TABLE 30. Indications for Hepatitis B Virus Testing[a]
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
Persons with HIV infection
Persons undergoing predialysis, hemodialysis, peritoneal dialysis, or home dialysis
Persons with developmental disabilities and staff in residential facilities for persons with developmental disabilities
Pregnancy
Before initiation of immunosuppressive or cytotoxic therapy
Elevated aminotransferase levels of unknown cause

[a]Recommendations collated from the CDC, U.S. Preventive Services Task Force, and American Association for the Study of Liver Diseases.

Hepatitis B

Hepatitis B virus (HBV) is a DNA virus affecting 240 million persons worldwide. See MKSAP 19 General Internal Medicine 2 for HBV vaccination strategies. HBV can be transmitted perinatally; through sexual exposure, direct contact with blood, or percutaneous exposure; or by close person-to-person contact. The risk for chronic HBV infection decreases with increasing age at time of infection. Newborns acquiring HBV have the highest risk (90%), whereas adults have an approximately 5% risk. Screening for HBV infection with hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B antigens (anti-HBs and anti–hepatitis B core antigen [HBc]) is recommended in individuals with risk factors and before initiation of immunosuppressive or cytotoxic therapy (**Table 30**); anti-HBV prophylactic treatment should be considered in patients with chronic HBV infection. Interpretation of screening test results is listed in **Table 31**.

HBV infection presents as acute hepatitis in a minority of patients. Approximately 30% of adults may develop jaundice from acute infection, with aminotransferase levels as high as 3000 U/L and nonspecific symptoms (e.g., malaise, nausea, and right-upper-quadrant pain). Acute liver failure develops in approximately 0.5% of patients. Chronic HBV infection is diagnosed after 6 months in patients with persistent HBsAg detected in serum.

The four phases of chronic HBV infection are differentiated on the basis of immune response: immune tolerant,

TABLE 31. Interpretation of Hepatitis B Serology Test Results

Interpretation	HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBe	HBV DNA (IU/mL)	ALT
Immunized	–	+	–	–	–	–	Normal
Acute infection	+	–	+(IgM)	+	–	+	Increased
Resolved infection	–	+	+(IgG)	–	+/–	–	Normal
Chronic HBV infection							
Immune tolerant chronic HBV infection	+	–	+(IgG)	+	–	>1 million	Normal or mildly elevated
Immune active chronic HBV infection	+	–	+(IgG)	+	–	>2000 HBeAg negative; >20,000 HBeAg positive	Increased (intermittent or persistent)
Inactive chronic HBV infection	+	–	+(IgG)	–	+	<2000 (when measured every 3-4 months for 1 year)	Normal

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

Data from Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67:1560-99. [PMID: 29405329] doi:10.1002/hep.29800.

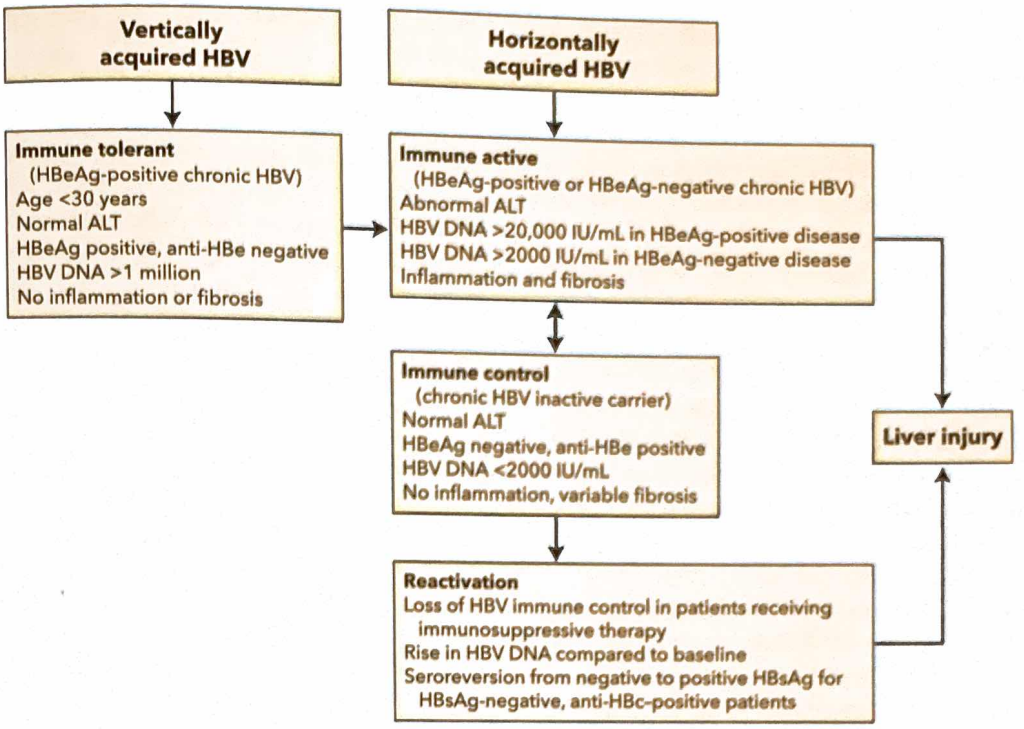

FIGURE 30. Phases of chronic hepatitis B virus infection. It is assumed that patients progress through the phases in sequence, although not all patients develop HBeAg-negative chronic hepatitis B, and only patients with vertical transmission of hepatitis B have a clinically recognized immune tolerant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

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

Data obtained from Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67:1570. PMID: 29405329 doi:10.1002/hep.29800.

immune active, immune control (inactive chronic HBV infection, which occurs at a rate of 10% per year in previously immune active patients), and reactivation.

Reactivation of chronic HBV infection results from loss of immune control in patients with HBsAg-positive/anti-HBc-positive disease or with HBsAg-negative/anti-HBc-positive disease. This often occurs in patients receiving immunosuppressive therapy. Reactivation is characterized by a rise in HBV DNA compared with baseline and seroconversion from HBsAg negativity to HBsAg positivity in HBsAg-negative/anti-HBc-positive patients. Reactivation may be asymptomatic, result in a hepatitis flare (evidenced by an ALT greater than 100 U/L and more than threefold above baseline), or result in hepatic failure (**Figure 30**).

Approximately 40% of deaths in HBV-infected persons older than 40 years are related to hepatocellular carcinoma or decompensated cirrhosis. Risk factors for these conditions in patients with chronic HBV infection are listed in **Table 32**; see Hepatocellular Carcinoma for recommendations on hepatocellular carcinoma screening and surveillance.

Treatment is advised for patients with acute liver failure, infection in the immune-active phase or reactivation phase, and cirrhosis as well as in selected immunosuppressed patients. First-line treatment is entecavir or tenofovir. Lamivudine, adefovir, and telbivudine are less commonly used because of resistance. Pegylated interferon can be used for 48 weeks in patients without cirrhosis who have high ALT levels and low HBV DNA levels.

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

TABLE 32. Risk Factors for Cirrhosis or Hepatocellular Carcinoma in Patients With Chronic Hepatitis B Virus Infection

Age >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

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

Rarely, patients with HBV infection develop membranous nephropathy, membranoproliferative nephropathy, polyarteritis nodosa, or cryoglobulinemia, all of which should prompt oral antiviral therapy.

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.

Hepatitis C

Worldwide, approximately 150 million individuals are infected with hepatitis C virus (HCV). HCV is most commonly transmitted through intravenous or intranasal drug use, blood transfusions before 1992, or sexual intercourse, although the efficiency of viral spread through vaginal intercourse is low. All patients aged 18 to 79 years should be screened for HCV, followed by HCV RNA testing if those results are positive. Although guidelines from the U.S. Preventive Services Task Force suggest not screening patients older than 79 years in the absence of specific risk factors, the CDC does not specify an upper age limit. Other patients with risk factors may also require testing (**Table 33**). Patients with positive HCV antibody and RNA results have active infection and should undergo genotyping.

Acute HCV infection is usually asymptomatic, but jaundice, nausea, right-upper-quadrant pain, dark urine, and acholic stools can occur. Evaluation of suspected acute infection includes HCV antibody and RNA tests. The HCV RNA result becomes positive first, followed by HCV antibody within 12 weeks of infection. The antibody remains positive for life but does not confer immunity from reinfection. Spontaneous clearance (usually within 6 months) is more common in women, younger patients, and patients with symptoms, high ALT levels, or the *IL-28 CC* genotype. Monitoring HCV RNA levels for clearance at 3 and 6 months is recommended in patients with acute infection.

HCV results in chronic infection in 60% to 80% of patients; up to 30% progress to cirrhosis over two to three decades. Risk for hepatocellular carcinoma in patients with cirrhosis is 2% to 4% per year.

Several extrahepatic diseases are associated with chronic HCV infection, including non-Hodgkin lymphoma, membranoproliferative glomerulonephritis, and mixed cryoglobulinemia. Chronic HCV infection is also the most common cause of porphyria cutanea tarda, although it is also associated with alcohol-induced liver damage and hemochromatosis. It presents with increased skin fragility noted on sun-exposed areas, most frequently the dorsal hands. Small vesicles rupture, leaving erosions (**Figure 31**). Treatment of porphyria cutanea tarda is aimed at avoiding sun exposure

TABLE 33. Conditions Requiring Testing for Hepatitis C Virus

Age 18-79 years[a]
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 pre-exposure prophylaxis for HIV
Undiagnosed chronic liver disease
Elevated alanine aminotransferase level
Living organ donors before donation

[a]This age range is recommended in guidelines from the U.S. Preventive Services Task Force. The CDC does not specify an upper age limit for screening.

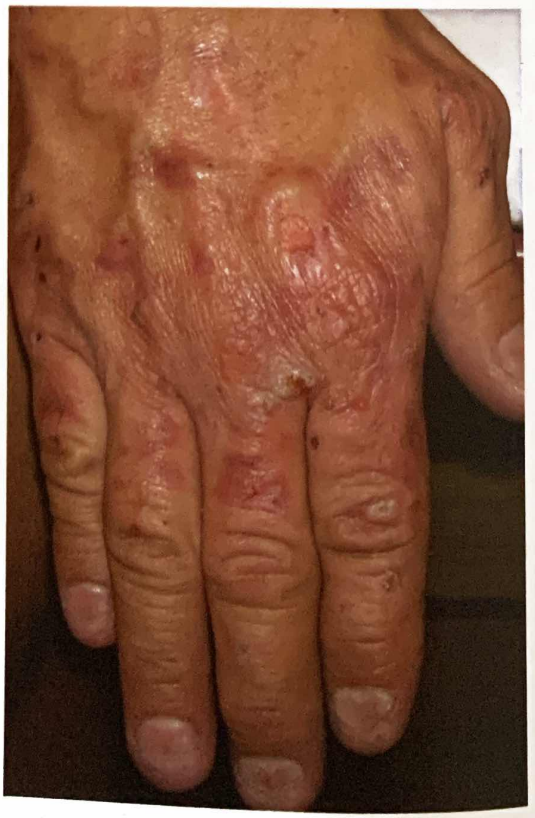

FIGURE 31. Porphyria cutanea tarda manifests as a chronic blistering disease with epidermal erosions on sun-exposed skin, especially on the backs of the hands.