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

Consensus and Voting

The consensus was formally achieved through nominal group technique, a structured quantitative method. The members of the working group anonymously voted on each recommendation. A 9-point scale was used (1—strongly disagree to 9—fully agree), and votes are reported for each recommendation. It was decided in advance that consensus was reached, if >75% of the working group members voted 6, 7, 8, or 9. The consensus was reached for all of the questions. The final draft of the paper was sent to all of the committee members for approval in October 2019.

SCREENING

Should Children Planned for Immune-Suppressive, Cytotoxic, or Biological Modifier Therapies Be Screened for HBV Infection Before Starting Treatment and Which Test(s) Should Be Done for Screening?

Cost-effectiveness studies of routine HBV screening before starting immune-suppressive therapies have never been done in children and are limited in adults (18–20). There is heterogeneity in the approaches that various professional medical societies have taken to address this issue. Routine HBV screening by HBsAg and anti-hepatitis B c (HBc) testing followed by a sensitive HBV DNA test if positive is recommended by the American Association for the Study of Liver Diseases (AASLD) (16), EASL (5), the Asian Pacific Association for the Study of the Liver (APASL) (21) and ESPGHAN (22) in all patients (adults and children) who are about to undergo immune-suppressive, cytotoxic, or biological modifier therapies. Only the American Gastroenterological Association argues against routinely screening for HBV in patients who will undergo immune-suppressive drug therapy but are at low risk of HBV reactivation (see below for definition of risk categories) (2). Anti-HBs testing is needed in order to evaluate, together with the medical history, the responsiveness to HBV vaccination. In case of isolated anti-HBc positivity, false-positive reactivity should be ruled out and retesting is needed (23).

Position. **Routine HBV screening is recommended among all children who are at risk of HBV reactivation. Screening should be done by HBsAg, anti-HBs, and anti-HBc testing.**

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

HEPATITIS B VIRUS VACCINATION

Should HBV Vaccination Be Done and When?

There is agreement across the published guidelines towards vaccination against HBV for all those who are negative for HBsAg, anti-HBc, and anti-HBs (2,5,16,21,22). Although, no real data can support the choice of the proper timing for HBV vaccination, it is conceivable that the sooner HBV vaccine is administered the better. Antibody responses to HBV vaccination in adults undergoing immune-suppressive treatment is good but it wanes rapidly during immune-suppressive treatment and more rapidly than in healthy subjects (24,25). It has been suggested that in adults, anti-HBs titres should be checked approximately 4 weeks after the last dose of vaccine to document protective titres. By comparison, multiple studies have shown that about two-third of children vaccinated before transplant will lose anti-HBs protection with time following liver or kidney transplant (26–31). No data is available on the use of more highly immunogenic vaccines, on the use of booster doses or of different vaccination schedules on the level and durability of protection during immune-suppressive drug therapy in children. Serial anti-HBs titres could be assessed periodically if the patient has ongoing risk for HBV exposure (12), and although not routinely performed in the immunocompetent host, it is widely accepted to perform serological monitoring to confirm acceptable immunity in children awaiting liver or nonliver solid organ transplant. Revaccination can be done in nonresponders or those with waning immunity (anti-HBs <10 mIU/mL) by either administering a complete series again or giving 1 dose and checking anti-HBs (10). Although, anti-HBs <10 mIU/mL has usually been referred to as the threshold lower limit for revaccination, in clinical practice, revaccination is usually performed in immunosuppressed children when anti-HBs are <50 mIU/mL.

Vaccination has also been evaluated as a tool to increase anti-HBs titres in both anti-HBc-positive and anti-HBs-positive patients but the threshold level of neutralizing anti-HBs titres that may offer protection against HBV reactivation has not been clearly identified in children (32,33). Due to a lack of studies that have used anti-HBs titres to guide initiating antiviral prophylaxis or infer protection, it can be concluded that there is insufficient evidence to support the use of anti-HBs titres in making a recommendation regarding prophylaxis (2).

Position. **All the children and adolescents who are negative for HBsAg, anti-HBc, and anti-HBs should be vaccinated against HBV as soon as possible before starting immune-suppressive, cytotoxic, or biological modifier therapies**.

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

RISK OF HEPATITIS B VIRUS REACTIVATION

How Can the Risk of Hepatitis B Virus Reactivation Be Stratified for Children?

The risk of HBV reactivation has been extensively studied in adults but not in children and adolescents. According to adult studies, the risk of HBV reactivation can be divided broadly into 3 categories: low-risk (if the rate of reactivation is <1%); moderate risk (if the rate of reactivation is between 1% and 10%), and high risk (if the rate of HBV reactivation is >10%) (1,2). The risk of HBV reactivation is dependent on the baseline diagnosis, which in turn correlates with the type of treatment, and on the serologic and virologic characteristics of the patients as detailed in Table 5. In general, this risk for HBV reactivation is higher in patients with high baseline HBV DNA levels, HBeAg positivity, non-A genotype infection (34–36) and 5 to 8 times higher in patients who are HBsAg-positive when compared with those who are HBsAg-negative and anti-HBc-positive (37). Male sex, older age, and the presence of cirrhosis are additional risk factors for reactivation (38,39). With regard to the type of disease, the greatest risk of reactivation that mandates antiviral prophylaxis, is in the setting of bone marrow, haematologic stem cell, or solid-organ transplant (1,2). Patients receiving cancer chemotherapy for lymphomas and acute myeloid leukaemia usually receive immune-suppressive therapies or high-dose pulse steroids and should be also considered at high risk of reactivation (1,2). Regarding treatment, the greatest risk of reactivation is described with the use of B-cell-depleting therapies (40,41). Treatment with systemic chemotherapy for diseases other than the ones described earlier can be considered at moderate risk of reactivation (1,2).

Position. **Due to the lack of paediatric data, the risk of HBV reactivation in children and adolescents should be extrapolated from adult studies and can be divided broadly into high risk (if the rate of HBV reactivation is >10%), moderate risk (if the rate of reactivation is between 1% and 10%), and low risk (if the rate of reactivation is <1%)** (Table 5)**. Patients undergoing bone marrow or haematologic stem cell transplant or solid organ transplant are at high risk of HBV reactivation.**

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

TABLE 5. Risk of hepatitis B virus reactivation based on the type of immune-suppressive, cytotoxic, and biological modifier therapy stratified by the virologic characteristics of the patient

Therapeutic class	Drugs	HBsAg-positive and anti-HBc-positive	HBsAg-negative and anti-HBc-positive with or without anti-HBs
B-cell-depleting agents (40–42)	Rituximab Ofatumumab Alemtuzumab Natalizumab Ibrimtumomab	High risk	High risk
Anthracycline derivatives (43)	Doxorubicin Epirubicin	High risk	Moderate risk
Corticosteroids (44)	Prednisone moderate-dose (10–20 mg/day) or high-dose (>20 mg) for more than 4 weeks	High risk	Moderate risk
	Prednisone low-dose (<10 mg/day) for more than 4 weeks	Moderate risk	Low risk
	Intra-articular corticosteroids	Extremely low risk	Low risk
	Any dose of oral corticosteroids for ≤1 week	Low risk	Low risk
Tumour necrosis α inhibitors (more potent) (45–47)	Infliximab Adalimumab Certolizumab Golimumab	High risk	Moderate risk
Tumour necrosis α inhibitors (less potent) (46–48)	Etanercept	Moderate risk	Low
Other cytokine or integrin inhibitors (49,50)	Abatacept Ustekinumab Mogamulizumab Natalizumab Vedolizumab	Moderate risk	Moderate risk
Tyrosine kinase inhibitors (51–53)	Imatinib Nilotinib	Moderate risk	Moderate risk
Proteasome inhibitors (54,55)	Bortezomib	Moderate risk	Moderate
Other traditional immune-suppressive agents	Azathioprine 6-Mercaptopurine Methotrexate	Low risk	Low risk
Histone deacetylase inhibitors (56)	Romidepsin	Moderate risk	Moderate risk
Immunophilin inhibitors (57)	Cyclosporine Tacrolimus	Moderate risk	Moderate risk
Systemic chemotherapy	Other drugs not listed above	Moderate risk	Moderate

HBc = hepatitis B c; HBsAg = hepatitis B s antigen.

ANTIVIRAL PROPHYLAXIS, WATCHFUL MONITORING AND PRE-EMPTIVE THERAPY

When Should Antiviral Prophylaxis Be Initiated?

The therapeutic management of HBV reactivation is based on the assessment of the risk of reactivation of the individual patient, that is, on the type of immunosuppressant used and on the virological profile of the patient as described earlier. When the risk of HBV reactivation is either high or moderate, prophylactic anti-HBV therapy should be considered (1,2). Antiviral prophylaxis should be initiated at least 1 week before or in concomitance with starting immune-suppressive, cytotoxic, or biological modifier therapies. No prophylaxis but monitoring may be considered on a case-by-case basis when the risk of HBV reactivation is moderate, depending on the comorbid conditions, the prevalence of anti-HBc positivity in the population, the cost and long-term availability of treatment (Table 6) (1,2).

Position. **Antiviral prophylaxis initiated before starting immune-suppressive, cytotoxic, or biologic modifier therapy is recommended for children and adolescents at a high or moderate risk of reactivation.**

VOTES: 4/7/8/8/9/9/9/9/9/9/9/9/9/9/9 Accepted.

When Should Watchful Monitoring and Pre-emptive Therapy Be Suggested?

When the risk of HBV reactivation is low (<1%), generally no antiviral prophylaxis is suggested in adults (1,2). In most scenarios, watchful monitoring may be a reasonable choice for patients who are HBsAg-negative and anti-HBc-positive. Monitoring HBV DNA and aminotransferase levels during immune-suppressive therapy may allow for early detection of HBV reactivation and pre-emptive treatment. The most appropriate HBV DNA monitoring interval cannot be determined from existing adult and paediatric data. Furthermore, it should be considered that the cost and the access to routine HBV DNA testing could be

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

HBV-positive organs should be transplanted to HBV-negative children is beyond the scope of the present position paper. The aim of the working group on this issue was to provide recommendations on the correct management of these patients. The second possible scenario is made by HBsAg- and/or anti-HBc-positive patients undergoing solid organ transplant. The mainstream of treatment is based for both groups on the use of antivirals with or without HBV immunoglobulins (HBIg). The risk and the therapeutic management change according to the solid organ transplanted, that is, liver, kidney, heart, and lungs.

Liver Transplant Recipients

Hepatitis B Virus-infected Recipient

HBsAg-positive liver transplant recipients with detectable serum HBV DNA should start antiviral therapy as soon as possible before transplant with the aim of achieving an undetectable HBV DNA level at the time of transplant (17,67). The treatment should be continued indefinitely, regardless of HBeAg or HBV DNA status (17,67,68). Although the combined long-term use of HBIg after the transplant could be considered in patients at high risk of recurrence (ie, those with questionable adherence, with confirmed drug resistance, or with high HBV DNA at time of liver transplant, or with HIV and/or HDV and/or hepatitis C virus [HCV] co-infection), a short course (5–7 days) of HBIg in patients at low risk for recurrence has been demonstrated to be highly effective to prevent the reinfection in adults (69–71). The use of HBIg for only 5 to 7 days combined with NAs is, therefore, an option for HBsAg-positive liver transplant recipients without additional risk factors and only if NAs with a high barrier to resistance (ie, entecavir or tenofovir) are simultaneously used (1,2,72). Although lamivudine combined with HBIg could be effective and may be used in resource-limited settings for the prevention of HBV reactivation, it is not considered the agent of choice because it has a low barrier for the development of drug resistance. Weaning of HBIg (when used on the long term) and/or of NA could be considered in the few patients who present sustained (>6–12 months) HBsAb seroconversion.

HBsAg-negative, anti-HBc-positive liver transplant recipients are at risk of HBV reactivation after transplant. These patients have been commonly treated with lifelong lamivudine prophylaxis. We suggest use of antiviral drugs with a high barrier to resistance over lamivudine for this group of patients according to the setting (resources and long-term availability of treatment) where the treatment is prescribed.

Hepatitis B Virus-infected Donor

The use of grafts from anti-HBc-positive donors in HBsAg-negative recipients may be unavoidable despite this risk of infection, especially in countries where the prevalence of anti-HBc-positive donors is high. The risk of HBV transmission for HBsAg-negative liver transplant recipients receiving a HBsAg-negative, anti-HBc-positive graft, in adults and children, in the absence of any intervention, varies significantly (between 19% and 94%) as it is dependent on the HBV immune status of the recipient being lower for anti-HBs-positive recipients and highest in those without anti-HBs (73–78). The use of antivirals has reduced the rate of HBV reinfection rate to less than 10% and the combined use of HBIg and antiviral in adults does not seem to have an additional impact on the transmission rate (73,77–79). Though lamivudine has been used widely because of the lower rate of replication risk, entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide are the preferred antivirals because of their high potency and low rate of drug resistance with long-term use. Tenofovir alafenamide or entecavir are preferred in patients who are at higher risk of renal disease (80,81). Discontinuation of antiviral prophylaxis has been considered after 1 year in adult recipients with confirmed persistence of immunity (anti-HBs >10 mIU/mL) (82). The role of vaccination given pre- or post-transplant as a tool to increase anti-HBs titres in recipients of anti-HBc-positive liver grafts to prevent HBV infection has been evaluated in children (32,33,79). Anti-HBs titre >200 mIU/mL before liver transplant and >1000 mIU/mL in the first 2 years after liver transplant were identified and suggested as sufficient to prevent HBV infection in HBsAg-negative recipients (32,33). The data available on vaccination given pre or posttransplant to prevent HBV infection are limited and further studies are needed in order to provide evidence-based recommendations.

Position. **We recommend that:**

1. **HBsAg-positive liver transplant recipients with detectable serum HBV DNA start antiviral therapy as soon as possible before transplant with the aim of achieving an undetectable HBV DNA level at the time of transplant;**
   VOTES: 5/7/9/9/9/9/9/9/9/9/9/9/9/9 Accepted.
2. **HBsAg-positive liver transplant recipients are treated after liver transplant with the combination of HBIg and lifelong entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide for the prevention of HBV recurrence. HBIg could be discontinued shortly (5–7 days) after transplant only in patients at low risk of recurrence;**
   VOTES: 7/8/8/8/9/9/9/9/9/9/9/9/9/9 Accepted.
3. **anti-HBc-positive and HBsAg-negative liver transplant recipients are treated with lifelong entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide;**
   VOTES: 8/8/8/8/9/9/9/9/9/9/9/9/9/9 Accepted.
4. **HBsAg-negative patients receiving livers from anti-HBc-positive donors should receive lifelong antiviral prophylaxis with entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide.**
   VOTES: 8/8/8/8/9/9/9/9/9/9/9/9/9/9 Accepted.
5. **Vaccination of the anti-HBc and HBsAg-negative recipients or booster dose when anti-HBs titre if <10 mIU/mL is recommended in addition to antivirals.**
   VOTES: 2/6/8/8/8/9/9/9/9/9/9/9/9/9 Accepted.

Nonliver Solid Organ Transplant Recipients

Hepatitis B Virus-positive Donor

The risk of HBV transmission from anti-HBc-positive, HBsAg-negative donors is much higher for HBV-uninfected (HBs and anti-HBc-negative) liver transplant recipients when compared with nonliver solid organ transplant recipients. Transmission is significantly lower in kidney (<3%) (83) and negligible in heart and lung transplant adult recipients. Antiviral prophylaxis should be administered to anti-HBc-negative nonliver transplant recipients receiving grafts from anti-HBc-positive, HBsAg-negative donors, irrespective of anti-HBs status, and titre of the recipient, to prevent de novo HBV infection. Vaccination of the anti-HBs-negative recipients or booster dose when anti-HBs titre is <10 mIU/mL is recommended. The optimal duration of antiviral prophylaxis has not been determined in randomized controlled trials and it is generally suggested for 6 to 12 months (84).

Hepatitis B Virus-positive Recipient

Anti-HBc-positive and HBsAg-negative recipients who undergo a nonliver solid organ transplant are at low risk of reactivation post-transplant. In these patients either no prophylaxis

but monitoring of HBsAg (5) or limited duration of prophylaxis for 6 to 12 months and during periods of intensified immunosuppression (16) have been suggested as reasonable preventive strategies in adults (5,16). When prophylaxis is stopped, these patients should be monitored using aminotransferases every 3 months followed by HBV DNA levels if aminotransferases rise.

HBsAg-positive nonliver recipients have a higher mortality rate, and liver-related complications have been recognized as major cause of death (85,86). The mortality risk is mitigated by the use of antiviral therapy (85,87,88). Anti-HBc- and HBsAg-positive nonliver solid organ transplant recipients should, therefore, start antiviral therapy as soon as possible before transplant and continue it indefinitely. Tenofovir alafenamide or entecavir are preferred over tenofovir disoproxil fumarate in patients who are at higher risk of renal disease (80).

Position. **We recommend that:**

1. **HBsAg-positive nonliver solid transplant recipients receive lifelong antiviral therapy with entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide;**
   VOTES: 8/8/8/8/9/9/9/9/9/9/9/9/9/9/9 Accepted.
2. **anti-HBc-positive and HBsAg-negative non-liver solid transplant recipients are treated with entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide for 6 to 12 months after transplant and during periods of intensified immunosuppression;**
   VOTES: 7/8/8/8/8/8/8/9/9/9/9/9/9/9 Accepted.
3. **anti-HBc- and anti-HBs-negative children receiving nonliver solid transplant from anti-HBc-positive, HBsAg-negative donors are treated with entecavir, tenofovir disoproxil fumarate, or tenofovir alafenamide for 6 to 12 months.**
   VOTES: 6/7/7/7/9/9/9/9/9/9/9/9/9/9/9 Accepted.
4. **Vaccination of anti-HBc- and HBsAg-negative recipients or booster dose when anti-HBs titre is <10 mIU/mL is recommended.**
   VOTES: 8/8/8/8/9/9/9/9/9/9/9/9/9/9/9 Accepted.

How Should Children Undergoing Haematologic Stem Cell Transplantation Be Managed

Patients undergoing haematologic stem cell transplantation should be considered at high risk of HBV reactivation (89). Both HBsAg-positive and HBsAg-negative, anti-HBc-positive haematologic stem cell transplant recipients should receive antiviral prophylaxis. Entecavir and tenofovir are the preferred drugs although lamivudine has been suggested in HBsAg-negative, anti-HBc-positive adult recipients (89) and has been successfully used in children (90). The duration of antiviral prophylaxis, ideally, should be based on immune recovery (ie, increased CD4-positive cells counts above 200–400/μL), which can take years after allo-transplantation. Due to the risk of HBV reactivation with viraemic rebound after withdrawal of antiviral therapy (66), it is recommended that children and adolescents undergo routine testing for HBV DNA and serum aminotransferases after discontinuation of antiviral therapy. HBsAg- and anti-HBs-negative patients receiving allo-haematologic stem cell transplantation with anti-HBc-positive donors should receive antiviral prophylaxis.

Position. **We recommend that antiviral prophylaxis is initiated in:**

1. **anti-HBc-positive haematologic stem cell transplantation recipients regardless of their HBsAg status (positive and negative).**
2. **HBsAg- and anti-HBs-negative patients receiving allo-haematologic stem cell transplantation with anti-HBc-positive donors.**

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

How Should Children With Acquired Immunodeficiencies Be Managed?

Adults and children who are HIV-HBV co-infected are at increased risk of liver fibrosis progression, cirrhosis, and hepatocellular carcinoma. European and American guidelines on the management of HBV in HIV-infected patients recommend the initiation of antiretroviral therapy in all co-infected patients irrespective of CD4 cell count (5,16). Lamivudine, emtricitabine, and tenofovir all have antiviral activity against HIV and HBV but, nowadays, the preferred treatment protocol should include either tenofovir disoproxil fumarate or tenofovir alafenamide (5,67,91). The existing data on the use of tenofovir alafenamide in HIV-HBV co-infected adults are limited (92). Treatment with tenofovir disoproxil fumarate or tenofovir alafenamide should not be stopped in HIV/HBV co-infected patients because of the high risk of severe hepatitis flares and decompensation following HBV reactivation hepatitis. At the same time, the immune reconstitution during the first few weeks of treatment could be associated with hepatitis flares (93).

Position. **We recommend that:**

1. **all HIV-positive children with HBV co-infection should start antiretroviral therapy irrespective of CD4 cell count;**
2. **HIV-HBV co-infected children should be treated with a tenofovir disoproxil fumarate or tenofovir alafenamide-based antiretroviral regimen.**

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

CONCLUSIONS

Reactivation of HBV is an increasingly recognized but often lately and misdiagnosed clinical problem. The aim of the present position paper was to raise the awareness on this condition and present a rigorous, evidence-based summary of literature describing the prevention and treatment of HBV reactivation in children and adolescents. A large number of studies have been published in adults on this topic and very few in children. The quality of the paediatric data available is limited. No data is available on the overall risk of HBV reactivation in children and adolescents and on its stratification and neither there is convincing evidence on the balance between risks and benefits for a particular therapeutic strategy. In most cases, therefore, the positions presented are based on the experts' opinion and on adult data. Overall, recognizing this major limitation, it should be pointed out that each recommendation included in this paper, including those on the use of prophylaxis in children and adolescents at high and moderate high risk of HBV reactivation, is aimed at protecting the patient by a prudent approach in order to facilitate effective decision-making with children and adolescents at risk for HBV reactivation. The large knowledge gap should be addressed by well-conceived prospective, multicentre studies.

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