

VIRAL HEPATITIS



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Learning Objectives

1. Distinguish among viral hepatitis A, B, C, D, and E's virology, epidemiology, and serological response to infection and clinical manifestation.
2. Design a prophylactic and therapeutic plan identifying the risk factors associated with the transmission of viral hepatitis A, B, C, D, or E in a clinical situation.
3. Develop an appropriate prophylactic regimen for preventing viral hepatitis A, B, C, D, and E.
4. Develop a therapeutic regimen for treating viral hepatitis B and C.
5. Evaluate the common adverse effects associated with viral hepatitis B and C treatment and implement a therapeutic regimen to manage the potential side effects.

Introduction

History

Viral hepatitis is inflammation of the liver caused by viruses. The first signs of hepatitis were first described as jaundice by Hippocrates in 5th century B.C. It was not until the 8th century B.C. that hepatitis was thought to be infectious in nature. Finally, in 1947, F.O. MacCallum classified viral hepatitis into two types, infectious hepatitis, now known as hepatitis A, and serum hepatitis known as hepatitis B. More recently, in 1987, Michael Houghton, Qui-Lim Choo, and George Kuo cloned and identified hepatitis C virus as the source of non-A, non-B transfusion-related hepatitis. Currently, viral hepatitis affects more than 500 million people and remains a significant public health threat worldwide. In the United States alone, more than 300,000 acute cases occur per year. At present, there are five types of viral hepatitis, hepatitis A (HAV), hepatitis B (HBV), hepatitis C (HCV), hepatitis D (HDV) and hepatitis E

(HEV). These are listed and compared in Table 1-1. Recently, a sixth virus, hepatitis G (HGV), has emerged and currently is undergoing extensive evaluation to determine its role in causing liver damage.

Definitions of Acute and Chronic Hepatitis

Viral hepatitis may present as either acute or chronic, and it is differentiated based on the duration of the illness. Acute hepatitis can last up to and rarely exceeds 6 months in duration. All viral hepatitis, A–E, may induce acute hepatitis. In contrast, chronic hepatitis is defined as having the disease for more than 6 months. At present, hepatitis B, C, and D can lead to the development of chronic hepatitis. The clinical presentation of hepatitis G is still under investigation.

Hepatitis A

Virology and Pathogenesis

Hepatitis A is a nonenveloped single-stranded ribonucleic acid (RNA) virus that was identified under the electronic microscope in 1973. This 27–32-nm diameter virus was classified in 1982 as an enterovirus in the *Hepatovirus* genus under the Picornaviridae family. Before 1973, hepatitis A was known as “infectious hepatitis” because of its easy person-to-person, oral-fecal transmission route. Still, as of today, hepatitis A outbreaks continue in areas of poor sanitation. The infections may be associated with the virus's ability to become resistant to extreme environments, such as elevated temperatures. For example, the virus may survive for at least 1 hour at 60°C and in dried feces for up to 4 weeks at room temperatures. This unique property may be related to the fact that hepatitis A is a single-stranded RNA virus that is 7.48 kilobase in length consisting of 2235 amino acids encoding a single polyprotein. There are three functional domains on the RNA strand, known as the P1, P2, and P3, where cleavage

Abbreviations in this Chapter

ALT	Alanine aminotransferase	HCV	Hepatitis C virus
anti-HAV	Hepatitis A virus antibody	HDV	Hepatitis D virus
anti-HBc	Hepatitis B core antibody	HEV	Hepatitis E virus
anti-HBe	Hepatitis B e antibody	HIV	Human immunodeficiency virus
anti-HBs	Hepatitis B surface antibody	IFN	Interferon
CHB	Chronic hepatitis B	Ig	Immunoglobulin
DNA	Deoxyribonucleic acid	NS	Nonstructural
HAV	Hepatitis A virus	PCR	Polymerase chain reaction
HAVAg	Hepatitis A virus antigen	PEG-IFN	Pegylated interferon
HBcAg	Hepatitis B core antigen	RNA	Ribonucleic acid
HBeAg	Hepatitis B e antigen	RT	Reverse transcriptase
HBsAg	Hepatitis B surface antigen	SVR	Sustained virological response
HBV	Hepatitis B virus	YMDD	Tyrosine, methionine, aspartate, aspartate
HCC	Hepatocellular carcinoma		

produces viral proteins. Once the HAV enters the hepatocyte, the RNA strand translates into a polyprotein, producing a template to replicate more RNA and causing more virions to be produced. The only host for the HAV is humans, with its primary site of viral replication in the hepatic cells; however, in small quantities, the virus may be detected in the kidney, spleen, and lymph nodes. As part of the viral degradation process, the HAV is released into the biliary system, causing elevated concentrations of the virus in the feces, therefore explaining its endemic potential in underdeveloped parts of the world.

Epidemiology and Risk Factors

About 1.4 million cases of hepatitis A occur worldwide yearly. Endemics associated with hepatitis A occur most commonly in underdeveloped countries. Prevalence is highest in Africa, parts of South America, the Middle East, and Southeast Asia. In comparison, developed countries, including Australia, Japan, and the United States, and parts of Western and Northern Europe, have low hepatitis A endemicity. Outbreaks of hepatitis A have occurred in every decade since 1960, with the last one in 2003 in Pennsylvania. According to the National Health and Nutrition Examination Survey, 31.3% of the American population has been infected with HAV. Those at greatest risk are Mexican Americans, followed by African Americans, then Caucasians. Almost 80% of all individuals older than 40 years of age have been infected with hepatitis A compared to less than 25% in individuals younger than 20 years of age. About 11–22% of those infected with HAV require hospitalization, costing the health care system more than \$300 million in the United States alone. It is estimated that 100 people will die annually from fulminant hepatitis.

No identifiable risk factor is found in about 50% of the reported hepatitis A cases. Of those with an identifiable cause, international travelers make up about 5% of the cases and 11–16% are associated with children and employees of day care centers. About 12–26% of household or sexual contacts with individuals infected with the virus are at greatest risk of acquiring hepatitis A infections. The highest concentration of the virus is found in stools. It also may be

present in serum and saliva, but is undetectable in urine. The infection rate in men is 20% more than in women, and is higher among homosexually active men. Other people at risk of contracting hepatitis A include health care workers, intravenous drug users using unsterilized needles, those working with nonhuman primates, food service handlers, those with clotting factor disorders, and individuals residing in health care institutions.

Clinical Course and Clinical Manifestations

The clinical course of hepatitis A infection may be separated into four different phases. The preclinical phase is the most infectious as the virus is actively replicating and in almost all situations the individual is asymptomatic. This phase or incubation period may range from 10 to 50 days and on average usually lasts for 30 days. The prodromal phase, known as preicteric, may last from several days to a week. Symptoms that may arise during this period include flu-like symptoms, including fevers, fatigue, nausea, vomiting, diarrhea with or without dark urine, and pale looking stools. However, during the icteric phase, symptoms of jaundice and pruritus are most apparent (70% of adults) and cause the individual to seek medical attention. Children younger than 6 years of age are mostly asymptomatic (70%). On physical examination, hepatomegaly, postcervical lymphadenopathy and splenomegaly may be palpable in any patient population. On occasion, extrahepatic manifestations, including arthritic-type symptoms, cryoglobulinemia or vasculitis, may be present. Death is rare in those younger than 40 years of age, occurring in 0.2% of patients due to massive necrosis of the liver from fulminant hepatitis. However, the mortality rate increases to about 2% in those older than 40 years. Hepatic encephalopathy and seizures may be observed and prothrombin time may be prolonged. Laboratory values such as total bilirubin concentrations and serum aminotransferases may be elevated. The last phase is resolution of the disease known as the convalescent period. Currently, no chronic liver disease associated with hepatitis A has been documented.

Table 1-1. Characteristics of Hepatitis A, B, C, D, E, and G

Virus	HAV	HBV	HCV	HDV	HEV	HGV
Genome	RNA	DNA	RNA	RNA	RNA	RNA
Size (nm)	27–32	42	30–60	40	32	Unknown
Incubation (days) [mean]	15–50 [30]	45–180 [80]	15–160 [50]	21–140 [35]	15–60 [42]	14–35 [unknown]
Transmission						
Oral	Yes	Rare	Rare	Rare	Yes	Unknown
Percutaneous	Rare	Common	Common	Common	Unknown	Yes, rare
Sexual	No	Common	Rare	Common	Yes, rare	Yes, rare
Perinatal	No	Common	Rare	Common	Rare	Yes, rare
Onset	Sudden	Insidious	Insidious	Insidious	Sudden	Unknown
Acute illness	70–80% adults 5% children	10–15% < 5 years: < 10% ≥ 5 years: 30–50%	5–10% > 5 years: < 10% < 5 years: 30–50%	10%	70–80% adults	Unknown
Case-fatality rate (acute infection)	0.15–1.7%	0.5–1%	1–2%	< 1% coinfect	1–3% 1.5–25% pregnant women	Unknown
Incidence of chronic infection	0%	< 5 years: 30–90% > 5 years: 2–10%	75–80%	80% superinfect ≤ 5% coinfection	0%	Unknown
Carrier state	No	Yes	Yes	Yes	No	Unknown
Risk of hepatocellular carcinoma	No	Yes	Yes	Yes	No	Unknown

ALT = alanine aminotransferase; DNA = deoxyribonucleic acid; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; HEV = hepatitis E virus; HGV = hepatitis G virus; RNA = ribonucleic acid.

Diagnosis and Serological Testing

Diagnosing hepatitis A may be difficult because most patients are asymptomatic. However, symptoms alone cannot distinguish which type of hepatitis may be present. The definitive diagnostic test to identify hepatitis A is the detection of immunoglobulin (Ig) antibody to the capsid proteins of the HAV. Acute infection is indicated when IgM HAV antibody (anti-HAV) is present in the serum about 3 weeks after exposure. These levels eventually become undetectable within 6 months. In contrast, IgG anti-HAV appears in the serum about at the same time as IgM anti-HAV develops. However, these antibodies remain detectable for individuals' lifetimes, indicating protection and immunity against hepatitis A. Liver function tests, including bilirubin, aspartate aminotransferase, alanine aminotransferase (ALT), alkaline phosphatase, and prothrombin time are not diagnostic for hepatitis A nor do concentrations correlate with the severity of the hepatic injury. Hepatitis A virus RNA currently is used in research studies and is not obtained as part of the standard of care. In addition, a liver biopsy is not routinely done to identify acute infection but may be useful in determining the severity of hepatic damage.

Managing of Hepatitis A

There is no specific treatment for hepatitis A. Historically, because it is mainly spread by the fecal-oral route, the primary method of minimizing the transmission of

the virus is good personal hygiene and proper disposal of sanitary waste. However, serum immune globulin and vaccination against hepatitis A are now commercially available, and are the most effective ways of preventing disease transmission. Therefore, those at greatest risk, such as travelers to developing countries, men who have sex with other men, or household contacts living with infected people, should receive prophylaxis or vaccination against hepatitis A.

Immune Globulin

Immune globulin from pooled human plasma is a sterile preparation of antibodies. Immune globulin given intramuscularly administration provides passive immunization by transfer of antibodies against hepatitis A. It may be used for either preexposure or postexposure prophylaxis; however, it does not provide long-lasting immunity. A thiomersal-free preparation should be used in pregnant women or infants. Intramuscular immune globulin should be administered in the deltoid or gluteal muscle. Adverse events associated with Ig are rare; however, a few reports of anaphylaxis have been documented in patients who have developed IgA deficiency. The response to inactivated vaccines such as poliovirus or yellow fever vaccine is not affected by Ig administration. However, the immunity of live vaccines such as measles, mumps and rubella vaccine may decrease significantly if Ig is concomitantly administered. Therefore, after Ig

Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 1999;48(RR-12):1–37.

administration, live vaccines should not be given for at least 3 months and live attenuated vaccines should not be given for at least 2 weeks.

Preexposure Prophylaxis

Immune globulin given intramuscularly 0.02 ml/kg provides passive immunization for less than 3 months. Those requiring longer duration of coverage, defined as more than 3 and less than 5 months, should receive 0.06 ml/kg. Readministration of immune globulin given intramuscularly may be required if continuous protection is warranted beyond 5 months. People who would benefit from preexposure immune globulin given intramuscularly prophylaxis are individuals who did not receive the hepatitis A vaccination within 4 weeks of exposure, such as international travelers to endemic areas. Administration of immune globulin given intramuscularly within 2 weeks of exposure can reduce the incidence of hepatitis A by up to 90%.

Postexposure Prophylaxis

Immune globulin given intramuscularly also is effective in preventing hepatitis A when administered within 2 weeks of exposure. If 0.02 ml/kg is given early during the incubation period, protection from disease exceeds 85%. developing the infection. It may still decrease the severity of liver disease even if given after the incubation period. Postexposure prophylaxis is recommended for those who are in contact with a person with acute viral hepatitis A. These individuals may include household and sexual partners, staff and children from day care facilities, and food handlers of restaurant establishments.

Hepatitis A Vaccine

Hepatitis A infection can be prevented with the hepatitis A vaccine, which provides active immunity against HAV. People who are at high risk (i.e., men who have sex with other men, international travelers to endemic areas, or people who work with nonhuman primates) are excellent candidates for vaccination. Inactivated or attenuated hepatitis A vaccines have been developed to provide active immunization against the HAV; however, only inactivated vaccines have been clinically studied for their efficacy. In the United States, there are two hepatitis A vaccines commercially available: VAQTA (Merck & Co., Inc.) and Havrix (GlaxoSmithKline). The differences between the two are that VAQTA is preservative-free, whereas Havrix is formulated with 2-phenoxyethanol. In addition, both products' final vaccine potency is determined by the

reactivity of the hepatitis A virus antigen (HAVAg). The dose for Havrix is expressed as enzyme-linked immunosorbent assay unit and the dose for VAQTA is expressed as units. Vaccine doses according to age are compared in Table 1-2. People who are at high risk for acquiring hepatitis A and are allergic to the vaccine (e.g., alum or 2-phenoxyethanol in Havrix) should be protected with hepatitis A immune globulin given intramuscularly. Repeated dosing of immune globulin given intramuscularly is required if protection beyond 5 months is necessary. The vaccine is of no benefit for those who have already been exposed to hepatitis A.

Both brands of hepatitis A vaccine are highly effective. Protective antibody levels develop after the first dose in 94–100% of adults and 97–100% of children and adolescents. When the second dose is administered, all recipients older than 2 years of age have 100% antibody coverage. Protective antibody response is defined with Havrix as concentrations greater than 20 mIU/ml measured by modified enzyme immunoassay and with VAQTA as concentrations greater than 10 mIU/ml measured by modified radioimmunoassay. Therefore, the brands are considered interchangeable. Children younger than 2 years of age are more likely to develop immunity with the hepatitis A vaccine if they have not passively acquired maternal antibodies. If maternal anti-HAV are present in children younger than 2 years of age, their geometric mean antibody concentration may be reduced after vaccination. Immune globulin should be recommended for high-risk infants in this population. The long-term protectiveness of the vaccines is unknown. At this time, the longest clinical trial was in adults receiving Havrix, 720 enzyme-linked immunosorbent assay units at months 0, 1, and 6, who had antibody levels of more than 20 mIU/ml for 8 years. Similar results were observed with VAQTA for up to about 6–7 years in adults and children. Based on pharmacokinetic models, though not confirmed in clinical trials, it is theorized that immunity with the hepatitis A vaccine may be greater than 20 years.

Adverse events associated with VAQTA or Havrix are minimal. The most common complaints from adults include injection site reaction (56%), headaches (14%), and fatigue (7%). Children have similar symptoms and also may have feeding disturbances (8%). Injection site reactions (e.g., tenderness, pain, and warmth) and headaches may occur within 5 days of giving the vaccine. The incidence of serious adverse effects (e.g., brachial plexus neuropathy, encephalopathy, erythema multiforme, Guillain-Barré syndrome, multiple sclerosis, and transverse myelitis) is not

Table 1-2. Recommended Doses for Hepatitis A Vaccines

Product	Recipient's Age (years)	Dose	Volume (ml)	Number of Doses	Schedule (months)
VAQTA (Merck & Co., Inc)	2–17	25 units	0.5	2	0, 6–18
	> 17	50 units	1	2	0, 6
Havrix (GlaxoSmithKline)	2–18	720 EL.U	0.5	2	0, 6–12
	2–18	360 EL.U	0.5	3	0, 1, 6–12
	> 18	1440 EL.U	1	2	0, 6–12

EL.U = enzyme-linked immunosorbent assay unit.

higher than the unvaccinated population. However, about 33% of the patients were receiving other vaccines at the same time hepatitis A vaccine was administered, making evaluation of adverse effects complex.

The use of the hepatitis A vaccine during pregnancy has not been evaluated. It can be hypothesized that the risk of developing complications to the fetus would be low because Havrix and VAQTA are made from inactivated HAV. Risk versus benefit must be assessed before administration. No special considerations are needed for immunocompromised people; however, they may not mount a similar rate of immunity as those who have a competent immune system.

An appropriate needle length should be used according to the person's age and size when administering the vaccine intramuscularly in the deltoid muscle. Obtaining serum anti-HAV before hepatitis A vaccination is only indicated if it is cost-effective. For example, individuals who are at high risk, such as men who have sex with other men or international travelers to endemic areas, may already be immune to HAV; thus, the cost of the screening may be less than the vaccine series. Postvaccination serological testing is not required because protective antibody concentrations occur more than 94% of the time with the first dose and 100% of the time with booster doses. The vaccine should not be frozen and should be stored at temperatures between 35.6°F (2°C) and 46.4°F (8°C) to maintain its efficacy.

Treatment

There is no specific pharmacological treatment for hepatitis A because, in most cases, it is a self-limiting disease requiring supportive care only. Patients with mild to moderate symptoms do not require hospitalization. However, those displaying signs of encephalopathy, severe nausea, vomiting, or diarrhea should seek medical attention immediately. Alcohol use should be avoided, especially during the acute incubation period. Alcohol ingestion may resume once the convalescence phase has been reached. There is no special dietary modification except for those with encephalopathy who may require a decrease in protein intake. Fluid intake should be encouraged for those with nausea, vomiting, and diarrhea. If these symptoms are severe, hospitalization may be required for intravenous fluid and electrolyte replacement. Liver transplantation may be the only treatment for some people who develop fulminant hepatitis.

Hepatitis B

Hepatitis B, first known as serum hepatitis, affects more than 300 million people worldwide. It was first discovered in 1947 by F.O. MacCallum who noticed a trend of individuals developing hepatitis from blood transfusions. In 1963, Baruch S. Blumberg and Harvey J. Alter discovered the Australian antigen from an aborigine, now known as hepatitis B surface antigen (HBsAg), and by 1967, the association between the antigen and the development of hepatitis was confirmed. The discovery was significant because by 1972, laws were passed in the United States requiring all donated blood to be tested for hepatitis B by screening HBsAg. With this legislation, the incidence of

hepatitis B decreased. Another significant decline in the incidence was observed when the hepatitis B vaccine was commercially available in 1981. However, this disease continues to be a worldwide problem as more than 300,000 new infections occur every year despite having an effective vaccine against hepatitis B.

Virology and Serology

Hepatitis B is an enveloped virus known as the Dane particle. This hepatitis B virion is 42-nm in diameter and belongs to the family Hepadnaviridae, which has been found in the woodchuck, and less observed in ducks and ground squirrels. It is a unique and complex genome in that it is a partially double-stranded deoxyribonucleic acid (DNA) with a phospholipid layer containing HBsAg that surrounds the nucleocapsid. The presence of HBsAg may indicate either acute or chronic hepatitis B (CHB) infections or carrier status (Table 1-3). In most cases, when hepatitis B surface antibodies (anti-HBs) develop, long-term immunity is indicated. The nucleocapsid contains the core protein which generates a capsid structure recognized as the hepatitis B core antigen (HBcAg). When this is expressed on the surface of liver cells, a cytotoxic immune reaction occurs; however, HBcAg is not detectable in serum. Therefore, to measure antibodies to the hepatitis B core antigen, hepatitis B core antibody (anti-HBc) to IgM is required to identify active infection and anti-HBc to IgG would be used to identify chronic infection or possible immunity against hepatitis B. The precore protein produces circulating peptides known as the hepatitis B e antigen (HBeAg) that is eventually released into the circulation, causing viral replication. To assess and quantify viral replication, HBV DNA is the most accurate test to determine viral infectivity. If the infectivity period is over, then HBV DNA should be undetectable and the HBeAg may have seroconverted to antibodies against HBeAg, referred as hepatitis B envelop antibody (anti-HBe).

The likelihood of developing CHB depends on the host immune system at the time the infection was acquired. The disease usually resolves spontaneously in immunocompetent individuals. The CD8⁺ cytotoxic T lymphocytes are active against the HBV-infected hepatic cells, thereby destroying the genome and inhibiting viral replication. However, in immunocompromised patients, there may be a decreased recognition between the HBV surface proteins and the host major histocompatibility complex, which may complicate resolution of the infection, promoting the development of CHB.

Hepatitis B viral replication is complex, involving several steps. In the first steps called fusion, the virus must attach and enter the host hepatocytes. The uncoating of the virus in the cytoplasm, causes the release of viral genomes leading to the synthesis of complete double-stranded DNA. Viral transcription occurs when RNA from the host produces a template for viral DNA production. In the next step, the translation forms viral proteins, including the surface (HBsAg), core (HBcAg), and envelope (HBeAg). With the production of viral cores, assembly of the virus occurs by packaging the RNA in the cytoplasm. Next, reverse transcriptase (RT) allows the synthesis of RNA

Table 1-3. Interpretation of the Hepatitis B Panel

Tests	Results	Interpretation
HBsAg	Negative	Susceptible
Anti-HBc	Negative	
Anti-HBs	Negative	
HBsAg	Negative	Immune due to natural infection
Anti-HBc	Positive	
Anti-HBs	Positive	
HBsAg	Negative	Immune due to hepatitis B vaccination
Anti-HBc	Negative	
Anti-HBs	Positive	
HBsAg	Positive	Acutely infected
Anti-HBc	Positive	
Anti-HBc IgM	Positive	
Anti-HBs	Negative	
HBsAg	Positive	Chronically infected
Anti-HBc	Positive	
Anti-HBc IgM	Negative	
Anti-HBs	Negative	
HBsAg	Negative	Four interpretations possible ^a
Anti-HBc	Positive	
Anti-HBs	Negative	

^a1. May be recovering from acute hepatitis B virus infection.

2. May be distantly immune and test not sensitive enough to detect very low levels of anti-HBs in serum.

3. May be susceptible with a false-positive anti-HBc.

4. May be undetectable level of HBsAg present in the serum and the person is actually a carrier.

Anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; IgM = immunoglobulin M. Centers for Disease Control Prevention. National Center for Infectious Diseases. Viral Hepatitis B. <http://www.cdc.gov/ncidod/diseases/hepatitis/b/Bserology.htm>. Accessed June 10, 2005.

minus strand DNA. Finally, viral replication is complete when mature, infectious virions are released into the blood.

Epidemiology

Hepatitis B is a worldwide infection affecting more than 2 billion individuals, including 360 million who are chronically infected. Epidemiological studies have shown that the prevalence of hepatitis B differs geographically. The rate of CHB in North America and Western Europe is about 1% and usually is acquired during adulthood. This rate is lower than that of developing areas such as in Southeast Asia, where infection occurs during the perinatal or childhood years at a rate of 10–15%. These areas have yet to or recently only implemented hepatitis B vaccination programs. For example, in China, with a total population of more than 1.6 billion, immunizations were initiated in 2000 and in the Philippines, only 30–40% have been vaccinated. Moreover, Japan, with a similar gross national income to the United States, does not routinely vaccinate newborns against hepatitis B. Most individuals who are carriers of

hepatitis B in the United States are immigrants from China and Southeast Asia. Although vaccines are available to prevent this disease, more than 300,000 new infections occur in the United States alone, with an estimated 1.25 million carriers of HBV. Almost 17,000 hospitalizations are due to CHB, with 5000 deaths/year from disease complications.

Risk Factors

Blood and serous fluids contain the highest concentration of the HBV followed by semen, vaginal fluid, and saliva. Thus, the primary mode of hepatitis B viral transmission is either by blood or body fluids through perinatal, sexual, or percutaneous exposure. In rare instances, close personal contacts with people with open cuts may be a source of transmission. Infants born of mothers who are infected with hepatitis B and are HBeAg-positive have a 90% risk of developing chronic infection. If not infected at birth, infants are still at risk for the first 5 years of life from a horizontal transmission if they reside in an endemic environment. The risk is about 30–60% for developing chronic infection in children 1–5 years of age. In addition, children of certain ethnic groups, Alaskan Natives, Pacific Islanders, and those with mothers from Asia have higher rates of childhood hepatitis B infections.

Homosexual men and those having multiple heterosexual partners are at greater risk of acquiring hepatitis B than those in monogamous relationships. In addition, because this virus is transmitted from blood-related items, individuals using intravenous drugs, recipients of blood products, household contacts with acute hepatitis B with cuts or sores, health care providers with accidental needle sticks, and patients undergoing dialysis are at increased risk of acquiring the infection. Unfortunately, about 33% of the individuals with the infection will never know how they obtained the virus.

Natural History

Most individuals who have been infected with HBV recover and develop anti-HBs, resulting in lifelong immunity against the disease. However, about 2% may develop acute infections, leading to fulminant hepatitis, which is associated with a 60–90% mortality rate. About 15% of the patients will develop CHB by not being able to eliminate HBsAg. Of this population, the chance of developing chronic disease is less than 20% if patients were infected during adult age. The risk of chronic infection increases to more than 40% if the infection occurred perinatally. As most of these patients are asymptomatic, it may take up to 20–40 years before complications such as cirrhosis or hepatocellular carcinoma (HCC) develop. The estimated mortality rate for this population ranges from 15% to 25%.

Clinical Course and Clinical Manifestation

The incubation period for hepatitis B ranges from 45 to 160 days and averages 120 days. It is difficult to distinguish and diagnose acute hepatitis B compared to other types of hepatitis because the clinical manifestations are fairly similar. There is an inverse relationship among age, symptoms, and chronic infections. Children usually are

asymptomatic but are more prone to developing chronic liver disease, whereas adults are more likely to become symptomatic but their disease resolves completely. The clinical course may be separated into three different phases. The preicteric phase is mostly asymptomatic lasting 3–10 days. Symptoms include flu-like symptoms, fevers, fatigue, loss of appetite, nausea, vomiting, abdominal pain, with or without dark urine, and pale stools. Symptomatology during the icteric phase includes jaundice, liver tenderness, and pale stools lasting up to 3 weeks. The last phase is resolution of the disease, known as the convalescent period, where jaundice dissipates, but fatigue may persist for months.

Diagnosis

There are several clinical scenarios for hepatitis B (Table 1-3). If all hepatitis B serologies are negative, patients susceptible to infection and should be immunized if they are at high risk for viral hepatitis (Table 1-4). However, if anti-HBs is present and HBsAg and anti-HBc are undetectable, then patients have already received the hepatitis B vaccination and are immune. The presence of HBsAg indicates that patients are infectious but do not distinguish if they have acute or chronic disease. Aminotransferases, specifically ALT concentrations, may or may not be elevated in either condition. Acute hepatitis B is defined as having anti-HBc to IgM. When this marker becomes undetectable, the acute phase has resolved. At that time, anti-HBc to IgG is present indicating either lifelong immunity against hepatitis B or chronic infection if HBsAg has not converted to anti-HBs after 6 months from acquiring the virus. As previously discussed, people with CHB continue to have detectable HBsAg with anti-HBc to IgG. In addition, HBeAg will be present, indicating active viral replication. Hepatitis B virus DNA may be used to quantify the amount of viral replication. Effective treatment against CHB may decrease HBV DNA to possibly undetectable levels and seroconvert HBeAg to anti-HBe and HBsAg to anti-HBs.

Though this description of CHB seems simplistic, it is far more complex as CHB has three major clinical patterns. In HBeAg-positive CHB, HBsAg and HBeAg are present along with elevated ALT concentrations and HBV DNA ranging between 7 and 11 log₁₀ copies/ml. In contrast, HBeAg-negative CHB does not have HBeAg present, but anti-HBe, known as a precore mutant, is detectable. It appears that in this population, virus replication has ceased, yet HBV DNA concentrations are elevated and usually range between 4 and 8 log₁₀ copies/ml in conjunction with a high ALT. In both scenarios, there is necroinflammation in the hepatic cells on liver biopsy. Finally, there is a carrier state where HBsAg and anti-HBe are detectable with normal ALT concentrations and HBV DNA concentrations less than 4 log₁₀ copies/ml. There are minimal changes on the liver biopsy in those who are hepatitis B carriers.

Managing of Hepatitis B

Managing hepatitis B can be separated into two categories: prevention and treatment. Hepatitis B

vaccination is used for prevention, whereas treatment consists of drug therapy with interferon (IFN), lamivudine, or adefovir dipivoxil.

Prevention

Immunization with the hepatitis B vaccine is the most effective method to prevent acquiring the virus, developing acute infection, and preventing the development of hepatic complications associated with hepatitis B. According to the Advisory Committee on Immunization Practices from the Centers for Disease Control and Prevention, all pregnant women should be screened for HBsAg to determine what type of immunoprophylaxis is required for the infant at birth, and to vaccinate naive household contacts who are at risk. Regardless of the HBsAg status of the mother, all infants should be vaccinated against hepatitis B. Children and adolescents who have not received any hepatitis B vaccination early in life should be immunized. Finally, adults at high risk for acquiring the infection should be vaccinated (Table 1-4).

Hepatitis B Vaccine

Immunizations should be recommended for high-risk individuals listed in Table 1-4. In the United States, there are two hepatitis B vaccines currently available, Recombivax HB (Merck & Co., Inc.) and Engerix-B (GlaxoSmithKline). The only major difference between the two vaccines is that Recombivax HB contains no thiomersal where Engerix-B has trace amounts from the manufacturing process (pediatric formulation contains less than 0.5 mcg mercury and adult formulation contains less than 1 mcg mercury). Currently, overexposure to thiomersal is not a concern. In July 1999, the Food and Drug Administration and other federal agencies, including the American Academy of Pediatrics, United States Public Health Service, American Academy of Family Physicians, and Advisory Committee on Immunization Practices, raised concerns regarding mercury exposure from vaccines with mercury as a preservative. The Food and Drug Administration, as part of an ongoing review

Table 1-4. High-risk Groups Recommended for Immunoprophylaxis Against Hepatitis B Infection

Newborn infants
Health care workers
Public safety workers
Clients and staff of institutions for the developmentally disabled
Hemodialysis patients
Recipients of blood products
Household contacts and sex partners of hepatitis B virus carriers
Adoptees from countries where hepatitis B infection is endemic
International travelers going to endemic areas for more than 6 months
Intravenous drug users
Sexually active homosexual and bisexual men
Sexually active heterosexual men and women having one or more partners in the previous 6 months
Inmates of long-term correctional facilities
Patients with hepatitis C

Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR Recomm Rep 1991;40(RR-13):1–19.

of biological agents of the Food and Drug Administration Modernization Act of 1997, determined that infants receiving several doses of thiomersal-containing vaccines within the first 6 months of life may be overexposed to mercury, causing neurotoxicity. Eventually, by March 2000, hepatitis B vaccines were essentially free of thiomersal as a preservative.

The hepatitis B immunization is a recombinant vaccine produced by using HBsAg expressed in *Saccharomyces cerevisiae* cells that are packaged to contain 10–40 mcg of HBsAg protein/ml after adsorption to aluminum hydroxide. The vaccines are recommended for intramuscular administration in the deltoid muscle, yet in some instances, subcutaneous administration may be used for those at risk for hemorrhage after intramuscular injections. However, after subcutaneous injections, the geometric mean antibody titer may be suboptimal. The results of clinical trials of both vaccines confer protective antibody levels, which are defined as concentrations greater than 10 mIU/ml, in more than 96% of recipients after a three-dose regimen at months 0, 1, and 6. Antibody response may be reduced to about 90% in patients older than 40 years of age. In addition, certain patient populations who are immunocompromised (e.g., hemodialysis patients, patients who are positive for human immunodeficiency virus [HIV], or patients taking immunosuppressive drugs) may not mount an antibody response as effectively as those who are not immunocompromised. The long-term protective effect of the hepatitis B vaccine is unknown, and the need for additional booster doses beyond the three-dose series is still in question. At present, results of the longest follow-up trial of 9 years showed that individuals receiving the hepatitis B vaccine continue to have detectable anti-HBs concentrations.

Table 1-5 indicates the dosing regimens for the available hepatitis B vaccines. The two brands are interchangeable for nondialysis formulations; however, it is recommended that the same brand should be used for the entire three-dose series. The vaccine dose is age-specific, and for newborns, dictated by the HBsAg status of the mother.

Postvaccination serological testing is not routinely recommended except in certain populations, including infants born to mothers who are HBsAg-positive, patients who are receiving dialysis or who have HIV, and occupational accidental needle sticks. If testing is required, it should be performed 1–6 months after the vaccination series has been completed.

The most common side effects associated with the hepatitis B vaccines are injection site reactions with or without elevated temperatures. In rare cases, anaphylaxis and hypersensitivity reactions have been reported within the first few hours of vaccine administration. Serious adverse events reported among adults include Guillain-Barré syndrome; however, this condition occurred only when the no longer commercially available plasma-derived vaccine was used. Currently, no association has been found linking severe adverse effects to Recombivax HB or Energix.

Twinrix, a combination vaccine that is made up of inactivated hepatitis A and recombinant hepatitis B, is indicated for immunization against HAV and HBV in people 18 years of age and older. A 1-ml dose contains the antigenic components of not less than 720 enzyme-linked immunosorbent assay units of Havrix (HAV vaccine) and 20 mcg of recombinant HBsAg protein of Engerix-B (HBV vaccine). Trace amounts of thiomersal (less than 1 mcg of mercury) are present because of the manufacturing process and 2-phenoxyethanol is used as a preservative. Patients who are at high risk for developing hepatitis A and B infections may receive Twinrix to protect them against both infections with one injection. These individuals include travelers to areas of high or intermediate endemicity for both hepatitis A and hepatitis B, patients with chronic liver disease and health care providers in contact with HAV and HBV. The combination vaccine dosing regimen is to be administered at months 0, 1, and 6. Seroconversion for antibodies against HAV was achieved in 99.9% of those receiving vaccine, and protective antibodies against anti-HBs were elicited in 98.5% of adult volunteers 1 month after a three-dose vaccination series. Twinrix has a similar frequency for side effects as if the vaccines were given separately.

Postexposure

Treatment with either hepatitis B immune globulin and/or hepatitis B vaccine are effective in preventing the development of hepatitis B infections. Hepatitis B immune globulin is recommended over the vaccine because it provides greater passive immunization because it contains a higher anti-HBs titer against HBV. Administering both the hepatitis B vaccine and hepatitis B immune globulin 0.5 ml to infants of HBsAg-seropositive mothers is typically more effective than the vaccine alone. Postexposure prophylaxis may benefit patients with the following

Table 1-5. Recommended Dosing Regimens for the Available Hepatitis B Vaccines^a

Product	Categories	Dose (in mcg)	Volume (ml)	Number of Doses	Schedule (months)
Recombivax HB	0–19	5	0.5	3	0, 1, 6
	11–15	10	1	2	1, 4–6
	> 19	10	1	3	0, 1, 6
	Hemodialysis	40	1	3	0, 1, 6 ^a
Energix	0–19	10	0.5	3	0, 1, 6
	11–19	20	1	3	0, 1, 6
	> 19	20	1	4	0, 1, 6
	Hemodialysis ^b	40	2	4	0, 1, 2, 6

^aThe two brands are interchangeable for nondialysis patients; however, it is recommended that the same brand be used for the entire three-dose series.

^bTwo doses of 20 mcg in one or two injections.

Table 1-6. Recommendations for Postexposure Immunoprophylaxis for Exposure to Hepatitis B Virus

	Source is HBsAg-positive	Treatment Source is HBsAg-negative	Source is Unknown or not Available for Testing
Unvaccinated	One dose of HBIG and initiate HB vaccine series	Initiate HB vaccine series	Initiate HB vaccine series
Previously vaccinated			
Known responder	No treatment	No treatment	No treatment
Known nonresponder	One dose of HBIG and initiate revaccination or two doses of HBIG	No treatment	If known high-risk source, treat as if source was HBsAg positive
Antibody response	Test exposed person for anti-HBs	No treatment	Test exposed person for anti-HBs
Unknown	1) if adequate, no treatment 2) if inadequate, one dose of HBIG and vaccine booster		1) if adequate, no treatment 2) if inadequate, vaccine booster and recheck titer in 1–2 months

Anti-HBs = hepatitis B surface antibody; HB = hepatitis B; HBIG = hepatitis B immunoglobulin; HBsAg = hepatitis B surface antigen.

exposures: perinatal exposure of an infant born to an HBsAg-positive mother, exposure to HBsAg-positive blood through percutaneous or permucosal route (intravenous drug use or sexual contact), and contact with a person with acute hepatitis B. If possible, the HBsAg status of the source should be known to determine which postexposure immunoprophylaxis should be implemented (Table 1-6). As with hepatitis A Ig therapy, treatment should be given as soon as possible after exposure, preferably within 14 days. A single hepatitis B immune globulin dose of 0.06 ml/kg administered intramuscularly is 75% effective in preventing hepatitis B infections.

Chronic Hepatitis B

Chronic hepatitis B is defined as the presence of HBsAg that has not cleared after 6 months of exposure in addition to active viral replication (HBeAg-positive or detectable HBV DNA). Patients who are carriers of the HBV (HBsAg-positive, normal ALT concentrations, or HBeAg-negative) do not need therapy, but should be followed on a yearly basis.

The goals of hepatitis B treatment are several-fold: 1) suppress viral replication by loss of HBV DNA and seroconversion of HBeAg; 2) normalize aminotransferases; 3) prevent and treat symptoms; 4) improve histology on liver biopsy; 5) decrease morbidity and mortality by preventing cirrhosis, HCC, and end-stage liver disease; and 6) eliminate the chronic carrier status through loss of HBsAg. Treatments available for CHB in the United States include IFN, lamivudine, and adefovir dipivoxil (Table 1-7).

Interferon

Interferon is a cytokine having antiviral, antiproliferative, and immunomodulatory effects. Several types of IFN drugs are available; however, only IFN- α 2b (Intron A by Schering-Plough) is indicated for treating

CHB. It is efficacious in suppressing and, in some cases, ceasing viral replication in certain populations.

A meta-analysis of 15 clinical trials in patients with HBeAg-positive CHB showed that HBeAg loss was observed in about 33% of the patients. The HBeAg seroconversion for patients who were treated with IFN was 18% greater than those not receiving therapy. The HBsAg loss is expected in 10–15% of patients treated for 12–24 weeks. In addition, IFN has an 80–90% durability of response after HBeAg seroconversion. Unfortunately, the results are much more variable for patients infected with HBeAg-negative CHB. End-of-treatment responses were high, ranging from 40% to 90%, while patients were being treated with IFN. However, sustained virological response (SVR) decreased to 15–25% when therapy was discontinued. Sustained virological response may be increased, with the possibility of loss of HBsAg, if treatment is extended beyond 12 months. As a result, patients should be maintained on IFN beyond 12 months. Patient factors associated with a higher likelihood of response to therapy include elevated ALT concentrations and low HBV DNA concentration before starting treatment.

Interferon has adverse effects. Because treatment is administered subcutaneously, injection site reactions may occur. In addition, flu-like symptoms, malaise, irritability, depression, thyroid abnormalities, leukopenia, and thrombocytopenia are the most common complications requiring either dose reduction or therapy discontinuation. (see the Hepatitis C section). Interferon- α 2b for HBV should be administered subcutaneously either 5 mU/day (better tolerated) or 10 mU 3 times/week.

Lamivudine

Lamivudine is a synthetic nucleoside analogue with an enantiomer of 3'-thiacytidine that has potent inhibitory antiviral effects against HBV and HIV. It is indicated for treating CHB infections. In HBV, it inhibits the reverse

Keeffe EB, Dieterich DT, Han SH, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States. *Clin Gastroenterol Hepatol* 2004;2:87–106.

Wong DK, Cheung AM, O'Rourke K, Naylor CD, Detsky AS, Heathcote J. Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B. A meta-analysis. *Ann Intern Med* 1993;119:312–23.

Table 1-7. Comparison of Three Treatments of Chronic Hepatitis B

	IFN- α	Lamivudine	Adefovir
Indications			
HBeAg +, normal ALT	Not indicated	Not indicated	Not indicated
HBeAg + chronic hepatitis	Indicated	Indicated	Indicated
HBeAg – chronic hepatitis	Indicated	Indicated	Indicated
Duration of Treatment			
HBeAg + chronic hepatitis	4–6 months	≥ 1 year	≥ 1 year
HBeAg – chronic hepatitis	1 year	> 1 year	> 1 year
Route	Subcutaneous	Oral	Oral
Side Effects	Many	Negligible	Potential nephrotoxicity
Drug Resistance	–	About 20%, year 1 About 70%, year 5	None, year 1 About 3%, year 2
Cost ^a	High	Low	Intermediate

^aBased on treatment duration of 1 year.

ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; IFN- α = interferon- α .

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transcription replication process, thus acting as a chain terminator. Lamivudine is effective in suppressing HBV DNA viral replication, normalizing ALT concentrations, and improving liver histology. Its efficacy is similar, and may be superior, to IFN in patients who are HBeAg-positive with CHB. Undetectable HBV DNA concentrations are seen in 44% of treated patients after 52 weeks of therapy compared to 16% in the placebo-treated group. About 40–75% of patients have normalization of ALT concentrations and histological improvement can be observed in about 50% of the patients treated with lamivudine. Hepatitis B envelope antigen loss occurs in 30% of the patients with HBeAg seroconversion rates being similar to IFN, ranging from 16% to 18%; however, the durability of seroconversion is roughly 77%. For this reason, long-term treatment is required to prevent relapse. The HBeAg seroconversion rate increases to 50% at 5 years compared to 17% at 1 year. Longer duration of lamivudine therapy means increasing the possibility of drug resistance from 14% at 1 year to 70% at 5 years. In patients developing drug resistance, ALT and HBV DNA concentrations return to baseline.

Treatment with lamivudine for HBeAg-negative CHB is not as favorable. About 70% of the patients who are treated for 12 months with lamivudine will have undetectable HBV DNA and close to 100% will have normalization of ALT concentrations. However, this response is not sustained once treatment is discontinued. Continuing lamivudine for more than 12 months may be reasonable to maintain these results, but biochemical and virological breakthrough commonly occurs because of the development of YMDD (tyrosine, methionine, aspartate, aspartate) mutant HBV. About 50% of patients continue to have undetectable viral loads and normal ALT concentrations when treated for 2 years. The response decreases to 40% after 3 years of treatment. There is a 10% SVR rate at the end of 1 year of therapy, but this is yet to be determined in HBeAg-negative patients treated for longer durations. Lamivudine may be the best treatment for patients with HBV who cannot tolerate or have contraindications to IFN.

The lamivudine dose for treating hepatitis B infections is 100 mg/day. The dose must be reduced in patients with renal insufficiency, usually when creatinine clearance is less than 50 ml/minute. Lamivudine is well tolerated in patients treated for hepatitis B infections. In clinical trials, the adverse effect profile for lamivudine was comparable to the placebo group. The most common side effects include fatigue, diarrhea, nausea, vomiting, and headaches. No major laboratory abnormalities are observed as seen with IFN. Although rare, serious adverse effects, including lactic acidosis, pancreatitis, and hepatomegaly have been reported. Lamivudine should be discontinued immediately if signs and symptoms associated with lactic acidosis develop as this can be fatal. In some cases, a flare in disease activity observed by elevated ALT concentrations can occur after ceasing treatment and can be associated with the development of YMDD mutants. These patients should be monitored carefully as the liver disease may progress to hepatic decompensation.

Adefovir Dipivoxil

Adefovir dipivoxil is an acyclic nucleotide analogue prodrug of adefovir that is effective against HIV and HBV. Adefovir dipivoxil inhibits DNA polymerase through RT acting as a DNA chain terminator. Adefovir dipivoxil has excellent biochemical and virological effects against HBV and is superior to lamivudine in that it has activity against the YMDD mutant in HBeAg-positive CHB. Results after 12–24 weeks of treatment are comparable to lamivudine, with greater efficacy rates if treatment continues for 72 weeks. Undetectable HBV DNA and loss of HBeAg is observed in about 45% of the patients treated with adefovir dipivoxil for 72 weeks in contrast to 20% with 48 weeks of treatment. In addition, more than 75% of the patients had a biochemical response with adefovir treatment and about 50% had histological improvement by week 72. At present,

Lai CL, Chien RN, Leung NW, et al. A one-year trial of lamivudine for chronic hepatitis B. *Asia Hepatitis Lamivudine Study Group. N Engl J Med* 1998;339(2):61–8.

Dienstag JL, Goldin RD, Heathcote EJ, et al. Histological outcome during long-term lamivudine therapy. *Gastroenterology* 2003;124:105–17.

Marcellini P, Chang TT, Lim SG, et al; Adefovir Dipivoxil 437 Study Group. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003;348:808–16.

the drug resistance rate is less than 4% when patients received adefovir dipivoxil 10 mg/day for 3 years.

For HBeAg-negative CHB, the results for treatment beyond 1 year are still being investigated. At present, a significant decrease in the HBV DNA concentration to 3.91 log₁₀ copies/ml was observed in the treatment arm in contrast to a 1.35 log₁₀ copies/ml drop in the placebo group after 52 weeks of therapy. Also, undetectable viral loads and ALT normalization were achieved in 50% and 72% of the treated patients compared to 0% and 29% in the placebo arm, respectively. Currently, clinical trials with adefovir dipivoxil for more than 1 year of therapy are under evaluation for this patient population.

The adefovir dipivoxil dose for treating CHB infections is 10 mg/day. In clinical trials, adefovir is well tolerated with a similar adverse effect profile as lamivudine and comparable to placebo. These side effects include asthenia, abdominal pain, diarrhea, dyspepsia, headaches, nausea, and flatulence. A rare but serious dose-related adverse effect is nephrotoxicity. The adverse effect was mostly observed in patients treated for HIV and HBV who received daily doses greater than 60 mg and 30 mg, respectively. Nephrotoxicity was defined as a gradual decrease in serum phosphorus and elevated concentrations of serum creatinine. However, patients with baseline renal insufficiency are at a greater risk for nephrotoxicity than those with normal kidney function. Therefore, caution is required when prescribing adefovir dipivoxil for patients with creatinine clearances less than 50 ml/minute and/or who are receiving other nephrotoxic therapies such as aminoglycosides. Other unlikely but potentially fatal adverse effects that have been reported with adefovir include lactic acidosis, pancreatitis, and hepatomegaly. Similar to lamivudine, therapy should be discontinued immediately if signs and symptoms of lactic acidosis develop. However, therapy can be restarted if an acute exacerbation of hepatitis occurs with treatment discontinuation.

Recommendations for Treating HBeAg-positive CHB

Figure 1-1 and Table 1-8 summarize treatment for patients who are HBeAg-positive. No therapy for HBV is required for patients with HBeAg-positive CHB with HBV DNA concentrations of less than 5 log₁₀ copies/ml measured by polymerase chain reaction (PCR). Patients should be monitored every 3 months for the first year to ensure stability after initial diagnoses. Monitoring includes biochemical (ALT), virological (HBV DNA by PCR), and clinical progression. Monitoring may be extended to every 6–12 months if all values are stable the first year after diagnosis. In some patients, a liver biopsy may be indicated if histological activity for active liver disease is in question as well as to follow the progression of necroinflammatory changes over time.

For patients with an HBV DNA concentration greater than 5 log₁₀ copies/ml, hepatitis B therapy should be considered. However, the recommended therapy depends on whether an ALT elevation is present. If patients have normal ALT concentrations, a liver biopsy is indicated to determine

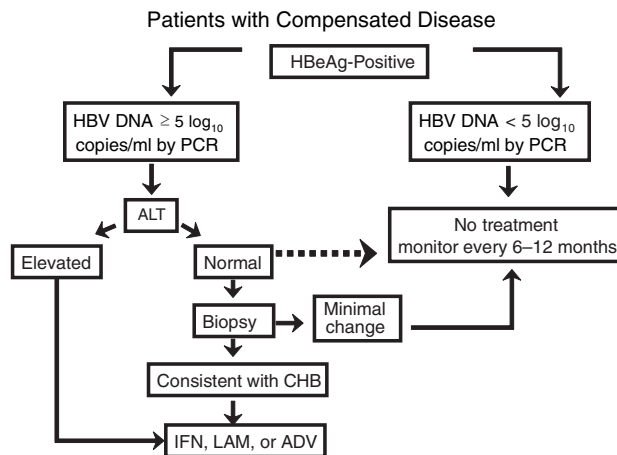


Figure 1-1. Recommendations for treating HBeAg-positive chronic hepatitis B.

ADV = adefovir; ALT = alanine aminotransferase; CHB = chronic hepatitis B; DNA = deoxyribonucleic acid; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; IFN = interferon; LAM = lamivudine; PCR = polymerase chain reaction.

the severity of liver disease. If there is active disease, lamivudine or adefovir therapy can be considered rather than IFN. No therapy is required if there is no disease activity. In those with elevated ALT and HBV DNA concentrations greater than 5 log₁₀ copies/ml, IFN, lamivudine, or adefovir can be initiated.

Therapy duration for these patients is still under investigation; however, it is recommended by the National Institutes of Health Consensus Development Conference that treatment should be continued for an additional 6 months after HBeAg seroconversion occurs with either stable detectable or undetectable HBV DNA concentrations by PCR. Indefinite treatment should be considered to possibly increase the chance of seroconversion if the loss of HBeAg does not occur.

Recommendations for Treating HBeAg-negative CHB

Patients with HBeAg-negative CHB tend to have active disease with lower HBV DNA concentrations compared to HBeAg-positive patients. Thus, patients with HBV DNA concentrations of more than 4 log₁₀ copies/ml measured by PCR should be considered for HBV therapy and those with less than 4 log₁₀ copies/ml do not require treatment. The treatment algorithm is similar to the one for HBeAg-positive patients in that it depends on the elevation of the ALT concentration. If ALT concentrations are normal, then a liver biopsy is indicated to determine the severity of liver disease (Figure 1-2 and Table 1-8). Treatment is required if active disease is present, but not if there is no disease in activity. Interferon, lamivudine, or adefovir should be considered if patients have an elevated ALT and a HBV DNA concentration greater than 4 log₁₀ copies/ml. It would not be unusual to treat a patient indefinitely because HBsAg seroconversion occurs rarely. Adefovir dipivoxil can be a

Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al; Adefovir Dipivoxil 438 Study Group. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med* 2003;348:800–7.

first-line therapy because of its low viral resistance with long-term treatment.

Investigational Drugs for CHB

Even though the pharmacotherapy of CHB has advanced, it is far from perfect. At present, three drugs are available. Lamivudine and adefovir are oral drugs with low virological and seroconversion rates. In addition, lamivudine is associated with high drug resistance, limiting its use. Interferon is an injectable drug that is expensive with several significant adverse effects requiring, in many cases, discontinuation of therapy. There are many drugs undergoing extensive review for treating hepatitis B, including entecavir, clevudine, emtricitabine, telbivudine, and pegylated interferon (PEG-IFN).

Entecavir

Entecavir is a cyclopentyl guanosine analogue that inhibits HBV DNA polymerase and eventually prevents DNA replication. It is unique compared to other nucleoside analogues in that it does not have any activity against HIV but is effective against lamivudine-resistant mutants such as YMDD. Entecavir is 30 times more potent than lamivudine in ceasing HBV replication. So far, entecavir has undergone Phase I and II clinical trials. In a dose-ranging study, 25% of the patients had undetectable HBV DNA concentrations by day 28 of therapy; however, this response was not maintained when treatment was discontinued. In another

safety and dose-ranging, double-blind, randomized, multicenter trial, entecavir was superior in suppressing viral replication compared to lamivudine after 24 weeks of treatment. Undetectable viral loads were observed in 84% of the patients receiving 0.5 mg of entecavir in contrast to only 58% in the lamivudine group. Despite this positive response, seroconversion and HBeAg loss was not different between the two populations. Entecavir may be effective in patients who were treated with lamivudine and developed YMDD mutants. In patients receiving a 1-mg dose, 79% had undetectable HBV DNA concentrations compared to only 13% of those treated with lamivudine. Entecavir and lamivudine have similar adverse effect profiles. Currently, Phase III multicenter, clinical trials are ongoing to further determine entecavir's role in treating CHB.

Clevudine

Clevudine is a pyrimidine analogue effective in inhibiting hepatitis B DNA polymerase. Phase I and II open-label, clinical studies have been completed. In a dose-ranging trial, 25 patients received 10 mg, 50 mg, or 100 mg of clevudine. All three treatment arms had a median reduction in HBV DNA concentration of 2.48 log₁₀, 2.74 log₁₀, and 2.95 log₁₀, respectively, at the end of a 28-day treatment period. At the end of the 20-week post-treatment period, HBV DNA concentrations were still suppressed at 1.84 log₁₀ and 2.38 log₁₀ for doses at 10 mg and 50 mg, respectively. Similar results were observed in

Table 1-8. Recommendations for Treating Chronic Hepatitis B

HBeAg	HBV DNA ^a	ALT	Treatment Strategy
+	+	≤ 2 x ULN	Low efficacy with current treatment Observe; consider treatment when ALT becomes elevated
+	+	> 2 x ULN	IFN-α, LAM, or ADV may be used as initial therapy End point of treatment—seroconversion from HBeAg to anti-HBe Duration of therapy <ul style="list-style-type: none"> • IFN-α: 16 weeks • Lamivudine: minimum 1 year, continue for 3–6 months after HBeAg seroconversion • Adefovir: minimum 1 year IFN-α nonresponders/contraindications to IFN-α → LAM or ADV LAM resistance → ADV
–	+	> 2 x ULN	IFN-α, LAM, or ADV may be used as initial therapy, IFN-α or ADV is preferred because of the need for long-term therapy End point of treatment—sustained normalization of ALT and undetectable HBV DNA by PCR assay Duration of therapy <ul style="list-style-type: none"> • IFN-α: 1 year • Lamivudine: > 1 year • Adefovir: > 1 year IFN-α nonresponders/contraindications to IFN-α → LAM or ADV LAM resistance → ADV
–	–	≤ 2 x ULN	No treatment required
±	+	Cirrhosis	Compensated: LAM or ADV Decompensated: LAM (or ADV); coordinate treatment with transplant center. Refer for liver transplant. IFN-α contraindicated
±	–	Cirrhosis	Compensated: Observe Decompensated: Refer for liver transplant

^aHBV DNA > 10⁵ copies/ml; this value is arbitrarily chosen.

ADV = adefovir; ALT = alanine aminotransferase; DNA = deoxyribonucleic acid; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; IFN-α = interferon-alfa; LAM = lamivudine; PCR = polymerase chain reaction; ULN = upper limit of normal.

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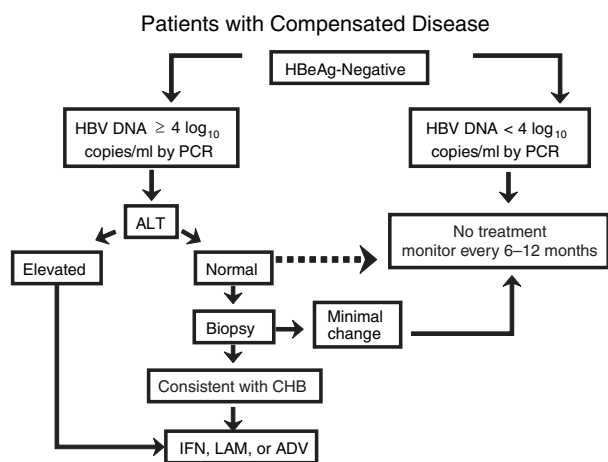


Figure 1-2. Recommendations for the treatment of HBeAg-negative chronic hepatitis B.

ADV = adefovir; ALT = alanine aminotransferase; CHB = chronic hepatitis; DNA = deoxyribonucleic acid; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; IFN = interferon; LAM = lamivudine; PCR = polymerase chain reaction.

another dose-ranging study of 30 patients receiving clevidine 50–200 mg/day for 28 days. Patients had a median reduction in HBV DNA concentration of 2.5 log₁₀, 2.7 log₁₀, 3.0 log₁₀, and 2.6 log₁₀, in the 10, 50, 100, and 200 mg treatment arms at the end of 28 days of treatment, respectively. In this trial, 28% of the patients had HBeAg loss, whereas 19% had HBeAg seroconversion. Treatment with clevidine in both trials was well tolerated with minimal adverse effects. However, despite these promising results, clinical trials associated with clevidine have been terminated because of licensing agreement issues as of August 2003.

Emtricitabine

Emtricitabine is a cytosine nucleoside analogue that has potent antiviral activity against HBV and HIV. In a 48-week dose-ranging, double-blind, clinical trial of 98 patients with CHB, emtricitabine produced undetectable HBV DNA concentrations in 38%, 42%, and 61% in the 25 mg, 100 mg, and 200 mg treatment arms, respectively. At the end of 48 weeks in 77 HBeAg-positive patients, 40% had HBeAg loss. Hepatitis B virus drug resistance had developed in 12% of the patients receiving 100 mg and 6% in patients receiving 200 mg. The similar resistance rate may be because of emtricitabine's structural similarity to lamivudine. Currently, emtricitabine is indicated for treating HIV. At present, Phase III clinical studies of this drug are in development to evaluate the safety and efficacy of long-term therapy for HBV.

Telbivudine

Telbivudine is an L-nucleoside analogue that inhibits HBV replication. Unlike lamivudine, which inhibits the negative strand of the HBV, telbivudine inhibits the positive strand, which possibly can translate into a slower onset of viral resistance development. In a randomized, multicenter trial, the safety and efficacy of telbivudine were compared with or without lamivudine for a 1-year period. Patients

received either 400 or 600 mg of telbivudine combined with or without lamivudine 100 mg. Another treatment group of lamivudine monotherapy was added in this study for adults with HBeAg-positive HBV. At the end of the treatment, patients had a median reduction in HBV DNA concentrations of 4.66 log₁₀, 6.43 log₁₀, 6.09 log₁₀, 6.4 log₁₀, and 6.05 log₁₀ in the lamivudine, telbivudine 400 mg/day, telbivudine 600 mg/day, telbivudine 400 mg/day plus lamivudine, and telbivudine 600 mg/day plus lamivudine groups, respectively. In all treatment arms, no major adverse effects were experienced. Overall, undetectable HBV DNA concentrations were observed in 61% of the telbivudine groups compared to 32% in the lamivudine arm. In addition, only 49% of patients receiving combination therapy with telbivudine and lamivudine cleared the virus. Telbivudine was superior in normalization of ALT concentrations compared to lamivudine and combination therapy, 86%, 63%, and 78%, respectively. Hepatitis B envelope antigen loss was observed in about 33% of the patients treated with telbivudine, which was not statistically different compared to 28% in the lamivudine group. At present, a multicenter, international, Phase III, clinical trial is ongoing to determine telbivudine's role in treating CHB.

Pegylated Interferons

Pegylated interferons currently are only available for treating chronic hepatitis C. Clinical trials currently are evaluating PEG-IFN for patients infected with hepatitis B. A dose-ranging, clinical study compared PEG-IFN-α2a at 90 mcg, 180 mcg, and 270 mcg to IFN 4.5 mIU. In this study, 291 patients were screened and 194 HBeAg-positive patients met inclusion criteria. The main end points were HBV DNA concentrations less than 4.69 log₁₀ copies/ml, loss of HBeAg, and normalization of ALT concentrations. When each factor was individually evaluated, no statistical differences were observed. However, there was a significant difference when the end points were combined, IFN of 12% versus all doses of PEG-IFN of 24% (p=0.036). In a 48-week, Phase III clinical trial of HBeAg-negative patients, PEG-IFN-α2a 180 mcg/week plus placebo was evaluated against PEG-IFN-α2a 180 mcg/week plus lamivudine 100 mg/day, and lamivudine 100 mg/day. Normalization of ALT concentrations was observed in 59%, 60%, and 44% of patients, respectively. Virological response, defined as HBV DNA concentrations less than 4.3 log₁₀ copies/ml, was similar between the two groups receiving PEG-IFN (43–44%) compare to 29% of the patients receiving lamivudine. Hepatitis B surface antigen loss was observed in 12 patients in both PEG-IFN-α2a groups but in no patients in the lamivudine arm. Further investigations are ongoing for PEG-IFN-α2a for treating CHB.

Hepatitis C

Hepatitis C, first known as non-A, non-B hepatitis, was first identified in 1974 by Albert Prince. Much was involved in studying this unknown infectious agent. Finally, in 1988, scientists at the Chiron Corporation cloned and discovered

the cause of non-A, non-B hepatitis as a virus and labeled the disease as hepatitis C. Extensive research led to the first blood antibody screening test for HCV in 1990. Since then, hepatitis C infections have decreased significantly as all donated blood is now screened for the virus. Despite the decrease, more than 170 million people are infected, making hepatitis C the most common cause of liver disease worldwide.

Virology and Pathogenesis

Hepatitis C is a single-stranded RNA virus belonging to the Flaviviridae family and the *Hepacivirus* genus. The 9.6 kilobase long virion contains structural and nonstructural (NS) peptides. A nucleocapsid core and glycoproteins are within the structural part of the genome that functions to assemble and enter the host. The NS genome contains proteins labeled NS2 to NS5. The function of each protein is still in question; however, it is known that NS5 may be responsible for RNA viral replication. What makes HCV unique is there are at least six identifiable genotypes and more than 90 subtypes. The genotypes are numbered 1 to 6, and are further divided into subtypes (e.g., genotype 1a, 1b, 2a, or 2b). Genotypes are geographically specific. For example, genotype 1a is commonly found in patients located in the United States and in Northern Europe, whereas genotype 4 is common in Africa and the Middle East. In the United States, about 75% of those infected with HCV have either genotype 1a or 1b, followed by about 14% for genotype 2a or 2b, and a little more than 5% for genotype 3a. There is no difference in disease severity or clinical outcomes based on genotype. Its primary function may be used to determine the likelihood of therapeutic response. For example, those with genotype 2 are more likely to benefit from treatment than those who have genotype 1. Regardless of genotype, hepatitis C is a chronic disease that persists for years. Viral resistance may be associated with the host's ineffective immunity against the HCV. It is believed that the cytotoxic T lymphocytes against the HCV infection are ineffective in eradicating the virus, thus allowing it to continue damaging the hepatic cells. Thus, immunocompromised individuals are less likely to eliminate HCV.

Epidemiology and Risk Factors

Hepatitis C is a bloodborne infection that affects individuals worldwide. In the United States alone, it is estimated that close to 4 million people are infected with HCV and almost 75% of this population have chronic hepatitis C infections. The prevalence is highest among non-Hispanic blacks (3.2%) compared to non-Hispanic whites (1.3%) and men are more likely to be infected than women. The incidence of hepatitis C has decreased significantly from 230,000 new cases in the 1980s to 38,000 cases in the 1990s. The decreased incidence is a result of screening blood donors for the hepatitis C antibodies. By and large, the most common risk factors associated with acquiring the HCV are blood transfusions before the 1990s and intravenous drug use. Currently, the risk for HCV infection from blood transfusions is minimal (0.001% per unit transfused) compared to before 1990s where the risk was about 0.02% per unit transfused. At present,

intravenous drug use is responsible for most hepatitis C transmissions. The risk includes the use of contaminated paraphernalia used for drug preparation which is shared among the users. It is encouraging that awareness is increasing on how to decrease the transmission of the virus through needle programs. Another risk factor (2%) is accidental needle sticks in the health care environment (e.g., surgeons, correctional facility personnel, or emergency medical technicians). The rate of becoming anti-HCV-positive is about 2% for those who are infected with an accidental needle stick from a HCV-positive source. Individuals engaged with multiple sexual partners are at greater risk of being infected with HCV compared to individuals in long-term monogamous relationships, where the prevalence of HCV infection is less than 5%. There also is a 5% prenatal risk for infants born to mothers who are anti-HCV-positive; however, this rate increases to about 15% when coinfecting with both HCV and HIV. The HCV transmission is more likely to occur when the mother has active viremia at the time of birth. Transmission of HCV through breast milk is unknown. Percutaneous exposures such as body piercing and tattooing performed unprofessionally may be a possible transmission mode of the virus. About 10% of the individuals infected with HCV have no identifiable risk factors.

Natural History

Morbidity associated with hepatitis C infections is a significant burden on the health care cost where, in 1998, more than \$1 billion in hospital charges alone were incurred. The increased cost is because of hepatitis C developing into a chronic disease in more than 85% of the cases. The remaining 10–15% mostly develop acute hepatitis C which, fortunately, resolves without any further sequelae. Of those developing chronic infections, about 70% progress to mild, moderate, or severe hepatitis. Although the natural history of the progression to cirrhosis is not clear and is estimated to occur in 10–20% of cases, it may take up to 20–40 years from the time of exposure to advance from fibrosis to cirrhosis. Factors contributing to the development of cirrhosis include alcohol use, gender, infection at an older age, and coinfection with HIV or HBV. The rate of developing HCC increases 1–4% per year when cirrhosis is confirmed. The estimated death rate is 1.8 deaths per 100,000 people per year. Cirrhosis caused by HCV is one of the primary reasons for liver transplantation in the United States.

Clinical Course and Clinical Manifestation

As with other types of hepatitis, individuals infected with HCV usually are asymptomatic; less than 30% actually present with symptoms that affect quality of life. Elevated serum aminotransferases associated with acute hepatitis C may develop 2–26 weeks after exposure. The incubation period may span between 7 and 12 weeks; however, almost all cases occur within 5–12 weeks. When an acute infection is documented, it is not uncommon to have ALT concentrations elevated to more than 15 times the upper limit of normal. In addition to having positive anti-HCV, HCV RNA is detectable early in the disease course and the presence of anti-HCV develops 5–6 weeks after exposure.

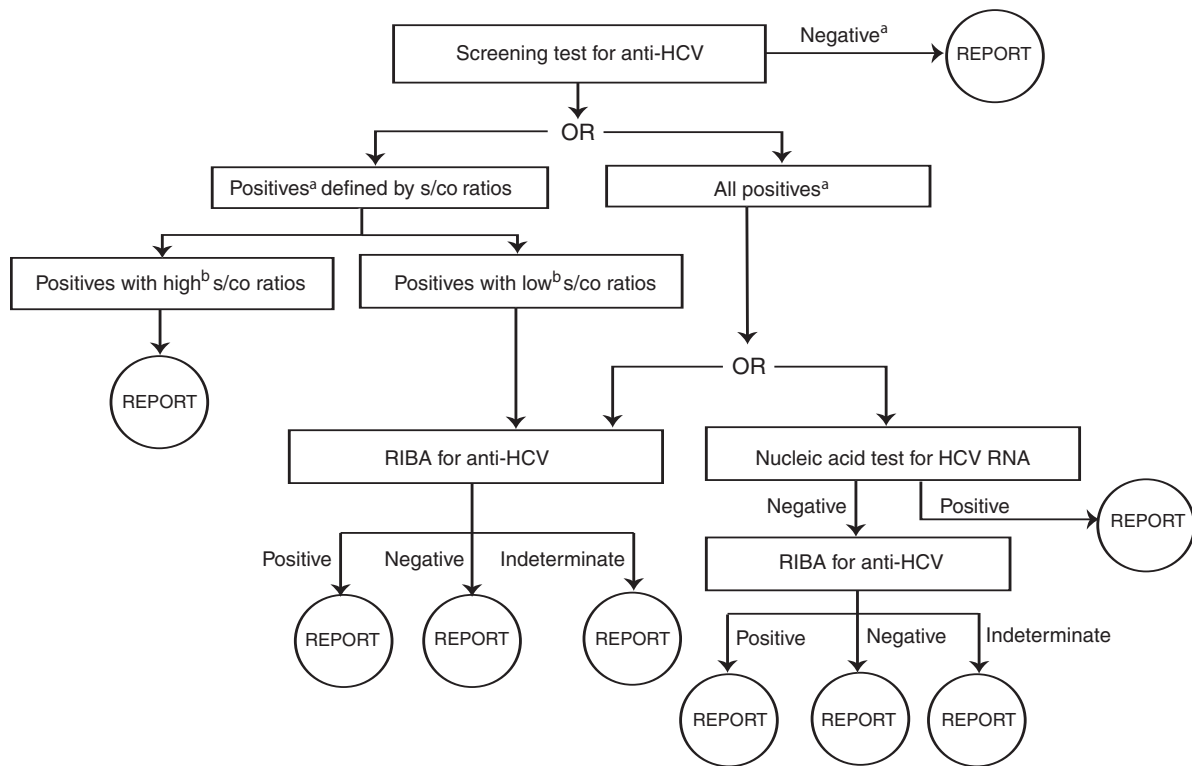


Figure 1-3. Laboratory algorithm for antibody to hepatitis C virus testing and result reporting.

^aInterpretation of screening immunoassay test results based on criteria provided by the manufacturer.

^bScreening-test-positive results are classified as having high s/co ratios if their ratios are at or above a predetermined value that predicts a supplemental-test-positive result of 95% or more of the time among all populations tested; screening-test-positive results are classified as having low s/co ratios if their ratios are below this value.

Anti-HCV = hepatitis C virus antibody; HCV = hepatitis C virus; RIBA = recombinant immunoblot assay; RNA = ribonucleic acid; s/co = signal to cutoff. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention. MMWR Recomm Rep 1998;47(RR-19):1-39.

Symptoms are mostly nonspecific, consisting of weight loss, anorexia, flu-like complaints, fatigue, abdominal pain, and arthralgias. In less than about 33% of the cases, jaundice can occur with other uncommon symptoms such as fever and rash. Acute hepatitis C resolves within 6 months from the time of exposure. However, when disease persists beyond 6 months, it is then considered chronic hepatitis C. The most common symptoms are fatigue and dull upper right quadrant pain. Uncommon symptoms include nausea, pruritus, arthralgia, and anorexia. Serum aminotransferases, specifically ALT concentrations, are mildly elevated, with about 25% having a level more than 2 times the upper limit of normal. About 30–40% of the chronic hepatitis C cases have detectable HCV RNA with ALT concentrations less than 2 times the upper limit of normal. Those with documented bridging fibrosis or cirrhosis may have splenomegaly and/or hepatomegaly on examination. They also may present with complications of cirrhosis, such as encephalopathy or ascites.

Diagnosis and Serological Testing

As with hepatitis A and B, diagnosing patients with hepatitis C may be difficult because most patients present with minimal or no complaints. Moreover, acute hepatitis C often is dismissed by the patient because of the flu-like symptoms. Serological screening assays for anti-HCV are

used to identify individuals who are infected with HCV. These assays include either the enzyme immunoassays or the chemiluminescence immunoassay. These tests are effective in screening and detecting the virus in more than 97% of infected individuals. However, a confirmation test is required because of high false-positive rates with enzyme immunoassays and chemiluminescence immunoassay tests. Confirmation tests include either the recombinant immunoblot assay or the nucleic acid test that may qualitatively or quantitatively measure HCV RNA. The Centers for Disease Control and Prevention has developed recommendations for laboratories to assist health care professionals in confirming the diagnosis of HCV (Figure 1-3).

Managing Hepatitis C Prevention

The Centers for Disease Control and Prevention has recommended primary and secondary methods for reducing the risk of contracting HCV infection and minimizing the development of chronic liver disease and its complications. Primary prevention strategies include screening and testing blood, plasma, organ, tissue, and semen donors; virus inactivation of plasma-derived products; risk-reduction counseling and services; and implementation and maintenance of infection-control practices. No vaccines are

currently available to immunize against hepatitis C; thus, identifying and counseling patients at high risk are reasonable to decrease their chance of acquiring the infection. Secondary prevention is done by identifying people who are HCV-positive through diagnostic testing and initiating treatment if necessary. Those who should be routinely screened for the HCV include past and current intravenous drug users, people with clotting factor disorders who received products manufactured before 1987, long-term hemodialysis patients, and those having persistently elevated ALT concentrations. Others who should be screened include people who received transfusions or organ transplants who received blood from a donor who later tested positive for HCV and/or who received blood products or an organ transplant before July 1992. Health care providers, emergency medical technicians, and public safety workers who are exposed to HCV-positive blood after an accidental needle stick also are at risk. Baseline and follow-up testing of anti-HCV and ALT should be obtained immediately and 4–6 months after exposure. Finally, infants born to mothers who are HCV-positive should be screened for HCV no sooner than 1 year of age, as the anti-HCV usually will be undetectable before this time. Hepatitis C virus RNA levels should be measured at 1–2 months of age if earlier testing is sought. Immunoglobulin, which is effective for postexposure prophylaxis against hepatitis A and B, is ineffective for hepatitis C.

Treating Hepatitis C

The primary treatment goal for hepatitis C is HCV eradication measured by undetectable HCV RNA concentrations (virological). Other goals include normalization of ALT concentrations (biochemical) and improving fibrosis scores to minimize the risk of developing cirrhosis (histological) and the progression to end-stage liver disease and HCC. Ultimately, treatment should improve signs and symptoms associated with hepatitis C and its complications to decrease morbidity and mortality. In 1997 and 2002, the National Institutes of Health Consensus Development Conference guidelines on managing hepatitis C defined several therapeutic end points (virological, biochemical, and histological). A virological response is defined as an undetectable HCV RNA concentration in the serum measured by RT-PCR assays with a sensitivity of at least $2 \log_{10}$ copies or 50 IU/ml or less. Biochemical response is defined as having normalization of serum ALT concentrations. Finally, when comparing pretreatment biopsy to 24 weeks after treatment biopsy, a histological response is when there is a 2-point or greater decrease in the total biopsy inflammatory score or a 1-point decrease in fibrosis score. The National Institutes of Health recommends measuring these end points at the end of treatment to determine the end of treatment response and at 24 weeks after treatment to determine the sustained response. There are different response patterns to hepatitis C therapy (Figure 1-4). Ideally, individuals treated should sustain virological and biochemical response as observed in panel A of Figure 1-4, yet there are several factors that may prevent this from happening. For reasons not clearly understood, treatment fails more often in African Americans. In addition, men, older age at the time of initial treatment, and those with bridging fibrosis or cirrhosis are

less likely to respond. Although it is unknown to what extent ethanol abuse alters the treatment response, it increases the risk for developing cirrhosis and HCC. More recently, obesity, defined as a body mass index of greater than 30 kg/m^2 , is associated with decreased SVR and possible progression of chronic hepatitis. Iron overload also may decrease response, and it has been suggested that phlebotomy may be an adjunctive therapy in increasing SVR. Regardless, the most important factor in determining a positive SVR is the viral genotype. Patients with non-genotype 1 and 4 have a more favorable response and require a shorter therapy duration. Unfortunately, in the United States, about 70–75% of the patients are infected with genotype 1.

In 1986, IFN- α 2b, the same drug used to treat CHB, was reported to be effective against hepatitis C. Since then, IFN- α 2b (Intron-A) in 1991 and IFN- α 2a (Roferon) in 1996 were available for treating chronic hepatitis C. Finally, by 1997, IFN alfacon 1 (Infergen), also known as consensus IFN, became available for use. The first National Institutes of Health Consensus Development Conference met in 1997 and recommended IFN 3 mU 3 times/week for 48 weeks to treat chronic hepatitis C. Although this was the preferred treatment, the SVR rate was only 12–16%. The SVR rates increased when ribavirin, a synthetic guanosine analogue, was added to IFN. Ribavirin is effective in reducing and normalizing serum ALT concentrations with no effect on HCV RNA levels. The mechanism of action of ribavirin is still under investigation, but it is thought to inhibit viral polymerase by depleting intracellular phosphate reserves. The combination approach of using both IFN and ribavirin for treating HCV was not applied until 1998 when ribavirin was finally available. Response rates improved significantly, ranging from 35% to 45%, when ribavirin was added to IFN therapy and it was considered the standard treatment for hepatitis C from 1998 to 2001. In 2002, the National Institutes of Health Consensus Development Conference again discussed the recommendations for treating hepatitis C. Much has changed since the last meeting, and more efficacious therapies, such as PEG-IFN, are available.

Pegylated interferon is IFN that is covalently attached to the inert molecule polyethylene glycol, which prolongs the IFN half-life. Interferon has a half-life of a few hours, but the half-life with the new formulation is several days, allowing for dosing once a week. At present, there are two PEG-IFNs: PEG-IFN- α 2b (PegIntron) and PEG-IFN- α 2a (Pegasys). A comparison between the two drugs is provided in Table 1-9; a randomized, clinical trial is under way to assess head-to-head comparative efficacy.

With either formulation of PEG-IFN, monotherapy achieves an SVR rate (25–40% for 48 weeks of treatment) similar to combination therapy with IFN and ribavirin. As expected, ribavirin with PEG-IFN significantly increased genotype nonspecific SVR to about 55%. Pretreatment factors for a favorable SVR include low HCV RNA levels, younger age, lower body weight, and minimal fibrosis scores. However, genotype is the most important factor. Patients with genotype 2 or 3 have an SVR of 75–85% compared to an SVR of 40–50% with genotype 1. Therapy duration and dosing of ribavirin also is dictated by genotype. Patients with genotype 1 will require 48 weeks of treatment

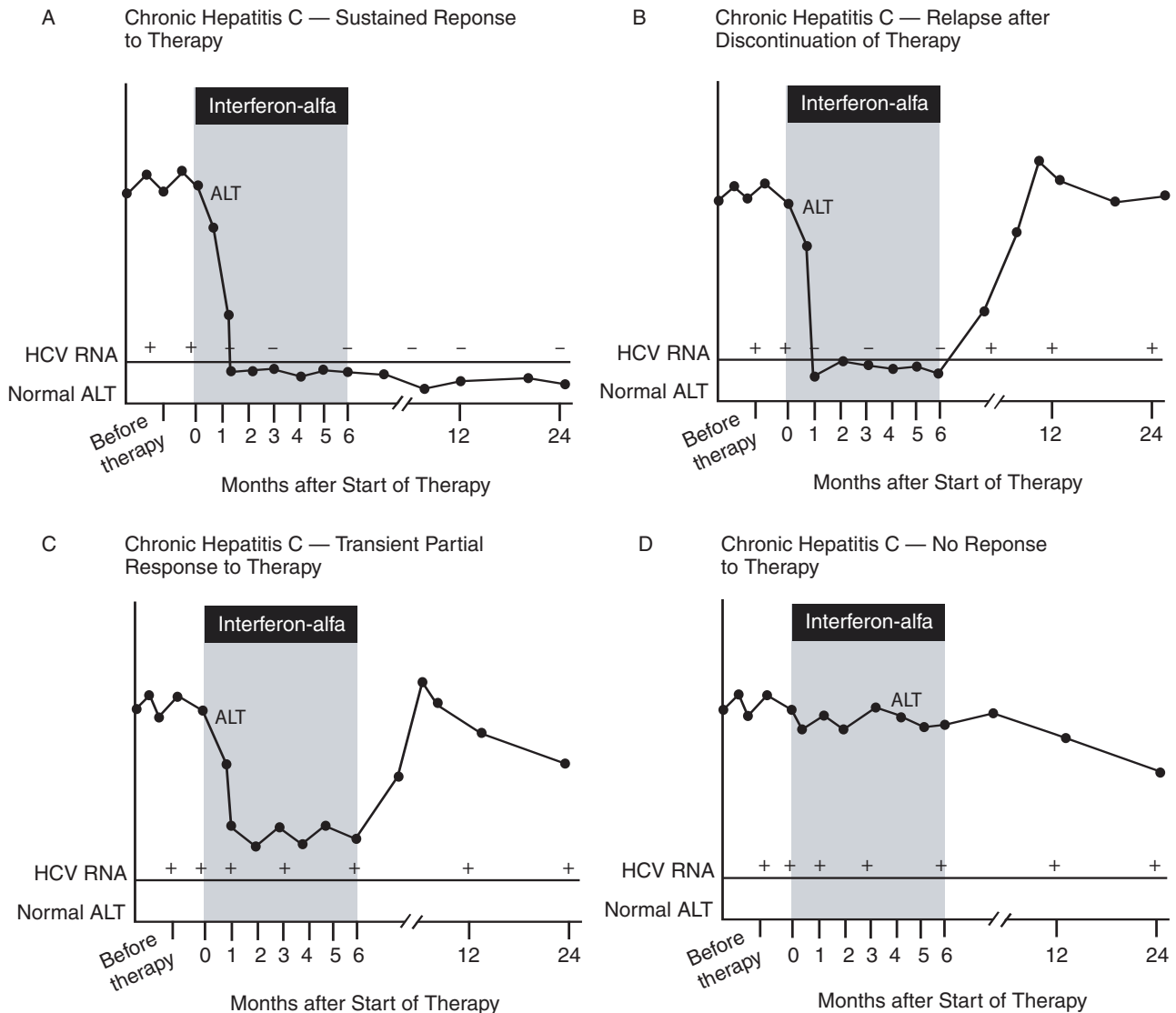


Figure 1-4. Serum alanine aminotransferase concentrations and viral markers in patients with chronic hepatitis C during and after 6-month courses of interferon- α .

Panel A shows the course of disease in a patient with chronic hepatitis C who had a sustained response to therapy. Panel B shows the course in a patient who had a transient response to therapy but relapsed after therapy was discontinued. Panel C shows the course in a patient who had a transient partial response to therapy. Panel D shows the course in a patient who had no response to therapy. Plus signs indicate the presence of detectable HCV RNA and minus signs indicate its absence. HCV RNA was measured by the polymerase chain reaction.

ALT = alanine aminotransferase; HCV = hepatitis C virus; RNA = ribonucleic acid.

Reprinted with permission from the Massachusetts Medical Society. Hoofnagle JH, Di Bisceglie AM. The treatment of chronic viral hepatitis. *N Engl J Med* 1997;336:347–56.

with weight-based dosing of ribavirin (less than 75 kg receives 1000 mg/day and 75 kg or more receives 1200 mg/day), whereas a treatment duration of 24 weeks is sufficient for genotypes 2 or 3, and all will receive ribavirin 800 mg/day, regardless of weight.

Adherence to hepatitis C therapy significantly increases response rates. In a recent study, patients receiving more than 80% of the total IFN dose with more than 80% of the ribavirin dose for more than 80% of the expected treatment duration are more likely to have an SVR. Patients receiving IFN and ribavirin who were not compliant with treatment had an SVR of 44% compared to an SVR of 52% for those

who were compliant. Similar rates also were observed in the PEG-IFN and ribavirin treatment arm, where those who had not missed any doses had an SVR of 63% compared to an SVR of 54% in the noncompliant arm. Nevertheless, certain patient populations are more ideal candidates for treatment than others, and individual risk versus benefit must be weighed in each case.

According to the 2002 National Institutes of Health Consensus Development Conference guidelines on managing hepatitis C, treatment is recommended for patients at an increased risk of developing cirrhosis. The overall rate of response is about 50–60% for patients with

Table 1-9. A Comparison Between the Pegylated Interferons

	Pegasys	PegIntron
Drug company	Roche	Schering
Approved for HCV	October 16, 2002	January 22, 2001
Type of IFN	α 2a	α 2b
# Kilodalton	40	12
Attachment	Branched	Linear
Half-life	50–80 hours	30–50 hours
Excretion	Liver	Kidney
Dosing	180 mcg fixed dose	0.35–1.5 mcg/kg based on body weight

HCV = hepatitis C virus; IFN = interferon.

genotype 1 and 70–85% for patients with genotype 2 and 3. Those at higher risk have detectable HCV RNA measured by RT-PCR assay, persistently elevated ALT concentrations, and either have portal or bridging fibrosis on liver biopsy with moderate degrees of inflammation and necrosis. However, there are several groups where initiation of treatment is in question. As previously discussed, 30–40% of the patients have persistently normal or minimally elevated ALT concentrations with detectable HCV RNA. Despite this, some may have histologically mild disease, whereas others have fibrosis and cirrhosis.

Historically, patients with normal ALT concentrations have mild disease with no progression. Yet, this may not be true as up to 29% of the patients with normal ALT concentrations have bridging fibrosis or cirrhosis. Thus, with the advent of more effective therapies, this patient population may warrant treatment even though the ALT concentrations are not elevated. More recently, studies using PEG-IFN with ribavirin have been evaluated. Overall, the SVR is about 30%; however, genotype 2 or 3, treated for either 24 or 48 weeks, had an SVR of 72% and 78%, respectively. In comparison, patients with genotype 1 treated for 48 weeks had an SVR of 40% versus 13% when treated for only 24 weeks. Besides preventing cirrhosis, other treatment factors can include prevention of virus transmission, improvement in quality of life, and elimination of signs and symptoms of liver disease. Nevertheless, treatment may be deferred until more effective and better tolerated therapies become available. Treatment initiation should be based on liver biopsy activity, comorbid conditions (i.e., coinfecting with HIV), extrahepatic manifestations (i.e., cryoglobulinemia), patient's motivation level, and, most important, favorable genotype (2 or 3).

Patients with mild liver disease, defined as no fibrosis and minimal necroinflammatory changes on liver biopsy, may not need therapy despite having elevated ALT concentrations and detectable HCV RNA. These patients should be monitored periodically. In contrast to patients with advanced liver disease demonstrated with bridging fibrosis and compensated cirrhosis, the risk of developing HCC and other hepatic complications, including bleeding esophageal varices, ascites, and infections, is much less in patients with mild disease. If decompensated liver disease is present, the only treatment option available is liver transplantation. Hence, treatment for chronic HCV should

be initiated before the development of advanced disease because the virological response rates and tolerability to treatment will decrease disease after complications of liver disease develop. Studies devoted to evaluating patients with cirrhosis or bridging fibrosis treated with PEG-IFN and ribavirin are not available; however, there are data derived from post hoc subgroup analyses. Patients with advanced disease treated with PEG-IFN and ribavirin have an SVR of 41–43% compared to 57–58% of the patients with no fibrosis or portal fibrosis. Of interest, histological response, defined as a decrease of two or more points in the histological activity index score, was not statistically different when either IFN or PEG-IFN was used, even though the response was high. Also for either treatment group where about 20% of patients had histological improvement in their fibrosis scores.

HIV/HCV Coinfection

Patients coinfecting with HIV should be considered for hepatitis C therapy as end-stage liver disease can develop much faster compared to those without HIV. The development of cirrhosis may be associated with highly active antiretroviral therapy; however, this is still being debated. Even though highly active antiretroviral therapy significantly decreased hospital admissions for opportunistic infections, hospitalizations associated with liver complications have increased. In addition, immune deficiency may support fibrosis progression; however, this is controversial. Conflicting studies have shown fibrosis scores increased and decreased when CD4 cell counts were less than 250 cells/mm³; further studies are being conducted to determine who is more likely to develop fibrosis. The severity of liver disease also may depend on patient age at onset of the infection, as those older than 40 years of age are more likely to have significant scarring of the liver. Regardless, early treatment may achieve SVR, minimize the risk of developing active necroinflammation or fibrosis, and prevent end-stage liver disease. Coinfecting patients treated with PEG-IFN and ribavirin have an overall end of treatment response of 41–47% and a more variable SVR between 27% and 40%. Similar to monoinfected patients, genotype is a significant factor in determining SVR. Only 14–29% of individuals infected with genotype 1 sustain response compared to 62–73% in patients infected with genotype 2 or 3. In addition, patients are more likely to achieve SVR (37–51%) if HCV RNA levels become undetectable by week 12 of therapy compared to those who did not achieve SVR. Therefore, week 12 of treatment is the significant time point in determining the likelihood of responding to therapy.

Treating Recurrent HCV after Liver Transplantation

Treatment for the recurrence of hepatitis C after liver transplantation should be decided on a case-by-case basis. It is known that as early as 2–4 days after the transplantation, HCV RNA levels may become detectable. About 25% develop moderate hepatitis confirmed by liver biopsy at 1 year after liver transplantation. It is estimated that by 5 years after transplantation, about 20% will develop cirrhosis and increase their risk of allograft rejection.

Bacon BR. Treatment of patients with hepatitis C and normal serum aminotransferase levels. *Hepatology* 2002;36(5 suppl 1):S179–84.

Factors associated with the progression of fibrosis can include immunosuppressants such as corticosteroids and monoclonal antibody treatments. These drugs have been documented to increase serum HCV RNA levels. Prior IFN use is hypothesized but not validated to produce a more virulent and aggressive HCV, and cause more hepatic damage. Other causes that can influence post-transplantation fibrosis include the use of organs from marginal and older donors, the time the transplantation took place (i.e., before the 1990s), and the pretransplantation HCV RNA level. Thus, it may be warranted to treat these orthotopic liver transplantation patients before the progression to cirrhosis. In liver transplant recipients infected with HCV, treatment with IFN with or without ribavirin resulted in a poor SVR (20–25%). Side effects were the major limitation preventing the use of maximal doses. Treatment with PEG-IFN and ribavirin produced an end of treatment response of about 55% and an SVR of 30%. Studies using preemptive therapy, meaning treating HCV immediately after the transplant in the presence of active disease, are disappointing, with SVR only achieved in less than 25% of patients. Most patients are too sick to tolerate the side effects associated with treatment, and about 33% of the patients require therapy to be discontinued. Thus, according to the First International Liver Transplantation Society Expert Panel Consensus Conference on Liver Transplantation and Hepatitis C, the time to recommend treatment for HCV after liver transplant would be with the diagnosis of progressive grade II fibrosis or greater.

Treating Nonresponders

Currently, the Hepatitis C Antiviral Long-term Treatment against Cirrhosis trial is ongoing to determine if maintenance therapy would be beneficial in delaying fibrosis progression and reducing the risk for hepatic decompensation and HCC in patients who did not respond to retreatment with PEG-IFN and ribavirin. Patients enrolled in the study have detectable HCV RNA levels, a liver biopsy performed 12 months before participating in the study with documented bridging fibrosis or cirrhosis, and did not respond to 12 weeks of IFN treatment with or without ribavirin. All patients were treated with PEG-IFN- α 2a 180 mcg/week with weight-based dosing of ribavirin (1000 mg for 75 kg or less or 1200 mg for more than 75 kg). Therapy continued to week 48 in patients with undetectable virus at week 20, whereas those who did not have undetectable viral levels received a reduced PEG-IFN- α 2a dose of 90 mcg/week (known as “maintenance therapy”) for 3.5 years. At present, 604 patients have been enrolled in the Hepatitis C Antiviral Long-term Treatment against Cirrhosis trial. Study results indicated that 35% of the patients who did not respond to IFN monotherapy had undetectable HCV RNA levels at week 20 and 18% had SVR. Results of the “maintenance phase” of the therapy will not be known until the study is completed.

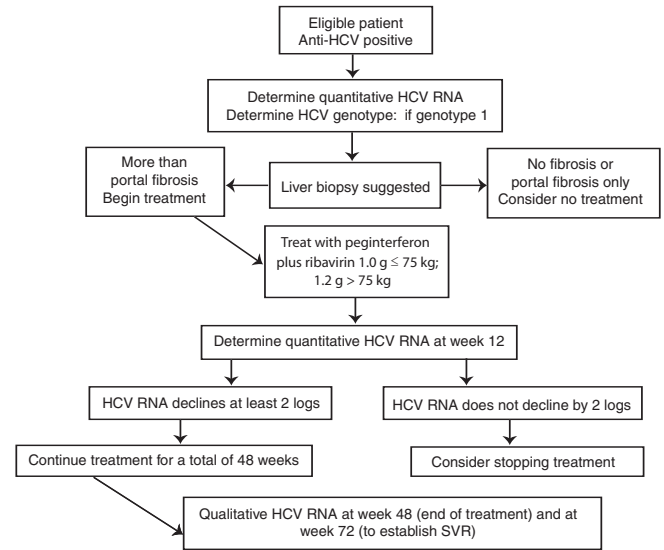


Figure 1-5. Sequential steps for managing and treating patients with chronic HCV infection, genotype 1. Anti-HCV = hepatitis C virus antibody; HCV = hepatitis C virus; RNA = ribonucleic acid; SVR = sustained virological response. Reprinted with permission from John Wiley & Sons, Inc. Strader DB, Wright T, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C. *Hepatology* 2004;39(4):1147–71.

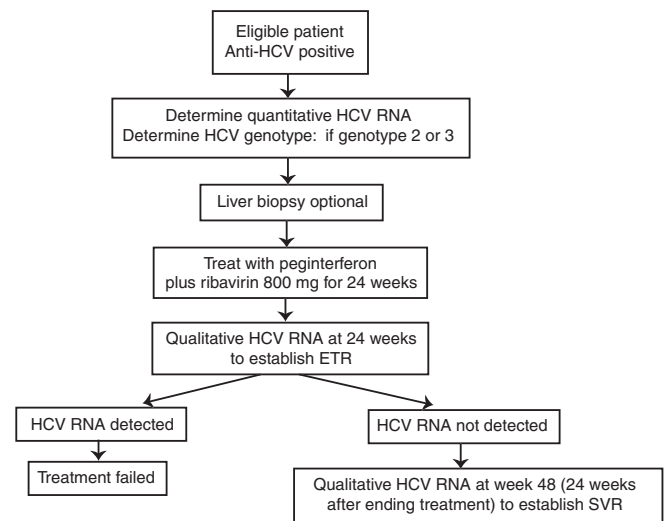


Figure 1-6. Sequential steps for managing and treating patients with chronic HCV infection, genotype 2 or 3. Anti-HCV = hepatitis C virus antibody; ETR = end of treatment response; HCV = hepatitis C virus; RNA = ribonucleic acid; SVR = sustained virological response. Reprinted with permission from John Wiley & Sons, Inc. Strader DB, Wright T, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C. *Hepatology* 2004;39(4):1147–71.

Wiesner RH, Sorrell M, Villamil F; International Liver Transplantation Society Expert Panel. Report of the first International Liver Transplantation Society expert panel consensus conference on liver transplantation and hepatitis C. *Liver Transpl* 2003;9:S1–9.

Shiffman ML, Di Bisceglie AM, Lindsay KL, et al; Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis Trial Group. Peginterferon alfa-2a and ribavirin in patients with chronic hepatitis C who have failed prior treatment. *Gastroenterology* 2004;126:1015–23.

Table 1-10. Adverse Effects Associated with Interferon, Pegylated Interferon, and Ribavirin for Hepatitis C

Most Common Adverse Effects	Uncommon Adverse Effects
Alopecia	Cardiovascular disorders: arrhythmia, angina
Anemia	Endocrine disorders: diabetes mellitus, hypothyroidism, hyperthyroidism
Anorexia	Musculoskeletal disorders: arthritis
Arthralgia	Reproductive system disorders: amenorrhea, impotence
Depression	Other: vision disturbances
Dermatitis	
Diarrhea	
Fatigue	
Fevers	
Headache	
Insomnia	
Irritability	
Myalgia	
Nausea	
Neutropenia	
Rigors	
Thrombocytopenia	

Treatment Duration for Hepatitis C

Patients with genotype 1 should be treated with PEG-INF and ribavirin (1 g if patient weighs 75 kg or less and 1.2 g if patient weighs more than 75 kg) for 48 weeks (Figure 1-5), whereas patients with genotype 2 or 3 should be treated with PEG-INF and ribavirin 800 mg for 24 weeks (Figure 1-6). In most cases where patients have compensated liver disease, SVR is achieved in 75–85% of those with non-genotype 1 disease. However, patients infected with genotype 1 have an SVR between 45% and 55%. One factor that determines the likelihood of SVR is early virological response, defined as an undetectable HCV RNA concentration or a 2 log₁₀ drop. An estimated 60–80% of the patients achieving an early virological response have a 50–60% chance of an SVR. This response is true for other subgroups. For example, about 40% of the coinfecting HIV patients achieving an early virological response at week 12 had SVR rates of 51% compared to an SVR of 0% if there was no early response. Adherence to therapy is extremely important in achieving an SVR. However, the therapy for hepatitis C is not tolerated well, as up to 75% of the patients may either have dosage reductions or therapy discontinued because of adverse events.

Side Effects Associated with HCV Therapy and Management. There are several side effects associated with treating hepatitis C (Table 1-10). The overall rate of discontinuing therapy ranges between 10% and 20%. Dose reductions associated with either drug usually range from 25% to 35%. The side effect profile is quite comparable for both PEG-INF formulations (Table 1-9).

Flu-like Symptoms. Almost all patients treated with any IFN formulation will experience mild to moderate flu-like symptoms (fevers, chills, rigors, myalgias, arthralgias, and fatigue) and some will have headaches. Temperatures up to 104°F are not uncommon. These initial symptoms usually subside with continued therapy, and diminish by the second

to fourth IFN dose. Administering antipyretic drugs (acetaminophen and nonsteroidal anti-inflammatory drugs) before the IFN injection is effective in minimizing flu-like symptoms. It is important to ensure adequate hydration, drink at least 64 ounces/day of fluid, and to avoid caffeinated beverages. If symptoms persist, administering either a PEG-IFN or IFN injection before bedtime may be beneficial to decrease the patients’ awareness of the fevers and chills.

Psychological Symptoms. Cases of psychiatric adverse effects have been reported with IFN treatment. The most common adverse effects include depression and irritability and rarely suicidal ideations have occurred. An estimated 30–60% of patients may have pretreatment depression. Interferon-induced depression occurs in about 20–35% of patients who have no psychiatric history before starting HCV therapy. Patients complaining of depression describe it as slow thinking, fatigue, decreased attention or increased restlessness, and in some cases hopelessness, sadness, and anger. Less than 2% of patients have suicidal ideation. The risk versus benefit for hepatitis C treatment must be weighed, especially in patients with a history of or uncontrolled neuropsychiatric disorders, as treatment may exacerbate or worsen their psychiatric illness. The mechanism by which IFN induces depression and irritability is still in question, but it is thought to be associated with the depletion of serotonin stores. For this reason, it would not be unreasonable to initiate an antidepressant drug, such as a selective serotonin reuptake inhibitor. Mood stabilizers and anxiolytic drugs often are useful adjuncts to address irritability and insomnia. In several open-label trials, 80–85% of patients with HCV who were treated with IFN developed depression and were treated with a selective serotonin reuptake inhibitor, allowing them to complete therapy. Patients with preexisting neuropsychiatric disorders can be considered for prophylactic therapy with an antidepressant drug before initiating IFN. Pretreatment with antidepressant drugs has proven effective in patients treated with high doses of IFN for malignant melanoma.

Hematological Adverse Effects. About 10–20% of the patients treated with IFN with or without ribavirin will develop hematological abnormalities, including neutropenia, thrombocytopenia, and/or anemia. In most cases, dosage reduction and discontinuation of therapy are required, but when this occurs, the response to viral clearance decreases. Adherence to treatment is significant in increasing SVR. Thus, with the advent of adjunctive therapy, achieving an SVR may be a possibility.

Anemia. The primary toxicity associated with ribavirin is a dose-dependent hemolytic anemia that usually resolves within 7–8 weeks after drug discontinuation. The mechanism by which this side effect occurs is red blood cell uptake of ribavirin and transformation into ribavirin triphosphate. This formation in the red blood cells depletes intracellular adenosine triphosphate that normally acts as an antioxidant. Thus, with the depletion of adenosine triphosphate, the antioxidant defense mechanism is impaired, causing oxidative membrane damage to the red blood cells and leading to premature extravascular red blood cell destruction by the reticular endothelial system. In

Musselman DL, Lawson DH, Gumnick JF, et al. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med* 2001;344:961–6.

addition, IFN also may play a minor role in producing anemia by bone marrow suppression of erythroprogenitor cells. Therefore, it is believed that ribavirin and IFN cause a “mixed” anemia. In most cases, hemoglobin drops between 2.9 g/dl and 3.7 g/dl within 4 weeks of treatment initiation. A decrease in hemoglobin concentrations to less than 10 g/dl is seen in about 10–15% of the patients taking PEG-IFN and ribavirin. Dosage reductions are more commonly required in women than men. A decrease in hemoglobin by more than 3 g/dl from baseline is observed in at least 50% of the patients treated. About 10–25% of the patients will require dosage reductions when hemoglobin concentrations are low and 5–26% of the patients require all therapies to be discontinued because of intolerable symptoms associated with anemia.

Hemoglobin and hematocrit concentrations should be monitored after initiating therapy at weeks 2 and 4 as these concentrations usually decrease within the first 1–2 weeks of treatment. Thereafter, these concentrations can be monitored on a monthly basis if results are clinically stable. Laboratory monitoring is imperative, especially in patients with a history of cardiac disease, and appropriate screening for cardiac abnormalities should be done before beginning treatment.

According to the manufacturer’s package labeling, for patients with no history of cardiac disease, the ribavirin dose should be decreased by 200 mg/day if the hemoglobin concentration is less than 10 g/dl and therapy should be discontinued if levels decrease below 8.5 g/dl. In patients with preexisting and stable cardiac disease and a 2 g/dl drop in hemoglobin in any 4-week period, the ribavirin dose should be decreased by 200 mg/day and the IFN dose should be reduced by 50%. In addition, individuals with preexisting and stable cardiac disease, all therapies should be discontinued if the hemoglobin concentration is less than 12 g/dl. When dosage reductions are done, the efficacy of treatment decreases significantly.

Another option for managing anemia is the use of recombinant human erythropoietin. Erythropoietin doses of 40,000 IU/week administered subcutaneously should be considered when hemoglobin concentrations decrease below 12 g/dl or by 3 g/dl from baseline, or symptoms of anemia (e.g., dyspnea on exertion and fatigue) are present. Erythropoietin is effective in maintaining initial ribavirin doses, improving quality of life, and increasing hemoglobin concentrations during the course of therapy. A mean increase of 2.2–2.8 g/dl in hemoglobin concentrations has been observed in patients supplemented with erythropoietin during IFN and ribavirin treatment. More important, 88% of the patients treated with erythropoietin were able to maintain the initial ribavirin dose compared to only 60% who did not receive adjunctive therapy. At this point, it can be speculated that adding erythropoietin in certain patients may enhance adherence rates, yet it is unknown whether this will translate into an improved SVR. Ongoing studies will answer this important question.

Neutropenia. Neutropenia is another common hematologic abnormality associated with IFN with an even more pronounced effect with PEG-IFN. The decrease in white blood cell count is a reversible phenomenon with treatment discontinuation. White blood cell counts rapidly decrease within the first 2 weeks of therapy and usually stabilize by week 4. Neutropenia is defined as an absolute neutrophil count of less than 1000 cells/mm³. The decrease in neutrophil counts is thought to be associated with IFN-stimulating cytokines which promote the migration of the white blood cells into the peripheral vascular space. Roughly 50% of patients will experience either a grade 3 or 4 neutropenia (more than 0.5 to less than 1.0 x 10⁹/L neutrophils and 0.5 or less x 10⁹/L neutrophils, respectively) with PEG-IFN compared to 25% with IFN. In extreme cases, an absolute neutrophil count of less than 500 cells/mm³ has been observed in 5% and 1% of the patients treated with PEG-IFN and IFN, respectively.

White blood cell counts should be monitored with a differential before initiating therapy and at weeks 2 and 4. Specifically, the absolute neutrophil counts (multiplying the white blood cell count by the percentage of bands and segmented neutrophils) should be monitored. According to the manufacturer’s package labeling, the IFN dose should be decreased by 50% if the absolute neutrophil count is less than 750 cells/mm³ and therapy discontinued if the absolute neutrophil count is less than 500 cells/mm³. However, similar to dosage reduction associated with anemia induced by HCV therapy, treatment response can be altered when the IFN dose is decreased. Thus, managing this adverse effect can include the initiation of granulocyte colony-stimulating factor. Granulocyte colony-stimulating factor given at 300 mcg 1–3 times/week can be effective in increasing absolute neutrophil count concentrations when levels decrease below 750 cells/mm³. The most common side effects associated with granulocyte colony-stimulating factor are bone pain, myalgias, and skin rashes. At present, small clinical trials have shown that granulocyte colony-stimulating factor increases white blood cell counts; however, larger trials are needed to confirm these results. If this is confirmed, then adjunctive therapy using this growth factor can promote adherence and possibly increase the SVR.

Thrombocytopenia. Thrombocytopenia is an adverse effect related to IFN associated with bone marrow suppression. In addition, patients with an underlying liver disease such as cirrhosis may already have a low platelet count before therapy. Individuals treated with IFN may have a 25–30% decrease in platelet count, which usually occurs within the first 8 weeks of treatment and slowly stabilizes thereafter. Dosage reductions because of thrombocytopenia are rare, occurring in less than 3% of patients. Bleeding occurs infrequently in patients with platelet counts less than 50,000 cells/mm³. Similar to the monitoring guidelines for hemoglobin and white blood cells, platelet counts should be evaluated before starting therapy, at weeks 2 and 4, and then every 4 weeks thereafter if the platelet count is stable. According to the manufacturing package label for either

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formulation of IFN- α 2b, the dose should be reduced when platelet counts are less than 80,000 cells/mm³ and discontinued when less than 50,000 cells/mm³. The threshold is lower for IFN- α 2a, where the dose should be reduced when platelet counts are less than 50,000 cells/mm³ and discontinued if less than 25,000 cells/mm³. Nevertheless, IFN can induce severe thrombocytopenia in a patient with established cirrhosis. In most cases, the IFN dose should be reduced; however, this may not be an option in patients who are in need of treatment to prevent the complications associated with liver disease. Pilot trials using oprelvekin, a recombinant human interleukin-11 for treating thrombocytopenia in patients undergoing chemotherapy, have been evaluated for IFN-induced thrombocytopenia. Oprelvekin 50 mcg/kg 3 times/week improved platelet counts in patients who were treated with IFN and ribavirin. The improvement in platelet counts with oprelvekin must be weighed against some serious adverse effects (e.g., pulmonary edema, papilledema, cardiovascular events, and electrolyte abnormalities) compared to the infrequency of severe thrombocytopenia due to IFN.

Other Adverse Effects. There are several uncommon adverse effects that can occur with IFN, PEG-IFN, or ribavirin treatment. If side effects do occur, HCV therapy may need to be discontinued. Therefore, patients should be screened for any of these disorders before initiating therapy as treatment may exacerbate or worsen these medical conditions (Table 1-10).

Contraindications and Warnings. Ribavirin is documented to cause significant teratogenic and embryocidal effects and is pregnancy category X. Animal trials have shown that ribavirin causes malformation of the eye, jaw, limbs, palate, skeleton, skull, and gastrointestinal tract. Therefore, precaution must be taken to prevent pregnancy. Women of childbearing age and men with female partners should use two forms of contraception during therapy and 6 months after therapy.

Ribavirin should not be used in patients with renal insufficiency, especially if the creatinine clearance is less than 50 ml/minute. Patients with uncontrolled endocrine disorders (e.g., diabetes or thyroid disease), ophthalmic conditions, and cardiac disturbances must first have the disease stabilized before starting HCV therapy.

Role of the Pharmacist in Treating Chronic Hepatitis C

Pharmacists can play a significant role in preventing hepatitis C infection and treating patients who are infected with HCV. Pharmacists can identify and educate patients who are at high risk for acquiring the infection and recommend screening. For patients infected with hepatitis C, pharmacists should encourage abstaining from alcohol use and hepatotoxic drugs (e.g., dietary supplements or over-the-counter drugs). In addition, they can recommend vaccination against hepatitis A and B for those who are not already immunized. Pharmacists can educate patients on proper injection techniques for PEG-IFN and appropriate disposal of used needles. Because the combination treatment has a significant adverse effect profile, pharmacists can discuss this with patients before initiating

treatment so they are fully aware of the possible complications that can arise during therapy. One topic of importance for both men and women is preventing pregnancies during treatment and 6 months after treatment with ribavirin as it is pregnancy category X. More important, pharmacists may have a significant impact in encouraging adherence as trials have shown noncompliance decreases the SVR.

Investigational Drugs for Chronic Hepatitis C

The highest overall SVR rate is about 50–60% for the treatments available for HCV, which is far from perfect. In addition, the drugs used for hepatitis C have significant adverse effects profiles, and in most cases require dosage reductions or discontinuations. Currently, several drugs are in clinical trials for HCV treatment.

Viramidine

Viramidine is a prodrug that is converted by adenosine deaminase *in vivo* to the active component, ribavirin. This investigational drug is associated with less erythrocyte uptake, thus causing less hematological toxicity. In addition, it has at least a 3-fold increased duration within the hepatic cells, which could result in better outcomes. Preliminary studies comparing viramidine to ribavirin indicate similar HCV RNA level response. In a dose-ranging study, five treatment arms consisting of either viramidine 800 mg/day, 1200 mg/day, or 1600 mg/day were compared to ribavirin 1000 mg/day or 1200 mg/day in combination with PEG-IFN- α 2a. In both groups, 83% had either undetectable HCV RNA levels or a 2 log₁₀ drop at week 24 of therapy. A drop in hemoglobin concentrations of 2.5 g/dl or more or to less than 10 g/dl during 24 weeks of treatment was significantly more common with ribavirin (82%) than with any of the viramidine regimens (ranging between 45% and 67%). This drug is in Phase III clinical trials and may potentially be as effective as current therapies for treating hepatitis C with fewer hematological adverse effects.

Merimepodib

Merimepodib (VX-497) is a selective inhibitor of inosine monophosphate dehydrogenase, an enzyme that decreases DNA and RNA replication by regulating and decreasing the production of intracellular guanosine triphosphate. Merimepodib exhibits potent antiviral effects, including activity against HCV. In a Phase IIa trial, 31 patients with genotype 1 whose disease did not respond to IFN and ribavirin were randomized to either one of the treatment arms: PEG-IFN- α 2a 1.5 mcg/kg/week plus ribavirin 1000–1200 mg/day plus placebo; PEG-IFN- α 2a 1.5 mcg/kg/week plus ribavirin 1000–1200 mg/day plus merimepodib 25 mg 2 times/day; or PEG-IFN- α 2a 1.5 mcg/kg/week plus ribavirin 1000–1200 mg/day plus merimepodib 50 mg 2 times/day. Hepatitis C virus RNA levels were obtained at week 24, revealing an 86% undetectable viral load in those receiving merimepodib 50 mg 2 times/day compared to about 33% in both treatment arms receiving either 25 mg of merimepodib or placebo. Currently, patients are being recruited for a Phase IIb clinical trial with merimepodib for HCV.

Thymosin Alpha 1

Thymosin alpha 1 (Thymosin) is a synthetic, nonglycosylated, 28 amino acid peptide that acts as an immunomodulator by stimulating type 1 helper T-cell and natural killer cell production. In addition, it stimulates the activity of IFN- γ , interleukin-2, and interleukin-3. In a recent trial, patients naïve to treatment were randomized to receive either thymosin alpha 1 900 mcg/m² subcutaneously 2 times/week with IFN- α 3 mU 3 times/week or IFN alone. Patients were treated for 6 months with a 6-month follow-up period. There was a significant end of treatment response difference in the thymosin alpha 1 group (41%) compared to the monotherapy (10.5%). However, for the primary end point, SVR, there was no difference, 9% versus 16%, respectively. Thymosin is well tolerated with minimal side effects, with the primary complaint being injection site reactions. Phase III clinical trials with thymosin alpha 1 and PEG-IFN currently are being conducted.

Therapeutic Vaccine

The most effective therapy for treating hepatitis C includes PEG-IFN and ribavirin. However, not all patients respond to treatment. It has been theorized that therapeutic vaccines can enhance the immune response and possibly treat the disease rather than prevent it. The first hepatitis C therapeutic vaccine developed is a 135 amino acid recombinant HCV E1 protein derived from the HCV genotype 1b strain. In a Phase II trial, 35 patients infected with HCV genotype 1 who were either treatment naïve or had been treated with 6 months of IFN received either the HCV E1 vaccine 20 mcg at weeks 0, 4, 8, 12, and 24 or placebo. They were followed for up to 48 weeks and later all were enrolled in an open-label trial where the vaccine was given every 3 weeks from weeks 50–65 with follow-up visits at weeks 69 and 73. Results indicate that those treated with the vaccine had a 23% decrease in ALT concentrations with no change observed in the placebo group, and neither group showed an effect on HCV RNA concentrations. Of the patients who received the vaccine, 88% had a T-cell proliferation response. Liver biopsy scores obtained before and after vaccinations had improved in 38% of treated patients. There was no change or the histological score worsened in 41% and 21%, respectively. The most common side effects associated with the vaccine were flu-like symptoms and headaches. Currently, a Phase IIb European, multicenter, placebo-controlled study of 150 patients with HCV genotype 1 is under way to confirm results that were earlier reported.

Hepatitis D

Virology and Pathogenesis

Hepatitis D, also known as delta hepatitis, is a defective single-stranded RNA virus that depends on the presence of HBV to replicate. This 35–37 nm spherical particle is a member of the genus *Deltavirus* of the Deltaviridae family that was first described in 1977 and cloned and sequenced by 1986. The HDV virion is made up of a circular RNA and HDV Ag that is coated by HBsAg of HBV. There are three major genotypes associated with HDV that are

geographically specific. Genotype 1 can be classified into 1a, which primarily affects patients in the United States, or 1b, which affects the Asian population. Both 1a and 1b are equally represented in the Mediterranean Basin. Genotype 2 is found mostly in individuals residing in Japan and Taiwan. Patients in South America, specifically Columbia, Venezuela, and Peru, are mostly infected with genotype 3. The HDV causes hepatic damage; however, the mechanism of action of the toxicity is still under investigation. The replication of HDV cannot occur without HBV DNA being present causing either coinfections (HBV and HDV occur simultaneously) or superinfections (HDV superimposes HBV).

Epidemiology

The primary transmission mode for HDV is identical to hepatitis B, as the only way an individual can be infected with hepatitis D is if they are already infected with HBV. Therefore, percutaneous exposure routes are the most likely mode of transmitting the virus. Sexual transmission and perinatal transmission are rare for HDV. About 5% of hepatitis B carriers are coinfecting with HDV. Thus, 15 million individuals are infected with HDV. Of interest, HDV infection is uncommon in Southeast Asia and China where HBV has the highest prevalence. Areas with the highest prevalence are in southern Italy and parts of Russia and Romania. Northern Italy, Spain, Turkey, and Egypt have a moderate prevalence of HDV, 30–50%, among those with CHB. In rare incidences, hepatitis D epidemics have occurred in CHB carriers, especially in some South American countries, causing fulminant hepatitis and death.

Diagnosis, Clinical Course, and Clinical Manifestation

To diagnose patients with hepatitis D, it is important to confirm that they also are infected with hepatitis B (see Hepatitis B Serology section). The most accurate method of confirming infection is by measuring HDV RNA levels in the serum by PCR. The presence of IgM anti-HDV Ag indicates active disease. It becomes a chronic infection if the disease persists and IgG anti-HDV becomes detectable. Unlike the antibodies developed in hepatitis A, these antibodies do not confer immunity.

The two clinical courses for hepatitis D are coinfections and superinfections. A coinfection is defined when both hepatitis B and hepatitis D infections occur simultaneously. In most cases, IgM and IgG anti-HDV are present along with HBV DNA and HDV RNA. Yet, about 15% of patients only have evidence of HDV either by detectable IgM anti-HDV in the preclinical phase or IgG anti-HDV during the convalescence period. When infection resolves, anti-HDV levels may still either be positive or negative, making it difficult to determine if patients were ever infected with HDV. Hepatitis D antigen can be detected in serum in about 25% of patients with a coinfection. Eventually, HDVAg is lost with the disappearance of HBsAg, indicating no development of a chronic infection. Symptom onset is severe with biphasic elevations of ALT concentrations. The first increase in ALT concentrations usually is associated with HBV followed by an increase due to HDV a few weeks later. The risk of fulminant hepatitis

ranges from 2% to 20%, which is much higher than when infected with HBV alone. The development of a chronic HBV infection occurs less often in patients infected with both HBV and HDV concurrently.

A superinfection is defined as acquiring HDV after having long-standing disease with HBV. Unlike coinfections, which do not lead to chronic disease, more than 90% of superinfections progress to chronic hepatic disease with 70–80% of patients developing cirrhosis. Serologically, HBsAg titers decline when HDVAg appears. In addition, HDVAg and HDV RNA levels remain detectable and finally, IgM and IgG anti-HDV become detectable, and persist indefinitely. In contrast to coinfections, superinfections rarely progress to fulminant hepatitis. These patients have a similar clinical picture as those infected with acute hepatitis B.

Managing Hepatitis D Prevention

Because hepatitis D replication primarily depends on the presence of HBV in the host, the most effective method of preventing hepatitis D is immunizing individuals against hepatitis B (see the Hepatitis B Vaccine section). There is no specific vaccine available for HDV.

Treating Hepatitis D

The only effective therapy for hepatitis D infection is IFN. Antiviral therapies, including acyclovir, famciclovir, and lamivudine, have little benefit in treating HDV. A meta-analysis of five randomized, controlled trials reviewed the effectiveness of IFN for treating hepatitis D. Patients received either IFN- α 2a, α 2b, α 2c, or lymphoblastoid IFN- α with a dose ranging from 3 mU/m² to 9 mU/m² administered 3 times/week with a treatment duration spanning 3–12 months. Results indicate that 18.4% of patients had a complete response defined as improvement of quality of life, normal ALT concentrations, loss of HDV, and a decrease in hepatic progression to cirrhosis for at least 12 months after therapy was ceased. In another trial using induction doses of 5 mU/m² 3 times/week for 4 months followed by 3 mU/m² for an additional 8 months, 25% (eight of 31 patients) had normalized ALT at the end of treatment; however, only one patient was able to sustain a biochemical response. The most effective treatment used is IFN 9 mU 3 times/week. Normalization of ALT concentrations occurred in 71% of patients who were treated for 48 weeks. In a recently published trial, patients were treated with IFN 9 mU, IFN 3 mU, or placebo 3 times/week for 48 weeks and were followed for up to 14 years after therapy. Results indicated that 58.3% of the patients treated with 9 mU (seven of 12) were still alive and continued to have normal ALT concentrations compared to 50% (two of four) who received 3 mU. Yet, when the therapy was discontinued, only 36% sustained biochemical response. Therefore, it is recommended to treat patients with IFN 5–9

mU 3 times/week or 5 mU/day for at least 12 months after ALT concentrations have normalized. In some patients, biochemical response may not occur until 10 months after therapy has begun. Treatment should continue for at least 1 year before being deemed a failure. The side effect profile for IFN is similar to that in patients treated for hepatitis C. Liver transplantation may be needed for those with end-stage liver disease associated with HDV.

Hepatitis E

Virology and Pathogenesis

Hepatitis E is a nonenveloped virus that was first discovered in 1983 in a healthy volunteer study requiring volunteers to ingest feces from a patient who was infected with non-A and non-B hepatitis. It was then that hepatitis E was identified as a 27–30 nm in diameter particle and the genome of the virus was cloned in 1990. Hepatitis E virus is a single-stranded messenger RNA virus that is about 7.2 kilobase in length. Hepatitis E virus was initially classified under the family of Caliciviridae, but was removed from the class as sequence analyses suggested the virus to be more related to the Togaviridae family. At this time, HEV is unclassified.

Similar to hepatitis A, hepatitis E is an infection transmitted by the fecal-oral route. Elevated viral concentrations in the bile eventually lead to viremia due to viral shedding in the feces. Hepatitis E virus causes liver damage with the severity dependent on the virus strain. Three strains have been studied in animal models; the Mex 14 strain is the most virulent strain followed by the Sar 55 strain and then the US 2 strain. It still needs to be determined if the severity of the disease is due to genotype or strain characteristics. The disease only produces acute infections and does not progress to a chronic condition.

Epidemiology

Because hepatitis E primarily is transmitted by the fecal-oral route, this virus is more prominent in underdeveloped countries where sanitation is poor and inadequate. Hepatitis E causes more than 50% of the acute hepatitis cases in endemic areas, such as Afghanistan, Bangladesh, Burma, China, India, Indonesia, Kazakhstan, Kyrgyzstan, Malaysia, Mongolia, Nepal, Pakistan, Tajikistan, Turkmenistan, Uzbekistan, Mexico, the Middle East, Northern Africa, and sub-Saharan Africa. These outbreaks occur mostly in young adults and rarely in children. Mortality can be as high as 25% in pregnant women who develop acute infections. Rarely does HEV cause endemics in industrialized countries where the seroprevalence is 1–5%. Sporadic cases have been documented in the United States, Europe, Australia, and South America. In these cases, HEV usually occurs in people who have traveled to or lived in an endemic area. To

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determine the prevalence of hepatitis E in developed countries, researchers collected sewage samples from Spain, France, Greece, Sweden, and the United States. Hepatitis E virus strains were found in Barcelona, Spain; Nancy, France; and Washington, D.C.

Diagnosis, Clinical Course, and Clinical Manifestation

The diagnosis of hepatitis E is done by detecting anti-HEV. During acute infections, IgM anti-HEV appears and persists for up to 5 months. Shortly after acquiring the infection, the patient develops IgG anti-HEV, which may remain for several years and which indicates immunity against hepatitis E.

The incubation period may range from 15 to 60 days, with an average of 40 days. In most cases, patients are asymptomatic. When symptoms occur, they include fevers, fatigue, nausea, vomiting, abdominal pain, and diarrhea with or without dark urine and pale looking stools. Hepatitis E often is a self-limiting disease similar to hepatitis A, lasting up to 4 weeks. A minority of patients may have persistent jaundice and pruritus that can last up to 6 months due to cholestatic hepatitis. Fulminant hepatitis associated with hepatitis E occurs in a small proportion of patients with a mortality rate of 0.5–4%.

Managing Hepatitis E

Treating acute hepatitis E is similar to that of other hepatitis infections, which includes supportive care. Because the infection primarily is spread by the fecal-oral route, good personal hygiene is needed. Individuals traveling to endemic areas should drink bottled water and avoid uncooked vegetables and shellfish and unpeeled fruits.

Currently, a recombinant hepatitis E vaccine is undergoing a Phase II/III efficacy trial in the Katmandu Valley of Nepal. Results from the preclinical study showed that the vaccine was highly effective in preventing hepatitis E. More clinical studies are needed to confirm these exciting results.

Conclusion

Viral hepatitis, specifically HBV and HCV, is a major cause of end-stage liver disease and HCC. In most cases, liver transplantation is needed to treat and sustain life. Because blood products have been actively screened for these diseases, the incidence of chronic hepatitis has decreased significantly. However, many individuals are still at risk for viral hepatitis. Thus, it is important to educate the public on the importance of preventing infection by encouraging vaccinations against HAV and HBV. In addition, newer and more effective treatment options are available for patients infected with chronic HBV and HCV. Pharmacists can play a significant role in identifying, educating, and preventing infections. In addition, pharmacists can participate in the care of patients infected with chronic hepatitis by providing initial and ongoing support regarding therapy. Pharmacists can educate patients about the potential adverse effects associated with treatment and encourage them to remain adherent to their regimen.

Annotated Bibliography

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These updated guidelines, approved by the American Association for the Study of Liver Diseases, represent the position of the association for treating hepatitis B. Recommendations for treating children with hepatitis B infection also are included. The use of interferon (IFN) for chronic hepatitis B (CHB) is reviewed. The guidelines summarize the recently published literature for lamivudine and adefovir dipivoxil and provide recommendations for treating hepatitis B e antigen (HBeAg)-positive and HBeAg-negative patients. Patients who are not candidates for hepatitis B treatment also are discussed. The guidelines do not include drugs that currently are being investigated in clinical trials.

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These are the American Association for the Study of Liver Diseases, the Infectious Diseases Society of America, and the American College of Gastroenterology recommendations for diagnosing, managing, and treating hepatitis C. The paper summarizes pivotal trials for treating hepatitis C virus (HCV) for treatment-naïve patients as well as nonresponders and relapsers. Hepatitis C treatment for special populations, including patients with normal alanine aminotransferase (ALT); children; patients with human immunodeficiency virus (HIV), renal disease, decompensated cirrhosis, and acute infections; injection drug users; and patients who have had solid organ transplantation, are discussed. The paper does not discuss managing adverse drugs associated with hepatitis C infection treatment.

3. Afdhal NH, Dieterich DT, Pockros PJ, et al; Proactive Study Group. Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized, controlled study. *Gastroenterology* 2004;126:1302–11.

This trial evaluated whether epoetin 40,000 units/week subcutaneously could increase hemoglobin concentrations in patients developing anemia due to ribavirin and increase their quality of life while receiving HCV therapy. Enrolled were 185 patients who received IFN and weight-based dosing of ribavirin for HCV. Epoetin weekly or placebo for 8 weeks was initiated if hemoglobin concentrations reached less than 12 g/dl in the first double-blind, placebo-controlled, parallel-group phase, followed by the second 8-week open-label, modified, crossover phase. Results indicated that at the end of the double-blind phase, 88% of the patients receiving epoetin were able to maintain the ribavirin dose that was initiated at the beginning of therapy in contrast to 60% who received placebo ($p < 0.001$). In addition, mean hemoglobin concentrations also increased in the epoetin arm by 2.2 ± 1.3 g/dl and only 0.1 ± 1.0 g/dl in the placebo arm ($p < 0.001$). These results are significant as one of the factors limiting treatment response is dosage reduction or discontinuation because of side effects associated with ribavirin (e.g., shortness of breath, fatigue, or a significant decrease in hemoglobin concentrations). Thus, the use of epoetin is able

to not only maintain hemoglobin concentrations but also improve all domains of the Linear Analog Scale Assessment for the quality of life evaluation. At this point, it can be speculated that adding epoetin may enhance adherence rates, yet it is unknown whether this will translate into improving sustained virological response (SVR) until ongoing studies are completed.

compliance with hepatitis C drugs, thereby increasing SVR rates.

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This article discusses the results of the AIDS Pegasys Ribavirin International Coinfection Trial. This first international, randomized, placebo-controlled trial enrolled 868 treatment-naïve patients into one of the treatment arms: 1) pegylated interferon (PEG-IFN)- α 2a 180 mcg/week plus ribavirin 400 mg 2 times/day, 2) PEG-IFN- α 2a 180 mcg/week plus placebo, or 3) IFN- α 2a 3 mIU 3 times/week plus ribavirin 400 mg 2 times/day. Treatment duration was for 48 weeks with a 24-week follow-up after treatment. All patients were HCV-positive, had a CD4⁺ count greater than 100 cells/mm³, and had compensated liver disease with stable HIV disease with or without highly active antiretroviral therapy. The overall SVR rate was 40% for those treated with PEG-IFN- α 2a and ribavirin compared to 12% receiving only IFN- α 2a ($p < 0.001$). The difference in SVR with PEG-IFN- α 2a and ribavirin also was statistically significant compared to PEG-IFN monotherapy (20% SVR; $p < 0.001$). When these results were stratified according to genotype, 62% of patients with HCV genotype 2 or 3 achieved SVR when treated with PEG-IFN combination therapy compared to 36% for PEG-IFN alone and 20% with IFN with ribavirin. Sustained virological response among genotype 1 patients was less significant; however, those treated with PEG-IFN combination therapy were more likely to achieve SVR (29%) than those receiving IFN with ribavirin (7%). The low SVR may be accounted for by the low ribavirin dose. As other trials have shown, ribavirin doses of 1 g/day or 1.2 g/day are required to increase SVR in genotype 1 disease. This is a landmark study of patients coinfecting with HCV and HIV, concluding that PEG-IFN- α 2a plus ribavirin is safe and effective against hepatitis C.

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This significant paper indicates that adherence to therapy for hepatitis C can increase SVR. Patients evaluated received IFN- α 2b plus ribavirin or PEG-IFN- α 2b plus ribavirin. Adherence was defined as receiving greater than 80% of the total IFN or PEG-IFN dose and greater than 80% of the ribavirin dose for more than 80% of the expected therapy duration. Patients adherent to IFN and ribavirin had an overall SVR rate of 52% compared to 44% in those who were noncompliant ($p < 0.0018$). Similar rates were observed for those receiving PEG-IFN and ribavirin in that adherence to therapy led to a 63% SVR in contrast to only 54% who had not taken their drugs regularly ($p < 0.01$). These results are even more significant for genotype 1 patients administered the combination PEG-IFN therapy, as they were more likely to have an increased SVR rate ($p = 0.034$). This paper is noteworthy, showing how pharmacists can encourage patient