Natural history of hepatitis B virus infection

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KEY POINTS

- Birth in highly endemic regions such as sub-Saharan Africa and East Asia is a risk factor for developing chronic hepatitis B (CHB) infection (1). The primary mode of transmission in such cases is vertical (i.e., mother to child).
- The risk of developing CHB is highest in those who acquire hepatitis B virus (HBV) infection perinatally and lowest in those who acquire the infection in adulthood.
- The natural history of HBV infection depends on complex interactions between host, virus and environment.
- There are four phases of CHB, and the host immune response in each phase determines the outcome of infection and the severity of liver injury.
- Liver damage is caused by the host immune response rather than the HBV itself.
- Complications of CHB include cirrhosis with hepatocellular failure and hepatocellular carcinoma. All complications can be minimised with effective antiviral therapy.

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Transmission of hepatitis B

Hepatitis B virus (HBV) is transmitted through infected blood or bodily fluids (semen and vaginal fluids). The virus enters the bloodstream either through a break in the skin or through mucous membranes (eyes, nose and mouth). The modes of transmission are summarised in Table 4.1.

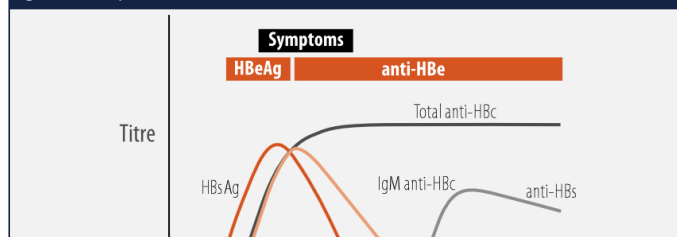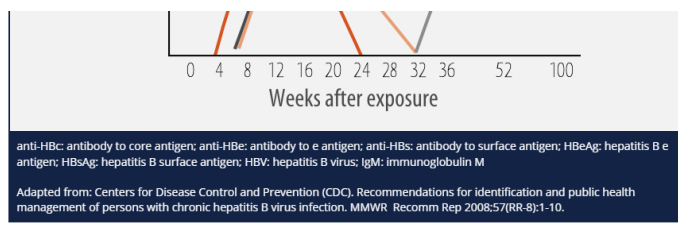| Table 4.1 Modes of transmission of hepatitis B virus	
Vertically	From mother to child during childbirth, the most common way the virus spreads in high-prevalence countries. Breastfeeding does not appear to increase the risk of HBV transmission to the infant, and it should not be discouraged if vaccination and HBIG are administered at birth. Most guidelines do not recommend caesarean section as an intervention to reduce vertical transmission (2).
Horizontally	From a person with hepatitis B to other household contacts who are unvaccinated (e.g. through sharing toothbrushes, razors, nail files or other personal items that may lead to exchange of body fluids). Infection acquired in early childhood after delivery is well recognised and has been attributed to parent-to-child contact (3-5), sibling contact (5, 6) and medical procedures such as intramuscular injections (6).
Sexually	Through unprotected vaginal, anal or oral sex with a person who has hepatitis B.
Percutaneously	Through the sharing or re-use of injecting equipment, tattooing, body piercing, acupuncture, cupping and some other cultural practices.
Medically acquired	There are still countries where blood transfusions, organ transplants and other medical interventions pose an extreme risk because donors are not screened for HBV. In most countries where screening is in place, the risk of infection is low. Medical procedures – including dentistry, surgery, dialysis and alternative health-care procedures – pose a risk if appropriate infection control procedures are not adhered to. Needlestick injury or splashing of infected blood or body fluids are a particular concern for health-care workers and emergency services providers.
HBIG: hepatitis B immune globulin; HBV: hepatitis B virus	

Acute hepatitis B virus infection

Acute HBV infection, as with other acute viral hepatitis infections, is asymptomatic in most people. Symptoms are more likely to occur in adults acquiring the infection, and will usually be mild, comprising arthralgia and nausea with or without right upper quadrant abdominal pain preceding any overt jaundice. HBV infection can be associated with a range of extrahepatic manifestations, more common in chronic hepatitis B (CHB). Those who acquire HBV perinatally or in infancy are likely to progress from acute to chronic infection. The acute illness can be described as having four stages.

1. **Incubation**:
   The incubation period of acute HBV infection can last up to 12 weeks.
2. **Symptomatic hepatitis**:
   Acute hepatitis develops after the incubation period, and is characterised by elevated alanine transaminase (ALT) levels lasting 4–12 weeks. Symptoms and signs include anorexia, dark urine, jaundice and right upper quadrant abdominal discomfort. Acute symptoms are common in adults but not in infants and children.
3. **Recovery**:
   A recovery period follows with normalisation of the levels of ALT.
4. **Viral clearance and immunity**:
   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). Hepatitis B core antibodies (anti-HBc) appear much earlier than anti-HBs and, in those who clear the infection, hepatitis B e antigen (HBeAg) appears and is cleared before the appearance of anti-HBs (Figure 4.1).

Figure 4.1 Acute hepatitis B virus infection with clearance

anti-HBc: antibody to core antigen; anti-HBe: antibody to e antigen; anti-HBs: antibody to surface antigen; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; IgM: immunoglobulin M

Adapted from: Centers for Disease Control and Prevention (CDC). Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR Recomm Rep 2008;57(RR-8):1-10.

Progression from acute to chronic hepatitis B virus infection

The transition from acute to chronic infection (Figure 4.2) signifies a failure of the immune response to eradicate the virus. Progression from acute to CHB infection is influenced by the age at which the subject acquires the virus. The overall risk of chronic infection is highest in those who acquire the virus perinatally (80–90%) (8). This is related to the inability of the immune system to recognise the virus and the high level of viral replication; it results in immunological tolerance. In adults, a cell-mediated response to foreign HBV proteins results in acute hepatitis, which may be asymptomatic; the response leads to clearance of the infection in all but 1–5% of patients (9).

In those who acquire the infection in childhood, the risk of chronic hepatitis is 30% (10) (Table 4.2).

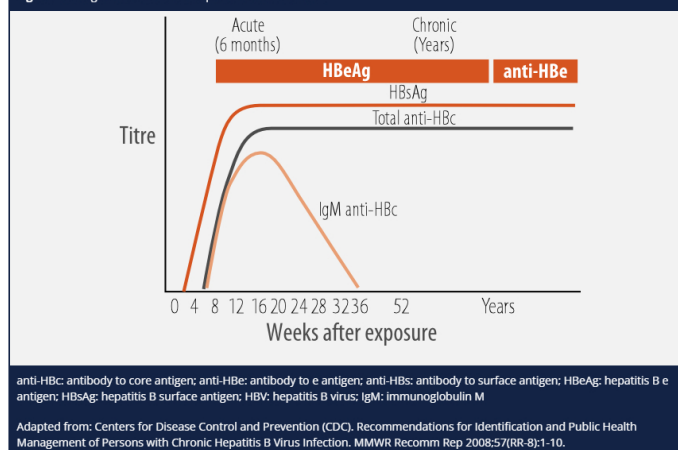### Figure 4.2 Progression to chronic hepatitis B virus infection

anti-HBc: antibody to core antigen; anti-HBe: antibody to e antigen; anti-HBs: antibody to surface antigen; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; IgM: immunoglobulin M

Adapted from: Centers for Disease Control and Prevention (CDC). Recommendations for Identification and Public Health Management of Persons with Chronic Hepatitis B Virus Infection. MMWR Recomm Rep 2008;57(RR-8):1-10.

Table 4.2 Risk of progression, by age at infection (11)

	Perinatal	Childhood	Adult
Risk of development of chronic infection (%)	80–90	30	< 5
Risk of advanced liver disease (% exposed to HBV)	20-30	5-10	1-2
Risk of advanced liver disease (% of those with chronic liver disease)	20-30	20-30	20-30
Length of immune tolerance phase (also known as HBeAg-positive chronic HBV infection)	Prolonged	Variable	Short

HBV: hepatitis B virus; HbeAg: hepatitis B e antigen

Chronic infection – definition and preferred terminology

The American Association for the Study of Liver Diseases (AASLD) practice guidelines define CHB as a chronic necroinflammatory disease of the liver caused by persistent infection with HBV. CHB is defined serologically as HBsAg positivity for more than 6 months (12).

The terminology used to describe the different phases in the natural history of HBV infection varies considerably, and has been the subject of much debate and confusion. In particular, HBeAg-negative chronic HBV infection, also known as the immune control phase, has been incorrectly referred to as the healthy carrier state, or the inactive carrier state of CHB. There is no such thing as a healthy carrier – the term fails to reflect the fluctuating nature of CHB over time.

In 2017 the European Association for the Study of the Liver (EASL) released guidelines on hepatitis B virus, which included new nomenclature for the phases of HBV infection (Table 4.3) (13). The clinical outcome of chronic HBV infection is dependent on the complex interaction between host immune responses and viral and environmental factors. Not all patients with chronic HBV infection develop chronic hepatitis and the new nomenclature aims to distinguish this characteristic. Using this new terminology patients can now be differentiated into four phases, which are determined by both serum HBV markers (HBeAg positivity and HBV DNA levels) as well as the presence or absence of liver inflammation (liver biopsy, and ALT) (Table 4.4). The four phases of chronic HBV infection are not necessarily consecutive, and it should be noted that not all patients can be classified to one of these phases. Serial monitoring of serum HBeAg, HBV DNA and ALT levels is required in most instances, and specialist advice may be required.

The new terminology has now gradually replaced the prior terminology although both remain still in use. (Table 4.3).

Table 4.3 Terminology of phases of chronic hepatitis B (13)

Phase	New terminology	Previously used terminology	Alternative name
Phase 1	HBeAg-positive chronic HBV infection	Immune tolerance	Immunotolerant phase Replicative state
Phase 2	HBeAg-positive chronic hepatitis	Immune clearance	Immune competence phase Immune (re) active phase
Phase 3	HBeAg-negative chronic HBV infection	Immune control	Non-replicative state
Phase 4	HBeAg-negative chronic hepatitis	Immune escape	HBeAg-negative CHB Precore mutant disease Reactivation phase

Note: Occult HBV infection or OBI is defined as the persistence of HBV DNA in serum or hepatocytes of a person with a negative HBsAg test result, using currently available assays. See below for more information.

CHB: chronic hepatitis B; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen

Table 4.4 Natural history and assessment of patients with chronic hepatitis B virus infection based upon hepatitis B virus and liver disease markers

Characteristic	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
Phase	1	2	3	4
HBsAg	High	High/Intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10^7 IU/mL	10^4-10^7 IU/mL	<2000 IU/mL**	>2000 IU/mL
ALT	Normal	Elevated	Normal	Elevated*
Liver Disease	None/minimal	Moderate/severe	None	Moderate/severe
Previously used terminology	Immune tolerance	Immune clearance	Immune control	Immune escape

HBsAg: hepatitis B surface antigen; HBeAg: hepatitis B e antigen; HBV DNA: hepatitis B virus DNA; ALT: alanine transaminase

*Persistently or intermittently. **HBV DNA levels can be between 2000 and 20,000 IU/mL in some patients without signs of chronic hepatitis

Phase 1 – HBeAg positive chronic infection

Previously known as immune tolerance, this phase is characterised by hepatitis B e antigen (HBeAg) positivity, high HBV DNA levels (> 20,000 IU/mL, and commonly over 1 million IU/mL), normal ALT levels (elevated ALT is >30 IU/L for men, and >19 IU/L for women) and minimal level liver injury. During this phase, which may persist for decades, liver inflammation or fibrosis is either absent or minimal. This phase is associated with a low risk of progression to advanced liver disease, and it is thought to occur most commonly in those who acquire the infection vertically from HBeAg-positive mothers (14). Patients are highly contagious in this phase.

Phase 2 – HBeAg-positive chronic hepatitis

Previously known as immune clearance, this phase is characterised by HBeAg positivity, and fluctuating levels of HBV DNA and ALT. The liver injury in HBV is determined by the immune response to the virus. The host's immune system recognises the HBV as foreign, and mounts a cytotoxic response to infected hepatocytes. Recurrent bouts of active inflammation and, eventually, fibrosis can occur 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 a lower level of viraemia. The observed rate of clearance of HBeAg in those with or without elevated ALT levels averages 8–12% per year (15). However, a number of people will still develop active liver disease after HBeAg seroconversion, generally owing to emergence of HBV mutant variants, particularly the core or precore mutation that renders the virus unable to encode for HBeAg (16) (see: Virology: viral replication and drug resistance).

Phase 3 – HBeAg-negative chronic infection

Previously known as immune control, patients in this phase were previously inaccurately described as inactive carriers of the infection. In this phase, liver inflammation is minimal, HBV DNA is undetectable or low level (< 2000 IU/mL), anti-HBe is detected in the serum, and liver function tests (LFTs) are usually normal. Minor fluctuations of ALT may occur in relation to intercurrent infections, medication reactions and, possibly, early attempts to clear the virus. These patients are at low risk of developing advanced liver disease and its related complications (17). In a study assessing the long-term outcomes for HBsAg-positive people who had normal LFTs and normal or minimal changes on liver biopsy, liver histology and ALT remained unchanged over a 12-year follow-up period.

Some patients in phase 3 can have HBV DNA levels > 2000 IU/mL (usually < 20,000 IU/mL) with normal ALT and minimal hepatic inflammation and low fibrosis. One study found that approximately 40% of HBeAg-negative chronic infection patients had had HBV DNA of > 2000 IU/mL (18). Such patients are at a low risk of progression to cirrhosis or hepatocellular carcinoma (HCC) if they remain in this phase, but progression to chronic hepatitis (immune escape) can occur (13).

About 10–20% of patients who are anti-HBe positive may develop subsequent reactivation of HBV, with progression to chronic hepatitis after many years (19). This is associated with flares of hepatitis with HBV reactivation and ALT elevation (3). In addition, some patients may enter phase 3 with already moderate to severe fibrosis. Therefore, all patients should be followed up indefinitely with 6-monthly ALT and annual measurement of HBV DNA to monitor whether if they have progressed to phase 4 – immune escape (HbeAg-negative chronic hepatitis).

In addition, there is now emerging evidence that, in patients with an HBV DNA level of less than 2000 IU/mL who were thought to have a comparable risk of HCC, an HBsAg level greater than 1000 IU/mL is an independent risk factor for HCC development (20). However, it is currently not routine practice to measure HBsAg titres, and the role of measuring this antigen in clinical practice is an area for further study.

Phase 4– HBeAg-negative chronic hepatitis

Previously known as immune escape, this phase is characterised by negative HBeAg, positive anti-HBe and persistently detectable viral load (HBV DNA > 2000 IU/mL) with fluctuating or elevated ALT levels. It may also be termed precore mutant HBV, because a mutation in the precore region of the DNA results in a lack of HBeAg production.

HBeAg-negative immune escape is more common in Asian and Mediterranean countries. It occurs due to the selection of a mutant HBV that does not produce HBeAg but is still able to replicate. This immune selection process is likely to occur late in the natural history of CHB.

Patients who are HBeAg negative tend to be older and have more advanced liver disease. The natural course of patients with HBeAg-negative disease (immune escape) is characterised by fluctuations in clinical status, and in biochemical and viral load parameters, caused by recurrent hepatic flares. About 70% of those in this phase have a fluctuating course characterised by periods of apparent inactivity (21). 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 (22). Consequently, the annual incidence of cirrhosis is significantly higher (8–10%) in HBeAg-negative CHB patients than in those with HBeAg-positive CHB (2–5%) (23).

Occult HBV infection

Also known as the HBsAg-negative phase, this phase refers to the presence of HBV DNA in the blood or liver, in the absence of HBsAg in the serum, with or without detectable antibodies to HBsAg (anti-HBs). The presence of HBV may be related to the persistence of HBV DNA within hepatocytes, in the form of covalently closed circular DNA (cccDNA), which remains present even in people who are HBsAg negative (24). In approximately 1% of cases, the absence of HBsAg may be related to the sensitivity of the assay to detect HBsAg (25).

HBsAg loss before the onset of cirrhosis is associated with a low risk of cirrhosis and HCC. However, if cirrhosis precedes HBsAg loss, patients remain at risk of HCC and should receive ongoing HCC surveillance. The reactivation of hepatitis B following immunosuppression has been described in patients with HBsAg-negative hepatitis B infection. Occult hepatitis B infection may also accelerate the progression of liver disease in the context of hepatitis C virus (HCV) co-infection (26).

Reactivation of hepatitis B virus following immunosuppression

Low levels of HBV DNA remain in hepatocytes after recovery from acute hepatitis B. Patients who have been exposed to HBV are at risk of reactivation of hepatitis B in the context of immunosuppression (27) (see: Complex situations: Co-infection and immunosuppression) . Reactivation of HBV can occur in those who are HBsAg positive, and even in those who are both HBsAg negative and anti-HBc positive if there is potent immunosuppression. Reactivation may be characterised by positive anti-HBc immunoglobulin M (IgM), but at lower titres than acute infection. Current AASLD guidelines suggest that patients who are at high risk of HBV infection should undergo testing for HBsAg and anti-HBc before chemotherapy or immunosuppressive therapy (28). Reactivation has been reported in 20–50% of those who are HBsAg positive and who undergo immunosuppressive treatment; the reactivation may result in hepatic decompensation and death (29). Thus, it is important for people with HBV infection undergoing immunosuppressive therapy to be carefully monitored, and managed appropriately with prophylaxis as indicated (see: Complex situations: Co-infection and immunosuppression). Current Australian recommendations for management of immunosuppressed

individuals with hepatitis B are contained in the document: Hepatitis B Management during immunosuppression for haematological and solid-organ malignancies: an Australian Consensus J statement 2019 (see: https://www.asid.net.au/documents/item/1741)

Complications of hepatitis B virus infection

Sequelae of HBV infection range from asymptomatic disease, decompensated liver failure, to extrahepatic manifestations. Cirrhosis and HCC are major causes of morbidity and mortality. It is estimated that 887,000 people worldwide die annually from HBV-related liver disease (30). The cumulative 5-year survival rate once decompensated cirrhosis ensues is 35% (31). The development of cirrhosis is influenced by several factors, most of which are virus and host related (Table 4.4).

Table 4.4 Factors influencing progression to cirrhosis and hepatocellular carcinoma

Risk factor	Reference
Active HBV DNA replication / viral load	Chen CJ, et al. (2006) (32)
HBV genotype C	Yang HI, et al. (2002) (33)
HBeAg-negative core promoter mutation	Yang HI, et al. (2002) (33)
Cirrhosis	Schiff ER, et al. (2006) (34)
Male sex	Bosch FX, et al. (1999) (35)
Asian/African/Aboriginal and Torres Strait Islander ethnicity	Fattovich G. (2003) (36)
	Parker C, et al. (2014) (37)
Coexisting non-alcoholic fatty liver disease and diabetes	El-Serag HB, et al. (2001) (38)
Smoking, alcohol, obesity	Marrero JA, et al. (2005) (39)
Positive family history, first-degree relative	Loomba R, et al. (2013) (40)

HBeAg: hepatitis B e antigen; HBV: hepatitis B virus

Studies provide strong evidence that the risk of HCC in HBV is linked to levels of serum HBV DNA. In HBV-related HCC, 30–40% of HCC cases develop in the absence of cirrhosis (HBeAg-positive chronic HBV infection) (41). HBV has the ability to integrate its genome into the host's hepatocyte DNA. Over many decades, especially during the immune tolerance phase, persistently high levels of HBV DNA lead to an accumulation of multiple sites of integration, thus increasing the risk of HCC even in the absence of active inflammation and fibrosis (42).

Risk stratification for development of HCC

Multiple risk models have been developed for predicting development of HCC in CHB patients. These included GAG-HCC, CU-HCC and REACH-B, which were developed and validated in Asian untreated CHB patients (43). The recently developed PAGE-B model offers good predictability for development of HCC during the first 5 years of entecavir or tenofovir therapy in European CHB patients. This is a simple scoring system based on **p**latelets, **a**ge, and **ge**nder (44). Although developed for patients undergoing treatment, the PAGE-B score appears to be applicable for untreated CHB patients (45,46). The main limitation to the models in the Australian context is the lack of validation of the models for the diverse population affected by CHB.

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 (32,47). The study showed that virus serum HBV DNA level was an independent risk factor for the development of cirrhosis and HCC after adjusting for other risk factors (e.g. male gender, alcohol use, cigarette smoking and older age).

There are ample data to suggest that patients who achieve long-term HBV DNA suppression through antiviral medications have reduced incidence of both HCC (48) and cirrhosis (49). Newer, more potent agents such as entecavir and tenofovir have replaced lamivudine and adefovir as first-line antiviral medication for CHB given their high barrier for resistance (4) (see: Treatment of chronic hepatitis B virus infection).

Hepatitis B reactivation after treatment with direct-acting antiretrovirals

The introduction of direct-acting antiretroviral (DAA) therapy for HCV has reshaped the landscape of hepatitis C virus (HCV) treatment. Sustained virological response (SVR) rates for patients with HBV/HCV co-infection are equivalent to those seen in patients with HCV mono-infection (50). A number of case reports have described reactivation of HBV infection in patients with HBV/ HCV co-infection taking DAA therapy. The US Food and Drug Administration (FDA) has issued a warning following 24 cases documented over a period of 31 months (51-54). Based on these findings, all patients fulfilling the standard criteria for HBV receiving treatment with DAA therapy should be treated with a nucleos(t)ide analogue (NA). Any HBsAg-positive patients receiving DAA should receive prophylaxis for 12 weeks with a NA. HBsAg-negative, anti-HBc positive patients undergoing DAA should be monitored and tested for HBV reactivation in case of ALT elevation (13).

Conclusion

The outcome of HBV infection and progression to chronicity is determined particularly by age at acquisition. The natural history of CHB virus infection is characterised by four distinct phases that depend on complex interactions between host, virus and environment. 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 (55). Effective antiviral therapy can alter the natural course of HBV infection and reduce long-term complications related to the disease.

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Authors

Amany Zekry - Department of Gastroenterology & Hepatology, St George Hospital, Kogarah NSW

Karen Bensted - Department of Gastroenterology & Hepatology, St George Hospital, Kogarah NSW

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