

# Chapter 2: Hepatitis B - Epidemiology, transmission and natural history

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## Introduction

It is estimated that 40% of the world's population has had contact with or are carriers of the hepatitis B virus (HBV). This corresponds to an estimated 350 million HBV carriers (Goldstein 2005). Thus, HBV infection is one of the most important infectious diseases worldwide. Around one million persons die of HBV-related causes annually. There is a wide range of HBV prevalence rates in different parts of the world. HBV prevalence varies from 0.1% up to 20%. Low prevalence areas (0.1-2%) are Western Europe (with wide variation within Europe), United States and Canada, Australia and New Zealand; intermediate prevalence (3-5%) are the Mediterranean countries, Japan, Central Asia, the Middle East, and Latin and South America; and high prevalence areas (10-20%) southeast Asia, China, and sub-Saharan Africa. This diversity is probably related to differences in the age at infection, which correlates with the risk of chronicity. The progression rate from acute to chronic HBV infection decreases with age. It is approximately 90% for an infection acquired perinatally, and is as low as 5% (or even lower) for adults (Stevens 1975; Wasley 2008).

The incidence of new infections has decreased in most developed countries, most likely due to the implementation of vaccination strategies (Rantala 2008). However, exact data are difficult to generate as many cases will remain undetected due to the asymptomatic nature of many acute and chronic infections (RKI 2007). Nevertheless, in Germany 2524 cases of acute hepatitis B were documented in the year 2006, corresponding to an incidence rate of 1.4 per 100,000 inhabitants. In 1997 there were 6135 documented cases of acute hepatitis B. Likewise, the incidence of acute hepatitis B in the United States has decreased by 78% from 1990 to 2005 (Wasley 2008). It is expected that this number will further decrease in countries with implementation of vaccination programs. In Germany 87% of all children starting school were completely vaccinated in 2006 with a trend toward increasing coverage (Poethko-Muller 2007).

Although the incidence of acute HBV infection has decreased in most countries due to the implementation of vaccination programs, HBV-related complications such as cancers and deaths have been on the increase (Gomaa 2008). Reasons might be the delay of vaccination effects, improved diagnosis, and better documentation of HBV cases. Although a drop in prevalence has been observed in many countries, estimates are difficult due to a continuously growing migration from high or medium prevalence areas to low prevalence areas (Belongia 2008).

## Transmission

The routes of HBV transmission:

- Sexual
- Percutaneous (Intravenous Drug Use)
- Perinatal

- Horizontal
- Transfusion
- Nosocomial infection (including needle-stick injury)
- Organ transplantation

There is considerable variation in the predominance of transmission modes in different geographic areas. For example, in low prevalence areas such as Western Europe, the routes are mainly unprotected sexual intercourse and intravenous drug use. In high prevalence areas like Sub-Saharan Africa perinatal infection is the predominant mode of transmission. Horizontal transmission, particularly in early childhood, is regarded as the major route of transmission in intermediate prevalence areas.

### **Sexual transmission**

In low prevalence areas sexual transmission is the major route of transmission. Approximately 40% of new HBV infections in the United States is considered to be transmitted via heterosexual intercourse, and 25% occur in men who have sex with men (MSM) (Wasley 2008). Measures to prevent HBV transmission are vaccination and safer sex, i.e., use of condoms. However, there is ongoing debate regarding what to advise low-viremic patients.

### **Percutaneous inoculation**

Percutaneous transmission seems to be an effective mode of HBV transmission. The most important route is sharing of syringes and needles in intravenous drug users. In low prevalence areas such as Europe and the United States about 15% of newly diagnosed HBV infections is in IVDU (Wasley 2008). The risk of HBV transmission increases with the number of years of drug use, frequency of injection, and sharing of drug preparation equipment.

Other situations with possible percutaneous inoculation of HBV are sharing shaving razors or toothbrushes, although the exact number remains unknown. In addition, certain practices like acupuncture, tattooing, and body piercing have been associated with transmission of hepatitis B. Public health education and the use of disposable needles or equipment are important in preventing this mode of transmission.

### **Perinatal transmission**

Transmission from an HBeAg-positive mother to her infant may occur in utero, at the time of birth, or after birth. The rate of infection can be as high as 90%. However, neonatal vaccination is highly efficacious (95%). Its efficacy indicates that most infections occur at or shortly before birth. On the other hand, caesarean section seems not be protective as it is in other vertically transmitted diseases like HIV.

The risk of transmission from mother to infant is related to the HBV replicative rate in the mother. There seems to be a direct correlation between maternal HBV DNA levels and the likelihood of transmission. In mothers with highly replicative HBV the risk of transmission may be up to 85 to 90%, and it continuously lowers with lower HBV DNA levels (Burk 1994; Wang 2003). In some studies there has been almost no perinatal transmission if the mother has no significant replication ( $<10^5$  log copies/ml) (Li 2004).

It is possible to reduce the risk of perinatal transmission in several ways. The first step is identification of persons at risk. Testing for HBsAg should be performed in all women at the first prenatal visit and repeated later in pregnancy if appropriate. Newborns born to HBV-positive mothers can be effectively protected by passive-active immunization (>90% protection rate) (del Canho 1997). Hepatitis B immunoglobulin for passive immunization should be given as early as possible (within 12 hours), but can be given up to seven days after birth, if seropositivity of the mother is detected later. Active immunization follows standard schemes and is given at three time points (10 µg at day 0, month 1, and month 6). Anti-HBV treatment of the mother with nucleoside analogues may be discussed especially in mothers with high HBV DNA levels, although it is not known whether antiviral treatment has a protective effect in addition to immunization. At the moment there are no substantiated guidelines. If appropriate, lamivudine seems to be the treatment of choice. Telbivudine may be an alternative, whereas adefovir, entecavir and tenofovir are not recommended in pregnancy, unless clearly indicated (Cornberg 2007).

As mentioned earlier, caesarean section should not be performed routinely, whereas it is recommended in the setting of other infectious diseases like HIV (according to the viral replication rate). If vaccination was performed in the child, the child may be breastfed (Hill 2002).

### **Horizontal transmission**

Children may acquire HBV infection through horizontal transmission via minor breaks in the skin or mucous membranes or close bodily contact with other children. In addition, HBV can survive outside the human body for a prolonged period; as a result, transmission via contaminated household articles such as toothbrushes, razors, and even toys may be possible. Although HBV DNA has been detected in various bodily secretions of hepatitis B carriers, there is no firm evidence of HBV transmission via body fluids other than blood.

### **Transfusion**

Blood donors are routinely screened for hepatitis B surface antigen (HBsAg). Therefore incidence of transfusion-related hepatitis B has significantly decreased. The risk of acquiring posttransfusion hepatitis B depends on several factors like prevalence and donor testing strategies. In low prevalence areas it is estimated to be one to four per million blood components transfused (Dodd 2000; Polizzotto 2008). In high prevalence areas it is considerably higher (around 1 in 20,000) (Shang 2007).

There are different strategies for donor screening. Most countries use HBsAg screening of donors. Others, like the United States, use both HBsAg and anti-HBc. Routine screening of anti-HBc remains controversial, as the specificity is low and patients with cleared hepatitis have to be excluded. Screening of pooled blood samples or even individual samples may be further improved by nucleic acid amplification techniques. However, this is an issue of continuous debate due to relatively low risk reduction and associated costs.

## Nosocomial infection

Nosocomial infection can occur from patient to patient, from patient to health care worker and vice versa. HBV is considered the most commonly transmitted blood-borne virus in the healthcare setting.

In general, nosocomial infection of hepatitis B can and should be prevented. Despite prevention strategies nosocomial infections occur, and there are documented cases (Williams 2004). However, the exact risk of nosocomial infection is unknown. The number of infected patients reported in the literature is likely to be an underestimate of true figures as many infected patients may be asymptomatic and only a fraction of the exposed patients are recalled for testing.

Strategies to prevent nosocomial transmission of hepatitis B are use of disposable needles and equipment, sterilization of surgical instruments, infection control measures and vaccination of healthcare workers.

Due to the implementation of routine vaccination of health care workers the incidence of HBV infection among them is lower than in the general population (Duseja 2002; Mahoney 1997). Therefore, transmission from healthcare workers to patients is a rare event, while the risk of transmission from an HBV-positive patient to a health care worker seems to be higher.

Healthcare workers positive for hepatitis B are not generally prohibited from working. However, the individual situation has to be evaluated in order to decide on the necessary measures. Traditionally HBeAg-negative healthcare workers are considered not to be infective, whereas HBeAg-positive healthcare workers should perform measures such as wearing double gloves and not performing certain activities, to be defined on an individual basis. However, there have been cases of transmission of hepatitis B from HBsAg-positive, HBeAg-negative surgeons to patients (Teams 1997). Hepatitis B virus was identified that had a precore stop codon mutation resulting in non-expression of HBeAg despite active HBV replication. Therefore, HBV DNA testing has been implemented in some settings, although this may not be reliable in all situations due to fluctuating levels of HBV DNA. In most developed countries guidelines for hepatitis B positive healthcare workers have been established and should be consulted.

## Organ transplantation

Transmission of HBV infection has been reported after transplantation of extrahepatic organs from HBsAg-positive donors (e.g., kidney, cornea) (Dickson 1997). Therefore, organ donors are routinely screened for HBsAg. The role of anti-HBc is controversial, as it is in screening of blood donors. Reasons are the possibility of false positive results, the potential loss of up to 5% of donors even in low endemic areas, and the uncertainty about the infectivity of organs, especially extrahepatic organs, from donors who have isolated anti-HBc (De Feo 2005). There is an increased risk of HBV infection for the recipient if organs of such donors are transplanted as compared to anti-HBc negative donors.

## Postexposure prophylaxis

In case of exposure to HBV in any of the circumstances mentioned above, postexposure prophylaxis is recommended for all nonvaccinated persons. A passive-active immunization is recommended. The first dose of active immunization should be given as early as

possible. 12 hours after the exposure usually is considered the latest time point for effective postexposure prophylaxis. One dose of hepatitis B-immunoglobulin (HBIG) should be administered at the same time, if the source is known to be HBsAg-positive. The other two doses of vaccine should be administered according to the usual schedule.

Vaccinated individuals with a documented response do not need postexposure prophylaxis. Individuals who have had no postvaccination testing should be tested for anti-HBs titer as soon as possible. If this is not possible, or the anti-HBs titer is insufficient (<100 IE/l), they will require a second course of vaccination.

Individuals who are documented non-responders will require two doses of HBIG given one month apart.

### **Natural history and clinical manifestations**

The spectrum of clinical manifestations of 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 occur in both acute and chronic infection.

### **Acute hepatitis**

After HBV transmission, the incubation period lasts from one to four months. A prodromal phase may appear before acute hepatitis develops. During this period a serum sickness-like syndrome may develop. This syndrome manifests with fever, skin rash, arthralgia and arthritis. It will usually cease with the onset of hepatitis. At least 70% of patients will then have subclinical or anicteric hepatitis, while less than 30% will develop icteric hepatitis. The most prominent clinical symptoms of hepatitis are right upper quadrant discomfort, nausea, jaundice and other unspecific constitutional symptoms. In case of coinfection with other hepatitis viruses or other underlying liver disease the clinical course may be more severe. The symptoms including jaundice generally disappear after one to three months, but some patients have prolonged fatigue even after normalisation of serum aminotransferase concentrations.

Concentrations of alanine and aspartate aminotransferase levels (ALT and AST) may rise to 1000-2000 IU/L in the acute phase. ALT is typically higher than AST. Bilirubin concentration may be normal in a substantial portion of patients. In patients who recover, normalisation of serum aminotransferases usually occurs within one to four months. Persistent elevation of serum ALT for more than six months indicates progression to chronic hepatitis.

The rate of progression from acute to chronic hepatitis B is primarily determined by the age at infection (Ganem 2004; McMahon 1985). In adult-acquired infection the chronicity rate is 5% or less, whereas it is higher if acquired at younger ages. It is estimated to be approximately 90% for perinatally-acquired infection, and 20-50% for infections between the ages of one and five years.

Until recent years it has been assumed that patients who recover from acute hepatitis B actually clear the virus from the body. However, there is a lot of evidence now that even in patients positive for anti-HBs and anti-HBc HBV DNA may persist for long

periods of time and this latent infection maintains the T cell response that keeps the virus under control (Yotsuyanagi 1998). Complete eradication rarely occurs. This is an important finding, as immunosuppression can lead to reactivation of the virus, e.g., after organ transplant or during chemotherapy.

Fulminant hepatic failure is unusual, occurring in approximately 0.1-0.5% of patients. Reasons and risk factors for fulminant hepatitis B are not well understood (Garfein 2004). There may be correlation with substance abuse or coinfections with other viruses. Fulminant hepatitis B is believed to be due to massive immune-mediated lysis of infected hepatocytes. This is why many patients with fulminant hepatitis B have no evidence of HBV replication at presentation.

Antiviral treatment of patients with acute hepatitis B usually is not recommended (Comberg 2007). The likelihood of fulminant hepatitis B is less than 1%, and the likelihood of progression to chronic hepatitis B is less than 5% in adults. Therefore, treatment of acute hepatitis B is mainly supportive in the majority of patients. Treatment can be considered in certain subsets of patients, e.g., patients with a severe or prolonged course of hepatitis B, patients coinfecting with other hepatitis viruses or underlying liver diseases, patients with immunosuppression, or patients with fulminant liver failure undergoing liver-transplantation (Kondili 2004; Tillmann 2006). It should be checked whether any contacts could be exposed to hepatitis B.

## Chronic hepatitis

The HBV chronicity rate is around 5% or less in adult-acquired infection, as mentioned earlier. In perinatally acquired infection it is estimated to be approximately 90%, and 20-50% for infections between the age of one and five years (Ganem 2004; McMahon 1985). However, most patients will not have a history of acute hepatitis.

Most patients with chronic hepatitis B are clinically asymptomatic. Some may have nonspecific symptoms such as fatigue. In most instances, significant clinical symptoms will develop only if liver disease progresses to decompensated cirrhosis. In addition, extrahepatic manifestations may cause symptoms.

Accordingly, physical examination will be normal in most instances. In advanced liver disease there may be stigmata of chronic liver disease such as splenomegaly, spider angiomas, Caput medusae, palmar erythema, testicular atrophy, gynecomastia, etc. In patients with decompensated cirrhosis jaundice, ascites, peripheral edema, and encephalopathy may be present.

Laboratory testing shows mild to moderate elevation in serum AST and ALT in most patients, whereas normal transaminases occur rarely. During exacerbation, serum ALT concentration may be as high as 50 times the upper limit of normal. Alfa-fetoprotein (AFP) concentrations correlate with disease activity. In exacerbations of hepatitis B concentrations as high as 1000 ng/mL may be seen.

The natural course of chronic HBV infection is determined by the interplay between viral replication and the host immune response. 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). The outcome of chronic HBV infection depends upon the severity of liver disease at the time HBV replication is arrested. Liver fibrosis is potentially reversible once HBV replication is controlled.

There are two different states that are distinguished in chronic HBV infection: firstly, a high-replicative state with active liver disease and elevated serum ALT. HBV DNA and HBeAg are present. Secondly, a low or non-replicative phase, where serum ALT may normalize, HBeAg disappears, and anti-HBe antibodies appear. In some patients, virus replication stops completely, as demonstrated by sensitive HBV DNA assays, although they remain HBsAg-positive. These patients have undetectable HBV DNA in serum and normal ALT concentrations. No sign of ongoing liver damage or inflammation is found on liver biopsy. This state is called inactive carrier state.

A small percentage of patients continue to have moderate levels of HBV replication and active liver disease (elevated serum ALT and chronic inflammation on liver biopsies) but remain HBeAg-negative. These patients with HBeAg-negative chronic hepatitis may have residual wild type virus or HBV variants that cannot produce HBeAg due to precore or core promoter variants.

The first high-replicative phase may switch into the nonreplicative phase spontaneously or upon antiviral treatment. Conversely, the non-replicative phase may reactivate to the high-replicative phase either spontaneously or with immunosuppression (e.g., in HIV infection or with chemotherapy).

In perinatally acquired chronic HBV infection there are three different states: An immune tolerance phase, an immune clearance phase, and a late non-replicative phase.

The immune tolerance phase, which usually lasts 10-30 years, is characterized by high levels of HBV replication, as manifested by the presence of HBeAg and high levels of HBV DNA in serum. However, there is no evidence of active liver disease as seen by normal serum ALT concentrations and minimal changes in liver biopsy. It is thought that this lack of liver disease despite high levels of HBV replication is due to immune tolerance to HBV (Dienstag 2008), although the exact mechanisms are unknown. This phenomenon of immune tolerance is believed to be the most important reason for the poor response to interferon therapy in HBeAg-positive patients with normal ALT levels. During this phase there is a very low rate of spontaneous HBeAg clearance. It is estimated that the rate of spontaneous HBeAg clearance is only 15% after 20 years of infection.

During the second to third decade the phase of immune tolerance may convert to a phase of immune clearance. The spontaneous HBeAg clearance rate increases. It is estimated to be 10 to 20% annually. If HBeAg seroconversion occurs, very often exacerbations of hepatitis with abrupt increases in serum ALT are observed. These exacerbations follow an increase in HBV DNA and might be due to a sudden increase in immune-mediated lysis of infected hepatocytes. Most often there are no clinical symptoms during exacerbation, and rise of ALT is only detected by routine examinations. Some patients may develop symptoms mimicking acute hepatitis. Titers of anti-HBc IgM may rise as well as alpha-fetoprotein. If such patients are not known to be HBV infected, misdiagnosis of acute hepatitis B can be made. HBeAg-seroconversion and clearance of HBV DNA from the serum is not always achieved after exacerbations. In these patients recurrent exacerbations with intermittent disappearance of serum HBV DNA with or without HbeAg loss may occur. The non-replicative phase is usually characterized by the absence of HBV DNA and normalisation of serum ALT as in adult chronic HBV.

Very few patients with chronic HBV infection become HBsAg negative in the natural course of infection. The annual rate of HBsAg clearance has been estimated to be less than 2% in Western patients and even lower (0.1-0.8%) in patients of Asian origin (Liaw 1991). If loss of HBsAg occurs, prognosis is considered favourable. However, clearance of HBsAg does not exclude development of cirrhosis or hepatocellular carcinoma in some patients, although the exact rate of these complications is not known. This phenomenon is thought to be linked to the fact that HBV DNA may still be present in hepatocytes despite HBsAg loss.

## Prognosis

As clinical course varies among patients, there is a wide variation in clinical outcome and prognosis of chronic HBV infection. The lifetime risk of a liver-related death has been estimated to be 40-50% for men and 15% for women. The risk of progression appears to be higher, if immune activation occurs.

The estimated five-year rates of progression (Fattovich 2008; Lok 2008):

- Chronic hepatitis to cirrhosis – 10-20%
- Compensated cirrhosis to hepatic decompensation – 20-30%
- Compensated cirrhosis to hepatocellular carcinoma – 5-15%

Accordingly, the survival rates are:

- Compensated cirrhosis — 85% at five years
- Decompensated cirrhosis — 55-70% at one year and 15-35% at five years

There are several factors known to influence survival.

- **Viral replication:** In patients with signs of viral replication (i.e., HBeAg-positive) there is consistently worse survival than in patients who are HBeAg-negative. However, in recent decades, infections with HBeAg-negative precore mutants prevail by far in newly-acquired infections, resulting in a different pattern of HBeAg-negative and HBV DNA positive hepatitis with fibrosis progression and HCC in a substantial proportion of patients. In recent years, the amount of HBV DNA has also been linked to disease progression and has replaced HBeAg positivity as a marker for disease activity (Chen 2006). This is true both for progression to cirrhosis as well as for the risk of HCC. Therefore, most treatment guidelines today are based on the level of HBV viremia. A reasonable cut-off to distinguish patients with a low risk of progression from patients with a high risk of progression and indication for antiviral treatment is  $10^4$  copies/ml (corresponding to approximately  $2 \times 10^3$  IU/ml), although other cut-offs may be used. The duration of viral replication is obviously linked with the risk of development of cirrhosis and HCC. As necroinflammation may persist longer in patients with a prolonged replicative phase, the risk of disease progression is elevated. Conversely, even in patients with decompensated cirrhosis, suppression of HBV replication and delayed HBsAg clearance can result in improvement in liver disease (Fung 2008).

- **Alcoholism:** HBV infection in alcoholics is associated with faster progression to liver injury and an elevated risk of developing cirrhosis and HCC (Bedogni 2008; Marcellin 2008). Survival is reduced compared to HBV-negative alcoholics. However, there is no clear evidence that alcoholics have an enhanced risk of chronic HBV infection, although prevalence of HBV is estimated to be fourfold higher than in controls (Laskus 1992) with variation among regions and cohorts (Rosman 1996).
- **Hepatitis C coinfection:** If coinfection of HCV and HBV occurs, HCV usually predominates. This may lead to lower levels of transaminases and HBV DNA (Jardi 2001). The rate of HBsAg-seroconversion even appears to be increased, although this finding may be due to the fact that around one third of patients coinfecting with HBV and HCV lack markers of HBV infection (i.e., HBsAg) although HBV DNA is detectable. Despite lower aminotransferases and HBV DNA levels, liver damage is worse in most instances. The risk of severe hepatitis and fulminant hepatic failure seems to be elevated if both infections occur simultaneously regardless of whether it is an acute coinfection of HBV and HCV or acute hepatitis C in chronic hepatitis B (Liaw 2004).
- **Hepatitis D coinfection:** Acute HBV and HDV coinfection tends to be more severe than acute HBV infection alone. It is more likely to result in fulminant hepatitis. If HDV superinfection in patients with chronic HBV infection occurs, HDV usually predominates, and HBV replication is suppressed (Jardi 2001). Severity of liver disease is worse and progression to cirrhosis is accelerated in such patients (Fattovich 2000).

It is very difficult to predict the individual course of hepatitis B due to the many factors influencing disease progression. Several predictive models of disease progression that include clinical parameters (e.g., hepatic decompensation) and laboratory parameters (e.g., bilirubin, INR) have been evaluated, but none of these models is used routinely in the clinic at present. In patients with cirrhosis, the MELD score (Model for End-Stage Liver Disease) and the Child-Pugh score are used (see Chapter 3).

## Extrahepatic manifestations

The two major extrahepatic complications of chronic HBV are polyarteritis nodosa and glomerular disease. They occur in 10-20% of patients with chronic hepatitis B and are thought to be mediated by circulating immune complexes (Han 2004).

- **Polyarteritis nodosa:** The clinical manifestations are similar to those in patients with polyarteritis who are HBV-negative. There may be some clinical benefit to antiviral therapy.
- **Nephropathy/Glomerulonephritis:** HBV can induce both membranous nephropathy and, less often, membranoproliferative glomerulonephritis. Most cases occur in children. The clinical hallmark is proteinuria. In contrast to polyarteritis nodosa, there is no significant benefit of antiviral treatment.

For further details, please refer to extrahepatic manifestations in Chapter 16.

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