

Continuing Education for Pharmacists

Volume XXIV, No. 7

Acute Viral Hepatitis: Prevalence, Prognosis, and Prevention

Thomas A. Gossel, R.Ph., Ph.D.
Professor Emeritus
Ohio Northern University
Ada, Ohio

and

**J. Richard Wuest, R.Ph.,
Pharm.D.**
Professor Emeritus
University of Cincinnati
Cincinnati, Ohio

Goals. The goals of this lesson are to discuss acute viral hepatitis with emphasis on the biological characteristics of and physical responses to hepatitis viruses A, B, and C.

Objectives. At the conclusion of this lesson, successful participants should be able to:

1. summarize key points relative to the biological characteristics of hepatitis A, B, and C viruses;
2. identify the pathological responses to infection by hepatitis A, B, and C viruses; and
3. select from a list important points to convey to patients relative to acute viral hepatitis.

This continuing education activity
is supported by
an educational grant from
GlaxoSmithKline.



Gossel



Wuest

Acute viral hepatitis is a systemic infection of the liver predominantly. Most clinical cases are caused by one of five viruses: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV). Together, they infect nearly 5 million people in the U.S., and according to a World Health Organization estimate, more than 500 million people worldwide.

All human hepatitis viruses are RNA viruses with the exception of HBV, which is a DNA virus. All hepatitis viruses produce clinically similar illnesses ranging from asymptomatic disease to rapidly progressive and chronic liver disease that can lead to cirrhosis and hepatocellular carcinoma. The three viruses that cause most human cases of hepatitis in the U.S. are compared in Table 1.

Epidemiology

Viral hepatitis was formerly labeled either as "infectious" or "serum" hepatitis for HAV and HBV, respectively. Distinguishing between the various viral types cannot be accomplished solely on the basis of clinical or epidemiologic features. Today, classification involves specific serologic testing.

Hepatitis A. HAV is a highly contagious virus that causes

widespread human infection worldwide, particularly in developing countries. There are also areas in the U.S., which because of poor sanitation practices, have high HAV infection rates.

The course of hepatitis A infection is extremely variable. The majority of infections in children are asymptomatic, whereas most adult infections are symptomatic. Approximately 100 people in the U.S. die each year as a result of HAV.

HAV is transmitted almost exclusively by the fecal-oral route. Unlike HBV and HCV, the hepatitis A virus remains stable when hepatocytes secrete it into the bile, which passes into the digestive tract. Fecal matter from an infected person, therefore, contains a high concentration of the virus, and it can survive on a hand or other surface for three to four hours at normal room temperatures. The virus can also be transmitted via a contaminated eating utensil.

Person-to-person transmission of HAV is accelerated by poor hygiene and overcrowding. Large outbreaks have been traced to contaminated food, water, milk, and raw shellfish. Spread within families, children and employees in daycare facilities through diaper changing, and persons within institutions including the military and prisons is also common. Kissing on the mouth and anal sex are confirmed routes of transmission. Contaminated needles and/or syringes used for injecting illicit drugs is a route of transmission. It is not known how infection occurs in about 40 percent of reported cases. The Centers for Disease Control and Prevention (CDC) lists household or sexual contacts, daycare attendance

Table 1
Comparison of Hepatitis A, B and C

	Hepatitis A Hepatitis A virus (HAV)	Hepatitis B Hepatitis B virus (HBV)	Hepatitis C Hepatitis C virus (HCV)
Cause	Feces of persons with HAV	Blood and certain body fluids of persons with HBV	Blood and certain body fluids of persons with HCV
Detection	Close personal contact (including sex or sharing a household); food or water contaminated with HAV	Exposure to body fluid from person infected with HBV; unprotected sex; sharing needles; needlestick; mother-infant transmission at birth	Exposure to body fluid from person infected with HCV; sharing needles; needlestick; mother-infant transmission at birth; unprotected sex (rare)
Spread	15 to 50 days (20 average)	45 to 160 days (120 average)	14 to 180 days (45 average)
Incubation	Acute	Insidious or acute	Insidious
Onset	Mild	Occasionally severe	Moderate
Severity	Household contacts or sex partners of infected persons; children in US high-rate areas during 1987-97; travelers to countries with increased rates ¹ ; men who have sex with men; injecting and non-injecting drug users	Sex partners of infected persons or those with multiple sex partners; men who have sex with men; injecting drug users; household contacts of chronically ill persons; infants of infected mothers; infants/children from countries with high HBV rates ² ; workers exposed to blood; chronic hemodialysis patients	Injecting drug users; clotting factor recipients before 1987; hemodialysis patients; blood and solid organ transplant recipients prior to 1992; infants of infected mothers; sex partners of infected persons or those with multiple sex partners (rare, but may increase risk of infection)
Risk	Not chronic; once infected, HAV cannot recur; 15% have prolonged illness or relapsing symptoms over 6-9 months	Chronic for 90% infected at birth, 30% infected at age 1-5 years, 2-6% infected after age 5 years; 5000 die annually in US; higher risk of liver cancer or cirrhosis	Chronic for 75-85% of those infected; chronic liver disease for 70%; 8000 to 10,000 die annually in US; higher risk of liver cancer or cirrhosis; leading indication for liver transplant
Infection	None available; alcohol worsens prognosis	Interferon, pegylated interferon, lamivudine, adefovir, entecavir approved for chronic HBV; liver transplant; alcohol worsens prognosis; liver function testing every 6-12 months	Interferon, pegylated interferon, ribavirin; combination therapy can eliminate virus in approx. 50%; alcohol worsens prognosis; liver function testing every 6-12 months
Treatment	Hepatitis A vaccine; hand washing around food preparation, diaper changes and toilet use	Hepatitis B vaccine; safe sex; avoiding tattoos, shared needles/syringes; persons with HBV should avoid donating blood, organs, or tissues; get vaccinated against hepatitis A	No available vaccine; safe sex; avoiding tattoos, shared needles/syringes; persons with HCV should avoid donating blood, organs or tissues; get vaccinated against hepatitis A and B
Prevention			

¹Excluding Canada, Western Europe, Japan, Australia, New Zealand

²Including Asia, Africa, Pacific Islands, Eastern Europe, Middle East, Amazon basin

or employment, and international travel as the major risk factors for transmission of HAV.

There seems to be a predilection for hepatitis A outbreaks in late fall and early winter. The incidence of hepatitis A in developed countries has been declining in recent years,

most likely as a function of improved sanitation.

Hepatitis B. HBV belongs to a family of genetically related animal viruses that are hepatotropic (i.e., have a high affinity for the liver). The highest concentrations of infectious HBV are found in blood.

However, other fluids, such as semen, vaginal secretions, and saliva are also infectious. HBV can remain contagious in the environment for at least seven days. It can also be inactivated by disinfectants such as 1:10 dilutions of household bleach.

The mode of transmission may be by contact with contaminated body

secretions, percutaneously usually through accidental needlesticks or by sharing needles and/or syringes with infected persons, or by maternal-neonatal transmission. Transmission of HBV can also occur during close contact with an infected person. HBV infection via blood transfusion is now rare in the U.S. as a result of screening of blood donors. The means of transmission in 30 to 40 percent of cases remains unknown. Perinatal transmission is uncommon in the U.S.; most infections occur during delivery and are not related to breast feeding. Oral ingestion is a potential, but inefficient, route of exposure. There is a human reservoir of persistently infected persons nearly worldwide.

CDC estimates that more than 1.25 million individuals in the U.S. and 350 million people worldwide are HBV carriers. They constitute the primary reservoir of hepatitis B in humans. Approximately 90 percent of infants and 6 to 10 percent of adults in the U.S. who are infected with HBV will become carriers. Approximately 50,000 HBV cases are reported in the U.S. each year; the number of unreported cases may be 10 times greater. High rates of HBV infection occur in spouses of acutely infected persons, sexually promiscuous persons (especially men who have sex with men), health care workers exposed to blood, persons who require repeated transfusions especially with pooled blood product concentrates, residents and staff of custodial institutions for the developmentally handicapped, prisoners, and to lesser extent, family members of chronically infected patients.

Hepatitis C. Hepatitis C virus is a common chronic bloodborne infection in the U.S., accounting for an estimated 8000 to 10,000 deaths annually. Approximately four million persons in the U.S. have been infected; three million have chronic HCV infection.

Routine screening of blood donors for HBV, along with elimination of commercial blood sources in the early 1970s, reduced the fre-

quency of transfusion-associated hepatitis. Voluntary self-exclusion of blood donors at risk for AIDS in the 1980s, along with introduction of donor screening for HIV, further reduced the probability of acquiring HCV via transfusion.

Individuals who encounter infected blood or instruments or needles, such as illicit drug users, health care workers or public safety workers, are at risk of acquiring hepatitis C infection. Other potential risks include intranasal cocaine use, tattooing and body piercing. People who live with HCV infected individuals should not share personal items such as razors, toothbrushes, and nail clippers. Women with hepatitis C infection do not need to avoid pregnancy or breast feeding. Approximately 5 percent of infants born to HCV infected females may be infected. HCV-positive mothers should abstain from breast-feeding if their nipples are cracked or bleeding.

Chronic hepatitis C appears to be a slowly progressive disease that may gradually advance over two to four decades. Newly acquired cases of hepatitis C that are diagnosed in an otherwise healthy person can often be traced back to the individual's brief period of illicit injection drug use or promiscuous sexual encounters two to four decades earlier.

Pathogenesis

The hepatitis viruses do not directly cause damage to hepatocytes; rather, the clinical manifestations and outcomes following acute hepatic damage associated with viral hepatitis are determined by the immunologic response of the host. The pathogenesis of hepatitis B has been studied to greatest extent. Persons with defective cellular immune competence are more likely to remain chronically infected rather than to clear the virus from the body.

Signs And Symptoms

Following an incubation period that varies widely according to the responsible agent (see Table 1),

signs and symptoms of acute viral hepatitis appear. Prodromal symptoms of acute viral hepatitis are systemic and variable. Constitutional symptoms include anorexia, nausea, and vomiting; cough, runny nose, and sore throat; fatigue; malaise; arthralgias, myalgias, headache; and photophobia that may precede onset of jaundice by one to two weeks. Gastrointestinal symptoms are often associated with alterations in smell and taste. A low-grade fever of 100-102°F is usually more common in hepatitis A than in hepatitis B or C, except when hepatitis B occurs with the serum sickness-like syndrome. A fever of 103-104°F may accompany the symptoms, but this is rare. A dark urine and clay-colored stools one to five days before onset of clinical jaundice may be noted.

Weight loss of five to 10 pounds is common and may continue throughout the entire icteric (i.e., pertaining to jaundice) phase. The liver enlarges and may be tender, with pain and discomfort in the right upper quadrant. Ten to 20 percent of patients with acute hepatitis develop splenomegaly and cervical adenopathy.

Constitutional symptoms abate during recovery, but some liver enlargement and abnormalities in liver function tests remain. The duration of the posticteric phase may range from two to 12 weeks, and is usually more prolonged in acute hepatitis B and C. Complete recovery from hepatitis A occurs within one to two months, and in three to four months in 75 percent of persons with uncomplicated hepatitis B or C.

Prognosis

In general, hepatitis A is a self-limiting disease. Most previously healthy patients infected with HAV recover completely from their illness within weeks to six months without clinical complications. Recovery is generally complete, and followed by protection against future HAV infection. Illness may be prolonged. Relapse of clinical illness occurring

weeks to months after apparent recovery has been described. Cholestatic hepatitis, noted by protracted cholestatic jaundice with itching is another unusual variant of acute hepatitis A. Approximately 20 percent of adults with hepatitis A require hospitalization.

Ninety-five to 99 percent of otherwise healthy adults with acute HBV infection recover completely. Elderly patients and those with serious underlying medical disorders may have a prolonged recovery, and are more likely to develop severe hepatitis. The presence of ascites, peripheral edema, and hepatic encephalopathy suggest a poor prognosis. A low serum albumin and high serum bilirubin values, and hypoglycemia suggest severe hepatocellular pathology. The fatality rate in hepatitis A and B is low, but increased by old age and underlying debilitating disorders.

Hepatitis C causes signs and symptoms that are less severe than hepatitis B during the acute phase. Jaundice is less likely to occur. Fatalities are rare; the precise fatality rate is unknown. HCV ranks with alcohol as a major cause of chronic liver disease and cirrhosis in the U.S. Infection with this virus causes inflammation and low-grade damage to the liver that, over several decades, can lead to cirrhosis and hepatocellular carcinoma. HCV is the most frequent indication for liver transplantation.

Fulminant hepatitis (occurring suddenly and with great intensity) is the most feared complication of viral hepatitis. Fortunately, this massive hepatic necrosis is rare. It occurs in persons with both hepatitis B and D infections, but rare fulminant cases of hepatitis A also occur in older adults and others with underlying chronic liver disease, including chronic hepatitis B and C. More than half of all severe hepatitis cases are caused by HBV, a significant number of which are associated with HDV infection, and another portion with underlying chronic hepatitis C. Fulminant

hepatitis is rare in persons with HCV alone.

A late complication of acute hepatitis B is chronic hepatitis B that occurs in a small number of patients with acute disease. Acute hepatitis is more apt to advance to chronic hepatitis when there is incomplete resolution of clinical symptoms of loss of appetite, weight loss, and fatigue and persistence of hepatomegaly; signs of multilobular (widespread) hepatic necrosis on liver biopsy during protracted, severe acute viral hepatitis; and failure of aminotransferase, bilirubin, and albumin serum levels to return to normal within six to 12 months following acute illness. Pancreatitis, myocarditis, atypical pneumonia (pulmonary virus disease with symptoms resembling those of pneumonia), aplastic anemia, and peripheral neuropathy are rare complications of viral hepatitis.

Prophylaxis

Knowledge of the natural history of hepatitis infections has steadily evolved over the past several decades. Emphasis is upon prevention through immunization of viral hepatitis since antiviral therapy is effective in only a small number of patients. Prophylaxis differs for each type of viral hepatitis.

Hepatitis A and B. The first plasma-derived HBV vaccine was licensed in the U.S. in 1982. It is no longer available in this country. A recombinant HBV vaccine was licensed in the U.S. in 1986 (Engerix-B), followed closely by another vaccine in 1989 (Recombivax HB). The first HAV vaccine was licensed in the U.S. in 1995 (Havrix), followed by approval of a second vaccine in 1996 (Vaqta). Both vaccines are inactivated whole-virus vaccines that have demonstrated safety and efficacy in preventing HAV infection. A combined HAV/HBV vaccine (Twinrix) was approved for use in the U.S. in 2001.

Hepatitis C and D. Hepatitis D infection can be prevented by

vaccinating high-risk persons with hepatitis B vaccine. There is no vaccine to prevent HDV specifically. Likewise, there is no vaccine to immunize against HCV. Prevention of infection is best achieved by screening donor blood, excluding blood donors in high-risk situations, and use of highly sensitive serologic screening tests for HCV infection. There are no recommendations for babies born to mothers with hepatitis C and no restrictions for their breast feeding.

Patient Advice

It is imperative that patients who are at risk or plan to travel to areas where the viruses are found speak with their physician about preventive measures for hepatitis immunization. Vaccines for HAV and HBV are safe and effective for prophylaxis against their respective viruses.

Overview and Summary

Hepatitis is a common infection caused by one or more contagious viruses. There are safe and effective vaccines that protect against hepatitis A and B. There is no vaccine for hepatitis C or D. Individuals at risk for hepatitis should seek immunization and avoid practices and conditions that increase their susceptibility.