Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHAPTER 6

Hepatitis Caused by Other Viruses

Elliot B. Tapper, MD ■ Michael P. Curry, MD

KEY POINTS

1. Systemic viral infections can cause liver injury that ranges from mild asymptomatic and transient elevation of serum aminotransferase levels to acute icteric hepatitis or rarely severe hepatitis with acute liver failure (ALF).
2. The clinical presentation may be indistinguishable from liver injury caused by the principal hepatotropic viruses.
3. Mild liver enzyme elevations are a common feature of many systemic viral infections and can occur as a bystander effect.
4. In general, specific antiviral therapy is not available.

Overview

1. Hepatic dysfunction is frequently encountered in systemic, nonhepatotropic viral infections and may reflect the host immune response rather than direct viral injury.
2. Hepatic involvement in systemic viral infections does not result in chronic liver injury.
3. Although most systemic nonhepatospecific viral infections cause mild hepatocellular dysfunction, more severe liver disease may occur.
4. These nonhepatotropic viruses include cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), varicella-zoster virus (VZV), human herpesvirus 6 (HHV-6), and nonherpes viruses including adenovirus, Dengue virus, Chikungunya virus, Ebola virus, and influenza virus (Table 6.1).
5. Serologic testing is available for most viruses that have the potential to cause liver injury.

Viruses with Frequent Hepatic Involvement

CYTOMEGALOVIRUS

1. CMV has a seroprevalence rate of 30% to 70% in the general population, reflecting prior infection.
2. Primary infection of immunocompetent hosts is usually clinically indistinguishable from infectious mononucleosis caused by EBV. Symptoms include fever, myalgia, cervical lymphadenopathy, and, in >75% of patients, mild elevations in the liver enzymes.
3. Recovery from a primary infection results in lifelong latent infection with the possibility of replication and reactivation if the host immune response becomes compromised.
4. CMV infection in an immunocompromised host can occur because of reactivation of latent infection or as a primary infection after first exposure.
5. CMV-induced liver injury can be more severe in the immunocompromised host. Symptoms and signs may include tender hepatomegaly and jaundice. Hepatic involvement by CMV is

TABLE 6.1 ■ **Viral Infections that May Involve the Liver**

Virus	Histology	Severity	Treatment
Viruses with Frequent Hepatic Involvement			
Cytomegalovirus	Lobular microabscesses, often surrounding hepatocytes with nuclear and/or cytoplasmic inclusions	Usually mild, rarely severe	Valganciclovir (if mild), ganciclovir (severe); cidofovir (refractory)
Epstein-Barr virus (EBV)	Diffuse sinusoidal lymphocytic infiltration, EBV-encoded RNA (EBER)–positive tissue staining	Usually mild, rarely severe	Case reports suggest ganciclovir
Viruses with Less Frequent Hepatic Involvement			
Herpes simplex virus	Hepatocyte necrosis, pauciinflammatory infiltrates, Cowdry type A inclusion bodies, and multinucleated hepatocytes	Always severe	Acyclovir
Varicella zoster virus	–	Usually mild, rarely severe	Acyclovir
Adenovirus	Staining for adenoviral antigens; randomly scattered punched-out lesions, large nuclei with inclusions consisting of waxy-appearing dense material with unstained clear zones	Usually mild, rarely severe	Case reports suggest cidofovir
Influenza virus	Inflammatory infiltrate without direct infection of hepatocytes	Always mild	Supportive care
Viruses Uncommon in the United States but with Frequent Hepatic Involvement			
Chikungunya	–	Always mild	Supportive care
Dengue virus	–	Usually mild	Supportive care
Ebola virus	Widespread necrosis with periportal mononuclear cells and Kupffer cell hypertrophy	Usually severe	Supportive care

frequently accompanied by gastrointestinal tract injury and symptoms (ulcers, nausea, vomiting) and pneumonia.

6. Severe CMV-induced liver injury is characterized histologically by small collections (microabscesses) of inflammatory cells (mainly neutrophils) throughout the hepatic lobule, often surrounding hepatocytes with nuclear and/or cytoplasmic inclusions, so-called "owl's eye" inclusions.
7. CMV is a common infection in patients with acquired immunodeficiency syndrome (AIDS) and has been associated with papillary stenosis and sclerosing cholangitis (AIDS cholangiopathy) (see Chapter 27).
8. The diagnosis is made in the appropriate clinical context with polymerase chain reaction (PCR) testing or histologic evidence of infection.
9. Infection is usually defined as *primary* if the patient has no evidence of prior exposure (i.e., negative immunoglobulin [Ig]G anti-CMV) or *recurrent* if the patient has detectable IgG anti-CMV.
10. Treatment of CMV infection is not always indicated in immunocompetent patients, unless the infection is severe or life threatening.
11. Many immunocompromised patients at risk for CMV are routinely tested by a PCR assay or treated prophylactically with an antiviral agent. Treatment of viremia before the onset of symptoms is considered preemptive.
12. Drugs approved for the treatment of CMV infection include oral ganciclovir, valganciclovir, intravenous ganciclovir, intravenous foscarnet, and intravenous cidofovir.

13. Ganciclovir-resistant strains of CMV are emerging.
14. The choice and duration of treatment are dependent on the severity of disease and the immune status of the patient. Repeated assessments for CMV viremia should be made.
15. Organ transplantation recipients at risk of CMV reactivation usually receive 3 to 6 months of prophylactic therapy after transplantation.

EPSTEIN-BARR VIRUS

1. Of the world's population, 90% have serologic evidence of prior EBV infection.
2. Primary infection typically manifests as infectious mononucleosis (fever, lymphadenopathy, and mild elevations in liver enzyme levels).
3. Of patients with EBV mononucleosis, 90% have mild elevations in serum aminotransferase levels.
4. Cholestasis with jaundice is reported in 45% of patients with primary EBV infection, with a 5% case-fatality rate reported in both immunocompetent and immunocompromised patients.
5. Half of the deaths from mononucleosis, while rare, are attributable to ALF. Less than 1% of all cases of ALF, however, are attributable to EBV. EBV-associated ALF carries with it a 25% transplant-free survival.
6. The monospot test, which detects heterophile antibodies, is sensitive but not specific.
7. Liver injury attributable to EBV mononucleosis can be diagnosed clinically by the combination of symptoms with consistent serology (IgM directed against the viral capsid antigens [IgM anti-EBV VCA]).
8. Definite severe EBV infection is confirmed by the combination of serologic evidence of virus (by a PCR assay) and evidence of EBV-associated hepatopathology on light microscopy (diffuse sinusoidal lymphocytic infiltration) with or without EBV-encoded RNA (EBER)–positive tissue staining.
9. Treatments with demonstrated efficacy in clinical trials are lacking. Acyclovir inhibits EBV in vitro and reduces viral shedding in the oropharynx but has little to no effect on symptoms. Ganciclovir use has been supported by a study of two children with EBV hepatitis.

Viruses with Less Frequent Hepatic Involvement

HERPES SIMPLEX VIRUS

1. The two types of HSV (HSV-1 and HSV-2) have seroprevalence rates of 57.7% and 17.0%, respectively, in the general population.
2. HSV infections typically manifest as orolabial or genital lesions. Rare presentations include meningitis, encephalitis, and hepatitis.
3. HSV hepatitis usually occurs in neonates, pregnant women, and immunocompromised patients.
4. Only 50% of patients have associated mucocutaneous involvement.
5. Mild asymptomatic elevations in serum aminotransferase levels are seen in 14% of patients with acute HSV genital infection.
6. HSV hepatitis is rare. Approximately 137 cases have been reported, and the frequency of HSV hepatitis in a cohort of patients with ALF is 0.3%. Patients present with fever, leukopenia, and elevated serum aminotransferase levels.
7. The prognosis of HSV hepatitis is poor, with a transplant-free survival rate of 24.8%.
8. Liver biopsy findings consistent with HSV infection include extensive hepatocyte necrosis with adjacent congestion, pauciinflammatory infiltrates, Cowdry type A inclusion bodies (purple nuclear inclusions with a clear halo), and multinucleated hepatocytes.

9. The diagnosis of primary infection complicated by hepatitis is made by the combination of viremia (detected by a PCR assay) and consistent histology, whereas reactivation hepatitis occurs when there is serologic evidence of prior infection (IgG anti-HSV-1 or anti-HSV-2).
10. Although prospective trials are lacking, treatment with intravenous acyclovir (10 mg/kg 3 times a day) may be effective.
11. Liver transplantation should be considered for patients who meet criteria for ALF that does not reverse with antiviral therapy.

OTHER VIRUSES

1. **Varicella zoster virus (VZV):** Disseminated varicella infection typically presents as pneumonia with infrequent, mildly elevated liver enzyme levels. Up to 25% of children with primary varicella infection have elevated liver enzymes. There are a few reports of ALF attributable to VZV in patients with a confluence of vesicular rash, positive VZV by a PCR assay, and severe liver injury. Primary varicella infection in organ transplant recipients has been associated with ALF. Treatment is the same as for HSV: Intravenous acyclovir, 10 mg/kg three times a day for 7 to 10 days.
2. **Adenovirus** is a double-stranded DNA virus that is frequently implicated in upper respiratory tract and ocular infections. Confirmation of adenoviral hepatitis requires evidence of systemic infection (positive PCR assay, antigenemia, or viral blood culture) and liver biopsy specimens consistent with a viral infection—either stains for adenoviral antigens or diagnostic morphology (randomly scattered punched-out lesions, large nuclei with inclusions consisting of waxy-appearing dense material with unstained clear zones). Most reported cases have been in organ transplant recipients. Severe adenoviral hepatitis has a poor prognosis with a low rate of spontaneous recovery. Treatment may be attempted with cidofovir.
3. **Influenza** is an RNA virus associated with pandemic infections and a predominance of respiratory symptoms. Mild asymptomatic elevations of liver enzyme levels are common. However, influenza does not directly infect hepatocytes. Influenza infection induces the expansion of CD8+ T cells, which cause "collateral damage" to the liver while interacting with Kupffer cells.
4. **Human herpesvirus 6** is a rare cause of liver injury, lymphadenopathy, and a nonspecific rash. A detectable viral load (positive PCR assay) or serology (IgM anti-HHV-6) in the absence of other potential causes for the symptoms is considered diagnostic. One study suggested that HHV-6 may be responsible for non-A-E–associated ALF; HHV-6 antigens were isolated in the liver tissue by immunohistochemistry in 12 of the 15 cases.

Viruses Uncommon in the Unites States but with Frequent Hepatic Involvement

1. **Chikungunya** is an RNA virus associated with an epidemic fever marked by flulike symptoms and arthralgia. In the early phase of infection (<14 days), serum aminotransferase levels range from 49 to 311 U/L without evidence of severe liver injury (i.e., coagulopathy or jaundice).
2. **Dengue** virus, the most common mosquito-borne RNA virus worldwide, is highly prevalent in tropical climates. Over 80% of patients with Dengue fever, including 84.4% of patients with hemorrhagic-type fever, present with elevated serum alanine aminotransferase (ALT) levels without severe liver injury. The mechanism of injury is not defined. The mortality rate associated with severe hepatitis associated with Dengue fever is 2.7% in affected adults and over 50% in the pediatric population.
3. **Ebola** virus is an epidemic RNA virus associated with hemorrhagic shock syndrome. Independent of shock, 77% of patients present with elevated liver enzyme levels, and 100%

develop liver injury during the index hospitalization. Serum aspartate aminotransferase (AST) and ALT levels rise to about 200 U/L, with an AST > ALT. Jaundice develops in over 50% of patients during the course of infection. A marked elevation in the alkaline phosphatase level (to 900 U/L) was noted in American patients treated in 2014. Fatalities were more frequent in patients with an AST level of 900 U/L during the Sudan Ebola virus epidemic in Uganda in 2000. Histology in this series showed widespread necrosis with periportal mononuclear cells and Kupffer cell hypertrophy, without prominent bile duct damage.

4. Liver injury was prominent in **severe acute respiratory syndrome (**SARS) caused by a coronavirus, with elevation of the serum aminotransferase levels, and may have reflected direct hepatic injury by the virus. After an outbreak of SARS in Asia in 2002, no further cases have been identified.

VIRUSES OF UNCLEAR PATHOGENICITY

1. **Transfusion transmitted (TT) virus** is a single-stranded, circular, hepatotropic DNA virus spread by both blood-borne and enteric transmission routes. Although it is prevalent in patients with specific risk factors (transfusions, intravenous drug use, and sex workers), TT virus is also found in the serum of some patients with ALF, cirrhosis, and liver cancer but has not been consistently implicated in liver injury.
2. **SEN virus** is a single-stranded, circular, hepatotropic DNA virus detected in 1.8% of American blood donors. In Japan, it was identified in 22% of healthy subjects and 38% of patients undergoing hemodialysis. It appears to be transmitted by transfusion. In a study of 12 patients with non-A-E-transfusion–related hepatitis, 11 (92%) had serologic evidence of SEN viremia; however, in a follow-up case-control study, no etiologic role for SEN in the cause of cryptogenic hepatitis could be established, nor was it associated with more severe hepatitis.
3. **Hepatitis G virus** (or GB virus C) is an RNA virus in the same family as hepatitis C virus (Flaviviridae*).* Although it was originally thought to cause transfusion-related hepatitis, no etiologic role has been established. Hepatitis G may be associated with favorable outcomes in patients with human immunodeficiency virus infection.

FURTHER READING

Adams DH, Hubscher SG. Systemic viral infections and collateral damage in the liver. *Am J Pathol*. 2006;168:1057–1059.

Adams LA, Deboer B, Jeffrey G, et al. Ganciclovir and the treatment of Epstein-Barr virus hepatitis. *J Gastroenterol Hepatol*. 2006;21:1758–1760.

Bradley H, Markowitz LE, Gibson T, et al. Seroprevalence of herpes simplex virus types 1 and 2—United States, 1999-2010. *J Infect Dis*. 2014;209:325–333.

Drebber U, Kasper HU, Krupacz J, et al. The role of Epstein-Barr virus in acute and chronic hepatitis. *J Hepatol*. 2006;44:879–885.

Gandhi MK, Khanna R. Human cytomegalovirus: clinical aspects, immune regulation, and emerging treatments. *Lancet Infect Dis*. 2004;4:725–738.

Härmä M, Höckerstedt K, Lautenschlager I. Human herpesvirus-6 and acute liver failure. *Transplantation*. 2003;76:536–539.

Kew M. Hepatitis viruses (other than hepatitis B and C viruses) as causes of hepatocellular carcinoma: an update. *J Viral Hepat*. 2013;20:149–157.

Khan E, Kisat M, Khan N, et al. Demographic and clinical features of Dengue fever in Pakistan from 2003-2007: a retrospective cross-sectional study. *PloS One*. 2010;5:e12505.

Lyon GM, Mehta AK, Varkey JB, et al. Clinical care of two patients with Ebola virus disease in the United States. *N Engl J Med*. 2014;371:2402–2409.

Mellinger JL, Rossaro L, Naugler WE, et al. Epstein-Barr virus (EBV) related acute liver failure: a case series from the US Acute Liver Failure Study Group. *Dig Dis Sci*. 2014;59:1630–1637.

Norvell JP, Blei AT, Jovanovic BD, et al. Herpes simplex virus hepatitis: an analysis of the published literature and institutional cases. *Liver Transpl*. 2007;13:1428–1434.

Papic N, Pangercic A, Vargovic M, et al. Liver involvement during influenza infection: perspective on the 2009 influenza pandemic. *Influenza Other Respir Viruses*. 2012;6:e2–e5.

Ronan B, Agrwal N, Carey EJ, et al. Fulminant hepatitis due to human adenovirus. *Infection*. 2014;42: 105–111.

Taubitz W, Cramer JP, Kapaun A, et al. Chikungunya fever in travelers: clinical presentation and course. *Clin Infect Dis*. 2007;45:e1–e4.

Uyeki TM, Mehta AK, Davey Jr RT, et al. Clinical management of Ebola virus disease in the United States and Europe. *N Engl J Med*. 2016;374:636–646.