Pediatric hepatitis B treatment

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Abstract: Although the introduction of hepatitis B vaccine has been contributing to the reduction in the prevalence of hepatitis B virus (HBV) carriers worldwide, the treatment of children with chronic HBV infection is a challenge to be addressed. HBeAg seroconversion, which induces low replication of HBV, is widely accepted as the first goal of antiviral treatment in children with chronic hepatitis B. However, spontaneous HBeAg seroconversion is highly expected in children with chronic HBV infection. Therefore, the identification of children who need antiviral treatment to induce HBeAg seroconversion is essential in the management of chronic HBV infection. Guidelines and experts' opinion show how to identify children who should be treated and how to treat them. If decompensated cirrhosis is absent, interferon-alpha is the first-line antiviral treatment. Nucleos(t)ide analogues (NAs), such as lamivudine, adefovir, entecavir and tenofovir, are also available for the treatment of children, although the approval age differs among them. If decompensated cirrhosis is present, NAs are the first-line antivirals. When the emergence of drug-resistant HBV variants is taken into consideration, entecavir (approved for age 2 years or older) and tenofovir (age 12 years or older), which have high genetic barriers, will play a central role in the treatment of HBV infection. However, the optimal duration of NA treatment and adverse events of long-term NA treatment remain unclear in children. In resource-constrained countries and regions, the financial burden of visiting hospitals, receiving routine blood examination and purchasing antiviral drugs is heavy. Moreover, there is no clear evidence that the induction of HBeAg seroconversion by antiviral treatment prevents the progression of liver disease to cirrhosis and hepatocellular carcinoma in children with chronic HBV infection. It is thus imperative to clarify the clinical impact of antiviral treatment in children with HBV infection.

Keywords: Seroconversion; interferon; nucleos(t)ide analogue (NAs); children; hepatocellular carcinoma (HCC)

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Introduction

Unlike in adults, the long-term effectiveness of antiviral treatment for chronic HBV (hepatitis B virus) infection in children has not yet been fully proven. Interferon (IFN) has been used for children with chronic HBV infection since the 1980s (1). However, it is unclear whether IFN therapy for children with chronic HBV infection will prevent disease progression to liver cirrhosis and hepatocellular carcinoma (HCC). In the past decade, several nucleos(t)ide analogues (NAs) have become available for the treatment in children. In addition to the consensus opinions of a US expert panel (2), guidelines have been published by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) 2013 (3), the American Association for the Study of Liver Diseases (AASLD) (4,5) and the Asian Pacific Association for the Study of the Liver (APASL) 2015 (6). Taking these recommendations into consideration, we herein discuss the potential of antiviral treatment for children with HBV infection.

Natural history

The chance of chronicity of HBV infection depends on the age of primary HBV infection. Chronic HBV infection occurs in more than 90% of infants that are infected perinatally. Among children exposed to HBV before 5 years of age, 25–50% develop chronic HBV infection. In individuals with primary HBV infection in adulthood, 5% to 10% will develop chronic HBV infection (2,7,8). In Asia, one of main sources of infection is mother-to-child transmission. Because genotype C is prevalent in Asia, and HBeAg seroconversion tends to occur later in individuals with this genotype compared to those with other HBV genotypes (9), pregnant mothers with chronic HBV infection have a high viral load. And because maternal high viral load is a risk factor for mother-to-child transmission, perinatal infection is common in Asia. On the other hand, genotypes A, E, and D are predominant in Africa. Because the rate of positivity for HBeAg is low in pregnant women in Africa, the chance of mother-to-child transmission is not high. Thus, horizontal transmission through family and household members with chronic HBV infection during early infancy and childhood is frequent (10).

The clinical course of chronic HBV infection is influenced by age at primary infection, gender, transmission route, HBV genotype and environmental factors. Chronic HBV infection is classified into four immunological phases: (I) the immune-tolerant phase; (II) immune-reactive phase (HBeAg-positive chronic hepatitis B); (III) low replicative phase; and (IV) reactivation phase (HBeAg-negative chronic hepatitis B) (2,6,7,11).

The immune-tolerant phase is the first phase in children infected with HBV. In this phase, the host immune is considered to be tolerant to HBV. Therefore, the immune-tolerant phase is characterized by the presence of HBeAg, a high level of serum HBV DNA, and normal or slightly elevated ALT levels. Liver biopsy shows normal histology or minimal histological changes. The duration of the immune-tolerant phase is variable and may last for more than 30 years in perinatally infected children. In contrast, this phase may be short or unrecognized in children who are infected after early infancy. Antiviral treatment is ineffective and not recommended in the immune-tolerant phase (2).

The immune-reactive phase is the second phase and characterized by high, fluctuating or gradually decreasing serum HBV DNA levels, the presence of HBeAg and persistent or intermittent ALT elevation. These ALT flare-ups precede HBeAg seroconversion. After HBeAg seroconversion, the ALT levels become normalized within 6 months (12). However, flare-ups of HBV DNA levels and ALT levels may remain after spontaneous HBeAg seroconversion (13). Liver histology shows active necroinflammation in the immune-reactive phase, as the host immune system begins to recognize HBV as a target and attacks the infected hepatocytes. The immunological response is reflected by the elevation of ALT levels, the decline of serum HBV DNA levels and the clearance of HBeAg with seroconversion to anti-HBe. The longer duration of this phase is associated with cirrhosis and HCC (6-8). The active necroinflammation during HBeAg seroconversion to anti-HBe is presumed to cause liver injury and to increase the risk of both cirrhosis and HCC. The rate of spontaneous HBeAg seroconversion is less than 2% per year among those aged 3 years or less and 4–5% per year in older children (14-16). An American study reported that 25% of Asian Americans underwent spontaneous HBeAg seroconversion by age 17 years and 50% by age 24 years (17). In a Canadian study, 37% of the enrolled children (Asian: 80%; perinatal transmission: 59%) underwent spontaneous HBeAg seroconversion at 14.5 years (18). In contrast to children with perinatal infection, children infected horizontally frequently show spontaneous HBeAg seroconversion. In two Italian studies of children who were mainly infected through horizontal transmission, the rate of spontaneous HBeAg seroconversion was 14–16% per year during the first 10 years of follow-up (19,20).

The third phase, the low-replicative phase, follows HBeAg seroconversion to anti-HBe. This phase is characterized by the absence of HBeAg, the presence of anti-HBe, persistently normal ALT levels, and low serum HBV DNA levels (<2,000 IU/mL). Liver histology shows minimal inflammation and minimal fibrosis. The low-replicative phase is also known as the "inactive carrier state." Because the potential for further disease flare-ups exists and complications such as HCC can supervene in this phase, the 2015 APASL guidelines suggest that the designation "inactive carrier state" is inappropriate for this phase. The majority of children with HCC are positive for anti-HBe and accompanied by cirrhosis. In a long-term follow-up study of Italian children (almost all of them with genotype D and horizontal transmission), those in the low-replicative phase and without cirrhosis showed a favorable outcome (20).

The reactivation phase is the fourth phase. This phase of the disease is also called "HBeAg-negative/anti-HB-positive chronic hepatitis B." After the achievement of HBeAg-

Table 1 Indication and first achievement goal of treatment

Clinical condition	HBeAg	ALT level	Serum HBV DNA (IU/mL)	Liver histology	Treatment	First achievement goal of treatment
HBeAg-positive chronic hepatitis B	Positive	Persistently elevated	>2,000	Moderate/severe; inflammation/fibrosis	IFN, NAs	HBeAg seroconversion
HBeAg-negative chronic hepatitis B	Negative	Persistently elevated	>2,000 or >20,000[†]	Moderate/severe; inflammation/fibrosis	IFN, NAs	Reduction of serum, HBV DNA level; normalization of ALT level
Compensated cirrhosis	Any	Any	Detectable	Cirrhosis	NAs (IFN[‡])	Undetectable HBV DNA
Decompensated cirrhosis	Any	Any	Detectable	Liver biopsy not needed	NAs	Undetectable HBV DNA

[†], European Society for Paediatric Gastroenterology Hepatology and Nutrition guideline, 2013; [‡], although IFN is not contraindicated in patients with compensated cirrhosis, NAs are considered to be safer than IFN.

seroconversion, the majority of patients with anti-HBe remain in the low-replicative phase. However, some patients re-develop significant HBV replication and progress to liver injury. The reactivation phase is usually characterized by the presence of anti-HB, elevated or fluctuating ALT levels, and detectable serum HBV DNA (>2,000 IU/mL). Moderate or severe necroinflammation with variable amounts of fibrosis is observed in liver biopsy. Reactivation of viral replication might sometimes induce the reversion back to the HBeAg-positive state. In a study on adults in Taiwan, 4% of subjects showed HBeAg reversion and 24% had HBeAg-negative chronic hepatitis B for a median of 8.6 years after spontaneous HBeAg seroconversion. Italian pediatric studies with a more than 20-year observation period showed that 4–5% of children with chronic HBV infection developed HBeAg-negative chronic hepatitis B after achieving HBeAg seroconversion (20,21). A recent pediatric study from Taiwan reported that 5.6% of children experienced HBeAg-negative chronic hepatitis B after spontaneous HBeAg seroconversion (22). Moreover, the pre-S2-deletion mutants are associated with HCC in Asian children (23).

Liver cirrhosis and HCC in children

In childhood, liver cirrhosis and HCC is rare. Long-term follow-up pediatric studies including treated children have reported that the prevalence rates of cirrhosis and HCC were 0.2% and 0.5% in Taiwan (24), 2.7% and 0% in the UK (25), 0.6% and 0.6% in Greece (26), 3.6% and 1.8% in Italy (20), 3.8% and 0% in Romania (27), 0.8% and 0.4% in Canada (18), and 0% and 1.5% in Japan (28), respectively. In adults, older age (>40 years), male gender, presence of cirrhosis, family history of HCC, race (Asian, African), high levels of HBV replication, HBV genotype (C > B), HBV variant (core promoter, pre-S), HDV/HCV concurrent infection and aflatoxin exposure are well known as risk factors of HCC (7). In children, however, the risk factors for HCC remain unknown, although two studies from Taiwan have suggested that early HBeAg seroconversion is a risk factor for HCC in children (24,29).

Treatment of children with chronic HBV infection

Who should be treated in childhood?

The aim of antiviral treatment of chronic HBV is to prevent the progression of liver disease. Activated host immunity against infected liver cells causes severe damage to the liver tissue. Therefore, children with a protracted immunoreactive phase (HBeAg-positive chronic hepatitis B) are considered to be indicated for antiviral treatment (*Table 1*). Similarly, the problem of necroinflammation caused by activated host immunity has not yet been resolved in children with HBeAg-negative chronic hepatitis B. The prolongation or re-emergence of liver inflammation after HBeAg seroconversion leads to advanced liver diseases. For this reason, children with HBeAg-negative chronic hepatitis B are considered to be indicated for antiviral treatment (*Table 1*). Cirrhosis is a risk factor for HCC, and is present in the majority of children with HCC (28). Therefore, children with cirrhosis due to chronic HBV infection should be immediately treated even if ALT levels are normal (6,30). If children suffer decompensated cirrhosis, preparation for liver transplantation might be needed. Conversely, children in the immune-tolerant phase should not be treated because antiviral treatment will be less effective in this phase. Unlike children with cirrhosis, children with normal ALT levels are not indicated to receive antiviral treatment regardless of HBeAg status and serum HBV DNA levels. In order to select

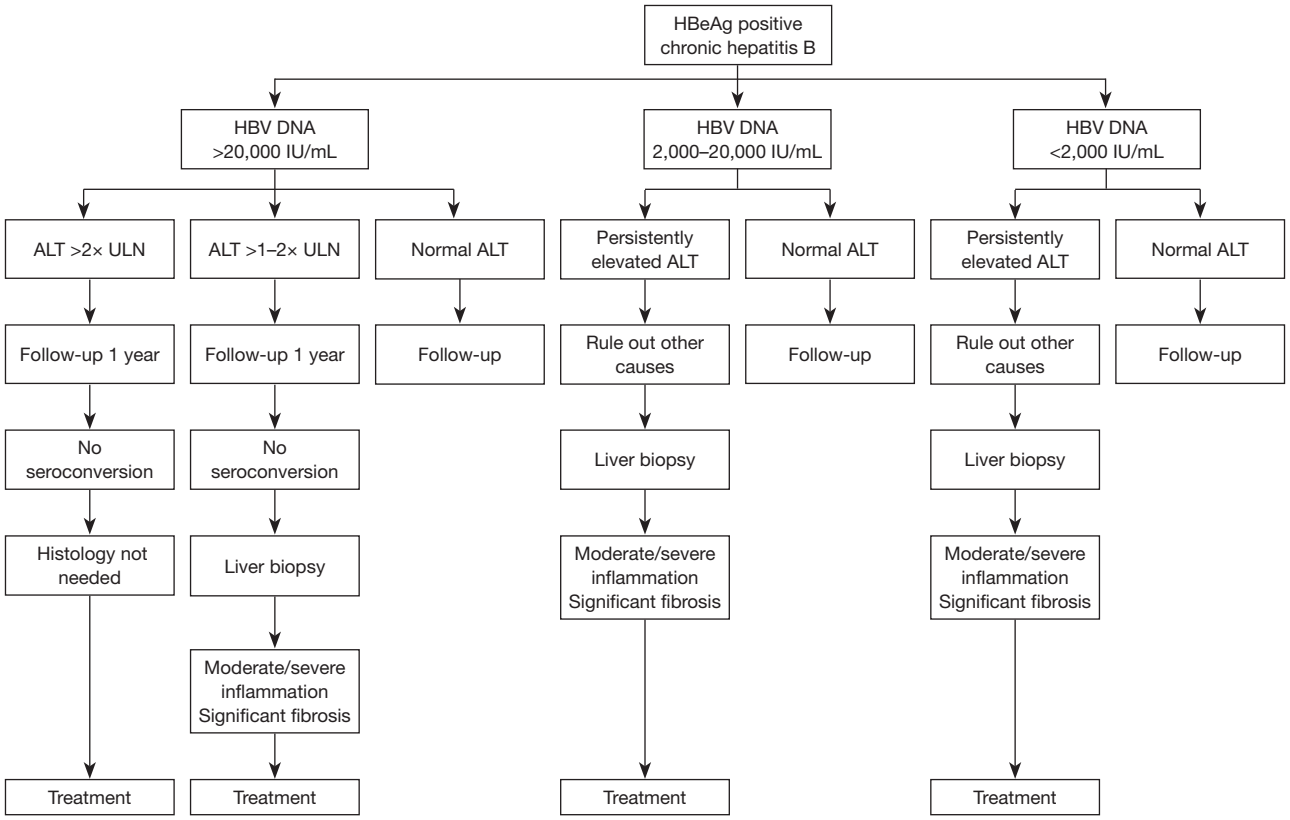

Figure 1 The treatment algorithm for children with HBeAg-positive chronic hepatitis B according to the 2015 guidelines of the Asian Pacific Association for the Study of the Liver. There is no definition of "persistently elevated ALT". However, routine blood examination is required for children every 3 months. If routine blood examination reveals a continuation of ALT elevation, liver biopsy is recommended except for the child with >2× ULN of ALT elevation and high viral load (>20,000 IU/mL). ULN, upper limit of normal.

the children who should be treated with antiviral drugs, the ALT levels (reflecting liver damage), HBeAg status, serum HBV DNA levels (reflecting the viral-replication activity) and liver histology (reflecting disease progression) are evaluated. The algorithm of the U.S. experts' opinion, ESPGHAN guideline 2013 and APASL guideline 2015 comprise these laboratory findings and histologic findings (2,3,6).

APASL guidelines 2015

According to the 2015 APASL guidelines, the treatment algorithms for non-cirrhotic children with chronic hepatitis B are as shown in *Figure 1* (HBeAg-positive) and *Figure 2* (HBeAg-negative). The guidelines recommend that ALT levels and serum HBV DNA levels should be monitored every 3 months. Surveillance for HCC should be performed by ultrasonography and alpha-fetoprotein every 6 months and preferably every 3 months in patients with cirrhosis. Only HBeAg-negative children with persistently normal ALT levels and low viral load (<2,000 IU/mL) should be monitored every 3 to 6 months. In cases of HBeAg-positive chronic hepatitis B with high viral load (>20,000 IU/mL), if the elevation of ALT levels [>2× upper limit of normal (ULN)] persists for 12 months and HBeAg seroconversion does not occur, antiviral treatment is recommended without liver biopsy. If the elevation of ALT levels ranges from 1× ULN to 2× ULN for 12 months, an evaluation of liver histology is required to determine the indication for antiviral treatment. In children with HBeAg-positive chronic hepatitis B with intermediate (2,000–20,000 IU/mL) or low viral load (<2,000 IU/mL), if ALT levels are persistently elevated for any length of time, other disease should be ruled out and liver histology should be evaluated prior to antiviral treatment. In cases of HBeAg-negative chronic hepatitis B with high viral load, a serum HBV DNA level of 2,000 IU/mL is a cut-off (*Figure 2*). If serum

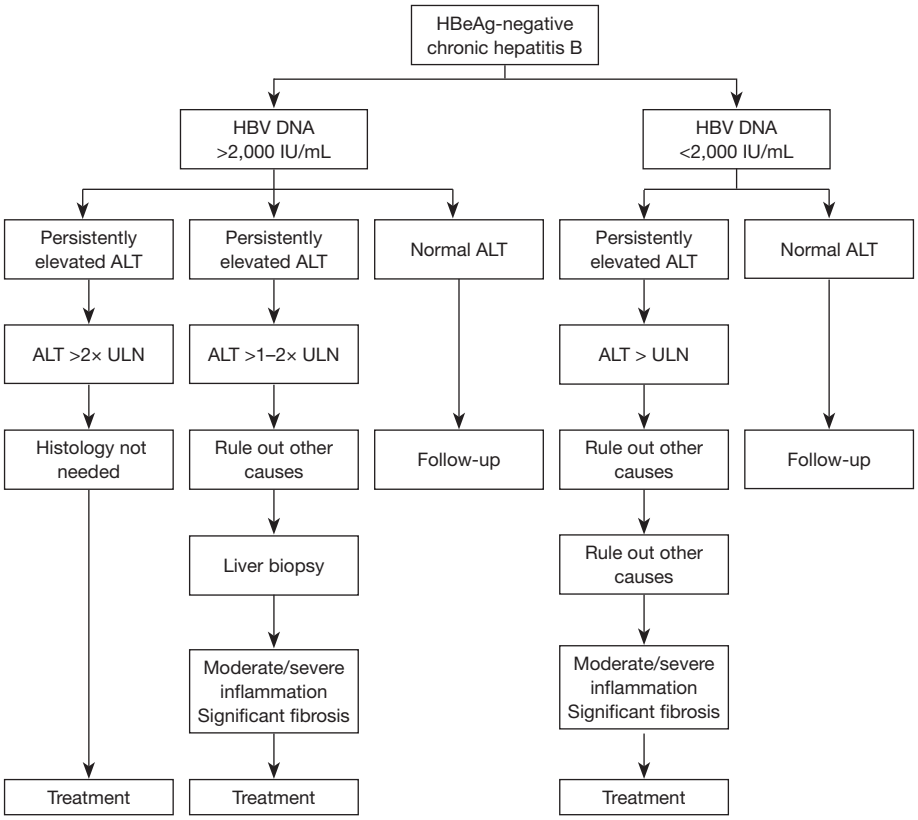

Figure 2 The treatment algorithm for children with HBeAg-negative chronic hepatitis B according to the 2015 guidelines of the Asian Pacific Association for the Study of the Liver. There is no definition of "persistently elevated ALT". However, routine blood examination is required for children every 3 months. If routine blood examination reveals a continuation of ALT elevation, liver biopsy is recommended except for the child with >2× ULN of ALT elevation and intermediate viral load (>2,000 IU/mL). ULN, upper limit of normal.

HBV DNA levels are >2,000 IU/mL and the elevation of ALT levels (>2× ULN) persists (monitor every 3 months) in children with HBeAg-negative chronic hepatitis B, antiviral treatment is recommended without liver biopsy. If the serum HBV DNA levels are >2,000 IU/mL and the elevation of ALT level ranges from 1× ULN to 2× ULN for at least 3–6 months in children with HBeAg-negative chronic hepatitis B, other disease should be ruled out and liver biopsy will be required to evaluate the histology prior to antiviral treatment. Even if the serum HBV DNA levels are <2,000 IU/mL, antiviral treatment is recommended when the ALT value is persistently elevated (monitor every 3 months) and liver histology shows moderate/severe inflammation and significant fibrosis. The 2015 APASL guidelines recommend that children with either decompensated cirrhosis or compensated cirrhosis should be treated. Analysis of the liver histology is not needed to initiate antiviral treatment in children with decompensated cirrhosis.

Consensus opinion of a US panel and ESPGHAN guidelines

Algorithms for selecting children for antiviral treatment have also been proposed by a panel of experts in the US and by the 2013 ESPGHAN guidelines (2,3). The selection algorithms for children with chronic HBV infection are summarized in *Figure 3*. In both the consensus panel opinion and 2013 ESPGHAN guidelines, children with normal ALT levels are not indicated for antiviral treatment. Except in cases of decompensated liver disease, both treatment algorithms always require liver biopsy prior to antiviral treatment. In children with HBeAg-positive chronic hepatitis B, both the consensus panel opinion and 2013 ESPGHAN guidelines have the same indications for antiviral treatment. Children with HBeAg-positive chronic hepatitis B, an elevated ALT level (>1.5× ULN or 60 IU/L) that persists for 6 months and a high level of viremia (serum

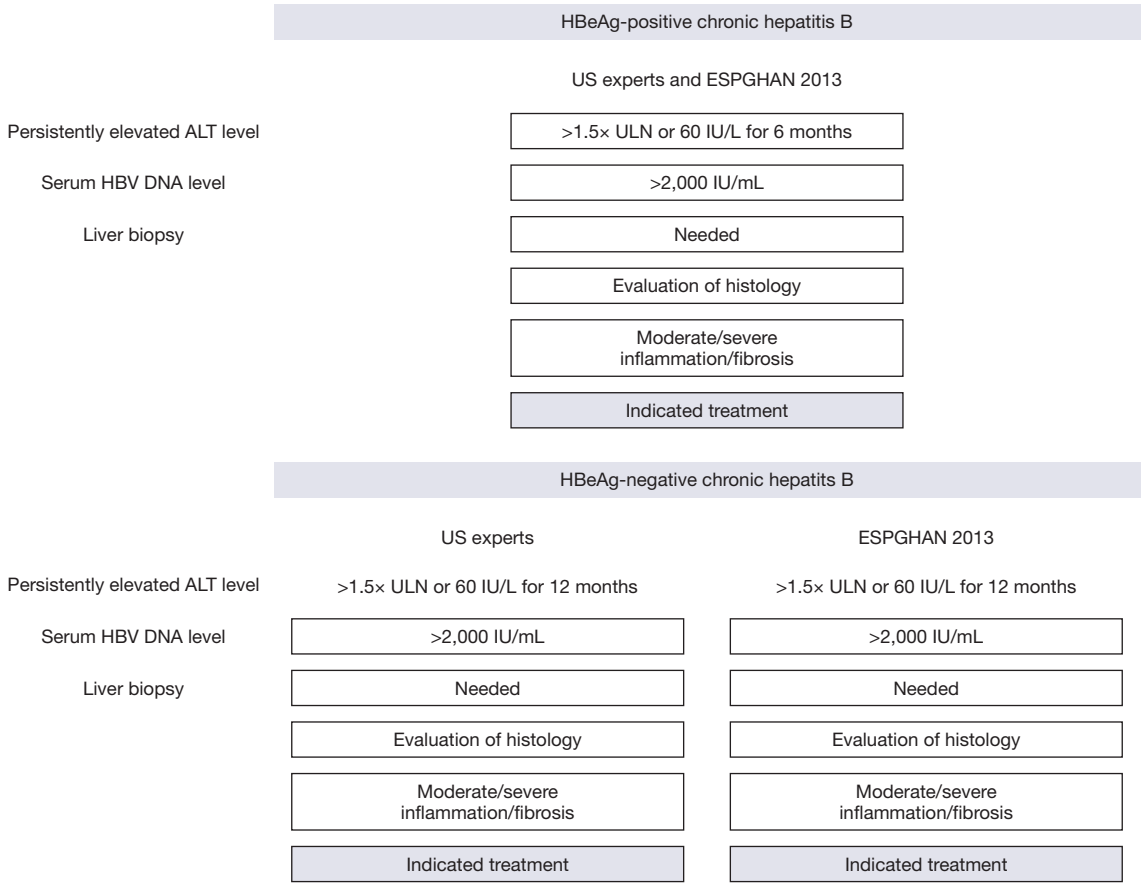

Figure 3 Indications for the treatment of children with chronic hepatitis B based on the consensus opinion of a US panel and the 2013 guidelines of the European Society for Paediatric Gastroenterology Hepatology and Nutrition.

HBV DNA levels >2,000 IU/mL) should be evaluated by liver histology. If moderate to severe inflammation and fibrosis are observed in liver histology, antiviral treatment is indicated. In HBeAg-negative chronic hepatitis B, however, the two algorithms employ different cut-off values for serum HBV DNA. The cut-off value of serum HBV DNA is 2,000 IU/mL in the panel opinion, versus 20,000 IU/mL in the 2013 ESPGHAN guidelines. This cut-off value in the 2013 ESPGHAN guidelines is higher than that in both the 2015 APASL guidelines and the US panel opinion. Presumably, the cut-off value of serum HBV DNA 20,000 IU/mL is adopted form the 2012 EASL clinical guidelines (30). Unlike in HBeAg-positive chronic hepatitis B, the elevation of ALT levels (>1.5× ULN or 60 IU/L) must be observed for 12 months before histological evaluation in HBeAg-negative cases. If liver histology shows moderate to severe inflammation and fibrosis, children with HBeAg-negative chronic hepatitis B are indicated for treatment. Although mild inflammation and fibrosis do not indicate treatment, family history of HCC is considered one indicator for antiviral treatment in children with mild liver damage.

Initial goals of treatment

The ultimate goal of treatment is the achievement of HBsAg seroconversion. However, the initial goals of antiviral treatment differ according to the clinical conditions (*Table 1*). In children with HBeAg-positive chronic hepatitis B, the achievement of HBeAg seroconversion is the first treatment endpoint. The occurrence of HBeAg seroconversion could lead to a low level of HBV replication and the normalization of ALT levels. In children with HBeAg-negative chronic hepatitis B, on the other hand, HBeAg seroconversion cannot be used to assess the treatment response. Because the suppression of serum HBV DNA is associated with an

Table 2 Antiviral drugs licensed for children with chronic HBV infection

Drugs	Approved age	Genetic barrier	Dose of treatment	Duration of treatment
IFN-alpha	≥12 months	No	5–10 M units/m^2 subcutaneous, 3 times a week	24 weeks
Nucleos(t)ide analogues				
Lamivudine	≥2 years	Low	3 mg/kg (Max. 100 mg), oral, once a day	>1 year
Adefovir dipivoxil	≥12 years	Low	10 mg, oral, once a day	>1 year (until 12 months after HBeAg seroconversion)
Entecavir	≥2 years	High	NAs treatment-naïve with compensated liver disease (≥16 years): 0.5 mg oral, once a day	>1 year (until 12 months after HBeAg seroconversion)
			NAs treatment-naïve or lamivudine-experienced children (>2 years and >10 kg), dosing is based on weight: treatment-naïve (10–11 kg/0.15 mg to >30 kg/0.5 mg); lamivudine-experienced (10–11 kg/0.3 mg to >30 kg/1 mg)	
			Lamivudine-refractory or known lamivudine or telbivudine Resistance substitutions rtM204I/V with or without rtL180M, rtL80I/V, or rtV173L (≥16 years): 1 mg oral, once a day	
			Decompensated liver disease (adults): 1 mg oral, once a day	
Tenofovir disoproxil fumarate	≥12 years	High	300 mg, oral, once a day	>1 year (until 12 months after HBeAg seroconversion)

improvement of liver histology, the reduction of serum HBV DNA and the normalization of ALT levels are the primary endpoints of treatment. In children with compensated cirrhosis, prolonged and adequate viral suppression could prevent the expansion of fibrosis and the progression to decompensated cirrhosis. Regression of liver fibrosis is expected by prolonged suppression of viral replication. Therefore, reducing HBV DNA to an undetectable level is the first endpoint in children with compensated cirrhosis. Although IFN is not contraindicated in patients with compensated cirrhosis, NAs are considered to be safer than IFN. Life-long treatment with NAs is recommended in cirrhotic adult patients (6). In children with decompensated cirrhosis, IFN is contraindicated and NAs are the fist-line drugs. Although undetectable serum HBV DNA is the first endpoint in children with decompensated cirrhosis, careful monitoring of liver function is indispensable.

Antiviral drugs and treatment duration

As of July 2016, five drugs (IFN-alpha and four NAs: lamivudine, adefovir, entecavir and tenofovir) had been licensed for the treatment of children with chronic HBV infection by the US Food and Drug Administration (FDA) (*Table 2*). IFN-alpha, which is administered by subcutaneous injection for a finite duration, has a risk of mild to moderate adverse reactions and is inferior to NAs in tolerability, but confers no risk of the emergence of drug-resistant variants and is superior to NAs in terms of the rate of HBsAg seroconversion. NAs, which are administered orally for indefinite duration, have a high efficacy for viral suppression but confer a risk of the induction of drug-resistant variants and unknown adverse reactions over the long-term. For antiviral treatment, the pros and cons of each drug must be taken into consideration. In general, except for children with decompensated cirrhosis, IFN-alpha is the first-line treatment for children with chronic HBV infection.

IFN-alpha

Conventional IFN-alpha can be administered at 12 months of age or older. The dosage of IFN is 5–10 M units per m^2 body surface area for 3 times a week by subcutaneous injection. A multinational randomized control pediatric study showed that HBeAg seroconversion and undetectable serum HBV DNA were achieved in 26% of children treated with IFN-alpha for 24 weeks but only 11% of children without treatment 24 weeks after the cessation of treatment

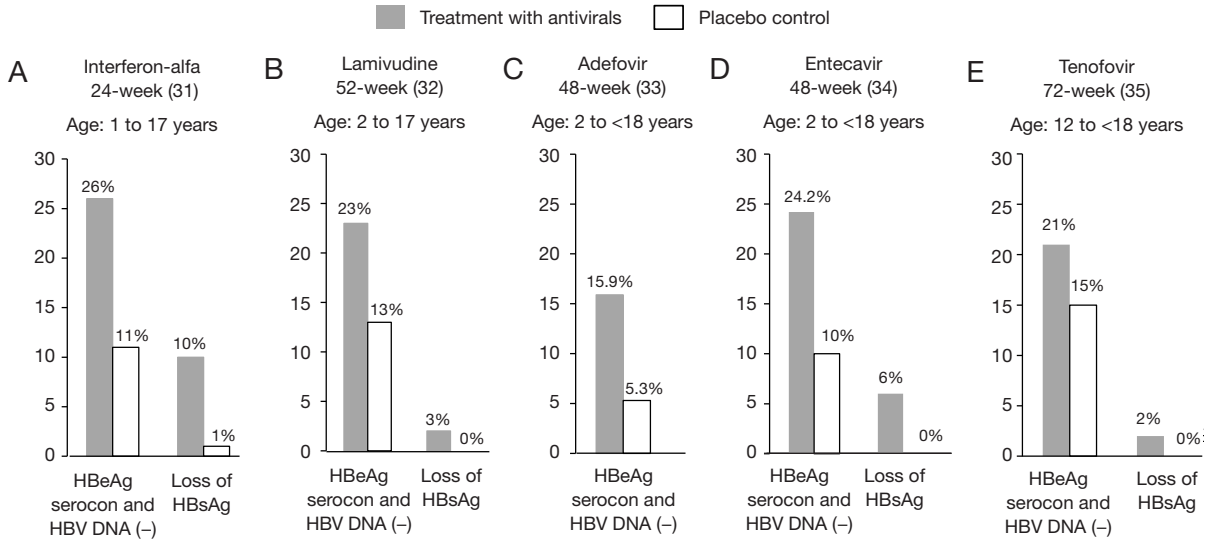

Figure 4 The efficacy of antiviral treatment for children with chronic hepatitis B. (A) Interferon alpha (31); (B) lamivudine (32); (C) adefovir (33); (D) entecavir (34); (E) tenofovir (35).

(P<0.05) (*Figure 4A*) (31). Short-term observation studies similarly showed that treatment with IFN therapy was significantly associated with HBeAg seroconversion and undetectable HBV DNA (36,37). Although a long-term follow-up study from the UK showed that the estimated 5-year HBeAg seroconversion rate was 54% for children treated with IFN plus prednisolone and 12% for untreated children (38), other long-term follow-up studies failed to show the significant effects of IFN therapy on the rate of HBeAg seroconversion in children (39-41). A meta-analysis showed that a sustained response (a combination of HBeAg seroconversion, an undetectable serum HBV DNA and the normalization of ALT levels) and loss of HBsAg were significantly more common in children treated with IFN compared to untreated children (42). Predictors for successful IFN therapy are a low level of serum HBV DNA, elevation of ALT levels, younger age, female gender and active inflammation of liver histology (2,3,31,37). In an adult study, pegylated IFN (PEG-IFN), which has a prolonged half-life and can be administered once a week, was proven to be superior to conventional IFN with respect to HBeAg seroconversion, the suppression of HBV DNA and normalization of ALT levels (43). Although PEG-IFN is available in children with chronic hepatitis C infection, PFG-IFN has not been licensed by the FDA for children with chronic hepatitis B. A clinical trial of PEG-IFN alpha-2a for children (age 3 years to <18, 48-week treatment) with HBeAg-positive chronic hepatitis B is ongoing (44).

Lamivudine

Lamivudine, a nucleoside analogue of cytosine and reverse-transcriptase inhibitor, is the first oral NA approved for the treatment of chronic HBV infection; approval for the drug was granted in 1998 for adults and in 2001 for children aged 2–17 years. Initially, lamivudine was developed to treat patients with human immunodeficiency virus (HIV) infection. As shown in *Figure 4B*, a large pediatric clinical trial (age: 2 to 17 years) of 52-week lamivudine treatment for HBeAg-positive children with chronic hepatitis B from North America, South America and Europe showed that the virologic response (loss of HBeAg and serum HBV DNA) rate was significantly higher in the treated children (23%) than in the placebo-treated children (13%) (P=0.04) (32). In this study, mutations in the tyrosine-methionine-aspartate-aspartate (YMDD) active site motif of the HBV DNA polymerase gene, which is associated with drug-resistance, was observed in 19% of treated children at 52 weeks. The cumulative rate of lamivudine-resistant variants in adults was as follows: year 1, 23%; year 2, 46%; year 3, 55%; year 4, 71%; year 5, 80% (6). In another report, however, although prolonged duration of lamivudine treatment clearly increased the virologic response rate, the emergence of YMDD mutations was also increased in treated children (45). Higher ALT levels, low viral load and older age are predictors of HBeAg clearance in children treated with lamivudine (46). Although lamivudine is well-tolerated

and inexpensive, this drug is not considered to be a first-line treatment for children with chronic HBV infection due to the low genetic barrier to drug-resistance.

Adefovir dipivoxil

Adefovir dipivoxil is a prodrug that is rapidly converted to adefovir after oral administration. Adefovir, an analogue of adeno monophosphate and an inhibitor of viral DNA polymerase, was approved by the FDA for treatment of chronic HBV infection in 2002 for adults and in 2008 for children aged 12–17 years. Adefovir was also initially developed as an antiretroviral drug for HIV infection, but was abandoned due to the high rate of nephrotoxicity at high doses. Although the suppression of viral replication is dependent on the dose of adefovir, a suboptimal dose (10 mg daily) has been approved to minimize nephrotoxicity (47). Adefovir exhibits potent antiviral activity against lamivudine-resistant HBV as well as the wild-type HBV. Therefore, either monotherapy with adefovir or a combination therapy of lamivudine plus adefovir is effective for lamivudine-resistant chronic hepatitis (48). Although the rate of emergence of drug-resistant variants is lower for adefovir than lamivudine, the incidence of drug-resistant variants increases with time of treatment. The cumulative rate of adefovir-resistant variants in adults is as follows: year 1, 0%; year 2, 3%; year 3, 11%; year 4, 18%; year 5, 29% (6). As shown in *Figure 4C*, a large pediatric study (subjects aged 2 to <18 years) of 48-week adefovir treatment conducted in North America and Europe showed that the frequency of HBeAg seroconversion in treated children was higher but not significantly higher than that in the placebo-treated children (treated *vs*. placebo-treated: 15.9% *vs*. 5.3%, P=0.051) at the end of treatment (33). In this study, the combination of HBeAg seroconversion, HBV DNA <1,000 copies /mL and normalization of ALT levels was observed in 10.7% of the treated children and 0% of the placebo-treated children (P=0.009) at the end of treatment. However, adefovir was found to be no more effective than placebo in children aged 2–11 years (33). Adefovir exhibited no adverse effect on renal function, and no adefovir-resistant variant was detected at the end of the 48-week treatment period (33). A pediatric study from Korea evaluated the efficacy of 48-week treatment with adefovir for children who developed lamivudine-resistance during lamivudine treatment (49). In that study, HBV DNA clearance at 24 weeks was significantly higher in children treated with the combination of lamivudine plus adefovir than in children treated with adefovir monotherapy (combination therapy, 50%; monotherapy, 0%; P=0.03). Because entecavir and tenofovir, which have more potent antiviral activity and a higher genetic barrier to resistance, are now available for children, the benefit of adefovir has become limited. In the 2015 APASL guidelines, add-on treatment of adefovir is recommended for adults with lamivudine resistance and entecavir resistance (6).

Entecavir

In 2005, entecavir was approved by the FDA for adults and adolescents (16 years of age or older) and in 2014 it was approved for children aged 2 or older. Entecavir is a potent inhibitor of HBV DNA polymerase, with 30- to 2,200-fold greater potency than lamivudine for reducing viral DNA replication *in vitro* (50). Moreover, entecavir has a high genetic barrier to drug resistance. A comparison of entecavir and lamivudine for adults with HBeAg-positive chronic hepatitis B showed that the rates of histological improvement (72% *vs*. 62%, P=0.009), undetectable serum HBV DNA (67% *vs*. 36%, P<0.001), and normalization of ALT levels (68% *vs*. 60%, P=0.02) were all significantly higher in patients treated with entecavir than in patients treated with lamivudine at the end of a 48-week treatment period (51). However, there was no significant difference in the rate of HBeAg seroconversion between entecavir (21%) and lamivudine (18%). Additionally, entecavir is effective for the treatment of lamivudine-refractory chronic hepatitis B. A comparison of entecavir and lamivudine for adults with lamivudine-refractory HBeAg-positive chronic hepatitis B showed that the rates of histological improvement (55% *vs*. 28%, P<0.001), undetectable serum HBV DNA (19% *vs*. 1%, P<0.001), and normalization of ALT levels (61% *vs*. 22%, P<0.001) were all significantly higher in patients treated with entecavir than in patients treated with lamivudine at the end of the 48-week treatment period (52). Although there was no significant difference in the rate of HBeAg seroconversion between entecavir (8%) and lamivudine (4%), the extension of the treatment period to 96 weeks resulted in a significantly higher rate of HBeAg seroconversion in children treated with entecavir (16%) than in patients treated with lamivudine (4%) (P=0.0012) (53). However, entecavir has shown 8-fold lower activity *in vitro* against lamivudine-resistant variants compared to the wild-type virus (54). In patients with lamivudine-refractory disease, a higher dose of entecavir is required to achieve adequate viral suppression. The emergence of entecavir-

resistant variants is closely associated with lamivudine-resistant substitutions (55). Therefore, entecavir is a potent treatment for NA-treatment-naïve patients, but not an optimal treatment for patients with lamivudine resistance (6). Recently, a large multinational pediatric study (age 2 to <18 years) of 48-week entecavir treatment for patients with NA-treatment-naïve HBeAg-positive chronic hepatitis B showed that the rates of undetectable serum HBV DNA (49.2% *vs*. 3.3%, P<0.0001), normalization of ALT levels (67.5% *vs*. 23.3%, P<0.0001) and HBeAg seroconversion (24.2% *vs*. 10.0%, P=0.021) were all significantly higher in children treated with entecavir than in children treated with placebo (*Figure 4D*) (34). In the pediatric study, a pretreatment HBV DNA level <8 $\log_{10}$ IU/mL and non-D HBV genotype were significant predictors of virologic response to entecavir. The safety profile of entecavir was similar to placebo. However, the cumulative rate of resistant variants was 0.6% at year 1 and 2.6% at year 2 of treatment (34). These figures are slightly higher than those in adults (<1% at year 2) (6). Further studies are necessary to evaluate whether the cumulative incidence of entecavir-resistant variants is higher in children compared to adults.

Tenofovir disoproxil fumarate

Tenofovir disoproxil fumarate is a prodrug of tenofovir, a nucleotide analogue. Tenofovir is a potent inhibitor of HIV reverse transcriptase and HBV polymerase. It remains equally effective against wild-type and lamivudine-resistant HBV. Tenofovir was first licensed for the treatment of HIV infection in 2001. Tenofovir was also licensed for adults with chronic HBV infection in 2008 and children (aged 12 years or older) with chronic HBV infection in 2014. Although tenofovir is similar in structure to adefovir, it has lower nephrotoxicity than adefovir. Therefore, a higher dose is used for treatment (300 mg tenofovir *vs*. 10 mg adefovir). In adults with chronic HBV infection, a head-to-head comparison study of 48-week treatment with tenofovir or adefovir showed that the rate of viral suppression was significantly higher in patients treated with tenofovir than in patients treated with adefovir (HBeAg-positive patients: tenofovir, 76%; adefovir, 13%; P<0.001; HBeAg-negative patients: tenofovir, 93%; adefovir, 63%; P<0.001). In the HBeAg-positive patients, the rates of normalization of ALT levels and HBsAg loss were significantly higher in patients treated with tenofovir than in patients treated with adefovir (ALT normalization: tenofovir, 68%; adefovir, 54%; P=0.03; HBsAg loss: tenofovir, 3.2%; adefovir, 0%; P=0.02) (56). In a retrospective study evaluating the efficacy of tenofovir in adults with chronic hepatitis B who were refractory to lamivudine and had high viral load during adefovir therapy, introduction of tenofovir led to undetectable HBV DNA in 19 of 20 patients within a median of 3.5 months (57). In addition, 10 of 14 patients who exhibited elevation of ALT achieved a normalization of ALT levels during the follow-up period (median 12 months) (57). A meta-analysis reported that tenofovir and entecavir were the most potent oral antivirals for HBeAg-positive patients and tenofovir was the most effective treatment for HBeAg-negative patients (58). As shown in *Figure 4E*, a pediatric study (age: 12 to <18 years; the vast majority of children had HBeAg-positive chronic hepatitis B and had experienced NA therapy) of 72-week tenofovir treatment conducted in Europe and the US showed that the rates of undetectable serum HBV DNA (tenofovir: 89%; placebo: 0; P<0.001), normalization of ALT levels (tenofovir: 74%; placebo: 31%; P<0.001) and HBeAg seroconversion (tenofovir: 21%; placebo: 15%; not significant) were higher in children treated with tenofovir than in children treated with placebo (35). The treatment response was not affected by prior treatment. No resistance to tenofovir developed over the 72-week study period. The frequency of adverse events in children treated with tenofovir was the same as that in children treated with placebo. In addition to nephrotoxicity, the reduction of bone mineral density has been reported in patients with HIV infection receiving long-term tenofovir treatment (59,60). However, there was no child treated with tenofovir who met the safety endpoint of a 6% decrease in spine bone mineral density during the 72-week treatment period in the HBV pediatric study (35). Tenofovir-resistant variants have not been detected yet (6). Tenofovir is not only a first-line treatment for treatment-naïve patients, but also the key therapy for lamivudine-refractory patients. A phase 3 clinical trial of tenofovir disoproxil fumarate (72-week treatment) for children aged 2 to <12 years with chronic HBV infection is ongoing (61).

Treatment for antiviral resistance in children

The 2015 APASL guidelines recommend that tenofovir (>12 years of age) or IFN (<12 years of age) should be used for the treatment of children who develop lamivudine resistance. When adefovir resistance develops, the guidelines recommend that entecavir (>2 years of age) or tenofovir (>12 years of age) should be used if the child has no history of NA treatment before receiving adefovir (6).

Optimal duration of NA treatment

There is no finite duration of NA treatment. In the clinical trials, NAs are usually administered for 48 weeks or more. HBeAg seroconversion is widely accepted as a therapy endpoint. The 2012 EASL guidelines and 2015 APASL guidelines recommend that NA treatment be continued for at least one year after HBeAg seroconversion occurs (6,30). In the patients with HBeAg-negative hepatitis, the continuation of NA treatment until HBsAg loss is recommended due to the high relapse rate after discontinuation (6).

Treatment of children with acute HBV infection

Children with acute HBV infection are usually asymptomatic. Those with fulminant hepatitis, severe acute hepatitis and protracted acute hepatitis might benefit from NA treatment. Lamivudine, adefovir, entecavir and tenofovir are considered acceptable options. IFN is contraindicated (6). Although an optimal duration of NA treatment has not been established, it is recommended that NA treatment be continued until HBsAg clearance, or at least 3 months after HBsAg seroconversion, or 1 year after HBeAg seroconversion without HBsAg loss (6,30).

Conclusions

Will antiviral drugs be able to improve the prognosis of children with chronic HBV infection? Because cirrhosis and HCC are rare in childhood, it will continue to be quite difficult to evaluate the impact of antiviral treatment on the prevention of cirrhosis and HCC in children. Nonetheless, we must make every effort to answer this question.

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Footnote

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References

1. Hashida T, Sawada T, Esumi N, et al. Therapeutic effects of human leukocyte interferon on chronic active hepatitis B in children. J Pediatr Gastroenterol Nutr 1985;4:20-5.
2. Jonas MM, Block JM, Haber BA, et al. Treatment of children with chronic hepatitis B virus infection in the United States: patient selection and therapeutic options. Hepatology 2010;52:2192-205.
3. Sokal EM, Paganelli M, Wirth S, et al. Management of chronic hepatitis B in childhood: ESPGHAN clinical practice guidelines: consensus of an expert panel on behalf of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition. J Hepatol 2013;59:814-29.
4. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009;50:661-2.
5. Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63:261-83.
6. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10:1-98.
7. Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. J Hepatol 2008;48:335-52.
8. Paganelli M, Stephenne X, Sokal EM. Chronic hepatitis B in children and adolescents. J Hepatol 2012;57:885-96.
9. Livingston SE, Simonetti JP, Bulkow LR, et al. Clearance of hepatitis B e antigen in patients with chronic hepatitis B and genotypes A, B, C, D, and F. Gastroenterology 2007;133:1452-7.
10. Kramvis A, Kew MC. Epidemiology of hepatitis B virus in Africa, its genotypes and clinical associations of genotypes. Hepatol Res 2007;37:S9-S19.
11. Hadziyannis SJ. Natural history of chronic hepatitis B in Euro-Mediterranean and African countries. J Hepatol 2011;55:183-91.
12. Marx G, Martin SR, Chicoine JF, et al. Long-term follow-up of chronic hepatitis B virus infection in children of different ethnic origins. J Infect Dis 2002;186:295-301.
13. Ni YH, Chang MH, Chen PJ, et al. Viremia profiles in children with chronic hepatitis B virus infection and spontaneous e antigen seroconversion. Gastroenterology 2007;132:2340-5.
14. Chang MH. Hepatitis B virus infection. Semin Fetal Neonatal Med 2007;12:160-7.
15. Chu CM, Liaw YF. Chronic hepatitis B virus infection acquired in childhood: special emphasis on prognostic and therapeutic implication of delayed HBeAg seroconversion. J Viral Hepat 2007;14:147-52.
16. Chang MH, Hsu HY, Hsu HC, et al. The significance

of spontaneous hepatitis B e antigen seroconversion in childhood: with special emphasis on the clearance of hepatitis B e antigen before 3 years of age. Hepatology 1995;22:1387-92.
17. Evans AA, Fine M, London WT. Spontaneous seroconversion in hepatitis B e antigen-positive chronic hepatitis B: implications for interferon therapy. J Infect Dis 1997;176:845-50.
18. Popalis C, Yeung LT, Ling SC, et al. Chronic hepatitis B virus (HBV) infection in children: 25 years' experience. J Viral Hepat 2013;20:e20-6.
19. Ruiz-Moreno M, Otero M, Millan A, et al. Clinical and histological outcome after hepatitis B e antigen to antibody seroconversion in children with chronic hepatitis B. Hepatology 1999;29:572-5.
20. Bortolotti F, Guido M, Bartolacci S, et al. Chronic hepatitis B in children after e antigen seroclearance: final report of a 29-year longitudinal study. Hepatology 2006;43:556-62.
21. Iorio R, Giannattasio A, Cirillo F, et al. Long-term outcome in children with chronic hepatitis B: a 24-year observation period. Clin Infect Dis 2007;45:943-9.
22. Wu JF, Chiu YC, Chang KC, et al. Predictors of hepatitis B e antigen-negative hepatitis in chronic hepatitis B virus-infected patients from childhood to adulthood. Hepatology 2016;63:74-82.
23. Abe K, Thung SN, Wu HC, et al. Pre-S2 deletion mutants of hepatitis B virus could have an important role in hepatocarcinogenesis in Asian children. Cancer Sci 2009;100:2249-54.
24. Wen WH, Chang MH, Hsu HY, et al. The development of hepatocellular carcinoma among prospectively followed children with chronic hepatitis B virus infection. J Pediatr 2004;144:397-9.
25. Boxall EH, Sira J, Standish RA, et al. Natural history of hepatitis B in perinatally infected carriers. Arch Dis Child Fetal Neonatal Ed 2004;89:F456-60.
26. Zacharakis G, Koskinas J, Kotsiou S, et al. Natural history of chronic hepatitis B virus infection in children of different ethnic origins: a cohort study with up to 12 years' follow-up in northern Greece. J Pediatr Gastroenterol Nutr 2007;44:84-91.
27. Manzat Saplacan RM, Mircea PA, Valean SD, et al. The long-term evolution of chronic hepatitis B acquired in childhood. J Gastrointestin Liver Dis 2009;18:433-8.
28. Komatsu H, Inui A, Sogo T, et al. Chronic hepatitis B virus infection in children and adolescents in Japan. J Pediatr Gastroenterol Nutr 2015;60:99-104.
29. Hsu HC, Wu MZ, Chang MH, et al. Childhood hepatocellular carcinoma develops exclusively in hepatitis B surface antigen carriers in three decades in Taiwan. Report of 51 cases strongly associated with rapid development of liver cirrhosis. J Hepatol 1987;5:260-7.
30. European Association For The Study Of The Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012;57:167-85.
31. Sokal EM, Conjeevaram HS, Roberts EA, et al. Interferon alfa therapy for chronic hepatitis B in children: a multinational randomized controlled trial. Gastroenterology 1998;114:988-95.
32. Jonas MM, Mizerski J, Badia IB, et al. Clinical trial of lamivudine in children with chronic hepatitis B. N Engl J Med 2002;346:1706-13.
33. Jonas MM, Kelly D, Pollack H, et al. Safety, efficacy, and pharmacokinetics of adefovir dipivoxil in children and adolescents (age 2 to <18 years) with chronic hepatitis B. Hepatology 2008;47:1863-71.
34. Jonas MM, Chang MH, Sokal E, et al. Randomized, controlled trial of entecavir versus placebo in children with hepatitis B envelope antigen-positive chronic hepatitis B. Hepatology 2016;63:377-87.
35. Murray KF, Szenborn L, Wysocki J, et al. Randomized, placebo-controlled trial of tenofovir disoproxil fumarate in adolescents with chronic hepatitis B. Hepatology 2012;56:2018-26.
36. Ruiz-Moreno M, Rua MJ, Molina J, et al. Prospective, randomized controlled trial of interferon-alpha in children with chronic hepatitis B. Hepatology 1991;13:1035-9.
37. Gregorio GV, Jara P, Hierro L, et al. Lymphoblastoid interferon alfa with or without steroid pretreatment in children with chronic hepatitis B: a multicenter controlled trial. Hepatology 1996;23:700-7.
38. Boxall EH, Sira J, Ballard AL, et al. Long-term follow-up of hepatitis B carrier children treated with interferon and prednisolone. J Med Virol 2006;78:888-95.
39. Bortolotti F, Jara P, Barbera C, et al. Long term effect of alpha interferon in children with chronic hepatitis B. Gut 2000;46:715-8.
40. Vo Thi Diem H, Bourgois A, Bontems P, et al. Chronic hepatitis B infection: long term comparison of children receiving interferon alpha and untreated controls. J Pediatr Gastroenterol Nutr 2005;40:141-5.
41. Hsu HY, Tsai HY, Wu TC, et al. Interferon-alpha treatment in children and young adults with chronic hepatitis B: a long-term follow-up study in Taiwan. Liver Int 2008;28:1288-97.

42. El Sherbini A, Omar A. Treatment of children with HBeAg-positive chronic hepatitis B: a systematic review and meta-analysis. Dig Liver Dis 2014;46:1103-10.
43. Cooksley WG, Piratvisuth T, Lee SD, et al. Peginterferon alpha-2a (40 kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B. J Viral Hepat 2003;10:298-305.
44. A study of Pegasys (Peginterferon Alfa-2a) versus untreated control in children with HBeAg positive chronic Hepatitis B. Available online: https://clinicaltrials.gov/ct2/show/NCT01519960
45. Sokal EM, Kelly DA, Mizerski J, et al. Long-term lamivudine therapy for children with HBeAg-positive chronic hepatitis B. Hepatology 2006;43:225-32.
46. Hagmann S, Chung M, Rochford G, et al. Response to lamivudine treatment in children with chronic hepatitis B virus infection. Clin Infect Dis 2003;37:1434-40.
47. Marcellin P, Chang TT, Lim SG, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. N Engl J Med 2003;348:808-16.
48. Peters MG, Hann HW, Martin P, et al. Adefovir dipivoxil alone or in combination with lamivudine in patients with lamivudine-resistant chronic hepatitis B. Gastroenterology 2004;126:91-101.
49. Chu M, Cho SM, Choe BH, et al. Virologic responses to add-on adefovir dipivoxil treatment versus entecavir monotherapy in children with lamivudine-resistant chronic hepatitis B. J Pediatr Gastroenterol Nutr 2012;55:648-52.
50. Robinson DM, Scott LJ, Plosker GL. Entecavir: a review of its use in chronic hepatitis B. Drugs 2006;66:1605-22.
51. Chang TT, Gish RG, de Man R, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med 2006;354:1001-10.
52. Sherman M, Yurdaydin C, Sollano J, et al. Entecavir for treatment of lamivudine-refractory, HBeAg-positive chronic hepatitis B. Gastroenterology 2006;130:2039-49.
53. Sherman M, Yurdaydin C, Simsek H, et al. Entecavir therapy for lamivudine-refractory chronic hepatitis B: improved virologic, biochemical, and serology outcomes through 96 weeks. Hepatology 2008;48:99-108.
54. Baldick CJ, Eggers BJ, Fang J, et al. Hepatitis B virus quasispecies susceptibility to entecavir confirms the relationship between genotypic resistance and patient virologic response. J Hepatol 2008;48:895-902.
55. Tenney DJ, Rose RE, Baldick CJ, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naive patients is rare through 5 years of therapy. Hepatology 2009;49:1503-14.
56. Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med 2008;359:2442-55.
57. van Bömmel F, Zollner B, Sarrazin C, et al. Tenofovir for patients with lamivudine-resistant hepatitis B virus (HBV) infection and high HBV DNA level during adefovir therapy. Hepatology 2006;44:318-25.
58. Woo G, Tomlinson G, Nishikawa Y, et al. Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. Gastroenterology 2010;139:1218-29.
59. Gafni RI, Hazra R, Reynolds JC, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: impact on bone mineral density in HIV-infected children. Pediatrics 2006;118:e711-8.
60. Cassetti I, Madruga JV, Suleiman JM, et al. The safety and efficacy of tenofovir DF in combination with lamivudine and efavirenz through 6 years in antiretroviral-naive HIV-1-infected patients. HIV Clin Trials 2007;8:164-72.
61. Evaluating the efficacy, safety and tolerability of tenofovir df in pediatric patients with chronic hepatitis B infection. Available online: https://clinicaltrials.gov/ct2/show/NCT01651403

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