

Medical microbiology

Virology..... Dr.Zaytoon Alkhafaji

Hepatitis Viruses

Viral hepatitis is a systemic disease primarily involving the liver. Most cases of acute viral hepatitis in children and adults are caused by one of the following six agents:

- 1- Hepatitis A virus (HAV), the etiologic agent of viral hepatitis type A (infectious hepatitis).
- 2- Hepatitis B virus (HBV), which is associated with viral hepatitis B (serum hepatitis).
- 3- hepatitis C virus (HCV) the agent of hepatitis C (common cause of posttransfusion hepatitis).
- 4- Hepatitis D (HDV), a defective virus dependent on co-infection with HBV.
- 5- Hepatitis E virus (HEV) the agent of enterically transmitted hepatitis.
- 6-Hepatitis G virus (HGV).

Additional well-characterized viruses that can cause sporadic hepatitis, such as Yellow fever virus, Cytomegalovirus, Epstein-Barr virus, Herpes simplex virus, Rubella virus, and the Enteroviruses. Hepatitis viruses produce acute inflammation of the liver, resulting in a clinical illness characterized by fever, gastrointestinal symptoms such as nausea and vomiting, and jaundice. Regardless of the virus type, identical histopathologic lesions are observed in the liver during acute disease.

Hepatitis Type A

HAV is a distinct member of the **picornavirus** family. HAV is a (**27-32**) nm **spherical particle** with **cubic symmetry** containing a linear single-stranded RNA genome with a size of 7.5 kb. It is assigned to picornavirus genus, Hepatovirus. Only one serotype is known. There is no antigenic cross-reactivity with HBV or with the other hepatitis viruses. isolates into seven genotypes.

HAV is stable to treatment with **20% ether**, **acid** (pH 1.0 for 2 hours), and **heat** (60°C for 1 hour), and its infectivity can be preserved for at least **1 month** after being dried and stored at **25°C** or for **years** at **-20°C**. The

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virus is destroyed by autoclaving (121°C for 20 minutes), boiling in water for 5 minutes, dry heat(180°C for 1 hour), ultraviolet irradiation (1 minute at 1.1 watts), treatment with formalin (1:4000 for 3 days at 37°C), or treatment with chlorine (10–15 ppm for 30 minutes).

Heating food to above 85°C (185°F) for 1 minute and disinfecting surfaces with sodium hypochlorite (1:100 dilution of chlorine bleach) are necessary to inactivate HAV. The relative resistance of HAV to disinfection procedures emphasizes the need for extra precautions in dealing with hepatitis patients and their products.

Diagnosis of HAV :

- 1-Identified the virus in **stool and liver** preparations by using **immune electron microscopy** as the detection system.
- 2 - **Sensitive serologic assays** , to measure specific antibody in serum.
- 3- **polymerase chain reaction** (PCR) methods have made it possible to detect HAV in stools and other samples.
- 4- **Various primate cell lines will support growth of HAV**, although fresh isolates of virus are difficult to adapt and grow. Usually, no cytopathic effects are apparent. **Mutations** in the viral genome are selected during adaptation to tissue culture.

Hepatitis Type B

HBV is classified as a hepadnavirus . HBV establishes chronic infections, especially in those infected as infants; it is a major factor in the eventual development of liver disease and hepatocellular carcinoma in those individuals.

A. Structure and Composition

Electron microscopy of hepatitis B surface antigen (HBsAg) positive serum reveals three morphologic forms. The most numerous are spherical

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particles measuring 22 nm in diameter . These **small particles** are made up exclusively of HBsAg—as are **tubular or filamentous forms**, which have the same diameter but may be more than 200 nm long—and result from overproduction of HBsAg. **Larger**, 42-nm spherical virions (originally referred to as **Dane particles**) are less frequently observed.

The outer surface, or envelope, contains HBsAg and surrounds a 27-nm inner nucleocapsid core that contains hepatitis B core antigen (HBcAg). The variable length of a single-stranded region of the circular DNA genome results in genetically heterogeneous particles with a wide range of buoyant densities.

The full-length DNA minus strand (L or long strand) is complementary to all HBV mRNAs; the positive strand (S or short strand) is variable and between 50% and 80% of unit length.

Important Properties of Hepadnaviruses

Virion: About 42 nm in diameter overall (nucleocapsids, 18 nm)

Genome: One molecule of double-stranded DNA, circular, 3.2 kbp.

In virion, negative DNA strand is full length, and positive DNA strand is partially complete. The gap must be completed at the beginning of the replication cycle.

Proteins: Two major polypeptides (one glycosylated) are present in HBsAg; one polypeptide is present in HBcAg.

Envelope: Contains HBsAg and lipid

B. Replication of Hepatitis B Virus

The infectious virion attaches to cells and becomes uncoated. In the nucleus, the partially double-stranded viral genome is converted to covalently closed circular double stranded DNA (cccDNA). The cccDNA

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serves as template for all viral transcripts, including a 3.5-kb pregenome RNA.

The pregenome RNA becomes encapsidated with newly synthesized HBcAg. Within the cores, the viral polymerase synthesizes by reverse transcription a negative-strand DNA copy. The polymerase starts to synthesize the positive DNA strand, but the process is not completed. Cores bud from the pre-Golgi membranes, acquiring HBsAg-containing envelopes, and may exit the cell. Alternatively, cores may be reimported into the nucleus and initiate another round of replication in the same cell.

The Hepatitis B blood tests interpreted:

The following table gives the usual interpretation for sets of results from hepatitis B blood (serological) tests.

Most Likely Status*	Tests	Results
Susceptible, not infected, not immune	HBsAg anti-HBc anti-HBs	negative negative negative
Immune due to natural infection	HBsAg anti-HBc anti-HBs	negative positive positive
Immune do to hepatitis B vaccination	HBsAg anti-HBc anti-HBS	negative negative positive
Acutely infected	HBsAg anti-HBc IgM anti-HBc anti-HBs	positive positive positive negative
Chronically infected	HBsAg anti-HBc IgM anti-HBc	positive positive negative negative

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Most Likely Status*	Tests	Results
	anti-HBs	

*Interpretation of the hepatitis B virus blood tests should always be made by an experienced clinician with knowledge of the patient's medical history, physical examination, and results of the standard liver blood tests.

Hepatitis Type C

Clinical and epidemiologic studies and cross-challenge experiments in chimpanzees in the past had suggested that there were several **non-A, non-B (NANB)** hepatitis agents that, based on **serologic tests**, were not related to HAV or HBV. The major agent was identified as HCV. **HCV** is a positive- stranded RNA virus, classified as family **Flaviviridae**, genus **Hepacivirus**. Various viruses can be differentiated by RNA sequence analysis into at least **six major genotypes** (clades) and more than 100 subtypes. Clades differ from each other by 25–35% at the nucleotide level; subtypes differ from each other by 15–25%. The genome is 9.4 kb in size and encodes a core protein, two envelope glycoproteins, and several nonstructural proteins . The expression of cDNA clones of HCV in yeast led to the development of serologic tests for antibodies to HCV. Most cases of post transfusion NANB hepatitis were caused by HCV.

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Most new infections with HCV are subclinical. **The majority** (70–90%) of HCV patients develop **chronic hepatitis**, and many are at risk of progressing to **chronic active hepatitis and cirrhosis** (10–20%). In some countries, as in Japan, HCV infection often leads to hepatocellular carcinoma.

HCV displays genomic diversity, with different genotypes (clades) predominating in different parts of the world. The virus undergoes sequence variation during chronic infections. This complex viral population in a host is referred to as “quasi-species.” This genetic diversity is not correlated with differences in clinical disease, although differences do exist in response to antiviral therapy according to viral genotype.

Hepatitis Type D (Delta Hepatitis)

An antigen–antibody system termed the delta antigen (delta-Ag) and antibody (anti-delta) is detected in some HBV infections.

The antigen is found within certain HBsAg particles. In blood, HDV (delta agent) contains delta-Ag (HDAg) surrounded by an HBsAg envelope. It has a particle size of 35–37 nm and a buoyant density of 1.24–1.25 g/mL in CsCl. The genome of HDV consists of single-stranded, circular, negative-sense RNA, 1.7 kb in size. It is the smallest of known human pathogens and resembles subviral plant pathogens (ie, viroids). No homology exists with the HBV genome. HDAg is the only protein coded for by HDV RNA and is distinct from the antigenic determinants of HBV. HDV is a defective virus that acquires an HBsAg coat for transmission. It is often associated with the most severe forms of

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hepatitis in HBsAg positive patients. It is classified in the *Deltavirus* genus, which is not assigned to any virus family.

Hepatitis Type E

HEV is transmitted enterically and occurs in epidemic form in developing countries, where water or food supplies are sometimes fecally contaminated. It was first documented in samples collected during the New Delhi outbreak of 1955, when 29,000 cases of icteric hepatitis occurred after sewage contamination of the city's drinking water supply.

Pregnant women may have a high (20%) mortality rate if fulminant hepatitis develops. The viral genome has been cloned and is a positive-sense, single-stranded RNA 7.2 kb in size. The virus is classified in the virus family, Hepeviridae, in the genus *Hepevirus*. HEV resembles, but is distinct from, caliciviruses. Animal strains of HEV are common throughout the world. There is evidence of HEV or HEV-like infections in rodents, pigs, sheep, and cattle in the United States. There is the possibility of spread of virus from animals to humans. contaminated water.

Hepatitis G virus (HGV, also termed [GBV-C](#)) was recently discovered and resembles HCV, but more closely, the flaviviruses; the virus and its effects are under investigation and some investigators do not recognize it as a cause of hepatitis.

Laboratory Features

Liver biopsy permits a tissue diagnosis of hepatitis. Tests for abnormal liver function, such as serum alanine aminotransferase (ALT) and bilirubin, supplement the clinical, pathologic, and epidemiologic findings.

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