CME

A clinical review of viral hepatitis

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ABSTRACT

Viral hepatitis remains a significant public health problem in the United States, despite advances in antiviral therapy and effective vaccines. According to the CDC, about 20,000 deaths each year are attributed to viral hepatitis, and 5 million people are chronically infected and at risk for serious liver disease and hepatocellular cancer. This article reviews the three most common causes of viral hepatitis, screening guidelines, clinical features, medical management, approaches for primary prevention, and the natural history of untreated disease.

Keywords: hepatitis, antiviral, public health, hepatocellular cancer, liver transplant, cirrhosis

Learning objectives

- Contrast the risk factors, clinical course, and treatment of viral hepatitis A, B, and C.
- Understand the screening recommendations for viral hepatitis.
- Recognize the prevalence of viral hepatitis and HIV coinfection.

Despite advances in antiviral therapy and access to effective vaccines, viral hepatitis remains a significant public health problem in the United States. The condition is most commonly caused by infection from the hepatitis A virus (HAV), hepatitis B virus (HBV), or hepatitis C virus (HCV). Liver injury can result from nearly any viral infection with systemic involvement, however, including cytomegalovirus and herpes simplex virus. Clinical features of viral hepatitis, including risk for progression to chronic infection with development of cirrhosis, vary considerably and are virus-specific. As frontline healthcare providers, physician assistants (PAs) can reduce the burden of disease through infection prevention, early detection, and collaborative care with specialists.

HEPATITIS A

HAV is an RNA virus transmitted person-to-person via the fecal-oral route, typically after consuming contaminated food or handling contaminated objects. Risk factors for HAV exposure include traveling to countries with high endemic rates of infection as well as being in close contact with HAV-infected persons. The overall incidence of HAV has declined since the HAV vaccine was added to the childhood immunization schedule. Peak outbreaks of the disease occurred

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Key points

- Chronic viral hepatitis frequently is asymptomatic.
- Normal liver function tests do not exclude cirrhosis or hepatocellular cancer.
- Patients who test negative for anti-HBs should be vaccinated against HBV.
- One-time screening for HCV is recommended for anyone born between 1945 and 1965, regardless of risk factors.

in the United States in 2012-2013 and again in 2015-2016.[1] In 2016, more than 2,000 cases were reported to the CDC, although the actual number was estimated to be closer to 4,000.[1] Recent nationwide outbreaks have been linked to imported food, but state health departments have reported that person-to-person transmission affecting homeless persons and those who use illicit drugs is becoming more widespread.[2]

Screening Because HAV has a low prevalence, self-limited clinical course, and is associated with lifelong immunity after exposure, routine HAV screening of the general population is not recommended (**Table 1**).

Clinical features After the average incubation period of 28 days, HAV may cause fatigue, abdominal discomfort, vomiting, pruritus, or fever. Patients with severe illness may develop jaundice and dark-colored urine. Most adults are symptomatic, but the condition is asymptomatic in about 70% of infections among children under age 6 years.

Diagnosis and management Clinical suspicion for acute hepatitis should prompt laboratory testing for the HAV immunoglobulin M antibody (IgM anti-HAV) (**Table 1**). Associated laboratory abnormalities may include elevated alanine transaminase (ALT) and aspartate transaminase (AST) enzymes; total serum bilirubin and alkaline phosphatase will be normal or mildly elevated. Cases of viral hepatitis due to HAV, HBV, and HCV are nationally notifiable conditions, though local and state-specific reporting requirements may vary.

Management is largely supportive because symptoms typically resolve within several weeks. Advise patients to avoid alcohol and medications associated with potential hepatotoxicity, such as acetaminophen, until they have recovered. Encourage good hand hygiene and administration of the HAV vaccine for unvaccinated caregivers and close contacts.

Older adults and patients with underlying chronic liver disease are at increased risk for severe infection. Fewer than 1% of patients develop acute liver failure and need to be considered for emergency transplant evaluation.[3] Acute hepatitis due to HAV does not progress to chronic infection (**Table 1**).

Prevention Vaccination provides long-term protection and should be offered to groups at increased risk for infection, such as military personnel, travelers to endemic areas, IV drug users, persons with chronic liver disease, and those with occupational risks for infection or who are in close contact with international adoptees. Also consider administering vaccine to any unvaccinated person who requests immunity. In 2018, the CDC's Advisory Committee on Immunization Practices (ACIP) updated its guidelines with recommendations to vaccinate infants ages 6 to 11 months who are traveling internationally.[4]

A single dose of HAV immune globulin (IG) administered IM offers short-term protection and is recommended for postexposure prophylaxis (PEP) for all immunocompetent patients age 12 months or older.[4] Positive HAV immunoglobulin G antibody (IgG anti-HAV) testing indicates immunity (**Table 1**).

HEPATITIS B

HBV is a DNA virus transmitted by percutaneous or perinatal exposure, or from direct mucosal contact with HBV-infected blood or body fluid.

In 2016, more than 3,000 new cases of HBV hepatitis were reported to the CDC, considerably lower than the estimate of 20,000 cases.[1] In the same year, the number of

TABLE 1. Serologic testing for hepatitis

	HAV	HBV*	HCV
Initial screening test in the general population	Not recommended	HBsAg and anti-HBs, plus IgG anti-HBc in patients who plan to start immunosuppressive therapy	Anti-HCV
Acute infection	IgM anti-HAV	HBsAg, IgM anti-HBc	Anti-HCV, HCV RNA
Chronic infection	Not applicable because HAV does not progress to chronic infection	Repeat HBsAg testing at 6 months*	
Immunity due to past infection or vaccination	IgG anti-HAV	Anti-HBs	Not applicable because HCV reinfection is always possible

* Additional serologic markers may be needed depending on clinical circumstance. See www.cdc.gov/hepatitis/hbv/pdfs/serologicchartv8.pdf.

patients with hepatitis due to chronic HBV was projected at 850,000 to 2.2 million.[1]

Screening All pregnant women regardless of vaccination status, and patients at increased risk for HBV infection (**Table 2**), should be screened for the HBV surface antigen (HBsAg) and HBV surface antibody (anti-HBs) (**Table 1**).[5] A positive HBsAg test indicates acute or chronic infection regardless of HBV DNA level. Even if immunity has been established, testing for the antibody to the HBV core antigen (IgG anti-HBc) is recommended for patients who need immunosuppressive therapy and would be at risk for HBV disease reactivation.[6]

Clinical features Following HBV transmission and an incubation period ranging from 4 weeks to 6 months, 30% to 50% of immunocompetent persons age 5 years and older will develop clinical signs and symptoms of infection.[7] Symptoms may include fever, fatigue, loss of appetite, vomiting, abdominal pain, dark-colored urine, clay-colored stools, arthralgias, and jaundice. Symptoms generally are present for several weeks but can persist for up to 6 months. As with HAV, severe illness is more prevalent among older adults. The rate of progression to acute liver failure is estimated at 1% to 2%, and without transplantation, the prognosis is poor.[7]

The risk for developing chronic infection is inversely related to patient age at the time of transmission, with fewer than 5% of immunocompetent adults developing chronic infection, compared with 90% of newborns.[7]

Diagnosis and management Serologic testing differentiates acute versus chronic HBV infection and identifies patients who have acquired immunity, either through vaccination or natural immune clearance. Positive HBsAg and immunoglobulin M antibody to the HBV core antigen (IgM anti-HBc) establishes acute infection. If clinical suspicion for infection is high, perform repeat testing to exclude a window period where both HBsAg and anti-HBs are undetectable. Chronic infection is confirmed by the presence of HBsAg for at least 6 months. If HBV e-antigen also is positive, active viral replication is occurring and the patient is considered highly contagious. An isolated positive anti-HBs generally is consistent with immunity conferred by vaccination; the additional finding of positive IgG anti-HBc indicates recovery from previous infection (**Table 1**).

All patients diagnosed with chronic hepatitis due to HBV should be counseled about the importance of lifelong monitoring with serial laboratory testing, practicing universal precautions to reduce the risk of disease transmission, and testing for HCV coinfection. Additionally, sexual and household contacts should be offered vaccination against HBV. Although HBV cannot be cured, viral suppressive therapy is highly effective. The goal of treatment is to reduce HBV viral load and the risk for histologic progression of liver disease. The decision to initiate pharmacologic therapy is based on review of HBeAg status, ALT level, HBV DNA, and evidence of advanced liver fibrosis.[6] Antiviral therapy is recommended for all patients with previous HBV exposure who are undergoing chemotherapy or other immunosuppressive therapy, because they need prophylaxis against HBV reactivation.[6]

TABLE 2. Risk factors for HBV infection in adults[5]

- IV drug use
- Sexual exposure (heterosexual and men having sex with men)
- Household contacts of patients with HBV
- Residence in a long-term care facility
- Residence in a correctional facility
- Occupational exposure to HBV
- Hemodialysis
- HCV infection
- Chronic liver disease
- Travel to countries where HBV is endemic
- HIV infection

First-line antiviral agents include tenofovir and entecavir, although medication selection may be individualized according to anticipated treatment duration, resistance patterns, and adverse reaction profile.

Prevention The first dose of the HBV vaccine should be administered at birth as part of the routine series and immunity typically is achieved within 18 months.[5] The HBV vaccine also is recommended for anyone who screens negative for anti-HBs. In 2018, Heplisav-B was approved by the FDA for adults age 18 years and older; the two doses of the vaccine are administered 4 weeks apart. Testing for serologic evidence of immunity postvaccination is not routinely performed and is only indicated if knowing the patient's immune status will affect clinical management (for example, in the case of healthcare workers who are at risk for exposure to HBV-infected body fluids).

HEPATITIS C (HCV)

HCV is an RNA virus transmitted by exposure to HCV-infected blood or blood-containing body fluid (for example, by sharing HCV-contaminated needles during IV drug use). Cases of HCV infection have been associated with occupational injuries, perinatal transmission, sexual transmission, receiving piercings or tattoos from unregulated body art studios, and transfusion of unscreened blood before 1992.

In 2016, nearly 3,000 new cases of acute hepatitis due to HCV were reported to the CDC, and the number of chronic cases was estimated at 3.5 million.[1] An estimated 50% of patients with chronic hepatitis due to HCV are unaware that they are infected; this figure includes more than 800,000 people who are institutionalized, incarcerated, or homeless.[8]

Screening One-time HCV screening with HCV antibody (anti-HCV) testing is recommended for the following groups:

• Anyone born between 1945 and 1965, regardless of risk factors
• Anyone with recent or remote history of IV drug use
• Anyone with increased risk for HCV exposure, such as persons on chronic hemodialysis, children born to mothers with HCV infection, patients who received an organ transplant or blood transfusion before 1992, patients with HIV infection, and those with unexplained ALT abnormalities.[9]

A positive anti-HCV indicates previous exposure and does not confirm immunity. Perform both anti-HCV and HCV RNA testing if the patient was exposed to the virus within the past 6 months (**Table 1**). Patients who continue to engage in high-risk behaviors or have ongoing risk exposures should also be screened annually, even if they have been previously treated for HCV.[10]

> Recognizing patients who have cirrhosis can be challenging because often they are asymptomatic.

Clinical features Acute hepatitis due to HCV often is unrecognized because patients who are infected frequently are asymptomatic. Regardless, 75% to 85% of these patients will go on to develop chronic infection after the 6-month acute phase.[11] Chronic infection due to HCV also is asymptomatic; the diagnosis is typically established through routine screening or diagnostic workup of an incidental abnormal finding on routine laboratory tests. Chronic infection is associated with increased risk for hepatic fibrosis, and 10% to 20% of patients with HCV infection eventually develop cirrhosis.[11]

Extrahepatic conditions associated with HCV infection include cryoglobulinemia vasculitis, membranoproliferative glomerulonephritis, porphyria cutanea tarda, and B-cell non-Hodgkin lymphoma.

Diagnosis and management Qualitative HCV RNA testing usually confirms the presence of hepatitis C, which is detectable within 21 days of an exposure (**Table 1**). Of the six known HCV genotypes, genotype 1 is the most common in patients from the United States. HCV viral load does not correlate with disease severity or prognosis. Like HBV infection, evidence of coexisting hepatic fibrosis can be assessed by a clinical examination revealing stigmata of cirrhosis, serum biomarkers, vibration-controlled transient elastography, or cross-sectional imaging. Liver biopsy is not needed to assess the extent of fibrosis but can be considered when there are discordant results.

HCV treatment has evolved significantly in the last decade with the development of direct-acting antiviral (DAA) medications. The primary goal of therapy is to achieve an undetectable HCV RNA level or sustained viral response at 12 weeks post-treatment, which is associated with reduced morbidity and mortality.[12] DAA regimens are pan-genotypic and well tolerated with minimal drug interactions. FDA-approved medications include ledipasvir-sofosbuvir, sofosbuvir-velpatasvir, elbasvir-grazoprevir, sofosbuvir-velpatasvir-voxilaprevir, and glecaprevir-pibrentasvir. Once sustained viral response has been achieved, repeat HCV RNA testing is not recommended unless there is clinical concern for reinfection.

The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) have partnered to develop *HCV Guidance*, an online resource that offers guidelines about medication selection and treatment duration, including recommendations for specific populations such as pregnant patients and those with decompensated cirrhosis, coinfections with HBV or HIV, or renal impairment.[10] The online resource also provides recommendations for when to refer a patient to a liver specialist.

Prevention No approved vaccines are protective against HCV, and PEP is not recommended.

HIV COINFECTION

An estimated 25% of patients with HCV infection and 10% of patients with HBV infection are coinfected with HIV, a fact that highlights the importance of HBV/HCV screening in patients with HIV infection.[10] In the era of DAA therapy, treating HCV in HIV/HCV-coinfected patients is now comparable to HCV monotherapy.[10] Liver transplant also can be considered if the patient has satisfactory immune function and persistent HIV viral suppression. In 2013, the HIV Organ Policy Equity (HOPE) Act was enacted so that HIV-positive organs can be offered to patients who are HIV-positive.[13]

RISK OF HEPATOCELLULAR CANCER

Hepatocellular cancer is a leading cause of cancer-related death in the United States, and its incidence has steadily increased over the past 20 years.[14,15] Risk factors associated with the development of hepatocellular cancer include cirrhosis (regardless of etiologic factors) and chronic hepatitis due to HBV or HCV. Patients diagnosed with cirrhosis due to chronic HCV have an estimated 1% to 5% annual risk for developing hepatocellular cancer.[16] Screening is recommended for patients who have cirrhosis or chronic HBV with a family history of hepatocellular cancer and who are likely to tolerate hepatocellular cancer treatment.[16] AASLD guidelines recommend screening for hepatocellular cancer with abdominal ultrasound, with or without alfa-fetoprotein (AFP) level, every 6 months.[16]

Having a sustained viral response does not eliminate the need for hepatocellular cancer surveillance in patients with cirrhosis due to chronic HCV.

CIRRHOSIS

HBV and HCV account for almost all cases of chronic viral hepatitis. Repeated inflammatory insults and injury to the liver parenchyma cause structural changes that lead to fibrosis. The degree of fibrosis is described by stage, using one of several histopathology scoring systems (for example, METAVIR or Batts-Ludwig) and ranges from no fibrosis (stage 0) to cirrhosis (stage 4).[17]

Clinical features The features and complications of cirrhosis arise from decreased hepatic function (altered protein synthesis, metabolic disturbances) as well as structural changes to the liver resulting in progressive portal hypertension. Recognizing patients who have cirrhosis can be challenging because often they are asymptomatic. As a result, patients are often diagnosed after seeking care for symptoms of cirrhosis decompensated by jaundice, ascites, hepatic encephalopathy, or variceal bleeding.

- *Jaundice* is the yellowing of the skin due to increased concentrations of serum bilirubin.
- *Ascites* results from portal fluid leaking into the peritoneal cavity due to increased resistance to hepatic flow secondary to fibrosis and reduced albumin synthesis. Management includes strict adherence to a low-sodium diet, diuretic therapy, and therapeutic paracentesis as clinically indicated. A transjugular intrahepatic portosystemic shunt (TIPS) procedure can be considered for patients with refractory ascites.
- *Hepatic encephalopathy* is a disturbance in brain function related to an accumulation of toxic nitrogenous byproducts crossing the blood-brain barrier in patients with reduced filtration due to hepatic dysfunction. Hepatic encephalopathy is treated with lactulose, a nonabsorbable disaccharide that titrated to effect, may be given with rifaximin, a nonabsorbable antibiotic. Secondary prophylaxis is recommended after the first episode of hepatic encephalopathy.[18]
- *Esophageal varices* form in response to increased intraportal pressures with splanchnic vascular dilation. Varices can spontaneously rupture and are associated with life-threatening gastrointestinal bleeding. Patients with newly diagnosed cirrhosis should undergo a screening endoscopy to assess for esophageal varices. Timing of ongoing surveillance varies and depends on endoscopy findings.

Patients also may seek consultation for dermatologic manifestations of liver disease such as spider angioma, palmar erythema, or pruritus.

Diagnostic approach Although liver biopsy is considered the gold standard test, it is possible to diagnose cirrhosis caused by chronic viral hepatitis by review of viral serologies, physical examination notable for stigmata of chronic liver disease, and/or cross-sectional imaging. As liver disease progresses, laboratory results consistent with decreased synthetic function of the liver may include an elevated International Normalized Ratio with hypoalbuminemia. Thrombocytopenia is suggestive of hypersplenism due to portal hypertension and decreased thrombopoietin produced by the liver. Normal liver function tests do not exclude cirrhosis.

Nonsurgical management With few exceptions, management of cirrhosis is independent of cause. A comprehensive approach involves counseling patients about their disease and prognosis, using evidence-based guidelines to screen for complications, and employing strategies to minimize further decompensation. Patients with cirrhosis also should receive vaccinations against HAV and HBV when applicable, and receive counseling about the importance of avoiding alcohol and hepatotoxic medications.

Liver transplantation According to AASLD guidelines, patients with chronic viral hepatitis should be referred for liver transplant evaluation if they develop decompensated cirrhosis, hepatocellular cancer (depending on size and number of lesions), or have a calculated Model for End-Stage Liver Disease (MELD) score of 15 or greater.[13] The MELD score, calculated using serum INR, total bilirubin, creatinine, and sodium values, was originally developed to predict 3-month mortality for patients with cirrhosis undergoing TIPS, and is used to assess the severity of disease.

For patients undergoing transplant for HCV who have not achieved virologic cure, recurrent infection in the graft is universal. DAA therapy can be considered post-transplant despite immunosuppression. Following transplant for cirrhosis due to chronic HBV, lifelong (suppressive) antiviral therapy is recommended to reduce the risk for development of HBV hepatitis in the allograft.

CONCLUSION

The World Health Organization recently announced a goal of eliminating viral hepatitis as a major public health threat by 2030.[19] Because PAs practice in nearly every clinical setting and specialty, they likely will encounter patients with liver disease due to viral hepatitis, and are appropriately positioned to drive change to achieve this goal. In addition to contributing to public awareness campaigns that support elimination efforts, PAs can promote safe and effective vaccinations that provide long-term protection against HAV and HBV, use screening tools to detect HCV earlier to mitigate patient risk for cirrhosis, and collaborate with specialists to initiate DAA therapy to achieve virologic cure in select patients with HCV. **JAAPA**

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