Review

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Chronic hepatitis B in children and adolescents

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Introduction

Hepatitis B virus (HBV) infection is still one of the most important causes of liver disease, with 2 billion people infected worldwide and more than 600,000 deaths each year, caused in 94% of cases by chronic infection-related cirrhosis and hepatocellular carcinoma (HCC) [1–3]. The World Health Organization (WHO) estimates more than 360 million persons being chronic carriers worldwide (6% of the world population). The incidence of HBV infection has been declining over the last two decades thanks to the introduction of universal immunization programs and the implementation of blood-donor screening. Nevertheless, a significant number of adults and children are still infected each year, the latter often developing chronic infection and requiring an appropriate follow-up. In spite of a rather benign course of chronic disease during childhood and adolescence, HBV chronic carriers have a lifetime risk of developing HCC up to 25%, and an incidence of cirrhosis of 2–3% per year [4]. Safe and partially effective antiviral therapies are available, but few are licensed for use in children, and an accurate selection of subjects to treat and of the right timing for treatment is needed to optimize efficacy and reduce viral resistance.

Epidemiology

HBV is transmitted by percutaneous and mucous membrane exposure to infectious blood, semen, vaginal secretions and saliva [5]. The extreme resilience of HBV, allowing its survival for more than a week on dry surfaces, explains the increased risk of horizontal intrafamilial transmission and the need of carriers counseling and household members vaccination [6–9]. Nonetheless, after 20 years from the introduction of immunization programs, most infants and children are protected against HBV [10], and chronic carriers should not be isolated in schools or prevented from practicing sports. Transmission occurs rarely in childcare settings [7], but the risk is higher in detention centers, where adolescents are less likely to be immunized and have high-risk behaviors [11,12].

In highly endemic areas, infection occurs mainly in infancy and early childhood, with mother-to-child transmission accounting for more than half of chronic infections. After exposure, the risk of developing CHB is indeed higher for newborns (90%) than for infants and children <5 years of age (25–30%) or adolescents and adults (<5%) [13,14]. To further reduce mother-to-child transmission, WHO recommends the administration of both the vaccine and hepatitis B immunoglobulins (HBIG) to newborns of HBsAg-positive mothers within 24 h from birth (90–98% protection rate) [7,15–17]. HBIG administration to newborns of HBeAg-negative mothers does not change the overall protection rate but decreases the risk of fulminant hepatitis (higher in this group), proving to be cost-effective [16,18–20].

Newborns of highly viremic HBeAg-positive mothers are at increased risk of HBV infection despite proper immunization (breakthrough infection), compared to babies born to HBeAg-negative mothers (16.8% *vs.* 1.6%), and are at increased risk for chronicity [16,21]. Breakthrough infection is more likely to occur in newborns of mothers with genotype C, who have higher viral loads. Vaccination programs are therefore changing the HBV genotype distribution [22]. Intrauterine infection, hyporesponsiveness to vaccine, and vaccine escape mutants could play a role as well [16,21,23,24]. The risk of mother-to-child transmission also depends on maternal serum HBsAg titer and mode of delivery (10.5% for elective cesarean section *vs.* 28% for vaginal delivery) [21,25,26]. Vertical transmission can be further reduced by treating highly viremic mothers during the last trimester of pregnancy with either lamivudine, telbivudine, or tenofovir (1–2% risk reduction for lamivudine and 8% for telbivudine) [27–30].

HBsAg and HBV DNA can be detected in breast milk of chronic carriers, but no increased risk of transmission to a breastfed infant has been shown and breastfeeding is currently recommended after proper infant immunization [31–33].

WHO has recommended universal HBV vaccination since 1991, with the first dose to be administered within 24 h from birth, followed by at least two doses at 1 and 6 months of life [15,34–36]. By the end of 2010, 179 of the 193 WHO member states had implemented a nationwide childhood HBV immunization program and global HBV vaccine coverage was estimated at 75% [37]. In countries where such programs have been imple-

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Abbreviations: HBV, hepatitis B virus; HCC, hepatocarcinoma; HBIG, hepatitis B immunoglobulins; CHB, chronic hepatitis B; ALT, alanine aminotransferases; cccDNA, covalently closed circular DNA; WHO, World Health Organization; ULN, upper limit of normal; IFN, interferon; FDA, Food and Drug Administration; VR, virologic response; PegIFN, pegylated interferon.

Key Points

- Incidence of HBV infection declined over the last two decades in countries where universal immunization programs have been implemented
- Newborns, infants and young children are at higher risk for chronicity
- To reduce mother-to-child transmission, newborns of HBsAg-positive mothers should receive both the vaccine and HBIG at birth
- Vertical transmission of HBV to properly immunized newborns (breakthrough infection) is an unsolved problem, which is changing HBV genotype distribution
- CHB in childhood is a mild disease but can lead to cirrhosis and HCC in few, not yet well identified cases
- The goal of antiviral therapy is to reduce the risk of infection-related complications
- Response to the few treatments currently available for children is partial and limited to specific subgroups
- Decision to treat should weight the risk of disease progression against side effects and the risk of developing antiviral resistance
- A chronic delay in licensing new drugs for children has limited treatment options
- Treatment with IFNα should be considered for patients with elevated serum ALT, high HBV DNA and moderate to severe fibrosis/inflammation at liver biopsy
- Children in the immunotolerant phase should not be treated outside of clinical trials
- Pediatric clinical trials for telbivudine, PegIFN and tenofovir are currently ongoing

mented, prevalence of HBV infection decreased dramatically [38–40]. Many countries with high HBsAg seroprevalence (⩾8%) before vaccination programs (like China and Taiwan) are now considered at intermediate (2–7%) or low prevalence (<2%) [38,41–43]. In Taiwan, prevalence of HBsAg in children younger than 15 years of age decreased from 9.8% to 0.5% after 20 years of vaccination [42]. In China, HBsAg prevalence in children aged 1–14 years decreased by 83% (from 8% in 1992 to 1.36% in 2006) [44]. In a recent study, 4.6% of the total population of the Unites States has been exposed to HBV (past or chronic infection), with up to a 50-fold variation as age, ethnicity and country of birth vary. HBsAg seroprevalence in children and adolescents aged 6–12 years and 13–17 years is 0.03% and 0.02%, respectively. Prevalence of both exposure and chronic carrier state is higher among people coming from high or intermediate prevalence countries, and among those with lower family income or with high-risk behavior [45].

Although, among children born in Western Europe and North America, prevalence of HBV infection is low, pediatricians and hepatologists are confronted with an increasing number of children adopted from higher prevalence countries (Table 1). Between 2% and 5% of all internationally adopted children, all coming from ⩾2% prevalence areas, are still infected with HBV [46,47]. CDC and American Academy of Pediatrics recommend screening all children adopted from these countries for HBV (HBsAg, HBsAb, HBcAb), at arrival and after 6 months, in order to provide vaccination to those without protective antibody levels (anti-HBs ⩾10 mIU/ml) [15,48] or diagnose a previously unknown infection and proceed to immunization of household contacts [6,34,49].

Ten genotypes (A–J) and several subtypes have been described for HBV, with a distinctive geographic distribution. Although in most of Europe and North America, genotype A is predominant, many of the children coming from high or intermediate endemicity countries are infected with genotype B, C, D, or F (Table 1), are at increased risk of complications and may have a worse response to therapy [50–52].

Natural history

Chronic HBV infection is defined as a positive HBsAg for 6 months or longer. Chronic hepatitis B (CHB) in childhood is a mild disease, and infected children are mostly asymptomatic, have normal growth and a normal physical examination [53]. Most perinatally infected subjects present a positive HBeAg and high serum levels of HBV DNA, with normal or minimally elevated serum alanine aminotransferases (ALT). A transplacental transfer of maternal HBeAg has been proved both in mice and in humans, and could elicit HBe/HBcAg-specific Th cell tolerance in utero [40,54–56]. Such an induced tolerance could explain the higher chronicity rate in babies born to HBeAg-positive mothers and the different rate of chronicity between neonatal and adult infection. The synthesis of large amounts of HBeAg by the wild type virus could be necessary to maintain the tolerance [57]. This immunotolerant phase is characterized by high viral replication and little liver damage, although in Italian children, after 7 years of disease, 7–10% of subjects showed severe hepatitis at liver biopsy and 1.7–4.5% had cirrhosis [53,58]. It lasts 10–30 years when infection is acquired perinatally, whereas it is of minimal duration in subjects infected later in life.

Viral mutants not capable of secreting HBeAg are then slowly selected (pre-core mutants are detected in 89% of HBeAg-positive patients) [59]. Selection seems to be secondary to an advantage of such mutants over wild type HBV, as hepatocytes infected by the latter are more susceptible to cytotoxic T lymphocyte-mediated clearance [60]. Pre-core mutants selection leads to a lower secretion of HBeAg. When the decreased amount of secreted tolerogen is no more sufficient to maintain immunotolerance, the immune system starts attacking infected hepatocytes [56,57]. ALT levels rise, reflecting the bioptic finding of necroinflammation of liver parenchyma, and HBV DNA levels fluctuate. This phase of active hepatitis leads to seroconversion to anti-HBe antibodies in 60–95% of patients on long-term follow-up [58,61]. ALT levels significantly increase before HBeAg clearance and may remain elevated for 6 months after seroconversion [53,62–64]. Up to 20% of spontaneous seroconverters may have ALT flare-ups in the years following seroconversion, which seems to be more likely in subjects carrying a pre-core mutant [63]. Spontaneous seroconversion occurs earlier and more frequently in subjects who have

Table 1. Estimated HBsAg seroprevalence and HBV genotype in countries of origin of internationally adopted children. (See below-mentioned references for further information.)

Country [Ref.]	HBsAg prevalence %		Predominant genotypes	Adopted children per year			
	Total	<16 yr		United States[a]	Italy[b]	France[c]	Canada[d]
China [41]	7.2	1.8	B, C	3401	116	100	230
Russian Federation [149]	1.4-8	-	D	1079	707	301	66
Ethiopia [150]	4.7	-	A	2511	274	352	159
Haiti [151,152]	5	-	A	133	0	992	94
Korea [153,154]	5.9	0.9	C	865	4	6	87
Colombia [155]	5.7	3.1	F	235	592	369	25
Vietnam [156]	10	7.5	B, C	9	251	469	29
Ukraine [157]	1-2	-	D	450	426	59	35
Brazil [158,159]	1	0.8	A, D, F	26	318	13	1
Taiwan [16,42]	1.1*	0.5	B, C	282	3	3	6
India [160]	2-8	-	A, D	241	124	21	36
Philippines [152]	10	-	B, C	216	30	14	96
Poland [149,157]	1-2	-	A	50	193	26	0
Nigeria [161-163]	4-12	12.4	E	189	5	23	6
Kazakhstan [164]	3.8	-	D	181	28	46	45
Bulgaria [149]	2-7	-	D	40	128	8	2
Ghana [165]	11.4	-	A	117	0	2	9
Belarus [166]	4.8	-	D	0	99	0	1
Cambodia [167]	8	2-14	B, C	0	87	2	1
Peru [149]	0.8-5.2	-	F	35	83	1	3
Hungary [149]	<1	-	A, D	5	78	5	0
Others				993	584	692	261
Total				11,058	4130	3504	1192

*Prevalence obtained from a study on 18-year old freshmen.
[a]Data refer to year 2010 (Bureau of Consular Affairs, US Department of State. US Intercountry Adoption [Internet]. adoption.state.gov 2011; [cited 10.01.12] Available from: http://adoption.state.gov/about_us/statistics.php). HBsAg seroprevalence in the United States is 0.27% (0.03% in 6–12 years old) [45].
[b]Data refer to year 2010 (Commission for intercountry adoptions. Data and perspectives in intercountry adoptions in Italy. Report on files from January 1 to December 31, 2010. Commission for intercountry adoptions; 2011. Available from: http://commissioneadozioni.it/it/per-una-famiglia-adottiva/rapporto-statistico.aspx). HBsAg seroprevalence in Italy is 0.9% [168].
[c]Data refer to year 2010 (Agence française de l'adoption. Statistiques de l'adoption international 2010. [Internet]. France Diplomatie 2011; [cited 10.01.12] Available from: http://www.diplomatie.gouv.fr). HBsAg seroprevalence in France is 0.65% [169].
[d]Data refer to year 2008 (HCCH Hague Conference Statistics. Canada: annual adoption statistics 2005–2009. [Internet]. HCCH 2012; [cited 10.01.12] Available from: http://www.hcch.net). HBsAg seroprevalence in Canada is 0.3–0.6% (0.4% for preadolescents) [170].

acquired HBV horizontally than in those infected perinatally (14–16% *vs.* 4–5% per year) [53,58,62,65]. It usually occurs after puberty, with about 90% of children <15 years of age still HBeAg positive [65]. It was shown that boys with earlier-onset puberty seroconverted at younger age (13 *vs.* 22 years), suggesting that androgens play a role in this process [64]. Environmental factors, such as nutritional status, have been suggested to influence immune response to HBV, accelerating seroconversion in children after adoption from developing countries [62]. Genotype C and maternal HBeAg-positive status were also associated with delayed spontaneous seroconversion [24,61,62,66–68].

HBsAg-positive, HBeAg-negative, and anti-HBe-positive patients are considered inactive carriers, express absent or low viral replication, with low or undetectable HBV DNA, and have inactive liver histology, with normal ALT levels. Inactive carriers with no signs of cirrhosis at seroconversion did not show progression to cirrhosis over 24–29 year follow-up [53,58].

On the contrary, 1–5% of HBeAg-positive children developed cirrhosis [53,58,69]. Between 2% and 5% of children with CHB developed HCC during childhood [24,58,70]. Incidence of HCC in high prevalence areas was significantly reduced after the implementation of immunization programs [71]. Children developing HCC are more likely to be males (70%), with cirrhosis (80%) and undergoing early seroconversion, suggesting that necroinflammation during seroconversion to anti-HBe may be severe and lead to cirrhosis and HCC [24,58,70]. Long-term risk of both HCC and cirrhosis is directly correlated to viral replication and serum HBV DNA levels [72,73]. The role of viral genotype on the risk of developing HCC is still to be defined: in children, 80% of HCCs are present in cirrhotic genotype B patients, whereas young adults with HCC are mostly non-cirrhotic [24,66]. In adults, genotypes C and F increase the risk for HCC [66,74–76]. Furthermore, such a risk is higher in persons with a family history of HCC, and a new susceptibility locus has been recently

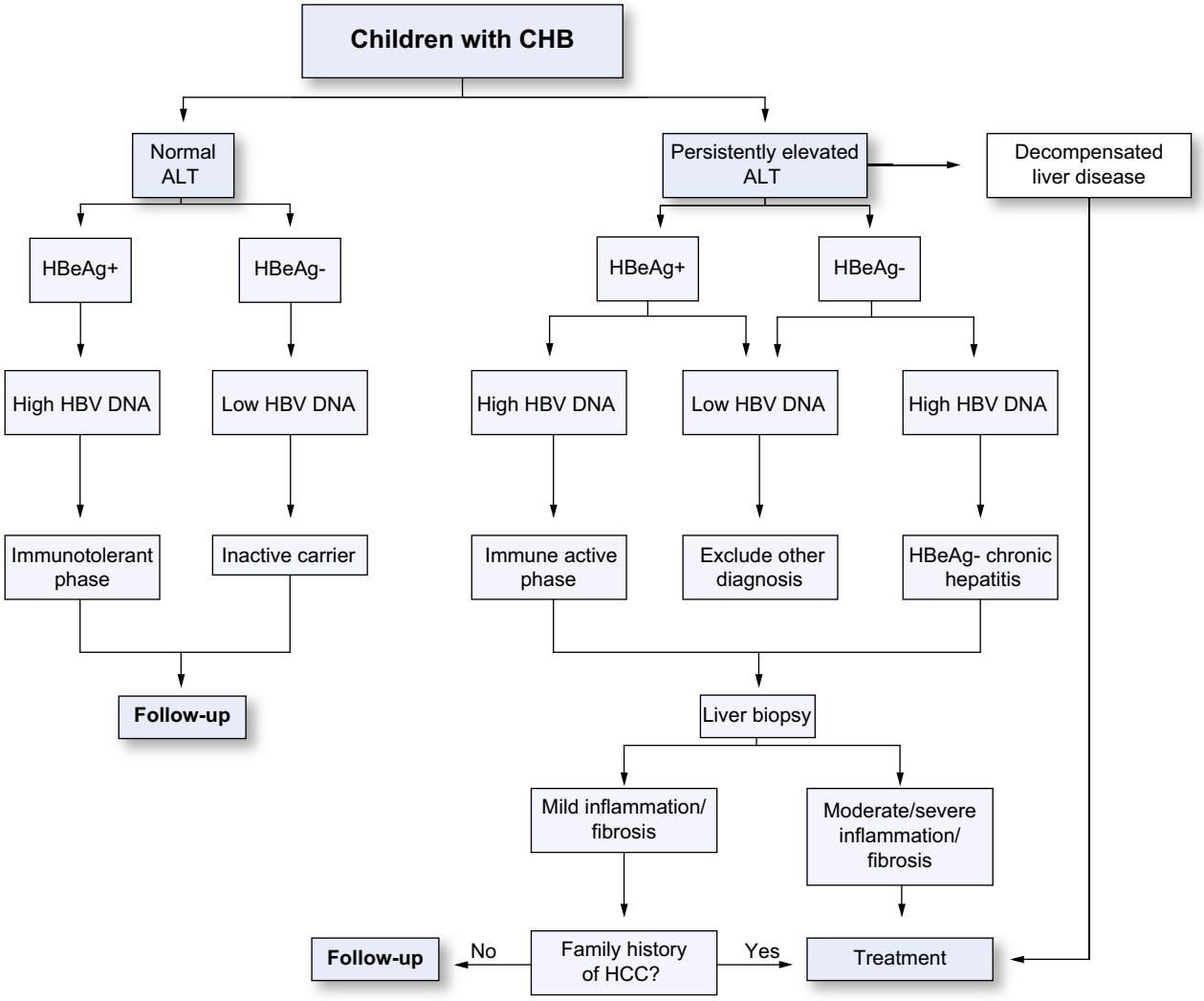


Fig. 1. Who and when to treat: algorithm for treatment of children and adolescents with chronic hepatitis B.

described in 1p36.22 [77,78]. Seroconversion to anti-HBe reduces the overall risk of developing HCC later in life, but an annual incidence of 0.2% has been described in HBeAg-negative adults (1.6% of asymptomatic HBsAg carriers) [79].

In 5% of anti-HBe-positive children, a pre-core mutant is selected, with persistent viral replication, abnormal ALT levels and histologically active hepatitis (HBeAg-negative chronic hepatitis). The latter progresses slowly in children, whereas adult patients are at increased risk of cirrhosis and HCC [53,58,79,80]. A stronger immune response with a faster turnover of infected cells could account for such an increased severity, and could be secondary to the reduced secretion of the tolerogen HBeAg [55,81].

In long-term longitudinal studies, it was shown that 7–14% of inactive carriers lost HBsAg and became anti-HBs-positive. Spontaneous seroconversion to anti-HBs is a rare event in childhood (1%/year and 0.6%/year in horizontally and perinatally infected children, respectively) [53,58,62,80]. HBsAg clearance and anti-HBs seroconversion mark the resolution of HBV infection, and are accompanied by improved liver histology. Long-term prognosis after HBsAg seroclearance is excellent if it occurs before the development of cirrhosis or HCC and in the absence of concomitant infections [82]. Nevertheless, cccDNA persists indefinitely in hepatocytes, and low-level viral replication or reactivation upon immunosuppression are still possible.

Who and when to treat

Even though several guidelines have been published by major international societies on the management of adult patients with CHB, treatment strategies for children are still evolving and are mostly based on consensus of expert panels (Fig. 1) [83–86]. Decision to start a therapy must take into account the mild evolution of the disease during childhood for most of the patients and the potentially severe complications in few, not yet well identified cases, and it is complicated by the limited number of drugs labeled for use in children.

The goal of the anti-HBV therapy, in children as in adults, is to reduce the risk of progressive liver disease, cirrhosis, and HCC. It can be achieved by suppressing viral replication through durable HBeAg seroconversion and undetectable serum HBV DNA levels. Reduction of viremia levels leads to decreased liver inflammation

and subsequent normalization of ALT levels. The final goal is anti-HBs seroconversion, as it stops disease progression and reduces the risk of HCC, although it occurs in a minority of treated subjects [87].

Need for treatment should be evaluated at each follow-up visit, in order to treat as soon as early signs of liver damage are detected. Children with CHB should undergo physical examination and measurement of serum ALT, HBeAg/anti-HBe, and alpha-fetoprotein levels every 6 months. ALT should be monitored every 3 months at diagnosis (for 1 year) and if persistently elevated, and every 12 months in HBeAg-negative patients with low viral load (<2000 IU/ml). HBV DNA levels should be assessed every 12 months, along with a complete blood count, a full liver panel and a liver ultrasound [83,85,88]. Lifetime follow-up is warranted even for inactive carriers, because of the risk of cirrhosis (7.8% of patients at 25 years), HCC (2.2%) and reactivation of HBV infection, with seroreversion to HBeAg positivity (1–4% of patients) or progression to HBeAg-negative hepatitis (15–24%) [79,89].

Decision to treat should be based on the following parameters: ALT levels, HBeAg positivity, HBV DNA levels, liver histology, family history of cirrhosis, and/or HCC, co-existing liver diseases, and patient's treatment history. Serum ALT level is the most useful marker of liver damage and should be used to identify patients who could be considered for possible antiviral therapy. Published evidence suggests that patients with normal or mildly elevated ALT respond poorly to available treatments [90,91]. Benefit of treating children with normal ALT has not been established, and the risk of developing antiviral resistance could turn it deleterious when considering the future of these patients [92]. Therefore, children in the immunotolerant phase should not be treated outside of clinical trials, and should be monitored and treated when the increase of ALT levels reveals immune activation. The three largest clinical trials of antiviral drugs in children used ALT levels higher than 1.5 times the laboratory ULN or more than 60 IU/L, whichever was lower, as inclusion criteria [90,91,93]. Unfortunately, the upper limit of normal (ULN) for ALT levels has not yet been established for children [94].

Serum ALT level has to be elevated for at least 6 months (12 months if HBeAg-negative), in order to avoid treating patients who are undergoing spontaneous HBeAg seroconversion. Persistent ALT elevation mandates assessment of serum HBV DNA levels. High HBV DNA values warrant treatment, whereas low HBV DNA levels should lead to the exclusion of other causes of liver disease. The cut-off value for HBV DNA has not been defined, and arbitrary values are used in clinical trials and guidelines. As children have a higher HBV replication rate, a value of 20,000 IU/ml has been chosen by different authors [85,95]. However, lower values have been associated with progressive liver disease in adults and latest management guidelines identified 2.000 IU/ml to be a good cut-off [83].

In adult patients older than 40 years of age, treatment can be started solely upon detection of a high viral load, as it is an independent risk factor of cirrhosis and HCC [72,73]. No data exist in children to support such an approach. Therefore, as response to currently available treatments for children is partial and limited to specific subgroups, histologic assessment of the grade of inflammation and the stage of fibrosis remains recommended before treating a child. Response to both interferon(IFN)-alfa and nucleos(t)ide analogues is more likely when at least moderate necroinflammation or moderate fibrosis are found at liver histology [90,96]. Although the benefit of treatment has not been established for children with mild inflammation or fibrosis, a family history of HCC may warrant treatment even in children with mild histological changes, as they are at increased risk of developing HCC [77].

There are other special populations of children at increased risk of rapid disease progression (cirrhosis, HBV-related glomerulonephritis, co-infection with HDV, HCV, or HIV). These patients could benefit from treatment even if ALT, HBV DNA levels, and liver histology do not match the above listed cut-offs. An antiviral treatment should be always considered in recipients of a liver graft from an anti-HBc-positive donor and to prevent (or treat) a recurrent HBV infection in children undergoing liver transplantation [83,97–99]. Furthermore, prophylactic treatment should be administered to HBsAg-positive patients who have to receive immunosuppressive or cytotoxic therapy, as it decreases the risk of mortality and morbidity related to HBV reactivation [100].

Several studies conducted in adults showed a better response to interferon for viral genotypes A and B, compared to D and C, respectively [25,101–103]. On the contrary, no significant difference was found when nucleoside analogues were used [104]. No studies have investigated the role of genotype on treatment response in pediatric patients, and genotype determination before treatment is not currently recommended [86].

Treatment options

The US Food and Drug Administration (FDA) approved four medications for treatment of children with CHB: IFNα, lamivudine, adefovir, and entecavir. IFNα can be used in children older than 12 months of age, lamivudine starting at 3 years of age, adefovir in children aged 12 years and older and entecavir starting from 16 years of age. Each of these treatments, together with others currently studied or used off-label in reference centers, has advantages and disadvantages (Table 2), and different response and resistance rates (Fig. 2).

Interferon-alfa

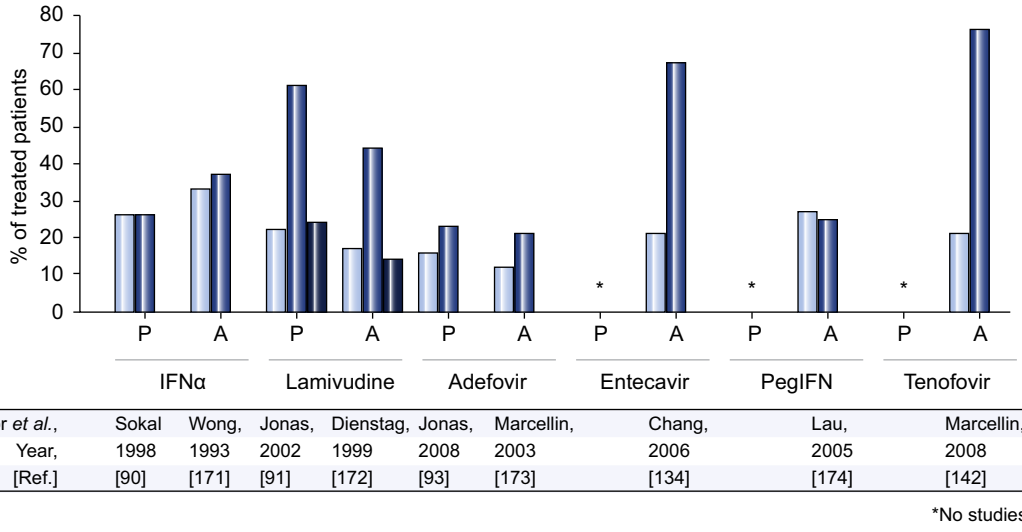
IFNα-2b has been the first drug to be approved and it has been used to treat CHB in children for about 15 years. Efficacy in children is similar to that in adults. In the largest multinational randomized controlled trial of IFNα therapy in children, 26% of patients achieved virologic response (VR: undetectable HBV DNA and loss of HBeAg) after 24 weeks of treatment, compared to 11% of untreated controls, and an additional 7% responded during the 24 weeks after treatment cessation. Response rate rose to 35% when only patients with ALT at least twice the ULN were considered. ALT levels decreased in all responders, and they were normal in 44% of cases at the end of treatment. Histological activity index improved in responders and loss of HBsAg occurred in 10% of treated children, as compared to 1.2% in the control group. Likeliness of a response was associated with low HBV DNA levels before treatment, younger age and female sex [90]. A better response in young patients was subsequently confirmed in children younger than 5 years of age [105].

IFNα is thought to simply accelerate seroconversion, as many patients who do not respond to treatment may still seroconvert to anti-HBe later in life. In three different series of 108, 107, and 174 children with CHB, IFNα treatment was shown to

Table 2. Available treatments for chronic hepatitis B in pediatric age.

Treatment	Licensing	Dose	Duration	Advantages	Disadvantages
IFNα	≥12 mo	5-10 M units/m^2 sc 3 x/wk	6 mo	No resistance Usable in young children Short treatment	Heavy side effects Parenteral administration Not usable if decompensated cirrhosis or transplantation
Lamivudine	≥3 yr	3 mg/kg po once daily (max 100 mg/d)	≥1 yr	Few side effects Usable in young children Oral administration Usable in 3rd trimester of pregnancy	High resistance rate (increasing with time of treatment)
Adefovir	≥12 yr	10 mg po once daily	≥1 yr (+ 6 mo after HBeAg seroconversion)	Partially effective in lamivudine resistant patients Oral administration	Not approved for children <12 yr Emergence of resistant mutations
Entecavir	≥16 yr + Phase III (2-17 yr)	0.5 mg/d once daily (1 mg/d for lamivudine-resistant pts)	≥1 yr (+ 6 mo after HBeAg seroconversion)	Partially effective in lamivudine resistant patients Oral administration	Resistance rate on the long term Not approved for children <16 yr No available preparation for young children
PegIFN	Phase III (2-18 yr)	180 μg/wk	6 mo	No resistance Once weekly administration Short treatment	Heavy side effects Parenteral administration Not usable if decompensated cirrhosis or transplantation
Telbivudine	Phase I (2-18 yr)	600 mg/d once daily	≥1 yr	Few side effects Oral administration Usable in 3rd trimester of pregnancy	High resistance rate
Tenofovir	Phase III (12-17 yr)	300 mg/d once daily	≥1 yr	High response rate No resistance identified Few side effects Oral administration Usable in 3rd trimester of pregnancy	No available preparation for young children Reduced mineral density in children

pts, Patients.

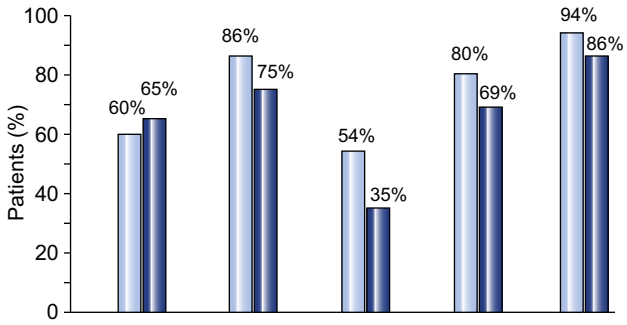


Studies	Author *et al.*,	Sokal	Wong,	Jonas,	Dienstag,	Jonas,	Marcellin,	Chang,	Lau,	Marcellin,
	Year,	1998	1993	2002	1999	2008	2003	2006	2005	2008
	[Ref.]	[90]	[171]	[91]	[172]	[93]	[173]	[134]	[174]	[142]

*No studies

Fig. 2. Comparison between available treatments in term of HBeAg seroconversion (light blue bars), undetectable HBV DNA (blue bars) and resistant mutations emergence (dark blue bars). Pediatric clinical trials (P) are compared to studies on adult patients (A). (See below-mentioned references for further information.)

accelerate HBeAg seroconversion, but treated and untreated patients had a similar rate of HBeAg clearance at long-term follow-up (Fig. 3) [53,62,106]. These data were confirmed in a recent study on Asian children [107]. Furthermore, children of Asian origin seroconverted slower than those of other ethnic origin, but they reached the same proportion of seroconversion in the long-term [62]. In a series of 74 children followed-up for 7 years, treated patients with elevated baseline ALT levels



Studies					
Author *et al.*,	Bortolotti,	Marx,	Vo Thi Diem,	Iorio,	Hsu,
Year,	2000,	2002,	2005,	2007,	2008,
[Ref.]	[106]	[62]	[108]	[53]	[107]
Follow-up (yr)	5	13	7	12	6
n treated/ untreated	107/59	27/147	37/37	41/67	17/21

Fig. 3. HBeAg seroconversion rates in children treated with INF-alfa (light blue bars) as compared to untreated subjects (dark blue bars). Differences between the two groups in each study are not statistically significant.

showed a higher long-term seroconversion rate, whereas elevated ALT at baseline did not significantly influence the long-term natural seroconversion rate in untreated children [108].

HBsAg clearance was observed in 4–15% of children treated with IFN (15–25% of responders), compared to 0–10% of controls [53,62,90,106–108]. The difference in HBsAg seroconversion rate between treated and untreated patients was shown to be significant in the randomized controlled trial, whereas none of long-term studies was able to find such a difference to be statistically significant. Nevertheless, children who responded promptly to IFN were more likely to lose HBsAg than late or no-responders [106].

Overall, although pediatric studies failed to show an impact of treatment over time, large case–control studies and meta-analyses in adults showed that IFNα reduced the risk of cirrhosis (RR 0.65) and HCC (RR 0.59–0.66) in the long-term [109–111].

European consensus recommendations for IFNα treatment suggest to treat HBeAg-positive children aged 2 years or older, with abnormal ALT and low-intermediate HBV DNA levels. The recommended regimen is 5–10 million units per square meter, three times weekly for 6 months [86,112]. The benefit of priming with corticosteroids has not been proven [113,114]. IFNα is contraindicated in children with decompensated cirrhosis, cytopenia, autoimmune disorders, cardiac or renal failure, and in transplanted patients [112]. As VR may be achieved in the 6 months following the end of treatment, at least 6–12 months should pass by before another therapy is started.

Side effects of IFNα treatment included fever and flu-like symptoms, behavioral disorders, gastrointestinal disorders and neutropenia [90]. Furthermore, IFNα was shown to temporarily affect growth [115]. All side effects resolve after treatment is stopped.

Pegylated interferon-alfa (PegIFN) has not yet been approved for the treatment of CHB in children. Polyethylene glycol addition to IFNα enhances its half-life, allowing a once-weekly administration. Such a formulation is licensed for the use in children with chronic hepatitis C. In adults with CHB, PegIFN proved to have superior efficacy than conventional IFNα, with the same safety profile [116]. Clinical trials of PegIFN in children with CHB are ongoing. Preliminary reports in children with HCV infection showed that it was well tolerated, while leading to better response rates than IFNα [117,118].

Lamivudine

Lamivudine is a pyrimidine nucleoside analogue approved for children aged 3 years and older. In the largest pediatric randomized, controlled trial, VR was achieved by 23% of patients receiving lamivudine after 1-year treatment (compared to 13% in the control group). Response increased to 35% when considering only children with ALT levels of at least twice the ULN [91]. An open label extension study was then carried out on the same cohort, reaching a total of 2 or 3 years of treatment. At the end of the extension period, response rate was 56% for children receiving lamivudine in the absence of resistant mutations (being 5% in patients with a YMDD mutant HBV). Resistance rate increased over time (24% after 1 year of treatment, 49% at 2 years, and 64% at 3 years) [119]. Likeliness of response was greater in patients with higher ALT levels and histologic activity index at baseline. In children, no data is yet available on the long-term impact of treatment with lamivudine (or any other nucleoside analogue) on the natural history of the disease.

Lamivudine is well tolerated with no significant side effects. The recommended treatment dose is 3 mg/kg/day (maximum 100 mg/day), administered orally once daily. Such a dose provides levels of exposure and trough concentrations similar to the 100 mg dose in adults [120]. Optimal treatment duration is more difficult to determine. Published data suggest continuing treatment until VR is achieved, and possibly for 6 months following seroconversion [119]. As a longer treatment duration leads to higher resistance rates, it is recommended to discontinue lamivudine after 6 months if a complete suppression of viral replication is not achieved or if YMDD mutations emerge. As post-treatment ALT flares are possible, children should be carefully followed and an alternative therapy should be started in the rare cases of severe and protracted ALT elevation [121].

Combination of lamivudine with IFNα (either concurrent or sequential) proved to be more effective that the single drugs alone in adult patients with elevated ALT levels [122,123]. The two drugs were shown to have a synergistic effect on cells *in vitro* [124]. In children, fewer data are available. Three studies investigated combined therapy in 32, 33, and 45 treatment-naïve children with elevated ALT levels. Although no difference was found between different combination strategies, the children reached 30–60% seroconversion to anti-HBe and 9–17% to anti-HBs [125–127]. An 8-week treatment with lamivudine followed by 10-month combination therapy with lamivudine and IFN has been tested on 23 immunotolerant children: complete suppression of viral replication was achieved in 78% of subjects and 22% of children seroconverted to anti-HBe. The concurrent administration of IFNα appeared to be protective against mutations emergence [128]. No difference was seen on histological response between monotherapy and combined therapy [129]. As no large clinical trials have been conducted so far, advantages of combination therapy over monotherapy in children are still to be confirmed.

Adefovir

Adefovir dipivoxil is a purine analogue approved to treat children with CHB aged 12 years and older. In a large pediatric

randomized controlled trial, 23% of patients aged 12–17 years achieved VR after 48-week treatment with adefovir (compared to 0% of placebo-treated subjects). The efficacy on HBV DNA suppression and ALT normalization was less evident in younger children (15% *vs.* 3%), with differences between groups not being statistically significant [93]. Adefovir was well tolerated by children of all age groups, with no resistance-associated mutation registered. However, adefovir resistant mutations are reported in more than 20% of HBeAg-positive adults after a 5-year treatment [130]. A dose-dependent proximal renal tubular toxicity, with occasional Fanconi-like renal tubular acidosis, is a known side effect of adefovir, which has been rarely reported in adults, but never in children. The nephrotoxicity is usually reversible if the therapy is rapidly stopped [131,132]. The recommended dose in patients 12–18 years of age is 10 mg orally once daily [133]. Treatment duration has not been established, but experts agree to continue for at least 6 months after HBeAg seroconversion. Adefovir should be discontinued if a complete VR is not achieved after 24 weeks or if a resistant mutation emerges. As with other nucleos(t)ide analogues, patients should be monitored after discontinuation because post-treatment flares are not uncommon.

Entecavir

Entecavir is a carbocyclic analogue of 2′-deoxyguanosine that proved to be more potent than both lamivudine and adefovir in adult patients [134,135]. Furthermore, entecavir resistance is rare, even after 5 years of treatment, and entecavir is active (although less effective) on lamivudine-resistant strains [136–138]. The safety profile of entecavir is similar to that of lamivudine. Based on adult studies, entecavir has been approved by the FDA for treatment of adolescents aged 16 years or older. The recommended dose is 0.5 mg once daily for nucleoside-naïve patients and 1 mg/day for lamivudine-resistant patients. A phase III clinical trial in children as young as 2 years old is underway [139].

New drugs

Telbivudine is an L-nucleoside analogue with a potent antiviral activity and a safety profile similar to lamivudine (although myopathy and peripheral neuropathy were reported in adults) [140]. Resistance rate is lower than lamivudine but higher than adefovir. For such a reason, telbivudine is only used in combination with other antiviral drugs. A phase I clinical trial is ongoing on children 2–18 years of age [141].

Tenofovir disoproxil fumarate is a nucleos(t)ide analogue originally licensed for treatment of HIV infection, which is structurally similar to adefovir and of equal antiviral activity. Nevertheless, as it proved to be less nephrotoxic than adefovir, the approved dose for adults is higher than that of adefovir (300 mg/day). For such a reason, tenofovir was shown to have a greater antiviral activity than adefovir in clinical trials (undetectable HBV DNA in 76% of patients *vs.* 13% of adefovir-receiving subjects after 48 weeks of treatment) [142]. After three years of treatment, 72% of HBeAg-positive and 87% of HBeAg-negative patients have HBV DNA levels <400 copies/ml [143]. The safety profile of tenofovir is similar to that of adefovir, although associated with decreased bone mineral density in children with HIV [144]. No genotypic resistance to tenofovir has yet been confirmed [143,145]. Tenofovir is currently used to treat HIV infection in children, and it proved to be well tolerated in phase I studies conducted in patients 4–18 years of age [146,147]. As there is no preparation suitable for young children, a phase III trial is ongoing on 12–17 year old CHB patients [148].

Proposition of a treatment scheme

Outside clinical trials, until new drugs are licensed for pediatric patients, IFNα is still the drug of choice, unless decompensated cirrhosis is present. The impossibility of developing a genotypic resistance against such a drug is a big advantage, even though adverse effects are more pronounced and a clear benefit on the long-term period remains to be confirmed. Furthermore, IFNα is the only treatment licensed for treating children younger than 3 years of age, although patients in this age group requiring treatment, are extremely rare. Currently available nucleos(t)ide analogues are second-line therapies, as the risk of emergence of resistant mutant strains is high. In adolescents older than 16 years of age, entecavir is the best choice, as resistance is less likely. Such a risk is higher with both lamivudine and adefovir, the latter being preferable in children aged 12–15 years. The use of lamivudine is currently limited to young children unresponsive to IFNα, in special populations (co-infection with HIV, transplant recipients or patients with HBV-related glomerulonephritis) or to prevent reactivation in children receiving immunosuppressive therapies. Combination therapy is promising, but further data are needed in children.

Newer drugs such as PegIFN and tenofovir are extremely promising and their licensing for children could change management of pediatric CHB. As the emergence of resistant mutant strains is becoming a major public health problem, pediatric practitioners should refrain from treating children who are not likely to benefit from a licensed therapy and consider waiting for safer and more effective drugs made available through clinical trials or future market approval.

Conclusions

A dramatic reduction of pediatric HBV infection prevalence has been observed in countries where global immunization programs have been implemented. Nevertheless, an important number of children are still infected every year. Prevention and management of breakthrough infection, along with a better identification of children at higher risk for disease progression and complications, are the current challenges.

Overall, management of pediatric patients with CHB is satisfactory, but hampered by a chronic delay in licensing new drugs as compared to adults. As the approval by regulatory agencies is based on the completion of appropriate clinical trials, studies on treatments that, in adults, have already been proved safe and more effective than available drugs should be conducted without undue delays. The current (2007) European regulation on medicines for children offers the appropriate regulatory framework to speed up this process.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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