

NATURAL HISTORY OF CHRONIC HEPATITIS B VIRUS INFECTION

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KEY POINTS

- Birth in a highly endemic country is a risk factor for developing chronic hepatitis B infection (CHB). The primary mode of transmission in such cases is vertical (mother-to-child).
- The risk of developing chronic hepatitis B infection is highest in those who acquire hepatitis B virus (HBV) perinatally and lowest in those who acquire the infection in adulthood.
- The natural history of HBV infection depends on complex host, viral, and environmental interactions.
- There are four phases of chronic HBV infection and the host immune response in each phase determines the outcome of infection and the severity of liver injury.
- Complications of chronic HBV infection include cirrhosis with hepatocellular failure and hepatocellular carcinoma (HCC).

Transmission routes and risks

Hepatitis B virus (HBV) infection is a viral infection spread by contact with infected blood or bodily fluids, including semen and saliva. The virus may be transmitted:

- Vertically, between a mother with chronic infection and her baby
- Horizontally, through close person-to-person contact, usually in childhood (e.g. through open cuts or sores)
- Parenterally, via injecting drug use (IDU)
- Sexually.

Risk factors

- Birth in a highly endemic country, e.g. East or South Asia, European Mediterranean countries, the Middle East, Eastern Europe, South America, the Caribbean and South Pacific Islands
- High-risk sexual behaviour, including men who have sex with men (MSM) and sex workers
- Indigenous Australians
- Household contacts of people who are HBsAg positive
- Injecting drug use (IDU)
- Contaminated blood products
- Contaminated surgical equipment
- Tattoos
- Previous imprisonment
- Haemodialysis.

Natural history of acute hepatitis

B virus infection

There are four phases in the natural history of acute hepatitis B:¹

1. Incubation phase: the incubation period of acute HBV infection can last up to twelve weeks.
2. Symptomatic hepatitis: acute hepatitis develops following the incubation period, evidenced by elevated aminotransferase levels, and lasts 4–12 weeks. Symptoms include anorexia, dark urine, jaundice and right upper quadrant abdominal discomfort. Acute symptoms are uncommon in infants and children, but common in adults.
3. A recovery period follows with normalisation of the levels of alanine aminotransferase (ALT).
4. Hepatitis B surface antigen (HBsAg) clearance in the serum follows after a few months, coinciding with the development of hepatitis B surface antibodies (anti-HBs).

Progression from acute to chronic hepatitis B virus infection

The transition from acute to chronic infection signifies a failure of the immune response to eradicate the virus. The overall risk of chronic infection is highest in those who acquire the virus perinatally (80–90%),² in those who acquire the infection in childhood or adulthood, the risk is 30% and 5% respectively³ (Table 4.1).

Table 4.1: Risk of development of chronic hepatitis B infection by the patient's age at infection

	Perinatal	Childhood	Adult
Development of chronic infection	80–90%	30%	<5%
Risk of advanced liver disease	20–30%	5–10%	1–2%
Immuno-tolerant phase	Prolonged	Variable	Short

The host immune responses determine the outcome of infection and the severity of liver injury.

Definition and preferred terminology

The American Association of the Study of Liver Diseases (AASLD) practice guidelines define chronic hepatitis B as chronic necroinflammatory disease of the liver caused by persistent infection with HBV. Diagnostically, chronic hepatitis B is defined as HBsAg positivity for more than six months.⁴

The terminology used to describe the different phases in the natural history of chronic hepatitis B infection varies considerably and has been the subject of much debate (refer to Table 4.2). In particular, the phase of immune control is, or has been, referred to as the 'healthy carrier' state, the 'inactive carrier' state and the 'non-replicative' state of chronic hepatitis B. Many of these terms may be potentially misleading and fail to reflect the fluctuating nature of CHB over time. The terms used below to describe the phases of CHB reflect the importance of the immune system in controlling this infection.

The natural history of chronic hepatitis B infection

The natural history of chronic HBV infection is characterised by four distinct phases (Table 4.2).

Table 4.2: Terminology of chronic hepatitis B

	Preferred term	Also known as
Phase I	Immune tolerant	Replicative state
Phase II	Immune clearance	Immune competence phase Immunoactive phase
Phase III	Immune control	Non-replicative state Inactive carrier 'Healthy' carrier
Phase IV	Immune escape	HBeAg negative CHB Pre-core mutant disease Reactivation phase

These phases are dependent on a complex interaction between host, viral and environmental factors, and the age at infection particularly (Table 4.3).

Table 4.3: Phases of chronic hepatitis B infection

Phase	Liver histology	HBV DNA	ALT	HBeAg	Anti-HBe	Duration	Natural history
Immune tolerance	Minimal inflammation	>20 000 IU/mL	Normal	Present	-	20-30 years	Low risk of progression to advanced liver disease
Immune clearance	Variable inflammation +/- fibrosis	>20 000 IU/mL (fluctuating)	Elevated (fluctuating)	Present	+/-	Can be protracted	Associated with hepatic flares
Immune control	Minimal inflammation and liver damage	< 2000 IU/mL	Normal	Absent	+	Years	Low risk of advanced liver disease HBsAg loss: 1% per year 10–20% have reactivation of HBV replication after many years
Immune escape (HBeAg-negative CHB)	Inflammation and often significant fibrosis	2000–20,000 IU/mL	Elevated	Absent	+	-	Can enter this phase from immune clearance or immune control phase High risk of progression to advanced liver disease

1. Immune tolerance phase

This initial phase is characterised by hepatitis B e antigen (HBeAg) positivity, high HBV DNA levels (> 20,000 IU/mL), normal ALT levels and minimal level liver injury. It is prevalent in those who acquired the infection vertically. This phase may persist for decades and is associated with a low risk of progression to advanced liver disease.

2. Immune clearance phase

The liver injury in HBV is determined by the immune response to the virus. This phase, also called the immune competence phase, is characterised by fluctuating HBV DNA and ALT levels as an active, immune-mediated cytotoxic response to the infected liver cells. Active inflammation and eventually fibrosis can be found in

the liver following these repeated immune-mediated attacks. An important outcome of this phase is the seroconversion of HBeAg to HBe antibody (anti-HBe), which is associated with lower level viraemia. Importantly, after HBeAg seroconversion, a small number of patients can still have active liver disease, most likely due to the emergence and activation of HBV mutant variants, particularly the precore variant (see Chapter 2: Virology: viral replication and drug resistance).

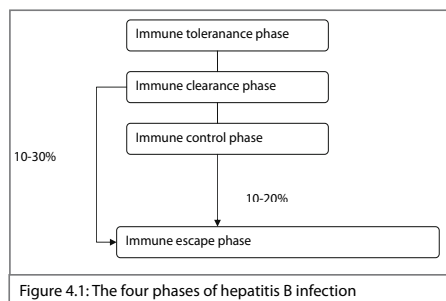
3. Immune control phase

Patients in this phase have also been described as 'inactive carriers' of the infection. Liver inflammation is minimal, HBV DNA is undetectable or at a low level (<2000 IU/mL) and liver function tests (LFTs) are normal. These patients are at low risk of developing advanced liver disease and its related complications.⁵ In

a study assessing the long-term outcome of HBsAg positive individuals who had normal LFTs and normal or minimal changes on liver biopsy, the liver histology and ALT remained unchanged over a 12-year follow-up period. A small minority (2%) of these subjects developed HBV reactivation with ALT flares. In contrast to the subjects with normal ALT, subjects with evidence of active liver disease (high ALT or inflammation on liver biopsy) had a worse prognosis, with an annual risk rate of developing cirrhosis and HCC of 1% and 0.5%, respectively.⁶ However, 10–20% of subjects in the immune control phase may have subsequent reactivation of HBV with immune escape, even after many years.⁷

4. Immune escape phase (HBeAg-negative chronic hepatitis B)

This phase is characterised by negative HBeAg, positive anti-HBe and detectable viral load (HBV DNA > 2000 IU/mL). It is often termed precore mutant HBV because a mutation in the precore region of the DNA results in a lack of HBeAg production. Patients can reach this phase from the immune control state (5–10%),⁸ or can progress directly from HBeAg-positive chronic hepatitis to HBeAg-negative chronic hepatitis (10–30%)⁶ (Figure 4.1).



HBeAg-negative chronic HBV infection is reported in all parts of the world, but is more common in Asian and Mediterranean countries. It occurs due to the selection of a mutant HBV, which does not produce HBeAg but is still able to replicate. This immune selection process is likely to occur late in the natural history of chronic HBV infection.

Thus, patients who are HBeAg negative tend to be older and have more advanced liver disease. The natural course of patients with HBeAg-negative disease is characterised by fluctuations in clinical status, and biochemical and viral load parameters caused by recurrent hepatic flares. Although patients with HBeAg-negative disease tend to have lower HBV viral load than those with HBeAg-positive infection (< 20,000 IU/mL vs > 20,000 IU/mL), they display more hepatic inflammation on liver biopsy.⁹ Consequently, the annual incidence of cirrhosis is significantly higher (8–10%) in HBeAg-negative chronic hepatitis B patients, compared to that in HBeAg-positive patients (2–6%).¹⁰

Reactivation of HBV following immunosuppression

In the context of immunosuppression, subjects in the immune control phase of CHB may experience a reactivation of the disease. Reactivation can occur in subjects who are HBsAg positive, and even in those who are HBsAg negative/anti-HBc IgG positive (occult HBV). The Reactivation is characterised by positive anti-HBc IgM but at lower titre than acute infection. It has been reported in 20–50% of those with hepatitis B infection undergoing immunosuppressive treatment, and may result in fulminant hepatic failure.¹¹ It is important for people with HBV infection undergoing immunosuppressive therapy to be carefully monitored and managed appropriately with prophylaxis, as indicated (see Chapter 10: Managing hepatitis B virus infection in complex situations).

Occult HBV

With the emergence of highly sensitive HBV DNA PCR assays, a population of patients have been identified with occult HBV infection. Occult hepatitis B infection refers to the presence of the hepatitis B virus in the blood or liver without the detection of HBsAg. Its presence may be related to the long-term persistence of HBV DNA reservoir in hepatocytes in the form of covalently-closed-circular DNA (cccDNA). The reactivation of hepatitis B following immunosuppression has been described

in patients with occult infection. Occult hepatitis B infection may also contribute to the development of hepatocellular carcinoma. Currently in clinical practice, the exact role of HBV occult infection remains unclear.

Complications of hepatitis B virus infection

Sequelae of HBV infection range from asymptomatic disease to decompensated liver failure to extrahepatic manifestations. Cirrhosis and hepatocellular carcinoma (HCC) are major causes of morbidity and mortality. It is estimated that over 250,000 patients worldwide die annually from HBV-related liver disease. The cumulative 5-year survival rate once decompensated cirrhosis ensues is 35%.¹² The development of cirrhosis is influenced by several factors, mostly viral and host related (Table 4.3). Patients with HBV infection have a 100-fold increased risk of developing HCC relative to patients without HBV infection.¹³ The risk of progression to HCC is also related to host, viral and environmental factors (Table 4.4).

Table 4.4: Factors influencing chronic hepatitis B progression to cirrhosis and hepatocellular carcinoma

Host factors	Viral factors	Other factors
Older age	High HBV DNA level	Alcohol consumption
Male	Genotype C ¹⁴	Co-infection with hepatitis C, human immunodeficiency virus (HIV), hepatitis D
Obesity, diabetes ¹⁵		

In a large prospective cohort study of CHB from Taiwan (the REVEAL study), elevated HBV DNA level (>10⁴ copies/mL or approximately 2000 IU/mL) at the time of initial evaluation was closely linked to the subsequent development of HCC.^{16,17} A further study demonstrated that if the HBV DNA level fell over the follow-up period, the risk of HCC also declined.¹⁷ These

studies provide strong data that the risk of HCC in HBV is linked to levels of serum HBV DNA. It should be noted that in HBV-related HCC, 30–40% of hepatoma cases develop in the absence of cirrhosis.¹⁸

Impact of antiviral therapy on the natural course of chronic hepatitis B virus infection

The importance of HBV viral replication to the natural history of the infection has been reported in the REVEAL HBV study.^{16,17} These data strongly support a role for antiviral therapies to alter the natural course of HBV infection, mitigating the rate of progression to end-stage liver disease and HCC through the suppression of viral replication. This finding was confirmed in a recent study evaluating the effect of lamivudine in Asian patients with high HBV DNA (>700,000 copies/mL or approximately 125,000 IU/mL) and advanced liver fibrosis.¹⁹ In these patients, lamivudine has been shown to delay the progression of liver disease and the development of HCC.

Conclusion

The outcome of HBV infection and progression to chronicity is determined particularly by age at acquisition. The natural history of chronic HBV infection is characterised by four distinct phases that depend on complex host, viral and environmental interactions. In each phase, it is the host's immune response that determines the outcome of infection and the severity of liver injury. Sequelae of HBV infection range from asymptomatic carrier status to decompensated liver failure and HCC.²⁰ Antiviral therapy can alter the natural course of HBV infection.

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