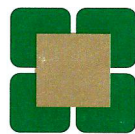


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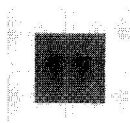


VIRAL HEPATITIS GUIDE FOR PRACTICING PHYSICIANS

SUPPLEMENT 1 TO VOLUME 67, 2000

SPECIAL ISSUE

CLEVELAND
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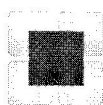
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Acknowledgment

Printed with an unrestricted educational grant from
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The statements and opinions expressed in the *Cleveland Clinic Journal of Medicine* are those of the authors and not necessarily of The Cleveland Clinic Foundation or its Board of Trustees.

The *Cleveland Clinic Journal of Medicine* (ISSN 0891-1150) is published 12 times yearly by The Cleveland Clinic Foundation.

Subscription rates: U.S. and possessions: personal \$90; institutional \$113; single copy/back issue \$13. Foreign: \$113; single copy/back issue \$13. Institutional (mul-

tiplier rate) applies to libraries, schools, hospitals, and federal, commercial, and private institutions and organizations. Individual subscriptions must be in the names of, billed to, and paid by individuals.

Postmaster address changes: *Cleveland Clinic Journal of Medicine*, NA32, 9500 Euclid Avenue, Cleveland, OH 44195. Subscription orders, editorial, reprint, and production offices (same address): Phone (216) 444-2661; Fax (216) 444-9385; E-mail ccjm@ccf.org. World Wide Web address: <http://www.ccjm.org>

Printed in USA.



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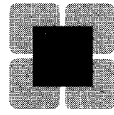
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From the Editor

VIRAL HEPATITIS, both in its acute and chronic form, has evolved into a national and worldwide public health concern. According to recent statistics, as many as 1.25 million people in the United States (US) are infected with hepatitis B, and nearly 4 million test positive for hepatitis C.¹ In the US alone, 700,000 new cases of acute viral hepatitis are reported annually. The disease burden for viral hepatitis is significant. Nearly 300 deaths per year are attributed to fulminant acute disease, and an estimated 15,000 persons succumb each year to chronic infection as a result of chronic liver disease. In fact, viral hepatitis is the leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC) worldwide, and is the principal reason for liver transplantation in adults.

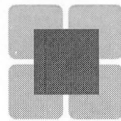
In the last decade, concerns regarding the clinical and economic impact of hepatitis C virus (HCV) are growing. It is estimated that between 8,000 and 10,000 people infected with HCV die each year. In the absence of effective intervention, hepatitis C deaths are expected to nearly triple, to over 22,000 annually, within the next 10 years.² Despite recent advances in treating HCV, less than 50% of patients completing a full course of treatment achieve durable response. Additionally, only the minority of patients with chronic hepatitis C are referred for appropriate treatment or are candi-

dates for interferon-based therapy. With no definitive treatment for hepatitis C, and considering the fact that from 1989 to 1998 the median waiting time for a liver transplant increased from approximately 40 days to 506 days,³ measures for slowing the development of cirrhosis and liver failure are vital.

To address this growing health concern, a steering committee consisting of generalists and of specialists in Gastroenterology, Infectious Disease, and Clinical Virology developed a guide to assist clinicians in preventing, diagnosing, and managing viral hepatitis. This guide was peer reviewed by an expert panel and updated for 2000 to include new information on emerging hepatotropic viruses and new therapies for viral hepatitis.

This guide provides an easy-to-use algorithmic approach to the diagnosis and treatment of viral hepatitis as well as the most in-depth and updated information on the epidemiology, diagnosis, and treatment of viral hepatitis. Special sections have been devoted to the issues of viral hepatitis in transplant, immunosuppressed, and pediatric populations. The ultimate goal of this guide is to provide easily accessible information to both primary care and specialty physicians involved in the care of patients with viral hepatitis.

ZOBAIR M. YOUNOSSEI, MD, MPH, FACP, FACG



Viral hepatitis guide for practicing physicians

ZOBAIR M. YOUNOSSI, MD, MPH, FACP, FACG

EPIDEMIOLOGY AND CLINICAL FEATURES OF HEPATITIS VIRUSES

Hepatitis A

Epidemiology. Hepatitis A is a disease with worldwide distribution;^{4,5} its principal mode of transmission is via food or water contaminated with fecal material, or from person to person. The NHANES II survey reported that 38% of the population in the US showed antibodies to the hepatitis A virus (HAV). Approximately 23,000 cases of hepatitis A

were reported in 1992, with 6% of these in travelers.^{6,7} Hepatitis A is the third most important foreign travel-associated infection after diarrhea and malaria.^{4,8,9}

The features of all known hepatitis viruses are summarized in **Table 1**.^{10,11}

Clinical features. As summarized in **Table 2**, parenteral transmission of HAV can occur but is relatively rare due to the short period of viremia during the illness. There is no evidence of vertical transmission from mother to baby.^{5,12} Hepatitis A virus viremia is relatively brief; the incubation period is

ABBREVIATIONS

ACIP: Advisory Committee on Immunization Practices

ACOG: American College of Obstetricians and Gynecologists

AFP: alpha fetoprotein

ALT: alanine aminotransferase

bdNA: branched-chain DNA

CDC: Centers for Disease Control and Prevention

EIA: enzyme immunoassay

ELISA: enzyme-linked immunosorbent assay

ETR: end-of-treatment response

FDA: US Food and Drug Administration

FHF: fulminant hepatic failure

GBV-C: hepatitis G virus

HAART: highly active antiretroviral therapy

HAV: hepatitis A virus

HBcAg: hepatitis B core antigen

HBsAg: hepatitis B surface antigen

HBIG: hepatitis B immune globulin

HBsAg: hepatitis B surface antigen

HBV: hepatitis B virus

HCC: hepatocellular carcinoma

HCV: hepatitis C virus

HDV: hepatitis D virus

HELLP: hemolysis, elevated liver enzymes, and low platelet count

HEV: hepatitis E virus

HIV: human immunodeficiency virus

Ig: immunoglobulin

IU: International Units

IV: intravenous

MU: million Units

ORF: open reading frame

PCR: polymerase chain reaction

RIA: radioimmunoassay

RIBA: recombinant immunoblot assay

RT: reverse transcriptase

SR: sustained response

TIW: three times weekly

U: Units

US: United States

TABLE 1
FEATURES OF KNOWN HUMAN HEPATITIS VIRUSES

Features	HAV	HBV	HCV	HDV	HEV
Virion structure*	28 nm No envelope	42 nm Enveloped	38–50 nm Enveloped	43 nm Enveloped	32 nm No envelope
Genome size and nature*	7.5 kb RNA ss, pos	3.2 kb DNA Partial ds	9.4 kb RNA ss, pos	1.7 kb RNA ss, neg	7.8 kb RNA ss, pos
Incubation period†	15–60 days	45–160 days	14–180 days	42–180 days	15–60 days
Clinical severity†	Mild	Occasionally severe	Mild	Occasionally severe	Mild
Fulminant disease†	0.1%	1.0%	< 0.1%	5%–20%	1%–2%
Progression to chronic viremia	No	Yes	Yes	Yes	No
Progression to chronic liver disease	No	Yes	Yes	Yes	No

HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; HEV = hepatitis E virus; ss = single-stranded; pos = positive-sense; ds = double-stranded; neg = negative-sense.

*Data from Versalovic C.¹⁰

†Data from Dienstag IL, Isselbacher KJ.¹¹

typically 15 to 60 days (mean, 30 days) after exposure, with maximal infectivity occurring prior to clinical symptoms. Treatment of HAV infection is primarily symptomatic and the disease is usually self-limiting. Severity of HAV infection can vary with age of the patient. In children hepatitis A is usually asymptomatic, whereas in adults symptomatic infection is characteristic and jaundice common.^{13,14} Fulminant hepatitis A is rare and is also age-dependent, occurring more frequently in older patients.

The onset of hepatitis A is often abrupt, and characteristic prodromal symptoms of anorexia, nausea, fatigue, and others are followed, within a few days to a week, by dark urine and jaundice. Mild-to-moderate tenderness over an enlarged liver is usually detected. Serum alanine aminotransferase (ALT) and aspartate aminotransferase levels usually both rise rapidly during the prodromal period, whereas serum bilirubin concentrations reach peak levels later and decline less rapidly than serum aminotransferases. In approximately 85% of cases, the duration of jaundice persists less than 2 weeks.¹³ The majority of adults having clinically apparent disease will recover, with restoration of normal serum bilirubin and aminotransferase values within 6 months. Antibodies of the immunoglobulin (Ig)M class can be detected during the acute illness phase but decline after 6 months; during recovery IgG antibodies to HAV develop and persist indefinitely.

The presence of anti-HAV IgG antibodies confers immunity to reinfection. Relapses and prolonged cholestasis are rare. Hepatitis A is an acute infection; no chronic form of HAV exists. Recovery usually occurs in 1 to 2 months.^{4,5,15} The case fatality rate for HAV is 0.35% overall, but may rise to 2.5% in older adults.⁷

Hepatitis B

Epidemiology. Between 1988 and 1994 (NHANES III), the prevalence of serologic markers of HBV infection was 4.9%, while the prevalence of chronic HBV infection was 0.4%. In the past 2 decades, the actual rate of HBV infection in the US is estimated at approximately 300,000 cases per year.^{16,17} Since 1987, the actual incidence of HBV has declined by 70%. Approximately 200 to 300 deaths occur annually due to hepatitis B.^{6,18,19} Infection occurs primarily in young adults because of lifestyle or occupational exposure.¹⁷ A recent report of a large-scale screening program for viral hepatitis revealed that the prevalence of infection with the hepatitis B virus (HBV) in the sampled cohort was 17.8%, with hepatitis B disease present in 0.7% of the overall US population.²⁰

Hepatitis B virus is a small, double-stranded member of the Hepadnaviridae family of hepatotropic DNA viruses (Table 1).^{10,11} Hepatitis B virus replicates in hepatocytes but is secreted and

TABLE 2
MODES OF TRANSMISSION AND PREVENTION

Virus	Transmission	Incubation period	Prevention
HAV	Fecal/oral from food and water Parenteral (relatively rare)	15–60 days	Immunization Sanitation with clean water and separate waste disposal Hand washing Cooking food Peeling vegetables and fruits
HBV	Parenteral and injection drug use Sexual contact Perinatal Transfusion-associated (rare)	45–160 days	Immunization Protection against exposure to body fluids (including blood) Safe sexual practices including use of condoms Adherence of healthcare professionals to practices of universal precautions
HCV	Parenteral and injection drug use Transfusion-associated (rare) Sexual contact	14–180 days	Similar to hepatitis B No vaccine available Universal precautions
HDV	Parenteral Sexual contact Perinatal	Depends on superinfection vs co-infection	Sterilization and disinfection of medical equipment and environmental surfaces Hepatitis B vaccine Universal precautions
HEV	Drinking water in endemic areas Person-to-person transmission rate appears low	15–60 days	Personal hygiene Boil drinking water Avoid eating uncooked food

HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; HEV = hepatitis E virus.

maintained in extrahepatic sites, including blood, saliva, and other body fluids. The virus is transmitted parenterally, by sexual contact, and perinatally. Transfusion-associated HBV has become rare in the US since routine screening of the blood supply has been in place. Risk factors continuing to be associated with HBV infection include hemodialysis, intravenous (IV) drug use, sex with an IV drug user,^{20,21} as well as unsafe injection practices, tattooing, and body piercing.^{22–25} The majority of HBV surface antigen (HBsAg)-positive mothers with active HBV infection (ie, HBV e antigen [HBeAg]-positive) will transmit the disease to their offspring; HBsAg-positive asymptomatic carriers with anti-HBe antibodies (HBeAg-negative) do so less frequently (10% to 15%).^{26–28}

Clinical features. The incubation period following HBV acquisition is 45 to 160 days. After acute infection, the first detectable virologic marker is the envelope protein surface antigen, HBsAg. Detectable serum HBsAg usually precedes elevations in serum transaminases as well as clinical symptoms, and remains detectable during the acute

icteric period and beyond. In most cases the HBsAg becomes undetectable 1 to 2 months following the onset of jaundice, rarely persisting beyond 6 months. After HBsAg disappears, antibody to HBsAg (anti-HBs) appears in serum and remains detectable indefinitely.^{11,29} There may be a lag period (window) between the disappearance of HBsAg and the appearance of anti-HBs, during which time patients with HBV infection may not be identified by routine serologic testing. The HBV core antigen (HBcAg) itself is sequestered inside an HBsAg coat and is not usually detectable in the serum of HBV-infected patients.³⁰ Anti-HBc IgM, however, may be detectable and can be used to identify acute HBV infection during the silent window period.^{28,31}

Clinical symptoms of acute HBV infection are typical of viral hepatitis and include nausea, anorexia, fatigue, and malaise, followed by jaundice. Elevations in serum transaminases precede the onset of jaundice. Approximately 25% of HBV-infected adults manifest an overt illness; however, most have a subclinical infection.^{32,33} Approximately 10% of adults develop a chronic infection manifest-

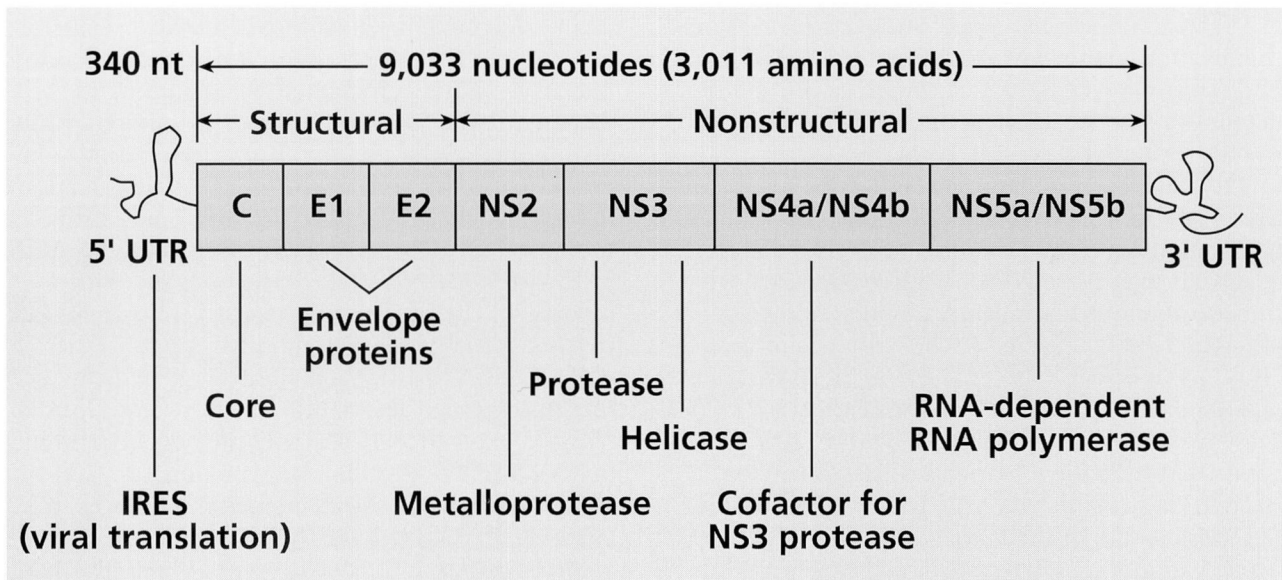


FIGURE 1. Genomic organization of hepatitis C virus. C = core; E = envelope; NS = nonstructural; UTR = untranslated regions; IRES = internal ribosome entry site. Adapted with kind permission from Fang JWS, et al.⁵²

ed by persistence of HBsAg in the serum and in some cases along with production of other viral antigens and HBV DNA.^{34,35}

The risk of becoming a chronic carrier of HBsAg is dependent on the mode of acquisition of infection as well as the age and immune status of the individual at the time of infection.³³ Children infected during the first few months of life almost invariably develop a chronic infection. Patients with chronic HBV infection are generally separated into those who manifest hepatitis with high viral replication (detectable HBeAg and HBV DNA) and abnormal liver histology versus the so-called “healthy carriers” or inactive carrier state who have normal or minimally abnormal liver histology and no symptoms of chronic liver disease, very low viral replication (ie, undetectable HBeAg or HBV DNA by hybridization method), and normal liver blood tests.^{36–38} Healthy carriers rarely transmit the infection to others and usually do not have progressive liver disease.³⁹

For those individuals with high levels of viral replication, chronic hepatitis with progression to cirrhosis, liver failure, and HCC is common.³³ In a recent study, overall mortality for patients with chronic HBV infection was increased several-fold over that of the general population ($P \leq .0001$).⁴⁰ Several variables were useful in predicting improved survival and survival without hepatic decompensation, including young age, absence of cirrhosis at

baseline, and sustained normalization of aminotransferases during follow-up, as well as interferon treatment. Persistent necroinflammatory changes markedly increased the risk of death, whereas specific virologic profiles at presentation were not reliable predictors.⁴⁰

Hepatitis C

Epidemiology. Approximately 3.9 million Americans (1.8% of the population) and over 170 million people worldwide have evidence of HCV infection.¹ Of the 3.9 million Americans infected with HCV, 2.7 million are chronically infected.⁴¹ Because institutionalized individuals were not represented in these surveys, these numbers very likely underestimate the true prevalence of HCV. Minority populations are typically overrepresented among HCV-positive patients, adding to the healthcare burden of populations least likely to have access to adequate and effective medical care. Chronic HCV infection leads to 8,000 to 10,000 deaths annually. The frequency of patients presenting with complications associated with HCV infection is expected to triple within the next 20 years, corresponding to a 61% increase in incidence of cirrhosis, a 68% increase in the incidence of HCC, a 279% increase in decompensated liver disease, and a 528% increase in the demand for liver transplantation.^{42–48}

HCV is a complex, single-stranded RNA virus that belongs to the Flaviviridae family.⁴⁹⁻⁵¹ Although HCV has not yet been cultivated in cell culture, details of its molecular structure have been revealed in recent years (Figure 1).⁵²

The envelope glycoproteins are coded for by the hypervariable region of the HCV genome, and the high mutation rates associated with these protein structures may be responsible for viral escape from the host immune responses. Variability of these protein structures is reflected in the existence of several HCV variants with different geographic distribution and response to therapy.⁵³⁻⁵⁶ At least 6 different HCV genotypes, as well as subtypes within genotypes, have been identified by nucleotide sequencing.⁵⁷⁻⁵⁹ In addition, variants may arise within a host that are not sufficiently distinct to be termed genotypes. These variants are referred to as quasispecies,⁶⁰⁻⁶⁴ the generation of which may relate to infectivity, chronicity, and resistance to therapy.^{61,62,65-69}

The HCV is now known to have caused most cases of non-A, non-B hepatitis prior to identification of HCV and was the major cause of transfusion-associated hepatitis until screening of the blood supply became feasible in the early 1990s.⁷⁰⁻⁷² Currently, the risk of transfusion-associated HCV is less than 1 unit per 103,000 units transfused.⁷³ Injection drug users continue to account for over half of the new infections reported annually, with other parenteral exposures such as tattooing, body piercing, and needlestick accidents accounting for the other cases.⁷⁴⁻⁷⁶ Despite these known risk factors, 30% to 40% of patients with acute HCV deny specific exposure associated with acquiring the infection in the 6 months prior to the onset of illness.²⁰ The risk of transmission of HCV via sexual activity for patients with a steady partner appears to be low,⁷⁶⁻⁷⁹ and transmission by sexual or household exposures accounts for less than 10% of cases. The likelihood of perinatal transmission is approximately 5%, with a very low risk of chronic infection developing in the infant.^{80,81}

Clinical Features. The clinical course of untreated HCV infection can be highly variable, with the majority of patients experiencing an indolent, fluctuating course that may take 20 years or more for full expression. Fulminant hepatitis C is extremely rare and the association with HCV has not been fully confirmed. Acute infection is associated with an incubation period of 6 to 7 weeks, with a range of 2 to 26 weeks. After initial exposure, HCV RNA

can be detected in serum within a few weeks; within a few months of exposure most patients develop liver cell injury as indicated by elevations in ALT values. A large percentage of patients are physically asymptomatic and anicteric. A "silent period" may ensue for weeks to months after initial infection, during which viral titers are low and antibody responses are not detectable. Seroconversion to HCV-antibody positive status occurs within 3 months in the majority of exposed individuals but in some may take up to 6 months.^{33,42,82-85}

The HCV is not efficiently cleared by the immune system after acute infection, and 75% to 85% of exposed patients will progress to chronic infection.^{41,42,51,86} In addition, approximately 20% to 30% of chronically infected patients will progress to cirrhosis.^{82,86} Studies have shown an estimated interval from infection to development of liver disease of 13.7 years for chronic hepatitis, 18.4 years for chronic active hepatitis, 20.6 years for cirrhosis, and 28.3 years for HCC.^{87,88} A variety of factors (eg, age, gender, amount of alcohol consumption) may affect the rate of progression. Military recruits who were infected at a young age and Irish women recipients of anti-D Ig appear to be slow progressors.^{89,90} Excessive alcohol use (consumption over 50 grams per day) appears to be an important cofactor that speeds progression.^{91,92} As with chronic HBV infection, chronic HCV infection is associated with an increased risk of HCC.^{86,93-97} This risk is 1% to 4% over a 20-year period in chronic HCV without cirrhosis, but increases 1% to 4% per year if cirrhosis develops.

Chronic HCV infection typically follows an insidious course involving episodes of elevated serum aminotransaminases and hepatocellular injury, often associated with fluctuations or increases in HCV titer. Nonspecific physical symptoms such as intermittent weight loss, fatigue, muscle or joint pain, irritability, nausea, malaise, anorexia, and upper quadrant pain develop in about 20% of cases.^{42,98,99} Inflammatory cells infiltrate portal tracts and may invade hepatic parenchymal tissue. Invasion of the parenchyma near the portal tracts is usually associated with inflammation and tissue necrosis (termed interface hepatitis), with fibrosis developing as parenchymal cells die off. More severe fibrosis leads to the development of bridging fibrosis between portal tracts and hepatic veins, ultimately leading to diffuse fibrosis and cirrhosis. The rate of progression from the asymptomatic, chronically viremic state to the expression of frank liver

disease is often indolent (years to decades). Significant morbidity is associated with chronic HCV infection once liver disease is evident, and the development of severe fibrosis and necroinflammatory changes is a poor prognostic sign indicating potential for progression to cirrhosis. Once cirrhosis is established, progression to decompensation and liver failure occurs in some of the cases.⁴²

Hepatitis D

Epidemiology. The epidemiology of hepatitis D infection closely parallels that of HBV, with hepatitis D having affected more than 10 million people worldwide who are also infected with HBV.¹⁰⁰⁻¹⁰⁴ The hepatitis D virus (HDV) or delta agent is endemic in many parts of the developing world,^{45,105-108} and is an important health problem worldwide in terms of morbidity and mortality.^{100,101,105,109} Hepatitis B and HDV co-infection in injection drug users has been well described in Europe, the latter agent appearing to have been introduced there in the mid-1970s.^{104,108,110} Currently, similar data are scanty for the US. In the CDC sentinel counties hepatitis study for 1983 to 1984, 2% of HBsAg-positive homosexual men were also positive for HDV markers. Out of 290 men with new HBV infections during follow-up, 1% had serologic evidence of HDV hepatitis. This study indicates that HDV is an infrequent cause of viral hepatitis in homosexual men in the US,¹¹¹ although some reports suggest increased risk in this population.¹⁰²

In contrast, in a study of samples obtained from HBV-infected drug users in the US, anti-HDV was detected in 42.1% of HBsAg-positive and in 3.3% of anti-HBs positive subjects. No correlation was found between detection of HBeAg (active HBV infection) and the presence of anti-HDV, but anti-HDV was found more frequently in those diagnosed with chronic active hepatitis than in those with chronic persistent hepatitis. These results indicate that HDV infection has been common in HBsAg-positive drug addicts in the US dating back to at least 1972 and probably earlier. In 1990, 250,000 acute HBV infections occurred, 7,500 of which had confirmed HDV co-infection or superinfection.^{112,113}

Hepatitis D virus is the most unusual of all hepatotropic viruses (Table 1).^{10,11} It is essentially a defective virus that requires the simultaneous presence of HBV or other Hepadnaviridae to assist in viral replication and expression.^{100,101,104} Slightly smaller than HBV, HDV has a hybrid structure that

includes a 1,700-nucleotide, single-stranded RNA genome nonhomologous with the HBV genome, a nucleocapsid protein also bearing no sequence homology to any HBV proteins (the delta antigen), and an outer envelope of HBsAg indistinguishable from that of HBV. The replication strategy of HDV is similar to that of plant satellite viruses or viroids.^{114,115} It is also the only virus in the satellite family known to infect animal species.^{101,104} Viral replication is absolutely dependent on the helper function of HBV, and HDV infection does not outlast the duration of HBV infection.¹¹⁶

Transmission of HDV is thought to occur by person-to-person contact in areas where HDV is highly endemic, whereas it is thought to occur only through parenteral exposure to blood or body fluids in low-prevalence areas such as the US. Intravenous drug users and hemophiliacs have the greatest risk of HDV infection in the US. Transmission of HDV includes the following mechanisms: 1) direct percutaneous exposure to contaminated blood through the parenteral use of drugs or through a blood product transfusion, 2) horizontal, nonparenteral transmission of HBV among siblings (may play a major role in transmission between household members who are HBsAg carriers), 3) sexual contact, and 4) inapparent transmission through open skin lesions or environmental contamination.^{45,102,104,117} Perinatal transmission does not appear to be of great importance.^{118,119}

Clinical features. Hepatitis D infection usually carries some risk of increased severity of liver disease.¹²⁰⁻¹²³ In a recently reported retrospective study in patients with compensated cirrhosis associated with HBV infection, the risk for HCC, decompensation, and mortality was increased by a factor of 3.2 (1.0 to 10), 2.2 (0.8 to 5.7), and 2.0 (0.7 to 5.7), respectively, for patients also positive for HDV.¹²⁴ Two patterns of HDV infection are recognized, depending on the initial HBV status of the host.^{120,125,126} In patients simultaneously co-infected with HBV and HDV, the disease is self-limiting in the majority of cases (90%), with only 2% progressing to chronic infection. Fulminant hepatic failure (FHF) occurs in less than 10% of cases of co-infection.¹²⁰⁻¹²³ The clinical course, however, may be quite different in HBV carriers subsequently infected with HDV. Termed "superinfection," 70% to 90% of cases result in chronic HDV carrier status, often with active liver disease. Fulminant hepatic failure can occur in 5% to 20% of cases of superinfection.^{121,127-129}

Hepatitis E

Epidemiology. The hepatitis E virus (HEV) is responsible for large epidemics of acute hepatitis and a proportion of sporadic hepatitis cases in southeast and central Asia, the Middle East, parts of Africa, and Mexico.¹³⁰⁻¹³⁴ Of note is that recent isolation of a swine virus resembling human HEV has opened the possibility that zoonotic HEV infection may occur in areas where animal hosts are abundant,^{132,135-140} including some pig-farming regions of the US.¹⁴¹ In addition, case-control and other study data indicate that seroreactive persons are more likely than seronegative persons to have traveled to countries where HEV is endemic.¹⁴²⁻¹⁴⁴ These findings suggest that travelers to regions in which HEV is endemic can acquire subclinical HEV infection.

Hepatitis E virus is a 32-nm to 34-nm, nonenveloped virus with a 7,600-nucleotide, single-stranded, positive-sense RNA genome encoding 3 open reading frames (Table 1).^{10,11,136,145} All HEV isolates to date appear to belong to 1 serotype, despite genomic heterogeneity of up to 25%. There is no genomic sequence homology between HEV and HAV or other picornaviruses; indeed, HEV most closely resembles calciviruses¹³⁶ yet is distinct enough to merit its own classification within the alphavirus group. Hepatitis E virus replicates in hepatocytes and is excreted in stool during the late incubation period; transmission of HEV is predominantly by the fecal-oral route, usually through contaminated water.¹⁴⁶ Direct person-to-person transmission is rare.^{134,147-150}

Clinical features. Hepatitis E presents after an incubation period of 15 to 60 days with a clinical illness resembling other forms of acute viral hepatitis.^{132,145} Only acute forms are recognized; asymptomatic and anicteric infections may occur in a significant number of cases. Clinical occurrence rates are the highest among young adults. Although the mortality rate is usually low (0.07% to 0.6%), the illness may be particularly severe for pregnant women, in whom mortality rates from acute liver failure may reach 20%.^{132,151}

Viral excretion begins approximately 1 week prior to the onset of clinical symptoms and persists for nearly 1 to 2 weeks; viremia can typically be detected during the late phase of the incubation period. Immunoglobulin M antibody (anti-HEV) appears early during clinical illness, then disappears over the next several months. Immunoglobulin G anti-HEV appears a few days later and persists for several years.¹³²

Hepatitis G/GBV-C

Epidemiology. Hepatitis G (also referred to as GBV-C) is a novel viral agent transmitted mainly through blood and blood products^{152,153} that frequently occurs as a co-infection with HCV or other hepatitis viruses due to common modes of transmission.^{154,155} However, the data presently available do not support a major role for this virus in causing liver disease. Indeed, at this time, hepatitis G virus and its role as a true hepatitis virus is controversial and will not be further discussed.¹⁵⁶

Hepatitis A and Hepatitis E

Prevention of HAV and HEV infection is primarily through sanitation. Clean water for drinking and cooking is essential; waste disposal must be separate from the water supply.^{4,8,157} Hand washing, boiling water, thorough cooking of food, and peeling of vegetables and fruit can prevent exposure. Hepatitis A virus is inactivated by chlorination, ultraviolet radiation, and boiling water for 20 minutes.

Every year, millions of travelers from the US will visit developing countries where HAV is endemic. Passive immunization with immune globulin before exposure or within 2 weeks following HAV exposure protects against clinical disease in 70% to 90% of immunized individuals; the duration of protection, however, is short, measured in months.^{8,11,157-159} Active immunization with a single dose of inactivated HAV vaccine generates protective antibodies and appears to provide better protection that lasts for several years. In order to extend the duration of protection by a decade or more, it is recommended that a booster is given between 6 and 12 months after the initial administration. The two inactivated hepatitis A vaccines that are approved for use in the US have been clinically well tolerated; mild transient soreness at the injection site is the most frequently reported adverse reaction. Immunization with inactivated hepatitis A vaccine is a safe and effective method for travelers to endemic areas to protect themselves against this infection.^{8,11,157-159} Immune globulin may be given concomitantly with HAV vaccine in persons requiring both immediate and long-term protection, with care taken to use different injection sites. Although active and passive immunization can be given concurrently, some reports indicate the mean antibody titers generated

TABLE 3
IMMUNIZATION STRATEGIES

Hepatitis A virus (HAV)

Whom to immunize	<p>Infants > age 2 years who are at risk</p> <p>Travelers to endemic areas</p> <p>Military personnel, others with occupational exposure</p> <p>Individuals with intravenous drug use or high-risk sexual activity</p> <p>Individuals from ethnic groups with high rates of HAV (eg, Native Americans and Native Alaskans)</p> <p>Individuals in communities experiencing outbreaks</p> <p>Individuals with clotting factor disorders, chronic liver disease</p>
Preparations and dosage	<p>HAV (Havrix)</p> <p>Children (2–18 years): 360 EL.U./0.5 mL, 2 doses given 1 month apart; then 360 EL.U./0.5 mL, 6 to 12 months after primary series</p> <p>Adults: 720 EL.U./0.5 mL, 1 dose; then 720 EL.U./0.5 mL, 6 to 12 months after primary series</p> <p>Vaqta</p> <p>Children (2–17 years): 25 U/0.5 mL, 1 dose; then 25 U/0.5 mL, 1 dose 6 to 18 months after primary dose</p> <p>Adults: 50 U/mL, 1 dose; then 50 U/mL, 1 dose 6 months after primary dose</p>

Hepatitis B virus (HBV)

Whom to immunize	<p>Infants (universal vaccination); infants born to HBsAg-positive mothers may receive HBIG in addition</p> <p>Healthcare workers</p> <p>Individuals with intravenous drug use or high-risk sexual activity</p> <p>Travelers to endemic areas</p> <p>Military personnel, morticians, embalmers, others with occupational exposure</p> <p>Adolescents</p> <p>Immigrants from endemic areas</p> <p>Persons from ethnic groups with high rates of HBV (eg, Native Alaskans, Pacific Islanders)</p> <p>Family members and sexual partners of chronic hepatitis B carriers</p> <p>Internationally adopted children</p> <p>Individuals with other types of chronic liver disease</p>
Preparations and dosage	<p>Engerix-B</p> <p>Usual dosing schedule: 0, 1, 6 months</p> <p>Alternative dosing schedule: 0, 1, 2, and 12 months</p> <p>Children (0–10 years): individual dose 10 µg/0.5 mL via either dosing schedule</p> <p>Adolescents (11–19 years): 10 µg/0.5 mL via the usual dosing schedule or 20 µg/1.0 mL via either dosing schedule</p> <p>Adults (> 19 years): 20 µg/1.0 mL via either dosing schedule</p> <p>Hemodialysis patients: 40 µg/2.0 mL at 0, 1, 2, and 6 months</p> <p>Recombivax-HB</p> <p>Dosing schedule: 0, 1, 6 months</p> <p>Neonates born to HBsAg-positive mothers: 5.0 µg/0.5 mL + HBIG</p> <p>Children (1–10 years): 2.5 µg/0.5 mL</p> <p>Adolescents (11–19 years): 5 µg/0.5 mL</p> <p>Adults (> 19 years): 10 µg/1.0 mL</p> <p>Predialysis and hemodialysis patients: 40 µg/1.0 mL</p>

HBsAg = hepatitis B virus surface antigen; HBIG = hepatitis B immune globulin.

in patients receiving both passive and active immunization against HAV were about 2-fold lower than in patients receiving active vaccine alone.¹⁶⁰ These findings suggest the immune globulin may interfere to some degree with the immune response that forms the basis of active immunity. In patients requiring both short-term and long-term protection against HAV by means of both passive and active immunization, a vaccine booster dose may be required sooner.¹⁶⁰

A vaccine against HEV is currently in clinical trials.

Recommendations. Recommendations for immunization for hepatitis A are summarized in **Table 3**. Routine immunization of children with active vaccine against HAV is the most effective way to prevent hepatitis A in individuals and the overall incidence of hepatitis A nationwide. This strategy has been implemented incrementally in the US, starting with the recommendation of the

Advisory Committee on Immunization Practices (ACIP) in 1996 to vaccinate children living in communities with the highest rates of infection and disease. These recommendations have recently been updated. They provide for the routine vaccination of children in states, counties, and communities with rates that are twice the 1987 to 1997 national average or greater (ie, ≥ 20 cases per 100,000 population), and consideration of routine vaccination of children in states, counties, and communities with rates exceeding the 1987 to 1997 national average (ie, ≥ 10 but ≤ 20 cases per 100,000 population).¹⁵⁹ Previous recommendations regarding the vaccination of adults in groups at increased risk for hepatitis A or its adverse consequences and recommendations regarding the use of immune globulin for protection against hepatitis are unchanged.¹⁶¹ Currently, HAV vaccine is indicated for individuals > 2 years of age who are at risk, including travelers to endemic areas, military personnel, certain ethnic groups with high rates of HAV (such as Native Americans and Native Alaskans), persons engaging in high-risk sexual activity, IV drug users, and individuals in communities experiencing outbreaks. Those with occupational exposure, such as laboratory researchers and persons with clotting factor disorders, should also be offered the vaccine.

For HEV, no passive immunization with immune globulin is currently available or recommended.

Active vaccines. Two vaccines are available in the US for prevention of HAV. These are Havrix (SmithKline Beecham, Philadelphia, Pa) and Vaqta (Merck & Co., Whitehouse Station, NJ); both require a series of 2 injections (6 to 18 months apart) for full, long-term protection.¹⁶²⁻¹⁶⁴ Under these schedules seroconversion rates of 95% or greater have been reported. The recommended schedule of Vaqta for adults is a 1.0-mL (50 Units [U] of HAV viral antigen) intramuscular dose initially, followed by a booster dose 6 to 12 months later; children 2 to 17 years of age should receive 0.5 mL initially (25 U of HAV antigen), followed by a booster dose 6 to 18 months later. Similarly, the adult dosage schedule for Havrix and Vaqta is a 1.0-mL (1,440 U) intramuscular dose initially, followed by a 1.0-mL booster dose 6 to 12 months later.^{163,165} Over 96% of normal adult patients had titers when measured 1 month after vaccination. A booster dose increases this to 100%.

Hepatitis B and Hepatitis D

Prevention of HBV is primarily through vaccination and protection against exposure to bodily fluids. This includes safe sexual practices, avoiding sharing needles, and, for healthcare providers, adhering to practices of universal precautions and safe injection techniques.^{16,166}

Hepatitis B must now be considered a preventable disease because acute infection can be effectively eliminated by either passive immunization with hepatitis B immune globulin (HBIG) or active immunization.^{32,167} In October 1997, the ACIP expanded its HBV vaccination recommendations to include all unvaccinated children aged 0 to 18 years, children in populations at high risk for HBV infection (eg, Native Alaskans, Pacific Islanders, and children who reside in households of first-generation immigrants from countries where HBV infection is moderately or highly endemic), previously unvaccinated children aged 11 to 12 years, older adolescents and adults in defined risk groups, and spouses or sexual partners of HBV-positive individuals.^{16,168-171} Vaccination of susceptible persons will save medical costs for populations with annual HBV infection rates above 5%; vaccination may even be considered cost effective (or cost saving when indirect costs are included) for populations with infection rates as low as 1% to 2%.^{172,173}

Both passive and active immunization have a role in prevention of HBV transmission.^{16,32,167-170}

- The first dose of an HBV vaccine series and HBIG are frequently administered together for post-exposure prophylaxis. A single sexual exposure to an HBsAg-positive individual is an indication for HBIG if given within 2 weeks of exposure.
- Passive immune prophylaxis with HBIG, combined with the active vaccination series, may be appropriate in certain situations in which rapid development of antibody titers is desirable. For example, postexposure prophylaxis with immune globulin using the 2-dose series (administered 1 month apart) provides about 75% protection for acute exposure to blood containing HBsAg.
- Infants born to HBsAg-positive mothers should receive both immune globulin and HBV vaccine.
- Postexposure prophylaxis with HBIG (0.06 mL/kg) is indicated for exposure to blood containing HBsAg in a nonimmune individual. The first dose of an HBV vaccine series should be administered concomitantly, but at a different intramuscular site. If the person refuses the HBV vaccine,

another dose of HBIG should be administered 1 month later. This postexposure prophylaxis is most effective if initiated within 1 week of exposure.

- Postexposure prophylaxis in patients with a sexual exposure consists of 1 dose of HBIG 0.06 mL/kg intramuscularly, preferably within 2 weeks of exposure.
- Hepatitis B immune globulin is always given intramuscularly for prophylaxis, never intravenously (except in liver transplant recipients).

Active vaccines. The previous plasma-derived HBV vaccine has been replaced by recombinant HBV vaccines (Engerix-B [SmithKline Beecham], Recombivax-HB [Merck & Co.]). The vaccines are highly effective and safe.

For Engerix-B, the usual dosing schedule is 0, 1, and 6 months; the alternate dosing schedule is 0, 1, 2, and 12 months.

- For children 0 to 10 years of age, the individual dose is 10 μ g/0.5 mL. Adolescents 10 to 19 years of age may receive 10 μ g/0.5 mL via the usual dosage schedule, or 20 μ g/1.0 mL via either dosage schedule.
- Adults older than 19 years can receive 20 μ g/1.0 mL via either dosage schedule.
- Hemodialysis patients can receive 40 μ g/2.0 mL at 0, 1, 2, and 6 months.

The recommended dosing schedule for Recombivax-HB is as follows (all are 0, 1, and 6 month dosing schedules):

- 2.5 μ g/0.5 mL for children 1 to 10 years of age;
- 5 μ g/0.5 mL for children 11 to 19 years of age; and
- 10 μ g/1.0 mL for adults 20 years of age and older.
- There is a special formulation for predialysis and hemodialysis patients, 40 μ g/1.0 mL.

Some adult patient populations may have suboptimal responses to active vaccination, including hemodialysis patients, alcoholics, immunocompromised patients, the elderly, and diabetics, who may fail to mount an effective immune response.¹⁷⁴⁻¹⁷⁹ For these patients, modified dosing schedules may be needed to engender effective immunization. A booster dose at Month 4 has been suggested for diabetics who do not develop a titer of 10 International Units (IU)/L by Month 4 of a 0-, 1-, 2-, and 12-month dosing schedule;¹⁷⁶ a randomized trial demonstrated that a fifth dose of Engerix-B in vaccine nonresponders will elicit titers in approximately half of vaccinees.^{180,181} There is some evidence that an accelerated HBV vaccination schedule (0, 1, and 2 weeks) can also provide persistent protec-

tive immunity.^{182,183} In contrast, some authors have advocated half of the recommended dose in healthy young adults and in children in underdeveloped areas as a cost-saving measure; this may result in a significant cost savings but has yet to become widely accepted.^{184,185}

Prevention of HDV exposure is also based on universal precautions, adequate sterilization, and disinfection of medical equipment and environmental surfaces. Because HDV replication is completely dependent on HBV helper function, HDV can be prevented by effective HBV vaccination.

Hepatitis C

Methods for prevention of HCV exposure are similar to those for HBV. Hepatitis C virus-positive patients should refrain from donating blood, organs, tissues, or semen. Among household contacts, toothbrushes and razors should not be shared. Safe sexual practices, including the use of latex condoms, are encouraged for individuals with multiple sexual partners. Additionally, expansion of needle exchange programs may reduce HCV transmission among injection drug users.¹⁸⁶

For HCV, no passive immunization with immune globulin is currently available or recommended. In animal models of HCV, postexposure immune globulin prolonged the incubation period of acute hepatitis C but did not prevent HCV infection, nor did it affect the course of infection.¹⁸⁷ However, 1 randomized trial demonstrated that the administration of immune globulin every 2 months in sexual partners of HCV patients reduced the risk of sexual transmission.¹⁸⁸ These data are yet to be repeated and at this point a role for immune globulin administration is not established.

Currently, there is no effective vaccine for preventing HCV infection.

The role of vaccine in patients with chronic liver disease

Recent reports of severe cases of hepatitis A occurring in patients with preexisting chronic hepatitis C suggest that individuals with chronic liver disease who are HAV- and/or HBV-seronegative should receive prophylactic vaccination against both HAV and HBV.^{189,190} Vaccine efficacy in patients with chronic hepatitis C is well maintained in the absence of severe disease or immune dysfunction; in cirrhotics, the seroconversion occurs in approximately 50% of patients. Studies of

vaccine immunogenicity in this population suggest lower immunogenicity in patients with advanced liver disease.¹⁹¹ For patients who have undergone liver transplantation, the current strategies for vaccination are not very effective.¹⁹¹ Following the guidelines suggested for patients susceptible to liver disease, those who do not have detectable levels of HAV IgG and anti-HBsAg are candidates for vaccination. One approach is to screen first for the presence of these antibodies and then institute both HAV and HBV vaccines in patients who do not have evidence of immunity. Depending on the prevalence of HAV and HBV in different regions of the country, other strategies may also prove useful and cost-effective, including vaccinating individuals under 40 years of age without prior evidence of immunity.

DIAGNOSTIC TESTS

Diagnosis of viral hepatitis is a complex, multi-stage procedure. Clinical symptomatology, abnormalities in serum transaminases, and histologic pathology are hallmarks of both acute and chronic hepatitis regardless of etiology. As summarized in **Table 4**, the diagnosis of viral hepatitis can be confirmed using serologic and molecular biologic test methods. These methods can be employed to confirm either the existence of a host immune response to infection, the presence of viral antigens, or the presence of viral particles. Quantitation of these markers often has prognostic and clinical value, and many of these tests can be used to evaluate patient responses to therapy (**Figure 2**).

Hepatitis A

Theoretically, the diagnosis of acute HAV infection can be made by identifying the presence of HAV in tissues, body fluids, or excretions. However, the feasibility and clinical utility of virologic tests, if available, are severely limited, as the period of HAV viremia is usually short and typically precedes the onset of symptoms.^{192,193} Of more general clinical value are tests that detect the presence of HAV by demonstration of a specific host immune response.^{192,194-196} Acute HAV is diagnosed by positive anti-HAV IgM in serum taken during the acute illness. Antibody titers reach a peak within a few weeks of symptom onset and rapidly decline thereafter to low or undetectable levels, typically within 6 to 12 months.^{5,193,197,198} Established

immunity to HAV or evidence of prior infection is determined by the presence of total antibodies to HAV.

Third-generation radioimmunoassay (RIA) and enzyme-immunoassay (EIA) techniques have superseded older, second-generation *in vitro* tests such as complement fixation or immune adherence hemagglutination. Two approaches are employed in the use of these tests. The hepatitis A-IgM antibody test is a simple, rapid, and reliable means to diagnose acute HAV infection, reflecting the initial immune response to infection. Stable levels of total anti-HAV (all classes) are considered a reliable indicator of established immunity. Rapidly increasing titers of total anti-HAV in sequential specimens from a given patient, however, may also indicate an active HAV infection and the host's ongoing efforts to mount an immune response.¹⁹²

Currently, the most widely used tests (RIA and EIA) employ a "sandwich immunoassay" in an antibody-class capture approach.

Hepatitis B

Serologic markers for HBV infection are numerous, and the diagnosis and assessment of HBV infection are complex. In addition to the traditional markers of e antigen (HBeAg) and surface antigen (HBsAg),^{192,196,199,200} the clinical utility of new serologic markers is being explored (eg, antibodies to the HBsAg epitopes pre-S1 and pre-S2 proteins).^{192,201} The serologic diagnosis of HBV infection is established by detecting either antibodies and/or their respective antigens (ie, the HBsAg and anti-HBs, HBeAg and anti-HBe, or the HBeAg and anti-HBe).^{39,202} An algorithm for HBV testing and management is illustrated in **Figure 3**.

HBsAg and anti-HBs. These tests target the mature viral envelope protein of HBV present in serum either as excess protein or complete viral particles. Highly sensitive, specific, and rapid test systems for the HBsAg include RIA, enzyme-linked immunosorbent assay (ELISA), as well as reverse passive hemagglutination methods. These techniques have been developed to meet the needs of extensive screening programs such as those for the US blood supply. Enzyme immunoassay is the most commonly used test for HBsAg, whereas the most commonly used tests for anti-HBs employ both EIA and RIA methods.¹⁹²

HBeAg and anti-HBe. Tests for HBeAg are generally limited for use in testing liver biopsy samples.

TABLE 4
SEROLOGIC MARKERS AND DIAGNOSTIC TESTS

Hepatitis A virus (HAV)	
Markers	HAV IgM: indicator of initial immune response to acute infection HAV total antibody: indicates established immunity
Tests available	HAV-IgM antibody test (IMx system) HAV antibody test: total antibody to HAV (IMx system)
Liver biopsy	Not indicated
Hepatitis B virus (HBV)	
Markers	HBsAg: first serologic marker to appear; disappears with clinical improvement; persistence beyond 6 months indicates chronic infection HBeAg: marker of infectivity for both acute and chronic infection; persistence beyond 10 weeks indicates likely chronic liver disease Anti-HBs: marker of recovery and immunity Anti-HBe: conversion from HBeAg to anti-HBe usually indicates a benign outcome Anti-HBc IgM: marker of recent acute infection (first 6 months); helps to distinguish acute from chronic infection Anti-HBc total: indicates current or previous infection, not associated with recovery or immunity Anti-HBc in the presence of anti-HBs distinguishes natural immunity from vaccination
Tests available	EIA on detection of anti-HBs in serum or plasma Qualitative EIA for detection of HBsAg in human serum or plasma EIA for detection of total anti-HBc Microparticle EIA for the detection of anti-HBc IgM (IMx system) EIA for detection of anti-HBe EIA for the detection of HBeAg HBV DNA
Liver biopsy	Indicated in chronic cases
Hepatitis C virus (HCV)	
Markers	Anti-HCV: indicates current or past infection HCV RNA: indicates active infection HCV genotype: indicates genetic heterogeneity
Tests available	ELISA-2 anti-HCV* RIBA II anti-HCV† RT-PCR HCV RNA bDNA HCV RNA
Liver biopsy	Indicated in chronic cases
Hepatitis D virus (HDV)	
Markers	Anti-HDV: indicates exposure Anti-HDV IgM: indicates recent exposure HDV RNA: indicates active infection
Tests available	Anti-HDV HDAg Anti-HDV IgM HDV RNA
Liver biopsy	Indicated in chronic cases with HBV
Hepatitis E virus (HEV)	
Markers	HEV RNA: indicates active infection
Tests available	EIA (CDC only) HEV RNA using RT-PCR (CDC only)
Liver biopsy	Not indicated

Ig = immunoglobulin; HBsAg = HBV surface antigen; HBeAg = HBV e antigen; anti-HBs = antibody to HBsAg; anti-HBe = antibody to HBeAg; anti-HBc = antibody to HBV core antigen; EIA = enzyme immunoassay; anti-HCV = antibody to HCV; ELISA = enzyme-linked immunosorbent assay; RIBA = recombinant immunoblot assay; RT-PCR = reverse-transcriptase polymerase chain reaction; bDNA = branched-chain DNA; anti-HDV = antibody to HDV; HDAg = HDV antigen; CDC = Centers for Disease Control and Prevention.

*ELISA-3 is currently only available for screening of donated blood.

†RIBA is a confirmatory antibody test used to reduce false positive ELISA test results in low-risk individuals.

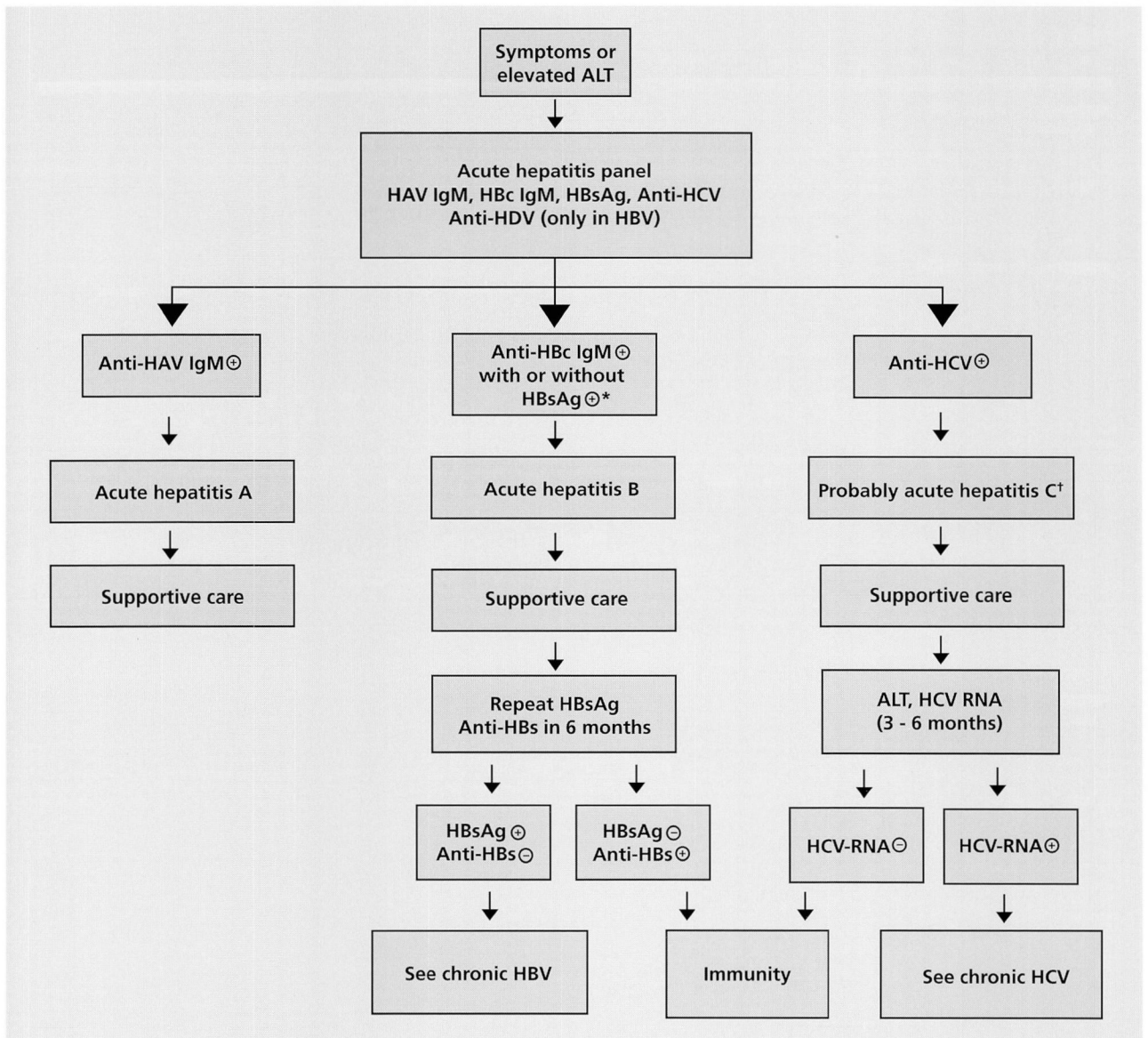


FIGURE 2. Algorithm of suggested diagnostic testing in patients with acute viral hepatitis. ALT = alanine aminotransferase; HAV = hepatitis A virus; Ig = immunoglobulin; HBc = HBV core; HBsAg = HBV surface antigen; HCV = hepatitis C virus; HDV = hepatitis D virus; HBV = hepatitis B virus; HAV = hepatitis A virus.

*Anti-HDV should only be considered in those who carry HBsAg.

†Many physicians recommend early treatment of acute hepatitis C.

Hepatitis B core antigen is detected by immunostaining in liver. The presence of HBcAg in liver tissue indicates ongoing viral replication and is often interpreted as a measure of infectivity. Measurement of anti-HBc IgM (principally by RIA or ELISA) can discriminate between acute HBV infection (positive) and chronic HBV cases (negative), as increased anti-HBc is indicative of

decreased viral replication. Positive anti-HBc IgM indicates acute hepatitis B infection.¹⁹²

HBeAg and anti-HBe. Hepatitis B e antigen is a viral protein secreted by HBV-infected cells. Its presence indicates high levels of virus in the blood, and it is an indicator of the infectiousness of the carrier. If this test is negative, but a person is known to be HBsAg positive, then it indicates low levels of

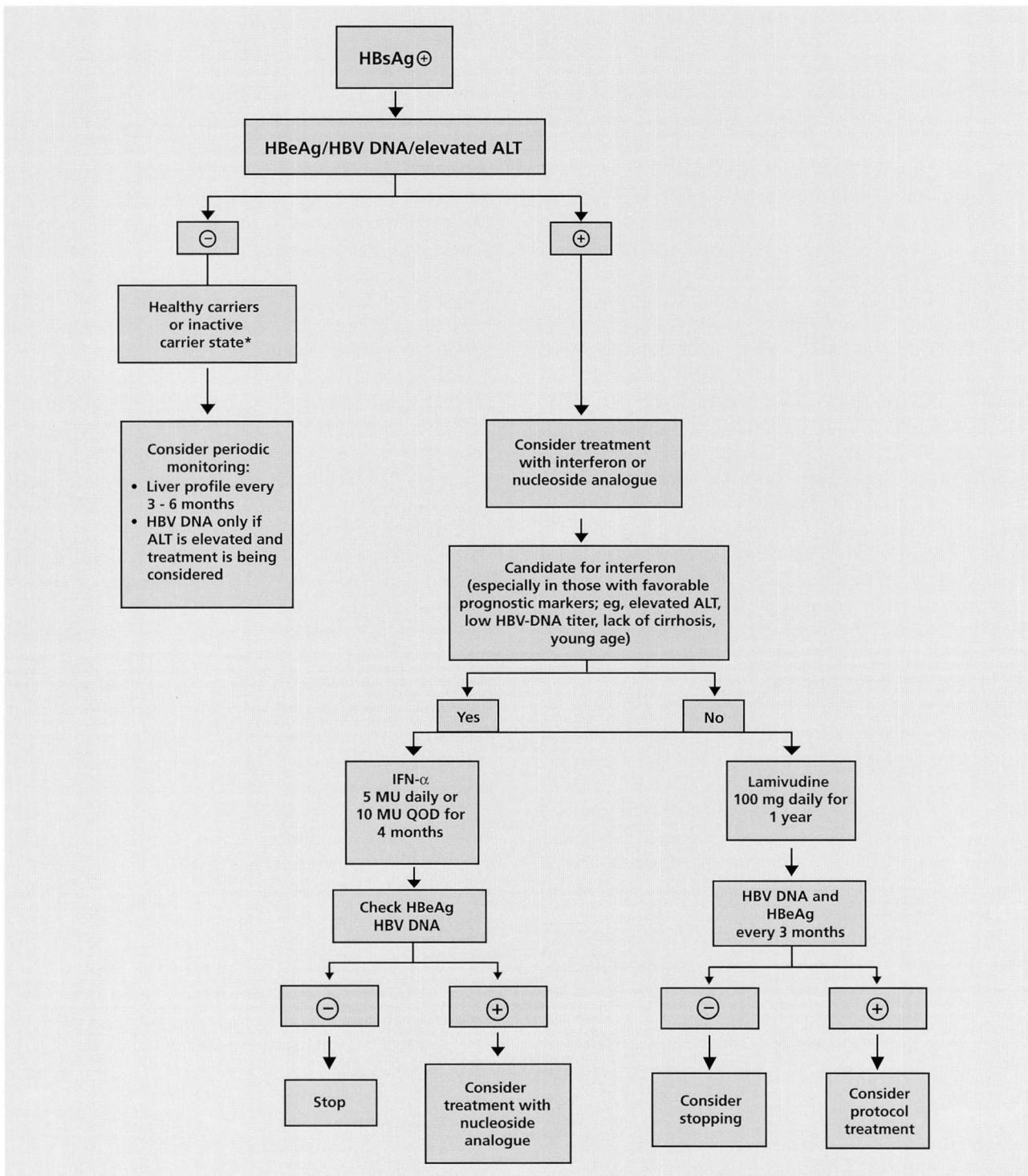


FIGURE 3. Algorithm of suggested diagnostic testing in patients with positive hepatitis B virus (HBV) surface antigen (HBsAg). HBeAg = HBV e antigen; HCC = hepatocellular carcinoma; IFN- α = interferon alfa; MU = million Units; QOD = every other day.

*If suspicion exists (ie, increased alanine aminotransferase) HBV DNA may be positive in those patients with precore mutants (HBsAg⁺, HBeAg⁻, and HBV DNA⁺).

virus in the blood or an “integrated phase” of HBV in which the virus is integrated into the host’s DNA. This test is often used to monitor the effectiveness of some HBV therapies, whose goal is to convert an actively replicating state to “e-antigen negative” state.

HBV DNA. The presence of HBV DNA (the viral genome) indicates active viral replication. Hepatitis B virus DNA is assayed by polymerase chain reaction (PCR) methods, branched-chain DNA (bDNA) methods, and by nucleic acid hybridization methods. Polymerase chain reaction-based assays tend to be more sensitive, but bDNA- and hybridization-based assays may provide more specificity, although the latter point is controversial.^{200,203} All of these assay methods detect HBV DNA in serum and are important in monitoring the effect of antiviral therapy on hepatitis B replication.

The most important thing to remember about these tests is that these assays yield different results, and their results cannot be used interchangeably. It is also important to note that the challenge of the next decade is to standardize these assays, which could make their clinical application more useful. Finally, it is also important to remember that none of these tests is currently approved by the US Food and Drug Administration (FDA).

Monitoring of HBV infection and response to treatment can be performed using combinations of these tests.¹⁹² Typical test panels for specific situations include 1) diagnosis of acute viral hepatitis B by HBsAg and anti-HBc; 2) for diagnosis of remote, prior HBV infection: HBsAg, total anti-HBc, and anti-HBs; and 3) for monitoring ongoing HBV infection: HBsAg, total anti-HBc, anti-HBs, HBeAg, anti-HBe, and HBV DNA.

It is also important to remember that some HBV patients from the endemic areas may be HBsAg-positive, HBeAg-negative but HBV-DNA-positive. These so-called “precore mutants” are unable to secrete HBeAg and may have more aggressive disease.

Hepatitis C

Since the HCV genome was cloned in 1989,²⁰⁴ the extensive use of molecular techniques has led to the development of serologic and molecular tests for detecting the virus and its subtypes, as well as to an increase in our understanding of the pathogenesis of chronic liver disease. Two categories of virologic assays are used for the diagnosis and management of

HCV infection: serologic assays based on HCV immunologic characteristics and molecular-based assays based on the quantitation and characterization of the HCV RNA.^{192,193,205–208}

Antibody tests in hepatitis C. Serologic assays include screening tests based on EIAs and immunoblot assays. Numerous serologic tests exist to detect antibodies to HCV antigens,^{209,210} but the utility of these assays is limited by the observation that not all patients infected with HCV generate an immune response.^{211–213} The ELISA has been the major screening test for the detection of anti-HCV against different HCV antigens. Supplemental semiquantitative assays developed to refine the specificity of a positive anti-HCV EIA assay include recombinant immunoblot assay (RIBA). The utility of RIBA testing is to decrease false positive ELISA tests that may still be seen in individuals with no apparent risk factors for HCV and those with other immune-mediated disease (eg, rheumatoid arthritis). In high-risk individuals, the positive predictive value of the ELISA-2 test is over 95% and in the presence of elevated ALT levels virtually establishes the diagnosis.

HCV-RNA tests. Notably, serologic methods may fail to detect HCV infection in the small proportion of patients unable to mount an effective immune response. Additionally, although a positive antibody response to HCV generally indicates infection, it does not distinguish between active and previous infection and therefore is of no benefit in assessing recovery after antiviral treatment. In this context, identification of the presence of HCV RNA in serum or plasma is clearly more useful. Molecular assays for HCV include qualitative assays detecting HCV RNA in body fluids and liver biopsy specimens; quantitative assays measuring HCV viral load, a parameter that estimates the level of HCV replication; and tests analyzing the sequence of HCV genomes, or “genotyping” assays (see below).²⁰⁸ Sensitive qualitative tests for detection of HCV RNA in serum by reverse transcriptase (RT)-PCR or bDNA methods have been shown to be useful in the diagnosis of active HCV infection.^{214–217} Accurate quantitative methods for measuring viral nucleic acid levels (ie, counting the number of viral particles) in patient serum have also been shown to correlate with the clinical stage of disease.

Detection of HCV RNA is definitive proof of HCV infection, and changes in the titer of HCV

RNA can indicate patient response to antiviral therapy.²¹⁸ The goal of therapy is to clear HCV RNA from the serum. To assess whether this goal is met, HCV RNA is typically measured prior to initiating therapy, after 6 months of combination therapy (at 3 months of interferon monotherapy), at the completion of therapy (ie, end-of-treatment response [ETR]), and 6 months after the completion of treatment (ie, sustained response [SR]). Typically, an SR represents the gold standard of HCV treatment, and HCV-RNA clearance 6 months after therapy completion is associated with durable remission in most patients.²¹⁹ However, in patients who fail to clear HCV RNA, the value of quantitative changes in HCV-RNA levels should not be underestimated. Interim results obtained during the course of treatment can be used to direct further treatment or lead to discontinuation of treatment. For example, patients receiving combination therapy without viral clearance after 24 weeks of treatment are unlikely to respond to further treatment.

Currently, both RT-PCR-based and bDNA-based assays are commercially available for accurately quantifying the amount of HCV in patient serum. Despite their availability, these tests are not fully approved by the FDA. It should be noted that bDNA measurement of HCV RNA is less sensitive, with a detection threshold of 200,000 copies/mL. There are two common quantitative HCV-RNA assays: Roche Monitor assay (Amplicor HCV Monitor, Roche Diagnostic Corporation, Indianapolis, Ind) and Quantiplex HCV RNA 2.0 Assay (bDNA-2.0; Bayer Diagnostics; Emeryville, Calif). Reverse transcriptase-PCR methods are more sensitive, with a threshold for detection in some tests of < 100 copies/mL. In several recent large studies,²²⁰⁻²²² the HCV Superquant assay (National Genetics Institute, Culver City, Calif) was employed, with the threshold for detection of 100 copies/mL. In an attempt to standardize the reporting of HCV-RNA levels between different laboratories using different methods, reporting viral levels in IU/mL was recently established. Because RT-PCR-based assay systems are more sensitive, they are more appropriate for determining ETR and SR to therapy.²¹⁶ Irrespective of which amplification/detection system is superior, physicians should be consistent in their choice of methodologies and/or laboratories that they use to measure HCV-RNA levels.

HCV genotyping and subtyping. In recent years, HCV has been classified into multiple strains or genotypes on the basis of the identification of their genomic sequence differences (genotypes 1 to 6). Hepatitis C viral genotypes have subsequently been further differentiated into subtypes and quasi-species.⁵⁷⁻⁵⁹ Specific HCV genotypes and subtypes are prevalent at different frequencies in various populations and geographic areas. In a US population sample, the distribution of HCV genotypes was 71.5% for genotype 1, 13.5% for genotype 2, 5.5% for genotype 3, and 1.1% for genotype 4.⁵⁹ In contrast, the distribution of HCV genotypes in a French population sample was 57% for genotype 1 (41% for genotype type 1b, 16% for genotype 1a), 11% for genotype 2, 22% for genotype 3, 4% for genotype 4, and 4% for mixed infection with multiple genotypes.²²³ In the US sample, subtypes 1a and 1b were equally frequent in patients with HCV genotype 1. Mixed infection was detected in 3.7% of patients, and 4.8% could not be typed. Genotype 4 appears to be more common in the Middle East and Egypt.

Although still controversial, liver disease outcomes may vary according to HCV genotype, with HCV genotype 1b considered to have a more aggressive course.²²⁴⁻²²⁸ However, HCV genotypes are consistently associated with response to antiviral therapy;^{66,224-226} in fact, the main role of HCV genotyping is to predict the likelihood of maintenance of long-term responses to therapy.^{223,224,226-228} Hepatitis C viral genotype 1 is resistant to interferon-based therapies, which has been confirmed in recent trials of interferon and ribavirin.²²⁰⁻²²² Additionally, a recent report also indicates that infection with HCV genotype 4 is also associated with a poor response to alpha interferons.²²⁸ In recent large, randomized controlled trials of combination interferon alfa-2b plus ribavirin therapy for previously untreated chronic hepatitis C patients, patients with genotype 1 benefited from extending their duration of therapy from 6 to 12 months.^{221,222}

The evolution of HCV quasiespecies represents the emergence of point mutations in the genome of HCV infecting an individual patient. Quasiespecies typically develop during active viral replication and have the potential for the evolution of so-called escape variants.⁶⁰⁻⁶⁴ These are thought to develop under the pressure of immunity or treatment and may potentially enable HCV infection to become chronic and resist the effect of interferon thera-

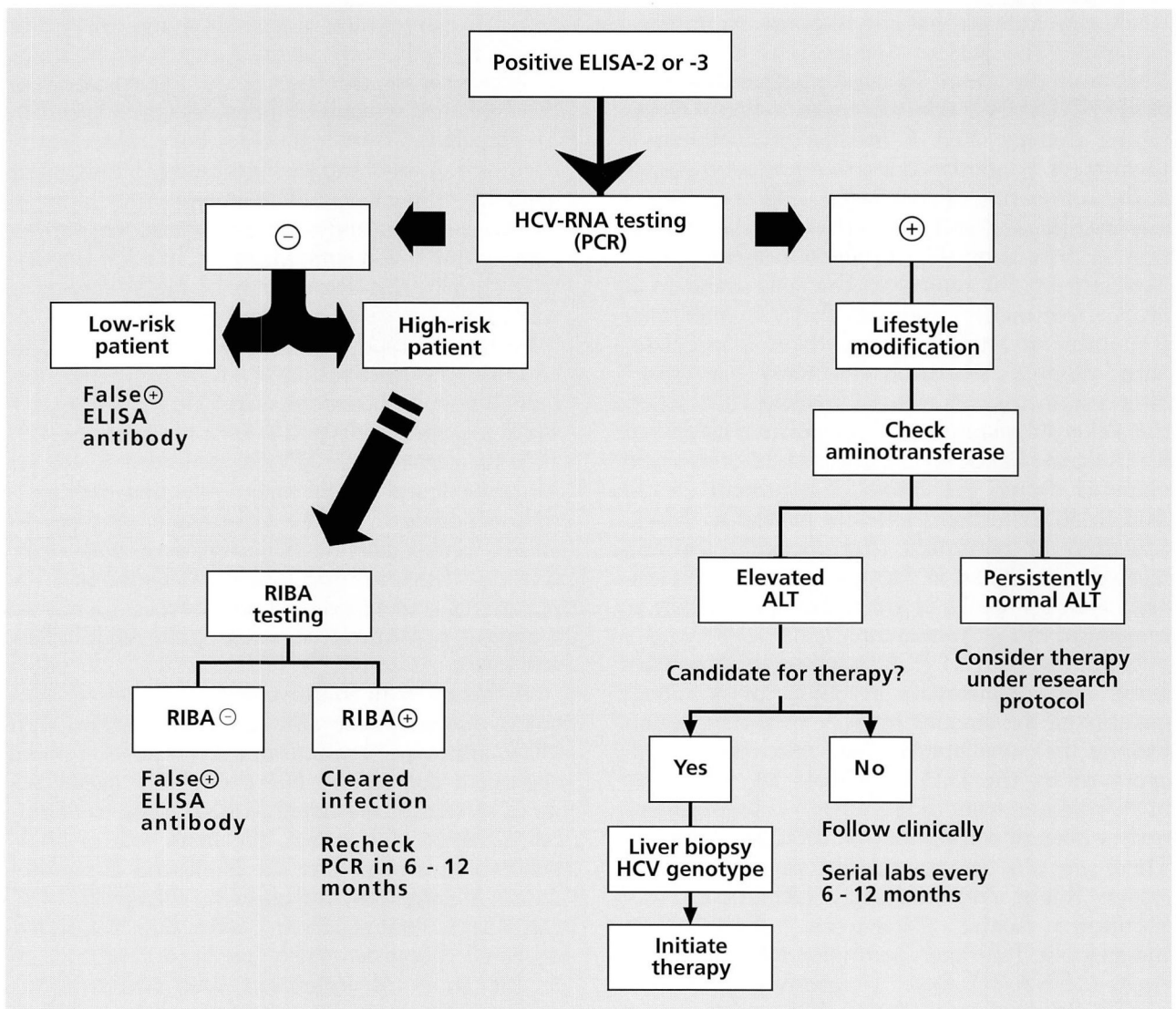


FIGURE 4. Algorithm of suggested diagnostic testing in patients with positive HCV antibody. ELISA = enzyme-linked immunosorbent assay; HCV = hepatitis C virus; PCR = polymerase chain reaction; RIBA = recombinant immunoblot assay; ALT = alanine aminotransferase. Adapted with permission from Sarbah SA, Younossi ZM. Hepatitis C: an update on the silent epidemic. *J Clin Gastroenterol.* 2000;30(2):125-143.⁴⁸

py.^{61,62,65-69} The precise clinical significance of quasi-species has yet to be determined.

Finally, the level of viremia is also considered an important predictor of response to interferon-based therapies. In several large trials of interferon-based therapy, patients with pretreatment HCV RNA > 2 million copies/mL were less likely to respond.²²⁰⁻²²² Additionally, those with detectable HCV RNA after 3 months of interferon monotherapy or after 6 months of interferon plus ribavirin therapy are unlikely to respond. Conversely, those who remain

HCV-RNA negative 6 to 12 months after discontinuation of antiviral therapy (sustained responders) seem to enjoy long-term benefit and remain HCV-RNA negative.

One strategy that can be used for HCV testing is illustrated in **Figure 4**.⁴⁸ Patients who are positive for HCV antibody by second-version or recently available third-version ELISA (third-version assays have limited availability) may undergo further testing directly for HCV RNA by PCR. A positive HCV-RNA test confirms the ELISA result. This

strategy differs somewhat from that recommended by the CDC, in which RIBA or RT-PCR is used as a supplemental assay to confirm ELISA-2 positive results in low-risk settings such as blood donor group. In most clinical settings the prevalence of HCV is higher than in the general population. As HCV-RNA tests become approved, widely available, standardized, and less costly, the role of anti-HCV RIBA testing will become less important. In some centers and in most clinical scenarios, the HCV-RNA test has replaced RIBA because it also provides information on viral load. However, RIBA may still be used to distinguish between recovered infection and a false-positive ELISA test (ie, in the patient with positive risk factors and positive ELISA test but negative PCR).

Hepatitis D

Coinfection with HDV/HBV is associated with severe and sometimes fulminant hepatitis. The possibility of HDV infection should be entertained in the clinical background of fulminant acute HBV or chronic HBV that has suddenly decompensated. It is first necessary to establish a diagnosis of HBV by testing for HBV serologies. A commonly used method for detecting anti-HDV uses EIA for the detection of antibody to HDV antigen. A definitive diagnosis is based on the detection of HDV antigen in liver biopsy samples by immunostaining. For many physicians, immunostaining is a more practical and accessible tool than PCR quantitation. Quantitative analysis of total antibody to HDV is an important clinical tool; antibody titers correlate with the severity of infection, and antibody levels > 1:1000 are considered indicative of ongoing viral replication.²⁰⁷ In these cases specific anti-HDV IgM should be measured, especially in acute infections. Other methods of determining HDV infection include detection of HDV RNA in serum by direct nucleic acid hybridization or with RT-PCR; liver biopsies may also be examined for the presence of HDV RNA by immunofluorescence, immunoperoxidase, or in situ hybridization.²²⁹

Hepatitis E

Current methods for the diagnosis of HEV are EIA and RT-PCR.^{230,231} Recombinant antigens encoded by 2 open reading frames (ORF-2 and ORF-3) of the HEV genome have been used to develop immunoassays to detect anti-HEV IgG and IgM. The immunoassays are solid-phase assays

in which anti-HEV is captured by the recombinant HEV antigens. The HEV antigen-antibody complex is detected by a goat-anti-human IgG labeled with horseradish peroxidase. However, this test is still investigational and not currently approved by the FDA for clinical use. Molecular diagnosis of HEV RNA using RT-PCR has also been developed using the sequences at the 3' end of ORF-2. These approaches have been successful in identifying presymptomatic and clinical HEV infection. Currently, these tests are available through the CDC.^{192,193,230,232}

Role of liver biopsy in viral hepatitis

Infection with only 3 (HBV, HCV, HDV) of the currently recognized hepatitis viruses is associated with progression to chronic disease. The role of liver biopsy in the management of the patient with chronic viral hepatitis remains quite important. Liver biopsy can be used to confirm a diagnosis (mainly for HBV) or exclude another diagnosis, but its most important role is to determine the stage of liver disease (degree of fibrosis or cirrhosis), which has potentially important prognostic implications. Liver biopsy is a commonly performed outpatient procedure that allows physicians to obtain liver specimens as an adjunct in the management of viral hepatitis. Information obtained from a liver biopsy specimen will help clinicians assess the activity of infection and provide important prognostic factors for the course of the patient's disease. Additionally, liver biopsy can be used to assess the efficacy of antiviral therapy, mainly in clinical trials. The main disadvantages of liver biopsy are related to the risks (pain, organ perforation, bleeding) and expense associated with this procedure. Although the risks of complication from liver biopsy are real, the risk of major complication is usually less than 1 in 1,000. Patient charges for liver biopsy and interpretation are estimated to be between \$1,500 to \$2,000 US dollars.

Histologic scoring. Chronic hepatitis is characterized by hepatic inflammation and necrosis of varying degrees that continues beyond 6 months after acute infection. Although the clinical characteristics and time course of chronic hepatitis vary somewhat with the specific etiologic agent, chronic hepatitis has been classified by histopathologic characteristics based on the localization and extent of liver injury. Ranging from milder forms (previously labeled chronic persistent or chronic lobular hepatitis) to the

more severe form (formerly labeled chronic active hepatitis), a contemporary structured classification scheme has been developed employing combinations of serologic, clinical, and histologic variables with demonstrated prognostic significance.²³³

Classification is based on etiology (viral, toxic, autoimmune, cryptogenic), histologic activity or grade (degree of inflammation and necrosis), and the stage (degree of fibrosis) of liver disease. Assessment of grade requires histologic evaluation of liver biopsy specimens, and includes the determination of the degree of periportal necrosis, the degree of confluent or bridging necrosis (ie, between the portal tract and portal vein, or between the portal tract and central vein), the degree of focal necrosis within the hepatic lobules, and the degree of portal inflammation. Stage is assessed by the degree of fibrosis present in the specimen, typically scored on a scale from 0 (no fibrosis) to 4 (cirrhosis). Several scoring systems have been used to evaluate these aspects of chronic hepatitis; the most commonly used is the modified Histologic Activity Index, which combines histologic evaluation of grade with the assessment of fibrotic stage of disease into a single score.

Liver biopsy and hepatitis B. In the setting of HBV, liver biopsy specimens not only allow the clinician to assess the extent of activity (inflammation) and the stage (fibrosis or cirrhosis), but will also allow for the detection of evidence of active viral replication. Immunoperoxidase staining to HBcAg can be performed on the liver biopsy specimens. In patients with active viral replication, both HBcAg and HBsAg are usually present. In patients with no viral replication, although HBsAg staining is present, HBcAg staining is usually absent. One of the most important prognostic indicators of chronic HBV infection, cirrhosis, can only be definitively excluded by liver biopsy. Confirmation of cirrhosis is not only important in assessing the potential for development of liver failure, but also in the risk for development of HBV-related HCC.

Liver biopsy and hepatitis C. Sensitive and specific serologic markers have provided valuable tools for the diagnosis of HCV. Because the pathologic features of HCV are nonspecific, liver biopsy is not as important in establishing the diagnosis of HCV. On the other hand, establishing the presence of cirrhosis or stage of liver disease has become an important prognostic factor not only for development of HCC, but in predicting the future course of chronic hepatitis C. The presence of histologic fibrosis is

increasingly recognized as the most important prognostic factor in predicting the development of cirrhosis. At the moment, both histologic fibrosis and cirrhosis can only be definitely established by a liver biopsy. Given the importance of histologic fibrosis, there is tremendous research interest in developing accurate serologic markers of fibrosis. Although there are several potential candidates, these markers are in the development stage and are not expected to be available clinically in the near future. Once developed and tested, these markers may negate the need for sequential liver biopsies to assess progression of fibrosis.

MANAGEMENT OF ACUTE VIRAL HEPATITIS

Clinical characteristics of acute viral hepatitis

Acute viral hepatitis is a systemic infection that predominantly affects the liver. It can be caused by any of 5 viral agents: HAV, HBV, HCV, HDV or delta agent (only in those clinically infected with HBV), and HEV. The majority of cases of acute hepatitis are caused by HAV and HBV. Under most circumstances none of the hepatitis viruses is known to directly damage hepatocytes; liver damage and subsequent clinical symptoms associated with acute hepatitis are generally a result of the host's immune response to infection.^{11,234} Acute hepatitis is associated with a characteristic set of symptoms; the symptoms caused by HAV, HBV, and HCV are indistinguishable, except that acute HCV infection is more frequently subclinical. Although the majority of cases of acute hepatitis are mild to moderate in severity and usually self-limiting, a small percentage may be fulminant (see below). The most frequent symptoms of acute hepatitis are anorexia, nausea, myalgias, and fatigue, with or without jaundice.

Treatment of acute viral hepatitis

The clinical management of viral hepatitis (acute and chronic) is summarized in Table 5. The treatment of acute viral hepatitis is primarily symptomatic, irrespective of the etiologic agent involved.²³⁵⁻²³⁷ Sporadic reports of benefit from pharmacologic therapies for acute hepatitis from HAV, HBV, or HCV are available in the literature, but none has been confirmed by large-scale controlled trials, and no guidelines exist for administration of therapy (eg, interferon, ribavirin, lamivudine) dur-

TABLE 5
CLINICAL MANAGEMENT OF ACUTE AND CHRONIC HEPATITIS

Acute viral hepatitis (HAV, HBV, HCV, HDV, HEV)

Symptoms	Anorexia, nausea, myalgias, fatigue, low-grade fever, abdominal pain
Signs	Jaundice, hepatomegaly
Treatment	Primarily symptomatic Metoclopramide and phenothiazines for severe nausea Oxazepam if sedation is required Avoidance of other hepatotoxic agents
Activity	For most patients, minimal activity Strict bed rest for frail, sicker patients Full activity may be resumed with resolution of symptoms, jaundice, and improvement of liver enzymes
Other	Hospitalization necessary when symptoms of nausea and vomiting preclude adequate nutrition considerations OR When clinical and biochemical deterioration suggest fulminant hepatic failure

Chronic viral hepatitis (HBV, HCV, HDV)

Symptoms	Mostly asymptomatic; fatigue, malaise, arthralgia
Signs	None (common), hepatomegaly, evidence of cirrhosis (rare)
Treatment	See Table 6
Activity	Patient education Limit or avoid alcohol Practice safe sex
Other	Vaccination for other viruses (HAV ± HBV) if not immune

HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; HEV = hepatitis E virus.

ing the acute phase of infection. The majority of patients with acute hepatitis can be treated at home. Hospital admission only becomes necessary when symptoms of nausea and vomiting preclude adequate nutrition and hydration, or when clinical and biochemical deterioration suggest progression to FHF. Fulminant hepatic failure is defined by the presence of hepatic encephalopathy and severe impairment of liver function (eg, elevated serum bilirubin and prothrombin time with decreasing serum albumin concentrations). In this situation, the patient should be immediately referred to a center with the capacity to perform liver transplantation.

Although not tested in randomized clinical trials, symptomatic and supportive care are recommended. These should include a combination of rest, limited activity, nutritional support, and symptomatic treatment,²³⁵⁻²³⁹ as follows:

- For most patients minimal to moderate activity is recommended; activity strenuous enough to cause fatigue should be avoided.
- Bed rest may be needed for frail and more sickly individuals.

- Activity is gradually increased, and most individuals with an uneventful course can resume full activity as tolerated with resolution of symptoms, jaundice, and improvement of liver enzymes.
- No dietary restrictions except for avoidance of alcohol and other potentially hepatotoxic agents are recommended. Good caloric intake and maintenance of hydration are important.
- Drugs, particularly sedatives, should be avoided. Metoclopramide and phenothiazines may be given in the minimal effective doses for severe nausea, and oxazepam can be used if sedation is required.

Progression to chronic viral hepatitis

Whereas hepatitis viruses A, B, C, D, and E are important causes of acute viral hepatitis; only HBV, HCV, and HDV (only in HBsAg carriers) are commonly associated with progression to chronic disease. Whereas over 95% of adults recover from acute hepatitis B, HBV usually progresses to the chronic form in children.^{240,241} For acute HBV infection, progression to chronicity is associated with

high levels of viral replication appearing early during the acute phase of infection.^{234,242,243} In contrast, HCV is associated with high rates (75% to 85%) of chronicity. Although mild chronic inflammation is present in most cases, progressive liver disease leading to cirrhosis occurs in approximately 25% of patients (over 2 to 3 decades).

Fulminant hepatic failure

Acute liver failure is an uncommon, devastating complication of acute viral hepatitis. Fulminant hepatic failure or acute liver failure is defined by development of hepatic encephalopathy occurring less than 8 weeks after the onset of jaundice in a patient without preexisting liver disease.²⁴⁴⁻²⁴⁶ The likelihood of progression to FHF varies widely with the etiologic agent. In the US, less than 0.1% of cases of acute HAV hepatitis and about 1% to 2% of acute HBV hepatitis cases can cause FHF. Association of HCV with FHF remains to be fully established. Hepatitis D virus can cause a fulminant course in approximately 5% to 20% of HBV-infected patients depending on the underlying extent of liver disease, whereas HEV can cause a fulminant course in patients who are pregnant (20% incidence during the third trimester).

Viral hepatitis, however, remains a major cause of FHF worldwide. In about one third of cases of presumed viral FHF, no specific agent can be identified.²⁴⁷ Fulminant hepatic failure can also be associated with infection with multiple viruses.^{248,249} In 1 French study, 15% of patients with FHF were affected with acute viral hepatitis, HBV either alone (32%) or together with HDV (13%), HAV (4%), and non-A, non-B, non-C virus (2%) and herpes virus (1%).²⁴⁴⁻²⁴⁷ In a similar British study between 1972 and 1988, the viral causes of FHF included HAV in 6%, HBV in 13%, and non-A, non-B virus in 13%. Another 7% of patients were presumed infected with a virus that was not identifiable.²⁴⁴⁻²⁴⁷

Once the diagnosis of FHF has been established by presence of encephalopathy, jaundice, and coagulopathy, prognosis is extremely poor, with survival expected from days to weeks.^{244,245} Liver failure in this setting can be classified into hyperacute, acute, and subacute forms, reflecting different clinical patterns of illness, etiology, and prognosis. In addition to the hallmark symptoms of encephalopathy and coagulopathy, clinical symptoms and signs in FHF may include those of multiorgan failure developing secondary to tissue hypoxia, endotoxemia, cytokine release, and

macrophage activation.²⁴⁷ Intensive care and support of hemodynamic, septic, and cerebral complications are essential.²⁴⁵ Liver transplantation is the primary treatment modality recognized for patients with severe FHF. The early identification of patients unlikely to survive without liver transplantation is important to maximize the efficiency of listing for liver transplantation. Survival in those patients who undergo transplantation may be in excess of 75%.²⁴⁴

Therapeutic options and treatment modalities for chronic viral hepatitis

Treatment options for chronic viral hepatitis are limited, consisting primarily of 3 drug classes: the interferons, synthetically produced versions of the naturally occurring cytokine typically produced as part of the immune response to infection; antiviral nucleoside analogues, such as ribavirin, lamivudine, and famciclovir; and nonnucleoside antiviral drugs such as amantadine and rimantadine. The interferons, ribavirin, and lamivudine are FDA-approved for use in chronic viral hepatitis or other viral diseases, whereas famciclovir is currently in late-stage clinical development in the US. An overview of these drug classes, their mechanisms of action, clinical efficacy, and safety is provided below.

Interferons. Alpha interferons are a family of naturally occurring proteins that are secreted by many mammalian cells. There are many structurally related classes of alpha interferons recognized; however, out of 20 or more subtypes only 5 forms have been successfully evaluated and proven effective in large, controlled trials: 1) interferon alfa-2b (INTRON A; Schering-Plough Corporation; Kenilworth, NJ); 2) interferon alfa-2a (Roferon-A; Hoffmann-LaRoche, Inc., Nutley, NJ); 3) interferon alfa-n3 (Alferon; Interferon Sciences, Inc.; New Brunswick, NJ); 4) interferon alfacon-1 (Infergen; Amgen Inc., Thousand Oaks, Calif); and 5) interferon alfa-n1 (Wellferon; Glaxo Wellcome Inc., Research Triangle Park, NC). Interferon alfacon-1 is a consensus product that contains approximately 16 forms of interferon, whereas interferon alfa-n1 is a naturally occurring interferon molecule. Interferons interfere with viral replication by an as-yet-unknown mechanism. Nevertheless, in addition to antiviral activity, they possess immunoregulatory and anti-inflammatory properties. The potency of most alpha interferon products is indirectly determined by measuring activity in biologic assays relative to an international reference standard, expressed in million Units (MU).

In contrast, the potency of interferon alfacon-1 is standardized in micrograms. Given the disparate assays that are used to determine potency of these biologic products, dosing comparisons between them are difficult at best. Although the different interferons may have slightly different structures and profiles of action, their overall clinical efficacy and side-effect profiles are similar.

Numerous alpha interferon treatment regimens for hepatitis B, C, and D have been explored in controlled and uncontrolled clinical trials.²⁵⁰⁻²⁵⁶ Response to therapy for HCV is defined on the basis of both biochemical responses (normalization of ALT) or virologic responses (undetectable serum HCV RNA) or both.^{43,257} Hepatitis C viral RNA is the most reliable indicator of response to treatment, particularly if the most sensitive assay systems based on RT-PCR are used. Response is determined at the end of an initial course of therapy (ETR) and again after some period of time has elapsed (usually 6 months) after completion of therapy (SR). Ideally, both ETR and SR are goals of therapy; persistence of normal ALT and/or undetectable HCV RNA for at least 6 months posttreatment is a typical definition of an SR. Once SR is achieved, over 90% of patients remain in short-term (2 to 10 years) durable responses and the overall prognosis is good. Low-dose, high-dose, and escalation schemes have all been employed for alpha interferons; high-dose therapy has shown little improvement over the conventional regimens recommended in the product labels and is associated with increased side effects.²⁵⁸⁻²⁶¹ Long-term sustained response rates for interferon monotherapy are disappointing and range from 14% to 45% for HBV²⁶²⁻²⁶⁹ and 15% to 20% for HCV.^{42,43,270} Improved response rates were associated with longer-term therapy, with 12 months of treatment now becoming the standard for hepatitis C monotherapy.^{42,43}

A wide range of side effects associated with alpha interferons have been described;²⁷¹ approved labeling for the specific interferon product selected should be reviewed for dosing recommendations and side-effect profile before initiation of therapy. Common side effects consistent with the known actions of these cytokines include fever, myalgia, headache, fatigue, and arthralgia, which together are described as a "flulike" syndrome. These side effects are most prominent early in therapy and can occur in up to 82% of individuals, but do not require dose reduction unless the intensity is severe.

Symptoms tend to decrease with continued exposure or dose adjustment, and it is recommended for most interferons that they be administered at bedtime, with acetaminophen pretreatment to reduce symptom severity.

One category of significant side effects not clearly related to the mechanism of action of interferon includes neuropsychiatric complications such as depression (including suicidal thoughts and, rarely, attempts), irritability, and anxiety.^{272,273} These side effects can occur in up to 20% of treated patients, and represent a significant risk of comorbidity.²⁷²⁻²⁷⁴ Emergence of depressive symptoms appears to be related to duration and intensity of interferon therapy in several surveys.^{221,273,275} Other than a prior history of affective disorders,²⁷⁵ no specific patient characteristics have been identified that predict the potential for emergence of neuropsychiatric symptoms. Thus, treatment with interferon requires the clinician to pay significant attention to changes in mood, behavior, and cognitive performance of patients during therapy. Neuropsychiatric symptoms may or may not respond to drug withdrawal or dose adjustment, but in refractory cases antidepressant therapy may prove useful.^{273,276}

Other major side effects commonly observed with interferon include suppression of bone marrow, with resulting granulocytopenia, thrombocytopenia, anemia, and alopecia. Induction of autoimmune thyroid disease is rare, but has been reported to develop in approximately 5% of patients. It should also be noted that these side effects are usually dose-related.²⁷² Contraindications for interferon included in product labeling for some but not all interferons include hepatic decompensation, severe chronic obstructive pulmonary disease, severe myelosuppression, severe cardiovascular disease, or preexisting severe psychiatric conditions such as major depression.

Nucleoside analogues. Drugs typically employed against human immunodeficiency virus (HIV), respiratory syncytial virus, and other viral diseases that act through interference with RNA (ribavirin) or DNA (lamivudine, famciclovir) synthesis have shown some clinical utility against viral hepatitis. Ribavirin is a guanine nucleoside analogue with broad antiviral properties. The mechanisms of action of ribavirin are not fully understood but may include inhibition of synthesis of viral RNA (guanosine triphosphate incorporation) by an effect on inosine monophosphate dehydrogenase, as well as

enhancement of type 1 helper T-cell responses to increase viral clearance. Ribavirin has no discernible effect on RNA polymerase.²⁷⁷ Results from multicenter and multinational trials in HCV indicate that combination therapy with interferon alfa-2b and ribavirin (REBETRON Combination Therapy, Schering-Plough Corporation) significantly improves the overall response rate compared with interferon alone and produces clinically significant improvements in histologic markers. Effectiveness of combination therapy exceeds that of either treatment alone, indicating a favorable potentiation of interferon effects by the immune-modulating actions of ribavirin.^{221,278-281} The most prominent side effect of ribavirin is a dose-dependent hemolytic anemia that occurs in the majority of patients,^{272,282-284} with hemoglobin decreasing up to 2 g/dL during the first 4 to 6 weeks after initiation of therapy. The decrease in hemoglobin is accompanied by a parallel decrease in red cell count and a rise in total bilirubin levels, typical for hemolytic anemia. Depressed hemoglobin levels reversed after the drug was discontinued and were comparable with baseline by approximately 4 weeks after treatment. Individuals with coronary artery disease may be at increased risk of angina or myocardial infarction if they develop severe anemia secondary to ribavirin treatment; thus, individuals with preexisting anemia or baseline hemoglobin of less than 12 g/dL should not be considered for this form of therapy.²⁷² An additional side effect of ribavirin is its potential for teratogenicity. Individuals (both male and female) receiving this form of therapy should be on a reliable birth control method. The most frequent side effects of the combination of interferon and ribavirin show no signs of synergy. Fatigue, malaise, flulike symptoms, and anemia are mild to moderate and reversible with dose modification or discontinuation.^{272,285} Other minor side effects for ribavirin include dry cough, itching, and mild shortness of breath.

More recently, 2 nucleoside analogues, lamivudine and famciclovir, have been used in chronic hepatitis, exclusively for HBV. Early results were equivocal; treatment with lamivudine resulted in significant suppression of serum HBV DNA within 4 weeks of therapy, but viral suppression appeared to be temporary and virologic and clinical relapse occurred after treatment was stopped.²⁸⁶ Subsequent studies employing longer treatment regimens of lamivudine (12 to 18 months) provided better responses; daily doses of 100 and 300 mg reduced

HBV DNA to undetectable levels that were maintained after cessation of therapy.^{287,288} In 1 report the sustained HBeAg seroconversion rate increased from 17% after 1 year of treatment to 27% after 2 years of treatment. Histologic improvements of 38% to 52% over those of placebo treatment have also been observed.²⁸⁹

The emergence of drug-resistant mutant (variant) HBV strains (YMDD-variant strain of HBV) remains an issue of concern,²⁹⁰⁻²⁹² particularly in transplant recipients, in whom emergence of resistant strains has been associated with increased rates of graft rejection.^{293,294} Several studies indicate that combination therapy with interferon or other agents may improve these results.²⁹⁵⁻²⁹⁷ In 1 study HBeAg seroconversion rates were similar for lamivudine monotherapy (1 year) and standard alpha interferon therapy (4 months). The combination of lamivudine and interferon increased the HBeAg seroconversion rate over either treatment alone.²⁹⁷ Lamivudine is likely to be of most benefit to patients with reduced ability to clear HBV (ie, immunocompromised patients,^{298,299} transplant recipients,^{300,301} or patients with active chronic hepatitis B and/or active cirrhosis).³⁰²

Although initially promising, fully published data on the efficacy and safety of famciclovir in HBV are not currently available. Newer nucleoside analogues (eg, adefovir) may have better antiviral effects, but their efficacy and safety are currently under investigation.

Amantadine and rimantadine. Amantadine and its structural congener, rimantadine, are antiviral agents active against the influenza A virus. Both agents appear to interfere with the early stages of influenza viral replication and produce nonspecific inhibition of HCV replication in the absence of direct effects on HCV protease, helicase, ATPase, or RNA-dependent RNA polymerase.³⁰³ Both agents have been evaluated as monotherapy against chronic hepatitis C, with equivocal and disappointing results.³⁰⁴⁻³⁰⁷ Although monotherapy improved biochemical (ALT) responses, no effect was seen on viral clearance per se, indicating a possible anti-inflammatory mechanism rather than direct antiviral action. Amantadine and interferon combination therapy, although initially promising, does not seem to hold great promise. Combining amantadine with both interferon and ribavirin remains promising and is currently being investigated.³⁰⁷

Other therapeutic options. Numerous other

treatments are being explored for therapy of chronic viral hepatitis. Several excellent reviews are available on these treatments,¹⁸ which include non-specific immunomodulatory therapy with thymosin,^{308,309} interleukins^{310,311} or levamisole,^{312,313} and specific anti-HBV immunomodulatory therapy such as pre-S or S peptide vaccines^{201,314} or DNA vaccines.³¹⁵⁻³¹⁷

Another important advance in the treatment of viral hepatitis is the development of pegylated forms of alpha interferon. Two recent additions to the treatment armamentarium for chronic hepatitis C include pegylated forms of interferon. The 2 drugs are PegIntron (Schering-Plough), a pegylated form of INTRON A, and Pegasys (Hoffmann-La Roche), a pegylated form of Roferon-A. Both drugs significantly enhance the pharmacokinetic properties of their respective interferon molecules and provide a more sustained suppression of HCV. In recent unpublished trials of PegIntron and Pegasys, sustained virologic response rates were approximately 2-fold greater compared with their respective interferon molecules (ie, interferon alfa-2b and interferon alfa-2a, respectively). From these preliminary reports, it seems that pegylated interferon monotherapy may not be superior to interferon alfa-2b and ribavirin combination therapy. However, combining pegylated interferons with ribavirin may further enhance sustained virologic response, especially in treatment-resistant genotype 1 virus. Studies to investigate the activity of pegylated interferons in combination with ribavirin are underway and may provide the best short-term alternative for patients with chronic hepatitis C.

Role of referral to specialist centers

As noted above, treatment of acute viral hepatitis is mainly supportive and can be provided by primary care physicians. However, in cases of severe hepatitis with development of coagulopathy or any indication of hepatic encephalopathy, early referral to a gastroenterologist/hepatologist is crucial. It would be important not only to provide the most up-to-date evaluation (Figure 2), but at the same time to make sure the appropriate treatment, including consideration of liver transplantation, is provided.

In terms of the role of referral for chronic viral hepatitis, the initial diagnosis of chronic hepatitis B and C (evaluation with serologic testing and

establishment of chronicity by abnormal ALT for 6 months) can be performed by primary care physicians (Figures 3 and 4¹⁸). The role of gastroenterology referral may be important not only for liver biopsy, but also to ensure that the most up-to-date treatment is provided. However, in noncomplicated patients with chronic hepatitis B or C, treatment may be initiated by a primary care physician well versed in managing side effects of antiviral agents and monitoring tests. In this setting, close and periodic consultation with an expert gastroenterologist/hepatologist remains crucial, and a team approach is the best alternative.

Role of liver transplantation for viral hepatitis

Both HBV and HCV are important causes of liver failure requiring liver transplantation. It is estimated that HCV accounts for 20% to 25% of all transplant cases, whereas HBV accounts for less than 5%.^{189,300,318} In a recent study of US veterans, 45% of liver recipients were infected with HCV.³¹⁹ Both HBV and HCV can recur after liver transplantation.

Hepatitis B. The probability of HBV recurrence after liver transplantation is very high without therapy, and the prognosis is dismal.³⁰¹ Therapy with HBIG in patients with HBV (without HCC) can improve short-term survival;^{189,190,320} thus, HBV is currently not a contraindication to transplantation. The role of newly developed nucleoside analogues in the posttransplant setting is currently being evaluated.^{300,301,321,322} In 1 study, lamivudine therapy was able to produce suppression of viral DNA and viral antigens in almost all patients. Disease-free survival of 81% at 24 months is similar to results obtained with HBIG therapy. Lamivudine was effective, safe, and well tolerated, and is changing the outlook of liver transplantation for patients with chronic hepatitis B.³²²

Hepatitis C. In patients with chronic hepatitis C, posttransplant recurrence of viremia is almost universal. Although mild, chronic hepatitis C can occur in 50% to 60% of transplant patients, and aggressive and progressive hepatitis with cirrhosis occurs in approximately 10% to 15% of posttransplant patients.^{189,318} Although interferon alone has been used in some studies,^{323,324} the efficacy of this type of therapy to achieve sustained virologic response is low.^{325,326} An increased risk of graft rejection has been suggested for interferon thera-

py³²⁵ but this has not been observed in all studies.^{323,324,327} Thus, interferon monotherapy is not recommended as routine for treatment of post-transplant HCV. Preliminary data from a single small study using short-term interferon and ribavirin²⁷⁸ showed modest virologic responses in the absence of increased rejection, but long-term data on sustained virologic response are lacking. It is important to remember that ribavirin-induced hemolysis could be severe, requiring smaller doses and very careful monitoring. This combination therapy remains promising³²⁸ and is currently being evaluated in large, multicenter, randomized clinical trials.

Screening for hepatocellular carcinoma

Patients with HBV and HCV are at increased risk for development of HCC,^{94,329,330} although this risk appears to be reduced in patients successfully treated. Interferon-associated reduction in HCC risk may be greater for chronic hepatitis C patients with no evidence of HBV infection.³³¹ In 1 report, the incidence of HCC per 100 person-years of follow-up was 3.7 for HCV-positive and 2.0 for HBsAg-positive patients, and 6.4 in those with dual infection. Multivariate analysis indicated that age > 50 years (hazard ratio, 4.5), male sex (hazard ratio, 2.8) and HBsAg/HCV co-infection (hazard ratio, 2.3) were independent predictors of HCC development.⁹⁴ The presence of cirrhosis dramatically increases the risk of HCC. Indeed, the risk of HCC in HCV-infected individuals increases to 1% to 4% per year after cirrhosis has developed, in contrast to a more modest 1% to 4% over 2 decades in the absence of cirrhosis. In hepatitis B, the risk of HCC is especially increased in those with active viral replication and histologic cirrhosis. The risk of HCC in the so-called "healthy carriers" remains controversial. Although healthy carriers born in HBV endemic regions may be at an increased risk of HCC, similar data for the Western populations do not support such an association.

Because of the substantial mortality associated with HCC, screening regimens are advocated for chronic viral hepatitis.^{329,332-334} However, for a screening program to be effective, it has to meet a number of objectives: 1) the screening test should be inexpensive and simple, 2) the population should be well defined with relatively high prevalence of the disease, and 3) the therapy should be effective in reducing morbidity and mortality. In the case of

HCC only some of these criteria are met, with the most problematic issue being effective treatment modality. In the era of liver transplantation for small, limited HCC, outcomes may be changed. The most common screening methods for HCC include alpha fetoprotein (AFP) and ultrasound. Elevated AFP levels are commonly found in HCC; however, sensitivity and specificity depend on the cut-off level used.³³⁵⁻³³⁷ The finding of hypoechoic lesions detected by ultrasound is strongly suggestive of HCC.³²⁹ However, the presence of nodular liver in cirrhosis can reduce the specificity of ultrasound scanning.^{329,332} The literature contains numerous studies concerning screening using 1 test, or a combination with various frequencies (every 3 to 12 months). One screening procedure that is commonly practiced in all patients with HBV infection and in cirrhotic patients infected with HCV is AFP and liver ultrasound (every 6 to 12 months). To date, no method of screening has been definitively proven to affect mortality related to HCC.^{335,338,339}

Treatment recommendations for specific viral etiologies

Chronic hepatitis B. The goal of therapy in chronic HBV infection is to reduce or arrest the progression of liver injury by suppressing viral replication and clearing the virus from the body.¹⁸ Successful therapy is associated with sustained loss of markers of viral replication (HBeAg) and for the viral genome (HBV DNA)³⁴⁰ as well as by histologic improvement. Seroconversion from HBeAg positive to anti-HBe positive status is typically a good prognostic sign associated with clearance of viral DNA markers.³⁴¹

Treatment options for adult patients with well-compensated chronic HBV include interferons, or lamivudine and other nucleoside analogues in clinical trials.^{18,264,265,342,343} Treatment with alpha interferon is associated with HBeAg seroconversion in over 50% of patients, with an apparent cure rate of 14% to 45%.²⁶²⁻²⁶⁹ The use of alpha interferon therapy in hepatitis B (and C and D) is summarized in **Table 6**. Factors associated with a more favorable response to interferon therapy include elevated ALT, low titers of HBV DNA, adult-acquired HBV infection, and HIV and HDV negativity. In hepatitis B patients who have low or near-normal ALT levels, efficacy of interferon is considered to be low. Although interferon therapy reduces the risk of HCC in patients with HBV-associated cirrhosis,^{263,344,345} safety is a

TABLE 6
INTERFERON THERAPY* FOR CHRONIC HEPATITIS

Hepatitis B virus (HBV)

Regimens	Interferon alfa-2b 30 to 35 million units a week subcutaneously for 4 months Interferon alfa-n1 Lamivudine 100 mg/day Experimental protocols with famciclovir or adefovir
Primary end points [†]	Suppress hepatitis B viral replication (hepatitis B e antigen and HBV DNA) Loss of hepatitis B surface antigen
Secondary end points [†]	Development of anti-HBs Improvement in histology
Comments	Elevated alanine aminotransferase level (> twice upper limit of normal), low titers of HBV DNA, absence of cirrhosis on biopsy Adult-acquired HBV infection, and HIV and hepatitis D negativity, are associated with favorable response Prednisone pretreatment may enhance the response to interferon, but should be used in specialized centers only In most cases, HBV-DNA suppression occurs within 4 weeks (lamivudine) Development of drug-resistant, YMDD-variant strains usually develop approximately 8 months after lamivudine therapy

Hepatitis C virus (HCV)

Regimens	Interferon alfa-2b 3 million units three times a week subcutaneously plus ribavirin 1,000 to 1,200 mg in divided (twice a day) daily doses for 6 to 12 months [‡] For those who are not candidates for ribavirin, 3 choices are available: Interferon alfa-2b 3 million units three times a week subcutaneously for 12 months [§] Interferon alfa-2a 3 million units three times a week subcutaneously for 12 months [§] Interferon alfacon-1 9–15 µg three times a week subcutaneously for 6–12 months [§]
End points [†]	Disappearance of virus at the end of therapy that is sustained for at least 6 months [†] follow-up (HCV RNA by polymerase chain reaction) Improvement in histology
Comments	Factors associated with a more favorable response to interferon therapy include a low level of virus, early eradication of virus, genotype other than genotype 1 and absence of cirrhosis on liver biopsy

Hepatitis D virus (HDV)

Regimen	5 million units/day or 9 million units three times a week for 1 to 6 months
End point [†]	Disappearance of virus at the end of therapy that is sustained for at least 6 months [†] follow-up

*Contraindications to interferon therapy include severe depression or psychiatric disease, decompensated cirrhosis, or thrombocytopenia and leukopenia.

[†]Common side effects of interferon therapy include fever, myalgia, headache, fatigue, arthralgia, and "flu like" syndrome. Less common side effects include neuropsychiatric problems such as depression, irritability, and anxiety. Serious but uncommon potential side effects include suppression of bone marrow with potential resulting granulocytopenia, thrombocytopenia, anemia, alopecia. Rare side effects include induction of autoimmune thyroid disease.

[‡]Common side effects for ribavirin are not synergistic with interferon, and may include dose-dependent hemolytic anemia and potential teratogenicity. Patients of childbearing potential (male and female) should use effective contraceptive methods while taking ribavirin.

[§]12 month course of interferon monotherapy only in those with HCV RNA negative after 12 weeks of therapy.

major concern in patients with decompensated cirrhosis.³⁴⁶ Interferon treatment in these patients is associated with increased risk of severe thrombocytopenia or leukopenia and infection,³⁴⁷ and interferon monotherapy should not be considered routine in

decompensated HBV cirrhosis. Lamivudine is now considered the treatment of choice for patients with decompensated cirrhosis and HBV.³⁴⁸ Increasing data suggest that lamivudine can result in sustained viral suppression with minimal side effects. The efficacy is

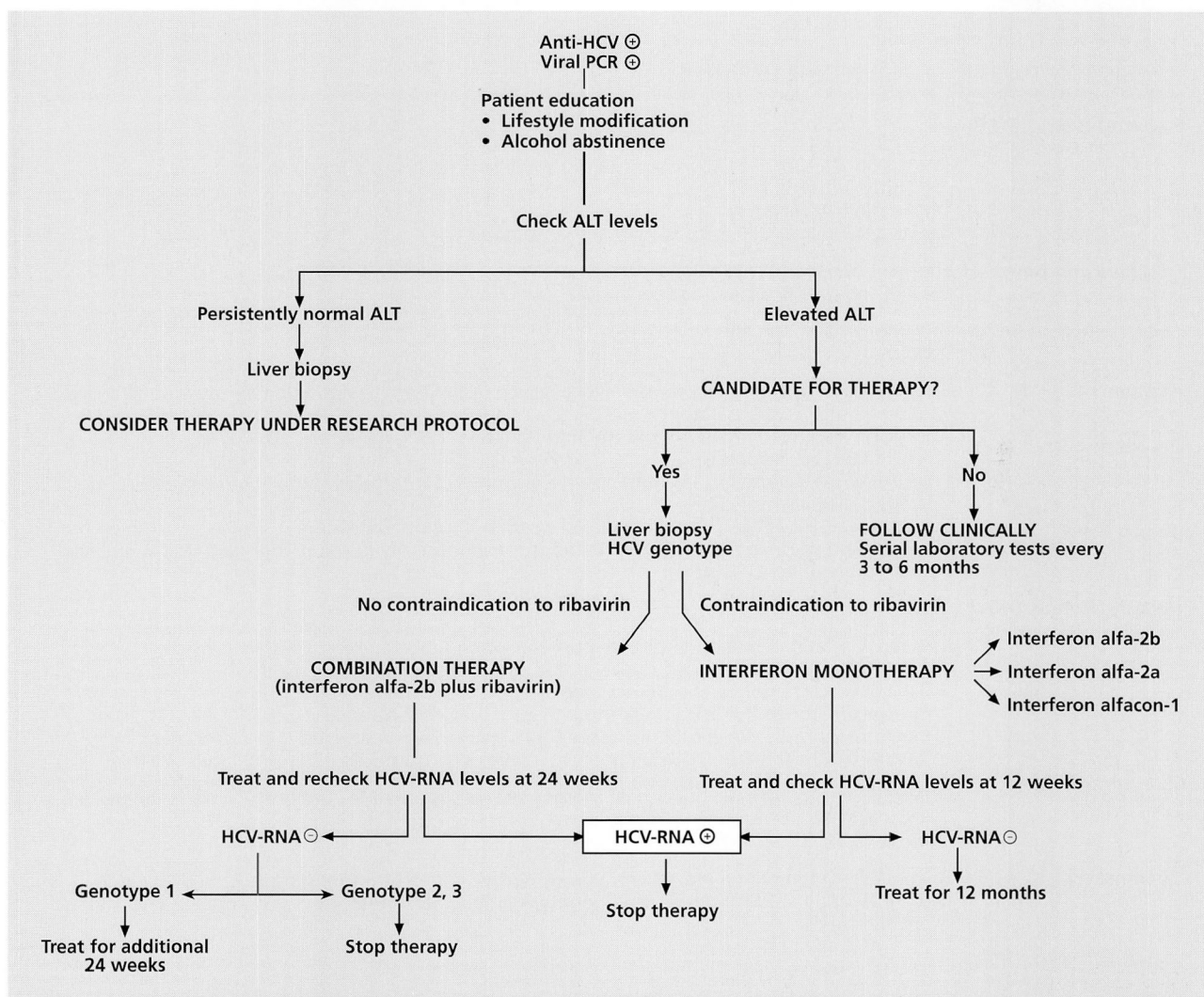


FIGURE 5. Algorithm for treatment of hepatitis C virus (HCV) infection. PCR = polymerase chain reaction; ALT = alanine aminotransferase.

higher in those with ALT greater than 5 times normal. The YMDD variant of hepatitis B can develop during therapy in cumulative rates (with 60% to 70% of treated patients developing it over 4 years of treatment). Despite this, continued treatment may result in HBeAg seroconversion, although in lower rates (Table 6). Newer antiviral agents such as the nucleoside analogues are available in the context of clinical trials or compassionate-use programs in the US.^{342,349} One approach to treatment of chronic hepatitis B is summarized in Figure 3.

Chronic hepatitis C. The National Institutes of Health Consensus Development Conference on the management of hepatitis C, which took place in

March 1997 and was published in September 1997, established guidelines for the diagnosis and management of chronic hepatitis C.⁴² Because strides have been made in the treatment of chronic hepatitis C, some investigators have attempted to informally update these guidelines.⁴³ Interferon-based therapy was recommended for those patients at highest risk for progression to cirrhosis, namely those with persistent elevations of ALT for greater than 6 months, detectable serum HCV RNA, and liver biopsy exhibiting some fibrosis with at least moderate inflammation or necrosis (Figure 5). The indication for therapy is less obvious in patients with milder histologic changes, persistently normal ALT,

and age < 18 years or > 60 to 65 years.

In order to optimize interferon therapy for patients with chronic hepatitis C there are some pretreatment and treatment factors that are associated with a more favorable response to therapy. The pretreatment factors associated with better response include low viral load (less than 2 million copies/mL), HCV genotype other than 1, and absence of advanced fibrosis or cirrhosis on liver biopsy.³⁵⁰⁻³⁵² Although patients with high viral titers and infection with genotype 1 usually have a lower rate of response, these factors cannot be used to select against patients with the so-called "poor prognosticators." In multiple studies of interferon monotherapy, the best predictor of sustained virologic response was early eradication of virus within the first 3 months of therapy.³⁵³ For those patients who clear HCV within the initial 3 months of treatment, a full 12-month course is associated with 15% to 20% SR.

Given the suboptimal response to alpha interferon monotherapy, alternative agents have been used, alone or in combination with interferon. These agents include ribavirin, amantadine, ursodeoxycholic acid, nonsteroidal anti-inflammatory drugs, quinolone, and corticosteroids. Although most of these studies are small, the only agent with proven efficacy for treatment of HCV is ribavirin (REBETOL; Schering-Plough Corporation). When ribavirin at doses between 1,000 to 1,200 mg daily is combined with interferon alfa-2b (REBETRON Combination Therapy), the sustained virologic response rate is increased to 31% to 43% in patients previously untreated with interferon.^{221,222} The response to combination therapy with interferon alfa-2b plus ribavirin was affected by several factors, with HCV genotype and pretreatment viral load representing the most important. In a large, randomized, controlled trial of over 1,000 patients with HCV (previously untreated), SR was 17% for genotype 1, which increased to 29% after a full 12-month course.^{221,222} This extension in duration of therapy to full 12-month course was not applicable to HCV genotypes 2 and 3. Additionally, the early response rule (undetectable HCV RNA after 3 months of therapy) does not apply to the combination regimen (ie, patients can achieve HCV-RNA eradication after 3 months with continuing treatment). However, patients who are treated with a 6-month course of combination therapy with detectable HCV RNA are unlikely to respond to

continued therapy. These patients should be considered for an alternative treatment protocol in a clinical trial setting.

In patients who are considered to have relapsed to alpha interferon monotherapy, higher dose alpha interferon (eg, Infergen 15 μ g three times weekly [TIW]) or combination therapy (interferon alfa-2b plus ribavirin) have been used with good response. In this group, sustained virologic response rates ranged from 44% to 52% of patients retreated (ie, after relapse) with 6 months of interferon alfa-2b plus ribavirin therapy.²²⁰ In addition, in a large study conducted using interferon alfacon-1 9 μ g TIW for 6 months, 12% of patients achieved sustained virologic responses.³⁵⁴ In a separate trial using higher doses of interferon alfacon-1 (15 μ g TIW for 6 months) in HCV-relapsed patients, sustained virologic responses were observed in 28%.³⁵⁴ Sustained responses improved to 58% in relapsers treated for 1 year with high-dose interferon alfacon-1.

Finally, re-treatment of alpha interferon-resistant patients is especially problematic. Re-treatment of the so-called nonresponders with combination interferon alfa-2b plus ribavirin therapy has been associated with an SR of 5% to 20%. This compares with 13% of interferon nonresponders retreated with interferon alfacon-1 15 μ g TIW for 12 months.³⁵⁴ Given the dissimilarity of patients included in these trials, these rates cannot be compared directly. Trial results comparing high-dose interferon alfacon-1 with interferon alfa-2b plus ribavirin therapy in alpha interferon nonresponders have not been available. Patients who do not respond or relapse after combination therapy are especially problematic because there are at present no further established treatment options for this patient subgroup. Using pegylated interferon in combination with ribavirin as treatment or pegylated interferon monotherapy as a maintenance regimen is promising and is the subject of recent large-scale clinical trials.

The 1997 NIH Consensus Conference suggested to treat patients with persistently normal ALT in a protocol setting. Most trials of patients with normal ALT with interferon monotherapy have suggested very low SR. On the other hand, preliminary unpublished data using interferon and ribavirin in combination are promising, but the full data on the efficacy and safety of these agents await full publication.

Chronic hepatitis D. The mainstay of treatment for chronic hepatitis D remains interferon

therapy, despite relatively low response rates and high rates of relapse after cessation of therapy. Because HDV is entirely dependent on HBV for replication, strategies aimed at eliminating HBV will also be effective in reducing HDV infection. In approximately half of patients with chronic hepatitis D treated with high doses of interferon alfa-2a (9 MU TIW for 1 year), serum ALT returns to normal, HDV RNA becomes undetectable in serum, and liver histology improves. However, relapse is common after treatment cessation.³⁵⁵ A recently published meta-analysis assessed the efficacy of interferon in 5 controlled and 10 uncontrolled trials conducted between 1987 to 1994.³⁵⁶ Doses ranged from 1.5 MU/day to 18 MU TIW for 1 to 9 months. Sustained response occurred in approximately 6% of patients. However, in other controlled studies that evaluated doses of up to 5 MU/m² for short periods of time, reported SRs were between 20% to 25%.³⁵⁷ Finally, another recent randomized clinical trial used a dose of 9 MU TIW for 1 year. Serum ALT levels normalized or significantly improved within 3 months of initiating treatment and remained improved in 54.5% of treated patients after 1 year of treatment, compared with 18% of untreated patients.³⁵⁸ Moreover, 79% of treated patients cleared HDV RNA and exhibited improvement in histologic scores compared with 36% of untreated patients. Following cessation of therapy, all patients but 1 experienced a biologic and/or virologic relapse over the 6-month follow-up. In conclusion, these data confirm that HDV is sensitive to inhibition by alpha interferon, although the schedule used did not achieve permanent control of the disease.³⁵⁸

MANAGEMENT OF SPECIAL GROUPS

Management issues in pediatric hepatitis

Hepatitis A. Pediatric infections account for more than one third of the recognized cases of hepatitis A. Children generally experience a milder clinical course than adults, and clinical manifestations of HAV in children may go unrecognized.³⁵⁹⁻³⁶¹ By far the most favored option for management of HAV in children is prevention. Previously, passive immunization with pooled immune serum globulin was the only available option for providing temporary immunity to HAV infection. Pooled immune globulin is effective when administered within 2 to

3 weeks of exposure; unfortunately, the window of opportunity is often missed because the majority of cases may be asymptomatic or unrecognized.³⁶² Vaccination is replacing the use of passive immunization as the prophylaxis of choice for HAV.

The pediatric dosage for the 2 available vaccines is quantitated in **Table 3**. Under these schedules seroconversion rates of 95% or greater have been reported.^{164,165,363,364} These vaccines have been proven safe and effective in children across the entire pediatric age range, from preschool age³⁶⁵ to 2 to 5 years of age³⁶³ and up to 15 years of age.³⁶⁶ Hepatitis A vaccination has also been shown safe and effective in children at increased risk of parenteral transmission of HAV, such as children with hemophilia.³⁶⁷

Once HAV infection has been acquired, treatment is comparable with that recommended in adults. Intervention is primarily symptomatic, with recommendations for adequate rest, hydration, and nutritional support.

Hepatitis B. Although children account for a relatively small number of new HBV cases each year (4,000 to 6,000),³⁶⁸ most HBV infections occur during the first year and are attributed to vertical transmission from HBV-infected mothers. Vertical transmission rates in viremic patients can be as high as 90%.³⁶⁹ A large number of perinatally acquired cases of HBV will become chronic "healthy carriers" of HBsAg.

In a 20-year follow up of children with HBV infection, only 4% developed severe outcomes such as cirrhosis or HCC; in all cases cirrhosis was an early complication.¹⁶⁷ The exact incidence of HCC in children is unknown, although cases have been reported in children as young as 8 months of age.⁹³ No current guidelines exist for monitoring children with chronic HBV infection, although in chronically infected adults periodic ultrasonographic examinations and serum AFP levels are performed.

As for all hepatitis viruses, prevention of infection is preferred over treatment of acute or chronic infection. Since 1991 it has been recommended that all infants, and all children who have not previously been vaccinated, receive the vaccine series. Two recombinant vaccines are available for prevention of HBV.¹⁶² Following vaccination, protective levels of anti-HBs are demonstrated in 95% of children.^{162,370}

As in adults, postexposure immunoprophylaxis with HBV vaccine and HBIG can effectively prevent infection after exposure to HBV. Serologic

testing of all pregnant women for HBsAg is essential for identifying infants who require postexposure immunoprophylaxis beginning at birth to prevent perinatal HBV infection.

Recombinant interferon alfa-2b is effective and is the only approved antiviral agent for chronic hepatitis B in children older than 2 years. Recent studies suggest that a 3- to 6-month course of interferon in doses ranging from 5 to 10 MU (5 MU/m²) given daily or TIW results in a clinical, biochemical, and serologic remission in 30% to 40% of HBV-DNA-positive HBeAg-positive patients with well-compensated liver disease.³⁷¹ Favorable prognostic factors are similar to adults. Nevertheless, > 50% of children with chronic hepatitis B do not respond to interferon treatment and many continue to exhibit high viral replication rates and progressive liver disease. For these patients, re-treatment has been considered as an option, but with little formal support from clinical data. In 2 HBV re-treatment trials the response rate to a second course of interferon ranged from 11% to 44% in children.³⁷² Seroconversion occurred in 33% of the re-treated children and in 26% of the controls. These data indicate that re-treatment with interferon monotherapy in nonresponding children with chronic HBV is safe but does not significantly increase HBeAg/anti-HBe seroconversion compared with the spontaneous seroconversion rate of patients without retreatment.³⁷² Future studies should focus on the safety and efficacy of newer antiviral agents alone or in combination with interferon.³⁷³⁻³⁷⁷

Hepatitis C. The seroprevalence of HCV infection is 0.2% for children less than 12 years of age and 0.4% for children/adolescents 12 to 19 years of age.³⁷⁸ To date, blood transfusion has been the principal route of acquisition of HCV in children, but vertical transmission may also play a role.^{81,378} The risk of perinatal transmission may increase with HIV co-infection and high levels of maternal viremia. The mode of delivery and breast feeding do not seem to affect the vertical transmission of HCV.³⁷⁸

The natural history of HCV in childhood is not well understood. The clinical picture of acute disease in children is indistinguishable from HAV or HBV. Although most pediatric patients are asymptomatic, HCV infection acquired early in life may be associated with biochemical features of liver damage during the first 12 months of life. Chronicity seems to occur in the majority of cases.³⁷⁸

Compared with adults, chronic hepatitis C in children is characterized by both low ALT levels and low viral load, as well as mild histologic changes.³⁷⁹ Finally, cirrhosis is rare. The prognosis seems to be worse in children receiving multiple exposures to blood products.^{367,380,381}

As noted previously, immune globulin provides no protective immunity to HCV, and vaccines are not available.

Diagnosis of perinatal transmission relies on HCV-RNA testing. Maternal anti-HCV may persist until 18 months of life, giving rise to false-positive tests. During early life, accuracy of anti-HCV testing is variable; thus, detection of HCV RNA may be necessary for accurate diagnosis.³⁷⁸ Recommendations for HCV screening include the following.

- Infants \geq 18 months of age born to HCV-infected women should be tested with anti-HCV. Passively acquired maternal antibody is unlikely to persist longer than 18 months.
- Children with a risk for HCV (eg, blood product transfusion) should be screened for HCV.
- All children who are known to be chronically infected with HCV should receive periodic testing, but definitive recommendations on what type of tests and the frequency of these tests are not known.

Recombinant interferon alfa-2b is licensed in the US for the treatment of chronic HCV infection in adults, but is not yet approved for use in children. Several small- to moderate-sized trials have assessed the efficacy of interferon in children at doses ranging from 3 to 5 MU 2 to 3 times per week for up to 12 months.³⁸²⁻³⁸⁴ Response rates appear to be similar to adults.³⁸²⁻³⁸⁴ Trials of interferon-based combination regimens or pegylated products are currently underway.

Children with HCV RNA and persistently elevated serum aminotransaminase levels should be referred to a pediatric gastroenterologist for additional evaluation and management.

Hepatitis D. Perinatal transmission of HDV is rare, but horizontal, nonparenteral transmission of HBV and HDV among siblings may play a major role in transmission within a household.¹¹⁷ In children, as in adults, superinfection of a chronic HBV carrier with HDV can exacerbate previously stable chronic HBV disease.¹²¹ In 1 series of HDV cases,³⁸⁵ 66% were co-infections with HBV and HDV, and 34% had HDV superinfection. The clinical course was fulminant in 3 cases (2 cases of HBV and HDV

co-infection and 1 case of HDV superinfection). The majority of co-infected cases progressed to chronic HBV/HDV with active chronic hepatitis.

Prevention and vaccination are similar to that recommended for adults.

There are no currently licensed drugs for the treatment of chronic hepatitis D in children. Similar to adults, interferon therapy has met with variable success in children with HDV infection. In about 50% of HDV-infected patients treated with high doses of interferon alfa-2a (9 MU TIW for 1 year), serum ALT levels normalize, HDV RNA becomes undetectable in serum, and liver histology improves.^{355,386} However, most patients relapse when interferon is discontinued.^{355,387-390}

Hepatitis E. In 1 series of children exposed to HEV, the rate of HEV infection was found to be 85%, which is mainly self-limited.^{144,391} Viremia was observed in 50% of exposed and 60% of anicteric patients compared with 66% of icteric patients.³⁹¹ These findings suggest that children have a high susceptibility to HEV infection and that viremia is frequently prolonged in those infected.

Management issues in pregnancy and birth

Many complementary changes occur in a pregnant woman's immune system to protect the fetus while maintaining maternal defenses against disease. Enhancements occur in immune elements that fight bacterial infections. Conversely, increased production of progesterone during pregnancy leads to down-regulation of cellular (cell-mediated) immune functions. Many food-borne pathogens (and other pathogens) are intracellular pathogens, and infections caused by these pathogens are controlled by cell-mediated immunity. The pregnancy-induced decrease in cell-mediated immune functions leads to increased susceptibility of the pregnant woman to certain infections.³⁹² In particular, suppression of T-cell activity causes increased susceptibility to viral infections, such as hepatitis.^{392,393}

With the exception of HEV infection, in which maternal and fetal mortality rates are significantly increased,³⁹⁴ the clinical course and histologic findings do not differ between pregnant and nonpregnant patients.^{119,394-396} Jaundice during pregnancy may be the result either of disease uniquely associated with the pregnant state or disease totally unrelated to the pregnancy. In the US, the most common cause of jaundice in pregnant women is viral hepatitis.^{394,396} Other causes of jaundice include cholelithi-

asis, HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count) and acute fatty liver of pregnancy.

The roles of various viruses during pregnancy are discussed below.

Hepatitis A. Acute HAV in pregnancy is typically self-limiting and does not appear to carry a different prognosis than that in the nonpregnant patient,^{151,395} nor have teratogenic effects of acute HAV during pregnancy been noted. Transmission to the neonate from an infected mother can occur by the usual fecal-oral route during delivery and the postpartum period; intrauterine transmission, however, is rarely reported.³⁹⁷ The HAV vaccines should only be used during pregnancy when clearly needed. Newborn infants of HAV-infected mothers whose symptoms first manifested between 2 weeks before and 1 week after delivery should receive supplemental immune globulin.^{157,158,163,398,399}

Hepatitis B. Between 0.5% and 1.5% of pregnant women in the US are chronic carriers of HBV. Acute HBV is reported in approximately 1 to 2 women out of 1,000 pregnancies. The clinical course and histologic findings of chronic HBV infection do not differ between pregnant and nonpregnant patients.^{119,151,394-396} Hepatitis B viral infection, however, may be transmitted to neonates, with the majority of transmission occurring in the perinatal period. The risk of transmission to the neonate is dependent on maternal viral replication status and increases with increasing viral replication. Mothers positive for both HBsAg and HBeAg have a 70% to 90% risk of transmitting the disease to their offspring, with 85% or more of these children ultimately becoming chronic carriers of HBsAg.^{400,401} For carriers of HBsAg alone, however, the rate of transmission is reduced.⁴⁰² Factors that increase the risk of vertical transmission include concurrent HIV infection,^{403,404} high maternal viral load, high titers of HBsAg, or the presence of HBeAg.

Both the CDC and the American College of Obstetricians and Gynecologists (ACOG) recommend that all pregnant women be screened for HBsAg during an early prenatal visit.^{16,118,405,406} The prevention of vertical transmission is the most effective measure to control HBV virus. As noted previously, HBV transmission is effectively prevented with perinatal hepatitis B vaccination and prophylaxis with HBIG.^{119,394,395,407} It is also recommended that the HBV vaccine series be administered to all infants, regardless of maternal status. Although

HBsAg can be found in breast milk, there is no evidence that breast feeding increases the risk of HBV acquisition in neonates who have been given immunoprophylaxis.⁴⁰⁶

Hepatitis C. Hepatitis C virus can be transmitted perinatally, parenterally, and sexually. Seroprevalence of HCV is similar in pregnancy to the US general population.^{85,119,394-396} In Western countries, a history of IV drug use appears to be the most common risk factor for HCV infection in pregnancy.^{408,409} Pregnancy does not adversely affect the course of hepatitis C. A modest rebound in ALT levels, but not HCV RNA, occurs after delivery in some viremic women. Hepatitis C infection does not affect pregnancy complications and outcomes.⁴⁰⁹ In pregnant women with chronic infection, serum ALT levels decrease during the third trimester and increase again after delivery. Conversely, HCV-RNA levels tend to increase late in pregnancy and return to baseline levels within 1 year after delivery. These findings suggest the importance of immune-mediated mechanisms in controlling viral replication and contributing to liver injury in chronic hepatitis C.^{85,410,411} The rate of cholestasis in pregnant women is significantly higher in anti-HCV-positive compared with anti-HCV-negative women, and mean gestational age at onset of symptoms and at delivery tends to be lower among antibody positive women. These findings suggest that early occurrence of cholestasis of pregnancy may be an indication for serologic testing for HCV.⁴¹²

The rate of vertical transmission of HCV (mean, 5%; range, 0% to 25%) is lower than for HBV infection, but transmission rates have been reported to increase in some studies when the mother is co-infected with HIV (mean, 14%; range, 5% to 36%). Vertical transmission of HCV is limited to infants whose mothers are viremic; risk increases with maternal viral load > 1 million copies/mL. There is no specific HCV genotype that is preferentially transmitted, and the mode of delivery (cesarean versus vaginal) does not appear to affect the rate of transmission. There is no evidence to suggest an increased risk of HCV transmission through breast feeding.^{85,151,404,413-415}

The American Academy of Pediatrics and the CDC recently recommended that all children born to women who are infected with HCV be screened for this virus. Most infected women are asymptomatic and unaware of their infection, so routine prenatal testing may be needed to fully

meet that goal.⁴¹⁶ Anti-HCV testing after the first year of life is used by most experts. Finally, pregnant women cannot be treated with alpha interferon or with ribavirin, which is a well-known teratogen.

Hepatitis D. Although perinatal transmission of HDV does occur, it is rare. Strategies to prevent vertical transmission of HBV also effectively prevent neonatal HDV infection.

Hepatitis E. In developing countries HEV infection is more common than in Western countries, and the frequency of HEV infection in pregnant women also appears to be higher. Hepatitis E viral infection has a high fatality rate during pregnancy, particularly during the second and third trimesters; the death rate may reach 20%.^{396,417,418}

Although intrafamilial spread of HEV appears to be negligible,¹³⁴ vertical transmission of HEV can occur at high rates, with significant perinatal morbidity and mortality.⁴¹⁹ Currently, there are no effective passive or active immunization protocols.

Management issues in hemodialysis patients

Due to the frequent contact with blood during the hemodialysis procedure, patients on chronic dialysis are at increased risk for acquisition of hepatitis B, C, or D through parenteral or nosocomial routes of transmission. Biochemical abnormalities are typically detected in 10% to 44% of patients on chronic hemodialysis.⁴²⁰ The prevalence of anti-HCV was 10% among patients and 2% among hospital staff.^{421,422} Today, stringent infection control practices as well as widespread use of HBV vaccination in dialysis centers have decreased these risks,^{179,423-427} but recent reports indicate the risks of exposure and infection by blood-borne hepatitis viruses in the dialysis setting have not vanished.^{421,424,428-433}

Uremic patients, whether dialyzed or not, tend to have some degree of immune dysfunction and suboptimal responses to some types of vaccines, including those against HBV.^{170,174,179} This may be due to macrophage Fc-receptor dysfunction, nutritional and metabolic factors, or other factors.⁴³⁴ Currently, no effective vaccines exist for prophylaxis against HCV. Altered responsiveness to HAV vaccines has not been reported in dialysis patients; reported response rates to currently available HBV vaccines, however, have ranged from 70% to 88% in the hemodialysis population.^{174,177,434} Frequently, the antibody response to HBV vaccine is transient.¹⁷⁴

Nevertheless, routine use of HBV vaccines can reduce the risk of HBV infection by as much as 70%.¹⁷⁰ A number of studies have attempted to assess the efficacy of booster doses and/or different vaccination schedules to elicit the best possible response in this immunocompromised population.^{181,435} The use of immunoadjuvants such as alpha and gamma interferon has been explored, with variable results.^{436,437}

The course of chronic hepatitis B infection does not appear to be adversely affected by hemodialysis. Evaluation and treatment of chronic active HBV or active HCV infection in hemodialysis patients should follow the general management guidelines for HBV. Although HBV infection in hemodialysis patients appears to result in chronic carriage of HBsAg and chronic elevation of liver enzymes more frequently than in normal hosts, fibrosis may develop in the absence of histologic evidence of severe necrosis or inflammation.^{438,439} Delayed clearance or persistence of HBsAg in hemodialysis patients is commonly observed;⁴⁴⁰ antigenemia is not, in itself, associated with increased morbidity or mortality in the hemodialysis population.⁴⁴¹

Hepatitis C virus remains a common pathogen in the hemodialysis population.⁴⁴²⁻⁴⁴⁴ In a recent report, related and unrelated isolates of HCV were detected from an HCV outbreak in a plasmapheresis center. These findings provide strong evidence for nosocomial transmission of the virus, despite initiation of strict general hygiene precautions. The production of anti-HCV may be delayed significantly, or seroconversion may not occur at all in newly infected HCV-RNA-positive patients,⁴³⁰ and *de novo* HCV infection may be undetected or underdetected by antibody assays.⁴⁴⁵ Serial ALT measurements supplemented by determination of HCV RNA by RT-PCR in suspected cases remains the best means of detecting HCV infection in the hemodialysis setting.^{430,446} Hepatitis C virus-related liver disease may follow a generally more benign course in dialyzed patients. This may relate to the marked and prolonged release of hepatocyte growth factor commonly associated with dialysis.⁴⁴⁶ Similar SR rates after interferon monotherapy have been reported in dialysis patients;⁴⁴⁷ however, ribavirin may pose a substantial risk of hemolytic anemia in this group as it is excreted by the kidney. At this point, treatment of HCV-infected dialysis patients should be considered in a protocol setting.⁴⁴⁸

It is now recommended that all hemodialysis

patients and healthcare workers should be vaccinated against HBV. Preferably, patients who may require hemodialysis should be vaccinated before they develop end-stage renal disease. Additionally, consideration should be given to a 4-dose, higher-dose vaccine series for hemodialysis patients, with or without verification of antibody titers and administration of a fifth dose for nonresponders (see vaccine recommendations). Finally, stringent infection control policies should be followed in dialysis units.

Management issues for transplant recipients

Hepatitis B. *Transplantation from an HBsAg-positive donor.* Traditionally, these donors have not been used for liver transplants because the risk of HBV transmission is high. In the current era, with the shortage of transplantable organs, the possibility of pretransplant vaccination of the recipient, and the availability of more effective drugs for hepatitis B treatment, this position may need to be reassessed.

With respect to nonhepatic (kidney, heart, lung) organ donation, there are conflicting reports regarding the risk of HBV transmission. In 1 survey of renal transplant recipients, the cumulative risk of developing posttransplant hepatitis was significantly higher in HBsAg-positive patients ($P = .001$).⁴⁴⁹

In bone marrow transplantation, abnormal ALT levels in donors are a significant predictor of potentially lethal liver complications in HBsAg-positive individuals.⁴⁵⁰ Hepatitis B virus carriers receiving a marrow graft from an HBsAg-positive donor have been shown to be at increased risk.⁴⁵¹ In another report, the use of HBsAg-positive donors, particularly if they were also positive for anti-HBc, increased the risk of severe liver disease in bone marrow transplant recipients.^{450,452} At the moment, organs from HBsAg carriers cannot be used.

Transplantation from an HBsAg-negative, anti-HBc-positive donor. HBsAg-negative and anti-HBc-positive donors generally have not been used in liver transplants, as *de novo* posttransplantation HBV infection occurs in recipients of donors with anti-HBc. Transmission of HBV through transplantation suggests that the virus may persist in the liver despite serologic resolution of infection.²¹ In 1 study of 332 transplants performed before exclusion of anti-HBc-positive liver donors, 3% of donors were anti-HBc-positive; 33% of recipients developed transplant-associated *de novo* HBV infections compared with only 0.5% of recipients who received

anti-HBc–negative donor livers ($P = .00014$). Of the 9 recipients of anti-HBc–positive livers, 67% were alive at the time of publication, and no deaths or allograft failures have been related to complications of hepatitis B. One of 5 patients with *de novo* hepatitis B and high levels of viremia developed graft dysfunction after follow-up of more than 7 years (range, 63 to 124 months).⁴⁵³ Of note, in the current era of organ shortage, the usefulness of these “suboptimal organs” is being reassessed.

However, for nonhepatic transplants the risk is thought to be relatively low, especially in the vaccinated recipient, and these organs may be considered. Data on the efficacy of prophylaxis with anti-HBV agents such as lamivudine and famciclovir are not established.

Transplantation into an HBsAg-positive recipient. Liver transplantation into an HBsAg-positive recipient would be performed for end-stage liver failure secondary to HBV. These transplants are performed with standard intermittent HBIG prophylaxis, which is costly but effective, and clinical judgment as well as input from transplant hepatologists are important. A positive HBV-DNA level at the time of transplant predicts recurrence of HBV posttransplant and is a poor prognostic sign; subsequent immunosuppression may be associated with reactivation of HBV after orthotopic liver transplantation.^{454,455} Recent work suggests that aggressive intravenous HBIG is more effective than the previous standard schedule in preventing recurrence.¹⁸⁹ However, patients appear to require lifelong treatment to prevent reinfection. One potential alternative to HBIG is lamivudine therapy. Although not currently used routinely for posttransplant patients, lamivudine therapy has been shown to prevent HBV recurrence after liver transplantation.⁴⁵⁶ Other nucleoside analogues are also under investigation.

For patients receiving nonhepatic transplants, in recent years programs have avoided transplanting the HBsAg-positive recipient because of the requirements for immunosuppression. Although the incidence of HBV reactivation and the development of chronic liver disease or FHF is increased while the patient is still in an immunosuppressed state,^{457,458} this risk is again being reassessed in the current era of newer agents for prophylaxis and therapy. This issue is especially important for life-saving transplants such as heart or bone marrow transplants.

Transplantation from an HCV-positive donor. There is a significant risk of transmission of HCV in liver transplantation using an HCV-positive donor, especially when the donor is HCV-RNA positive. Liver transplantation from an HCV-positive donor may be considered only in special situations and only for those already infected with HCV.

The clinical effect of HCV-positive donor status in nonhepatic transplant recipients has not been entirely defined. Hepatitis C viral infection after renal transplantation is associated with an increased risk of liver disease, and, according to recent data, with negative long-term outcomes.⁴⁵⁹ A few cases of severe cholestatic hepatitis have occurred following heart transplantation, and these were associated with prolonged course and poor prognosis.⁴⁶⁰ Concern has been raised about the possible transmission of HCV via bone, ligament, and tendon allografts. Testing of donors of such allografts for HCV has been recommended; informed consent is extremely important for all patients receiving any transplant from an HCV-positive donor.

The issue of whether HCV infection adversely affects patient outcome following bone marrow transplantation is still unclear.^{450,461–463} Hepatitis C viral infection in donor or recipient is not considered an absolute contraindication for bone marrow transplant, but viremia should be carefully evaluated before disregarding HBV- or HCV-positive siblings with normal transaminase levels in favor of unrelated donors.⁴⁵⁰

Transplantation into an HCV-positive recipient. Whereas newly acquired disease is uncommon in patients negative for HCV pretransplant, recurrent infection is nearly universal in those with HCV viremia pretransplant. The natural history of post-transplant disease suggests that there is no significant impact on graft or patient survival, at least in the short term.⁴⁶³ Progressive liver disease secondary to HCV can occur in 20% of patients. An aggressive cholestatic form of post-orthotopic liver transplantation HCV with very poor prognosis has been seen in < 5% of patients.^{464,465}

Alpha interferon therapy in transplant recipients appears to be less effective than in other patient groups and carries a theoretical risk of causing graft rejection. The combination of interferon alfa-2b and ribavirin has been recently studied with promising results.²⁷⁸ A large, multicenter study is currently evaluating this combination. Ribavirin-induced hemolysis in liver transplant recipients may be

especially severe, requiring lower doses and frequent monitoring protocols.

Diagnosis of HBV/HCV in the transplant recipient. Serologic responses to HBV and HCV in the transplant recipient, especially bone marrow transplant recipients, may be blunted and may not be used to exclude clinical HBV and HCV. Methods of direct molecular detection, such as HCV RNA and HBV DNA determinations, are more accurate in this setting. The following issues need to be considered in transplant patients:

- Issues surrounding hepatitis in transplant recipients, liver and otherwise, are complex and should be managed by a hepatologist with experience in transplantation.
- HBsAg-positive donors are generally not used.
- HBV liver transplant recipients should receive HBIG prophylaxis, or should be considered for enrollment in clinical trials investigating newer forms of prophylaxis.
- HBsAg-negative, anti-HBc-positive donors are generally considered low risk for nonhepatic transplant recipients; they are high risk for hepatic recipients and generally not used for liver transplants (except for protocols that are being developed to consider these organs for patients with end-stage liver disease from HBV). For nonhepatic recipients, antiviral prophylaxis may be considered without proven efficacy.
- Hepatitis C virus-positive donors may be considered with awareness of the potential risks outlined above; mainly in those with previous infection (HCV-related cirrhosis).
- Hepatitis C viral RNA and HBV DNA are far more useful for detecting transmission or reactivation of these viruses after transplant. Serologic responses are usually inaccurate in this population.
- Insofar as possible, all potential transplant recipients should be vaccinated against HBV pre-transplant, preferably before the onset of end-stage organ disease.
- Solid organ and bone marrow transplant donors and recipients should be tested for serology to HBV and HCV prior to transplant. It has also been suggested that donors of bone, ligament and tendon allografts be tested for HCV.

Management issues in immunocompromised patients

The therapeutic effect of most immunosuppressive agents is nonspecific and therefore often limit-

ed by an increased risk of infection by viral, bacterial, or fungal organisms as well as by an increased incidence of malignant neoplasms. Hepatotoxicity has been reported among patients receiving azathioprine (cholestatic hepatitis) and methotrexate (elevated aspartate aminotransferase levels and, rarely, liver fibrosis or cirrhosis).⁴⁶⁷ Immunosuppressants may impair T-cell function and thereby reduce immune-mediated hepatocytolysis and virus clearance. In addition, corticosteroids may activate the glucocorticoid responsive element in the HBV genome to enhance HBV replication and gene expression. These combined effects result in an increase of viremia association with decreased ALT levels, histologic necrosis, and inflammation. In acute hepatitis infection, immunosuppressants tend to increase the rate of progression to chronic disease.⁴⁶² Such patients would benefit from consultation with a hepatologist. In general, serologies may not be reliable and HCV RNA and HBV DNA are much more useful. Vaccination for HBV should be offered, if possible, before severe immunocompromise has occurred.

Long-term protection against HBV infection and chronic carrier status depends on immunologic memory, which supports protective anamnestic antibody responses to antigen challenge. Memory seems to last for at least 15 years in immunocompetent individuals, and no data support the need for booster doses of HBV vaccine in immunocompetent individuals who have responded to a primary course. However, the long-term effectiveness of HBV vaccine in immunocompromised hosts is uncertain; regular testing for anti-HBs, and a booster injection when the titer falls below 10 MU/mL, is advised, along with long-term monitoring to confirm the absence of clinically significant breakthrough episodes or evolution to the HBsAg carrier state.^{177,468}

Hepatitis C viral infection progresses faster in immunosuppressed patients and patients with hypogammaglobulinemia, with a potential for a cholestatic course with poor prognosis. Response to interferon is typically poor in these patients;^{213,469,470} however, early treatment with high-dose alpha interferon may result in a high clearance of HCV.⁴⁷¹

Managing patients with human immunodeficiency virus

As deaths from acquired immunodeficiency syndrome continue to decline with effective antiretroviral therapy, liver disease is becoming an increasing

cause of hospital admission and death in HIV and HCV co-infected persons. The problem is particularly relevant among hemophiliacs or intravenous drug users, many of whom may be co-infected not only with HBV or HCV but also with multiple genotypes of HCV.^{472,473} Concomitant HIV infection may alter the course of HBV and HCV infection, and vice versa through effects of one virus on the replication and immunopathology of the other as described above.⁴⁷³ In co-infected patients, a low CD4 T-cell count, high alcohol consumption rate, and increased age at the time of acquisition of HCV infection are associated with a higher liver fibrosis progression rate.⁴⁷⁴

Hepatitis B virus infection (either active or prior) is particularly frequent in HIV-positive IV drug users, and most carry markers of past infection.⁴⁷⁴ Isolated detection of anti-HBc (absence of anti-HBs) is more common in HIV-positive than in HIV-negative drug users. Despite progressive immunosuppression, HBV reactivation is rare.⁴⁷⁵ Human immunodeficiency virus seropositivity accelerates HCV-related liver fibrosis progression.⁴⁷⁴ Serum HBV-DNA polymerase activity tends to be higher and ALT levels lower, and loss of serum HBeAg occurs at a lower rate compared with HIV-uninfected HBV carriers. Chronic hepatitis B infection does not appear to adversely affect the rate of progression of HIV disease.⁴⁷⁶

In the era of highly active antiretroviral therapy (HAART), a significant upgrading of immune function may theoretically increase liver damage due to immunopathology from HBV or HCV, but these effects are not yet fully understood. The use of lamivudine as a highly effective drug in antiretroviral combinations may have an impact on HBV in that lamivudine is also highly effective against HBV,²⁹⁸ although resistant HBV strains are estimated to develop in co-infected patients under long-term therapy at a rate of 20% per year.²⁹⁰ Patients are frequently switched from 1 antiretroviral combination to another, and this may lead to inadvertent discontinuation of lamivudine in a patient with chronic hepatitis B. Response to HBV vaccine is typically suboptimal (24% to 43%) in HIV-infected patients with immune dysfunction, but it should still be offered.

In patients chronically infected with HCV, co-infection with HIV may be associated with increased HCV viremia.⁴⁷⁷ The frequency of HCV transmission to sexual partners is 5 times higher

when HIV is also transmitted.⁴⁷⁸ In addition, infants of mothers with an HCV and HIV co-infection or with a high HCV-RNA titer are at high risk for HCV infection, and 81% may progress to chronic infection.^{85,479}

Although HIV infection and possibly HIV progression are associated with increased HCV-RNA levels, other factors appear to affect biochemical and virologic markers of HCV infection in some co-infected persons.⁴⁸⁰ Liver damage in patients co-infected with HIV and HCV may be influenced by HCV subtypes; subtype 1b may be associated with more severe forms of liver pathology.^{472,481-483} Furthermore, the presence of HIV infection is an independent factor associated with more aggressive histologic damage with higher degrees of piecemeal necrosis and fibrosis.⁴⁸¹ Treatment with alpha interferon provides a similar rate of response in non-severely immunosuppressed HIV-positive patients versus HIV-negative patients, although some have reported decreased effectiveness of interferon regimens.^{484,485} Preliminary results from trials using the combination of interferon alfa-2b plus ribavirin in HIV/HCV co-infection look promising.⁴⁷³ Two variables are independently associated with a response in HIV-infected patients: a CD4⁺ T-lymphocyte count of $> 500 \times 10^6/L$ and a new baseline HCV viremia. In the 12 months following treatment, relapses occurred in 30.8% of the HIV-infected patients and 12.5% of non-HIV-infected patients ($P = .403$).⁴⁸⁶ Ribavirin-induced hemolytic anemia may be more problematic in this population, requiring lower dosage and careful monitoring.

The long-term efficacy and safety of combination therapy (especially interaction of ribavirin with other HAART medications) needs further assessment. In addition to previously described advantages of the newer pegylated interferons, they may also have additional anti-HIV activity and are currently under investigation. The following issues should be considered for immunocompromised individuals:

- Caution should be exercised in the patient with concomitant HBV and HIV in terms of inadvertent discontinuation of lamivudine.
- The interactions of HBV and HCV with HIV are complex, and patients who are candidates for therapy would benefit from consultation with an experienced gastroenterologist/hepatologist or infectious disease specialist.

- HIV-positive, nonimmunocompromised individuals should receive an HBV vaccine series, although the response is suboptimal.

Alcohol and viral hepatitis

Considerable epidemiologic data are becoming available to support the negative synergistic effects of alcohol in chronic hepatitis B and C. Chronic hepatitis in the presence of excessive alcohol (> 50 g/day) seems to lead to a more aggressive disease course.^{92,487-489} Development of HCC may be higher in alcoholics infected with HBV or HCV than others.^{92,487,490,491} Whether this increased risk of HCC represents proof of synergy between hepatitis and alcohol or an independent effect of alcohol on the liver is not clear.⁴⁹²

Similarly, there is now significant evidence that both serologic markers of HCV infection and HCV viremia are higher in alcoholics than in the general population.^{92,493,494} Although the first-version serologic testing (ELISA-1) for HCV was plagued with high false-positive rates in alcoholics,⁴⁹⁵ the subsequent supplemental testing confirmed that the prevalence of anti-HCV is 7- to 10-fold higher in alcoholics than in the general population. In patients with alcoholic liver disease who have serologic evidence of HCV infection, the majority are viremic as measured by the HCV PCR method.⁹¹ Results suggest that, in addition to a higher prevalence of HCV in alco-

holics, these patients also have a higher viral load.

The clinical course of HCV infection in patients with excessive alcohol use (> 50 g/day) seems to be more aggressive, accelerating the development of progressive fibrosis and cirrhosis.^{92,487-489,496} Among the 3 independent risk factors associated with increased progression (age > 40 years, alcohol consumption > 50 g/day, male sex), excessive alcohol consumption is the most consistent finding.⁴⁹⁶ The exact mechanism and interaction of HCV and alcohol is not known. Direct hepatotoxic effects of alcohol and higher levels of viremia have been implicated. Alcoholics also have higher hepatic iron content, a factor that has been suspected as a cofactor in the pathogenesis of HCV-related liver injury.⁴⁹⁷ Finally, chronic alcohol use can negatively impact hosts' immunity and nutritional status, thereby rendering them more susceptible to damage by HCV.^{82,498}

In addition to the potential impact of excessive alcohol use on the course of HCV, it may also negatively affect interferon-based antiviral therapy against HCV.

Although excessive alcohol is consistently associated with enhanced hepatic fibrosis, the effect of lower amounts of alcohol on progression of HCV-related cirrhosis is not fully established. Patients with viral hepatitis should be counseled against alcohol intake.

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