

Management of Hepatitis B Virus Infection and Prevention of Hepatitis B Virus Reactivation in Children With Acquired Immunodeficiencies or Undergoing Immune Suppressive, Cytotoxic, or Biological Modifier Therapies

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ABSTRACT

Reactivation of hepatitis B virus (HBV) is a known complication of immune-suppressive, cytotoxic, and biological modifier therapies in patients currently infected with HBV or who have had past exposure to HBV. Nowadays, newer and emerging forms of targeted biologic therapies are available for the management of rheumatologic conditions, malignancies, inflammatory bowel disease, dermatologic conditions and solid-organ, bone marrow, or haematologic stem cell transplant but there is currently a lack of a systematic approach to the care of patients with or at risk of HBV reactivation. The Hepatology Committee of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) together with a working group of ESPGHAN members with clinical and research expertise in viral hepatitis developed an evidence-based position paper on reactivation of HBV infection in children identifying pertinent issues addressing the diagnosis, prevention, and treatment of this condition. Relevant clinical questions were formulated and agreed upon by all the members of the working group. Questions were answered and positions were based on evidence resulting from a systematic literature search on PubMed and Embase from their inception to July 1, 2019. A document was produced and the working group and ESPGHAN Hepatology Committee members voted on each recommendation, using a formal voting technique. A recommendation was accepted provided upon agreement by at least 75% of the working group members. This position paper provides a comprehensive update on the diagnosis, prevention and treatment of HBV reactivation in children.

Key Words: antiviral, hepatitis B virus, position paper, reactivation, systematic review, transplant, treatment

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What Is Known

- Reactivation of hepatitis B virus is a known complication of immune-suppressive therapies.
- The clinical course of hepatitis B virus reactivation is unpredictable and ranges from mild hepatitis to liver failure and even death.
- Reactivation of hepatitis B virus is preventable or amenable to treatment with the appropriate use of antiviral drugs.

What Is New

- Enhanced awareness of the risk of reactivation of hepatitis B virus is crucial for its correct therapeutic management.
- All patients at moderate or high-risk of hepatitis B virus reactivation should undergo prophylaxis.
- Entecavir or tenofovir are the drugs of choice for prophylaxis or pre-emptive therapy of hepatitis B virus reactivation.

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OBJECTIVES

Reactivation of hepatitis B virus (HBV) is a known complication of immune suppressive, cytotoxic, and biological modifier therapies (1,2). This condition can lead to hepatocellular injury, elevated alanine aminotransferase levels, symptoms of acute hepatitis, liver failure, and even death but it is preventable or curable with the appropriate use of antiviral drugs. The aim of the present position paper by the Hepatology Committee of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) is to provide its position on the optimal prophylactic, therapeutic, and clinical management regarding HBV reactivation in children and adolescents.

BACKGROUND

Hepatitis B in Children

HBV can cause both acute and chronic infection in children (3). Age at acquisition of the infection is the key determinant of the outcome, with chronic infection occurring in 90% of infected neonates and infants but in <5% of older children (>5 years of age), adolescents and adults (4). The natural history of chronic HBV infection is dynamic and progresses nonlinearly through several phases of variable duration (3). According to the new nomenclature adopted by the European Association for the Study of the Liver (EASL) in 2017 (5), chronic HBV infection can be characterized with regard to presence or absence of active hepatitis (defined as raised or normal aminotransferase levels, respectively) and with

regard to hepatitis B e antigen (HBeAg) status (Table 1). The main characteristic of HBV infection acquired vertically, perinatally, or in early childhood is the decades long duration of a high-replication, low-level inflammation phase whereby hepatitis B s antigen (HBsAg) and HBeAg are detectable in serum, serum HBV deoxyribonucleic acid (DNA) concentrations are high, but serum aminotransferases may be normal or only minimally increased. Overall, cirrhosis has been reported in 1% to 5% of HBeAg-positive children (6,7). The earlier HBeAg seroconversion (before 3 years of age, consistent with severe necroinflammatory activity) and the longer duration of the immune-active phase (Table 1) (6,8), which is in turn associated with HBV genotype C infection (9), are considered risk factors for development of cirrhosis. The risk of developing hepatocellular carcinoma in childhood is very low (8).

Hepatitis B Virus Vaccine

HBV vaccine represents the most effective way to prevent HBV infection (10,11) For children and adults with normal immune status, routine anti-HBs testing following a standard vaccination course and booster doses of HBV vaccine are not recommended. For immunocompromised people (eg, human immunodeficiency virus [HIV]-infected people and those receiving immune suppressive, cytotoxic, or biological modifier therapies), the need for booster doses has not been determined but annual anti-HBs testing and booster doses when anti-HBs concentrations decrease to <10 mIU/mL should be considered if they have an ongoing risk for HBV exposure (12). Although larger vaccine doses are required

TABLE 1. Phases in natural history of chronic hepatitis B virus infection

Old terminology	New terminology	Characteristics
Immune-tolerant phase	HBeAg-positive infection	HBsAg: high Aminotransferases: normal HBV DNA: >10 ⁷ IU/ml Liver disease*: none/minimal Progression to cirrhosis: none Treatment: not generally indicated
Immune-active phase	HBeAg-positive hepatitis	HBsAg: high Aminotransferases: elevated HBV DNA: >2000 IU/ml (constantly raised or fluctuating) Liver disease: moderate to severe Progression to cirrhosis: possible Treatment: may be indicated
Inactive carrier/immune-control phase	HBeAg-negative infection	HBsAg: low Aminotransferases: normal HBV DNA: <2000 IU/mL Liver disease: none Progression to cirrhosis: none Treatment: not indicated
Immune-escape phase	HBeAg-negative hepatitis	HBsAg: intermediate Aminotransferases: elevated HBV DNA: >2000 IU/mL Liver disease: moderate to severe Progression to cirrhosis: more rapid than in other phases Treatment: may be indicated
Occult HBV infection (anti-HBc-positive)	HBsAg-negative infection	HBV DNA: undetectable Aminotransferases: normal Liver disease: none Progression to cirrhosis: none Treatment: not indicated

Data from (5). HBeAg = hepatitis B e antigen; HBsAg = hepatitis B s antigen; HBV = hepatitis B virus.

*Necroinflammatory changes.

TABLE 2. Antiviral drugs approved for children and adolescents with chronic hepatitis B virus infection

Drug	Licensed age for use in children and adolescents	Dose
Interferon α 2b	≥ 1 year	6 million IU/m ² 3 times a week (subcutaneous injections)
Pegylated interferon α 2a	≥ 3 years	180 μ g/1.73 m ² once a week (subcutaneous injections)
Lamivudine	≥ 3 years	3 mg/kg once daily or in 2 divided doses (max 100 mg) (oral)
Entecavir	≥ 2 years	0.015 mg/kg once daily (max 0.5 mg) (oral)
Adefovir	≥ 12 years	10 mg once daily (oral)
Tenofovir disoproxil fumarate	≥ 12 years	300 mg once daily (oral)
Tenofovir alafenamide	≥ 12 years	25 mg once daily (oral)

and have been used to induce protective anti-HBs concentrations in immunocompromised adults and in those undergoing hemodialysis, few data exist concerning the response to higher doses of vaccine in children and adolescents, and no specific recommendations has been made for these age groups (10).

Antihepatitis B Virus Drugs

None of the anti-HBV drugs currently available can be considered curative or eradicated for HBV. Two different classes of anti-HBV drugs are available: immune-modulators and nucleos(t)ide analogues (NA) (13). Interferon (IFN) α and pegylated (PEG) IFN α act as immune-modulators and can be administered for a predefined duration with the aim of inducing an immune-mediated control of HBV infection to achieve long-lasting suppression of viral replication off-treatment (13). NA have been characterized as carrying low (lamivudine, adefovir, telbivudine) or high (tenofovir and entecavir) genetic barrier to resistance (Table 2). Tenofovir and entecavir have no significant drug-drug interactions and excellent safety records (14,15) confirmed by real-world experiences in adults, which makes them suitable for long-term use. Tenofovir and entecavir are potent HBV inhibitors and are used as long-term oral treatment to suppress viral replication or, less frequently, for treatment of finite duration (with or without IFN) to obtain sustained off-treatment virological response. Treatment duration with NA, once commenced, could be lifelong, as HBeAg seroconversion, or HBsAg loss is relatively uncommon and virological relapse is frequent upon treatment withdrawal (13).

Immune-suppressive, Cytotoxic, and Biological Modifier Therapies

Every treatment that suppresses or reduces the strength of the body's immune system can be considered immune-suppressive. There are several different types of immunosuppressant drugs as described in Table 3. Cytotoxic drugs used to treat cancer prevent cell division or cause cell death acting predominantly on rapidly dividing cells, such as T lymphocytes, and are therefore, immune-suppressive (1,2). Biological response modifiers are substances that can either enhance or suppress an immune response. A rapidly increasing number of newer and emerging forms of targeted immune-suppressive biologic therapies are becoming available for the management of rheumatologic conditions, malignancies, inflammatory bowel disease, dermatologic conditions, and solid-organ or bone marrow transplant.

Reactivation of Hepatitis B Virus

The population at risk for HBV reactivation includes those who either have active HBV replication (ie, HBV DNA detectable in serum) or have serologic evidence of exposure to the virus without detectable HBV DNA in serum (1,2). There is no consensus on the definition and on the diagnostic criteria for HBV reactivation (1,2,16,17). Reactivation occurs whenever the dynamic balance between HBV and the host's immune system changes resulting in a reduction in host's immune control. The possible consequences of the new balance are: the enhancement of the viral replicative

TABLE 3. Main classes of immune-suppressive, cytotoxic, and biological modifier therapies, and relative common therapeutic indications

Therapeutic class	Main therapeutic indications
B-cell-depleting agents	Non-Hodgkin lymphoma, rheumatologic conditions (rheumatoid arthritis and vasculitides)
Anthracycline derivatives	Lymphoma/leukemia, idiopathic thrombocytopenic purpura, cryoglobulinemia
Immunophilin inhibitors	Hepatocellular carcinoma (transarterial haemoembolization)
Corticosteroids	Breast, ovarian, uterine, and lung cancers; lymphoma and leukemias
Tumour necrosis factor α inhibitors	Postsolid organ transplant immune suppression
Other cytokine or integrin inhibitors	High dose and long-term: inflammatory bowel disease, vasculitis, sarcoidosis, autoimmune disorders, nephrotic syndrome
Other immune-suppressive agents	Inflammatory bowel disease, rheumatologic (rheumatoid arthritis), and dermatologic conditions, ankylosing spondylitis
Histone deacetylase inhibitors	Inflammatory bowel disease, rheumatologic, and dermatologic conditions
Tyrosine kinase inhibitors*	Plaque psoriasis
Proteasome inhibitors*	Inflammatory bowel disease, psoriasis, sarcoidosis, autoimmune liver disease, arthritis
Cancer chemotherapy*	T-cell lymphomas
	Chronic myeloid leukaemia, gastrointestinal tumours
	Multiple myeloma
	Breast cancer, pancreatic cancer, lung cancer

*Drugs of limited or null relevance for children.

fitness; the possible reappearance of active HBV-related necroinflammatory liver disease, usually several weeks later; and the possible change in the HBV serological pattern of the patient. Consequently, HBV reactivation has been defined as: a sudden and rapid increase in HBV DNA level (by a 10 to above 100-fold the baseline level) or as the reappearance of detectable HBV DNA viremia having been undetectable before the initiation of the immune-suppressive therapy; with or without an increase in alanine aminotransferase level to at least 3 times the baseline value or to a predefined level above the upper limit of the normal range (1,2). HBV reactivation may be classified into 2 broad categories based on the baseline virologic profile: HBV reactivation in patients who are positive for HBsAg in the serum with or without detectable HBV DNA viremia in the blood and reverse seroconversion defined as a reappearance of HBsAg and HBV DNA in individuals who initially are negative for HBsAg and HBV DNA in the serum before the exposure to immunosuppressive therapies. Most children and adolescents belong to the first category.

For the purpose of this position paper and because of the peculiarity of the natural history of HBV infection acquired vertically or in early childhood, the following definition of HBV reactivation has been accepted by the authors of the present position paper:

1. a sudden and rapid increase in HBV DNA level or the de novo detection of HBV DNA viremia whenever undetectable before the initiation of the immune-suppressive, cytotoxic, or biological modifier therapy;
2. irrespective of alanine aminotransferase level and of HBsAg reverse seroconversion.

The clinical outcome of HBV reactivation is unpredictable. Reactivation can be subclinical and resolve spontaneously or can lead to clinically apparent acute hepatitis, which can be severe and result in acute liver failure and even death, or can result in persistent infection, which may go undetected until advanced liver disease is present (1,2).

Prophylactic Antihepatitis B Virus Therapy

The management of HBV reactivation in adults is based on the likelihood of the risk of reactivation, which, in turn, is based on the profile of the individual patient, that is, the baseline diagnosis, the type of immune-suppressive therapy, and on the

serologic and virologic characteristics of the patient (1,2). Prophylactic anti-HBV therapy before starting immune-suppressive, cytotoxic, and biological modifier therapies is generally recommended in all patients who are either at moderate or high risk of HBV reactivation (1,2). In selected patients, such as those who are HBsAg-negative, additional factors could be taken in account on a case-by-case basis before starting antiviral prophylaxis. Patient's perceptions, the cost of treatment, the long-term availability, the overall prevalence, and the risk of HBV transmission in the population and the resources of the local health care system could justify a strict monitoring approach with HBV DNA, HBsAg, and aminotransferases rather than routine prophylaxis. When the risk of HBV reactivation is low (<1%) generally no antiviral prophylaxis is suggested (1,2).

METHODS

The project started in April 2019, when under the auspices of Hepatology Committee of the ESPGHAN, a working group consisting of selected ESPGHAN members (G.I., B.F., E.S., S.B., M.H.A.) who have a long-term clinical and research expertise in viral hepatitis was formed to prepare a position paper to be reviewed and approved by all 12 Hepatology committee members, representing the European paediatric hepatologist community. The aim of this paper is to formulate evidence-based positions on current knowledge for the clinical and therapeutic management of HBV reactivation in children undergoing immune-suppressive, cytotoxic, or biological modifier therapies. Relevant clinical questions were formulated (Table 4) by the lead of the working group (G.I.) and agreed upon by the other members. Questions were answered and relative positions were based on evidence resulting from a selection of key publications on the topic published and cited in PubMed (www.ncbi.nlm.nih.gov/pubmed) and Embase (www.embase.com/#search). The following search words were used "hepatitis B virus," "immunosuppressive agents," "viruses," "reactivation," "infant," "child," and "adolescent." Fundamental characteristics of the abstracts judged pertinent to the review were noted, and full-length articles/reviews were selected from the abstracts. Citations were chosen on the basis of their relevance to the text. Furthermore, all of the members of the working group were asked to search the literature relevant to the topic to possibly uncover further studies that may have been missed by the former search. Due to the lack of original paediatric data, relevant adult studies and guidelines were evaluated. Extrapolations from adult literature were clearly highlighted throughout the manuscript.

TABLE 4. Overview of relevant clinical questions

Screening	1. Should children planned for immune-suppressive, cytotoxic, or biological modifier therapies be screened for hepatitis B virus infection before starting treatment and which test(s) should be done for screening?
HBV vaccination	2. Should HBV vaccination be done and when?
Risk of HBV reactivation	3. How can the risk of HBV reactivation be stratified for children?
Antiviral prophylaxis, watchful monitoring and pre-emptive therapy	4. When should antiviral prophylaxis be initiated?
Management of specific cases	5. When should watchful monitoring and pre-emptive therapy be suggested?
	6. Which are the preferred drugs?
	7. How long should the antiviral prophylaxis last?
	8. How should children undergoing solid organ transplant be managed?
	a. Liver transplant recipients
	b. Nonliver solid organ transplant recipients
	9. How should children undergoing haematologic stem cell transplant be managed?
	10. How should children with acquired immunodeficiencies be managed?

HBV = hepatitis B virus.

TABLE 6. Suggested management of hepatitis B virus infection according to the risk of reactivation

Risk category	Anticipated risk of hepatitis B virus reactivation	Management
High risk	>10%	Antiviral prophylaxis continued for at least 6 months after discontinuation of immune-suppressive therapy (12 months for B-cell-depleting agents)
Moderate risk	1% to 10%	Antiviral prophylaxis continued for at least 6 months after discontinuation of immune-suppressive therapy; no prophylaxis could be a reasonable approach in HBsAg-negative, anti-HBc-positive children and adolescents. In these cases, monitoring of HBV DNA (or HBsAg when HBV DNA testing is impractical and could not be performed in regular care) and aminotransferases may be considered. The decision on whether doing or not the antiviral prophylaxis in this group of patients should be on a case-by-case basis, depending on the comorbid conditions, the prevalence of anti-HBc positivity in the population, on the cost and long-term availability of treatment and on the patient's and parent's perception
Low risk	<1%	No antiviral prophylaxis suggested; monitoring is not mandatory for adults but is considered prudent for children and adolescents

HBc = hepatitis B c.

impractical and difficult to reproduce in regular care in many low- and middle-income countries (3). In this case, monitoring HBsAg for reverse seroconversion in HBsAg-negative children could be considered as an alternative. Although in adults, monitoring is also not mandatory when the risk of HBV reactivation is low, the working group feels that a prudent approach is recommendable for children and adolescents.

Position. Watchful monitoring of HBV DNA and aminotransferase levels and prompt pre-emptive therapy are recommended for children and adolescents when the risk of HBV reactivation is low (<1%).

VOTES: 7/7/7/8/8/8/8/9/9/9/9/9/9/9/8 Accepted.

Which Are the Preferred Drugs?

The clinical effectiveness of oral antiviral drugs with a high barrier to resistance as compared with earlier generation antiviral drugs has never been directly explored in any trial in children and adolescents who developed reactivation of HBV. The higher effectiveness in terms of control of HBV DNA replication and decreased development of virological resistance with the use of the new generation drugs as compared with lamivudine has been largely demonstrated in nonimmunosuppressed patients (14,15,58,59).

Although lamivudine has been effectively used for the prevention of HBV reactivation both in adults and children and is cheaper than the new drugs and more easily available in resource-limited settings, it cannot be considered the drug of choice because it has a low barrier for the development of drug resistance. Rates of lamivudine resistance of 20% at 1 year and 30% at 2 years have been reported in nonimmunocompromised adults and would be anticipated to be higher in patients undergoing immunosuppressants (60,61). Two studies have demonstrated the superiority of entecavir over lamivudine in reducing the risk of HBV reactivation in HBsAg-positive adults receiving chemotherapy treatment for B-cell lymphoma and solid tumours (62,63). A network meta-analysis has shown that tenofovir and entecavir may be the most efficacious therapies for the prevention of HBV reactivation (64). Therefore, extrapolating from adult data, we suggest the use of antiviral drugs with a high barrier to resistance over lamivudine for prophylaxis and for established HBV reactivation in patients undergoing immune-suppressive, cytotoxic, and biological modifier therapy. However, according to the setting where the treatment is prescribed, less expensive drugs could be preferred to the expensive antiviral drugs with a higher barrier to resistance. This is particularly true in patients who have extremely low or undetectable HBV DNA levels

and who are expected to use antiviral prophylaxis for less than 6 months.

Position. We recommend the use of antiviral drugs with a high barrier to resistance (entecavir or tenofovir) over lamivudine for prophylaxis, pre-emptive treatment, and for treatment of HBV reactivation in patients undergoing immune-suppressive, cytotoxic, and biological modifier therapy.

VOTES: 9/9/9/9/9/9/9/9/9/9/9/9/9/9/9 Accepted.

How Long Should the Antiviral Prophylaxis Last?

The overall accepted and agreed duration of antiviral prophylaxis is at least 6 months after discontinuation of immune-suppressive therapy (1,2,5,16). When high risk treatments, such as B-cell-depleting agents are used and in patients undergoing bone marrow or haematologic stem cell transplant, the duration of antiviral prophylaxis should be extended to at least 12 months (1,2,5,16). The rationale of the suggested duration of antiviral prophylaxis lies in the data derived from the onset of risk of reactivation. Immune recovery may be delayed for up to 1 year (and even more) after the last dose of rituximab and other B-cell-depleting agents (65). Due to the risk of HBV reactivation after withdrawal of antiviral therapy (66), it is recommended that children and adolescents undergo routine testing for HBV DNA and serum aminotransferases at 3 to 6 months after discontinuation of antiviral therapy.

Position. The duration of antiviral prophylaxis is at least 6 months after discontinuation of immune-suppressive, cytotoxic, and biological modifier therapy. The duration of antiviral prophylaxis should be extended to 12 months when high-risk treatments, such as B-cell-depleting agents are used and in patients undergoing bone marrow or haematologic stem cell transplant.

VOTES: 7/8/8/9/9/9/9/9/9/9/9/9/9/9/9 Accepted.

MANAGEMENT OF SPECIFIC CASES

How Should Children Undergoing Solid Organ Transplant be Managed?

Two scenarios are possible with regard to HBV reactivation in solid organ transplant recipients. First, HBsAg- and anti-HBc-negative patients receiving organs from donors with evidence of past HBV infection (anti-HBc-positive). The debate around whether

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