Virology
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Done By
Dana Alnasra

Contributed in the Scientific Correction
8: Mohammad Yousef 9: Abod Suliman

Contributed in the Grammatical Correction
Abod Suliman + Ibrahim N. Dbyabo

Doctor
Malik Sallam
Hey there, this sheet is for the 8th and 9th virology lectures. We’re going to talk about the Hepatitis virus in details.

**Viral Hepatitis**: a systemic disease that causes inflammation of the liver tissue.

It’s important for us to know that there are various infectious agents that cause inflammation in the liver e.g. yellow fever virus -causes jaundice-, herpes simplex virus, Epstein-Barr virus, and Coxiella bacteria. However, the MOST common is hepatitis virus.

**Liver functions:**

a. **Synthesizing coagulation factors:**

They have a very short half-life (hours). So, if the liver is injured, it cannot synthesize these proteins leading to increased bleeding. Therefore, levels of the PT test are elevated.

(PT test measures how long it takes the blood to clot). One of the fastest lab markers of liver injury is an elevated Prothrombin time (PT) results.

Elevated PT → it takes more time for the blood to clot → low levels of coagulation factors → liver injury

b. **Bilirubin metabolism**: Bilirubin is metabolized in:

1. Mainly liver and GI tract; two thirds of it.
2. Kidney; one third.

Hepatitis causes post hepatic jaundice (obstructive jaundice); blockage of bilirubin passage through liver → bilirubin goes to kidneys instead → this is associated with clay colored stool and tea colored urine.

c. **Detoxification of lipid soluble wastes**

When severe damage occurs in the liver, toxic waste products accumulate in the body, and they can cross the blood brain barrier leading to CNS disturbances like encephalopathies, which is characterized by the sudden onset of high fever, marked abdominal pain, vomiting, and jaundice and associated with deep coma and seizures.

**There are 5 types of hepatitis virus**: (general concepts):

★ Hepatitis A, B, C, D, and E viruses.

★ In acute infection, they ALL have the same signs and symptoms; fever, nausea, vomiting, and jaundice. Thus, we cannot differentiate between them clinically or histopathologically.
★ Manifestations of ALL the hepatitis viruses is due to immune response
★ Types A and E are very similar:
  1. Both are naked, non-enveloped. Therefore, they both have the same mode and route of transmission; fecal-oral.
  2. They’re NOT associated with chronic infections.
  3. Complete resolution in few weeks, there’s no latency, the virus is not detected in the body.
★ Types B, C, and D are:
  1. Enveloped
  2. Blood borne; transmitted through blood, or things contaminated with blood.
  3. can cause chronic infection but NOT necessarily.
★ Hepatitis B: highly related to sexual transmission. And vertical (mother to child) transmission in unvaccinated mothers.
★ Hepatitis C: can be transmitted through homosexual men.
★ Incubation period:
  – Types A & E: a few weeks
  – Types B & C: a few months
**What determines if the infection turns into chronic or not?**

In hepatitis B, it’s age associated; a well-developed immune system will produce a severe acute manifestation. Therefore, it’s less likely to turn into chronic.

Infants have 90% chance to develop chronic hepatitis. On the contrary, adults have only 10%
Now let’s study each one in details:

1. Hepatitis A virus (HAV):
   - An RNA virus that belongs to the Picornaviridae family.
   - Naked (non-enveloped).
   - Positive-sense single-stranded RNA. ssRNA(+)
   - Genomic sequence analysis divided HAV isolates into seven genotypes.
   - Has ONE single serotype; when you get infected with HAV, you develop life-long immunity, because you developed antibodies against the one and only form that causes hepatitis. Which means reinfection is not possible.
   - The fact that it has a single serotype led to the production of a very effective vaccine for hepatitis A. (up to 99.9% potency).

Let’s talk about vaccines a little bit:

Let’s all agree that most effective vaccines (>99% potency) are the live attenuated vaccines; created by reducing the virulence of a pathogen, but still keeping it viable (live). Attenuation takes an infectious agent and alters it so that it becomes harmless or less virulent.

HEV vaccine is a protein (antigen); the only response is going to be producing antibodies. But, when giving vaccines as whole pathogens (live attenuated), there will be multiple antigens and more cell interactions. Therefore, it will induce cell mediated immunity and produce antibodies.

Hepatitis B vaccines are only 90% effective (10 out of a hundred people will not develop antibodies enough to cause immunity against the virus). But WHY??

This depends on the host genetics and the fact that there is NOT a single serotype of HBV

*Effectiveness of vaccines depend on:

   a. Virus-related factors, e.g. variability (serotypes) in HBV. (there might be vaccine escaped mutants)
   b. Host genetics, e.g. Immune response is weak.
   c. Formulation of the vaccine, e.g. proteins, antigen, a whole pathogen.

Pathogenesis of HAV:

- The receptor for HAV is called Hepatitis A virus cellular receptor 1 (HAVcr-1) also known as T-cell immunoglobulin and mucin domain 1 (TIM-1).
- HAV is spread by the fecal–oral route, most commonly by person-to person contact.
- Can occur sporadically or as outbreaks; like when a restaurant serves contaminated food.
- HAV is stable at low pH, and heating. The relative resistance of HAV to disinfection procedures emphasizes the need for extra precautions in dealing with hepatitis A patients and their products.
- HAV has been found to survive for days to months in experimentally contaminated fresh water, seawater, waste water, soils, marine sediment and live oysters.
- The primary site of replication for HAV is the liver, as demonstrated by virus detection in hepatocytes within days after infection.
- Part of the manifestations is elevated liver enzymes; found in blood (ALT and AST). A relatively high concentrations of HAV are shed in the feces before the alanine aminotransferase (ALT) level initially becomes elevated (for 1 to 3 weeks) and before the onset of clinical symptoms or jaundice. (HAV is one of the most common causes of jaundice).

Cell mediated immunity is activated by interaction between lymphocytes and the MHC-1 molecule expressed on hepatocytes, leading to the killing of hepatocytes, which will release the liver enzymes to the blood.

Now, we know that there are two classes of MHC molecules. But the surprise is that there is a third class (MHC-3); Its gene is located between MHC-1 and MHC-2 genes. And it encodes for some cytokines and complement proteins involved in immune responses.

Clinical and lab findings in HAV:

Principal age distribution: Children, young adults.

The onset is abrupt (sudden), fever is common

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.

HAV communicability is apparently highest during the clinically silent incubation period when virus replication reaches a peak.

Liver function tests (LFTs):
groups of blood tests that provide information about the state of a patient's liver.
These tests include prothrombin time (PT), albumin, bilirubin (direct and indirect), and others.
Diagnosis can be achieved through: Liver function tests, IgM anti-HAV.

Hospitalization is not ordinarily indicated. Therapy should be supportive and aimed at maintaining comfort and adequate nutritional balance.

Formaldehyde inactivated vaccines are available worldwide.

2. Hepatitis E virus (HEV):

- HEV is an enterically 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.
- Although resembling caliciviruses, it is distinct and is classified in the genus, Hepevirus, within the Hepeviridae family.
- This agent, with epidemiologic features resembling those of hepatitis A, is a 32- to 34-nm, non-enveloped, HAV-like virus with a small genome of 7.6 kb, single-stranded positive-sense RNA genome (+)ssRNA.
- All HEV isolates appear to belong to a single serotype, despite genomic heterogeneity of up to 25% and the existence of five genotypes, 4 of which have been detected in humans (1 and 2 are more virulent, while 3 and 4 are more attenuated and may account for subclinical infections).
- No genomic or antigenic homology between HEV and HAV.
- Contributing to the perpetuation (increase in the cases) of this virus are animal reservoirs, most notably in swine.

**Pathogenesis:**

- Entry of the virus into the host is by the oral route (fecal-oral), with incubation period ranging from 2 weeks to 2 months.
- Viral replication occurs in the cytoplasm of hepatocytes, then it’s released back to bile and blood.
- Viremia and fecal shedding are first detected after 3 weeks of exposure and one week before the onset of the disease.
- Liver enzymes peak about 7-8 weeks after exposure, viremia may diminish at that time, but fecal shedding may continue for days to weeks.

**Serotypes:** surface antigens that are able to react with specific antibodies.

**Genotypes:** differences in the genome.

HEV genotypes have one form that can be recognized by antibodies. But, they have differences in the genome that make differences in other characteristics.
**Epidemiology:**

- Mortality of hepatitis E has varied in different reports but has been as high as 1%, compared to 0.2% for hepatitis A. (mostly due to fulminant hepatitis cases; a rare syndrome of massive necrosis of liver parenchyma and a decrease in liver size that usually occurs after infection with certain hepatitis viruses). Fulminant hepatitis can lead to encephalopathies, as discussed above.
- More important, however, is the severity of hepatitis E in pregnant women, which may reach 20%, especially if infection is attributed to the genotype 1. 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.
- Although most hepatitis E infections are self-limiting, organ transplant patients and those with other immune-suppression conditions 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.

**Diagnosis and treatment:**

- **Diagnosis** can be achieved using serology and RT-PCR. (reverse transcriptase-PCR)
- No specific treatment exists for acute hepatitis E.
- Both interferon alpha and ribavirin been used successfully to treat chronic HE infection among the reported cases of immune-suppression.
- Candidate recombinant vaccines in trials

### 3. Hepatitis B virus (HBV):

- One of the blood-borne viruses
- HBV is the only human virus that belongs to the family **Hepadnaviridae**.
- HBV in hosts is characterized by the circulation of three EM morphologically recognized structures: The largest 42-nm **virion particles**, the 22-nm **spherical particles** (most abundant, non-infectious), 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, so the antibodies will neutralize these non-infectious particles instead of neutralizing the infectious virions.
About the genome:

- HBV is a DNA virus with a peculiar genome that is a circular partially double-stranded DNA of about 3.3 kb. The extraordinary short length of HBV genome with the overlapping nature of its genes makes HBV a unique human pathogen from an evolutionary point of view.

- It consists of four open reading frames (sequences that can be translated) that encode for seven proteins. The most important of which are:
  1. The s gene: encodes 3 surface proteins

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 gene 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). (see picture below).

  2. x: trans-activator for transcription

  3. c: 2 core proteins:
     a. Hepatitis B core antigen (HBcAg) forms the capsid and exists as a dimer.
     b. Translation of the preCore region results in the production of the soluble form of core protein Hepatitis B e antigen (HBeAg) with its presence in serum marking higher transmissibility; High infectivity.

  4. P: HBV polymerase (has DNA polymerase, RT and RNase H); it 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 (reverse transcriptase) and RNase H which is an RNA endonuclease.

Remember that HBV is a DNA virus, but the replication happens through an intermediate we’ll call it the pre-genomic RNA, This RNA will use reverse transcriptase at the end of the process to convert back to DNA.

In a single-stranded DNA virus, a plus strand is one contained in the virus particle or any strand having the same base sequence. A minus strand has a base sequence complementary to the plus strand.
HBV replication is unique in the way that its replication occurs through an RNA intermediate (the pre-genomic RNA) from the minus DNA strand. Then, the (+) strand is transcribed from the (-) strand DNA template by DNA dependent DNA polymerase, followed by transfer to the nucleus and forms the covalently closed circular DNA (CCCDNA) that is the template for the mRNA and the pre-genomic RNA.

- For genetic variability HBV is the only pathogenic human virus that replicates its DNA through reverse transcriptase, this is characterized by low fidelity (low accuracy) in spite of restriction in the allowed mutations due to the overlapping nature of some parts of the genome.

**Classification:**

- HBV is currently classified into at least eight (+2 hypothetical yet to be fully determined) genotypes designated with capital letters (A-H). with pair wise intragenomic distance of more than 8%.
- HBV genotypes are further divided into sub-genotypes designated with Arabic numerals, with molecular divergence of 4-8 %.
- The genotypic classification of HBV nowadays replaces the obsolete serotyping system that was based on the serologic features of the HB surface antigen.

**Pathogenesis:**

- The percutaneous (through skin) 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.
- HBV can cause both acute and chronic infections, with age as one of most determinants of chronicity. Fulminant hepatitis can follow acute infection.
- Because HBV doesn’t cause cytopathic effects on the infected hepatocytes, the time from the infection to the development of immune response with clinical signs and symptoms might take months. (incubation period).
- 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:**

- After HBV infection, one of the **first markers** of the disease is the presence of viral DNA in the **liver and plasma** together with circulating HBsAg (HB surface antigen). High levels of viremia are 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.**
- The persistence of HBsAg beyond 6 months marks HBV **chronicity**. Meaning that **chronic hepatitis b** is defined as the presence of HBsAg in the patient for more than 6 months.
- HBcAb (antibodies) **appears within the first two weeks** after the appearance of HBsAg and preceding HBsAb.
- The window between the **decline** of HBsAg and **rise** HBsAb is associated with HBcAb of **igM type** as the only serologic evidence of infection.
- **Clearance** is associated with the appearance of HBsAb. (no more antigens detected).
- NAT (nucleic acid amplification testing) is also available for screening blood and blood products.
Treatment:

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 e.g. lamivudine (drug).

For prevention of HBV infection, an effective vaccine (recombinant HBsAg) has been available from mid1980s, with many countries worldwide implementing universal vaccination of infants.

4. Hepatitis D virus (HDV); delta hepatitis: (note: only words highlighted in yellow are required)

- Was firstly recognized following detection of a novel (new) protein (the delta antigen) by immunofluorescence staining in the nuclei of hepatocytes from some patients suffering from hepatitis B.

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

- Two types of infection are described:
  a. 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 viruses at the same time.
  b. 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.

Structure:

- 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.
- HDV is slightly smaller than HBV, its nucleocapsid expresses delta antigen which bears no antigenic homology with any of the HBV antigens that contains the viral genome.
- The delta core is encapsidated by the outer envelope of hepatitis B surface antigen that is indistinguishable from that of HBV except for the composition of middle and large surface antigen components.

About the genome:

The genome consists of a single-stranded, circular RNA of around 1700 nucleotides (very small), the delta antigen being encoded by antigenomic RNA; The complementary strand of RNA from which the genome of a virus is constructed.
HDV RNA requires host RNA polymerase II for its replication via RNA directed RNA synthesis by transcription of genomic RNA to complementary antigenomic (+) strand RNA. Then, the antigenomic RNA serves as a template for the subsequent genomic RNA synthesis.

I have the original strand of RNA and I want to replicate it, so I make a complementary strand of RNA then use this complementary strand as a template for another strand that’s going to be the same as the original RNA.

Between genomic and antigenomic RNAs of HDV there are coding regions for 9 proteins.

**Epidemiology:**

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

1. 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 non-percutaneous means, especially close personal contact.
2. In non-endemic 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; a disorder in which your blood doesn't clot normally because it lacks sufficient clotting factors.

HDV can be introduced to a population through injection blood users or by the migration of persons from the endemic to nonendemic areas.

**Diagnosis and prevention:**

- The presence of HDV infection can be identified by demonstrating intrahepatic HDV antigen or anti-HDV Ab. Circulating HDV antigen which is also diagnostic of acute infection, is detectable only briefly, if at all.
- Early diagnosis of acute infection may be hampered by delay up to 30-40 days in the appearance of anti-HDV antibodies.
- Although IgM anti-hepatitis B core does not distinguish absolutely between acute and chronic infections, its presence is a reliable indicator of recent infection. And its absence is a reliable indicator of an infection in the past.
- When a patient presents with acute hepatitis and has hepatitis B surface antigen and anti-HDV antibodies, serum determination of the class of anti-hepatitis B core antigen is helpful in establishing the relationship between infection with HBV and HDV; In simultaneous acute HBV and HDV infections IgM anti-core antibodies will be detectable, while in acute HDV infection superimposed by chronic HBV infection anti-core antibody will be of the IgG class.
- 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 except for the diagnosis of questionable cases.

Delta hepatitis can be prevented by vaccinating HBV susceptible persons with hepatitis B vaccine. However, vaccination can’t protect HBV carriers from super-infection of the HDV because the infection had already been established.

5. Hepatitis C virus (HCV): (note: only words highlighted in yellow are required)

✓ Before the identification of HCV, it was evident that the culprit infectious agent responsible for the majority of non-A, non-B hepatitis cases was a novel virus that was unrelated to hepatitis viruses known at that time, namely hepatitis A, B, D, and E viruses.

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

✓ HCV is a member of the genus Hepacivirus that belongs to the family Flaviviridae.

About the genome:

- Phylogenetic attempts to study the genetic diversity of HCV revealed the enormous divergence of the virus into at least 7 genotypes designated with Arabic numerals, substantial variability among intergenotype lineages revealed further divisions of each genotype into sub-genotypes designated by small English letters. Depending on the genome region studied, the distinct genotypes differ by more than 30% in the nucleotide sequences. Whereas, the inter-genotypes and sub-genotypes 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 1-2 * 10^-3 substitutions per site per year.

- Considering the enormous divergence of HCV genotypes from their common ancestors, differences in the clinical manifestations and response to treatment appear as a likely outcome.

- As a positive-sense single-stranded RNA virus (+)ssRNA, HCV genome can be viewed as a single ORF (open reading frame) which encodes a polyprotein of about 3000 amino acids. The HCV polyprotein is processed by cellular and viral proteases and end products of structural and non-structural proteins.

Now look at the figure next page (it’s required):

- At the 5’ end of the HCV resides the highly conserved 5’ untranslated region (5’-UTR); the region with internal ribosomal entry site (IRES). The 5’ untranslated region is followed by the genes that encode the structural proteins. Namely, the core protein, the envelope glycoprotein E1 and E2, and the ion channel, viroporin; the P7.
• In contrast to the conserved nature of the core protein, the E1 and E2 proteins display a high level of sequence variability most likely as a result of immune selection.

• The **non-structural** genes are located towards the 3’ end of the genome and include the following proteins:
  1. NS2 which is a **cysteine protease** that cleaves NS3 from NS2
  2. NS3, together with NS4A forms a serine protease that cleaves all the downstream non-structural proteins of the virus.
  3. NS4b acts as a membrane anchor for the replication complex together with the NS5a forming the endoplasmic reticulum membranous web, which has an important role in the induction and regulation of HCV replication.
  4. NS5b is an RNA dependent RNA polymerase acting as the replicating enzyme of the virus.

![Diagram of HCV replication](image)

**Epidemiology:**

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

**Transmission:**

− The major route of HCV transmission worldwide is the exposure to contaminated blood mainly through injection drug users particularly in the high-income countries.
− After the introduction of effective screening of blood and blood products used for transfusion, health-care-related spread of HCV became less common.
Other lower-risk modes of transmission include high risk sexual behavior, vertical transmission, health-care associated infections (percutaneous exposure through needlestick injuries, hemodialysis (غسيل الكلى), surgeries or dental procedures).

- Other modes of transmission: 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.

Pathogenesis:

- The hepatocyte tropism is related to HCV cellular receptors namely CD81, claudin, occludin and scavenger receptor class b type1.
- Hepatic injury is mainly related to immune attack by T-helper type 1 mediated cytotoxic T lymphocytes response on the infected hepatocytes through viral cytopathic effects.
- After a variable period of incubation; one week to several months, acute HCV infection develops, which is mainly asymptomatic. Nevertheless, about 15-50% of infected individuals develop signs and symptoms of hepatitis; including mild fever, malaise, myalgia, and obstructive jaundice (characterized by dark colored urine and clay colored stool and itching). With elevated liver enzymes mainly ALT.
- Spontaneous clearance of HCV occurs in a minority of patients with variable rates in different studies. Higher rates of clearance are associated with symptomatic acute infection, indicating a strong immune response; IL-28b that favors the clearance of the CC genotype as opposed to CT and TT genotypes. Spontaneous clearance has been shown to occur even in the absence of the seroconversion, which means even if antibodies were not detected. (seroconversion is the time period during which a specific antibody develops and becomes detectable in the blood).

Chronicity:

- 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 hepatitis B virus and lower viral load.
- In individuals with chronic infection, progression of the disease is associated with old age, male gender, simultaneous co-morbidities causing hepatic damage like alcoholism, chronic HBV infection, steatohepatitis, and co-infection by HIV-1.
- In the chronically infected individuals, the main risk is the progression towards fibrosis, cirrhosis and hepatocellular carcinoma. Following hepatic cirrhosis, the rate of hepatocellular carcinoma development is about 7% each year.
The role of HCV development genotype in disease progression and severity is less certain though some studies suggested that genotype-3 is associated with increased risk.

**Diagnosis:**

- It starts with serologic screening through enzyme or Chemiluminescent immunoassays; a modified version of ELISA.
- The third generation have epitopes from NS4, the core NS3 and NS5 proteins, 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.

**Treatment and prevention:**

- The traditional treatment of HCV relied on interferon-based regimens with Ribavirin that were limited by severe adverse effects and variable efficiency depending on variables like HCV like genotype.
- 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.
- The main goal of HCV treatments is to achieve sustained virologic response that’s undetectable for HCV RNA 24 weeks following the completion of treatment course.

**DAAs (Very important):**

- 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. DAAs were used initially in combination with interferon-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 interferon.
- The efficacy of DAAS is generally high with slight differences among HCV genotypes observed in different reports.
- **High cost** remains the major obstacle for the wide spread use of DAAS.

So far, four classes of DAAS have been approved for the treatment of chronic HCV:

1. Protease inhibitors that target the NS3 protein: e.g. simeprevir and telaprevir
2. Nucleotide inhibitors that target the NS5B, e.g. sofosbuvir
3. Non-nucleotide inhibitors that target NS5B e.g. basabuvir, and beclabuvir
4. NS5A inhibitors that target the NS5A protease e.g. daclatasvir, and velpatasvir.

Due to absence of an effective vaccine to HCV infection so far, prevention of transmission relies on identifying individuals at risk and consulting on behavioral changes to decrease the likelihood of forward transmission.

In the low-income countries strict testing of blood and blood products before transfusion is of prime importance. And in high-income countries where injection drug use represents the major risk factor for HCV spread, awareness, behavioral changes, opioid substitution treatment (drugs that in enable people to reduce or cease injecting drug use) and needle exchange programs (which provide access to sterile syringes and facilitate safe needle disposal for injection drug users at little or no cost) represent important intervention measures to control the HCV epidemic.

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<th>Transmission and pathogenesis</th>
<th>Incubation period</th>
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<td>HAV (+)ssRNA</td>
<td>Naked; non-enveloped</td>
<td>Fecal-oral (Binds to HAV cellular receptor-1 (TIM))</td>
<td>Several weeks</td>
<td>No specific treatment</td>
<td>Effective vaccine</td>
<td>Acute infection</td>
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<td>Naked; non-enveloped</td>
<td>Fecal-oral</td>
<td>Several weeks</td>
<td>No specific treatment</td>
<td>Vaccines still in trials</td>
<td>Acute infection</td>
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<tr>
<td>HBV dsDNA</td>
<td>Enveloped</td>
<td>Blood-borne Percutaneous Parenteral Vertical sexual</td>
<td>Several months</td>
<td>Lamivudine</td>
<td>Effective surface antigen vaccine</td>
<td>Acute Can be chronic</td>
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<tr>
<td>HDV (-)ssRNA</td>
<td>Enveloped</td>
<td>Blood-borne Parenteral (need a helper function from HBV)</td>
<td>Several months</td>
<td>No specific treatment</td>
<td>If HBV vaccinated, person is not susceptible</td>
<td>Acute Can be chronic</td>
</tr>
<tr>
<td>HCV (+)ssRNA</td>
<td>Enveloped</td>
<td>Blood-borne Parenteral Sexual Vertical intrafamilial (HCV cellular receptors e.g. CD81)</td>
<td>Several months</td>
<td>DAAs (protease inhibitors) e.g. sofosbuvir</td>
<td>No vaccine available</td>
<td>Acute and usually progresses into chronic (85% of the cases)</td>
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