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Treatment of hepatitis B virus infection in children and adolescents

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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

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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.

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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 mainly 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

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 > 10 ⁷ 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 10 ⁴ -10 ⁷ 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.

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].

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/m ² three times a week | Subcutaneous injection |
| Peginterferon alfa-2a | ≥ 3 yr | 180 µg/1.73 m ² 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) > 30 kg: 0.5 mg daily | Oral solution (0.05 mg/mL) or tablets (0.5 mg and 1 mg) |
| Adefovir | ≥ 12 yr | 10 mg daily | Tablets (10 mg) |
| Tenofovir disoproxil fumarate | ≥ 2 yr ¹ ≥ 12 yr ¹ | 8 mg/kg daily (maximum 300 mg) 300 mg daily | Oral powder (40 mg per 1 g) or tablets (150 mg, 200 mg, 250 mg and 300 mg) |
| Tenofovir alafenamide | ≥ 12 yr ² | 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.

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

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

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.

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