hepatitis E resembles hepatitis A, but a key difference is that HEV infection often presents with higher bilirubin levels and more intense, prolonged jaundice.
- In endemic and developing regions, hepatitis E has the highest attack rate among young adults.
  - Most cases occur in areas with poor sanitation, where recurrent epidemics have been reported.

❖ **Transmission:**

- The infection is typically associated with the consumption of contaminated food and water.
- Does not appear to spread from person to person.

Hepatitis E virus (HEV)

- **Incubation period:** it's approximately 40 days, but usually 2-8 weeks.
- **Diagnosis:** confirmed by detecting specific anti-HEV IgM antibodies in the patient's serum. Also, by excluding other types, and **molecular real-time PCR.**
- **High risk group:** include pregnant women and malnourished individuals, these patients are most likely to develop severe hepatitis E, e.g. fulminating hepatitis.
- **Treatment:** no specific treatment, but supportive treatment as in HAV is used.
- **Case fatality rate:** normally it's 1-2% but significantly increased to 10-20% in high-risk group.
  - The case fatality rate (CFR) measures the proportion of confirmed deaths among confirmed cases of a disease and is expressed as a percentage or a decimal ratio, (measure severity).

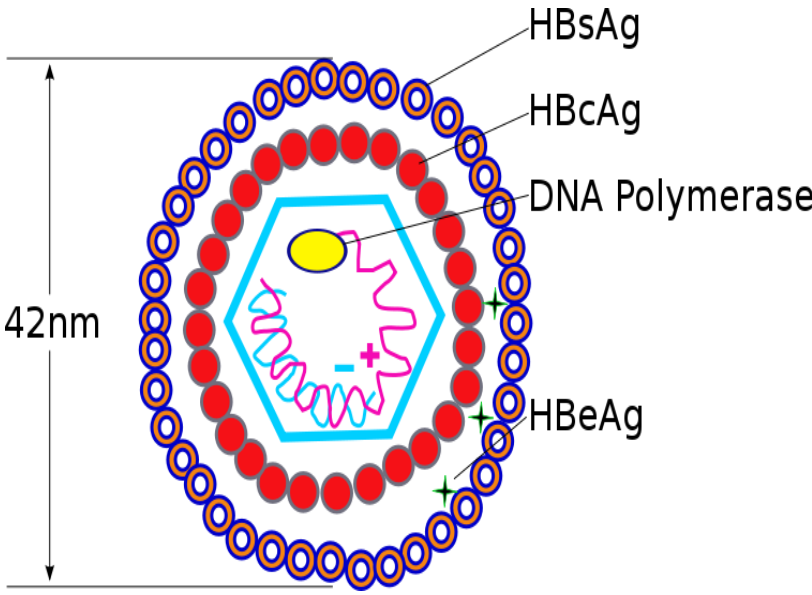


eLearning question: **What is the primary mode of transmission of the Hepatitis E virus in developing countries?**

A. Vertical transmission from mother to fetus
B. Blood transfusions
C. Sexual contact
D. Contaminated water

ANS: D

Hepatitis B virus



- **The smallest DNA virus known, with 3200 nucleotides.** (in terms of genome not size)
- Hepadnavirus, Partially Double stranded circular DNA **with a short and a single stranded piece** genome.
- Enveloped.
- Icosahedral nucleocapsid.
- Antigens:
- The main components of the virus include the (1)core - hepatitis B core antigen (HBcAg) and the (2)pre-corehepatitis B e antigen (HBeAg), and the (3)envelope of the virus contains the hepatitis B surface antigen (HBsAg).

Hepatitis B virus – Notes (pt.1)

- The pre-core hepatitis B e antigen (HBeAg) indicates active replication and infectivity.
- For replication, HBV has its own DNA-dependent DNA polymerase. and exists as a single serotype.

❖ **Hepatitis B infection:** asymptomatic or presents as a mild, **self-limited** illness in approximately 90% of cases, typically with jaundice and fever lasting a **few days to weeks.**

- However, up to 10% of patients may develop **chronic infection**, which can lead to liver **cirrhosis** or **hepatocellular carcinoma**. (unlike HAV infection)

❖ **HBV particle forms:** virions, spheres, and filaments.

Hepatitis B virus – Notes (pt.2)

- **HBV serotypes:** serotypes are classified based on a common group-specific antigen (A) and two pairs of mutually exclusive epitopes (either D or Y, and W or R) which are determined by the serological properties of the hepatitis B surface antigen (**HBsAg**). This classification results in **four** main serotypes.
  - The four serotypes are: adr, adw, ayr, ayw

- **Treatment:** there's an HBV vaccine.

Hepatitis B virus

- **Transmission:**
  - Parenteral via blood or plasma.
  - Needle stick injury, pose a high risk of transmission especially among medical personnel.
  - Vertically: mother to baby, during or soon after birth.
  - Body fluids, for example semen and saliva.
- **Risk groups:**
  - Health care workers
  - Drug abusers
  - Recipients of blood or its products (blood should be ideally screened)
  - Dialysis patients, Homosexual men...

Hepatitis B virus – Epidemiology.

- HBV has a global distribution, with an estimated 2 billion people showing serological markers of past or present HBV infection.
  - Among them, around 400 million have **chronic HBV infections**, thus carriers.
- The global incidence of death due to HBV-related complications is approximately 1 million people per year.
- Infection of hepatitis B is called **serum hepatitis**.

❖**Transmission:** transmitted through **intravenous routes** such as transfusions of infected blood or the use of contaminated needles, including among people who inject drugs. It may also spread via **practices**, such as tattooing and acupuncture. Additionally, transmission can occur through **close personal contact**, including sexual intercourse, particularly among men who have sex with men (MSM).

Hepatitis B virus

- **Pathogenesis**:
  - Blood borne > liver cells > hepatocytes injury and necrosis (piecemeal necrosis) -Largely cell mediated.
- **Clinically**:
  - Incubation period: 1-4 months – 7 to 160 days with an AVG of 70 days (10 weeks) – (infectious dose)
- Based on the immune response, patients can be:
  - ✓**Asymptomatic**: 90% of children and 50% of adults (increased liver enzymes)
  - ✓**Symptomatic**:
    - Pre-icteric phase: flu like symptoms nausea, anorexia, malaise
    - Icteric phase: Jaundice, pale stool, dark- coloured urine, increased liver enzymes and bilirubin.
  - ✓Also, acute and chronic.
- ✓ Rule: increased involvement of the liver, increased risk of cholestasis.
- Hepatitis can cause cholestasis, leading to light-colored stools, dark urine, and **jaundice** due to impaired bile flow.
- Having antibodies to the Hepatitis B **surface** antigen (HBsAg) gives lifelong immunity

Hepatitis B virus infection

❖ **Piecemeal necrosis** (interface hepatitis):

- Common form of necrosis, with a characteristic histological finding in hepatitis.
- Involves an inflammation that extends from the portal tract into the surrounding periportal zone (around portal vein), leading to necrosis of the **periportal hepatocytes** and destruction of limiting plate. (“**hepatocytes injury and necrosis** ”)

- **Acute hepatitis B infection** often begins gradually, with symptoms such as fatigue, reduced appetite, nausea, and discomfort or a sense of fullness in the right upper abdominal area.
  - Early in the illness, some patients may also report joint pain and swelling, and occasional frank arthritis (Antigen – Antibody mediated).
  - A skin rash may also appear in some individuals as part of the body’s immune reaction to the virus.

Hepatitis B virus infection

❖ Fulminant hepatitis:

- A rare complication of hepatitis B infection, occurring in less than 1% of cases, and can be life-threatening; leads to death.
  - ✓ Remember most HBV deaths are due to complications.
- Characterized by extensive liver necrosis.

❖ Chronic hepatitis B:

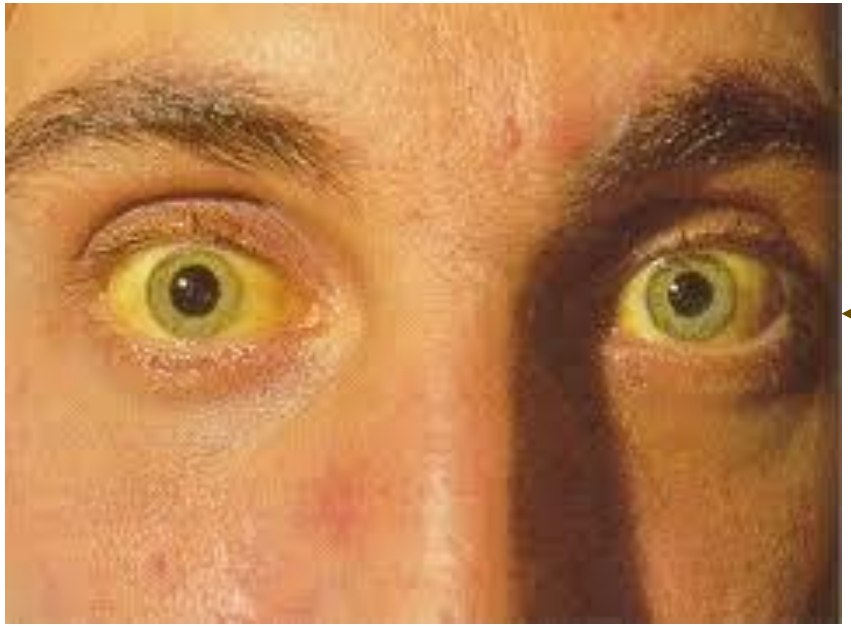
- Develops in approximately 10% of infected individuals, with a significantly higher risk among younger patients, especially neonates. Around 20% of those with chronic hepatitis B may eventually develop hepatocellular carcinoma.
- Approximately 90% of neonates infected with hepatitis B become chronic carriers.
  - ➢ The likelihood of developing chronic disease is inversely related to the age at which the infection occurs.

❖ **Hepatocellular carcinoma:** caused by the integration of the viral DNA with the DNA of the hepatocyte.

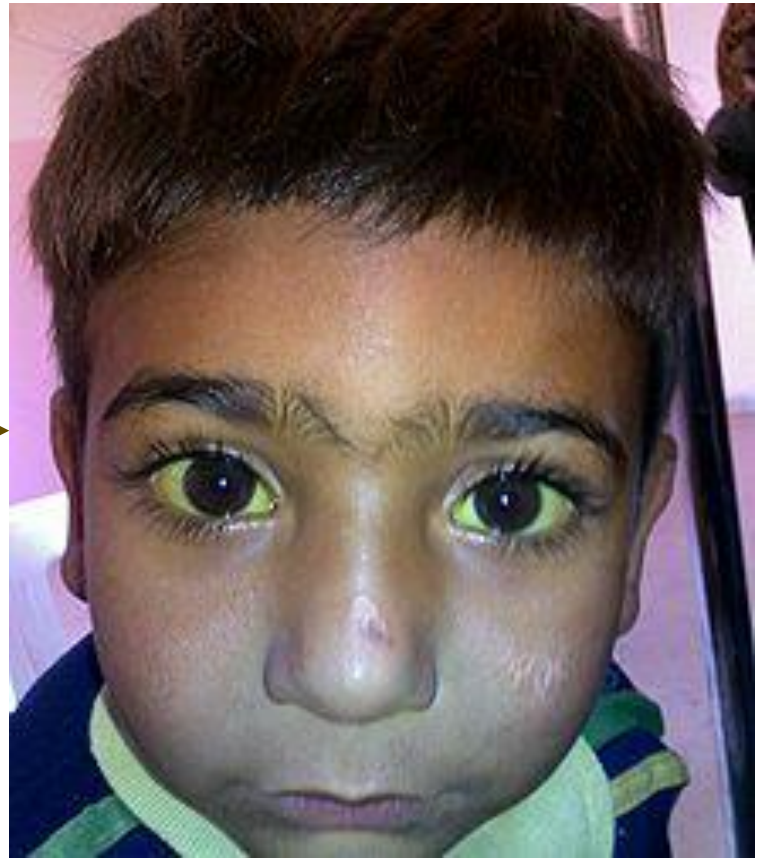
Hepatocellular injury in hepatitis B infection is primarily mediated by the host immune response, especially **$CD8^+$ cytotoxic T lymphocytes**.

While **extrahepatic manifestations** such as arthritis and vasculitis result from circulating **antigen-antibody complexes**.

Hepatitis B



Jaundice



Increased involvement of the liver.

Caused by cholestasis. Patients are in icteric phase

Symptoms may persist for several months before resolving.

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

See next slides for explanation

Summarizing HBV infection – Pt. 1

- HBV in children is generally less severe than in adults and is often asymptomatic.
- Clinically apparent illness occurs in about 25% of infected patients.
  - Fulminant hepatitis occurs in about 1% of icteric patients and can be fatal.
- The majority (~90%) recover, typically marked by declining fever and return of appetite.
- Chronic hepatitis develops in 5–10% of cases, often following mild or asymptomatic initial disease.

Summarizing HBV infection – Pt.2

- In those who develop chronic hepatitis:
  - About **one-third** progress to chronic active hepatitis, which may lead to:
    1. Liver scarring (cirrhosis)
    2. Liver failure
    3. Primary hepatocellular carcinoma
  - The other **two-thirds** develop chronic passive (inactive carrier) hepatitis, which is less likely to cause serious issues.
- Chronic hepatitis is often discovered incidentally through elevated liver enzyme levels in routine blood tests.
- Chronically infected individuals:
  - Are the **main source** of HBV transmission.
  - Are at increased risk of fulminant hepatitis, especially when **co-infected with HDV**.

Diagnosis of HBV:

1. Clinical picture
2. Liver, kidney function tests, other tests to role out other causes e.g: CMV, EBV infection
   - Also, to determine the grade of the inflammation and stage of fibrosis, thus prognosis, liver biopsy is examined.
3. Serology:
   - We rely on:
     - S, e antigens and antibodies.
     - Anti core antibodies.

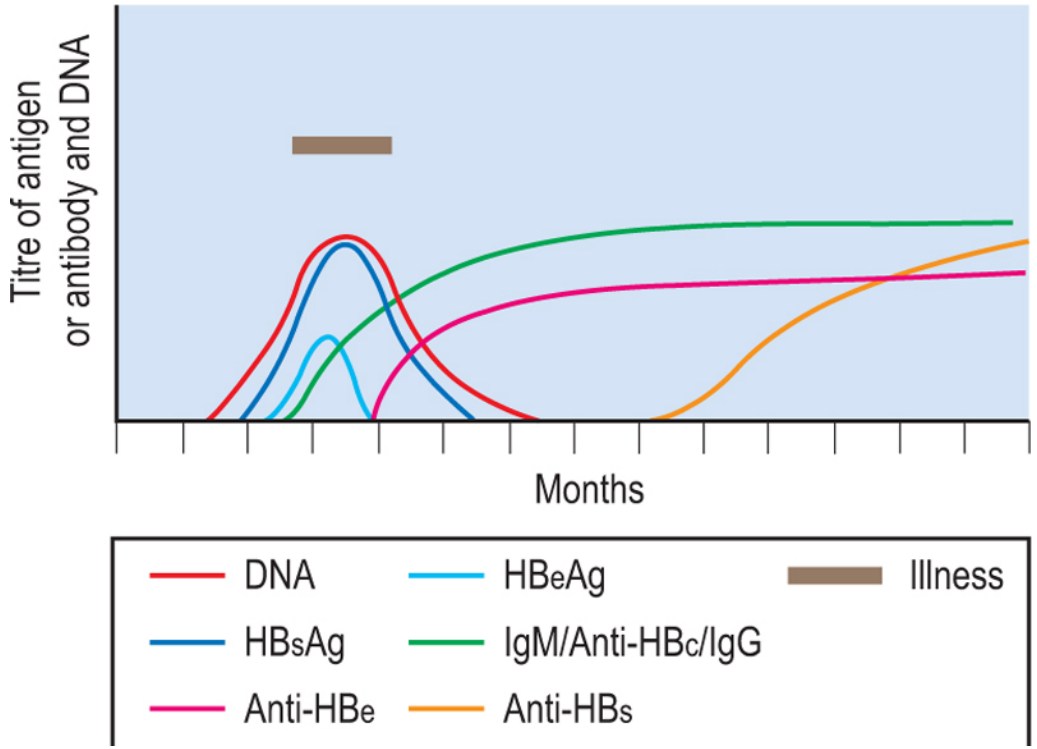
Patients with jaundice tend to have IgM antibodies against the hepatitis B core antigen (HBcAg) and may also test positive for hepatitis B surface antigen (HBsAg).

Previous infections show (either or both) anti-core and anti-surface antibodies in the form of IgG; as it's a past infection not acute.

- Viral DNA detection by PCR is the most accurate marker.

- Hepatitis B surface antigen (HBsAg) is a **general marker** of HBV infection, regardless of the stage. Its persistence for more than 6 months indicates **chronic infection**.

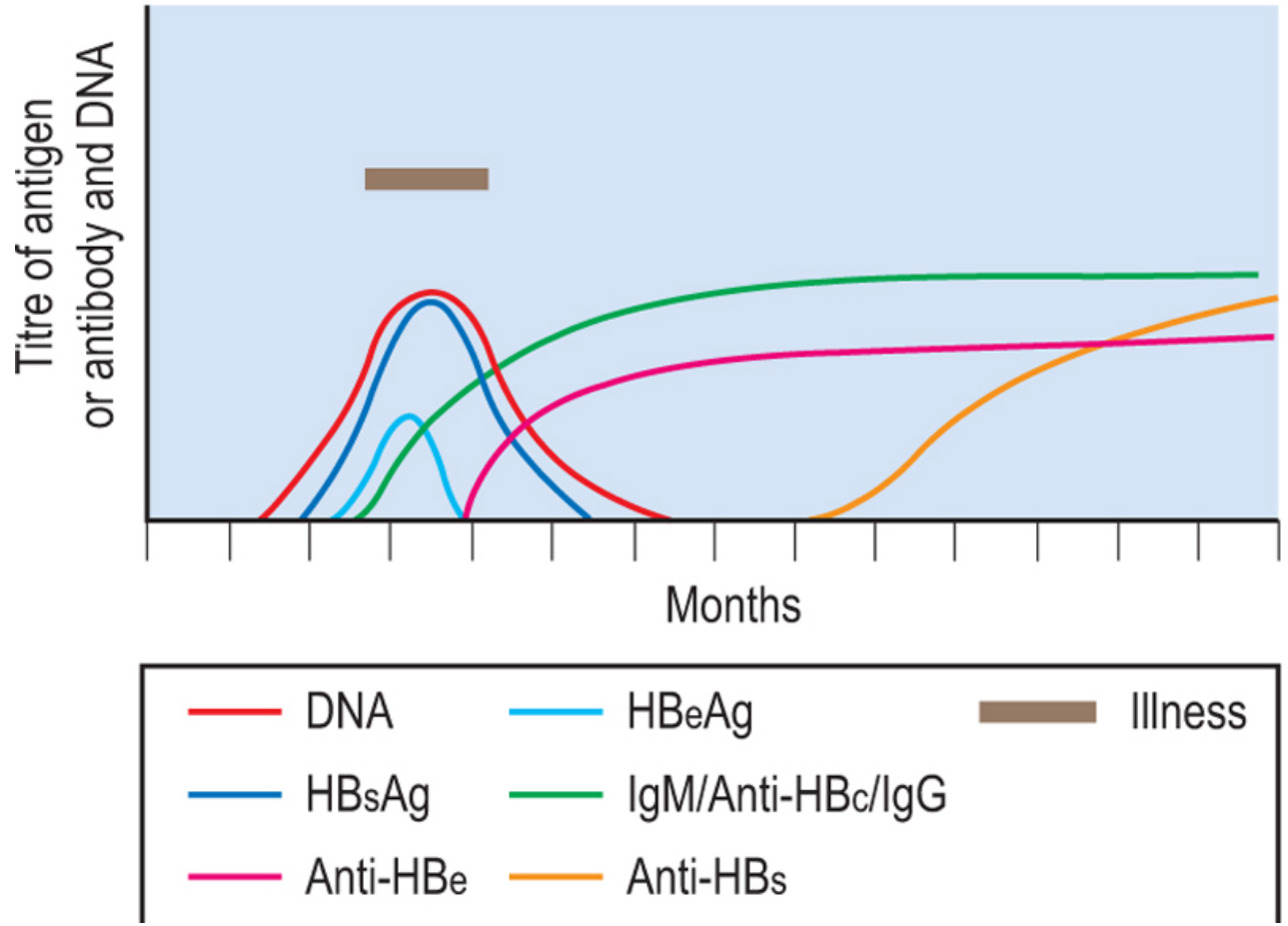
- The presence of antibodies against HBsAg (anti-HBs) signifies that the immune system has successfully **cleared** the virus and **recovery and immunity**.



- It is important to distinguish between detecting the antigen (e.g., HBsAg, HBeAg), which indicates active infection, and detecting antibodies (e.g., anti-HBs, anti-HBe), which typically indicate immune response or the resolution of infection.

- IgM antibody to hepatitis B core antigen (Anti-HBc IgM) indicates an acute infection. While, IgG antibody to hepatitis B core antigen (Anti-HBc IgG) suggests either a past resolved infection or chronic hepatitis B.

- The presence of hepatitis B e antigen (HBeAg) indicates active viral replication and infectivity.
- The appearance of **antibodies** to HBeAg (anti-HBe) suggests a cessation of viral replication. however, patients may still test **positive** for hepatitis B surface antigen (HBsAg) made by the integrated HBV, indicating ongoing **infection**.



- HBV DNA detected by PCR is a more accurate indicator of active viral replication than HBeAg, especially in cases of escape mutants.
- DNA is used for monitoring the response to therapy.

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

- This table summarizes serology of HBV infection.
- One can notice that the antibody for HBs antigen doesn't appear in blood spontaneously with the antigen itself.
  - For example, in the acute phase HBsAg is detected while HBsAb is not. Also, after complete recovery HBsAb is detected, while HBsAg is not.
- **Window phase:** the virus is still active, but the surface antigen (HBsAg) is no longer detectable, and antibodies against the surface antigen (anti-HBs) have not yet appeared. Here, HBcAb is detectable.
  - How to detect the virus in the window phase? By Anti-HBc IgM.

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

- In case of antibodies produced:
  - Prior infection results in the production of Ab to all Ag.
  - While immunization results in the production of Ab to only the HBsAg.

Treatment of ***Hepatitis B virus****:*

1. No specific treatment for HBV is present.
2. *Peg Interferon alpha*, used in cases of chronic hepatitis, provides a long-term benefit for 1/3 of patients.
3. High calorie diet is desirable.
4. *Lamivudine, Tenofovir, entecavir*

!! Corticosteroid therapy has no proven benefit in the management of uncomplicated acute viral hepatitis

❖ Chemical agents:

1. *Lamivudine:*

- A potent inhibitor of HIV and also shows activity against hepatitis B virus (HBV), both in vitro and initial clinical trials. However, **resistance** to the drug develops in approximately 25% of patients after 12 months of therapy.

2. *Tenofovir, entecavir*

- Because of resistance to Lamivudine, these agents are used.
- **Nucleotide analogs of adenosine monophosphate**.
- Newly approved for the treatment of chronic hepatitis B.

Prevention of ***Hepatitis B virus****:*

1. Avoidance of needle stick injuries by safe practices, for medical personnel and injection drug users.
2. *Immunoglobulin / passive*
   - *Accidental exposure in non vaccinated*
   - *Newborns of infected mothers*
3. *Vaccine (Recombinant HBsAg), 3 I.M doses at 0, 1, 2 OR 6 months*
   - Vaccination is highly effective.
   - Vaccine can be given for individuals at increased risk of infection, such as healthcare workers. It is also routinely administered to neonates in many countries.
   - *Fridge storage*
   - *Check response to vaccine by measuring anti HBsAg antibodies 2 months after last dose (>10mIU/ml is protective)* → if more than 10 million international units per ml, it's protective.
   - *Part of ministry of health vaccination program (2, 3, 4 months)*

Prevention – *Immunoglobulin*

- **Hepatitis B immunoglobulin (HBIG) may be used to:**
  1. Protect individuals exposed to hepatitis B virus (HBV):
     - It is effective as post-exposure prophylaxis if administered within 48 hours of exposure.
  2. Provide protection to neonates at high risk of HBV infection:
     - Especially those born to HBsAg-positive mothers, HBIG is given at birth in combination with the first dose of the hepatitis B vaccine.

- **Other measures of prevention:**
  - Screening of blood donors, blood, and body fluids.
- **Prevention of HBV in Jordan:**
  - The Hepatitis B virus component is included in the Hexaxim vaccine (المطعوم السداسي), which is typically administered in 3 doses at the 2nd, 3rd, and 4th months of an infant's life.

Hepatitis D virus

- Small ssRNA virus.
- Causes Delta hepatitis (Hepatitis D).
- *It needs HBV to replicate and to be transmitted.*
  - HBV *provides the envelop,* so HDV requires the HBsAg for transmission, that's why HDV is only found in presence of chronic or acute hepatitis B infection
- *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*

- Delta hepatitis is most prevalent among groups at high risk for hepatitis B, such as injection drug users, up to 50% of these individuals may have IgG antibodies to the delta virus antigen.
- Other at-risk populations include patients undergoing dialysis.

HDV Infection

❖ **Two Major Types of Hepatitis D (Delta) Infection:**

1. **Co-infection with HBV and HDV:**
   - Occurs when an individual is simultaneously infected with both Hepatitis B virus (HBV) and Hepatitis D virus (HDV).
   - Results in acute clinical hepatitis that is clinically indistinguishable from acute hepatitis A or B.
   - Fulminant hepatitis is significantly more common than with HBV infection alone.

2. **Superinfection with HDV:**
   - Occurs when a person with chronic HBV infection later acquires HDV.
   - Clinical consequences include:
     - **Relapse of jaundice**
     - High risk of developing **chronic cirrhosis**

HDV – Diagnosis, treatment, and prevention

❖ Diagnosis:

- Most diagnosed by detecting IgM and/or IgG antibodies against delta antigen in serum.
  - **IgM** appears within 3 weeks of infection and persists for several weeks.
  - **IgG** persists for years.

❖ Treatment:

- The response to treatment (interferon alpha) is poorer in HDV-HBV co-infection compared to HBV infection alone.
- Treatment usually requires:
  - Higher doses.
  - Sustained improvement is seen in only ~25% of patients.
  - ➢ This is due in part to HDV's dependence on HBsAg for its replication.

❖ Prevention: (limiting transmission of HBV, limits transmission of HDV)

- Individuals with hepatitis B or D should not donate blood, organ tissues or semen.
- Reducing the use of contaminated needles and syringes among people who inject drugs will decrease HBV transmission.
- Use of needle safety devices by healthcare workers.

eLearning question: **Regarding the Hepatitis D virus (HDV), which statement is <u>true</u>?**

A. HDV is a non-enveloped virus.
B. HDV is a defective virus that requires the Hepatitis B virus to replicate.
C. HDV requires co-infection with Hepatitis A virus to cause disease.
D. HDV can independently infect and replicate in a host cell.

ANS: B

Hepatitis C virus

- Flavivirus, Enveloped, single stranded, positive sense RNA virus; a very simple genome, consisting of just 3 structural and 5 non-structural genes. Also, there're regions called **quasi species**, which are hyper variable regions in the envelop glycol protein.
- No polymerase in the virion (unlike HBV)
- 6 genotypes, and multiple subtypes: needed for Rx and medicolegal
- Spread is still less well understood when compared to transmission of HAV, HBV, and HDV. But can be via:

1. Infected blood, well documented, until screening blood for transfusions was introduced, it caused the great majority of cases of post-transfusion hepatitis.
   - Hepatitis C was the major cause of post-transfusion hepatitis until a serologic test for screening blood donors was developed.
2. Sexual contact, but to a lesser extent than HBV.
3. Needle sharing, accounts for 40% of the cases.

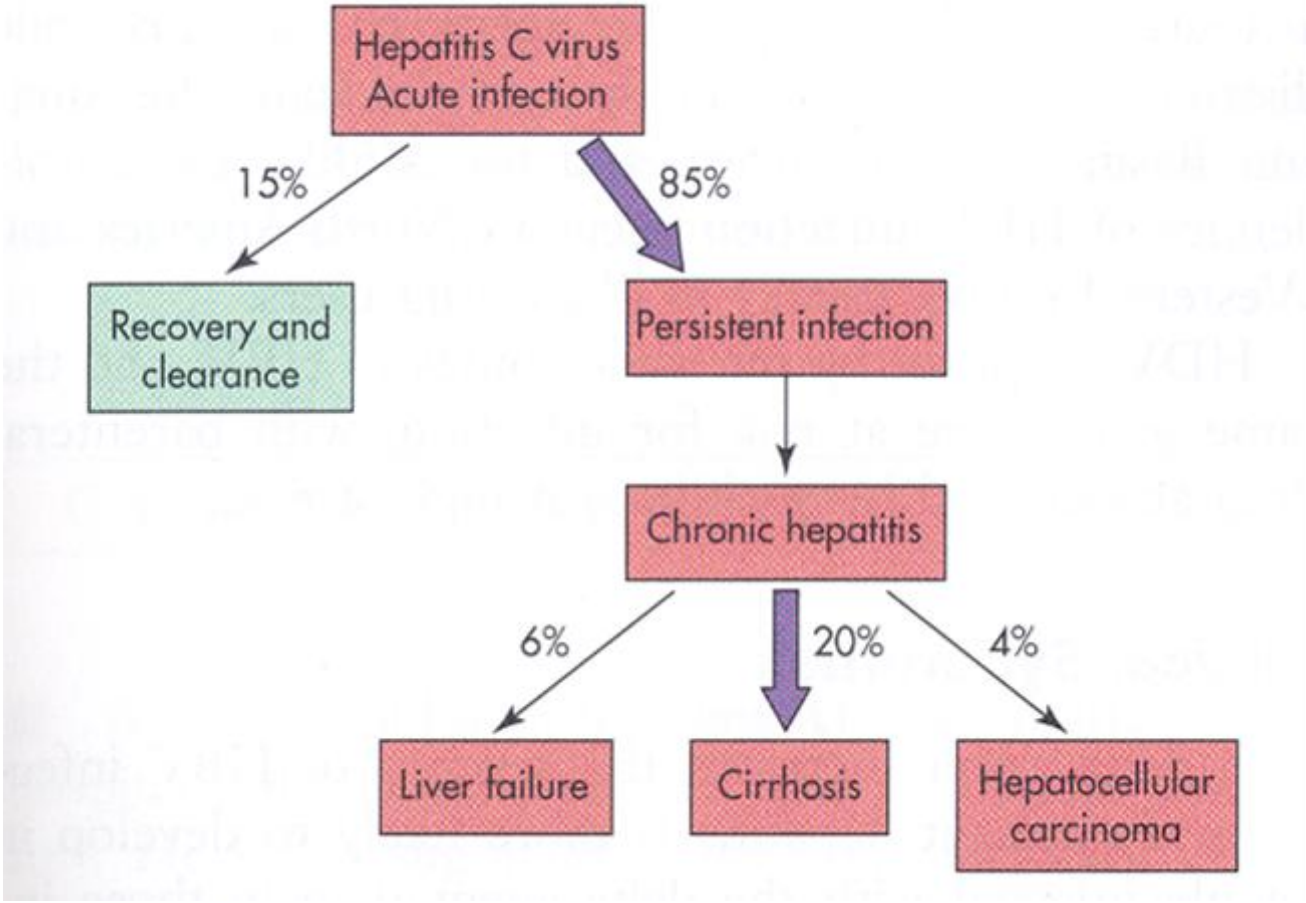
Hepatitis C virus

- 6 - 8 weeks incubation period / most infections are sub-clinical.
  - Hepatitis C is an insidious disease that typically does not cause a clinically apparent acute illness.
  - In about one-quarter of infected individuals, the first manifestation may be smoldering chronic hepatitis, which can eventually progress to liver failure.
- Clinical infections are generally less severe than HBV, damage due to cell mediated immune response.
- HVC 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.
- Screening donor blood for hepatitis C antibodies has significantly reduced the incidence of post-transfusion hepatitis C, with an 80% to 90% decrease in transmission through blood transfusions.
- Individuals at risk of HCV infection include chronic hemodialysis patients and spouses of those infected with hepatitis C.
- In the United States, approximately 3.5 million people have antibodies to the hepatitis C virus (HCV).

Hepatitis C virus

Incubation period in slides is 6-8 weeks. The doctor said 6-12 weeks. Resources indicated that it's 2 weeks to 6 months. so...

- After the incubation period, HCV infection can either be:
  - Asymptomatic.
  - Mild and anicteric, that can result in a chronic infection (carrier state) in up to 85% of infected persons.
- Chronic hepatitis can result in a liver failure and some late sequelae like liver cirrhosis and hepatocellular carcinoma.
- The average time from hepatitis C virus infection to the development of chronic liver disease typically ranges from 10 to 18 years.



Hepatitis C virus

Diagnosis:

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

- Quantitative assays of hepatitis C RNA can be used for diagnosis, prognosis estimation, prediction of response to interferon therapy, and monitoring treatment. However, there is a poor correlation between viral load and liver histology.

Treatment:

- *Antivirals.*
- The current treatment of choice for hepatitis C is combination therapy with **interferon-alpha** and **ribavirin**.

! Corticosteroids are not beneficial in the management of hepatitis C infection.

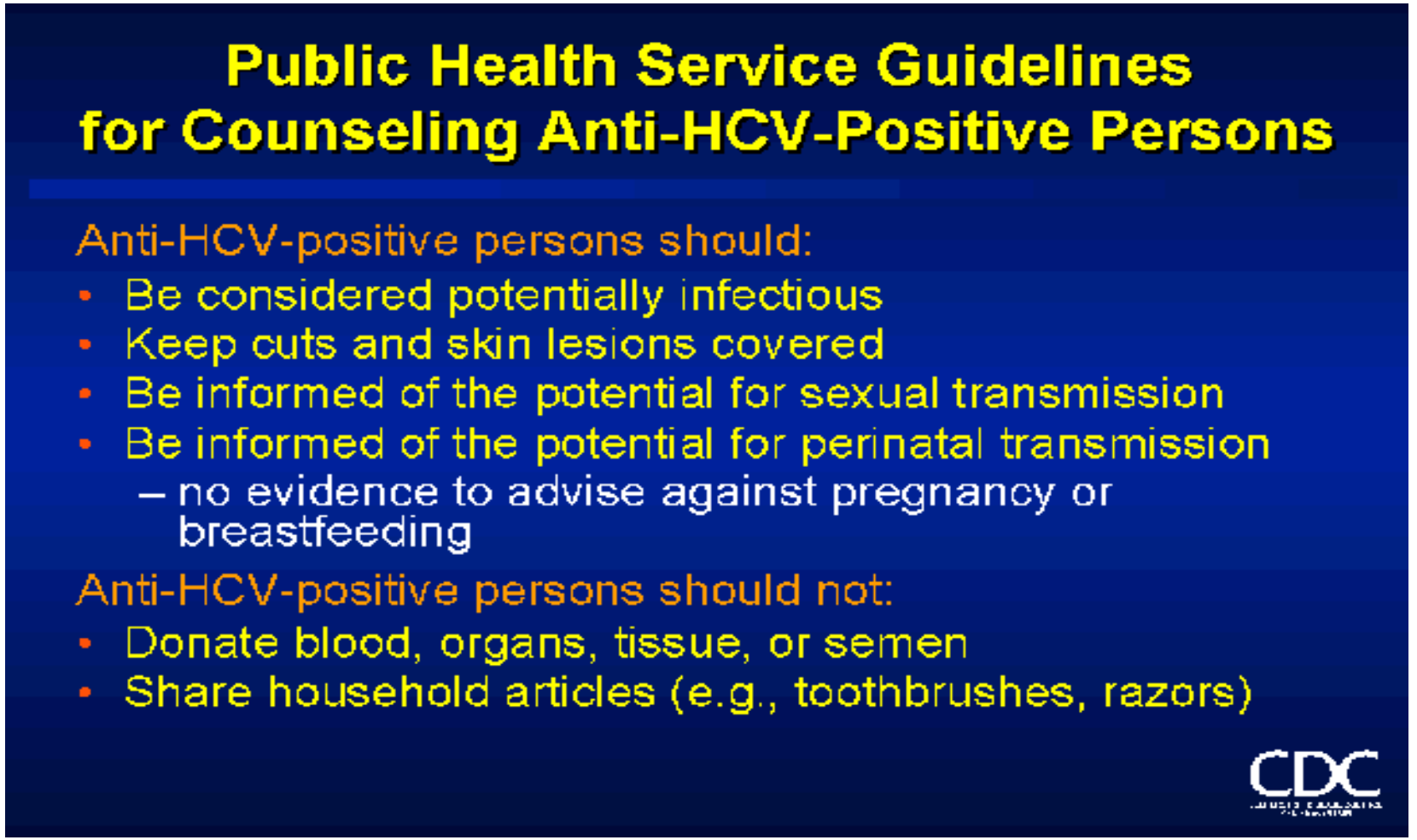
Hepatitis C virus

❖ ***Diagnosis:*** ***Anti HCV IgM***

- Antigens of hepatitis C are not detectable in the blood; therefore, diagnostic tests rely on detecting antibodies to HCV.
- Unfortunately, the antibody response during acute infection remains **negative for 1 to 3 weeks** after the onset of clinical symptoms and **may** never become positive in up to 20% of patients with self-limited acute hepatitis C.
- Now, antibody testing and detection is done by:
  - Enzyme immunoassay (EIA)
  - Immunoblot assay
- Even with newer assays, IgG antibodies to hepatitis C may take up to 4 months to develop, making the serological diagnosis of acute hepatitis C challenging.

Hepatitis C virus / prevention

- No vaccine; not clear whether prophylactic immune serum globulins protect against Hepatitis C.
- Blood screening.



Important preventive measures include:

1. Avoidance of injection drug use.
2. Screening the blood products.

Post exposure prophylaxis

This high-value table explains post-exposure prophylaxis for 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	?

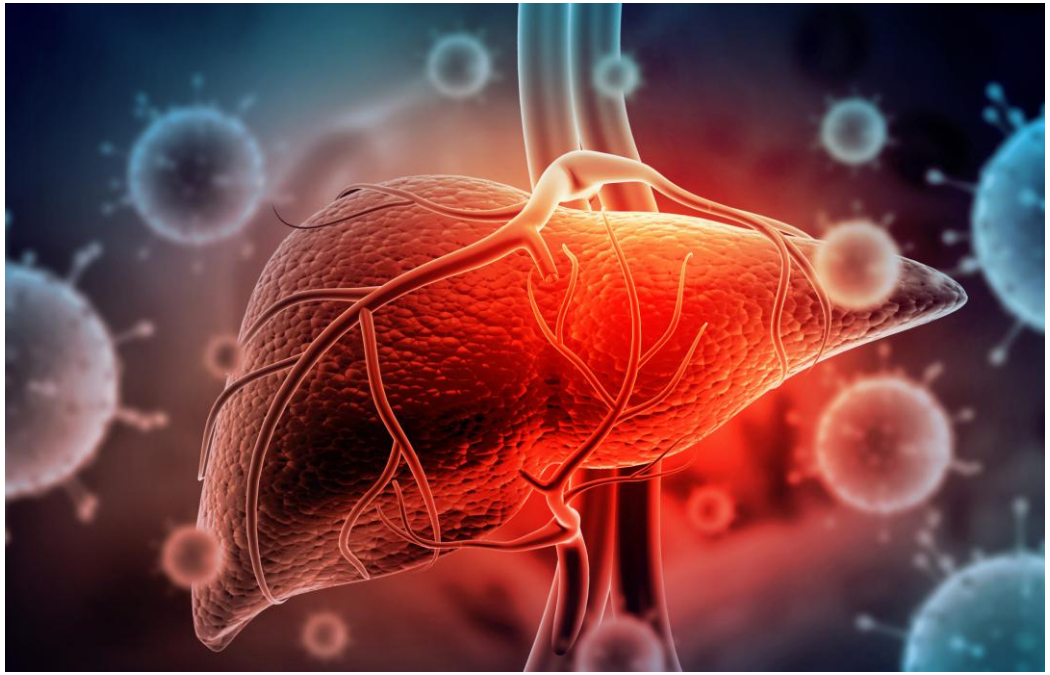
Abbreviation: Plus and minus signs indicate relative frequencies.

[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.

Quiz on this lecture



الحمدلله الذي بنعمته تتم الصالحات

The End

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	27	-	(in terms of genome not size), note added.
	43	Here, **HBcAg** is detectable.	Here, **HBcAb** is detectable.
	48	that's why **HBV** is only found in presence of chronic or acute hepatitis B infection	that's why **HDV** is only found in presence of chronic or acute hepatitis B infection
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

References:

1. Liver Function Test.
2. Case fatality rate.
3. WHO: Hepatitis B.
4. المطعوم السداسي
5. Dirty medicine: hepatitis B serology.