**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 67180

**Manuscript Type:** MINIREVIEWS

**Treatment of hepatitis B virus infection in children and adolescents**

Stinco M *et al*. HBV infection therapy in children

Mariangela Stinco, Chiara Rubino, Sandra Trapani, Giuseppe Indolfi

**Mariangela Stinco, Chiara Rubino, Sandra Trapani,** Department of Health Sciences, Pediatric Section, Meyer Children’s University Hospital, Florence 50139, Italy

**Giuseppe Indolfi,** Department Neurofarba, University of Florence and Meyer Children’s University Hospital, Florence 50139, Italy

**Author contributions:** Stinco M and Indolfi G wrote the paper; Rubino C and Trapani S reviewed it critically for significant intellectual content.

**Corresponding author: Giuseppe Indolfi, MD, Professor,** Department Neurofarba, University of Florence and Meyer Children’s University Hospital, 6 Gaetano Pieraccini, Florence 50139, Italy. giuseppe.indolfi@meyer.it

**Received:** April 17, 2021

**Revised:** June 30, 2021

**Accepted:** August 13, 2021

**Published online:** September 28, 2021

**Abstract**

Hepatitis B virus (HBV) infection is one of the main causes of morbidity and mortality worldwide. Most children acquire the infection perinatally or during early childhood and develop a chronic hepatitis characterized by a high viral replication and a low-inflammation phase of infection, with normal or only slightly raised aminotransferases. Although a conservative approach in children is usually recommended, different therapies exist and different therapeutic approaches are possible. The main goals of antiviral treatment for children with chronic HBV infection are to suppress viral replication and to warn the disease progression to cirrhosis and hepatocellular carcinoma, although these complications are rare in children. Both United States Food and Drug Administration (US-FDA) and European Medicines Agency (EMA) have approved interferon alfa-2b for children aged 1 year and older, pegylated interferon alfa-2a and lamivudine for children aged 3 years and older, entecavir for use in children aged 2 years and older, and adefovir for use in those 12 years of age and older. Tenofovir disoproxil fumarate is approved by EMA for children aged 2 years and older and by US-FDA for treatment in children aged 12 years and older. Finally, EMA has approved the use of tenofovir alafenamide for treatment of children aged 12 years and older or for children weighing more than 35 kg independent of age. This narrative review will provide the framework for summarizing indications to antiviral therapy in the management of chronic HBV infection in children and adolescents.

**Key Words:** Hepatitis B; Children; Adolescents; Antiviral therapy; Tenofovir disoproxil fumarate; Entecavir; Interferon

**©The** **Author(s) 2021.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Stinco M, Rubino C, Trapani S, Indolfi G. Treatment of hepatitis B virus infection in children and adolescents. *World J Gastroenterol* 2021; 27(36): 6053-6063

URL: https://www.wjgnet.com/1007-9327/full/v27/i36/6053.htm

DOI: https://dx.doi.org/10.3748/wjg.v27.i36.6053

**Core Tip:** Hepatitis B virus (HBV) is a major cause of acute and chronic liver disease. During childhood, asymptomatic chronic hepatitis B is the most common outcome of the infection, and a conservative approach is usually recommended. In selected patients there is a strict indication for treatment. Different drugs have been approved by United States Food and Drug Administration and European Medicines Agency for treatment of children and adolescents with chronic HBV infection. The main goal of the treatment is to reduce the risk of progression to cirrhosis and hepatocellular carcinoma through the suppression of HBV replication.

**INTRODUCTION**

Hepatitis B virus (HBV) infection is one of the major causes of acute and chronic liver disease and associated morbidity and mortality worldwide. In 2015, 257 million people were estimated as being chronically infected by the World Health Organization (WHO), with a global prevalence of 3%-5%, and 887,000 people died due to chronic HBV infection (CHB)[1].

Hepatitis B is a vaccine-preventable disease but, despite the availability of effective vaccine and vaccination programs, it remains a global health problem[2]. It has been estimated that annually there are almost 2 million new infections in children younger than 5 years of age. Most of the infected children acquire the infection around the time of birth through vertical transmission or during early childhood through horizontal transmission[3-5].

**NATURAL HISTORY OF HBV INFECTION IN CHILDREN**

The natural history and the long-term outcome of HBV infection acquired in childhood vary depending upon the age at infection. CHB is the most common outcome (90%) of the infection acquired vertically in neonates and infants. The risk of CHB is reduced to 30% when infection occurs during the first 5 years of life and < 5% for older immunocompetent children and adults[5].

HBV infection is usually asymptomatic during childhood, but sometimes acute infection could present with severe symptoms and fulminant hepatitis both in adult and children[6]. The development of complications of CHB, such as cirrhosis, hepatocellular carcinoma, and extrahepatic manifestations, is manly observed in adulthood but can also present in infancy and early childhood[7-10].

In 2017 the European Association for the Study of the Liver (EASL) proposed a new nomenclature for CHB that is no more based on the concept of immune-tolerant, immune-active, immune-control, and immune-escape, which have been previously used to describe the different phases of infection[7]. The new nomenclature emphasizes the distinction between infection and active hepatitis (defined basing on the presence of normal or raised alanine aminotransferase levels, respectively) and is based on Hepatitis B e Antigen (HBeAg) status, HBV viremia, and liver histology (Table 1)[11].

Another biomarker to monitoring HBV infection is the covalently closed circular DNA (ccc-DNA), a new biomarker related to viral replication and persistence of infection. A “complete cure” of HBV infection requires also the clearance of ccc-DNA, as well as HBsAg loss and undetectable serum HBV DNA (otherwise it is defined “functional cure”)[12].

**TREATMENT FOR CHRONIC HBV INFECTION**

The common and main goals of antiviral treatment for adults, adolescents, and children with chronic HBV infection are the effective and sustained suppression of HBV replication and consequently to decrease the risk of disease progression to cirrhosis and hepatocellular carcinoma[13-15]. Guidelines for treatment of children and adolescents have been issued by the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), EASL, American Association for the Study of Liver Diseases (AASLD), and Asian Pacific Association for the Study of the Liver (APASL)[11,16-18].

The aim of this narrative review is to summarize the available evidence on the use of drugs for treatment of CHB in children and adolescents, to summarize the main recommendations for treatment, and to highlight research gaps.

***Interferon alfa-2b***

Interferon alfa-2b has both antiviral and immunomodulatory actions. Binding to the specific transmembrane receptor, it activates intracellular signaling and gene transcription, resulting in the reduction of viral DNA level and viral injury. Furthermore, it directly stimulates the cell-mediated immune response against HBV-infected hepatocytes, thus reducing the number of cells containing ccc-DNA[19].

Interferon alfa-2b for subcutaneous injection is approved by European Medicines Agency (EMA) and United States Food and Drug Administration (US-FDA) for treatment of children and adolescents (1-17 years of age) with CHB. Treatment duration is 16 to 24 wk. The recommended dose is 6 million IU/m2 three times a week (Table 2).

A large open-label, multinational randomized controlled trial evaluated the safety and efficacy of interferon alfa-2b[20]. Interferon alfa-2b was started at a dose of 3 million IU/m2 of body surface area three times a week for 1 week. The dose was increased to 6 million IU/m2 of body surface area at the second week, and this was continued for a minimum of 16 wk and a maximum of 24 wk based on results of virological testing for evidence of response (treatment was stopped at 16 or 20 wk if HBeAg was undetectable on two serum determinations taken 1 month apart). One hundred and forty-nine children were enrolled, 144 were evaluable of whom 70 received the treatment and 77 were untreated controls. Patients in the treatment arm had a better response (loss of HBV DNA and HBeAg at 24 wk of follow-up) compared to the untreated controls (26% *vs* 11%, *P* = 0.02). Loss of HBsAg occurred in 7 treated children (10%) but in only 1 untreated child (1.2%) (*P* = 0.03). Patients with lower baseline HBV DNA (< 50 pg/mL) were more likely to respond to interferon alfa-2b therapy than patients with a baseline HBV DNA greater than 200 pg/mL (41% *vs* 7%, respectively). All children in the treatment group reported at least one adverse event, the most common being influenza-like symptoms (100%), irritability, sleep disturbance and depression (40%), nausea or vomiting (40%), diarrhea or gastrointestinal distress (46%), alopecia (17%), and neutropenia (19%). The dose of interferon alfa-2b was reduced in 17 children (23%), most commonly because of neutropenia, thrombocytopenia, and fever. Three children discontinued treatment because of an adverse event. Subsequent studies confirmed the same efficacy and safety results[21-23].

***Peginterferon alfa***

Peginterferon alfa comprises an inert, branched, 40 kD polyethylene glycol molecule attached to interferon alfa. Through the direct stimulation of immune system, it is effective in the achievement of serological response and reduction of ccc-DNA level[19].

***Peginterferon alfa-2a***

Peginterferon alfa-2a for subcutaneous injection is approved by EMA and US-FDA for treatment of children and adolescents (3-17 years of age) with CHB. Treatment duration is 16 to 24 wk. The recommended dose is 180 μg/1.73 m2 once a week (Table 2).

The efficacy and safety of peginterferon alfa-2a treatment in children with CHB was assessed in the PEG-B-ACTIVE study, a phase III randomized, controlled, open-label, multicenter study[24]. Peginterferon alfa-2a was prescribed at a dose of 180 μg/1.73 m2 once a week and was continued for a minimum of 48 wk. One hundred and sixty-one HBeAg-positive children with raised aminotransferase levels without advanced fibrosis or cirrhosis were enrolled. One hundred and fifty-one were evaluable, of whom 101 received the treatment and 50 were untreated controls. Twenty-four weeks after the end of treatment, patients who received peginterferon alfa-2a had a better response compared to untreated controls with higher HBeAg seroconversion rates (25.7% *vs* 6%, *P* = 0.0043), higher rates of hepatitis B surface antigen (HBsAg) clearance (8.9% *vs* 0%, *P* = 0.03), HBV DNA < 2000 IU/mL (28.7% *vs* 2%, *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). Loss of HBsAg occurred in 9 treated children (8.9%) and in none of those who were untreated. The most common adverse events included fever (49%), headache (30%), abdominal pain (19%), and neuropsychiatric disorder (12%). Laboratory abnormalities reported during treatment were ALT flares (53%) and neutropenia (10%) and were managed without dose modification. Short-term effects on growth appeared minimal. The study highlighted the efficacy and positive benefit/risk profile of peginterferon alfa-2a for the treatment in children and adolescents with CHB, consistent with the extensive data available in adults.

***Peginterferon alfa-2b***

Peginterferon alfa-2b is not approved by the US-FDA or EMA for treatment of children or adolescents with CHB but is approved for treatment of chronic hepatitis C for children 3 years of age or older (Table 2)[25-30].

***Lamivudine***

Lamivudine is a synthetic nucleoside analogue (analogue of cytidine) that inhibits viral replication in human cells by interfering with the DNA polymerase enzyme of HBV, and it acts as a chain terminator of DNA synthesis. If the nucleoside analogue is incorporated in the DNA chain, it prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, consequently terminating viral DNA growth[31].

Lamivudine is approved by EMA and US-FDA for treatment of children and adolescents (3-17 years of age) with CHB. The recommended dose is 3 mg/kg daily, oral (maximum 100 mg; Table 2).

The efficacy and safety of lamivudine treatment in children with CHB was originally assessed in one randomized, double-blind, placebo-controlled study[32]. Children and adolescents aged between 2 and 17 years received either oral lamivudine (*n* = 191) or placebo (*n* = 97) once daily for 52 wk. This study demonstrated that treatment with lamivudine was safe, efficacious, and superior to placebo, consistent with the results observed in adults with CHB. Virologic response defined by the loss of serum HBeAg and by the reduction of serum HBV DNA to undetectable levels occurred by week 52 in 23% of the children in the treatment group, as compared with 13% of children in the placebo group (*P* = 0.04). The rate of virologic response increased with higher baseline ALT values and scores on the histologic activity index. Loss of HBsAg occurred in 3 treated children (2%) and in none of those who were untreated. The treatment was highly safe and the nature, incidence, and severity of adverse clinical events and abnormal laboratory values in patients receiving lamivudine were similar to those receiving placebo. The emergence of YMDD-variant HBV was detected in 19% of patients who received lamivudine for 52 wk. YMDD-variant HBV may reverse the response in some patients and has been considered a limitation of lamivudine therapy.

The efficacy of lamivudine was explored in other studies. According to a recent systematic review with meta-analysis, lamivudine, when compared to placebo, was associated with significantly higher likelihood of ALT normalization, HBeAg clearance or loss, and HBV DNA suppression but not HBeAg seroconversion or HBsAg clearance after 48 wk of treatment[33-35].

Although lamivudine is a safe drug, it has low barrier to resistance.

***Entecavir***

Entecavir is a nucleoside analogue (analogue of deoxyguanosine). In the intracellular environment, it is rapidly phosphorylated to the active intracellular 50-triphosphate form; this active metabolite competes with the natural substrate (*i.e.*, deoxyguanosine triphosphate) of HBV polymerase and inhibits HBV replication[36].

Entecavir is approved by US-FDA and EMA for treatment of children and adolescents aged 2 years and older with CHB. The recommended treatment dose is 0.015 mg/kg daily (maximum 0.5 mg; weight > 30 kg: 0.5 mg daily; Table 2).

The efficacy and safety of entecavir were studied in a randomized, double-blind, multicenter study including children and adolescents (2 to < 18 years) with CHB[37]. Blinded treatment was administered for a minimum of 48 wk. One hundred and seventeen patients received entecavir treatment, and 56 received placebo. Patients who achieved HBeAg seroconversion continued blinded treatment while those who did not (*n* = 50) were switched to open-label entecavir up to week 96 of treatment. Response rates for the combined endpoint of HBeAg seroconversion and HBV DNA < 50 IU/mL at treatment week 48 occurred in 24.2% in the entecavir group, as compared with 3.3% in the placebo group (*P* = 0.0008). After 48 wk of treatment, patients who received entecavir had a better response compared to untreated controls with higher rates of virological suppression (49.2% *vs* 3.3%, *P* < 0.0001), ALT normalization (67.5% *vs* 23.3%, *P* < 0.0001), and HBeAg seroconversion (24.2% *vs* 10, *P* = 0.02). At week 96, loss of HBsAg occurred in 7 treated children (5.8%) and in none of those who were untreated. The rate of virologic response increased with low baseline HBV DNA (< 8 Log10 IU/mL) and high baseline ALT (> 2 × upper limit of normal). The cumulative probability of emergent entecavir resistance through years 1 and 2 of entecavir was 0.6% and 2.6%, respectively. The treatment was well tolerated with no observed differences in adverse events or changes in growth compared with placebo. A subsequent study confirmed the same efficacy and safety results[38].

***Adefovir***

Adefovir is an acyclic nucleotide analogue (analogue of deoxyadenosine-5´-monophosphate). It is converted by adenylate kinase to adefovir diphosphate, an active derivate that selectively inhibits the HBV polymerase. Adefovir diphosphate competes with deoxyadenosine-5´-triphosphate during HBV DNA synthesis, and, when incorporated into the HBV DNA chain, it discontinues further elongation of DNA chain, stopping HBV replication[39].

Adefovir is approved by US-FDA and EMA for treatment adolescents aged 12 years and older with CHB. The recommended treatment dose is 10 mg daily (Table 2).

The efficacy and safety of adefovir were studied in a randomized, double-blind, multicenter study including children and adolescents (2 to < 18 years) with CHB[40]. Treatment was administered for 48 wk. One hundred and eighteen patients have received adefovir treatment and 58 received placebo. Response rates for the combined endpoint of HBV DNA < 1000 copies/mL and normal ALT at treatment week 48 occurred in 19.1% in the adefovir group, as compared with 1.7% in the placebo group (*P* < 0.001). This result was primarily due to response in the 12 to 17 years age group as in the younger children, although there were apparent differences in response to those treated with adefovir compared to those who received placebo, they did not reach statistical significance. After 48 wk of treatment, patients who received tenofovir had a better response compared to untreated controls with higher rates of ALT normalization (56% *vs* 21%, *P* < 0.0001) and HBeAg seroconversion (15.9% *vs* 5.3%). More patients treated with adefovir met the combined endpoint of HBeAg seroconversion and HBV DNA < 1000 copies/mL plus normal ALT (10.6% *vs* 0/57, *P* = 0.009). Only 1 patient in the adefovir group achieved HBsAg seroconversion. The rate of virologic response increased with low baseline HBV DNA (< 8.8 Log10 IU/mL) and high baseline ALT (> 2.3 X upper limit of normal). No subject developed the rtA181V or rtN236T mutation associated with adefovir resistance by treatment week 48. The treatment was well tolerated with no observed differences in adverse events compared with placebo.

A subsequent study confirmed the same efficacy and safety results[41].

***Tenofovir disoproxil fumarate***

Tenofovir disoproxil fumarate (DF) is an inhibitor of DNA polymerase. *In vivo* it is converted by diester hydrolysis to tenofovir, an acyclic nucleotide analogue (analogue of deoxyadenosine-5´-monophosphate), and after two phosphorylation steps to its active metabolite, tenofovir diphosphate. In this form, tenofovir binds to active site of enzyme, avoiding the attaching of the natural substrate deoxyadenosine-5´-triphosphate, and inhibits the HBV DNA polymerase activity[42].

Tenofovir DF is approved by EMA for children aged 2 years and older and by US-FDA for treatment of children aged 12 years and older with CHB. The recommended treatment dose is 8 mg/kg daily (maximum 300 mg) for younger children and 300 mg daily for those older than 12 years (Table 2).

The efficacy and safety profile of tenofovir DF were studied in a randomized, double-blind, multicenter study including adolescents (12 to < 18 years) with CHB[43]. Blinded treatment was administered for 72 wk. One hundred six patients were enrolled, and 101 completed 72 wk of treatment. Fifty-two patients have received tenofovir DF treatment and 54 received placebo. Virologic response (HBV DNA < 400 copies/mL) at treatment week 72 was observed in 89% of patients who received tenofovir DF and none of those who received placebo (*P* < 0.001). The treatment was well tolerated with no observed differences in adverse events compared with placebo. No resistance to tenofovir DF developed through week 72.

***Tenofovir alafenamide***

Tenofovir alafenamide is a pro-drug of tenofovir diphosphate, thus it presents the same action mechanism of tenofovir DF causing causes viral DNA chain termination and preventing viral DNA transcription[42].

Tenofovir alafenamide is approved by EMA for treatment of children aged 12 years and older and, independent of age, for children weighing more than 35 kg. The recommended treatment dose is 25 mg daily. Tenofovir alafenamide was approved on the basis of studies in children with human immunodeficiency virus infection[44,45].

***Telbivudine***

Telbivudine is not approved by the FDA or EMA for pediatric use.

***Pros and cons of anti-HBV treatment***

Overall interferon based treatments are associated with higher HBeAg and HBsAg seroconversion rates and could be used for treatment of finite duration. Concerns are present with regard to tolerance and safety, and recently the availability of the drug on the market has been questioned. Furthermore, interferon and peginterferon treatments have the disadvantage of subcutaneous administration that is relevant for treatment of children.

Nucleot(s)ide analogues have been classified as having low (lamivudine, adefovir, telbivudine) and high (tenofovir, entecavir) genetic barrier to resistance and are generally used for oral treatment of indefinite duration, with an overall good safety profile[14,15].

***New prospective antiviral treatment strategies***

Recently, there is a growing interest in some new therapeutic strategies, targeting viral life cycle or improving antiviral immune response, that could eliminate all replicative intermediates, including ccc-DNA. The drugs targeting different steps of HBV life cycle include entry inhibitors; polymerase inhibitors; core protein (nucleocapsid) inhibitors; HBsAg release inhibitors; RNA silencers. On the other hand, the new therapies to improve anti-HBV immunity response include therapeutic vaccines, generating “new” T cells; toll-like receptor 7 and toll-like receptor 8 agonists, stimulating antiviral effector cells; retinoic acid-inducible gene I agonist; anti-HBV antibodies; checkpoint inhibitors; programmed cell death protein 1 (PD1) and PD1 ligand inhibitors, rescuing the T-cell exhaustion that can be observed in chronic HBV infection. Results of preclinical and early clinical studies are promising; thus, soon, these treatment options could be available and could potentially transform the future indications for hepatitis B treatment[46-49].

**INDICATION FOR TREATMENT**

The decision to start treatment in a child with CHB is based on the combined assessment of stage of liver disease, HBV DNA and ALT concentrations, and HBeAg status. Presence of other features, such as a family history of hepatocellular carcinoma, human immunodeficiency virus coinfection or other concomitant liver disease, is an additional factor to support treatment initiation. Regardless of age, all guidelines recommend treatment for children with cirrhosis, histological evidence of necroinflammation and fibrosis (active hepatitis), and fulminant or severe acute hepatitis B infection and for those undergoing immunosuppression or chemotherapy with evidence of past or ongoing HBV infection[11,13,16-18].

There are some differences between recommendations provided by the available guidelines for the treatment of CHB in children not satisfying the above treatment criteria that are highlighted in Table 3[14].

Interferon, entecavir, and tenofovir DF are recommended for treatment of chronic HBV infection in children by ESPGHAN, AASLD, and APASL. Entecavir is recommended for children aged 2–12 years in WHO guidelines while interferon is not included because its use in resource limited settings is often not feasible as a result of its high cost, requirement for injection, and high rate of adverse effects that require careful monitoring. The advantages of interferon and peginterferon as compared with nucleoside and nucleotide analogues are the absence of viral resistance and the predictable finite duration of treatment. However, the use of interferon and peginterferon requires subcutaneous injections and is associated with a high risk of adverse events. Tenofovir (tenofovir DF or tenofovir alafenamide) or entecavir have high genetic barrier and are recommended as preferred initial therapies for adults by EASL, AASLD, and WHO.

**CONCLUSION**

Treatment guidelines provided by the different major scientific international societies (ESPGHAN, AASLD, APASL, EASL) clearly agree on treating all patients with advanced liver disease (cirrhosis) and histological features of active hepatitis and patients with fulminant or severe acute hepatitis B infection, preventing uncontrolled HBV replication and serious complications such as cirrhosis and hepatocellular carcinoma in young adult life. The guidelines also recommended antiviral therapy for children and adolescents with HBV infection (immune-tolerant patients) undergoing immunosuppressive therapy, such as those patients who will be receiving chemotherapy or stem cell or solid organ transplantation.

All others HBV infected children who not satisfy the above treatment criteria are not typically candidates for treatment. For these patients a tight clinical, biochemical and no invasive imaging (abdominal ultrasound) follow-up will be important to monitoring the natural course of HBV infection, to identify patients undergoing spontaneous HBeAg seroconversion, and above all to recognize rapidly those children with chronic HBV infection who may benefit from treatment (*e.g.*, patients with persistently abnormal ALT levels).

The establishment of pediatric treatment registries and of new international associations would be the most important strategy to inform best practices for the management, care, and treatment of children with HBV infection and to promote collaborative research.

**REFERENCES**

1 **World Health Organization.** Global hepatitis report 2017. [cited 17 April 2021]. Available from: [https://www.who.int/publications/i/item/global-hepatitis-report-2017](about:blank)

2 Hepatitis B vaccines: WHO position paper – July 2017. *Wkly Epidemiol Rec* 2017; **92**: 369-392 [PMID: 28685564]

3 **Schweitzer A**, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet* 2015; **386**: 1546-1555 [PMID: 26231459 DOI: 10.1016/S0140-6736(15)61412-X]

4 **Polaris Observatory Collaborators**. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol* 2018; **3**: 383-403 [PMID: 29599078 DOI: 10.1016/S2468-1253(18)30056-6]

5 **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 [PMID: 3973412 DOI: 10.1093/infdis/151.4.599]

6 **Tseng YR**, Wu JF, Kong MS, Hu FC, Yang YJ, Yeung CY, Huang FC, Huang IF, Ni YH, Hsu HY, Chang MH, Chen HL. Infantile hepatitis B in immunized children: risk for fulminant hepatitis and long-term outcomes. *PLoS One* 2014; **9**: e111825 [PMID: 25380075 DOI: 10.1371/journal.pone.0111825]

7 **McMahon BJ**. The natural history of chronic hepatitis B virus infection. *Hepatology* 2009; **49**: S45-S55 [PMID: 19399792 DOI: 10.1002/hep.22898]

8 **Nguyen VT**, Law MG, Dore GJ. Hepatitis B-related hepatocellular carcinoma: epidemiological characteristics and disease burden. *J Viral Hepat* 2009; **16**: 453-463 [PMID: 19302335 DOI: 10.1111/j.1365-2893.2009.01117.x]

9 **Sun YH**, Lei XY, Sai YP, Chen JH, Sun YC, Gao X. Relationship between genotypes and clinical manifestation, pathology, and cccDNA in Chinese children with hepatitis B virus-associated glomerulonephritis. *World J Pediatr* 2016; **12**: 347-352 [PMID: 27059747 DOI: 10.1007/s12519-016-0015-0]

10 **Arnone OC**, Serranti D, Bartolini E, Mastrangelo G, Stinco M, Trapani S, Ricci S, Resti M, Indolfi G. Chronic hepatitis B in children, report of a single-centre longitudinal study on 152 children. *J Viral Hepat* 2020; **27**: 1344-1351 [PMID: 32853482 DOI: 10.1111/jvh.13382]

11 **European Association for the Study of the Liver**. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67**: 370-398 [PMID: 28427875 DOI: 10.1016/j.jhep.2017.03.021]

12 **Allweiss L**, Dandri M. The Role of cccDNA in HBV Maintenance. *Viruses* 2017; **9** [PMID: 28635668 DOI: 10.3390/v9060156]

13 **World Health Organization.** Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. 2015 [cited 17 April 2021]. Available from: [https://www.who.int/publications/i/item/9789241549059](about:blank)

14 **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**: 466-476 [PMID: 30982722 DOI: 10.1016/S2468-1253(19)30042-1]

15 **Jonas MM**, Lok AS, McMahon BJ, Brown RS Jr, Wong JB, Ahmed AT, Farah W, Mouchli MA, Singh S, Prokop LJ, Murad MH, Mohammed K. Antiviral therapy in management of chronic hepatitis B viral infection in children: A systematic review and meta-analysis. *Hepatology* 2016; **63**: 307-318 [PMID: 26566163 DOI: 10.1002/hep.28278]

16 **Sokal EM**, Paganelli M, Wirth S, Socha P, Vajro P, Lacaille F, Kelly D, Mieli-Vergani G; European Society of Pediatric Gastroenterology, Hepatology and Nutrition. Management of chronic hepatitis B in childhood: ESPGHAN clinical practice guidelines: consensus of an expert panel on behalf of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition. *J Hepatol* 2013; **59**: 814-829 [PMID: 23707367 DOI: 10.1016/j.jhep.2013.05.016]

17 **Terrault NA**, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; **67**: 1560-1599 [PMID: 29405329 DOI: 10.1002/hep.29800]

18 **Sarin SK**, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, Chen DS, Chen HL, Chen PJ, Chien RN, Dokmeci AK, Gane E, Hou JL, Jafri W, Jia J, Kim JH, Lai CL, Lee HC, Lim SG, Liu CJ, Locarnini S, Al Mahtab M, Mohamed R, Omata M, Park J, Piratvisuth T, Sharma BC, Sollano J, Wang FS, Wei L, Yuen MF, Zheng SS, Kao JH. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016; **10**: 1-98 [PMID: 26563120 DOI: 10.1007/s12072-015-9675-4]

19 **Yeh ML**, Huang JF, Dai CY, Yu ML, Chuang WL. Pharmacokinetics and pharmacodynamics of pegylated interferon for the treatment of hepatitis B. *Expert Opin Drug Metab Toxicol* 2019; **15**: 779-785 [PMID: 31593639 DOI: 10.1080/17425255.2019.1678584]

20 **Sokal EM**, Conjeevaram HS, Roberts EA, Alvarez F, Bern EM, Goyens P, Rosenthal P, Lachaux A, Shelton M, Sarles J, Hoofnagle J. Interferon alfa therapy for chronic hepatitis B in children: a multinational randomized controlled trial. *Gastroenterology* 1998; **114**: 988-995 [PMID: 9558288 DOI: 10.1016/s0016-5085(98)70318-x]

21 **Hu Y**, Ye YZ, Ye LJ, Wang XH, Yu H. Efficacy and safety of interferon alpha-2b versus pegylated interferon alpha-2a monotherapy in children with chronic hepatitis B: a real-life cohort study from Shanghai, China. *World J Pediatr* 2019; **15**: 595-600 [PMID: 31487005 DOI: 10.1007/s12519-019-00303-w]

22 **van Zonneveld M**, Flink HJ, Verhey E, Senturk H, Zeuzem S, Akarca US, Cakaloglu Y, Simon C, So TM, Gerken G, de Man RA, Hansen BE, Schalm SW, Janssen HL; HBV 99-01 Study Group. The safety of pegylated interferon alpha-2b in the treatment of chronic hepatitis B: predictive factors for dose reduction and treatment discontinuation. *Aliment Pharmacol Ther* 2005; **21**: 1163-1171 [PMID: 15854180 DOI: 10.1111/j.1365-2036.2005.02453.x]

23 **Zhao H**, Si CW, Wei L, Wan MB, Ying YK, Hou JL, Niu JQ. [A multicenter, randomized, open-label study of the safety and effectiveness of pegylated interferon alpha 2b and interferon alpha 2b in treating HBeAg positive chronic hepatitis B patients]. *Zhonghua Gan Zang Bing Za Zhi* 2006; **14**: 323-326 [PMID: 16732903]

24 **Wirth S**, Zhang H, Hardikar W, Schwarz KB, Sokal E, Yang W, Fan H, Morozov V, Mao Q, Deng H, Huang Y, Yang L, Frey N, Nasmyth-Miller C, Pavlovic V, Wat C. Efficacy and Safety of Peginterferon Alfa-2a (40KD) in Children With Chronic Hepatitis B: The PEG-B-ACTIVE Study. *Hepatology* 2018; **68**: 1681-1694 [PMID: 29689122 DOI: 10.1002/hep.30050]

25 **Wirth S**, Ribes-Koninckx C, Calzado MA, Bortolotti F, Zancan L, Jara P, Shelton M, Kerkar N, Galoppo M, Pedreira A, Rodriguez-Baez N, Ciocca M, Lachaux A, Lacaille F, Lang T, Kullmer U, Huber WD, Gonzalez T, Pollack H, Alonso E, Broue P, Ramakrishna J, Neigut D, Valle-Segarra AD, Hunter B, Goodman Z, Xu CR, Zheng H, Noviello S, Sniukiene V, Brass C, Albrecht JK. High sustained virologic response rates in children with chronic hepatitis C receiving peginterferon alfa-2b plus ribavirin. *J Hepatol* 2010; **52**: 501-507 [PMID: 20189674 DOI: 10.1016/j.jhep.2010.01.016]

26 **Indolfi G**, Bailey H, Serranti D, Giaquinto C, Thorne C; PENTAHep Study Group. Treatment and monitoring of children with chronic hepatitis C in the Pre-DAA era: A European survey of 38 paediatric specialists. *J Viral Hepat* 2019; **26**: 961-968 [PMID: 30980773 DOI: 10.1111/jvh.13111]

27 **Indolfi G**, Easterbrook P, Dusheiko G, El-Sayed MH, Jonas MM, Thorne C, Bulterys M, Siberry G, Walsh N, Chang MH, Meyers T, Giaquinto C, Wirth S, Chan PL, Penazzato M. Hepatitis C virus infection in children and adolescents. *Lancet Gastroenterol Hepatol* 2019; **4**: 477-487 [PMID: 30982721 DOI: 10.1016/S2468-1253(19)30046-9]

28 **Indolfi G**, Nebbia G, Cananzi M, Maccabruni A, Zaramella M, D'Antiga L, Grisotto L, Azzari C, Resti M; Italian Study Group for Treatment of Chronic Hepatitis C in Children. Kinetic of Virologic Response to Pegylated Interferon and Ribavirin in Children With Chronic Hepatitis C Predicts the Effect of Treatment. *Pediatr Infect Dis J* 2016; **35**: 1300-1303 [PMID: 27636721 DOI: 10.1097/INF.0000000000001325]

29 **Bortolotti F**, Indolfi G, Zancan L, Giacchino R, Verucchi G, Cammà C, Barbera C, Resti M, Marazzi MG, Guido M. Management of chronic hepatitis C in childhood: the impact of therapy in the clinical practice during the first 2 decades. *Dig Liver Dis* 2011; **43**: 325-329 [PMID: 21111693 DOI: 10.1016/j.dld.2010.10.008]

30 **Serranti D**, Indolfi G, Nebbia G, Cananzi M, D'Antiga L, Ricci S, Stagi S, Azzari C, Resti M; Italian Study Group for Treatment of Chronic Hepatitis C in Children. Transient Hypothyroidism and Autoimmune Thyroiditis in Children With Chronic Hepatitis C Treated With Pegylated-interferon-α-2b and Ribavirin. *Pediatr Infect Dis J* 2018; **37**: 287-291 [PMID: 28953189 DOI: 10.1097/INF.0000000000001791]

31 **Porche D**. Treatment review: lamivudine. *JANAC* 1996; **7**: 51-53

32 **Jonas MM**, Mizerski J, Badia IB, Areias JA, Schwarz KB, Little NR, Greensmith MJ, Gardner SD, Bell MS, Sokal EM; International Pediatric Lamivudine Investigator Group. Clinical trial of lamivudine in children with chronic hepatitis B. *N Engl J Med* 2002; **346**: 1706-1713 [PMID: 12037150 DOI: 10.1056/NEJMoa012452]

33 **Figlerowicz M**, Kowala-Piaskowska A, Filipowicz M, Bujnowska A, Mozer-Lisewska I, Słuzewski W. Efficacy of lamivudine in the treatment of children with chronic hepatitis B. *Hepatol Res* 2005; **31**: 217-222 [PMID: 15799860 DOI: 10.1016/j.hepres.2005.02.003]

34 **Luo A**, Jiang X, Ren H. Lamivudine therapy for chronic hepatitis B in children: a meta-analysis. *Virol J* 2019; **16**: 88 [PMID: 31272463 DOI: 10.1186/s12985-019-1193-x]

35 **Jonas MM**, Little NR, Gardner SD; International Pediatric Lamivudine Investigator Group. Long-term lamivudine treatment of children with chronic hepatitis B: durability of therapeutic responses and safety. *J Viral Hepat* 2008; **15**: 20-27 [PMID: 18088241 DOI: 10.1111/j.1365-2893.2007.00891.x]

36 **Robinson DM**, Scott LJ, Plosker GL. Entecavir: a review of its use in chronic hepatitis B. *Drugs* 2006; **66**: 1605-22; discussion 1623-4 [PMID: 16956310 DOI: 10.2165/00003495-200666120-00009]

37 **Jonas MM**, Chang MH, Sokal E, Schwarz KB, Kelly D, Kim KM, Ling SC, Rosenthal P, Oraseanu D, Reynolds L, Thiry A, Ackerman P. Randomized, controlled trial of entecavir versus placebo in children with hepatitis B envelope antigen-positive chronic hepatitis B. *Hepatology* 2016; **63**: 377-387 [PMID: 26223345 DOI: 10.1002/hep.28015]

38 **Lee KJ**, Choe BH, Choe JY, Kim JY, Jeong IS, Kim JW, Yang HR, Chang JY, Kim KM, Moon JS, Ko JS. A Multicenter Study of the Antiviral Efficacy of Entecavir Monotherapy Compared to Lamivudine Monotherapy in Children with Nucleos(t)ide-naïve Chronic Hepatitis B. *J Korean Med Sci* 2018; **33**: e63 [PMID: 29441755 DOI: 10.3346/jkms.2018.33.e63]

39 **Hadziyannis SJ**, Papatheodoridis GV. Adefovir dipivoxil in the treatment of chronic hepatitis B virus infection. *Expert Rev Anti Infect Ther* 2004; **2**: 475-483 [PMID: 15482214 DOI: 10.1586/14787210.2.4.475]

40 **Jonas MM**, Kelly D, Pollack H, Mizerski J, Sorbel J, Frederick D, Mondou E, Rousseau F, Sokal E. Safety, efficacy, and pharmacokinetics of adefovir dipivoxil in children and adolescents (age 2 to <18 years) with chronic hepatitis B. *Hepatology* 2008; **47**: 1863-1871 [PMID: 18433023 DOI: 10.1002/hep.22250]

41 **Jonas MM**, Kelly D, Pollack H, Mizerski J, Sorbel J, Frederick D, Mondou E, Rousseau F, Sokal E. Efficacy and safety of long-term adefovir dipivoxil therapy in children with chronic hepatitis B infection. *Pediatr Infect Dis J* 2012; **31**: 578-582 [PMID: 22466329 DOI: 10.1097/INF.0b013e318255ffe7]

42 **Grim SA**, Romanelli F. Tenofovir disoproxil fumarate. *Ann Pharmacother* 2003; **37**: 849-859 [PMID: 12773076 DOI: 10.1345/aph.1C388]

43 **Murray KF**, Szenborn L, Wysocki J, Rossi S, Corsa AC, Dinh P, McHutchison J, Pang PS, Luminos LM, Pawlowska M, Mizerski J. Randomized, placebo-controlled trial of tenofovir disoproxil fumarate in adolescents with chronic hepatitis B. *Hepatology* 2012; **56**: 2018-2026 [PMID: 22544804 DOI: 10.1002/hep.25818]

44 **Gaur AH**, Kizito H, Prasitsueubsai W, Rakhmanina N, Rassool M, Chakraborty R, Batra J, Kosalaraksa P, Luesomboon W, Porter D, Shao Y, Myers M, Ting L, SenGupta D, Quirk E, Rhee MS. Safety, efficacy, and pharmacokinetics of a single-tablet regimen containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in treatment-naive, HIV-infected adolescents: a single-arm, open-label trial. *Lancet HIV* 2016; **3**: e561-e568 [PMID: 27765666 DOI: 10.1016/S2352-3018(16)30121-7]

45 **Lockman S**, Brummel SS, Ziemba L, Stranix-Chibanda L, McCarthy K, Coletti A, Jean-Philippe P, Johnston B, Krotje C, Fairlie L, Hoffman RM, Sax PE, Moyo S, Chakhtoura N, Stringer JS, Masheto G, Korutaro V, Cassim H, Mmbaga BT, João E, Hanley S, Purdue L, Holmes LB, Momper JD, Shapiro RL, Thoofer NK, Rooney JF, Frenkel LM, Amico KR, Chinula L, Currier J; IMPAACT 2010/VESTED Study Team and Investigators. Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet* 2021; **397**: 1276-1292 [PMID: 33812487 DOI: 10.1016/S0140-6736(21)00314-7]

46 **Gane EJ**. Future anti-HBV strategies. *Liver Int* 2017; **37 Suppl 1**: 40-44 [PMID: 28052637 DOI: 10.1111/liv.13304]

47 **Testoni B**, Durantel D, Zoulim F. Novel targets for hepatitis B virus therapy. *Liver Int* 2017; **37 Suppl 1**: 33-39 [PMID: 28052622 DOI: 10.1111/liv.13307]

48 **Lin CL**, Yang HC, Kao JH. Hepatitis B virus: new therapeutic perspectives. *Liver Int* 2016; **36 Suppl 1**: 85-92 [PMID: 26725903 DOI: 10.1111/liv.13003]

49 **Soriano V**, Barreiro P, Benitez L, Peña JM, de Mendoza C. New antivirals for the treatment of chronic hepatitis B. *Expert Opin Investig Drugs* 2017; **26**: 843-851 [PMID: 28521532 DOI: 10.1080/13543784.2017.1333105]

**Footnotes**

**Conflict-of-interest statement:** The authors declare that they have no competing interests.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** April 17, 2021

**First decision:** June 3, 2021

**Article in press:** August 13, 2021

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Italy

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

1. **Reviewer:** Kayesh MEH, Kishida Y **S-Editor:** Gong ZM **L-Editor:** Filipodia **P-Editor:** Li JH

**Table 1 Patients’ categories and phases in natural history of chronic hepatitis B virus infection defined by European Association for the Study of the Liver guidelines 2017[11]**

|  |  |  |  |
| --- | --- | --- | --- |
|  | HBeAg positive | HBeAg negative | HBsAg negative |
| HBV infection (normal ALT) | High HBsAg | Low HBsAg | HBcAb-positive with/without positive HBsAb |
| HBV DNA > 107 IU/ml | HBV DNA < 2000 IU/ml | HBV DNA usually undetectable |
| None/minimal liver disease | No liver disease | No liver disease |
| Old terminology: Immune-tolerant | Old terminology: Inactive carrier/immune control | Old terminology: Occult HBV infection |
| Hepatitis B (abnormal ALT) | High or intermediate HBsAg | Intermediate HBsAg |  |
| HBV DNA 104-107 IU/ml | HBV DNA > 2000 IU/ml |
| Moderate to severe liver disease | Moderate to severe liver disease |
| Old terminology: immune-active | Old terminology: immune escape |

HBV: Hepatitis B virus; ALT: Alanine aminotransferase levels; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B s antigen; DNA: Deoxyribonucleic acid; HBcAb: Hepatitis B c antibodies.

**Table 2 Antiviral drugs approved for children and adolescents with chronic hepatitis B virus infection[14]**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Ages approved for drug administration | Drug dosage | Drug formulations |
| Interferon alfa-2b | ≥ 1 yr | 6 million UI/m2 three times a week | Subcutaneous injection |
| Peginterferon alfa-2a | ≥ 3 yr | 180 µg/1.73 m2 once a week | Subcutaneous injection |
| Lamivudine | ≥ 3 yr | 3 mg/kg daily (maximum 100 mg) | Oral solution (5 mg/mL) or tablets (100 mg) |
| Entecavir | ≥ 2 yr | 10-30 kg: 0.015 mg/kg daily (maximum 0.5 mg) | Oral solution (0.05 mg/mL) or tablets (0.5 mg and 1 mg) |
| > 30 kg: 0.5 mg daily |
| Adefovir | ≥ 12 yr | 10 mg daily | Tablets (10 mg) |
| Tenofovir disoproxil fumarate | ≥ 2 yr1 | 8 mg/kg daily (maximum 300 mg) | Oral powder (40 mg per 1 g) or tablets (150 mg, 200 mg, 250 mg and 300 mg) |
| ≥ 12 yr1 | 300 mg daily |
| Tenofovir alafenamide | ≥ 12 yr2 | 25 mg daily | Tablet (25 mg) |

1Approved for ≥ 2 yr by the European Medicines Agency and ≥ 12 yr by the United States Food and Drug Administration.

2Approved independent of age for weight > 35 kg.

**Table 3 Differences among recommendations and indications for treatment of chronic hepatitis B virus infection in adults, adolescents, and children from five professional societies or international organizations**

|  |  |
| --- | --- |
| Organization |  |
| ESPGHAN[16] | HBeAg-positive adolescents and children with persistent alanine aminotransferase elevation for at least 6 mo |
| HBeAg-negative adolescents and children with persistent alanine aminotransferase elevation for at least 6 mo for at least 12 mo |
| HBV DNA > 2000 IU/mL and either |
| Moderate necroinflammation or fibrosis |
| Mild inflammation or fibrosis with a family history of hepatocellular carcinoma |
| AASLD[17] | HBeAg-positive adolescents and children with both elevated alanine aminotransferase and measurable HBV DNA concentrations |
| Therapy should be deferred when HBV DNA is < 10000 IU/mL, until spontaneous HBeAg seroconversion is excluded |
| APASL[18] | Non-cirrhotic HBeAg-positive adolescents and children when HBV DNA level is higher than 20000 IU/mL and alanine aminotransferase is more than twice the upper limit of normal for more than 12 mo |
| Non-cirrhotic HBeAg-positive adolescents and children either HBV DNA > 20000 IU/mL and ALT more than two times ULN for more than 12 mo, or a family history of hepatocellular carcinoma or cirrhosis and moderate-to-severe inflammation or pronounced fibrosis |
| Non-cirrhotic, HBeAg-positive chronic HBV infection, HBV DNA < 20000 IU/mL and moderate to severe inflammation or pronounced fibrosis |
| Non-cirrhotic, HBeAg-negative chronic HBV infection, HBV DNA > 2000 IU/mL, and ALT more than two times ULN  Non-cirrhotic, HBeAg-negative chronic HBV infection and moderate to severe inflammation or pronounced fibrosis, regardless of HBV DNA concentration |
| EASL[11] | A conservative approach is warranted |

ESPGHAN: European Society for Paediatric Gastroenterology Hepatology and Nutrition; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus; DNA: Deoxyribonucleic acid; AASLD: American Association for the Study of Liver Diseases; APASL: Asian Pacific Association for the Study of the Liver; ALT: Alanine aminotransferase levels; ULN: Upper limit of normal; EASL: European Association for the Study of the Liver.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2021 Baishideng Publishing Group Inc. All rights reserved.**