Chapter 58: Viral Hepatitis

Paulina Deming

UPDATE SUMMARY

Update Summary

May 15, 2023

The following sections, tables, and figures were updated:

- Hepatitis B, Epidemiology: additional information added regarding screening.
- Table 58-10: minor updates are done.
- Hepatitis C, Treatment, Pharmacologic Therapy, Special Populations, Patients with Decompensated Cirrhosis: information for ribavirin treatment added.
- Self-Assessment Questions: questions 9 and 14 updated along with their answers.

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 25, Hepatitis, Viral.

KEY CONCEPTS

KEY CONCEPTS

1. Hepatitis A virus (HAV) is transmitted via the fecal–oral route, most often from ingestion of contaminated food or water, or through contact with an infected person.
2. HAV causes an acute, self-limiting illness and does not lead to chronic infection. There are three stages of infection: incubation, acute hepatitis, and convalescence. Rarely, the infection progresses to liver failure.
3. HAV vaccination is highly effective. There is no pharmacological treatment specifically for HAV; treatment consists of supportive care.
4. Hepatitis B virus (HBV) causes both acute and chronic infection. Chronic infections are responsible for high rates of liver disease, liver cancer, and death.
5. Vaccination can prevent HBV and is the most effective strategy in preventing complications of HBV infections. Prevention of HBV infections focuses on immunization of all children and at-risk adults.
6. The purpose of anti-HBV drug therapy is for viral suppression and immune control and to prevent progression of liver disease and the complications associated with HBV infections.
7. Initial therapy of chronic HBV is with tenofovir or entecavir because these agents have a high barrier to resistance. Therapy is often long term.
8. Patients undergoing immunosuppressive therapy or chemotherapy should be screened for HBV infections and may require HBV therapy to reduce the risks of reactivating their HBV and developing fulminant liver failure.
9. The hepatitis C virus (HCV) is an insidious, blood-borne infection. Universal, one-time screening is recommended for all persons aged 18 and over.
10. Hepatitis C infections can cause significant morbidity (including extrahepatic manifestations) and mortality. Patients with chronic hepatitis C are at risk for end-stage liver disease, cirrhosis, liver transplant, and death as a result of their infection.
11. The goal of anti-hepatitis C virus (HCV) drug treatment is cure. Drug therapy with direct-acting antivirals (DAAs) is highly effective and well tolerated.

BEYOND THE BOOK

BEYOND THE BOOK

Watch “Hepatitis C: Test, Treat, Cure” available at: Npaihb.org/hcv/

This short video includes a review of epidemiology of HCV infections, risks for HCV infection, tests for HCV diagnosis, and patient experiences with HCV as well as with HCV treatment.

INTRODUCTION

The major hepatotrophic viruses responsible for viral hepatitis are hepatitis A, hepatitis B, hepatitis C, delta hepatitis (hepatitis D), and hepatitis E. All share clinical, biochemical, immunoserologic, and histologic findings. Hepatitis A and E are spread through fecal–oral contamination, whereas hepatitis B, C, and delta are transmitted parenterally. Infection with delta hepatitis requires coinfection with hepatitis B. This chapter focuses on

hepatitis A, B, and C.

Viral hepatitis remains a major cause of morbidity and mortality with a significant impact on healthcare costs in the United States. Compared with human immunodeficiency virus (HIV), there are three to five times as many people infected with chronic viral hepatitis. In the United States, a national strategy for the elimination of hepatitis B and C was established by the National Academies of Science, Engineering, and Medicine.[1] Despite the national strategy, many challenges persist in achieving elimination goals. Although unprecedented therapeutic advances occurred for the treatment for hepatitis C; the rates of acute infection are on the rise and challenges in screening and access to treatment persist. Both hepatitis A and B are vaccine preventable, yet many vulnerable patients remain unvaccinated and susceptible to infection.

HEPATITIS A

Hepatitis A virus (HAV) is often a self-limiting and acute viral infection of the liver posing a health risk worldwide. The infection is rarely fatal. According to the Centers for Disease Control and Prevention (CDC), rates of reported cases of acute clinical HAV infection in the United States were declining until multi-state outbreaks were reported in 2013 and 2016. Since 2016, 38 multi-state outbreaks were reported with an increase of over 1,300% in the number of acute cases. As of May 2021, nearly 40,000 cases were reported with a 61% hospitalization rate and 374 deaths.[2]

Epidemiology

1 Infection primarily occurs through the fecal–oral route, by person-to-person, or by ingestion of contaminated food or water. HAV's prevalence is linked to resource-limited regions and specifically to those with poor sanitary conditions and overcrowding. Travel to areas with poor sanitation poses a risk for travelers. In areas with good sanitation and hygiene, HAV outbreaks are observed among specific patient groups, such as persons who inject drugs (PWID) and in men who have sex with men (MSM). Household or close personal contacts of an infected person are at high risk for infection. Children can contribute to the spread of the disease because they often remain asymptomatic and are infectious for longer periods of time than adults.

In the United States, recent HAV outbreaks were identified in persons who use drugs, persons experiencing homelessness, and in MSM.[3] Foodborne outbreaks occur with local and widespread outbreaks reported annually. Although HAV infections were previously mostly identified in children, since 2018 adults aged 30 to 39 accounted for the highest number of cases, followed by adults aged 40 to 49.[2] In 2019, HAV rates were highest among White, non-Hispanic males aged 30 to 39. Of patients with a known history of risk factors, 46% were linked with injection drug use. Mortality rates are low and were previously recognized to be most likely in elderly patients with underlying comorbid conditions. However, in 2019 death was most likely to occur in males aged 45 and above.[2] Patients with preexisting chronic liver disease, such as HCV, are at an increased risk of developing fulminant HAV.[4]

Despite low endemic rates and successful vaccination programs in the United States, travel to HAV endemic areas is a recognized risk for acquiring acute HAV infections and includes "standard" tourist itineraries. Rural and backcountry travel or consumption of food or drink in areas of poor sanitation pose the highest travel-related risk.[5]

Etiology

1 Hepatitis A is a nonenveloped ribonucleic acid (RNA) virus in the *Picornaviridae* family. The virus is stable in low pH environments and in freezing to moderate temperatures.[5] Inactivation requires disinfecting with a 1:100 dilution of sodium hypochlorite (bleach) in tap water or heating foods to a minimum of 85°C (185°F) for 1 minute.[5] Chlorination of water also effectively kills HAV in water systems. Transmission occurs primarily through the fecal–oral route because HAV is shed in the feces of infected people.[5] Contaminated water or ice are common modes of transmission, as are any foods which may be prepared using contaminated water including shellfish harvested from contaminated water. Access to clean water and proper handwashing are critical in preventing the transmission of HAV.

Pathophysiology

HAV infection is usually acute, self-limiting, and confers lifelong immunity. HAV's life cycle in the human host classically begins with ingestion of the virus. Absorption in the stomach or small intestine allows entry into the circulation and uptake by the liver. Replication of the virus occurs within hepatocytes and gastrointestinal epithelial cells. New virus particles are released into the blood and secreted into bile by the liver. The virus is then

either reabsorbed to continue its cycle or excreted in the stool. The enterohepatic cycle will continue until interrupted by antibody neutralization.[5]

Clinical Presentation

The incubation period of HAV is approximately 28 days, with a range of 15 to 50 days.[5] Table 58-1 summarizes the clinical features of acute hepatitis. There are no specific distinguishing features of HAV compared to other types of hepatitis; thus, serological testing for immunoglobulin (Ig) M antibody to HAV (anti-HAV) is needed to confirm a diagnosis of acute HAV. In the majority of patients, IgM anti-HAV will be detectable within 5 to 10 days of symptom onset. Symptom severity varies according to age. Children younger than 6 years typically are asymptomatic and can shed the virus for long periods of time, serving as a reservoir for the spread of HAV. Peak fecal shedding of the virus precedes the onset of clinical symptoms and elevated liver enzymes. Acute hepatitis follows, beginning with the preicteric or prodromal period. The phase is marked by an abrupt onset of nonspecific symptoms, some mild.[6] More unusual symptoms include chills, myalgia, arthralgia, cough, constipation, diarrhea, pruritus, and urticaria. The phase generally lasts 2 months.

TABLE 58-1

Clinical Presentation of Acute Hepatitis

	Hepatitis A (HAV)	Hepatitis B (HBV)	Hepatitis C (HCV)
Signs and symptoms	>70% of patients are symptomatic with fever, jaundice, and scleral icterus. Hepatomegaly is evident on physical exam. Less common signs include splenomegaly, skin rash, arthralgia.	Approximately 70% of patients are anicteric or subclinical. Younger patients most likely to be asymptomatic. If symptoms occur, jaundice, dark urine, white stool, abdominal pain, fatigue, fever, chills, loss of appetite, and pruritus are possible.	Approximately 70% of patients are asymptomatic. If symptoms occur, jaundice, dark urine, white stool, abdominal pain, fatigue, fever, chills, loss of appetite, and pruritus are possible.
Laboratory Findings in Acute Phase of Infection			
Aminotransferase (ALT, AST) Elevations	• >1,000 IU/L (16.7 µkat/L) • ALT>AST	• 1,000-2,000 IU/L (16.7-33.3 µkat/L) • ALT>AST	• Highly variable, can be approximately 1,000 IU/L (16.7 µkat/L) • ALT>AST
Bilirubin	Elevated and preceded by aminotransferase elevations	Can be normal or elevated	Elevated and preceded by aminotransferase elevations
Virus Specific Tests	IgM anti-HAV for acute HAV; IgG anti-HAV for prior infection or vaccination	IgM anti-HBc (+), HBsA g (+) for active, acute infection	HCV RNA (+) or quantifiable; HCV antibody reactive within 12 weeks of exposure

ALT, alanine aminotransferase; anti-, antibody; AST, aspartate aminotransferase; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; IU, international units; L, liter.

Liver enzyme levels rise in serum within the first weeks of infection, peaking approximately in the fourth week and normalizing by the eighth week. Conjugated bilirubinemia, clinically evident as dark urine, precedes the onset of the icteric period. Gastrointestinal symptoms may persist or subside during this time and some patients may have hepatomegaly. Duration of the icteric period varies and corresponds to disease duration, averaging between 7 and 30 days.[6]

The diagnosis of acute HAV is made through the IgM anti-HAV which is detectable 5 to 10 days prior to symptomatic HAV infections in the majority of

patients. The IgG anti-HAV replaces IgM and indicates host immunity following the acute phase of the infection.[6] Serological testing is available for IgM anti-HAV, IgG anti-HAV, and total (anti-IgM and IgG) anti-HAV. Patients who have detectable total anti-HAV with a negative IgM have resolved their infection. Concentrations of antibody often fall to 10 to 100 times lower than what would be expected after a natural course of infection. Detectable antibodies may persist for over 40 years. Although a positive anti-HAV result confirms protection, undetectable concentration of anti-HAV may not necessarily imply that protective levels were not achieved.[6] Booster, or challenge doses, may be given after an HAV vaccine series is completed to provide rapid immunity when there is concern for serious infection.[6]

HAV does not lead to chronic infections; however, some patients may experience symptoms for up to 9 months. Rarely, patients experience complications from HAV including relapsing hepatitis, cholestatic hepatitis, and fulminant hepatitis. These severe effects are more likely in patients who are immunocompromised, have underlying liver disease, or are greater than 40 years of age.[6] Fatalities from HAV are generally rare, although more likely in patients older than 50 years and in persons with preexisting liver disease.[6]

A diagnosis of HAV is based on clinical criteria of an 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. Testing for IgM anti-HAV in the absence of symptoms is not recommended.[6] Serologic testing is necessary to differentiate the diagnosis from other types of hepatitis.

Treatment

Desired Outcomes

The majority of people infected with HAV can be expected to fully recover without clinical sequelae.[7] Nearly all individuals will have clinical resolution within 6 months of the infection and a majority will have done so by 2 months. Rarely, symptoms persist for longer or patients relapse. The ultimate goal of therapy is complete clinical resolution. Other goals include reducing complications from the infection, normalization of liver function, and reducing infectivity and transmission. Prevention of HAV infection is important because significant costs are accrued during acute HAV infections, including costs of administration and use of immunoglobulin and vaccine, hospitalizations, and indirect costs from loss of workdays.

General Approach to Treatment

3 Prevention and prophylaxis are keys to managing this vaccine-preventable virus. No specific treatment options exist for HAV infections. Instead, patients should receive general supportive care. The importance of good hand hygiene should be emphasized in preventing disease transmission. Passive immunity with Ig is used for preexposure and postexposure prophylaxis. Active immunity is achieved through vaccination. Vaccines were approved for use since 1995 and implemented in the routine vaccination of children, as well as at-risk adults, to reduce the overall incidence of HAV.[6] Despite HAV vaccine availability, vaccine coverage in adults is low.

Prevaccination serologic testing to determine susceptibility is generally not recommended. In some cases, testing may be cost-effective if the cost of the test is less than that of the vaccine and if the person is from a moderate-to-high endemic area and likely to have prior immunity. Similarly, because of high vaccine response, postvaccine serologic testing is not recommended.[6]

Prevention of Hepatitis A

HAV is easily preventable with vaccination. Because children often serve as reservoirs of the disease, vaccine programs have targeted children as the most effective means to control HAV. Two vaccines for HAV are available and are incorporated into the routine childhood vaccination schedule. The Advisory Committee on Immunization Practices (ACIP) recommends expanding vaccine coverage to all children, including catch-up programs for children not previously vaccinated. Vaccination is also recommended for adults. The recommendations were enacted in the attempt to further reduce HAV incidence rates and possibly to eradicate the virus.[6] Complete HAV vaccination recommendations are available from the CDC (Table 58-2).

TABLE 58-2

Recommendations for Hepatitis A Virus Vaccination

- All children at 1 year of age
- Any unvaccinated children ages 2-18 years
- Persons traveling to or working in countries that have high or intermediate endemicity of infection[a]
- Men who have sex with men
- Users of injection and noninjection drugs
- Persons with occupational risk for infection (eg, persons who work with HAV-infected primates or with HAV in a research laboratory)
- Persons with chronic liver disease including persons with hepatitis B virus infection, hepatitis C virus infection
- All previously unvaccinated persons anticipating close personal contact (eg, household contact or regular babysitter) with an international adoptee from a country of high or intermediate endemicity within the first 60 days following the arrival of the adoptee
- Anyone who would like HAV vaccine

[a]Travelers to Canada, Western Europe, Japan, Australia, or New Zealand are at no greater risk for infection than they are in the United States. All other travelers should be assessed for HAV risk.

Data from Reference 6.

Persons at risk for worse outcomes with HAV infection are also recommended to receive vaccination and include persons over the age of 40, persons with immunocompromising conditions, persons with chronic liver disease planning on traveling, and persons with HIV. In response to the HAV outbreaks beginning in 2016, ACIP revised its vaccination recommendations to persons ≥1 year of age who are at risk for HAV infection including PWIDs, persons experiencing homelessness, MSM, or persons at risk for severe outcomes with HAV infection such as persons with chronic liver disease or persons with HIV. Vaccination is recommended in settings providing services to adults in which a high proportion have risk factors for HAV infection such as healthcare settings with a focus on injection or noninjection drug use, group homes, and non-residential day care facilities for developmentally disabled persons.

Vaccines to Prevent Hepatitis A

The inactivated virus vaccines licensed in the United States are the single-antigen HAVRIX® and VAQTA® and the combination of HAV and HBV antigen vaccine TWINRIX®. Both single-antigen vaccines are available for pediatric (12 months and older) and adult (18 years and older) use, while the TWINRIX® is indicated for adults only (Table 58-3). The differences in the vaccines are in the use of a preservative and in expression of antigen content. VAQTA® is formulated without a preservative and uses units of HAV antigen to express potency. HAVRIX® and TWINRIX® use 2-phenoxyphenol as a preservative and antigen content is expressed as enzyme-linked immunosorbent assay (ELISA) units.[6] High seroconversion rates of more than or equal to 94% are achieved with the first dose; however, VAQTA® and HAVRIX® recommend a booster shot to achieve the highest possible antibody titers. Although seroconversion exceeds 90% for HAV after the first dose of TWINRIX®, the full three-dose series is required for maximal HBV seroconversion. An accelerated dosing schedule of TWINRIX® is available but requires four doses for optimal response. The combined vaccine offers the advantage of immunization against both types of hepatitis in a single vaccine.

TABLE 58-3

Recommended Dosing of Hepatitis A Vaccines

Vaccine	Age (Years)	Dose of Hepatitis A Antigen (Volume)	No. of Doses	Schedule[a]
HAVRIX	1-18	720 ELISA units (0.5 mL)	2	0, 6-12 months
	≥19	1,440 ELISA units (1 mL)	2	0, 6-12 months
VAQTA	1-18	25 units (0.5 mL)	2	0, 6-18 months
	≥19	50 units (1 mL)	2	0, 6-18 months
TWINRIX[b]	≥18	720 ELISA units (1 mL)	3	0, 1, 6 months
	≥18 (accelerated schedule)	720 ELISA units (1 mL)	4	0, 7 days, 21-30 days, +12 months

[a]Zero (0) denotes initial dose, subsequent numbers denote time after initial dose for timing of additional doses.

[b]Combination hepatitis A and B vaccine, also contains 20 mcg of hepatitis B surface antigen and requires a three-dose schedule for adequate HBV response.

Data from Reference 6.

In situations of postexposure prophylaxis, either the vaccine or Ig can be used, although vaccine is preferred because it confers the benefit of long-term immunity against HAV. In patients older than 40 years or with underlying medical conditions, vaccine experience is limited, thus vaccine and immunoglobulin may be preferred for optimal protection.[5] Both vaccines may be given concomitantly with Ig and the two brands are interchangeable.[6]

Vaccination is recommended for international travel to areas of high or intermediate endemicity and can be given regardless of scheduled dates of departure. For older patients, immunocompromised, or any patients with chronic liver disease or any other chronic medical conditions traveling within 2 weeks, both Ig and vaccine are recommended.[5] Vaccination is preferred because it confers long-term protection.

The most common side effects of the vaccines include soreness and warmth at the injection site, headache, malaise, and pain. More than 65 million doses of the HAV vaccine have been administered and despite routine monitoring for adverse events, there are no data to suggest a greater incidence of serious adverse events among vaccinated people compared with nonvaccinated. The vaccine is considered safe.[4–6]

Post serological testing after vaccination is not recommended due to the high efficacy of vaccination. However, anti-HAV levels can be measured against a World Health Organization (WHO) standard. Although the lowest level of protective anti-HAV has not been established, a general standard is ≥10 mIU/mL (IU/L).[6]

Immunoglobulin

Immunoglobulin (Ig) is a sterile preparation of concentrated antibodies against HAV that provides protection by passive transfer of antibody. In 2017, recommendations for increased dose of Ig were established due to concerns for declining HAV antibody from donors. Active immunity is achieved through vaccination, although preexposure prophylaxis is used in situations where protective effects of vaccine may either be inadequate or take too long to develop. Specifically, Ig is recommended with vaccination if travel to an HAV high or intermediate risk country will begin in <2 weeks and the individual is an older adult, immunocompromised, or has chronic liver disease or other chronic medical condition. Ig is used when preexposure or postexposure prophylaxis against HAV infection is needed in persons for whom vaccination is not an option. Vaccination is preferred for multiple reasons, including that it induces active immunity and, therefore, a longer time of protection against HAV than Ig.

Immunoglobulin is most effective if given in the incubation period of the infection. Receipt of Ig within the first 2 weeks of infection will reduce

infectivity and moderate the infection in 85% of patients. Patients who receive at least one dose of the HAV vaccine at least 1 month prior to exposure do not need preexposure or postexposure prophylaxis with Ig.[6] Although Ig is available as both an intravenous (IV) and intramuscular (IM) injection, for HAV exposure only the IM formulation is used.

Serious adverse events from Ig are rare. Anaphylaxis has been reported in patients with IgA deficiency. Patients who had an anaphylaxis reaction to Ig should not receive it. There is no contraindication for use in pregnancy or lactation.

Dosing of Ig is the same for adults and children. For postexposure prophylaxis and for short-term preexposure coverage of less than 3 months, a single dose of 0.02 mL/kg IM is given. For long-term preexposure prophylaxis of less than or equal to 5 months, a single dose of 0.06 mL/kg is used. Either the deltoid or gluteal muscle may be used. In children younger than 24 months, Ig can be given in the anterolateral thigh muscle.[6]

Vaccination is also preferred in most patients who were recently exposed to HAV and who had not been previously vaccinated. In contrast, prophylaxis with Ig may be preferred in patients younger than 12 months or who have an allergy to a vaccine component.[5]

Ig can be given concomitantly with the HAV vaccine. Although the antibody titer will be significantly lower than with the vaccine administered alone, the response is still protective and coadministration should be considered for the advantages of long-term HAV protection. However, Ig can interfere with the response of other live- attenuated vaccines and should be delayed.

Vaccine efficacy may be reduced in certain patient populations. In HIV-infected patients, greater immunogenic response may correlate with higher baseline CD4-cell counts. Patients with lower CD4 counts or HIV viremia at vaccination have a reduced response rate.[7]

HEPATITIS B

4 Viral hepatitis B infections pose a substantial global disease burden. Hepatitis B is highly infectious, approximately 50 to 100 times more so than HIV.[8] In 2015, 3.5% of the population, or 257 million people, had chronic HBV. In comparison, 0.8% of the adult population, or 38 million people, were living with HIV. Screening and diagnosis also vary between the two viral infections; only 10% of patients with chronic HBV are aware of their infection in comparison to 79% of people living with HIV.

Globally, the majority of adults with chronic HBV were infected prior to the availability and use of the HBV vaccine in infancy.[9,10] Chronic infection with HBV is a major public health issue as it serves as a reservoir for continued HBV transmission and poses a significant risk of death resulting from liver disease including liver cirrhosis and hepatocellular carcinoma (HCC). According to the WHO, 650,000 people per year die as a result of complications from HBV.[9] In the United States, there is no national chronic hepatitis surveillance program; however, estimates suggest between 850,000 and 2.2 million people have chronic HBV.[1] Although HBV infection is uncommon among the general population in the United States, prevalence is high among certain groups.

Low public awareness, low perceived risk, and misinformation about HBV can result in discrimination and stigma.[1] In 2013, the Department of Justice recognized patients with chronic HBV infection to be protected under the Americans with Disabilities Act after students with HBV were denied enrollment in health professional schools. Although not curable, HBV infections can be successfully managed with viral suppression. Importantly, vaccination prevents HBV infection. In 2021, the CDC's ACIP recommended universal HBV vaccination for all adults aged 19 to 59.

Epidemiology

According to the WHO, chronic HBV infections disproportionately affect low- and middle-income countries.[9,10] Prevalence can vary regionally; however, areas commonly associated with high infectivity rates include sub-Saharan Africa, East Asia, followed by the Amazon and southern parts of Eastern and Central Europe.[10] Most new HBV infections are in children in areas of high HBV prevalence, approximately 45% of the global population. Infections of infants and children are of special concern because more than 90% of cases lead to chronic infections and serve as ongoing source of infectivity. Major public health initiatives focused on pediatric vaccination have successfully reduced HBV infection. In the United States, acute HBV cases declined by approximately 90% since vaccination recommendations were first issued in the 1980s.[11] Annual rates of acute cases vary but in 2019, the number of new HBV cases was 20,700. Substantial increases in the number of cases of acute HBV were first reported in 2016 and were attributed to injection drug use and the opioid epidemic. The highest rates of acute HBV continue to be among White non-Hispanic or Black non-Hispanic men between the ages of

30 to 49 years.[2] Injection drug use continues to be the most commonly identified risk factor for new HBV infections, followed by sexual contact.

HBV is transmitted sexually, parenterally, and perinatally because concentration of HBV is high in blood, serum, and wound exudates of infected persons. The virus can be stable in the environment for at least 7 days and can cause infection during this time. Even in the absence of visible blood, HBV can cause infection and transmission may occur through the reuse of contaminated needles, syringes, or sharp objects. In areas of high HBV prevalence, perinatal transmission from mother to child at birth is most common. Horizontal transmission, such as from an infected child to an uninfected child, is also common. In the United States, injection drug use and sexual contact continue to be key routes of transmission although a large percentage of patients with acute HBV had no identified risk factor. [10] In 2023, the CDC recommended HBV screening for all adults aged 18 and older and least once and for all pregnant people during each pregnancy. The recommended tests for screening are anti-HBs, HBsAg, and total anti-HBc. Periodic screening is also recommended for persons at increased risk of HBV infection, including persons who are incarcerated, have a history of sexually transmitted infections or multiple sex partners, and people with HCV (Table 58-4).[11]

TABLE 58-4

Persons at High Risk for HBV

Individuals from the Following Areas	Other Groups
• Africa (all countries) • Asia (all countries in North, Southeast, East Asia) • South Pacific Islands (all countries except Australia and New Zealand) • Middle East (all countries except Cyprus and Israel) • Malta • Spain • Arctic (indigenous populations of Alaska, Canada, Greenland) • South America (Ecuador, Guyana, Suriname, Venezuela, and Amazonian areas) • Central America (Mexico, Guatemala, and Honduras) • Eastern Europe (all countries except Hungary) • Caribbean (Antigua-Barbuda, Dominica, Granada, Haiti, Jamaica, St. Kitts and Nevis, St. Lucia, Turks and Caicos)	• US-born persons not vaccinated as infants whose parents were born in high HBV endemic regions • Household, needle-sharing, and sexual contacts of HBsAg-positive patients • Infants born to HBsAg-positive mother • Persons who have ever injected drugs • Persons with multiple sex partners • Persons seeking evaluation or treatment for an STD • Men who have sex with men • Inmates of correctional facilities • Individuals with chronic liver disease • Individuals with elevated AST or ALT of unknown etiology • Individuals with HIV • Individuals with HCV • Patients with end-stage kidney disease including those receiving dialysis • All pregnant women • Persons requiring immunosuppressive therapy (chemotherapy, organ transplantation, rheumatological, or gastroenterologic) • Donors of blood, plasma, organs, tissues, or semen • Residents/staff of facilities for developmentally disabled persons • Travelers to countries of high or intermediate HBV prevalence • Healthcare, public safety workers at risk for occupational exposure to blood or blood-contaminated body fluids • Persons who may require postexposure prophylaxis following blood or fluid exposures

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBsAg, hepatitis B surface antigen; STD, sexually transmitted disease.

Data from Reference 11.

Up to half of all children infected before the age of 6 will develop chronic HBV.[9] Children infected in the first year of life have a 90% likelihood of developing chronic HBV infection; thus, prevention of perinatal transmission and pediatric vaccination is critical.

Etiology

The HBV is a deoxyribonucleic acid (DNA) virus that infects hepatocytes.[12] There are at least 10 HBV genotypes (GTs) (A-J) with distinct geographic and ethnic distribution. Although particular HBV GTs can affect the course of HBV infections, testing for HBV GT is not recommended for clinical practice.[13]

Pathophysiology

On infection, replication of the virus begins by attachment of the virion to the hepatocyte cell surface receptors. The virion contains an internal capsid shielding a partially double stranded DNA which is released within the hepatocyte nucleus and integrates into the host chromosomal DNA.[12] In the nucleus the DNA is converted into closed, circular DNA that serves as a template for pregenomic RNA to transcribe various viral proteins and begins the viral life cycle. The viral genome has four reading frames coding for various proteins and enzymes required for viral replication. Several of these proteins are used diagnostically (Table 58-5).

TABLE 58-5

Interpretation of Serologic Tests in Hepatitis B Virus

Tests	Result	Interpretation
HBsAg	(–)	Susceptible
Anti-HBc	(–)	
Anti-HBs	(–)	
HBsAg	(–)	Past HBV infection, resolved
Anti-HBc	(+)	No further management needed unless undergoing immunosuppressive therapy or chemotherapy
Anti-HBs	(+)	
HBsAg	(–)	Immune because of vaccination (valid only if test performed 1-2 months after third vaccine dose)
Anti-HBc	(–)	
Anti-HBs	(+)	
HBsAg	(+)	Acute infection
Anti-HBc	(+)	
IgM anti-HBc	(+)	
Anti-HBs	(–)	
HBsAg	(+)	Chronic infection
Anti-HBc	(+)	Further evaluation needed
IgM anti-HBc	(–)	
Anti-HBs	(–)	
HBsAg	(–)	Possible interpretations: (1) Resolved infection or (2) false positive. If patient immunocompromised, check
Anti-HBc	(+)	HBV DNA[a]
Anti-HBs	(–)	

[a]Some patients may experience occult HBV infection, defined by the presence of low-level HBV DNA levels in the setting of negative HBsAg.

Note: Unless otherwise specified, anti-HBc includes total (both IgM anti-HBc and IgG anti-HBc) or IgG anti-HBc. IgM anti-HBc is present during acute phase of infection.

Anti-, antibody; HBc, hepatitis B core; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen.

Data from References 12.

The hepatitis B surface antigen (HBsAg) is the most abundant of the three surface antigens and is detectable at the onset of clinical symptoms. Its

persistence past 6 months after initial detection corresponds to chronic infection and indicates an increased risk for cirrhosis, hepatic decompensation, and HCC. Patients with detectable HBsAg are considered to have active HBV infection. The loss of HBsAg (defined as negative or non-reactive HBsAg) is a goal of therapy and considered an optimal endpoint because it indicates that viral replication and protein expression is suppressed. The loss of HBsAg may occur with or without the development of antibody to HBsAg (anti-HBs).[13]

The precore polypeptide encodes for the secretory protein hepatitis B e-antigen (HBeAg) and the hepatitis B core antigen (HBcAg) proteins. HBeAg is present in an acute infection. In children, HBeAg is responsible for chronic HBV infection because it promotes immune tolerance to HBV.[12] In patients where HBeAg is replaced by antibodies (anti-HBe), the HBV DNA is undetectable, and alanine aminotransferase (ALT) levels normalize, the HBV infection is considered to be resolving. If after a year the patient continues to have HBeAg seroconversion (HBeAg is replaced by anti-HBe), the HBV DNA remains undetectable and the ALT levels remain in the normal range, antiviral therapy may be discontinued with close follow to monitor for HBV reactivation.[14]

The HBcAg is a nucleocapsid protein that, when expressed on hepatocytes, promotes immune-mediated cell death. It is not readily detectable by current laboratory techniques, instead antibodies to HBcAg (anti-HBc) are used for diagnostic purposes. High levels of antibodies (IgM anti-HBc) are detectable during acute infections. Patients who were infected with HBV at any point will be anti-HBc positive (either as total or IgG anti-HBc). Patients who respond to vaccine will have anti-HBs only.[10]

Some patients can have HBeAg negative chronic HBV infections. Due to substantial genetic variability of HBV and propensity for viral mutation, there are viral mutants that have down-regulated expression of HBeAg without affecting viral replication.[12] HBeAg-negative mutants pose a particular clinical challenge because they are refractory to treatment and have been implicated in acute liver failure.[12] Patients with HBeAg-negative mutants will continue to have detectable HBV DNA.

Immune response to HBV affects patient outcomes. In patients who have acute resolving infections, a robust immune response is necessary to quickly neutralize and destroy infected cells before the virus can infect other hepatocytes.[13] Chronic infections are associated with a progressive impairment in immune response. Liver injury is likely caused by secondary, nonspecific inflammation activated by the initial cytotoxic lymphocyte response and as an attempt by the immune system to clear the virus by destroying HBV antigen–presenting hepatocytes. HBV itself is not pathogenic to hepatocytes.[12] Destruction of hepatocytes results in release of circulating, and hence increased ALT levels.

Chronic Hepatitis B Virus

4 Chronic HBV is defined as detectable HBsAg for more than 6 months.[11] Chronic infections can be controlled in many cases, but cure is not possible because the HBV template is integrated into the host genome. The most predictive factor for developing a chronic infection is age. Perinatal infections almost always result in chronic infections because of immune tolerance to the virus. The risk of chronicity declines to less than 5% in adult-onset infections. Importantly, chronic HBV infections are often dynamic and disease progression may not necessarily be sequential.[13]

Clinical Presentation and Phases of Infection

The clinical symptoms and course of an HBV infection are indistinguishable from other types of viral hepatitis (Table 58-1).

During the initial phase of the infection, profuse HBV DNA replication results in high levels of HBV DNA and HBeAg secretion (positive or detectable levels of HBeAg). Patients with HBV >1 million IU/ml (kIU/L) are highly contagious.[13] This phase has been described as “immune tolerant” because hepatic injury is limited.[11] ALT levels remain within normal limits (historically defined as <40 IU/L [0.67 μkat/L]) and no or minimal evidence of fibrosis is seen on liver biopsy.[13] In perinatal or early childhood infections, the phase can persist for years and the likelihood for spontaneous HBeAg seroconversion (loss of HBeAg) is low.[13]

As the immune system responds to HBV-infected hepatocytes, ALT elevants may be intermittent or persist. This immune activity against HBV-infected hepatocytes can lead to liver injury with progression of fibrosis.[11,13] During this time high levels HBeAg and HBV DNA may be present. This phase is more likely in adults and progresses more rapidly.[13] With the increase in immune activity against HBV-infected hepatocytes, the outcome can include HBV DNA suppression. Another scenario where immune response is minimized to the infection is characterized by undetectable or low (<2,000 IU/mL

[kIU/L]) HBV DNA, reactive antibody to HBeAg (anti-HBe positive), and normal ALT. Progression of liver disease is unlikely in this phase if ALT remains persistently normal. However, some patients will not see immune control of HBV.

A less common state, described as HBeAg negative chronic HBV, is characterized by viral mutation. Mutations within the virus result in loss of HBeAg production but viral replication is not affected and HBV DNA levels range from moderate to high. ALT levels can also fluctuate or be elevated and patients have more advanced liver disease. Guidelines recognize this mutation in HBV with a lower threshold for initiating HBV treatment.

An uncommon but important clinical state is the "occult HBV infection," where HBcAg (anti-HBC) antibody is positive with negative HBsAG, yet HBV DNA is present, frequently in low levels. Patients may or may not have detectable anti-HBs and the ALT levels are often within normal limits. The risk of ongoing liver damage is minimal unless HBV reactivation occurs, such as if a patient is started on immunosuppressive therapies which may allow rapid increases in HBV replication.[14–16]

Reactivation of hepatitis B, defined as the recurrence or abrupt rise in HBV replication by an increase in serum HBV DNA of at least 1 $\log_{10}$ and a marked increase in transaminase levels, is well described in the literature in patients receiving cancer chemotherapy, steroids, and other immunosuppressive agents.[15,16] Reactivation is the loss of HBV immune control and can occur in anyone with a prior or current HBV infection, but patients who are HBsAg positive are at particular risk. Patients who are HBsAg positive and undergoing treatment with B-cell depleting agents (eg, rituximab), anthracycline derivatives (eg, doxorubicin), or moderate-to-high dose steroid therapy (10-20 mg per day of prednisone or equivalent for 4 weeks or longer) are considered high risk for reactivation.[15] Risk of reactivation is especially high among patients undergoing B-cell depleting therapy (eg, rituximab), where reactivation can occur even in the setting of HBsAg negativity but anti-HBc positivity.[15] Antiviral prophylactic therapy is often indicated to prevent reactivation and continued for at least 6 months, or at least 12 months for B cell–depleting agents, after discontinuation of immunosuppressive therapy.[15]

Cirrhosis

Cirrhosis results as the liver attempts to regenerate while in an environment of persistent inflammation, such as HBV or HCV infections. The development of cirrhosis is mostly insidious and patients can remain stable for years before disease progression. Most patients with compensated cirrhosis either are asymptomatic or have mild symptoms of epigastric pain. The diagnosis is made by laboratory or imaging findings. A decline in albumin, increase in bilirubin, and/or increase in prothrombin time (PT)/international normalized ratio (INR), and/or evidence of portal hypertension (thrombocytopenia) typically demonstrate a gradual decline in synthetic function as blood perfusion through the liver is affected. On imaging, the classical appearance of a small and knobby liver reflects nodules of regenerating cells integrated with infiltrates of inflammation-induced fibrous tissue. Progression of liver disease is variable and affected by both viral and host factors; in particular, the immune response to HBV plays a key role in clinical outcomes (Table 58-6). Patients without cirrhosis have a 5% to 20% risk of progression to cirrhosis over a 5-year period. Subsequently, 20% of all patients with chronic hepatitis B infection and cirrhosis progress to decompensated cirrhosis within a 5-year period.[13] Progression to decompensated cirrhosis is marked by the development of clinical complications of hepatic insufficiency and portal hypertension such as ascites or hepatic encephalopathy. Risks for death and decompensation increase with underlying liver disease. All patients with cirrhosis, irrespective of severity or receipt of HBV treatment, are at an annual risk of developing HCC and require routine surveillance for HCC as per guidelines.[11]

TABLE 58-6

Factors Associated with Hepatitis B Virus Cirrhosis and Risk of HCC

Host Factors	Viral Factors
Older age at diagnosis	Persistence of high HBV serum DNA and or HBsAg levels
African ancestry (greater likelihood for early onset HCC)	Infection with genotype C > B
Asian ethnicity	Specific HBV mutations
Alcohol misuse	
Chronic coinfection with HCV, delta hepatitis, or HIV	
Diabetes or metabolic syndrome	
Active smoking	
Family history of cirrhosis/HCC Presence of cirrhosis (as a risk for HCC)	

Data from References 13 and 17.

Hepatocellular Carcinoma

HBV is a known risk factor for the development of HCC and in areas of high HBV endemicity, a major complication of the infection.[9] There is a known annual risk of developing HCC in patients with cirrhosis because of the years of inflammatory processes provoked by ongoing HBV infection. Several factors influence the development of HCC (Table 58-6), in particular, the presence of cirrhosis. In the United States, the majority of cases of HCC are in patients >60 years of age, male, with cirrhosis, and of Asian race. Patients of African ancestry are more likely to develop HCC at a younger age (median 44 years).[17] HBV itself is an oncogenic virus and HCC can occur in patients with HBV who do not have cirrhosis.[9]

Vaccine Prevention of Hepatitis B

5 Vaccination is the most effective strategy to prevent HBV infection. Despite substantial declines in HBV, gaps in HBV vaccination persist that contribute to ongoing HBV transmission. Birth dose vaccination of infants born to HBsAg-positive women remains below target levels.[18] Similarly, the three-dose vaccine coverage for adults, including patients with chronic liver disease, travelers, persons with diabetes, and healthcare personnel, are lower and far below target levels.[18] Vaccination for HBV is less effective than for HAV and requires multiple doses for improved response. Many patients start a vaccine series but do not complete it. All infants and all previously unvaccinated children less than 19 years of age should receive HBV vaccine. Additionally, in 2021 ACIP voted to recommend universal HBV vaccination for all adults aged 19 to 59. Adults 60 and older are recommended for vaccination based on risk factors (Table 58-7).

TABLE 58-7

Risk Factor-Based Vaccine Recommendations for Adults 60 and Older

- Sex partners of persons who are HBsAg positive
- Sexually active persons not in a long-term monogamous relationship (>1 partner/6 months)
- Men who have sex with men
- Persons seeking evaluation or treatment for sexually transmitted infection
- Persons with HIV
- Current or recent injection drug use
- Household contacts of persons with chronic hepatitis B infection; clients and staff of institutions for the developmentally disabled
- Healthcare and public safety workers with anticipated risk for exposure to blood or blood-contaminated fluid in the workplace
- Chronic dialysis/ESRD patients including predialysis, peritoneal dialysis, and home dialysis patients
- Correctional facilities inmates
- International travelers to regions with high or intermediate levels (HBsAg prevalence >2%) of endemic HBV infection
- Persons with chronic HCV infection
- Persons with chronic liver disease (eg, patients with alcoholic liver disease, cirrhosis, fatty liver disease, autoimmune hepatitis)
- All unvaccinated adults seeking vaccination (specific risk factor not required)

ESRD, end-stage renal disease.

Data from Reference 18,19.

The development of the HBV vaccine represented the first vaccine against a major human cancer.[9] Vaccines use HBsAg to prompt active immunity. The HBsAg is produced using recombinant DNA technology using yeast. The HBsAg itself is not infectious; only the complete HBV is infectious. Available vaccines include HBV antigen only products and combination products. The two single-antigen products are Recombivax® HB and Engerix-B®. The PreHevbrio™ vaccine, approved in 2021, contains three hepatitis B surface antigens to elicit a more robust vaccine response. TWINRIX® is a combination vaccine for HAV and HBV in adults. Comvax® and Pediarix® are used for children along with other scheduled vaccines. Unlike the HAV vaccine, the HBV vaccine response is generally lower and often requires at least three doses for optimal protection. Most vaccines use aluminum as an adjunct; however in 2017 the Food and Drug Administration approved the Heplisav-B® vaccine which uses a novel adjuvant for immunogenicity, a toll-like receptor ligand to enhance immunity that allows for a two-dose vaccine schedule in adults (Table 58-8).

TABLE 58-8

Recommended Dosing of Hepatitis B Vaccines (HBV Antigen Vaccines)

Vaccine	Age (Years)	Dose (Volume)	No. of Doses	Schedule[a]
Engerix-B	0-19	10 mcg IM (0.5 mL)	3	0, 1, 6 months
	>20	20 mcg IM (1 mL)	3	0, 1, 6 months
Recombivax	1-19	10 mcg IM (0.5 mL)	3	0, 1, 6 months
	>20	10 mcg IM (1 mL)	3	0, 1, 6 months
Heplisav-B[b,c]	≥18	0.5 mL	2	0, 1 months
PreHevbrio[c]	≥18	1 mL	3	0, 1, 6 months

[a]Zero (0) denotes initial dose, subsequent numbers denote time after initial dose for timing of additional doses.

[b]Utilizes different adjuvant; cannot be interchanged with other HBV vaccines.

[c]Cannot be interchanged with other HBV vaccines.

Data from Reference 6.

The most commonly reported adverse events for single-antigen vaccine are nausea/dizziness, and fever/headache; for combination vaccines, fever, injection site erythema, and vomiting. For Heplisav-B, the most common adverse reactions reported within 7 days of vaccination included injection site pain, fatigue, and headache.

Vaccination is the standard for HBV prevention. Passive immunity with hepatitis B Ig offers temporary protection against HBV and is used in conjunction with the hepatitis B vaccine for postexposure prophylaxis in infants born to HBsAg-positive mothers and for select other prophylaxis.[11]

Treatment

Desired Outcomes

Prevention of HBV, in particular preventing mother-to-child transmission, is a primary goal with substantial public health benefits. HBV infections are not curable; thus, the goals of therapy are to suppress HBV replication and prevent disease progression to cirrhosis and HCC. Another important goal is preventing HBV reactivation in patients with inactive HBV infections.

General Approach to Treatment

HBV viral suppression is a goal of all therapies.[13] In patients who are HBeAg positive, HBeAg loss, with or without seroconversion to anti-HBeAg, indicates immune control. Normalization of ALT is another goal associated with viral suppression. An ultimate goal of therapy is the loss of HBsAg with or without anti-HBs seroconversion. This is a goal not often realized but one associated with suppression of HBV replication and viral protein expression and indicates antiviral therapy that can be safely discontinued.

Indications for treatment consider HBV DNA levels, ALT levels, and whether or not the patient has cirrhosis (Table 58-10). All patients with cirrhosis require HBV treatment, irrespective of DNA or ALT levels. In patients without cirrhosis, HBV DNA and ALT levels can determine the need for treatment because active viral replication predicts disease progression.[13] In persons without cirrhosis, elevated ALT levels are used to recognize inflammation

within the liver and thus the need for HBV treatment to minimize disease progression. Not all persons with chronic HBV are candidates for treatment. Persons without cirrhosis who have low levels of HBV DNA (<2,000 IU/mL [kIU/L]) may be managed by periodic monitoring. The rationale for deferring HBV treatment includes the concern that therapeutic response is unlikely and does not outweigh the risks and costs associated with treatment. The major organizations providing comprehensive guidelines on the management of HBV infections are the WHO, American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver, and the Asian Pacific Association for the Study of the Liver. A more simplified approach to treatment for primary care providers is also available through the online resource from the HBV Primary Care Workgroup (https://www.hepatitisb.uw.edu/page/primary-care-workgroup/guidance).

TABLE 58-10

Generally Accepted Criteria for Treatment of HBV

Characteristics:

Anyone with active HBV defined as: HBsAg positive (with HBeAg [+] or HBeAg [−])

- HBV DNA >2,000 IU/mL (kIU/L)
- ALT 2 × upper limit of normal[a] and/or with evidence of histological disease[b]

Anyone with compensated or decompensated cirrhosis with any HBV DNA level[c]

Anyone not fulfilling above criteria with ALT < 2 × ULN and any detectable HBV DNA (<2,000 IU/mL [kIU/L]), consider:

- Patient's age (especially age >40 years)
- Family history of HCC or cirrhosis
- Prior history of HBV treatment
- Extrahepatic manifestations of HBV

[a]Per European guidelines, any elevations in ALT.

[b]Moderate or greater fibrosis as determined by biopsy or noninvasive measures.

[c]Per AASLD 2018 guidelines, HBV DNA level >2,000 IU/mL (kIU/L).

Patient Counseling and Nonpharmacologic Therapy

All persons with chronic HBV should be counseled on preventing disease transmission. Sexual and household contacts should be vaccinated against HBV. Barrier protection methods are recommended for sex partners who have not completed vaccination series.[11] Concomitant metabolic syndrome and insulin resistance increase hepatic liver disease progression and the development of HCC.[20,21] Other lifestyle factors known to potentiate liver disease include alcohol use and smoking.[11,20] Herbal medicines are an intriguing option to many patients, although no data support their use and some may have harmful effects on liver function.

Pharmacologic Therapy

HBV virological cure, or HBV virus eradication, is not an achievable goal of therapy because of persistence of the closed, circular DNA in hepatocytes and lifelong risk for HBV reactivation. Instead, the loss of HBsAg and the development of anti-HBs is considered a "functional cure" because it indicates a loss of HBV replication. This is a rare event even in patients on HBV therapy and rarely occurs spontaneously in the absence of HBV therapy.[10]

Because hepatic damage is sustained by ongoing viral replication, drug therapy aims to suppress viral replication by either antivirals—the nucleos(t)ide agents (NAs)—or immunomodulating agents. A major difference in therapy between the NAs and the immune-mediating agents is duration of use: interferon (IFN)-based therapies are typically administered for a predefined duration, whereas NAs are used until a specific end point is achieved. Antiviral agents are the preferred therapy for several reasons, including that they are all oral agents, are well tolerated, and can be safely used even in patients with decompensated cirrhosis.[22]

The preferred NAs are those considered to have a high barrier to resistance and include entecavir, tenofovir diprovoxil, and tenofovir alafenamide. All of these agents also have some level of activity against HIV; thus, it is important to understand a patient's HIV status before starting HBV therapy.

In the United States, the immune-mediating agents approved for use are pegylated interferon (peg-IFN)-alfa and IFN-alfa. These agents are injectable. Due to the substantial side effects, need for monitoring, and toxicities of IFN-based therapies, their role in HBV treatment is limited. IFN is not recommended as a first-line therapy by the WHO.[9]

Entecavir

Entecavir is an oral guanosine analogue that inhibits the HBV polymerase, thus preventing HBV replication. It has weak activity against HIV.[9] Entecavir is considered to be a first-line agent for HBV therapy because of its efficacy and low rates of resistance.[8,11–13] It is more potent than lamivudine and adefovir in suppressing serum HBV DNA levels, improving liver histology, and normalizing ALT levels.[9] Rates of HBeAg seroconversion increase with subsequent years of treatment.[13] The dose is 0.5 mg orally daily for adults with treatment-naïve or non–lamivudine-resistant infections and 1 mg daily in lamivudine-experienced patients or patients with decompensated cirrhosis. Entecavir resistance remains low in treatment-naïve persons, demonstrating the high barrier to resistance of the drug.[13] However, resistance to lamivudine is a risk factor for entecavir resistance; thus, guidelines do not recommend use of entecavir in patients with prior lamivudine experience.[11] Entecavir is safe and well tolerated.

Tenofovir

Due to its high barrier to resistance, tenofovir is considered a first-line therapy in the treatment of HBV.[11,13] For HBV, it is available as a single-agent oral tablet. Tenofovir is a nucleotide analog which competitively inhibits HBV polymerase, thus interrupting viral replication. There are two forms of tenofovir available: tenofovir disoproxil fumarate (tenofovir DF) and tenofovir alafenamide. Tenofovir DF is available as a 300-mg dose for HBV. Tenofovir alafenamide is a prodrug converted to the active tenofovir in the hepatocyte, allowing for a lower dose at 25 mg. Tenofovir DF was used for HBV where it was highly effective in HBV DNA viral suppression demonstrating regression of fibrosis.[11,23] It is effective even in patients previously treated with other HBV therapies. Tenofovir DF is associated with acute renal injury and hypophosphatemia, thus renal function should be monitored before and during treatment.[11] It is also associated with decreased bone mineral density. In persons with suspected tenofovir DF renal or bone disease, HBV treatment should be switched to entecavir or tenofovir alafenamide.

Tenofovir alafenamide offers several advantages over tenofovir DF as it allows more efficient delivery of tenofovir directly to the hepatocytes and thus a more direct action against HBV replication. In both HBeAg-positive and HBeAg-negative patients, tenofovir alafenamide was as effective as tenofovir DF and was more likely to result in normalization of ALT.[24] The ability to reduce the systemic exposure to tenofovir allows for an improved safety profile. Compared to tenofovir DF, tenofovir alafenamide demonstrated improved bone safety and smaller changes in estimated glomerular filtration rates.[24]

Resistance to tenofovir has not been seen in clinical studies. No resistance was identified to tenofovir DF through a 7-year study period and viral suppression was seen in nearly all patients, regardless of HBeAg status.[23] Similarly, there was no resistance to tenofovir alafenamide with 96 weeks of follow-up.[25]

Alternative Drug Treatments

Other available NAs which have a low barrier to resistance and are thus not preferred for treatment of HBV include lamivudine, telbivudine, and adefovir.[11] Lamivudine has antiviral activity against both HIV and HBV but is not recommended as first-line therapy for chronic HBV infections. The main limitation to lamivudine use is its likelihood for resistance, which is considered inevitable and can undermine the value of treatment. Adefovir's role in HBV therapy is unclear. It is no longer recommended as monotherapy because it also has a relatively low barrier to resistance. Telbivudine is similar to lamivudine and also has a high rate of mutations that limits its efficacy. It has been discontinued in the US market. Combination therapy has been proposed for chronic HBV treatment; however, it is not recommended for initial HBV treatment.[13] Patients who are treatment adherent but have incomplete HBV DNA viral control on entecavir or tenofovir DF/tenofovir alafenamide should be switched to the other drug. In rare instances combination therapy can be considered, such as if adherent patients continue to have suboptimal HBV DNA viral suppression or in patients with

multiple underlying HBV resistance mutations.[11,13,26] If combination therapy is considered, guidance should be sought from a clinician with expertise in HBV treatment.

Special Populations

Cirrhosis

All patients with cirrhosis should receive HBV treatment irrespective of HBV DNA, HBeAg status, or ALT elevations. The presence of cirrhosis is a risk for worsening complications of end-stage liver disease thus an independent reason to initiate HBV treatment. Patients with decompensated cirrhosis should be on HBV therapy and evaluated for liver transplant.[11] Recommended therapies in patients with decompensated cirrhosis include entecavir and tenofovir DF. There are no data using tenofovir alafenamide in patients with decompensated cirrhosis; however, if renal function or bone disease is a concern, it is reasonable to use tenofovir alafenamide. Treatment in these patients is continued indefinitely.[11]

Coinfection with Hepatitis C Virus

Coinfection with HCV increases the progression of liver disease including the risk of HCC; thus, all patients with HBV should be screened for HCV. Moreover, reactivation of HBV can occur in patients undergoing treatment with direct-acting antivirals (DAAs) for HCV and may require HBV prophylaxis.[11,13] The exact mechanism of this is unknown but is primarily a concern in patients undergoing HCV DAA therapy who also have detectable HBsAg. Patients with both HBV and HCV should be evaluated for HBV treatment according to HBV treatment criteria.

Coinfection with Hepatitis D

Infection with hepatitis D requires infection with hepatitis B. No NAs have demonstrated efficacy against HDV; however, IFN does have some efficacy against HDV and treatment may include either IFN monotherapy or a combination of IFN with an NA.[9,13]

Coinfection with Human Immunodeficiency Virus

In HIV-coinfected patients, initiation of highly active antiretroviral therapy (HAART) is strongly recommended as it may improve overall survival. Therapy should include either tenofovir alafenamide or tenofovir DF since both have efficacy against HIV and HBV.[13]

Pediatric Patients

Most children with chronic HBV are asymptomatic and do not meet the established criteria for HBV treatment.[13] Treatment is recommended in HBeAg-positive children aged 2 to 18 who have elevated ALT and measurable HBV DNA.[11] A limitation to the recommendations is a lack of clarity regarding the upper limit of normal for ALT in pediatric patients with guidelines using an upper limit of normal of 35 IU/L (0.58 µkat/L) for males and 25 IU/L (0.42 µkat/L) for females.[11] Entecavir and tenofovir DF are approved for children 2 years and older and are preferred due to their high barrier to resistance. Adefovir and lamivudine are not preferred due to the low barrier to resistance. Although IFN is approved for use in children 1 year and older, its side effect profile and need for injection limit its use.

Chronic HBV in Pregnancy

Perinatal transmission of HBV is a major cause of chronic HBV. In pregnant females who are HBeAg positive and have an HBV DNA >200,000 IU/mL (kIU/L), tenofovir DF is recommended in the third trimester. Tenofovir alafenamide has been shown to prevent transmission with no safety concerns in one small retrospective study, and may be a potential option once additional evidence is available.[27] To prevent mother-to-child transmission, all infants born to HBsAg-positive women should receive HBV vaccination and immunoglobulin within 12 hours of birth.[18] Assessment of HBsAg status, a complete HBV vaccine series, and post-vaccination serological testing to document vaccine response (anti-HBs) is recommended. Revaccination is recommended in infants who are HBsAg negative and do not have a post-vaccination anti-HBs titer ≥10 mIU/mL (IU/L). Infants born to females with an unknown HBsAg status should also receive the first dose of vaccine within 12 hours of birth while maternal serological tests are pending. The rationale for this birth dose vaccination approach is that timely prophylaxis against HBV can disrupt the vertical transmission associated with perinatal HBV infections. Completion of the vaccine series is critical to long-term HBV prevention.

Immunosuppressive or Cytotoxic Therapy

Patients who will undergo chemotherapy or immunosuppressive therapy should be assessed for risk of HBV. The American Gastroenterological Association recommends antiviral prophylaxis for persons who are at high risk of HBV including persons who are (1) HBsAg-positive or negative and anti-HBc-positive and undergoing B-cell depleting agents such as rituximab; (2) HBsAg-positive and anti-HBc-positive treated with anthracycline derivatives such as doxorubicin; (3) HBsAg-positive and anti-HBc-positive undergoing 10 to 20 mg prednisone daily or equivalent therapy or on high-dose (>20 mg prednisone daily or equivalent) corticosteroids for 4 weeks or more.[15,16] Due to moderate risks of reactivation, other immunosuppressive therapies such as tumor necrosis factor alpha inhibitors, cytokine or integrin inhibitors, tyrosine kinase inhibitors, and corticosteroids are also identified as requiring antiviral prophylaxis in patients with specific HBV serological results.[15,16] The CDC recommends testing for hepatitis B for all patients who are to receive chemotherapy or other immunosuppressive agents.

Patients who are at high risk of HBV reactivation and are expected to be on chemotherapy or immunosuppressive treatment for 1 year or less should receive prophylactic HBV antiviral therapy and be treated for at least 6 months after completion of chemotherapy or immunosuppressive therapy.[15]

Hepatitis B Virus Mutations and Resistance Concerns

Although a DNA virus, HBV uses reverse transcriptase, similar to a retrovirus such as HIV. The similarities between HIV reverse transcriptase and HBV polymerase prompted the development of NAs for the treatment of HBV. The preferred therapies have a high barrier to resistance. Resistance potential in HBV is evaluated by an antiviral agent's genetic barrier to resistance, or the number of primary mutations needed for antiviral drug resistance to occur. Other factors include cross-resistance and drug potency. Treatment adherence is important.

Viral resistance in HBV is a concern given HBV's high replication rate and an estimated 10 mutations generated daily.[9–11] Viral suppression is important because the HBV virus mutates and risks the development of resistance when ongoing viral replication occurs in the setting of antiviral drug pressure.

Patients who experience treatment interruptions risk treatment failure because HBV can archive drug-resistant mutations that allow the virus to quickly select the mutation if the antiviral agent is reintroduced. Cross-resistance among antiviral agents also occurs, further limiting therapeutic options. Lamivudine is most commonly associated with resistance due to (1) its low barrier for developing resistance with a single mutation able to overcome efficacy and (2) widespread use of lamivudine in some regions.[9]

Resistance to the NA agents occurs by alteration of the active site of the HBV DNA polymerase. Long-term use of lamivudine is associated with resistance mutations of this active site and cross-resistance occurs which also affects telbivudine.[28] Prior treatment with lamivudine and the expected resistance with ongoing lamivudine therapy is an established risk for entecavir resistance. In these patients with prior lamivudine experience, a tenofovir-based therapy is preferred due to concerns for entecavir resistance. Resistance to tenofovir alafenamide was not identified in clinical trials and is rare is clinical practice.[25]

Guidelines favor the use of entecavir, tenofovir DF, and tenofovir alafenamide because these are potent agents able to suppress viral replication and maintain a high barrier to resistance. However, another major factor in resistance is patient adherence to therapy. Barriers to adherence include forgetting doses, limited understanding of the importance of adherence, and changes to routine.[29]

HEPATITIS C

Approximately 2.4 million people in the United States are chronically infected with HCV.[2] Considering that HCV infection is prevalent in high-risk populations such as prisoners, PWIDs, and homeless individuals, and that this population is generally excluded from most surveys, the actual number of chronically infected people is not known. Routine screening for HCV remains a barrier to diagnosis given the substantial stigma associated with HCV. Most acute HCV infections are asymptomatic. Chronic infections are often insidious, leading to delays in HCV diagnosis and significant disease progression. The current HCV epidemic is linked to the opioid crisis. HCV therapies are curative in the overwhelming majority of patients. These treatments are all-oral and well tolerated with few adverse effects or laboratory abnormalities. However, HCV treatment access is variable and may include a number of stipulations which act as barriers to care and ultimately, the ability to cure HCV.

Epidemiology

9 10 HCV is the most common blood-borne pathogen. Since 2010, the number of acute HCV cases increased, due to both improved surveillance and increase in incidence. There were 50,300 new HCV infections in 2018 compared to 16,500 in 2011.[2] Since 2014, acute HCV cases increased by 71% and most were among people aged 20 to 39. Universal HCV screening is recommended for all persons aged 18 and older by the CDC and the United States Prevention Services Task Force, in an attempt to address this rising epidemic.[30]

Transmission of HCV occurs through percutaneous exposure.[31] Injection-drug use is a major factor in the cycle of HCV transmission and the most common reason for the current increase in new infections. In Indiana in 2015, an outbreak of 135 new cases of HIV among PWIDs identified coinfection with HCV in over 84% of patients.[32] Some experts also consider other illicit drug use, for example, intranasal cocaine, as a risk factor because of the possible contamination of drug paraphernalia not limited to syringes and needles. Unsafe injection practices are associated with HCV transmission and include tattoos received in a nonregulated setting and needle stick injuries. Less common routes of transmission include sexual transmission and infants born to HCV-infected women.[33] Although sexual contact is considered an inefficient means of HCV transmission, anal sex, multiple sexual partners, and coinfection with sexually transmitted diseases, including HIV, increase the risk for HCV sexual transmission. Outbreaks of HCV were demonstrated in MSM with guidelines recommending annual HCV screening for adolescent and adult MSM including HIV-uninfected men seeking HIV preexposure prophylaxis.[31] Blood transfusion posed a major risk for infection, but improved screening of blood in 1992 decreased the risk of transfusion-related HCV.[31] Healthcare-associated transmission is rare; however, unsafe injection practices are often identified as the cause of HCV transmission.

9 The CDC recommends hepatitis C screening at least once in all adults aged 18 and above.[30] More frequent screening is recommended if there are risk factors for infection (Table 58-11). Because of the increase in HCV infections among women of reproductive age, HCV screening should also be done with each pregnancy.[30] The AASLD, in conjunction with the Infectious Diseases Society of America (IDSA), publish online guidelines for testing, managing, and treating HCV (see www.hcvguidelines.org).[31] The AASLD recommends children born to mothers with HCV be screened at or after 18 months of age. More frequent screening is also warranted in persons who are at high risk for infection, especially among PWIDs or who have a history of injection drug use (Table 58-11).[31] Any needle-borne exposure in an unregulated setting poses a risk for infection.

TABLE 58-11

Recommendations for Hepatitis C Virus Screening

All adults ≥18 years

All pregnant females during each pregnancy

Routine periodic testing for persons with ongoing risk factors:

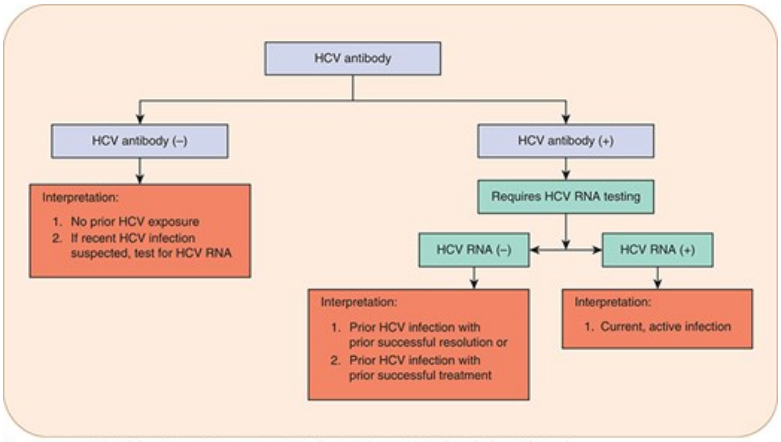
- Persons who inject drugs, share needles, syringes, or other drug preparation equipment
- Persons undergoing maintenance hemodialysis
- Sexually active MSM with HIV
- MSM at initiation of HIV pre-exposure prophylaxis

Data from References 30 and 31.

The initial test for HCV infection is the anti-HCV or antibody test (Fig. 58-1). Patients who are antibody positive for HCV require confirmatory testing for HCV RNA to verify current HCV infection. Some laboratories offer reflex testing where confirmatory testing is done on all samples where the anti-HCV is reactive. Patients who are anti-HCV positive but who do not have a detectable HCV RNA do not have a current HCV infection and no further workup is required in the majority of cases.[34] The presence of antibody does not infer immunity and patients are at risk for HCV infection should they be reexposed.[35]

FIGURE 58-1

HCV testing.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Etiology

HCV is a single-stranded RNA virus notable for lacking a proofreading polymerase which enables frequent viral mutations and poses a challenge for vaccine development.[35] The virus replicates within hepatocytes and, like hepatitis B, is not directly cytopathic. HCV replicates copiously posing an immense challenge for host immune control.[35] Viral mutations can affect DAA therapy.

HCV is differentiated into seven major GTs, numbered 1 to 7. GTs are further classified into subtypes (a, b, c, etc.). The most widely distributed GTs are 1 and 2, with GT1 being the most common. In the United States, GT1a and GT1b, followed by GT2 and GT3, cause most infections. Chronic HCV infection with any of the GTs can lead to cirrhosis, end-stage liver disease (ESLD), or HCC. Preferred therapies on most formularies are those that are pan-genotypic (active against all GTs).

Pathophysiology

In most cases, an acute HCV infection leads to chronic infection. The immune response in an acute HCV infection is mostly insufficient to eradicate the virus. HCV poses a daunting challenge for immune control because of its rapid viral diversification. Resolved cases of HCV are defined by a vigorous T-cell response with highly active CD8 and persistent CD4-cell response. CD8 activity mediates protective immunity but requires the aid of CD4 cells to maintain the response during viral mutations.[35]

Clinical Presentation

In an acute HCV infection, most patients are asymptomatic and thus undiagnosed. HCV RNA is detectable within 1 to 2 weeks of exposure and levels rise quickly during the initial weeks. Approximately one-third of adults will experience some mild and nonspecific symptoms of hepatitis, including fatigue, anorexia, weakness, jaundice, abdominal pain, or dark urine.[36] Acute infections rarely progress to fulminant hepatitis, although the course can be severe and prolonged. Patients who have self-limiting infections may experience symptoms as the immune response attempts to clear the infection. This can result in clinical symptoms and elevated ALT levels. If symptomatic, patients generally see symptom improvement as ALT and HCV RNA levels subside. In patients who are immunosuppressed or have been infected with HCV for less than 6 months, antibody testing could be negative because the immune system is unable or has not yet developed an antibody response. In these cases, confirmation of HCV infection requires HCV RNA testing.[31]

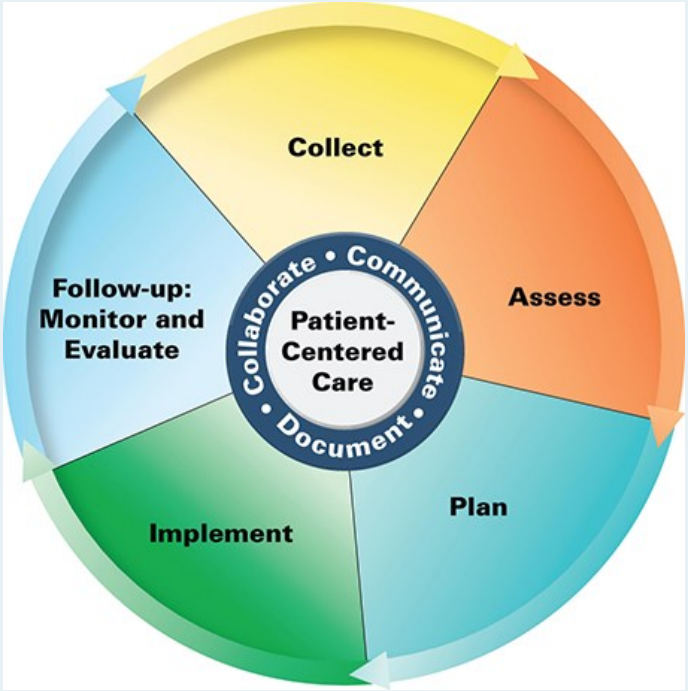
Up to 85% of acutely infected patients will go on to develop a chronic HCV infection, defined as persistently detectable HCV RNA for 6 months or more. HCV RNA levels and ALT levels can fluctuate. Most patients will have few, if any, specific symptoms of chronic HCV infection. Chronic inflammation of the liver from chronic HCV infection may result in fibrosis. Fibrosis is defined by altered hepatic perfusion creating a distorted structure and affecting normal function. Fibrosis leads to cirrhosis, although the speed of fibrosis progression is variable. Patients with cirrhosis require follow-up care specifically for management of the complications associated with cirrhosis. Once a patient is diagnosed with cirrhosis, staging is necessary to differentiate patients who have compensated cirrhosis (Child's class A cirrhosis) versus decompensated (Child's class B or C cirrhosis). Patients with

decompensated cirrhosis generally require management by specialists due to severe liver damage and potential complications.

10 The development of HCV cirrhosis poses a 30% risk over 10 years for the development of ESLD, as well as a 1% to 2% risk per year of developing HCC.[30] Progression to cirrhosis is the primary concern in patients infected with HCV for two decades or longer. Disease progression is not uniform or linear, making it difficult to identify which patients will have progressive liver damage and when. Other concomitant viral infections, comorbidities, and lifestyle factors can contribute to disease progression. Ongoing alcohol use, obesity, and metabolic syndrome can potentiate fibrosis.[31] Viral load is not a factor for disease progression and not associated with degree of fibrosis. Coinfection with HIV or HBV is associated with disease progression as is infection with HCV GT3.[31,37]

10 Although HCV is thought of as a liver disease, chronic HCV is associated with extrahepatic manifestations, or HCV-associated systemic disease. The most common is cryoglobulinemia, a local deposition of immune complexes that cause vasculitis.[31] Typical manifestations involve the skin and internal organ damage, predominantly affecting the kidneys and associated with worsening renal function. Other systemic diseases associated with HCV include cardiovascular disease, diabetes, B-cell non-Hodgkin lymphoma, Sjögren syndrome, glomerulonephritis, arthritis, corneal ulcers, thyroid disease, neuropathies, and skin diseases such as vasculitis, porphyria cutanea tarda, and lichen planus.[38]

Patient Care Process for Hepatitis C



Collect

- Patient history (past medical, family, social) and medical record summary
- Thorough medication history (include prescription, nonprescription medications, and other substances) and drug allergies and intolerances. Previous HCV therapy, if applicable
- Laboratory results (see Table 58-1)
- Laboratory results to assess if patient has cirrhosis (see Table 58-2)
- Abdominal imagining or transient elastography results (if available)

Assess

- Determine if the patient is a candidate for the simplified treatment algorithm (see Table 58-3)
- If the patient has cirrhosis, assess the level of liver dysfunction using the Child-Pugh Score to determine options for HCV therapy
- Review insurance company formulary preferences for HCV therapy
- Review national guidelines for updated treatment recommendations
- Assess if patient assistance programs may be utilized

Plan*

- Determine goals of therapy with monitoring parameters for each goal
- Based on severity of underlying liver disease, determine the appropriate therapy, treatment duration, and monitoring plan
- Counsel patients on avoiding pregnancy and need for contraception during treatment
- Identify potential obstacles to treatment success such as insurance requirements regarding refills
- Check for drug interactions with prescribed medications, any over-the-counter medications, herbals, or supplements

Implement

- Initiate HCV direct-acting antiviral (DAA) therapy
- Discontinue or modify adjunct medications if drug interactions anticipated with HCV DAAs
- Discuss with the patient and patient's family what to expect for monitoring while on therapy, strategies to address any potential adverse effects and strategies to minimize likelihood for therapy interruptions

Follow-Up: Monitor and Evaluate

- Continually reassess patient's use of HCV antivirals, any changes in other medications or herbals and supplements which could compromise HCV therapy, and any adverse effects
- Patients not on the simplified algorithm require monitoring of laboratory tests
- Monitor for any interruptions in therapy which could risk treatment failure
- Evaluate patient for cure at least 12 weeks after completion of therapy
- Reassess patient's risk for reinfection and counsel on harm-reduction strategies

* ***Collaborate with patients, caregivers, and other healthcare professionals.***

Treatment

Desired Outcomes

11 The primary goal of therapy is to eradicate HCV infection. Virologic cure, or sustained virologic response (SVR), is defined as a nondetectable HCV RNA at least 12 weeks after completing HCV therapy. Patients who achieve SVR will continue to have detectable HCV antibody indefinitely. The persistence of HCV antibody should not be confused with the potential to reactivate HCV and it does not confer protection against subsequent exposure to HCV. Patients can be reinfected with the same or different HCV GT. Resolving the infection prevents the development of chronic HCV infection sequelae including ESLD, HCC, and death. Patients with extrahepatic manifestations of HCV are expected to benefit with reductions in

symptoms and disease severity of their extrahepatic disease while experiencing improvements in quality of life measures.[31] As more patients are cured, the risk of transmission is expected to decline and reduce HCV disease prevalence.[31]

General Approach to Treatment

Treatment for HCV is recommended for all persons with HCV. Initiating HCV therapy early in the disease state can provide substantial benefit by preventing complications of liver disease as well as preventing extrahepatic manifestations of HCV. In persons at high risk of transmitting HCV such as PWIDs, HCV treatment may help reduce rates of HCV transmission.[31] There are no clearly identified contraindications for HCV therapy. Patients with a short-life expectancy who are unlikely to benefit from HCV therapy, liver transplantation, or other directed therapy are the only populations for whom treatment is not recommended.[31]

The initial evaluation for HCV treatment is intended to stage the patient's level of liver disease, specifically to differentiate patients with cirrhosis from those without (Table 58-12). Patients without cirrhosis may be candidates for a much more simplified treatment approach if the patient does not have cirrhosis, is HCV treatment naïve, has no history or suspicion of HCC, has not received a liver transplant, and has no evidence of HIV or active HBV infection (Table 58-13). In contrast, patients with cirrhosis must be further evaluated to determine if the cirrhosis is compensated (Child–Turcotte–Pugh [CTP] A) or decompensated (CTP B or C). Patients with cirrhosis will likely require on-treatment monitoring as well as additional post-treatment follow-up to manage the complications associated with cirrhosis (eg, need for endoscopy or screening and surveillance for HCC). Patients with decompensated cirrhosis should be treated by clinicians with expertise in managing advanced liver disease.[31]

TABLE 58-12

Tools Used for Assessment of Cirrhosis

Any of the Following	
FIB-4 score[a]	Scores >3.25 suggestive of cirrhosis
Transient elastography	Scores >12.5 kPa indicate cirrhosis
Clinical evidence of cirrhosis	Liver nodularity and/or splenomegaly on imaging; thrombocytopenia (platelets <150,000/mm^3 [150 × 10^9/L]); etc.
Serological tests (eg. FibroSure)	Scores above specific test thresholds
Prior biopsy findings[b]	

[a]FIB-4 includes age, AST, ALT, and platelet level.

[b]Biopsy not required for diagnosis of cirrhosis.

TABLE 58-13

Simplified Treatment Candidates

Candidates for Simplified Treatment Approach		
HCV treatment naïve	AND	• No cirrhosis • No coinfection with HIV or active HBV infection[a] • Not pregnant • No history or suspicion of HCC • No history of liver transplant

[a]Active HBV defined as patients who have HBsAg positivity

The suggested laboratory tests prior to treatment are listed in Table 58-14. Quantitative HCV RNA testing is performed to confirm HCV infection. Genotyping is often performed although not required per national guidelines. Patients should be evaluated for HAV and HBV and offered vaccinations if not previously vaccinated. On-treatment laboratory monitoring is not necessary for patients without cirrhosis who meet the criteria for the simplified algorithm. Patients with cirrhosis may need on-treatment monitoring, with the most monitoring required for patients undergoing HCV therapy with the addition of ribavirin.

TABLE 58-14

Suggested Laboratories Prior to Initiating HCV Treatment

Test	Timeframe	Comments
HCV RNA	Any point before starting HCV therapy	Confirm HCV infection
Complete blood count	Within 6 months of starting HCV therapy	Thrombocytopenia (platelets <150,000/mm^3 [150 × 10^9/L] suggest cirrhosis)
Liver function tests	Within 6 months of starting HCV therapy	Albumin, bilirubin used to assess synthetic function of liver and for calculating Child Pugh in patients with cirrhosis; AST/ALT used to assess level of liver inflammation
International normalized ratio	Within 6 months of starting HCV therapy	In patients with cirrhosis used to assess synthetic function of the liver and for calculating Child–Pugh score
Estimated glomerular filtration rate	Within 6 months of starting HCV therapy	Renal insufficiency may indicated extrahepatic manifestations of HCV
HIV antigen/antibody	Any point before starting HCV therapy	Patients with HIV are not candidates for simplified algorithm; HIV and HCV share common routes of transmission (injection drug use)
Hepatitis B serologies (anti-HBs, anti-HBc, HBsAg)	Any point before starting HCV therapy	Patients with detectable HBsAg are at risk for HBV reactivation; patients who are HBV susceptible should be offered HBV vaccine
Anti-HAV	Any point before starting HCV therapy	Patients susceptible to HAV should be offered HAV vaccine

Data from Reference 31.

Counseling and Nonpharmacologic Therapy

Lifestyle changes are an important factor in reducing health consequences in hepatitis C. Continued alcohol use is a known risk factor for disease progression and severity. There is no established lower limit of alcohol consumption at which disease progression is not seen. Obesity is also a factor and patients should be encouraged to eat a balanced diet and exercise regularly to maintain a normal weight. Progression of fibrotic changes is associated with obesity. The use of herbal therapy is ineffective and potentially a source of drug interaction with HCV therapies. Patients should be counseled on minimizing HCV transmission risks and harm reduction strategies are recommended by national guidelines.[31]

Pharmacologic Therapy

11 The treatment of chronic HCV was revolutionized with the approval of DAAs. The DAAs act on one of three targets on the HCV virion. The DAAs must be used in combination with at least two drugs acting on different targets. The drug nomenclature identifies where the drug is inhibiting viral replication: the N3/4A protease inhibitors end with –previr; NS5A inhibitors end with –asvir; and the NS5B polymerase inhibitors end with –buvir. Early DAAs acted on specific HCV GTs. Sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, and sofosbuvir/velpatasvir/voxilaprevir are pangenotypic, meaning they are effective in all HCV GTs. The ability to treat without pretreatment GT testing favors the use of these agents and is an increasingly appealing strategy because it can streamline HCV treatment and reduce costs. As a group, the DAAs are well tolerated and cause few laboratory abnormalities.

The guidelines offer a simplified treatment algorithm which takes advantage of the safety and efficacy of pangenotypic therapies and shortened

duration of therapy with either an 8- or 12-week treatment course (Table 58-15).[31] Patients who do not have cirrhosis or any other major medical comorbidity are candidates for the simplified treatment (see Table 58-16 for exclusion criteria). Laboratory monitoring is not necessary; patients are re-assessed 12 weeks after the end of therapy with an HCV RNA and LFTs. A negative HCV RNA 12 weeks after completing treatment is consistent with cure, or sustained virologic response (SVR or SVR12 to denote that the HCV RNA was done 12 weeks after completing treatment). The LFTs are determined to confirm resolution of inflammation and identify patients which may need further workup of their liver disease if inflammation persists.[31]

TABLE 58-15

AASLD/IDSA Recommended Treatment Regimens for Treatment-Naïve Patients with Hepatitis C (All Genotypes)

Simplified Treatment Algorithm		
Glecaprevir/pibrentasvir 3 tabs orally daily with food × 8 weeks	Or	Sofosbuvir/velpatasvir 1 tab orally daily with or without food × 12 weeks
Repeat HCV RNA and LFTs 12 weeks after completing HCV therapy to assess for cure (SVR) and resolution of hepatic inflammation		

Data from Reference 31.

TABLE 58-16

AASLD/IDSA Recommended Treatment Regimens for Treatment-Naive Patients with No Cirrhosis (NC) or Compensated Cirrhosis (CC) and Hepatitis C Genotypes 1-6

	GT1a NC	**GT1a CC**	**GT1b NC or CC**	**GT2 NC or CC**	**GT3 NC**	**GT3 CC**	**GT4 NC or CC**	**GT5, 6 NC or CC**
DAA Therapy								
Glecaprevir/Pibrentasvir	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ledipasvir/Sofosbuvir	Yes	Yes	Yes	No	No	No	Yes	Yes
Sofosbuvir/Velpatasvir	Yes	Yes	Yes	Yes	Yes	Yes[b]—but with RAS testing	Yes	Yes
Elbasvir/Grazoprevir	No[a]	No	Yes	No	No	No	Yes	No

[a]Considered an alternative regimen because NS5A resistance testing is required prior to treatment start.

[b]Pre-treatment resistance testing for NS5A resistance-associated substitutions (RAS) should be done; if the Y93 RAS is identified, an alternative therapy is recommended.

Data from Reference 31.

Patients without cirrhosis or those with compensated cirrhosis are treated similarly with no difference in treatment duration. A main difference in the treatment approach is the necessary monitoring. Patients with cirrhosis may have laboratories (eg, AST/ALT) checked every 4 weeks while on treatment to monitor their underlying liver disease. In contrast, patients with decompensated cirrhosis (CTP class B or C) often require concomitant ribavirin and have fewer treatment options due to the underlying level of liver disease and concerns for safety. In general, patients with decompensated cirrhosis should be managed by clinicians with experience with end-stage liver disease due to the potential for complications related

to cirrhosis (eg, ascites, encephalopathy) developing while on HCV treatment.[31]

Prior treatment experience does not substantially alter retreatment except that there are more limited options for retreatment if patients were previously treated with more recent DAA therapies. Patients previously treated with IFN or IFN and a first generation protease inhibitor (boceprevir, teleaprevir, or simeprevir) who did not achieve cure can be retreated with a DAA therapy and expect cure rates comparable to those in patients who are treatment naïve. As a result the national guidelines no longer recognize separate recommendations for IFN-experienced patients. For patients previously treated with a DAA therapy (sofosbuvir- or NS5A-based regimen) who experience treatment failure, the only recommended retreatment is with the combination of sofosbuvir/velpatasvir/voxilaprevir.[31]

Clinically significant drug-drug interactions are expected with carbamazepine, phenobarbital, phenytoin, oxcarbazepine, rifampin, and St. John's wort and concurrent use of these agents with any of the HCV therapies is expected to result in HCV treatment failure. The clinical management of concomitant use of statins can vary from holding statins during HCV therapy to changing or dose reducing the statin. An important resource for timely and updated guidance on HCV-drug interactions is available for free through the University of Liverpool: https://www.hep-druginteractions.org/checker.

Previously, HCV treatment included the injection of peg-IFN and was associated with a substantial side-effect profile as well as a prolonged duration of therapy. The current standard of care for all chronic HCV infections, regardless of GT, is an all-oral drug regimen. Despite the change in pharmacological therapy, many patients are aware of the substantial side effects associated with IFN-based therapy and are wary of all HCV therapy. For patients familiar with IFN treatment, it is important to clearly distinguish current therapies from IFN-based ones as the concern for side effects of IFN-based HCV therapy can prevent patients from seeking HCV treatment with DAAs.

Sofosbuvir

Sofosbuvir was approved in 2013 for HCV GT1 to 4 at a dose of 400 mg. Although available as a single product, its use is mostly as the backbone of combination therapies including ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, and sofosbuvir/velpatasvir/voxilaprevir. Sofosbuvir is metabolized to its primary circulating active metabolite GS-331007. Sofosbuvir is well tolerated and has few drug-drug interactions; the majority of drug interactions are related to the agents used in combination with sofosbuvir. Serious symptomatic bradycardia was identified in patients treated with sofosbuvir and taking amiodarone in combination with other DAAs; thus, this combination is not recommended.

Ledipasvir/Sofosbuvir

The fixed dose combination tablet of ledipasvir/sofosbuvir (90 mg/400 mg) is a recommended therapy in patients with HCV GT1 or 4. A 12-week treatment course is highly effective in treatment-naïve patients with or without cirrhosis with an estimated SVR of 95%.[39] Initial studies also demonstrated a high SVR of 94% in patients without cirrhosis, treatment-naïve, and with a baseline viral load of less than 6 million IU/mL (kIU/L) treated for 8 weeks. However, due to limited data, the level of evidence to support this shorter course of therapy is lower than the 12-week course of treatment and the shorter course is not recommended in patients who have cirrhosis, have a viral load greater than 6 million IU/mL (kIU/L), are Black, or have HIV–HCV coinfection.[31,40] There are no differences in treatment whether patients have GT1a, 1b, or 4; however, there are differences in treatment duration depending on underlying cirrhosis.[41,42] The use of ribavirin did not affect SVR rates and is not routinely recommended. Patients with decompensated cirrhosis are more difficult to treat with lower SVR rates. In these patients, ledipasvir/sofosbuvir plus ribavirin is recommended for 12 weeks of treatment. If patients are unable to tolerate ribavirin due to its hematological effects, ledipasvir/sofosbuvir for 24 weeks is an alternative.[31,43] National guidelines also recommend ledipasvir/sofosbuvir for treatment of HCV GT4 for a 12-week course of therapy.[31]

The combination of ledipasvir/sofosbuvir is well tolerated and can be used in patients with cirrhosis, including CTP Class A, B, and C cirrhosis. It may also be used in patients with renal insufficiency including patients with end-stage renal disease on dialysis. Headache and fatigue are the most common side effects. Laboratory abnormalities do not frequently occur. The drug-drug interaction potential is also limited, although amiodarone use is not recommended because of the symptomatic bradycardia observed with the concomitant use of sofosbuvir. Acid suppressive therapy poses a challenge to treatment because ledipasvir requires an acidic environment for absorption. Antacids must be spaced apart by 4 hours whereas histamine blockers should be taken either at the same time or 12 hours apart from ledipasvir/sofosbuvir. The use of proton pump inhibitors is controversial with omeprazole 20 mg once daily recommended by the manufacturer; however, more frequent dosing or higher dosages are expected to compromise the efficacy of ledipasvir.[44] The effect of other proton pump inhibitors is not established and concomitant histamine blockers or antacids must be timed

appropriately to avoid a clinically significant drug-drug interaction.

Sofosbuvir/Velpatasvir

Sofosbuvir/velpatasvir is a pan-genotypic agent with activity against GT1 to 6. It is available as a fixed-dose tablet (400 mg/100 mg for adult dosing or 200 mg/50 mg for pediatric dosing) and as oral pellets for pediatric use (200 mg/50 mg or 150 mg/37.5 mg). In patients with HCV GT1, 2, 4, 5, and 6, 99% SVR was achieved with sofosbuvir/velpatasvir, irrespective of prior treatment experience or whether patients had cirrhosis or not.[40] In GT3 patients, pretreatment resistance testing is recommended for any patients with cirrhosis or prior treatment experience with peg-INF and ribavirin. If the Y93 substitution is detected, ribavirin should be added or an alternative therapy chosen.[31] Studies showed a numerically higher SVR in patients with HCV GT3 and cirrhosis who had received concomitant ribavirin, although this did not reach statistical significance.[45]

Sofosbuvir/velpatasvir is well tolerated with few side effects or laboratory abnormalities. It is recommended for use in patients with all levels of liver disease including decompensated cirrhosis where it is used in combination with ribavirin in order to maximize SVR. Patients with HCV GT1, 2, 3, 4, or 6 and decompensated liver disease treated with sofosbuvir/velpatasvir and ribavirin for 12 weeks achieved an SVR of 94%.[46] Patients with decompensated cirrhosis who cannot tolerate ribavirin may be treated with an extended duration of sofosbuvir/velpatasvir alone for 24 weeks. Most patients with decompensated cirrhosis also demonstrated an improvement in their liver disease (eg, reductions in their Child–Pugh score) as a result of treatment. Sofosbuvir/velpatasvir may also be used in patients with renal impairment, including patients on dialysis. Velpatasvir, like ledipasvir, requires an acidic environment for absorption; thus, patients must be appropriately counseled to avoid the use of proton pump inhibitors and on timing of other acid suppressive therapy to minimize the drug-drug interaction.

Elbasvir/Grazoprevir

Elbasvir/grazoprevir as a fixed-dose tablet (50 mg/100 mg) is approved for use in patients with HCV GT1 and 4. In treatment-naïve patients with HCV GTs 1, 4, and 6, the overall SVR rate was 95%.[47] Among patients with HCV GT1a, SVR rates were lower than for GT1b and this difference was attributed to the presence of baseline resistance–associated substitutions (RASs). When comparing patients with GT1a versus 1b who did not have any RASs, there was no difference in SVR (99 vs 100% SVR, respectively). For patients with baseline RASs and GT1a, the SVR rate dropped to 58%. Therefore, in patients with HCV GT1a, pretreatment resistance testing is required. If specific mutations are identified, treatment must be modified to include ribavirin and extended to 16 weeks, thus making it an alternative treatment as per guidelines in favor of shorter, ribavirin-free treatments.[31] Elbasvir/grazoprevir is approved for use in patients with HCV GT1 or 4, including those with renal insufficiency receiving hemodialysis. Because it contains a protease inhibitor, it should not be used in patients with decompensated cirrhosis.

Glecaprevir/Pibrentasvir

Glecaprevir/pibrentasvir is a pan-genotypic agent with activity against the major HCV GTs. It is available as a combination tablet (100 mg/40 mg) and as oral pellets (50 mg/20 mg) for pediatric use. It is recommended for use in both treatment-naïve and treatment-experienced patients with HCV GTs1 to 6. It is also recommended for use in patients with renal insufficiency including patients on hemodialysis. For patients who are treatment naïve, without cirrhosis or with compensated cirrhosis (CTP class A), the combination is recommended for an 8-week treatment regimen.[31] The approved combination tablet demonstrated the highest SVR rates ranging from 94% to 100% in patients with HCV GTs1 to 6. The lowest SVR at 94% was seen in patients with HCV GT3.[48] An 8-week treatment course is recommended for patients with cirrhosis and HCV GT1 to 6 due to SVR results comparable to those seen in patients without cirrhosis.[49] A smaller number of patients with cirrhosis and HCV GT3 in the clinical trial led to a lower level of recommendation for the use of the 8-week treatment course in these patients.[31] Baseline mutations for NS3 or NS5A did not affect SVR in clinical trials.[50] Because it contains a protease inhibitor, glecaprevir/pibrentasvir should not be used in patients with decompensated cirrhosis due to concerns for worsening liver injury, including liver failure.

Although approved for use in patients with prior DAA failure, guidelines limit the use of glecaprevir/pibrentasvir in this patient population pending further data.[31] Glecaprevir/pibrentasvir is recommended in patients with prior NS3/4A treatment experience (eg, boceprevir or simeprevir). However, it is an alternative treatment for patients with prior NS5A (eg, ledipasvir) treatment in part due to limited data and the need for an extended 16-week treatment duration in this patient population.[31]

Similar to other DAAs, glecaprevir/pibrentasvir is not associated with laboratory abnormalities and is well tolerated. The most common adverse events include headache and nausea. It is contraindicated with ethinyl estradiol products including hormone replacement and oral contraceptives due to a potential for ALT increases.

Sofosbuvir/Velpatasvir/Voxilaprevir

The addition of the pangenotypic protease inhibitor voxilaprevir to sofosbuvir/velpatasvir represents the first triplet regimen against all three targets on the HCV virion. It is available as a combination tablet (100 mg voxilaprevir/400 mg sofosbuvir/100 mg velpatasvir). Although effective in both treatment-naïve and treatment-experienced patients, the triplet regimen is reserved for patients who have failed prior DAA therapies and represents the last available combination for HCV therapy.[31] Although sofosbuvir/velpatasvir can be safely used in patients with decompensated cirrhosis, due to the presence of the protease inhibitor voxilaprevir, the triplet regimen cannot be used in patients with decompensated cirrhosis.

In patients with HCV GT1 to 6 who were previously treated with a DAA course including an NS5A agent, a retreatment course of sofosbuvir/velpatasvir/voxilaprevir achieved an SVR of 99%.[51] A lower SVR was seen in patients with cirrhosis at 93%; however, baseline resistance mutations were not associated with reduced SVR. The combination is also recommended in patients with HCV GT3 who are more difficult to treat including patients with cirrhosis or a known Y93 mutation (ie, patients with prior treatment experience with peg-INF and ribavirin tested for GT3 mutations).[31]

Ribavirin

Ribavirin continues to be used in combination with DAAs, although its use has been minimized when alternative treatments are available that are highly effective and ribavirin-free. There are some situations that continue to require ribavirin in order to improve SVR rates, such as in patients with decompensated cirrhosis or those with HCV GT3. The mechanism of action of ribavirin is not well understood. Ribavirin is a synthetic guanosine analog and is ineffective as a monotherapy for HCV. The most common adverse effect of ribavirin is hemolytic anemia, necessitating close monitoring during HCV therapy and contributing to complaints of fatigue during treatment. In addition, ribavirin is a teratogenic agent, Pregnancy Category X, and women of childbearing age as well as female partners of male patients who undergo HCV treatment with ribavirin need to practice two forms of contraception during HCV treatment and for 6 months after to avoid pregnancy.[31]

Special Populations

Clinical trials are conducted with a patient population that generally does not reflect the patient spectrum encountered in clinical practice. HCV infections are associated with patients who may be less likely to be engaged in routine healthcare and underrepresented in clinical trials. Treatment guidelines address some of these higher-risk populations and include recommendations for enhanced screening as well as treatment.[31] Published recommendations for treatment in various populations are as follows.

Patients with Decompensated Cirrhosis

Patients with decompensated cirrhosis, defined as CTP class B or C cirrhosis, are at high risk for developing complications of their end-stage liver disease and thus are recommended to be treated by clinicians with expertise in managing decompensated cirrhosis.[31] As a class, the protease inhibitors are not recommended in patients with decompensated cirrhosis due to the risk of further decompensation including liver failure. The only therapies recommended for use in decompensation include ledipasvir/sofosbuvir and sofosbuvir/velpatasvir. Ribavirin is indicated for use in patients with decompensated cirrhosis. In patients unable to tolerate ribavirin, the treatment course is extended to 24 weeks.

Persons Who Inject Drugs

Injection drug use is not a contraindication to therapy and treatment of PWIDs will be necessary to reduce HCV transmission.[52] Treatment of PWIDs is recommended as part of a comprehensive harm-reduction effort, ideally in a multidisciplinary setting.[31,52] Treatment outcomes are comparable to rates in those in clinical trials among persons without injection drug use and reinfection rates among PWID are low.[53] However, access to HCV therapies is limited as many insurers refuse coverage of HCV therapies in the setting of active drug use.

Persons with Ongoing Alcohol Use

Alcohol cessation is recommended for all patients with liver disease. However, due to the short-treatment course, safety profile of the DAAs, and the ability to cure HCV, ongoing alcohol use is not a reason to withhold or defer HCV treatment.[31]

End-Stage Renal Disease

There are no dose adjustments needed for the DAAs in patients with chronic kidney disease including for patients on hemodialysis. In contrast, ribavirin elimination is dependent on renal function and significant dose adjustments may be necessary.

Patients with HCV GT3

In patients with HCV GT3 and cirrhosis, a more aggressive treatment strategy may be recommended due to the concerns for lower SVR rates in some patients. For patients who are to be treated using sofosbuvir/velpatasvir and who have cirrhosis or prior TE, pretreatment resistance testing is recommended.[31] If the Y93 mutation is identified, ribavirin should be added to the treatment course. Alternatively, a different regimen should be used, such as sofosbuvir/velpatasvir/voxilaprevir. In contrast, glecaprevir/pibrentasvir is recommended for an 8-week treatment course for patients with HCV GT3 and cirrhosis although the level of evidence to support the 8-week treatment duration in patients with cirrhosis is lower than the 12-week course.[31] As a result, some clinicians will prefer to use a 12-week course of glecaprevir/pibrentasvir in patients with cirrhosis and HCV GT3. Guidelines do recommend a 12-week treatment course for HIV-HCV coinfection in persons with cirrhosis and HCV GT3 infection.[31]

DAA-Experienced Patients

Patients without cirrhosis or those with compensated cirrhosis who failed any course of DAA therapy (eg, elbasvir/grazoprevir, glecaprevir/pibrentasvir) or any prior HCV regimen which included sofosbuvir can be retreated with sofosbuvir/velpatasvir/voxilaprevir. For patients with cirrhosis who were previously treated with glecaprevir/pibrentasvir and experienced treatment failure, the addition of ribavirin may be considered to sofosbuvir/velpatasvir/voxilaprevir. Glecaprevir/pibrentasvir is an alternative retreatment strategy; however, its use is limited to specific patient populations and to specific prior treatment experience and requires an extended treatment duration of 16 weeks. For patients who failed multiple prior DAA therapies, including sofosbuvir/velpatasvir/voxilaprevir or the combination of sofosbuvir plus glecaprevir/pibrentasvir, there are limited options for retreatment. Using available therapies, the recommended retreatment in these unique circumstances includes the addition of ribavirin and retreatment for a longer duration of therapy.[31,51] There are no recommendations for pretreatment resistance testing in this population, and given the small number of patients who failed DAA therapy, it is difficult to predict who will fail DAA treatments.

HIV Coinfection

Patients with HIV HCV coinfection should be treated as having HCV monoinfection. Despite this, patients with HIV HCV coinfection are not candidates for the simplified algorithm. Similarly, the 8-week treatment duration is not recommended for patients with compensated cirrhosis and HCV and HIV coinfection. Potential drug-drug interaction concerns between HCV DAAs and HIV antivirals do merit careful scrutiny and may necessitate antiretroviral drug changes.[31] The University of Liverpool HCV drug interaction checker is a useful resource for up to date information on drug interactions.

Preferred HCV therapies for treatment-naïve patients with HIV coinfection are the pan-genotypic agents—sofosbuvir/velpatasvir or glecaprevir/pibrentasvir. Elbasvir/grazoprevir and ledipasvir/sofosbuvir may also be used. Sofosbuvir/velpatasvir has few clinically significant drug-drug interactions but should be avoided with efavirenz, etravirine, or nevirapine. Ledipasvir and velpatasvir increase tenofovir disoproxil levels and may increase the risk of tenofovir-associated renal toxicity especially if combined with cobicistat or ritonavir; however, this risk is minimized with tenofovir alafenamide and thus is the preferred formulation of tenofovir. Glecaprevir/pibrenasvir can be used in patients concurrently on abacavir, bictegravir, cabotegravir, dolutegravir, doravirine, emtricitabine, fostemsavir, ibalizumab-uiyk, lamivudine, maraviroc, raltegravir, rilpivirine, and tenfovir. Glecaprevir/pibrenasvir exposure can increase when combined with elvitegravir/cobicistat with a concern for potential resultant hepatic toxicity. Pending more data, concomitant use necessitates more frequent monitoring for worsening liver function. For patients who are DAA treatment experienced, sofosbuvir/velpatasvir/voxilaprevir is recommended.

HIV treatment poses additional problems because of hepatotoxicity issues associated with HAART, hepatic complications from HIV-associated diseases, as well as flares in hepatitis as CD4 counts recover. In general, treatment is recommended with coadministration of HIV and HCV therapies

and is considered a priority due to more liver-related morbidity and mortality than in HCV mono-infected patients.

Children

Although the number of pediatric HCV cases is low, there are no good epidemiological studies to determine the actual prevalence of HCV in the pediatric population. Mother-to-child transmission is possible and of concern given the rise in HCV prevalence among younger females of childbearing age. Because maternal HCV antibody can persist and thus interfere with an infant's HCV antibody test, testing in newborns is not recommended until 18 months of age.[31] This delay in testing raises concerns for loss to follow up and potential missed opportunities for HCV diagnosis. Although fibrosis progression is generally considered slow in children, there is a general lack of data on the impact of persistent viremia on child development. Children with HCV as well as their families may face stigma and discrimination due to a general lack of knowledge about HCV and HCV transmission.

HCV DAA treatment is available; however, it is deferred until age 3 due to limited data in children. Both pan-genotypic agents are approved (sofosbuvir/velpatasvir and glecaprevir/pibrentasvir) as is ledipasvir/sofosbuvir. Pediatric dosing may be done with reduced dose tablets and pellets/granules which may be sprinkled over food.

Similar to adult clinical trial data, glecaprevir/pibrentasvir is highly effective in pediatric patients and is approved for children 3 years of age and older. The overall SVR was 96% in 80 children ranging in age from 3 to 12 years and with HCV GT1, 2, 3, or 4 infection.[54] The most common side effect was headache with patients also reporting vomiting and diarrhea. Glecaprevir/pibrentasvir is available as oral pellets for pediatric use.

Sofosbuvir/velpatasvir is also highly effective in pediatric patients and approved for children 3 years of age and older. SVR rates were 92% overall in 216 patients ranging in age from 3 to 17 years.[55] Virological failure was 1%, of the 17 patients who did not have a document SVR. The adverse effect profile was similar to what was observed in adult trials. Younger patients were more likely to report vomiting.

Ledipasvir/sofosbuvir is also an option and is available in a smaller dose tablet (45 mg/200 mg) as well as oral pellets (45 mg/200 mg or 33.75 mg/150 mg). The expected SVR is high at 98%.[56] The main limitation of this combination therapy is that it is not pan-genotypic; it is indicated for patients with HCV GT1, 4, 5, or 6.

Pregnancy

Transmission of HCV can occur during pregnancy and children born to mothers with HCV should be tested for HCV. HCV screening is recommended for each pregnancy; however, HCV therapy is not recommended during pregnancy.[31]

Post-Organ Transplant

Given the high efficacy of the DAAs and the number of HCV-positive organ donors, some organ transplant centers are offering HCV-positive organs to HCV-negative patients. Pan-genotypic agents are preferred in the transplant setting. Both glecaprevir/pibrentasvir and sofosbuvir/velpatasvir are recommended as soon as the patient is clinically stable but preferably within the first week after transplant. Experience in the transplant setting is increasing and includes liver, heart, lung, and kidney transplant.[31,57]

Prevention

No vaccine is available for HCV. It is unlikely that a vaccine will be developed in the near future because of the mutagenesis of the virus. Although the likelihood of household transmission is small, patients should minimize risks by avoiding possible blood or mucus exposure, such as not sharing razors or toothbrushes and covering open wounds. Sharing of any drug paraphernalia poses a risk of transmission. Where legally allowed, patients should be provided with resources for needle and syringe exchange programs.

Targeted HCV treatment in specific patient groups can reduce transmission and offer substantial public health benefits. Patients who achieve cure (SVR) cannot transmit virus, thus interrupting HCV transmission. Improved access to HCV DAA therapy and scale-up of treatment efforts is critical to prevention of new infections.

Treatment Interruptions

In real-world settings, treatment interruptions occur for a number of reasons. It is important to minimize treatment interruptions and identify solutions to help patients be successful in obtaining refills in a timely manner. Disruptions in the treatment course can cause treatment failure. It is important to review the most current guidance available.[31] Patients who miss a week or less of therapy should restart treatment immediately and complete the originally scheduled treatment course. Patients who miss 8 or more days during the first month of treatment should continue DAA therapy and ideally also obtain an HCV RNA. If the HCV RNA is negative, the original treatment duration should be completed. In contrast, if the HCV RNA is positive or unable to be obtained, or if the patient has HCV GT3 infection or cirrhosis, DAA therapy should be extended by an additional 4 weeks.

If a patient misses 8 to 20 days of therapy after receiving at least the first month of treatment, DAA therapy should be restarted immediately and an HCV RNA checked. If the RNA is negative, the originally scheduled therapy should be continued or extended by 4 weeks if the patient has GT3 or cirrhosis. If the RNA is positive or not obtained, treatment should be stopped.

If patients experience a treatment interruption of more than 20 days, DAA therapy should be stopped. Although not common, it is possible that some patients may experience cure. The recommendation is to wait and recheck HCV RNA 12 weeks after the last known dose of medication was taken to assess for possible cure (SVR12).[31]

ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
ACIP	Advisory Committee on Immunization Practices
ALT	alanine aminotransferase
Anti-HAV	antibody to hepatitis A virus
Anti-HBsAg	antibody to HBsAg
CDC	Centers for Disease Control and Prevention
CTP	Child–Turcotte–Pugh
DAA	direct-acting antiviral
DF	disoproxil fumarate
DNA	deoxyribonucleic acid
ELISA	enzyme-linked immunosorbent assay
ESLD	end-stage liver disease
GT	genotype
HAART	highly active antiretroviral therapy
HAV	hepatitis A virus
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B e-antigen

HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IDSA	Infectious Diseases Society of America
IFN	interferon
Ig	immunoglobulin
IM	intramuscular
IV	intravenous
MSM	men who have sex with men
NAs	nucleos(t)ide analogs
peg-IFN	pegylated interferon
PWID	persons who inject drugs
RAS	resistance–associated substitution
RNA	ribonucleic acid
SVR	sustained virologic response
WHO	World Health Organization

REFERENCES

1. Department of Health and Human Services. *National Viral Hepatitis Action Plan 2021-2025*. Available at: https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf. Accessed November 10, 2021.

2. Centers for Disease Control and Prevention. Surveillance for Viral Hepatitis—United States. Available at: https://www.cdc.gov/hepatitis/statistics/2019surveillance/index.htm. Accessed July 28, 2021.

3. Centers for Disease Control and Prevention. Hepatitis A outbreaks in the United States. Available at: https://www.cdc.gov/hepatitis/outbreaks/hepatitisaoutbreaks.htm. Accessed June 1, 2021.

4. Centers for Disease Control and Prevention. Hepatitis A. In: Hall E, Wodi AP, Hamborsky J, et al., eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 14th ed. Washington, DC: Public Health Foundation; 2021.

5. Centers for Disease Control and Prevention. Hepatitis A. In: *CDC Yellow Book 2020: Health Information for International Travel*. 13th ed. New York: Oxford University Press; 2017.

6. Centers for Disease Control and Prevention. Prevention of hepatitis A through active or passive immunizations: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 2020;69(5):1–38. [PubMed: 31917782]

7. Huang SH, Huang CH, Wang NC. Taiwan HIV Study Group. Early seroconversion after 2 doses of hepatitis A vaccination in human inmmunodeficiency virus positive patients: Incidence and associated factors. *Hepatology*. 2019;70:465–475. [PubMed: 30614542]

8. World Health Organization. Hepatitis B. July 21, 2021. Available at: http://www.who.int/news-room/fact-sheets/detail/hepatitis-b. Accessed September 14, 2021.

9. World Health Organization. Guidelines for the prevention, care, and treatment of persons with chronic hepatitis B infection. 2015. Available at: http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf?ua=1ua=1. Accessed September 25, 2021.

10. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and Testing for Hepatitis B Virus Infection: CDC Recommendations - United States, 2023. MMWR Recomm Rep 2023;72(1):1–25. 10.15585/mmwr.rr7201a1 [PubMed: 36893044] .

11. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B; AASLD 2018 Hepatitis B Guidance. *Hepatology*. 2018;67:1560–1599. [PubMed: 29405329]

12. Tong S, Revill P. Overview of hepatitis B viral replication and genetic variability. *J Hepatol.* 2016;64:S41–S48. [PubMed: 27084036]

13. European Association for the Study of the Liver. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol.* 2017;67:370–398.

14. Tang AS, Thornton K, HBV Primary Care Workgroup. Hepatitis B management: Guidance for the primary care provider. February 25, 2020. Available at: https://www.hepatitisb.uw.edu/page/primary-care-workgroup/guidance. Accessed October 25, 2021.

15. Reddy RK, Beavers KL, Hammond SP, et al. American Gastroenterological Association Institute guideline on prevention and treatment of hepatitis B reactivation during immunosuppressive drug therapy. *Gastroenterology*. 2015;148:215–219. [PubMed: 25447850]

16. Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology*. 2015;148:221–244. [PubMed: 25447852]

17. Kennedy K, Graham SM, Arora N, et al. Hepatocellular carcinoma among US and non–US-born patients with chronic hepatitis B: Risk factors and age at diagnosis. *PLoS One*. 2018;13:e0204031. [PubMed: 30252863]

18. Schillie S, Vellozzi C, Reingold A, et al. Centers for Disease Control and Prevention (CDC). Prevention of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep.* 2018;67:1–31. [PubMed: 29324727]

19. Weng MK, Doshani M, Khan MA, et al. Universal Hepatitis B Vaccination in Adults Aged 19-59 Years: Updated Recommendations of the Advisory Committee on Immunization Practices - United States, 2022. MMWR Morb Mortal Wkly Rep 2022;71(13):477–483. 10.15585/mmwr.mm7113a1 [PubMed: 35358162] .

20. Yu MW, Lin CL, Yang SH, et al. Influence of metabolic risk factors on risk of hepatocellular carcinoma and liver-related death in men with chronic hepatitis B: A large cohort study. *Gastroenterology*. 2017;153:1006–1017. [PubMed: 28711626]

21. Kim JH, Sinn DH, Gwak GY, et al. Insulin resistance and the risk of hepatocellular carcinoma in chronic hepatitis B patients. *J Gastroenterol Hepatol.* 2017;32:1100–1106. [PubMed: 27862289]

22. Terrault N, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology*. 2016;63:261–283. [PubMed: 26566064]

23. Buti M, Tsai N, Petersen J, et al. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. *Dig Dis Sci.* 2015;60(5):1457–1464. [PubMed: 25532501]

24. Agarwal K, Brunetto M, Seto WK, et al. 96 weeks treatment of tenofovir alafenamide vs tenofovir disoproxil fumarate for hepatitis B virus infection. *J Hepatol.* 2018;68:672–681. [PubMed: 29756595]

25. Cathcart AL, Chan HL, Bhardwaj N, et al. No resistance to tenofovir alafenamide detected through 96 weeks of treatment for chronic hepatitis B infection. *Antimicrob Agents Chemother.* 2018;62(10): e01064–18. doi: 10.1128/AAC.01064-18.

26. Lim YS, Yoo BC, Byun KS, et al. Tenofovir monotherapy versus tenofovir and entecavir combination therapy in adefovir-resistant chronic hepatitis B patients with multiple drug failure: Results of a randomized trial. *Gut.* 2016;65:1042–1051. [PubMed: 25800784]

27. Ding Y, Cao L, Zhu L, et al. Efficacy and safety of tenofovir alafenamide fumarate for preventing mother-to-child transmission of hepatitis B virus: A national cohort study. *Alimentary Pharmacol Ther.* 2020 Aug 27;52(8):1–10. doi: 10.1111/apt.16043.

28. Gupta N, Goyal M, Wu CH, Wu GY. The molecular and structural basis of HBV-resistance to nucleos(t)ide analogs. *J Clin Transl Hepatol.* 2014;2:201–211.

29. Ford N, Scourse R, Lemoine M, Hutin Y, Bulterys M. Adherence to nucleos(t)ide analogue therapies for chronic hepatitis B infection: A systematic review and meta-analysis. *Hepatol Commun.* 2018;25:1160–1167.

30. Schillie S, Wester C, Osborne M, Wesolowski L, Ryerson AB. CDC recommendations for hepatitis C screening among adults—United States, 2020. *MMWR Recomm Rep.* 2020;69(RR-2):1–17.

31. AASLD/IDSA. Recommendations for testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org. Accessed August 20, 2021.

32. U.S. Preventive Services Task Force. Final Recommendation Statement: Hepatitis C Virus Infection in Adolescents and Adults: Screening. March 2020. Available at: http://www.uspreventiveservicestaskforce.org/uspstf/recommendation/hepatitis-c-screening. Accessed August 27, 2021.

33. Terrault NA, Dodge JL, Murphy EL, et al. Sexual transmission of HCV among monogamous heterosexual couples: The HCV partners study. *Hepatology*. 2013;57:881–889. [PubMed: 23175457]

34. Centers for Disease Control. Testing for HCV infection: An update of guidance for clinicians and laboratorians. *MMWR.* 2013;62(18):362–365.

35. Kanto T, Hayashi N. Immunopathogenesis of hepatitis C virus infection: Multifaceted strategies subverting innate and adaptive immunity. *Intern Med.* 2006;45:183–191. [PubMed: 16543687]

36. Centers for Disease Control and Prevention. Hepatitis C FAQs for health professionals. Available at: http://www.cdc.gov/hepatitis/hcv/hcvfaq.htm. Accessed September 17, 2021.

37. Kanwal F, Kramer JR, Ilyas J, Duan Z, El-Serag HB. HCV genotype 3 is associated with an increased risk of cirrhosis and hepatocellular cancer in a national sample of U.S. veterans with HCV. *Hepatology*. 2014;60(1):98–105. [PubMed: 24615981]

38. Sherman AC, Sherman KE. Extrahepatic manifestations of hepatitis C: Navigating CHASM. *Curr HIV/AIDS Rep.* 2015;12(3):353–361. [PubMed: 26208812]

39. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med.*

2014;370:1879–1888. [PubMed: 24720702]

40. Feld JJ, Jacobson IM, Hézode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med.* 2015;373(27):2599–2607. [PubMed: 26571066]

41. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med.* 2014;370(20):1889–1898.

42. Afdhal N, Reddy KR,, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med.* 2014;370(16):1483–1493.

43. Charlton M, Everson GT, Flamm SL, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. *Gastroenterology*. 2015;149:649–659. [PubMed: 25985734]

44. Tapper EB, Bacon BR, Curry MP, et al. Real-world effectiveness for 12 weeks of ledipasvir-sofosbuvir for genotype 1 hepatitis C: The Trio Health Study. *J Viral Hepat.* 2017;24:22–27. [PubMed: 27730717]

45. Esteban R, Pineda JA, Calleja L, et al. Efficacy of sofosbuvir and velpatasvir, with or without ribavirin, in patients with HCV genotype 3 infection and cirrhosis. *Gastroenterology*. Oct 2018;155(4):1120–1127. doi: 10.1053/j.gastro.2018.06.042.

46. Curry MP, O'Leary JG, Bzowej N, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. *N Engl J Med.* 2015b;373(27):2618–2628. [PubMed: 26569658]

47. Zeuzem S, Ghalib R, Reddy KR, et al. Grazoprevir-elbasvir combination therapy for treatment-naive cirrhotic and noncirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: A randomized trial. *Ann Intern Med.* 2015;163(1):1–13. [PubMed: 25909356]

48. Kwo PY, Poordad F, Asatryan A, et al. Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis. *J Hepatol.* 2017;67:263–271. [PubMed: 28412293]

49. Brown RS, Buti M, Rodrigues L, et al. Glecaprevir/pibrentasvir for 8 weeks in treatment naïve patients with chronic HCV genotype 1-6 and compensated cirrhosis. *J Hepatol.* 2020;72:441–449. [PubMed: 31682879]

50. Gane E, Poordad F, Wang S, et al. High efficacy of ABT-493 and ABT-530 treatment in patients with HCV genotype 1 or 3 infection and compensated cirrhosis. *Gastroenterology*. 2016b;151:651–659. [PubMed: 27456384]

51. Bourliere M, Gordon SC, Flamm SL, et al. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. *N Engl J Med.* 2017;376:2134–2146. [PubMed: 28564569]

52. Doyle JS, Aspinall EJ, Hutchinson SJ, et al. Global policy and access to new hepatitis C therapies for people who inject drugs. *Int J Drug Policy*. 2015;26(11):1064–1071. [PubMed: 26118794]

53. Aspinall EJ, Corson S, Doyle JS, et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: A systematic review and meta-analysis. *Clin Infect Dis.* 2013;57(suppl 2):S80–S89. [PubMed: 23884071]

54. Jonas MM, Rhee S, Kelly DA, et al. Pharmacokinetics, safety, and efficacy of glecaprevir/pibrentasvir in children with chronic HCV: Part 2 of the DORA study. *Hepatology*. 2021;74:19–27. [PubMed: 33811356]

55. Sokal E, Schwarz K, Rosenthal P, et al. Safety and efficacy of sofosbuvir/velpatasvir for the treatment of chronic hepatitis C infection in adolescents and children aged 3 to 17 years old through 24 weeks posttreatment. Poster session presented at: The American Association for the Study of Liver Diseases (AASLD) Liver Meeting Digital Experience 2020; 2020 November 13-16.

56. Balistreri WF, Murray KF, Rosenthal P, et al. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12-17 years old with hepatitis C

virus genotype 1 infection. *Hepatology*. 2017;66:371–378. [PubMed: 27997679]

57. American College of Obstetricians and Gynecologists. Practice Advisory: Routinehepatitis C virus screening in pregnant individuals. May 2021. Available at: acog.org/clinical-guidance/practice-advisory/articles/2021/05/routine-hepatitis-c-virus-screening-inpregnant individuals. Accessed November 11, 2021.

SELF-ASSESSMENT QUESTIONS

1. Which of the following is correct regarding viral hepatitis infections?

   A. Hepatitis A virus is transmitted through contaminated food, water, or ice and can cause acute or chronic infections.

   B. Hepatitis B virus is transmitted through blood, mucosal fluids, or contaminated food or water and can cause acute or chronic infections.

   C. Hepatitis C virus is transmitted through blood or contaminated food or water and can cause acute or chronic infections.

   D. Hepatitis B and C are transmitted through blood and can cause acute or chronic infections.

2. Which of the following patients is at risk for hepatitis A virus infection?

   A. A 51-year-old male who received two doses of vaccine and is traveling to a high-end resort in a country with high rates of HAV

   B. A 21-year-old female who received one dose of vaccine 4 weeks before a known HAV exposure

   C. A 1-year-old child who received a dose of HAV vaccine 2 months before traveling to a country with high rates of HAV

   D. An unvaccinated 49-year-old homeless male living in a homeless encampment

3. A 26-year-old female is worried about HAV because she ate at a restaurant implicated in a HAV outbreak. Her records indicate she received 2 doses of the hepatitis A vaccine as a child. Which of the following is the best action?

   A. Serological tests are needed to assess her risk of HAV.

   B. Immunoglobulin should be given to prevent symptoms of HAV.

   C. No vaccine or immunoglobulin necessary now.

   D. She should receive a booster shot of HAV vaccine now to stimulate her immune response.

4. The immunization records of a child indicate that the first dose of the hepatitis A vaccine was with one of the available single antigen products approximately 1 year ago. Which of the following is correct?

   A. A second dose should be given today with any single antigen HAV vaccine to complete the series.

   B. A dose should be given today but with the same single antigen HAV vaccine as was given previously to complete the series.

   C. A dose should be given today but if with a different product than previously given, will require restarting the vaccine series.

   D. A dose should be given today with any HAV vaccine and will require a second shot in 6 months to complete the series according to the schedule.

5. Which of the following Hepatitis B serological test results are consistent with successful vaccination?

   A. HBsAg (+), anti-HBc (+), anti-HB (+)

   B. HbsAg (+), anti-HBc (−), anti-HB (−)

C. HbsAg (−), anti-HBc (+), anti-HB (−)

D. HbsAg (−), anti-HBc (−), anti-HB (+)

6. A patient is scheduled to start rituximab. On routine labs, anti-HBs is negative, HBsAg is positive, and an HBV DNA is found to be 1,000 IU/mL (kIU/L). All other laboratories are within normal limits. Which of the following is correct?

A. The patient is at risk for HBV reactivation and requires vaccination prior to starting rituximab.

B. The patient is at risk for HBV reactivation and should be started on HBV therapy.

C. The patient should receive vaccination against HBV. Treatment for HBV is not necessary now.

D. The patient has HBV but treatment is not necessary because the patient's viral load is low and there is no diagnosis of cirrhosis.

7. Which of the following statements regarding HBV vaccination is correct?

A. The Engerix-B, Recombivax, and Heplisav-B vaccines are interchangeable.

B. Serological response to HBV vaccine is high even after a single dose of vaccine.

C. Engerix-B and Recombivax are given as two doses, given 6 months apart.

D. The Heplisav-B vaccine is given in as two doses, given 4 weeks apart.

8. Which of the following therapies are recommended for treatment of HBV?

A. Adefovir, tenofovir diprovoxil, or entecavir

B. Entecavir, adefovir, or lamivudine

C. Tenofovir diprovoxil, tenofovir alafenamide, or entecavir

D. Tenofovir alafenamide, adefovir, or entecavir

9. When should infants born to a mom whose HBV status is unknown receive the first HBV vaccine?

A. Within 6 hours of birth

B. Within 12 hours of birth

C. Within 24 hours of birth

D. Within the first 6 months of birth

10. A patient is screened for HCV and found to be HCV antibody positive. What is the correct interpretation of this lab finding?

A. Acute HCV infection

B. Chronic HCV infection

C. Either current or prior HCV infection, requires further evaluation

D. Immune protected against HCV

11. Which of the following is recommended for treatment of chronic HCV in DAA experienced patients?

A. Glecaprevir/pibrentasvir X 8 weeks

B. Sofosbuvir/velpatasvir X 12 weeks

C. Ledipasvir/sofosbuvir X 12 weeks

D. Sofosbuvir/velpatasvir/voxilaprevir X 12 weeks

12. Which of the following therapies is indicated for treatment of HCV genotype 1, 4, 5, or 6 only?

A. Glecaprevir/pibrentasvir X 8 weeks

B. Sofosbuvir/velpatasvir X 12 weeks

C. Ledipasvir/sofosbuvir X 12 weeks

D. Sofosbuvir/velpatasvir/voxilaprevir X 12 weeks

13. Which of the following therapies is indicated for use in patients with chronic HCV and decompensated cirrhosis?

A. Glecaprevir/pibrentasvir X 8 weeks

B. Elbasvir/grazoprevir X 12 weeks

C. Sofosbuvir/velpatasvir X 24 weeks

D. Sofosbuvir/velpatasvir/voxilaprevir X 12 weeks

14. Which of the following is preferred for use in a treatment naïve patient with HCV, genotype unknown?

A. Glecaprevir/pibrentasvir X 8 weeks

B. Sofosbuvir/velpatasvir X 12 weeks

C. Ledipasvir/sofosbuvir X 12 weeks

D. Sofosbuvir/velpatasvir/voxilaprevir X 12 weeks

15. Which of the following is correct regarding the treatment of HCV in patients with HIV?

A. Treatment is extended and is longer than in HCV monoinfected patients.

B. Treatment is limited because of substantial drug–drug interactions.

C. Treatment is the same as in HCV monoinfected patients.

D. Treatment includes agents with activity against HCV and HIV.

SELF ASSESSMENT QUESTION-ANSWERS

1. **D.** Hepatitis B and C are transmitted through blood and can cause acute or chronic infections. Hepatitis A is an acute infection and is transmitted through contaminated food, water, or ice.

2. **D.** An unvaccinated 49-year-old homeless man living in a homeless encampment. Vaccination for HAV is highly effective even with one dose of vaccine as long as it is administered at least 2 weeks prior to exposure.

3. **C.** No vaccine or immunoglobulin necessary now. The HAV vaccine is highly effective and serological testing to prove vaccine efficacy is not routinely recommended. The use of immunoglobulin is limited and considers also the circumstances, age, and underlying health status of the exposed individual. Post-exposure prophylaxis with vaccine is recommended but for unvaccinated persons.

4. **A.** A second dose should be given today with any single antigen HAV vaccine to complete the series. Ideally the vaccine series is completed with the same vaccine; however, it is preferable to complete the series with any HAV vaccine so that optimal vaccine efficacy is achieved rather than risk patient loss to follow up or risk HAV infection.

5. **D.** HBsAg (−), anti-HBc (−), anti-HBs (+). In a patient without prior exposure to HBV (anti-HBc [−]), successful vaccination results in a reactive (+) anti-HBs. Patients who have replicating HBV will have a reactive HBsAg.

6. **B.** The patient is at risk for HBV reactivation and should be started on HBV therapy. The patient already has replicating HBV (as identified by HBsAg reactivity and a quantifiable HBV DNA). The use of rituximab in this setting is expected to suppress immune activity and allow more robust HBV replication, thus necessitating HBV treatment for the duration of rituximab therapy. Since the patient already has HBV, vaccine will not be helpful.

7. **D.** The Heplisav-B vaccine is given in as two doses, given 4 weeks apart. Engerix-B and Recombivax share a similar adjuvant for vaccination; however, this is different to the one used in Heplisav-B, thus these vaccines are not recommended to be used interchangeably. Unlike the HAV vaccine, the HBV vaccine is less effective and requires the full dosing regimen to maximize response.

8. **C.** The standard of care is with entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide because these agents have a high barrier to HBV resistance.

9. **B.** Infants born to females with an unknown HBsAg status should receive the first dose of vaccine within 12 hours of birth. Infants born to moms with known HBsAg positivity should receive both the vaccine and immunoglobulin. It is important to document mom's HBV serology results to guide the management of infants to minimize HBV transmission.

10. **C.** Either current or prior HCV infection, requires further evaluation. To confirm HCV infection, an HCV RNA must be checked and only patients who have a quantifiable HCV RNA have HCV infection. Patients can spontaneously clear HCV infection or undergo HCV treatment and achieve cure but will continue to have an HCV antibody detected. For patients with known prior HCV antibody positivity, it is not necessary to repeat the HCV antibody test.

11. **D.** Sofosbuvir/velpatasvir/voxilaprevir is indicated for patients who were previously treated and failed by other DAA agents. Patients who were previously treated with an interferon-based regimen are treated as DAA naïve.

12. **C.** Ledipasvir/sofosbuvir has efficacy for genotypes 1, 4, 5, and 6. It is not considered a pan-genotypic agent because it is not effective for genotypes 2 or 3. Options A, B, and D are considered pan-genotypic.

13. **C.** Sofosbuvir/velpatasvir X 24 weeks. DAA therapies which include a protease inhibitor (those agents ending in –previr) are not recommended in patients with decompensated cirrhosis due to concerns for exacerbating further liver injury. Decompensated cirrhosis poses additional challenges to successful HCV treatment and in these cases either ribavirin is added to the 12-week therapy or the treatment course is extended. In patients with decompensated cirrhosis who cannot tolerate the addition of ribavirin, a 24-week course of sofosbuvir/velpatasvir is recommended.

14. **A.** Glecaprevir/pibrentasvir is a pan-genotypic agent used for 8 weeks in patients with HCV. Options B and C are not preferred because both require genotype testing prior to use to confirm their activity against specific HCV genotypes. Sofosbuvir/velpatasvir/voxilaprevir is used in patients with DAA treatment failure, thus not preferred in this patient who is treatment naïve.

15. **C.** Treatment is the same as in HCV monoinfected patients. Although drug–drug interactions need to be assessed prior to starting HCV therapy, most current HIV HAART can be used with current DAAs. Unlike HBV therapy, HCV DAAs do not have activity against HIV.