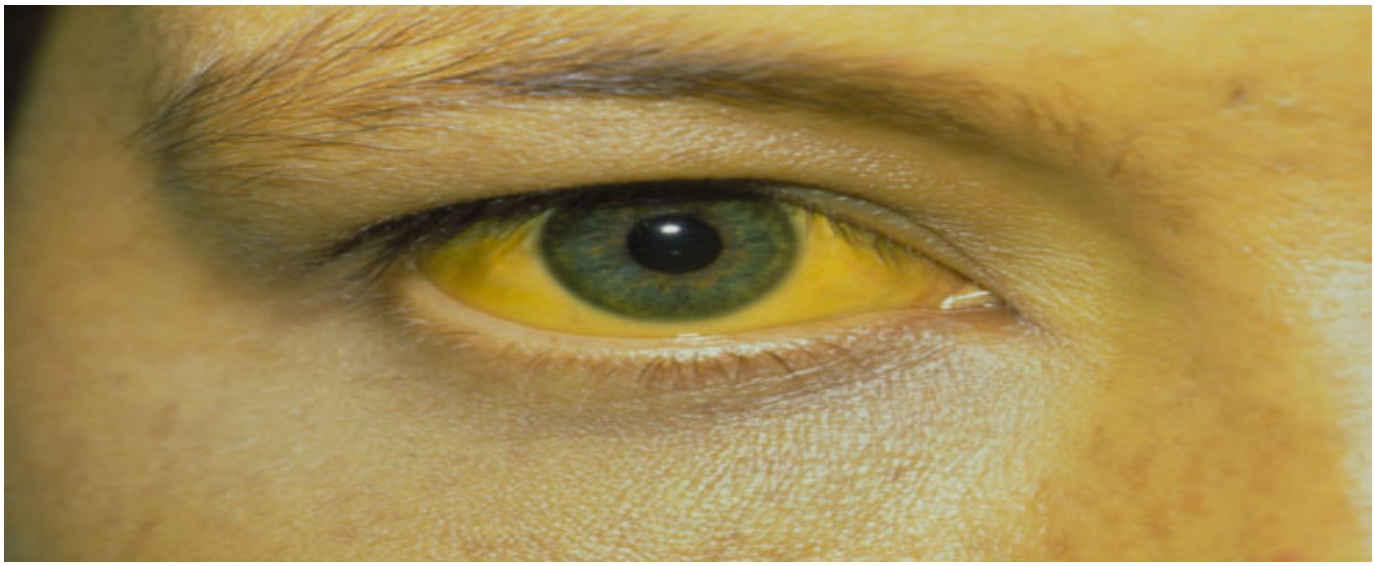
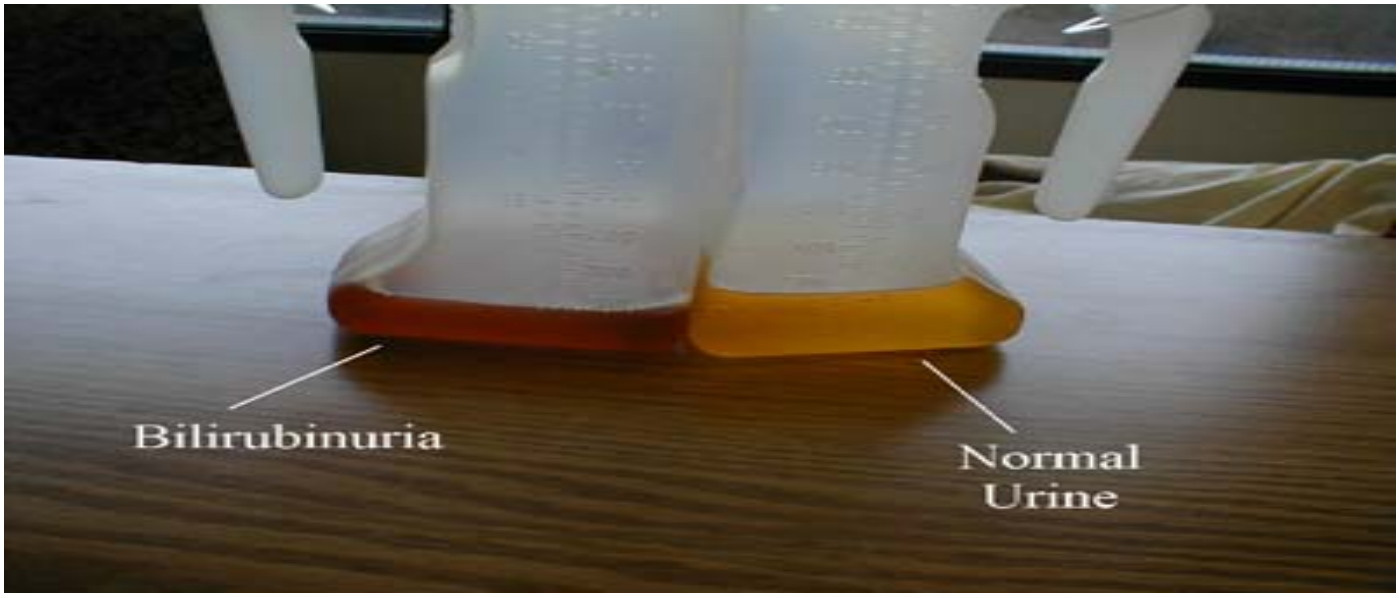
VIRAL HEPATITIS

Hepatitis viruses (Infectious hep A&E)



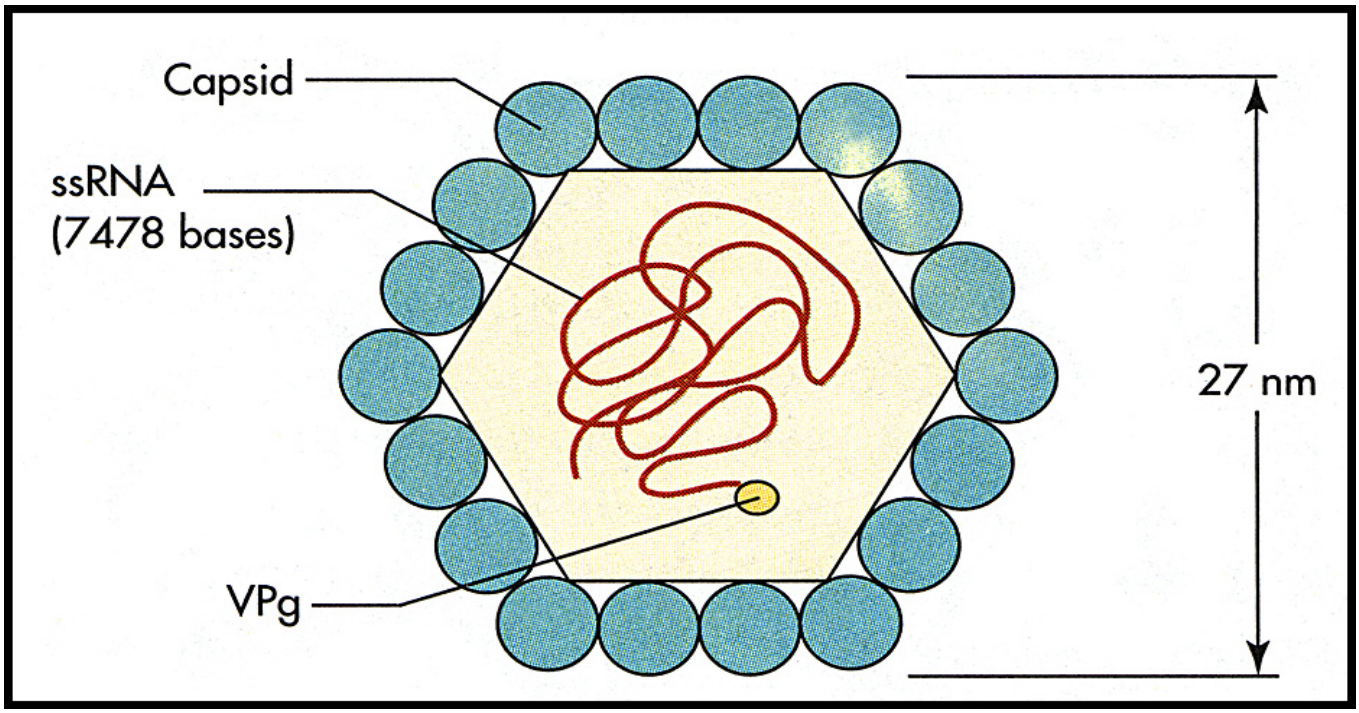


Acute Viral Hepatitis

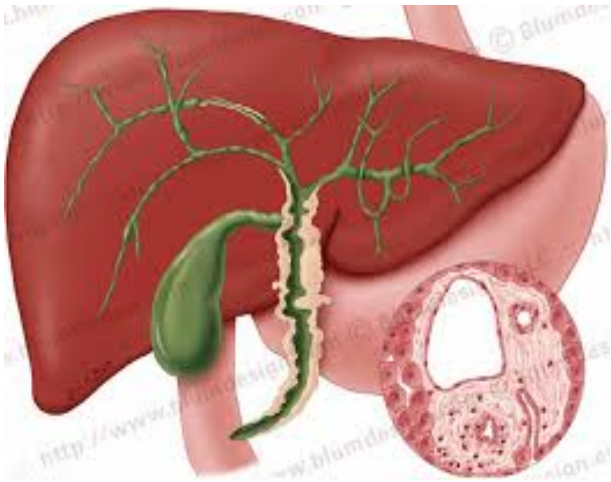
Causes of acute hepatitis :

Viruses	Others
Hepatitis A	*- Drug*
Hepatitis B	*- Toxin*
Hepatitis C	*- Alcohol*
Hepatitis D	*- Ischemia*
Hepatitis E	*- Wilson's disease*
Herpes simplex	*- Others*
Cytomegalovirus	
Epstein-Barr	
Adenoviruses	

Hepatitis A Structure and classification



- ❑ **RNA Picornavirus**
    - **Separate genus because of differences with other enteroviruses**
    - **Naked icosahedral capsid SS RNA (740 nucleotides)**
    - **Single serotype worldwide, Humans only reservoir**
    - **Fecal-oral transmission**
- ❑ **Incubation 4 weeks (range 2-6 weeks)**
- ❑ **Oral cavity→GI tract→liver via blood**
- ❑ **Replicates in hepatocytes (little damage to cells) released via bile to intestines 7-10 days prior to clinical symptoms shedding in stool**
- ❑ **Liver damage and clinical syndrome result of immune response and not direct effect of virus**



HEPATITIS A - CLINICAL FEATURES

• Jaundice by age group:	<6 yrs	<10%
	6-14 yrs	40%-50%
	>14 yrs	70%-80%
• Rare complications:	Fulminant hepatitis Cholestatic hepatitis Relapsing hepatitis	
• Incubation period:	Average 30 days Range 15-50 days	
• Chronic sequel:	None	

The average incubation period of hepatitis A is 30 days(range 15-50 days). Patients characteristically have abrupt onset of symptoms include fever, malaise, anorexia, nausea , abdominal discomfort, dark urine and jaundice (icterus). The severity of clinical disease associated with HAV infection increases with increased age. Jaundice occur among less than 10% of children younger than 6 years, 40-50% of older children and 70-80% of adults. Complications of HAV include fulminant hepatitis in fatality rate can be greater than 50% despite medical intervention with very high bilirubin levels can persist for months. Chronic infection does not occur following HAV infections.

An acute illness with:

- **discrete onset of symptoms (e.g. fatigue, abdominal pain, loss of appetite, intermittent nausea, vomiting)**
- **jaundice or elevated serum aminotransferase levels, dark urine, light stool**
- **Adults usually more symptomatic**
- **Patients are infective while they are shedding the virus in the stool-usually before the onset of symptoms**
- **Most cases resolve spontaneously in 2-4 weeks**

Complete recovery 99%

Hepatitis A Diagnosis

- **Detection of IgM antibody**
- **IgG positive 1-3 weeks later; suggests prior infection or vaccination.**
- **Viral Ag in stool or liver biopsies**
- **Molecular detection**

HEPATITIS A VACCINES

Inactivated vaccine, Highly immunogenic

- **97%-100% of children, adolescents, and adults have protective levels of antibody within 1 month of receiving first dose; essentially 100% have protective levels after second dose. Highly efficacious**
- **In published studies, 94%-100% of children protected against clinical hepatitis A after equivalent of one dose**

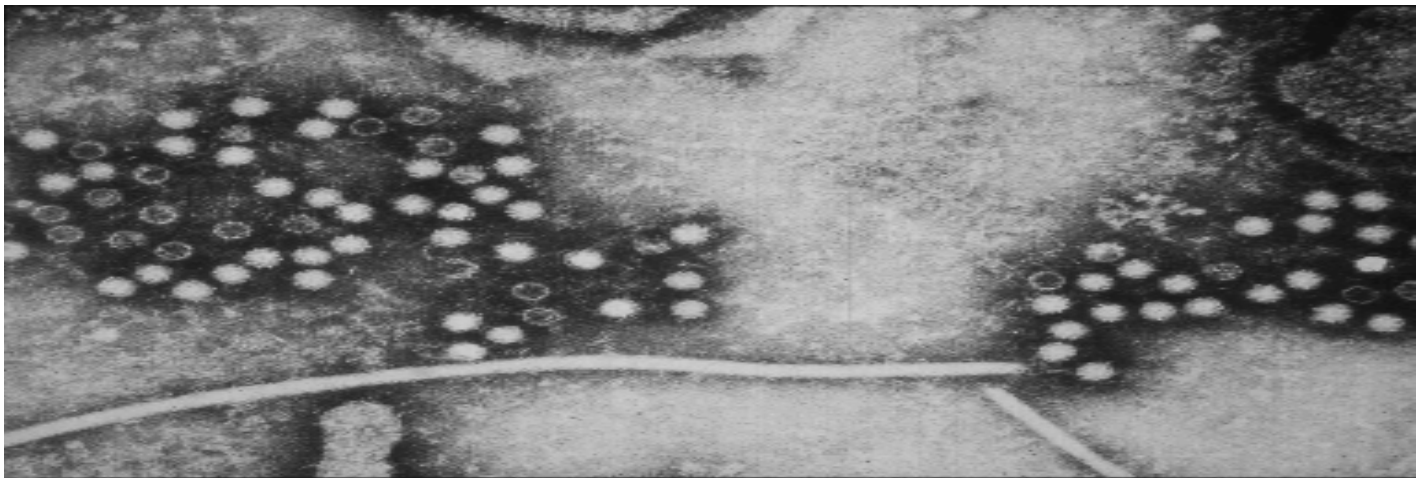
- **1st dose at 0 time , 2nd dose at 6-12 months afterward**

Hep A Passive Immunization

- **Hepatitis A immune globulin can be given up to 2 weeks after an exposure**

Immunity temporary (4-5 months) Also given in travelers leaving for endemic area on short notice (not enough time for the vaccine to be effective)

Hepatitis E virus



- Non-enveloped single stranded RNA virus
- Resembles calicivirus or Norwalk agent
- Similar illness to Hep A except high mortality in pregnant women

Hepatitis E - Epidemiologic Features

- Most outbreaks associated with fecally contaminated drinking water
- Minimal person-to-person transmission

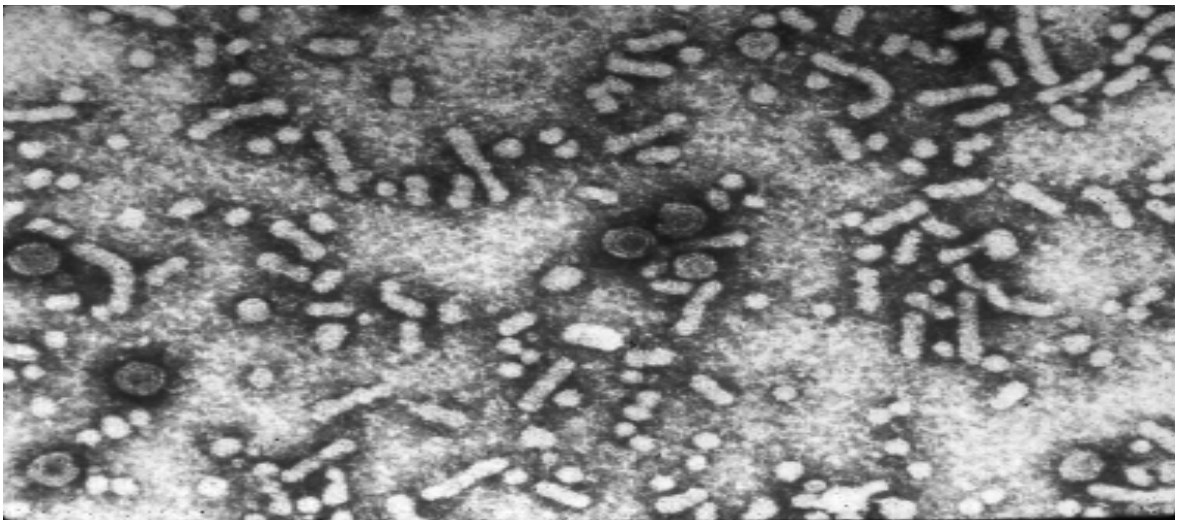
CONCEPT QUESTIONS

- What are the structure and classification bases of HAV
- - What are the possible mode of HAV transmission ?
- - Describe the pathogenesis of HAV .
- - What are the clinical feature of HAV ?
- - What are the diagnostic methods of HAV ?

- - What are the prevention consideration of HAV ?
- - What are the values of HAV vaccination ?
- - For whom the HAV vaccination is recommended ?

(Hepatitis viruses-Parenteral:B,D & C)

Hepatitis B Virus



Hepatitis B: Structure and replication

- **Member of the hepadnavirus group**
- **Virion also referred to as Dane particle**
- **42nm enveloped virus**
- **Core antigens located in the center (nucleocapsid)**
  - **Core antigen (HbcAg)**
  - **e antigen (HBeAg)- an indicator of transmissibility (minor component of the core- antigenically distinct from HBcAg)**

- **22nm spheres and filaments other forms- no DNA in these forms so they are not infectious (composed of surface antigen)- these forms outnumber the actual virions**
- **Circular partially double stranded DNA of virus**
- **Initial replication to complete circular DNA with subsequent transcription to make several mRNAs some of which are translated into viral proteins**
- **One of the mRNAs is replicated with a reverse transcriptase making the DNA that will eventually be the core of the progeny virion**
- **Some DNA integrates into host genome causing carrier state**
- **Virus stable and resist many stresses making them more infectious**

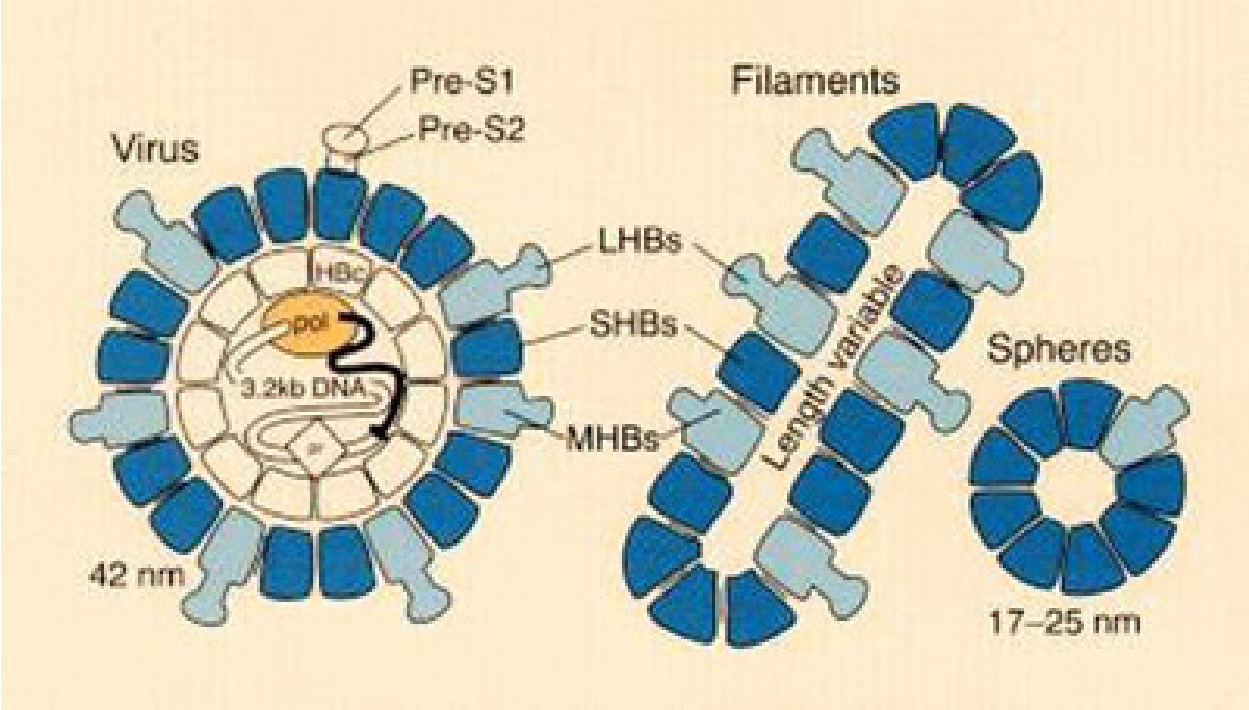


Fig. HBV particle. The schematic diagram shows the 42 nm , tubular filaments and spherical particles composed of the HBV envelope protein, which also appear in the circulation of HBV –infected individuals. The envelope contains small, medium and large size envelope proteins(HBV surface antigens=HBsAg). Th small proteins of HBsAg

specified by S gene, the medium by S and pre-S2,and the large by S, Pre-S1 and pre-S2 genes.The 3.2Kb DNA, HBV DNA polymerase are shown within capsid (HBc)

HBV Markers

Marker	*interpretation*
HB_sAg	Active HBV infection; may be acute or chronic
HB_sAb	immunity to HBV natural or following vaccination
HB_cAb-IgM	acute infection (sensitive technique detect reaction of chronic)
HB_eAg	High infectivity, active viral replication (window period)
HB_eAb	Low or no infectivity , need measuring in chronic
HBV-DNA	Direct measure of infectivity or replicative state

Hepatitis B Vaccine

Infants: **several options that depend on status of the mother**

- **If mother HepBsAg negative: birth, 1-2m,6-18m**
- **If mother HepBsAg positive: vaccine and Hep B immune globulin within 12 hours of birth, 1-2m, <6m**

- **Adults**
  - Vaccine recommended in doses at 0,1, 6 months
  - Those at high risk

Hepatitis B: Passive Immunization

- Infants of surface antigen positive mothers
  - Exposures to infected blood or infected body fluids in individuals who are unvaccinated, or unknown vaccination ; Ideally within 24 hours
  - Probably not effective >7days post exposure

High risk group:

Persons with multiple sex partners or diagnosis of a sexually transmitted disease

Men who have sex with men , Sex contacts of infected persons •
Injection drug users •
Household contacts of chronically infected persons •
Infants born to infected mothers •
Health care and public safety workers •

Hepatitis D (Delta) Virus

- **Defective virus that requires co-infection with hepatitis B for replication**
- **Enveloped with SS RNA genome, Only antigen encoded in the delta antigen**

Modes of Transmission

- **Percutanous exposures , injecting drug use**
- **Permucosal exposures and sex contact**

Pathogenesis

- **Immune mediated**
- **Co-infection- infection with B at the same time (more severe)**
- **Superinfection: acquisition of Hep D in chronically Hep B**

HDV prevention:

- **<u>HBV-HDV Coinfection</u>**

  Pre or post exposure prophylaxis to prevent HBV infection

- **<u>HBV-HDV Superinfection</u>**

  Education to reduce risk behaviors among persons with chronic HBV infection

- **Alpha interferon may help to reduce hepatocellular damage**

CONCEPT QUESTIONS

- What are the structure and classification of HBV?

- **What are the replication strategies of HBV?**
- **What are tthe main modes of HBV transmission?**
- **Who are at greater risk of acquiring HBV carriage?**

- **In what types of body fluids HBV more concentrated**
- **Mention the pathogenesis of HBV .**
- **How HBV genome reflect the complexicty of virus?**
- **What are the clinical features of HBV ?**
- **What are the possible outcome of HBV infection?**
- **What are the main HBV markers?**
- **Mention the main diagnostic methods of HBV.**
- **Give the interpretation for the presence for HBV markers ,**

. What are the options for HBV treatment?

. What are the types of HBV vaccines ?

. What is the schedule for HBV vaccination?

. Who are at high risk of HBV infections?

. To whom passive HBV immuniation is recommended ?

- **Describe the structure of HDV .**
- **- What is the nature of HDV infection?**
- **- What are the mode of HDV transmission?**
- **- Mention the pathogenesis of HDV ?**
- **- What are the clinical feature of HDV infection?**
- **- What are clinical outcome of HDV coinfection?**
- **- Mention the diagnostic methods for HDV.**
- **-What are the methods for HDV prevention?**

Hepatitis C

HCV is a positive sense , single stranded RNA virus, HCV represent a distinct genus in Flaviviridae family. A viral envelope comprising a lipd layer and envelope protein, surround a core (capsid) strucrure enclosing the viral nucleic acid. HCV RNA is 9.4 kb.

- **Member of the flavivirus family**
- **Enveloped single stranded RNA virus**
- **Humans and chimpanzees only known reservoirs**
- **6 serotypes (genotypes) and multiple subtypes based on high variability of envelope glycoproteins**

Hep C: Pathogenesis

- **Blood-borne pathogen that infects hepatocytes**
- **Much like Hep A and B, liver damage and clinical illness due more to elicited immune response as opposed to direct cytopathic effect of the virus**
- **Likely cytotoxic T cells that mediate most of the damage**
- **Like other chronic liver diseases (Hep B and chronic alcoholism), can cause hepatocellular ca (HCC)**

Clinical feature of HCV :

- **Incubation period** — **Average 6-7 weeks**; **Range 2-26 weeks**
- **Acute illness (jaundice)** — **Mild (≤20%)**
- **Case fatality rate** — **Low**
- **Chronic infection** — **60%-85%**

- **Chronic hepatitis** **10%-70% (mostasx)**
- **Cirrhosis** **<5%-20%**
- **Mortality from CLD** **1%-5%**

Acute infection asymptomatic in over 80% of patients, when present, acute illness usually mild

- **Acute symptoms include jaundice, nausea, abdominal pain, loss of appetite, dark urine**

Clinical manifestations of HCV:

Acute infection

- **Symptoms are uncommon. Malaise ,Weakness, Anorexia jaundice**
- **Symptoms subside after several weeks as ALT levels decline.**

Preventing HCV Transmission to Others

Avoid Direct Exposure to Blood

- **Do not donate blood, body organs, other tissue or semen**
- **Do not share items that might have blood on them**
  - **personal care (e.g., razor, toothbrush)**
  - **home therapy (e.g., needles)**
- **Cover cuts and sores on the skin**
- **Inefficient by occupational exposures**
- **Average incidence 1.8% following needle stick from HCV-positive source**
  - **Associated with hollow-bore needles**
- **Case reports of transmission from blood splash to eye**

- **Prevalence 1-2% among health care workers**
  - **Lower than adults in the general population**
  - **10 times lower than for HBV infection**
- **Chronic Hepatitis C : Factors Promoting Progression or Severity**
  Increased alcohol intake, Age > 40 years at time of infection

  HIV co-infection

  Other : Male gender and Chronic HBV co-infection

Hepatitis C: Extrahepatic Manifestations

- **Seen with chronic infection**
- **Due to immune complexes**
- **Extrahepatic manifestations**
  - **Vasculitis, skin rash, fatigue**
  - **Cutaneous porphyria**
  - **Glomerulonephritis**
  - **Diabetes mellitus**
  - **Other autoimmune disease**
  - **Lymphoma**

Hepatitis C: Diagnosis

- **ELISA-a serological test which is usually. positive within 2-5 months after infection**
- **Confirmatory testing**
  - **PCR (positive 1-2 weeks post infection)**

- **RIBA (recombinant immunoblot assay)- looks for 2 or more antibodies to HCV viral antigens**

Quantitative estimates of HCV –RNA:

- **Acute or chronic HCV infection in a patient with a positive EIA test should be confirmed by a qualitative HCV RNA assay.**
- **The specificity of these assays for detecting HCV RNA exceeds 98 percent.**
- **A single positive qualitative assay for HCV RNA confirms active HCV replication.**
- **A single negative assay does not exclude viremia and may reflect only a transient decline in viral level below the level of detection of the assay.**

A follow up quantitative HCV RNA should be performed to confirm an acute infection

Estimation of viral load and genotyping are important parameters for case assessment

HCV serologic assay

- **EIA tests are reproducible, inexpensive.**
- **A negative EIA test is sufficient to exclude a diagnosis of chronic HCV infection in immunecompetent patients.**
- **On hemodialysis and patients with immune deficiencies may have false-negative EIAs.**
- **False-positive EIAs may occur in patients with autoimmune disorders. In these patients, an assay for HCV RNA is necessary for diagnosis of chronic infection.**

CONCEPT QUESTIONS

- **What are the structure & classification of HCV?**
- **Describe the pathogenesis of HCV .**
- **What are the clinical feature of HCV infections?**
- **What are the outcome of HCV infections?**

- What are the possible extrahepatic manifestation of HCV infections?

- **What are the factors promoting progression or severity of HCV chronicity?**
- **Mention the main diagnostic methods for HCV?**
- **What is the the benefit of HCV therapy?**