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HEPATITIS B (JK LIM, SECTION EDITOR)

Viral Hepatitis B—Management in Children

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Abstract

Purpose of Review Chronic hepatitis B (CHB) infection is a worldwide health problem with significant morbidity. Children with CHB require a lifetime of monitoring for infection activation, hepatic disease and its complications, and hepatocellular carcinoma (HCC). Children with CHB which is in the immune active stage are candidates for antiviral treatment. As new medications have been approved for children, the treatment recommendations have changed. This review summarizes the recent data.

Recent Findings With the demonstration of safety and efficacy of entecavir and tenofovir in children, previously used medications like lamivudine and adefovir are no longer recommended as the first-line treatments.

Summary Health care providers should provide counseling regarding monitoring, natural history, and transmission to children with CHB and their families. Children in the immune active stage are candidates for antiviral treatment. With more approved therapies over the last few years for a wider age range of children, there are safe, effective, and well-tolerated therapeutic options.

Keywords Children · Pediatric · Chronic hepatitis B · Treatment · Management · Viral hepatitis

Background

The natural history of chronic hepatitis B virus infection in children varies with age at infection, acquisition, ethnicity, and endemic region. Around the world, most chronic hepatitis B virus (HBV) infection is transmitted perinatally or during early childhood. The global burden of disease was recognized by the World Health Organization (WHO) in 2016 when it started the Global Health Sector Strategy on Hepatitis 2016–2021 [1, 2]. This initiative is aimed at elimination of hepatitis B as a public health threat by 2030 by reducing the incidence of chronic infection by 90%. This will be measured by a reduction of the prevalence of chronic HBV in children age 5 years. This is because the risk of chronic infection when acquired in infancy is 90%, 30% when acquired during the first 5 years of life, and < 5% in older childhood and adulthood [3]. Loss of hepatitis B e antigen (HBeAg), or seroconversion to anti-HBe can occur spontaneously, and the annual rate differs by age < 2% in children under 3 years, 4–5% after age 3, with higher rates during puberty [4, 5]. Children from non-endemic areas are less likely to have been perinatally infected and will often undergo HBeAg seroconversion in the first 2–3 decades of life [6].

Although most children are in the immune tolerant stage of HBV infection, those with immune active HBV by definition have abnormal alanine aminotransferase (ALT) values. In children, as in adults, with cessation of HBV replication, serum alanine aminotransferase (ALT) becomes normal, HBeAg is lost with or without the development of anti-HBe, and there is improvement in liver histology. Due to the persistence of covalently closed circular DNA (ccc DNA), the transcriptional template of HBV, in the nucleus of hepatocytes, patients who have undergone HBeAg seroconversion cannot be considered "cured" [7, 8]. These patients are at lifelong risk for reactivation of infection. If patients lose the hepatitis B surface antigen (HBsAg), typically with persistent HBV DNA suppression, this is considered to be an "immunological cure." This is true whether seroconversion occurs spontaneously or as a result of treatment, although HBsAg loss is rare during the childhood years.

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The most serious sequelae of chronic hepatitis B (CHB), cirrhosis and hepatocellular carcinoma (HCC), are not commonly seen during childhood and adolescence. In a study of 292 consecutive HBsAg-positive children with elevated ALT levels, 10 patients (3%) had cirrhosis [9]. In adults, HCC is thought to be related to HBV DNA level, degree of liver injury, and duration of infection. HCC can occur in children who have had HBeAg seroconversion, indicating that the risk of HCC continues even after viral replication has ceased [10].

AASLD [11, 12], WHO [13], European Association for the Study of the Liver (EASL) [14, 15], and the ESPGHAN [16], guidelines all agree that the goal of treatment is to improve long-term survival and decrease the morbidity associated with chronic HBV infection. Although these guidelines also agree the optimal endpoint of treatment is persistent HBsAg clearance, which indicates a halting of disease progression and thereby a reduction in the risk for HCC, this endpoint occurs rarely in treated patients. If this is not attained, the next goal of therapy is to reach sustained undetectable HBV DNA levels and anti-HBe seroconversion in patients who were previously HBeAg-positive, along with ALT normalization. Alternatively, undetectable HBV DNA while under prolonged antiviral therapy is also a reasonable goal, although this is not ideal for pediatric patients.

Indication for Treatment

Selecting patients who can benefit from treatment and determining the optimal time for treatment are important decisions in order to maximize benefit while limiting the duration of therapy to minimize the risk for drug resistance later in life.

There are no data regarding the treatment of acute HBV infection in children. Most children who are infected perinatally are asymptomatic. If children develop acute fulminant hepatitis, typically the viremia and HBsAg rapidly clear without treatment. Most children who develop chronic HBV after maternal-to-child transmission have persistently normal ALT levels, high HBV DNA levels and HBeAg in keeping with an immune-tolerant state, but immune activation can occur [11].

Children with ALT levels ≤ 1.3–2 times the upper limit of normal (ULN), positive HBeAg, and high HBV DNA levels (> 10 million IU/ml) are in the immune tolerant phase of HBV infection. These children are not candidates for treatment because current therapies have not been shown to induce HBeAg seroconversion when compared with no treatment [12, 13]. Thus, the American Association for the Study of Liver Diseases (AASLD) recommends against the use of therapy in these children, regardless of the HBV DNA level [11]. In addition, children with ALT values greater than 10 times the ULN may be in the process of spontaneous HBeAg seroconversion and should be observed for several months before the decision to proceed with treatment is finalized. For patients with DNA level < 10^4 IU/mL but elevated ALT, therapy can be deferred until other etiologies of liver disease and spontaneous HBeAg seroconversion are evaluated.

The AASLD recommends treatment for children ages 2 to < 18 years who are HBeAg-positive with persistently elevated ALT (> 1.3 times the ULN at least 2 occasions over at least 6 months in HBeAg + or 12 months in HBeAg—children) and HBV DNA levels of ≥ 2000 IU/ml [11, 12]. The AASLD guidelines recommend using ALT 35 U/L for adult males and 25 U/L for adult females for the ULN thresholds for treatment [12]. The 2015 World Health Organization (WHO) and 2013 European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines state that treatment priority should be given to children with clinical evidence of compensated or decompensated cirrhosis, regardless of ALT levels, HBeAg status, or HBV DNA levels [13, 16]. In addition, according to those guidelines, treatment of patients with advanced inflammation or fibrosis or family history of HCC should be considered [16].

Treatment Options

Therapies for children with chronic hepatitis B include biologic preparations (pegylated interferon-alfa 2a, interferon-alfa), oral nucleoside (lamivudine, entecavir), and nucleotide (adefovir dipivoxil, tenofovir disoproxil fumarate, tenofovir alafenamide) analogs (NA). There are currently 6 agents (interferon-α-2b, pegylated interferon alfa- 2a, lamivudine, adefovir, tenofovir disoproxil fumarate, entecavir) approved for treatment for children or adolescents in the United States by the Food and Drug Administration (FDA). Current treatment options for children in the USA have acceptable safety profiles (Table 1).

Therapeutic trials in children have included HBeAg-positive patients with at least mildly elevated ALT (> 1.3 times the ULN with the usual ULN of 30 U/L). Since endpoints such as cirrhosis, HCC, and death are rare in children, these studies typically invoked intermediate endpoints including the normalization of ALT, HBV DNA clearance/suppression, HBeAg loss, and seroconversion, or a combination of these factors. Studies used different assays for the measurement of HBV DNA level, but all studies included only HBeAg-positive patients. There have been no studies of therapy for HBeAg-negative children, since this is rare during childhood and adolescence.

A meta-analysis examined randomized controlled trials (RCT) and observational studies of children < 18 years with chronic HBV infection [17]. After searching 2321 citations, 14 qualifying studies with children were identified, in which some of the patients were followed for up to

Table 1 Recommended antiviral therapies approved for use in children in the USA

Drug	Age	Dose	Possible Side Effects	Monitoring while on treatment
Pegintereron alpha-2a	3 to < 18 years	180 mcg/1.73 m^2 x BSA SC weekly Max dose-180 mcg/dose	- Flu-like symptoms -Fatigue - Mood changes -Nausea, anorexia and weight loss - Cytopenias	- CBC (q 1–3 months) - TSH (q 3 months) - Monitor for autoimmune, ischemic, neuropsychiatric and infectious issues
Interferon-α-2b	≥ 1–18 years	6 million IU/m^2 TIW	- Flu-like symptoms - Fatigue - Mood changes - Cytopenias - Autoimmune disorders	- CBC (q 1–3 months) - TSH (q 3 months) - Monitor for autoimmune, ischemic, neuropsychiatric and infectious issues
Entecavir	≥ 2 years	For treatment naïve For 10–30 kg, there is weight-based dosing - 0.15 mg (10–11 kg) - 0.2 mg (> 11–14 kg) - 0.25 mg (> 14–17 kg) - 0.3 mg (> 17–20 kg) - 0.35 mg (> 20–23 kg) - 0.4 mg (> 23–26 kg) - 0.45 mg (> 26–30 kg) - 0.5 mg (> 30 kg) For lamivudine experienced - 0.3 mg (10–11 kg) - 0.4 mg (> 11–14 kg) - 0.5 mg (> 14–17 kg) - 0.6 mg (> 17–20 kg) - 0.7 mg (> 20–23 kg) - 0.8 mg (> 23–26 kg) - 0.9 mg (> 26–30 kg) - 1 mg (> 30 kg)	Lactic acidosis	Lactic acid levels if concerned
Tenofovir DF	≥ 2 yrs and weighing ≥ 10 kg	8 mg/kg/dose once daily Max dose: 300 mg daily	-Nephropathy -Fanconi syndrome -Osteomalacia, decrease in bone density -Lactic acidosis	-CrCl at baseline -If at risk for renal impairment, CrCl, serum phos, urine glucose, and protein yearly - In patients with fractures or risk for osteopenia, bone density at baseline and during treatment - Lactic acid levels if concerned

Abbreviations: *BSA* body surface area, *CBC* complete blood counts, *TSH* thyroid-stimulating hormone, *CrCl* creatinine clearance

15 years. Twelve of the RCTs studied intermediate treatment endpoints: ALT normalization, HBV DNA suppression, HBeAg/HBsAg seroconversion, and HBeAg/HBsAg loss. Looking at all RCTs with post-treatment follow-up both < 12 months and ≥ 12 months, anti-viral treatment was more effective than placebo to achieve all intermediate endpoints: ALT normalization, HBeAg clearance loss, HBV DNA suppression, HBeAg seroconversion, and HBsAg clearance.

Biologic Therapies

Interferon (IFN) is a cytokine with immunomodulatory and antiviral properties [18]. IFN-α affects HBV by binding to its cellular receptor and activates secondary messengers which then help promote defense of the cell against viruses. IFN-α also enhances immunomodulation by increasing antigen presentation to the immune system, activation of natural killer cells, and increased production of cytokines. Antiviral effects include degradation of viral mRNA, inhibition of viral protein synthesis, and prevention of cell infection.

In a RCT in children, IFN-α did not significantly reduce the risk of either HCC (RR 0.3) or cirrhosis (RR 0.2) [19, 20]. In RCTs looking at < 12-month follow-up from therapy, pediatric patients treated with IFN-α were found to have statistically improved HBeAg clearance/loss (RR 3.2) [21–24] and HBV DNA suppression (RR 2.2) [21–26] compared to no treatment. However, IFN-α treatment did not result in ALT normalization (RR 1.4) [21–23, 26], HBeAg seroconversion (RR 2.8) [24], or HBsAg clearance (RR

7.4) [23]. When followed for ≥ 12 months post-IFN-α treatment, there was improved HBeAg clearance/loss (RR 2.0) [21, 24, 26, 27] and HBeAg seroconversion (RR 3.1) [24, 27], but not ALT normalization (RR 1.4) [28], HBV DNA suppression(RR 1.5) [21, 22, 27], HBsAg clearance (RR 3.3) [25, 29], or HBsAg seroconversion (RR 2.5) [23, 28].

In the USA, for children older than 1 year of age, interferon-α-2b is approved for a course of 24 weeks. Peginterferon (PegIFN) alfa-2a is recommended for the treatment of adults with CHB and chronic hepatitis C and has replaced IFN because of its once-weekly injection requirement and improved efficacy and safety. In 2017, the FDA and European Medicine Agency (EMA) approved PegIFN alfa-2a for pediatric patients age 3 to < 18 years with CHB for once weekly therapy for 48 weeks. A randomized, controlled, open-label, international multicenter phase III study studied PegIFN alfa-2a in children (age 3 to < 18 years) with HBeAg-positive (≥ 6 months), HBV DNA (> 2000 IU/mL), and elevated ALT (> 1 × but ≤ 10 × ULN), without advanced fibrosis [29]. Patients were randomized to receive either PegIFN alfa-2a or no treatment for 48 weeks HBeAg seroconversion rates at 24 weeks post-treatment were significantly higher in treated children (25.7% vs. 6%; $P = 0.0043$), as were the rates of hepatitis B surface antigen (HBsAg) clearance (8.9% vs. 0%; $P = 0.03$), hepatitis B virus (HBV) DNA < 2000 IU/mL (28.7% vs. 2.0%; $P < 0.001$) or undetectable (16.8% vs. 2.0%; $P = 0.0069$), and alanine aminotransferase (ALT) normalization (51.5% vs. 12%; $P < 0.001$). Overall, PegIFN alfa-2a treatment was efficacious, well tolerated, and associated with a higher incidence of HBsAg clearance than in adults.

The major advantage of interferon treatment is the lack of resistance and the possibility of off-treatment sustained virological response, chance of HBsAg loss, and undetectable HBV DNA. Like in adults, children can experience flu-like symptoms with interferon treatment. Body weight and growth have also been reported to be influenced transiently in children [15]. While it is advantageous to have a defined treatment course, the three times per week injection schedule can be more challenging in children. There are several relative contraindications for its use in patients with decompensated cirrhosis, hypersplenism, thyroid disease, autoimmune disease, severe coronary artery disease, renal transplant status, pregnancy, seizures, psychiatric illness, thrombocytopenia, leucopenia, retinopathy, and certain concomitant medication use [13].

Oral Therapies

The oral antiviral therapies currently approved for children in the USA are lamivudine, adefovir, tenofovir DF, and entecavir. Of these medications, lamivudine and adefovir are no longer recommended as the first-line therapies. The main advantage for the NA over IFN is the once-daily oral dosing and tolerability. A disadvantage of NAs is it may require a long-term, potentially life-long therapy, with high long-term costs and the risk of developing drug resistance [13]. In addition, all NAs carry a black box warning from the US FDA for lactic acidosis, although this is exceedingly rare in CHB. NAs are primarily renally excreted, and dose adjustments are necessary with renal functional impairment. The cost of therapy is also quite variable especially in resource-poor areas with a higher cost of TDF and entecavir in these areas. Regardless of oral NA chosen, treatment with oral antivirals has been studied for 1–4 years with the main therapeutic endpoint in children of HBeAg seroconversion. An additional 12 months of consolidation therapy (after HBeAg seroconversion) is recommended, as in adults. Once therapy is completed, monitoring every 3 months for the 1st year is recommended for signs of recurrent viremia, ALT elevations, and decompensation of clinical status.

Lamivudine was the first oral nucleoside analog reverse transcriptase inhibitor approved in the USA for the treatment of children younger than 12 years with chronic HBV.

In a RCT which studied lamivudine treatment for 48 weeks in children, patients were found to have a significant advantage in 3 of the intermediate endpoints including ALT normalization (RR 4.5), HBeAg clearance/loss (RR 1.8), and HBV DNA suppression (RR 3.9) but not HBeAg seroconversion (RR 1.7) or HBsAg clearance (RR 3.5) [30]. In children, resistance to lamivudine was developed in 19% at 1 year [30] of therapy and 67% after 2 years [31]. For this reason, lamivudine is not considered the first-line agent and has been largely replaced by entecavir or tenofovir in clinical practice.

Entecavir is a guanosine nucleoside analog active against HBV polymerase. When entecavir was studied in children for 48 weeks, compared to placebo, treated patients had higher rates of ALT normalization (RR 2.9), HBV DNA suppression (RR 14.8), and HBeAg seroconversion (RR 2.4) [32]. The only statistically significant difference with treatment at 96 weeks was for HBeAg seroconversion. The frequency for entecavir resistance is low due to a high genetic barrier. Entecavir-resistant variants are seen almost exclusively in lamivudine-experienced patients; when entecavir is used in that setting, a higher dose (double) is recommended. Entecavir is approved for children 2 years and older and dosing is based on body weight for children weighing less than 30 kg. Entecavir is well tolerated with the only side effect reported in patients with entecavir is lactic acidosis. For patients who do not undergo seroconversion, treatment duration is indefinite. If/when seroconversion is achieved, the general practice is to continue treatment for 1 year after seroconversion and/or indefinitely.

Adefovir dipivoxil is a nucleotide analog. In 1 RCT of pediatric patients treated for 48 weeks, adefovir was found

to produce a higher rate of ALT normalization (RR 2.7) and HBV DNA suppression (RR 1.1) but not HBeAg seroconversion (RR 3, 95% CI 0.9–9.9) when compared to placebo treatment [33]. When the same cohort of patients was followed in an open-label study for 192 weeks, adefovir-treated patients showed continued viral suppression and ALT normalization [34]. The rate of development of adefovir resistance mutations is lower than those reported for lamivudine. It has been predicted to be 5% at 12 months and 17% at 24 months in adults [35]. While adefovir is approved for the treatment of adolescents (≥ 12 years of age) in the USA, it has less potent antiviral activity than newer agents; therefore, its use is no longer recommended.

Tenofovir disoproxil fumarate (TDF) has been shown to be effective against wild-type and lamivudine-resistant HBV strains. Tenofovir DF is phosphorylated into the active form with a long half-life [36]. Like the other NAs, it also functions as a chain terminator but also is a poor substrate for cellular DNA polymerase [37]. Tenofovir DF is well tolerated with a similar safety profile to adefovir, but is more potent. Long-term studies of TDF in adults have not reported detectable resistance [38]. When TDF treatment was studied in an adolescent RCT for 72 weeks, in comparison to the placebo, there were higher rates of ALT normalization (RR 2) and HBV DNA suppression (RR 92.4) but no difference in the rate of HBeAg clearance/loss (RR 1.4) [39]. In a study of 89 children, 2 years to < 12 years old treated for 48 weeks, there was HBV DNA suppression in 77% of treated subjects when compared to 7% placebo [40].

Tenofovir disoproxil fumarate (TDF) is currently approved for children > *2 years and weight* > 10 kg. TDF has been reported to cause renal dysfunction, hypophosphatemia, and Fanconi syndrome (glycosuria, hypophosphatemia, metabolic acidosis) and the associated reduced bone density and osteomalacia/osteoporosis [41]. The AASLD practice guidelines recommend that patients on TDF should be assessed for renal safety with serum creatinine, phosphorus, urine glucose, and urine protein before treatment initiation and at least annually or more frequently during treatment [11, 14]. There is insufficient evidence to recommend monitoring of bone mineral density for pediatric patients on TDF, as the long-term effects on children's bone health is yet unknown.

Tenofovir alafenamide (TAF) is a nucleotide reverse transcriptase inhibitor and has the same mechanism of action as TDF. TAF is the more stable prodrug than TDF which leads to decreased plasma exposure to tenofovir and therefore reduces the risk of long-term TDF toxicities like nephrotoxicity and decreased bone mineral density. In November 2016, the FDA-approved tenofovir alafenamide (TAF), the prodrug of TDF, for use in adults with chronic HBV. It is reported to have similar efficacy but with greater plasma stability. Thus, the effective dose of TAF is much lower than TDF, resulting in lower rates of renal and bone adverse effects. Like other NAs, TAF also carries a black box warning for lactic acidosis, but also carries an additional warning for hepatomegaly with steatosis. The 2017 EASL clinical practice guidelines do include TAF in the recommendations for children, though no specific details on specific dosing or age groups were included [15]. In 2018, the European Medicines Agency approved the use of TAF for children aged 12 years and older who weigh more than 35 kg. Meanwhile, in the USA, the TAF trial (NCT02932150) is studying 25 mg once daily vs. placebo—a randomized, placebo-controlled trial in treatment-naïve and treatment-experienced adolescents aged 12 to < 18.

Monitoring

Patients and their caregivers should be counseled on the indications, possible benefits, and side effects of treatment. Practitioners should also assess their understanding of the need and willingness for long-term treatment and regular monitoring. In addition to immunizations for hepatitis A, patients should receive counseling regarding the risk of transmission to others, including the risk of environmental transmission. Household members should not share toothbrushes or razors, which can be contaminated with blood. However, there is no definitive evidence of HBV transmission from body fluids [12]. So, children with HBV infection should be allowed to participate in regular school, childcare, and sports activities without special arrangements other than following universal precautions [42]. Adolescents should also be counseled to prevent sexual transmission and avoid alcohol.

In all phases of HBV infection, children should undergo regular laboratory surveillance. While in the immune tolerance phase, they should have liver biochemical tests (ALT) every 6–12 months and HBeAg and HBeAb every 12 months. Hepatitis B DNA level is likely to be elevated and does not require regular monitoring during this phase.

For patients who are in the immune active phase, liver tests and serologies should be checked more frequently (3–6 months) to monitor for natural seroconversion. If seroconversion does not occur, then the patient can be considered for treatment. Liver biopsy is indicated for patients in the immune-active phase who are being considered for treatment or in patients with signs of advanced liver disease. For patients who are in the inactive chronic HBV phase (HBsAg-positive, HBeAg-negative, HBeAb positive, persistently normal ALT levels, and serum HBV DNA < 10^5 copies/mL), serum ALT should be checked every 6–12 months and HBeAg and HBeAb every 12 months. If the ALT is elevated, then the HBV DNA levels and HBV serologies should be rechecked to see if the disease is reactivating. The infection may reactivate even after years of quiescence; 4 to

20% of inactive "carriers" have one or more reversions back to HBeAg, and approximately 20–25% will develop HBeAg-negative chronic HBV [12].

For all patients with chronic HBV infection, HCC surveillance is warranted as HCC can develop regardless of active viral replication. We maintain surveillance of HCC in patients of all phases of HBV infection even though HCC is rare in children. This includes serial abdominal ultrasound and/or alpha-fetoprotein (AFP) levels, although data regarding optimal frequency and sensitivity are lacking in young patients. As HCC risk increases with age, young children are monitored less frequently (every 2–3 years), if the first AFP and ultrasound are normal.

Summary

Though most children with chronic hepatitis B infection typically do not develop advanced liver disease, complications such as HCC and cirrhosis are reported in childhood. Therapeutic trials in children show improvement in intermediate outcomes including ALT normalization, HBeAg loss, HBV DNA suppression, HBeAg seroconversion, and HBsAg loss when compared to no treatment or placebo. Unfortunately, the RCT evidence in children is limited due to a small number of studies, short duration of follow-up, and minimal data on significant outcomes—cirrhosis and HCC. Since cirrhosis and HCC development in childhood is rare, RCT in children uses intermediate outcomes (HBeAg seroconversion and viral suppression) to inform clinical decisions when treating children. Like in adults, the currently approved therapies for children are well tolerated. Care must be taken to determine the best regimens in order to minimize the development of resistance and side effects. Caregiver and patient preferences and capabilities must also be considered when decided the appropriate therapy and treatment course.

References

1. United Nations. Transforming our world: the 2030 agenda for sustainable development. New York: United Nations; 2015.
2. Indolfi G, Easterbrook P, Dusheiko G, Siberry G, Chang MH, Thorne C, Bulterys M, Chan PL, El-Sayed MH, Giaquinto C, Jonas MM, Meyers T, Walsh N, Wirth S, Penazzato M. Hepatitis B virus infection in children and adolescents. Lancet Gastroenterol Hepatol. 2019;4:466–76.
3. McMahon BJ, Alward WL, Hall DB, Heyward WL, Bender TR, Francis DP, Maynard JE. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. J Infect Dis. 1985;151:599–603.
4. Chang MH, Sung JL, Lee CY, Chen CJ, Chen JS, Hsu HY, et al. Factors affecting clearance of hepatitis B e antigen in hepatitis B surface antigen carrier children. J Pediatr. 1989;115(3):385–90.
5. Liaw YF, Chu CM, Lin DY, Sheen IS, Yang CY, Huang MJ. Age-specific prevalence and significant of hepatitis B e antigen and antibody in chronic hepatitis B virus infection in Taiwan: a comparison among asymptomatic carriers, chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. J Med Virol. 1984;13(4):385–91.
6. Bortolotti F, Cadrobbi P, Crivellaro C, Guido M, Rugge M, Noventa F, et al. Long-term outcome of chronic type B hepatitis in patients who acquire hepatitis B virus infection in childhood. Gastroenterology. 1990;99:805–10.
7. Moraleda G, Saptuelli J, Aldrich CE, Averett D, Condreay L, Mason WS. Lack of effect of antiviral therapy in nondividing hepatocyte cultures on the closed circular DNA of woodchuck hepatitis virus. J Virol. 1997;71:9392–9.
8. Wong DK, Seto WK, Fung J, Ip P, Huang FY, Lai CL, et al. Reduction of hepatitis B surface antigen and covalently closed circular DNA by nucleos(t)ide analogues of different potency. Clin Gastroenterol Hepatol. 2013;11:1004-1010.e1.
9. Bortolotti F, Calzia R, Cadrobbi P, Giacchini R, Ciravegna B, Armigliato M, et al. Liver cirrhosis associated with chronic hepatitis B virus infection in childhood. J Pediatr. 1986;108:224–7.
10. Livingston SE, Simonetti JP, McMahon BJ, Bulkow LR, Hurlburt KJ, Homan CE, et al. Hepatitis B virus genotypes in Alaska Native people with hepatocellular carcinoma: preponderance of genotype F. J Infect Dis. 2007;195:5–11.
11. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63(10):261–83.
12. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67(4):1560–99.
13. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. World Health Organization. March 2015. http://www.who.int/hiv/pub/hepatitis/hepatitis-b-guidelines/en/.
14. European Association For The Study of the Liver. EASL Clinical Practice Guidelines: management of chronic hepatitis B virus infection. J Hepatol. 2012;57(1):167–85.
15. European Association For The Study of the Liver. EASL Clinical Practice Guidelines: management of chronic hepatitis B virus infection. J Hepatol. 2017;67:370–98.
16. Sokal EM, Paganelli M, Wirth S, Socha P, Vajro P, Lacaille F, et al. Management of chronic hepatitis B in childhood: ESPGHAN clinical practice guidelines. J Hepatol. 2013;59:814–29.
17. Jonas MM, Lok A, McMahon BJ, Brown RS, Wong JB, Ahmed AT, et al. Antiviral therapy in management of chronic hepatitis B viral infection in children: a systemic review and meta-analysis. Hepatology. 2016;63:307–18.
18. Rijckborst V, Janssen HLA. The role of interferon in hepatitis B therapy. Curr Hepat Rep. 2010;9(4):231–8.
19. Bortolotti F, Jara P, Crivellaro C, Hierro L, Cadrobbi P, Frauca E, et al. Outcome of chronic hepatitis B in Caucasian children during a 20-year observation period. J Hepatol. 1998;29:184–90.
20. Fujisawa T, Inui A, Sogo T, Komatsu H. Long-term history of chronic hepatitis B virus infection in children [Japanese]. Nippon Rinsho. 2004;62(Suppl 8):303–8.
21. Barbera C, Bortolotti F, Crivellaro C, Coscia A, Zancan L, Cadrobbi P, et al. Recombinant interferon-alpha 2a hastens the rate of HBeAg clearance in children with chronic hepatitis B. Hepatology. 1994;20:287–90.
22. Utili R, Sagnelli E, Galanti B, Aprea L, Cesaro G, Digilio L, et al. Prolonged treatment of children with chronic hepatitis B

with recombinant alpha 2a-interferon: a controlled, randomized study. Am J Gastroenterol. 1991;86:327–30.
23. Sokal EM, Conjeevaram HS, Roberts EA, Alvarez F, Bern EM, Goyens P, et al. Interferon alfa therapy for chronic hepatitis B in children: a multinational randomized controlled trial. Gastroenterology. 1998;114:988–95.
24. Gregorio GV, Jara P, Hierro L, Diaz C, de la Vega A, Vegnente A, et al. Lymphoblastoid interferon alfa with or without steroid pretreatment in children with chronic hepatitis B: a multicenter controlled trial. Hepatology. 1996;23:700–7.
25. Ruiz-Moreno M, Rua MJ, Molina J, Moraleda G, Moreno A, Garcia-Aguado J, Carreno V. Prospective, randomized controlled trial of interferon-alpha in children with chronic hepatitis B. Hepatology. 1991;13:1035–9.
26. Ruiz Moreno M, Jimenez J, Porres JC, Bartolome J, Moreno A, Carreno V. A controlled trial of recombinant interferon-alpha in Caucasian children with chronic hepatitis B. Digestion. 1990;45:26–33.
27. Lai CL, Lin HJ, Lau JN, Flok AS, Wu PC, Chung HT, et al. Effect of recombinant alpha 2 interferon with or without prednisone in Chinese HBsAg carrier children. Q J Med. 1991;78:155–63.
28. Vajro P, Tedesco M, Fontanella A, De Vincenzo A, Vecchione R, Ammendola R, et al. Prolonged and high dose recombinant interferon alpha-2b alone or after prednisone priming accelerates termination of active viral replication in children with chronic hepatitis B infection. Pediatr Infect Dis J. 1996;15:223–31.
29. Wirth S, Zhang H, Hardikar W, Schwarz KB, Sokal E, Yang W, et al. Efficacy and safety of peginterferon-alfa-2a (40KD) in children with chronic hepatitis B: the PEG-B-ACTIVE study. Hepatology. 2018;68:1681–94.
30. Sokal EM, Kelly DA, Mizerski J, Badia IB, Arelas JA, Schwarz KB, et al. Long-term lamivudine therapy for children with HBeAg-positive chronic hepatitis B. Hepatology. 2006;43(2):225–32.
31. Jonas MM, Kelley DA, Mizersky J, Badia IB, Areias JA, Schwarz KB, et al. Clinical trial of lamivudine in children with chronic hepatitis B. N Engl J Med. 2002;346:1706–13.
32. Jonas MM. Chang M-H, Sokal E, Schwarz KB, Kelly D, Kim KM, et al. Randomized controlled trial of entecavir versus placebo in children with HBeAg-positive chronic hepatitis B. Hepatology 2015; published on-line July 2015; https://doi.org/10.1002/hep.28015.
33. Jonas MM, Kelly D, Pollack H, Mizerski J, Sorbel J, Frederick D, et al. Safety, efficacy, and pharmacokinetics of adefovir dipivoxil in children and adolescents (age 2 to <18 years) with chronic hepatitis B. Hepatology. 2008;47:1863–71.
34. Jonas MM, Kelly D, Pollack H, Mizerski J, Sorbel J, Frederick D, et al. Efficacy and safety of long-term adefovir dipivoxil therapy in children with chronic hepatitis B infection. Pediatr Infect Dis J. 2012;31:578–82.
35. Gallego A, Sheldon J, Garcia-Samaniego J, Margall N, Romero M, Hornillos P, et al. Evaluation of initial virological response to adefovir and development ofa defovir-resistant mutations in patients with chronic hepatitis B. J Viral Hepat. 2008;15:392–8.
36. Delaney WE 4th, Ray AS, Yang H, Qi X, Xiong S, Zhu Y, et al. Intracellular metabolism and in vitro activity of tenofovir against hepatitis B virus. Antimicrob Agents Chemother. 2006;50:2471–7.
37. Delaney WE 4th, Borroto-Esoda K. Therapy of chronic hepatitis B: trends and developments. Curr Opin Pharmacol. 2008;8:532–40.
38. Kitrinos KM, Corsa A, Liu Y, Flaherty J, Snow-Lampart A, Marcellin P, et al. No detectable resistance to tenofovir disoproxil fumarate (TDF) after 6 years of therapy with chronic hepatitis B. Hepatology. 2014;59(2):434–42.
39. Murray KF, Szenborn L, Wysocki J, Rossi S, Corsa AC, Dinh P, et al. Randomized, placebo-controlled trial of tenofovir disoproxil fumarate in adolescents with chronic hepatitis B. Hepatology. 2012;56:2018–26.
40. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021356s058,022577s014lbl.pdf. Accessed 14 May 2021.
41. Fontana RJ. Side effects of long-term antiviral therapy for hepatitis B. Hepatology. 2019;49:S185–95.
42. American Academy of Pediatrics. Red Book Online 2018: Section 2: recommendations for care of children in special circumstances. 2018. https://redbook.solutions.aap.org. Accessed 1 May 2021.

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