**5th Year Therapeutics 2015**

# Viral Hepatitis

## Introduction

1-There are **five types** of viral hepatitis: hepatitis A (**HAV**), B (**HBV**), C (**HCV**), D (**HDV**), and E (**HEV**). These types may present as either **acute** or **chronic illnesses**, which are primarily differentiated based on **disease duration** [(1)].

**2-Acute hepatitis may be associated with *all five types* of hepatitis and *rarely exceeds 6 months in duration*. Chronic hepatitis** (disease lasting ***longer than 6 months***) is usually associated **with hepatitis *B, C, and D.*** *Chronic viral hepatitis may lead to the development of* ***cirrhosis****, which may induce* ***end-stage liver disease*** (ESLD) [(1)].
Identification and subsequent management of HBV and HCV are central to preventing **long-term** complications.

3-One of the serious complication of viral hepatitis is **fulminant hepatitis** (massive hepatic necrosis); fortunately, **this is a rare event**. Fulminant hepatitis is primarily seen in **hepatitis B and D, as well as hepatitis E**, but **rare fulminant cases of hepatitis A** occur primarily in older adults and in persons with underlying chronic liver disease [(2)].

[(**fulminant hepatitis**, a rare and frequently **fatal** form of acute hepatitis in which the patient's condition rapidly deteriorates, with hepatic encephalopathy, necrosis of the hepatic parenchyma, coagulopathy, renal failure, and coma.(Mosby's Medical Dictionary, 8th edition. © 2009, Elsevier)].

## Clinical Presentation of Viral Hepatitis

1-The **symptoms of acute viral hepatitis** caused by HAV, HBV, HCV, HDV, and HEV are ***similar*** [(3)].

2-Signs and Symptoms of viral hepatitis are summarized by table 1 [(1)].

3-Acute viral hepatitis **occurs after an *incubation period*** that varies according to the responsible agent [(4)].

**Table 1 Clinical Presentation of Viral Hepatitis**

| |
|---|
| **Symptoms** |
| • Most patients infected with any type of viral hepatitis have no symptoms. |
| • Those who have symptoms may experience any of the following: flulike symptoms, fevers, fatigue/malaise, anorexia, nausea, vomiting, diarrhea, dark urine, pale-appearing stools, pruritus, and abdominal pain. |
| **Signs** |
| • Jaundice may be evident in the whites of the eyes (scleral icterus) or skin. |
| • An enlarged liver (hepatomegaly) and spleen (splenomegaly) may be present. |

4-***Constitutional prodromal symptoms*** of anorexia, nausea and vomiting, fatigue, and malaise may **precede the onset of jaundice** by 1–2 weeks [(4)].

5- **Dark urine** (caused by bilirubin) and **clay-colored stools** may be noticed by the patient from 1–5 days before the onset of clinical jaundice .With the onset of **clinical jaundice** (***icteric phase***), the constitutional prodromal symptoms usually **diminish** [4].
6-During the **recovery phase**, constitutional symptoms **disappear** [4].

### Laboratory tests: [1].

1-laboratory ***serologies*** must be obtained to identify the specific type of hepatitis).

2-**liver function tests** (AST , ALT , ……) may be obtained to assess the extent of cholestatic and hepatocellular injury.

3-The definitive test to determine the amount of damage and inflammation of hepatic cells is **a liver biopsy.**

## Hepatitis A

### Mode of Transmission:

1-The primary mode of transmission is person-to-person via **the fecal-oral route**. Fecally contaminated water or food is a significant mode of transmission [3].

2-The **virus resists degradation by environmental conditions**, gastric acid, and digestive enzymes in the upper gastrointestinal (GI) tract, thus, is readily spread within a population [3].

3-The period of greatest infectivity **is 2 weeks before the onset of clinical illness**; fecal shedding **continues for 2-3 weeks after** the onset of symptoms [2].

### Clinical Course

1-**HAV is typically a benign, self-limited infection**. Fulminant hepatitis A (**Acute liver failure**) is rare, occurring in 0.014% to 3.0% of the population infected with HAV, but often fatal [3].

2- Complete clinical recovery is usually seen within 2 months in 60% of patients and virtually all patients within 6 months after HAV infection [3].

3-HAV ***does not induce chronic hepatitis, chronic carriers or cirrhosis*** [2].

### Diagnosis

Diagnosis of acute HAV infection depends on clinical symptoms, mild elevation of aminotransferases (AST and ALT) and bilirubin, and a **positive anti-HAV antibodies** [5].

## Treatment

1-Management of HAV infection **is primarily supportive**, including a healthy **diet**, **rest**, **maintenance of fluid** balance, **avoidance of hepatotoxic** drugs and alcohol [5].
(e.g. **paracetamol** should not be used because the risk of fulminant hepatitis could increase) [3].
2-Pharmacologic agents offer **no clear benefit** in the treatment of HAV [5].

## Prevention

1-The spread of HAV can be best controlled by avoiding exposure. The most important measures to avoid exposure include **good hand-washing techniques and good personal hygiene practices** [5].
2-**Vaccination:** The current vaccination strategy includes vaccinating all children at 1 year of age [5]. Vaccination is recommended to groups at increased risk for HAV infections, such as for laboratory staffs who work with the virus [5].

# Hepatitis B

Hepatitis B is a leading cause of **chronic hepatitis**, **cirrhosis**, and **hepatocellular carcinoma (HCC)** [5].

## Mode of Transmission [2]:

1-**Parenteral routes** (e.g., injection drug use, and transfusion)
2-**Sexual contact.**
3-**Vertical or perinatal transmission** (from mother to infant)

## Clinical Course

1-Hepatitis B may cause an **acute** or **chronic hepatitis** [5]. The acute infection is often **asymptomatic, particularly when acquired at birth**. Many individuals with chronic hepatitis B are also asymptomatic. Chronic hepatitis, **can lead to cirrhosis, usually after decades of infection** [6].
2-Approximately *90% of infants but 10% of adolescents or adults* with acute infection **progress to chronic HBV**[5].

## Diagnosis

Hepatitis B is diagnosed when Hepatitis B surface antigen **(HBsAg)** is detectable in the serum [1]. **The persistence of HBsAg for longer than 6 months indicates chronic infection** [2].
The presence of serum **HBsAg** indicates **infection**, while **antibodies** against HBsAg indicate **recovery**.

## Treatment

### Acute Hepatitis B:

Treatment is **supportive** with monitoring for acute liver failure which can occurs in less than 1 % of cases [7]

## Chronic Hepatitis B:

Recommendations for treatment consider the patient's age, serum HBV DNA (marker of viral replication) and ALT levels. Not all chronic HBV patients are candidates for treatment [3]. Current treatment guidelines recommend treating patients with elevated ALT and high HBV DNA levels [8].

## Pharmacologic Therapy

1-Because hepatic damage is increased by ongoing viral replication, drug therapy aims to suppress viral replication by either immune mediating (Interferon ) or antiviral agents [2].

2-**Seven** therapies approved by the U.S. Food and Drug Administration (FDA) for the treatment of HBV:

- ***Interferon***: **interferon alfa**-2b and **pegylated interferon** alfa-2a (Peg-IFN).
- ***Nucleoside analogues***: **lamivudine** , **telbivudine** , and **entecavir** .
- ***Nucleotide analogues***: **adefovir** and **tenofovir** [9].

Lamivudine has activity against HBV and HIV. **It** is potent in preventing HBV replication and improving liver disease; however, it is associated with a **high rate of resistance** which limits its usefulness as a first-line agent for chronic HBV.

Telbivudine is prone to high rates of resistance development, and telbivudine resistance usually confers resistance to lamivudine as well. Therefore, telbivudine monotherapy has a limited role in the treatment of HBV.

**Adefovir** may cause nephrotoxicity at higher doses, thus limiting its utility as a first-line agent.

***Entecavir*** is more effective than lamivudine and adefovir [6] and associated with less **emergence of viral resistance** [10]. Entacavir maintains activity against lamivudine-resistant HBV mutants.

The most **recently** approved therapy for treatment of chronic HBV is **tenofovir.** Treatment with tenofovir yielded a significantly greater histologic response and normalization of ALT compared with other antivirals.

**Peg-IFN, tenofovir, or entecavir is preferred as initial therapy** [11]. So peginterferon alfa is an option for the initial treatment of chronic hepatitis B. If contraindication or no response, use entecavir and tenofovir [12, 13].

Interferons are glycoproteins with antiviral, immunomodulatory, and antiproliferative actions. **The addition of polyethylene glycol (PEG)** to the standard IFN molecules (pegylation) results in **prolonged half-life with improved bioavailability** [2].
Conventional IFN is administered subcutaneously or intramuscularly **three times per week**, and **pegylated forms are administered *once weekly*** [8].

Adverse effects of interferons include an **initial influenza-like illness**, including fever, chills, headache, malaise, and myalgia. Other noted adverse effects include anxiety, irritability, depression, and suicidal tendency. **IFN has myelosuppressive effects**, and patients should be monitored closely for potential neutropenia or thrombocytopenia [(11)].

3-Treatment for a **minimum of 12 months** [(5)].
**Note**: response to treatment is achieved when there is HBeAg (Hepatitis B envelope antigen ) seroconversion (the loss of HbeAg), HBV DNA suppression, and alanine transaminase (ALT) normalization [(11)]. **HBeAg is a qualitative marker and HBV DNA a quantitative marker of replication phase** [(4)].

In HBeAg-negative patients, no such marker of treatment success exists, and there is a high likelihood of relapse when therapy is discontinued. These patients are usually treated indefinitely or until surface antigen HBsAg seroconversion occurs [(12)].

### Liver transplantation:

For patients with **end-stage liver disease** due to chronic hepatitis B infection, transplantation is an option [(8)].

### Prevention :

1-**Two products** are available for prevention of hepatitis B infection: hepatitis B vaccine, which provides **active immunity**, and hepatitis B immune globulin (HBIG), which provides temporary **passive immunity** [(5)].

2- HBV vaccine should be considered for everyone, particularly in individuals with a history of multiple blood transfusions, patients on hemodialysis, health care workers, injection drug users, Infants born to HBsAg-positive mothers, ……[(2)].

## Hepatitis C Virus

### Epidemiology

HCV is the most common blood-borne pathogen [(5)]. HCV is a **global health problem with approximately 200 million** carriers worldwide [(2)]. HCV is the leading cause of liver transplantation. HCV-related mortality is attributed to complications of end-stage liver disease as well as death from development of HCC.

### Modes of Transmission [(2)].

**1-Parenterally** (e.g., transfusion, injection drug use, needlestick injury)
**2-Sexually and from mother to offspring**, although at a much lower frequency than HBV

## Clinical Features

1- Nearly 85% patients with HCV infection eventually develop **chronic hepatitis** and about 20% of patients with chronic HCV infection will develop cirrhosis and half of those patients will progress to **decompensated cirrhosis** or **hepatocellular carcinoma** HCC [5].

## Diagnosis

Hepatitis C is diagnosed by testing for antibodies against HCV (anti-HCV) in the serum [1] and HCV RNA.

**Table 58.4** Distribution of hepatitis C virus genotypes

| Genotype | Geographical predominance |
|---|---|
| 1a | USA and developed Western countries |
| 1b | USA, Japan, and Europe |
| 2 | Developed countries |
| 3 | Developed countries |
| 4 | Middle East and North Africa |
| 5 | South Africa |
| 6 | Asia |

Prevalence in USA: 74% genotype 1, 26% genotype 2 and 3.
Genotypes 1 and 4 are less responsive to antiviral therapy.

## Treatment

Before therapy is initiated, **genotyping (of virus)** is performed because response to therapy and duration of therapy vary depending on the infecting genotype [5]. (table 58.4) [14].

## Acute infection

Main benefit of treatment is prevention of chronic infection [12]. ***Treatment for acute HCV is necessary because nearly 85% of acutely infected patients develop chronic infections and are at risk of developing cirrhosis, ESLD, and hepatocellular carcinoma*** [5].
Treatment of acute hepatitis C patients with interferon alfa or peginterferon for 8-24 weeks (depending on genotype) appreciably decreases the risk of chronic hepatitis. **Ribavirin** (a synthetic guanosine analog) **may be added** if HCV fails to clear after 3 months of peginterferon or interferon alfa [10].

## Chronic infection:

1-The current standard of care for chronic HCV patients is a **combination therapy of a once-weekly injection of peginterferon and a daily oral dose of Ribavirin** [5] (a synthetic nucleotide analogue).
While monotherapy with IFN may be used in individualized cases where ribavirin is contraindicated, ribavirin should never be used as monotherapy.
**The main side-effect of ribavirin is haemolytic anaemia** [6] which may occur in up to 10% of patients (usually within 1–2 weeks of initiating therapy) [12].
Duration: 24-48 weeks (depending on genotype) [5]

Ribavirin is an abortifacient, carcinogenic and teratogenic. As a result, adequate contraception must be present with female patients as well as female partners of male patients who are of childbearing age and should be continued for 6 months following treatment cessation**.**

Specific dosage reductions or treatment cessation for ribavirin is necessary with the development of anemia and or severe renal failure. Dosage reductions of pegIFN may also be necessary with elevated liver enzymes or renal insufficiency.

2- Treatment for genotype 1 hepatitis C changed dramatically in 2011 [9]. **Boceprevir** and **telaprevir** are oral protease inhibitors that were approved in 2011 for the treatment of hepatitis C (genotype 1) in combination with peg-IFN and ribavirin. They target thee protease responsible for processing proteins essential for the HCV replication cycle.
**Both agents showed increased rates of response when used in combination with peg-IFN-alfa and ribavirin compared to peg-IFN-alfa and ribavirin alone** [11].

### Prevention:

**1-No HCV vaccine** is currently available. Current recommendations for prevention of HCV include **universal precautions for the prevention of blood-borne infections** [5].

## Hepatitis D Virus

1-The **modes of transmission of HDV are similar to those reported for HBV infection** [1]. ***HDV requires the presence of HBV for infection and replication*** [2].

2- Generally two major patterns of infection occur with HBV: **coinfection** and **superinfection** [3].

**A-Coinfection** (***acute hepatitis B and D***)[2] : Co-infection occurs when an individual is infected with both HBV and HDV at the same time [9].
The infection is generally ***similar in severity to acute hepatitis B alone*** [10]. ***The rate of progression to chronicity is similar to the one reported for acute HBV*** [2].

**B-Superinfection** (***chronic hepatitis B with acute hepatitis D***) [2]: HDV infection of a chronically HBV-infected individual is referred to as superinfection [9].
In chronic hepatitis B, superinfection by HDV appears to carry a worse short-term prognosis, **often resulting in fulminant hepatitis or severe chronic hepatitis which progresses rapidly to cirrhosis** [10] (patient with superinfection may eventually develop chronic infection of both types and eventually cirrhosis) [7].
(So the rate of chronic disease after coinfection with HDV is similar to that of HBV infection alone, whereas superinfection with HDV is linked to a high rate of chronicity) [3].

3-**Diagnosis** is made by finding HDV antigen in serum and by detecting **antibody to the HDV** [2].

### Treatment

**IFN-alfa is the treatment of choice for chronic hepatitis D** [2]. The only drug shown to be of benefit in treating chronic HDV is interferon-alfa. However, although interferon-alfa is capable of suppressing viral replication, **its antiviral effect is not sustained after withdrawal of therapy** [9].
Although there is **no vaccine to prevent HDV** in carriers of HBV, ***both infections can be prevented by timely administration of the HBV vaccine*** [2].

# Hepatitis E Virus

1-Transmission closely **resembles that of HAV** (i.e., fecal-oral route) [2].

2- The clinical presentations of hepatitis E are similar to that of hepatitis A [6]. Infection with HEV is typically a self-limited disease [9]. It differs from HAV in that infection **during pregnancy is associated with the development of liver failure, which has high mortality rate** [7]. For reasons that are not well understood, women in the second and third trimesters of pregnancy are at risk for a more severe clinical course. Mortality due to acute liver failure from HEV ranges from 20% to 25% in pregnant woman [9].

3-There **is no chronic infection** associated with HEV [2].

4-The diagnosis of HEV is made by serologic detection of anti-HEV antibodies [9].

5-Treatment: There is no specific treatment for HEV infection; **therapy is supportive**. There are currently **no commercially available vaccines for HEV** [9].

**Table 2 : Clinical and Epidemiologic Features of Hepatitis Viruses** [2]

| Organism | Hepatitis A | Hepatitis B | Hepatitis C | Hepatitis D |
|---|---|---|---|---|
| **Incubation** | 15-45 d | 30-180 d | 15-150 d | 30-150 d |
| **Transmission** | Fecal-oral | Blood<br>Sexual<br>Perinatal | Blood<br>Sexual (rare)<br>Perinatal (rare) | Blood<br>Sexual (rare) |
| **Fatality rate** | 1.0% | 1.0% | <0.1% | 2%-10% |
| **Carrier state** | No | Yes | Yes | Yes |
| **Chronic hepatitis** | None | 2%-10% in adults;<br>90% in children <5 yr | 70%-85% | Variable |
| **Cirrhosis** | No | Yes | Yes | Yes |

The following table from reference 6.

| Features of the main hepatitis viruses | | | | | |
|---|---|---|---|---|---|
| | Hepatitis A | Hepatitis B | Hepatitis C | Hepatitis D | Hepatitis E |
| **Spread** | | | | | |
| Faeces | Yes | No | No | No | Yes |
| Blood | Uncommon | Yes | Yes | Yes | No |
| Saliva | Yes | Yes | Yes | Unknown | Unknown |
| Sexual | Uncommon | Yes | Uncommon | Yes | Unknown |
| Vertical | No | Yes | Uncommon | Yes | No |
| Chronic infection | No | Yes | Yes | Yes | No |
| **Prevention** | | | | | |
| Active | Vaccine | Vaccine | No | Prevented by | No |
| Passive | Immune serum globulin | Hyperimmune serum globulin | No | hepatitis B vaccination | No |
| **Note** All body fluids are potentially infectious, although some (e.g. urine) are less infectious than others. | | | | | |

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