

Viral Hepatitis

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Faculty

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Faculty Disclosure

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

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

Audience

This course is designed for dental professionals in all specialties.

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Course Objective

The purpose of this course is to provide dental 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 select the appropriate tests to assess the nature and degree of hepatic injury in the patient who presents with hepatitis.
3. Describe the classification of the various hepatitis viruses.
4. Discuss the epidemiology, 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.



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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, 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), formerly known as serum glutamic pyruvic transaminase or SGPT, and aspartate aminotransferase (AST), formerly called serum glutamic-oxaloacetic transaminase or SGOT. 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 (acetaminophen), and poisonings (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 best determined by liver biopsy, though noninvasive imaging techniques are now available to assess this indirectly by measuring organ stiffness. 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.

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.

By law, 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, there was an 850% increase in incidence by 2018, reaching 12,474 reported cases, the highest number in more than a decade [12]. According to the CDC, the drastic increase in incidence between 2014 and 2018 was "primarily due to unprecedented person-to-person outbreaks reported in 24 states among people who use drugs and people experiencing homelessness" and foodborne transmission [12]. The World Health Organization (WHO) estimates the annual worldwide incidence to be 1.5 million per year [13].

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. The cellular immune system responds 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]:

- All children ≥ 1 year of age who are infected with HIV
- Unvaccinated children and adolescents 2 to 18 years of age
- Persons who are at increased risk for infection (e.g., international travelers, 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. It is suggested that travelers to endemic regions receive the initial injection at least one month prior to travel. A booster dose six months after the initial injection is useful and may provide lifelong protection [15].

An alternative 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].

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 for 30 seconds is not effective against HAV [17]. Therefore, handwashing with soap and water for at least 20 seconds is recommended rather than hygiene using hand sanitizers. If handwashing facilities are not available, an alcohol-based sanitizer may be used for a minimum of one minute of contact time.

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 have been identified; these have been labeled A through J [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 United 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 under-ascertainment and under-reporting, an estimated 14,000 cases of acute hepatitis B infection occurred in 2018 [23].

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. 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 coinfecting 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].



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. 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 HBeIgG, 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 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 α 2b) 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/IFN α 2b therapy and are HBeAg positive will usually respond to reinstitution of therapy [32].

While somewhat successful in clearing HBV from the blood, PegIFN/IFN α 2b 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 α 2b [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, telbivudine, 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, lamivudine, and telbivudine 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 coinfecting 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].



The American Association for the Study of Liver Diseases (AASLD) recommends antiviral therapy for adults with immune-active chronic hepatitis B infection (hepatitis B 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. 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 born to persons with HBV infection within 12 hours of birth, followed by completion of the vaccine series and postvaccination serologic testing. All neonates should receive hepatitis B vaccination within 24 hours of birth, followed by completion of the vaccine series. 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 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.

As noted, the FDA has approved the combination HAV/HBV vaccine known as Twinrix. It is administered on the same schedule as hepatitis B vaccine, with doses at 0, 1, and 6 months. Although this vaccine does not shorten the immunization schedule, the combination vaccine provides dual protection with three injections instead of five. This vaccine is particularly popular with travelers. HBV vaccine is also a component of the pediatric combination vaccine Pediarix and combines HBV, diphtheria, acellular pertussis, tetanus, and inactivated polio virus vaccines [16].

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 coinfecting 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 coinfecting 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]. At this time, seven distinct genotypes and more than 80 subtypes of HCV have been identified [18; 45; 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 HCV were reported, compared with 2,194 in 2014, an increase of 129% [49]. After adjusting for under-ascertainment and under-reporting, an estimated 69,800 acute hepatitis C cases occurred 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].

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].

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



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 health-care 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

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, indicating resolution of the infection and clearance of the virus from the body. 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.

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]. Two methods have been developed for performing quantitative tests: polymerase chain reaction (PCR) and branched deoxyribonucleic acid signal amplification (bDNA). Because the two methods are performed using different standards, the results obtained cannot be compared with each other. Therefore, for purposes of monitoring therapy, the same type of quantitative test should be used consistently.

As noted, based upon genetic characteristics, seven genotypes and many 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

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 IDSA and the AASLD recommend reviewing current recommendations online, available at <https://www.hcvguidelines.org> [64].

The IDSA/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]. 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]:

- Evaluation for advanced fibrosis using the FIB-4 score (calculator available at <https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4>)
- Cirrhosis assessment
- Medication reconciliation, including over-the-counter drugs and herbal/dietary supplements
- Potential drug-drug interaction assessment
- Education regarding proper administration of medications, adherence, and prevention of reinfection

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:
 - Quantitative HCV RNA (HCV viral load)
 - 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 child-bearing 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 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]. Selection of treatment options is based on determination of the infecting HCV genotype.

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 coinfecting with HIV and HCV should be evaluated for HCV therapy [36].

Interferon-Based Regimens for Treatment of HCV Infection

Historically, the regimen most commonly prescribed for persons with progressing liver damage from HCV was IFN α 2a or IFN α 2b, 3 million units administered subcutaneously three times per week, for 6 to 12 months. With IFN α 2b alone, an SVR and improvement on post-treatment biopsy could be achieved in only about 50% of treated patients. Persons with genotype 1 were less likely to respond to medication therapy than those infected with other genotypes. When therapy was stopped, 50% to 70% of responders experienced a relapse.

The co-administration of an antiviral agent, ribavirin, twice daily in conjunction with the usual IFN regimen received approval by the FDA in 1999. After 24 weeks of dual-drug therapy, 40% of patients previously untreated and 50% of patients who had relapsed after IFN alone demonstrated a sustained response to therapy [50].

As mentioned in the treatment of chronic hepatitis B, PegIFN α 2b, the sustained-release form of the medication, was approved in 2002. It has an injection schedule of only once a week. This form of interferon demonstrates response rates of 25% to 40% when used alone and has fewer patient reports of side effects [67].

Between 2002 and 2011, the standard treatment for patients with chronic HCV infection was the combination regimen of pegylated interferon and ribavirin. In clinical trials, groups treated with the combination of pegylated interferon and ribavirin showed better drug tolerance and a significantly higher SVR rate than those groups treated with conventional interferon and ribavirin [68].

The limitations of interferon-based (cytokine) therapy alone or in combination with ribavirin are multiple: the need for parenteral administration, long duration of treatment, less than satisfactory sustained response, and high adverse effects profile. Side effects of interferon, as discussed in the treatment of hepatitis B, include irritability, flu-like symptoms, nausea, weight loss, cytopenia, depression, suicidal tendencies, thyroid dysfunction, hyperlipidemia, alopecia, skin rash, ophthalmic changes, and dyspnea. Ribavirin has also been associated with negative side effects, the most profound of which is birth defects. Women should not become pregnant and men should not impregnate a woman during therapy or for six months after therapy is discontinued [16]. In addition to the side effects occurring during treatment with an immunomodulator, the risk of hepatocellular carcinoma may increase in persons who have undergone interferon therapy.

Because it has the poorest safety profile of all the HCV antiviral agents, with few exceptions Peg-IFN is no longer recommended in combination regimens [50].

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]. In 2013, the FDA approved two additional direct-acting antiviral drugs: simeprevir, a protease inhibitor that blocks a specific protein needed for HCV replication, and sofosbuvir, a nucleotide analogue that inhibits HCV NS5B polymerase, an enzyme necessary for viral replication [16]. While simeprevir is no longer recommended by the AASLD and the IDSA, sofosbuvir, in combination with other appropriate agents, is recommended for HCV infection (all genotypes) in limited situations [16]. In 2015, the combination of ombitasvir, paritaprevir, and ritonavir (as a single agent under

the brand name Technivie) was approved for use in combination with ribavirin for the treatment of genotype 4 HCV infection [70]. This combination regimen is no longer recommended by the AASLD and IDSA for treatment of HCV infection [16]. It should be noted that none of the drugs were discontinued due to safety profile [16; 70].

In 2017, the FDA approved the combination glecaprevir and pibrentasvir, and in 2020, combination sofosbuvir and velpatasvir was approved for the treatment of HCV infection in patients with any of the six HCV genotypes with mild or no cirrhosis [16; 65; 71; 72].

Since 2015, the therapy of chronic HCV infection has advanced further as the results of new clinical trials demonstrate that non-interferon combinations of oral direct-acting antiviral agents can achieve even higher SVR rates in less time with fewer side effects [64; 73; 74]. These studies selected patients with genotype 1 and include patients with varying degrees of chronic liver disease. All were treated with the combination of sofosbuvir and ledipasvir, an oral direct-acting antiviral drug with potent activity against HCV administered as a single oral dose once daily. Multiple trials of 8-, 12-, and 24-week duration showed consistent and comparable results, with SVR rates of 93% to 99% (without need for interferon or ribavirin) [74]. In previously untreated patients without cirrhosis, an 8-week course of therapy was as effective as 12 weeks (SVR rate 94% vs. 95%).

The efficacy and safety of therapy directed at HCV has improved greatly in recent years with the advent of these newer, highly potent antiviral agents. Standard interferon-based regimens in combination with older antivirals have been superseded by combination oral regimens that are safer, of shorter duration, and achieve SVR rates greater than 90% [73]. The downside of these combination direct-acting antiviral drug regimens is their high cost, which compromises accessibility for some patients [74].

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 initial treatment of HCV with glecaprevir (300 mg)/pibrentasvir (120 mg) for a duration of 8 weeks or sofosbuvir (400 mg)/velpatasvir (100 mg) for a duration of 12 weeks for treatment-naïve patients without cirrhosis [64; 65]. For treatment-naïve patients with compensated cirrhosis, glecaprevir (300 mg)/pibrentasvir (120 mg) for a duration of 8 weeks is recommended for genotypes 1–6, and sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks is recommended for genotypes 1, 2, 4, 5, or 6 [64; 65]. In patients in whom prior therapy failed, guidelines for retreatment can be found at <https://www.hcvguidelines.org/treatment-experienced> [64].

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 Flaviviridae, the same family as HCV but different genus. Because the virus was not implicated in human liver disease, it was renamed GBV-C [75].

This virus is transmitted through blood, either through percutaneous injury or blood transfusion, or through sexual contact. Persons coinfecting 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].

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, and uncorrectable life-threatening congenital anomalies remain contraindications for liver transplantation.

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.

Various combinations of immunosuppressive drugs (monoclonal and polyclonal antibodies) have been used to reduce the probability of post-transplant rejection. It is desirable to try to prevent or minimize the adverse effects of these drugs, including infections, malignancy, and general drug toxicity. In the immediate post-transplant period, a common drug regimen includes a combination of a monoclonal antibody, mycophenolate mofetil, corticosteroids, and a calcineurin inhibitor such as cyclosporine or tacrolimus [25]. According to Hanto, the addition of an anti-IL-2 receptor monoclonal antibody (basiliximab or daclizumab) can result in a decrease in rejection rate from 43.5% to 35.1% [84]. Sirolimus is a newer drug that appears to be useful, especially in patients with renal insufficiency.

Chronic suppressive therapy is usually accomplished with tacrolimus and mycophenolate mofetil. Steroids are weaned within a few weeks of transplantation, except in the presence of autoimmune hepatitis. Liver transplant recipients require lower doses of immunosuppressive therapy than patients receiving other solid organ transplants. Nevertheless, providers should be attentive to drug-drug interactions and therapeutic monitoring of these medications [85].

The process of rejection is insidious in the majority of liver transplantation cases; hyperacute rejection rarely occurs. Most episodes of acute rejection occur within the first six months after the transplant (usually between three and six months) but can be reversed with steroids. In approximately 10% to 20% of patients, steroid resistance occurs, requiring treatment with a monoclonal antibody, such as muromonab-CD3, or a polyclonal antibody, such as thymoglobulin [84]. Acute rejection episodes seldom threaten graft survival. Patient survival rates are 84% with living-donor grafts and 83% with deceased-donor grafts at one year and 34% with living-donor grafts and 46% with deceased-donor grafts at five years [85].

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.

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

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 at 12 years of age 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 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 qualitative 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 PT. A gastroenterology specialist is consulted for further evaluation and possible liver biopsy and to co-manage the patient. The PT is within normal range. The liver biopsy reveals chronic inflammatory infiltration of the por-

tal areas with minimal fibrosis. Genotype identifies the virus as type 3. HCV RNA viral load is 350,000 phages/cc.

Treatment options appropriate for HCV genotype 3, and the timing of therapy in relation to biopsy findings 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 than either condition alone. 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 356 Units/L and AST is 418 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. Treatment is discontinued and Patient B is asked to return in three months, six months, and one year after cessation of therapy to repeat HCV viral load and confirm a sustained virologic response.

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 PPD is negative.

The NP informs Patient C that he is coinfecting 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 bicitgravir, 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 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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