Viral Hepatitis

Viruses commonly affect the liver, resulting in a transient and harmless hepatitis. Viruses that target the liver are primarily described as hepatotropic viruses, and each of these can lead to clinically significant hepatitis and in some cases to the development of chronic viral hepatitis with viral persistence.

Five human viruses have been well described to date, including: hepatitis A, B, C, D and E. Each type of viral hepatitis causes a similar pathology with acute inflammation of the liver.

Types A and E are classically associated with an acute and sometimes severe hepatitis which is invariably self-limited, but occasionally fatal.

Hepatitis B causes acute hepatitis in adults and 5% of patients become chronic carriers, while 95% of patients infected in the neonatal period are chronically infected. Hepatitis C rarely causes an acute hepatitis but up to 85% of patients become chronic carriers. Both viruses cause chronic liver inflammation or hepatitis, cirrhosis and hepatocellular carcinoma.

Hepatitis A

Hepatitis A virus (HAV), or infectious hepatitis, is often a self-limiting and acute viral infection of the liver posing a health risk worldwide.
Although vaccine preventable, HAV continues to be one of the most commonly reported infections.

Clinical Presentation and Diagnosis

HAV infection primarily occurs through transmission by the fecal-oral route, person to person, or by ingestion of contaminated food or water. The incidence of HAV correlates directly with low socioeconomic status, poor sanitary conditions, and overcrowding. Rates of HAV infection have increased among international travelers and injection drug users.

Under physical examination, patient will shows icteric (or yellowish) sclera, skin and secretions, mild weight loss of 2–5 kg and hepatomegaly.

The disease exhibits three phases:

- Incubation (or preicteric phase) - averaging 28 days, range 15–50 days. Patients experience nonspecific influenza-like symptoms consisting of anorexia, nausea, fatigue and malaise. Then, Abrupt onset of anorexia, nausea, vomiting, malaise, fever, headache and right upper quadrant abdominal pain with acute illness
- Acute hepatitis or Icteric hepatitis generally lasting 2 months. It is generally accompanied by dark urine, alcoholic (light-colored) stools, and worsening of systemic symptoms. Pruritus is often a major complaint of icteric patients.
- Convalescence.

Most patients have full clinical and biochemical recovery within 12 weeks. Nearly all individuals will have clinical resolution within 6 months of the infection. HAV does not lead to chronic infections.

The diagnosis of acute HAV infection is based on clinical criteria of acute onset of fatigue, abdominal pain, loss of appetite, intermittent nausea and vomiting, jaundice or elevated serum aminotransferase levels and serologic testing for IgM anti-HAV.

Treatment

The goal of treatment is complete clinical resolution, including avoidance of complications, normalization of liver function and reduction of infectivity and transmission.

No specific treatment options exist for HAV. Management of HAV infection is primarily supportive.

Corticosteroids may be used in cholestatic HAV. A brief course may shorten the illness; however, this may be most effective in patients with milder disease.

The current international vaccination strategy includes vaccinating all children at 1 year of age. Vaccination is recommended for children and adolescents in addition adults who are under risk of HAV.

Hepatitis B

HBV is a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma. The HBV is a DNA virus of the family *Hepadnaviridae*. Seven HBV genotypes exist (A to H) with distinct geographic distribution. Genotype D is the most common in Mediterranean region, Middle East and India (*more than 90% in Iraq*).

Transmission of HBV occurs sexually, parenterally and perinatally. Transmission occurs predominantly through sexual contact or injection-drug use. Mother-to-child transmission of hepatitis B most commonly occurs at birth, when the neonate is exposed to maternal blood and bodily fluids, or during early childhood.

Approximately 20% of patients with chronic HBV infection develop complications of decompensated cirrhosis, including hepatic insufficiency and portal hypertension as their compensated cirrhosis progresses to decompensated cirrhosis within a 5-year period. HBV is a risk factor for development of hepatocellular carcinoma.

There are three phases of HBV infection:

- The incubation period for HBV is 4 to 10 weeks during which patients are highly infective.
- Symptomatic phase with intermittent flares of hepatitis and marked increases in aminotransferase serum levels.
- Seroconversion to anti–hepatitis B core antigen (anti-HbcAg).

Patients who continue to have detectable hepatitis B surface antigen (HbsAg) and HBcAg and a high serum titer of HBV DNA for longer than 6 months have chronic HBV.

Signs and symptoms:

Signs and symptoms may include anorexia, nausea and vomiting, low-grade fever, myalgia, fatigability, disordered gustatory acuity and smell sensations and right upper quadrant and epigastric pain

Patients with fulminant and subfulminant hepatitis may present hepatic encephalopathy, somnolence and disturbances in sleep pattern, mental confusion, coma, ascites, gastrointestinal bleeding and coagulopathy.

Examination in patients with acute hepatitis may demonstrate low-grade fever, jaundice (10 days after appearance of constitutional symptomatology; lasts 1-3

months) and hepatomegaly. Splenomegaly can be noticed in some cases in addition to rarely happened palmar erythema and spider nevi.

Prophylaxis and treatment

Prophylaxis of HBV can be achieved by ***vaccination*** (by HBV vaccine) or by passive immunity in post-exposure cases with HBV Ig. The first dose of HBV vaccine is recommended within 24 hours of birth with either two or three more doses given after that.

The goals of therapy are to increase the likelihood of seroclearance of the virus, prevent disease progression to cirrhosis or hepatocellular carcinoma, and minimize further liver injury. Successful therapy is associated with loss of HBcAg status and seroconversion to anti-HBcAg.

HBV infection can be self-limited or chronic. No specific therapy is available for persons with acute hepatitis B; treatment is supportive.

The immune-mediating agents approved as first-line therapy are **interferon (IFN)-alfa** and **pegylated (peg) IFN-alfa**. The antiviral agents **entecavir** and **tenofovir** are all approved as first-line therapy options for chronic HBV. **Lamivudine**, **telbivudine** and **adefovir** are of historical interest. These agents are currently considered second- or third-line therapy. Emtricitabine is approved for use in HIV and with activity against HBV. It is currently not approved for HBV but has been used in combination with tenofovir.

For HBeAg-positive patients, treatment is recommended until HBeAg seroconversion and an undetectable HBV viral load are achieved and for 6 months of additional treatment. In HBeAg-negative patients, treatment should be continued until HBsAg clearance.

Hepatitis C

HCV is the most common blood-borne pathogen and is most often acquired through injection drug use. Previously, it was known as Non-A, Non-B viral hepatitis. Transmission may occur by sexual contact; hemodialysis; or household, occupational or perinatal exposure. In up to 85% of patients, acute HCV infection leads to chronic infection defined by persistently detectable HCV RNA for 6 months or more.

Patients with acute HCV are often asymptomatic and undiagnosed. One third of adults will experience some mild and nonspecific symptoms, including persistent fatigue. Additional symptoms include right upper quadrant pain, nausea, or poor appetite.

An estimated 20% of patients with chronic HCV infection will develop cirrhosis, and half of those patients will progress to decompensated cirrhosis or hepatocellular carcinoma.

The diagnosis of HCV infection is confirmed with a reactive enzyme immunoassay for anti-HCV. Serum transaminase values are elevated within 4 to 12 weeks after exposure.

Treatment:

No HCV vaccine is currently available.
All patients with chronic HCV infection should be vaccinated for HAV and HBV. Patients should be advised to maintain good overall health, stop smoking and avoid alcohol and illicit drugs.

Treatment of chronic HCV infection has 2 goals:

- The first is to achieve sustained eradication of HCV (i.e., sustained virologic response (SVR)), which is defined as the persistent absence of HCV RNA in serum 6 months or more after completing antiviral treatment.
- The second goal is to prevent progression to cirrhosis, hepatocellular carcinoma (HCC), and decompensated liver disease requiring liver transplantation.

Patients with acute hepatitis C virus (HCV) infection appear to have an excellent chance of responding to standard therapy with **antiviral agents**. 6-12 months of **interferon (IFN)** or **pegylated interferon (Peg-INF)** with **ribavirin** would become a historical treatment.

Antiviral agents in HCV

Hepatitis C has become a curable disease with the use of antiviral agents (>95%). Antiviral therapy for chronic hepatitis C should be determined on a case-by-case basis.

Currently agents in use:

Drug	Trade name	Genotypes	Notes
Sofosbuvir	Sovaldi	1	With Peg-IFN + ribavirin Or with ribavirin only
		4	With Peg-IFN + ribavarin
		2, 3	With ribavarin
Ledipasvir / Sofosbuvir	Harvoni	1	With ribavarin
		4	With or without ribavarin
		5, 6	without ribavarin
Elbasvir / Grazoprevir	Zepatier	1, 4	With or without ribavarin
Ombitasvir/Paritaprevir/Ritonavir With Dasabuvir	Viekira Pak	1	With or without ribavarin
Ombitasvir/Paritaprevir/Ritonavir	*Technivie - Viekirax*	*4*	*With ribavarin*
Velpatasvir/Sofosbuvir	Epclusa	1,2,3,4,5,6	Pan-genotypic, with ribavarin
Velpatasvir/Voxilaprevir/Sofosbuvir	Vosevi	1,2,3,4,5,6	Pan-genotypic
Glecaprevir/Pibrentasvir	Mavyret - Maviret	1,2,3,4,5,6	Pan-genotypic
Daclatasvir + Sofosbuvir	Darvoni, Sovodak	1, 3	*Available in combination in Bangladesh and Iran. It is considered Pan-genotypic in China.*
Simeprivir + Sofosbuvir		*1a, 1b*	
Daclatasvir + Asunaprevir			*Asunaprevir (Sunvepra) is available in Japan, Russia and China*

Hepatitis E

Hepatitis E virus (HEV) is endemic in India, Asia, the Middle East and parts of Latin America. It is an RNA virus, which is transmitted enterically and leads to acute hepatitis. The symptoms of HEV are no different from other causes of viral hepatitis, with an average incubation period of 42 days.

Treatment of patients infected with hepatitis E virus (HEV) infection is supportive in nature.

Hepatitis D

Hepatitis D virus (HDV) is an incomplete virus that can establish infection only in patients simultaneously infected by HBV. It is estimated that 5% of HBV carriers worldwide are infected with HDV. It is endemic in the Mediterranean basin and is transmitted permucosally, percutaneously or sexually. In other geographical areas, it is confined to intravenous drug users.

The only effective treatment for HBV/HDV coinfection is pegylated interferon (PEG-IFN); antiviral nucleos(t)ide analogues have limited or no effect on HDV replication.

Thrombopoietin-Receptor Agonists

Eltrombopag is an oral thrombopoietin (TPO) receptor agonist. It directly stimulates bone marrow platelet production to provide stable platelet counts to allow therapy with interferons.

This agent is indicated for the treatment of ***thrombocytopenia in patients with chronic hepatitis C*** to allow the initiation and maintenance of interferon-based therapy.

Note:

This indication is not listed for other oral thrombopoietin (lusutrombopag and avatrombopag) or romiplostim.