Viral Hepatitis B , C , D and G

Lecture objectives:

- Introduction to hepatitis
- Characteristics of viral hepatitis
- Mode of transmission
- Markers of hepatitis infections Serological profile Stages of hepatitis infection
- Lab diagnosis
- Management & treatment

Color index:

- Important
- Doctors' note
- Extra
- Found in Girls' slides
- Found in Boys' slides

EDITING FILE

Hepatitis

Definition:

Is inflammation of the liver.

Etiology:

- **Primary infections:**
  - Hepatitis A virus (HAV).
  - **Hepatitis B virus (HBV).**
  - **Hepatitis C virus (HCV), was known as non-A non-B hepatitis.**
  - **Hepatitis D virus (HDV) or delta virus.**
  - Hepatitis E virus (HEV).
  - Hepatitis F virus (HFV).
  - **Hepatitis G virus (HGV).**
- **As part of generalized infection:**
  - CMV[1].
  - EBV[2].
  - Yellow fever virus.

- Hepatitis F has been reported in the literature but not confirmed.
- Viral hepatitis is divided into two large groups, based on the **mode of transmission:**
  1. Enterically transmitted hepatitis or **water borne hepatitis**. This group includes **hepatitis A and E viruses.**
  2. **Parenterally transmitted hepatitis or blood borne hepatitis. This group includes hepatitis B, C, D & G viruses.**

Hepatitis B Virus

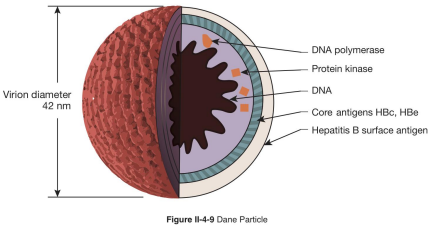
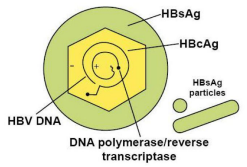
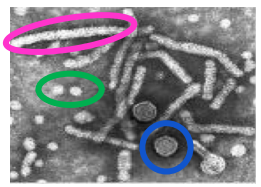


Figure II-4-9 Dane Particle

Characteristics:

- Family of **Hepadnaviridae.**
- There are 8 known genotypes (A-H), genotype D is the dominant in Saudi Patients
- **Virion consists of:**
  - **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[3].**
  - The virus contains the enzymes reverse transcriptase, protease enzyme.





- **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 form filaments.**
  - **The complete HBV particles (Dane particles)** and they are 42-nm in diameter

1. Cytomegalovirus
2. Epstein-Barr virus
3. All hepatitis viruses are **RNA** viruses EXCEPT hepatitis B which is a **DNA** virus

Hepatitis B Virus

Transmission:

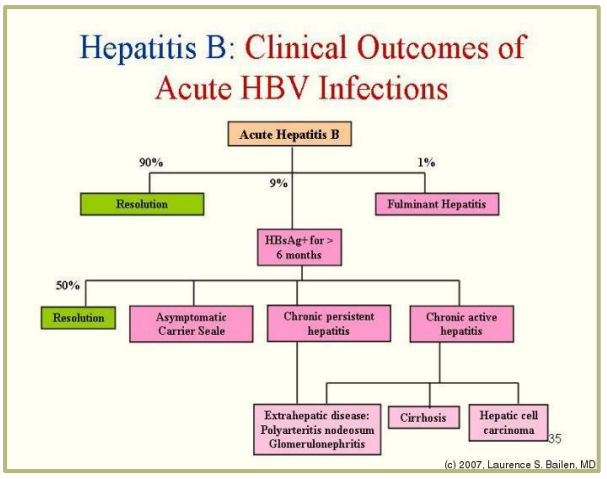
Transmission		
Parentally	**Sexually**	**Perinatally**
• Direct exposure to infected blood or body fluids (e.g. **receiving blood** from infected donor). • Using contaminated or not adequately sterilized tools in surgical or cosmetic practice (**dental**, tattooing, body piercing)[4]. • Sharing contaminated needles, razors, or tooth brushes.	• The virus is present in blood and body fluids. • By having sexual contacts with infected person, virus is present in semen and vaginal secretion (Homosexual[1])	• Infected mothers can transmit HBV to their babies mostly **during delivery.** • **Breastfeeding** is also way of perinatal transmission. • Mostly(perinatally) during delivery,nursing , breastfeeding and **less likely through placenta**[2] (vertical transmission)

Risk Factors:

- **Intravenously drug users.**
- Hemodialysis patients.
- Patients receiving clotting factors.
- Recipient of blood transfusion, before 1992.
- Individuals with multiple sexual partners
- Health care workers with frequent blood contact.
- Individuals who exposed to tattooing , body piercing or cupping.

Clinical Outcomes:

- 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**[3], characterized by massive liver necrosis, liver failure and death.



1. Because the rectum is a highly vascularized area
2. It's less likely for the mother to transmit the virus to the baby during pregnancy
3. Seen in about 1% in ALL types of viral hepatitis
4. It stays on the surfaces and resist the environment (very virulent virus) , unlike HIV which dies outside the human body.

Hepatitis B markers

(Important)

Types	Description	Serological profile of acute HBV infection
HBV DNA	- **Markers of infections.** - Contagious	**1st marker that appears in circulation**, 3-4 weeks after infection.
HBsAg Hepatitis B surface antigen	- **Markers of infections.** - Contagious	- The **2nd** marker that appears in the blood and persists for **<6** months, then disappears. **- In chronic infection:** **- HBsAg** may persist in the blood **for life** OR - Some patients will become immune after years and the **HBsAg** disappears and **anti-HBs Ab[3]** will be detected in the serum and persists for life. (for several years)
HBeAg Hepatitis B e antigen	- Markers of **active virus replications** - the patient is **highly** infectious, the virus is present in **all body fluids.** **- Highly Contagious**	- The **3rd** maker that appears in circulation and disappears before HBsAg. - it indicates active viral replication.
Anti-HBe Antibody to hepatitis B e antigen	- Markers of **low** infectivity - the patient less infectious. - Contagious	After the disappearance of HBeAg, it Appears and usually persists for several weeks to several months.
Anti-HBc[2] Antibody to hepatitis B core	- Markers of **exposure** to hepatitis B infections. - Contagious	Is the **1st antibody that appears in the blood** and usually persists for several years.
Anti-HBs[1] Antibody to hepatitis B surface antigen	**- Markers of immunity.** **- Not Contagious.**	-Anti-HBsAb 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 infections**

Acute phase: (For figure 1)

- The first antibody to appear in blood: **Anti-HBc(IgM)**
- Anti-HBc indicates viral infection in the past.
- Laboratory findings in **Vaccinated** patients: **Only Anti-HBs**
- Laboratory findings in patients who **recovered from previous HBV** infection **(Immune patients)**: **Anti-HBs and Anti-HBc**

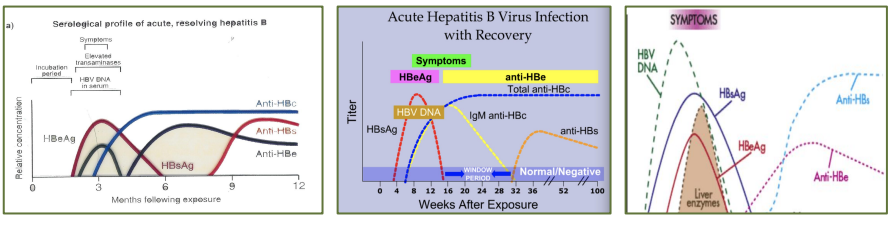
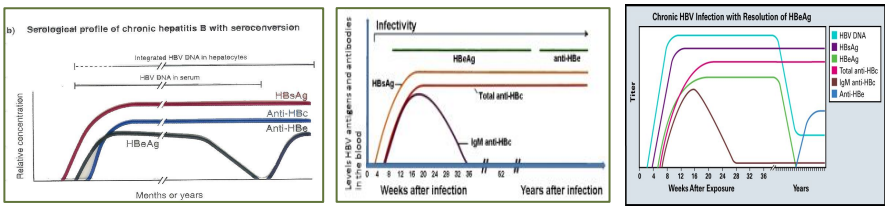


Figure (1)

Chronic phase:

- Notice the Anti- HB cAg founded in the chronic HBV infected patient



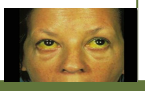
1- In a **vaccinated** person , anti-HBsAg would be positive with a negative HBsAg
2- What's the first antibody to appear in blood? Anti-HBc followed by Anti-HBe then Anti- HBs
3- The period between end of detection of HBsAg and beginning of detection of HBsAb is called window period or window phase.
- CLICK here for a cool pic from first aid

Acute and Chronic hepatitis infection

Acute Hepatitis B Infection

- Acute viral hepatitis usually lasts for several weeks or < 6 months.
- Incubation period varies from 2 to 4 months.
- most acute hepatitis B is asymptomatic or anicteric.

If symptomatic hepatitis as

Anicteric Hepatitis (phase) (No jaundice)	Icteric[1] Hepatitis (phase) (With Jaundice)	Convalescent phase
Low grade fever, anorexia, malaise, nausea, vomiting and pain at the right upper quadrant of the abdomen with raised liver enzymes.	about 25% of the patient become icteric Jaundice with raised bilirubin, dark bile containing urine and pale stools. 	Recovery phase

Chronic Hepatitis B Infection

- Chronic hepatitis is limited to hepatitis B, C , D and may be G viruses.
- **Defined by:**
  the presence of **HBsAg** or **HBV-DNA** in the blood for **> 6 months.**
- **The majority of patients with chronic Hepatitis B are Asymptomatic** or have mild fatigue only, may only be detected by elevated liver enzyme on a routine blood chemistry profile.
- symptoms include right upper quadrant abdominal pain, enlarged liver & spleen. Jaundice may or may not developed, fatigue.
- **Chronic active hepatitis :** The major long term risk of chronic HBV infection are **cirrhosis** with **hepatic failure** and **hepatocellular carcinoma** ,when HBV genome integrates into hepatocytes DNA

Three phases of chronic hepatitis infection

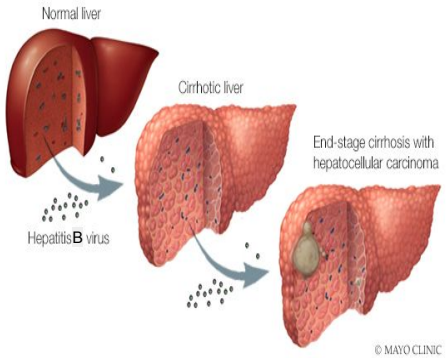
The replicative phase	Inflammatory phase	Inactive phase
- The patient is **positive** for HBsAg, **HBeAg** and HBV-DNA, - High viral load > 10^5 copies/ml -**ALT** is **normal** or nearly normal -Liver biopsy shows minimal damage.	- HBsAg positive for > 6 months, HBeAg positive, Decline in HBV-DNA in the blood - VL is > 10^5 copies/ml, - **ALT** is **elevated**, - The immune system attacks hepatocytes harboring the virus, -Liver biopsy shows damage to hepatocytes.	- **Negative** for **HBeAg**, Positive for anti-HBe, HBV-DNA - VL < 10 5 copies/ml - **Normal ALT**.

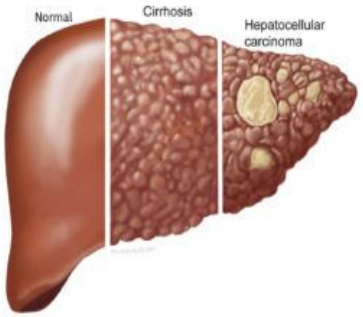
1- Icterus is also known as jaundice or yellow jaundice.

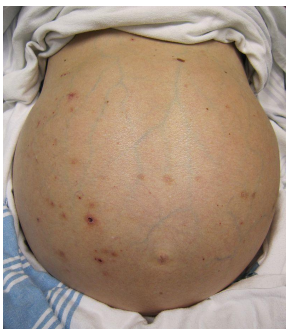
Complication of Chronic hepatitis infection

Hepatocellular carcinoma	
Definition	-One of the most common cancers in the world. - Also, one of the most deadly cancers if not treated.
Cause of chronic liver diseases	Hepatitis B and C viruses
Symptoms	Abdominal pain, abdominal swelling, weight loss, anorexia, vomiting, jaundice.
Physical examination	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.

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







Hepatic cirrhosis

Hepatitis B

Lab diagnosis of hepatitis B infection

- **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.**
  - **Detection of HB-DNA by PCR.**
- **Additional lab investigations:**
  - Liver function tests (LFT).
  - Ultrasound of the liver.
  - Liver biopsy to determine the severity of the diseases.

Treatment of hepatitis B infection

- There are several approved antiviral drugs:
  1- Pegylated alpha interferon, one injection per week, for 6- 12 months.
  2- Lamivudine, antiviral drug, nucleoside analogue. One tablet a day for at least one year.
  3- Adefovir, antiviral drug, nucleoside analogue. One tablet a day for at least one year.

Hepatitis B vaccine

Prevention and Control

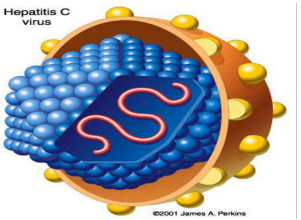
Pre Exposure prophylaxis:	Post exposure prophylaxis[3]

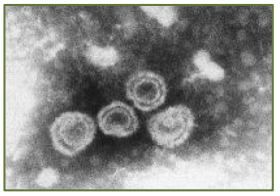
• Active vaccination given to all newborn, children or adult.
• The vaccine is safe and protective.
• Recombinant hepatitis B subunit vaccine:
  ○ Contains highly purified preparation of **HBsAg** particles, produced by genetic engineering(cloning) in **yeast**
• It is **not** live attenuated or killed vaccine
• The vaccine is given in 3 IM injection at 0[1]-1-6 months and booster dose may be required after 3-5 years[2].
	• **Persons exposed to needle prick or infant born to +ve HBsAg mother should immediately receive both:**
	  ○ Active vaccine and hepatitis B specific immunoglobulin.

1. Newborn
2. Due to the decrease in immunity.
3. An active immunization by vaccine , and a passive immunization by Ig. To insure that even if the patient is infected it's going to be killed in the early IP.

Hepatitis C virus

Hepatitis C virus:





- 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.

Transmission[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 & tooth brushes.
- Sexually
- From mother to child perinatally.

Hepatitis C markers

- hepatitis C virus RNA.

- Is the **1st** marker that appears in circulation, it appears as early as 2-3 weeks after exposure.

- It is a marker of infection.

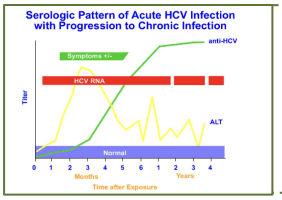
- hepatitis C core antigen.

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

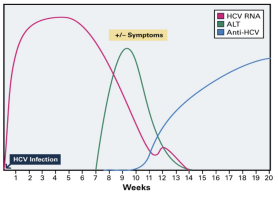
- Marker of infection

- IgG antibody to hepatitis C.[2]

- Antibodies to hepatitis C virus is the **last/2nd[3]** marker that appears in the blood, usually appear 50 days after exposure (long window period)
- it is **not** marker of immunity,
- can be detected in completely recovered patient and chronic and acute.



Serological pattern of acute Hepatitis C infection not progress to chronic and patient become cured(infection resolved).



1. Same as HBV.
2. It's not a specific marker, so along with it you need to check the liver enzymes in order to assess the patient's condition.
3. It's last in male slides and 2nd in female slides

Hepatitis C virus

Risk Factors[1]:

- Intravenously drug users.
- Hemodialysis patients.
- Patients receiving clotting factors.
- Recipient of blood transfusion
- Individuals with multiple sexual partners
- Health care workers with frequent blood contact.
- Individuals who exposed to tattooing , body piercing or cupping.

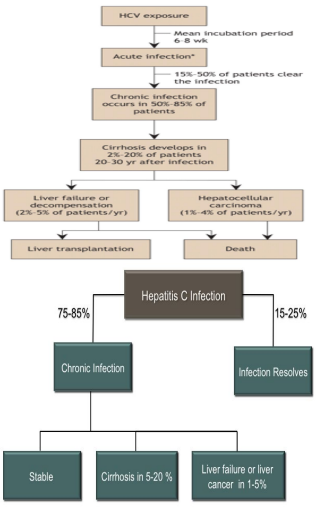
The clinical picture of HCV:

- Incubation period from 2 to 7 weeks[2].
- 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

Acute hepatitis	Chronic hepatitis
Symptoms : - jaundice, fatigue & nausea. - Elevated serum ALT (usually greater than 10 folds). - Presence of anti-HCV (-ve in 30-40%) in early stages of disease. - HCV-RNA is +ve even before the onset of symptoms.	- Defined as the presence of anti-HCV & elevated serum level of ALT for > 6 months. - Almost all patients with chronic hepatitis C have the genome HC RNA in serum. - Usually asymptomatic, but if symptom present it's usually mild, non-specific & intermittent. - Lab findings: Elevated ALT & AST ranging from 3-20 times - ALT > AST

Clinical Outcomes:

- **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 , about 10%-30% of them can develop cirrhosis within 30 years and liver cancer.**
- **< 1 %** will develop **fulminant hepatitis C**, liver failure and death.



1. Same as HBV
2. Shorter than hep A.

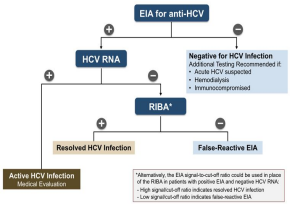
Hepatitis C virus

Lab diagnosis:

- By detection of both:

  1- Antibody to HCV in the blood by ELISA, if positive the result must be confirmed by **Recombinant ImmunoBlot Assay (RIBA) or PCR.**

  2- HCV-RNA in the blood using RT-PCR.



- Molecular: Dr.mona said it's **not imp**

  1- Qualitative Assay:

  It's the most specific test for indicating ongoing infection & almost +ve in chronic hepatitis.
  it's usually –ve after recovery & effective treatment.
  It's the best method for diagnosis of early sages of acute hepatitis & HCV in immunocompromised patient.
  PCR & TMA (transcription mediated amplification) can detect low level of virus (50-100 copies/ml) # 25-50 IU

  2- Quantitative Assay:
  It gives indirect assessment of viral load by measuring the concentration or level of virus in serum.
  Methods includes quantitative PCR & branched DNA test.
  Most patient have viral load between 100.000-10.000.000 copies/ml # 50.000-500.000 IU.
  It correlate with the likelihood response to therapy.
  Response is higher with low level viraemia <2 million copies/ml # one million IU

Treatment and Vaccine

- **The currently used treatment is the combined therapy using:**
  - **Pegylated alpha interferon** and **Ribavirin**.
  - The dose: for pegylated alpha interferon, one injection per week.
  - For ribavirine two capsules a day.
- 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.
- New drugs: There are number of approved therapies as SOVALDI may be given together with or without RIBAVIRIN & 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 therap
- **Hepatitis C vaccine:**
  - At the present time, there is **no vaccine** available to hepatitis C.

Hepatitis D and G viruses

Hepatitis D virus (delta virus)

- 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.

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.**

Hepatitis G virus: Dr.mona said it's **not imp**

- 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
- Transmitted **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.

Dr.Mona's Questions

- The only hepatitis virus that is ds-DNA is HBV
- What is the marker of infections in HBV? HBs Ag & HBV DNA
- What is the earliest serum marker seen viral hepatitis ? DNA or RNA (depending on the causative virus)
- What is the most common Antigen screened for in HBV? HbsAg
- What does it mean to find AntiHBs ? Immunity
- Patient A have AntiHBs and AntiHBc +ve → got HBV and recovered, and developed immunity.
- Patient B have AntiHBs +ve only → developed immunity from vaccine.
- What is the confirmatory test for HBV? Neutralization test
- Which of the following is a defective virus ?

  A. HAV B. HBV C. HCV D. HDV
- What is the marker of infection in HCV ? RNA by PCR
- What is the treatment of HCV ? Peglyated alpha interferon and **Ribavirin**
- What are the characteristics of HBV seen under the EM ?
  1- Small spherical HBsAg
  2- HBsAg filaments
  3- Dane particles (complete HBV particles)

Quiz:

MCQ:

Q1:C, Q2:C, Q3:D, Q4:C, Q5:A

Q1: Which ONE of the following Markers indicates active viral replication?
A- HBV DNA
B- Hepatitis B surface antigen
C- Hepatitis B e antigen
D- Antibody to hepatitis B e antigen

Q2: Which one of the following is TRUE regarding Hepatitis B infection?
A- Most patients will develop chronic Hepatitis
B- Most patients will develop Fulminant Hepatitis
C- infected adults will develop acute hepatitis B infection and recover completely.
D- All patients will die within a couple of weeks

Q3: Which one of the following viruses is Ds-DNA virus?
A- HAV
B- HDV
C- HCV
D- HBV

Q4: A 44-year-old woman with end-stage renal disease and on hemodialysis presents to the physician with abdominal pain. The physician suggests that she has Hepatitis B infection. What is the classic laboratory finding that would confirm the physician's diagnosis?
A- Detection of IgM to HAV in blood
B- Detection of IgA to HBeAg in CSF
C- Detection of HBsAg in blood
D- Detection of Hepatitis D Ab in CSF

Q5: A medical student accidently sticks himself while attempting to recap a needle. The patient he was treating is known to have chronic, active hepatitis C virus infection. The student has blood drawn for antibody testing, which is found to be negative for anti-HCV Ab. Four weeks later, the medical student is still negative for anti-HCV antibody, but at 8 weeks, results of antibody testing are positive. What's the appropriate treatment?
A- Pegylated alpha interferon and Ribavirin.
B- Acyclovir
C- Oseltamivir
D- Metronidazole

SAQ:

CASE: A 34-year-old man with a history of alcohol and drug abuse comes to the emergency department complaining of nausea and vomiting. He notes no recent change in diet or lifestyle and has been in a monogamous relationship for the past year. Physical examination reveals a fever of 38.3°C, a heart rate of 80/min, and a respiratory rate of 18/min. Scleral icterus is present and there is tenderness in the right upper quadrant and midepigastric region. Workup is negative for gonorrhea and chlamydia. Relevant laboratory finding are as follows:

ALT: 1310 U/L
AST: 1200 U/L
Alkaline phosphatase: 98 U/L

HBsAg: **Positive**
HBeAg: **Positive**

Anti-HBc: **Positive**
Anti-HBs: **Negative**

Anti-HBe: **Negative**

Q1: What is the most likely diagnosis?
Hepatitis B virus (HBV) infection

Q2: What's the first antibody to appear in blood?
Anti-HBc

Q3: What's the first marker to appear in blood?
HBV DNA

Q4: What are the laboratory findings in patients who had HBV in the past and recovered completely?
Positive for Anti-HBs, Anti-HBc, EXTRA: the may also be positive for Anti-HBe.
Negative for HBsAg, HBeAg

Q5: What's the appropriate treatment for this patient?
1- Pegylated alpha interferon(main)
2- Lamivudine
3- Adefovir

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