

Viral hepatitis

A and E & others

Lecture objectives:

- Distinguish the etiology of enteric viral hepatitis (HAV, HEV) from other viruses causing hepatitis such as EBV, CMV, Yellow fever virus.
- Describe the main characteristics of HAV ,HEV,EBV, CMV, and Yellow fever virus
- Describe the epidemiology and the mode of transmission of these viruses.
- Describe the clinical manifestations of enteric viral hepatitis.
- Describe the laboratory methods used to diagnose enteric hepatitis.
- Describe the treatments and the prevention measures available for these viral infection

Color index:

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

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:**

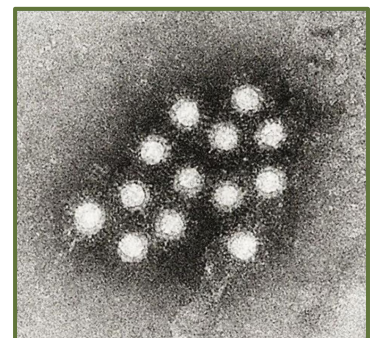
- CMV.
- EBV.
- Yellow fever virus.

- 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 A

- **Characteristics:**

- Family: **Picornaviridae**.
- Genus: **Hepatovirus**.
- **Non-enveloped**¹ virion consisting of:
 - **Icosahedral capsid**.
 - **Positive sense ss-RNA**.
- **Presentation:**
 - Short incubation hepatitis²
 - Infectious hepatitis³
 - Epidemic hepatitis⁴

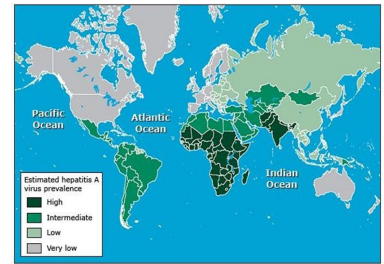


1. Nonenveloped → more resistance to the harsh environment
 2. Due to its short incubation period
 3. Transmitted easily
 4. Causes outbreaks

Hepatitis A

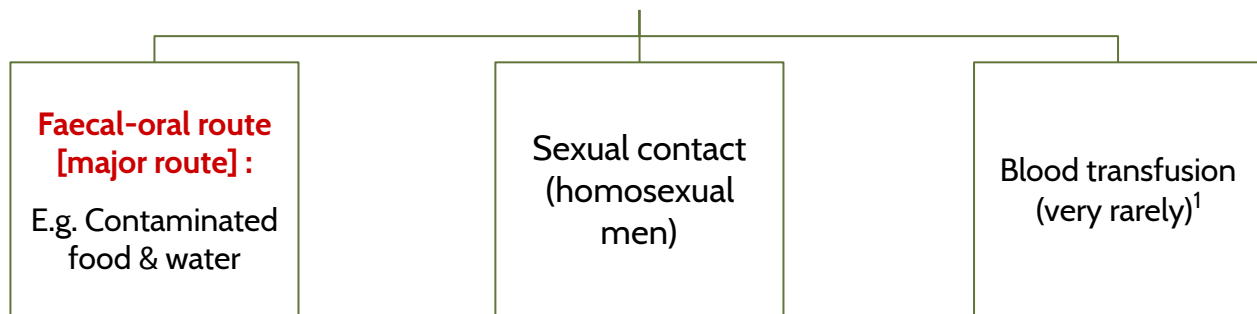
● Epidemiology:

- **Distribution:**
 - Worldwide, endemic in **tropical countries**
- **Age:**
 - In **developing countries**; children
 - In **developed countries**; young adults

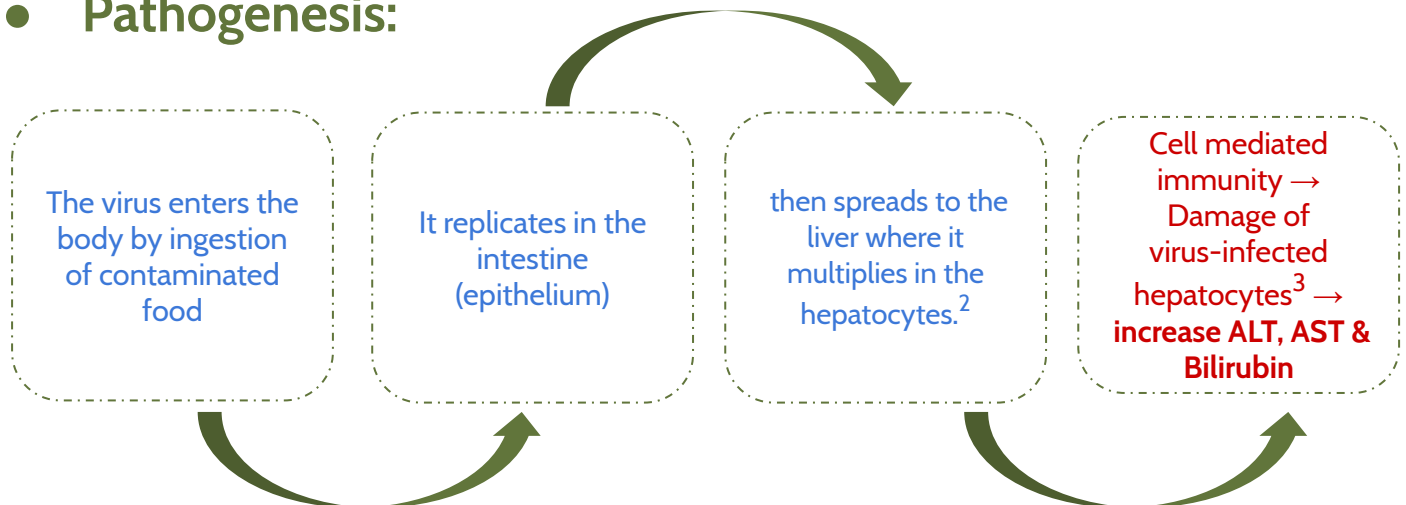


Geographic Distribution of HAV Infection

Transmission



● Pathogenesis:



● Manifestations:

- **Incubation Period (IP): 2-6 weeks.**
- **Pre-icteric phase:** Fever, Fatigue, Nausea, Vomiting, & Right upper quadrant pain (RUQP).
- **Icteric phase:** Dark urine, Pale stool & Jaundice.
 - Asymptomatic & Anicteric infection⁴: Common (more in children)
 - Symptomatic illness: Increases with age (more in adult)

1. Because HAV don't cause chronic infection (short/ transient viremia)
 2. The virus is present in the stool two weeks before the symptoms and one week after the symptoms → spreading the infection before the symptoms even begin
 3. Rather than complications of the virus itself (no cytopathic change), thereby antiviral are not effective.
 4. Presenting with symptoms of pre-icteric phase

Hepatitis A

Diagnosis & Management

| | | |
|-----------------------------|---|--|
| <p>Lab Diagnosis</p> | <p>Serology:</p> <ul style="list-style-type: none"> • Detection of anti-HAV IgM <ul style="list-style-type: none"> ○ Indicates Current infection • Detection of Anti-HAV IgG <ul style="list-style-type: none"> ○ Previous infection ○ Immunity (Vaccinated patients) | |
| <p>Treatment</p> | <p>Supportive therapy (self-limiting)</p> | |
| <p>Prevention</p> | <p>Sanitation & hygiene measures</p> <p>Hig (human immunoglobulin):¹ Given before or within 2 Weeks of exposure (shorter immunity²) Indication: travellers, unvaccinated, exposed patients.</p> <p>Vaccine:¹</p> <ul style="list-style-type: none"> - Inactivated (killed) - Given IM in two doses - >1 Y of age - Side effects: mild local reaction - Indication: Patients at high risk of infection and severe disease³ - Combination vaccine (HAV & HBV) | |

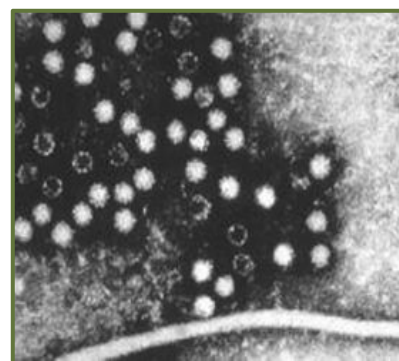
● **Prognosis:**

- **Self-limited disease**
- Fulminant hepatitis rare (severe necrotic infection of liver lead to liver failure)
- Mortality rate ~ 0.1 - 0.3% (low)
- No chronicity or malignancy changes

Hepatitis E

● **Characteristics of HEV:**

- Family: **Hepeviridae.**
- Genus: **Hepevirus.**
- **Non-enveloped** virion consisting of:
 - **Icosahedral capsid.**
 - **Positive sense ss-RNA.**



● **Epidemiology**

- **Outbreak of water-borne** & sporadic cases of viral hepatitis.
- **Age; young adults.**

1. If someone is living with a person who has been diagnosed with Hepatitis A, will you give him vaccine or Hig? Hig, because it gives immunity against HAV faster than the vaccine, but only for a short-term. Unlike vaccines which will provide long-term protection.
 2. 3-6 months.
 3. E.g. Chronic liver diseases

Hepatitis E

Transmission



● Clinical Features:

Similar to HAV infection with exceptions:

- **Longer** IP =4-8 Ws
- **Chronic hepatitis, cirrhosis, but not HCC².**
- **Fulminant disease**
- **Mortality rate ~10 times higher than HAV**
 - ~ 1-3% **[20% in pregnancy]**

Diagnosis & Management

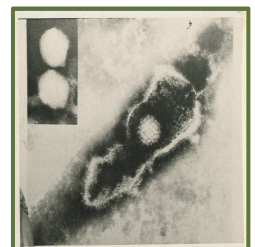
| | |
|---------------|--|
| Lab Diagnosis | Serology: <ul style="list-style-type: none"> ● Detection of anti-HEV IgM by ELISA |
| Treatment | Not specific |
| Prevention | Sanitation & hygiene measures <ul style="list-style-type: none"> - No Immunoglobulin - No vaccine (remember HAV/HBV) |

Herpesviridae³

● General features:

● dsDNA , Icosahedral & Enveloped Viruses:

- 1- Herpes simplex virus type-1 HSV-1 → causes symptoms above the waist (e.g. meningitis)
- 2- Herpes simplex virus type-2 HSV-2 → causes symptoms below the waist
- 3- Varicella –Zoster virus VZV HSV → causes chicken pox
- **4- Epstein-Barr virus** **EBV HSV**
- **5- Cytomegalovirus** **CMV HSV**
- 6- Human herpes virus type-6 HHV-6
- 7- Human herpes virus type-7 HHV-7 } → cause mild skin rash
- 8- Human herpes virus type-8 HHV-8 → can cause Kaposi sarcoma in patients with AIDS



1. Unlike HAV, HEV can be transmitted from animal to human especially through uncooked pork or beef,
 2. MAY cause in immunocompromised. However, benign self limiting in immunocompetent.
 3. Herpesviridae is family of 8 viruses that cause infections in humans and share some features. EBV & CMV cause hepatitis as part of their systemic infections, and they establish latency .

Epstein – Barr Virus EBV



● Characteristics:

- **It's lymphotropic.¹**
- it has **oncogenic properties**: :
 - Burkitt's lymphoma
 - Nasopharyngeal carcinoma

● Epidemiology:

- **Distribution:** Worldwide
- **Age:** Depends on SE (Socio-Economic status)
 - 1- Low SE : early childhood (developing countries)
 - 2- High SE : adolescence (developed countries)
- **Transmission:**
 - **1- Saliva (kissing disease)**
 - 2-blood (rare)

Clinical Features

1- Immunocompetent host:

- Asymptomatic (usually).
- **Infectious mononucleosis** (or glandular fever).
 - Mainly in teenagers & young adults
 - IP= 4-7 weeks
 - Fever, **pharyngitis**, malaise, lymphadenopathy **hepatosplenomegaly**, abnormal LFT & hepatitis.
 - Complications (rare but serious): acute airway obstruction², splenic rupture, CNS infection
- - Chronic EBV infection³

2- Immunocompromised host:

- **Lymphoproliferative disease (LD)**
- **Oral hairy leukoplakia (OHL)⁴**

Diagnosis

Hematology:

- Increased WBC:
 - **Lymphocytosis** (atypical lymphocytes **20-30%**)

Serology:

- 1. Non-specific AB test** via Paul-Bunnell or Monospot test:
 - **Heterophile Abs +ve⁵**
- 2. EBV-specific AB test:** IgM Abs to EBV capsid antigen

Treatment and vaccines

- Treatment : Antiviral drug is not effective in Infectious mononucleosis⁶
- No Vaccine

1. Attracted to lymph cells and become latent in the B-lymphocytes.
 2. Due to the enlargement of the cervical lymph nodes
 3. **If the symptoms lasts for more than 6 months**
 4. White patches on the tongue, The patches may look hairy.
 5. **Important feature to differentiate EBV from CMV (Heterophile Abs -ve).**
 6. Because the symptoms are not due to the viral replication, it's due to the immunological Attack.

Cytomegalovirus (CMV)

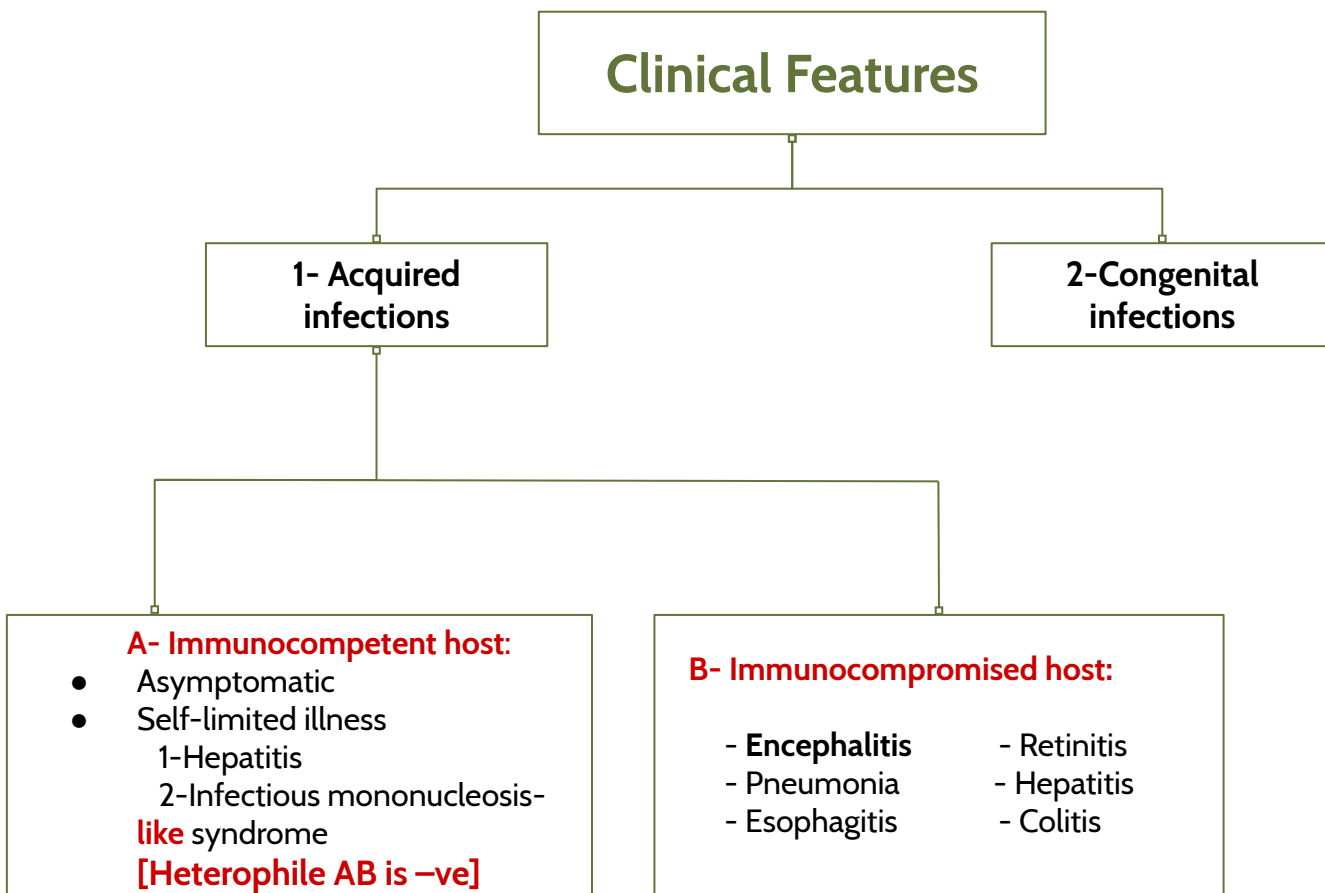
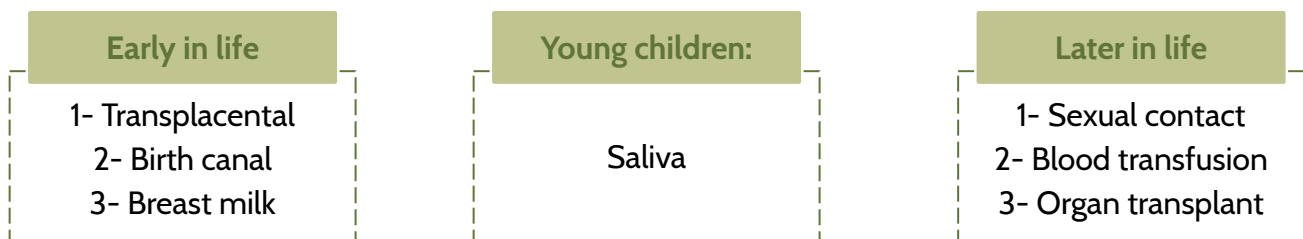
● Special features

- 1- Its replication cycle is longer
- 2- **Infected cell enlarged and multinucleated.** [cyto=cell, megal=big]
- 3- **Resistant to acyclovir¹**
- 4- **Latent in monocyte** (Mostly), lymphocyte & other.

● Epidemiology

- **Distribution:** Worldwide

● Transmission



1. In contrast to other herpes viruses
 2. Found in all the body fluids → different ways of transmission (but not airborne)

Cytomegalovirus (CMV) cont'

Diagnosis & Management

| | | | | |
|----------------------|---|--|--|------------|
| Lab Diagnosis | Histology: Intranuclear inclusion bodies [Owl's eye] (<u>sight</u> -o-megalo virus) | Culture: - In human fibroblast 1-4 weeks: CPE ¹ - Shell Vial Assay ² : 1-3 days | Serology : - Antibodies: IgM : current infection ³ IgG : previous exposure - Antigen: CMV pp65 Ag by IFA | PCR |
| Treatment | Ganciclovir : effective in the treatment of severe CMV infection Foscarnet: the 2nd drug of choice | | | |
| Prevention | <ul style="list-style-type: none"> • Screening: Organ donors, Organ recipients & Blood donors. • Leukocyte-depleted blood. (CMV replicate in the leukocytes) • Prophylaxis: Ganciclovir, CMV IG. (for immunocompromised) • No vaccine | | | |

Arthropod –borne Viruses (Arboviruses)⁴

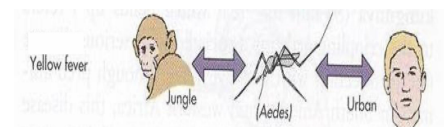
Yellow Fever virus

● Characteristics

- Family: Flaviviridae (enveloped, ss RNA +ve polarity, icosahedral)
- Asymptomatic to Jaundice (hepatitis) + Fever ± hemorrhage ± renal failure

● Epidemiology:

- **Distribution:** Tropical Africa & South America.
 1- jungle yellow fever
 2- Urban yellow fever



| Jungle Yellow Fever: | Urban Yellow Fever |
|---|---|
| <ul style="list-style-type: none"> ● Vector: Aedes mosquito⁵ ● Reservoir: monkeys ● Accidental host: humans ● It is a disease of monkeys | <ul style="list-style-type: none"> ● Vector: Aedes mosquito⁵ ● Reservoir: human ● It is a disease of humans |

1. Cytopathic effect
 2. Modified cell culture
 3. Diagnosis in immunocompetent only, because immunocompromised may be unable to produce detectable Antibody. (thus detecting for the antigen is needed)
 4. arthropod-borne viruses (arboviruses) are transmitted between vertebrate hosts by hematophagous (blood-feeding) arthropod vectors, including mosquitoes and ticks
 5. It's also vector for zika virus

Arthropod - borne Viruses (Arboviruses)

Yellow Fever virus

| Diagnosis & Prevention | | | |
|--|--|--|--|
| Lab Diagnosis | <p>A- Isolation (Gold standard) B - IgM-Ab - ELISA, IF: (most used) C - Arbovirus RNA by RT-PCR</p> | | |
| Prevention | <table border="0"> <tr> <td style="vertical-align: top;"> <p>1-Vector Control:</p> <ul style="list-style-type: none"> • Elimination of vector breeding sites • Using insecticides • Avoidance contact with vectors (repellants , net) </td> <td style="vertical-align: top;"> <p>2-Vaccine:</p> <p>Yellow Fever vaccine:</p> <ul style="list-style-type: none"> - (LAV¹, one dose /10 yrs) - recommended for travelers. </td> </tr> </table> | <p>1-Vector Control:</p> <ul style="list-style-type: none"> • Elimination of vector breeding sites • Using insecticides • Avoidance contact with vectors (repellants , net) | <p>2-Vaccine:</p> <p>Yellow Fever vaccine:</p> <ul style="list-style-type: none"> - (LAV¹, one dose /10 yrs) - recommended for travelers. |
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Summary (with Hep B lecture)

| 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- Live attenuated vaccine thus it's contraindicated in immunocompromised and pregnancy

Dr.Malak's Notes

Hepatitis A and E

- What is the most common cause of Waterborne outbreak? Hepatitis E virus
- What are the viruses that cause zoonotic disease ? HEV & yellow fever virus
- What are the fecal borne hepatitis viruses? HAV and HEV (the have similar structure but they are from different families)
- HAV → more seen in children
- HEV → more seen in Adult
- Epidemiology: mainly poor hygiene and sensitization.
- HEV and HAV mostly cause Benign self limiting disease (low risk for chronic or malignancy)
- HEV → **high mortality in pregnancy** and may cause chronic disease in immunocompromised.
- Diagnosis for HEV, HAV, & yellow fever: by specific IgM
- No treatment for HEV and HAV
- Prevention:
 - HAV → vaccine (killed) and HIg
 - Yellow fever virus → Live attenuated vaccine

- What are the viruses that transmit through saliva ? CMV and EBV
- Mosquito is the vector in yellow fever virus
- Viruses can be prevented by screening the blood before transfusion:
 - CMV
 - HAV
 - HCV
- What is the disease caused by EBV ? Infectious mononucleosis
- Immunoglobulin for the immunocompromised → HAV and CMV

MCQ:

Q1: B; Q2: D; Q3:D; Q4:B

Q1: Which of the following is available and effective for HAV?

- A- Acyclovir
- B- Killed virus vaccine
- C- Live virus vaccine
- D- Recombinant viral vaccine

Q2: Which of the following is transmitted by the fecal-oral route; can be acquired from shellfish; and often causes acute jaundice, diarrhea, and liver function abnormalities?

- A- Rotavirus
- B- Adenovirus 40/41
- C- Norwalk virus
- D- Hepatitis A virus

Q3: Malaise and hepatosplenomegaly with increased “atypical” lymphocytes and a reactive heterophil antibody test is most commonly caused by:

- A- HAV
- B- HEV
- C- HBV
- D- Epstein-Barr virus

Q4: Burkitt’s lymphoma is characterized by elevated “early antigen” tests with a restricted pattern of fluorescence. This disease is caused by:

- A- Cytomegalovirus
- B- Epstein-Barr virus
- C- HAV
- D- HEV

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 37.7°C. 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’s the most likely diagnosis?

Infectious mononucleosis

Q2: What’s the most likely causative agent?

Epstein-Barr virus

Q3: Which malignancies are associated with this infection?

Burkitt’s lymphoma, Nasopharyngeal carcinoma

Q4: How is this organism transmitted?

Saliva (kissing disease) , blood (rare)

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

Heterophile Abs +ve, increased atypical lymphocytes

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