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.

Outcome — Among patients who recover from acute hepatitis B, traces of HBV are often detectable in the blood by polymerase chain reaction testing for many years, despite the presence of serum antibodies to hepatitis B surface antigen (anti-HBs) and HBV-specific cytotoxic T cells, which can be present at high levels [5,6]. HBV-specific cytotoxic T cells may express activation markers, indicating recent contact with antigen in patients studied up to 23

years after clinical and serologic recovery. One study found that HBV DNA was detected in the liver tissues in 13 of 14 healthy liver transplant donors who were positive for hepatitis B core antibody (anti-HBc) and anti-HBs [7]. Persistent histologic abnormalities (including fibrosis and mild inflammation) were present for as long as 10 years in another series focusing on nine patients who demonstrated a complete serologic recovery after acute infection [8].

These observations suggest that complete eradication of HBV rarely occurs after recovery from acute HBV infection and that latent infection can maintain the T cell response for decades following clinical recovery, thereby keeping the virus under control [5]. Although some studies suggest that liver damage may be present in patients with latent infection, it is not clear how common this is since these studies were based on very few patients. However, immunosuppression in such patients can lead to reactivation of the virus. (See "Hepatitis B virus reactivation associated with immunosuppressive therapy".)

The rate of progression from acute to chronic hepatitis B in immunocompetent persons is determined primarily by the age at infection. The rate is approximately 90 percent for a perinatally acquired infection [9], 20 to 50 percent for infections between the age of one and five years [10,11], and less than 5 percent for an adult-acquired infection [12]. The factors responsible for the high rate of progression in neonates and children are discussed below. (See 'Phases of chronic HBV infection' below.)

Treatment — Treatment for acute HBV is mainly supportive. In addition, appropriate measures should be taken to prevent infection in exposed contacts.

The decision to hospitalize patients should be individualized. Patients who have a coagulopathy, are deeply jaundiced, or are encephalopathic should generally be hospitalized. Hospitalization might also be considered in patients who are older, have significant comorbidities, cannot tolerate oral intake, or have poor social support systems.

Whether patients should be treated with nucleos(t)ide analog therapy is unsettled since few studies have addressed the benefits of antiviral therapy during acute infection. We do not believe that all patients with acute HBV require antiviral treatment since the likelihood of fulminant hepatitis B is less than 1 percent, and in immunocompetent adults, the likelihood of progression to chronic HBV infection is less than 5 percent.

This recommendation was supported by a placebo-controlled study that included 71 patients with acute hepatitis B (31 randomized to lamivudine for three months and 40 to placebo), which showed no biochemical or clinical benefit to lamivudine, including the subset of 47 patients with severe acute hepatitis B [13]. There was also no difference in hepatitis B surface antigen (HBsAg) loss after 12 months (94 versus 97 percent in the groups that received lamivudine and placebo,

respectively). These data support that antiviral therapy is not indicated in the vast majority of patients with acute hepatitis B, but the role of antiviral therapy in patients with severe or protracted acute hepatitis B was not adequately addressed as the duration of illness was not mentioned, and only 3 of the 47 patients with severe acute hepatitis had encephalopathy.

As a general rule, we treat patients with a severe (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). We also suggest treating patients with fulminant hepatitis B to reduce the likelihood of reinfection post-liver transplant, those who are immunocompromised, have a concomitant infection with hepatitis C or D virus, have a preexisting liver disease, or are elderly.

Interferon should be avoided because of the increased risk of hepatic necroinflammation. Entecavir, tenofovir, lamivudine, adefovir or telbivudine are acceptable options given as monotherapy as the duration of treatment should be short. However, in situations in which it is unclear if the patient has acute HBV or an acute exacerbation of chronic HBV, entecavir or tenofovir (tenofovir disoproxil fumarate or tenofovir alafenamide) is preferred since these agents have a higher barrier to resistance. Treatment can be stopped after confirmation (two consecutive tests four weeks apart) that the patient has cleared HBsAg. More detailed information about these agents is found elsewhere. (See "Hepatitis B virus: Overview of management", section on 'Overview of antiviral agents'.)

Issues related to preventing HBV infection in individuals exposed to the patient are presented separately. (See "Epidemiology, transmission, and prevention of hepatitis B virus infection".)

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 [15]. 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 [16]. 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 [17-19]. 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".)

PHASES OF CHRONIC HBV INFECTION

The natural course of chronic hepatitis B virus (HBV) infection is determined by the interplay between virus replication and the host immune response (table 2). Other factors that may play a role in the progression of HBV-related liver disease include gender, alcohol consumption, and concomitant infection with other hepatitis virus(es). With the increasing prevalence of obesity, several studies have found that obesity and concomitant fatty liver disease may also accelerate progression of HBV-related liver disease [20-22]. The outcome of chronic HBV infection depends upon the severity of liver disease at the time HBV replication is arrested.

Chronic HBV infection generally consists of four phases, though not all patients go through all four phases and, while most patients move from one phase to the next, reversal to an earlier phase can occasionally occur (figure 1) [23-25].

Immune tolerance — In patients with a perinatally acquired HBV infection, the initial phase is characterized by high levels of HBV replication—the presence of hepatitis B e antigen (HBeAg) and high levels of HBV DNA in serum—but no evidence of active liver disease as manifested by lack of symptoms, normal serum ALT concentrations, and minimal changes on liver biopsy [26,27]. Two studies found that 30 to 50 percent of patients in this phase had stage 0 while the others had stage I fibrosis [28,29]. One of these studies showed that fibrosis scores on repeat biopsies were unchanged after five years among patients who remained in the immune tolerance phase [29].

The lack of liver disease despite high levels of HBV replication has typically been attributed to immune tolerance to HBV [30]. Experiments in mice suggest that the transplacental transfer of maternal HBeAg may induce specific unresponsiveness of T cells to HBeAg and to hepatitis B core antigen (HBcAg), resulting in ineffective cytotoxic T cell lysis of infected hepatocytes [31]. Immune tolerance is also believed to be the major reason for the poor response to interferon therapy in HBeAg positive Asian patients who have normal serum ALT concentrations. However, subsequent studies have found that the T cell response to HBV in patients during this phase is similar to those in the immune clearance phase, challenging the concept of immune tolerance [32].

The immune tolerance phase usually lasts 10 to 30 years, during which there is a very low rate of spontaneous HBeAg clearance [33,34]. Studies in Chinese children, for example, have found HBeAg in as many as 90 percent below the age of five, and up to 80 percent below the age of 20 [27,33]. The cumulative rate of spontaneous HBeAg clearance is estimated to be approximately 2 percent during the first three years and only 15 percent after 20 years of infection [34,35]. The low rate of viral clearance in adolescence and early adulthood accounts for the high frequency of maternal-infant transmission in Asian countries.

Immune-active, HBeAg-positive — The transition from the immune tolerance to the immune-active or clearance phase occurs during the second and third decades in patients with perinatally acquired HBV infection. During this phase, spontaneous hepatitis B e antigen (HBeAg) clearance increases to an annual rate of 10 to 20 percent [33,34]. A seroconversion rate of 70 percent during 10 years of follow-up was described in a population-based study of 1536 Alaskan natives who acquired HBV as adults [36]. Several studies from Asia found that patients with genotype B infection undergo HBeAg seroconversion at an earlier age than those with genotype C infection. (See "Clinical significance of hepatitis B virus genotypes".)

HBeAg seroconversion is frequently, but not always, accompanied by biochemical exacerbations (abrupt increases in serum ALT) [14,37,38]. Exacerbations are believed to be due to a sudden increase in immune-mediated lysis of infected hepatocytes. They are often preceded by an increase in serum HBV DNA [39] and a shift of HBcAg from nuclear to cytoplasmic sites within hepatocytes [40], suggesting that immune clearance may be triggered by an increase in viral load or a change in the presentation of viral antigens. How these changes occur is not known.

Most exacerbations are asymptomatic and are discovered during routine follow-up. However, some are accompanied by symptoms of acute hepatitis and may lead to the incorrect diagnosis of acute hepatitis B in patients who are not previously known to have chronic HBV infection [41]. Exacerbations may be associated with an elevation in the IgM hepatitis B core antibody (anti-HBc) titer, which may lead to misdiagnosis of acute HBV infection and an increase in the serum alpha-fetoprotein concentration, which may raise concerns about the diagnosis of hepatocellular carcinoma (HCC) [14,42].

Exacerbations are more commonly observed in men than in women [43,44]. The reason for the gender difference is not clear, but a higher frequency of exacerbations in men may at least in part account for a higher incidence of HBV-related cirrhosis and HCC among men.

In a small percentage of patients, exacerbations result in hepatic decompensation and rarely death from hepatic failure [45]. One report found that a serum HBV DNA level of 1.55×10^9 copies/mL (approximately 8 $\log_{10}$ international units/mL) or greater at the onset of a flare predicted decompensation in HBeAg positive patients without cirrhosis [46].

Patients with severe exacerbations should be referred to specialized centers for liver transplantation and receive treatment with nucleos(t)ide analogues. Interferon is not indicated in this setting since it can cause further exacerbation of the disease. (See "Hepatitis B virus: Overview of management".)

Not all exacerbations lead to HBeAg seroconversion and clearance of HBV DNA from the serum, a phenomenon termed **abortive** immune clearance [14,38]. These patients may develop

recurrent exacerbations with an intermittent disappearance of serum HBV DNA with or without a transient loss of HBeAg. Such repeated episodes of hepatitis may increase the risk of developing cirrhosis and HCC. One study of 151 patients with chronic HBeAg positive hepatitis B (all with genotype C infection) found that early HBeAg seroconversion was more likely in patients who acquired HBV infection after the perinatal period and those with HBV DNA levels ≤7 log copies/mL (approximately 6 $\log_{10}$ international units/mL) [47].

As noted above, the initial phase in patients with childhood or adult-acquired chronic HBV infection consists of virus replication (presence of HBeAg and high serum HBV DNA) and active liver disease (elevated serum ALT and chronic hepatitis on liver biopsy) (figure 1). The prevalence of HBeAg among non-Asian adults with chronic HBV infection is usually in the range of 10 to 20 percent, lower than the 30 to 50 percent seen among Chinese adults with chronic HBV infection. However, the rate of spontaneous HBeAg clearance during the immune clearance phase appears to be similar to Asians (10 percent to 20 percent per year) [23,24,34,48].

Inactive chronic HBV — Patients in the low or nonreplicating phase/inactive carrier state are HBeAg negative and anti-HBe positive. In some patients, HBV DNA is undetectable in serum, and liver disease is in remission as evidenced by normal serum ALT concentrations and the resolution of necroinflammation in liver biopsies. One study found that about 40 percent of inactive carriers had HBV DNA levels of 10^4 copies/mL (>2000 international units/mL) or greater [49].

HBeAg-negative patients with a persistently normal serum ALT can still have significant histologic inflammation and/or fibrosis [50,51], although a meta-analysis found that significant liver disease was rare in those with a persistently normal ALT and an HBV DNA level ≤20,000 international units/mL [52]. In another report, only patients with high serum HBV DNA >4 $\log_{10}$ copies/mL (>2000 international units/mL) were biopsied; in such patients, age was a predictor of significant histologic findings [50]. In a third study, the authors reported that 21 percent of HBeAg-negative patients with a persistently normal ALT and HBV DNA level of <5 log copies/mL (<20,000 international units/mL) had histologically active liver disease [51]. However, only 29 of 75 (39 percent) HBeAg-negative patients who had persistently normal ALT and HBV DNA <5 log copies/mL were biopsied, and only six had active liver disease. It was unclear if patients who were biopsied were representative of the entire population. These data indicate that significant liver disease can be found in HBeAg-negative patients with normal ALT, but this is rare in those with truly persistent normal ALT defined by at least three normal ALT over a 12-month period and HBV DNA <4 $\log_{10}$ copies/mL (<2000 international units/mL).

Because of the fluctuating nature of chronic HBV infection, patients should not be categorized as inactive carriers unless there are at least three ALT levels and two to three HBV DNA levels

over a 12-month period of observation. Studies suggest that combined quantification of hepatitis B surface antigen (HBsAg) level and HBV DNA at a single time point may help in differentiating inactive carrier phase versus HBeAg-negative chronic hepatitis. HBsAg <1000 international units/mL in an HBeAg-negative patient with serum HBV DNA <2000 international units/mL identifies the inactive carrier phase with a high diagnostic accuracy (94 percent) [53].

Immune-active, HBeAg-negative — Some patients continue to have moderate levels of HBV replication and active liver disease (elevated serum ALT and chronic inflammation on liver biopsies), but remain hepatitis B e antigen (HBeAg) negative [54,55]. Such patients are said to have HBeAg-negative chronic hepatitis. They have a residual wild-type virus or HBV variants that cannot produce HBeAg due to precore or core promoter genetic variations [56-59].

Patients with HBeAg-negative immune-active chronic hepatitis B are older and have more advanced liver disease. They also tend to have fluctuations in HBV DNA and ALT levels.

The frequency of flares was estimated in a study of 217 asymptomatic patients with chronic HBV who were HBeAg negative, anti-HBe positive, and had a normal ALT level at baseline [43]. During a median follow-up of almost six years, spontaneous ALT flares occurred in 43 patients (4.3 percent per year) with a cumulative probability of a flare of 11 and 47 percent after 5 and 10 years, respectively. On multivariable analysis, flares were significantly associated with age ≥30, male sex, and the presence of a precore mutation. The authors noted that follow-up every three months captured up to 90 percent of flares [44].

In one study, 283 patients who underwent spontaneous HBeAg seroconversion were followed for a median of 8.6 (range 1 to 18) years; 67 percent had sustained biochemical remission [60]. The risk of cirrhosis and HCC were negligible in those with sustained remission and significantly higher in those with ALT elevation after HBeAg seroconversion.

Resolution of chronic HBV infection — Some patients with chronic HBV infection become HBsAg negative. The annual rate of delayed clearance of HBsAg has been estimated to be 0.5 to 2 percent in Western patients and much lower (0.1 to 0.8 percent) in Asian countries [48,61,62]. A study from Taiwan estimated that the cumulative probability of HBsAg seroclearance was only 8 percent after 10 years, but increased to 25 and 45 percent, respectively, after 20 and 25 years [63]. Another report followed 3087 patients with chronic HBV [62]. The patients median age was 45, 65 percent were men, and the majority (84 percent) were HBeAg seronegative. HBsAg clearance occurred in 562 participants (an annual clearance rate of 2.26 percent). Clearance was preceded by a decrease in HBV DNA. The cumulative incidence of HBsAg clearance after 5 and 8 years were approximately 26 and 51 percent, respectively, in patients whose serum HBV DNA became undetectable. HBsAg clearance may be preceded by decreasing levels of HBsAg [64].

In most reports, patients who cleared HBsAg appeared to have a good prognosis [65-72]. In the absence of other causes of liver injury, progression to cirrhosis and hepatic decompensation after HBsAg clearance is rare. However, the risk of HCC remains [73,74], and surveillance should continue in those who have HCV or hepatitis D virus (HDV) coinfection, cirrhosis, or are older than 50 years at the time of HBsAg clearance.

One of the largest series to address this issue focused on 218 such patients who were followed for a median of 62 months [66]. Of 189 patients who did not have cirrhosis at the time of HBsAg clearance, three developed cirrhosis, two developed hepatocellular carcinoma, and one died of hepatocellular carcinoma. However, these complications developed only in patients who had concurrent HCV or HDV infection. Another report found that the likelihood of developing HCC was greater in those who cleared HBsAg when older than age 50 [69].

In a series of 55 patients who spontaneously cleared HBsAg, complications developed in 33 percent (11 hepatocellular carcinoma, 6 cirrhosis, and 1 subfulminant liver failure) during a mean follow-up of 23 months [68]. This study probably overestimated the frequency with which complications occur, as it included 20 patients (36 percent) who had coinfection with either hepatitis C or hepatitis D. Furthermore, some of the patients may have had undocumented cirrhosis or irreversible liver damage prior to seroconversion.

Many patients who clear HBsAg remain HBV DNA positive when tested by polymerase chain reaction assays, particularly during the first 10 years of HBsAg clearance [69] (see "Hepatitis B virus: Screening and diagnosis in adults"). A small proportion of these patients may be infected with a mixture of the wild-type virus and HBV variants with a deletion in the pre-S1 region, which are associated with a reduction in HBsAg synthesis [75]. A reactivation of HBV replication with reappearance of HBeAg and HBV DNA in serum and recrudescence of liver disease may occur when these patients are immunosuppressed. The reactivation can vary in severity from mild and asymptomatic to severe with possible fulminant hepatic failure. (See "Hepatitis B virus reactivation associated with immunosuppressive therapy".)

HBV DNA persists in the liver of the vast majority of patients after HBsAg clearance, although HBV DNA may not be detected in serum. These patients are anti-HBc positive and, over time, many seroconvert to anti-HBs. These patients are often considered to have occult HBV infection (HBsAg negative, HBV DNA positive in liver and/or serum, and generally also anti-HBc positive) [76].

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 [77-79]. 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 [77]. 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 [79]. 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 [80-83]. The estimated five-year rates of progression are [84]:

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

The cumulative survival rate at each of these stages of progressive disease is [81,83-86]:

- Compensated cirrhosis – 85 percent at five years
- Decompensated cirrhosis – 55 to 70 percent at one year and 14 to 35 percent at five years

Among Chinese patients with chronic HBV infection, the life-time risk of a liver-related death has been estimated at 40 to 50 percent for men and 15 percent for women [87]. The risk of progression appears to be greatest in patients who stayed in the immune clearance phase [29], in patients who have delayed hepatitis B e antigen (HBeAg) seroconversion [88], and in patients who had reactivation of HBV replication after HBeAg seroconversion [36,60,89].

It should be noted that the rates of progression and rates of survival cited above were based on data in the pre-nucleos(t)ide analogue era and prognosis of patients with chronic hepatitis B have improved markedly in the last 10 years.

A follow-up report of a placebo controlled trial evaluating lamivudine in patients with bridging fibrosis or compensated cirrhosis described the natural history in 215 patients randomized to placebo [90]. The primary endpoint of the study was defined as time to first occurrence of disease progression (an increase of ≥2 points in the Child-Pugh score, the development of

hepatocellular carcinoma, or bleeding varices). One of these endpoints was reached in 18 percent of patients after a median follow-up of 32 months (9 percent with an increase in the Child-Pugh score, 7 percent with the development of HCC, and 1 percent with bleeding varices). Disease progression was more likely in patients with higher baseline fibrosis scores. There was a possible association between HBV genotype C and disease progression, but there were insufficient data for detailed analysis. (See "Clinical significance of hepatitis B virus genotypes".)

Factors predictive of disease progression — Both virologic and nonvirologic factors influence disease progression and survival in patients with chronic HBV infection [85,86,90-92].

Factors related to HBV infection include the individual's HBeAg status, the HBV DNA and HBsAg levels, and the HBV genotype. Certain HBV variants (eg, core promoter or pre-S deletion variants) have also been associated with progressive liver disease and HCC. The HBV DNA level is the most important virologic predictor of disease progression in patients with a high HBV viral load (≥2000 IU/mL), whereas the HBsAg level helps determine the risk of progression in those with a HBV DNA <2000 IU/mL [93]. Other examples include:

- **HBeAg** – Patients with a prolonged replication phase (ie, HBeAg positive) have a worse prognosis, mostly due to the development of cirrhosis and HCC [85,86,94]:
  - In a study of 98 patients with HBsAg positive compensated cirrhosis, the five-year survival rate was significantly lower in patients who were HBeAg positive (72 versus 97 percent in those who were HBeAg negative) [85]. Clearance of HBeAg was associated with a 2.2-fold decrease in death rate.
  - In a cohort study of 11,893 men from Taiwan, 111 cases of newly diagnosed HCC were identified during 92,359 person-years of follow-up [94]. Compared to men who were negative for both HBsAg and HBeAg, the relative risk of HCC was 9.6 (95% CI 6.0 to 15.2) among men who were HBsAg positive but HBeAg negative, and 60.2 (95% CI 35.5 to 102.1) among those who were positive for both HBsAg and HBeAg.

  The worse prognosis in patients with a prolonged replicative phase may be related to a longer duration of necroinflammation [14,95]. Recurrent episodes of hepatitis may, either directly or indirectly through immune-mediated injury, increase the risk of fibrosis, cirrhosis, and perhaps carcinogenesis. Even among patients with decompensated cirrhosis, the suppression of HBV replication can result in an improvement in liver disease [65,96]. (See "Epidemiology and risk factors for hepatocellular carcinoma", section on 'Hepatitis B virus'.)

- **HBV DNA** – High HBV DNA levels are associated with an increased incidence of cirrhosis, hepatocellular carcinoma, and liver-related mortality [97,98]. As an example, in a population-based prospective cohort study (REVEAL HBV) in Taiwan, the cumulative incidence of cirrhosis during a mean follow-up of 11 years ranged from 4.5 percent for those with an HBV DNA level of less than 300 copies/mL (approximately 60 international units/mL) to 36 percent for those with an HBV DNA level of 10^6 copies/mL (approximately 200,000 international units/mL) or more at study entry. The HBV DNA level remained an independent predictor of cirrhosis after adjusting for HBeAg status, age, sex, ALT level, cigarette smoking, and alcohol consumption. High serum HBV DNA (>10^6 copies/mL) was also an independent predictor of HCC after adjusting for HBe antigen status, serum alanine aminotransferase, and the presence of cirrhosis (hazard ratio [HR] 5.3, 95% CI 2.9-9.7) [99]. However, the majority of persons in the REVEAL study acquired HBV infection in infancy or early childhood and the mean age of participants was 43 years. Thus, the significance of high HBV DNA levels in those with a shorter duration of infection (eg, younger individuals and in those with adult acquired HBV infection) is unclear.

- **HBsAg levels** – In patients with HBeAg negative chronic HBV with a low viral load, HBsAg levels >1000 IU/mL have been associated with an increased risk of disease progression and HCC [100,101]. In a prospective cohort study in Taiwan, 1068 patients with chronic HBV genotype B or C infection and a low viral load (HBV DNA <2000 IU/mL), HBsAg levels >1000 IU/mL were associated with an increased risk of HBeAg negative hepatitis, hepatitis flares, and cirrhosis after adjusting for age, HBV DNA, and ALT levels (HR 1.5, 2.3, and 4.1, respectively). These data indicate that among patients with low viral load, the narrow range of HBV DNA from undetectable to <2000 IU/mL, makes it difficult to stratify patients for risk of cirrhosis or HCC and other markers such as HBsAg level need to be considered.

Factors not associated with HBV include those related to the host (gender, age, diabetes) and environment (alcohol, smoking, carcinogens) as well as coinfection with other viruses (eg, HCV, HDV, HIV). (See "Clinical manifestations and natural history of chronic hepatitis C virus infection", section on 'Factors associated with disease progression' and "Epidemiology, clinical manifestations and diagnosis of hepatitis D virus infection" and "Epidemiology, clinical manifestations, and diagnosis of hepatitis B in patients living with HIV", section on 'Effect of HIV on liver-related mortality'.)

Reactivation following seroconversion — A subset of patients who achieve HBeAg seroconversion experience reactivation. Reactivation can occur in patients who receive immunosuppressive therapy, but can also occur spontaneously. (See "Hepatitis B virus reactivation associated with immunosuppressive therapy".)

Only a few studies have described risk factors for spontaneous reactivation. One of the most detailed reports described 133 asymptomatic blood donors who had documented HBeAg seroconversion and were followed regularly for an average of six years [89]. Reactivation occurred in 26 patients at a rate of 3.3 percent per year. On multivariate analysis, reactivation was associated with HBV genotype C, male sex, serum ALT levels >5 times the upper limit of normal during the HBeAg-positive phase, and age at HBeAg seroconversion ≥40.

Reactivation associated with immunosuppression — Hepatitis B virus reactivation associated with immunosuppression is discussed separately. (See "Hepatitis B virus reactivation associated with immunosuppressive therapy".)

Surveillance for hepatocellular carcinoma — Surveillance for HCC is recommended for chronic HBV carriers. Recommendations for surveillance for HCC have been issued by the American Association for the Study of Liver Diseases (AASLD) [102-104], which can be accessed through the AASLD website. Surveillance can lead to early detection of HCC, but available testing is far from satisfactory. (See "Surveillance for hepatocellular carcinoma in adults".)

HBV AND CHRONIC ALCOHOL ABUSE

The prevalence of serum HBV markers among alcoholics has been estimated to be two- to fourfold higher than a corresponding control population, suggesting an increased rate of HBV infection [105,106]. There is no clear evidence that alcoholics have an enhanced risk of chronic HBV infection. However, HBV DNA has been detected in the sera and liver tissues in some HBsAg negative alcoholics who present with liver disease, implying that occult HBV infection may have contributed to liver disease in these patients [107,108].

Alcoholics with HBV infection have been reported to have accelerated liver injury, increased risk of developing cirrhosis and hepatocellular carcinoma (HCC), and reduced survival compared with alcoholics who are not HBV-infected [109-112]. As an example, the odds of having HCC appear to be much higher in patients with heavy alcohol use compared with those who use less alcohol [111]. Obesity also increases the risk of HCC among patients who drink alcohol on a regular basis (ie, at least four drinks per week for at least one year) [113]. Obesity and alcohol are also with fatty liver disease. More detailed discussions of HCC and fatty liver disease are found elsewhere. (See "Epidemiology and risk factors for hepatocellular carcinoma", section on 'Risk factors' and "Clinical manifestations and diagnosis of alcohol-associated fatty liver disease and cirrhosis" and "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults".)

COINFECTION WITH HCV OR HDV

Hepatitis B infected patients may also be infected with hepatitis C virus (HCV) or hepatitis D virus (HDV).

Hepatitis C virus infection — Acute coinfection with HBV and HCV may shorten the duration of HBs antigenemia and lower the peak serum aminotransferase concentration compared with acute HBV infection alone [114]. These findings suggest that HCV coinfection may interfere with the replication of HBV, leading to attenuation of liver damage. However, acute coinfection of HCV and HBV, or acute HCV on preexisting chronic HBV have also been reported to increase the risk of severe hepatitis and fulminant hepatic failure [115-117]. Similarly, acute HBV in patients with chronic HCV can lead to severe hepatitis, but may also lead to clearance of HCV [118].

Approximately 10 to 15 percent of patients with HBV-associated chronic hepatitis, cirrhosis, or hepatocellular carcinoma (HCC) have coexistent HCV infection [119]. In a study of 1257 patients with chronic HCV infection, 62 percent had evidence of exposure to HBV, while 6 percent had concurrent chronic HBV [120]. The risk of developing HCC appears to be greater among those with dual-infection compared with those who are infected with HBV or HCV alone. As an example, the effect of HBV and HCV infection on the development of HCC was evaluated in a study of 23,830 individuals from Taiwan, of whom 477 developed HCC [121]. The incidence of HCC in men and women who were dually-infected (ie, positive for hepatitis B surface antigen [HBsAg] and antibodies against HCV [anti-HCV]) was 38 and 27 percent, respectively, whereas the incidence of HCC for men and women who were only positive for HBsAg was 27 and 8 percent, respectively.

HCV superinfection in HBsAg carriers appears to reduce HBV DNA levels in serum and liver tissues and to increase the rate of HBsAg seroconversion [122-126]. Most patients who have dual HCV and HBV infections have detectable serum HCV RNA but undetectable or low HBV DNA levels, indicating that HCV is the predominant cause of liver disease in these patients. On the other hand, levels of HBV DNA and HCV RNA fluctuate over time in about one-third of patients [127]. Liver disease is usually more severe than in patients infected by HBV alone [128]. Patients with dual HBV and HCV infection may also have a higher rate of HCC compared with patients infected by either virus alone, particularly those who are anti-HCV and hepatitis B e antigen (HBeAg) positive [126,129-131].

The treatment of HCV infection with peginterferon plus ribavirin or direct-acting antiviral agents (DAA) in patients with concomitant HBV infection can lead to a sustained virologic response. The rate of sustained virologic response is similar to that observed in patients with HCV alone [102].

However, HBV replication may increase after clearance of HCV [102,132]. Thus, close monitoring of both viruses is required, and testing of HBsAg and hepatitis B core antibody (anti-HBc) should be done prior to initiating DAA therapy [133]. (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection", section on 'HBV coinfection' and "Hepatitis B virus: Overview of management", section on 'Patients with hepatitis C coinfection'.)

Hepatitis D virus infection — Although HDV can replicate autonomously, the simultaneous presence of HBV is required for complete virion assembly and secretion. As a result, individuals with hepatitis D are **always** dually infected with HDV and HBV.

Acute HBV and HDV coinfection tends to be more severe than acute HBV infection alone and is more likely to result in fulminant hepatitis. HDV superinfection in patients with chronic HBV infection is usually accompanied by a suppression of HBV replication due to interference mechanisms that are not well understood [134]. HDV superinfection in such patients has been associated with more severe liver disease and accelerated progression to cirrhosis in most studies [135-137], although discordant data have been reported [138].

The clinical manifestations of persons with HBV/HDV infection are discussed in detail in a separate topic review. (See "Epidemiology, clinical manifestations and diagnosis of hepatitis D virus infection".)

Hepatitis C and D virus infection — The interaction of viral replication in patients coinfected with HBV, HCV, and HDV remains unclear. Triple infection was associated with inhibition of HCV and HBV replication, suggesting that HDV had the dominant role [125]. Similar results had been described by others [139]. In contrast, another study found that triple infection was usually dominated by HCV [1]. (See "Epidemiology, clinical manifestations and diagnosis of hepatitis D virus infection".)

HEPATITIS A VIRUS INFECTION

The Advisory Committee on Immunization Practices (ACIP) recommends the immunization of all patients with chronic liver disease against hepatitis A virus (HAV). (See "Hepatitis A virus infection: Treatment and prevention" and "Immunizations for adults with chronic liver disease".)

This recommendation is based upon theoretical grounds (that patients with chronic liver disease might have a worse prognosis if they developed superimposed acute hepatitis) rather than firm data, particularly with respect to HBV. In one study, in which 163 patients with chronic hepatitis B were prospectively followed for seven years, hepatitis A superinfection occurred in 10 patients [140]. An uncomplicated course occurred in nine of these patients; one patient who

also had preexisting cirrhosis developed marked cholestasis. The outcome was much worse in patients with chronic HCV. A more detailed discussion of HAV infection in patients with underlying liver disease is found elsewhere. (See "Hepatitis A virus infection in adults: Epidemiology, clinical manifestations, and diagnosis", section on 'Epidemiology'.)

Despite the sparse data, we follow the ACIP guidelines and recommend immunization with the Hepatitis A vaccine in patients with chronic hepatitis B (see "Hepatitis A virus infection: Treatment and prevention" and "Immunizations for adults with chronic liver disease"). However, countries with a high prevalence of HBV also have a high prevalence of HAV. Thus, testing for the HAV antibody should be performed, with the vaccine being given only to patients who are HAV antibody-negative.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Diagnosis of hepatitis B".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Hepatitis B (The Basics)")
- Beyond the Basics topics (see "Patient education: Hepatitis B (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Acute hepatitis B virus (HBV) infection**

  - **Clinical features** – In patients with acute HBV infection, the clinical manifestations can vary. Approximately 70 percent of patients with acute hepatitis B have subclinical or anicteric hepatitis, while 30 percent develop icteric hepatitis. Less than 1 percent develop fulminant hepatitis. The disease may be more severe in patients coinfected with other hepatitis viruses or with underlying liver disease. Extrahepatic manifestations (eg, serum sickness-like syndrome) also can occur. (See 'Clinical manifestations' above.)

  - **Outcome** – In general, most patients with acute HBV recover clinically; less than 5 percent go on to develop chronic HBV. Patients typically recover on their own, but patients with severe or persistent acute HBV may require treatment with a nucleos(t)ide analogue. For those who develop fulminant hepatitis, liver transplant may be needed. (See 'Outcome' above.)

    Although patients may recover clinically from acute HBV, complete eradication of HBV rarely occurs, and HBV remains latent in the hepatocytes. Latent infection maintains the T cell response for decades following clinical recovery, keeping the virus under control. However, reactivation of HBV can occur in the setting of certain immunosuppressive therapies (eg, rituximab). HBV reactivation is discussed detail elsewhere. (See "Hepatitis B virus reactivation associated with immunosuppressive therapy".)

- **Chronic hepatitis B virus infection**

  - **Clinical features** – During the chronic phase of HBV infection, manifestations range from an asymptomatic carrier state to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Extrahepatic manifestations, which are thought to be mediated by circulating immune complexes, can include polyarteritis nodosa and glomerular disease. (See 'Chronic hepatitis' above.)

  - **Natural history** – 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.

In some patients, reactivation of HBV replication occurs after a varying period of quiescence. (See 'Phases of chronic HBV infection' above.)

- **Factors predictive of disease progression** – Both virologic and nonvirologic factors influence disease progression and survival in patients with chronic HBV infection. These include the individual's hepatitis B e antigen (HBeAg) status, the HBV DNA and hepatitis B surface antigen (HBsAg) levels, and the HBV genotype. Certain HBV variants (eg, core promoter or pre-S deletion variants) have also been associated with progressive liver disease and hepatocellular carcinoma (HCC). (See 'Sequelae and prognosis of chronic HBV infection' above.)

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Topic 3627 Version 28.0

GRAPHICS

Glossary of clinical terms used in HBV infection

Definitions
Chronic hepatitis B
Chronic necroinflammatory disease of the liver caused by persistent infection with hepatitis B virus. Chronic hepatitis B can be subdivided into HBeAg-positive and HBeAg-negative chronic hepatitis B.
Inactive HBsAg carrier state
Persistent HBV infection of the liver without significant, ongoing necroinflammatory disease.
Resolved hepatitis B
Previous HBV infection without further virological, biochemical, or histological evidence of active virus infection or disease.
Acute exacerbation or flare of hepatitis B
Intermittent elevations of aminotransferase activity to more than 10 times the upper limit of normal and more than twice the baseline value.
Reactivation of hepatitis B
Reappearance of active necroinflammatory disease of the liver in a person known to have the inactive HBsAg carrier state or resolved hepatitis B.
HBeAg clearance
Loss of HBeAg in a person who was previously HBeAg positive.
HBeAg seroconversion
Loss of HBeAg and detection of anti-HBe.

HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; anti-HBe: hepatitis B e antibody.

Graphic 81182 Version 2.0

Diagnostic tests to determine phase of acute or chronic hepatitis B virus infection[1]

HBsAg	HBeAg	IgM anti-HBc	Total anti-HBc*	Anti-HBs	Anti-HBe	HBV DNA	ALT¶	Interpretati

Acute HBV infection								
+	+	+	±			+++	Elevated	Early phase
		+	±			+	Elevated	Window phase
			+	+	+	±	Normal	Recovery phas
Chronic HBV infection (HBsAg-positive for >6 months)								
+	+		+	-	-	+++ (Serum HBV typically >1 million international units/mL)	Normal or mildly elevated	Immune-tolera phase[Δ]
+	+		+	-	-	+++ (Serum HBV >20,000 international units/mL)	Persistently elevated	Immune-active HBeAg-positive
+	-		+	-	+	++ (Serum HBV >2000 international units/mL)	Elevated	Immune-active HBeAg-negativ
+	-		+		+	- to ++ (Serum HBV ≤2000 international units/mL)	Normal or mildly elevated	Inactive chroni HBV[§]
-	-		± (generally +)	±	±	+ in liver; - to + in serum	Normal	Occult HBV

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.

* This test is typically ordered as total anti-HBc, which includes IgM and IgG.

¶ The upper limits of normal for ALT in healthy adults are reported to be 29 to 33 units/L for males and 19 to 25 units/L for females. For healthy children after infancy, the upper limits of normal are 25 to 38 units/L and 22 to 31 units/L for boys and girls, respectively.

Δ For patients with immune-tolerant chronic hepatitis B, liver biopsy or noninvasive tests show no fibrosis and minimal inflammation. This is the initial phase seen in patients with perinatally acquired HBV infection.

◇ For patients with immune active chronic hepatitis B, liver biopsy or noninvasive tests show chronic hepatitis with moderate or severe necroinflammation with or without fibrosis. For patients who are HBeAg positive, immune-active chronic hepatitis B (also known as the clearance phase) can last for 10 to 20 years, and may be associated with the loss of HBeAg. For patients who are HBeAg negative, immune-active chronic hepatitis B is associated with immune reactivation and is also referred to as HBeAg-negative chronic hepatitis B or HBeAg-negative replicative phase.

§ Patients with inactive chronic hepatitis B are HBeAg negative. In such patients, liver biopsy confirms the absence of significant necroinflammation, but biopsy or noninvasive testing show variable levels of fibrosis. This stage has also been referred to as the nonreplicative or carrier phase.

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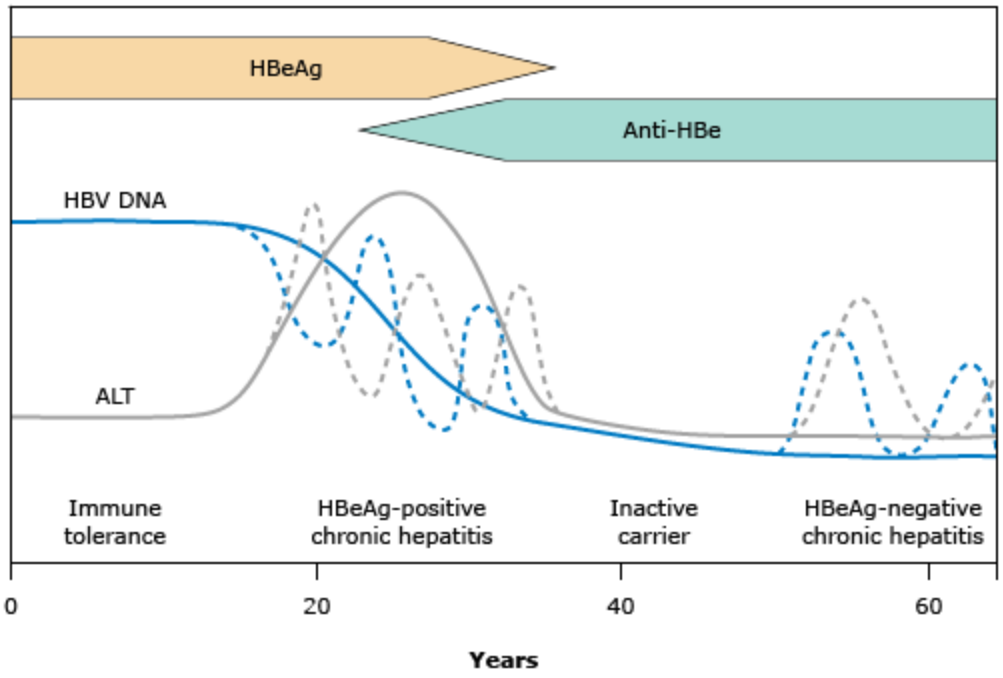
Graphic 60627 Version 8.0

Course of chronic HBV infection



The course of chronic HBV infection is considered to consist of four phases: immune tolerance, immune clearance (HBeAg-positive chronic hepatitis), inactive carrier, and reactivation (HBeAg-negative chronic hepatitis), although not all patients go through every phase.

Characteristics of each phase:

- Immune tolerance: HBeAg+, high HBV DNA (usually >10^8 IU/mL), and persistently normal ALT
- HBeAg-positive chronic hepatitis: HBeAg+, fluctuating high HBV DNA (usually >10^5 IU/mL), and fluctuating ALT (usually >ULN)
- Inactive carrier: HBeAg–, persistently low HBV DNA (usually <2000 IU/mL), and normal ALT
- HBeAg-negative chronic hepatitis: HBeAg–, fluctuating moderate HBV DNA (usually 10^3-10^7 IU/mL), and fluctuating ALT (usually >ULN but may be intermittently normal)

HBeAg: hepatitis B e antigen; anti-HBe: antibody to HBeAg; HBV: hepatitis B virus; ALT: alanine aminotransferase; ULN: upper limit of normal.

Graphic 67609 Version 4.0

Contributor Disclosures

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