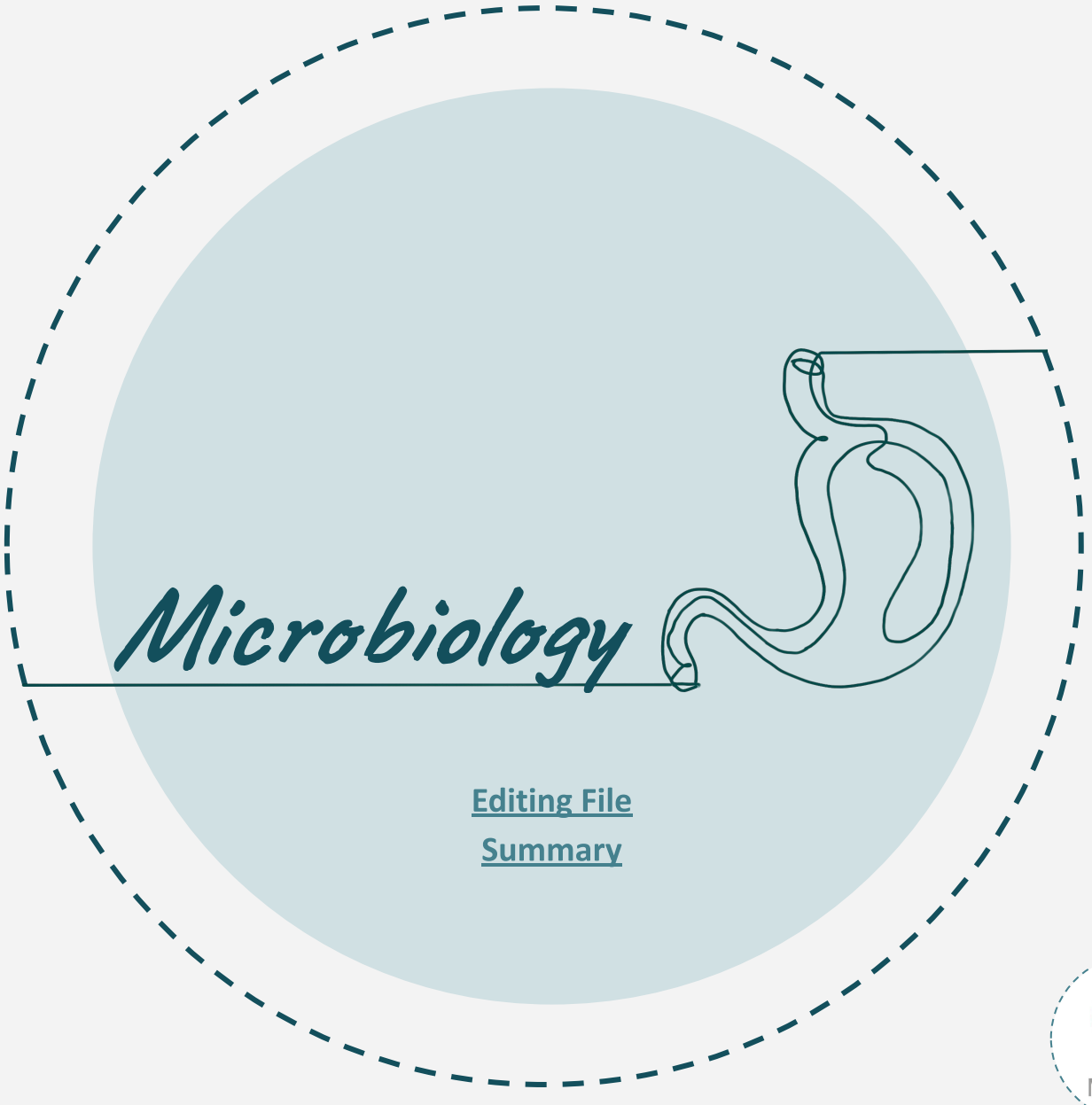
Viral Hepatitis A, E and others



Editing File

Summary

MED439
KING SAUD UNIVERSITY

MICROBIOLOGY
Team 439

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- Girls' slides
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Objectives:

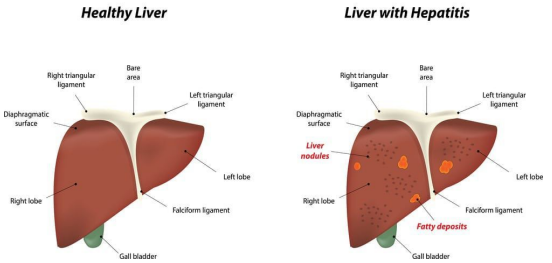
- Describe the structure, epidemiology, clinical presentation, lab diagnosis, treatment, and prevention of viruses causing enterically transmitted hepatitis: HAV and HEV

- Describe the structure, epidemiology, clinical presentation, lab diagnosis, treatment, and prevention of viruses that are causing hepatitis during their course of infection: Cytomegalovirus (CMV), Epstein-Barr virus (EBV), and Arbovirus (yellow fever virus)

Hepatitis A & E

Hepatitis

Is inflammation of the liver (Boys' Slide)



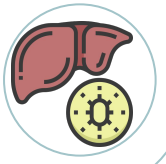
Etiology

Primary infection

- 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) has been reported in the literature but not confirmed
- Hepatitis G virus (HGV)

As part of generalized infection

- CMV
- EBV
- Yellow fever virus



Viral hepatitis is divided into two large groups based on the mode of transmission

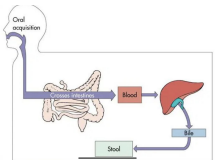
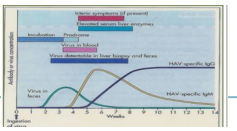
Water borne hepatitis

- Enterically transmitted hepatitis
- Includes hepatitis A and E viruses

Blood borne hepatitis

- Parenterally transmitted hepatitis
- Includes hepatitis B, C, D & G viruses

Hepatitis A

Virus	Hepatitis A virus (Acute Hepatitis)
Family	Pico**rna**viridae (Pico means small, and rna indicates that its genome is RNA)
Genus	Hepatovirus
Characteristics	Non-enveloped virion consisting of : ○ Icosahedral capsid ○ Positive sense ss-RNA
Presentation (Other names)	○ **Short incubation hepatitis** ○ Infectious hepatitis ○ Epidemic hepatitis
Epidemiology	**Distribution** ○ Worldwide endemic in tropical countries. **Age** (Depends on socioeconomic status) ○ In developing countries: children ○ In developed countries: young adults 
Transmission	○ **Fecal-Oral route (major route)** [1] E.g. contaminated food & water [2] ○ Sexual contact (homosexual men) ○ Blood transfusion (very rarely) [3]
Pathogenesis	1. The virus enters the body by ingestion of contaminated food 2. It replicates in the intestine (epithelium) 3. Spreads to the liver where it multiplies in the hepatocytes 4. Cell mediated immunity —> damage of virus-infected hepatocytes 5. increase ALT , AST & Bilirubin
Manifestations	○ Asymptomatic & anicteric infection (non-specific illness without jaundice) is common ○ Symptomatic illness increases with age ○ Incubation period (IP) : 2-6 weeks **Has two phases** [4] (short compared to other hepatitis viruses) ○ Pre-icteric phase : fever, fatigue, nausea, vomiting, right upper quadrant pain ○ Icteric phase : dark urine , pale stool , jaundice
Lab diagnosis	**Serology** (by ELISA) ○ Anti-HAV IgM : current infection ○ Anti-HAV IgG : previous infection - immunity 
Treatment	Supportive therapy (self-limiting)
Prevention	○ Sanitation and hygiene measures ○ **HIG:** [5] given before or within 2 weeks of exposure. Indication: travelers , unvaccinated, exposed patients. ○ **Vaccine** [6] : inactivated, given IM at 0.6-12 m, >1 year of age. ○ Side effects: mild local reaction. ○ Indication: people at high risk of infection ○ Combination of vaccine (HAV & HBV)
Prognosis	○ **Acute** self limited disease ○ Fulminant hepatitis: rare ○ Mortality rate: 0.1 - 0.3 % [7] ○ No chronicity or malignancy changes

[1] usually related to poor hygiene and overcrowding
[2] common source of outbreaks
[3] very rare because HAV usually causes acute low level / transient viremia (NOT chronic)
[4] Aka. prodromal phase. it is characterized by non-specific illness.
[5] passive immunization with human immunoglobulins.
[6] included in children routine vaccines in KSA
[7] very low but increases with the age

Hepatitis E & Herpesviridae

Virus	Hepatitis E virus
Family	Hepeviridae
Genus	Hepevirus
Characteristics	Non-enveloped virion consisting of : ○ Icosahedral capsid ○ Positive sense ss-RNA
Clinical features	**Similar to HAV infection with exceptions** ○ Longer IP (4-8 weeks) **Longer than HAV** ○ Chronic hepatitis[1], cirrhosis , but not HCC (Hepatocellular carcinoma) ○ Fulminate disease ○ Mortality rate **10 times higher** than HAV ~ 1-3% **(20% in pregnancy)**
Epidemiology	★ **Major cause of outbreak of water-borne hepatitis** & sporadic cases of viral hepatitis **HEV** على طول **water-borne** اول ما تسمعوا **Age** ○ Young adults
Transmission	○ Water-borne (most common: drinking contaminated water) ○ Zoonotic (food-borne) by eating undercooked meat or animal products ○ Perinatal ○ Blood-borne
Lab diagnosis	**Serology** ○ Detection of **anti-HEV IgM** by ELISA
Treatment	Not specific
Prevention	○ Sanitation & hygiene measures ○ No immunoglobulin ○ **No vaccine .**

Herpesviridae

dsDNA, Icosahedral, and Enveloped viruses

1- Herpes simplex virus type -1 (HSV-1)	2- Herpes simplex virus type -2 (HSV-2)
3- Varicella –Zoster virus (VZV) [1]	4- Epstein-Barr virus (EBV)
5- Cytomegalovirus	6- Human herpes virus type-6
7- Human herpes virus type-7	8- Human herpes virus type-8

[1] It's similar to hepatitis A which causes acute hepatitis but in case of hepatitis E it cause chronic hepatitis only in immunocompromised patients

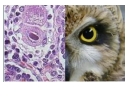
Epstein - Barr Virus (EBV)

Aka. The kissing disease

Virus	Epstein - Barr Virus (EBV)
Characteristics	○ It is lymphotropic (it infects and becomes latent in lymphoid cells mainly B lymphocytes) ○ It has oncogenic properties (association with malignancy): -Burkitt's lymphoma -Nasopharyngeal carcinoma
Epidemiology	**Distribution** ○ Worldwide. **Age :** Depends on SE (Socio - Economic status) ○ Low SE : early childhood by sharing items contaminated by saliva (such as spoons/forks) ○ High SE : Adolescent by kissing
Transmission NOT fecal-oral	○ **Saliva (Kissing disease)** ○ Blood (rare)
Clinical features [1]	**Immunocompetent host :** ○ Asymptomatic ○ **Infectious mononucleosis** (aka. glandular fever) : - Mainly in teenagers & young adults - IP = 4-7 weeks - Fever , pharyngitis , malaise , lymphadenopathy. , hepatosplenomegaly , abnormal LFT & hepatitis - Complications are rare (acute airway obstruction, splenomegaly, CNS infection) ○ Chronic EBV infection (if symptoms are present for more than 6 months)
	Immunocompromised host : ○ Lymphoproliferative disease (LD) ○ Oral hairy leukoplakia (OHL)
Lab diagnosis of Infectious mononucleosis	**Hematology :** ○ Increased WBC : lymphocytosis (atypical lymphocytes)
	Serology : ○ **Non - specific AB test via paul - bunnell or monospot test :** - **Heterophile Abs +ve** ○ **EBV - specific AB test :** - IgM Abs to EBV capsid antigen
Treatment	○ Antiviral drug is not effective in infectious mononucleosis
Prevention	○ **No vaccine**

[1] Mainly due to immunological attack of cells and infiltration of lymph nodes and spleen and immune-related cause (not due to viral replication itself)

Cytomegalovirus (CMV)

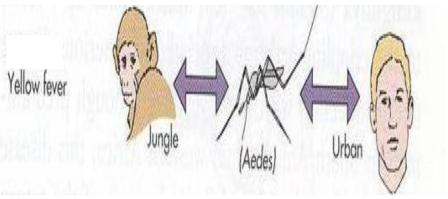
Virus	Cytomegalovirus	
Special Features	○ **Infected cell enlarged** with multiple nuclei [cyto=cell, megalo=big] ○ Resistant to acyclovir ○ Latent in monocyte, lymphocyte, and other cells. such as salivary glands cells and cells of the kidney ○ It's replication cycle is longer	
Epidemiology	○ Distribution: worldwide	
Transmission	Early in life	○ Transplacental ○ Birth canal ○ Breast milk
	Young children	○ Saliva (By sharing items, like EBV)
	Later in life	• sexual contact, blood transfusion, and organ transplant
Clinical features	**Immunocompetent host (acquired infection)** ○ Asymptomatic ○ Self-limited illness -Hepatitis -Infectious mononucleosis like syndrome [1] **(Heterophile AB is –ve)**	
	Immunocompromised host (acquired infection): ○ Systemic symptoms: Encephalitis , Retinitis , Pneumonia , ○ GIT symptoms: Hepatitis, Esophagitis, Colitis	
	Congenital Infections Almost all infants with clinically evident congenital CMV infection are born to mothers who experienced primary CMV infection during pregnancy. It causes a variety of congenital defects, and is a leading cause of deafness in children. (Sherris)	
Lab Diagnosis	**Histology (Best)** ○ Intranuclear inclusion bodies (Owl's eye)	
	Culture ○ In human fibroblast: CPE (Cytopathic effects) after 1-4 wks (Slow) ○ Shell Vial Assay results after 1-3 days	
	Serology ○ **AB** (Antibodies): 1- IgM : current infection 2-IgG : previous exposure ○ **Ag**: CMV pp65 (phosphoprotein 65) Ag by IFA (immunofluorescence assay)	
	PCR	
Treatment	○ **Ganciclovir** is effective in the Rx (treatment) of **severe** CMV infection ○ **Foscarnet:** the 2nd drug of choice (Ganciclovir **resistant** strains)	
Prevention	○ Screening [2]; - Organ donors - Organ recipients - Blood donors ○ By using Leukocyte-depleted blood (in blood transfusion to eliminate risk of latent CMV transfusion) ○ Prophylaxis: Ganciclovir , CMVIG (CMV immunoglobulin) ○ No vaccine .	

[1] same as infectious mononucleosis caused by EBV. However, the difference is that there will be no heterophile antibodies.

[2] screening the blood of donors for specific IgG against CMV (as IgG indicates latent CMV in lymphocytes and tissue).

Arthropod –borne Viruses(Arboviruses)

Virus	Yellow Fever virus[1] (Zoonotic virus)
Family	Flaviviridae
Epidemiology	Tropical Africa & South America
Clinical features High mortality rate (20-50%)	○ Asymptomatic ○ to Fever ± **Jaundice** ± hemorrhage[2] (hemorrhagic fever) ± renal failure
Types of fever	**1. Jungle Yellow Fever** ○ Vector: mosquito ○ Reservoir: Monkey ○ Accidental host: human[3] ○ It is a disease of Monkeys **2. Urban Yellow Fever** ○ Vector: mosquito ○ Reservoir: human ○ It is a disease of humans
Lab Diagnosis	**Lab. Methods:** 1. Isolation (Gold standard) 2. IgM-AB by ELISA or immunofluorescence: (**most used** because it is faster than culture isolation) 3. YFV- RNA by RT-PCR
Prevention	○ **Vector Control:** 1. Elimination of vector breeding sites 2. Using insecticides 3. Avoidance contact with vectors (repellants, net) ○ **Vaccine:** Yellow Fever vaccine - **LAV** (live attenuated virus), one dose /10 yrs



Summary (Extra)

Virus	HAV	HBV	HCV	HDV	HEV
FAMILY	RNA picornavirus	DNA hepadnavirus	RNA flavivirus	RNA deltavirus	RNA hepevirus
TRANSMISSION	Fecal-oral (shellfish, travelers, day care)	Parenteral (Blood), sexual (Baby-making), perinatal (Birthing)	Primarily blood (IVDU, post-transfusion)	Parenteral, sexual, perinatal	Fecal-oral, especially waterborne
INCUBATION	Short (weeks)	Long (months)	Long	Superinfection (HDV after HBV) = short Coinfection (HDV with HBV) = long	Short
CLINICAL COURSE	Asymptomatic (usually), Acute	Initially like serum sickness (fever, arthralgias, rash); may progress to carcinoma	May progress to Cirrhosis or Carcinoma	Similar to HBV	Fulminant hepatitis in Expectant (pregnant) women
PROGNOSIS	Good	Adults → mostly full resolution; neonates → worse prognosis	Majority develop stable, Chronic hepatitis C	Superinfection → worse prognosis	High mortality in pregnant women
HCC RISK	No	Yes	Yes	Yes	No
LIVER BIOPSY	Hepatocyte swelling, monocyte infiltration, Councilman bodies	Granular eosinophilic "ground glass" appearance; cytotoxic T cells mediate damage	Lymphoid aggregates with focal areas of macrovesicular steatosis	Similar to HBV	Patchy necrosis
NOTES	No carrier state	Carrier state common	Carrier state very common	Defective virus, Depends on HBV HBsAg coat for entry into hepatocytes	Enteric, Epidemic (eg, in parts of Asia, Africa, Middle East), no carrier state

[1] Called yellow fever because yellow is referring to jaundice

[2] signs of hemorrhage, nose bleeding, melena, and petechiae.

[3] Humans usually get infected by it when they enter a jungle by mosquito bite

Drs' notes

Dr. Malak

- Non-infectious hepatitis can be caused by fatty liver, alcohol (toxin-induced hepatitis), autoimmune diseases, and some drugs. However, infectious hepatitis is caused by viruses (most common) and parasites.
- Viruses that cause hepatitis are classified based on their route of transmission; (1) Enterically transmitted hepatitis (fecal-borne) such as hepatitis A and E. (2) Blood transmitted hepatitis (blood-borne) such as hepatitis B,C,G,D.
- Both **HAV** and **HEV** are non-enveloped viruses with icosahedral capsid and single stranded RNA genome. (the fact that they are non-enveloped explains how can they be transmitted by fecal-oral route as most enveloped viruses cannot resist stomach acidity).
- Human is the only reservoir of hepatitis A virus (it is not a zoonotic diseases). Upon consumption of contaminated food, it replicates in GIT cells (intestine) then it enters the blood causing transient low level viremia. Finally, it infects the liver and cause liver damage and disease (infected hepatocytes will have the viral antigen in their surface which can later be recognised by cytotoxic T cell and cause cell mediated damage). This damage will manifest as elevated liver enzymes & bilirubin → jaundice. Finally, the virus will be released to the bile and excreted in stool (can be infectious).
- Current infection of HAV is diagnosed by presence of **IgM**. Also, HAV is prevented by general measures such as proper hyagine, and by specific measures such as (1) passive human immunoglobulins and (2) inactivated vaccine.

★ **HEV is the major cause of outbreak of water-borne hepatitis**

- Hepatitis E virus can be zoonotic and have animal reservoir (Unlike hepatitis A virus).

★ **IMPORTANT:** Clinical features of HEV are generally similar to HAV that it **usually** cause ACUTE hepatitis. **However,** it can sometimes cause **chronic hepatitis** (almost exclusively in immunocompromised patients) and may cause cirrhosis (but it has no role in causing hepatocellular carcinoma).

- HEV has longer incubation period than HAV. Also, mortality rate of HEV is 10 times more and increases with pregnancy. In contrast to hepatitis A virus, there is no vaccine / human immunoglobulins to prevent hepatitis E virus (except in China).
- Epstein Barr virus (EBV) is lymphotropic (meaning that it infects and becomes latent in lymphoid cells. Mainly; B lymphocytes).
- Clinical features of EBV differs based on the immune-status and age of the patients.
  - **(1) In immunocompetent host:** majority of patients are asymptomatic (Especially young children). However, teenagers & young adults might develop **infectious mononucleosis** (glandular fever) which is characterized by fever, sore throat, etc.. In addition, significant number of patients may present with splenomegaly / hepatosplenomegaly / hepatitis.
  - **(2) In immunocompromised host:** it can cause lymphoproliferative disease (LD).
- Infectious mononucleosis of EBV can be diagnosed by two approaches;
  - **(1) Hematological**: (high WBCs, lymphocytosis, atypical lymphocytes).
  - **(2) Serological**:
    - **(2A) Non-specific antibodies test**: used to detect **heterophile antibodies** that resulted from B lymphocytes non- specific activation. Theses antibodies are detected by a test called (Paul Bunnell test / monospot test). However, these heterophiles can also be associated with other diseases as well hence called non specific test.
    - **(2B) Specific antibodies test**: **IgM** antibodies to EBV capsid antigen.
- Most patients infected with CMV are asymptomatic or have mild self limited disease. However, some patients may present with infectious mononucleosis syndrome which is almost similar to the one caused by EBV, **BUT it LACKS heterophile antibodies**. Splenomegaly and adenopathies are uncommon with this virus.
- Best diagnostic method of CMV is histology which will reveal intranuclear inclusion bodies [Owl's eye shape]. The CMV can be cultured on human fibroblast culture, and it takes a long time (1-4 weeks) to show cytopathic effect. However, there is a modified type of cell culture called shell viral assay that can show CMV antigen in 1-3 days (antigen NOT cytopathic effect). Also, serology and PCR can be used (see serology details in footnotes).
- Yellow fever virus can cause a wide spectrum of manifestations ranging from asymptomatic infection to severe systemic disease and organ failure. YFV is characterized by fever and jaundice, and it has two patterns; (1) Jungle yellow fever which is a monkey disease and human gets the infection by mosquito bite. (2) Urban yellow fever which is a human disease originally but it is transmitted by mosquitoes as well.

Dr. Alhetheel

- Non-enveloped viruses have a solid / rigid capsid that protects the virus from stomach acidity.
- HAV has a short incubation period so it can cause a fast outbreak of the virus.
- Clinical manifestations of enteric viral hepatitis and blood-borne hepatitis are very similar. A detailed clinical history is indicated to differentiate.
- Studies showed correlation between consumption of pork and hepatitis E infection.

Quiz

MCQ

Q1: Which of the following is the major route for HAV?

A- sexual route
B- Fecal-Oral route
C- Blood
D- liquid route

Q2: A 19 YO female patient has acute, primary Epstein-Barr virus infection, which of the following would be the most specific confirmatory test?

A- Heterophile ABS
B- Paul-Bunnell test
C- IgM Abs to EBV capsid antigen
D- PCR

Q3: Vaccines have been demonstrated to be efficacious in preventing which one of the following viruses?

A- Yellow fever virus
B- Cytomegalovirus
C- Epstein-Barr virus
D- Hepatitis E virus

Q4: Which is available and effective for HAV?

A- Killed vaccine
B- Live vaccine
C- Acyclovir
D- Antibiotics

Q5: Which if the following have a high mortality rate in pregnant women?

A- HAV
B- HBV
C- Epstien barr virus
D- HEV

Q6: A 23 YO man presents with a 6-day history of fever, sore throat, swollen lymph nodes, weight loss, and fatigue. Physical examination shows generalized lymphadenopathy, most prominent in the cervical lymph nodes, and mild hepatosplenomegaly. The peripheral blood smear shows 65% atypical lymphocytes. Heterophile antibody test is positive. Which of the following is the most probable causative agent?

A- Cytomegalovirus
B- Hepatitis A virus
C- Yellow fever virus
D- Epstein-Barr virus

Answers: Q1:B | Q2:C | Q3:A | Q4:A | Q5:D| Q6:D

SAQ

Case: A 19-year-old college sophomore presents to the university health center with a 7-day history of sore throat, headache, and fatigue. He has a temperature of 37.70C. Physical examination reveals enlarged, tender cervical lymph nodes in both the anterior and posterior cervical chain. The spleen is found to protrude 5cm under the costal margin with inspiration. Upon examination of his oropharynx, gray-green tonsillar exudate is noted.

Q1: What is the most likely diagnosis?

A: Infectious mononucleosis

Q2: What is the most likely causative agent?

A: Epstein-Barr virus

Q3: Which malignancies are associated with this infection?

A: Burkitt's lymphoma, Nasopharyngeal carcinoma

Q4: How is this organism transmitted?

A: Saliva (kissing disease) , blood (rare)

Q5: What are the main laboratory findings in this disease?

A: Heterophile Abs +ve, increased atypical lymphocytes

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