NATURAL HISTORY OF HEPATITIS B
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SUMMARY

Hepatitis B virus (HBV) infection can cause acute, fulminant or chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC). Perinatally or childhood acquired HBV infection usually causes subclinical or anicteric acute hepatitis and is associated with a high risk of chronicity (30 to 90% of cases), whereas adult acquired infection may cause acute symptomatic hepatitis (approximately 30% of patients) and is associated with a low risk of chronicity (less than 5%). Fulminant hepatic failure is unusual (0.1 to 0.5% of patients), but acute coinfection with other hepatitis viruses increases the risk of fulminant hepatitis. Chronic HBV infection is a dynamic process with an early replicative phase and active liver disease and a late low or non replicative phase with remission of liver disease. Perinatally acquired HBV infection is characterized by a prolonged "immunotolerant" phase with hepatitis B e antigen (HBeAg) positivity, high levels of serum HBV-DNA, normal levels of aminotransferases, minimal liver damage and very low rates of spontaneous HBeAg clearance. Patients with childhood or adult acquired infection and chronic hepatitis B usually present in the "immunoactive" phase with elevated aminotransferases and liver necroinflammation at histology (HBeAg positive chronic hepatitis) and approximately 50% will clear HBeAg within 5 years. The rate of spontaneous HBeAg seroconversion may vary in relation to the degree of the elevation of aminotransferases. Seroconversion from HBeAg to antibody to HBeAg marks the transition from chronic hepatitis to the inactive hepatitis B surface antigen (HBsAg) carrier state with low or undetectable serum HBV-DNA and normal aminotransferases, and confers favourable long-term outcome with very low risk of cirrhosis or HCC in the majority of patients. HBsAg clearance may occur at the rate of around 1% per year in chronic HBV infected adults (resolved hepatitis B). However a proportion of patients (about 20 to 30% of prospective cases) continue to have or redevelop high levels of HBV-DNA and active hepatitis despite HBeAg seroconversion; these patients may have HBV variants unable to express HBeAg (HBeAg negative chronic hepatitis). HBeAg negative chronic hepatitis represents a late phase in the natural history of chronic HBV infection and is associated with a very low rate of spontaneous disease remission. Longitudinal studies of patients with chronic hepatitis B indicate that the 5-year cumulative incidence of developing cirrhosis ranges from 8 to 20% (2 to 5.4 per 100 person years, but as high as 8 to 10 in HBeAg negative chronic hepatitis). Morbidity and mortality in chronic hepatitis B are linked to evolution to cirrhosis or HCC. The incidence of HCC appears to vary geographically and correlates with the underlying stage of liver disease (0.1 to 10 per 100 person years). The risk of HCC is highest for patients with cirrhosis and usually arises in the clinical setting of compensated cirrhosis which may be silent clinically. The 5-year cumulative incidence of hepatic decompensation is approximately 20% (3 to 4 per 100 person years). Survival is reasonably good, the 5-year probability of survival being approximately 80 to 86% in patients with compensated cirrhosis. Patients with decompensated cirrhosis have a poor prognosis (14 to 35% probability of survival at 5 years). The worst survival occurs in patients presenting with more than one complications, and the best in those with ascites alone. Factors predictive of a worse prognosis in chronic hepatitis B include the severity of the underlying liver disease, older patient age, male sex, recurrent episodes of acute exacerbations of hepatitis not followed by viral clearance and lengthy persistence of HBV replication, whereas viral clearance and biochemical remission correlate with an improved clinical outcome. As many as 20 to 30% of acute flares in chronic hepatitis B may be caused by superinfection with other hepatotropic viruses. Concurrent HDV or hepatitis C virus infection or concomitant alcohol abuse have been reported as negative prognostic factors in chronic hepatitis B. There is growing evidence of differences in severity of liver disease between HBV genotype B and C.
INTRODUCTION

Hepatitis B virus (HBV) infection is an important global health problem and may cause both acute and chronic infection in man (1). It is estimated that 400 million people worldwide are chronic HBV carriers (2). The clinical spectrum of HBV infection ranges from subclinical to acute symptomatic hepatitis or, rarely, fulminant hepatitis during the acute phase and from the inactive hepatitis B surface antigen (HBsAg) carrier state, chronic hepatitis of various degree of histologic severity to cirrhosis and its complications during the chronic phase (3, 4). Approximately 15% to 40% of people who develop chronic hepatitis B are expected to progress to cirrhosis and end stage liver disease (1). Understanding the natural history and prognosis of hepatitis B is of major importance for the disease management and for evaluating the efficacy of the chosen treatment strategy.

NATURAL HISTORY OF HBV INFECTION

Perinatal infection from infected mothers to their infants or horizontal infection early in childhood from exposure to HBsAg positive family members are the main routes of HBV transmission in high endemic area, such as South-East Asia, most Africa, Pacific Islands and the Arctic, whereas in low endemic regions, such as Western countries, hepatitis B is primarily a disease of adolescents and adults as a result of high risk sexual activity and injection drug use.

HBV infection is a dynamic process characterized by replicative and non replicative phases based on virus-host interaction, which are present in some form in all infected patients (Figure 1).

The presence of circulating HBsAg, hepatitis B e antigen (HBeAg) and high levels of serum HBV-DNA identifies the first immunotolerant phase. In adult acquired infection this phase marks the incubation period of acute HBV infection and lasts about two to four weeks, in contrast with perinatal infection this phase often lasts for decades. During this phase patients have no symptoms, normal or slightly increased serum alanine aminotransferase (ALT) levels and minimal histological activities, which implies that there is a lack or very week immune response against the infected hepatocytes. Experimental results in transgenic mice have suggested an immunoregulatory function for HBeAg in neonates, which is believed to induce a state of immunological tolerance to HBV (5). During the course of HBV infection, for unknown reasons, the tolerogenic effect is lost and patients may enter the second immunoactive phase which is associated with a decrease in HBV-DNA concentrations and increased ALT levels and histologic activity, reflecting the host immune mediated lysis of infected hepatocytes. In acute HBV infection this phase is the period of clinical symptoms and jaundice and usually lasts for three to four weeks, whereas in patients with chronic HBV infection has a variable duration from months to years.

The third low or non replicative phase involves seroconversion from HBeAg to antibody to HBeAg (anti-HBe) usually preceeded by a marked reduction of serum HBV-DNA levels below 105 copies per ml, that are not detectable by hybridization techniques, and followed by normalization of ALT levels and resolution of liver necroinflammation. Serum HBV-DNA remains detectable only by ultrasensitive technique of polymerase chain reaction (PCR) in many patients. In chronic HBV infection this phase is also referred as the inactive HBsAg carrier state (3, 4). The inactive carrier state may last for lifetime, but a proportion of patients may undergo subsequent spontaneous or immunosuppression induced reactivation of HBV replication with reappearance of high levels of HBV-DNA with or without HBeAg seroreversion and rise in ALT levels (3). For reasons that are not yet known during HBeAg clearance or later on after HBeAg seroconversion replication-competent HBV variants with mutations in the precore or core promoter regions preventing HBeAg production may be selected (6).

Patients who become HBsAg negative and develop antibody to HBsAg (anti-HBs) are diagnosed as having resolved hepatitis B (3,4). This is an uncommon phenomenon in chronic HBV infection. During this stage HBV-DNA may still be detectable by PCR assay both in serum and liver (7). In rare cases of severe immune suppression, such as cancer chemotherapy or after organ transplantation HBV can reactivate in patients with resolved hepatitis B (8).
CLINICAL OUTCOME OF ACUTE HEPATITIS B

Acute HBV infection is generally subclinical and anicteric in neonates and children, whereas in approximately 30 to 50% of adults may cause icteric hepatitis (9). Patients who recover from acute hepatitis B acquire protective levels of anti-HBs and gain lifelong immunity. However a proportion of patients may become chronically infected and approximately 0.1 to 0.5% of patients develop fulminant hepatitis. Acute HBV and hepatitis delta virus (HDV) coinfection is associated with high rate of fulminant hepatitis (10). Acute HBV and hepatitis C virus (HCV) coinfection has also been reported to increase the risk of fulminant hepatitis (11). It is generally believed that fulminant hepatitis is the consequence of an enhanced immune response of the host inhibiting viral replication and causing massive lysis of infected hepatocytes, thus explaining the absence of serological markers of HBV infection in many patients (12).

Persistence of HBsAg, HBeAg and HBV-DNA in high titer for more than 6 months implies progression to chronic HBV infection (13). Age at the time of primary HBV infection is the best established determinant of chronicity. Up to 90% of infants of highly infectious HBsAg and HBeAg positive mothers become chronic HBV carriers as compared with approximately 30% of children infected after the neonatal period but before the age of 5 years (9,14). In contrast only 1% to 5% of adults become persistently infected after clinically overt acute hepatitis (15). In addition to age at infection also the maternal HBeAg/anti-HBe status is an important determinant of the outcome of HBV infection. Indeed less than 10% of babies born to HBeAg negative/anti-HBe positive mothers become persistently infected, although a small proportion (approximately 5%) develop acute symptomatic or fulminant hepatitis within the first 3 to 4 months of life (14). High maternal viral load appears to increase the risk of persistently infected infant, on the other hand HBV mutants not producing HBeAg were detected both in babies with benign and fulminant hepatitis and their mothers, indicating that HBV genomic heterogeneity does not play a major role in the clinical outcome of perinatal HBV infection (16,17).

NATURAL HISTORY OF CHRONIC HEPATITIS B

HBeAg positive chronic hepatitis

Clinical data indicate that HBV infection acquired in the perinatal period is characterized by a prolonged immunotolerant phase and very low rate of spontaneous HBeAg clearance (14). Most carriers infected at birth or in the first few years of life present with HBeAg positive chronic hepatitis with normal serum aminotransferases and this clinical condition is likely to be maintained up to adulthood by a consistent proportion of patients (3,4). Many of these patients enter the immunoactive phase and develop HBeAg positive chronic hepatitis with elevated ALT levels only after 10 to 30 years of infection (18). In contrast patients who acquire HBV infection in the late childhood, during adolescence or adulthood and become chronic carriers usually present in the immunoactive phase with active liver disease.

The age of adult patients at the time of initial presentation with HBeAg positive chronic hepatitis B ranges between 24 and 36 years (median 31) in several reports and men usually outnumber women, the male to female ratio ranging from 1.5 to 4.9 (19-28). Liver damage ranges from mild (24% to 42%) to moderate or severe chronic hepatitis (44% to 63%) or active cirrhosis (10% to 24%) (20, 22, 24-26, 28). Chronic hepatitis B tends to be milder in children and liver histology reveals minimal to mild chronic hepatitis in the great majority of children (86% to 90%), nevertheless severe liver disease including cirrhosis may occur in a small proportion of patients during childhood (29, 30).

A key event in the natural history of HBeAg positive chronic hepatitis is HBeAg seroconversion. Several longitudinal studies conducted in cohorts of patients with HBeAg positive chronic hepatitis have shown that seroconversion from HBeAg to anti-HBe with marked reduction of HBV replication is associated with biochemical and histologic regression of inflammatory activity in the majority of patients (19-22, 30, 31). Histologic improvement occurs gradually months to years after HBeAg seroconversion (32).

In longitudinal studies the observed probability of clearing HBeAg was about 50% and 70% within 5 and 10 years of diagnosis, respectively (22, 28, 33, 34). Most studies have found that the mean annual rate of
spontaneous HBeAg seroconversion ranges from 8% to 15% in children or adults showing biochemical signs of liver disease activity (3, 4, 19, 20, 22, 28, 34-36). On the other hand in Asian children, most with normal ALT, the annual spontaneous HBeAg seroconversion occurs at a very low rate, less than 2% during the first 3 years of age and 4-5% in children older than 3 years (37).

Some determinants for HBeAg seroconversion have been reported, including sex, age, the degree of biochemical activity and more recently HBV genotypes. Older carriers and females are more likely to clear HBeAg (18, 33, 38); in a study of 532 Alaska Natives with HBeAg positive chronic hepatitis, a multivariate Cox proportional hazards model predicted clearance of HBeAg within 5 years in 33%, 52% and 76% for persons 0 to 18 years of age, 19 to 30 years of age, and 31 to 78 years of age, respectively (33).

Spontaneous HBeAg seroconversion within 1 year occurs in over 50% of patients with serum ALT levels over 5 times the upper limit of normal (ULN) as opposed to less than 10% of those with ALT levels less than 5 times the ULN (39). Frequently acute exacerbation of hepatitis, reflecting immune mediated lysis of HBV infected hepatocytes, with ALT elevations to more than 10 times the upper limit of normal range and more than twice the baseline value and with HBV-DNA levels rising before and falling during the flare, precede HBeAg to anti-HBe seroconversion and usually lasts for 2 to 4 months (40). The probability of HBeAg seroconversion correlates with the degree of histologic activity during the acute flare of hepatitis. A prospective study in Asian patients has indicated that approximately 70% of ALT flares with histological changes compatible with bridging hepatic necrosis sometimes associated with elevated serum alpha-fetoprotein level are followed by HBeAg seroconversion compared to only 20% of acute exacerbations without (41). Indeed in some cases these spontaneous flares of hepatitis are not followed by subsequent HBeAg seroconversion and these episodes can be viewed as an abortive attempt at seroconversion. These temporary flares of hepatitis are usually asymptomatic and frequently unrecognized, but some are accompanied by symptoms of acute hepatitis and very rarely, primarily in patients with slightly compensated chronic liver disease, may lead to hepatic decompensation and even death due to massive necrosis (42).

HBV can be classified into 7 genotypes A-G and recent studies, all from Asia, have indicated that HBV genotype B is associated with earlier HBeAg seroconversion than genotype C, thus most likely explaining the less progressive disease in patients with genotype B (43, 44).

HBeAg seroconversion associated with liver disease remission marks the transition from chronic hepatitis B to the inactive HBsAg carrier state, however a small percentage of patients (approximately 5%) may continue to show biochemical activity and high levels of serum HBV-DNA at the time of HBeAg seroconversion (22, 30, 31). These patients as well those undergoing reactivation of hepatitis B after HBeAg seroconversion may generate the group of patients with HBeAg negative chronic hepatitis B.

HBeAg negative chronic hepatitis

The diagnosis of HBeAg negative chronic hepatitis B is based on chronic HBsAg carriership, HBeAg negativity with anti-HBe positivity, detectable serum HBV-DNA by molecular hybridization techniques or by quantitative PCR assays, with HBV-DNA usually exceeding 105 and 106 copies per ml, increased ALT levels, liver necroinflammation at histology and exclusion of other concomitant or superimposed causes of liver disease, such as superinfection with other hepatitis viruses, alcohol abuse, hepatotoxic drug use, autoimmune or metabolic liver disease (3, 4, 6). The atypical serological profile is sustained by HBV variants which are unable to express HBeAg. The most frequent precore mutation is a G to A change at nucleotide 1896 (G1896A), which creates a stop codon in the precore region of HBV genome and completely abolishes the production of HBeAg (6). Other patients may harbour other changes in the precore region or mutations in the core promoter region, which reduces pre-core mRNA synthesis and HBeAg production; the most common core promoter mutation involve a 2 nucleotide substitution, A to T at nucleotide 1762 and G to A at nucleotide 1764 (TA) (45).

HBeAg negative chronic hepatitis has been reported to prevail in certain part of the world such as in the Mediterranean basin, the middle East and Asia (3, 6). Recent data suggest that HBeAg negative chronic hepatitis is more common than previously suspected and that is present worldwide (46). The geographical variations in the prevalence of HBeAg negative chronic hepatitis and associated precore and core promoter
variants is related to the predominant HBV genotype in each area. Indeed the most common precore mutant (G1896A) can be selected only in patients infected with HBV genotypes B, C, D, E harboring thymidine (T) at precore position 1858. On the other hand in HBV genotype A the nucleotide 1858 is a cytosine (C), precluding the selection of the G1896A mutation. This explains why HBeAg negative chronic hepatitis associated with precore stop codon variant is prevalent in the Mediterranean area where non-A genotypes, particularly D, predominate and is infrequent in North America, Northern Europe and parts of Africa where genotype A predominates (6). In Asian countries, where both A and non-A genotypes exist, HBeAg negative chronic hepatitis is associated with mutation in the core promoter region in addition to precore mutants (45). Clinical experience suggests that the prevalence of HBeAg negative chronic hepatitis is increasing during the last decade particularly in the Mediterranean area and in Asia, but this issue is supported only by few studies (45, 47).

Patients with HBeAg negative chronic hepatitis are usually older than patients with HBeAg positive chronic hepatitis and the age ranges between 36 and 45 years (median 40); males largely predominates and the reported male/female ratio ranges from 3.9 to 17 (26, 48-51). Current available data indicate that the clinical profile of HBeAg negative chronic hepatitis differs from that seen in patients with HBeAg positive chronic hepatitis. Indeed minimal or mild chronic hepatitis at histology is infrequent and severe necroinflammation is seen in more than 50% of HBeAg negative cases at diagnosis (26, 48, 51, 52). In large series of patients from the Mediterranean area from 29% to 38% had cirrhosis already developed at the time of their first presentation (25, 26, 51, 52). The older age and the high rate of advanced liver damage at presentation of HBeAg negative as compared to HBeAg positive patients suggest that HBeAg negative chronic hepatitis represents a late phase in the natural history of chronic HBV infection. To further support this concept a recent long term study has reported that HBeAg negative chronic hepatitis accumulated over time after HBeAg seroconversion with a cumulative incidence of approximately 25% at 16 years of follow-up (31). Thus the increasing prevalence of HBeAg negative chronic hepatitis may be only the reflect of the increased duration of infection in chronic HBV carriers and long term monitoring of patients.

Moreover the clinical course of HBeAg negative chronic hepatitis differs from the HBeAg positive forms in relation to large fluctuations over time of viremia and transaminases, with relapses of hepatitis alternate to periods of biochemical remission in most patients and a much lower rate of sustained spontaneous remission. During follow-up three main biochemical profiles are observed, namely recurrent flares of ALT with (pattern 1) or without (pattern 2) spontaneous ALT normalization between flares, and persistently increased ALT without tendency for spontaneous remission (pattern 3). In a recent longitudinal study approximately two-thirds of patients showed recurrent ALT flares and the frequency of patterns 1,2 and 3 was reported to be 45%, 20% and 35%, respectively (51). Flares of hepatitis may be severe and disease exacerbations correlate with progression to end stage complications of cirrhosis (51). Periods of remission with normal ALT and low serum HBV-DNA levels (< 105 copies per ml) may be long lasting, but usually the disease recurs and sustained spontaneous remission of disease activity is uncommon (6). The incidence of delayed spontaneous HBSAg clearance has been estimated to occur at a low rate of 0.5% per year (31, 52).

Inactive HBsAg carrier state

The inactive HBsAg carrier state is diagnosed by HBeAg negativity with anti-HBe positivity, no or low levels of HBV-DNA detectable by PCR based assays, repeatedly normal ALT levels, and minimal or no necroinflammation, slight fibrosis or even normal liver on biopsy, although inactive cirrhosis may be present in those cases who have worsened during the high replicative phases of infection (3, 4). The prognosis of the inactive HBsAg carrier state is usually benign. Long term follow-up (up to 16 years) of these carriers both referred to clinical centers or from population-based studies have indicated that the vast majority show sustained biochemical remission and very low risk of cirrhosis or HCC (31, 53, 54). Some patients, even non cirrhotics, may rarely develop liver cancer during the inactive HBsAg carrier state (31, 55). In addition in longitudinal studies approximately 20-30% of persons known to have the inactive HBsAg carrier state may undergo spontaneous reactivation of hepatitis B with reappearance of biochemical and necroinflammatatory activity of liver disease, high levels of serum HBV-DNA with or without seroreversion to HBeAg (18, 30, 31, 56, 57). Multiple episodes of reactivation or sustained reactivation may be observed and can cause progressive hepatic damage and even hepatic decompensation (56, 57). HBV reactivation is usually asymptomatic, but on occasion can mimic acute viral hepatitis (15).
Acute flares of hepatitis occurring during the inactive HBsAg carrier state or in patients who are in the replicative stage of chronic HBV infection (both HBeAg positive or HBeAg negative) should be differentiated by superinfection with other hepatotropic viruses. As many as 20 to 30% of these acute exacerbations may be caused by superinfection with HDV, HCV or hepatitis A virus and can be associated with an increased risk of fulminant hepatic failure (40, 58).

Some carriers eventually become HBsAg negative and develop anti-HBs. The incidence of delayed HBsAg clearance has been estimated to be 1% to 2% per year in Western countries, where HBV infection is usually acquired in adulthood (38, 59), but to occur at a lower rate from 0.05% to 0.8% per year in endemic area where HBV infection is mostly acquired perinatally or in the early childhood (28, 33, 60). Clearance of HBsAg has been reported to be higher in women than in men and in older than younger carriers (38, 61). Prognosis is improved by loss of HBsAg as there is no evidence of active or progressive liver disease, but HBsAg clearance does not prevent occurrence of decompensation or HCC both in Caucasian and Asian patients who have already developed cirrhosis (59, 62).

Progression to cirrhosis and risk factors

Longitudinal studies of untreated patients with predominantly HBeAg positive chronic hepatitis B have indicated that the incidence of developing cirrhosis ranges from 2 to 5.4 per 100 person years and that the 5 year cumulative incidence of progression to cirrhosis ranges from 8% to 20% (23, 24, 27, 63-65). It has been suggested a higher rate of cirrhosis occurrence in HBeAg negative compared with HBeAg positive chronic hepatitis B; indeed results of a few longitudinal studies of untreated patients with HBeAg negative chronic hepatitis B have indicated that the incidence of developing cirrhosis ranges from 8 to 10 per 100 person years (66, 67).

The variability in the rate of progression to cirrhosis may be related to differences in the clinical and serological features of HBV infected patients among different studies and indeed various risk factors for evolution to cirrhosis have been identified (table 1). In one study the severity of the fibrosis stage at presentation did correlate with the probability of developing cirrhosis, which was 0%, 6% and 17% after 5 years for stages F1, F2 and F3, respectively (64). In addition the severity of necroinflammation at diagnosis and recurrent episodes of severe acute exacerbation with bridging hepatic necrosis during follow-up are important pathologic factors that predict unfavorable evolution of the disease (23, 24, 40, 63).

Older age and ongoing HBV replication detected by sustained or intermittent HBV-DNA positivity by non-PCR assays have also been well established prognostic factors for cirrhosis occurrence (23, 24, 51, 63). Altogether these studies have underlined the relevant prognostic value of biochemical and virologic patterns during follow-up.

Studies in Asian patients suggest that HBV genotype C is associated with a higher risk of developing cirrhosis than genotype B and preliminary data suggest that genotype C, but not core promoter or precore stop mutations, correlates with more severe liver disease in HBeAg negative chronic hepatitis (68, 69).

Other clinical conditions have been implicated as predisposing factors for worsening of chronic hepatitis B, including concurrent HDV, HCV or human immunodeficiency virus (HIV) infection or concomitant alcohol abuse. Heavy drinking has been reported to increase the risk for progression to cirrhosis by 6 folds (64).

Concurrent HBV and HCV infection in chronic hepatitis B has been reported to occur in approximately 10-25% of patients, particularly among drug abusers (70,71). The interaction between the viruses that determine chronic hepatitis seems to be characterized by a reciprocal inhibition of the respective genome (72). Despite this the clinical presentation of the disease and prognosis have been reported to be generally more severe among patients with dual HBV and HCV infection than those with single infection, with a high prevalence of histologically proven severe chronic hepatitis or cirrhosis (70-72). In a longitudinal study of patients with dual HBV and HCV infection the incidence of progression to cirrhosis was 4.3 per 100 person years during 1 to 11 years of follow-up (70).
Recent data indicate a decline in HDV infection throughout the industrialized world as a consequence of the control of HBV infection (73). HDV superinfection in chronic HBV carriers has been extensively investigated and found to be associated with more severe forms of chronic liver disease and with a rapid progression to cirrhosis (73-75). In a large series of HDV infected patients the median time elapsed from acute hepatitis to the diagnosis of cirrhosis was 9 years and in only a minority of patients the disease has been non progressive (75). In another study patients with chronic delta hepatitis showed a significantly higher probability of evolution to cirrhosis (approximately 50% at 5 years) than HBsAg carriers with chronic hepatitis and no evidence of HDV infection (74).

It has been reported that in homosexual men with chronic hepatitis B, HIV infection is associated with high level of HBV replication, low rate of spontaneous HBeAg seroconversion and with 4.2 fold increased risk for cirrhosis relative to HIV negative homosexuals (95% confidence interval (CI) 1.3 to 13.8) (76).

**MORBIDITY**

In reports on chronic hepatitis B, the average age of patients at the time of diagnosis of cirrhosis was 41 to 52 years (median 46) and males usually predominates, the male to female ratio ranging from 2.2 to 18 (51, 77-81). In a European study of 366 patients with compensated cirrhosis due to hepatitis B, only a minority (24%) of patients were referred to the enrolling center because of non specific symptoms of fatigue, dyspepsia and upper abdominal discomfort, thus indicating that development of cirrhosis B is insidious and mainly asymptomatic (82).

**Development of hepatocellular carcinoma**

Chronic HBV infection and cirrhosis of the liver are well recognized risk factors for HCC (83). One main point that has emerged from clinical studies is the increased risk of HCC with significant liver disease. In high endemic area the incidence of liver tumor per 100 person years is about 0.1 for chronic asymptomatic HBsAg carriers (84, 85) and approximately 1.0 for untreated patients with chronic hepatitis B without preexisting cirrhosis at diagnosis (27, 86). In longitudinal studies of untreated patients with compensated cirrhosis type B from Asia the incidence of HCC was 3 per 100 person years, but even higher incidence of 6 to 8 has been reported in studies from Singapore and Japan (77, 78, 80, 87).

The natural history of compensated cirrhosis caused by hepatitis B was assessed in an updated analysis of the subgroup of 161 out of 366 patients enrolled in the above referred European study, who were delta negative at diagnosis and remained untreated during a mean follow-up of 6.4 years (88). The study was based on the collaboration of eleven European university hospitals participating in a Concerted Action on viral hepatitis named EUROHEP (82). In this evaluation there is an acceptable level of uniformity in the patient population by defining the zero-time point of follow-up as the time of histological diagnosis of cirrhosis, by including only untreated patients in Child class A and by excluding major cofactors of disease progression such as concurrent HCV or HDV infection and excessive alcohol consumption. In this study population the 5-year cumulative incidence of HCC was 9%, the incidence per 100 person years was 2.2 and the mean interval between the time of diagnosis of cirrhosis and the occurrence of HCC was 44 months (range 6-180) (Figure 2, A) (88). The majority (68%) of patients developing HCC did not experience hepatic decompensation before or by the time of diagnosis of liver cancer, indicating that HCC usually arises in the clinical setting of compensated cirrhosis which may be silent clinically (88).

Host factors, virus factors and extraneous factors may play a role in influencing the rate of progression of hepatitis to liver cancer. The incidence of HCC is three to six times higher in males than female, suggesting a tumorigenic effect of androgens (61, 83).

Several studies have indicated that older age, which may be a determinant in itself or simply a reflection of a presumable longer duration of infection and liver disease, is an important determinant of HCC (61, 83, 89, 90).

The relationship between ongoing HBV replication and the risk of HCC has been evaluated in the European cohort of patients with compensated cirrhosis B. The risk for liver cancer did not differ among patients who
were HBeAg positive or HBeAg negative/HBV-DNA positive or HBeAg negative/HBV-DNA negative at entry (5-year cumulative incidence of HCC: 9%, 14% and 8%, respectively (p=0.4 by log rank test)) and the RR (95% CI) for HCC was 0.89 (0.30 to 2.63) in HBV-DNA positive relative to HBV-DNA negative patients (88). These data suggest that the HBeAg and HBV-DNA status at the time of diagnosis of cirrhosis has no prognostic value for liver cancer occurrence and that in addition to chronic HBV infection, cirrhosis per se is a risk factor for HCC.

Alcohol and concurrent infection with HCV or HDV increases the risk of HCC (81, 90, 91). In a longitudinal study conducted in a cohort of 290 Italian patients with cirrhosis, age, male sex, previous alcohol abuse and coinfection with hepatitis C were independent risk factors for liver cancer by multivariate analysis (90). The effect of HDV infection as a risk factor for HCC has been evaluated in a EUROHEP longitudinal cohort study of 200 patients (20% infected by HDV) followed for a mean period of 6.6 years; in this study HDV infection was associated with 3-fold (95% CI 1.0 to 10) increased risk for liver cancer (81).

Development of hepatic decompensation

In the EUROHEP cohort study the 5-year cumulative incidence of hepatic decompensation was 16%, the incidence per 100 person years was 3.3 and the mean interval between the time of diagnosis of cirrhosis and the appearance of the first episode of decompensation was 31 months (range 6-109) (Figure 2, A) (88). The first episode of decompensation was caused by ascites in 49% of patients and by variceal bleeding, jaundice or more than one complications in 9%, 12% and 30% of patients, respectively. Longitudinal studies conducted in Asia including patients with recent development of cirrhosis (Child class A) have indicated similar rates of decompensation with a 5-year cumulative incidence of approximately 20% (4 per 100 person years) (77). These findings indicate that a significant proportion of patients presenting with compensated cirrhosis B do not worsen for several years and that hepatic decompensation usually occurs at a relatively late stage of the disease.

MORTALITY FROM LIVER DISEASE AND RISK FACTORS

HCC and liver failure are the main causes of death and currently more than 1 million people die each year from the consequence of HBV infection (1).

The mortality rate depends on the initial clinical features at which patients are studied. Among inactive HBsAg positive carriers both referred to clinical centers and in population-based studies none died from liver related causes when followed up to 16 years (31, 53, 54).

In patients with chronic hepatitis B the survival rate was 99% to 100% at 5 years following the diagnosis of chronic hepatitis (63, 64). In long term studies of untreated patients with chronic hepatitis B, both HBeAg positive and HBeAg negative, without preexisting cirrhosis at baseline and without HDV infection, the incidence of liver related death was low and ranged from 0 to 1.06 per 100 person years (personal communication thank to the courtesy of the Authors of references 26, 27, 52, 65).

The probability of survival is approximately 80-86% at 5 years in patients with compensated cirrhosis (77, 82, 92). In the EUROHEP cohort of 161 untreated patients with HBsAg positive, delta negative compensated cirrhosis the 5-year probability of survival was 86% and the incidence per 100 person years of liver related death was 3.5; there was a linear, although slow, rate of HCC, hepatic decompensation and liver related death in this cohort of patients (Figure 2, B) (88). The causes of death or liver transplantation included complications of HCC in 35%, liver failure in 53% and causes unrelated to liver disease in 12% (88).

Strong predictors for survival that have been identified are age and parameters that relate to hepatocellular function (albumin, bilirubin) and the presence of portal hypertension (platelets, splenomegaly); these are similar to the risk factors for the development of HCC and of decompensation and reflect the stage and severity of the underlying cirrhosis (table 1) (82, 88, 92).

Active HBV replication has been reported as a negative prognostic factor, whereas viral clearance and ALT
normalization correlated with increased survival (55, 92). In the EUROHEP cohort of patients with compensated cirrhosis B and with information on the HBeAg and HBV-DNA status at diagnosis, survival was significantly lower in patients who were HBeAg positive or HBeAg negative/HBV-DNA positive as compared with those HBeAg negative/HBV-DNA negative (5-year survival probability: 79%, 86% and 97%, respectively, p= 0.01); the risk of decompensation and mortality was 4.0 fold (95% CI 1.09 to 15.1) and 5.9 fold (95% CI 1.64 to 21.3), respectively, in HBV-DNA positive relative to HBV-DNA negative patients (88).

Moreover it has been reported that the change in HBeAg status from positive to negative during follow-up of cirrhotic patients was associated with a 2.2 fold decrease in death rate (92). In another study of HBeAg positive cirrhotic patients multivariate analysis found that ALT normalization during follow-up is a better predictor of improved survival than HBeAg clearance (55). This data is in agreement with the observation that in the natural course of HBV related chronic liver disease a proportion of patients do not benefit from HBeAg seroconversion, as shown by persistence of HBV viremia and disease activity or by HBV reactivation.

In a study of delta chronic hepatitis the 5 year probability of survival was 100% for patients with mild hepatitis, 90% for severe hepatitis and 81% for histologically asymptomatic cirrhosis (75). Chronic hepatitis D rapidly advances to cirrhosis, but available data indicate that thereafter the disease remains stable and asymptomatic in a high proportion of patients for more than one decade similarly to that observed in compensated cirrhosis B. On the other hand the prognosis of patients with hepatitis D and with clinical cirrhosis at presentation is worse with a 5 year probability of survival of 49% (75).

Survival after decompensation

Once decompensation occurs the prognosis is poor. The probability of survival ranges from 55% to 70% at 1 year and from 14% to 35% at 5 years, considerably lower than the survival for compensated cirrhosis due to HBV (figure 2, B) (89, 92). Moreover the type of decompensation may influence the rate of survival. The lowest survival rate was observed in patients with more than one complications (35% at 3 years; no patient in follow-up at 5 years) and the highest survival rate for decompensated patients who presented with ascites (50% at 3 years and 38% at 5 years) (88). A recent study has indicated encephalopathy and hypoalbuminemia as significant prognostic indicators of a worse prognosis after onset of hepatic decompensation (93). In decompensated patients with cirrhosis HBV clearance and delayed HBsAg loss can be associated with improvement of liver disease (94). Such information are helpful in guiding management decisions and timing for referral for liver transplantation.

**Table 1. Factors affecting prognosis of chronic hepatitis and compensated cirrhosis due to Hepatitis B Virus (HBV)**

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<tr>
<td>- HBV replication</td>
<td>- age at diagnosis</td>
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<td>- HBV variants</td>
<td>- gender</td>
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<tr>
<td>- virus genotype</td>
<td>- stage of liver disease at presentation</td>
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<td>- viral coinfection</td>
<td>- recurrent flares of hepatitis</td>
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<td>- sustained ALT normalization</td>
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<td>- alcohol intake</td>
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**LEGENDA TO FIGURES**

Figure 1. Natural course of hepatitis B virus (HBV) infection. The initial immunotolerant phase with hepatitis B
e antigen (HBeAg) positivity and high levels of serum HBV-DNA is followed by the immunoactive phase with a decrease in serum HBV-DNA and increase in alanine aminotransferase (ALT) levels and finally by the nonreplicative or minimally replicative phase with seroconversion to antibody to HBeAg (anti-HBe) and remission of liver disease. Reactivation of HBV and of liver disease activity may occur after seroconversion from HBeAg to anti-HBe. Resolved hepatitis B involves loss of hepatitis B surface antigen (HBsAg) and seroconversion to HBsAg (anti-HBs).

Figure 2. Cumulative incidence of hepatocellular carcinoma (HCC) and decompensation (A) and cumulative probability of survival and survival after the appearance of the first episode of decompensation (B) in 161 untreated Caucasian patients with compensated cirrhosis due to hepatitis B (88). The 5-year rate of HCC and decompensation was 9% and 16%, respectively. The 5-year probability of survival and survival after decompensation was 86% and 28%, respectively. The number of patients under observation refers to the survival probability.
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