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# Management of patients with hepatitis B virus-induced cirrhosis

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## 1. Introduction

Approximately 350 million people worldwide are chronically infected with hepatitis B virus (HBV). If left untreated, approximately 20% will develop cirrhosis and complications of end-stage liver disease [1,2]. Antiviral therapy may decrease the progression to cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC). Until recently, the only treatment for chronic hepatitis B was standard interferon (IFN). Interferon has limited efficacy, and may be associated with severe sepsis and worsening of hepatic failure in patients with decompensated cirrhosis [3,4]. The availability of oral antiviral agents with a better safety profile has significantly changed the management of end-stage liver disease caused by HBV. Lamivudine has been shown to suppress HBV replication, and to improve or stabilize liver function in patients with compensated as well as in those with decompensated cirrhosis [5,6]. Adefovir dipivoxil has also demonstrated efficacy in patients with decompensated cirrhosis and lamivudine-resistant HBV [7]. Oral nucleos(t)ide agents have delayed or obviated the need for liver transplantation in some patients, but transplantation is still required for those who present with advanced liver failure [8,9]. This article will focus on the use of antiviral agents for the treatment of HBV-cirrhosis.

## 2. Prognosis of hepatitis B virus-cirrhosis

### 2.1. Progression to cirrhosis

Based on studies of patients with hepatitis B e antigen (HBeAg)-positive chronic hepatitis, the incidence of cirrhosis was estimated to be 2–5 per 100 person-years [10–12]. The incidence of cirrhosis among patients with HBeAg-negative chronic hepatitis is higher, at 8–9 per 100 person-years [13]. This is not surprising since HBeAg-negative chronic hepatitis represents a later phase in the natural history of chronic HBV infection. Thus, patients with HBeAg-negative chronic hepatitis tend to be older and to have more advanced fibrosis on biopsy. Risk factors associated with an increased risk of progression to cirrhosis include active viral replication, older age, advanced fibrosis on biopsy, concomitant alcohol use, co-infection with other hepatitis viruses (C or D) or human immunodeficiency virus (HIV), and possibly HBV genotype [14–16]. Studies from Asia showed that patients with HBV genotype C have more active liver disease, delayed HBeAg seroconversion, and more rapid progression to cirrhosis, compared to those with genotype B [17,18]. However, the relation between other HBV genotypes and the risk of cirrhosis has not been examined.

### 2.2. Hepatic decompensation

Approximately 20% of patients with compensated HBV-cirrhosis will decompensate over 5 years [19]. Fig. 1 shows the marked decrease in survival among patients with decompensated cirrhosis, and lower survival among HBeAg-positive patients. The 5-year survival rates of HBeAg-positive and HBeAg-negative patients with compensated HBV-cirrhosis have been estimated to be 72 and 97%, respectively [20]. The corresponding figures for patients with decompensated cirrhosis are substantially lower, 0 and 28%, respectively. Factors associated with an increased risk of hepatic decompensation include active viral replication, regular alcohol consumption, and coinfection with HIV or HCV [20,21]. A study of 161 European patients (28% HBeAg-positive) with compensated HBV-cirrhosis followed for a median of 6.6 years found that those with HBeAg and detectable HBV DNA by hybridization assay had a higher cumulative probability of decompensation (18%), compared to HBeAg-negative/HBV DNA-positive patients (13%) and HBeAg-negative/HBV DNA-negative patients (4%) ($P = 0.04$) [19].

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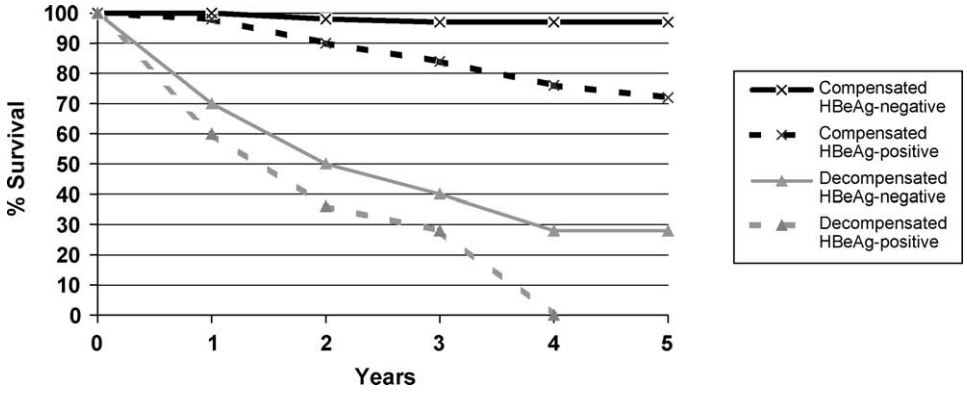


**Fig. 1. Survival of patients with HBV-cirrhosis. Modified from De Jongh et al. [20], the survival of patients with compensated and decompensated HBV-cirrhosis is illustrated. Black lines represent patients with compensated cirrhosis; gray lines represent those with decompensated cirrhosis. Solid lines represent patients with HBeAg-negative chronic hepatitis; dotted lines represent patients with HBeAg-positive chronic hepatitis.**

### *2.3. Hepatocellular carcinoma*

Chronic HBV infection is a major risk factor for hepatocellular carcinoma (HCC). Compared to hepatitis B surface antigen (HBsAg)-negative persons, HBV carriers have a 100-fold relative risk of developing HCC [22]. The age-adjusted incidence of HCC has been reported to be 18–35 per 100,000 in Asian men and 3–10 per 100,000 in European men [23]. Both viral and host factors are important in the development of HCC. Males and older patients have a higher risk of HCC [22,24,25]. Other risk factors include environmental exposures such as smoking, alcohol, aflatoxin B1, and coinfection with HCV [26–28]. Previous studies found that most patients with HCC were HBeAg-negative and had undetectable serum HBV DNA by hybridization assays. However, a recent study from Taiwan that prospectively followed 11,893 men found that those who were HBsAg and HBeAg-positive at enrollment had a relative risk of HCC of 60 (95% CI, 36–102) compared to 9.6 (95% CI, 6.0–15.2) for those who were HBsAg-positive but HBeAg-negative [29]. An increased risk among carriers who were HBeAg-positive remained after adjustment for smoking, alcohol use and HCV coinfection. These data suggest that suppression of HBV replication may reduce the risk of HCC development. The importance of HBV replication on liver disease progression is highlighted by the lack of clinically significant liver disease, HCC or liver-related mortality after a mean of 29 years of follow-up of 296 HBsAg-positive blood donors who were all HBeAg-negative with normal ALT at baseline [30].

## 3. General medical management

The general medical management of patients with HBV-cirrhosis is similar to that of patients with cirrhosis due to other causes. Regular follow-up with a hepatologist or gastroenterologist is recommended to screen for varices and HCC, to manage ascites, variceal bleeding and hepatic encephalopathy, and to assess the need for liver transplantation. Patients with HBV-cirrhosis are recommended to receive hepatitis A vaccine but response may be impaired in those with decompensated disease [31,32].

## 4. Hepatocellular carcinoma surveillance

Several studies have shown that periodic testing for alpha-fetoprotein (AFP) and ultrasound can lead to earlier detection of HCC and an increased likelihood of eligibility for ‘curative’ treatment [33–36]. An improvement in survival has also been reported among patients whose tumors were detected through surveillance as opposed to those who presented with symptomatic tumors. However, prospective data confirming a survival benefit of HCC surveillance is lacking. This is in part related to the poor accuracy of available screening tools, the difficulty in defining a target population for surveillance, and the limited number of treatment options.

The most common regimen for HCC surveillance includes 6-monthly testing for AFP and abdominal ultrasound. However, both AFP and ultrasound have limitations. AFP has a low sensitivity (40–65%) and variable specificity (75–90%) for the detection of HCC, depending on the cut-off value used [37]. AFP values more than 500 ng/ml are highly suggestive of HCC, but these values have also been reported in patients with exacerbations of chronic hepatitis B. This was illustrated in a retrospective study involving 290 patients in Hong Kong screened for HCC using AFP [38]. Forty-four patients had elevated AFP during a follow-up of up to 4 years, only six (14%) had HCC, most of the remaining patients with AFP increase (up to 1934 ng/ml) had flares in underlying chronic hepatitis B. High AFP levels can also be seen during pregnancy and in association with gonadal tumors. Conversely, AFP levels can be normal in 30–40% of HCC patients with small tumors [39]. Ultrasound can detect tumors that are not AFP-secreting, but the technique is operator-dependent and its accuracy in detecting diffuse HCC and in differentiating regenerative/dysplastic nodules