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Advances in the diagnosis and management of human viral hepatitis

Christine Wisnom, RN, BS[a,*],
Michael A. Siegel, DDS, MS[b]

[a]*Baltimore College of Dental Surgery Dental School, University of Maryland–Baltimore, 666 West Baltimore Street, Baltimore, MD 21201-1586, USA*
[b]*Department of Diagnostic Sciences, Nova Southeastern University, School of Dentistry, Fort Launderdale, FL 33328–2018, USA*

Virologists theorize that the human hepatitis viruses have existed for longer than 2500 years [1]; however, technology was not sophisticated enough to identify the first human hepatitis virus in a cell culture until 1979 [1]. Since that time, the science of hepatology has identified several types of viral hepatitis including hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), hepatitis E virus (HEV), hepatitis F virus (HFV), hepatitis G virus (HGV), and the newly discovered transfusion-transmitted virus (TTV) [2]. Undoubtedly, in the future, virologists will identify many more hepatitis viruses yet undiscovered.

Hepatitis is defined as an inflammation of the liver in which diffuse or patchy necrosis causes damage to the liver acini, resulting in destruction of the organ's architecture [3]. A multitude of etiologic agents are responsible for hepatitis. Most hepatitis is of viral origin; Box 1 [4] illustrates the major causes of this disease, with a few examples listed in each category.

The signs, symptoms, and stages of viral hepatitis vary greatly. Patients infected with hepatitis types A through G and TTV may be totally asymptomatic. When symptoms are experienced, they are often described as flulike. The signs and symptoms may include one or any combination of the following: fever, nausea, vomiting, diarrhea, joint and muscle pain, anorexia, jaundice, hepatomegaly, abdominal and gastric distention, dark urine, fatigue, bruising, rash, and chills [2,3].

* Corresponding author.
E-mail address: cjw002@dental.umaryland.edu (C. Wisnom).

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Box 1. Primary causes of hepatitis[a]

Viral
- Hepatitis A–G and TTV
- HIV
- Cytomegalovirus
- Herpes simplex virus

Bacterial
- Mycobacterium tuberculosis
- Bacteremia

Medications
- Prescribed psychotropic agents, acetaminophen (analgesic), ampicillin and tetrachcline (antibiotics), zidovudine (AZT; antiviral)
- Vitamins (niacin)
- Herbal remedies (bee pollen, chapparal)
- Abused substances (ie, cocaine, heroin)

Toxins
- Halothane
- Isoniazid
- Methyldopa

Alcohol

Obstruction
- Cholangitis (biliary tract)
- Cholecystitis (gallbladder)

[a] Note: This is an abbreviated table. There are hundreds of other etiologic agents that are responsible for hepatitis.

Adapted from Wisnom C. Viral hepatitis. In: Hupp J, Williams T, Vallerand W, editors. The five minute medical consult for dental professionals. 1st edition. Baltimore (MD): Williams and Wilkens; 1996. p. 240–7; with permission.

Diagnosis

Viral hepatitis occurs as either an acute or chronic infection. Hepatitis is initially diagnosed by monitoring an individual's history, physical symptoms, laboratory values and, as required, liver biopsy. The progression of the disease may be determined by monitoring the patient's symptoms, blood, and histologic findings. Imaging techniques such as CT, MR, and endoscopic retrograde cholangiopancreatography are used to evaluate patients with elevated levels on liver function tests including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) [5]. The use of ultrasound of the liver with alpha fetoprotein studies in asymptomatic and symptomatic carriers of viral hepatitis is used as a screening tool to detect cirrhosis with subsequent hepatocellular carcinoma (HCC) [6]. The blood is evaluated for

elevated levels on liver function tests including AST and ALT. The term *liver function test* is misleading: liver function tests reflect the degree of hepatocellular damage rather than the function of the liver. In adults, normal ALT levels range from 1 to 45 U/L. Normal AST levels range from 1 to 36 U/L. Patients are diagnosed as having mild elevations when liver function test levels are less than three times the normal levels; moderate elevations when values range from 3 to 20 times higher than normal; and severe elevations when values are greater than 20-fold higher [7]. Other blood tests include biliruben. Normal serum bilirubin levels are <1.1 mg/dL and reflect a balance between the degradation of hemoglobin and its hepatic elimination, with clinical jaundice associated with levels of 2 to 3 mg/dL. Prothrombin time is a universal indicator of liver failure. When patients suffer from severe hepatocellular disease, the prothrombin time is often prolonged [5]. Normal prothrombin time ranges from 10 to 12 seconds. Patients can safely be treated when prothrombin time falls within the normal range and a platelet count is above 60,000/mL [2]. Additional blood tests are performed to determine the patient's antigen and antibody markers for each of the specific viruses [3]. There are serum antigen and antibody tests available for hepatitis types A through E. No serologic assays are available for detecting HFG or TTV [2,3]. In 1995, HGV was discovered in serum by a reverse transcriptase polymerase chain reaction test (not commercially available) that identifies the RNA of HGV [8]. Use of liver function tests (AST/ALT), antigen/antibody reactions, and liver biopsy results assists practitioners in identifying whether patients have an acute (6 months or less) or chronic (>6 months) hepatitis infection [5]. After patients are diagnosed, a liver biopsy may be used to determine the severity or activity of the disease and the stage or degree of fibrosis. Results of liver biopsy are measured in terms of four histologic stages. Stage 1 refers to chronic, persistent or to mild chronic, active hepatitis. Stages 2 and 3 include chronic, active hepatitis with fibrosis (scarring). Stage 4 is cirrhosis. The stages do not correspond to the duration of infection. Some patients may live for many years or even decades while maintaining an early histologic stage. Other patients may progress to cirrhosis (stage 4) in less than a decade. Biopsies are also useful in ruling out other causes of liver disease such as alcoholic liver injury or iron overload [3,5].

Chronic hepatitis

In chronic hepatitis, inflamed cells infiltrate the portal tracts and may accumulate in small clusters in the parenchyma. When this occurs, focal liver cell necrosis may be observed. As chronic disease progresses, the inflammation and liver cell death may lead to fibrosis. Mild fibrosis is often localized in the portal tracts. More severe fibrosis may bridge between the portal tracts and hepatic veins. This fibrosis can progress to cirrhosis. The age at time of exposure, sex, use of alcohol, coinfection with other hepatitis

viruses, TTV, HIV, and viral load may cause complications in the patient with cirrhosis [2,9–11]. Complications that may occur as the result of liver failure include portal hypertension, jaundice, ascites, variceal hemorrhages, and encephalopathy. In summary, chronic hepatitis is defined as hepatitis inflammation, necrosis, and fibrosis. This massive destruction of liver tissue can result in cirrhosis, HCC, liver failure and, ultimately, death [12].

Acute and chronic types

Of the eight types of viral hepatitis (A–G and TTV), five have both acute and chronic forms and three occur only as acute diseases. HAV, HEV, and HFV are considered to be acute forms of hepatitis and have no carrier states [2–4,13,14].

Pathogenesis

Hepatitis is a disease affecting primarily the liver, but abnormalities are noted throughout the body. Table 1 [4] lists the pathologic effects of hepatitis on multiple body systems, with emphasis on the oral cavity. Regardless of the type of viral hepatitis, the scope of clinical manifestations may range from prodromal (anicteric; ie, without jaundice) to mild symptomatic infection, progressing to an icteric (jaundice) phase that may,

Table 1
Systems affected by hepatitis

System	Affects
Liver/abdomen	Primary organ affected. Hepatomegally, splenomegally
Thorax	Most common site of drainage from rupture of a liver abscess
Peritoneum	Second most common site of drainage from ruptured liver abscess
Kidney	Affected by severe forms
Esophagus	Varices often noted in alcoholic hepatitis
Biliary tract	Inflammation caused by bacterial infection or obstruction
Gall bladder	Inflammation commonly caused by gall stones (obstruction)
Skin/eyes	Hyperpigmentation, jaundice, purpura, vascular spider veins
Extremities	Pallor, erythematic, white or banded nails, peripheral edema
Nervous system	Peripheral neuropathy
Oral cavity	HCV implicated as the onset in Sjorgren's syndrome. In southern Europeans with chronic hepatitis, lichen planus has been noted. Breath odor is often described as musty and sweet, and gingival bleeding may occur. In alcoholic hepatitis, nutritional deficiencies may result in reduced papillae on the tongue, glossitis and/or labial angular cheilosis. Mucosal ecchymosis, petechiae, and reduced healing following trauma or surgery have been noted. Jaundiced mucosal tissues may also be present. Painless, parotid gland enlargement may also be seen in advanced liver disease.

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dependent on the viral strain, result in a carrier state [3]. Because the signs, symptoms, and stages are very similar, serologic tests are required for definitive diagnosis of hepatitis types A through E and HGV (currently no test for HFV or TTV) [2,3,13,14].

Hepatitis A virus

HAV is a 27 nm nonenveloped, single-stranded RNA picornavirus. It is transmitted enterically, primarily person-to-person by way of the fecal/oral route. Infection occurs by close personal contact. The onset of HAV is acute (approximately 2–6 weeks after exposure). The mortality rate is approximately 0.6%. Severity of disease is age related. Most children have asymptomatic infections (70%), and jaundice is present in only about 10% of the cases. Almost 30% of the cases occur in children <15 years of age. Most of the adults (76%– 97%) exhibit symptoms. Poor hygiene, contaminated food or water, ingestion of raw or undercooked shellfish (oysters, clams, mussels) from contaminated waters, crowded living conditions, travel to areas of the world with poor hygienic conditions, and intimate (intrahousehold or sexual) contact may increase the risk of transmission [15–17].

Settings such as day care centers, institutions providing care to the mentally and physically disabled, and schools (if an outbreak occurs) are considered to be situations where immune globulin (immunoglobulin sterile solution of antibodies from human plasma) postexposure prophylaxis may be beneficial. Many dental personnel work in areas where they are exposed to patients within these settings. In these instances, pre-exposure prophylaxis with the new HAV vaccines [HAVRIX, (SmithKline Beecham Biologicals, Rixensart, Belgium), VAQTA (Merck and Company, West Point, PA), and Twinrix (Glaxo-SmithKline, Triangle Park, NC)] is recommended. HAVRIX and VAQTA are prescribed for children (>2 years of age) and adults. Twinrix, a combination HAV and HBV vaccine, is indicated for immunization of persons 18 years or older. Studies of the protective levels of antibodies (anti-HAV) after completing the vaccine series indicate that virtually 100% of children, adolescents, and adults acquire adequate protection against HAV after completing the vaccine series [18]. Table 2 illustrates the recommended HAVRIX, VAQTA, and Twinrix vaccination schedules [18]. The Centers for Disease Control and Prevention (CDC) often lists countries as having either high, intermediate, or low rates of infectious diseases. The CDC recommends HAV vaccination as prophylaxis for travelers to countries with high and intermediate rates of HAV. Countries of high HAV endemicity (700–1000 cases per 100,000/year) include Africa, Asia (including the Middle East), South America, Central America, Mexico, Philippines, and Greenland. Countries with intermediate endemicity (50–200 cases per 100,000/year) include Russia and eastern Europe (including Italy and Spain). Countries with low endemicity include Australia, Canada, western Europe, and the United States (which averaged 121 cases per 100,000 infections in 1994) [18]. HAV

Table 2
Recommended vaccination schedules for hepatitis A virus vaccines

Age group (y)	Dose (U)	Volume (mL)	No. of doses	Schedule (months)[a]
HAVRIX[b]				
2–18	360[c]	0.5	3	0, 1, 6–12
>18	1440[c]	1.0	2	0, 8–12
VAQTA[d]				
2–17	25[e]	0.5	2	0, 6–18
>17	50[a]	1.0	2	0, 6
Twinrix[f]				
<18	Not established	N/A	N/A	N/A
>18	720 HAV 20 μg HBV	1.0	3	0, 1–6

[a] 0 months represents timing of the initial dose; subsequent numbers represent months after the initial dose.

[b] Hepatitis A vaccine, inactivated (SmithKline Beecham Biologicals).

[c] ELISA units.

[d] Hepatitis A vaccine, inactivated (Merck and Company).

[e] Units.

[f] Hepatitis A vaccine, inactivated; hepatitis B, recombinant (Glaxo-Smith Kline).

Abbreviations: HAV, hepatitis A virus; HAV, hepatitis B virus.

Adapted from Centers for Disease Control and Prevention. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 1999;48(RR-12):1–37; with permission.

vaccine is also recommended in the United States for children residing in states having a rate of infection of at least 20 cases per 100,000. These states include Arizona, Alaska, Arkansas, California, Colorado, Idaho, Missouri, Montana, Nevada, New Mexico, Oklahoma, Oregon, South Dakota, Texas, Wyoming, Utah, and Washington [18].

While the fecal/oral route causes the majority of HAV cases, recent cases of HAV transmission have been linked to blood. Intravenous drug users, patients with a history of blood transfusions, and hemophilia patients who received clotting factor concentrate have developed HAV [16–19].

Epidemiologically, in the United States, 32% of the reported acute hepatitis cases are HAV. Over the past several decades, there has been a decline in the overall incidence of HAV; however, high rates of diseases still occur in many segments of the population (see the previously listed risk groups). The CDC estimates that 200,000 new cases of HAV occur annually in the United States. Approximately 22% of adults with HAV require hospitalization, resulting in 80 to 100 deaths annually [16]. It has been estimated that between 1989 and 1991, approximately one third of the population of the United States was exposed to HAV [16].

Hepatitis B virus

HBV is a 42 nm enveloped, double-stranded DNA hepadnavirus. It is a highly infectious agent capable of being transmitted sexually, perinatally,

and parenterally. In dentistry, it may be transmitted by blood and saliva. The incubation period is approximately 120 days. The fatality rate is approximately 1.4% [2–4,6]. Only about 20% of patients exhibit clinical symptoms, which usually subside in 2 to 4 weeks. Risk groups for HBV are well defined and include parenteral drug users, hemodialysis patients, health care workers with frequent exposure to blood, infants born to infected mothers, individuals born in countries endemic for HBV, household and sexual contacts of HBV carriers, institutionalized populations (institutions for the physically and mentally handicapped and prisons), and recipients of organs and plasma-derived products [19]. Relative to occupational transmission, it is estimated that dental health care workers have a three to five times higher rate of HBV infection than the general population [2,19]. In addition, dental health care workers with frequent exposure to blood have approximately a 5% rate of chronic HBV [2,19]. HBV vaccine and infection control practices, however, have reduced infections in health care workers. A primary contributing factor may be the high HBV concentrations (10^{10} virions/mL) found in body fluids of infected individuals [2]. Therefore, only a very small amount of inoculum is required to cause an infection. Sexual contact with an HBV carrier patient is an effective mechanism for transmission; therefore, partners of infected individuals should be considered at high risk for HBV infection [3,4,6].

HBV has an acute and a chronic state. The younger an individual is when he or she becomes infected with HBV, the higher the carrier state and the more serious the sequelae. Infants who become perinatally infected have a 90% to 95% risk of developing chronic HBV, and up to one fourth will die of liver disease as adults. Children aged 1 to 5 years who do not become infected at birth have a 30% to 60% risk of becoming carriers during the first 5 years of life, resulting from horizontal transmission from HBV carrier mothers. HBV infections that occur in adolescents and adults have only a 6% to 10% carrier state [6]. Due to the high rates of infection in infants and children, public health policy has emphasized early vaccination of all children against HBV [12].

Epidemiologically, the CDC estimates that there are approximately 350 million HBV carriers worldwide, with HBV being the most frequent cause of chronic hepatitis. Between 1 and 1.5 million people die each year, making it a major cause of morbidity and death. There are seven known genotypes of HBV (A–G). All seven types are present in the United States. Forty-two percent of the acute cases and 5% of the chronic cases (lasting 6 months or greater) of hepatitis are caused by HBV in the United States annually. Approximately 67% of cases are diagnosed as HBV genotypes A and C. Patients infected with these strains have a higher incidence of cirrhosis [20]. Before 1982, the estimated pool of hepatitis carriers in the United States ranged from 750,000 to 100,000, with approximately 300,000 new cases yearly [29]; however, 2002 marked the 20-year anniversary of the HBV vaccine. From 1982 to 2002, an estimated 40 million infants and children and

30 million adults have received the HBV vaccine. Because of vaccination and changes in risk behaviors, the number of HBV infections in the United States declined to approximately 79,000 in 2001 [21]. Table 3 [22] illustrates CDC recommendations for HBV vaccinations. Worldwide, other countries that are considered highly endemic (chronic infection rates 8%–15%) for HBV include China, southeast Asia, Africa, Pacific Islands, parts of the Middle East, and the Amazon Basin. Russia, western block countries, India, southern Europe, and South America are moderately endemic (chronic infection rates 5%–7%). In the United States, western Europe, New Zealand, and Australia, there are low rates (0.2%–0.9%) of endemicity for HBV [3,17,19].

Hepatitis C virus

HCV is a 55 nm enveloped RNA flavivirus. It is a blood-borne virus, with an incubation period ranging from 15 to 90 days and a mortality rate of approximately a 1% to 2% [16,23]. Risk groups for HCV include the following: intravenous drug abusers, hemodialysis patients, health care workers with exposure to blood, and recipients of organs and plasma-derived products. Fig. 1 demonstrates the reported cases of HCV by risk group in the United States from 1983 to 1996 [23,24]. The perinatal, sexual, and lateral transmission of HCV from infected individuals is low [16,23].

HCV is transmitted primarily through blood; however, it has also been detected in the saliva of 50% of the patients suffering from chronic HCV and has been transmitted by a human bite [20]. Currently, no vaccine exists to protect dental health care workers against HCV. This is due primarily to the fact that HCV has six major genetic types, multiple subtypes, and mutates frequently [2,16,23]. Therefore, developing one vaccine that would provide protection against all HCV genotypes would be a monumental task.

Table 3
Recommended doses and schedules of the hepatitis B virus vaccine Engerix-B

Group	Dose (μg)	(mL)
Infants of HBV-carrier mothers: 3 doses plus 1 dose of HBIG (0.06 mL/kg IM at birth)	10	(0.5)
Other infants at birth: 3 doses	10	(0.5)
Children < 11 y: 3 doses	10	(0.5)
Other children < 11–12 y: 3 doses	10	(0.5)
Children and adolescents 12–19 y: 3 doses	20	(1.0)
Adults > 19 y: 3 doses	20	(1.0)
Dialysis patients and other immunocompromised persons: 3 doses	40	(2.0)

Abbreviations: HBIG, hepatitis B immune globulin; HBV, hepatitis B virus, IM, intramuscularly.

Adapted from Centers for Disease Control and Prevention. Protection against viral hepatitis: recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR Morb Mortal Wkly Rep 1999;48:33–4; with permission.

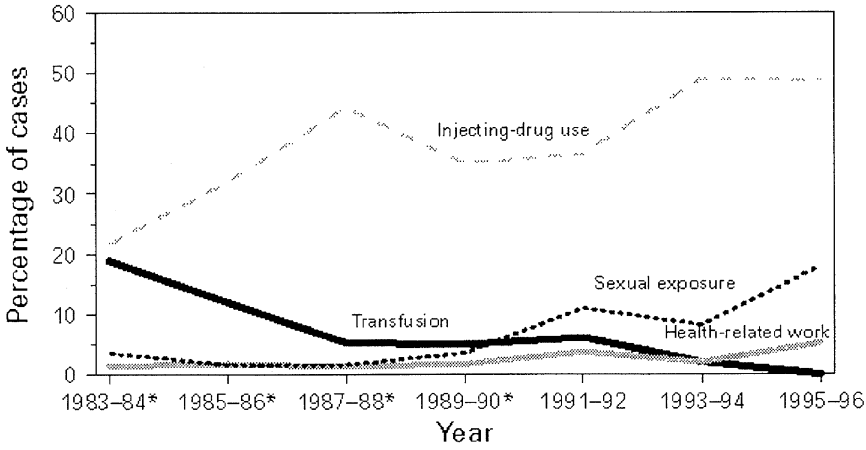

Fig. 1. Reported cases of acute HCV by selected risk factors—United States, 1983–1996. Asterisk indicates data presented for non-A and non-B hepatitis. (*From* Centers for Disease Control and Prevention. Recommendations for the prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR Morb Mortal Wkly Rep 1998;47(RR-19):1–39; with permission.)

HCV virus has an acute (15%) and a chronic (85%) state. After initial exposure, HCV RNA can be detected in serum as early as 1 to 3 weeks (average 50 days). Approximately 20% to 30% of acutely infected individuals exhibit symptoms. Females and individuals infected when young are among the 15% who spontaneously clear the virus. African American males are the least likely to clear the virus [23]. Perinatal transmission of HCV occurs in approximately 3% to 5% of infants born to HCV-infected women. The rate of perinatal transmission of HCV infection to infants from mothers who are infected with both HCV and HIV ranges from 15% to 35%. Breast-feeding appears to be safe, with no cases of mother-to-infant transmission being reported. Chronic HCV is usually a slow, insidious disease, progressing without signs or symptoms for the first 2 decades after infection until patients have advanced liver disease. Approximately 80% of the chronic cases are stable, having mild to moderate histologic disease. The other 20% develop cirrhosis (average time 20 years following infection). Seventy-five percent of the patients with cirrhosis progress slowly, with 1% to 5% developing HCC approximately 30 years following infection. Although fulminant disease is rare in HCV, it has been reported. The natural history of this disease differs according to geographic location and viral characteristics (genotype, viral load). Being male, being infected at >40 years of age, use of alcohol, and coinfection with HAV, HBV, and HIV have been associated with an increased risk for the development of cirrhosis and HCC [5,23].

Epidemiologically, in the United States, an estimated 3.9 million people (1.8%) are infected with HCV, with approximately 2.7 million being chronic

carriers, making it the most common form of viral hepatitis in the population today [23]. Annually, 20% of the acute cases and 85% of the chronic cases of hepatitis in the United States are caused by HCV. There are six different genotypes of HCV (A–F), with 70 to 90 subtypes. Approximately 75% of the cases of HCV in the United States are genotype 1. Limited evidence exists regarding differences in clinical features, disease outcome, or progression to cirrhosis or HCC based on genotypes or subtypes. Response rates in individuals infected with genotype 1, however, are substantially lower (46%) than response rates in patients with other genotypes. Patients with genotype 2 or 3 demonstrate a favorable response to antiviral therapy approximately 80% of the time [23]. The incidence of HCV declined in the late 1980s, and transmission from transfusion with contaminated blood products was virtually eliminated by a highly sensitive HCV test in 1992. Fig. 2 [25] illustrates the prevalence of HCV infections by age and race/ethnicity in the United States from 1988 to 1994. Due to the high rate of chronicity (>85%), however, a fourfold increase in chronic HCV infections is projected to occur from 1990 to 2015 [12,16,19,23]. Yearly, 35,000 acute cases occur, with 25% experiencing symptoms. Ten thousand deaths occur annually from cirrhosis and HCC, with the number expected to expand greatly in the next 10 to 20 years, making it the primary reason for liver transplantation in this country [16,19,23]. Countries endemic for HCV include Russia, Asia, Africa, Burma, India, and Mexico [19].

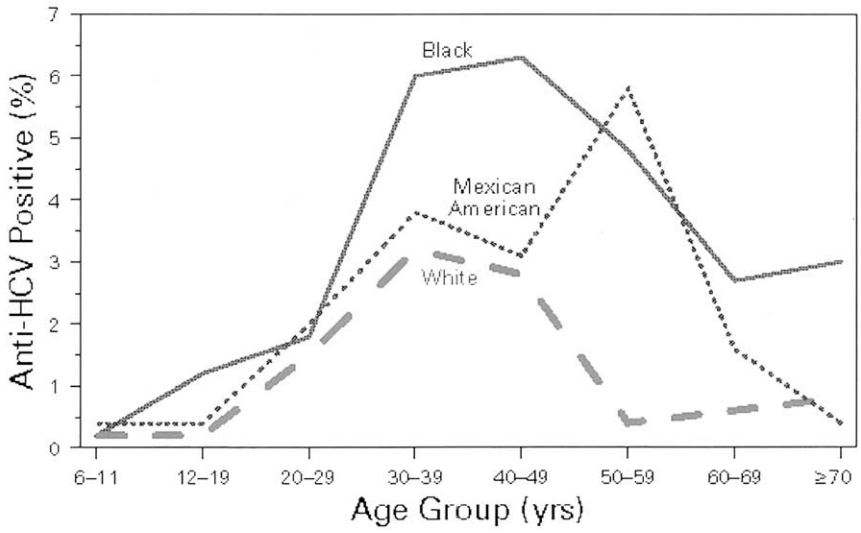

Fig. 2. Prevalence of HCV infection by age and race/ethnicity—United States, 1988–1994. HCV infection occurs among persons of all ages, but the highest incidence rates of acute HCV are found among persons (predominately men) aged 20 to 39 years. (*From* Centers for Disease Control and Prevention. Third National Health and Nutrition Examination Survey (NHANES) 1998–1994. MMWR Morb Mortal Wkly Rep 1998;47(RR-19):1–39; with permission.)

Hepatitis D virus

HDV is a 1.7 kb single-stranded RNA viroid that requires the existence of the HBV envelope protein for viral replication and pathogenesis. It is transmitted parenterally, sexually, and through the transmucosal exchange of body fluids. The incubation period is from 3 to 13 weeks. HDV has the highest mortality rate of up to 30% [2–4,19]. It can be transmitted simultaneously with HBV (coinfection) or can infect an individual with an existing HBV infection (superinfection). Those who suffer coinfections have far better outcomes than those who develop a superinfection. In superinfections, HDV causes cirrhosis in up to 70% of the cases, causing severe and fulminant disease [2–4,19]. HDV has at least three genotypes that have been identified worldwide. Risk groups include transfusion recipients, hemophiliacs, hemodialysis patients, male homosexuals, and individuals with multiple sexual contacts. Sexual and parenteral contact with an HBV-infected individual may also result in HDV transmission. Limited data exist on the prevalence of HDV in dental health care workers. Dental health care workers are protected against HDV due to the fact that a concurrent HBV infection must exist for an HDV infection to occur. Therefore, HBV vaccination also provides preexposure prophylaxis against HDV infections [2–4,19].

HDV occurs as an acute and a chronic disease. It appears concurrent with HBV and becomes chronic at a rate of $<5\%$ as a coinfection and from 70% to 90% as a superinfection [19].

Epidemiologically, HDV accounts for less than 5% of the cases of chronic hepatitis in the United States annually. It has at least three genotypes that have been identified in various geographic locations. Genotype 1 is the most prevalent and has been identified in North Africa, western Europe, the Middle East, Turkey, Japan, Taiwan, and in the United States [26,27]. Genotype 2 has been detected in individuals from Japan and Taiwan, and genotype 3 has been detected in patients from Peru and Columbia. The genotype distribution reflects the migration of populations over time. Limited data exist on the relationship of the three genotypes to the severity of the disease. Current findings suggest that genotype 2 is a milder disease, whereas genotype 3 is a more severe disease. Disease severity in genotype 1, the predominant form of the disease, ranges from mild to severe. Worldwide, 3% to 25% of fulminant HBV cases are HDV coinfections [19]. HDV is endemic in Italy, isolated areas of South America, and some European countries. In the United States, HDV is responsible for approximately 7500 new infections and 1000 deaths annually [19,26,27].

Hepatitis E virus

HEV is a single-stranded RNA calicivirus, first identified in 1980. It is transmitted enterically by way of the fecal/oral route (contaminated drinking water/food). It is primarily seen as a waterborne epidemic in

developing countries but may also occur sporadically. The incubation period is usually 3 to 6 weeks. It occurs primarily in young to middle-aged adults. The mortality rate in the general population is approximately 1% to 2%; however, in pregnant females, it can be as high as 20%. Groups at risk for the acquisition of HEV include people having close personal contact with infected individuals, people traveling in endemic areas of the world, and those who consume contaminated food or water. Parenteral and lateral transmissions of HEV are rare. Prophylaxis with immune globulin prepared from plasma in the United States has not proved to be effective protection against HEV. To avoid infection, the CDC recommends consuming bottled or canned foods and beverages and avoiding foods that may have been prepared with contaminated water [19].

Epidemiologically, HEV occurs sporadically or in epidemics in parts of India, Asia, Mexico, and North and West Africa. Although HEV is detected at a rate of 1% to 5% in the United States blood pool, it is not endemic in the United States or western Europe [2–4,19]. In epidemics of HEV in third world countries, a high morality rate (30%) has been documented in pregnant females.

Hepatitis F virus

HFV is a sporadic waterborne human virus. Viral particles of HFV were isolated in the stools of patients who did not have hepatitis types A through E. Because of its French origin, the virus was identified as HFV. Isolated cases have also been documented in Italy, England, the United States, and India. To discover additional information about this novel virus, stool extracts from five icteric patients were inoculated into rhesus monkeys. In infected animals, the AST and ALT test levels remained elevated for an average of 20 days. The liver morphology also indicated an acute hepatitis. The disease in humans has a fatality rate of approximately 20% [28]. The chronicity of HFV is currently undetermined [19].

Limited data exist on the epidemiology of HFV, and it is referred to sporadically in many countries. HFV has been identified in England, northern Italy, France, the United States, and India. In India, a survey of non-HAV/non-HVB patients revealed that 40% of the cases were caused by HEV infections and 60% by HFV infections [24]. No specific epidemiologic information exists to date.

Hepatitis G virus

The newest hepatitis virus, HGV, is assumed to be a bloodborne virus and was first identified in a patient who developed post-transfusion hepatitis [2,3,8,19,29,30]. HGV RNA becomes positive in chimpanzees approximately 70 days after exposure. HGV is associated with acute and chronic

infections and often occurs concurrent with HCV. Risk groups for HGV include organ and transfusion recipients, intravenous drug users, dialysis patients, and health care workers with exposure to blood and chronic HCV patients [2,3,8]. HGV is transmitted by way of blood and is more prevalent in blood donors than HCV, occurring at a rate of 1.7% [8,29,30]. Its role in fulminant hepatitis and HCC remains to be determined. HGV may be a more benign form of hepatitis because in most of the cases monitored to date, there have been no obvious immune system responses to the virus and signs of an active disease state were minimal [8]. In a study of HGV/HIV-infected individuals, the presence of HGV had a beneficial effect, leading to a declined morbidity and mortality associated with the HIV infection [31].

HGV may present as either an acute or chronic disease and has been detected as persisting for 10 years. When it is present for >6 months, it is assumed to be a chronic form of hepatitis and may occur at a rate of approximately 50%. This rate was assessed by monitoring elevated levels of AST and ALT persisting for greater than 6 months in duration [29,30].

HGV is globally distributed and has been detected in North America, South America, Asia, Europe, and Africa. In Africa, the prevalence rate is approximately 15%. In the United States, HGV appears to be a highly infectious agent within high-risk groups such as intravenous drug users and recipients of contaminated blood products. Preliminary estimates based on surveys of blood samples indicate that the possibility exists for 2 to 5 million people to be infected with HGV in the United States today [8,19,32]. The disease is primarily detected in the previously identified risk groups [2,19,29].

Transfusion-transmitted virus

TTV was first identified in 1997 in a patient who developed post-transfusion hepatitis of unknown origin [2,33]. More than 40 genotypes have been identified [34]. Infection with TTV may be acquired in early childhood and persist throughout life. Prevalence rates among patients with liver disease have not been established. The association between TTV and human disease is not well defined; however, high TTV viral load has been linked to HCC and fulminant hepatic failure [13,14,34]. TTV has been documented by parenteral and nonparenteral routes [2,13,14,33,34].

TTV has been identified in Japan, the United Kingdom, Scotland, Australia, and the United States. The prevalence of TTV among individuals with hepatic disease has not been established. In North America, a prevalence of 1% in routine blood donors, 15% in patients with cirrhosis, 18% in post-transfusion patients, 27% in patients with end-stage liver failure, and 4% in patients without parenteral risk has been suggested [2,13,33,34].

Comprehension of the risk groups and the global distribution of viral hepatitis will assist practitioners in identifying which patients may be infected with the various strains of hepatitis.

Management

Hepatitis A virus

Improved sanitation and other preventive measures are the mainstays of managing HAV infection. Passive and active immunizations against HAV are available, including inactivated vaccines and immune globulin containing anti-HAV. Supportive care for the HAV-active patient includes a high-carbohydrate, low-fat diet to minimize nausea and limit the patient's physical activity during the infection [35]. No specific medication therapy is recommended and follow-up is not necessary.

Hepatitis B virus

Treatment of acute HBV infection is primarily supportive. Good nutrition and bed rest should be reinforced. Abstinence from alcohol and the use of hepatotoxic drugs is also necessary. Conversely, chronic HBV infection may be progressive and, therefore, requires management. The goals of therapy include minimization of hepatocellular damage and viral clearance. The only approved therapy for chronic HBV infection shown to have lasting effects is interferon alfa-2b (4–6 months of therapy remission in 25%–50% of patients). Possible adverse effects to interferon include arthralgias and myalgias, fever and chills, headache, depression, malaise, tachycardia, bone marrow suppression, alopecia and, on rare occasion, cardiac or renal failure.

A new therapeutic option includes oral nucleoside analogs such as lamivudine or famciclovir [36]. The Lamivudine Asia Hepatitis Study group reported that use of this nucleoside analog reduced serum HBV DNA levels and hepatic necrosis in 56% of treated patients with chronic HBV after 1 year [37]. Liver transplantation is a potential life-saving approach for the patient with end-stage chronic hepatitis; the transplanted liver often becomes infected with HBV.

Hepatitis C virus

Patients with HCV must use barrier protection during sexual activity, abstain from alcohol ingestion, and restrict exercise to low-level aerobics. The primary aim in the patient with HCV is to achieve a sustained virologic response, which is defined as undetectable HCV RNA 6 months after termination of antiviral therapy. Secondary goals of antiviral therapy include improvement in histology and quality of life and the prevention of HCC. Therapeutic intervention with antiviral medications is indicated in patients with HCV RNA seropositivity and who have elevated serum hepatic enzyme levels or positive liver biopsy disclosing moderate degrees of fibrosis, inflammation, or hepatocellular necrosis [35]. Combination therapy with injected interferon alfa-2b with orally administered ribavirin has been

shown to induce a significantly prolonged response in patients compared with those on monotherapy [38]. A pegylated form of interferon is currently being tested in clinical trials [39]. This form of interferon has an increased half-life of 90 hours when used alone or with ribaviron.

The rate of complementary medicine use by HCV patients dissatisfied with conventional medications is estimated to be as high as 60% [40]. Various agents and approaches are used in this setting, including milk thistle, vitamin therapies, Chinese herbal therapies, acupuncture, and lifestyle-modification techniques. Despite the widespread use of these modalities, few well-designed clinical trials have been published that evaluate the efficacy of these therapies. The flavanoid silymarin, found in milk thistle contains documented hepatoprotective properties [41]. Their mechanism of action is still poorly understood. Silymarin, which exhibits antioxidant properties and may function as a free-radical scavenger, has been used to treat all forms of liver disease for 2000 years. It appears to be safe for use in patients with active hepatitis [42]. The effects of this agent specifically on HCV have not yet been evaluated. Recently, results of a controlled trial showed no benefit of silymarin use in patients with primary biliary cirrhosis [43]. Many patients who take alternative therapies either do not seek or delay the use of conventional therapies that may be effective in controlling their hepatitis.

Hepatitis D, E, and G viruses

Supportive care is the only measure currently available for HDV, HEV, and HGV infections. Sanitary precautions offer the only protection from these viruses. HBV vaccine will protect against HDV in the absence of HBV infection, but is not effective in HBV carriers. No vaccine against HDV is currently available. There is no vaccine for preventing HEV.

Summary

This article presents a comprehensive review of viral hepatitis types A through G and TTV. The information that is provided includes the definition, causes, signs and symptoms, diagnosis, pathogenesis, and acute and chronic forms of hepatitis. The modes of transmission, risk groups, morbidity and mortality, epidemiology, and treatment modalities are also presented. The primary objective for this extensive review is to provide dental health care workers with the most current information on the subject, which will allow them to identify the patients who will potentially have complications as the result of invasive dental treatment. By using this information, dental health care workers can be assured that they are practicing ''state-of-the-art dentistry'' while ensuring the health of their patients, staff, and families.

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