Viral Hepatitis

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- Complete the questions at the end of the course.
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Faculty

Kalynn Matisco, APRN, PhD, received an Associate Degree in Nursing from Wallace College in Dothan, Alabama, her BSN from Troy State University, her Masters and Doctoral degrees from University of Alabama at Birmingham, and her Nurse Practitioner education at the University of South Alabama. Dr. Matisco has practiced in a variety of settings, including obstetrics, medical-surgical, dialysis, critical care, nursing education, nursing research, and, most recently, infectious disease. She retired from the University of Florida Division of Infectious Disease and Global Medicine in 2018 and now practices in temporary assignments with underserved populations.

Faculty Disclosure

Contributing faculty, Kalynn Matisco, APRN, PhD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, nurses, pharmacists, and allied staff in all specialties.

Accreditations & Approvals

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This activity has been designated for 5 Lifelong Learning (Part II) credits for the American Board of Pathology Continuing Certification Program.

A complete Works Cited list begins on page 32.

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NetCE designates this activity for 5 hours ACPE credit(s). ACPE Universal Activity Numbers: JA4008164-0000-24-008-H01-P and JA4008164-0000-24-008-H01-T.

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About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement

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Course Objective

The purpose of this course is to provide healthcare professionals with a review of normal liver structure and function, common liver function tests used to assess liver disease, and an overview of the current diagnosis and management of primary viral hepatitis.

Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the structure and function of the liver.
2. Describe the common laboratory measures of liver function and compare and contrast diagnostic testing methods to evaluate the degree of hepatic injury in the patient who presents with hepatitis.
3. Describe the classification of the various hepatitis viruses.
4. Discuss the epidemiology, diagnosis, management, and prevention of hepatitis A and E.
5. Identify the appropriate approach to diagnosis and management of hepatitis B and D, including a strategy for using selective serologic testing.
6. Design a best practice approach to clinical staging and management of chronic hepatitis C infection.
7. Discuss the current options for, and efficacy of, directed antiviral therapy of chronic hepatitis C.
8. Educate patients on the role of liver transplantation in the treatment of end-stage liver disease, including benefits, limitations, and patient selection.

Pharmacy Technician Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the physiology of the liver and the pathophysiology of hepatitis infections.
2. Describe the various hepatitis virus infections and their management.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Hepatitis is an inflammatory state of the liver and may be caused by exposure to toxic chemicals, autoimmune disease, fatty liver disease, or infection. Many common viral infections in humans are associated with mild, usually transient, secondary inflammation of the liver. The term "viral hepatitis" is applied to infection caused by a set of viruses unique in their primary trophism for the liver and their propensity to cause serious, often prolonged "primary" hepatitis. For clinical purposes, the viruses causing primary hepatitis are grouped and classified alphabetically in accordance with when each was identified: hepatitis A, B, C, D, and E. In 1994, hepatitis F was identified as a cause of fulminant liver failure [1]. This was later found to be a variant subspecies of another virus. Therefore, "F" is now omitted in the hepatitis alphabet. A virus similar in structure to hepatitis C was initially designated hepatitis G; however, this virus has been reclassified as a *Pegivirus* GB virus-C (GBV-C) [2]. This virus can cause subclinical infection in humans but is not linked to active disease.

This course will provide information describing normal anatomy and physiology of the liver and the effects of acute and chronic inflammation on the liver structure and function. Diagnostic tests commonly used to assess liver function and as markers of liver disease are reviewed. An overview of the viruses now known to cause primary hepatitis is presented. The history, etiology, pathophysiology, and clinical presentation of each type of viral hepatitis will be discussed. Therapeutic options will be presented, and methods of preventing transmission of viral hepatitis will be delineated.

THE LIVER

The liver is one of the largest organs in the body. The healthy adult liver typically weighs 1.3–1.8 kg and lies just under the diaphragm in the right upper quadrant of the abdomen, with its left lobe extending several centimeters past midline toward the spleen. At the mid-sternal line, the height of the liver is typically 4–8 cm, while at the right mid-clavicular line, it extends 6–12 cm. On inspiration, the edge of the liver may be just palpable in a healthy adult. Because downward displacement of the liver may occur in several conditions without true enlargement of the liver, percussion along with palpation should be used to estimate the size of the liver. Palpation should also be used to evaluate the consistency of the organ [3].

The liver is made up of small lobules. In the center of each lobule is a central vein. Extending from the vein, like the spokes of a wheel, are the hepatic sinusoids, which receive blood from the hepatic artery and the portal vein. Blood flows through these sinusoids and into the central vein. The blood from the central veins then flows into the hepatic vein.

The portal vein brings products of digestion from the intestines to the liver; in doing so, the blood in the portal vein may also contain small numbers of intestinal bacteria. The lining of the sinusoids consists of both epithelial cells, which permit transfer of nutrients, and Kupffer cells. The Kupffer cells are tissue macrophages—cells of the immune system that scavenge stray bacteria entering the liver through the portal circulation.

There are trapezoid-shaped structures between the sinusoid spokes that contain two columns of hepatic cells, sometimes referred to as the hepatic plate, between which lies the bile canaliculus. Bile canaliculi collect bile produced by the hepatic cells and form a conduit to the bile ducts, located in the fibrous tissue between lobules.

Surrounding the columns of hepatic cells is a narrow space entitled the space of Disse. Excess fluid collects in the space of Disse. These spaces connect to the lymphatic vessels, providing a mechanism for fluid removal from the liver.

The liver has many functions. Because of its vascular nature, the liver serves as a blood reservoir. Normally, the liver contains about 450 cc of blood. Because it is distensible, the liver can expand to accommodate up to a liter of extra blood, providing some compensation for fluid overload in conditions such as congestive heart failure or renal failure. Conversely, during hemorrhage or hypovolemic shock, the vessels in the liver respond to circulating vasoconstrictors (such as norepinephrine and angiotensin II), and blood is shunted from the liver into the general circulation.

The liver is responsible for a myriad of metabolic functions. In carbohydrate metabolism, the liver stores glycogen, converts fructose and galactose to glucose, performs gluconeogenesis (i.e., the conversion of constituent substances, such as fatty acids, into glucose), and forms enzymes and other chemicals from the intermediate products of glucose metabolism.

The liver metabolizes fats by oxidizing fatty acids to supply energy. It also synthesizes cholesterol, lipoproteins, and phospholipids. To enhance storage of nutrients, the liver converts excess ingested carbohydrates and protein to fat.

Protein metabolism is also a function of the liver. The liver modifies amino acids from the ingested proteins into a form that is usable by the body. The liver can also convert one amino acid into another in order to supply the body's needs. Urea formation by the liver facilitates the removal of nitrogenous wastes from the body. The liver is also responsible for monitoring plasma oncotic pressure and regulating the synthesis of albumin.

In addition to serving as a blood reservoir and coordinating metabolism, the liver has several other essential functions. The liver serves as a storage center for iron and vitamins A, D, and B12. At least one dozen substances necessary for normal blood coagulation are formed by the liver. Finally, the liver serves to detoxify the body of many drugs, hormones, and other substances, facilitating removal of these toxins in the urine or feces [4].

Chronic inflammation of the liver or injury from prolonged exposure to toxic substances leads to scarring, a replacement of the functioning lobules with fibrous tissue. This condition is commonly termed cirrhosis. Chronic inflammation and cirrhosis are carcinogenic and confer a substantial risk for the eventual development of hepatocellular cancer.

DIAGNOSTIC TESTS OF LIVER FUNCTION AND DISEASE

The role of laboratory tests in establishing a diagnosis of liver disease has gained increasing importance as newer methods of detection and analysis become available. Each of the types of viral hepatitis described in this course has specific tests for the virus and/or the antibody to the virus. The severity of the impact of these viruses upon the liver is measured by less specific tests of general liver function. Patterns of abnormality in liver function tests rather than specific values of a single test permit the clinician to interpret the functional status of the organ. In addition, it is important to note that diseases that are not hepatic in origin can produce abnormalities in liver function tests. These include, but are not limited to, hemolytic diseases, congestive heart failure, sepsis, and other disorders that alter liver perfusion.

Though viral hepatitis can occur without the presence of jaundice, this sign has historically been considered a diagnostic marker for hepatitis. Jaundice results from elevations in the serum bilirubin. The normal level for total serum bilirubin is ≤1.6 mg/dL. In order for clinical jaundice to become detectable, the total serum bilirubin must exceed 2.5 mg/

dL. In most cases of viral hepatitis, the peak serum bilirubin does not exceed 10 mg/dL; levels higher than this are indicative of intra-hepatic cholestasis or extra-hepatic biliary obstruction (e.g., stone or tumor) [5].

Hepatic inflammation leads to excessive release of cellular enzymes into the circulation that serve as sensitive markers of hepatic injury and indicators of disease severity. Two such enzyme markers of liver injury used for clinical purposes are alanine aminotransferase (ALT). Elevated serum levels are seen early in the course of viral hepatitis and in other forms of toxic liver injury, such as caused by alcohol, drugs (e.g., acetaminophen), and poisonings (e.g., carbon tetrachloride). Elevations in ALT and AST are also associated with centrilobular necrosis due to inadequate perfusion in shock states and in cases of biliary obstruction. The normal range for ALT is 7–56 Units/L; the normal range for AST is 5–40 Units/L [6]. There may be slight differences in normal values between men and women.

Albumin levels (normal range: 3.5–5.5 mg/dL) are typically decreased in hepatocellular disease such as hepatitis but are unchanged in uncomplicated obstructive liver disease. Alkaline phosphatase levels (normal range: 44–147 IU/L) remain in the normal range in hemolytic disease, are slightly elevated in hepatocellular disease, and are greatly increased in obstructive liver disease [7].

The presence and degree of liver scarring and cirrhosis are most accurately assessed by liver biopsy. However, liver biopsy is resource-intensive, invasive, and prone to sampling area. Noninvasive techniques, including laboratory testing and imaging techniques, are more readily available and more cost effective. These tests can be used as a starting point in the evaluation of cirrhosis caused not only by chronic viral hepatitis but also due to other etiologies, including alcoholic liver disease, fatty liver disease, and autoimmune hepatitis. If advanced cirrhosis is suggested by these noninvasive tests, referral to a specialist and a liver biopsy are recommended [88].

Estimates of cirrhosis in persons with chronic (not acute) liver disease can be performed using only blood tests. These are commercially available as Fibrotest or the Enhanced Liver Fibrosis (ELF) score. The Fib-4 is a method calculated by the provider, or via an online calculator, using the patient's age, platelet count, ALT, and AST. The Fib-4 score has been found to be efficacious for estimation of minimal to moderate cirrhosis but is less reliable in advanced disease [89]. The prothrombin time (PT), which is dependent on clotting factors produced in the liver, is a sensitive screening test for advanced liver disease (cirrhosis). Prolongation of the PT related to inadequate production of clotting factors begins to occur when 80% or more of the synthetic function of the liver has been lost.

Noninvasive imaging techniques are available to indirectly determine the degree of cirrhosis by measuring organ stiffness. These methods involve sending a sound wave through the liver tissue while imaging with ultrasound or magnetic resonance. Because liver stiffness is affected not only by cirrhosis but also by inflammation and fluid overload, the accuracy of these techniques can be affected by congestive heart failure, renal failure, acute hepatitis, and recent ingestion of ethanol or other liver toxins [90].

The most common method of assessing hepatic elastography, vibration-controlled transient elastography (VCTE), uses a specialized probe that sends a transient acoustic wave through the liver tissues; liver movement is then measured by ultrasound. This method does not produce images but has been found to assess degree of fibrosis with an accuracy of >84% [91]. The presence of ascites or abdominal fat (BMI >35) can adversely affect accuracy. Shear wave elastography (SWE) uses an ultrasound probe and can not only assess the degree of liver stiffness but also produce a two-dimensional image of the study, allowing for visualizing images of liver tissues and decreasing the likelihood of errors due to ascites, masses, or adipose tissue [91].

Magnetic resonance elastography (MRE) also uses an acoustic shear wave to displace liver tissue. As the name implies, magnetic resonance is used to create images during this process. MRE is more costly than VCTE or ultrasound SWE. However, MRE demonstrates improved accuracy in all stages of fibrosis. In addition, variations in the amount of fibrosis in each liver segment are more easily visualized. MRE is considered the most accurate of the elastographic techniques [90; 93].

High-risk patients, persons with HCV who have previously failed HCV treatment, and those whose screening tests do not rule out advanced cirrhosis should be referred to a hepatologist for further evaluation, likely including liver biopsy. For persons without cirrhosis or with only mild-to-moderate cirrhosis, monitoring and treatment by the primary care provider can be considered.

OVERVIEW OF VIRUSES AND VIRAL DISEASES

Viruses are the cause of some of the earliest disease processes recorded in the medical literature. Though the natural history of diseases such as polio, rabies, measles, and smallpox had been described for millennia, the identification of a viral etiology was not made until the beginning of the 20th century. The knowledge of specific viruses, viral life cycle, and viral/host interaction increased dramatically over the next 50 years, leading to the development of vaccines. More recent techniques such as electron microscopy, electrophoresis, x-ray crystallography, and polymerase chain reaction have permitted in-depth studies of viral structure and more precise identification of the viruses that cause specific diseases [8].

Classification of viruses has changed as knowledge of them has increased. Initially, viruses were primarily classified by size, method of transmission, or organ affected in the disease process. Viruses are now classified in relation to the type of nucleic acid in the viral core, either ribonucleic acid (RNA) or deoxyribonucleic acid (DNA). Other determinants include the method of nucleic acid replication, the presence or absence of an envelope, and the symmetry of the viral capsid (protein coat).

The structure of viral core RNA or DNA consists of either a single strand or double strand of nucleic acid. These nucleic acid strands can be circular or linear. Viruses replicate nucleic acid in one of five different methods. Discussion of these complex methods of replication is beyond the scope of this course, but the method by which a virus replicates contributes to its classification.

In the majority of viruses, the nucleic acid is covered with a protein coat called a capsid. Most capsids are either shaped as a helical spiral or as an icosahedral sphere. Some virus capsids are enveloped in an outer lipid layer (the envelope) derived from the host cell.

Using this classification system, poliovirus is classified as a single-stranded RNA virus with an icosahedral capsid and no lipid envelope. Similarly, the herpes simplex virus is classified as a double-stranded DNA virus with an icosahedral capsid and a lipid envelope.

Viruses are unable to replicate outside the host. Therefore, in order to survive and multiply, the virus must interact with host cells in such a way as to "hijack" the cell's mechanism for nucleic acid replication. The first step of this process is attachment, which occurs when proteins on the surface of the virus attach to receptors on the surface of the host cell. After attachment has been accomplished, the virus penetrates the cell membrane. Within the cell, the virus undergoes a process of uncoating as the capsid is removed. After removal of the capsid, replication of the nucleic acid takes place. Next, the nucleic acid of the new viral particles is coated with a capsid. Finally, the new virus leaves the host cell, either through budding or through rupture of the host cell.

Viruses can be transmitted through inhalation of respiratory droplets, percutaneously, or via direct introduction into the gastrointestinal (GI), genitourinary (GU), or respiratory tract. The virus may cause a localized infection at the area of entrance or may travel through the blood stream, lymphatics, or nerve pathways to the target organ(s). In response to viral invasion, nonspecific defense mechanisms and a specific immune response are activated.

Because viruses are intracellular invaders, phagocytosis, the inflammatory response, and antigen/antibody reactions not only result in destruction of viral particles but also may injure or destroy host cells.

CLASSIFICATION OF HEPATITIS VIRUSES

Viral hepatitis can be classified by mode of transmission, by the type of virus, and by chronicity. Hepatitis A (HAV) and E (HEV) are both transmitted by the fecal-oral route while hepatitis B (HBV), C (HCV), and D (HDV) are considered bloodborne pathogens. HBV is a DNA virus; HAV, HCV, HDV, and HEV are RNA viruses. Hepatitis A and E cause acute, usually self-limited illness; hepatitis B, C, and D present with both acute and chronic disease manifestations. The hepatitis viruses represent different families of viruses: hepatitis A is a member of the Picornavirus family; hepatitis B is a Hepadnavirus; hepatitis C is a Flavivirus; hepatitis D is sometimes classified as a Hepadnavirus and sometimes as a satellite virus of HBV; and hepatitis E is of the family Calicivirus. The commonality in these viruses is their trophism for the liver and the ability to cause hepatic inflammation. The differences in the individual viruses account for the tremendous variation in outcome of infection, chronicity of the disease, and the ease with which tests to diagnose the virus and vaccines to prevent the virus are developed.

Because hepatitis A and E share similarities in transmission and absence of chronic sequelae, these disorders, their etiology, pathophysiology, prevention, diagnosis, and treatment will be presented first. The bloodborne hepatitis viruses will then be similarly discussed.

HEPATITIS A

Documents from ancient China describe a contagious jaundice in which the victims experienced symptoms consistent with hepatitis A or E. In the fifth century B.C.E., epidemics of jaundice occurred in Greece and Rome. Outbreaks of jaundice associated with unsanitary conditions during wartime were reported in Europe during the 17th, 18th, and 19th centuries. Analysis of outbreaks of hepatitis during World War II supported the theory that some forms of jaundice resulted from unsanitary conditions while others seemed to be related to a shared percutaneous source of infection (contaminated needle, transfusion, or vaccine). Therefore, hepatitis was classified into two categories: infectious hepatitis and serum hepatitis [9; 10].

The virus associated with hepatitis A was initially identified when viewed in an electron microscope in 1973. Since that time, the virus and the body's response to the virus have been extensively studied.

The World Health Organization (WHO) estimates the annual worldwide incidence of hepatitis A to be 1.5 million per year [13]. Within the United States, diagnosed cases of HAV must be reported to the local health authorities, who in turn report the incidence to the Centers for Disease Control and Prevention (CDC). Many persons who contract HAV, however, do not have clinical symptoms. Therefore, the CDC must estimate the actual incidence of HAV infection based upon CDC reports and projections. For the 10-year period 1999 to 2009, the CDC estimates that 749,000 cases occurred within the United States [11].

Since the introduction of hepatitis A vaccine in 1995, the incidence of hepatitis A in the United States has declined by 95% [11]. However, after falling to a low of 1,239 cases reported in 2014, a series of outbreaks from 2013 to 2023 resulted in a dramatic increase in cases, reaching 12,474 reported cases in 2018 and 18,846 in 2019 [12]. According to the CDC, the drastic increase in incidence was primarily the result of contaminated organic fruit, including strawberries, pomegranate seeds, blackberries, and a mixed antioxidant blend [12].

During a multistate outbreak in 2017, the initial onset of the outbreak followed the usual pattern of a contaminated food source, but outbreaks occurring in intravenous drug users were noted in four states. The initial hypothesis was that transmission occurred through needle sharing while the source patient was viremic in the acute phase of HAV infection. This hypothesis was supported when HAV RNA was extracted from IgM-positive serum samples. Specimens from 1,169 cases in four states were tested, and 1,054 were found to be positive for HAV RNA. The strain of HAV in three of the states was identical, but the strain in the fourth state was unique. While foodborne transmission remains the primary factor identified in multistate outbreaks, after HAV has been introduced into the population, person-to-person spread through both fecal/oral and percutaneous routes can occur [94].

As noted, hepatitis A is transmitted via the fecal-oral route, most commonly from contaminated water or food. After the virus is ingested, it is transported from the intestines to the liver, where it invades the hepatocytes. The virus uses the hepatocytes for viral replication and is then released into the bloodstream and excreted in the stool. HAV that is acquired percutaneously travels directly from the bloodstream to the liver to invade the hepatocytes; viral replication and excretion follow the same pattern as in fecal-oral transmission.

The cellular immune system responds to invasion of hepatocytes with infiltration of the liver by lymphocytes and cytokines. These lymphocytes are toxic to HAV-infected liver cells, thus producing the inflammatory damage to the liver. IgM antibody against HAV is produced, followed by IgG antibody. Levels of IgM antibody appear in the acute stage and decrease to undetectable levels over time. IgG antibody appears later and persists throughout life.

Signs and symptoms of hepatitis A infection can vary from subclinical disease to fulminant (sudden and intense) illness. In symptomatic patients, the incubation period (i.e., time from exposure to onset of illness) is in the range of 15 to 50 days (average: 28 days). Clinical symptoms and signs include nausea, vomiting, headache, fever, chills, abdominal discomfort, hepatomegaly, and right upper quadrant tenderness. For most patients, symptoms are mild and subside in three to seven days. Others will have more significant disease and will progress to an icteric phase (jaundice). For these patients, recovery typically occurs after about three weeks.

Fulminant infection occurs in less than 1% of the cases. Some of these patients may have such severe damage that they require a liver transplant. Fatalities from hepatitis A are extremely rare. There is no known chronic carrier state.

Laboratory studies reflect leukopenia, atypical lymphocytes, and elevated ALT and AST levels. As discussed, anti-HAV IgM can be detected early in the disease, usually appearing in detectable levels 2 to 3 weeks after exposure, then declining to undetectable levels in 12 to 24 weeks. IgG levels begin to rise three to four weeks after exposure and remain elevated throughout life.

Treatment of HAV is supportive and directed at maintaining adequate nutrition and controlling symptoms. Ingestion of alcohol and/or hepatotoxic medications is avoided. For patients with fulminant hepatic failure resulting from HAV, corticosteroids may be used. However, clinical research has not demonstrated improved outcomes in patients receiving corticosteroids when compared to those who did not receive steroid treatment [14].

HEPATITIS A VACCINATION

As with any other disease, prevention is the most effective strategy. Hepatitis A vaccine is licensed in the United States for use in individuals 1 year of age and older. Immunoglobulin (Ig) can provide short-term protection, both pre- and post-exposure (administered within two weeks after exposure for maximum protection). The Advisory Council for Immunization Practices (ACIP) recommends that the following persons be vaccinated against hepatitis A [15; 95]:

- All children at 12 through 23 months of age
- Infants 6 to 11 months of age who will be traveling outside the United States, regardless of the incidence of HAV in the area to which they are traveling. (This dose is not counted as part of the two-dose series.)
- Unvaccinated children and adolescents 2 to 18 years of age
- Healthy persons 1 to 40 years of age who have not previously completed the two-dose series and will be traveling to an area in which HAV is highly or intermediately endemic. These persons should receive the first dose of vaccine as soon as travel is anticipated, whether or not the second dose of vaccine can be completed prior to the trip. Persons older than 40 years of age, persons with immunocompromising conditions, and persons with chronic liver disease planning on traveling to an area with high or intermediate HAV endemicity should receive a single dose of vaccine as soon as travel is considered. Persons traveling in less than two weeks should receive the initial dose of the vaccine and simultaneously may be administered Ig in a different anatomic injection site (e.g., separate limbs).
- Persons who are at increased risk for infection (e.g., men who have sex with men, persons who use injection or non-injection drugs, persons with occupational risk for exposure, persons who anticipate close personal contact with an international adoptee, persons experiencing homelessness)
- Persons at increased risk for complications of hepatitis A (e.g., individuals with chronic liver disease, persons with human immunodeficiency virus [HIV])
- Any person who wishes to obtain immunity (protection)
- Pregnant women at risk for HAV infection or severe outcome from HAV infection
- Unvaccinated persons ≥1 year of age in outbreak settings who are at risk for HAV infection or at risk for severe disease from HAV
- Persons in settings that provide services to adults in which a high proportion of those persons have risk factors for HAV infection

The U.S. Food and Drug Administration (FDA) has approved two single-antigen HAV vaccines and one combination vaccine for use in the United States, all of which are inactivated vaccines. The single-antigen vaccines are Havrix and VAQTA. Both are administered to adults in a dose of 1 mL intramuscularly. The dose for children is 0.5 mL [15]. Single-antigen vaccines are considered interchangeable. A second dose of either vaccine can be administered, regardless of which vaccine was administered as the first dose. Although the manufacturer recommends that the second dose be administered 6 to 12 months after the first, persons who receive the second dose more than 12 months after the first are still considered fully vaccinated. The duration of protection from the vaccine is not fully known. However, studies have shown that immunity persists for at least 25 years [96]. Because the vaccine was not approved until 1995 and became a two-dose series in 1999, studies of persistence beyond 25 years are not available.

An alternative to single-antigen HAV vaccines is Twinrix, which contains inactivated HAV and HBV recombinant vaccines. It is immunogenic against HAV and HBV but requires three injections of 1 mL intramuscularly. The suggested schedule is an initial injection followed by boosters at one and six months. This vaccine is not approved for use in children. Immunity is expected to persist for at least 20 years (and possibly longer) in those who receive all three doses [9; 15].

For individuals who are immunologically intact and do not have chronic liver disease, administering the first dose of HAV is considered to be protective, even if administered less than four weeks prior to HAV exposure. Studies of seroconversion found that the "vast majority of vacinees develop antibodies within two weeks of vaccination, some as early as 12 days after vaccination" [97]. The incubation period for HAV is typically at least 28 days; therefore, in immunologically intact persons without significant liver disease, receiving HAV vaccine just a few days

before travel remains a better option than using Ig for protection. A combination of HAV vaccine and Ig should be considered for persons with chronic liver disease or an immune-compromising condition that inhibits vaccine response [97].

IMMUNOGLOBULIN

Passive immunization with human Ig, preferably administered within two weeks of known or anticipated exposure, provides short-term protection against HAV infection for persons who have not been vaccinated. The single human Ig product licensed for hepatitis A prophylaxis in the United States is GamaSTAN S/D. In July 2017, because of declining levels of anti-HAV IgG in pooled human plasma, the dosing instructions for GamaSTAN S/D were updated. The dosage recommendations for pre- and post-exposure prophylaxis against hepatitis A infection are [15; 16]:

- Pre-exposure:
  - Up to one month of travel: 0.1 mL/kg
  - One to two months of travel: 0.2 mL/kg
  - More than two months of travel: 0.2 mL/kg (repeat every two months)
- Post-exposure: 0.1 mL/kg

DISINFECTION AND HAND HYGIENE

Sanitation strategies are also important in controlling HAV. If in water, the virus is inactivated by boiling the water for five minutes. Hand hygiene using alcohol-based hand sanitizers containing 60% to 95% ethanol are ineffective against HAV, even when in contact with the virus for a full two minutes [17; 98]. Therefore, handwashing with soap and water for at least 20 seconds is recommended rather than hygiene using hand sanitizers. If handwashing with soap and water is not an option, cleansing the hands with povidone-iodine for at least 30 seconds may be considered. While there is no available research supporting the use of povidine-iodine against HAV, a standard povidine-iodine solution has been found to be effective in eliminating coxsackievirus and polio virus from the skin [98; 99]. Coxsackievirus and polio virus are both in the same viral family (Picornavirus) as HAV and have very similar viral structure. Thus, povidine-iodine is anticipated to be effective against HAV when utilized for hand hygiene for at least 30 seconds [99].

HAV is not inactivated by vinegar and may not be inactivated by plant-based disinfectants. A 1:10 solution of bleach in water is effective against HAV, as are hospital-grade disinfectants. If a household cleaner has been tested and found effective against HAV, this will be reflected on the label.

HEPATITIS E

Like hepatitis A, hepatitis E virus is spread through the fecal-oral route, and like HAV, HEV was also first identified via electron microscope examination of stools of infected patients. HEV has been associated with outbreaks in India, Burma, Pakistan, Russia, China, northern and central Africa, Peru, and Mexico. Outbreaks are usually associated with a contaminated water supply. No outbreaks have occurred in the United States or Western Europe, though individual cases have been identified in persons who have recently traveled to areas in which the virus is endemic [18; 19].

HEV most often affects young adults. The incubation period is two to nine weeks, with an average of six weeks. Signs and symptoms are similar to HAV, but with a higher incidence of jaundice, which can be prolonged. The disease is self-limited in the majority of patients. The fatality rate in acute HEV is between 1% and 2%, except in pregnant women. In pregnant women with HEV infection, mortality can reach as high as 30% [19]. No cases of chronic liver disease associated with HEV have been reported.

The treatment of HEV is nonspecific and is directed toward supportive care. Because the incidence of HEV is low and most cases resolve without negative sequelae, the development of a vaccine against HEV has not been a priority for pharmaceutical companies or national and international health agencies. Primary preventive strategies, therefore, concentrate on improved sanitation [19; 20].

HEPATITIS B

The first documented outbreak of "serum hepatitis," as hepatitis B was originally termed, occurred in 1833 among shipyard workers in Bremen, Germany, who had received smallpox vaccine administered with contaminated needles [9]. Throughout the early part of the 20th century, clusters of cases were reported in venereal disease clinics and diabetic clinics in which reuse of contaminated needles and/or syringes had occurred.

In 1965, medical researcher Baruch Blumberg identified a specific antigen in the serum of an Australian Aborigine who had received numerous blood transfusions [18]. This "Australia antigen" was later found to be associated with hepatitis B; its discovery led to rapid advancement in the knowledge of HBV. This antigen has now been renamed the hepatitis B surface antigen (HBsAg). The virus, as well as the typical serologic response pattern of the host, has been extensively studied.

The hepatitis B virus is one of the smallest viruses known to cause disease in animals. Ten HBV genotypes, labeled A through J, and 30 subtypes have been identified [21]. The genotype of the virus influences the likelihood of developing cirrhosis and the response of the virus to therapy with interferon.

HBV consists of a core and an envelope. The envelope contains HBsAg proteins, glycoprotein, and lipids. The core of HBV includes viral DNA, enzymes necessary for replication, and antigenic protein particles distinctly different from those found in the envelope. The viral DNA is circular and predominantly double stranded, but with a single-stranded arc. The core antigen is termed HBcAg.

The virus is resistant to heat and cold and has been shown to survive for more than 15 years when frozen. However, infectivity is lost in albumin and serum after heating for 10 hours at 60°C or 20 minutes at 90°C, respectively. When dry heat is used, HBV is destroyed after one hour at 160°C [22].

Prior to the availability of hepatitis B immunization, 75,000 to 160,000 new cases of hepatitis B were acquired in the Unites States each year, with the highest incidence of new HBV cases being among persons 20 to 39 years of age. The rate of new HBV infections declined between 1990 and 2014, following the recommendation for routine vaccination of children. According to the CDC, only 2,157 cases of acute hepatitis B were reported in the United States during 2020, an incidence rate of 0.7 cases per 100,000 population. After adjusting for underascertainment and under-reporting, an estimated 14,000 cases of acute hepatitis B infection occurred in 2018 [23]. The incidence of new cases is lowest among persons 18 years of age and younger, most likely due to widespread immunization of children in the United States [100]. The exact timing of vaccination for infants differs slightly depending on the infant's birth weight, maternal HBsAg status, and the vaccine used. Often, the first dose of vaccine is administered in an infant's first two days after birth [101].

The natural history of HBV infection is variable and in large part dependent on age at onset. In general, 6% to 10% of persons newly infected will progress to a state of chronic persistent infection [24]. The rate of progression to chronic disease is highest in infants (90%) and children (25% to 50%), with only 5% of adults becoming chronically infected. An estimated 580,000 to 1.17 million people were living with chronic HBV infection in the United States in 2018, with approximately two-thirds of these persons unaware of their infection [102]. Foreign-born people account for 69% of the U.S. population living with chronic HBV infection. There were an estimated 1,752 HBV-related deaths in 2020, which corresponds to an age-adjusted death rate of 0.45 cases per 100,000 population [23]. HBV hepatitis is the leading cause of liver failure leading to transplantation in the world [25].

HBV is a bloodborne pathogen that is typically acquired parenterally, perinatally, or through sexual interaction. As with HIV infection, sexual contact and use of contaminated needles for drug injection are the primary risk factors for HBV [26]. However,

HBV is considered 50 to 100 times more infectious than HIV, requiring a much smaller inoculum for transmission. Thus, a needlestick injury from a source patient who is coinfected with both HBV and HIV is more likely to transmit HBV, even when the needle is solid (e.g., a suture needle) and even when blood is not visible. Because HBV does not transfer across the placenta, perinatal transmission occurs when an infant is exposed to the blood of an infected mother at the time of delivery. Parenteral exposures include occupational exposure of healthcare workers (1%), use of injected drugs (15%), tattoos, ear and body piercing, acupuncture, and blood transfusions received prior to 1980. Rare cases of transfusion-associated HBV continue to occur, indicating that the virus was present in the blood but with antigen levels below the level of laboratory detection [22].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The U.S. Preventive Services Task Force recommends screening for hepatitis B virus infection in adolescents and adults at increased risk for infection. (https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/hepatitis-b-virus-infection-screening. Last accessed February 19, 2024.)

Strength of Recommendation: B (There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.)

The CDC recommends that all adults 18 years and older be screened for hepatitis B at least once in their lifetime using a triple panel test [86]. Those at increased risk for infection (e.g., injecting drug users, those with HCV, incarcerated persons) should be screened periodically. Persons at increased risk for infection include:

- Persons currently or formerly incarcerated in jail, prison, or another detention setting
- Persons with current or past sexually transmitted infections or multiple sex partners
- Persons with current or past HCV infection
- Persons born in regions with an HBV prevalence ≥2%
- United States-born persons who were not vaccinated as infants and whose parents were born in a region of high HBV prevalence (≥8%)
- Persons with HIV infection
- Persons with current or past injection drug use
- Men who have sex with men
- Infants born to people who are HBsAg-positive who have not been fully vaccinated
- Household contact with a person who has HBV infection
- Needle-sharing or sexual contacts of persons with known HBV infection
- Patients receiving predialysis, hemodialysis, peritoneal dialysis, or home dialysis
- Persons with elevated ALT or AST levels of unclear etiology
- Persons who request HBV testing due to the potential reluctance to disclose stigmatizing risk factors

In addition, all pregnant patients should be screened for HBsAg during each pregnancy, preferably in the first trimester, regardless of vaccination status or history of testing. Infants born to HBsAg-positive people should be screened for HBsAg and anti-HBs seromarkers [86].

The incubation period for HBV can be as little as 45 days or as long as 180 days, but most commonly is 60 to 90 days. The severity of primary HBV infection varies from subclinical to fulminant illness. The age of the patient, the integrity of the immune system, and the infecting dose of the virus influence the severity of acute disease. Persons younger than 5 years of age exhibit mild symptoms or no symptoms, while 70% of infected adults exhibit significant clinical symptoms [23].

Signs and symptoms associated with acute HBV infection are similar to those of other acute viral hepatitis syndromes and include malaise, nausea, abdominal discomfort, icterus, and dark urine.

SEROLOGIC MEASURES OF ACUTE AND CHRONIC HBV DISEASE				
Disease State	**HBsAg**	**HBcIgM**	**HBcIgG**	**HBsAb**
Acute HBV infection	+	+ (early)	+ (late)	
Resolved acute HBV infection			+	+
Chronic HBV infection	+		+	
Immunity after vaccination				+

Source: Compiled by Author *Table 1*

Physical examination of the patient typically reveals an enlarged, tender liver and a yellowish hue to the skin. The spleen is palpable in some patients. In patients with fulminant hepatitis, progressive signs of hepatic encephalopathy (e.g., somnolence, confusion, stupor, coma) are common.

HEPATITIS B SEROLOGY

The use of serology for diagnosis and management of HBV infection is important and somewhat complicated. The CDC offers online training for health professionals that covers hepatitis B and other types of viral hepatitis [27].

Serologic testing in hepatitis B typically follows one of two patterns. Within two to four weeks after exposure, HBsAg is detectable in the serum [23]. In acute HBV infection, the antigen remains through the course of the clinical illness, then is cleared after 20 to 24 weeks. Persistence of detectable HBsAg is diagnostic of chronic HBV infection.

The IgM core antibody, also known as anti-HBc IgM, is detectable within two weeks after the HBsAg. In acute HBV infection, soon after the anti-HBc-IgM begins to rise, clinical symptoms are apparent. Anti-HBc-IgM declines after three to six months. The IgG core antibody (anti-HBc-IgG) appears within four to eight weeks after exposure and persists indefinitely.

In acute HBV infection, surface antibody (HBsAb) appears concurrently with clearance of HBsAg from the serum. HBsAb does not develop in patients chronically infected with HBV. Persons who have been immunized against HBV also exhibit a positive HBsAb. See ***Table 1*** for summaries of serologic measures of acute and chronic HBV disease [28].

Serologic testing for hepatitis B occasionally reveals presence of hepatitis B core IgG antibody alone (HBc-IgG or HBcAb total). According to the CDC, four possible interpretations of this result are possible [29]:

- A false positive
- Resolved acute infection in which HBsAb has declined to non-detectable levels (most common)
- Low-level chronic infection in which the HBsAg level is lower than detectable by the laboratory method used
- Resolving acute infection in which the HBsAg level has dropped to non-detectable but the HBsAb level has not yet risen to the detectable range

Subsequent testing, guided by patient history, is advised.

As previously stated, approximately 6% to 10% of persons infected with HBV will develop chronic disease. Those who develop chronic HBV infection have few if any acute symptoms. Development of chronic disease occurs most often in infants, children, and persons with immune compromising conditions such as HIV. Chronic HBV infection is the leading cause of liver failure and liver cancer in the world [9].

There is no specific treatment for acute HBV infection; management is primarily supportive. Control of nausea and vomiting, maintenance of fluid and electrolyte balance, avoidance of potentially hepatotoxic drugs and alcohol, and extended periods of rest are the typical therapies.

In less than 1% of cases, fulminant acute liver failure develops. Treatment for fulminant hepatic failure includes compensating for coagulation defects, correcting acid-base as well as fluid and electrolyte disturbances, prevention of hypoglycemia, administering prophylactic antibiotics, and therapies to reduce ammonia levels and combat cerebral edema. With aggressive therapy, improved intensive care and the use of orthotopic liver transplantation, the mortality rate for fulminant acute hepatic failure has gone down to 40% [30].

CHRONIC HEPATITIS B

Persons diagnosed with chronic HBV infection should be counseled regarding the risk of transmission to others through sexual activity or sharing sharps [31]. In addition, the patient should be cautioned to avoid ingesting alcohol or other hepatotoxic substances. If not previously vaccinated, HAV vaccine should be offered. Household members and sexual partners should be offered HBV vaccine as well.

Immune-directed and specific antiviral therapies are available for the treatment of selective patients with chronic HBV infection. The decision to initiate therapy is based on multiple factors, such as serologic profile, genotype, severity of inflammation, anticipated benefit, and the risks of side effects. Regular follow-up and clinical monitoring are necessary to ensure the safety and efficacy of therapy, detect emerging signs of cirrhosis, and screen periodically for hepatocellular carcinoma. Specific clinical guidance is available from the American Association for the Study of Liver Diseases (AASLD) *Practice Guidelines for the Treatment of Chronic Hepatitis B* [21].

In patients with positive HBsAg and HBcIgG, normal liver enzymes, and a negative hepatitis B early antigen (HBeAg), therapy is usually withheld and the patient's liver function and quantitative HBV-DNA are monitored on a regular basis (every 3 to 6 months). Patients chronically infected with HBV who have abnormal ALT levels should have DNA testing performed to detect pre-core mutants. Pre-core mutants have a defect in the gene necessary to produce HBeAg. Therefore, in patients with a viral type that contains a pre-core mutant, active viral replication of HBV can be occurring without the presence of HBeAg in the blood. This particular mutation of the virus produces a much more rapid demise of the patient's liver and is typically resistant to interferon therapy. A final assessment in the patient with elevated ALT is noninvasive testing for liver fibrosis using blood tests and elastography or referral to a specialist for a liver biopsy to assess the character and extent of liver damage.

At one time, few pharmacologic options were available for the treatment of chronic hepatitis B. Interferon (pegylated in adults, standard for children) is the recommended first-line agent for the treatment of chronic HBV infection, as no other agent with the potential to produce a sustained virologic response (SVR) after the removal of the drug has been identified. SVR is the closest equivalent to a cure for this chronic condition. However, even interferon is less than 40% effective in producing an SVR and is fraught with unpleasant side effects. Because of these factors, patients and providers often choose suppressive therapy instead. The number of medications that can successfully suppress HBV has tripled since 2000, enabling sequential and/or combination dosing for long-term viral suppression.

Immunomodulator therapy with interferon alfa-2b (IFN α2b) has been recognized as helpful in the treatment of chronic HBV since the 1970s. Pegylated interferon contains the addition of a polyethylene glycol, which permits the drug to be administered once weekly rather than the thrice weekly dosing required with standard interferon. Immunomodulators act both by destroying infected hepatocytes and by elevating the body's production of cytokines. Cytokines in turn promote control of viral replication.

After four months of therapy, 32% of persons will demonstrate a sustained loss of HBV from the serum. This viral suppression remains sustained unless the patient becomes immune suppressed. Patients who relapse after PegIFN/IFNα2b therapy and are HBeAg positive will usually respond to reinstitution of therapy [32].

While somewhat successful in clearing HBV from the blood, PegIFN/IFN α2b has significant side effects. These include irritability, flu-like symptoms, nausea, weight loss, cytopenias, depression, suicidal tendencies, thyroid dysfunction, hyperlipidemia, alopecia, skin rash, ophthalmic changes, and dyspnea. Side effects are reportedly milder with PegIFN α2b [21].

Hepatitis B suppressive therapy is accomplished with medications categorized as nucleoside or nucleotide analogues. The available nucleoside and nucleotide analogues target viral transcription of HBV at three different locations in the process of DNA synthesis. Medications available for this indication include adefovir, lamivudine, entecavir, and tenofovir. Entecavir and tenofovir (both tenofovir dipovoxil fumarate [TDF] and tenofovir alafenamide [TAF]) are recommended individually as first line therapy, with TDF the preferred agent for pregnant patients [33]. Adefovir and lamivudine are classified as "non-preferred" therapy [21]. While the manufacturers of emtricitabine have never sought approval for HBV monotherapy, the drug is very similar chemically to lamivudine and many single-tablet regimens available for treatment of HIV include tenofovir and emtricitabine. Based on these facts, research has been conducted to confirm the efficacy of emtricitabine in the treatment of chronic HBV and have found it to be non-inferior to lamivudine [33]. Studies have shown that combination therapy is only advantageous in limited circumstances in which there is resistance to one of the approved first-line monotherapy agents [16; 34; 35].

Several of the medications effective in suppressing HBV are also useful in HIV treatment, with higher doses indicated for HIV suppression than for HBV suppression. In persons coinfected with HIV and HBV, utilizing tenofovir along with lamivudine or emtricitabine in the HIV regimen will also produce HBV suppression. Because use of HBV suppressive doses of adefovir, entecavir, lamivudine, tenofovir, and emtricitabine can result in resistance of HIV to these agents and/or other closely related HIV medications, even at the higher HIV dosages, HIV treatment guidelines now recommend that patients with HIV/HBV co-infection persons be placed on an antiretroviral two-drug combination effective against both HBV and HIV [36].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The American Association for the Study of Liver Diseases (AASLD) recommends antiviral therapy for adults with immune-active chronic hepatitis B infection (hepatitis Be antigen negative or positive) to decrease the risk of liver-related complications.

(https://journals.lww.com/hep/pages/articleviewer.aspx?year=2018&issue=04000&article=00034&type=Fulltext. Last accessed February 19, 2024.)

Level of Evidence/Strength of Recommendation: Moderate/Strong

HEPATITIS B VACCINATION AND PREVENTION

As with hepatitis A and E, prevention is the best method for dealing with hepatitis B. Hepatitis B vaccine has been available since the 1980s and has been recommended as a routine childhood immunization since the early 1990s. Hepatits B vaccine is available in the United States in seven different formulations. Of those seven formulations, only Engerix-B and Recombivax-HB are approved for neonates and in pregnancy. Other HBV vaccines include Heplisav-B and PreHevbrio. Combination vaccines that include HBV vaccine in the formulation include Twinrix (providing immunization against HAV and HBV), Pediarix (containing diphtheria toxoid, tetanus toxoid, acellular pertussis antigens, recombinant HBsAg, and inactivated poliovirus) and Vaxelis (containing diphtheria toxoid, tetanus toxoid, acellular pertussis antigens, inactivated poliovirus, recombinant HBsAg, and *Haemophilus influenzae* type b) [23].

Hepatitis B vaccine is typically administered as a series of three intramuscular injections, the second and third doses given at one month and six months, respectively, after the first dose [23]. In 2017, a two-dose series hepatitis B vaccine for unvaccinated or incompletely vaccinated individuals 18 years of age and older was approved by the FDA [16; 37]. In addition, evidence has indicated that two injections may be sufficient to achieve protection if administered in adolescence [23]. The ACIP recommends all adults 19 to 59 years of age and adults 60 years of age and older with risk factors for hepatitis B infection should receive hepatitis B vaccination [38]. Hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) should be administered to infants weighing at least 2,000 grams born to persons with HBV infection within 12 hours of birth, followed by completion of the vaccine series and postvaccination serologic testing. These neonates should receive hepatitis B vaccination within 24 hours of birth, followed by completion of the vaccine series. If the HBsAg-exposed neonate weighs less than 2,000 grams, the first dose of vaccine should not be counted as part of the three-dose series. Instead, the series is administered when the infant attains a weight of 2,000 grams or 1 month of age, whichever comes first, and at 2 and 7 months of age. All unvaccinated children and adolescents younger than 19 years of age also should receive the vaccine [39].

More than 90% of persons who received HBV vaccine in accordance with the recommended schedule and method of administration will be protected against HBV infection. Therefore, confirmation of protection is not recommended for the general public. Assessment of HBsAb following immunization is recommended for persons who are considered at high risk for HBV exposure, such as healthcare workers. For these persons, the HBsAb level should be assessed one to two months after the third injection. If detectable HBsAb levels are not achieved, the series should be repeated. If the second series fails to produce detectable antibody levels,the vaccine recipient should be tested for HBsAg or HBV qualitative PCR, as chronic HBV would prevent the development of HBsAb. If the vaccine recipient tests negative for HBV, other factors, such as age, obesity, smoking, chronic illness, or an immune-compromising condition that inhibits vaccine response, may be preventing development of protective antibody. In this case, the individual should be considered a nonresponder, and this fact should be documented in the medical record and in the individual's occupational health record.

Persons who have not been immunized (or did not respond to the vaccine) and are exposed to HBV may achieve passive protection from infection by receiving HBIG within seven days of exposure. The usual dose of HBIG is 0.06 mL/kg. For persons who have not been immunized, an accelerated schedule of immunizations is recommended following the dose of HBIG. For documented nonresponders, a second dose of HBIG is appropriate.

Strict adherence to Standard Precautions is recommended in order to prevent exposure to HBV or other bloodborne pathogens. Careful handling of needles is also imperative. Because of the hardiness of HBV even in adverse conditions, caution should be used when cleansing objects contaminated with blood or body secretions, regardless of whether or not the body fluids have dried.

Hepatitis B can be inactivated on surfaces with the use of 1:10 bleach solution or hospital-grade disinfectant. Unlike HAV, alcohol-based hand sanitizers, used for 30 seconds, are effective against HBV [17].

HEPATITIS D

In 1977, a new antigen was detected in patients with hepatitis B. At first it was thought to be a variant of HBV. By 1980, HDV was determined to be a separate virus, but a virus that was dependent upon the presence of HBV in order to replicate [40].

HDV is an RNA virus, the core of which is distinctively different from other viruses. However, due to a defect in replication, HDV is unable to synthesize a viral coat. It must borrow a coat from HBV in order to complete the replication process. Therefore, HDV cannot cause infection independently but instead must exist as a coinfection (acquired at the same time as HBV) or a superinfection (HDV acquired in a patient who is chronically infected with HBV). In the United States, the infection primarily occurs as a coinfection among intravenous drug users. In some areas of the world in which chronic HBV infection is endemic (including the Amazon Basin of South America, China, and Southeast Asia), HDV is more commonly a superinfection [18; 41].

Patients coinfected with HBV and HDV tend to have a more severe case of acute hepatitis. The mortality rate in coinfection has been reported to be as high as 20%. Superinfection with HDV results in rapid progression of cirrhosis, with 70% to 80% of coinfected individuals showing signs of liver failure, compared to 15% to 30% of patients with chronic HBV and no cirrhosis [42]. Prevention of HDV is accomplished through the same means as prevention of hepatitis B. A 12-month course of peginterferon alfa-2a is the recommended treatment for patients with elevated HDV-RNA levels and ALT elevation [21]. Nearly 25% of patients involved in an efficacy study of peginterferon alfa-2a treatment showed sustained clearance of HDV RNA over 48 weeks [43]. Given the limited efficacy of current therapies, it is reasonable to refer patients to specialized centers that offer access to experimental therapies for HDV [21]. Immunization against hepatitis B is effective prevention of HDV also because if the individual is immune to HBV, he/she cannot become infected with HDV. Avoidance of bloodborne pathogen exposure through observance of Standard Precautions is a primary mechanism of prevention for persons already chronically infected with HBV.

HEPATITIS C

After the agents responsible for hepatitis A and hepatitis B were identified and laboratory tests to detect the presence of these agents were available, it became obvious that these two viruses were not the only agents associated with hepatitis. Non-A, Non-B hepatitis became the designation for cases of hepatitis that followed a course indicative of a viral cause, but did not produce laboratory evidence of HAV or HBV. Two separate syndromes of non-A, non-B hepatitis were distinguished; one was present in developing countries and resulted from ingestion of contaminated water (this is now known as HEV), and one was related to blood exposures, particularly transfusions. For more than 10 years, attempts to identify the causative agent for chronic post-transfusion non-A, non-B hepatitis were unsuccessful. In 1989, a cooperative effort between the CDC and a private clinical laboratory was successful in discovering the virus-specific antigen for hepatitis C [44]. Prior to 2014, six genotypes of HCV were known. The commercially available laboratory tests for HCV were developed to detect these genotypes and their subtypes. Likewise, the direct-acting medication developed for treatment of HCV focused on these six genotypes. Because HCV testing could not always recognize a genotype, and medication response was inconsistent in patients for whom a genotype could be designated, unrecognizable viral strains were investigated further. In 2014, genotype 7 was discovered in central Africa, and in 2021, genotype 8 was identified in India [103; 10than as of 2024, eight distinct genotypes and more than 90 subtypes have been identified [46].

Hepatitis C virus is the leading cause of end-stage liver disease and the leading reason for liver transplantation in the United States [45; 47]. Chronic HCV infection has also been associated with membranoproliferative glomerulonephritis, cryoglobulinemia, and B-cell lymphoma [45]. Coinfection of HCV with HIV occurs in 50% to 90% of persons who acquired HIV through injection drug use [48].

HCV occurs throughout the world, with endemic rates varying widely. The WHO estimates that 10% of the population of the Middle East, Africa, and Eastern Europe are infected with HCV. In the United States, an estimated 1.8% of the population (approximately 4 million people) is infected with HCV, and only about half of those infected are aware that they are. Rates of HCV in the United States have increased dramatically since 2010. This has been primarily attributed to the nation's opioid crisis and increased infection among injecting drug users. In 2021, 5,023 new cases of acute HCV were reported, an increase of 492% since 2010 and 129% since 2014 [49]. After adjusting for under-ascertainment and under-reporting, an estimated 69,800 acute hepatitis C cases occurred in 2021 [49]. In addition, 107,540 cases of newly identified chronic hepatitis C were reported in 2021 [49]. The highest incidence rates of newly acquired HCV infection occurs in persons 30 to 39 years of age (3.5 per 100,000 population) followed by persons 20 to 29 years of age (2.5 cases per 100,000 population), similar to the age groups at highest risk for fatal overdose and age at initiation of injection drug use among certain U.S. populations [49]. Compared with 2006, rates in 2021 were substantially higher among all race and ethnicity categories [49]. During 2021, rates of reported cases of acute HCV ranged from a low of 0.3 cases per 100,000 population among non-Hispanic Asian/Pacific Islander persons to a high of 2.7 cases per 100,000 population among non-Hispanic American Indian/Alaska Native persons [49].

The demographic data for those currently living with HCV are somewhat different from that of new cases. The highest prevalence of persons living with HCV is among persons 30 to 39 years of age. The rate is higher among American Indian/Alaska Natives than among other ethnicities and higher among men than women [49]. Educational level and income are independent predictors of HCV acquisition, with the rate of HCV higher in persons who have not completed high school and in those living below the poverty level [50].

In the United States, the mortality rate attributable to HCV infection is now greater than the rate associated with 60 other infectious diseases reported to the CDC, including HIV infection [51; 52]. Individuals born between 1945 and 1964, or "baby boomers," account for the vast majority of HCV fatalities, often acquiring HCV during adolescence or young adulthood through experimentation with injection or inhaled drugs [53]. Between 1999 and 2007, approximately 75% of HCV fatalities occurred among this population, increasing to 82.5% of HCV fatalities between 2014 and 2018 [51]. A 2023 report from the CDC suggests that the majority of people with HCV still have not been cured nearly a decade after direct-acting antiviral agents were first approved in the United States [54]. The U.S. Preventive Services Task Force recommends one-time screening for HCV infection in all adults 18 to 79 years of age regardless of risk level [55]. In addition, the CDC recommends universal HCV screening for all U.S. adults, for all pregnant women during every pregnancy, for any requesting screening, and periodically in those persons with risk factors [45].

The U.S. Preventive Services Task Force recommends screening for hepatitis C virus infection in adults 18 to 79 years of age. (https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/hepatitis-c-screening. Last accessed February 19, 2024.)

Strength of Recommendation: B (There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.)

HCV is considered a bloodborne pathogen. The most common source of infection is percutaneous or parenteral exposure through transfusion, use of injectable drugs, and occupational injury of healthcare providers with a contaminated sharp object. The blood supply in the United States has been tested for hepatitis C since the early 1990s. Now that more advanced screening tests for HCV are used in blood banks, the risk is considered to be

less than 1 chance per 2 million units transfused [45]. Therefore, the annual incidence rate of HCV transmission from transfusion therapy since 1994 is less than one case per 100,000 population. In 2016, the CDC issued a health advisory due to an increasing number of acute HCV infections among persons undergoing hemodialysis [56].

The overall risk of transmission from patients with HCV infection to their infants is approximately 4% to 8% per pregnancy [45]. Transmission occurs during pregnancy or childbirth. There is no prophylaxis available to protect the newborn from infection. The risk is significantly higher if the mother has a high HCV viral load or is co-infected with poorly controlled HIV. Among pregnant women co-infected with HCV and poorly controlled HIV, the rate of transmission ranges from 8% to 15% [57]. Most infants infected with HCV at birth have no symptoms [45]. As such, the CDC recommends testing all infants perinatally exposed to HCV at 2 to 6 months of age, or up to 18 months of age if not previously tested [87]. Because infants of HCV-infected mothers carry maternal antibodies for up to 18 months, regardless of whether or not the infant is infected with the virus, antibody testing of infants should not be performed [87].

Transmission of HCV through vaginal intercourse is inefficient, with the transmission rate in long-term mutually monogamous partners who were not using barrier protection reported by various studies as 0% to 21% [44]. HCV is present in menstrual blood; therefore, intercourse during the menstrual period is considered to be higher risk than intercourse when menstrual blood is not present. Studies of transmission among men who have sex with men indicates rates of transmission similar to that in heterosexual intercourse, with the highest incidence of infection among those with more than 50 partners per year [55]. For persons whose first sexual experience occurs before 18 years of age, prevalence of HCV infection is almost three times higher than in those who are celibate until after the age of 18 years [55].

Intranasal cocaine use has been associated with HCV transmission, presumably resulting from sharing nasal straws contaminated with blood. History of tattoo is considered a risk factor for HCV infection, although no cases of transmission have been linked to licensed, commercial tattoo parlors [45]. Unregulated tattooing and piercing (as is done in prisons and other informal settings) is often not in accordance with infection control practices and may be a risk; however, it is unclear the extent to which these practices occur in the United States [45]. Transmission of HCV has also been documented through sharing of toothbrushes or razors [31].

The incubation period for HCV varies widely, from a mean of 7 to 10 weeks and a range of 2 to 20 weeks. HCV antibody is detectable in 80% of cases 15 weeks after exposure and in 97% of cases by 6 months after exposure. People with recently acquired acute infection typically have detectable HCV RNA levels as early as one to two weeks after exposure to the virus [45]. During the acute phase of the infection, 60% to 70% of HCV positive persons will be asymptomatic; approximately 20% of patients will develop mild jaundice, and the remaining persons will have generalized nonspecific symptoms, such as anorexia, nausea, fatigue, malaise, and abdominal pain. During this phase, serum ALT and AST levels are elevated then return to normal range. Fulminant acute hepatitis associated with HCV is rare [30; 58].

After the acute infection, 15% to 25% of patients will demonstrate an absence of HCV RNA in the serum and normalization of liver enzymes, within six months indicating resolution of the infection and clearance of the virus from the body. The presence of detectable HCV RNA in persons who test positive for HCV antibody is 74% in the general population. However, the rate of progression to chronic infection is higher in some subpopulations. In particular, the progression rate is more than 90% in African American individuals and as high as 98% in African American men. In those persons in whom HCV RNA remains detectable, indicating continued

presence of the virus, 30% to 40% will maintain normal ALT levels and will show no evidence of chronic liver disease. The remaining 60% to 70% of chronically infected patients will have fluctuating ALT levels indicative of chronic liver disease and risk of subsequent progression to cirrhosis. On rare occasions, a patient will demonstrate positive HCV RNA without the presence of HCV antibody. Therefore, in a patient who exhibits chronic hepatitis without apparent cause, assessment of HCV RNA may be indicated [45; 59].

Chronic hepatitis from HCV infection usually progresses slowly, with cirrhosis developing in 20% to 25% of patients over a period of 20 to 30 years. However, persons with HCV infection whose daily ethanol consumption exceeds 50 g (about 3.5 standard drinks) per day are twice as likely as nondrinkers to develop cirrhosis and progress to cirrhosis more quickly (in as little as 10 years) [60]. Of those with cirrhosis, 25% eventually develop hepatocellular carcinoma. Persons who ingest alcohol or who were older than 40 years of age at the onset of infection have a more rapid progression of cirrhosis. Men have a higher incidence of cirrhosis than women. Persons with non-alcoholic fatty liver disease (NAFLD) and those receiving immunosuppressive therapy are also more likely to progress to cirrhosis [105].

Because acute HCV infection can be asymptomatic, the first indication of the presence of chronic HCV infection may be elevated liver enzymes on laboratory testing obtained in connection with another clinical condition or routine health examination. In evaluating the cause of liver enzyme elevation, a hepatitis panel is typically ordered. The first tests FDA approved specifically for HCV infection were tests for HCV antibody (anti-HCV). The presence of anti-HCV does not differentiate between acute, chronic, or resolved HCV infection.

Testing for the presence of HCV RNA has become the accepted method of confirming current HCV infection (acute or chronic) [45]. Qualitative HCV RNA testing determines whether or not hepatitis C viral particles are present in the blood and can therefore differentiate between resolved and continued infection. Quantitative HCV RNA testing evaluates the amount of hepatitis C virus in the blood and can be used to guide therapy [45; 61]. In most commercial laboratories, a positive HCV antibody test triggers a reflex test for quantitative HCV RNA; qualitative HCV RNA is rarely performed.

As noted, based upon genetic characteristics, eight genotypes and more than 90 different subtypes of HCV virus have been identified. Because the genotypes respond differently to therapy, genotypic testing should be performed for persons with chronic progressive HCV infection who are considering antiviral therapy [45]. In the United States, genotype 1 accounts for 60% to 75% of HCV infections and genotypes 2 and 3 account for about 25% [62].

MANAGEMENT OF PATIENTS WITH CHRONIC HCV INFECTION

All persons diagnosed with HCV should be instructed regarding prevention of transmission to others, as well as the natural history of the disease, self-care (including avoidance of alcohol and toxins), and treatment options. Clinical management of HCV-positive patients, including decisions with respect to antiviral therapy, varies in relation to age, severity of the hepatitis and associated fibrosis, the presence or absence of complications and comorbidities, and the genotype of the infecting strain. The patient discovered to be HCV-positive should be evaluated for the presence and severity of liver disease, including signs of chronic liver disease and complications. This assessment, along with the decision to begin specific antiviral therapy, is usually initiated by primary care providers in consultation with a specialist in gastroenterology or infectious diseases. Consultation with a healthcare provider with expertise in pediatric hepatitis C management is recommended for all infants and children with detectable HCV RNA [87].

Prior to 2011, HCV therapy relied on interferon-based regimens (standard IFN with or without ribivirin prior to 2002, and PegIFN with ribavirin from 2002 to 2011). Treatment was prolonged, cumbersome, and fraught with adverse effects and high relapse rates. Consequently, healthy patients with normal hepatic enzymes or only mild elevations and no overt evidence of chronic liver disease were often managed expectantly while monitoring the clinical course and laboratory parameters every 6 to 12 months [63]. In patients with fluctuating ALT levels or those in whom ALT levels remained elevated, liver biopsy provided an assessment of the degree of hepatic inflammation and fibrosis. If the biopsy revealed anything more than mild inflammatory change, such as portal or bridging fibrosis, moderate inflammation, or focal necrosis, then antiviral therapy was recommended.

The treatment of HCV infection has advanced rapidly following the introduction of anti-HCV protease inhibitors in 2011. These newer, direct-acting antiviral drug combinations are highly effective and relatively free of side effects; thus, therapy is now considered for virtually all patients diagnosed with HCV infection [64]. In order to provide healthcare professionals with timely guidance, the IDSA and the AASLD have developed evidence-based recommendations for the diagnosis and management of hepatitis C infection, last updated in 2023. However, due to the rapidly evolving nature of new therapies and other developments, the ISDA and the AASLD recommend reviewing current recommendations online, available at https://www.hcvguidelines.org [64].

The ISDA/AASLD 2023 guidelines emphasize that treatment is recommended for all patients with chronic HCV infection, except those with a short life expectancy that cannot be remediated by HCV therapy, liver transplantation, or another directed therapy [64]. Prior to treatment, patients should be educated regarding proper administration of medications, adherence, and prevention of reinfection. Pretreatment assessment to facilitate decision making regarding the treatment strategy and to determine the need for initiating additional measures for the management of cirrhosis (e.g., hepatocellular carcinoma screening) is recommended in all patients, and should include [64]:

- HCV quantitative RNA and genotype
- Evaluation for degree of fibrosis using the FIB-4 score (calculator available at https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4) and noninvasive elastography
- HBsAg, HBcAb, and HBsAb testing (with HBV vaccine for those without evidence of immunity)
- HAV antibody testing (with HAV vaccine for those without evidence of immunity)
- Medication reconciliation, including over-the-counter drugs and herbal/dietary supplements
- Potential drug-drug interaction assessment

Recognizing that incomplete medication adherence is well known, HCV guidance includes an algorithm for the management of incomplete adherence as part of treatment monitoring [65].

In addition, pretreatment laboratory testing should include [64]:

- Within six months:
  - Complete blood count (CBC)
  - International normalized ratio (INR)
  - Hepatic function panel
  - Estimated glomerular filtration rate (eGFR)
- Any time prior to starting antiviral treatment:
  - HIV antigen/antibody test
  - Hepatitis B surface antigen
- Before initiating antiviral therapy with a regimen that includes ribavirin:
  - Serum pregnancy testing and counseling to women of childbearing age

Patients are candidates for antiviral therapy when there is ongoing active infection over a six-month period, as evidenced by detectable HCV in the blood. The 2023 AASLD/IDSA HCV treatment guidelines recommend treating acute HCV infection defined as patients positive for HCV RNA for less than six months) as well as those with chronic HCV. Selection of the treatment approach is based on determination of the infecting HCV genotype, prior treatment failure, and degree of advanced liver disease. Treatment-naive individuals with no-to-moderate liver fibrosis (F-score of F0 to F2) are typically candidates for management in the primary care office [106; 107]. Patients with scores of F3 (bridging fibrosis) or F4 (cirrhosis) should be referred to a gastroenterologist, hepatologist, or infectious disease specialist for consultation and/or care. In persons with decompensated cirrhosis, referral for evaluation for liver transplantation should be considered [64]. The goal of antiviral therapy in patients with chronic HCV infection is to clear demonstrable viral RNA from the blood stream, reducing the burden of viral replication to such a low level that the patient's own immune system will be able to eradicate the infection. This in turn changes the natural history of this chronic illness, alleviating morbidity and the risk of further complications or need for transplantation. The criterion for achievement of this goal is a sustained virologic response (SVR), defined as undetectable HCV RNA by PCR for at least 12 weeks after completion of a course of therapy. SVR is a marker for cure of HCV infection and has been shown to be durable in large prospective studies in more than 99% of patients followed up for five or more years [66].

Coinfection with HIV and HCV results in a much higher rate of progression to liver failure than infection with HCV alone. Low CD4 levels cannot effectively inhibit HCV replication. Hepatotoxicity of antiretroviral agents may also accelerate the rate of fibrosis, even in immunocompetent persons with HIV. Therefore, all patients coinfected with HIV and HCV should be evaluated for HCV therapy [36].

Direct-Acting Antiviral Therapy for HCV Infection

In 2011, the FDA approved the first protease inhibitors for the treatment of chronic HCV: boceprevir and telaprevir. Both agents were withdrawn in 2015 due to availability of more effective and better tolerated agents [69]. Since 2013, additional agents were approved for treatment, then single agents were replaced with combination regimens. As of 2024, available combination direct-acting antiviral therapy medications include elbasvir-grazoprevir, glecaprevir-pibrentasvir, ledipasvir-sofosbuvir, sofosbuvir-velpatasvir, and sofosbuvir-velpatasvir-voxilaprevir. Protease inhibitors are not advised for use in patients with severe liver disease (Child-Turcotte-Pugh B or C cirrhosis). Therefore, combination medications containing voxilaprevir, glecaprevir, and grazoprevir have limited use in this population. However, in patients with decompensated cirrhosis and few treatment options, clinicians may offer therapy that contains one of these, with careful monitoring and adjustment of therapy as necessary.

Guidance for treatment of chronic HCV changes frequently. In making treatment decisions, clinicians should review current guidelines provided jointly by the ISDA/AASLD online at https://www.hcvguidelines.org. As of updated guidance published in 2023, the ISDA/AASLD guideline recommends, for treatment of adults with genotype 1, 2, 4, 5, or 6 and no advanced liver disease, a regimen of either sofosbuvir/velpatasvir for 12 weeks or glecaprevir/pibrentasvir for 8 weeks. For genotype 3, testing for the presence of genetic mutation Y93H should be completed. Those without this mutation can take either of these two regimens. If Y93H mutation is present, glecaprevir/pibrentasvir is the recommended regimen [64; 65].

Glecaprevir/pibrentasvir has a lower success rate in genotypes 3 and 4 (96%, compared with 98% in genotypes 1, 2, 5, and 6). Sofosbuvir/velpatasvir exhibits 99% efficacy in genotypes 1, 2, 4, 5, and 6 and 97% efficacy in genotype 3. Sofosbuvir/velpatasvir can also be utilized in persons with advanced firbrosis (F3) or cirrhosis (F4). At present,

glecaprevir/pibrentasvir is available in the branded form only, while sofosbuvir/velpatasvir is available in generic form. The decreased cost of the generic drug paired with the fact that it can be used for persons with and without advanced liver disease makes sofosbuvir/velpatasvir the often preferred agent for third party payors or organizations with restricted formularies (e.g., correctional facilities).

The ISDA/AASLD provides specific guidance regarding treatment regimens for persons with comorbidities such as renal failure, HIV/HCV coinfection, history of solid organ transplantation, decompensated cirrhosis, and those who fail initial treatment with direct-acting antiviral therapy.

During treatment, routine laboratory monitoring of hepatic function or inflammation is not indicated in persons without advanced liver disease. Because of drug-drug interactions between warfarin and direct-acting antiviral therapy, periodic INR should be assessed for patients on warfarin in order to evaluate for subtherapeutic anticoagulation. Drug-drug interactions of direct-acting antiviral therapy and medications used to treat type 2 diabetes can lead to hypoglycemia. Thus, persons on oral diabetes medications should be counseled about the potential for this interaction. No other laboratory studies are required for monitoring.

HCV quantitative RNA should be assessed 12 to 24 weeks after the conclusion of the recommended course of therapy. Persons with sustained virological response at 12 weeks or greater have less than 1% chance of re-emergence of the original infection. They can, however, become re-infected if high-risk practices are continued or re-initiated.

Achieving and maintaining SVR has positive effects on both hepatic and extrahepatic manifestations of HCV infection. These improvements include fibrosis regression, reduction in portal hypertension, reduction in the incidence of hepatocellular carcinoma, reduced incidence of myocardial infarction, reduced incidence of stroke, lower rate of insulin resistance and type 2 diabetes, improved quality of life, and lower all-cause mortality rate [109].

Even in compliant patients, treatment failures can occur. Factors that correlate with treatment failure include degree of fibrosis; the presence of advanced fibrosis in genotype 3 is particularly prone to treatment failure. Other factors that can affect treatment success include age older than 55 years, male sex, and Hispanic or Black ethnicity/race. Fortunately, prior treatment with interferon-based regimens does not usually prevent achieving SVR with direct-acting antiviral therapy. However, prior incomplete or inconsistent treatment with direct-acting antiviral therapy can lead to medication-resistant infection and treatment failure [110]. Patients who experience treatment failure should be referred to a specialist for re-treatment. Monitoring of liver function should be continued by the specialist or primary care provider at least every six months until retreatment is initiated [64].

As noted, infants who are noted perinatally exposed to HCV should have HCV RNA testing at 2 to 6 months of age. Repeat HCV RNA testing, with genotype determination, should be performed when the child is 3 years of age. If viremia remains and genotype 1, 4, 5, or 6 is identified, a weight-based course of ledipasvir-sofosbuvir can be initiated, with an expected SVR in 98% of children. For children with genotype 1-6 and no evidence of fibrosis level 3 or 4, treatment with a weight-based dose of either sofosbuvir-velpatasvir or glecaprevir-pibrentasvir can be accomplished. After successful treatment with any of these three regimens, liver damage caused by HCV usually resolves and these children show no evidence or residual effects three [64; 65].

For patients with cirrhosis secondary to chronic HCV or HBV infection that has gone untreated or failed therapy, liver transplantation may be indicated. Replacing the liver, however, does not cure the infection. The transplanted liver will also become infected, and immunosuppressive agents facilitate the progression of this infection. At present, chronic viral hepatitis is the most common diagnosis of persons receiving liver transplants in the United States [45].

Because hepatitis C is a bloodborne pathogen, prevention is similar to that for hepatitis B. Observing Standard Precautions is essential. No vaccine is as yet available for prevention of hepatitis C, and Ig has no role in prophylaxis.

HEPATITIS G

In 1995, a virus similar to the HCV was identified and designated hepatitis G. This discovery was confirmed by another laboratory the following year. Although this virus was often found in the blood of patients with Hepatitis C, it was never found to independently cause liver disease in humans. Upon further study, the virus was classified within the Pegivirus genus of Flavivirdiae, the same family as HCV but different genus. Because the virus was not implicated in human liver disease, if was renamed GBV-C [75].

This virus is transmitted through blood, either through percutaneous injury or blood transfusion, or through sexual contact. Persons coinfected with GBV-C and HIV-1 exhibit slowed progression of HIV disease. At least eight different mechanisms of GBV-C interference HIV/T-cell interaction have been identified. However, because highly active antiretroviral medications are more effective in preventing HIV progression than GBV-C co-infection, development of an HIV treatment using GBV-C is unlikely [2].

LIVER TRANSPLANTATION

Liver transplantation, one of the most common types of solid organ transplant, is the replacement of the diseased liver by an allograft from a brain-dead donor or a partial replacement of the liver by a living related donor. Dr. T.E. Starzl and associates at the University of Colorado pioneered this treatment modality in the early 1960s. By the end of the decade, surgeons in Pennsylvania and England were performing the procedure. By the beginning of the 21st century, liver transplantation had been performed at dozens of medical centers in the United States, Canada, and Western Europe. Although survival rates in the early programs were only 30%, improvements in technique and timing of the transplant have now brought the one-year survival rate to approximately 90% and the five-year survival rate to approximately 75% [76]. The rate of recurrence of liver disease in the transplanted organ varies depending upon the disease or liver injury that necessitated transplantation. Untreated viral hepatitis infects the allograft as soon as the organ is reperfused with the recipient's blood and can lead to failure of the graft in as little as five years. As anticipated, the rate of recurrence in transplants that occur as a result of acute liver failure from toxic exposures (e.g., acetaminophen overdose, mushroom poisoning) is essentially zero [112].

Children and adults who have irreversible liver disease or defects that cannot be overcome or managed by medical options are candidates for liver transplants. In children, the most common reasons for liver transplantation include biliary atresia, neonatal hepatitis, congenital hepatic fibrosis, alpha 1-antitrypsin deficiency, and disorders of metabolism that result in inappropriate storage within the liver or significant liver damage from the buildup of metabolites. The most common diseases necessitating liver transplantation in adults are chronic viral hepatitis (HCV in the United States, HBV in Europe), biliary cirrhosis, alcoholic cirrhosis, sclerosing cholangitis, cryptogenic cirrhosis, Caroli disease, primary hepatocellular malignancies, hepatic adenomas, and hepatic vein thrombosis [25; 77]. Biliary atresia remains a common indication for liver transplantation in pediatric patients [78].

The Model for End-Stage Liver Disease (MELD) is a prognostic system that is now widely accepted as a tool for predicting survival of patients with cirrhosis. MELD, in conjunction with international normalized ratio, serum creatinine, serum bilirubin, and sodium, has been evaluated as a prognostic indicator for cirrhosis regardless of cause. Transplant centers utilize the MELD score in prioritizing clients for transplant [76; 79]. The Pediatric End-Stage Liver Disease (PELD) is used for children younger than 12 years of age [76].

Though patients may have a disease process that is an indication for liver transplant, the presence of compounding factors may provide a contraindication for the therapy. At one time, HIV disease was considered a contraindication for liver transplant. While patients with advanced HIV disease are not transplant candidates, HIV disease that is in an early stage or is controlled by antiretroviral therapy is no longer a contraindication for transplantation therapy. Similarly, persons older than 60 years of age were at one time excluded from this therapy, but persons older than 60 years of age who are healthy other than their liver disease can now be considered for candidacy. Active drug or alcohol use, metastatic cancer, uncontrolled bacterial or fungal infections, advanced cardiac or lung disease, uncorrectable anatomic anomalies that preclude transplantation, persistent non-adherence to medical care, and acute liver failure with a sustained intracranial pressure >50 mm Hg or a cerebral perfusion pressure <40 mm Hg are considered contraindications to liver transplantation in most centers [112].

Relative contraindications for liver transplantation are those factors that in isolation would not preclude a patient from receiving a transplant but in combination might decrease the probability that the patient would be approved. Examples of relative contraindications include chronic HBV with rapidly replicating virus, significant psychiatric disorder that may interfere with the patient's ability to follow the post-transplant regimen, significant renal disease not associated with the hepatic disease, and previous hepatic or biliary surgery [77].

Historically, donor organs have been obtained from cadavers. In 1998, the use of living related donors became an option in certain cases [80; 81]. Partial liver transplantation from living related donors results in a 20% morbidity rate for the donor. Therefore, cadaveric transplant remains the procedure of choice. The following discussion addresses only cadaveric transplants.

In 2020, the Organ Procurement and Transplantation Network implemented a new liver distribution system called the acuity circle policy, which emphasizes the medical urgency of liver transplant candidates and the distance between the donor and transplant hospitals. The new system replaces the use of decades-old geographic boundaries of 58 donation service areas and 11 transplant regions [82]. Under the new policy, livers from all deceased donors will first be offered to the most urgent liver transplant candidates listed at transplant hospitals within a radius of 500 nautical miles of the donor hospital. Following offers to the most urgent candidates, livers from adult donors will be offered to candidates at hospitals within distances of 150, 250, and 500 nautical miles of the donor hospital. These offers are grouped by medical urgency [76].

Donor livers are usually obtained from brain-dead persons younger than 60 years of age who are free from bloodborne pathogen infections (HCV, HBV, HIV), are not septic, have no existing liver disease, and have not recently experienced abdominal trauma. Some centers consider the use of livers from HBV- or HCV-infected donors for recipients infected with the same strain or subspecies of virus [83]. When donor livers are infected but not yet showing signs of cirrhosis, preliminary results indicate that recipient outcomes are not significantly different from those receiving uninfected livers.

Donor and recipient should have compatible body size and A, B, O blood groups. Unlike kidney transplants, however, donor and recipient do not have to have matching tissue types. The liver is viable for up to 20 hours after removal from the donor, but most centers prefer for the transplant surgery to be completed within 12 hours after organ harvest.

Liver transplantation surgery typically requires a procedure of 6 to 12 hours in duration; in more complex circumstances, the surgery has lasted up to 18 hours. During the procedure, the patient is at risk for coagulopathies, electrolyte disturbances, hypoglycemia, and a large volume of blood loss.

In order to prevent rejection of the transplanted organ, immunosuppressive agents are initiated at the time of transplant. Therapy is then adjusted and continued long-term at maintenance doses for the life of the graft. In most transplant centers, initial therapy consists of a glucocorticoid, a calcineurin inhibitor (usually tacrolimus;), and an antimetabolite (usually mycophenolate mofetil). Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, can be useful as a replacement for tacrolimus in patients with renal insufficiency [92]. For patients who have contraindications to glucocorticoids, monoclonal antibody therapy with basiliximab intraoperatively and on day 4 can be used as an alternative to glucocorticoids.

For maintenance immunosuppression, various combinations of immunosuppressive drugs are used to reduce the probability of post-transplant rejection. The choice of medications and the dose of these medications varies depending upon factors such as the recipient's renal function and tolerance of the drug, as well as the underlying disease process that led to transplantation. For example, glucocorticoids are typically continued in patients with autoimmune hepatitis. It is desirable to try to prevent or minimize the adverse effects of these drugs, including infections, malignancy, and general drug toxicity. Therefore, the lowest effective dose and least toxic regimen that is still efficacious in preventing rejection is selected for each patient and adjusted as needed. For most patients, an effective single-drug regimen for maintenance therapy is established within six months of transplantation. Continued attention to therapeutic drug monitoring and drug/drug interactions is essential [92].

Post-transplant patients require regular monitoring for transplant-related complications, including rejection and complications of immunosuppressive medications, including, but not limited to, infection, renal insufficiency, hypertension, malignancy, diabetes mellitus, obesity, hyperlipidemia, and bone disease. The process of rejection is insidious in the majority of liver transplantation cases; acute rejection occurs in 10% to 30% of liver transplant recipients, typically within the first three to six months after transplant [108]. Acute rejection can usually be reversed with methylprednisone with transition to oral prednisone. Approximately 10% to 20% of patients do not respond to initial or repeat dosing of antirejection steroids. For these patients, antithymocyte globulin monoclonal antibody (typically basiliximab) may be used. Acute rejection episodes seldom threaten graft survival; approximately 5% of patients who experience acute rejection will progress to chronic rejection despite immunosuppressive therapy. As of 2022, overall graft failure rate was 14.6% at three years and 21.6% at five years [111].

Five-year survival rates following liver transplant vary based upon recipient age, the disease process that necessitated transplant, and presence of comorbid conditions. The lowest survival rate is among recipients of transplants who are older than 65 years of age at the time of transplant, persons whose transplants were the result of acute liver failure, and those who received transplants due to hepatocellular carcinoma. However, the overall five-year survival rates for adults with deceased donors exceeds 75%. Except for recipients receiving transplants due to acute liver failure, five-year survival rates for adults with living donors was at least 80% [111].

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

Obtaining a detailed patient history is a vital aspect of diagnosing viral hepatitis, particularly those that are rare or that display similar signs and symptoms to other conditions. Furthermore, communication with patients regarding diagnostic procedures, treatment regimens, and prevention of hepatitis depends on clear communication between the patient and clinician. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required.

In the increasingly multicultural landscape of the United States, interpreters are a valuable resource to help bridge the communication and cultural gap between patients or caregivers and practitioners. Interpreters are more than passive agents who translate and transmit information from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter. When interacting with patients for whom English is a second language, the consideration of the use of an interpreter and/or patient education materials in their native language may improve understanding and outcomes.

CASE STUDIES

HEPATITIS A

Patient A is 19 years of age and a college sophomore who presented to her physician's office with mild jaundice. The patient reports being in good health until a week before, at which time she began having flu-like symptoms of headache, low-grade fever, nausea, loss of appetite, and malaise. She self-treated the fever with acetaminophen. The symptoms persisted. Upon awakening this morning, she noticed that her eyes were yellow. She therefore contacted her physician's office.

In response to her physician's questions, she indicated that her urine has been darker than usual and she has been experiencing joint pain for the last three days. She also acknowledged that her stools have been lighter than usual.

Her medical history is positive for mild exercise-induced asthma, for which she uses a prophylactic bronchodilating inhaler. Her only other routine medication is a daily vitamin/mineral supplement. She reports no surgeries. Family history is positive for cardiovascular disease (father and both sets of grandparents) and breast cancer (mother).

Other significant history includes that she was immunized against hepatitis B in infancy and she recently participated in a two-week mission trip to Central America. Although she was very cautious about the foods she ingested during the mission trip, the patient indicated that a primary recreational activity after the day's work was to swim in the lagoon near the village. The lagoon was fed both by the stream in which the natives washed their clothes and the adjacent bay. Rainfall averaged 2–3 inches per day. Patient A returned to the United States five weeks ago.

Physical examination revealed a well-developed, well-nourished female who was alert and oriented. Her temperature was 99.7°F; other vital signs were within normal limits. Abnormal physical findings included mild icterus of sclera and skin, abdominal tenderness, hepatomegaly, and palpable spleen. Results of laboratory tests are indicated in ***Table 2***.

Case Study Discussion

Patient A has presented with classic signs and symptoms of acute hepatitis. Based on her past history, travel, and exposure history, the most likely diagnosis is acute hepatitis A infection. The hepatic chemistry profile and serologic studies confirm this diagnosis. Exposure probably resulted from accidental ingestion of contaminated water while swimming in the lagoon.

Because acute viral hepatitis is usually a self-limited disease and Patient A is alert with no evidence of coagulopathy, she can be managed as an outpatient with close follow-up. Liver enzymes and PT should be monitored every 5 to 7 days for the first two weeks, then, if convalescence is satisfactory, at 14-day intervals until function test results have returned to normal. Bed rest is not indicated, but the patient should avoid strenuous activity. She should eat a well-balanced diet and abstain from alcohol for the duration of the illness. Because acetaminophen can be toxic to the liver, ibuprofen would be a better alternative for controlling fever. No other alterations in the patient's medications are necessary at this point. If nausea precludes the patient from ingesting food and fluids, IV replacement of fluids

PATIENT A LABORATORY TEST RESULTS		
Test	**Patient's Results**	**Normal Value or Range**
Hematocrit (Hct)	40%	37% to 47%
Hemoglobin (Hgb)	13.3 mg/dL	12.0–16.0 mg/dL
White blood cell count	6200 cell/microliter	4300–10,800 cells/microliter
Aspartate aminotransferase (AST)	323 Units/L	5–40 Units/L
Alanine aminotransferase (ALT)	358 Units/L	5–35 Units/L
Total bilirubin	3.7 mg/dL	0.2–1.6 mg/dL
HBsAg	Negative	Negative
HBsAb	Positive	Positive indicates previous disease or immunization; negative indicates no exposure
Anti-HAV IgM	Positive	Negative
Anti-HCV antibody	Negative	Negative
Alkaline phosphatase (ALP)	85 Units/mL	30–115 Units/mL
Prothrombin time (PT)	11.6 seconds	Control 10.4 seconds (normal is ±2.0 seconds from control)
Albumin	3.8 mg/dL	3.5–5.5 mg/dL
Glucose	84 mg/dL	70–110 mg/dL
Sodium	142 mEq/L	135–150 mEq/L
Chloride	102 mEq/L	100–108 mEq/L
Potassium	3.8 mEq/L	3.6–4.8 mEq/L

Source: Compiled by Author *Table 2*

and electrolytes may be necessary. In the event the patient develops bleeding tendencies or signs of encephalopathy, she should immediately be taken to the hospital or her physician's office.

Hepatitis A virus is a reportable disease. The health department should be informed of the case immediately. Because the exposure probably occurred outside the geographical area, follow-up will be limited to those with similar exposure (i.e., persons who were also on the mission trip) and to her intimate and/or household contacts. A single dose of HAV immunoglobulin is recommended for close contacts. If immunoglobulin is not available, administration of hepatitis A vaccine may prevent illness or lessen the severity of the contact's symptoms if infection does occur. Immunoglobulin is not recommended for those who may have been exposed on the mission trip, as those exposures occurred more than two weeks prior to the diagnosis. Follow-up with these persons is primarily to determine if they too are experiencing symptoms and are possible sources of spreading the disease.

CHRONIC HEPATITIS C

Patient B is a paramedic, 48 years of age. Laboratory work obtained during his annual physical examination reveals hyperlipidemia; CBC, glucose, BUN, and electrolytes were within normal range. With the exception of his weight (15 lbs heavier than indicated for his height), his exam identifies no abnormalities.

After two months of a diet and exercise program, his cholesterol level is 256. Therefore, his physician elects to begin a lipid-lowering agent. A baseline liver profile is drawn prior to initiation of the medication. Because the patient is in a profession that is high-risk for bloodborne pathogen exposure, an HCV antibody test with reflex to qualitative HCV RNA is ordered. The liver profile reveals an AST of 226 Units/L and an ALT of 282 Units/L. HCV antibody and reflex quantitative HCV RNA are both positive.

The physician reviews Patient B's history and medications. He has been a paramedic for 25 years. He was immunized against HBV in 1988. During his career, he has experienced several exposures to blood (usually blood splashes, but also two needlesticks from IV needles), most before the advent of Standard Precautions. His most recent exposure was two years ago. An HIV test six months post-exposure was negative. He does not recall hepatitis testing being performed at that time.

Patient B's surgical history includes a hernia repair in childhood and removal of skin lesions three times in the past eight years. He has had no transfusions. He is the widowed father of two teenage children. His wife died six years ago from ovarian cancer.

The patient has never smoked. He drinks about six beers per week and rarely drinks hard liquor. He denies any history of illegal drug use. Although the patient has no current prescription medications, he uses several herbal preparations including garlic, ginkgo, and an antioxidant preparation. The patient takes ibuprofen for pain, consuming 6 to 10 tablets (200 mg each) per month.

Although alcohol consumption and herbal antioxidants can both cause liver inflammation, the degree of his liver inflammation is much higher than would be expected from limited use of these two factors. The patient is diagnosed with chronic HCV infection.

In order to evaluate the extent of liver damage and determine an appropriate treatment plan, the physician orders an HCV RNA quantitative PCR and genotype as well as a repeat hepatic panel, platelet count, and PT. Shear wave elastography is also ordered. The laboratory results are:

- Platelets: 237 × 10_9/L
- ALT: 253 Units/L
- AST: 214 Units/L
- PT INR: 1.0
- HCV RNA: 350,000 IU/L
- HCV genotype: 3

Based upon these laboratory results, the calculated Fib-4 score is 2.72.The elastography reflects a fibrosis score of F1. No masses are identified on ultrasound. Because the genotype of the virus is 3, resistance testing is ordered. Substitution mutation Y93H is not present.

Treatment options appropriate for HCV genotype 3, and the timing of therapy in relation to his degree of fibrosis and anticipated progression of disease are discussed with Patient B. He is advised to eat a nutritious, balanced diet and abstain completely from alcohol. Although he is not currently sexually active, the patient is educated about the low but present risk of sexual transmission of HCV and how to minimize the risk of transmission. A test for HAV antibody is found to be negative. Immunization against HAV is also recommended, as acquiring an acute case of HAV in a patient with pre-existing chronic hepatitis can be much more serious that either condition alone. He is also provided pneumococcal immunization, as persons with chronic liver disease are at increased risk of pneumococcal infection and complications. Because of uncertainty as to how recently he acquired the infection, the decision is made to defer treatment for three to four months while monitoring the course of the infection.

Four months after the initial diagnosis, there has been no improvement in Patient B's liver function tests: the ALT is 318 Units/L and AST is 287 Units/L. The HCV RNA remains detectable in the blood, and the viral load has increased to 450,000 phages/cc. He is advised to begin antiviral treatment; therapeutic options are discussed in relation to efficacy, potential drug interactions, and cost reimbursement priorities, bearing in mind that he is a treatment-naïve patient with no evidence of cirrhosis. The recommended course of therapy is the 12-week, two-drug oral regimen of sofosbuvir (400 mg) and velpatasvir (100 mg) for a duration of 12 weeks (reported SVR rate: 95% in clinical trials for genotype 3).

On treatment, the patient experiences transient nausea and persistent mild fatigue, but is compliant with the recommended duration of therapy. At 12 weeks, the ALT and AST are both within normal range and HCV RNA is undetectable. Patient B is asked to return in three months to continue his hyperlipidemia treatment follow-up.

HIV AND CHRONIC HBV COINFECTION

Patient C is a man, 32 years of age, with a history of injection drug use, who participated in a free HIV testing day. His screening test was found to be positive. A confirmatory test conducted at the health department was also positive. He has therefore been referred to the Infectious Disease Clinic of a large university medical center for follow up.

During his first visit, the patient indicates that he injected drugs off and on beginning at 19 years of age. His first two experiences with rehabilitation failed, but he has been "clean" for two years, since his best friend died of an overdose. He reports that he also snorted cocaine occasionally during the years he used injected drugs.

The patient's medical history includes a hospitalization for a motorcycle accident at age 24, with surgery on his right leg both on that admission and again about a year later. He received 2 units of blood during the first admission. The patient denies a history of heart disease, neurologic disorders, or endocrine disorders. He has had pneumonia both in adolescence and again last year.

The patient's parents are living and in good health. Grandparents all have hypertension, and maternal grandmother has type 2 diabetes. The patient smokes 1/2 to 1 pack of cigarettes per day and consumes two or three drinks per day. The patient's current medications include acetaminophen or ibuprofen as needed for leg pain and paroxetine for anxiety and depression.

Physical examination reveals no acute distress. Vital signs are within normal limits, and sclerae are non-icteric. Oral cavity is free from thrush and leukoplakia. Cervical lymph nodes are palpable but moveable and nontender. Heart sounds are normal; lungs are clear. Abdomen is soft; both liver and spleen are palpable. Neurologic exam is normal. The patient has full function in upper extremities and left leg; right leg has a slight decrease in strength and a moderate decrease in range of motion.

Initial laboratory tests ordered by the nurse practitioner (NP) include an HIV PCR viral load, a CD4 count, a CBC, a chemistry panel, and a liver profile. Because of the high incidence of HCV and/or HBV coinfection in persons whose HIV was acquired percutaneously, the NP also orders a hepatitis profile. Baseline tuberculosis testing is also recommended for persons with HIV who are entering care. Therefore, a T-SPOT interferon gamma release assay is also ordered. The patient is instructed to return in 72 hours to review lab results and formulate a treatment plan.

Upon his return, all results except the HIV PCR are available. His CD4 count is 246. Hematocrit is 44%, hemoglobin 15 gm/dL, and WBC is 3,800. The liver profile reveals an alkaline phosphatase of 143 Units/mL, AST 358 Units/L, ALT 383 Units/L, total bilirubin 1.2 mg/dL, and albumin 2.8 gm/dL. The remainder of the chemistry panel is unremarkable. Hepatitis profile is positive for HBsAg, HBeAg, and total anti-HBc. The anti-HAV, anti-HCV and anti-HBc IgM are negative. The T-SPOT TB test is negative.

The NP informs Patient C that he is coinfected with HIV and HBV and instructs him about the problems associated with HIV/HBV coinfection. He is given HAV and pneumococcal immunizations and options for antiretroviral therapy are discussed. Because of its effectiveness against both HIV and HBV, a medication regimen including tenofovir with lamivudine or tenofovir with emtricitabine should be utilized. A third medication for HIV viral suppression should be added, with consideration of the hepatotoxicity profile of the medication. After discussing available options with limited hepatotoxicity, an integrase inhibitor is selected as the third active agent in the combination. A single tablet medication containing bictegravir, emtricitabine, and tenofovir alafenamide in a once daily formulation was therefore selected to treat both HIV and HBV.

Information is provided to Patient C regarding safe sex practices. He is also instructed to abstain from alcohol and to use ibuprofen (or no more than 2 g acetaminophen in 24 hours) for pain control. The NP also orders a PT to be drawn; in addition, the patient is referred to hepatology for a liver biopsy to be performed in order to evaluate the progression of the liver disease. The patient is scheduled for a follow-up visit in four weeks, with a repeat HIV PCR performed at that time. In the interim, his baseline HIV PCR is found to be 123,000.

Upon his return to the office, Patient C is advised that the liver biopsy revealed periportal inflammation with focal necrosis and bridging fibrosis. PT is 15.6 seconds (control: 12 seconds). These findings indicate severe, advanced liver disease and the guarded prognosis. Because of the severity of his liver disease, he is not a good candidate for PegIFN therapy. The patient's current HIV status precludes his being a transplant candidate at the time. The recommended treatment plan for Patient C is to maximize his HIV suppression while minimizing his continued liver damage. If he is compliant with his therapy, he should be able to maintain a fairly good quality of life and postpone liver failure for three years or more. Prolonging the time until liver failure also provides the opportunity to improve immunocompetency. Some liver transplant centers now accept HIV-positive patients, provided that HIV viral loads are undetectable and CD4 counts are sufficiently high (usually >500). Patient C's future, therefore, depends upon his tolerance of the regimen, his compliance with the treatment plan, and his body's response to therapy.

The patient will initially be followed on a monthly basis. The viral load will be checked one month after the initiation of therapy, then every three months thereafter. Liver profile, CBC, and amylase will be assessed after one month, then bimonthly. After three months, HIV and HBV quantitative PCRs will be measured. If both are well suppressed, follow-up will be extended to every two to three months. If the patient's liver function significantly deteriorates, supportive therapy for end-stage liver disease will be instituted.

CONCLUSION

Viral hepatitis represents a diverse spectrum of causative agents. These agents can cause an equally diverse spectrum of severity of symptoms and outcomes. Prevention is the most effective strategy for dealing with viral hepatitis. When preventive efforts fail, therapy for acute disease is primarily supportive. Treatment of chronic hepatitis disease is an evolving process, with new medications and combinations producing promising results.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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