MICROBOILOGY
TEAM 432

Lecture (11)

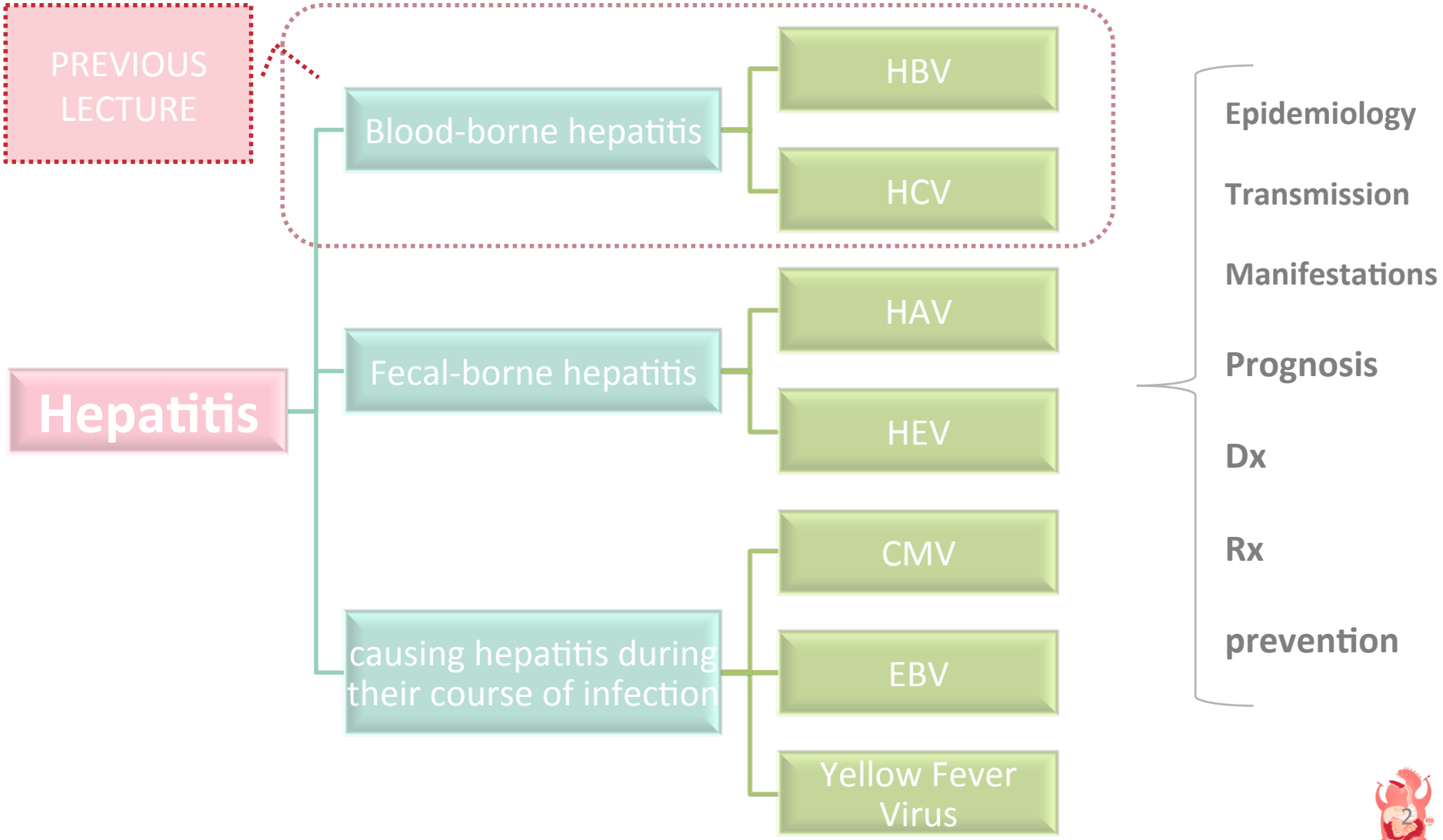
HEPATITS A,E & OTHERS.

Objectives:

- Know the classification of viruses causing hepatitis.
- viruses causing entericaly transmitted hepatitis
  - HAV
  - HEV
- viruses that are causing hepatitis during their course of infection ;
  e.g. Cytomegalovirus (CMV),
  Epstein-Barr virus (EBV),
  Arbovirus (yellow fever virus)

Done by: Deema Alturki & Sahar Alharthi **Reviewed by:** Joharah Almubrad & khalid Alosaimi

MIND MAP
(HEPATITS)



VIRAL HEPATITIS

As part of generalized infection. (liver + other organs)
(CMV, EBV, Yellow fever virus)

Infect primarily the liver.
- Fecal-borne hepatitis (A & E) → fecal oral route
- Blood-borne hepatitis (B , C , D & G) → transmitted by blood

FECAL-BORNE HEPATITS

HAV
- *Hepatovirus*
- *Picornaviridae*

- *Nonenveloped*
- *Icosahedral*
- *ss,+ sense RNA*
- *One serotype*

HEV
- *Hepevirus*
- *Hepeviridae*

Hepatitis A

Other names :
Short incubation hepatitis - Infectious hepatitis - Epidemic hepatitis

Epidemiology And transmission

It is the most common type of hepatitis

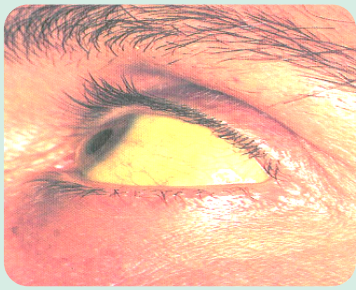
Distribution:
- a worldwide, endemic in tropical countries

Age:
- In developing countries; children*
- In developed countries ; young adults

Transmission:
- **Fecal-oral route [major route]**
- Contaminated food &water
- Sexual contact (homosexual men)
- Blood transfusion (rarely)

Manifestations (Clinical features)

- IP=2-6 Ws
- Pre-icteric (prodromal=before illness) phase: fever, fatigue, nausea, vomiting ,& RUQP (right upper quadrant pain)
- Icteric phase: dark urine, pale stool, jaundice
- Asymptomatic & anicteric infection → common
- Symptomatic illness → ↑ age

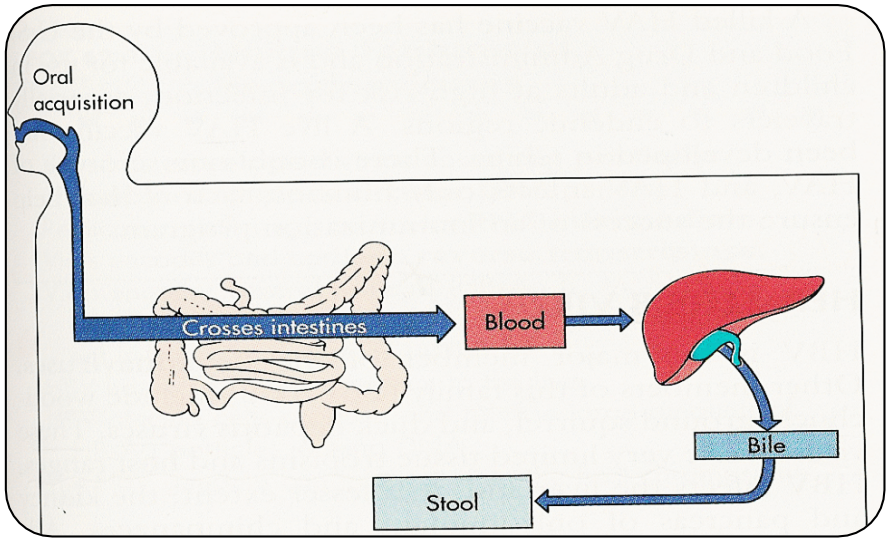


Prognosis

- Self-limited disease
- Fulminant hepatitis → rare
- Mortality rate ~ 0.1 - 0.3% (increased with age)
- No chronicity or malignancy changes

It doesn't cause chronic infection like B & C
- Hepatitis B: presence of hepatitis B surface AG in blood >6 months
- Hepatitis C : presence of hepatitis C surface AG in blood >6 months

pathogenesis



CMI cell mediated immunity → Damage of virus-infected hepatocyte

→ ↑ ALT ,AST & Bilirubin

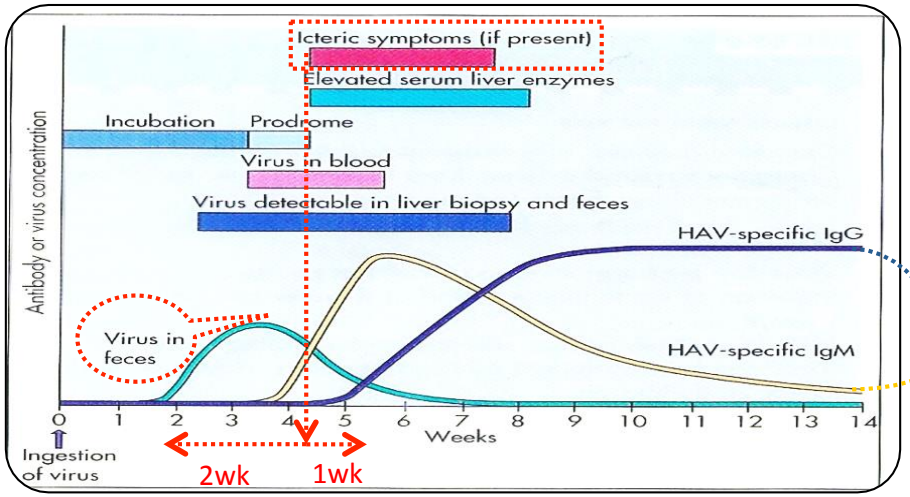
reach intestine and stomach →

replicate in the cells of GIT→

transient varemia →

infect hepatocytes and damage them (due to the action of CMI "cell mediated immunity"

not the replication of the virus) → ↑ enzymes & Bilirubin



the virus will be present in the stool of pt 2WKs before onset of symptoms (late stage of the IP and prodromal phase) and after 1 wk of the onset of the symptoms

(THE PT IS INFECTIOUS AT THIS STAGE)

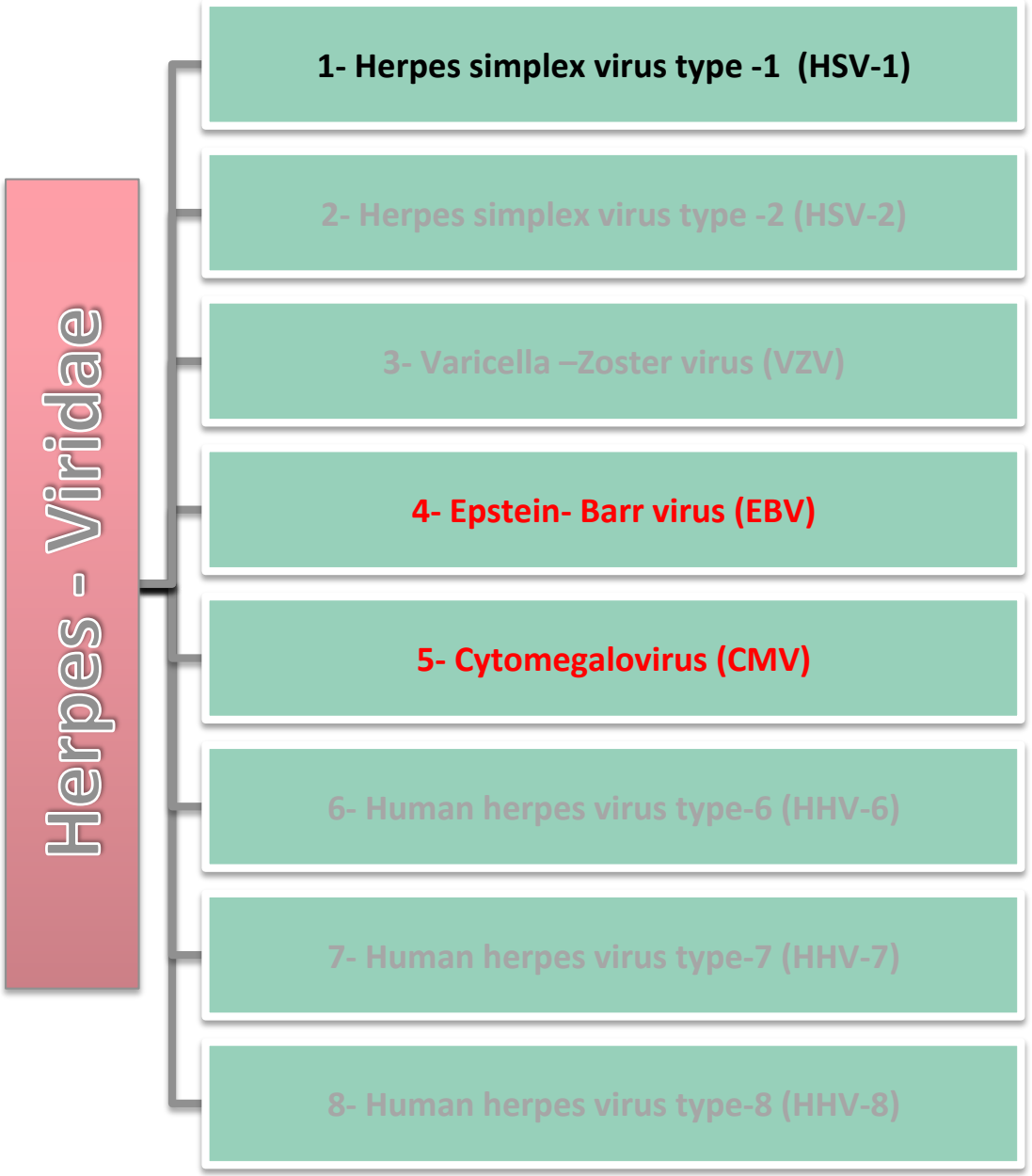
- IgM → acute (decline in few months)
- **IgG** after 1-3 wks → persist for life → immunity

Hepatitis (A)

Lab. Diagnosis	**Serology:** ○ Anti-HAV IgM → Current infection (acute infection) ○ Anti-HAV IgG → previous infection (vaccine) → **immunity**
Management	○ Supportive therapy (because it is self limited)
prevention	○ Sanitation & hygiene measures. ○ Hig "human immunoglobulin" (passive immunization) : - Given before or within 2 WKs of exposure. Not after the onset of the symptoms → the body will produce AB. - Indication : → travelers. → unvaccinated , exposed people. ○ Vaccine (active immunization) : - inactivated (killed) - Given IM at [6-12 Months] - >1 Y of age - S/E : mild local reaction - Indication : → person at high risk of infection. → person at high risk of severe disease (e.g. immunocompromised). - A combination vaccine (HAV &HBV) (called Twinrix).

HEPATITIS (E) Hepevirus ,Hepeviridae

– Epidemiology And transmission	outbreak of waterborne & sporadic cases of VH **Age:** ○ young adults ○ Severity increased with age **Transmission**: 4 routes of transmission; ○ Waterborne* (most common) ○ Zoonotic foodborne (e.g. undercookd meat) Bloodborne ○ Perinatal				
Manifestations (Clinical features)	○ ~ HAV infection & exceptions: ○ Longer IP =4-8 Ws ○ **Fulminant disease** (more common than A) ○ Mortality rate ~10 times > HAV ○ ~ 1-3%[20%in pregnancy]				
Lab. Diagnosis	Serology: ELISA → Anti-HE IgM	Treatment	Not specific	Prevention	○ Sanitation & hygiene measures ○ No Ig ○ No vaccine



Doctor's Notes:-

- At present, 8 Human Herpes Viruses are recognized.
- In immuno-competent patient, any of these viruses, especially from 1 to 7, can cause hepatitis. Usually cause mild hepatitis.
- In immuno-compromised patient, will cause severe hepatitis & sometimes cause fulminant hepatitis.
- We'll talk about only 2 (Epstein Barr Virus & Cytomegalovirus) as a causative agents of hepatitis

- dsDNA
- Icosahedra
- Enveloped Virus

Epstein – Barr Virus (EBV)

It is lymphotropic (because it infects and becomes latent in the lymphoid cells, **mainly B lymphocytes**).

It has oncogenic properties (associated with malignancies), such as:

- Burkitt's lymphoma
- Nasopharyngeal carcinoma

Epidemiology

Distribution	• World Wide
Transmission	• Saliva "kissing Disease" (Mainly) • Blood. (Rarely)
Age	• Low SocioEconomic class ➔ early childhood • High SocioEconomic class ➔ adolescence

Clinical Features

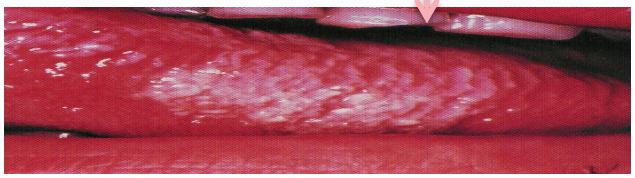
(clinical manifestations of EBV differ according to the age and the immune status of the patient)

Immuno-Competent Host

- ✧ Asymptomatic (especially in children)
- ✧ Infectious Mononucleosis "glandular fever"
  - Mainly in teenagers & young adults
  - IP (Incubation Period) = 4-7 weeks
  - Fever, pharyngitis, malaise, LAP, hepatosplenomegaly, abnormal LFT, hepatitis
  - Complications (acute air way obstruction, splenic rupture, CNS infections)
- ✧ Chronic EBV Infection (usually these symptoms resolve within few weeks. and rarely last for more than 4 months. If such symptoms last for more than 6 months, so it's called "chronic EBV infection")

Immuno-Compromised Host

- ✧ Lymphoproliferative Disease "LD"
- ✧ Oral Hairy Leukoplakia "OHL" (which is characterized by non-specific whitish lesion in the lateral boarder of the tongue)
- ✧ Malignancies



➢ N.B:- EBV can cause infectious mononucleosis with hepatitis in immuno-competent host and NOT in the immuno-compromised patient.

Diagnosis

Haematology

- ⇧ WBC Lymphocytosis (atypical lymphocytes)

Serology

- Non-Specific Anti-Body Test
  - ✓ **Heterophile Abs +ve**
  - ✓ Paul-Bunnell OR Mono-Spot Test
- EBV-Specific Anti-Body Test
  - ✓ IgM Abs to EBV capsid antigen

Management

Treatment

- Antiviral drug is not effective in IMN (No specific treatment)

Prevention

- No Vaccine

Doctor's Notes:-

The infectious mononucleosis is diagnosed by 2 approaches:

1- Hematological Approach

- There is increased WBC with absolute lymphocytosis and about 20-30% show abnormal or atypical lymphocytes with deformed nucleus and irregular rim of cytoplasm.
- This happens because the cytotoxic T cells are acting against the B cells infected with EBV.
- **So these atypical lymphocytes are cytotoxic T cell reacting against B cells infected with EBV.**

2- Serological Approach (2 types of tests):

- *(Non-Specific AB Test)*
  - is used to detect non-specific Abs that are called "heterophille" Abs. Those non-specific Abs are produced by non-specific activation of B cells.
  - As we know, B cells are responsible for the production of antibodies. When B cells are infected with EBV, they produce non-specific antibodies due to non-specific activation of B cells caused by the infection of EBV.
  - So, these antibodies are non-specific for EBV. So, these antibodies can be seen in patients with hepatitis, or patients with serum sickness.
  - It is detected by Paul-Bunnell or mono-spot test. It is a slight agglutination test. it is based on the ability of this viruses to agglutinate with RBCs. So, when the suspicious RBCs mix with serum containing the heterophille antibodies, the agglutination takes place.
- *(Specific AB Test)*
  - However, the definitive diagnosis is by the detection of IgM Abs to EBV capsid antigen.

IMN can be detected by:

- Presence of atypical lymphocytes in the blood
- Heterophille Antibodies
- IgM antibodies to EBV capsid antigen (Most Definite).

CytoMegaloVirus (CMV)

- Its replication cycle is longer (longer incubation period, up to 4 weeks to produce cytopathic effect)
- Infected cells enlarge and become multinucleated (Cyto = Cell , Megalo = Big)
- Resistant to acyclovir
- Latent in monocyte , lymphocyte & other (infect variety of cells and become latent in variety of cells. Mainly, leukocytes)

Epidemiology

Distribution

- World Wide

Transmission

- Early In Life
  - ✓ Transplacental (from mother to infant through the transplacental causing congenital infections)
  - ✓ Birth canal (birth canal & breast milk causing prenatal infections, including hepatitis)
  - ✓ Breast milk
- Young Children
  - ✓ Saliva
- Later In Life
  - ✓ Sexual Contact
  - ✓ Blood Transfusion
  - ✓ Organ Transplant

Acquired Infections

Immuno-Competent Host

- ✧ Asymptomatic (especially in children)
- ✧ Self-limited illness
- Hepatitis
- Infectious mononucleosis **like** syndrome (Heterophile Abs is –ve)
  - ✓ Characterized by: fever, malaise, splenomegaly, mild hepatitis.
  - ✓ Atypical lymphocytes in blood.
  - ✓ It differ from infectious mononucleosis caused by EBV in number of ways:
    1. Heterophille antibodies are -ve (because there is no activation of B lymphocytes. CMV do NOT infect the B lymphocytes)
    2. Pharyngitis & Tonsillitis are usually uncommon presentation in the infectious mononucleosis like syndrome

Immuno-Compromised Host

- ✧ Encephalitis, Retinitis, Pneumonia
- ✧ Hepatitis, Esophagitis, Colitis

Congenital Infections

Lab. Diagnosis

✧ **Histology** (The best way to diagnose CMV pneumonia or GI diseases caused by CMV is by the histological diagnosis of the tissue obtained from the site of the infection)

- Intranuclear inclusion bodies "Owl's – eye"

✧ **Culture** (CMV can be isolated from different types of tissue or samples such as the blood, saliva and urine)

- In human fibroblast (grow ONLY in the human fibroblast)
- 1-4 weeks ➔ CPE „Cyto Pathic Effect" (grow SLOWLY)
- Shell Vial Assay 1-3 days (it's a more modified test. it's a modified cell culture that is based on detection of CMV antigen in cell culture by the use of Immunofluorescence. Results takes from 1-3 days)

✧ **Serology**

- AB ➔ IgM (CMV can be detected by the presence of IgM specific for the CMV. However, it's not usually easy or possible to diagnose CMV in immuno-compromised patient and in neonate by the detection of IgM)

  ➔ IgG : Previous Exposure (detection of IgG in the blood indicates the previous exposure to CMV and the presence of latent infection. It does NOT indicate that the patient is immune against CMV, because of reactivation)

- AG ➔ CMV pp65 Ag by IFA (in case "AB Test" didn't work, detection of CMV antigen, CMV phosphoprotein 65 "pp65" in the peripheral leukocytes by the indirect IF Test)

✧ **PCR**

Treatment	✧ **Ganciclovir** (The drug of choice is "Ganciclovir", as CMV is resistant to acyclovir) ✓ is effective in the Rx of severe CMV infections ✧ **Foscarnet** ✓ the 2nd drug of choice (to treat the disease caused by resistance strain of CMV to the Ganciclovir)
Prevention	✧ **Screening** ✓ Organ donors (As we know, CMV can be transmitted by blood and by organ transplant. So, spread by these 2 ways can be prevented by screening of the donors for the presence of IgG, which indicates the previous exposure of CMV and the presence of latent virus) ✓ Organ recipients ✓ Blood donors ✧ **Leukocyte-depleted blood** (or by the use of "leukocyte-depleted blood" which is blood without leukocytes, because the CMV becomes latent in the leukocytes. So, using blood without leukocytes, means there is no risk or very low risk of transmission of the virus by the blood transfusion) ✧ **Prophylaxis: Ganciclovir , CMVIG** (has been used effectively to reduce the incidence and the severity of the disease in the immuno-compromised patient) ✧ **No vaccine**

Arthropod-borne Viruses (Arbo Viruses)

Yellow Fever Virus

(as the name indicates, yellow fever virus causes fever with jaundice)

Flaviviridae Family (an other important member of this family causes chronic hepatitis is “hepatitis C virus”. But “hepatitis C” does NOT transmit by the arthropods)

yellow fever virus cause a wide spectrum of illnesses range from an asymptomatic infections to systemic diseases. characterized by jaundice, fever, hemorrhage, and renal failure.

Epidemiology

Distribution

- Tropical Africa & South America (there are 2 types of epidemiological patterns):
  1. Jungle Yellow Fever
  2. Urban Yellow Fever

Transmission

- It is transmitted by the arthropod by the "mosquito".

Jungle

Mosquito

Urban

- Disease of Monkeys
- Vector is Mosquito
- Transmitted from the animal to the human through the bite of mosquito (zoonotic disease)

- Disease of Humans
- Vector is Mosquito

Diagnosis	✧ **Reference Lab** ✧ **Lab Methods** (diagnosed mainly by the isolation of the virus form different clinical samples, or by the detection of specific IgM in the blood, or by the detection of Yellow Fever Virus RNA genome) ✓ Isolation "(Gold standard)" ✓ IgM -AB* - ELISA, IF (however, the **most common** method used to diagnose yellow fever is by the detection of IgM specific antibodies by the use of the ELISA) ✓ YFV- RNA by RT-PCR
Prevention	✧ **Vector Control** ✓ Elimination of vector breading sites (vector control depends on the elimination of the growth conditions, such as removing of stagnant water) ✓ using insecticides (to kill mosquitos) ✓ Avoidance contact with vectors (wearing protective clothes or using repellants and net) ✧ **Vaccines** ✓ Yellow Fever vaccine (LAV, one dose /10 years) • Vaccine is available "life attenuated vaccine", one dose provide immunity for 10 years. • So, booster dose should be given after 10 years to maintain the immunity in the body. • Given mainly to travelers to endemic areas

SUMMARY

MICROBIOLOGY

Vr.	HAV	HEV	EBV	CMV	Yellow Fever Virus
Transmission	○ Fecal-oral route [major route] ○ Contaminated food &water ○ Sexual contact ○ Blood transfusion	4 routes of transmission; ○ Waterborne* (most common) ○ Zoonotic Foodborne ○ Bloodborne ○ Perinatal	○ Saliva (Mainly) ○ Blood (Rare)	○ Transplacental ○ Birth Canal ○ Breast Milk ○ Saliva ○ Sexual Contact ○ Blood Transfusion ○ Organ Transplant	○ Arthropod (Mosquito)
Clinical features	○ Pre-icteric phase: fever, fatigue, N, V,& RUQP ○ Icteric phase: dark urine, pale stool, jaundice ○ Asymptomatic	○ Fulminant disease > HAV ○ Mortality rate ~10 times > HAV	○ Asymptomatic ○ IMN ○ Chronic EBV Infection ○ LD ○ OHL	○ Asymptomatic ○ Hepatitis ○ IMN Like Syndrome ○ Encephalitis ○ Pneumonia ○ Retinitis ○ Esophagitis ○ Colitis	○ Jaundice ○ Fever ○ Hemorrhage ○ Renal Failure
Dx	○ Anti-HAV IgM → Current inf ○ Anti-HAV IgG → previous inf → immunity	ELISA → Anti-HE IgM	○ Atypical Lymphocytes In Blood ○ Heterophille Abs ○ IgM Abs to EBV	○ Histology (Best) Owl's Eye ○ Culture ○ IgM (Not Common) ○ IgG ○ CMV pp65 ○ PCR	○ Isolation Gold standard" ○ IgM Abs (ELISA, IF) **Most Used** ○ YFV-RNA by RT-PCR
Rx	Supportive therapy	Not specific	No Specific Treatment	○ Ganciclovir (1st drug of choice) ○ Foscarnet(2st drug of choice)	-
Prevention	○ Sanitation & hygiene measures ○ Hig ○ Vaccine	○ Sanitation & hygiene measures. ○ No Vaccine	○ No Preventive Measures ○ No Vaccine	○ Screening ○ Leuko-Cyte Depleted Blood ○ Prphylaxis ○ No Vaccine	○ Vector Control ○ Vaccine

QUESTIONS

1. You are a public health physician working at a city health department and receive a report of a case of hepatitis A virus (HAV) infection in a 32-year-old man who lives with his wife and one-year-old twins. He is a self-employed contractor who often eats on the run. His wife works part-time at a bookstore and his children attend day care. He has no history of travel, eating raw fish, or known contact with other cases of HAV infection. The first step in investigating this case is to confirm the diagnosis of HAV with is ..

A. HAV RNA
B. Stool cultures
C. Total anti-HAV antibodies
D. IgM anti-HAV

2. The initial infection with human cytomegalovirus most commonly occurs:

A. during early childhood, by exchange of body fluids
B. in utero, by transplacental transmission from a latently infected pregnant woman
C. by transfer of saliva between young adults
D. by sexual intercourse
E. as a result of blood transfusion or organ transplantation

answers : 1=D 2=A, , , , ,

FOR ANY SUGGESTIONS AND PROBLEMS PLEASE CONTACT:
MICROBIOLOGY TEAM LEADERS
KHALED ALOSAIMI AND JOHARAH ALMUBRAD
MICROBIOLOGY432@GMAIL.COM

QUESTIONS

3. The cellular response typical of infectious mononucleosis caused by Epstein-Barr virus is due to:

A. stimulation of B-cell proliferation by the EBV early proteins synthesized in the infected cells
B. proliferation of cytotoxic T cells responding to EBV antigens expressed on the surface of infected B cells
C. a primary humoral immune response to the EBV infection
D. macrophages responding to the death of EBV-infected cells
E. Activation of an oncogene resulting from a chromosome translocation in EBV-infected lymphocytes

4. Acyclovir is largely ineffective in the treatment of human cytomegalovirus infections because:

A. HCMV exhibits a high rate of mutation in the target enzyme
B. HCMV depends upon the host cell's DNA polymerase for replication of its DNA
C. HCMV lacks the thymidine kinase required for activation of acyclovir
D. the tissues in which HCMV multiplies are largely inaccessible to the drug
E. HCMV codes for an enzyme that inactivates the drug

answers : 3=B 4=C , , , ,

Questions from 2-4 are copied from Lippincott's Microbiology Book, 2nd edition, page 272.
If you're interested to read about answers, please refer to the page number mentioned above.

FOR ANY SUGGESTIONS AND PROBLEMS PLEASE CONTACT:
MICROBIOLOGY TEAM LEADERS
KHALED ALOSAIMI AND JOHARAH ALMUBRAD
MICROBIOLOGY432@GMAIL.COM