LEARNING GUIDE

HEPATITIS

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ABOUT THIS LEARNING GUIDE

This learning guide presents a discussion of each type of viral hepatitis and how serological assessments of the patients can aid in differential diagnosis.

The overview of each type of viral hepatitis has been developed in a case study format to demonstrate the materials' practicality better. As you progress through the sections, review the learning objectives, and complete the quizzes on significant points covered in the text.

CONTENTS

INTRODUCTION

HEPATITIS LEARNING GUIDE

Viral hepatitis continues to be a disease of major significance in terms of both morbidity and mortality. Because most persons infected with viral hepatitis are asymptomatic and not identified or reported, summaries created by the Centers for Disease Control and Prevention (CDC) are estimated trends. In 2011, the CDC began using a different but unpublished statistical methodology as a basis to create such estimates such that new reports cannot be compared with prior estimates. In 2018, the CDC estimated that in the United States, there were 24,900 new HAV infections, 21,600 new HBV infections, and 50,300 new HCV infections.[1] In 2016, the CDC estimated that there were 862,000 people chronically infected with HBV, and estimated that from 2013–2016 there were 2.4 million people chronically infected with HCV.[2,3] Unlike HBV and HCV, HAV does not cause chronic infection.[4] HDV is uncommon in the United States and occurs only in people infected with HBV.[5] HEV is believed to be uncommon in the United States.[6]

Hepatitis is largely a nondiscriminatory disease. Although each type may target a specific population and there is greater prevalence in specific groups or areas (e.g., HBV in Asian/pacific islanders and people born outside the United States) the disease is not limited to a small geographical, social, or socioeconomic group and anyone may become infected. Therefore, the control and diagnosis of viral hepatitis demand that physicians, clinicians, and other healthcare providers be aware of the:

- Known and potential risks for acquiring the different types
- Risk behavior histories of their patients
- Appropriate diagnostic tests for each type of hepatitis
- Appropriate preventive and therapeutic measures

Diagnosing the specific agent responsible for viral hepatitis can be difficult because the signs and symptoms of each type are similar. Furthermore, many individuals who contract the disease have few or no symptoms. Hepatitis presents a challenge to physicians who must try to integrate epidemiological, clinical, and serological data before making patient management decisions.

SECTION 1

THE PATHOLOGY OF VIRAL HEPATITIS

LEARNING OBJECTIVES

After completing this section, you should be able to:

1. Name the viruses that cause viral hepatitis
2. Describe the symptoms of viral hepatitis
3. Indicate the use of liver function tests in the diagnosis of viral hepatitis
4. Identify the viral hepatitis panels

Hepatitis, an inflammation of the liver, can be caused by viruses, bacteria, drugs, toxins, or excess alcohol intake. Physicians are able to differentiate the five major types of viral hepatitis using the serological tests developed for specific markers.

The five distinct viruses currently known to cause hepatitis which will be discussed in this text are hepatitis A, B, C, D, and E. Although these are the most common causative viruses that cause acute hepatitis, other viruses, such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus, varicella-zoster virus, and adenovirus, can rarely cause acute hepatitis.[7]

BRIEF HISTORY OF VIRAL HEPATITIS

Outbreaks of epidemic jaundice were known in both Greek and Roman times, but viral hepatitis was first recognized as a distinct clinical entity in the United States and Europe during the late 18th and early 19th centuries. Scattered outbreaks of "infectious hepatitis," "epidemic hepatitis," or "catarrhal jaundice" were reported in the medical literature of the times.[8,9]

During World War II, two types of viral hepatitis—subsequently designated **hepatitis A** and **hepatitis B**—were distinguished.[10] Later studies demonstrated that other viruses could cause hepatitis. One agent, the delta virus, was identified in 1977 and later became known as the **hepatitis D** virus (HDV).[8]

With the development of serological assays for HAV and HBV and their use as aids in the diagnosis of hepatitis and with the implementation of HBV screening of blood donors, it became evident that there were additional viruses involved. Hepatitis due to viruses other than the hepatitis A, hepatitis B, or hepatitis D viruses were called **non-A, non-B (NANB) hepatitis**.[8] In the late 1980s, this NANB population was further differentiated with the identification of two viruses: **hepatitis C** virus (HCV) and **hepatitis E** virus (HEV).

HAV, HBV, HCV, HDV, AND HEV

There are five distinct viruses currently known to cause hepatitis:

- hepatitis A virus (HAV)
- hepatitis B virus (HBV)
- hepatitis C virus (HCV)
- hepatitis D virus (HDV)
- hepatitis E virus (HEV)

THE LIVER

To understand the effects of hepatitis on the liver, it is essential to know some of the functions of the liver:

- Storage of substances such as glycogen, iron, and vitamins
- Disposal of metabolic wastes such as urea and bile
- Metabolism of sugar, protein, and fat
- Production of proteins that circulate in the blood, such as factors that regulate blood clotting and plasma proteins that influence blood pressure and blood viscosity
- Filtration of toxic substances that could damage the body if allowed to accumulate

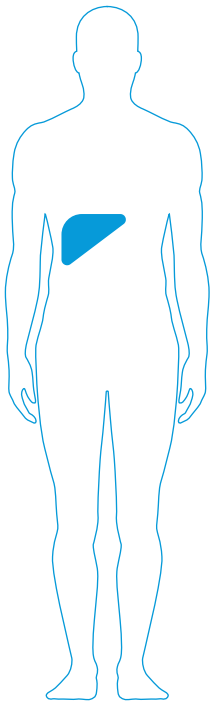
EFFECTS ON THE LIVER

Regardless of the cause, all types of viral hepatitis affect liver cells. This accounts for the fact that many signs and symptoms of the various types are similar.

SIGNS AND SYMPTOMS

Because the liver is involved with so many metabolic functions, individuals infected with a hepatitis virus tend to have generalized symptoms, which in the early stages are similar to the flu.

- Fatigue
- Joint and muscle pain (myalgia)
- Loss of appetite
- Nausea
- Diarrhea
- Constipation
- Fever
- Jaundice



As the disease progresses, the liver, located in the right upper abdomen, may become enlarged and tender. At this stage, other symptoms may occur:

- Chills
- Weight loss
- Distaste for cigarettes and food
- Darker urine and lighter feces

JAUNDICE (ICTERUS). When the liver's ability to dispose of metabolic waste is impaired, bilirubin accumulates in the blood. Bilirubin is derived from the breakdown of red blood cells and contains a yellow pigment. When high levels of bilirubin accumulate in the blood, the skin and the whites of the eyes turn yellow.

VARIABILITY OF SYMPTOMS. The symptoms of hepatitis vary considerably from one individual to another, even when the same causative agent is involved. **Because symptoms are not specific to the causative agent, it is impossible to distinguish among the various causative agents of hepatitis based on clinical symptoms alone; serological testing is required.**

TESTS OF LIVER FUNCTIONS

The numerous biochemical tests that detect abnormal liver function can help to confirm the presence of liver disease but do not define the cause. Three commonly used blood tests that assess liver function include bilirubin and specific enzymes: alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Blood levels of all three substances are roughly elevated in proportion to the degree of liver damage. ALT and AST are contained within the liver cells. Inflammation of the liver causes these enzymes to be released in abnormally high amounts into the blood. An elevated test result for one or all of these substances is often the first indication that the patient has an inflamed liver and is usually the first step in diagnosing hepatitis.

Elevated test results may also be caused by alcoholic hepatitis, acetaminophen overuse or overdose, cirrhosis of the liver, biliary tract disease, or viral hepatitis. Until the development of serological assays for specific viral hepatitis markers, physicians determined the diagnosis by integrating liver function tests with patient history, physical examination, and the physician's knowledge of liver diseases.

BILIRUBIN, ALT, AST

An elevated test result for one or all of these substances is often the first indication that the patient has an inflamed liver, and is often the first step in diagnosing hepatitis.

VIRAL HEPATITIS TESTING

A definitive diagnosis of viral hepatitis is only achievable by the use of viral-specific hepatitis serological tests.

SEROLOGICAL MARKERS

Serology pertains to antigen/antibody reactions in vitro. Viral hepatitis assays detect the presence of specific viral antigens and/or antibodies in serum. A physician uses these results to identify, differentiate, and monitor a hepatitis infection.

VIRAL HEPATITIS PANELS

Panels, or groups of assays, to detect serological markers of viral hepatitis are used by physicians for the following purposes:

DIAGNOSE

- To differentiate between HAV, HBV, and HCV
- To diagnose acute hepatitis A (anti-HAV IgM), acute hepatitis B (anti-HBc IgM), and acute or chronic hepatitis C (HCV Ag or RNA, anti-HCV antibodies)

SCREEN

- To screen blood or blood products to prevent the spread of viral hepatitis
- To test exposed persons for immunity to HBV using anti-HBc and anti-HBs (in particular, dialysis patients, healthcare workers, recipients of frequent transfusions, and injecting drug users)
- To identify HBsAg positive pregnant women who may transmit hepatitis B virus to their newborn infants. Infants who become infected with HBV by perinatal transmission have a 90 percent risk of developing chronic hepatitis B
- To identify HBV infected individuals
- To test sex partners of individuals with acute or chronic HBV to minimize the spread of infection by the initiation of prophylaxis
- To identify HCV infected individuals
- To determine if an individual is currently infected or has antibodies to HBV
- To determine individuals who require secondary testing to determine HCV viremia

MONITOR

- To evaluate for late seroconversion and/or disease resolution in a known HBV carrier
- To monitor the success of immunoprophylaxis in cases of potential perinatal transmission of HBV (9–15 months after birth)
- To ensure immunity has been achieved after vaccination for HBV

The Acute Viral Hepatitis Panel* is the first laboratory tool for identifying the specific virus responsible for a patient's hepatitis. The Acute Viral Hepatitis Panel tests for four serological markers: anti-HAV IgM (IgM antibody directed against HAV), HBsAg (hepatitis B surface antigen), anti-HBc IgM (IgM antibody directed against the hepatitis B core antigen), and anti-HCV (antibody to HCV).[11] HCV RNA or Ag tests are performed on anti-HCV positive individuals to determine active viral replication or resolved infection.

Additional panels will be discussed in the upcoming sections.

*As defined in CPT code #80074

ACUTE VIRAL HEPATITIS PANEL

The Acute Viral Hepatitis Panel tests for four serological markers: anti-HAV IgM (IgM antibody directed against HAV), HBsAg (hepatitis B surface antigen), anti-HBc IgM (IgM antibody directed against HBcAg), and anti-HCV (antibody to HCV).

QUIZ QUESTIONS

PATHOLOGY OF VIRAL HEPATITIS

1. Name the five major viruses currently known to cause viral hepatitis:

   _____

   _____

2. List four general symptoms associated with viral hepatitis:

   _____

   _____

3. Physicians are able to differentially diagnose cases of viral hepatitis based on symptoms alone.

   A. True

   B. False

4. How are liver function tests used in the diagnosis of viral hepatitis? (Choose one or more of the following)

   A. To indicate the status of liver function

   B. To indicate roughly the amount of liver damage

   C. To indicate the viral agent involved

5. Viral hepatitis panels are used to:

   A. Diagnose

   B. Monitor

   C. Screen

   D. All of the above

SECTION 2

HEPATITIS A

LEARNING OBJECTIVES

After completing this section, you should be able to:

1. Indicate how the hepatitis A virus (HAV) is transmitted
2. Identify individuals at risk for infection by the hepatitis A virus
3. Recognize the incidence and prevalence of hepatitis A
4. Describe the symptoms and clinical course of the disease

CASE STUDY #1

JANET, MARKETING MANAGER

Janet, a 34-year-old marketing manager, felt fatigued, had diarrhea, and was running a fever after returning from a trip to China, which included travel to a rural area. Assuming it was just the flu, she rested for a couple of days. When symptoms continued for more than a week, she went to her physician. Janet told her physician about her symptoms, including the fact that her stools had changed color. Upon examination, the physician observed that both her skin and the whites of her eyes were slightly yellow.

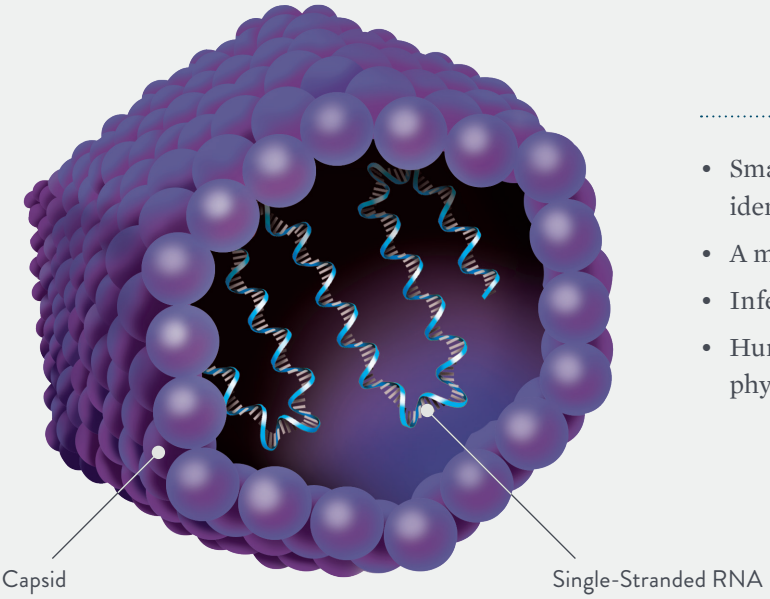
Together with travel history, this last observation prompted the physician to check Janet's bilirubin and liver enzymes. Laboratory tests showed that Janet's bilirubin and ALT levels were abnormally elevated. At this point, the physician ordered the Acute Viral Hepatitis Panel. Below are the results of the Acute Panel:

ACUTE VIRAL HEPATITIS PANEL

ASSAY	HBsAg	Anti-HAV IgM	Anti-HBc IgM	Anti-HCV
Results	–	+	–	–

In this case, the panel definitively diagnosed an acute infection with HAV. While the hepatitis A **virus** is rarely detectable in serum, the IgM **antibody** to HAV (anti-HAV IgM) is detectable in serum and indicated that Janet had hepatitis A.

HEPATITIS A VIRUS



- Small, single-stranded RNA virus first identified in 1973
- A member of the Picornaviridae family
- Infects the liver
- Humans and vertebrates are natural hosts, phylogenetic analysis suggest rodent origin

ROUTES OF TRANSMISSION

Transmission usually occurs enterically (fecal-oral) through:

- Close person-to-person contact
- Ingestion of contaminated food or water

These routes could be facilitated by poor personal hygiene and poor sanitation.

Evaluation of the risk factors associated with HAV infection relative to Janet's history suggested that she was probably exposed to HAV during the course of her trip. Most likely, she ate some food or water contaminated with the HAV virus while traveling in this HAV endemic area.

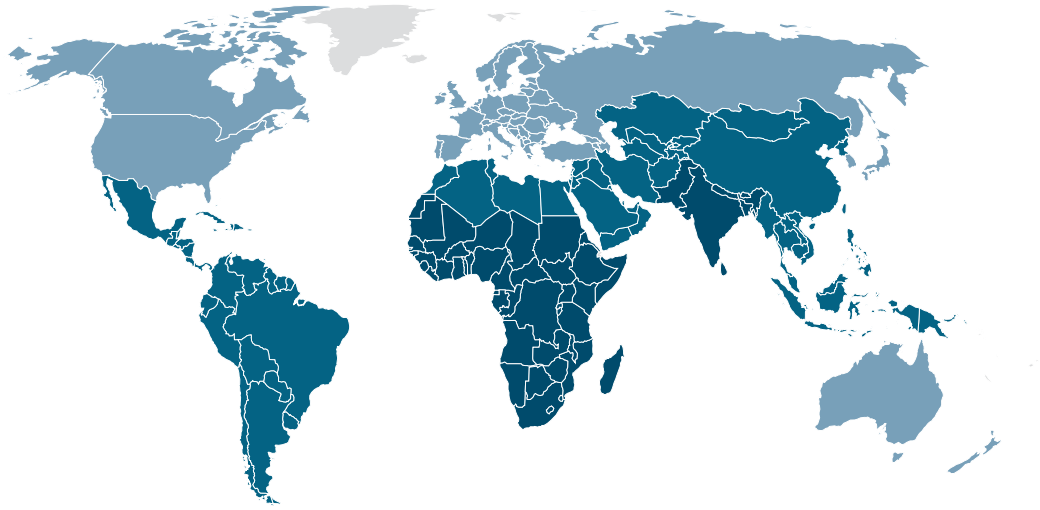
INDIVIDUALS AT RISK[10,12,13]

- Those in close contact with an infected individual
- Travelers to countries with high or intermediate endemicity of HAV infection
- Men having sex with men
- Users of injection and non-injection drugs
- Persons working with non-human primates
- Household members and other close personal contacts of adopted children newly arriving from countries with high or intermediate hepatitis A endemicity

As she had traveled to an area where HAV is endemic, Janet was at risk for HAV infection.

INCIDENCE/PREVALENCE[1,33,36–39]

GEOGRAPHIC DISTRIBUTION OF HAV INFECTION*



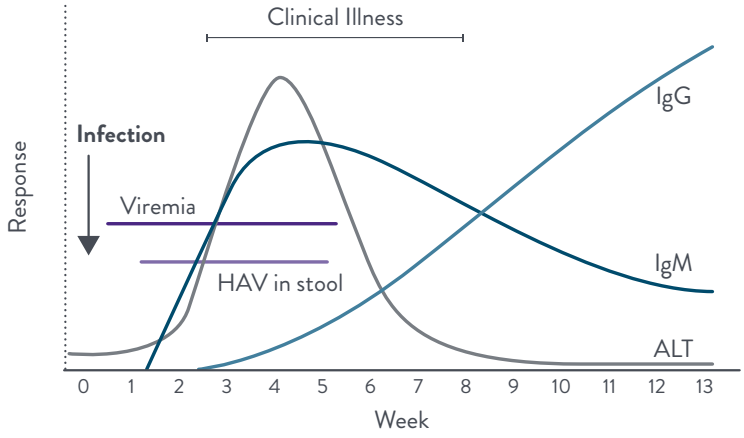
*Note: This map has been generalized from available data.

- Rates of HAV in the United States have declined almost 95 percent since the HAV vaccine introduction in 1995. Vaccination provides long-lasting immunity, thought to be a lifetime, when properly administered with two doses, spaced six months apart.[10]
- In the United States, HAV incidence fluctuates and is associated with outbreaks, usually foodborne outbreaks. In 2018 there were an estimated 24,900 total infections in the United States.[1]
- The CDC reports that the increase in HAV infections in the United States in 2018 was primarily due to person-to-person spread during outbreaks of HAV that have occurred among people who use drugs and experience homelessness. Approximately 55 percent of cases occurring in people 30–49 years of age.
- In terms of morbidity, the CDC notes that in rare cases, HAV can cause liver failure and death and that this is more common in people over 50 or who have other liver diseases. In the pre-vaccine era, this 'fulminant liver failure' caused by HAV resulted in approximately 100 deaths per year. Case-fatality estimates currently range from 0.3–0.6 percent for all ages up to 1.8 percent for adults aged 50 years and greater.[10]
- Since 2006, it has been recommended that all children less than one year be routinely vaccinated against HAV, but unfortunately, vaccination rates remain lower than for other infectious diseases.[1] New efforts focused on routine vaccination of children at 12 months of age are designed to enhance not replace vaccination programs for older children.[10]
- HAV occurs commonly in countries with poor sanitation and lack of safe water and food. Countries at high risk for transmission include those in Africa, Asia, and Central and South America. The map above represents prevalence patterns of HAV infections worldwide.

CLINICAL COURSE[4,10]

- The onset of symptoms is usually abrupt, with symptoms lasting approximately two to eight weeks.
- Importantly, hepatitis A has never been reported to cause chronic infection, although 10 percent of those infected can experience a relapse during the six months following initial infection.
- Jaundice develops in more than 70 percent of adults and older children, but young children typically do not develop jaundice.
- In children under age six, 70 percent of infections are asymptomatic.
- HAV replicates in the liver, is excreted in the bile, and is shed in the stool. HAV is a stable virus and can survive for months outside the body, depending on environmental conditions.
- Peak infectivity occurs during the two-week period before the onset of jaundice or elevation of liver enzymes when the concentration of virus in stool is highest.
- The concentration of virus in stool declines after jaundice appears.
- Children and infants can shed HAV up to several months after onset of clinical illness.
- HAV IgG can be used to detect past HAV infection and to determine if immunity has developed from a previous infection, possibly to determine if vaccination is necessary. There is no recommendation to test for immunity post-vaccination.

HEPATITIS A VIRUS INFECTION



Within three weeks, Janet's symptoms had disappeared. She can now be considered immune to the hepatitis A virus. There is no chronic carrier state for hepatitis A.

PREVENTION/PROPHYLAXIS[10,12]

- Vaccination with the full, two-dose series of hepatitis A vaccine is the best way to prevent HAV infection. Hepatitis A vaccine has been licensed in the United States for use in persons one year of age and older.
- The CDC advisory committee recommends that the following populations be vaccinated: 1) All children at age one year; 2) Persons who are at increased risk of infection; 3) Persons who are at increased risk of complications from hepatitis A; 4) Any person who wishes to obtain immunity (protection).
- Immune globulin can provide short-term protection against hepatitis A, both pre- and post-exposure. Immune globulin must be administered within two weeks after exposure for maximum protection.
- Given that the virus is transmitted through the fecal-oral route, good hand hygiene, including handwashing after using the bathroom, changing diapers, and before preparing or eating food, is integral to hepatitis A prevention.
- Two vaccines are commercially available in the United States—Havrix® (GlaxoSmithKline) and VAQTA™ (Merck & Co., Inc.). In addition, there is a combination vaccine, Twinrix® (GlaxoSmithKline), that provides immunization for HAV and HBV.

VACCINATION

Hepatitis A vaccinations, providing long-term protection, are available for individuals older than one years of age.

Had Janet received the HAV vaccine—even just the initial dose—before she left on her trip, she could have prevented her infection.

THERAPY

HAV is usually a self-limited infection, and treatment and management of HAV infection are supportive.

VIRAL HEPATITIS OVERVIEW

	Hepatitis A Virus[10,12]	Hepatitis B Virus	Hepatitis C Virus	Hepatitis D Virus	Hepatitis E Virus
Virus Family	*Picornaviridae*				
Route of Transmission	Fecal-oral route				
Onset	Usually abrupt				
Incubation	15–50 days				
Chronicity	None				
Mortality	All: 0.3–0.6% ≥50 years: 1.8%				

QUIZ QUESTIONS

HEPATITIS A

1. Cite two routes of HAV transmission:

   _____

2. Individuals most at risk for contracting HAV include:

   A. Food handlers

   B. Children in daycare centers as well as their families

   C. Individuals in close contact with an infected individual

   D. Law enforcement personnel

3. Which of the following describes the incidence of hepatitis A?

   A. In the pre-vaccine era, approximately 100 deaths from fulminant HAV were reported each year in the United States

   B. Since the introduction of the HAV vaccine in 1995, rates of HAV in the United States have fallen 95 percent

   C. Almost all reports of HAV in the United States are associated with outbreaks, usually foodborne

   D. All of the above

4. Which of the following describe the most common symptoms and clinical course associated with HAV? (Choose one or more of the following)

   A. Jaundice always occurs

   B. Onset is usually abrupt

   C. Most cases involving children under age six are asymptomatic (70 percent)

   D. Patients are potentially infectious for up to several weeks before the onset of symptoms

SECTION 3

HEPATITIS B

LEARNING OBJECTIVES

After completing this section, you should be able to:

1. Recognize the incidence and prevalence of hepatitis B
2. Describe the symptoms and clinical course of the disease
3. Indicate the physical features of the virus
4. Indicate how the hepatitis B virus (HBV) is transmitted
5. Identify individuals at risk for infection by the hepatitis B virus
6. Recognize that hepatitis B is a sexually transmitted disease
7. Identify the types of hepatitis B panels and describe their purpose

CASE STUDY #2

SUSAN, 32-YEAR-OLD SALESPERSON

Susan, a 32-year-old salesperson, had been experiencing the following symptoms for over a week: persistent fatigue, loss of appetite, nausea, vomiting, and abdominal pain. She scheduled an appointment with her primary care doctor. After completing her patient history, this is what the physician learned:

- About one week ago, Susan had become sexually active with a new boyfriend
- Both Susan and her new partner had multiple sex partners before they started dating
- Susan had not always used condoms with her partners
- The symptoms appeared about one week ago and were still present

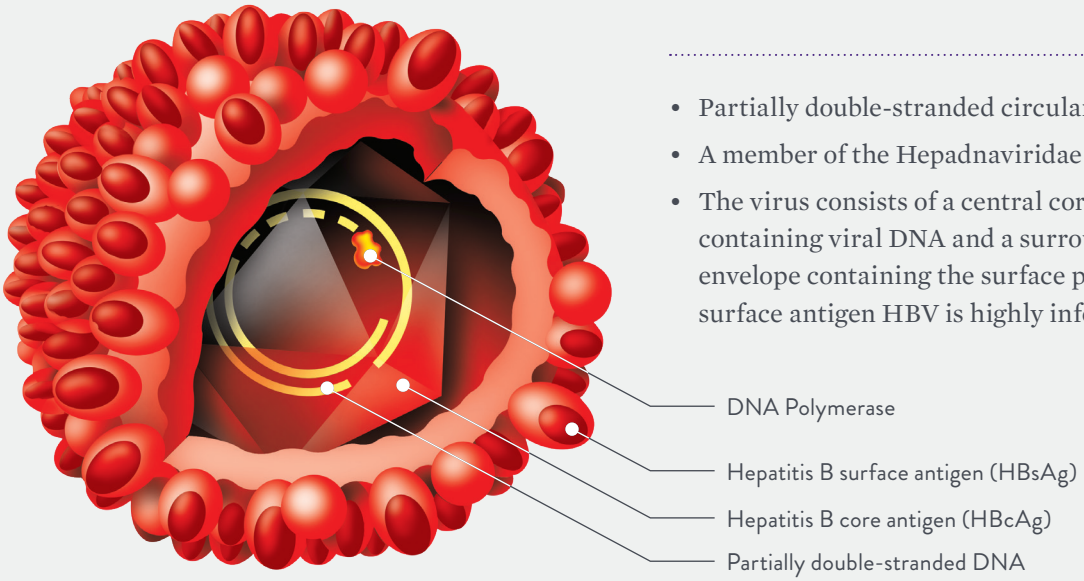
The physician ordered tests for other sexually transmitted diseases, HIV, and pregnancy; all came back negative. Because of Susan's persistent abdominal tenderness, the physician ordered liver function tests. Susan's bilirubin and liver enzyme results were elevated, prompting the physician to order an Acute Viral Hepatitis Panel. Below are the results:

ACUTE VIRAL HEPATITIS PANEL

ASSAY	HBsAg	Anti-HBc IgM	Anti-HAV IgM	Anti-HCV
Results	+	+	–	–

Susan was HBsAg positive, indicating that she was infected with HBV. Susan's test results also showed that anti-HBc IgM was present, indicating an acute HBV infection.

HEPATITIS B VIRUS

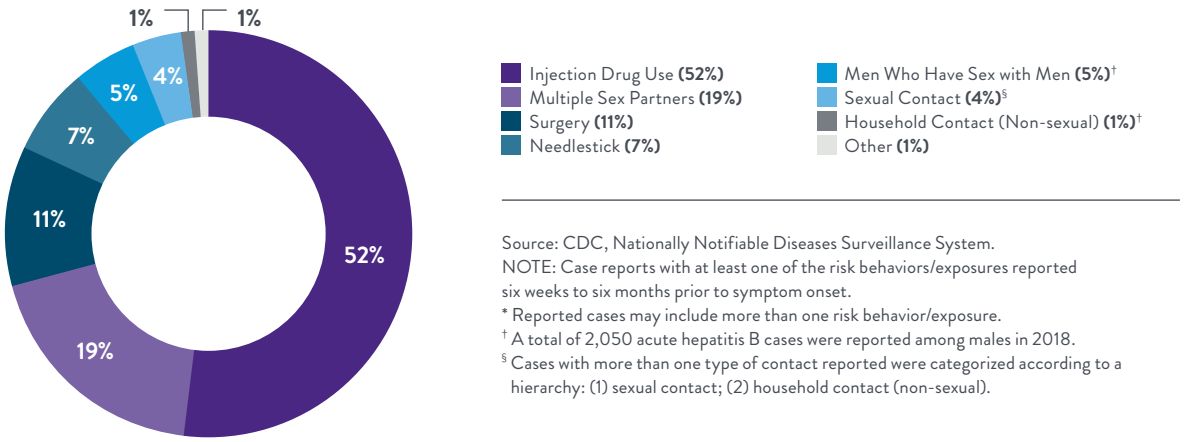


- Partially double-stranded circular DNA virus[9]
- A member of the Hepadnaviridae family
- The virus consists of a central core nucleocapsid containing viral DNA and a surrounding envelope containing the surface protein, or surface antigen HBV is highly infectious

ROUTES OF TRANSMISSION[2,9]

- Percutaneous
  - Contaminated needlestick (injecting drug use and occupational exposure)
  - Hemodialysis
  - Human bite
  - Transplant or transfusion of unscreened blood or blood products
  - Acupuncture, tattooing, and body-piercing with unsterilized needles
  - Sharing razors
- Permucosal
  - Sexual intercourse
  - Perinatal—infant born to an HBV infected mother
  - Contact with infected household objects (i.e., toothbrush or razor that may have blood on it)

REPORTED RISK BEHAVIORS/EXPOSURES* AMONG REPORTED CASES OF ACUTE HEPATITIS B—UNITED STATES, 2018



Source: CDC, Nationally Notifiable Diseases Surveillance System.
NOTE: Case reports with at least one of the risk behaviors/exposures reported six weeks to six months prior to symptom onset.
* Reported cases may include more than one risk behavior/exposure.
† A total of 2,050 acute hepatitis B cases were reported among males in 2018.
§ Cases with more than one type of contact reported were categorized according to a hierarchy: (1) sexual contact; (2) household contact (non-sexual).

Most likely, due to the long incubation period characteristic of an HBV infection, which averages 60 to 90 days, Susan had probably contracted the virus from a previous partner. Her current partner was not experiencing any symptoms, but because many individuals infected with HBV are asymptomatic, her previous and current partners should also be tested and counseled. Her physician advised her of this and also inquired about her previous partners to try to determine which one may have transmitted the infection to Susan. Susan reported that about four months ago, she had been intimately involved with a young immigrant from Ghana. She noted that he did not appear 'sickly' and that they had not used condoms during their sexual relations. Her primary care doctor visited the CDC and NIH websites and found that there is a high prevalence of HBV in Ghana.

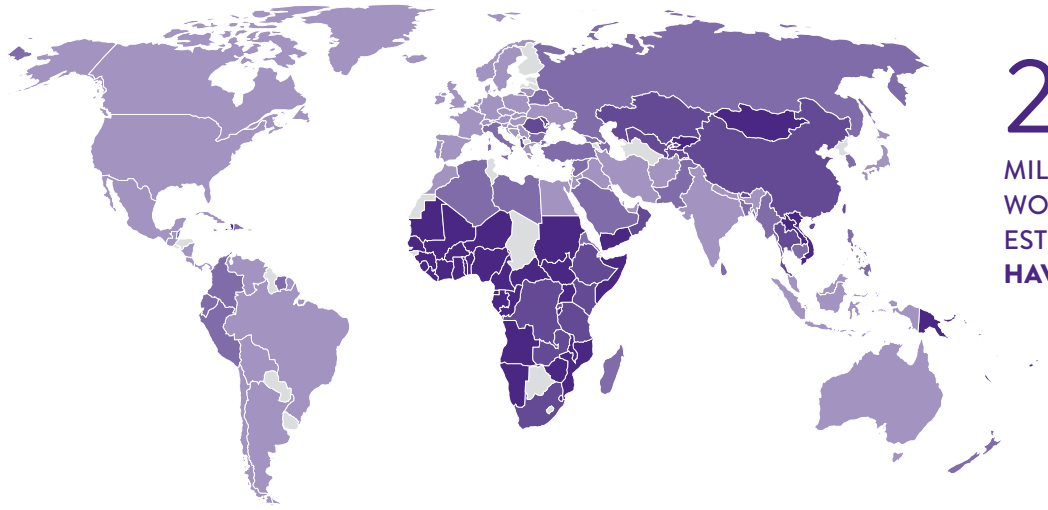
INDIVIDUALS AT RISK[2]

- Sexual contacts of an acute or chronically infected person
- Intravenous drug users/abusers
- Persons with multiple sex partners or a history of sexually transmitted diseases
- Infants born to HBV infected mothers
- Individuals who have occupational contact with blood:
  - Medical and dental workers
  - Laboratory and support personnel
  - Public service employees (i.e., paramedics, EMTs)
- Hemodialysis patients (due to poor equipment sterilization, not blood)
- Household contacts of HBV infected individuals
- Institutionalized populations (i.e., individuals in prisons and facilities for the developmentally disabled)
- Persons born in HBV endemic areas (i.e., Africa, Asia, Eastern Europe, and South America)

Susan had unprotected sex with multiple partners, which placed her at risk for HBV infection, particularly because of her exposure to someone who immigrated from a region known to have a high prevalence of HBV.

INCIDENCE/PREVALENCE

GEOGRAPHIC DISTRIBUTION OF CHRONIC HBV INFECTION*



257

MILLION PEOPLE WORLDWIDE ARE ESTIMATED TO **HAVE CHRONIC HBV**[14]

*Note: The map of HBsAg prevalence generalizes available data; patterns may vary within countries.
Source: CDC 2020.

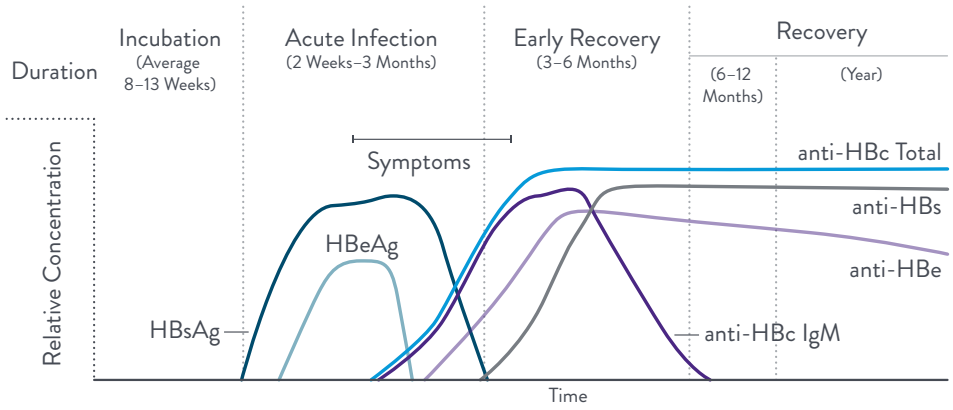
- In 2015, the World Health Organization (WHO) estimated that there were approximately 257 million people worldwide with chronic HBV infection.[14]
- The rate of new HBV infections had declined from 1990 to 2014, with the greatest decline among children born since 1991 when routine vaccination of children was first recommended. There has been an increase in new HBV infections beginning in 2014, likely due to an increasing rate of injection drug use.
- In the United States, the CDC estimated in 2016 that were 862,000 people chronically infected with HBV with an estimated 21,600 new infections in 2018.[1,2]
- From 2001 to 2016, the incidence of new cases of HBV was consistently highest in people aged 30–39.[2]
- Approximately 30–50 percent of patients greater than five years old with HBV infection develop clinical illness/symptoms; 5–15 percent of children one to five years of age develop symptoms with acute infection, but less than one percent of infants who acquire the infection develop symptoms.[2,14]
- Approximately 1,650 individuals in the United States were reported to have died in 2018 due to chronic liver disease associated with HBV.[2]

Susan's age placed her in the population with the largest percentage of new cases that occur each year.

CLINICAL COURSE[2,9,14]

- The incubation period averages 60–90 days, with the range being 60–150 days.
- Onset is often insidious and many of those infected, especially children, have no symptoms.
- HBV causes clinical illness (jaundice) in 30–50 percent of all individuals age five and older, but less than 10 percent of those aged under five years.
- Symptoms include anorexia, fatigue, nausea, vomiting, abdominal pains, muscle or joint aches, mild fever, dark urine, clay-colored stools, skin rashes, and jaundice.
- Most HBV infected adults (95 percent) will recover within six months and develop immunity.
- Of those infected with HBV, 25–50 percent of children one to five years of age, 90 percent of infants, and approximately five percent of the population over five years of age will progress to chronic infection.
- Patients with chronic HBV infection are often asymptomatic but may infect others and are referred to as carriers. More than 25 percent of these carriers develop chronic active hepatitis, often resulting in cirrhosis.
- Approximately 25 percent of those with chronic HBV infection die prematurely from cirrhosis or liver cancer.
- Approximately 25 percent of those who become chronically infected with HBV during childhood and 15 percent who become chronically infected after childhood die prematurely as a result of cirrhosis or liver cancer. The remainder remains asymptomatic until the onset of cirrhosis or end stage liver disease.

ACUTE HEPATITIS B DIAGNOSTIC PROFILE



Since Susan's symptoms were so persistent, the physician followed up the initial Acute Viral Hepatitis Panel with the Hepatitis B Monitoring Panel. It was important for the physician to understand the stage of Susan's infection.

HEPATITIS B PANELS

HEPATITIS B MONITORING PANEL

When a patient tested with the Acute Viral Hepatitis Panel has positive results for surface antigen (HBsAg) and IgM antibody to the core antigen (anti-HBc IgM), the diagnosis of acute hepatitis B is established. To follow the patient's progress, serial testing with the monitoring panel is indicated. This panel consists of four hepatitis B markers: HBsAg, HBeAg, anti-HBe, and anti-HBs.* With the hepatitis B monitoring panel, a physician can:[2,9]

- Determine the patient's potential for developing chronic HBV infection due to the persistence of the surface antigen (HBsAg)
- Determine relative infectivity (HBeAg)
- Monitor seroconversion from HBeAg to anti-HBe, which usually indicates progress toward a resolution of the disease
- Monitor seroconversion from HBsAg to anti-HBs positivity, which indicates a resolution of the disease and establishment of immunity

In Susan's case, the results of the monitoring panel would help identify her degree of infectivity.

ACUTE VIRAL HEPATITIS PANEL

ASSAY	HBsAg	HBeAg	Anti-HBe	Anti-HBs
Results	+	+	–	–

*Example of a hepatitis B monitoring panel used by a large reference laboratory.

The results show that Susan was highly infectious. At this point, the physician informed Susan of the following:

- Need to advise sex partners and household contacts of her infectious state
- The clinical course of the hepatitis B virus infection and possible outcomes
- Importance of NOT DONATING BLOOD

The physician also informed her that she was going to be monitored every month until the resolution of the disease. Six months later, the results were negative for HBsAg and HBeAg and positive for anti-HBe and anti-HBs. This indicated that Susan had resolved the infection.

Susan did contact all of her previous partners to advise them of her infection and recommend that they be tested. When she talked with the young man who had immigrated from Ghana, he did mention to her that his mother had died when he was an adolescent of an illness that left her thin and weak but with a bloated abdomen. When he was tested for viral hepatitis, he was found to be HBsAg positive, and as he was not ill, he was identified as an HBV carrier. With the information he provided, it appears that his mother succumbed to hepatocellular carcinoma secondary to HBV infection and that she passed this to him at his birth. His risk of significant liver disease is great.

If Susan's HBsAg had persisted for more than six months, she would have been considered chronically infected with HBV.

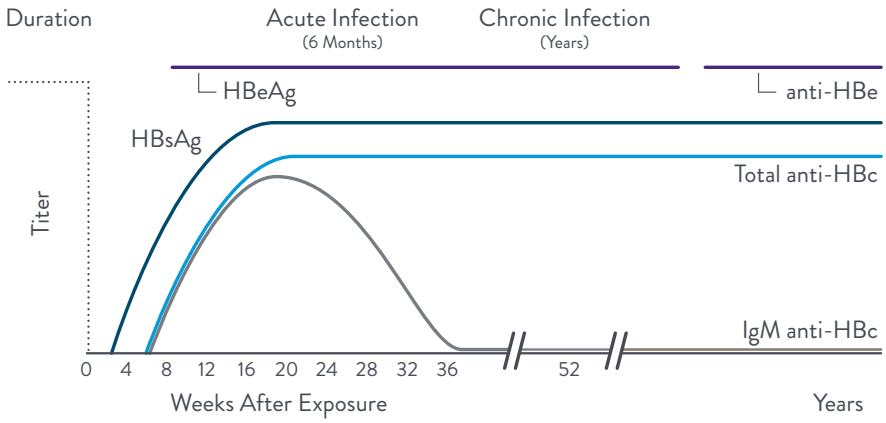
CHRONIC HBV INFECTION

An individual is considered chronically infected if HBsAg is present for more than six months.[2,9]

Three markers are used to determine the stage of chronic infection: HBsAg, HBeAg, and anti-HBc total. HBsAg and anti-HBc total will almost always be present; HBeAg may or may not be present, depending on the stage of disease progression.[2,9]

Chronically infected individuals with HBeAg typically have higher viral loads than those with anti-HBe. Both patient groups should be considered infectious.[2,9,15]

PROGRESSION TO CHRONIC HBV INFECTION TYPICAL SEROLOGIC COURSE



TESTING TO DETERMINE IMMUNITY: Anti-HBs[2]

Anti-HBs (antibody to the surface antigen) is the only marker for determining immunity to an HBV infection. Anti-HBs appears early in recovery, and the titer may eventually decline. Other indicators of recovery are normal liver enzyme levels and negative tests for HBsAg.

Anti-HBs testing is recommended for:

- Healthcare workers
- Pregnant women
- Babies born to HBV infected mothers
- Sex partners of persons with chronic HBV infection
- Immunocompromised individuals

PREVENTION: HBV VACCINE[16,17]

The first hepatitis vaccine available in the United States was produced from the plasma of persons chronically infected with HBV. The hepatitis B vaccines currently available are produced by recombinant DNA technology. HBV infection cannot result from the vaccine produced by recombinant technology as it does not contain viral DNA or complete viral particles.

Since its introduction, the use of this vaccination has helped reduce the incidence of HBV infections, both acute, and over time, chronic. The conventional regimen is a series of three intramuscular doses of the vaccine given over a six-month period: initial vaccination, again at 30 days, and the third dose at six months.

- Immunization is one of the most medically efficient and cost-effective means of controlling viral hepatitis.[18,19]
- Countries with universal vaccination programs are seeing declines in chronic HBV infections.[18,19]
- Achieving universal immunity requires an increase in public awareness of the severity of health problems caused by HBV.[18,19]

Immunity following vaccination is as high as 95 percent in those receiving it prior to age 19 and drops to approximately 90 percent at age 40 and 75 percent when received by age 60.[9] Increased vaccine dosage is required in those who are immune-compromised. It is generally reported the vaccine is 80–100 percent effective in preventing clinical hepatitis in patients who receive the complete vaccine series.

In the United States, the CDC recommends that hepatitis B vaccination be part of childhood immunization programs with vaccination of all infants soon after birth, children, and adolescents through age 18, and all adults at risk for HBV as well as those who want to attain protection from HBV infection.[2,9] Currently, the World Health Organization (WHO) strongly recommends universal vaccination against HBV in all countries, and nearly all are adopting programs to accomplish this.[2,18]

PRE-VACCINATION TESTING

Anti-HBc total, total antibody (i.e., IgM and IgG) to the hepatitis B core antigen, is an indicator of a current or previous HBV infection. It is also used with anti-HBs and HBsAg for screening at-risk populations for hepatitis B to determine their immune status. The CDC currently recommends that adult populations that have risk factors for HBV transmission or reinfection should receive complete serologic testing (HBsAg, anti-HBs, anti-HBc). Following the collection of the blood sample for this testing, the first dose of the vaccine should be administered as vaccination of a person who is immune to HBV because of prior infection or vaccination is not harmful. Individuals who are found to be positive for both anti-HBc and anti-HBs are presumed to be immune by prior natural infection. Should the serologic testing results indicate that the person is HBsAg negative, without evidence of immunity, the two remaining doses of vaccination can be completed. Those that are HBsAg positive should be referred to a specialist for antiviral treatment and counseling. Those who are anti-HBc positive should be referred for counseling regarding the risk of reactivation.[2] The CDC now recommends a prevention strategy that includes recommendations for vaccination, for prenatal testing for HBsAg to identify pregnant women whose newborns require prophylaxis and whose household members require vaccination.[9]

VACCINATION RECOMMENDATIONS

The current CDC vaccine recommendations include all infants and unvaccinated children under 19, people at risk of infection through sexual exposure, people at risk for infection via percutaneous or mucosal exposure to blood, international travelers to countries with high or intermediate levels of endemic HBV, people with HCV, HIV infection and chronic liver disease, those who are incarcerated and anyone seeking protection from HBV infection.[2]

Hepatitis B vaccines are produced by Merck & Co., Inc. (Recombivax HB®), and GlaxoSmithKline Pharmaceuticals (Engerix-B®), and both are available in both pediatric and adult formulations. Additional vaccines are also available, which combine the hepatitis B vaccine with other childhood vaccines, Comvax® (Merck & Co., Inc.), and Pediarix® (GlaxoSmithKline). Twinrix® is a combined vaccination for HBV and HAV.[9]

POST-VACCINATION TESTING

The higher the vaccine-induced anti-HBs concentration after the primary vaccination course, the longer the antibodies will persist. The hepatitis B vaccine is designed to induce only anti-HBs (the protective antibody) and will not induce an anti-HBc response; the presence of anti-HBc indicates immunity acquired through past HBV infection. In the United States, an antibody level of 10 mIU/mL or higher indicates immunity.[9] Outside the United States, other levels of antibody may be used to determine immunity. These levels may vary from country to country.

The CDC recommends that testing for immunity should only be done in persons whose subsequent clinical management depends on the knowledge of their immune status.[2] This includes:

- Infants born to HBsAg positive mothers
- Healthcare workers and public safety workers at risk for percutaneous or mucosal blood exposure
- Chronic hemodialysis patients, HIV infected patients, or other immunocompromised patients
- Sex partners of persons with chronic HBV infection

PREVENTION/PROPHYLAXIS

Beginning in 1991, the CDC initiated a comprehensive strategy to eliminate HBV transmission. This plan included prenatal testing of pregnant women for HBsAg to identify infants who were exposed and required immunoprophylaxis to prevent neonatal infection and to permit the identification of household contacts who should receive the vaccination, initiated the routine vaccination of infants, and vaccination of adolescents and high-risk adults. In 2011, recommendations were made to enhance the vaccination of at-risk adults.[9,20]

Additional measures to prevent HBV infection include:[20]

- Worldwide screening of blood and blood products
- Destruction of disposable needles and adequate sterilization of reusable materials such as surgical or dental instruments
- Effective use of universal precautions and barrier techniques (such as the use of sterile equipment, the wearing of gloves, and the wearing of eye/face protection)

Prophylaxis against HBV infection is essential in patients who are exposed to HBV but have not been vaccinated and lack immunity. Prophylaxis can be effective using hepatitis B immune globulin (HBIg), which is administered to provide temporary, passive protection. The hepatitis B vaccine is used to provide active, prolonged immunity.[9]

CDC recommendations currently include that in instances in which there is exposure either percutaneously through needlestick, laceration or bite, and also permucosally to HBV, that blood is drawn from the exposed individual to determine their immune status. Management will depend on their status and may include hepatitis B immune globulin (HBIg) and initiation of vaccination in the unvaccinated and in those who were vaccinated but were non-responders and remain vulnerable to HBV infection.[9]

PRENATAL SCREENING

Infants born to mothers who are chronically infected with hepatitis B have a high probability of contracting the infection, of becoming chronically infected, and of developing chronic liver disease later in life. Therefore, HBsAg testing is recommended in the United States for prenatal screening of all pregnant women.[9]

If the mother's HBsAg status is unknown at the time of admission for delivery, blood should be drawn for HBsAg testing. While awaiting test results, the infant should receive the hepatitis B vaccine. If the mother is identified as HBsAg positive, the infant should also be given hepatitis B immune globulin (HBIg) as soon as possible but not later than seven days after birth, and the vaccine series should be completed as scheduled. When a combination of HBV vaccination and one dose of HBIg is administered to infants born to women who are HBsAg positive within 24 hours of birth, there is an 85–95 percent effectiveness at preventing chronic HBV infection in the newborn. HBV vaccine alone, when administered within 24 hours after birth, is 70–95 percent effective at preventing infection.[9]

Routine vaccination of all infants is recommended.

HBV AND INFANTS

Infants born to mothers who are chronically infected with hepatitis B have a high probability of contracting the infection, of becoming chronically infected, and of developing chronic liver disease later in life.

DEVELOPMENTS IN HBV TESTING

Researchers have developed assays that detect and accurately measure HBV DNA. These assays detect the viral genome and measure the level of circulating virus in an infected individual. The level of HBV DNA in the blood is often referred to as "viral load."

Applications for hepatitis B virus DNA assays include:

- Directly assess circulating virus in an infected individual
- Predict response to antiviral therapy based on pretreatment viral load
- Monitor the effectiveness of antiviral therapy (HBV DNA falls rapidly in patients who respond to treatment)
- Provides additional information to help confirm a diagnosis in cases with ambiguous serology

If a physician can determine the viral load, then he or she can better gauge whether or not to initiate therapy, as well as more accurately monitor its effect.

THERAPY

Individuals with chronic HBV infection should be evaluated and monitored for evidence of chronic liver disease and the potential need for treatment. Although there several therapeutic antiviral agents currently available to treat HBV, including interferon (IFN) and nucleos(t)ide analogues (NAs), sustained remission off-treatment best measured with HBsAg loss, is infrequently attained. Other antiviral drugs are being studied experimentally. For acute HBV, there are no medications available, and supportive care is rendered.[9]

VIRAL HEPATITIS OVERVIEW

	Hepatitis A Virus[10,12]	Hepatitis B Virus[9,14]	Hepatitis C Virus	Hepatitis D Virus	Hepatitis E Virus
Virus Family	*Picornaviridae*	*Hepadnaviridae*			
Route of Transmission	Fecal-oral route	Percutaneous, permucosal			
Onset	Usually abrupt	Usually insidious			
Incubation	15–50 days	Average 60–90 days, range 60–150 days			
Chronicity	None	5% of Adults and those 5+ years of age; 90% infants; 25–50% of children (1–5 years of age)			
Mortality	All: 0.3–0.6% ≥50 years: 1.8%	Overall case fatality of 1.0%			

QUIZ QUESTIONS

HEPATITIS B

1. Which of the following is not a route of transmission for HBV?

   A Needlestick
   B Sexual contact
   C Tattoo
   D Contaminated water

2. Name the six serological markers for hepatitis B:

   _____

3. Chronic HBV infection worldwide is approximately:

   A 2 million
   B 150 million
   C 250 million
   D 1 billion

4. In the United States, about 860,000 people are chronically infected with hepatitis B.

   A True
   B False

5. Vaccination against HBV is more effective in achieving immunity when those who receive it are older than 60 years.

   A True
   B False

6. List five symptoms that may be associated with an acute HBV infection:

   _____

7. The average incubation period of hepatitis B is:

   A 20–30 days
   B 60–90 days
   C 90–120 days

8. Of those infected with HBV, _____ percent of children one to five years of age will progress to a chronic HBV infection.

   A 2–10%
   B 15–20%
   C 25–50%
   D 100%

9. Which of the following individuals are typically at risk for hepatitis B?

   A. Injecting drug users
   B. Travelers to endemic areas (for short periods of time)
   C. Sexual contact with HBV infected individuals
   D. Household contacts of persons with chronic HBV infections

10. What assays are included in the hepatitis B Monitoring Panel?

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11. Anti-HBc is used primarily to assess infectivity.

   A. True
   B. False

12. What test is used in the prenatal screening of pregnant women?

   A. Anti-HBs
   B. HBsAg
   C. HBeAg
   D. Anti-HBc Total

13. The hepatitis B vaccine is administered to provide temporary passive protection.

   A. True
   B. False

14. HBIg should be given to:

   A. Infants born to HBV infected mothers
   B. Sexual partners of individuals with acute HBV
   C. Unvaccinated healthcare workers involved in needlestick incidents where HBV is known
   D. All of the above

15. Anti-HBs is the only test available today to determine immunity to HBV.

   A. True
   B. False

SECTION 4

HEPATITIS C

LEARNING OBJECTIVES

After completing this section, you should be able to:

1. Indicate how the hepatitis C virus (HCV) is transmitted
2. Identify individuals at risk for infection by HCV
3. Recognize the incidence and prevalence of HCV infection
4. Describe the symptoms and clinical course of an HCV infection

CASE STUDY #3

DONALD, EMERGENCY ROOM NURSE

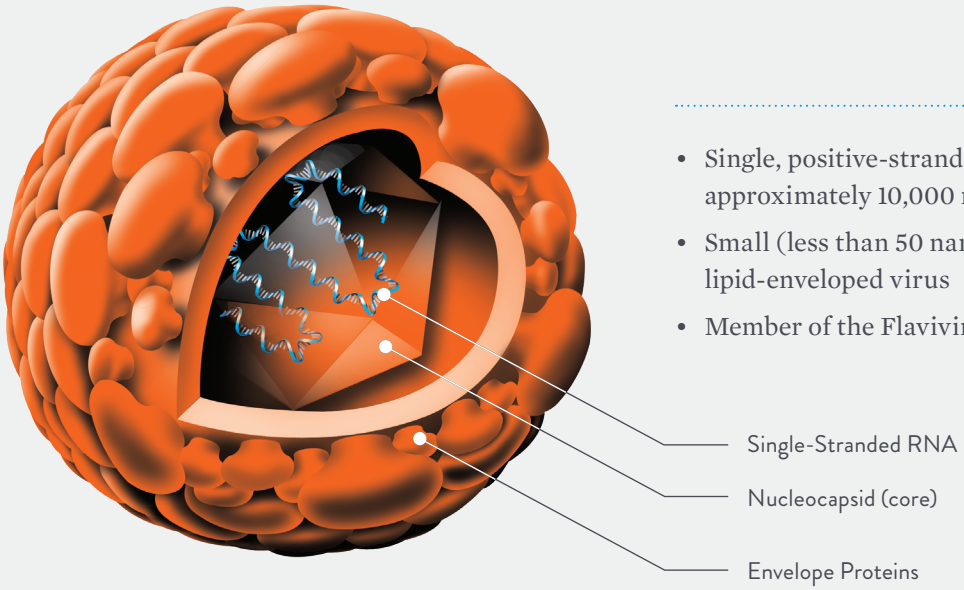
Donald, a 39-year-old emergency room nurse, accidentally stuck himself with a needle as he removed it from a patient's vein. When he reviewed the patient's chart, he noticed that this individual was anti-HCV positive. He immediately scheduled an appointment with his physician. Even though the needlestick occurred less than 24 hours previously (too soon for an antibody response), the physician still ordered an Acute Viral Hepatitis Panel to check for current infection with HAV, HBV, and/or HCV. An HIV test was also ordered.

ACUTE VIRAL HEPATITIS PANEL

ASSAY	HBsAg	Anti-HAV IgM	Anti-HBc IgM	Anti-HCV
Results	–	–	–	–

All tests came back negative, including HIV. Because of the recent exposure to the hepatitis C virus, the physician advised Donald that follow-up testing would be needed in order to rule out an HCV infection.

HEPATITIS C VIRUS



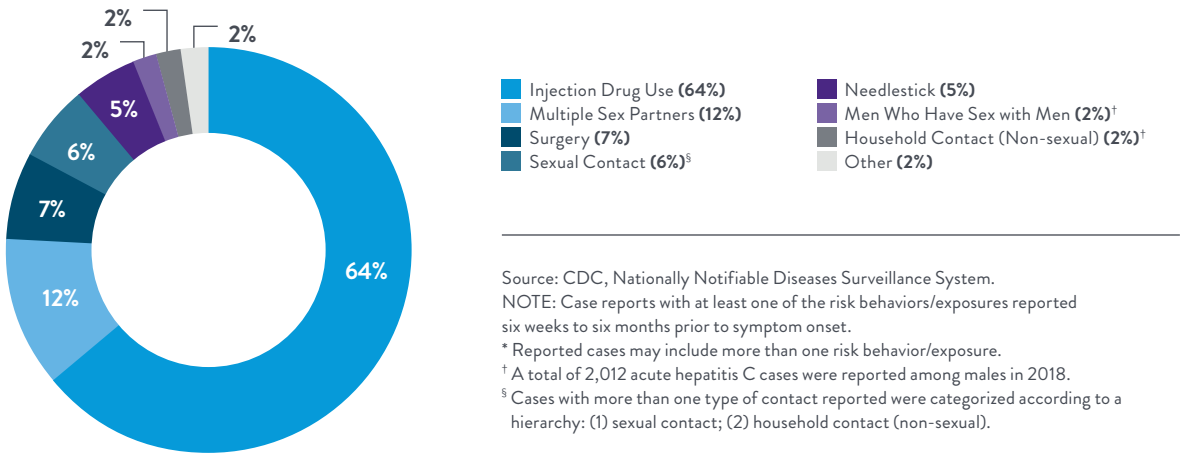
- Single, positive-stranded RNA virus of approximately 10,000 nucleotides
- Small (less than 50 nanometers in diameter); lipid-enveloped virus
- Member of the Flaviviridae family

ROUTES OF TRANSMISSION[3,21,22]

HCV is a blood-borne virus. There are no known cases of HCV transmitted enterically (oral-fecal) through breast milk, semen, or saliva. Today, most HCV is transmitted through sharing needles or other equipment to inject illicit drugs. The following routes of transmission are well-documented:

- Percutaneous
  - Contaminated needlestick (injecting drug use and occupational exposure)
  - Hemodialysis
  - Human bite
  - Transplant or transfusion of unscreened blood or blood products
  - Acupuncture, tattooing, and body-piercing with unsterilized needles
- Permucosal
  - Sexual intercourse
  - Perinatal—infant born to HCV infected mother
  - Contact with infected household objects (i.e., toothbrush or razor that may have blood on it)

REPORTED RISK BEHAVIORS/EXPOSURES* AMONG REPORTED CASES OF ACUTE HEPATITIS C—UNITED STATES, 2018



Source: CDC, Nationally Notifiable Diseases Surveillance System.
NOTE: Case reports with at least one of the risk behaviors/exposures reported six weeks to six months prior to symptom onset.
* Reported cases may include more than one risk behavior/exposure.
† A total of 2,012 acute hepatitis C cases were reported among males in 2018.
§ Cases with more than one type of contact reported were categorized according to a hierarchy: (1) sexual contact; (2) household contact (non-sexual).

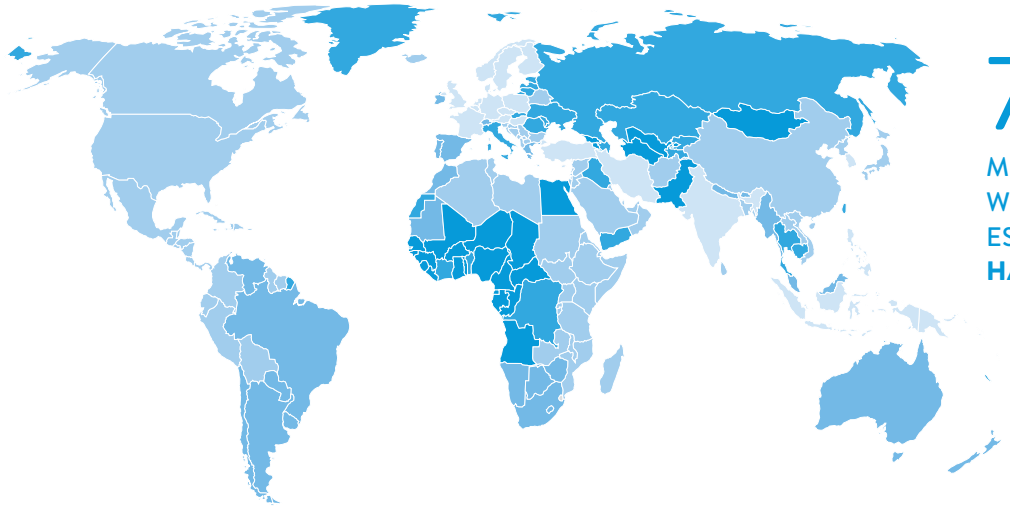
INDIVIDUALS AT RISK[3,21]

- Current or former injection drug users
- Persons with known exposures to HCV, including health care workers after needle sticks involving HCV-positive blood
- Chronic Hemodialysis patients
- Transfusion and transplant recipients (prior to 1992)
- Recipients of blood or organs from a donor who tested HCV-positive
- People with HIV infection
- Children born to HCV-positive mothers

The route by which Donald was exposed to HCV, as well as his occupation, put him at risk for an HCV infection.

INCIDENCE/PREVALENCE

GLOBAL DISTRIBUTION OF HEPATITIS C, 2020



71
MILLION PEOPLE WORLDWIDE ARE ESTIMATED TO **HAVE CHRONIC HCV**[21]

Source: CDC, 2020

Because an acute infection is asymptomatic in most cases, incidence data on a global scale is not well known.

It is important to note that since the availability of multi-antigen testing in 1992, the incidence of post-transfusion HCV has declined significantly. The risk is now less than 1 in 2,000,000 units transfused.[3]

- In the United States, the annual number of newly acquired acute HCV infections has declined from an estimated 240,000 in the mid-1980s[23] to an estimated 50,300 in 2018.[1] This number has been increasing recently, most likely due to the increase in illicit injection drug use. The CDC notes that the number of reported cases increased three-fold between 2010 and 2016, from 850 cases reported in 2010 to 2,967 in 2016.[24] In 2018, there were 3,621 new cases reported to the CDC.[1] As noted previously, because many who are infected are asymptomatic, the CDC provides both a reported number of cases and an estimate of the suspected number of infections.[3]
- In terms of prevalence, an estimated 2.4 million Americans have hepatitis C.[3]
- The WHO estimates that globally an estimated 71 million people have chronic HCV infection.[21]
- The WHO reports that approximately 399,000 people die each year from HCV infection, mostly due to cirrhosis and hepatocellular carcinoma.[21]

CLINICAL COURSE[3,21]

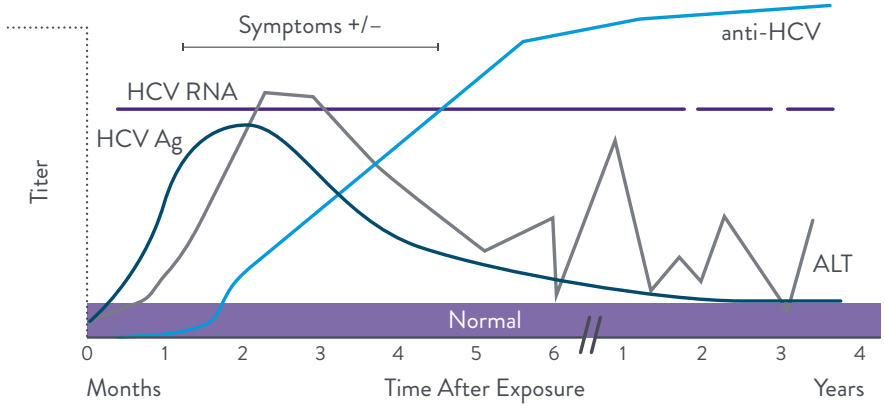
- The incubation period varies from 2–26 weeks; the average is six to seven weeks.
- Onset is usually insidious.
- The majority of infected persons, 70–80 percent, may be asymptomatic.
- 20–30 percent of patients develop nonspecific symptoms (e.g., anorexia, malaise, fatigue, or abdominal pain).
- 20–30 percent of individuals with acute HCV might have jaundice.
- Patients with acute HCV infection may take an average of four to ten weeks from exposure for seroconversion to occur; the average time from exposure to symptoms development is 2–12 weeks.
- Individuals positive for HCV antibody, even if liver enzyme tests are normal, are considered potentially infectious for the virus.
- About 70 percent (55–85 percent) of HCV infected individuals become chronically infected with the virus. Around 30 percent (15–45 percent) of infected persons spontaneously clear the virus within six months of infection without any treatment.
- Of persons with chronic hepatitis C, 15–30 percent will develop cirrhosis.
- Hepatocellular carcinoma develops in one to five percent of individuals with chronic HCV infection who develop cirrhosis over 20–30 years.
- Mortality—in the United States, it is conservatively estimated that 18,000 people died from HCV-associated chronic liver disease in 2016.
- HCV is now a common cause for liver transplantation in the United States.
- Various factors, including alcohol use and coinfection with HIV, can affect the clinical course of HCV (abstinence from alcohol in infected individuals is recommended).

CHRONIC HCV INFECTION

About 70 percent of HCV infected individuals become chronically infected. Of persons with chronic hepatitis C, 15–30 percent will go on to develop cirrhosis.

Three months after the needlestick incident, Donald's anti-HCV result was still negative, and his liver enzymes were normal. As a precaution, his physician routinely tested Donald for anti-HCV. At the one-year follow-up, he remained negative for anti-HCV, and the physician reassured him that although exposed to HCV, he had not become infected.

SEROLOGIC PATTERN OF ACUTE HCV INFECTION WITH PROGRESSION TO CHRONIC INFECTION



DIAGNOSTIC TESTING FOR HEPATITIS C

The serological testing required to make the diagnosis of HCV and identifying acute from chronic infection can be more challenging. Since the development of new antiviral drugs that first became available in 2011, with second-generation drugs approved in 2012, identifying active infection, distinguishing acute from chronic infection, and determining if the infection has been eradicated has become more important.[25]

The first step in diagnosing HCV serologically is by detecting antibodies specific to the hepatitis C virus (anti-HCV) and by ruling out other viruses such as HAV or HBV. Active HCV infection cannot be diagnosed by anti-HCV assay alone, and a secondary test, such as an HCV RNA or HCV Ag, should be used to confirm active viremia, either acute HCV or chronic HCV, following a positive anti-HCV result.[3]

As a screening assay for the blood supply, current anti-HCV assays have been very effective in the United States at reducing post-transfusion hepatitis to a very low level.

DEVELOPMENTS IN HCV TESTING

A major development was of assays that detect and accurately measure HCV RNA. These assays detect the viral genome and measure the level of circulating virus in an infected individual. The level of HCV RNA in the blood is often referred to as the "viral load." Several polymerase chain (PCR) tests for HCV RNA are now available.

Applications for hepatitis C virus RNA assays include:

- Directly assess circulating virus in an infected individual indicating viremia (active infection)
- Evaluate suspect HCV infection before seroconversion occurs
- Assess viral load before antiviral therapy is administered
- Monitor the effectiveness of antiviral therapy and determine if a resolution of the infection has occurred, resulting in a cure

Another major development was that of assays that detect HCV Ag. Because the antigen is part of the virus, its presence indicates active infection identifying viremia in acute and chronic HCV. It has been recommended in European Association for the Study of the Liver (EASL) guidelines that HCV Ag may be used as a surrogate marker of HCV replication in places where HCV RNA testing is not available or affordable.[26]

Viral genotyping, another serological test, is important to help determine the epidemiology of hepatitis C and to make recommendations for the appropriate treatment regimen. In the United States, the CDC reports that genotypes 1, 1a, 2, and 3 are the most common genotypes. With the advent of new HCV therapies that are effective against many genotypes, routine testing for genotypes prior to initiation of treatment is no longer necessary. It is recommended that genotype testing be undertaken, however, for patients with evidence of cirrhosis or who have failed past treatments to enable the selection of the treatment most likely to be effective.

PREVENTION/PROPHYLAXIS

There is currently no vaccine for HCV. The difficulty in developing a vaccine is due, in part, to the mutability of the HCV genome. In addition, there is no effective, short-term prevention such as HBIg or immune globulin. In the absence of the above, all precautions to prevent HCV infection must be taken.[3,21]

WHO recommendations on measures to prevent HCV include:[21]

- Hand hygiene, including surgical hand preparation, hand washing, and use of gloves
- Safe and appropriate use of health care injections
- Safe handling and disposal of sharps and waste
- Provision of comprehensive harm-reduction services to people who inject drugs, including sterile injecting equipment
- Testing of donated blood for hepatitis B and C (as well as HIV and syphilis)
- Training of health personnel
- Promotion of correct and consistent use of condoms

UNIVERSAL PRECAUTIONS

Effective use of universal precautions and barrier techniques (such as use of sterile equipment and the wearing of gloves) are some of the recommendations to prevent HCV infection.

THERAPY

- HCV does not always require treatment, and 15–25 percent of those infected will clear the acute infection. In most cases, patients presenting with acute HCV infection should be followed with treatment initiation if HCV RNA persists for more than six months.[21,22]
- No post-exposure prophylaxis is available for hepatitis C; immune globulin is not recommended.[22]
- The treatment of HCV was substantially improved with the introduction of protease inhibitor therapies beginning in 2011 with first-generation drugs, which were used in combination with pegylated interferon and ribavirin (RBV). Second-generation drugs were first approved in 2012 for use as stand-alone therapies. There are currently several different medications now available, and these can achieve cure rates of over 95-98 percent with 8-12 weeks of oral therapy. A cure is considered an achievement of sustained virologic response (SVR), defined as the absence of detectable HCV RNA or HCV Ag 12 weeks after completion of treatment. This class of drugs has changed the outcome of chronic HCV infection from persistent infection frequently leading to liver failure and death with most symptoms developing 20 or more years post-infection, to one where eradication of the virus and cure can prevent this fatal outcome.[3]
- Treatment of acute HCV infection may be recommended in limited populations where there is a risk of transmission, such as healthcare workers, especially surgeons, intravenous drug users, or in the rare cases where acute liver failure occurs.[26]
- Treatment with this class of drugs is recommended for patients with chronic HCV who have already developed cirrhosis or liver disease as eradication of the hepatitis C virus has resulted in patient improvement.[27]
- Patients undergoing HCV treatment who have also been infected with HBV can be at risk for HBV reactivation.[3]

VIRAL HEPATITIS OVERVIEW

	Hepatitis A Virus[10,12]	Hepatitis B Virus[9,14]	Hepatitis C Virus[3,21]	Hepatitis D Virus	Hepatitis E Virus
Virus Family	*Picornaviridae*	*Hepadnaviridae*	*Flaviviridae*		
Route of Transmission	Fecal-oral route	Percutaneous, permucosal	Percutaneous, permucosal		
Onset	Usually abrupt	Usually insidious	Insidious		
Incubation	15–50 days	Average 60–90 days, range 60–150 days	14–182 days		
Chronicity	None	5% of Adults and those 5+ years of age; 90% infants; 25–50% of children (1–5 years of age)	75–85%		
Mortality	All: 0.3–0.6% ≥50 years: 1.8%	Overall case fatality of 1.0%	In 2016, >18,000 HCV associated		

QUIZ QUESTIONS

HEPATITIS C

1. Name two routes of transmission of the hepatitis C virus:

   _____

2. The number of persons with chronic HCV infection worldwide is approximately:

   A. 2 million
   B. 30 million
   C. 70 million
   D. 450 million

3. What percent of individuals infected with the hepatitis C virus go on to develop chronic infections?

   A. 10 percent
   B. 30–45 percent
   C. 50 percent
   D. 75–85 percent

4. Approximately what percent of those chronically infected who receive treatment with the current HCV antivirals released in 2012 attain SVR and cure?

   A. 1–5 percent
   B. 10–20 percent
   C. 50 percent
   D. 95–98 percent

5. Which of the following is NOT a recommendation by the World Health Organization to prevent the spread of HCV:

   A. Worldwide screening of blood and blood products
   B. Implementation of water purification systems in developing countries
   C. Adequate sterilization of reusable materials such as surgical or dental instruments
   D. Effective use of universal precautions and barrier techniques (i.e., disposable gloves)

SECTION 5

HEPATITIS D

LEARNING OBJECTIVES

After completing this section, you should be able to:

1. Understand the relationship of the hepatitis D virus (HDV) to the hepatitis B virus (HBV)
2. Recognize how and when HDV is transmitted
3. Identify individuals at risk for HDV infection
4. Describe the symptoms and clinical course of the disease

CASE STUDY #4

WILLIAM, PATIENT WITH CHRONIC HBV INFECTION AND A 20-YEAR HISTORY OF ILLEGAL INJECTION DRUG USE

William, a patient with chronic HBV infection and a 20-year history of illegal injection drug use, had been experiencing the following symptoms for about two weeks: nausea, abdominal pain, and diarrhea. Given William's chronic HBV infection, the physician suspected superinfection with another virus. He ordered the Acute Viral Hepatitis Panel and an HIV test.

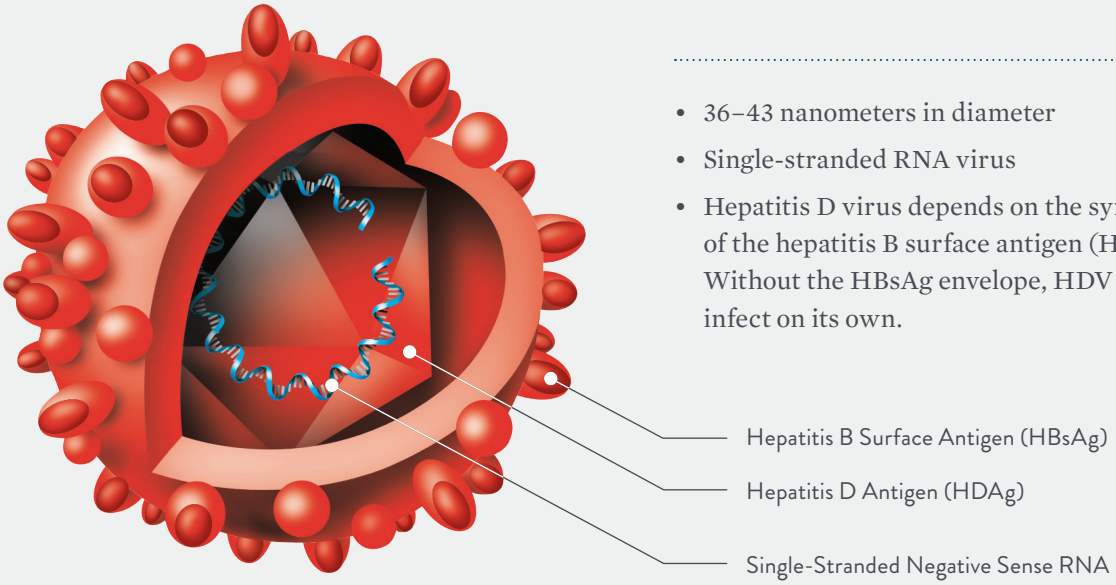
ACUTE VIRAL HEPATITIS PANEL

ASSAY	HBsAg	Anti-HAV IgM	Anti-HBc IgM	Anti-HCV
Results	+	–	–	–

The lab results came back negative for HIV, HAV, and HCV. In order to rule out a superinfection with hepatitis D, the physician ordered an anti-HDV test as well.

The lab result was positive for anti-HDV, confirming an HDV superinfection of this chronically infected patient. William was counseled on the severity of his situation. A superinfection can often lead to fulminant hepatitis or hepatocellular carcinoma. The physician continued to periodically run the chronic hepatitis B panel, anti-HDV, and liver enzymes. This individual was never able to resolve his HBV and HDV infections and died one year later of liver failure.

HEPATITIS D VIRUS



- 36–43 nanometers in diameter
- Single-stranded RNA virus
- Hepatitis D virus depends on the synthesis of the hepatitis B surface antigen (HBsAg). Without the HBsAg envelope, HDV cannot infect on its own.

ROUTES OF TRANSMISSION[28]

- Percutaneous or mucosal contact with infectious blood
- Percutaneous
  - Contaminated drug use equipment
  - Transfusion of infected blood and blood products
- Permucosal
  - Sexually transmitted

HDV AND HBV

HDV prevalence corresponds (proportionally) to the prevalence of chronic HBV infection worldwide; however, several distinct features have been documented.

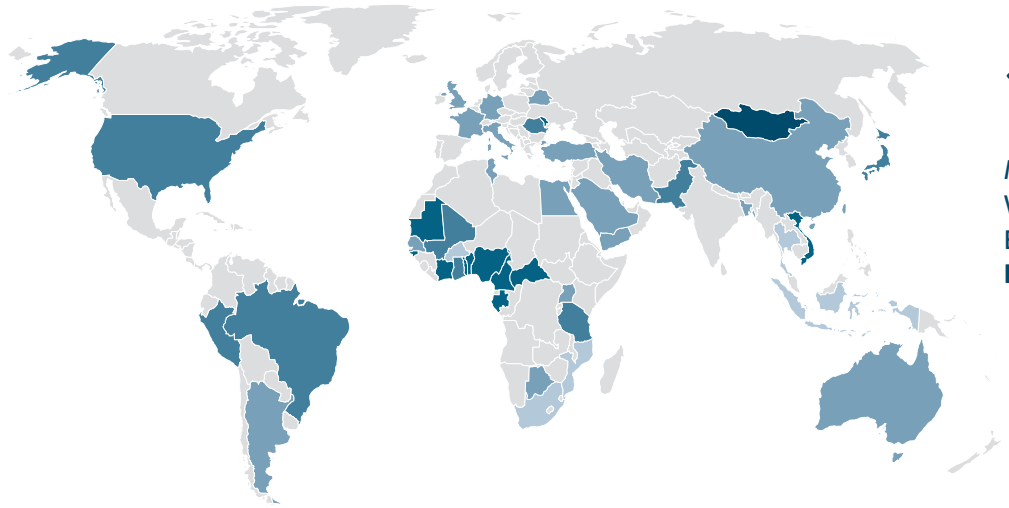
INDIVIDUALS AT RISK[28]

Because HDV is an incomplete virus that requires the helper function of HBV to replicate, it only occurs in people infected with HBV. HDV can be a short, acute infection or a long-term chronic infection and coinfection with HBV or superinfection in people with HBV.

- Individuals with HBV
- Anyone at risk for HBV
- Injecting drug users
- Hemophiliacs/hemodialysis patients
- Homosexuals and heterosexuals with multiple sex partners

INCIDENCE/PREVALENCE[34]

GEOGRAPHIC DISTRIBUTION OF HDV INFECTION



30.1%–50% 10.1%–30% 5.1%–10% 2.1%–5% <1%–2% No Data

*Note: The map of anti-HDV prevalence generalizes available data, and patterns may vary within countries.

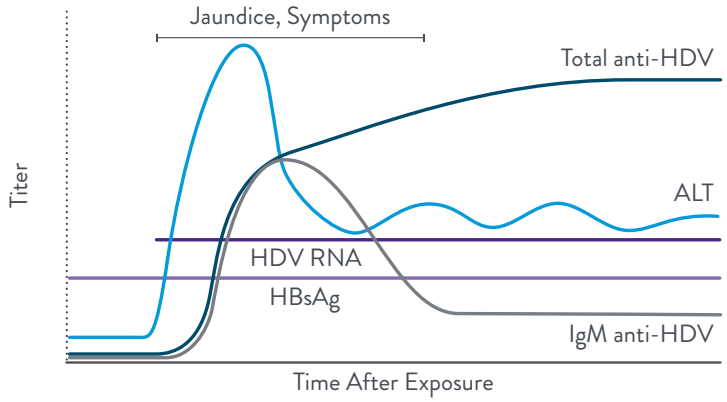
15–20
MILLION PEOPLE WORLDWIDE ARE ESTIMATED TO BE **INFECTED WITH HDV**[28]

The WHO estimates that globally approximately five percent of people with chronic HBV infection are coinfected with HDV. Approximately 15–20 million persons are thought to be infected with HDV worldwide. The WHO reports that high-prevalence areas include Africa, Asia, Pacific Islands, Middle East, Eastern Europe, South America, and Greenland. It is noted, however, that the estimation of HDV is incomplete because many countries do not report its prevalence.[28]

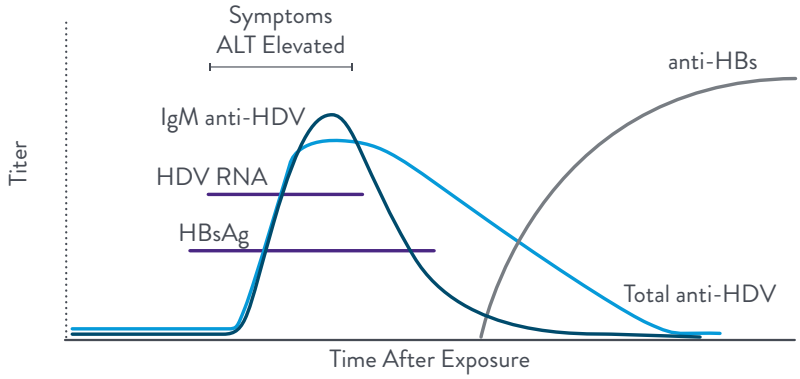
CLINICAL COURSE[28–30]

- HDV can be acquired either as a coinfection or as a superinfection in persons already infected with HBV.
- The incubation period averages 90 days (45–160 days) for coinfection and two to eight weeks for superinfection.
- Symptoms of a coinfected HBV-HDV patient are similar to those of HBV alone but can be more severe.
- HDV suppresses HBV markers such as viral load or HBsAg.
- HDV has the most rapid progression to liver-related death and hepatocellular carcinoma.
- The mortality rate for HDV infections is estimated at 2–20 percent.
- Approximately five percent of HBV acquired as a coinfection, and 80 percent acquired as superinfection develops into chronic infections.
- 70–80 percent of chronic HBV carriers with HDV superinfection develop evidence of chronic liver disease with cirrhosis, compared to 15–30 percent of patients with chronic HBV infection alone.

HEPATITIS D SUPERINFECTION OF A CHRONIC HBV CARRIER—TYPICAL SEROLOGIC COURSE



HEPATITIS D COINFECTION—TYPICAL SEROLOGIC COURSE



PREVENTION/PROPHYLAXIS[28]

- No vaccine specific for HDV exists, but HDV can be prevented in people who are not already infected with HBV by vaccination against HBV.
- HDV is dependent on HBV for replication, and although the most important tool for preventing HBV-HDV coinfection is immunization with a hepatitis B vaccine; it is also important to employ safe injection practices, blood safety screening, and harm reduction services with clean needles and syringes.
- Follow pre- and post-exposure prophylaxis recommendations for HBV infection to prevent HBV-HDV coinfection.
- Education to reduce risk behaviors is the primary tool for the prevention of HBV-HDV superinfection.

THERAPY[28]

- Individuals with chronic HDV and HBV infection should follow HBV therapy.
- There is no therapy specifically for chronic hepatitis D, but the WHO currently generally recommends 48 weeks of pegylated interferon alpha but notes that sustained virological response is low.

VIRAL HEPATITIS OVERVIEW

	Hepatitis A Virus[10,12]	Hepatitis B Virus[9,14]	Hepatitis C Virus[3,21]	Hepatitis D Virus[28–30]	Hepatitis E Virus
Virus Family	*Picornaviridae*	*Hepadnaviridae*	*Flaviviridae*	*Deltavirus*	
Route of Transmission	Fecal-oral route	Percutaneous, permucosal	Percutaneous, permucosal	Percutaneous, permucosal	
Onset	Usually abrupt	Usually insidious	Insidious	Usually abrupt	
Incubation	15–50 days	Average 60–90 days, range 60–150 days	14–182 days	Coinfection 45–160 days; Superinfection 2–8 weeks	
Chronicity	None	5% of Adults and those 5+ years of age; 90% infants; 25–50% of children (1–5 years of age)	75–85%	5% of coinfections, 80% of superinfections	
Mortality	All: 0.3–0.6% ≥50 years: 1.8%	Overall case fatality of 1.0%	In 2016, >18,000 HCV associated	2–20%	

QUIZ QUESTIONS

HEPATITIS D

1. HDV is transmitted via:

   A. Percutaneous routes
   B. Enteric routes
   C. Permucosal routes
   D. Community contact
   E. A and C

2. Who is at risk for an HDV infection?

   A. Anyone at risk for HBV infection
   B. Injecting drug users
   C. Hemophiliacs
   D. Homosexuals and heterosexuals with multiple sex partners
   E. All of the above

3. A patient who develops an HDV infection:

   A. Is not coinfected with any other hepatitis virus
   B. Rarely suffers direct liver damage
   C. Has a mortality rate of 2–20 percent
   D. When compared to HBV infection shows less evidence of chronic liver disease with cirrhosis
   E. All of the above

4. Hepatitis D prevalence generally corresponds proportionally to the prevalence of chronic HBV infection worldwide.

   A. True
   B. False

5. Immunity to HDV relies solely on vaccination against HDV.

   A. True
   B. False

6. HDV can be acquired as a _____ or _____ in persons with HBV infection.

SECTION 6

HEPATITIS E

LEARNING OBJECTIVES

After completing this section, you should be able to:

1. Indicate how the hepatitis E virus (HEV) is transmitted
2. Identify individuals at risk for infection by HEV
3. Recognize the incidence and prevalence of HEV infection
4. Describe the symptoms and clinical course of HEV infection

CASE STUDY #5

ELIZABETH VACATIONED IN CENTRAL AMERICA EIGHT WEEKS AGO

Eight weeks after Elizabeth returned from her vacation in Central America, she went in for her annual physical. She joked with her physician about consuming both unbottled beverages and food from local vendors without getting a typical case of "traveler's diarrhea." Elizabeth had recently been experiencing what seemed to be the flu. She explained her symptoms of fatigue and abdominal pain to her physician.

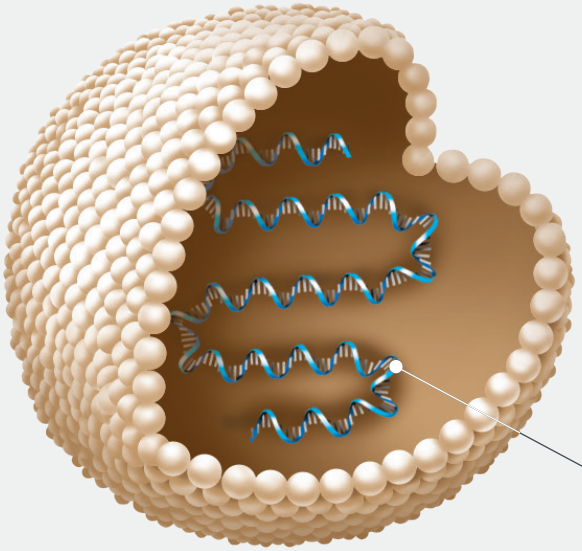
Due to the late onset of Elizabeth's symptoms in relation to her travel and comment about drinking unbottled water, the physician wanted to rule out a parasite or viral infection as the cause of her abdominal pain and fatigue. He ordered a liver panel, and the results showed an elevation of bilirubin and ALT, indicating inflammation of the liver. Next, the physician ordered an Acute Viral Hepatitis Panel.

ACUTE VIRAL HEPATITIS PANEL

ASSAY	HBsAg	Anti-HAV IgM	Anti-HBc IgM	Anti-HCV
Results	–	–	–	–

The results ruled out HAV, HBV, HCV, and HDV, and after ruling out parasites, the physician suspected HEV due to Elizabeth's recent vacation to an endemic area. Currently, a diagnostic test for anti-HEV is available in Europe, Asia, and Latin America, but none has been approved in the United States. There are several tests available for research purposes, and some commercial laboratories use commercially available assays from other countries.

HEPATITIS E VIRUS



- Single-stranded, nonenveloped, positive-sense RNA virus[31]
- Belongs to the Hepeviridae family
- Spherical, icosahedral, and nonenveloped virus, approximately 32–34 nanometers in diameter

ROUTES OF TRANSMISSION[31]

Transmission usually occurs enterically (fecal-oral) through:

- Ingestion of fecally contaminated drinking water supplies is the most common mode of transmission
- In developed countries, sporadic cases have occurred from ingestion of uncooked/undercooked pork, deer meat, or shellfish
- Other foodborne transmission has occurred

Since Elizabeth had recently visited a region where HEV is endemic, she was at risk for transmission through the ingestion of contaminated water or food purchased at open-air markets.

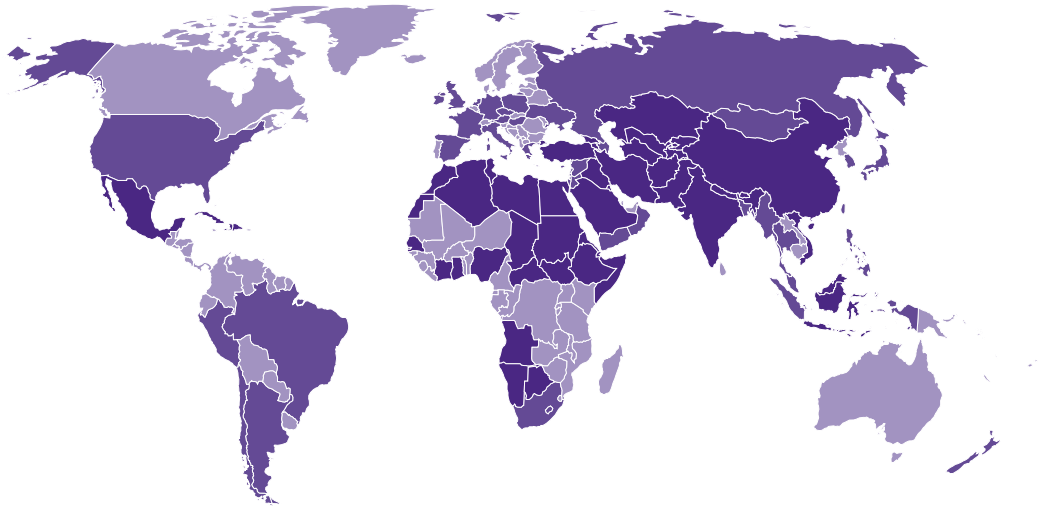
INDIVIDUALS AT RISK[6]

- Residents of endemic regions (developing countries) most commonly older adolescents and young adults (ages 15–44)
- Travelers to endemic regions, especially those who ingest potentially contaminated water or food

Elizabeth's exposure probably occurred during her visit to Central America.

INCIDENCE/PREVALENCE[35]

GEOGRAPHIC DISTRIBUTION OF HEPATITIS E*



Highly Endemic (HEV infection accounting for ≥25% of non-A, non-B hepatitis or waterborne outbreaks)
Endemic (HEV infection accounting for <25% of non-A, non-B hepatitis)
Not Endemic

Outbreaks or Confirmed Infection in >25% of Sporadic Non-ABC Hepatitis

*Note: The map of HEV infection generalizes available data; patterns may vary within countries.

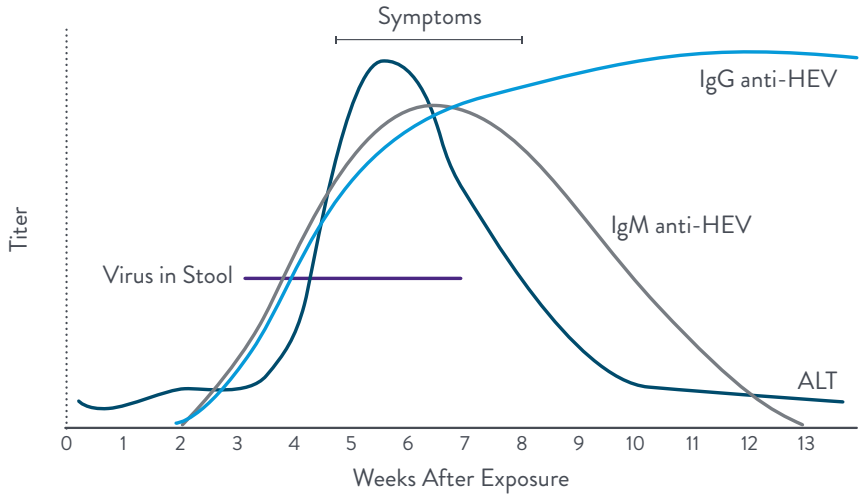
Globally, HEV is the most common cause of acute viral hepatitis. It is now believed that it occurs more frequently in developed countries than previously recognized. Occurrence in the United States usually is a result of travel to endemic regions.

There are four known genotypes of HEV. Types 1, 2, and 4 are associated with illness in developing countries and result only in acute infections, and for most people, the disease is self-limited. Pregnant women who contract HEV type 1, 2, or 4, however, have more severe disease, especially when infected in the third trimester, and may rapidly progress to liver failure or experience premature delivery or miscarriage. HEV genotype 3 is more frequently associated with developed countries and found in recipients of solid organ allografts.[31]

CLINICAL COURSE[6,31,32]

- The incubation period is 15–60 days, with an average of 40 days.
- Symptoms are usually abrupt.
- Symptoms are similar to other types of viral hepatitis infection—malaise, anorexia, nausea/vomiting, abdominal pain, jaundice, dark urine, clay-colored stool, joint pain, fever, and non-hepatic manifestations such as neurological symptoms.
- The highest rates of symptomatic disease (jaundice) have been in young to middle-aged adults.
- Acute but rarely chronic. There are no reports of chronic HEV in developing countries where HEV genotypes 1 and 2 are predominant. Reports of HEV genotype 3 progressing to chronic cases, mostly in persons on immunosuppressive treatment for an organ transplant, have been made.
- Disparate presentation due to unique epidemiologic transmission patterns that vary by HEV genotype is associated with disease presentation—frequently misdiagnosed by clinicians.
- HEV usually resolves without treatment, and care is supportive. In solid organ transplant recipients, oral ribavirin has been used to treat chronic hepatitis E.
- Pregnant women experience the most severe symptoms and have the highest mortality, which ranges from 10–30 percent.
- During HEV outbreaks, the overall case fatality rate is about one percent.

HEPATITIS E VIRUS INFECTION—TYPICAL SEROLOGIC COURSE



PREVENTION/PROPHYLAXIS[6]

- Immune globulin is not effective in preventing hepatitis E.
- Currently, there is no FDA approved vaccine available to prevent the transmission of HEV, but in China, a recombinant vaccine was approved for use in 2012.
- Long-term prevention relies primarily on the provision of safe drinking water, prudent hygiene, and avoiding potentially contaminated water, uncooked shellfish and meats, fruits, and vegetables in endemic areas.

THERAPY

There is currently no antiviral therapy available. Supportive care is recommended.[31]

VIRAL HEPATITIS OVERVIEW

	Hepatitis A Virus[10,12]	Hepatitis B Virus[9,14]	Hepatitis C Virus[3,21]	Hepatitis D Virus[28–30]	Hepatitis E Virus[6]
Virus Family	*Picornaviridae*	*Hepadnaviridae*	*Flaviviridae*	*Deltavirus*	*Hepeviridae*
Route of Transmission	Fecal-oral route	Percutaneous, permucosal	Percutaneous, permucosal	Percutaneous, permucosal	Fecal-oral (especially contaminated water)
Onset	Usually abrupt	Usually insidious	Insidious	Usually abrupt	Usually abrupt
Incubation	15–50 days	Average 60–90 days, range 60–150 days	14–182 days	Coinfection 45–160 days; Superinfection 2–8 weeks	15–60 days, average 40 days
Chronicity	None	5% of Adults and those 5+ years of age; 90% infants; 25–50% of children (1–5 years of age)	75–85%	5% of coinfections, 80% of superinfections	Rare but has occurred in developed countries following genotype 3 infection in recipients of solid organ transplants
Mortality	All: 0.3–0.6% ≥50 years: 1.8%	Overall case fatality of 1.0%	In 2016, >18,000 HCV associated	2–20%	About 1%, 10 – 30% in pregnant women

QUIZ QUESTIONS

HEPATITIS E

1. HEV is most commonly transmitted through _____.

2. _____ are most at risk for contracting HEV.

   A. Healthcare workers
   B. Infants born to infected mothers
   C. Residents of/travelers to endemic areas
   D. Injecting drug users

3. Which of the following statement(s) is/are true regarding HEV?

   A. Most common form of viral hepatitis reported in the United States
   B. Leading cause of acute sporadic hepatitis in both children and adults in some high endemic areas
   C. Not found in developed countries
   D. Both A and B

4. No chronic cases of HEV have been reported to date in developing countries.

   A. True
   B. False

5. Normal HEV incubation period is 5–15 days.

   A. True
   B. False

GLOSSARY, APPENDIX, AND REFERENCES

GLOSSARY

ACUTE | Of short and sharp course; not chronic (new infection).

ALT (ALANINE AMINOTRANSFERASE) | An enzyme normally produced by the liver; blood levels may increase in cases of liver damage, formerly known as SGPT.

Anti-HAV | Antibody to hepatitis A virus.

Anti-HAV IgM | M class immunoglobulin antibody to hepatitis A virus.

Anti-HBc | Antibody to hepatitis B core antigen.

Anti-HBc IgM | M class immunoglobulin antibody to hepatitis B core antigen.

Anti-HBe | Antibody to hepatitis B e antigen.

Anti-HBs | Antibody to hepatitis B surface antigen.

ANTIBODY (Ab) | A Y-shaped protein molecule (immunoglobulin) in serum or body fluid that either neutralizes an antigen or tags it for attack by other cells or chemicals; acts by uniting with and firmly binding to an antigen. The prefix anti- followed by initials of a virus refers to a specific antibody against the virus.

ANTIGEN (Ag) | A substance capable of causing the body to produce specific antibodies; any substance that stimulates lymphocytes (white blood cells) to initiate an immune response.

ASSAY | A test to determine the presence, absence, or quantity of one or more components of a substance.

ASYMPTOMATIC | Without overt symptoms.

CHRONIC HEPATITIS | A condition in which liver inflammation persists for more than six months.

CHRONIC INFECTION | An individual with evidence of infection for periods longer than six months is considered to be chronically infected and may or may not exhibit symptoms of hepatitis. For HBV, this is identified by the continued presence of HBsAg in the serum. For HCV, the persistence of HCV RNA or antigen indicates chronic infection.

CHRONICITY | The quality of being chronic or persisting over a long period of time.

CIRRHOSIS | Irreversible scarring of the liver that may occur with chronic hepatitis.

COINFECTION | A condition whereby an uninfected individual becomes infected with two or more different infectious agents.

CORE | The central part of the hepatitis B virus, as well as other viruses.

DELTA AGENT | Previously used name to identify a unique RNA virus that causes acute or chronic hepatitis; requires hepatitis B virus for replication and only infects patients who are HBsAg positive; comprised of delta antigen core and hepatitis B surface antigen coat; today referred to as hepatitis D virus (HDV).

DNA (DEOXYRIBONUCLEIC ACID) | The coded genetic material in the nucleus of most cells that controls heredity; automatically controls the formation of RNA, which spreads throughout the cell and controls the formation of specific proteins. The genome of HBV is DNA.

DNA POLYMERASE | An enzyme that catalyzes DNA synthesis; present in the core of the hepatitis B virus.

ENDEMIC | Present in a community at all times.

ENTERIC | Pertaining to the intestines.

ENTERIC ROUTE | The spread of organisms via the fecal-oral cycle of infection.

ENTEROVIRUS | One of a group of similar viruses infecting the gastrointestinal tract and discharged in the feces.

EPIDEMIOLOGY | The study of the incidence, distribution, and control of disease in a population.

FLAVIVIRUS | A family of small RNA viruses formerly referred to as the arboviruses. HCV is a member of the Flavivirus family.

FULMINANT HEPATITIS | The most severe form of hepatitis; it may lead to acute liver failure and death.

GENOME | The complete set of genetic information.

HAV Ag | Hepatitis A virus antigen.

HAV | Hepatitis A virus.

HBcAg | Hepatitis B core antigen.

HBIg | Hepatitis B immune globulin (specific to hepatitis B virus, see **immune globulin**).

HBsAg | Hepatitis B surface antigen.

HBV | Hepatitis B virus.

HCV | Hepatitis C virus.

HDV | Hepatitis D virus.

HEV | Hepatitis E virus.

HEMOPHILIA | A hereditary disorder in which the blood clots very slowly due to a deficiency of one of the coagulation factors.

HEPADNAVIRUS | One of a group of DNA viruses; HBV is a member of this group of viruses.

HEPATITIS | Inflammation of the liver.

HEPATITIS A | Viral hepatitis caused by the hepatitis A virus; formerly known as infectious hepatitis.

HEPATITIS B | Viral hepatitis caused by the hepatitis B virus; formerly known as serum hepatitis.

HEPATITIS C | Viral hepatitis caused by the hepatitis C virus.

HEPATITIS D | Viral hepatitis caused by the hepatitis D virus.

HEPATITIS E | Viral hepatitis caused by the hepatitis E virus.

HEPATOCELLULAR CARCINOMA | Cancer of the liver cells.

IgG | A form of immunoglobulin that occurs late in an infectious process.

IgM | A form of immunoglobulin that occurs early in an infectious process.

IMMUNE | A state of protection afforded against infection as the result of the presence of antibodies in the body's circulatory system.

IMMUNE GLOBULIN | A sterile solution of water-soluble proteins that contain those antibodies normally present in adult human blood; used as a passive immunizing agent against various viruses such as HAV. Other names include immune serum globulin (ISG) and gamma globulin.

INCIDENCE | The number of new episodes of illness arising in a population over an estimated period.

INCUBATION PERIOD | The interval of time between the moment of entrance of the infecting organism into the body and the first appearance of symptoms of the disease.

INFECTIOUS HEPATITIS | An old term for hepatitis A.

INSIDIOUS | Stealthy; denotes a disease that progresses with few or no symptoms to indicate its presence or its gravity.

INTERFERON | A substance that is produced by cells infected with a virus, which has the ability to inhibit viral growth.

JAUNDICE | A syndrome characterized by increased levels and deposits of bile pigment in the skin, giving the individual yellowish skin color and may include yellowing of whites of the eyes, usually caused by liver inflammation/disease.

MALAISE | A general feeling of being unwell; the feeling may be accompanied by identifiable physical discomfort and may indicate the presence of disease.

MARKER | An antigen or antibody used to indicate the status of disease or recovery.

MEDIATE | Act indirectly to affect a result.

MORBIDITY | The state of being diseased.

MYALGIA | Pain in the muscles.

NANB (non-A, non-B) HEPATITIS | Original name for HCV when first identified; naming it for what it was not.

PARENTERAL | Used to refer to entering the body subcutaneously (under the skin), intramuscularly (into a muscle), or intravenously (into a blood vessel); may refer to any other means whereby the organism reaches the bloodstream directly.

PERCUTANEOUS | Through the skin.

PERMUCOSAL | Through the mucous membranes.

PICORNAVIRUS | A virus family consisting of small RNA viruses, HAV belongs to the Picornavirus family.

PREVALENCE (OF A DISEASE) | The percentage of a population that is affected with a particular disease at a given time.

PROPHYLAXIS | Measures designed to preserve health and prevent the spread of disease.

REPLICATION | Production of a copy or image of itself; encompasses the steps that a virus goes through to reproduce (the term "duplication" is used for cells that split in two to reproduce themselves).

RNA (RIBONUCLEIC ACID) | A substance formed in the cell nucleus, under the control of DNA; transfers genetic code into the cell for the synthesis of proteins.

SEQUELA | An illness or condition that follows as a consequence of another disease (plural form: sequelae).

SEROCONVERSION | An immune response that is characterized by a conversion from the absence of a specific antibody to the presence of that specific antibody in a patient or the disappearance of an antigen followed by the appearance of its corresponding antibody.

SEROLOGICAL | Pertaining to antigen-antibody reactions in vitro.

SERONEGATIVITY | Blood serum showing a negative result to a specific test.

SEROPOSITIVITY | Blood serum showing a positive result to a specific test.

SERUM HEPATITIS | Old term for hepatitis B.

SUPERINFECTION | A condition whereby an already infected individual becomes infected with a virus different from the original infecting agent.

SUBCLINICAL | Without clinical manifestations or symptoms.

SYNDROME | A set or collection of symptoms and signs that occur together.

VIRAL LOAD | The amount or concentration of virus in the blood.

VIROLOGY | The study of viruses.

VIRUS | A collection of proteins and nucleic acids capable of infecting other cells; viruses can multiply only within the cells that they are infecting.

APPENDIX: QUIZ ANSWERS

SECTION 1 **PATHOLOGY**

1. A, B, C, D, E
2. Any four of the following: fatigue, myalgia, loss of appetite, nausea, diarrhea, constipation, fever, jaundice
3. B – False
4. A and B
5. D

SECTION 2 **HAV**

1. Close person-to-person contact, ingestion of contaminated food or water
2. C
3. D
4. B, C, D

SECTION 3 **HBV**

1. D
2. HBsAg, HBeAg, Total anti-HBc, anti-HBc IgM, anti-HBe, anti-HBs, and if listed, HBV DNA could be included in this list as well
3. C
4. A – True
5. B – False
6. Nausea, diarrhea, malaise, dark urine, jaundice
7. B
8. C
9. A, C, D
10. HBsAg, HBeAg, anti-HBe, and anti-HBs
11. B – False
12. B
13. B – False (provides prolonged immunization)
14. D
15. A – True

SECTION 4 **HCV**

1. Any two of the following: injecting drug use, use of inadequately sterilized or completely unsterilized healthcare equipment, transfused blood not screened for HCV, organ or tissue transplants from an HCV infected donor, sexual or household contacts, perinatal exposure, body piercing, tattooing
2. C
3. D
4. D
5. B

SECTION 5 **HDV**

1. E
2. E
3. C
4. A – True
5. B – False
6. Coinfection, superinfection

SECTION 6 **HEV**

1. Ingestion of contaminated water
2. C
3. B
4. A – True
5. B – False (incubation period averages 40 days)

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