Chapter 25: Hepatitis, Viral

INTRODUCTION

- *Viral hepatitis* refers to the clinically important hepatotropic viruses responsible for hepatitis A (HAV), hepatitis B (HBV), delta hepatitis, hepatitis C (HCV), and hepatitis E.

HEPATITIS A

- HAV infection usually produces a self-limited disease and acute viral infection, with a low fatality rate, and confers lifelong immunity. Outbreaks occur each year in the United States.
- HAV infection primarily occurs through transmission by the fecal-oral route, person-to-person, or by ingestion of contaminated food or water. The incidence of HAV correlates directly with low socioeconomic status, poor sanitary conditions, and overcrowding. Rates of HAV infection are increased among international travelers, injection drug users, the homeless population, and men who have sex with men.
- The disease exhibits three phases: 1) incubation (averaging 28 days, range 15–50 days), 2) acute hepatitis (generally lasting 2 months), and 3) convalescence. Acute hepatitis is marked by an abrupt onset of nonspecific symptoms; some very mild. Some patients may experience symptoms for up to 9 months. Nearly all individuals have clinical resolution within 6 months of the infection, and a majority have resolution by 2 months. HAV does not lead to chronic infections.
- The clinical presentation of HAV infection is given in **Table 25-1**. There are no specific symptoms unique to HAV. Children younger than 6 years of age are typically asymptomatic.
- The diagnosis of acute HAV infection is based on clinical criteria of acute onset of fatigue, abdominal pain, loss of appetite, intermittent nausea and vomiting, jaundice or elevated serum aminotransferase levels, and serologic testing for immunoglobulin (Ig) M anti-HAV. Detection of IgG anti-HAV replaces IgM and indicates host immunity following the acute phase of the infection.

TABLE 25-1

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, scleral icterus, hepatomegaly. Less common: splenomegaly, skin rash, arthralgia.	Approximately 70% of patients are anicteric or subclinical. Younger patients are 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			
Aminotransferase (ALT, AST) elevations	>1000 IU/L (6.7 µkat/L) ALT>AST	1000–2000 IU/L (16.7–33.3 µkat/L) ALT>AST	Highly variable, can be approximately 1000 IU/L (16.7 µkat/L) ALT>AST
Bilirubin	Elevated and preceded by aminotransferase elevations	Can be within normal or elevated	Elevated and preceded by aminotransferase elevations
Virus-specific tests	IgM anti-HAV	IgM anti-HBc (+), HBsAg (+)	HCV RNA (+) or quantifiable; HCV antibody reactive within 12 weeks of exposure

ALT, alanine aminotransferase; AST, aspartate aminotransferase; anti-, antibody to; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; IgM, immunoglobulin; IU, international units; L, liter; RNA, ribonucleic acid.

Prevention

- The spread of HAV can be best controlled by avoiding exposure. The most important measures to avoid exposure include good handwashing techniques and personal hygiene practices.
- The current vaccination strategy in the United States includes vaccinating all children at 1 year of age. Groups who should receive HAV vaccine are shown in **Table 25-2**.
- Three inactivated virus vaccines are licensed in the United States: Havrix, Vaqta, and Twinrix. Approved dosing recommendations are shown in **Table 25-3**. Seroconversion rates of 94% or greater are achieved with the first dose.
- Common vaccine side effects include soreness and warmth at the injection site, headache, malaise, and pain.
- Ig is used when pre- or postexposure prophylaxis against HAV infection is needed in persons for whom vaccination is not an option. It is most effective if given during the incubation phase of infection. A single dose of Ig 0.02 mL/kg is given intramuscularly for postexposure prophylaxis or short-term (≤5 months) preexposure prophylaxis. For lengthy stays, a single dose of 0.06 mL/kg is used. HAV vaccine may also be given with Ig.
- For people recently exposed to HAV and not previously vaccinated, Ig is indicated for patients older than 40 years or with underlying medical conditions, when vaccine experience is limited, or the vaccine is contraindicated. Combined vaccine and immunoglobulin may be preferred for optimal protection.

- 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.
- Anaphylaxis to Ig has been reported in patients with IgA deficiency.

TABLE 25-2

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 who have clotting factor disorders
Persons with chronic liver disease
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 after the arrival of the adoptee
Anyone who would like to obtain immunity

[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.

HAV, hepatitis A virus.

Source: Centers for Disease Control and Prevention

TABLE 25-3

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	1440 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 (accelerate 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.

ELISA, enzyme-linked immunosorbent assay.

Source: Centers for Disease Control and Prevention

Treatment

- Goals of Treatment: Complete clinical resolution, including reducing complications, normalization of liver function, and reducing infectivity and transmission. No specific treatment options exist for HAV. Management of HAV infection is primarily supportive. Corticosteroid use is not recommended.

HEPATITIS B

- HBV is a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC).
- Transmission of HBV occurs sexually, parenterally, and perinatally. In areas of high HBV prevalence, perinatal transmission from mother to child at birth is most common. In the United States, both homosexual and heterosexual contact are key routes of transmission.
- 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 hepatocellular carcinoma.
- The phases of chronic HBV, with patterns, are noted in **Table 25-4**.
- The interpretation of serologic markers for HBV is given in **Table 25-5**.
- The clinical presentation of HBV infection is given in **Table 25-1**.

TABLE 25-4

Patterns of Chronic Hepatitis B Virus Phases

State	HBeAg Status	ALT Level	HBV DNA IU/mL[a]	Other
Phase 1 (immune tolerant)	+	WNL[b]	>1 million	
Phase 2 (immune active)	+	High	>20,000	ALT intermittently or persistently elevated
	–	WNL	>2000	ALT intermittently or persistently elevated
Phase 3 (inactive carrier)	–	WNL	<2000	Anti-HBe+
Phase 5 (occult infection)	–	WNL	Undetectable	Anti-HBc+, HBsAg–, with or without anti-HBs
Reactivation	±	High	>20,000	Associated with immunosuppressive states or therapies

[a]IU/mL is numerically equivalent to the SI unit of kIU/L.

[b]Per AASLD guidelines, ALT normal limits are defined as <35 IU/L (0.58 µkat/L) (men); <25 IU/L (0.42 µkat/L) (women).

ALT, alanine aminotransferase; DNA, deoxyribonucleic acid; HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus; WNL, within normal limits.

TABLE 25-5

Interpretation of Serologic Tests in Hepatitis B Virus

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

Anti-, antibody to; HBsAg, hepatitis B surface antigen; HBc, hepatitis B core; HBs, hepatitis B surface; IgM, immunoglobulin M.

Note: Anti-HBc includes both IgM anti-HBc and IgG anti-HBc. IgM is present during acute phase of infection.

Source: Data from Hepatitis B Serology, Centers for Disease Control and Prevention. https://www.cdc.gov/hepatitis/hbv/pdfs/serologicchartv8.pdf.

Prevention

- Prophylaxis of HBV can be achieved by vaccination (HBV vaccine) or by passive immunity in postexposure cases with HBV Ig which provides temporary passive immunity.
- The goal of immunization against viral hepatitis is prevention of the short-term viremia that can lead to transmission of infection, clinical disease, and chronic HBV infection.
- Vaccination is the most effective strategy to prevent HBV infection, and a comprehensive vaccination strategy was implemented in the United States. Persons who should receive HBV vaccine are listed in **Table 25-6**.
- 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.

TABLE 25-6

Recommendations for Hepatitis B Virus Vaccination

All infants
All previously unvaccinated children <19 years
All unvaccinated adults aged 19–59 with diabetes; those aged ≥60 should be vaccinated at the discretion of treating clinician
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
STD clinic patients
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, etc.)
All unvaccinated adults seeking vaccination (specific risk factor not required)

ESRD, end-stage renal disease; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; MSM, men who have sex with men; STDs, sexually transmitted diseases.

Treatment

- Goals of therapy: The goals of therapy are to suppress HBV replication and prevent disease progression to cirrhosis and HCC. HBeAg loss, with or without seroconversion to anti-HBeAg in patients who are HBeAg positive, indicates immune control.
- Some patients with chronic HBV infection should be treated. Recommendations for treatment consider the patient's age, serum HBV DNA and ALT levels, and histologic evidence and clinical progression of the disease. Generally accepted criteria for treatment of HBV are given in **Table 25-7**.
- All patients with chronic HBV infection should be counseled on preventing disease transmission, avoiding alcohol, and on being immunized against HAV. Sexual and household contacts should be vaccinated against HBV.
- The immune-mediating agents approved for HBV treatment are interferon **(IFN)-alfa** and **pegylated (peg) IFN-alfa**. The nucleos(t)ide antiviral agents **lamivudine**, **telbivudine**, **adefovir**, **entecavir**, and **tenofovir** diprovoxil and tenofovir alafenamide are approved treatment options for chronic HBV.
- For HBeAg-positive patients, treatment is recommended until HBeAg seroconversion and an undetectable HBV viral load are achieved and for 6 months of additional treatment. In HBeAg-negative patients, treatment should be continued until HBsAg clearance.

TABLE 25-7

Generally Accepted Criteria for Treatment of HBV

Characteristics
Anyone with HBeAg (+) or HBeAg (−) active HBV defined as:
HBV DNA >2000 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 HBV DNA >2000 IU/mL (kIU/L)[c]
Anyone not fulfilling above criteria with ALT <2 × ULN and any detectable HBV DNA (<2000 IU/mL [kIU/L]), consider:
Patient's age
Family history of HCC
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 European guidelines, any detectable HBV DNA.

HEPATITIS C

- HCV is the most common blood-borne pathogen and is most often acquired through injection drug use. Screening for HCV infection is recommended in groups who are at high risk for infection (**Table 25-8**). The U.S. Preventive Services Task Force now recommends hepatitis C screening for everyone between the ages of 18 to 79 years.
- Transmission may occur by sexual contact; hemodialysis; or household, occupational, or perinatal exposure. Multiple sexual partners and coinfection with sexually transmitted diseases, including HIV, increase the risk for HCV sexual transmission.
- HCV is differentiated into six major genotypes (GT), numbered 1–6. GTs are further classified into subtypes (a, b, c, etc.). In the United States, GT1a and GT1b, followed by GT2 and GT3, cause most infections.
- In an acute HCV infection, most patients are asymptomatic and undiagnosed. HCV RNA is detectable within 1–2 weeks of exposure and levels rise quickly during the initial weeks.
- Patients with acute HCV are often asymptomatic and undiagnosed. One-third of adults will experience some mild and nonspecific symptoms, including fatigue, anorexia, weakness, jaundice, abdominal pain, or dark urine. Additional symptoms include right upper quadrant pain, nausea, or poor appetite.
- Up to 85% of acutely infected patients go on to develop chronic HCV infection, defined as persistently detectable HCV RNA for 6 months or more.
- HCV cirrhosis poses a 30% risk of developing end-stage liver disease over 10 years as well as a 1%–2% risk per year of developing hepatocellular carcinoma.

TABLE 25-8

Recommendations for Hepatitis C Virus Screening

All persons between the ages of 18 to 79 years.
Current or past use of injection drugs
Persons with current or past intranasal illicit drug use
Patients who have ever been on hemodialysis
Persons with percutaneous/parenteral exposures in an unregulated setting
Healthcare and public safety workers after a needle-stick or mucosal exposure to HCV-positive blood
Children born to HCV-positive mothers
Received blood transfusions or organ transplantations before July 1992
Received clotting factors before 1987
Persons who were ever incarcerated
Coinfection with HIV
Sexually active persons about to start preexposure prophylaxis for HIV
Patients with unexplained elevated ALT levels or evidence of liver disease
Solid organ donors

ALT, alanine aminotransferase; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

Treatment

- Goals of Treatment: The goal is to eradicate HCV infection, which prevents the development of chronic HCV infection, end-stage liver disease, HCC, and death.
- 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, though this does not imply HCV immunity.
- Treatment is recommended for all HCV-infected persons. Patients with a short life expectancy (<12 months) are currently the only populations for whom treatment is not recommended.
- Before therapy is initiated, quantitative HCV testing and genotyping are performed.
- Recommended treatment regimens for treatment-naïve patients with hepatitis C genotypes 1–3 (in alphabetical order) are given in **Table 25-9**.
- Recommended treatment regimens for treatment-experienced patients with hepatitis C genotypes 1–3 (in alphabetical order) are given in **Table 25-10**.
- 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.
- Adherence to therapy is a crucial component in response, especially among genotype 1–infected patients.
- All patients with chronic HCV infection should be vaccinated for HAV and HBV.
- No HCV vaccine is currently available.

TABLE 25-9

AASLD/IDSA Recommended Treatment Regimens for Treatment-Naïve Patients with Hepatitis C Genotypes 1–3 (in Alphabetical Order)

HCV Genotype	No Cirrhosis	Compensated Cirrhosis (CTP Class A)
1a	Elbasvir/Grazoprevir × 12 weeks[a] Glecaprevir/Pibrentasvir × 8 weeks Ledipasvir/Sofosbuvir × 12 weeks[b] Sofosbuvir/Velpatasvir × 12 weeks	Elbasvir/Grazoprevir × 12 weeks[a] Glecaprevir/Pibrentasvir × 12 weeks Ledipasvir/Sofosbuvir × 12 weeks Sofosbuvir/Velpatasvir × 12 weeks
1b	Elbasvir/Grazoprevir × 12 weeks Glecaprevir/Pibrentasvir × 8 weeks Ledipasvir/Sofosbuvir × 12 weeks[b] Sofosbuvir/Velpatasvir × 12 weeks	Elbasvir/Grazoprevir × 12 weeks Glecaprevir/Pibrentasvir × 12 weeks Ledipasvir/Sofosbuvir × 12 weeks Sofosbuvir/Velpatasvir × 12 weeks
2	Glecaprevir/Pibrentasvir × 8 weeks Sofosbuvir/Velpatasvir × 12 weeks	Glecaprevir/Pibrentasvir × 12 weeks Sofosbuvir/Velpatasvir × 12 weeks
3	Glecaprevir/Pibrentasvir × 8 weeks Sofosbuvir/Velpatasvir × 12 weeks	Glecaprevir/Pibrentasvir × 12 weeks Sofosbuvir/Velpatasvir × 12 weeks[c]

[a]If no NS5A resistance detected.

[b]Eight-week duration may be considered for patients who are not black, not HIV coinfected, and with an HCV RNA <6 million IU/mL (kIU/L).

[c]Pretreatment resistance testing recommended.

CTP, Child–Turcotte–Pugh.

TABLE 25-10

AASLD/IDSA Recommended Treatment Regimens for Treatment-Experienced Patients with Hepatitis C Genotypes 1–3 (in Alphabetical Order)

	Peg-Interferon/Ribavirin TE		NS3 PI + Peg-Interferon TE	
HCV Genotype	**Non-Cirrhotic**	**Compensated Cirrhosis**	**Non-Cirrhotic**	**Compensated Cirrhosis**
1	Elbasvir/Grazoprevir × 12 weeks[a] Glecaprevir/Pibrentasvir × 8 weeks Ledipasvir/Sofosbuvir × 12 weeks Sofosbuvir/Velpatasvir × 12 weeks	Elbasvir/Grazoprevir × 12 weeks[a] Glecaprevir/Pibrentasvir × 12 weeks Sofosbuvir/Velpatasvir × 12 weeks	Ledipasvir/Sofosbuvir × 12 weeks Glecaprevir/Pibrentasvir × 12 weeks Sofosbuvir/Velpatasvir × 12 weeks	Glecaprevir/Pibrentasvir × 12 weeks Sofosbuvir/Velpatasvir × 12 weeks
2	Glecaprevir/Pibrentasvir × 8 weeks Sofosbuvir/Velpatasvir × 12 weeks	Sofosbuvir/Velpatasvir × 12 weeks Glecaprevir/Pibrentasvir × 12 weeks		
3	Sofosbuvir/Velpatasvir × 12 weeks[b]	Elbasvir/Grazoprevir plus Sofosbuvir × 12 weeks Sofosbuvir/Velpatasvir/Voxilaprevir × 12 weeks		

[a]For GT 1a: Recommended treatment if no resistance for NS5A detected.

[b]Resistance testing for Y93 recommended before use; if Y93 present, add ribavirin or use different regimen.

See Chapter 57, Viral Hepatitis, authored by Paulina Deming, for a more detailed discussion of this topic.