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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

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Introduction

More than 360 million persons worldwide (6% of the world population) are chronically infected by the hepatitis B virus (HBV). Although the incidence of HBV infection has dramatically declined since the implementation of universal immunization programs in several countries and blood-donor screening, a significant number of children are still infected each year, often developing chronic infection and requiring appropriate follow-up [1]. Despite a rather benign course of chronic hepatitis B (CHB) during childhood and adolescence, 3–5% and 0.01–0.03% of chronic carriers develop cirrhosis or hepatocellular carcinoma (HCC), respectively, before adulthood [2,3]. Such a risk for HCC rises to 9–24% when considering the whole lifetime, with an incidence of cirrhosis of 2–3% per year [4,5]. Worldwide universal vaccination remains the goal for eliminating HBV infection and its complications. Treatment of CHB in childhood has been hampered by the chronic delay in licensing new drugs for pediatric use. Safe and effective antiviral therapies are available in adults, but few are labeled for the use in children, and an accurate selection of whom to treat and the identification of the right timing for treatment are needed to optimize response and reduce the risk of antiviral resistance. Although several guidelines on the management of adult patients with CHB have been published by major international societies, the clinical approach to infected children is still evolving, and is mostly based on consensus of expert opinion [6–9].

Context

Epidemiology and prevention

Since the WHO recommended global immunization programs for HBV in 1991, the prevalence of HBV infection has declined worldwide [5,10–12]. Although among children born in Western Europe and North America HBsAg-positivity is rare, pediatricians are confronted with an increasing number of children adopted from higher prevalence countries, 2–5% of whom are still infected with HBV and often carry HBV genotypes which expose them to a higher risk of complications [1,13–15].

In countries where donor screening and blood testing have been implemented, the current risk of acquiring HBV infection after blood transfusion is estimated at 1 in 500,000 per unit exposure [16,17]. Nevertheless, as HBV nosocomial transmission is still a critical problem, vaccination status of children needs to be checked regularly and all preventive measures have to be strictly respected [18].

Mother-to-child transmission accounts for more than 50% of chronic infections in highly endemic areas. After exposure, the risk of chronicity is higher for newborns (90%), infants and children younger than 5 years (25–30%) than for adolescents or adults (<5%) [19,20].

Vaccination is the most effective measure to prevent hepatitis B transmission. In highly endemic areas, it is also the most

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cost-effective medical intervention, offering the higher benefit-cost ratio, whereas in low-endemicity countries, such cost-effectiveness is not as clear [21–24]. Recombinant vaccine induces a seroprotective response (anti-HBs ⩾10 mIU/ml) in about 95% of subjects vaccinated with three doses [25,26]. The first dose of monovalent vaccine should be administered intramuscularly within 24 hours of birth, and should be followed by 2 or 3 doses (monovalent or combined) with a minimum interval of 4 weeks **(A1)** [26]. Preterm infants weighting <2000 g should receive 3 doses after the birth dose **(B1)** [26,147]. Postvaccination testing for a protective concentration of anti-HBs is recommended only for high-risk populations (infants born to HBsAg-positive mothers and HIV-infected or other immunocompromised subjects), and should be performed 1–2 months after the end of the vaccination schedule **(A1)** [26]. Revaccination with further 3 doses induces protective anti-HBs response in the majority of non-responders [27,28]. Immunocompromised subjects should be tested annually and revaccinated if anti-HBs <10 mIU/ml **(C1)** [148]. Although anti-HBs levels have been shown to decrease over time, long-lasting protection has been observed in vaccinated subjects with undetectable anti-HBs, and at present there is no clear evidence for recommending the administration of a booster dose in immunocompetent individuals [149,150]. Testing for coeliac disease, HIV or other causes of immune deficiency might be advisable for non-responders **(C2)** [29,30,151].

Vaccine failure and mother-to-child transmission of hepatitis B affect 17% of infants born to HBeAg-positive mothers [25]. The high viral load related to HBeAg-positivity seems to be the most important factor for breakthrough infection [25,31]. Moreover, when the mother is infected by genotype C HBV, intrauterine infection may occur before vaccination can be administred, in addition to hyporesponsivness to vaccination [31,32]. When the mother is a chronic carrier, vaccination at birth is not sufficient to avoid vertical transmission, and concurrent intramuscular administration of 0.5 ml of hepatitis B immunoglobulin (HBIG) is recommended to give immediate passive immunity to the newborn [26,33]. Administration of both the vaccine and HBIG to newborns of HBeAg-positive mothers within 12–24 h of birth allows the achievement of 90% protection rate (98% when mothers are HBeAg-negative), compared to vaccine alone [25,26,34]. Administration of both vaccine and HBIG is recommended for newborns of HBeAg-positive mothers **(A1)**. Although a clear benefit has not been shown for newborns of HBeAg-negative mothers, a reduction of the incidence of fulminant hepatitis justifies HBIG administration to all infants born of HBsAg-positive mothers [25], regardless of the maternal HBeAg status **(C2)**. High breakthrough infection (17%) and chronicity (54%) rates have been reported in newborns of HBeAg-positive mothers despite concomitant active and passive immunization at birth [25]. As breakthrough infection rates are directly correlated to maternal viral load (as well as to HBV genotype C, high HBsAg titer, vaginal delivery, hyporesponsiveness to vaccine and vaccine escape mutants) [25,31,152], treatment with nucleos(t)ide analogues (NA) of highly viraemic women during the last trimester of pregnancy is currently recommended to prevent vertical transmission **(B1**, see below) [8].

Breastfeeding has been shown not to contribute significantly to HBV transmission from infected mothers to infants who have received active and passive immunoprophylaxis [153,154]. In the absence of cracked or bleeding nipples, breastfeeding of properly immunized infants is encouraged **(B2)**. Unlike interferon (IFN), which is not excreted in breast milk, lamivudine and tenofovir are excreted (although no data are available yet for tenofovir in humans), but the dose adsorbed by the infants is negligible compared to standard oral doses [155,156]. Nevertheless, no systematic study has been conducted to evaluate the effects of nucleos(t)ide analogues (NA) absorbed from maternal milk on breastfed infants. Though there are data suggesting that breastfeeding while on lamivudine and tenofovir is safe [156] at present, breastfeeding cannot be recommended, and the risk of potential long-term effects on the infant should be weighed against the risk of stopping the antiviral therapy. Entecavir has not been studied in pregnant women as yet, but was shown to be excreted in breast milk in rats and to have carcinogenic potential both in mice and rats after placental transfer. No data are available yet for telbivudine.

Natural history

Chronic hepatitis B, defined as positivity for HBsAg for 6 months or longer, is a mild disease in childhood [1]. Most infected children are asymptomatic, with a normal growth and a normal physical examination [35]. The great majority of perinatally infected subjects are HBeAg-positive, with high serum levels of HBV DNA and normal serum alanine aminotransferases (immunotolerant phase). Transplacental transfer of maternal HBeAg has been suggested to elicit HBe/HBcAg-specific Th cell tolerance in utero [157–160]. Such mechanism could explain the different chronicity rates between neonatal and adult infection, as well as the higher chronicity rate in babies born to HBeAg-positive mothers, in whom high-level viral replication leading to large amount of HBeAg would maintain the tolerance to HBV [56]. This immunotolerant phase, which lasts 10–30 years, is usually marked by high viral replication and little liver damage. Nevertheless, 1.7–4.5% of children and adolescents infected at birth have cirrhosis at liver biopsy [35,36].

Over time, HBV DNA levels fluctuate and ALT levels rise, reflecting the histologic finding of necroinflammation of liver parenchyma. This phase of active hepatitis leads to seroconversion to anti-HBe antibodies in 60–95% of patients on long-term follow-up [36,37]. ALT levels increase before HBeAg clearance and may remain elevated (with flare-ups in 20% of subjects) for 6–12 months after seroconversion [11,35,38,39]. Most HBsAg-positive, HBeAg-negative, and anti-HBe-positive patients (i.e. those who undergo HBeAg seroconversion) are defined as inactive carriers, have absent or low viral replication (HBV DNA <2000 IU/ml) and usually inactive liver histology, with normal ALT levels. Over a long-term follow-up (24–29 years), inactive carriers with no signs of cirrhosis at seroconversion do not show disease progression, whereas 1–5% of HBeAg-positive children develop cirrhosis [2,35,36].

Although the incidence of HCC in high HBV prevalence areas has been significantly reduced by global immunization programs, between 0.01% and 0.03% of children with CHB develop HCC during childhood (32 per 100,000 person-year) [14,36,40,41]. Children developing HCC are more likely to be males (70%), with cirrhosis (80%), and to have undergone early seroconversion (suggesting that necroinflammation during seroconversion to anti-HBe may be severe enough to lead to cirrhosis and HCC) [14,36,40]. In adult patients, the long-term risk of both HCC and cirrhosis is directly correlated to serum HBV DNA levels and HBeAg positivity [42–44]. No conclusion can be drawn from pediatric studies because of the rarity of HCC during childhood [36,40]. The role of viral genotype on the risk of developing

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HCC is still to be clarified in the pediatric population (80% of HCC are in cirrhotic genotype B children, whereas in adults, genotypes C and F are considered at increased risk) [14,45–48]. Furthermore, the risk of HCC is higher in individuals with a family history of HCC [4]. Seroconversion to anti-HBe reduces the risk of developing HCC, but 0.2% of HBeAg-negative adults and 1.6% of asymptomatic HBsAg carriers still develop HCC [49].

A subgroup of anti-HBe-positive subjects has active viral replication with abnormal ALT levels and histologically active hepatitis (HBeAg-negative chronic hepatitis). HBeAg-negative hepatitis affects about 10% of pediatric patients, who show a more severe disease progression and have a higher incidence of HCC than HBeAg-negative patients in sustained remission [49].

Between 7% and 25% of inactive carriers lose HBsAg and become anti-HBs-positive over a 20-year follow-up [50]. Unfortunately, spontaneous seroconversion to anti-HBs is a rare event in childhood (0.6–1%/year) [35,36,38]. Such an event marks resolution of HBV infection, and leads to an improved liver histology. HBsAg seroclearance, if it occurs before the development of cirrhosis or HCC and in the absence of concomitant infections, has an excellent long-term prognosis [51]. Nevertheless, covalently closed circular DNA (cccDNA) persists indefinitely in hepatocytes, and low-level viral replication or reactivation upon immunosuppression is always possible. Moreover, the HBV genome may integrate in the host genome, increasing the risk of HCC development even after HBsAg seroclearance [52,53].

As a reflection of the transcriptional activity of cccDNA, HBsAg levels decrease with age and disease progression, being higher during the immunotolerance phase, lower after seroconversion to anti-HBe, and reaching the lowest levels in inactive carriers [161].

Methods

These guidelines were developed by a panel of experts chosen by the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). Recommendations were based on evidence from existing papers published before June 2012 and, when evidence was not available, on experts' personal experience. Evidence has been evaluated by the authors and classified as high (A), moderate (B), or low (C) quality according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system [54–56]. The strength of recommendations (1: strong; 2: weak) reflects the extent to which we can be confident that the desirable effects of the intervention outweigh the undesirable effects, and is based on the balance between desirable and undesirable effects, the quality of underlying evidence, variability in values and preferences and the costs of the intervention (Table 1).

End points of treatment and definitions of response

The goal of anti-HBV therapy, in children as in adults, is to improve long-term survival and quality of life by reducing the risk of progressive liver disease, cirrhosis, and HCC.

For all patients, the ideal end point of treatment is sustained HBsAg clearance, as it stops disease progression and reduces the risk of HCC, although it occurs in a minority of treated subjects **(A1)** [51,57].

When HBsAg seroclearance is not achieved, sustained off-therapy suppression of viral replication (undetectable HBV DNA levels with a sensitive real time polymerase chain reaction assay), associated with durable anti-HBe seroconversion in originally HBeAg-positive patients, is a good end point, being associated with improved prognosis, including decreased risk of HCC **(A1)** [44]. In the absence of off-therapy viral suppression, undetectable HBV DNA under long-term antiviral therapy (maintained virological response) is the next desirable end point **(A1)**. Reduction of viremia levels leads to decreased liver inflammation and subsequent normalization of ALT levels, reducing the risk of disease progression [2,35,36,42,43].

Response to treatment can be evaluated at biochemical, serological, virological and histological levels. In the few available pediatric trials, several end points have been used to evaluate response. A consensus on the definition of response would be required to compare the different clinical trials. Current AASLD and EASL definitions can be adapted to pediatric clinical trials [6,8]:

- Biochemical response: normalization of ALT levels, which reflects reduction of histological activity index. ALT level is, however, a difficult parameter to assess because it can fluctuate widely over time and can remain elevated up to 6–12 months after HBeAg seroconversion. ALT levels,

Table 1. Grading of evidence and recommendations according to the GRADE system [54].

| Grading of recommendation			
	Implications for clinicians	Implications for patients	Symbol
Strong recommendation warranted	Most patients should receive the recommended course of action	Most informed patients would choose the recommended management	1
Weaker recommendation	Different choices will be appropriate for different patients	Patients' choices will vary according to their values and preferences	2
Grading of evidence			
	Definition	Type of evidence	Symbol
High quality	We are very confident that the true effect lies close to that of the estimate of the effect	Randomized controlled trials	A
Moderate quality	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Randomized controlled trials with risk of bias, high quality observational studies	B
Low quality	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect	Observational studies, case reports, experts' opinion	C
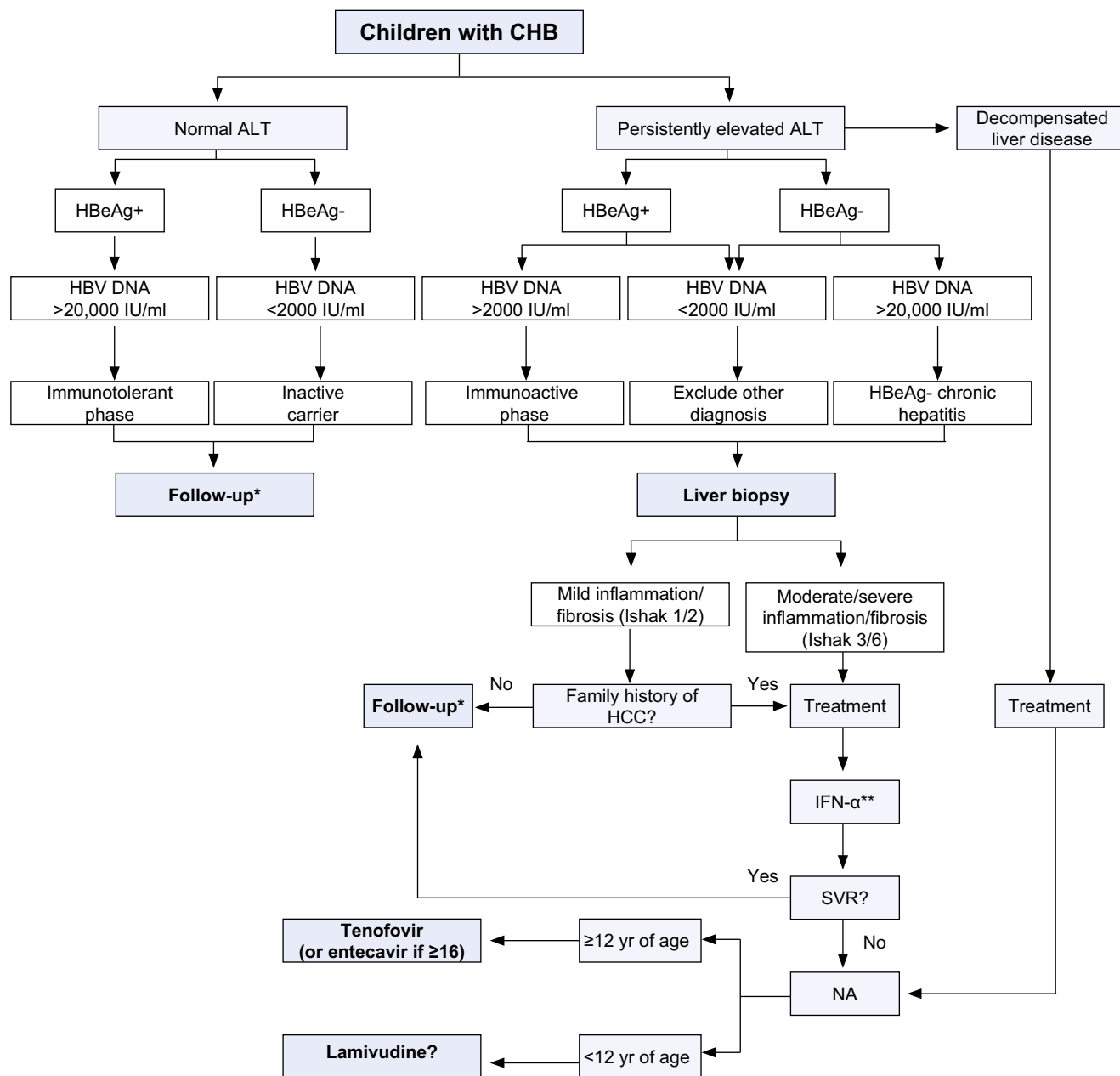
Fig. 1. Treatment algorithm for pediatric patients with CHB (modified from [1]). *Recommendation valid until results of ongoing trials on the treatment of immunotolerant children are available. **It is likely that PegIFN will replace IFN-α as the first-line treatment for CHB once the results of ongoing clinical trials are available.

therefore, should be monitored every 3 months during the first year post-treatment **(C1)** and every 6 months during the second year post-treatment **(C2)**.

- Serological response for HBeAg is defined as HBeAg loss and seroconversion to anti-HBe (only for HBeAg-positive patients); serological response for HBsAg is defined as loss of HBsAg and development of anti-HBs antibodies (valid for all chronic hepatitis B patients).
- Virological response (VR): undetectable levels of HBV DNA (as determined by a sensible PCR assay) after 3–6 months of treatment for NA-treated patients or HBV DNA <2000 IU/ml after 6 months and at the end of treatment for IFN-treated patients.

- Complete response: off-treatment virological response associated with HBsAg loss sustained on long-term follow-up.
- Sustained off-treatment virological response (SVR): VR persisting at least 12 months after cessation of treatment.
- Maintained virological response: undetectable HBV DNA under long-term antiviral therapy.
- Partial virological response: decrease in HBV DNA of more than 1 $\log_{10}$ IU/ml but detectable HBV DNA after at least 6 months of treatment with NA.
- Primary non-response: less than 1 $\log_{10}$ IU/ml decrease in HBV DNA levels from baseline after 3 months of therapy.

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- Virologic breakthrough: HBV DNA level increase of more than 1 $\log_{10}$ IU/ml during therapy, usually caused by poor adherence to treatment or emergence of a drug-resistant HBV mutant.
- Histologic assessment of necroinflammatory activity has not been used as a criterion to evaluate response to treatment in pediatric studies.

Who and when to treat

Decision to treat must take into account the mild evolution of the disease during childhood, the risk of disease progression later in life, the development of severe complications in few, not yet well identified children, the efficacy of current antivirals, their side effects, and the limited number of drugs labeled for use in this age group. A treatment algorithm is proposed in Fig. 1.

The need for treatment should be evaluated at each follow-up visit, in order to initiate antiviral drugs at the earliest signs of liver damage (C2). Children with CHB should undergo physical examination and measurement of serum ALT and HBeAg/anti-HBe levels every 6 months (C1). In HBeAg-positive patients with persistently elevated ALT, their levels should be monitored every 3 months for at least one year (B1). In HBeAg-negative patients, ALT and HBV DNA levels should be measured 4-monthly within the first year to rule out HBeAg-negative hepatitis. After confirmation of the inactive carrier status (normal ALT and HBV DNA <2000 IU/ml), patients should be monitored every 6 months (B1). Full blood count and liver function tests should be performed yearly (C1). HCC surveillance with liver ultrasound should be done every 6–12 months, depending on the stage of fibrosis [190]. Alpha-fetoprotein (AFP), although widely used, was recently shown to provide insufficient sensitivity and specificity for effective surveillance [191,192]. Lifetime follow-up is warranted even for inactive carriers, because of the risk of cirrhosis, HCC and reactivation of HBV infection, with seroreversion to HBeAg-positive status or progression to HBeAg-negative hepatitis (C1) [49,58].

Currently, decision to start treatment is based on ALT levels (which reflect ongoing liver damage), HBeAg positivity, HBV DNA levels, liver histology, family history of HCC, co-existing liver diseases and patient's treatment history.

As the upper limit of normal (ULN) for ALT levels in pediatric age has not been established yet, it is advised that a patient should be considered for antiviral treatment if ALT levels are more than 1.5 times the laboratory ULN or more than 60 IU/L (value used as inclusion criterion in the three largest trials in children [59–61]), whichever is lower (C2) [9]. Patients with lower transaminases have fewer chances to achieve serological response [59,60]. A lower threshold based on larger pediatric cohorts may be used in future studies to avoid underestimation of liver damage, but this approach may reduce the overall rate of serological response and increase the need of prolonged treatment of patients with maintained VR under antiviral drugs [62].

Antivirals should be considered for children with elevated serum ALT levels for at least 6 months (12 months if HBeAg-negative), in order to avoid treating patients who are undergoing spontaneous HBeAg seroconversion (C1).

In the presence of high ALT levels, assessment of serum HBV DNA levels is important, as high HBV DNA values warrant antiviral treatment, whereas low levels should instigate investigations to exclude other causes of liver disease. The cut-off value for HBV DNA, however, has not been defined for children. As young patients have a higher HBV replication rate than adults, a value of 20,000 IU/ml has been chosen by different authors [7,63]. However, lower values have been associated with progressive liver disease in adults, and latest management guidelines for adult patients identified 2000 IU/ml to be a more reliable cut-off [6,8]. Such a cut-off appears to be appropriate for children as well (C1).

In patients older than 40 years of age, antiviral treatment is advocated in the presence of a high viral load in isolation, as this is an independent risk factor for cirrhosis and HCC [42,43]. No data exist in children to support such an approach. Therefore, as response to currently available antivirals in children is partial and limited to specific subgroups, histologic assessment of the degree of inflammation and of the stage of fibrosis is recommended before considering treatment (A1). Response to both interferon(IFN)-α and NA is more likely when at least moderate necroinflammation or moderate fibrosis is found at liver histology (A1) [59,64]. 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 (B2) [4].

Although still not fully validated, non-invasive methods to assess the degree of hepatic fibrosis, such as FibroScan, could prove useful to avoid liver biopsy, especially during follow-up [8,162–165]. However, no sufficient data are available in children and, at present, these non-invasive methods cannot substitute for liver biopsy in the decision to treat a child or an adolescent with chronic hepatitis B, as these methods evaluate more fibrosis than necroinflammatory activity (C2).

Antiviral treatment with NA should be instituted in HBV infected children undergoing liver transplantation or in recipients of grafts from anti-HBc-positive donors to prevent (or treat) recurrent HBV infection (C1). Prophylactic anti-HBV therapy should also be administered to HBsAg-positive patients who are going to receive immunosuppressive or cytotoxic treatment, as it decreases the risk of mortality and morbidity related to HBV reactivation (B1) [65]. Children with cirrhosis, HBV-related glomerulonephritis, or co-infection with HDV, HCV or HIV are at increased risk for a rapid progression of liver disease. These patients might benefit from treatment even if ALT, HBV DNA levels, and liver histology do not match the criteria listed above (C2).

If antiviral treatments were able to achieve complete viral control (i.e., anti-HBs seroconversion), the ideal children to treat would be those tolerant to HBV, in order to obtain the production of neutralizing antibodies before the onset of complications. These children, who have normal or mildly elevated ALT levels and a high viral load, have been shown not to respond to isolated interferon treatment [59,60,66–68] and are not good candidates for current NA therapy because of the risk of developing antiviral resistance [69]. A pilot open study in small cohort of tolerant children has shown promising results with a combined protocol, in which 8 weeks of lamivudine treatment to decrease the viral load were followed by 44 weeks of combined lamivudine and IFN-α treatment [70]. On the basis of this study, two controlled trials in tolerant children are currently being conducted in the UK (lamivudine/pegylated IFN-α) and in the USA (entecavir/pegylated IFN-α) [71,72]. Until the results of these studies become available, children in the immunotolerant phase should

not be treated, but should be monitored, and treated only if an increase of ALT levels reveals immune activation (**A1**).

Efficacy of currently available therapies

The U.S. Food and Drug Administration (FDA) approved five medications for treatment of children with CHB: IFN-α, lamivudine, adefovir, entecavir and, recently, tenofovir. IFN-α can be used in children older than 12 months of age, lamivudine starting at 3 years of age, adefovir and tenofovir in children aged 12 years and older, and entecavir starting from 16 years of age. Each of these treatments has advantages and disadvantages (Table 2). Response rates and side effects are summarized in Fig. 2 and Table 3. So far, none of these medications have been approved by the European Medical Agency for the treatment of children.

Predictors of response

Several baseline and on-treatment predictors of response have been identified for children treated with IFN-α and lamivudine, whereas no data from pediatric studies exists for other NA.

In HBeAg-positive patients, likelihood of response to IFN-α is associated with low HBV DNA levels and elevated ALT levels (more than twice the ULN) before treatment, younger age and female sex (**A1**) [59,91–93]. Elevated ALT levels at baseline are
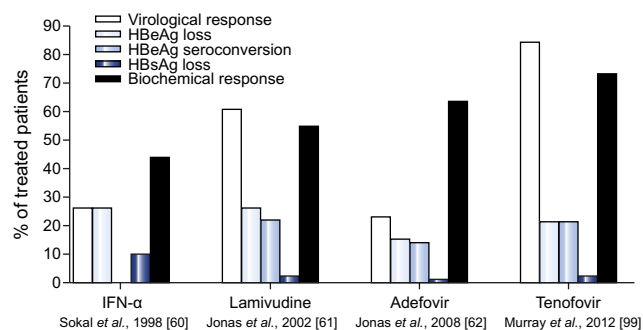

Fig. 2. **Response to antiviral treatments currently licensed for children: rates of virological (white bars), serological (HBeAg loss: light blue bars; HBeAg seroconversion: blue bars; HBsAg loss: dark blue bars) and biochemical (black bars) response in pediatric clinical trials.** Entecavir has not been included as no pediatric trials have been conducted so far.

associated with higher long-term seroconversion rate after treatment (**B2**) [74]. Early response to IFN-α is more likely to lead to HBsAg loss than late or no-response (**C2**) [73]. A better response to IFN-α has been shown in adults for viral genotypes A and B, compared to D and C [15,94–96]. No pediatric studies have yet investigated the role of genotype on response to antiviral therapy, and genotype determination before treatment is not currently recommended (**C2**), until the role of the viral genotype

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

Treatment	Licensing	Dose	Duration	Advantages	Disadvantages
IFN-α	≥12 mo	5-10 M units/m² sc three times weekly	6 mo	• No resistance • Licensed for young children • Short treatment	• Side effects • Parenteral administration • Not usable if decompensated cirrhosis or transplantation
Lamivudine	≥3 yr	3 mg/kg po once daily (max 100 mg/die)	≥1 yr	• Few side effects • 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 • High resistance rate (increasing with time of treatment)
Entecavir	≥16 yr + phase III (2-17 yr)	0.5 mg po once daily (1 mg/day for lamivudine-resistant pts)	≥1 yr (+ 6 mo after HBeAg seroconversion)	• Low resistance rate • Oral administration	• Not approved for children <16 yr
Tenofovir	≥12 yr	300 mg po once daily	≥1 yr	• High response rate • No resistance identified • Few side effects • Oral administration • Usable in 3rd trimester of pregnancy	• Not approved for children <12 yr • Reduced mineral density in children
PegIFNα	Phase III (2-18 yr)	180 µg/wk	6 mo	• No resistance • Once weekly administration • Short treatment	• Side effects • Parenteral administration • Not usable if decompensated cirrhosis or transplantation
Telbivudine	Phase I (2-18 yr)	600 mg po once daily	≥1 yr	• Few side effects • Oral administration • Usable in 3rd trimester of pregnancy	• High resistance rate

Table 3. Efficacy and safety of treatments for chronic hepatitis B [82,83,86,188]. (See below-mentioned references for further information.)

Treatment	Study	P/A	Type	Patients (N treat./cont.)-duration	VR % treat/cont (p value)	Serological response % HBe loss/HBe SC/HBs loss			Resist. %	HR % treat/cont (p value)	More frequent side effects (% treat./cont.)
						Treat	Cont	p value			
IFN-α	Sokal 1998 [60]	P	OL RCT (vs. PLB)	HBeAg+, ALT >1.5x (70/74)-24 wk	26/11 (0.029)	72/-/10	-/-/1	-/-/0.03	-		Flu-like symptoms (100/0), behavioral disorders (40/4), nausea/vomiting (40/8), diarrhea (46/16), neutropenia (19/5), alopecia (17/0)
	Wong 1993 [112]	A	Meta-analysis	HBeAg+ (498/339)	37/17 (-)	33/-/8	12/-/2	0.0001/-/0.001	-		Flu-like symptoms, leukopenia and thrombocytopenia, depression, alopecia. Dose reduction in 20%, termination in 5%
PegIFNα	Lau 2005 [103]	A	PDB RCT (vs. Lam)	HBeAg+, ALT >1x (271/272)-48 wk	25/40 (-)	30/27/3	22/20/0	-	-	I 49/51 (-)	Pyrexia (49/4), fatigue (40/14), headache (28/10), myalgia (26/3), alopecia (20/2), anorexia (15/2), pruritus (10/2), arthralgia (9/3), depression (5/1), ALT elevation, neutropenia, thrombocytopenia
	Janssen 2005 [104]	A	DB RCT (vs. PegIFN + Lam)	HBeAg+, ALT >2x (118/114)-52 wk	10/33 (<0.0001)	29/22/5	44/25/7	0.01/0.52/0.54	-	I 22/33 (-)	Flu-like symptoms (62/74), fatigue (43/42), headache (40/45), myalgia (30/32), alopecia (19/27), anorexia (16/16), arthralgia (16/15), depression (21/22), neutropenia (21/26), thrombocytopenia (13/11)
Lamivudine	Jonas 2002 [61]	P	DB RCT (vs. PLB)	HBeAg+, ALT >1.3x (191/95)-52 wk	23/13 (0.04)	26/22/2	15/13/0	0.03/0.06/-	19		Adverse events similar between treated and untreated children
	Sokal 2006 [81]	P	OL extension	HBeAg+, ALT >1.3x, Lam 52 wk (134)-36 mo	28/-	-/25/2	-	-	64		ENT infections (37), headache (19), abdominal pain (14), nausea/vomiting (13), ALT increase (3)
	Dienstag 1999 [210]	A	DB RCT (vs. PLB)	HBeAg+, ALT >1.3x (66/71)-52 wk	44/16 (<0.001)	32/17/2	11/6/0	0.003/0.04/-	32		Malaise/fatigue (19/20), nausea/vomiting (9/15), headache (9/8), abdominal discomfort (4/7), rash (6/8), diarrhea (6/6)
Adefovir dipivoxil	Jonas 2008 [62]	P	DB RCT (vs. PLB)	HBeAg+, ALT >1.5x (115/58)-48 wk	11/2 (-)	17/16/-	5/5/-	-/0.051/-	0		Mild CK increase (22/26), mild creatinine increase (16/11), severe hepatic flare (3/0)
	Jonas 2012 [89]	P	OL extension	HBeAg+, ADV 52 wk (108)-240 wk	35/-	-	-	-	0.9		Severe hepatic flare (3), mood disorders (2), growth retardation
	Marcellin 2003 [120]	A	DB RCT (vs. PLB)	HBeAg+, ALT >1.2x (172/170)-48 wk	21/0 (<0.001)	24/12/-	11/6/-	<0.001/0.049/-	0		Flu-like symptoms (16/19), headache (25/22), abdominal pain (18/19), nausea (10/14), diarrhea (13/8), ALT increase >10x (10/19)
	Marcellin 2008 [90]	A	OL extension	HBeAg+, ADV 2 yr (171)-240 wk	39/-	58/48/2	-	-	20		Asthenia (18), headache (14), abdominal pain (11), anorexia (6), nausea (6), diarrhea (6), ALT increased (18), creatinine increase (8)

Treatment	Study	P/A	Type	Patients (N treat./cont.)-duration	VR % treat/cont (p value)	Serological response % HBe loss/HBe SC/HBs loss			Resist. %	HR % treat/cont (p value)	More frequent side effects (% treat./cont.)
						Treat	Cont	p value			
Entecavir	Chang 2006 [91]	A	DB RCT (vs. Lam)	HBeAg+, ALT >1.3x (354/355)-48 wk	67/36 (<0.001)	22/21/2	20/18/1	0.45/0.33/0.52	0	K 72/62 (0.009) I 7/-	ALT elevation (10/17), post-treatment flare (2/12)
	Chang 2010 [197]	A	OL extension	HBeAg+, ALT >1.3x (94)-240 wk	94/-	31/-/5	-	-	0.7	-	Upper respiratory tract infections (31), headache (21), diarrhea (16), abdominal pain (10), ALT flare (0.7), increased ALT (1), liver abscess (1)
	Chang 2010 [198]	A	OL extension	HBeAg+/-, ALT >1.3x (57)-6 yr	100/-	55/33/0	-	-	1.2	K 96/- I 58/-	-
Tenofovir disoproxil fumarate	Murray 2012 [99]	P	DB RCT (vs. PLB)	HBeAg+/-, ALT >2x (51/50)-72 wk	89/0 (<0.001)	21/-/2	15/-/0	n.s./-/n.s.	0	-	Headache (4/15), upper respiratory tract infections (10/13), acne (19/4), abdominal pain (6/13), ALT increase (6/22), >4% decreased BMD (6/4)
	Marcellin 2008 [97]	A	DB RCT (vs. ADV)	HBeAg+, ALT >2x, 12-18 yr, (176/90)-48 wk	76/13 (<0.001)	-/21/3	-/18/0	-/0.36/0.02	0	K 78/71 (n.s.)	Headache (13/14), nasopharyngitis (10/11), nausea (9/3), fatigue (8/7), diarrhea (7/5), ALT flare (1/2), ALT increase (3/1), creatinine elevation (0/1)
	Marcellin 2013 [196]	A	OL extension	HBeAg+, TDF 48 wk, (266)-240 wk	65/-[b]	49/40/10	-	-	-	I 98/-	Serious adverse events (2%: ALT increase, osteoporosis, osteopenia, mild renal falure, acute pancreatitis, LDH increase), creatinine increase (1)
	Gordon 2013 [195]	A	OL extension	HBeAg+/-, TDF 48 wk, (489)-240 wk	98/-[a]	55/45/10	-	-	0	-	
Telbivudine	Liaw 2009 [108]	A	DB RCT (vs. Lam)	HBeAg+, ALT >1.3x (458/463)-104 wk	56/39 (<0.001)	35/30/1	29/25/1	0.06/0.1/0.99	25	-	CK elevation (13/4), ALT elevation (6/12), ALT flares (2/5), upper respiratory tract infections (18/16), fatigue (13/12), headache (12/13), diarrhea (7/6)
	Wursthorn 2010 [126]	A	OL extension	HBeAg+, ALT >1.3 (205)-3 yr	-	71/57/6	-	-	-	-	

Table 3 reports studies on HBeAg-positive chronic hepatitis as, in children and adolescents, it is much more common than HBeAg-negative hepatitis.P, pediatric study; A, adults study; VR, virological response; SC, seroconversion; DB, double-blind; PDB, partially double-blind; OL, open-label; RCT, randomized controlled trial; HR, histologic response [reduction of 2 or more points in the Knodell necroinflammatory score (K), with no worsening in the fibrosis score, or in the Ishak fibrosis score (I) at the end of the study protocol, as compared to baseline], n.s., not significant.
[a]On-treatment analysis.
[b]Intention-to-treat analysis.

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in assigning children to treatment and in predicting response has been clarified. A decrease of the HBsAg serum levels after the first 3 months of treatment predicts SVR and HBsAg loss in adults treated with pegylated IFN (PegIFN), but no data are available in children treated with IFN-α [97–99].

The likelihood to respond to lamivudine is greater in children with higher ALT levels (at least twice the ULN), and high histologic activity index at baseline **(A1)** [60,75]. In adult patients, the same parameters, as well as low HBV DNA levels (HBV DNA $<2 \times 10^8$ IU/ml), were predictive of response to all NA **(A1)** [85,90,100,101]. No significant difference in response to NA was found among different genotypes **(A1)** [102,103]. In adults, VR at 24 weeks during treatment with lamivudine or telbivudine (and 48 weeks during treatment with adefovir) is associated with a higher chance of HBeAg seroconversion, maintained virological response, and lower incidence of resistance **(B1)** [90,104–106]. The decline of HBsAg serum levels during NA treatment predicts HBeAg seroconversion or HBsAg loss **(C2)** [107–109].

Treatment strategy

Currently, a finite-duration IFN-α therapy remains the treatment strategy of choice for HBeAg-positive children with elevated ALT levels **(A1)**, as in this patient population seroconversion to anti-HBs is the main aim. IFN-α is the only available treatment offering a chance of sustained off-treatment VR. It is likely that, as soon as results of trials using PegIFN in children [89] are available, this medication will become the recommended drug. Although adverse effects may be serious and a clear benefit on the long-term remains to be confirmed, the use of IFN-α is not associated with the emergence of genotypic resistance. The recommended regimen is 5–10 million units per square meter, three times weekly for 6 months **(A1)**. For PegIFN, studies in adults show the highest HBeAg seroconversion rate with 48-week treatment schedules [166] **(A1)**. IFN-α is contraindicated in children with decompensated cirrhosis, cytopenia, autoimmune disorders, cardiac or renal failure, and in transplanted patients **(B1)** [68]. The possible benefit of priming with corticosteroids has not been proven **(C2)** [110–112]. On-treatment response was higher with the combination of IFN-α and lamivudine than with IFN-α alone, both in adults and in children, but no benefit was seen for off-treatment response rate [76–80,87,88,167]. Thus, the combination is currently not recommended **(C2)**. Furthermore, in adults combined IFN-α and telbivudine treatment has been reported to be associated with polyneuropathy **(A1)** [168]. IFN-α is the only treatment licensed for treating children younger than 3 years of age, who however rarely require therapy **(A1)**. In this age group, the risk of IFN-related neurotoxicity (although mostly minor and transient) has to be taken into account [59,113]. In case of no response, at least 6–12 months should elapse before considering other therapies, as VR may be achieved during the 6 months following the end of IFN-α treatment **(B1)**.

NA used to be second-line therapies because of the high risk of emergence of resistant mutant strains. Nevertheless, the recent FDA approval of NA with higher genotypic barrier to resistance has opened the way for the use of such drugs as first-line treatment for adolescents. In patients older than 12 years of age, tenofovir (or entecavir for patients ⩾16 years old) is the best choice, as response rate is high and resistance is less likely **(A1)**. The

recommended dose for tenofovir is 300 mg once daily, and for entecavir is 0.5 mg once daily (for nucleoside-naïve patients) **(A1)**. Although not yet approved for the treatment of CHB in patients <12 years of age, the use of tenofovir might be safe in younger children, as it is already widely used (and FDA-licensed) for patients older than 2 years of age with HIV infection. A phase 3 clinical trial in 2–11-year-old CHB patients is currently underway [189]. Since the approval of tenofovir for adolescents, adefovir is no more recommended because of the higher risk of resistance and the lower response rate **(B1)** [61,81].

A finite-duration treatment with tenofovir or entecavir is possible if seroconversion to anti-HBe is achieved on treatment **(C2)**. Duration of treatments with NA has not been established, but they should be continued for at least 12 months after reaching undetectable HBV DNA levels and HBeAg seroconversion **(B1)** [8,169]. As an important proportion of adult patients was shown not to maintain their serological and virological response, treatment up to HBsAg clearance could be a safer choice for patients with histological evidence of severe fibrosis **(C2)** [170]. Patients should be monitored after discontinuation because of the possibility of post-treatment flares **(B1)**.

Patients who do not undergo HBeAg seroconversion on treatment, the rare children with HBeAg-negative chronic hepatitis and cirrhotic patients need long-term treatment with NA **(B1)**. Tenofovir or entecavir, if allowed by the age, are the first choice **(A1)**. Long-term efficacy and safety data in adults support such a strategy, but no data are available for adolescents as yet [173–176]. During long-term treatment with NA, HBV DNA levels should be monitored every 3 months, as HBV DNA reduction to undetectable level is of paramount importance to avoid resistance **(B1)**.

Although guidelines in adults do not recommend the use of lamivudine monotherapy [6,8], the risk of the emergence of resistant strains has to be balanced against the fact that lamivudine is the only NA currently approved for younger children. Its use should be limited to the rare young children unresponsive to IFN-α and requiring immediate treatment and to special populations (see below) **(C1)**. The recommended treatment dose for lamivudine is 3 mg/kg/day (maximum 100 mg/day), administered orally once daily **(A1)** [114]. Optimal treatment duration is more difficult to determine. Treatment should be continued until VR is achieved, and possibly for 12 months after seroconversion **(B1)** [75,169]. As 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 resistant mutations emerge **(B1)**. As post-treatment ALT flares are possible, children should be carefully monitored and a reinstitution of lamivudine treatment (in patients who have not developed resistance) or an alternative therapy (tenofovir if possible for the age) should be started in the rare cases with severe and protracted ALT elevation **(A1)** [115]. For children with cirrhosis, who need antiviral treatment to be continued, switch to tenofovir (if ⩾12 years of age), alone or in combination with entecavir (if ⩾16 years of age) or maintenance of lamivudine (if <12 years of age) despite an incomplete VR is recommended **(C2)** [171,172]. Combination therapy with IFN-α and lamivudine is promising, but further data are needed in children **(C2)**. Combination therapy with adefovir and lamivudine has been tried only in children not responding to adefovir monotherapy, and its efficacy has not been compared to monotherapy [81].

Although no data are available from pediatric studies, current guidelines in adults suggest that, for HBeAg-negative patients who have persistently elevated ALT values (at least 3 measurements in 12 months) and high HBV DNA levels, the same treatment algorithm applied to HBeAg-positive children should be considered **(C1)** [6,8]. Nevertheless, attention should be paid to the higher relapse rate and the longer duration of treatment needed [116–118].

Treatment failure and antiviral resistance

Partial response to NA or primary non-response is often due to the emergence of genotypic resistant strains or to patient non-adherence to treatment. In non-responders, HBV genotypic analysis is warranted in order to differentiate between resistance and patient non-compliance **(C1)**. Non-compliance may be a major issue in adolescents, especially if long-term treatment is required to maintain response.

In responders, virologic breakthrough (which may be followed by biochemical breakthrough) is usually secondary to genotypic resistance. Likelihood of virologic breakthrough depends on the intrinsic barrier to resistance of the specific NA (lamivudine >telbivudine >adefovir >entecavir >tenofovir). All children receiving NA should be monitored for virologic breakthrough by measuring HBV DNA levels every 3 months **(C1)**. Ideally, identification of virologic breakthrough and consequent adaptation of treatment should be performed as early as possible, before ALT levels rise [6,69]. Because of the low number of effective drugs approved, when resistance to an NA develops in children, the decision on therapy adjustment is based on liver biopsy and the patient's age. If mild hepatitis is present, he/she should be switched to either entecavir (for adefovir-resistant, ⩾16 years old and lamivudine-naïve patients) or tenofovir (for ⩾12 years old, lamivudine-resistant patients or adefovir-resistant patients previously treated with lamivudine) **(C2)**. For younger children, for whom no other NA other than lamivudine is approved at the moment, switching to IFN-α (Peg-IFN when approved) can be a possibility **(C2)**. Treatment with lamivudine should be stopped and the child should be followed up in the eventuality of post-treatment flares **(C2)**. In case of moderate hepatitis/fibrosis, the patient should be switched to tenofovir if ⩾12 years old, or, if younger, to IFN-α **(C2)**. If severe hepatitis is found at liver biopsy, switching to tenofovir is the only available choice (as monotherapy or associated to entecavir if the child is ⩾16 years old and has high viral load) **(C2)** [171,172]. Both tenofovir and entecavir are effective in lamivudine-resistant patients [69], but an increased resistance rate has been observed for entecavir (8% after 2-year treatment) and higher dose (1 mg daily) is required **(B1)** [84,119]. Lamivudine should therefore be discontinued when switching to entecavir to decrease the risk of emergence of resistant mutants **(C2)** [6]. Tenofovir can be used in lamivudine-resistant mutant strains, as their activity is not hampered by such mutations **(B1)** [69,81].

In patients with partial virological response at week 24 (for those receiving lamivudine) or 48 (for those receiving adefovir), switch to tenofovir or entecavir (if allowed by the age) is recommended **(B1)**. The strategy for children younger than 12 years of age is difficult to define. Patients could be switched to IFN-α (or PegIFN) if not tried yet **(C1)**, or lamivudine could be either

continued up to the 12th birthday (the only choice in those with severe fibrosis or cirrhosis) or stopped (with proper post-treatment follow-up) **(C2)**.

As the emergence of resistant mutant strains is becoming a major public health problem, pediatric practitioners should not treat children who are not likely to benefit from a licensed therapy and consider waiting for market approval of more effective drugs **(C1)**.

Special populations

Treatment strategies for special populations of HBV infected children are rarely based on strong evidence. Indications and type of treatment are decided on the basis of few available case reports and are often extrapolated from evidence obtained in adult patients. Such children should be referred to specialized tertiary centers where individualized treatments (even with off-label newer antivirals) can be administered.

Immunocompromised children

All children candidate for chemotherapy or immunosuppressive therapy should be screened for HBsAg, anti-HBs, and anti-HBc, and seronegative patients should be vaccinated **(A1)**. Prophylactic treatment with NA should be considered for inactive carriers requiring immunosuppressive therapy (transplanted patients, patients undergoing cytotoxic chemotherapy, corticosteroids treatment, rituximab, anti-TNF-α or other monoclonal antibody therapies), in order to prevent reactivation **(A1)** [6,120]. NA treatment should be continued for 12 months after cessation of the immunosuppressive therapy **(C1)**. NA with high genetic barriers to resistance should be used for patients with CHB and for inactive carriers requiring long or repeated cycles of immunosuppressive therapy **(C1)**. Lamivudine could be sufficient for children with low viral load or requiring a short duration of immunosuppression **(C2)**. HBsAg-negative, anti-HBc-positive children (prior infection) should be treated as HBsAg-positive subjects if they have detectable HBV DNA **(C2)**. If they have undetectable HBV DNA levels, they should be followed and treated upon reactivation of HBV infection **(C2)**. Prophylaxis with lamivudine should be administered to HBsAg-negative, anti-HBc-positive children receiving rituximab or combined regimens for hematological malignancies or undergoing bone marrow or stem cell transplantation **(C1)** [177–181].

Organ transplantation

If the recipient has been successfully immunized before surgery, the risk of HBV infection after transplantation of non-hepatic solid organs from HBsAg-negative, anti-HBc-positive donors (i.e., with past HBV infection) is low, despite immunosuppression [121]. The risk of infection is higher after liver transplantation from anti-HBc-positive donors, with a 10% rate of *de novo* hepatitis in successfully vaccinated recipients and 69% recurrence rate in HBsAg-positive recipients [122–124]. Presence of anti-HBs antibodies *per se* does not guarantee protection against *de novo* HBV infection, whereas the achievement of a high anti-HBs titer (>200 mIU/ml) is protective [125]. Therefore, immunization (with the achievement of an adequate anti-HBs titer) and prophylaxis with lamivudine, tenofovir or entecavir (according to patient's

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age) for an indefinite period of time, and HBIG are recommended when transplanting an anti-HBc-positive liver to an HBV naïve recipient (**C1**) [126]. Anyway, because of the long post-transplant life expectancy, HBc-positive liver grafts should be discarded when transplanting pediatric patients (**C2**).

Co-infection with HIV, HCV or HDV

HIV infection should be ruled out in children from high-prevalence countries, as well as in adolescents who are injection drugs users. HBV/HIV-co-infected patients are at increased risk of disease progression [127]. Furthermore, they are at increased risk of developing resistance against lamivudine if used as monotherapy [128]. Because of the risk of inducing HIV resistance, entecavir should only be used in patients receiving effective antiretroviral therapy [129] (**A1**). In HBV/HIV-co-infected adult patients, the combination of tenofovir (approved for HIV-infected children ⩾2 years old) and emtricitabine or lamivudine is the recommended treatment (**A1**). Tenofovir monotherapy should not be administered to co-infected patients because of the risk of HIV resistance (**A1**). Until stronger pediatric evidence is available, such recommendations may be extrapolated to co-infected children (**C2**) [130,131]. The indications for therapy are the same as in HIV-negative patients. According to HHS pediatric guidelines, no HIV treatment is required if the CD4 count is ⩾500 cells/mm^3 in children ⩾5 years of age (⩾750 if aged 3 to <5 years and ⩾1000 if aged 1 to <3 years) [182]. In these cases, HBV may be treated before the institution of an anti-HIV therapy with drugs inactive against HIV (such as IFN-α or PegIFN) (**C2**).

HBV/HCV co-infection is rare, and few data are available. IFN-α (at doses recommended for HBV treatment) and ribavirin may be a good option (**C2**). HBV/HDV co-infected children have more severe liver disease than those with HBV alone. IFN-α is also the drug of choice for these patients, although the only pediatric study available has shown a transient effect with no therapeutic benefit in the long-term (24 months) compared to medium-term (12 months) treatment (**C2**) [132,133].

Acute hepatitis B

Acute symptomatic infection is rare in pediatric age, and it can vary from a mild to a fulminant hepatitis. Classic symptoms are present in 30–50% of older children and adolescents with acute hepatitis B and include fever, jaundice, nausea and vomiting, abdominal pain, liver tenderness, and fatigue, which last approximately 2–3 months. Less than 10% of infants born to HBeAg-positive mothers develop acute hepatitis, and jaundice may be the only sign [183,184]. Fulminant hepatitis is uncommon in infants and children but it is associated with a more than 40% mortality rate without liver transplantation [185,186]. Therefore, patients with fulminant hepatitis must be evaluated for liver transplantation (**A1**). Such patients may benefit from treatment with entecavir, tenofovir (according to the age of the patient) or lamivudine (**C2**) [187]. Although the duration of treatment is not defined, continuation of antiviral therapy for at least 3 months after anti-HBs seroconversion or 1 year after anti-HBe seroconversion may be recommended (**C2**) [8].

Pregnant women

No antiviral agent has been approved by the FDA for use in pregnancy. Lamivudine and entecavir are classified pregnancy class C by the FDA, while both tenofovir and telbivudine are class B. Although interference with organogenesis secondary to the activity of the drug on replication of mitochondrial DNA cannot be excluded, data from the Antiretroviral Pregnancy Registry has shown no increased incidence of birth defects with the use of lamivudine (3.1% when used during the first trimester and 2.7% during the second or third trimester) or tenofovir (2.4% and 2%, respectively) compared to the CDC's population-based birth defects surveillance system (2.72% of total prevalence) [134]. PegIFN is contraindicated during pregnancy (**A1**). Children of lamivudine-treated mothers have 13–23% lower incidence of intrauterine infection and 1–2% lower mother-to-child transmission rate [135,136]. Treatment with telbivudine during the third trimester of pregnancy has proven effective in

Table 4. Unsolved issues in the management of pediatric CHB.

• A better identification of children at higher risk for disease progression and/or HCC development would allow early treatment without increasing the risk of antiviral resistance
• Response to treatment of immunotolerant patients needs further attention. Large clinical trials are ongoing to assess whether this population responds to currently available or newer antiviral treatments
• More clinical trials should be conducted to understand the role of age on response to treatment (and to verify whether younger patients respond better than older ones)
• The relationship between HBV genotype and response to therapy needs to be clarified in pediatrics
• Pediatric licensing of newer drugs that are already the standard of care in adults needs to be speed up. Among such drugs, PegIFNα is highly promising, and its licensing for children will probably change management of pediatric CHB
• Indications for treating children with nucleos(t)ide analogues need to be better defined
• Optimal duration of treatment with nucleos(t)ide analogues is still a debated issue for both adult and pediatric patients. The right balance between the advantages of viral suppression and the risk of resistance to antivirals needs to be further studied in pediatric patients
• Children are still mostly treated with monotherapy. Possible advantages of combination therapy need to be tested by large clinical trials
• Management of non-response, of antiviral resistance and of special populations is still largely based on experts' opinion, with evidence extrapolated from adult studies. In view of the small number of patients with these conditions, multicenter pediatric studies are needed to assess different treatment strategies

reducing maternal viral load and preventing perinatal transmission (0% *vs.* 8% in controls) [137]. No studies are yet available for tenofovir. Nevertheless, in order to reduce the risk of mother-to-child transmission, treatment of highly viraemic (serum HBV DNA $>10^6$ IU/ml) HBsAg-positive women during the last trimester of pregnancy with tenofovir is currently recommended because of its high genetic barrier to resistance and the possibility to continue therapy post-partum if needed (**B1**) [8]. Although no studies have been conducted in pregnant teens, the same recommendations for treatment in the third trimester of pregnancy may apply (**C1**).

Household contacts

The extreme resilience of HBV, which allows its survival for more than a week on dry surfaces, is the cause of the significant risk of horizontal intrafamilial transmission. Counseling of HBV carriers and vaccination of uninfected household members are therefore essential [33,138]. Surprisingly, although between 8% and 24% of household contacts of HBV infected subjects (children and adults) have been reported to be HBsAg-positive [139–143], vaccination coverage in this high-risk group is still low (15–25%) even in developed countries [141,144–146]. All household contacts of an HBV infected child should be screened for HBsAg, HBsAb, and HBcAb in order to offer vaccination to those without protective antibody levels and diagnose those with a previously unknown infection (**C1**).

Conclusions

CHB is a mild disease in most children and adolescents. Nevertheless, a minority of patients is at risk of rapid disease progression and early development of complications, and a quarter of infected individuals develop serious complications in adult life. Treatment of patients with elevated ALT levels is overall satisfactory, but several unsolved issues need to be addressed (Table 4). IFN-α is still the treatment of choice for most children. Although in specialized centres PegIFN is currently used, this drug cannot be recommended until the results of ongoing trials become available. Licensing of highly-effective NA for older children and adolescents has opened new possibilities of treatment. Nevertheless, the risk of emergence of drug resistant strains is a public health problem and a major long-term issue for young patients. Before starting a child on NAs, therefore, the risks of treatment should be carefully weighed against the possible benefits, and treatment should be offered only to those patients who need to be treated and are likely to respond. While waiting for the results of ongoing trials, immunotolerant patients should not be treated, but monitored routinely to identify early signs of liver damage. As the management of special patient populations is problematic and not evidence-based, their referral to highly specialized centers is highly recommended.

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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