Hepatitis B virus: Clinical manifestations and natural history

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Introduction

The spectrum of clinical manifestations of hepatitis B virus (HBV) infection varies in both acute and chronic disease. During the acute phase, manifestations range from subclinical or anicteric hepatitis to icteric hepatitis and, in some cases, fulminant hepatitis; during the chronic phase, manifestations range from an asymptomatic carrier state to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Extrahepatic manifestations can also occur with both acute and chronic infection.

The clinical manifestations and natural history of HBV infection will be reviewed here. Issues related to epidemiology, transmission, and treatment are discussed separately (see appropriate topic reviews). Terms used to define different clinical states are summarized in the table (table 1). These terms will be used throughout the discussion.

Acute hepatitis

Clinical manifestations — Approximately 70 percent of patients with acute hepatitis B virus (HBV) infection have subclinical or anicteric hepatitis, while 30 percent develop icteric hepatitis. The disease may be more severe in patients coinfected with other hepatitis viruses or with underlying liver disease [1].

Fulminant hepatic failure is unusual, occurring in approximately 0.1 to 0.5 percent of patients. Fulminant hepatitis B is believed to be due to massive immune-mediated lysis of infected hepatocytes. This explains why many patients with fulminant hepatitis B have no evidence of HBV replication at presentation [2].

The reasons why HBV has a fulminant course in some patients are not well-understood. A case-control study evaluated risk factors for a fulminant course in an outbreak among injection drug users [3]. Compared with control patients, case patients were more likely to have used acetaminophen during their illness ($p = 0.08$), used more alcohol and methamphetamine, and lost more weight in the six months before illness. Furthermore, all nine isolates were genotype D (see "Clinical significance of hepatitis B virus genotypes"). It is unclear whether viral or environmental factors led to the fulminant course in this outbreak [4], or if the risk factors identified in this outbreak can be generalized to acute HBV in other settings.

The method of acquiring HBV infection varies geographically. Perinatal transmission and occasionally horizontal transmission early in life are most common in high prevalence areas such as southeast Asia and China, while sexual contact and percutaneous transmission (eg, intravenous drug use) are most common in the United States, Canada, and western Europe (table 1). (See "Epidemiology, transmission, and prevention of hepatitis B virus infection".)

The incubation period lasts one to four months. A serum sickness-like syndrome may develop during the prodromal period, followed by constitutional symptoms, anorexia, nausea, jaundice, and right upper quadrant discomfort. The symptoms and jaundice generally disappear after one to three months, but some patients have prolonged fatigue even after normalization of serum aminotransferase concentrations.

Laboratory testing during the acute phase reveals elevations in the concentration of alanine and aspartate aminotransferase levels (ALT and AST); values up to 1000 to 2000 units/L are typically seen during the acute phase with ALT being higher than AST. The serum bilirubin concentration may be normal in patients with anicteric hepatitis. The prothrombin time is the best indicator of prognosis. In patients who recover, the normalization of serum aminotransferases usually occurs within one to four months. A persistent elevation of serum ALT for more than six months indicates a progression to chronic hepatitis.

Chronic hepatitis

A history of acute hepatitis is elicited in only a small percentage of patients with chronic hepatitis B virus (HBV) infection. In low or intermediate prevalence areas, approximately 30 to 50 percent of patients with chronic HBV infection have a past history of acute hepatitis; such a history is lacking in the remaining patients in these areas and in the majority of patients in high prevalence areas (predominantly perinatal infection).

Many patients with chronic HBV are asymptomatic (unless they have decompensated cirrhosis or have extrahepatic manifestations), while others have nonspecific symptoms such as fatigue. Some patients experience exacerbations of the infection which may be asymptomatic, mimic acute hepatitis, or manifest as hepatic failure.

Physical examination may be normal, or there may be stigmata of chronic liver disease. Jaundice, splenomegaly, ascites, peripheral edema, and encephalopathy may be present in patients with decompensated cirrhosis. Laboratory tests may be normal, but most patients have a mild to moderate elevation in serum AST and ALT. During exacerbations, the serum ALT concentration may be as high as 50 times the upper limit of normal, and alpha-fetoprotein (AFP) concentrations as high as 1000 ng/mL may be seen [14]. A progression to cirrhosis is suspected when there is evidence of hypersplenism (decreased white blood cell and platelet counts) or impaired hepatic synthetic function (hypoalbuminemia, prolonged prothrombin time, hyperbilirubinemia).

Extrahepatic manifestations — Extrahepatic manifestations are thought to be mediated by circulating immune complexes. As mentioned above, acute hepatitis may be heralded by a serum sickness-like syndrome manifested as fever, skin rashes, arthralgia, and arthritis, which usually subsides with the onset of jaundice. The two major extrahepatic complications of chronic HBV are polyarteritis nodosa and glomerular disease.

- A variable proportion of patients with polyarteritis nodosa are HBsAg positive. The clinical manifestations are similar to those in patients with polyarteritis who are HBV-negative [15]. Patients with HBV-related polyarteritis may benefit from antiviral therapy. (See "Clinical manifestations and diagnosis of polyarteritis nodosa in adults" and "Kidney disease associated with hepatitis B virus infection".)

- HBV can induce both membranous nephropathy and, less often, membranoproliferative glomerulonephritis. Most cases of HBV-related glomerulonephropathy occur in children [16-18]. The typical presentation is with nephrotic range proteinuria. Approximately 30 to 60 percent of children with HBV-related membranous nephropathy undergo spontaneous remission, usually in association with hepatitis B e antigen to antibody (HBeAg to anti-HBe) seroconversion. A progression to renal failure can occur, particularly in adults. The efficacy of antiviral therapy is uncertain. (See "Kidney disease associated with hepatitis B virus infection".)

- Aplastic anemia has been described in association with HBV infection, although most cases of post-hepatitis aplastic anemia are not due to HBV. (See "Treatment of acquired aplastic anemia in children and adolescents".)

Sequelae and prognosis of chronic HBV infection

The sequelae of chronic hepatitis B virus (HBV) infection vary from an inactive carrier state to the development of cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), extrahepatic manifestations, and death. The prognosis appears to vary with the clinical setting. Long-term follow-up studies of hepatitis B surface antigen (HBsAg) positive blood donors have shown that the majority remain asymptomatic with a very low risk of cirrhosis or HCC [72-74]. In a 16-year follow-up study of 317 HBsAg positive blood donors from Montreal, for example, only three died from HBV-related cirrhosis and none developed HCC

[72]. Another report included 296 potential blood donors who were excluded from donation after they were found to be HBsAg positive and were followed for 30 years [74]. The incidence of clinically significant liver disease, HCC, or other liver-related morbidity or mortality was not significantly greater than a control population of HBV negative blood donors. (See "Epidemiology and risk factors for hepatocellular carcinoma".)

The prognosis is worse in HBV-infected patients from endemic areas and in patients with chronic hepatitis B [75-78]. The estimated five-year rates of progression are [79]:

- Chronic hepatitis to cirrhosis – 12 to 20 percent
- Compensated cirrhosis to hepatic decompensation – 20 to 23 percent (figure 3)
- Compensated cirrhosis to HCC – 6 to 15 percent (figure 4) (see 'Surveillance for hepatocellular carcinoma' below)

The cumulative survival rate at each of these stages of progressive disease is [76,78-81]:

- Compensated cirrhosis – 85 percent at five years (figure 5)
- Decompensated cirrhosis – 55 to 70 percent at one year and 14 to 35 percent at five years (figure 6)

Summary and recommendations

- The spectrum of clinical manifestations of hepatitis B virus (HBV) infection varies in both acute and chronic disease. During the acute phase, manifestations range from subclinical or anicteric hepatitis to icteric hepatitis and, in some cases, fulminant hepatitis; during the chronic phase, manifestations range from an asymptomatic carrier state to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Extrahepatic manifestations also can occur with both acute and chronic infection.

- Approximately 70 percent of patients with acute hepatitis B have subclinical or anicteric hepatitis, while 30 percent develop icteric hepatitis. The disease may be more severe in patients coinfected with other hepatitis viruses or with underlying liver disease. (See 'Acute hepatitis' above.)

- In patients with acute hepatitis B, we suggest treatment with a nucleos(t)ide analogue in those who have severe hepatitis (such as those who develop a coagulopathy [INR >1.5]) or a protracted course (such as persistent symptoms or marked jaundice [bilirubin >10 mg/dL] for more than four weeks after presentation) (**Grade 2B**). We also suggest treating patients with fulminant hepatitis B to reduce the likelihood of reinfection post-liver transplant, those who are immunocompromised, have concomitant infection with hepatitis C or D virus, have preexisting liver disease, or are elderly. (See 'Acute hepatitis' above.)

- The natural course of chronic hepatitis B virus infection is determined by the interplay between virus replication and the host immune response (table 2). Chronic HBV infection generally consists of two phases: an early replicative phase with active liver disease (immune-active), and a late or low replicative phase with remission of liver disease (inactive chronic HBV) (figure 1). In patients with perinatally acquired HBV infection, there is an additional immune tolerance phase in which virus replication is not accompanied by active liver disease (figure 2). In some patients, reactivation of HBV replication occurs after a varying period of quiescence. (See 'Phases of chronic HBV infection' above.)

- The sequelae of chronic HBV infection vary from an inactive carrier state to the development of cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), extrahepatic manifestations, and death. The prognosis appears to vary with the clinical setting. (See 'Sequelae and prognosis of chronic HBV infection' above.)

SUMMARY AND RECOMMENDATIONS

- **Epidemiology** – Hepatitis B virus (HBV) is a double-stranded DNA virus belonging to the family of hepadnaviruses. It is estimated that there are more than 250 million HBV carriers in the world, of whom approximately 600,000 die annually from HBV-related liver disease. (See 'Introduction' above.)

- **Acute HBV infection** – The diagnosis of acute HBV infection is based upon the detection of hepatitis B surface antigen (HBsAg) and IgM antibody to hepatitis B core antigen (anti-HBc). For most patients, treatment is mainly supportive. The likelihood of liver failure from acute HBV is less than 1 percent, and in immunocompetent adults, the likelihood of progression to chronic HBV infection is less than 5 percent. However, preventive measures (eg, hepatitis B immune globulin and hepatitis B vaccine) should be administered to all household and sexual contacts who are not known to be immune. (See 'Acute infection' above.)

- **Chronic HBV infection** – The diagnosis of chronic HBV infection is based upon the persistence of HBsAg for more than six months. The management of chronic HBV infection is complex and depends upon multiple factors including clinical variables (eg, the presence or absence of liver inflammation and/or cirrhosis), the patient's immunologic response to infection (eg, hepatitis B e antigen [HBeAg]), virologic factors (eg, HBV viral load and genotype), and risk factors for disease progression (eg, age >40, family history of hepatocellular carcinoma) (table 4). (See 'Initial evaluation' above.)

- **Antiviral therapy for chronic HBV** – Antiviral agents for chronic HBV include pegylated interferon (PegIFN) or nucleos(t)ide analogs (eg, entecavir and tenofovir). The goals of antiviral therapy are suppression of HBV DNA, loss of HBeAg (in patients who were initially HBeAg-positive), and loss of HBsAg. (See 'Overview of antiviral agents' above.)

- **When to initiate treatment** – The decision to initiate treatment is primarily based upon the presence or absence of cirrhosis, the alanine aminotransferase (ALT) level, and the HBV DNA level (table 5). There are additional indications for patients with certain concurrent conditions, such as malignancy and pregnancy. Patients who are not deemed to be treatment candidates at presentation, and those who decide to defer treatment, should undergo monitoring of liver biochemical tests, HBV DNA, and HBeAg status since liver disease and/or HBV replication may become active later (table 4). (See 'Indications for antiviral therapy' above.)

DIAGNOSTIC ALGORITHMS

Tests for HBV markers are useful in confirming the diagnosis of HBV infection and in the selection and monitoring of patients for antiviral therapy.

Acute hepatitis — The diagnosis of acute hepatitis B is based upon the detection of hepatitis B surface antigen (HBsAg) and IgM hepatitis B core antibody (anti-HBc) (table 3A-B and figure 1). During the initial phase of infection, markers of HBV replication, hepatitis B e antigen (HBeAg) and HBV DNA, are also present. Recovery is accompanied by the disappearance of HBV DNA, HBeAg to hepatitis B e antibody (anti-HBe) seroconversion, and subsequently HBsAg to hepatitis B surface antibody (anti-HBs) seroconversion.

Rarely, patients present during the window period when HBsAg has become negative but anti-HBs is not yet positive. In this setting, which is more common in patients with fulminant hepatitis B in whom virus clearance tends to be more rapid, IgM anti-HBc is the sole marker of acute HBV infection (figure 2).

The differential diagnosis of HBsAg-positive acute hepatitis includes acute hepatitis B, exacerbations of chronic hepatitis B (eg, around the time of HBeAg seroconversion), reactivation of chronic hepatitis B, superinfection of a hepatitis B carrier with hepatitis A, C, D, or E virus [14,20,56], and acute hepatitis due to drugs and other toxins in a hepatitis B carrier.

Past HBV infection — Previous HBV infection is characterized by the presence of anti-HBs and IgG anti-HBc (figure 1). Immunity to HBV infection after vaccination is indicated by the presence of anti-HBs only.

Chronic HBV infection — The diagnosis of chronic HBV infection is based upon the persistence of HBsAg for more than six months (table 3A-B and figure 1). Additional tests for HBV replication, HBeAg and serum HBV DNA and ALT, should be performed to determine if the patient should be considered for antiviral therapy.

SUMMARY AND RECOMMENDATIONS

- **Overview** – Approximately two billion people worldwide have evidence of past or present infection with hepatitis B virus (HBV), and 257 million individuals have chronic HBV infection.

  Hepatitis B surface antigen (HBsAg) is the serologic hallmark of HBV infection (acute and chronic). Hepatitis B e antigen (HBeAg) is a secretory protein that is processed from the precore protein. It is generally considered to be a marker of HBV replication and infectivity. Hepatitis B core antibody (anti-HBc) can be detected throughout the course of HBV infection and persists in those with chronic or past HBV infection. (See 'Serologic markers' above.)

- **Screening for HBV infection**

  - **Whom to screen** – Screening for HBV is indicated in certain asymptomatic patients (table 1). Screening is important to identify those with chronic HBV infection and those with prior infection who are at increased risk for HBV reactivation (eg, patients receiving immunosuppressive therapy, those with chronic hepatitis C virus infection [HCV] receiving direct-acting antiviral therapy). The results of screening can also be used to identify those who would benefit from vaccination. (See 'Asymptomatic patients' above.)

  - **What tests to order** – For most asymptomatic persons, we screen for HBsAg and hepatitis B surface antibody (anti-HBs). We also perform testing for anti-HBc (total or anti-IgG) in the following groups: persons with HIV, those with HCV infection who will receive direct-acting antivirals, patients who require immunosuppressive therapy, and blood and organ donors. (See 'What to test' above.)

- **Evaluating symptomatic patients for HBV infection** – Patients with signs and symptoms of acute or chronic hepatitis should be tested for HBV infection. In such patients, we typically test for HBsAg, anti-HBc (IgM and IgG), and anti-HBs. Additional tests may be warranted in those with evidence of acute or chronic HBV infection.

- **Interpretation of serologic test results**:

  - The diagnosis of acute HBV infection is based upon the detection of HBsAg and IgM anti-HBc (table 3A-B and figure 1). (See 'Acute hepatitis' above.)

  - Previous HBV infection is characterized by the presence of anti-HBs and IgG anti-HBc (figure 1). Immunity to HBV infection after vaccination is indicated by the presence of anti-HBs only. (See 'Past HBV infection' above.)

  - The diagnosis of chronic HBV infection is based upon the persistence of HBsAg for more than six months (table 3A-B and figure 1). (See 'Chronic HBV infection' above.)

- Additional tests for HBV replication – HBeAg and serum HBV DNA should be performed in those with chronic HBV infection to determine if the patient should be considered for antiviral therapy. (See 'Chronic HBV infection' above and 'Clinical use' above.)

- **Occult HBV infection** – Occult HBV infection is defined as the presence of detectable HBV DNA by polymerase chain reaction (PCR) in patients who are negative for HBsAg. Such patients have been further subclassified as having "seropositive" or "seronegative" occult HBV depending upon whether they are positive or negative for other HBV markers, most commonly anti-HBc. Most of these patients have very low or undetectable serum HBV DNA levels though HBV DNA is often detected in the liver. (See 'Occult HBV infection' above.)