

# Chapter 12

## Viral Hepatitis: Other Viral Hepatides

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### Questions from Patients

1. *How do I know I have viral hepatitis?*

Hepatitis means inflammation of the liver. Drugs, toxins, heavy use of alcohol, reduced blood supply to the liver, and microorganisms including viruses may cause it. However, signs and symptoms of hepatitis from any virus are similar and the specific cause is often undistinguishable without blood tests. Sometimes patients have no symptoms. When patients do experience symptoms, these may include jaundice (yellowing of the eyes and skin), fatigue, lethargy, nausea, vomiting, loss of appetite, abdominal pain, and fever. In severe cases, patients may start noticing swelling of feet, abdomen, or confusion and drowsiness. If any combination of these symptoms occurs, medical care should be sought immediately.

2. *How does it occur? Is it contagious?*

Most viral hepatitis occurs from human-to-human transmission, though animal-to-human transmission may also occur. Different viruses may be transmitted either from contaminated water and food; bodily secretions like blood, semen, and saliva (e.g., herpesviruses); or droplets when people cough or sneeze (influenza). The mechanism of transmission and its contagiousness is specific to each virus.

3. *How are these infections treated?*

Hepatitis caused by viruses is usually treated symptomatically, meaning treating the symptoms of liver inflammation rather than the virus itself. However, some

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viruses may have a specific antiviral that can be used to eradicate it and prevent progression of the disease.

4. *How do I know if I am getting better?*

Recovery after viral hepatitis typically starts with gradual resolution of nausea, vomiting, abdominal pain, and return of appetite and energy. The jaundice is usually the last to resolve.

## Introduction

1. *Besides the known hepatitis viruses, which other viruses cause hepatitis?*

The hepatotropic viruses are the most common cause of viral hepatitis worldwide, of which hepatitis B and C cause chronic hepatitis. However, non-hepatotropic viruses only cause acute hepatitis and/or acute liver failure, without causing any chronic damage to the liver. These viruses do not primarily target the liver; hence the term non-hepatotropic is used in their description. These viruses include the herpesviruses (Epstein-Barr virus (EBV), cytomegalovirus [CMV], and herpes simplex virus), parvovirus, adenovirus, influenza, and severe acute respiratory syndrome (SARS)-associated coronavirus [1].

The risk of acquiring infection from any of the non-hepatotropic viruses is specific to each virus and is detailed below. Considerations for determining the risk of infection include sanitary conditions, prior exposure, host immune status, and duration of infection in the contact.

## Human Herpesviruses

This class of viruses includes varicella zoster (VZV), EBV, CMV, and herpes simplex virus (HSV).

### *Herpes Simplex Virus*

Approximately 90% of people worldwide have been exposed to one or both HSV viruses [2]. HSV-1 is more common, with 65% of persons in the USA being seropositive to HSV-1 [3]. It is almost universal in the developing world, usually acquired in childhood secondary to close contact with infected family members and causes oral cold sores [2]. HSV-2 on the other hand is less ubiquitous and incidence varies from 15 to 80%, depending on the population. Transmission is almost exclusively during sexual activity [2].

2. Which subgroups are at a particularly high risk for liver involvement with HSV?

The infection in the liver with HSV is uncommon. However, when it does occur, it frequently leads to acute liver failure with a high mortality. Severe HSV

infections are typically associated with impaired cell-mediated immunity that may occur in a transplant recipient or in patients on high-dose steroids. Females in the third trimester of pregnancy are also particularly at risk for acute liver failure.

The diagnosis is often missed as skin lesions that provide clinical clues to the diagnosis are often lacking in patients with HSV-associated hepatitis. A high degree of suspicion, even in the absence of skin lesions, combined with early diagnostic modalities and early institution of appropriate therapy with parenteral acyclovir may dramatically improve survival [4].

Four mechanisms of HSV dissemination and resultant hepatitis have been hypothesized [5]: (a) a large HSV inoculant overwhelming the defense system; (b) an impairment in host macrophages, cytotoxic T lymphocytes, and delayed-type hypersensitivity reactions; (c) enhanced virulence; and (d) activation of a latent hepatovirulent strain.

HSV hepatitis is characterized by rapid development of fulminant hepatic necrosis with serum aminotransferase levels 100- to 1000-fold above normal and hyperbilirubinemia [4]. Positive serology often points at the diagnosis with polymerase chain reaction (PCR) confirming the diagnosis. In the era of widespread availability of PCR testing, a liver biopsy is now less commonly needed to secure the diagnosis. Common findings on liver biopsy include massive liver necrosis with almost complete absence of portal tracts and central veins. Presence of typical intranuclear viral inclusions is the hallmark finding on a liver biopsy, confirmed with immunohistochemical staining.

Given the time-sensitive nature of the disease, initiation of empiric therapy with acyclovir is indicated while awaiting diagnostic confirmation in a patient with acute liver failure.

## ***Varicella Zoster***

Varicella zoster (VZV) causes chicken pox which is a very common, albeit usually benign, contagious disease. It spreads easily from infected people via direct contact and droplets from coughing and sneezing. Individuals at highest risk include those who have never had chicken pox or are unimmunized [6].

Chicken pox occurs in epidemics among preschool and school-aged children and is characterized by generalized vesicular rash which is extremely pruritic. In addition to widespread systemic involvement, varicella may also cause a rare congenital varicella syndrome.

Similar to herpes virus, hepatitis secondary to varicella zoster can be life threatening [7, 8]. The disease severity and pattern of liver injury are similar to those seen in HSV hepatitis, and it usually occurs in the adult population that has not been previously exposed to varicella. Diagnosis is made based on serology, PCR, and liver biopsy, which show diagnostic inclusions on immunohistochemistry. Treatment is with parenteral acyclovir.

## ***Epstein-Barr Virus***

EBV is one of the most common viruses worldwide. It is usually asymptomatic, though it may cause infectious mononucleosis (IM). Its transmission is via saliva and is most common among teens and adults [6].

The pattern of liver injury is again hepatocellular, though it may rarely be cholestatic with marked hyperbilirubinemia. Majority of the patients who develop hepatitis do not have concomitant signs and symptoms of IM, though it is accompanied by lymphocytosis and/or splenomegaly. EBV hepatitis affects an older demographic compared to IM, with nearly half of patients over 60 years old. It is usually a self-limiting hepatitis which improves with supportive management [9].

## ***Cytomegalovirus***

CMV is usually spread by infected saliva, urine, and other body fluids. Most healthy individuals infected with CMV are asymptomatic, though occasionally it may cause systemic disease with primarily upper respiratory symptoms. When acquired vertically from pregnant woman to fetus it causes serious congenital disease [6].

Mild elevations in transaminases are almost always present, though the elevations are rarely higher than five times of the normal value. Patients are usually anicteric, and improve with supportive management.

## **Adenovirus**

Adenovirus is a common virus capable of infecting multiple organ systems. It is transmitted via direct conjunctival inoculation, fecal-oral route, aerosolized droplets, or exposure to infected tissue or blood. It causes various diseases and syndromes, including acute viral gastroenteritis, acute respiratory disease, keratoconjunctivitis, and acute hemorrhagic cystitis amongst others.

It can also cause adenoviral hepatitis, which can lead to severe fulminant failure and be life threatening, typically in the immunocompromised transplant-recipient host. The injury to liver is hepatocellular, with transaminases five to ten times upper limit of normal. Serum levels of AST are often markedly more elevated than the ALT values, and may run into several thousands. Total bilirubin and GGT on the other hand are only moderately elevated [10]. Diagnosis is with secured with PCR. There is no specific treatment, though several antivirals including ribavirin, ganciclovir, cidofovir, and vidarabine have been tried in small populations with modest success [11].

## Parvovirus B19

Parvovirus B19 (PV-B19) most commonly infects children and pregnant women. It spreads primarily via respiratory droplets, though infection may also occur via blood products.

It is most commonly associated with erythema infectiosum, otherwise known as the fifth disease of childhood. Its hallmark is fever and a rash classically known as “slapped-cheek appearance.” Mild upper respiratory tract symptoms begin approximately 1 week after exposure to PV-B19 and last for 2–3 days. The virus then spreads to the bone marrow and enters the erythroid progenitor. It subsequently causes lysis of blood cells which leads to fever with IgM-mediated lacy exanthema. In adults it is more commonly associated with marked arthropathy, and during pregnancy may cause aplastic anemia. Post-transplant patients are another at-risk population which can manifest refractory anemia [12].

While diagnosis of erythema infectiosum is clinical, blood tests are indicated for confirmation in patients with atypical symptoms or in adults. This is typically with an enzyme-linked immunosorbent assay (ELISA) for IgM antibodies and/or PCR assay. Viral DNA is typically present in serum up to 6 months after onset of symptoms [13].

Presentation as acute hepatitis or fulminant liver failure has been mostly reported in children. While it may also occur in adults, PV-B19-associated hepatitis course is less severe than in children. The pattern of injury is typically hepatocellular, with ALT and AST often three to five times the normal value, with a preferential elevation in alanine transferase. Fulminant hepatic failure secondary to PV-B19 remains a rare clinical entity. There is no specific antiviral therapy or vaccine available for prevention.

## Influenza

Influenza spreads via respiratory droplets, with humans and birds as the primary reservoir. While most flu activity occurs from October to May in the USA, it can occur year-round [6].

Influenza is often associated with mild elevations in liver enzymes, which typically resolve after clearance of the virus. This is somewhat intriguing as the virus typically infects the respiratory endothelial lining and the hepatocytes are not exposed to the viral antigen. It has been proposed that the process of CD8<sup>+</sup> T-cell infiltration of the liver in influenza infection can lead to clinically significant hepatitis [1]. The pattern of injury is typically hepatocellular with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) usually two to three times above the normal limit. Alkaline phosphatase (ALKP) and gamma-glutamyl transpeptidase

(GGT) are often normal. Another observation was significantly higher serum levels of AST, ALT, and GGT in patients with pandemic influenza in 2009 caused by the H1N1 strain compared to seasonal influenza [14]. Diagnosis is confirmed with immunoassays and PCR.

Hepatitis secondary to influenza rarely progresses to acute liver failure, and when it does occur the process is more due to multiorgan failure from sepsis and ischemia than direct viral injury.

Treatment is with oseltamivir. The incidence has reduced and outbreaks have diminished in severity due to active recruitment of care providers at grassroots levels to encourage annual immunization in all with no contraindications. However, occasional viral mutations lead to resistant strains against which the efficacy of vaccine is diminished.

## **Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV)**

SARS-CoV is a relatively recently recognized virus, being first recognized in 2003 as the perpetrator of a massive outbreak of respiratory illness with high mortality in China. It has been virtually eradicated with no further cases reported since 2004, though CDC declared it a select agent in 2012 [6]. Another viral outbreak identified as MERS-CoV in 2012 in Saudi Arabia has been reported recently. There is a current outbreak of the MERS-CoV in South Korea since May 2015.

Both SARS- and MERS CoV-associated liver injury is reported in up to 60 % of the patients and is associated with clinically significant hepatitis. It is usually associated with focal lobular lymphocytic infiltrates and has been reported in patients with SARS. In these cases, although SARS-associated coronavirus was detected in the liver tissues by reverse transcriptase-PCR, no viral particles were seen at electron microscopy [1].

There is no specific therapy for either of the viruses. Various antivirals have been tried with little success, apart from interferon which showed modest improvement in symptoms.

## **Ebola Hemorrhagic Fever (EHF)**

Ebola is an extremely contagious virus transmitted from direct contact with infected body fluid. Humans and primates are the primary reservoir. The most recent outbreak started in March 2014 in West Africa and is currently ongoing, and has so far resulted in over 10,000 deaths.

The disease is associated with severe fulminant liver failure, resulting in massive internal hemorrhage. Diagnosis is confirmed by IgM ELISA, PCR, and virus isolation [6].

The elevations in liver enzymes are hepatocellular in pattern, with AST being much higher than ALT. Bilirubin, ALKP, and GGT are only modestly elevated.

Treatment is supportive, with no FDA-approved specific antiviral therapy available. Experimental vaccines and treatments for Ebola are under development, but they have not yet been fully tested for safety or effectiveness [6]. Mortality remains very high.

3. *What is the management of patients who develop acute liver failure due to non-hepatotropic virus infection?*

Acute liver failure is defined by elevation in liver enzymes, an INR >1.5, and development of encephalopathy in someone without known underlying liver disease. It is associated with rapid progression and very high mortality. The first step towards appropriate management is prompt transfer of the patient to the nearest transplant center. These patients are preferably admitted to the critical care unit, and should have close frequent monitoring of sensorium and the basic chemistry panel. Their management is very similar to management of other patients with non-acetaminophen-associated liver failure and the use of *N*-acetylcysteine may also have a role [15].

Management of advanced encephalopathy is arguably the most challenging in acute liver failure. Management is aimed at reducing intracranial pressure. When sedation is indicated, propofol is the preferred agent as it reduces brain edema [16].

Early transplant consideration and evaluation offer the best chance at survival in patients with acute liver failure. Even with appropriate management, mortality remains high. Prior to transplantation, most series suggested less than 15% survival. Currently, overall short-term survival (1 year) including those undergoing transplantation is greater than 65% [17].

4. *Do the non-hepatotropic viruses cause chronic disease or result in an elevated risk of liver cancer?*

None of the non-hepatotropic viruses, with the possible exception of PV-B19, has been shown to cause chronic liver disease. PV-B19 has been postulated as a rare and unusual etiology of chronic hepatitis. This observation is based on identification of viral DNA from the hepatocytes years after the original infection. However, the extent to which it results in actual fibrosis and chronic damage is unclear. Furthermore, interest has focused on a possible effect of co-infection with PV-B19 on the natural history of chronic hepatitis B and C [18]. Similarly, none of the above viruses have been associated with liver cancer.

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