Microbiology

Hepatitis

435's GIT SAQs and OSPE

- This document includes both males and females tutors' notes. In addition to the original practical material, we added the most important theoretical aspects and extra team notes in order to cover for SAQs as well. You can skip it if you want!
- Remember that the cases usually change in the exam, therefore, please avoid pure memorization and do not skip a statement unless 100% understood.

Important **Males note** **Females note** **Team's note** **Theoretical** **Practical** **Edited**

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Introduction

As we previously know, a primary hepatitis infection can be caused by a number of viruses (HAV, HBV, HCV, HEV... etc.) For each type, we will briefly go through their main theoretical aspects in order to distinguish each type from the other by highlighting the key informations embedded in the scenario, and hopefully, we will answer any possible follow-up question regarding the case, weather SAQ or OSPE.

- Hepatitis viruses are mainly diagnosed by **SEROLOGY**, therefore you should know what the findings are and how to detect them.
- In case of hepatitis, you must request blood **MARKERS** which can be an antigen, an antibody, or a part of the virus's genome (DNA / RNA).
- **Diagnosing hepatitis A, E and C is very simple**, we only confirm if the marker is positive. On the other hand, **diagnosing hepatitis B is difficult** because depending on the markers we find, we determine whether it is an acute infection, chronic infection, infected patient, carrier patient, immune patient... etc.

- **Hepatitis A and E** are common, acute, and self limiting.
- **Hepatitis B and C** are less common, can be acute or chronic, and sometimes associated with bad complications.
- **Hepatitis E** is associated with pregnancy and common in India.
- **Hepatitis A** is common worldwide.
- **All types of hepatitis are usually asymptomatic.**

- **IgM** = **ACUTE** disease.
- Acute hepatitis produces gastrointestinal symptoms.
- **IgG** = **CHRONIC** disease.
- Chronic hepatitis produces non-specific symptoms.

- **There are some general roles in hepatitis virus markers, which are:**
  1. Usually, a part of the virus's **DNA or RNA** appears as the **earliest marker**.
  2. Every Antigen (Ag) should have an antibody (Ab) in response. When the antibody appears, the antigen will disappear from the circulation.
  3. Each virus has its own markers, so we can use them to indicate the virus's type and the stage of disease (Acute or Chronic). This is mainly in **Hepatitis B**.

- **Screening** is the use of a **very sensitive**, yet **non-specific** test to make sure not to miss any positive case possible. (We end up with positive + false-positive cases).
- **Confirming** is the use of a **very specific** test to **confirm the result of screening**, hence, rule out any false-positive cases. (We end up with positive cases only).

Hepatitis A	
Characteristics	Non-enveloped ssRNA with positive polarity.
Prevalence	Common worldwide, especially in developing countries with poor hygiene.
Transmission	Mainly fecal-oral (contaminated food and water).
Age Group	Mainly children.
Pathogenesis	Eating contaminated food → Replicate in the intestine → Spread to the liver → Multiply inside the hepatocytes → Human cell mediated immunity attack the infected hepatocytes → Damage → Increase in ALT, AST and Bilirubin levels.
Presentation	Mainly acute and asymptomatic. If symptomatic, fever and right upper quadrant pain are noticed.
Diagnosis	Markers by ELISA: IgM = Current infection. IgG = Previous infection or vaccine.
Treatment	Self-limiting with good prognosis.
Prevention	1. Human Immunoglobulin (HIg) within two weeks of exposure. 2. Inactivated virus vaccine. 3. Twinrix vaccine.

Hepatitis E	
Characteristics	Non-enveloped ssRNA with positive polarity.
Prevalence	Common in developing countries with poor hygiene, especially India.
Transmission	Mainly fecal-oral (contaminated food and water). Possibly zoonotic foodborne (animal to human).
Age Group	Mainly pregnant ladies and young adults.
Pathogenesis	Eating contaminated food → Replicate in the intestine → Spread to the liver → Multiply inside the hepatocytes → Human cell mediated immunity attack the infected hepatocytes → Damage → Increase in ALT, AST and Bilirubin levels.
Presentation	Mainly acute and asymptomatic. If symptomatic, fever and right upper quadrant pain are noticed.
Diagnosis	Markers by ELISA: Anti-HV IgM = Current infection.
Treatment	Self-limiting with good prognosis.
Prevention	No Human Immunoglobulin (HIg) or vaccine available.

Hepatitis C

Characteristics	• Envelope contains **s**urface antigens (HC**s**Ag). • Core contains **c**ore antigens (HC**c**Ag). • SsRNA genome. • 6 genotypes (1 to 6), genotype 4 is common in KSA.
Prevalence	Less common than A and E.
Transmission	**Parenteral:** via blood from sharp tools or infected transfusions. 1. **Sexual:** via body fluids from unprotected sex. 2. **Perinatal:** during delivery or breastfeeding. 3. Idiopathic.
Presentation	• Can be acute or chronic and is mainly asymptomatic. • If symptomatic, jaundice, black urine, and upper right quadrant pain are noticed. • Associated with complications e.g. liver cirrhosis or hepatocellular carcinoma.
Diagnosis	1. Markers by ELISA. HCV-RNA, Anti-HCV, HCcAg, and IgG Hepatitis C antibody. 2. RIBA or PCR for confirmation.
Treatment	Pegylated alpha interferon + Ribavirin (combined).
Prevention	No vaccine available.

Hepatitis B

Characteristics	• Envelope contains **s**urface antigens (HB**s**Ag) and **e**nvelope antigens (HB**e**Ag). • Core contains **c**ore antigens (HB**c**Ag) but it cannot be detected in the serum. • DsDNA genome. • 8 genotypes (A to H), genotype D is common in KSA.
Prevalence	Less common than A and E.
Transmission	1. **Parenteral:** via blood from sharp tools or infected transfusions. 2. **Sexual:** via body fluids from unprotected sex. 3. **Perinatal:** during delivery or breastfeeding.
Presentation	• Can be acute or chronic and is mainly asymptomatic. • If symptomatic, jaundice, black urine, and upper right quadrant pain are noticed. • Associated with complications e.g. liver cirrhosis or hepatocellular carcinoma.
Diagnosis	1. Markers by ELISA **(next page is required and VERY IMPORTANT)**. HB**s**Ag, Anti-HB**s**, Anti-HB**e**, IgM Anti-HB**e** and Anti-HB**c**. 2. Neutralization test for confirmation. 3. Liver function test.
Treatment	• Pegylated alpha interferon. • Lamivudine. • Adifovir.
Prevention	HBsAg particles vaccine.

Interpretation of Hepatitis B Serologic Test Results

Hepatitis B serologic testing involves measurement of several hepatitis B virus (HBV)-specific antigens and antibodies. Different serologic "markers" or combinations of markers are used to identify different phases of HBV infection and to determine whether a patient has acute or chronic HBV infection, is immune to HBV as a result of prior infection or vaccination, or is susceptible to infection.

MEMORIZE THE FIRST 5 RAWS OF THE TABLE.

HBsAg **anti-HBc** **anti-HBs**	negative negative negative	Susceptible Uninfected and non-immunized.
HBsAg **anti-HBc** **anti-HBs**	negative positive positive	Immune due to natural infection Immunization is due to the presence of Anti-HBc.
HBsAg **anti-HBc** **anti-HBs**	negative negative positive	Immune due to hepatitis B vaccination The difference between a vaccinated person and a previously infected one is the presence of Anti-HBc.
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive positive negative	Acutely infected Note that IgM always indicates an acute infection.
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive negative negative	Chronically infected Note that the absence of IgM indicates a chronic infection.
HBsAg **anti-HBc** **anti-HBs**	negative positive negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection

- **Hepatitis B surface antigen (HBsAg):** A protein on the surface of hepatitis B virus; it can be detected in high levels in serum during acute or chronic hepatitis B virus infection. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part of the normal immune response to infection. HBsAg is the antigen used to make hepatitis B vaccine.
- **Hepatitis B surface antibody (anti-HBs):** The presence of anti-HBs is generally interpreted as indicating recovery and immunity from hepatitis B virus infection. Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B.
- **Total hepatitis B core antibody (anti-HBc):** Appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with hepatitis B virus in an undefined time frame.
- **IgM antibody to hepatitis B core antigen (IgM anti-HBc):** Positivity indicates recent infection with hepatitis B virus (≤6 mos). Its presence indicates acute infection.

As a follow-up question on a case of Hepatitis B infection, **they can ask you any question about the first 5 rows of the table above.** For example: What are the HBV serological findings for a patient who is susceptible? Answer must be: HbsAg (-ve), Anti-HBc (-ve), and Anti-HBs (-ve). **The notes in purple are important too. The last row is complicated and unimportant (you will not be asked about it).**

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Didn't quite get it? This is for you.

CASE - 1

Mohammed Khan is a 20 year-old male who has recently arrived from India[1] to work as a food handler[2] in a restaurant in Riyadh. Three weeks after his arrival he was seen in the ER of KKUH because of repeated vomiting, abdominal pain and fever.[3] On examination, his temperature was 38°C, he was jaundiced[4] and had tenderness in the right upper quadrant of his abdomen.

Q1: What are the possible causes for his presentation?[5]

1. Viral Hepatitis (Has to be the first).
2. Acute Cholecystitis.
3. Leptospirosis.
4. Malaria.
5. Typhoid fever.

Q2: What investigations would you like to order for him? Explain how these investigations would help you.

1. **CBC & ESR** → Shows non-specific signs of infection or inflammation.
2. **Liver function test** → Assesses liver function.
3. **Kidney function test** → Assesses kidneys function.
4. **Viral Hepatitis screening serology test for all types** → Excludes viral hepatitis.
5. **Viral Hepatitis confirming serology test for a specific type** → Confirms the diagnosis if screening was positive.
6. **Thin and thick blood film** → Excludes malaria.
7. **Blood Culture** → Excludes typhoid fever (because they cause bacteremia).

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[1] Most common hepatitis virus in india is E, and the most common worldwide is A.
[2] Means that oro-fecal transmission to other people is possible.
[3] Gastrointestinal symptoms indicate acute Hepatitis.
[4] Important sign of Hepatitis.
[5] According to the presentation, viral hepatitis is on top of the list. However, he is a traveller, hence, we cannot exclude malaria and typhoid fever unless we have an evidence. Leptospirosis is common in India and it causes jaundice.

Complete Blood Count[6]		Liver Function Test[7]	
Hb	14.2 g/L	**AST**[8]	**1557** (Normal = 12-37 IU/L)
WBCs	6100 mm3	**ALT**[9]	**1879** (Normal = 20-65 IU/L)
Platelet	271 g/L	**ALP**[10]	**441** (Normal = 175-476 IU/L)
ESR	4 mm/h	**Albn**[11]	**42.3** (Normal = 30-50 g/L)
Malaria Blood film	NEGATIVE	**Bilirubin**	**86** (Normal = 3-17 µmol/L)
Blood culture	NEGATIVE		

Q3: Based on the findings above, what is the most likely diagnosis?

Viral hepatitis A, B, C, or E (Write them all, but mention "it's most likely A or E").

TEST	RESULT
Anti-HAV-IgM	Positive
HBsAg	Negative
Anti-HCV	Negative
Anti-HEV-IgM	Negative

Q4: Interpret the serology results found above?[12]

Anti-HAV-IgM positive → indicates an acute[13] hepatitis A infection.

HBsAg negative → excludes hepatitis B infection.

Anti-HCV negative → excludes hepatitis C infection.

Anti-HEV IgM negative → excludes acute hepatitis E infection.

Q5: Based on the findings above, what is your final diagnosis?

Acute Hepatitis A Infection.

Q6: Briefly outline the management of this patient?

Supportive. Stop working to prevent any transmission. Contact tracing.[14] Follow up (clinical and laboratory).

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[6] All normal.
[7] Very high liver enzymes indicate acute hepatic injury.
[8] Aspartate aminotransferase: marker of hepatocellular injury.
[9] Alanine aminotransferase: marker of hepatocellular injury.
[10] Alkaline phosphatase: marker for cholecystitis Since it is normal, we exclude any obstruction causing cholecystitis.
[11] If the case was chronic, Albumin would be low. Since it is normal, we exclude chronic hepatic injury.
[12] Don't confuse between interpretation and diagnosis. Interpret = explain the positive and negative findings. Whereas diagnose = Identify the disease (the positive finding only).
[13] IgM indicates acute. However, hepatitis A does not have a chronic presentation anyways.
[14] Diagnosis of people who may have come into contact with the infected case.

CASE - 2

Mohammed Abdullah is a 34 year old married Saudi male who has donated two units of blood at KKUH for a relative undergoing an operation. Two days later, the Blood Bank called him because of abnormal blood test results[15] and advised him to see his physician. On arrival to the blood bank, the doctor informed him that his blood is not suitable for transfusion because of the presence of infection.

Q1: What type of infectious agents can be transmitted through blood transfusion? (List 4 infections).

1. Hepatitis B Virus (HBV).
2. Hepatitis C Virus (HCV).[16]
3. Human Immunodeficiency Virus (HIV).
4. Human T-Lymphotropic Virus (HTLV).
5. Malaria.
6. Syphilis.

TEST		RESULT
1	HBsAg	Negative
2	Anti-HBc	Negative
3	Anti-HCV	Positive
4	HIV-Ag/Ab	Negative
5	Anti-HTLV	Negative
6	ALT	49 (Normal = 20-65 IU)
7	AST	29 (Normal = 12-37 IU)
8	Bilirubin	4 (Normal = 3-17 mol/L)

[15] The vast majority of hepatitis patients are diagnosed by accident because it is usually an asymptomatic disease.
[16] Hepatitis A and E on the other hand are mainly transmitted oro-fecally.

Q2: The next day Mohammed came to see his general practitioner with a letter from the Blood Bank. The letter revealed the result shown above. What is your interpretation?

Test 1: Not infected with HBV.

Test 2: Was never exposed to HBV.

Test 3: Infected with HCV and is asymptomatic.

Test 4: Not infected with HIV.

Test 5: Not infected with HTLV.

Tests 6, 7, and 8: Liver enzymes are normal, this indicates a chronic presentation.

Q3: What is your diagnosis, and how do you define it?

Chronic Hepatitis C infection:
The presence of Hepatitis C RNA (HCV-RNA) in the blood for more than 6 months.

Q4: How can you diagnose HCV?

- Screening test for Anti-HCV by ELISA.
- Confirmatory test by recombinant[17] immunoblot assay (RIBA) or PCR.
- Molecular assay for detection of RNA (For early detection).

Q5: How do you confirm HCV infection?

RIBA with PCR (Must mention both and stress that they are used together).

Q6: What type of management would you do for a patient with HCV? Mention their significance and how they help in management.

Genotype (viral load)[18] and PCR.

Test	Significance	How can it help?
PCR	**1. Qualitative[19]:** -ve or +ve HCV-RNA. **2. Quantitative:** viral load.	**1.** Confirm the Diagnosis. **2.** Monitor response to treatment.
Genotype	Identify the genotype of HCV.	Guide the choice and duration of therapy.

[17] Recombinant = مصنوع. They make it at the lab by adding the patient's serum to a plate of E. Coli, and if the serum had an antibody, it will bind to the antigen on the plate and hepatitis C can be confirmed.
[18] This test measures the actual amount of hepatitis virus in a blood sample, which helps determine if it is reproducing in the liver.
[19] Not being used nowadays.

CASE - 3

A 15-weeks pregnant[20] Saudi woman was seen for the first time at the antenatal clinic at KKUH. As part of the antenatal screening, the doctor arranged for blood screening for viral serology.

TEST		RESULT
1	HBsAg	Positive
2	HBeAg	Negative
3	Anti-HBe	Positive
4	Anti-HBc IgM	Negative
5	Total Anti-HBc	Positive
6	HIV Ag/Ab	Negative
7	Anti-HCV	Negative

Q1: How would you interpret these results?

Test 1, 3 and 5: The patient is infected with Hepatitis B.

Test 2: The patient's rate of infectivity is low.

Test 4: The patient's infection is chronic.

Test 6 and 7: The patient is not infected with HCV or HIV.

Q2: Which HBV marker indicate the rate of infectivity?

HBeAg and Anti-HBe.

Q3: Which HBV marker has no serological significance, and why?

HBcAg; because it is intracellular (inside the hepatocyte) not in the blood.

Q4: How can you differentiate between a patient who have taken the vaccine and another who had a previous infection?

- **Previous Infection:** both Anti-HBc and Anti-HBs are positive.
- **Vaccination:** Anti-HBs is positive and Anti-HBc is negative.

[20] Any pregnant lady is at high risk of having hepatitis, however, be careful, it is not always hepatitis E! لا تتخدع.

Q5: How can you confirm HBV?

Neutralizing test.

Q6: How would you manage the newborn?

We need quick post exposure prophylaxis:

- Hepatitis B immunoglobulin (HBIg) within 12 hours of birth.
- First dose of recombinant HBV vaccine (You have to mention "recombinant").

Q7: Is there a risk of transmission of HBV to the newborn?

- **Seropositive for HBsAg with no immunoprophylaxis:** vertical transmission[21] = 10-20%.
- **Seropositive for both HBsAg and HBeAg:** vertical transmission = 90%.
- **Acute hepatitis B occurs in the first trimester:** vertical transmission = 10%.
- **Acute hepatitis B occurs in the third trimester:** vertical transmission = 90%.

Q8: What further management would you offer to the mother?

- No donation of blood, body organs, or other tissues.
- No sharing of personal items (e.g. toothbrushes).
- Obtain vaccination against hepatitis viruses A as indicated.
- Be seen at least annually by their regular medical doctor.
- Discuss the risk for transmission with her partner.
- The partner must be tested and vaccinated.

Q9: You accidentally prick your finger with a needle stained by the mother's blood. What should you do?

1. Wash my hands with water immediately.
2. Report an occupational exposures immediately.
3. Review the hepatitis B vaccination status and the vaccine-response status.

Q10: What is the risk of infection to you?[22]

- **If the blood was (+ve) HBsAg (+ve) HBeAg:** risk of serological evidence is 37-62%.
- **If the blood was (+ve) HBsAg (-ve) HBeAg:** risk of serological evidence is 23-37%.

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[21] Passage of the virus from mother to baby during the period immediately before and after birth.

[22] Vary depending on the presence of the infectivity marker (HBeAg).