Microbiology (2) For Doctor of Dental Surgery (DDS) Students

Viral Hepatitis

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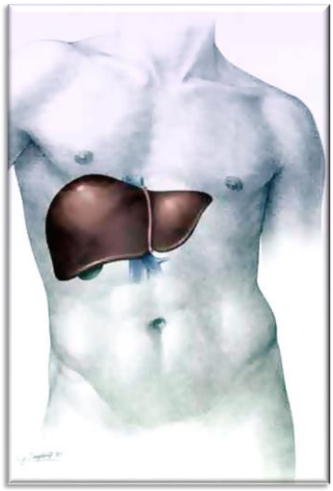
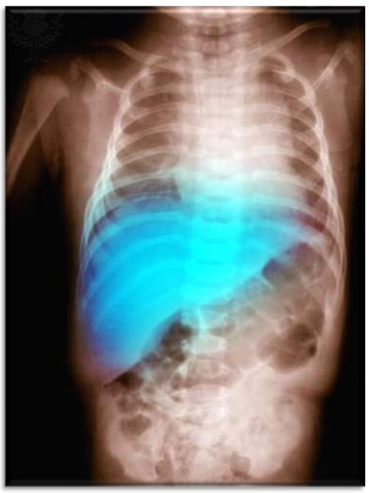
1

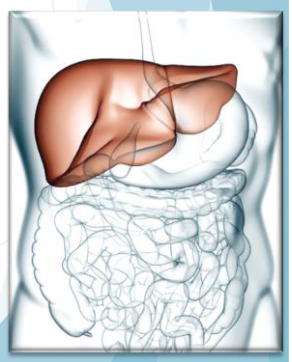
Normal Liver Function vs. Hepatitis





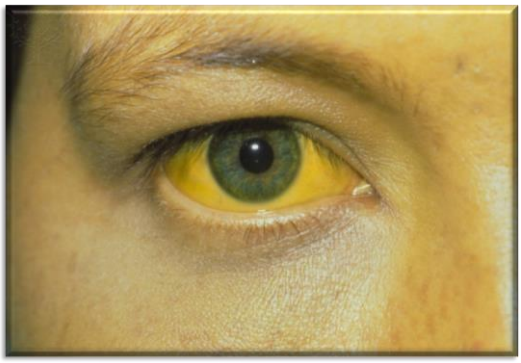
Viral Hepatitis-Introduction

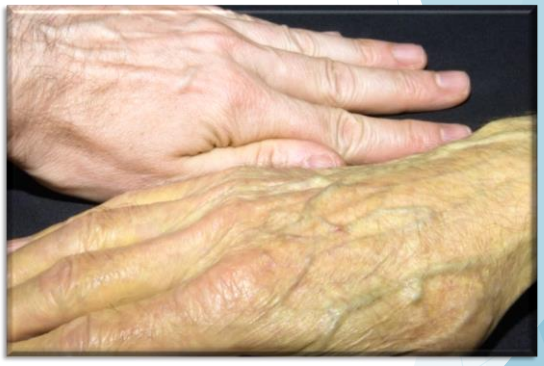
- Viral hepatitis is a systemic disease primarily involving the liver.
- Most cases of acute viral hepatitis are caused by one of the following agents: HAV, HBV, HCV, or HEV.
- Hepatitis viruses produce acute inflammation of the liver, resulting in a clinical illness characterized by fever, nausea, vomiting, and jaundice.
- Regardless of the virus type, **identical histopathologic lesions are observed in the liver during acute disease**.



3

Rabies Pathogenesis and Pathology





Jaundice is usually visible in the sclera or skin when the serum bilirubin value is (2.5 mg/dL).

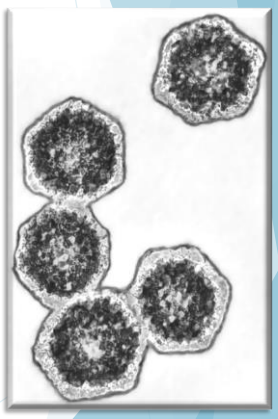
Viral Hepatitis-Summary

Virus	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Family	*Picornaviridae*	*Hepadnaviridae*	*Flaviviridae*	Unclassified	*Hepeviridae*
Envelope	No	Yes (HBsAg)	Yes	Yes (HBsAg)	No
Genome	Positive ssRNA	dsDNA	Positive ssRNA	Negative ssRNA	Positive ssRNA
Stability	Heat- and acid-stable	Acid-sensitive	Acid-sensitive	Acid-sensitive	Heat-stable
Transmission	Fecal-oral	Parenteral	Parenteral	Parenteral	Fecal-oral
Chronic disease	Never	Often	Often	Often	Rare?

5

Hepatitis A Virus (HAV)-Introduction

- An RNA virus.
- Belongs to the *Picornaviridae* family.
- Positive-sense single-stranded RNA.
- **Naked**.
- HAV is **stable at low pH**.
- HAV has been found to survive for days to months in experimentally contaminated fresh water, seawater, waste water, soils, marine sediment and live oysters.



Hepatitis A Virus (HAV)-Introduction

- Natural Host: Human, primates.
- Tropism: Hepatocytes (liver cells).
- Cellular receptors: HAVcr-1 (TIM-1).
- Transmission: Fecal–oral route (poor sanitation, overcrowding).
- Geography: Worldwide.

7

HAV Features

- HAV is a 27- to 32-nm spherical particle with a linear single-stranded RNA genome with a size of 7.5 kb.
- **Only one serotype is known**.
- Genomic sequence analysis divided HAV 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.

HAV Features

- The virus is destroyed by autoclaving (121°C for 20 minutes), boiling in water for 5 minutes, ultraviolet irradiation, treatment with formalin or treatment with chlorine.
- Heating food to above 85°C 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*.

9

Hepatitis A Pathogenesis

- HAV is spread by the fecal–oral route, most commonly by person-to-person contact. Common source outbreaks can occur.
- HAV is exceptionally stable at low pH.
- The primary site of replication for HAV is the liver, as demonstrated by virus detection in hepatocytes within days after infection.
- A relatively high concentrations of HAV are shed in the feces before the alanine aminotransferase (ALT) level initially becomes elevated and before the onset of clinical symptoms or jaundice.

10

Hepatitis A - Clinical & Lab. Findings

- Incubation period: 10–50 days (average, 25–30).
- Principal age distribution: Children, young adults.
- Seasonal incidence: Throughout the year but tends to **peak in autumn**.
- Route of infection: Predominantly fecal–oral.
- Occurrence of virus in blood: 2 weeks before to ≤1 week after jaundice.
- Occurrence of virus in stool: 2 weeks before to 2 weeks after jaundice.

11

Hepatitis A - Clinical & Lab. Findings

- Onset: Abrupt (sudden).
- Fever: Common.
- Duration of aminotransferase elevation: 1–3 weeks.
- Complications are uncommon, **no chronic state**.
- Patients with inapparent or subclinical hepatitis have neither symptoms nor jaundice.

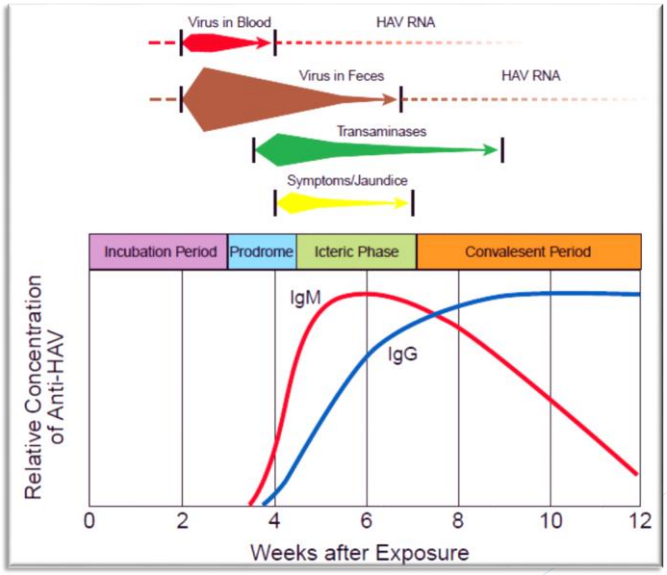
Hepatitis A - Clinical & Lab. Findings

- Other patients can develop anicteric hepatitis or icteric hepatitis.
- Symptoms ranging from mild and transient to severe and prolonged can accompany anicteric or icteric hepatitis.
- Most patients recover completely; however, some develop fulminant hepatitis and die.

Hepatitis A-Clinical & Lab. Findings

- Occasionally, more extensive necrosis of the liver occurs during acute viral hepatitis A, leading to severe impairment of hepatic synthetic processes, excretory functions, and detoxifying mechanisms.
- This entity, designated **fulminant hepatitis** if hepatic encephalopathy occurs during the first 6 to 8 weeks of illness or within 1 to 4 weeks after jaundice, is characterized by the sudden onset of high fever, marked abdominal pain, vomiting, and jaundice followed by the development of encephalopathy associated with deep coma and seizures.

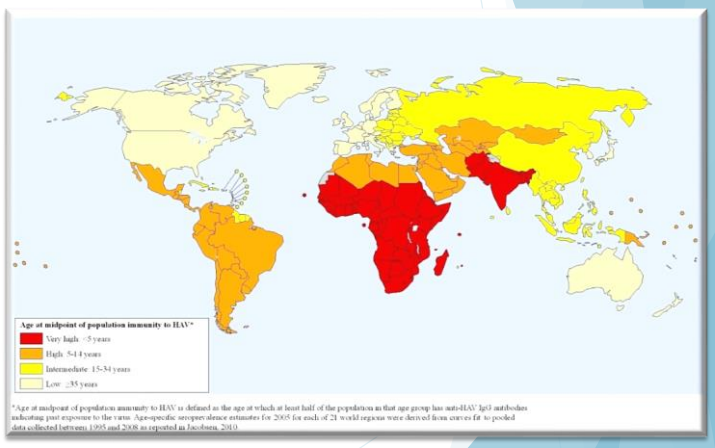
Hepatitis A



15

Hepatitis A - Epidemiology

- ✓ Hepatitis A is one of the most common causes of infectious jaundice in the world today and is frequently associated with recurrent epidemics.
- ✓ HAV communicability is apparently highest during the clinically silent incubation period when virus replication reaches a peak.



Hepatitis A - Dx, Rx & Prevention

- LFT, IgM anti-HAV.
- No specific treatment for acute viral hepatitis exists, and hospitalization is not ordinarily indicated. Therapy should be supportive and aimed at maintaining comfort and adequate nutritional balance.
- Formaldehyde inactivated vaccines are available worldwide.

17

Hepatitis E Virus (HEV)-Introduction

- Previously labeled **e**nterically transmitted non-A, non-B hepatitis, HEV is an **e**nterically transmitted virus that occurs primarily in India, Asia, Africa, and Central America; in those geographic areas, HEV is the most common cause of acute hepatitis.

- This agent, with epidemiologic features resembling those of hepatitis A, is a 32- to 34-nm, nonenveloped, HAV-like virus with a 7.6 kb, single-strand, positive-sense RNA genome.

Hepatitis E Virus (HEV)-Introduction

- All HEV isolates appear to belong to **a single serotype**, despite genomic heterogeneity of up to 25% and the existence of five genotypes, only four of which have been detected in humans; genotypes 1 and 2 appear to be more virulent, while genotypes 3 and 4 are more attenuated and account for subclinical infections.

- Contributing to the perpetuation of this virus are animal reservoirs, most notably in **swine**.

Hepatitis E Virus (HEV) - Introduction

There is no genomic or antigenic homology, however, between HEV and HAV or other picornaviruses; and HEV, although resembling caliciviruses, is sufficiently distinct from any known agent to merit a new classification of its own as a unique genus, Hepevirus, within the *Hepeviridae* family.

Hepatitis E-Pathogenesis

- Entry of the virus into the host is believed to be primarily by the **oral** route.
- The incubation period ranges from 2 weeks to 2 months.
- HEV replicates in the cytoplasm of hepatocytes and is released into the bile and blood.

Hepatitis E-Pathogenesis

- Viremia and fecal shedding are first detected about 3 weeks after exposure and about a week before onset of disease.
- Liver enzyme values peak about 7 to 8 weeks post exposure. Viremia may diminish at that time; however, fecal shedding may continue for days to weeks.
- Mortality of hepatitis E has varied in different reports but has been as high as 1%, compared to 0.2% for hepatitis A.

22

Hepatitis E-Pathogenesis

- More important, however, is the severity of hepatitis E in **pregnant women**, which may reach 20%.
- The reason for the excessive mortality of hepatitis E in pregnancy is unknown, although a high viral load and abnormalities of progesterone signaling pathways have been suggested.

Hepatitis E-Pathogenesis

- Although most HEV infections are self-limiting and resolve without sequelae, a significant proportion (>50%) of infected organ transplant patients or those with other types of **immunosuppression** may develop *chronic infection* that can progress to chronic hepatitis and cirrhosis.
- Individual cases of hepatitis E cannot be differentiated from other cases of hepatitis on the basis of clinical presentation.

Hepatitis E-Dx and Management

- Serology, RT-PCR.
- No specific treatment exists for acute hepatitis E. Both **interferon alpha and ribavirin** have been used successfully to treat chronic HEV infections.
- Candidate recombinant vaccines in trials.

Hepatitis B Virus (HBV)-Background

- HBV is **a DNA virus** with a peculiar genome that is a circular **partially double-stranded DNA** of about 3.3 kb (slight length differences are observed in different genotypes).

- HBV is the only human virus that belongs to the family *Hepadnaviridae*, while other animal viruses have been identified that belonged to the same family of viruses which can infect mammals and birds with characteristic tropism for **hepatocytes.**

Hepatitis B Virus (HBV)-Background

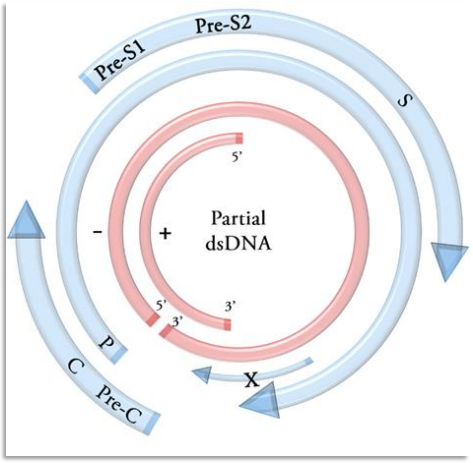
- The accidental discovery of association between Australia antigen (HBsAg) and serum hepatitis (type B, compared to type A [infectious hepatitis] caused by HAV) in 1965 by Blumberg *et al*, marked the start of great strides that were made in the investigation of hepatitis B epidemiology and pathogenesis which eventually led to development of a successful HBV vaccine.

HBV genome and virion structure

- The genome of HBV consists of four ORFs that encodes seven proteins (*S* that encodes three surface proteins, *X* which encodes the trans-activator of transcription, *C* which encodes two core proteins and the *P* which encodes the HBV polymerase that has DNA polymerase, RT and RNase H activities).

- The extraordinary short length of HBV genome together with the overlapping nature of its genes make HBV a unique human pathogen particularly from an evolutionary point of view

HBV genome and virion structure



The genomic structure of HBV with the blue arrows indicating the four open reading frames (S: surface, X: trans-activator of transcription, C: core and P: polymerase). The genomic DNA is shown in pink

HBV genome and virion structure

- In the host, HBV is characterized by the circulation of three electron microscope (EM) morphologically recognized structures: The 42-nm virion particles, the 22-nm spherical particles and the 22-nm tubular particles that are up to 200 nm in length.

- The 22-nm particles, that are non-infectious, are produced in excess compared to the virions which might be a viral decoy mechanism to trick the immune system.

HBV genome and virion structure

- HBV replication is unique in the way that its replication occurs through an RNA intermediate (the pregenomic RNA) from the minus DNA strand.

- Then plus DNA strand is transcribed from the minus-strand DNA template by the DNA-dependent DNA polymerase, followed by transfer to the nucleus and forms the covalently closed circular DNA that is the template for mRNA and pregenomic RNA.

HBV genome and virion structure

- The polymerase of HBV has the following activities in four domains: terminal protein at the amino end that has a role in initiation of DNA synthesis, a spacer domain that is not critical in function, RT and RNase H.
- The core protein (HBcAg) form the capsid and exists as a dimer.
- Translation of the preCore region results in the production of the soluble form of core protein (HBeAg) with its presence in serum marking higher transmissibility.

HBV genome and virion structure

- The surface proteins embedded in the envelope are small (S), medium (M) and large (L).
- The most abundant is the S protein that is the product of *S* while translation of both *PreS2* and *S* results in the production of M protein and translation of *PreS1*, *PreS2* and *S* all together results in L protein production. The pre-S1 domain of the L protein binds to the hepatic receptor of HBV namely sodium taurocholate co-transporting polypeptide (NTCP).

Genetic variability and classification

- HBV is the only pathogenic human virus that replicates its DNA through an RNA intermediate using reverse transcription which is characterized by low fidelity in spite of restriction in the allowed mutations due to the overlapping nature of some parts of the genome.
- HBV is currently classified into at least eight genotypes designated with capital letters (A-H) with pairwise inter-genotypic distances of more than 8.0%.

HBV genome and virion structure

- HBV genotypes are further divided into subtypes designated with Arabic numerals with molecular divergence of 4.0-8.0%.
- The genotypic classification of HBV nowadays replaced the obsolete serotyping system that was based on the serological features of HBsAg.
- Recently, two novel genotypes have been described, genotype I in Vietnam and Laos, and genotype J in Japan.

35

Epidemiologic features and transmission

- The percutaneous transmission is the major route for HBV infection. Other major routes of transmission include sexual spread and mother-to-child transmission (MTCT).
- In areas with high endemicity (sero-prevalence ≥8%, e.g. Southeast Asia), MTCT represents a frequent mode of spread with its subsequent high prevalence of chronicity.

Natural history and clinical features

- HBV can cause both acute and chronic infections, with age as one of determinants of chronicity.
- Fulminant hepatitis can follow acute infection.
- Because HBV does not induce a cytopathic effect on the infected hepatocytes, the time from infection till the development of immune response (with clinical signs and symptoms) might take months.

Natural history and clinical features

In adults, the majority clear the infection and a minority develops chronic infection during which, hepatocyte damage occurs as a result of T cell mediated immune attack on hepatocytes expressing HBV antigens on the context of their HLA molecules.

Diagnosis, treatment and prevention

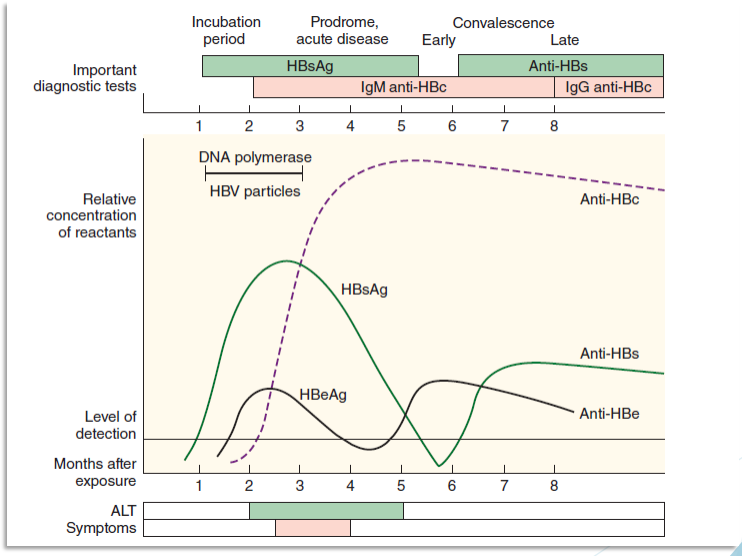
- After HBV infection, the first markers of the disease is the appearance of viral DNA in the liver and plasma together with circulating HBsAg. High levels of viremia is followed by rise in the level of markers of hepatocyte damage (mainly ALT) and the appearance of clinical features (fever, malaise and jaundice).
- HBsAg becomes undetectable 1–2 months after the appearance of jaundice.

Diagnosis, treatment and prevention

- The persistence of HBsAg beyond 6 months marks HBV chronicity.
- HBcAb appears within the first two weeks after the appearance of HBsAg and preceding HBsAb.
- The window between decline of HBsAg and rise HBsAb is associated with HBcAb as the only serologic evidence of infection.
- Clearance is associated with the appearance of HBsAb.
- NAT is also available for screening blood/blood products.

40

Diagnosis, treatment and prevention



41

Diagnosis, treatment and prevention

- Multiple options are available for treatment of chronic hepatitis B including IFNs and several nucleotide and nucleoside analogs with the goal of reducing the viral load to an undetectable level and to reach HBsAg clearance.
- For prevention of HBV infection, an effective vaccine (recombinant HBsAg) has been available from mid-1980s, with many countries worldwide implementing universal vaccination of infants.

Hepatitis D Virus (HDV) - Background

- Delta hepatitis was first recognised following detection of a novel protein, delta antigen (HDAg), by immunofluorescent staining, in the nuclei of hepatocytes from some patients with hepatitis B.

- HDV is now known to be defective and require a helper function from HBV for its transmission. HDV is coated with HBsAg, which is needed for release from the host hepatocyte and for entry in the next round of infection.

Hepatitis D Virus (HDV)-Background

- HDV is unique among human viruses, having an internal nucleocapsid comprising the genome surrounded by the delta antigen and enveloped by an outer protein coat of HBsAg.

- The genome consists of a single-stranded, circular RNA of around 1700 nucleotides, the delta antigen being encoded by antigenomic RNA.

44

Hepatitis D Virus (HDV)

- Two types of infection are described:

-Co-infection: Where a person who is susceptible to HBV is exposed to someone who is co-infected with HBV and delta virus, this results in acute co-infection with both the viruses at the same time.

-Super-infection: When an HBV carrier is exposed to infected blood from co-infected patients then the exposure results in super-infection of the existing HBV infection with delta virus; this may result in development of acute hepatitis (due to delta virus) in an HBV chronic carrier.

Hepatitis D Virus (HDV)

- HDV, is a defective RNA virus that coinfects with and requires the helper function of HBV for its replication and expression.
- Slightly smaller than HBV, delta is a formalin-sensitive, 35- to 37-nm virus. Its nucleocapsid expresses delta antigen, which bears no antigenic homology with any of the HBV antigens, and contains the virus genome.
- The delta core is "encapsidated" by an outer envelope of HBsAg, indistinguishable from that of HBV except in its relative compositions of major, middle, and large HBsAg component proteins.

Hepatitis D Virus (HDV) - Genome

- The genome is a small, 1700-nucleotide, circular, single-strand RNA (minus strand) that is nonhomologous with HBV DNA (except for a small area of the polymerase gene).

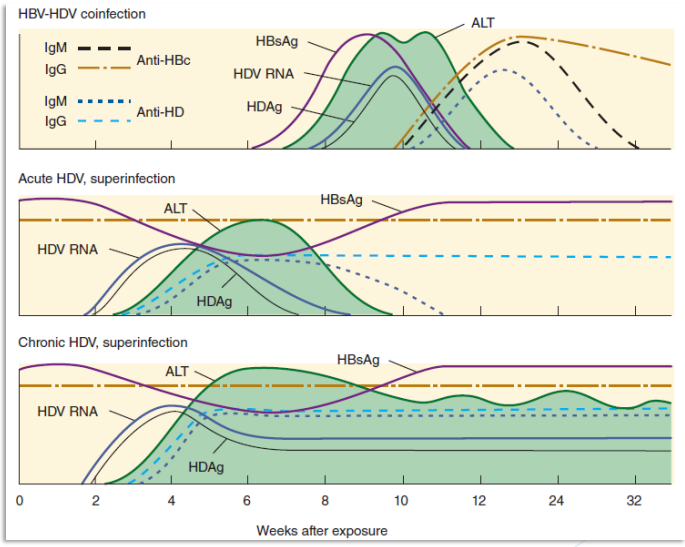
- HDV RNA contains many areas of internal complementarity; therefore, it can fold on itself by internal base pairing to form an unusual, very stable, rodlike structure.

Hepatitis D Virus (HDV) - Genome

- HDV RNA requires host RNA polymerase II for its replication via RNA-directed RNA synthesis by transcription of genomic RNA to a complementary antigenomic (plus strand) RNA; the antigenomic RNA, in turn, serves as a template for subsequent genomic RNA synthesis.

- Between the genomic and antigenomic RNAs of HDV, there are coding regions for nine proteins.

Hepatitis D-Serologic Markers



49

Hepatitis D - Epidemiology

- Infection with HDV has a worldwide distribution, but two epidemiologic patterns exist.

- In Mediterranean countries (northern Africa, southern Europe, the Middle East), HDV infection is endemic among those with hepatitis B, and the disease is transmitted predominantly by nonpercutaneous means, especially close personal contact.

Hepatitis D-Epidemiology

- In nonendemic areas, such as the United States and northern Europe, HDV infection is confined to persons exposed frequently to blood and blood products, primarily injection drug users and hemophiliacs.

- HDV infection can be introduced into a population through drug users or by migration of persons from endemic to nonendemic areas.

Hepatitis D - Dx

- The presence of HDV infection can be identified by demonstrating intrahepatic HDV antigen or anti-HDV Ab.
- Circulating HDV antigen, also diagnostic of acute infection, is detectable only briefly, if at all.
- Early diagnosis of acute infection may be hampered by a delay of up to 30–40 days in the appearance of anti-HDV.

Hepatitis D - Dx

When a patient presents with acute hepatitis and has HBsAg and anti-HDV in serum, determination of the class of anti-HBc is helpful in establishing the relationship between infection with HBV and HDV. Although IgM anti-HBc does not distinguish absolutely between acute and chronic HBV infection, its presence is a reliable indicator of recent infection and its absence a reliable indicator of infection in the remote past. In simultaneous acute HBV and HDV infections, IgM anti-HBc will be detectable, while in acute HDV infection superimposed on chronic HBV infection, anti-HBc will be of the IgG class.

Hepatitis D-Dx

- Tests for the presence of HDV RNA are useful for determining the presence of ongoing HDV replication and relative infectivity.

- Liver biopsy is rarely necessary or indicated in acute viral hepatitis, except when the diagnosis is questionable or when clinical evidence suggests a diagnosis of chronic hepatitis.

Hepatitis C Virus (HCV)-Background

- Before the identification of HCV, it was evident that the culprit infectious agent responsible for the majority of “non-A, non-B hepatitis (NANBH)" cases was a novel virus that is unrelated to other hepatitis viruses known at that time, namely HAV, HBV, HDV and HEV.

Hepatitis C Virus (HCV)-Background

- Epidemiologic investigation together with transmission studies in chimpanzees helped to unravel the role of parenteral transmission in the spread of the virus before its identification for the first time by Choo *et al.* through molecular cloning which helped to study its genome characteristics and to develop serological tests for diagnosis of HCV infection.

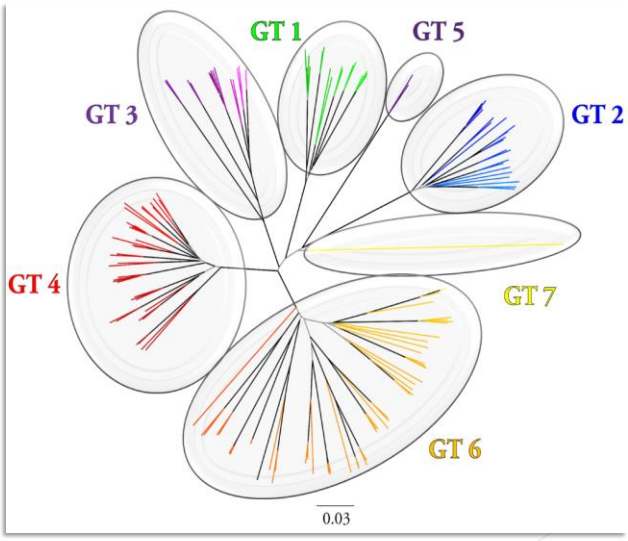
HCV classification

- HCV is a member of the genus Hepacivirus that belongs to the family *Flaviviridae*.
- Phylogenetic attempts to study the genetic diversity of HCV revealed the enormous divergence of the virus into at least seven genotypes, designated with Arabic numerals.

HCV classification

In addition, substantial variability among intra-genotype lineages was found that mandated further division of each genotype into subtypes, designated by small English letters. Depending on the genomic region studied, the distinct genotypes differ by more than 30% in the nucleotide sequences, whereas the intra-genotype subtypes differ by 20-25% in the nucleotide sequences. The evolutionary rate of HCV is considered high and is close to other RNA viruses in the range of $1\text{-}2 \times 10^{-3}$ substitutions/site/year. Considering the enormous divergence of HCV genotypes from their common ancestor(s), differences in the clinical manifestations and response to treatment appear as a likely outcome.

HCV classification

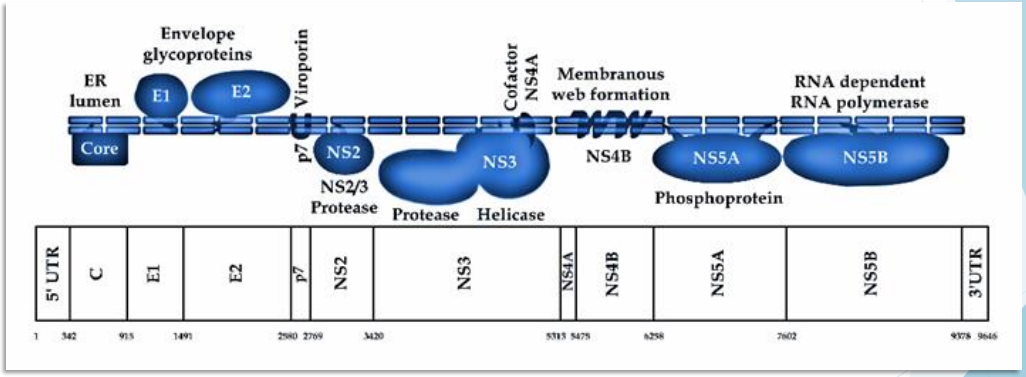


HCV genome

- As a positive-sense single-stranded RNA virus, HCV genome can be viewed as a single ORF which encodes a polyprotein of about 3000 amino acids.

- The HCV polyprotein is processed by cellular and viral proteases with end-products of structural and non-structural proteins. At the 5' end of the HCV resides the highly conserved 5' untranslated region (5' UTR), the region with an internal ribosomal entry site (IRES).

HCV genome



61

HCV genome

- The 5' UTR is followed by the genes that encode the structural proteins, namely the core protein (C), the envelope glycoproteins (E1 and E2) and the ion-channel viroporin (p7). In contrast to the conserved nature of C, the E1 and E2 display a high level of sequence variability likely as a result of immune selection.
- The non-structural (NS) genes are located towards the 3' end of the genome and encode the following proteins: NS2 which is a cysteine protease that cleaves NS3 from NS2. The second structural protein is NS3 that together with NS4A, forms a serine protease that cleaves all the downstream NS proteins of the virus.

HCV genome

- NS4B acts as a membrane anchor for the replication complex together with the NS5A forming the ER membranous web which has an important role in the induction and regulation of HCV replication.

- NS5B is an RNA-dependent RNA polymerase acting as the replicating enzyme of the virus.

HCV Epidemiology

Hepatitis C is considered a global health problem with about 70 million people living with chronic HCV infection and 700,000 mortalities by the end of 2015 (WHO, 2015). The morbidity and mortality from HCV infection stems from the hepatic disease including fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). The countries with highest prevalence of sero-positivity to HCV are Egypt and Cameroon with prevalence reported to be more than 10%. Of all genetic variants of HCV, genotype 1 represents that most prevalent genotype globally, followed by genotype 3. Genotype distribution follows a characteristic geographic distribution.

HCV Epidemiology

The major route of HCV transmission worldwide is the exposure to contaminated blood mainly through **IDU** particularly in the high-income countries. After the introduction of effective screening of blood/blood products used for transfusion, health-care-related spread of HCV became less common. Other lower-risk modes of transmission include high risk sexual behaviour, vertical transmission, health-care associated infections (percutaneous exposure through needlestick injuries, haemodialysis, surgeries or dental procedures), intrafamilial spread, tattooing, piercing and acupuncture. The per-act risk of infection is mainly related to the volume of inoculum together with the viral load of the source of infection, with transfusion as an efficient route.

Natural history of HCV infection

After a variable period of incubation (one week to several months), acute HCV infection develops which is mainly asymptomatic, nevertheless about 15-30% of infected individuals develop signs and symptoms of hepatitis (mild fever, malaise, myalgia and obstructive jaundice [dark urine, clay-coloured stool and itching]) with elevated liver enzymes (mainly alanine amino transferase [ALT]).

Natural history of HCV infection

- Spontaneous clearance of HCV (undetectable RNA within six months of infection) occurs in a minority of patients with variable rates in different studies.
- Higher rates of clearance is associated symptomatic acute infection (indicating a strong immune response) and *IL-28B* allele that favours clearance (CC genotype as opposed to CT and TT genotypes).
- The spontaneous clearance has been shown to occur even in the absence of sero-conversion.

Natural history of HCV infection

- Chronicity that is characterized by high viral load (usually associated with HIV-1 co-infection), follows acute infection in 50–85% of the cases.
- Clearance of RNA during chronic infection is a rare event, with association of clearance with young age, female gender, co-infection with HBV and lower viral load.
- In the chronically infected individuals, the main risk is the progression towards fibrosis, cirrhosis and HCC.

Pathogenesis, immune response and clinical features of hepatitis C

- The tropism of HCV is mostly towards hepatocytes.
- The hepatocyte tropism is related to HCV identified cellular receptors namely CD81, claudin, occludin and scavenger receptor class b type I.
- Hepatic injury is mainly related to immune attack by T helper 1 (Th1)-mediated cytotoxic T lymphocyte (CTL) response on the infected hepatocytes though viral cytopathic effects may play a role.

Pathogenesis, immune response and clinical features of hepatitis C

- In individuals with chronic infection, progression of the disease is associated with old age, male gender, contemporaneous co-morbidities causing hepatic damage (alcoholism, chronic HBV infection, and steatohepatitis) and coinfection by HIV-1.
- The role of HCV genotype in disease progression and severity is less certain though some studies suggested that genotype 3 is associated with increased risk.
- **Following the development of hepatic cirrhosis, the rate of HCC development is 1-7% each year**.

Diagnosis, treatment and prevention

- The diagnosis of HCV starts by **serologic screening** through enzyme or chemiluminescent immunoassays (3rd generation have epitopes from [NS4, C, NS3 and NS5] with a window period of approximately 66 days).
- The serologic assays confirm the history of HCV past infection, nevertheless, the diagnosis of ongoing infection relies on **nucleic acid testing** which is also used to monitor response to treatment.

Diagnosis, treatment and prevention

Based on the scientific evidence of genotype correlation with outcome of treatment, particularly for IFN-based therapies, **the identification of HCV genotype is considered to have a significant predictive value for treatment success**.

Diagnosis, treatment and prevention

- The main goal of HCV treatment is to achieve SVR (i.e. undetectable HCV RNA 24 weeks following the completion of the treatment course).
- The traditional treatment of HCV relied on IFN-based regimens (with ribavirin) that were limited by severe adverse effects and variable efficiency depending on variables like HCV genotype.
- The novel therapeutic options of HCV in the form of **direct-acting antivirals (DAAs)**, have resulted in rising hope among clinicians and patients for better response, less side effects and shorter duration of therapy.

Diagnosis, treatment and prevention

- DAAs were initially used in combination with IFN/ribavirin regimens to improve the overall response, however, this was limited by severe side effects.
- In the current time, DAAs have been shown to give the possibility of HCV eradication from the infected individuals without IFN.
- So far, four classes of DAAs have been approved for treatment of chronic HCV.
- **The efficacy of DAAs is generally high** with slight differences among HCV genotypes observed in different reports. High cost remains the major obstacle for widespread use of DAAs.

Diagnosis, treatment and prevention

Class	HCV target	Drugs
Protease inhibitor	NS3	Simeprevir, Boceprevir, Telaprevir.
Nucleotide inhibitor	NS5B	Sofosbuvir.
Non-nucleotide inhibitors	NS5B	Dasabuvir, Beclabuvir.
NS5A inhibitors	NS5A	Daclatasvir, Velpatasvir.

75

Diagnosis, treatment and prevention

- Due to *absence of an effective vaccine to HCV* infection so far, prevention of transmission relies on identifying individuals at risk and consulting on behavioural changes to decrease the likelihood of forward transmission. In the low-income settings, strict testing of blood/blood products before transfusion is of prime importance.

- In high-income countries where IDU represents the major risk factor for HCV spread, awareness, behavioural changes, treatment as prevention (TasP), opioid substitution treatment (OST) and needle exchange program (NEP) represent important intervention measures to control the HCV epidemics.

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