

Hepatitis B virus associated cirrhosis: overview of prognostic and management

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ABSTRACT

Hepatitis B virus (HBV) infection is a global public health problem ; two billion people worldwide have evidence of past or present infection with HBV, and 296 million individuals are chronic carriers (i.e., positive for hepatitis B surface antigen [HBsAg]), of whom approximately 887,000 dies annually from HBV-related liver disease: chronic hepatitis B-associated cirrhosis and hepatocellular carcinoma. There are described some risk factors to the development of cirrhosis to HBV-infected persons: alcohol consumption, HBeAg status, metabolic syndrome, HBV genotypes and variants, and the level of HBV replication. The observation of a strong association between the development and decompensation of cirrhosis as well as between the development of HCC and the level of HBV replication suggests that suppression of HBV replication by long-term antiviral treatment may decrease the risk of complications in patients with HBV-related cirrhosis. The indication for antiviral treatment is given if any HBV DNA levels are detectable in the serum of HBV-infected patients with cirrhosis. Into the new era of antiviral treatment with nucleos(t)ide analogs we can prevent the development of cirrhosis in patients with chronic HBV infection and hepatic decompensation in many patients with HBV-related cirrhosis.

Keywords: cirrhosis, hepatitis B virus, nucleos(t)ide analogs, hepatocellular carcinoma, HBeAg status

Hepatitis B virus (HBV) is a double-stranded DNA virus belonging to the family of hepadnaviruses. HBV infection is a global public health problem. It is estimated that approximately two billion people worldwide have evidence of past or present infection with HBV, and 296 million individuals are chronic carriers (i.e., positive for hepatitis B surface antigen [HBsAg]), of whom approximately 887,000 dies annually from HBV-related liver disease: chronic hepatitis B-associated cirrhosis and hepatocellular carcinoma [1]. The sequelae of chronic hepatitis B virus (HBV) infection vary from an inactive carrier state to the development of cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), extrahepatic manifestations, and death. The epidemiological features and transmission modes of hepatitis B virus infection are exemplified in Table 1.

The diagnosis of **acute HBV infection** is based upon the detection of hepatitis B surface antigen (HBsAg) and immunoglobulin M (IgM) antibody to hepatitis B core antigen (anti-HBc). The diagnosis of

TABLE 1. Epidemiology and modes of transmission of hepatitis B virus infection

	High	Intermediate	Low
Carrier rate	≥8%	2 to 7%	<2%
Geographic distribution	Parts of sub-Saharan Africa (e.g., Western Africa, South Sudan)	Eastern Europe; Central Asia; Southeast Asia; China; Japan; parts of Latin and South America (e.g., Peru, Colombia); Middle East	United States; Canada; Western Europe; Mexico; Australia; New Zealand
Predominant age at infection	Perinatal and early childhood	Early childhood	Adult
Predominant mode of infection	Mother to child; percutaneous	Percutaneous; sexual	Percutaneous; sexual

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TABLE 2. Diagnostic tests to determine phase of acute or chronic hepatitis B virus infection.

HBsAg	HBeAg	IgM anti-HBc	Total anti-HBc	Anti -HBs	Anti -HBe	HBV DNA	ALT	Interpretation
						Acute HBV infection		
+	+	+	±			+++	Elevated	Early phase
		+	±			+	Elevated	Window phase
			+	+	+	±	Normal	Recovery phase
Chronic HBV infection (HBsAg-positive for >6 months +++)								
+	+		+	-	-	(Serum HBV typically >1 million international units/mL) +++	Normal or mildly elevated	Immune-tolerant phase
+	+		+	-	-	(Serum HBV >20,000 international units/mL) ++	Persistently elevated	Immune-active, HBeAg-positive
+	-		+	-	+	(Serum HBV >2000 international units/mL) - to ++	Elevated	Immune-active, HBeAg-negative
+	-		+		+	(Serum HBV ≤2000 international units/mL)	Normal or mildly elevated	Inactive chronic HBV
-	-		(generally +)	±	±	+ in liver; - to + in serum	Normal	Occult HBV

Adapted from Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018; 67:1560 [4]

chronic HBV infection is based upon the persistence of hepatitis B surface antigen (HBsAg) for greater than six months (Table 2).

Advances in molecular biology techniques led to the development of hybridization and polymerase chain reaction (PCR) assays for direct determination of hepatitis B virus DNA (HBV DNA). The diagnosis of HBV infection can also be made by the detection of HBsAg or hepatitis B core antigen (HBcAg) in liver tissues by immunohistochemical staining and of HBV DNA by Southern hybridization, in-situ hybridization, or PCR. Several risk factors for HBV infection have been identified, providing a rationale for screening. Patient groups for rationale screening are: individuals born in areas with high (≥8%) or intermediate (≥2%) prevalence rates for HBV, including immigrants and adopted children; pregnant women; those requiring immunosuppressive therapy; donors of blood, plasma, organs, tissues, or semen; infants born to HBV-infected mothers; household and sexual contacts of HBsAg-positive persons; persons who have ever injected drugs; persons with multiple sexual partners and/or history of sexually transmitted diseases; individuals with chronic liver disease (e.g., cirrhosis, fatty liver disease, autoimmune liver disease, ALT or AST greater than twice the upper limit of normal); individuals with HIV infection. The development of cirrhosis is the most frequent complica-

tion of chronic hepatitis B virus infection [2-4]. There are clinical retrospective and prospective studies that indicated that 4-7% of patients with HBeAg-positive disease and 2-3% of patients with HBeAg-negative disease will develop cirrhosis per year if untreated [5-7]. The development of cirrhosis is mainly mediated by inflammatory activity in the liver, which represents an immune response to infection, and which may not be reflected by elevated ALT levels, but also other factors may contribute. At the first diagnosis of compensated cirrhosis, about 30-70% of patients still have active HBV replication associated with continued progression of liver disease and decreased survival [4,5]. Decompensation of cirrhosis can either develop unperceived over a long period or as a complication of an acute hepatitis flare, which was found to be the cause in 14% of decompensation in one study [6,7]. Another study in 161 patients showed that the risk of hepatic decompensation was four times higher in HBV DNA-positive patients (13-18%) than in HBeAg-negative/HBVDNA-negative patients (4%, P=0.04) during a median follow-up period of 6.6 years [8]. Without treatment, the cumulative probability of survival over 5 years in patients with HBV-related cirrhosis was shown to be 84% in two European studies [4,5]. Fattovich G and colab. illustrated the progression to decompensated HBV-related cirrhosis by Figure 1 [9].

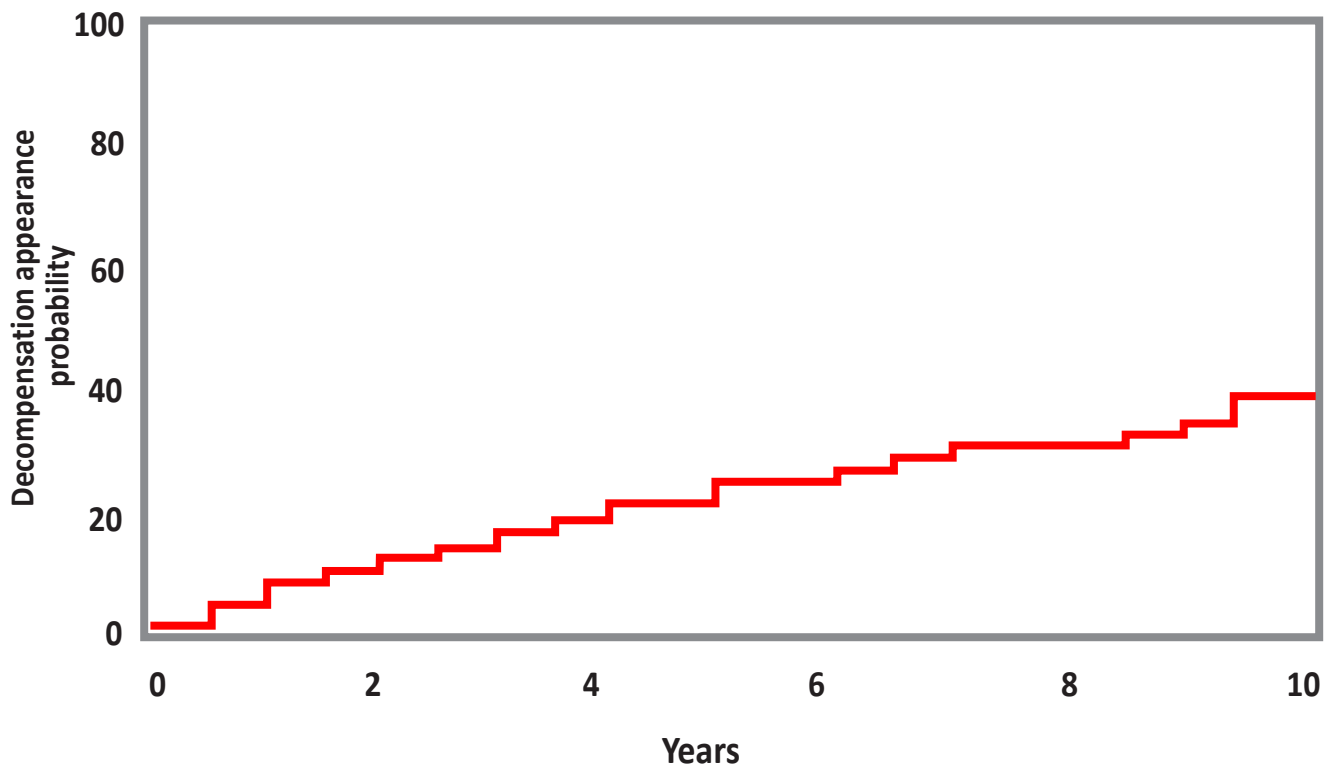


FIGURE 1. Cumulative probability of progression to decompensation in patients with compensated cirrhosis related to hepatitis B virus (HBV) infection.

Adapted from: Fattovich G, Giustina G, Schalm SW, et al. Hepatology. 1995; 21:77 [9]

RISK FACTORS FOR THE DEVELOPMENT OF CIRRHOSIS IN HBV-INFECTED PERSONS

Although a risk tool is the best way to identify an individual's future risk of cirrhosis and identify individuals who should undergo diagnostic testing, knowledge of the risk factors associated with cirrhosis is useful in predicting the likely effect of treatment or avoidance of risk factors, and in planning diagnostic investigations. If the probability of cirrhosis is very low ('good prognosis'), any adverse effects related to invasive diagnostic tests, even if rare, will play a big part in any decision to perform such tests. If instead the probability of cirrhosis is high ('bad prognosis'), the impact of new diagnostic information may be large, and patients may be ready to accept higher risks of diagnostic investigations. There is an increased risk of cirrhosis in people who: have hepatitis B virus infection, have hepatitis C virus infection, misuse alcohol, are obese (BMI of 30 kg/m² or higher) and have type 2 diabetes. To HBV-infected persons there are noted some risk factors to the development of cirrhosis: alcohol consumption, HBeAg status, metabolic syndrome, HBV genotypes and variants, and the level of HBV replication.

A. Alcohol consumption

Hepatitis B virus and alcohol are primary causes of cirrhosis. In individuals with HBV infection and

heavy alcohol use, the progression to cirrhosis and HCC is faster compared with those who consume alcohol without HBV infection and their survival is decreased [10,11]. Alcohol can result in replication of HBV, an increase in oxidative stress, a compromised immune response to the virus and an increase in liver inflammation, all of which can result in progression of cirrhosis. HBV-DNA plays an important role in the progress of cirrhosis and HCC. Previous studies have shown that an elevated serum HBV-DNA level ($\geq 10,000$ copies/mL) is a strong, independent predictor of disease progression to cirrhosis and liver cancer [12,13]. High HBV-DNA load activates the host's immune response to target and destroy infected liver cells, resulting in constant inflammation and necrosis of liver tissue. Repeated periods of immunologic activity with associated liver injury leads to liver fibrosis and HCC [14]. Discussion of whether alcohol synergizes with HBV to accelerate the progress of liver cirrhosis is limited. Certainly HBV-DNA load in the excessive drinking persons was much higher than in the moderate drinking persons. This result was consistent with previous work on HBV transgenic C.B-17 SCID mice fed a standard Lieber-DeCarli ethanol liquid diet, showing viral DNA in serum increased by up to 7-fold in the experimental mice compared with mice fed the control diet [15]. Similarly, Ganne-Carrié et al. [16] showed that in the HEP G2 hepatitis B DNA positive cell line the concentration of HBsAg in-

creased after exposure to ethanol, in both the cells and the culture medium, although the increase was only significant with 200 mM ethanol. Pre-S1 and Pre-S2 envelope proteins levels also increased in the culture medium. In addition, CYP2E1-induced oxidative stress potentiates the ethanol-induced transactivation of HBV [17]. Conclusions can also be drawn from clinical research results combined with laboratory research results that excessive alcohol may influence the HBV-DNA load, whereas moderate drinking may have less influence. Previous studies have shown that an elevated serum HBV-DNA level ($\geq 10,000$ copies/mL) is an independent risk predictor of disease progression to cirrhosis and HCC [18,19]. When the HBV-DNA load is high, specific cytotoxic T cells are at a low level, but HBV can be cleared by non-specific CD8⁺ cells. Excessive drinking can also elevate the HBV-DNA load by weakening the cellular immune response to viral structural proteins [20]. The weakening of the immune response causes the human body to be in an immune-tolerant state, compromising the clearance of HBV by the immune system, resulting in persistent inflammation.

B. HBeAg status

HBeAg positivity at first presentation of cirrhosis is associated with poorer survival, and HBeAg sero-clearance or undetectable HBV DNA during follow-up is associated with better survival [6,7].

C. Metabolic syndrome

Metabolic syndrome may lead to liver manifestations as non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD). Both represent risk factors for hepatic fibrosis and may lead to liver cirrhosis. Metabolic syndrome was strongly associated with increased risk of severe fibrosis and cirrhosis in patients with chronic HBV infection in a recent large-scale study [21]. Parameters associated with superimposed NASH in patients with chronic HBV infection are known components of the metabolic syndrome and include abdominal obesity, dyslipidemia, hyperglycemia, and arterial hypertension [22].

D. HBV genotypes and variants

For HBV, eight genotypes (A–H) have been identified based on an intergroup divergence of > 8% of the whole HBV genome [23,24]. Hepatitis B virus genotypes may play a role in the progression of disease to cirrhosis and HCC [25]. Thus, HBV genotype A is associated with a relatively low risk of development of cirrhosis. On the other hand, genotype C seems to be associated with a higher risk of HCC and cirrhosis than genotypes A, B or D [25-27]. However, because HBV genotypes have a typical geographical distribution, it must be considered that epidemiological and

environmental influences may contribute to the individual risk of developing cirrhosis as well as the mode of HBV transmission, the duration of HBV infection, exposure to liver-toxic agents and secondary diseases, which may have an impact on different dynamics of the development of cirrhosis in different parts of the world. Apart from HBV genotypes, other genetic variations of HBV such as pre-S mutations were also found to influence the development of cirrhosis. Thus, in a long-term follow-up study in 141 HBeAg-negative patients, a two-fold increase in the risk of developing cirrhosis was found in patients in whom pre-S mutations were detectable at baseline [25]. Also, mutations within the core promoter region, namely the mutations A1762T/G1764A and T1768A have been shown to be associated with an increased development of cirrhosis [28,29].

E. The level of HBV replication

Numerous studies have shown that in individuals with HBV infection, the progression to cirrhosis correlates with the serum level of circulating virus, despite their different methodology and study designs [30-32]. In the REVEAL study (Risk Evaluation of Viral Load Elevation and Associated Liver disease/cancer-HBV), which analyzed 3653 mono-infected HBV carriers over 12.5 years of follow-up, elevated HBV DNA levels at baseline were significantly associated with HBeAg positivity, cirrhosis, younger age, male sex, and elevated serum ALT levels [31]. In this study, the incidence of newly diagnosed cases of cirrhosis increased over time in proportion to serum HBV DNA levels at study entry, which were found to be the strongest independent predictors of the development of cirrhosis. A low incidence of the development of cirrhosis was found in patients with HBV DNA of less than 2000 IU/ml. Based on these results, an HBV DNA level of ≥ 2000 IU/ml was chosen as an indication of antiviral treatment for patients without cirrhosis by many recent treatment guidelines [33-35].

Persons who are HBsAg positive **should**:

- have sexual and household contacts vaccinated,
- use barrier protection during sexual intercourse if partner not vaccinated or naturally immune,
- not share toothbrushes or razors,
- cover open cuts and scratches,
- clean blood spills with detergent or bleach,
- not donate blood, organs, or sperm.

Children and adults who are HBsAg positive:

- **can** participate in all activities including contact sports,
- **should not** be excluded from daycare or school participation and should not be isolated from other children,
- **can** share food, utensils, or kiss others.

HBsAg-positive persons should be counseled regarding **prevention of transmission** of HBV:

- Sexual and household contacts of HBsAg-positive persons who are negative for HBV seromarkers should receive hepatitis B vaccination
- Newborns of HBsAg-positive mothers should receive HBIG and hepatitis B vaccine at delivery and complete the recommended vaccination series. In addition, antiviral therapy should be offered to mothers with a high HBV DNA level.
- Persons who remain at risk for HBV infection such as infants of HBsAg-positive mothers, healthcare workers, dialysis patients, and sexual partners of HBsAg-positive persons should be tested for response to vaccination
 - Postvaccination testing should be performed at 1 to 2 months after the last dose, except for infants born to HBsAg-positive mothers in whom testing should be performed at age 9 to 12 months or 1 to 2 months after the last dose of hepatitis B vaccine if immunization is delayed
 - Follow-up testing of vaccine responders is recommended annually for chronic hemodialysis patients.
- Abstinence or only limited use of alcohol is recommended in HBsAg-positive persons
- Persons who are positive only for anti-HBc (HBsAg-negative) and who are from a low endemic area with no risk factors for HBV should be given the full series of hepatitis B vaccine.

IS LIVER BIOPSY USEFUL FOR PATIENTS WITH HBV ASSOCIATED CIRRHOSIS?

Most patients with HBV infection **will not need** a liver biopsy. However, a liver biopsy may be useful in the following scenarios:

1. Patients who have persistently elevated ALT but persistently low HBV DNA to exclude other causes of liver disease.
2. Patients who do not meet criteria for treatment but are at risk for having histologically active or advanced liver disease that would benefit from treatment. These include patients who have ALT levels that are normal or mildly elevated ($<2 \times$ the upper limit of normal [ULN]), an HBV viral load that is persistently elevated (e.g., >6 months), and one of the following risk factors:
 - age >40 years.
 - a family history of HCC

An elevated HBV DNA is considered >2000 international units/mL (104 copies/mL) for HBeAg-neg-

ative patients or $>20,000$ international units/mL (>105 copies/mL) for HBeAg-positive patients. A normal serum ALT level alone in patients with active viral replication does not predict mild or normal histologic findings [36,37]. As an example, one report found that up to 37 percent of patients with persistently normal ALT and HBV DNA levels $>10,000$ copies/mL (approximately >2000 international units/mL) had significant fibrosis and inflammation on liver biopsy. On subgroup analysis, most such patients had an ALT in the high range of normal and were older than 40 years of age. By contrast, two studies in patients in the immune tolerant phase of chronic HBV infection found that despite high HBV DNA levels, most patients had no or minimal fibrosis [38,39]. The decision to obtain a liver biopsy should be made on a case-by-case basis in consultation with a specialist in liver diseases.

TREATMENT IN HBV-RELATED CIRRHOSIS: RISK AND BENEFITS

The aim of antiviral therapy is to stop HBV-associated liver injury, to improve hepatic dysfunction and decrease the risk of mortality. The goals of antiviral therapy are suppression of HBV DNA, loss of HBeAg (in patients who were initially HBeAg-positive), and loss of HBsAg. A sustained viral response, particularly in those who clear both HBeAg and HBsAg, is almost invariably accompanied by normalization of serum ALT, a decrease in necro inflammatory activity, and over time, a decrease in fibrosis as well. Antiviral treatment can also reduce the risk of long-term complications from chronic HBV (e.g., liver failure and hepatocellular carcinoma) as well as the transmission of HBV to others. For some patients, immediate antiviral therapy is indicated, whereas for others, treatment may be deferred with careful monitoring. The observation of a strong association between the development and decompensation of cirrhosis as well as between the development of HCC and the level of HBV replication suggests that suppression of HBV replication by long-term antiviral treatment may decrease the risk of complications in patients with HBV-related cirrhosis [35,40,41]. Antiviral therapy should therefore be begun as soon as the diagnosis is established to suppress HBV replication to undetectable levels as measured with a highly sensitive assay as recommended in recent treatment guidelines. The indication for antiviral treatment is given if any HBV DNA levels are detectable in the serum of HBV-infected patients with cirrhosis. The incidence of HCC is increasing slowly in patients with HBV-related cirrhosis and to date, only a few long-term studies of patients undergoing antiviral treatment are available. A randomized placebo-controlled study in 651 patients showed that lamivudine (LAM) therapy

for a median of 32.4 months could reduce the incidence of HCC in patients with advanced fibrosis or compensated cirrhosis (hazard ratio 0.49, $P = 0.047$) [42]. However, no protective effect was found in patients whose Child-Turcotte-Pugh-Score (CTP) was greater than 7 at the start of LAM treatment. Consistently, in a recent retrospective Greek study in 818 patients (517 with chronic hepatitis B only, 160 with compensated and 56 with decompensated cirrhosis, 85 with unclassified disease) who were retrospectively analyzed for a mean of 4.7 years of successful nucleosides analogue (NUC) treatment, the incidence of HCC in Child B and Child C patients was not decreased [43]. The probability of developing HCC was also strongly associated with an age >60 years. In patients with a longer duration of disease and more significant fibrosis, the conditions for the development of HCC may already exist regardless of the beneficial effects of an antiviral treatment.

How to treat?

For patients with decompensated cirrhosis, **interferon is contraindicated** [44]. Interferon may be used with caution in patients with compensated cirrhosis, normal hepatic synthetic function, and minimal or no evidence of portal hypertension, but **nucleos(t)ide analogs** are safer [51]. **Tenofovir or entecavir** can be used for patients with cirrhosis. We generally prefer entecavir (ETV) for patients with decompensated cirrhosis who are treatment naïve. [52]. Such patients are at risk for acute kidney injury secondary to the hepatorenal syndrome, and entecavir has not been shown to be nephrotoxic, whereas tenofovir disoproxil fumarate (TDF) has been associated with reduced kidney function. In patients with decompensated cirrhosis, the virologic and clinical outcomes with **entecavir** are comparable to tenofovir and better than **adefovir** and **lamivudine**. These findings are highlighted in the following studies:

1. A meta-analysis of 13 trials that included 873 patients compared **entecavir** with **lamivudine** for the treatment of HBV-related decompensated cirrhosis [55]. Entecavir produced significantly lower HBV DNA levels and significantly less drug resistance (0.3 versus 14.3 percent) as compared with lamivudine. Entecavir also resulted in not significantly greater HBeAg seroconversion (32 versus 25 percent at 48 weeks) and lower mortality (6.4 versus 7.9 percent). Both drugs significantly improved liver function, and both were safe and well tolerated.
2. A randomized, open-label study compared **entecavir** (1 mg daily) with **adefovir** (10 mg daily) in 191 patients with HBV and decompensated cirrhosis for up to 96 weeks [54]. The entecavir group had a greater decline in HBV

DNA levels and was more likely to achieve an HBV DNA level of <300 copies/mL (approximately 60 international units/mL: 57 versus 20 percent at week 48). About two-thirds of patients in both groups showed either improvement or stabilization in Child-Turcotte-Pugh status. Adverse events were similar between the groups.

3. A phase II randomized double-blind study evaluated safety in 112 patients with decompensated liver disease who were assigned to treatment with tenofovir, tenofovir plus **emtricitabine**, or **entecavir** [56]. Tenofovir and entecavir were both well tolerated and associated with similar improvements in virological, biochemical, and clinical features.
4. One study included 70 treatment-naïve patients who received **entecavir** (0.5 mg daily) for one year (957). During follow-up, 15 patients dropped out (nine because of death or the need for liver transplantation, and six were lost to follow-up). Of the remaining 55 patients, 49 percent had improvement in Child-Turcotte Pugh score of ≥ 2 points. On intention-to-treat analysis, 92 percent became HBV DNA negative, and 54 percent lost HBeAg. Adverse events were not discussed.
5. A retrospective cohort study compared clinical outcomes in 482 entecavir-treated and 69 treatment-naïve patients (i.e., historical controls who were untreated) with cirrhosis [58]. Entecavir-treated patients who achieved viral suppression had a reduced risk of all clinical outcomes (hazard ratio [HR] 0.51; 95% CI 0.34-0.78), including hepatocellular carcinoma and mortality (liver-related and all-cause mortality).

Although **entecavir** is well tolerated in most patients with cirrhosis, entecavir can result in severe lactic acidosis when used in patients with decompensated cirrhosis [59]. Lactic acidosis may be a class effect of nucleosides and/or related to sepsis, which occurs commonly in hospitalized patients with decompensated cirrhosis.

Tenofovir alafenamide (TAF) is an alternative agent, but efficacy and safety data in patients with decompensated liver disease are lacking. Recently there was reported a new protocol for administration of tenofovir: for most patients who are initiating therapy with tenofovir, it is recommended tenofovir alafenamide (25 mg daily), if available, rather than tenofovir disoproxil fumarate (TDF) (300 mg daily) (**Grade 1B**). Although there is more experience with TDF, tenofovir alafenamide appears to be equally effective and is associated with less renal and bone toxicity. In addition, for most patients who were origi-

nally started on TDF, we suggest switching to tenofovir alafenamide (**Grade 2B**). Lactic acidosis has been reported in patients with severe liver dysfunction receiving entecavir [45]; however, this is likely a class effect of nucleos(t)ide analogs. Several larger studies did not observe any clinical cases of lactic acidosis, but lactate levels were not monitored in those studies. Treatment of such patients should be coordinated with a transplant center. In general, there is no evidence that initiating combination therapy with two nucleos(t)ide analogs (e.g., entecavir and TDF) is superior to monotherapy [53]. Although combination therapy results in more rapid viral suppression in patients with high baseline HBV DNA, it has not been determined whether accelerating viral suppression improves clinical outcomes.

Patients with life-threatening liver disease secondary to HBV should initiate antiviral therapy. This includes patients with acute liver failure (e.g., fulminant acute HBV, severe exacerbation of chronic HBV), as well as those with decompensated cirrhosis and a detectable HBV DNA by polymerase chain reaction (PCR) assay (regardless of the ALT level) [46]. Such patients should also be evaluated for liver transplant.

A summary of the modality of treatment is presented below.

- I. To patients with cirrhosis **compensated** with any ALT and detectable HBV DNA (PCR) with HBV DNA >2000 international units/mL treat them with ETV, TAF, or TDF; treatment should be continued indefinitely.
- II. To patients with cirrhosis **compensated** with any ALT and detectable HBV DNA (PCR) with HBV DNA <2000 international units/mL consider treatment particularly if ALT elevated; close monitoring if treatment is not initiated.
- III. To patients with cirrhosis **decompensated** with any ALT and detectable HBV DNA (PCR) treat immediately, regardless of ALT or HBV DNA levels: ETV preferred. TDF may be used with close monitoring of renal function. There is an indication for liver transplant.
- IV. To patients with cirrhosis **compensated** with any ALT and **undetectable HBV DNA (PCR)** observe, recheck HBV DNA during follow-up, evaluate for other causes of cirrhosis if HBV DNA remains undetectable.
- V. To patients with cirrhosis **decompensated** with any ALT and **undetectable HBV DNA (PCR)** refer for liver transplant, recheck HBV DNA during follow-up, evaluate for other causes of cirrhosis.

Monitoring on therapy

To monitor the response to nucleos(t)ide therapy we measure:

- **HBV DNA** every three months until undetectable for at least two consecutive visits; we then decrease the frequency to every six months.
- **Aminotransferases** every three months; the frequency can be decreased to every six months in patients with an undetectable HBV DNA or normalized ALT.
- **HBeAg** and **anti-HBe** every 12 months in patients who are HBeAg positive to determine if seroconversion has occurred; if HBeAg seroconversion has occurred, we repeat the HBeAg and anti-HBe to confirm the result.
- **HBsAg** should be tested yearly in patients with undetectable HBV DNA.

In addition, we monitor for **adverse reactions** to the antiviral **medications**. If TDF or adefovir are used, **creatinine** and phosphate should be monitored every three to six months. For those with decompensated cirrhosis, the creatinine should be monitored more frequently (e.g., every one to three months). The frequency of monitoring can be reduced (but not eliminated) if tenofovir alafenamide is used, although there are no clear guidelines. Monitoring creatinine every 12 months is reasonable for patients at low risk of renal impairment.

Duration of treatment

For patients with cirrhosis, **lifelong therapy** with oral agents is typically administered to reduce the risk of clinical decompensation if a relapse occurs. Therapy should be continued even with those who are HBeAg-positive and have seroconverted to anti-HBe on nucleos(t)ide therapy, as well as those with decompensated cirrhosis who have resolution of cirrhosis complications on treatment. Although it is possible that treatment may be discontinued in those with compensated cirrhosis who have lost HBsAg, or those who have documentation of cirrhosis regression by histology or noninvasive assessment of liver fibrosis, there is insufficient evidence to guide treatment decisions for this group of patients.

Risk and screening for hepatocellular carcinoma

Chronic HBV infection has been associated with increased risk for HCC [60-63]. While HCC can develop in patients with chronic HBV but without cirrhosis, most patients with HBV who develop HCC will have cirrhosis [64]. Similarly, the annual incidence of HCC among those with HBV infection is higher in patients with cirrhosis compared with no cirrhosis (3.2 versus 0.1 cases per 100 person-years) [65].

In addition to cirrhosis, other HBV-related factors that were associated with HCC risk include:

- High viral load (i.e., HBV DNA levels >106 copies/mL) [66].
- HBeAg positivity (an indicator of a prolonged replication phase) [67].
- HBsAg levels >1000 IU/mL in patients with HBeAg negative chronic HBV with low viral load (i.e., inactive chronic HBV) [63,68,69].
- HBV genotype C [70].
- Male sex (for patients who are HBsAg positive) [68,71].
- Viral coinfection (HCV or hepatitis D virus) [72,73].
- Coinfection with HBV and hepatitis E virus (HEV) was associated with increased HCC risk compared with HEV infection alone [74]. However, coinfection was associated with lower HCC risk compared with HBV infection alone, implying that HEV infection served to mitigate rather than promote the effect of HBV on HCC carcinogenesis.
- HBsAg clearance – Despite a generally favorable prognosis, clearance of HBsAg did not eliminate the risk of HCC [75,76]. In a study including 1271 patients, chronic HBV with average follow-up of 20 years, HCC incidence was lower in patients who were HBsAg negative compared with those who were HBsAg positive (37 versus 196 per 100,000 person-years), but still higher than the general population [76].

Other risk factors that can concurrently exist in persons with HBV infection and are associated with HCC risk include [75,77-81]:

- Age – Young age of HBV acquisition or older age among those with chronic infection.
- Lifestyle factors – Alcohol or tobacco use.
- Blood group B (in males only) [82].
- Family history of HCC [81].

Periodic screening for hepatocellular carcinoma (HCC) should be performed in select patients with chronic HBV. Screening should be performed regardless of antiviral therapy. Several different guidelines issued by the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver, European Organization for Research and Treatment of Cancer (EASL-EORTC), the Japan Society of Hepatology [2,3,47,49,50], provide recommendations for HCC screening: perform ultrasound screening (with or without screening for alpha-fetoprotein) **every six months** for:

- All HBsAg-positive patients with cirrhosis
- HBsAg-positive adults at high risk for HCC: Asian men over 40 years of age; Asian women over 50 years of age; persons with a first-de-

gree family member with a history of HCC; persons with HDV; African Americans people.

2018 Practice Guidance by the American Association for the Study of Liver Diseases recommend HCC surveillance in all patients with cirrhosis (from any cause) who are treatment candidates, which includes the following groups [47]:

- patients with Child-Pugh class A or B
- patients with Child-Pugh class C, only if they are waitlisted for transplantation.

The annual incidence of HCC in these populations exceeds 1.5 percent, a threshold above which surveillance for HCC is thought to be cost effective in the identified subgroups [48]. Surveillance is **not** recommended in patients with Child-Pugh class C due to their limited expected lifespan and low hepatic functional reserve to tolerate treatment for detected cancer.

CONCLUSIONS

Until very recently, hepatitis B virus (HBV)-associated cirrhosis precipitated by alcohol consumption, HBeAg status, metabolic syndrome, HBV genotypes and a high level of HBV replication was often regarded as an irreversible condition. It is associated with strongly increased mortality and a high risk of the development of hepatocellular carcinoma (HCC). But the new era of antiviral treatment with nucleos(t)ide analogs show us how we can prevent the development of cirrhosis in patients with chronic HBV infection and hepatic decompensation in many patients with HBV-related cirrhosis. Nucleos(t)ide analogs treatment also results in better survival and improves recovery of liver function in patients with HBV-related decompensated cirrhosis as well as reverting fibrosis and cirrhosis in many patients. Nucleos(t)ide analogs treatment in patients with cirrhosis should be initiated as early as possible and should result in complete suppression of HBV replication, but the antiviral potency of the different nucleos(t)ide analogs did not influence the survival rate. Treatment with nucleos(t)ide analogs is generally safe and well tolerated in patients with decompensated cirrhosis. Lactic acidosis is a general risk in patients with decompensated cirrhosis; therefore, lactate levels should be monitored in all patients with HBV-related cirrhosis undergoing antiviral treatment. Although treatment can decrease the probability of the development of HCC in patients with cirrhosis, patients with a Child-Turcotte-Pugh-Score (CTP) score ≥ 7 remain at a high risk of developing HCC whatever the long-term response to antiviral treatment may be and thus require life-long screening for HCC.

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