rarely, acute liver failure. HAV is transmitted by the fecal-oral route. Risk factors include international travel, contacts with household members with HAV infection, men who have sex with men, and exposure to day care or institutionalized settings. The incidence of HAV infection declined dramatically after introduction of the HAV vaccination (see MKSAP 18 Infectious Diseases). Mortality is rare but may be increased in patients with preexisting chronic liver disease. The incubation period for HAV is 15 to 50 days. A prodrome of malaise, nausea, vomiting, fever, and right upper-quadrant pain is followed by development of jaundice, with physical examination findings of jaundice and hepatomegaly. HAV can be transmitted during the prodrome stage and up to 1 week after development of jaundice. Laboratory studies may show aminotransferase levels greater than 1000 U/L and total bilirubin level of 10 mg/dL (171 μmol/L) or higher, mostly direct (conjugated). A positive test for IgM antibodies to HAV is suggestive of acute illness, although false positives may occur in the setting of other viral infections. The presence of IgG antibodies to HAV indicates previous infection or vaccination and provides immunity from reinfection. Treatment is supportive, and 90% of patients or more recover fully within 3 to 6 months of infection. Postexposure vaccination is sufficient for immunocompetent patients, and HAV immunoglobulin can be administered to immunocompromised patients.

Hepatitis B

Hepatitis B virus (HBV) is a DNA virus affecting 240 million persons worldwide and 2.2 million in the United States. See MKSAP 18 General Internal Medicine for HBV vaccination strategies. HBV can be transmitted vertically, through sexual exposure, percutaneously, or by close person-to-person contact. The risk for developing chronic HBV infection differs by age. Newborns acquiring HBV have the highest risk (90%), whereas adults have an approximately 5% risk. Testing for HBV is recommended in individuals with risk factors (**Table 27**).

HBV infection presents as acute hepatitis in a minority of patients. Approximately 30% of adults may develop jaundice as a result of acute infection with aminotransferase levels as high as 3000 U/L and nonspecific symptoms including malaise, nausea, and right-upper-quadrant pain. Acute liver failure (ALF) develops in approximately 0.5% of patients. Typically, adult patients recover within 1 to 4 months. Chronic HBV infection is diagnosed after 6 months in patients with persistent hepatitis B surface antigen (HBsAg) detected in serum.

Interpretation of HBV serologies is shown in **Table 28**. There are four phases of chronic HBV infection: immune tolerant, immune active, immune control, and reactivation (**Figure 30**). Patients who have acquired HBV through vertical transmission remain in the immune-tolerant phase for the first two to three decades. This stage does not require treatment except in specific cases (patients older than 40 years with an HBV DNA level of at least 1 million IU/mL and significant inflammation or fibrosis).

Patients transition to hepatitis B e antigen (HBeAg)-positive, immune-active hepatitis later in life. Hallmarks of the immune-active phase include elevated ALT levels, an HBV DNA level of at least 20,000 IU/mL, and a positive HBeAg test. Moderate to severe inflammation can occur, fibrosis can progress, and treatment is warranted in this phase.

Spontaneous seroconversion to the immune-control (inactive) phase with a loss of HBeAg and development of anti-HBe occurs at a rate of 10% per year. To be considered inactive, the ALT level must be normal and the HBV DNA level must be 2000 IU/mL or lower when measured every 3 to 4 months for 1 year.

Approximately 60% to 80% of cases remain in the inactive phase, but up to 20% can revert to the HBeAg-positive, immune-active phase. In addition, the HBeAg-negative reactivation phase can develop in 10% to 30% of cases; this phase is marked by fluctuating elevations in ALT levels and an HBV DNA level that is low but at least 2000 IU/mL, accompanied by ongoing inflammation and fibrosis that require treatment. Not all patients progress through each one of these phases or in sequence.

TABLE 27. Risk Factors Requiring Testing for Hepatitis B Virus

Individuals born or raised in regions with high rates of hepatitis B virus infection, including Asia, Africa, the South Pacific, European Mediterranean countries, Eastern Europe, most of South America, Honduras, Guatemala, and the Middle East (except Israel and Cyprus)
U.S.-born persons not vaccinated as infants whose parents were born in endemic areas
Household or sexual contact with hepatitis B surface antigen-positive persons
Intravenous drug use
Multiple sex partners or history of sexually transmitted infection
Men who have sex with men
History of incarceration
History of hepatitis C virus or HIV infection
Hemodialysis
Pregnancy
Elevated aminotransferase levels of unknown cause

TABLE 28. Interpretation of Hepatitis B Virus Test Results

Clinical Scenario	HBsAg	Anti-HBs	IgM anti-HBc	IgG anti-HBc	HBeAg	Anti-HBe	HBV DNA (IU/mL)
Acute hepatitis B; occasionally reactivation of chronic hepatitis B	+	−	+	−	+	−	>20,000
Resolved previous infection	−	+	−	+	−	+/−	Undetected
Immunity due to previous vaccination	−	+	−	−	−	−	Undetected
False positive anti-HBc or resolved previous infection	−	−	−	+	−	−	Undetected
Immune-tolerant chronic hepatitis B (perinatally acquired, age <30 years)	+	−	−	+	+	−	>1 million
Inactive chronic hepatitis B	+	−	−	+	−	+	<10,000
HBeAg-positive immune-active chronic hepatitis B	+	−	−	+	+	−	>10,000
HBeAg-negative immune-reactive chronic hepatitis B	+	−	−	+	−	+	>10,000

Anti-HBc = hepatitis B core antibody; anti-HBe = hepatitis B e antibody; anti-HBs = hepatitis B surface antibody; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus.

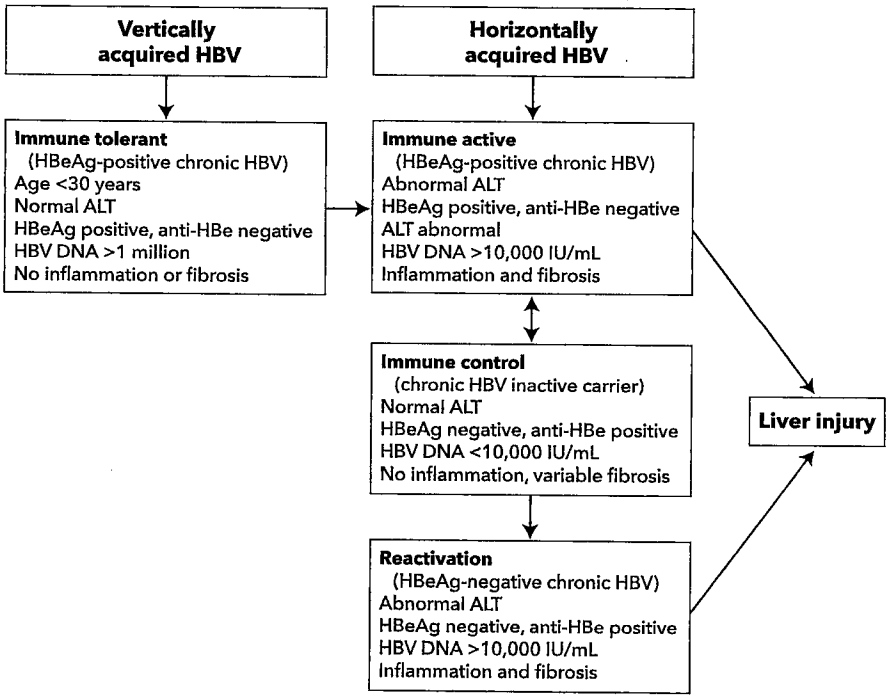

FIGURE 30. Phases of chronic hepatitis B infection. It is assumed that patients progress through the phases in sequence, although not all patients develop HBeAg-negative chronic hepatitis B, and only patients with vertical transmission of hepatitis B have a clinically recognized immune-tolerant phase. All phases have positive HBsAg, negative anti-HBs, and positive IgG anti-HBc.

ALT = alanine aminotransferase; anti-HBc = hepatitis B core antibody; anti-HBe = hepatitis B e antibody; anti-HBs = hepatitis B surface antibody; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HBV DNA = hepatitis B virus DNA.

Risk factors for the development of cirrhosis and hepatocellular carcinoma in patients with chronic HBV infection are listed in **Table 29**.

Treatment is advised for patients with acute liver failure, infection in the immune-active phase or reactivation phase, and cirrhosis, and in immunosuppressed patients. Treatment thresholds in chronic immune-active or reactivation HBV infection are an ALT level at least twice the upper limit of normal and an HBV DNA level of at least 20,000 IU/mL (HBeAg-positive, immune-active phase), or an HBV DNA level of at least 2000 IU/mL (HBeAg-negative, reactivation phase). First-line treatment is entecavir or tenofovir. Lamivudine, adefovir, and telbivudine are less commonly used due to resistance. Pegylated interferon can be used for 48 weeks in patients with

TABLE 29. Risk Factors for Developing Cirrhosis or Hepatocellular Carcinoma in Patients with Chronic Hepatitis B Virus Infection
Age older than 40 years
Hepatitis B virus DNA level >2000 IU/mL
Elevated alanine aminotransferase level
Genotype C infection
Heavy alcohol use
Development of hepatitis B e antigen-negative reactivation phase of chronic hepatitis B virus infection
HIV infection
Hepatitis C virus or hepatitis D virus infection

high ALT levels, low HBV DNA levels, and without cirrhosis. Candidates for interferon are those who have a desire for finite therapy, are not pregnant, and do not have significant psychiatric disease, cardiac disease, seizure disorder, cytopenia, or autoimmune disease.

Treatment goals for patients in the HBeAg-positive, immune-active phase are HBeAg loss and anti-HBe seroconversion, which should be followed by an additional 12 months of treatment. Goals of treatment in the HBeAg-negative, reactivation phase are HBV DNA suppression and ALT normalization; oral antiviral agents are generally continued indefinitely. Patients with cirrhosis should continue oral antiviral medications indefinitely. HBsAg seroconversion rarely occurs with oral antiviral treatment and, therefore, is not a goal of treatment. Regression of fibrosis and even of cirrhosis can occur with treatment.

Prophylactic oral antiviral therapy should be given to patients who are HBsAg-positive or isolated core antibody-positive and receiving B-cell depleting therapy (for example, rituximab, or ofatumumab), prednisone (≥10 mg/d for at least 4 weeks), or anthracycline derivatives. Patients undergoing therapy with tumor necrosis factor-α or tyrosine kinase inhibitors should be considered for prophylaxis.

Rarely, patients with HBV infection develop polyarteritis nodosa or cryoglobulinemia, which should prompt treatment with oral antiviral therapy. Membranous glomerulonephritis is a rare extrahepatic association.

The survival rate after liver transplantation for end-stage liver disease from HBV infection is greater than 90% at 1 year. Recurrence of HBV infection in transplant recipients is prevented with HBV immunoglobulin and/or oral antiviral therapy.

The prognosis for untreated individuals with HBV infection worsens with age, particularly with age older than 40 years. Approximately 40% of deaths in HBV-infected persons older than age 40 years are related to hepatocellular carcinoma or decompensated cirrhosis. The following characteristics are associated with an increased risk for hepatocellular carcinoma in patients with HBV infection and are indications for surveillance with ultrasound or cross-sectional imaging every 6 months: (1) cirrhosis; (2) Asian descent plus male sex plus age older than 40 years; (3) Asian descent plus female sex plus age older than 50 years; (4) sub-Saharan African descent plus age older than 20 years; (5) persistent inflammatory activity (defined as an elevated ALT level and HBV DNA levels greater than 10,000 IU/mL for at least a few years); and (6) a family history of hepatocellular carcinoma.

Hepatitis C

Worldwide, 130 to 150 million individuals are infected with hepatitis C virus (HCV), with 2.7 to 3.9 million individuals with HCV infection in the United States. HCV is most commonly transmitted through intravenous or intranasal drug use, blood transfusions before 1992, or sexual intercourse. The efficiency of the virus' spread through vaginal intercourse is low. Individuals born between 1945 and 1965 require one-time HCV testing, as the prevalence is nearly 3% in this group and these individuals account for 75% of cases of HCV infection. Patients with risk factors should be tested (**Table 30**).

Acute HCV infection is asymptomatic in most patients. Jaundice, nausea, right-upper-quadrant pain, dark urine, and acholic stools can occur in the symptomatic cases. Evaluation of suspected acute infection includes HCV antibody and RNA tests. The HCV RNA test becomes positive first, and the HCV antibody test becomes positive within 1 to 3 months. HCV antibody seroconversion within 12 weeks in the presence of an initial positive HCV RNA test confirms an acute HCV infection. Infection that clears spontaneously, usually within 6 months, is more common in patients with symptoms, high ALT levels, female sex, younger age, and the *IL-28 CC* genotype. Monitoring HCV RNA quantification for clearance for 6 months is recommended in patients with acute infection.

TABLE 30. Conditions Requiring Testing for Hepatitis C Virus
Birth year 1945-1965
Injection-drug use or intranasal illicit-drug use (ever)
Long-term hemodialysis (ever)
Percutaneous/parenteral exposures in an unregulated setting (nonsterile technique)
Needlesticks, sharps, or mucosal exposure to hepatitis C virus-infected blood
Children born to women infected with hepatitis C virus
Receipt of blood or blood-components transfusion or organ transplantation before 1992
Receipt of clotting-factor concentrates produced before 1987
History of incarceration
HIV infection
Sexually active persons about to start preexposure prophylaxis for HIV
Undiagnosed chronic liver disease
Elevated alanine aminotransferase level
Living organ donors, before donation

HCV results in chronic infection in 60% to 80% of patients, with up to 30% progressing to cirrhosis over two to three decades. Patients with cirrhosis have a 2% to 4% risk per year for developing hepatocellular carcinoma.

The first step in the diagnosis of chronic HCV infection is HCV antibody testing, and if positive, a HCV RNA quantification. Patients with positive HCV antibody and RNA tests have active infection, and a genotype test should be performed. Asymptomatic patients with a positive HCV antibody and a negative HCV RNA test, and without recent exposure to HCV, do not have active infection and generally do not require further testing.

All patients infected with HCV should be tested for HBV and HIV because of the potential shared routes of transmission. HBV testing should include HBsAg to assess for active infection (followed by HBV DNA if positive) and antibodies to hepatitis B antigens (anti-HBs and anti-HBc) to assess for past infection. Susceptible patients should receive HBV vaccination. HBV reactivation can be seen during treatment of HCV infection with direct-acting antiviral therapy. Patients who test positive for HBsAg with detectable HBV DNA and who do not meet standard HBV treatment criteria should undergo HBV DNA monitoring approximately every 4 weeks until 12 weeks after completion of treatment for HCV infection, or they can be treated with oral HBV therapy prophylactically.

Patients with chronic HCV infection require a fibrosis assessment with a transient or MRI elastography or liver biopsy, unless they have a documented short duration of disease, decompensated cirrhosis, or a radiologic diagnosis of cirrhosis.

All patients infected with HCV should be considered for treatment unless there are significant life-limiting comorbidities or major barriers to adherence to treatment.

Treatment regimens include a combination of direct-acting antivirals, using different mechanisms to prevent viral reproduction (**Table 31**). Regimens are chosen based on genotype, previous treatment experience and response, and fibrosis status. Patients whose infection does not respond to newer regimens are generally managed by a hepatologist or infectious disease specialist because resistance-associated substitution-guided retreatment may be necessary. Patients with decompensated cirrhosis should see a hepatologist before treatment and be considered for liver transplantation. Post-liver transplantation recurrence of HCV infection is universal in treatment-naïve patients. Success rates of HCV treatment after liver transplantation are excellent.

Cure is defined by the absence of HCV RNA in blood 12 weeks after completion of treatment. HCV antibodies remain positive indefinitely and should not be rechecked. Patients can become reinfected after new exposures, and HCV RNA testing is appropriate to identify new infection. Cure rates exceed 90% in the majority of patients. Virologic cure reduces the risk for progression to cirrhosis, complications of cirrhosis, hepatocellular carcinoma, and liver-related mortality. Patients with stage F3 fibrosis or cirrhosis require ongoing surveillance for hepatocellular carcinoma even after virologic cure. Patients with cryoglobulinemic vasculitis and non-Hodgkin lymphoma are more likely to experience remission when HCV is eradicated.

TABLE 31. Treatment Regimens for Hepatitis C Virus Infection

Drug Treatment Regimens
Grazoprevir[a] + elbasvir[b]
Paritaprevir[a] + ombitasvir[b] + dasabuvir[c]
Simeprevir[a] + sofosbuvir[d]
Daclatasvir[b] + sofosbuvir[d]
Ledipasvir[b] + sofosbuvir[d]
Velpatasvir[b] + sofosbuvir[d]

[a]Drug class: NS3/4A protease inhibitor (-previr)

[b]Drug class: NS5A inhibitor (-asvir)

[c]NS5B non-nucleoside polymerase inhibitor (-buvir)

[d]NS5B nucleotide polymerase inhibitor (-buvir)

Hepatitis D

Hepatitis D virus (HDV) is a defective RNA virus that requires HBV for human infection. HDV is endemic in the Mediterranean basin and Pacific islands and uncommon in Western countries. The diagnosis of HDV infection is made through detection of HDV IgG. The clinical course can range from inactive disease to progressive liver disease (in the case of simultaneous HBV-HDV coinfection) to fulminant hepatitis in HDV superinfection. Patients infected with HDV with evidence of progressive liver disease should receive treatment with pegylated interferon for 12 months; cure rates are 25% to 45%.

Hepatitis E

Hepatitis E virus (HEV) is an RNA virus with worldwide distribution. There are four different genotypes: genotypes 1 and 2 are more common in developing countries and are transmitted by the fecal-oral route through contaminated water; genotypes 3 and 4 are more common in developed countries where transmission occurs through contaminated food, mostly pork or deer meat. In developing countries, HEV infection generally occurs in young adults and can occur in large epidemics. In developed countries, HEV generally affects males older than age 40 years. The incubation period is 2 to 5 weeks. Approximately 50% of cases are asymptomatic. Symptoms of HEV infection are jaundice, malaise, nausea, vomiting, anorexia, and right-upper-quadrant pain. Aminotransferase levels are usually elevated to 1000 to 3000 U/L. Diagnosis relies on detection of HEV IgM or RNA. Treatment is supportive, and recovery is expected within 4 to 6 weeks. HEV infection should be considered in patients with an unknown cause of acute hepatitis and in immunocompromised patients with chronic hepatitis. Solid-organ transplant recipients with chronic hepatitis E have response rates of 70% with ribavirin treatment.