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Review article

Recommendations for the treatment of hepatitis B in 2017

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Abstract

The therapeutic goal which is currently unfrequent but realistic in HBV infected patients is sustained HBsAg clearance. It is preceded by the loss or significant suppression of HBV replication and leads to inhibition of the progression of liver fibrosis, normalization of biochemical indicators of liver damage, reduction in the risk of hepatocellular carcinoma, prolongation of survival, prevention of HBV infection in the transplanted organ in post-transplant patients, enhancement of the quality of life, inhibition or reversal of extrahepatic changes associated with HBV infection, and halting of the spread of HBV infections. Recommendations of Polish Group of Experts for HBV for 2017 provide guidelines to assess treatment eligibility, choice of the first-line drug, monitoring and duration of treatment, management of treatment failure as well as therapy of HBV associated cirrhosis or hepatocellular carcinoma. Moreover it contains advice for treatment of HBV infection in children, females planning pregnancy or pregnant. We also included recommendations for pre- and post-exposure prophylaxis, prevention of HBV transmission from mother to infant, after liver transplantation, on immunosuppressive therapy and during HCV treatment.

Key words: liver, HBV, therapy.

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Introduction

It is estimated that 350-400 million people globally are carriers of the surface antigen (HBsAg) of the hepatitis B virus (HBV) [1]. HBV infection may take a variety of forms ranging from acute viral hepatitis B (AHB) and the inactive carrier state which is normally, though not always, associated with the presence of HBsAg, to chronic hepatitis B potentially leading to liver cirrhosis and hepatocellular carcinoma (HCC) [2]. Among untreated patients with chronic hepatitis B (CHB), the risk of developing cirrhosis over a five-year period is 8-20%, and among those with cirrhosis, the risk of hepatic decompensation during the following five years reaches 20% [1]. At the same time, the annual incidence of HCC in patients with cirrhosis associated with HBV infection is 2-5% [3, 4]. The course of HBV infection may be affected by a range of factors including coinfections with hepatitis C and D viruses (HCV and HDV) and the human immunodeficiency virus (HIV) as well as hepatotoxic factors (primarily alcohol consumption) [1]. In 95% of CHB cases recorded in Poland no HBe antigen (HBeAg) is detected, which has important implications for the evaluation of prognosis, eligibility for treatment and selection of optimum therapy [5]. The choice of therapy may also be influenced to a certain extent by the HBV genotype. Out of ten known genotypes, genotype A is the dominant one in Poland, detectable in 67% of all HBV-infected patients, followed by genotype D found in 20% of patients [5].

Natural history of HBV infection

A characteristic feature of chronic HBV infection is that can be divided into phases reflecting the dynamic relationship between the host's immune system and the

virus [1, 6, 7]. Generally, HBV comprises two phases with active hepatitis and two phases with low disease activity (inflammatory vs. non-inflammatory). The four phases do not always occur in a sequence, and include:

(a) High replicative phase with HBeAg positivity (previously: immune-tolerant phase). In addition to HBsAg, HBeAg is detected in the serum, and HBV-DNA reaches high values (> 10^6 IU/ml) with normal or slightly elevated ALT levels (> 19 IU/ml in women and > 30 IU/ml in men). Signs of inflammation, necrosis and fibrosis determined in liver biopsies are minimal or nonexistent. The phase, which is known to be highly infectious, may be of short duration in patients infected during late childhood and in adults. With increasing age, there is an increased likelihood of transitioning to the immune-reactive phase.

(b) HBeAg-positive immune-reactive phase. The phase is claimed to be caused by changes in the expression of HBV antigens and increased anti-HBV immune responses associated with the inflammatory response [8]. The serum levels of HBV-DNA are variable, but lower than in the previous phase. The ALT levels periodically exceed the values listed in item a) above. Necroinflammatory changes in the hepatic tissue are moderate or severe, with different degrees of fibrosis (potentially progressive). The stage has a variable duration from months to years, and may culminate in the loss of HBeAg and the development of anti-HBe (2-15%). In approximately 1-4% of patients, reverse-seroconversion and re-emergence of HBsAg are observed. The higher the frequency of exacerbations, the greater the severity of liver fibrosis.

(c) Inactive HBV carrier phase. Anti-HBe antibodies are present, and HBV-DNA levels are low (typically below 2,000 IU/ml), but occasionally higher or, conversely, undetectable. The ALT levels remain within the range specified in item a). Histopathological changes are variable, reflecting the incidence and severity of lesions during the previous phase of the disease. Minimal inflammatory changes and variable degrees of fibrosis are noted. There is a risk of cirrhosis and HCC. The rate of spontaneous loss of HBs and emergence of anti-HBs is estimated at 1-3%/year. The concentration of HBsAg (hereinafter in the text – quantification of HBsAg : qHBs) is below 1,000 IU/ml in genotype D infection, however it is usually higher in patients infected with genotype A, the most common one in Poland [9].

(d) HBeAg-negative chronic hepatitis. Following seroconversion from HBeAg to anti-HBe, active inflammation in the liver is observed in 10-30% of patients. Anti-HBe antibodies are present, and considerable variation in HBV-DNA and ALT levels as well as necroinflammatory changes in the liver are noted. The key features of this phase of infection are intermittent disease exacerbations with intervening periods of remission. Most patients in this phase have detectable mutations in the HBV precore/core promoter gene, which is associated with the inability to synthesize the HBe antigen.

(e) Occult infection (HBsAg-negative) is most commonly associated with undetectable or periodically very low serum concentrations of HBV-DNA accompanied by its presence in the liver. Anti-HBc with or without anti-HBs are present in the serum. The loss of HBsAg is associated with a reduced risk of cirrhosis and liver failure, though the risk of HCC continues to be higher than in the general population. The state of immunosuppression may lead to the reactivation of the virus due to its episomal DNA form – HBV cccDNA.

Goals of therapy

The ultimate goal of antiviral therapy is HBV eradication. At the current stage of knowledge and therapeutic opportunities, the goal is unattainable due to the episomal DNA form of HBV (covalently closed circular DNA – cccDNA), which is a structure showing very high resistance to the activity of currently available antiviral drugs. The persistence of this form of HBV-DNA is responsible for recurrences of the infection [1].

The content of transcriptional active cccDNA reflects the concentration of HBsAg (qHBsAg) to a much higher extent than the level of HBV replication. Consequently, the test may be used for noninvasive assessment of the content of viral DNA in the liver. A gradually decreasing qHBsAg concentration is a good indicator of therapeutic efficacy and allows for preliminary assessment of the effect of treatment on cccDNA, which may be relevant in the process of HBV eradication and modify the ultimate goal of antiviral therapy in the future [1, 6].

Since HBV eradication is, for the time being, unattainable, the primary goal of therapy is complete suppression of HBV replication: sustained loss of HBV-DNA in the serum confirmed by a highly sensitive real-time PCR test together with elimination of the HBs antigen and formation of anti-HBs antibodies. In consideration of the above, the therapeutic goal both in HBeAg-positive and HBeAg-negative patients is sustained undetectability of HBsAg combined with seroconversion to anti-HBs [10]. In the majority of patients, the loss or significant suppression of HBV replication which precede the attainment of that goal, leads to the following effects:

a) inhibition of the progression of liver fibrosis and reversal of the process in the majority of patients, as demonstrated by long-term follow-up of patients treated successfully with entecavir and tenofovir;
b) normalization of biochemical indicators of liver damage; in a proportion of cases they may continue to be elevated for reasons other than HBV infection (e.g. non-alcoholic fatty liver disease, NAFLD);
c) reduction in the risk of progression to HCC; a number of studies indicate that HBV replication, particularly at a high level, is a factor contributing to the development of HCC; the incidence of HCC is reported to be lower in patients treated successfully with antiviral drugs, however the effect is not observed until four years after achieving stable suppression of viraemia, and does not occur in patients with cirrhosis;
d) prolongation of survival; sustained reduction of HBV-DNA viraemia in patients with advanced disease or cirrhosis slows down the progression of the disease/fibrosis, increasing survival, lowering the risk of liver failure and reducing the need for liver transplantation;
e) prevention of HBV infection in the transplanted organ in post-transplant patients; antiviral drugs have documented efficacy in promoting transplant survival;
f) enhancement of the quality of life through improved liver function which contributes to achieving a better mental state and cognitive functions in patients;
g) inhibition or reversal of extrahepatic changes associated with HBV infection;
h) halting of the spread of HBV infections; the loss or marked inhibition of HBV replication reduces the infectiousness of HBsAg-positive individuals.

Drugs used in the therapy of HBV infection

Drugs approved in the European Union for the therapy of HBV infections, the majority of which are reimbursed in Poland, include:

- interferons (IFN):
  – natural interferons,
  – α-2a and α-2b (IFNα-2a and IFNα-2b),
  – pegylated α-2a (PegIFNα-2a);
- analogues (NA):
  – nucleoside analogues: lamivudine (LMV), telbivudine (LdT) and entecavir (ETV),
  – nucleotide analogues: adefovir (ADV), tenofovir disoproxil (TDF) and tenofovir alafenamide (TAF).

PegIFNα-2a is the preferred choice among IFN, offering a clear advantage in terms of the highest efficacy, convenience of use and treatment regimen (once a week). The preferred NA drugs include ETV, TDF and TAF owing to the most potent antiviral activity and a high genetic barrier [1, 7, 11].

Eligibility for the treatment of chronic hepatitis B

To assess treatment eligibility both in HBeAg-positive and HBeAg-negative patients, HBsAg must be consistently detectable for at least six months, and at least two out of the three criteria below (evaluated concurrently) must be met:

1) HBV-DNA > 2,000 IU/ml;
2) ALT level exceeding the upper limit of normal;
3) signs of liver inflammation or fibrosis. Inflammation should be evaluated by histological examination of liver biopsy specimens, and fibrosis – by share wave elastography or transient elastography to measure the stiffness of the liver tissue expressed in kPa. However, attention should be given to different cut-off points compared to other liver diseases including those induced by HCV infection. If coexisting liver diseases of different aetiology are suspected, elastography results are inconsistent with the clinical state of the patient or discrepancies are observed between results obtained by various noninvasive examination methods, liver biopsy is recommended (unless contraindications are present). In such cases biopsy results are regarded as conclusive.

Patients in the high replicative HBeAg(+) phase, particularly younger (aged less than 30 years), without clinical features of liver disease and without family history of HCC, do not require liver biopsy and should not be treated. In such patients ALT levels should be determined at three-monthly intervals. In addition, fibrosis should be evaluated periodically using noninvasive methods. If elevated ALT levels or signs of liver fibrosis are found, antiviral therapy should be initiated. Patients with positive family history of HCC and/or cirrhosis of unestablished aetiology should be assessed for liver inflammation and fibrosis. If characteristic features of chronic hepatitis are found, the patient should be immediately referred for treatment. Also, immediate therapy should be initiated in patients with cirrhosis, regardless of their HBV-DNA level.

Before selecting the first-line drug, patients should be evaluated for HCV and HIV coinfection. During therapy, patients should be tested for anti-HDV IgG antibodies when their ALT levels rise or persist at an elevated level.

Choice of first-line drug

Regardless of the patient's HBeAg status, a drug with the highest proven efficacy and safety of use in a given patient group should be chosen as first-line therapy in treatment-naive patients with chronic HBV

infection. The preferred IFN is PegIFNα-2a, and the preferred NA include ETV, TDF and TAF [1, 7].

LMV and ADV should not be used as first-line treatment because of their low genetic barrier which carries the risk of resistant strain selection. The phenomenon narrows down the possibility for using other NA drugs as salvage therapy. Consequently, it restricts the therapeutic options available for HBV infections, and increases the risk of spread of NA-resistant HBV strains [1, 7].

PegIFNα-2a has been proven to be particularly effective in chronic HBV infections caused by genotype A which dominates in Poland (> 70%) [5]. In addition, PegIFNα-2a treatment has a defined duration [12, 13]. Based on the two arguments, PegIFNα-2a appears to be the optimum choice as first-line treatment in all patients without contraindications to a 48-week interferon therapy. If PegIFNα-2a therapy is determined to be futile during its course, or it is found to be ineffective after its scheduled completion, ETV, TDF or TAF should be used in patients who continue to meet treatment eligibility criteria. It is important to note, however, that PegIFNα-2a is contraindicated in patients with decompensated cirrhosis, so NA drugs are the preferred choice for first-line treatment in this patient group.

Monitoring of interferon therapy

PegIFNα-2a therapy should continue for 48 weeks, unless the treatment futility criteria listed below, related to the lack of therapeutic response, are met in the course of treatment. Response to therapy should be monitored by determining the HBV-DNA and qHBsAg levels at 12 and 24 weeks of therapy (see below).

The futility criteria for the discontinuation of PegIFNα-2a treatment include:

a) in HBeAg-positive patients [14]:
- infected with genotypes A or D – when the qHBsAg level fails to decrease after 12 weeks of treatment;
- infected with genotypes B or C – when the qHBsAg level exceeds 20,000 IU/ml after 12 weeks of treatment;
- regardless of the genotype or in cases where the genotype is unknown – when the HBV-DNA level fails to decrease by at least 2 $\log_{10}$ after 12 weeks of treatment or when the qHBsAg level is higher than 20,000 IU/ml after 24 weeks of treatment;

b) in HBeAg-negative patients regardless of the genotype [1, 15]:
- when the qHBsAg level fails to decrease by any degree after 12 weeks of treatment or
- when the level of HBV-DNA fails to decrease by at least 2 $\log_{10}$ after 12 weeks of treatment.

In the above situations PegIFNα-2a should be discontinued and NA treatment with potent antiviral activity (ETV or TDF) should be initiated promptly, also in patients with normal HBV-DNA and ALT levels.

As the effects of IFN treatment, i.e. HBsAg elimination and seroconversion to anti-HBs, are usually observed many years after the end of therapy, the minimum goal of interferon therapy immediately after its completion should be HBV-DNA suppression below 2,000 IU/ml. In patients achieving this response after the scheduled end of treatment, ALT, HBV-DNA and HBsAg levels should be tested every six months (using a qualitative method). A confirmed increase in ALT and/or HBV-DNA above the levels determining eligibility for treatment should be a basis for introducing NA with potent antiviral activity (ETV, TDF or TAF). There is no sufficient scientific support for IFN retreatment. If the loss of HBsAg is observed, the level of anti-HBs antibodies should be evaluated in the patient, as its subsequent monitoring makes it possible to determine the risk of possible reverse-seroconversion to HBsAg.

Monitoring and duration of NA treatment

For the treatment to be recognized as successful, HBV replication must be suppressed below the threshold of detection in blood serum (i.e. HBV-DNA < 15 IU/ml in accordance with current standards). The suppression usually corresponds to biochemical and histological improvements in the course of the disease.

Serum HBV-DNA and ALT levels should be systematically monitored throughout the therapy (two to four times a year). The therapy is deemed effective when seroconversion in the HBe system is achieved in HBeAg-positive patients, followed by HBsAg elimination – possibly with seroconversion to anti-HBs.

There are no universally accepted criteria to guide the cessation of NA treatment. It is commonly recognized that in HBeAg-positive patients the loss of HBeAg and the development of anti-HBe sustained for consecutive 12 months of therapy at normal ALT levels and viraemia below 2,000 IU/ml may justify the cessation of treatment. After the withdrawal of therapy, patients should undergo systematic (2-4 times a year) tests for HBV-DNA and HBeAg/anti-HBe in blood serum on account of the risk of reverse-seroconversion. HBsAg is determined every 12 months after the development of anti-HBe.

In HBeAg-negative patients the only serological criterion determining the success of therapy is HBsAg elimination followed by anti-HBs seroconversion. As they occur rarely, in practice patients receive NA treatment on a continuous basis. Every 12 months, patients

Table 1. HBV variants associated with drug resistance [47, 48]

HBV variants	Sensitivity level				
	LMV	LdT	ETV	ADV	TDF
Wild type	S	S	S	S	S
M204V	R	S	I	I	S
M204I	R	R	I	I	S
L180M + M204V	R	R	I	I	S
A181T/V	I	S	S	R	S
N236T	S	S	S	R	I
L180M + M204V/I ± I169T ± V173L ± M250V	R	R	R	S	S
L180M + M204V/I ± T184G ± S202I/G	R	R	R	S	S

LMV – lamivudine, LdT – telbivudine, ETV – entecavir, ADV – adefovir, TDF – tenofovir disoproxil, S – sensitive, I – reduced sensitivity, R – resistant

should be tested for HBV-DNA (to consider a change of therapy in patients with detectable viraemia) and HBsAg/anti-HBs (to consider the withdrawal of therapy). If HBsAg elimination is achieved, treatment continuation until the development of anti-HBs should be considered.

NA drugs are characterized by a high safety level due to relatively rare side effects, the most common of which is renal impairment, particularly in patients with reduced creatinine clearance. Potential nephrotoxic effects are mainly associated with nucleotide analogues (ADV and TDF), with the exception of TAF. During the course of therapy in this patient group regular monitoring of kidney function (creatinine and phosphate levels in blood serum and creatinine clearance) is necessary. The above parameters should be tested at least every three months during the first year of treatment, and twice a year after that. The dosage of NA drugs should be based on creatinine clearance, as specified in their SPC. Patients with renal impairment induced by TDF should switch to ETV or TAF [11, 16, 17].

In the absence of effective virological response, HBV drug resistance tests should be performed, and their results interpreted according to Table 1.

The following treatment response types can be observed during NA treatment:

- **complete response** – undetectable HBV-DNA and seroconversion to anti-HBs;
- **virological response** – undetectable HBV-DNA with HBsAg presence;
- **partial virological response** – decrease in HBV-DNA level by more than 1 $\log_{10}$ IU/ml in relation to the baseline value and its maintenance above the detection threshold over the six-month course of drug therapy; treatment with drugs with a high genetic barrier should be continued;
- **virological breakthrough** – increase in HBV-DNA level by at least 1 $\log_{10}$ IU/ml in patients with previously undetectable viraemia during the course of therapy; usually caused by the selection of drug-resistant HBV strains;
- **primary drug resistance** – no reduction in viraemia by at least 1 $\log_{10}$ IU/ml in relation to the baseline value during a three-month period of drug therapy; caused by infection with HBV strains dominated by drug-resistant variants.

Both primary drug resistance and partial virological response, or virological breakthrough, might be mistakenly diagnosed in cases of patient non-adherence to the therapeutic regimen.

Management of treatment failure and NA resistance

If PegIFNα-2 treatment is shown to be ineffective 24 weeks after its completion, a potent NA (ETV, TDF or TAF) should be promptly initiated [1, 7].

Patients treated with NA who develop primary drug resistance should be assessed for adherence to the prescribed therapy. If non-adherence to the drug regimen is excluded, tests determining the presence of substitutions responsible for resistance should be performed. The only exceptions are patients treated with ADV because its primary inefficacy in the vast majority of cases results from insufficient dose of the drug rather than resistance. However, if resistance to the drug used by the patient is proven, the patient should switch to another potent NA. The above applies to all patients regardless of their status in the HBeAg/anti-HBeAg system. The following NA regimens are recommended:

- LMV should be switched to TDF or TAF;
- ETV should be switched to TDF or TAF;
- ADV, TDF or TAF should be switched to ETV.

If secondary drug resistance or partial virological response is observed in patients on NA monotherapy (as previously, the above applies to all patients regardless of their status in the HBeAg/anti-HBe system), adherence to the prescribed therapy should be checked, and patients should be assessed for HDV superinfection/coinfection. If the current NA drug is used as prescribed, it should be substituted for another potent NA. The following NA regimens are recommended:

- LMV should be switched to TDF or TAF;
- ETV should be switched to TDF or TAF;
- TDF or TAF should be switched to ETV;
- ADV should be switched to ETV, TDF or TAF (particularly in patients previously treated with LMV).

In patients with partial virological response, adding a second NA to the one already used might be considered. The above applies in particular to patients with high baseline HBV-DNA levels and proven significant HBV-DNA decrease over the course of treatment. In practice, the combination of ETV and TDF is recommended [16, 17].

Also, the possibility of initiating PegIFNα-2a treatment should always be considered in patients treated with one NA who develop primary or secondary drug resistance or achieve partial virological response or virological breakthrough (regardless of their HBeAg/anti-HBeAg status).

Patients with detectable but low viraemia (< 100 IU/ml) during NA treatment who adhere to the prescribed drug regimen may continue the therapy.

It is important to note that the discontinuation of NA treatment may lead to disease exacerbation. Consequently, the patient's clinical condition and ALT level (and in the case of ALT elevation also the HBV-DNA level) should be monitored for six months after the withdrawal of the drug.

Treatment of cirrhosis and HCC associated with HBV infection

Patients with cirrhosis and HBV-DNA detectable in the serum, regardless of the ALT level, should be promptly treated with ETV (at 0.5 mg), TDF or TAF [18]. Patients before and after liver transplantation should receive prompt and indefinite treatment with ETV (at 1 mg) or TDF. Careful biochemical monitoring is necessary for the early diagnosis of potential metabolic complications.

Patients with hepatic decompensation (Child-Pugh category B or C), and a history of hepatic decompensation, as well as patients before and after liver transplantation with detectable HBV-DNA, are eligible for prompt and indefinite ETV (at 1.0 mg) or TDF treatment regardless of their ALT level. In this group of patients, PegIFNα-2a should not be used. Patients with HCC and detectable HBV-DNA should be treated with ETV or TDF [18, 19].

Treatment of severe acute HBV infection

At present, there are no unambiguous results from controlled trials on the effectiveness of NA therapy in acute hepatitis B with a severe (including fulminant) course. NA therapy may be considered in these patients only if liver transplantation is an option [20, 21].

Treatment should be started with NA drugs which show potent antiviral activity and high genetic barrier: ETV, TDF or TAF [1]. However, patient management should be oriented primarily toward actions leading to liver transplantation.

There may be difficulties with differentiating between acute or superacute hepatitis B and reactivation of chronic hepatitis B. Prompt NA treatment is also recommended in such cases, though it has little impact on reducing early mortality [22, 23].

Treatment of chronic viral hepatitis B in children

Following the introduction of mandatory HBV vaccination program for all neonates in Poland, which began in 1996, only isolated cases of viral hepatitis B are recorded in children and adolescents under 18 years of age.

The basic principles governing the treatment of chronic hepatitis B in adolescents over the age of 14 are similar to the treatment of adults. PegIFNα-2a is an approved treatment option in the European Union, and demonstrates high efficacy in children [24]. However, the only therapeutic agent which is currently reimbursed in Poland is recombinant interferon α-2b. Clinical trials have shown good tolerance and high efficacy of TDF in the suppression of HBV viraemia and normalization of ALT level in adolescents. TDF and TAF are approved in the UE for the treatment of children aged 12-18 years and weighing at least 35 kg. High efficacy and safety of use in children between 2 and 18 years of age have also been shown for ETV, which is approved in the EU for the treatment of patients in this age group with compensated liver disease [25-27].

Antiviral therapy is indicated in HBe antigen-positive children aged 2-18 years in cases involving elevated ALT levels and detectable HBV-DNA viraemia. Conversely, antiviral therapy is not recommended in HBe antigen-positive children aged 2-18 years with persistently normal ALT levels regardless of their HBV-DNA concentrations. The management

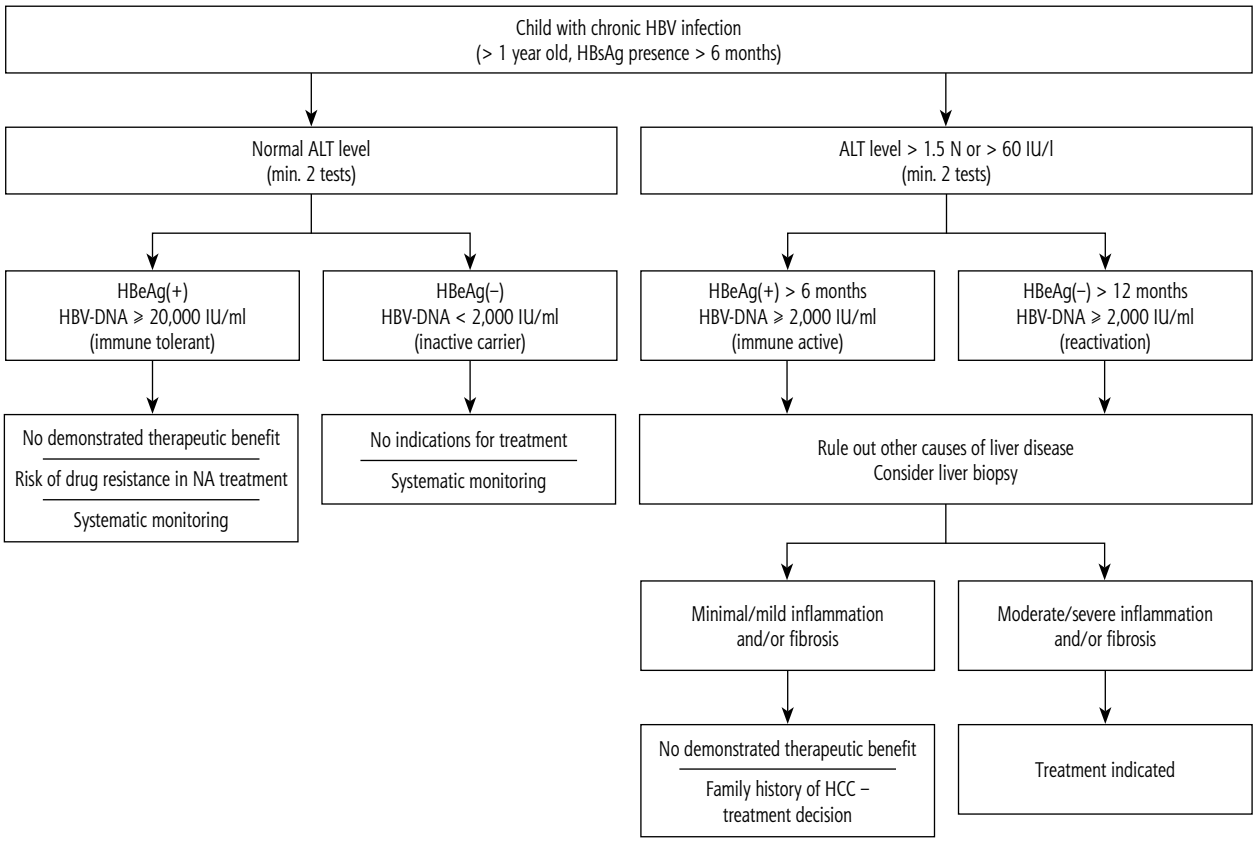

Fig. 1. Algorithm for the management of HBV-infected children under 14 years of age [49]

of chronic HBV infection in children (under 14 years of age), as shown in Figure 1, should consist of:

- determination of HBV viraemia and qHBsAg levels to identify inactive carriers;
- systematic monitoring (every six months) of ALT levels, HBV viraemia and AFP concentration, as well as liver ultrasound for the early detection of HCC. An elevated ALT level, AFP concentration > 10 ng/ml and HBV-DNA > 2,000 IU/ml, histopathological changes in the liver and family history of liver disease are factors determining eligibility for treatment [28].

Medical conditions requiring special consideration in the decision to initiate treatment in HBV-infected children include:

- impairment of liver function,
- cirrhosis,
- HBV-associated glomerulonephritis,
- recurrence of HBV infection in transplanted liver,
- recipients of transplants from anti-HBc (+) donors,
- immunosuppression/chemotherapy,
- HBV/HIV, HBV/HCV, HBV/HDV coinfection,
- family history of HCC.

Chronic HBV infection should not be considered as a contraindication to breastfeeding.

Antiviral therapy for chronic hepatitis B in women planning pregnancy

Before becoming pregnant, women infected with HBV should consult an infectious diseases specialist to discuss indications (or their lack) for anti-HBV therapy, and obtain information about the safety of treatment to be provided during future pregnancy.

Every pregnant woman should be tested for HBsAg. If the result of the test is negative, it should be repeated in the third trimester of pregnancy, i.e. prior to delivery. If the HBsAg test is positive, the level of HBV-DNA should be measured immediately [29].

In women who plan to get pregnant in the near future but display no features of advanced liver fibrosis (F3 or F4), the most rational option is to defer treatment until the birth of the child. However, in women with advanced fibrosis of the liver who plan a pregnancy in the near future, the most appropriate treatment is PegIFNα-2a in the pre-conception period (it is the physician's responsibility to inform patients about the need to use effective contraception during the therapy). Women with contraindications to PegIFNα-2a should be treated with TDF or telbivudine (LdT; registered in Poland but unavailable).

Antiviral therapy for chronic hepatitis B in pregnant women

Interferons are contraindicated in pregnancy. LMV, ETV and ADV are listed as category C under the FDA pregnancy categories, which means they have not been tested in pregnant women. LdT and TDF are rated as category B, which means that there have not been clinical trials in pregnant women, but case reports or clinical observations have not shown an adverse effect on the foetus. The risk of using ETV and TAF in pregnancy is not known. As a result, the preferred drug is TDF because of superior resistance profile and safety of use in pregnant women. The above recommendation also applies to women who are first diagnosed with HBV infection during pregnancy [30].

The following therapeutic management is recommended in women who become pregnant during anti-HBV treatment:

1) discontinue PegIFNα-2a or another IFN treatment, if used;
2) in patients treated with NA other than TDF, substitute the drug for TDF;
3) continue or modify the treatment depending on the stage of liver disease; continue antiviral treatment with NA in patients with stage F3 or F4 fibrosis; reevaluate indications for antiviral treatment in patients with stage F0-F2 fibrosis.

Pregnant women infected with HBV who, on account of low HBV viraemia (HBV-DNA < 2,000 IU/ml) and/or non-advanced liver fibrosis, receive no antiviral treatment or it has been discontinued because of pregnancy, should remain under the care of a hepatologist owing to the possibility of disease exacerbation.

Prevention of mother-to-infant HBV transmission

The risk of vertical transmission of HBV infection is 5-15%. The majority of vertical infections occur perinatally. The main risk factor for transmission is the level of HBV replication. The HBV-DNA level should be evaluated in every HBV-infected woman between the second and third trimesters of pregnancy. The following recommendations apply to women with high viraemia levels (> 200,000 IU/ml):

- treatment with analogues in the third trimester of pregnancy; the preferred drug is TDF (FDA pregnancy class B);
- consideration of termination of pregnancy by elective caesarean section.

Regardless of the woman's HBV-DNA level determined in pregnancy, during the first 12 hours of life every neonate born of an HBV-infected mother should receive anti-HBV immunoglobulin and the first dose of anti-HBV vaccine, to be followed by other doses at 1 and 6 months according to the vaccination schedule 0-1-6. Four doses of the vaccine, administered at 0, 1, 2 and 12 months, are recommended in neonates with a birth weight below 2,000 g. Children in this group require evaluation of the efficacy of vaccinations: every child born of an HBV-infected mother should be tested for the presence of HBsAg, anti-HBs and anti-HBc IgG at the age of nine months. An additional course of vaccinations according to 0-1-6 months schedule is recommended in uninfected infants not responding to vaccine, followed by reevaluation of anti-HBs one to two months after administering the last vaccine dose [31-34].

Preventive therapy in HBV-infected individuals after liver transplantation

All candidates for liver transplantation should be screened for HBsAg, anti-HBs and anti-HBc as part of assessing their eligibility for transplantation. Seronegative patients should be vaccinated against HBV before liver transplantation, and the effectiveness of vaccination should be assessed by measuring the anti-HBs level after the second or third vaccine dose depending on the urgency of transplantation and organ availability [35, 36]. If the basic vaccination course is shown to be ineffective, non-standard vaccination schedules should be considered. All patients awaiting liver transplantation with any serological evidence of contact with HBV (also HBsAg-negative individuals) should be tested to determine the level of HBV-DNA viraemia [35-37].

All patients with detectable HBV-DNA, regardless of the level of HBV viraemia, who are considered eligible for liver transplantation should start NA therapy prior to the transplantation and before the initiation of immunosuppressive therapy. The same procedure should be applied in HBsAg-negative patients with detectable HBV-DNA.

To prevent HBV reactivation, patients with occult HBV infection who are positive for anti-HBc-total antibodies with concurrent undetectability of HBsAg and HBV-DNA should receive anti-HBs (HBIG) serum in the peritransplant period and use NA over the whole period of immunosuppression. Similarly, HBIG in the peritransplant period and uninterrupted preventive NA treatment are necessary in HBV-uninfected recipients, regardless of their anti-HBsAg status, receiving liver transplant from an anti-HBc-positive donor. The preferred choices among NA are ETV or TDF [38-40].

Screening tests for early HCC detection

HBV and HCV infections are currently recognized as the most important risk factors for HCC, particularly in patients with cirrhosis who are at a risk of developing HCC even after the infection is eliminated. The risk of HCC in patients with cirrhosis decreases four years after achieving sustained suppression of viraemia [41]. This is why screening tests (liver ultrasound) should be performed every six months in HBV- and HCV-infected individuals, particularly in patients with cirrhosis. If a focal lesion found in the liver does not exceed 1 cm in diameter, the ultrasound should be performed every three months. However, if the lesion increases in size or changes its characteristics, the patient should be referred for a 4-phase CT scan or MRI [4, 42, 43]. If the focal lesion is stable during repeated tests, after one-year follow-up the frequency of checks may be changed to every six months. If an ultrasound screening test reveals a nodule ≥ 1 cm in size, 4-phase dynamic CT scan or NMR should be performed. Tumour hypervascularity in the arterial phase followed by the washout of the contrast agent in the venous phase support the diagnosis of HCC. Where radiological findings fail to meet the criteria, especially in cases involving lesions which are 1-2 cm in diameter, biopsy of the lesion should be performed. On account of considerable difficulties with differentiating between a dysplastic nodule and early HCC presentation, the evaluation should be carried out by an experienced pathologist.

Prevention of HBV reactivation in patients with planned or initiated immunosuppressive therapy including biologic treatment or anticancer chemotherapy

HBV reactivation is defined as an abrupt increase, at least 100-fold, in the HBV-DNA level in patients with previously detectable HBV-DNA or repeated detection of HBV-DNA in individuals without detectable viraemia before the initiation of immunosuppressive or biological treatment or anticancer chemotherapy [44].

Drugs carrying the highest risk of HBV reactivation (frequency > 10%) include: rituximab, ofatumumab, ustekinumab, natalizumab, alemtuzumab, ibritumomab, doxorubicin, epirubicin, prednisone (over 10 mg daily for more than four weeks), infliximab, adalimumab, certolizumab, golimumab. A moderate risk of reactivation (frequency 1-10%) is associated with: etanercept, abatacept, ustekinumab, mogamulizumab, natalizumab, vedolizumab, imatinib, nilotinib, bortezomib, romidepsin, glucocorticosteroids (prednisone up to 10 mg daily for four weeks), doxorubicin, epirubicin, ciclosporin, tacrolimus. Drugs with a low reactivation risk (frequency < 1%) include methotrexate, azathioprine, 6-mercaptopurine and low-dose glucocorticosteroids [44].

Candidates for this type of therapy should have their HBsAg and anti-HBc-total evaluated before the treatment is introduced. In HBsAg-positive individuals HBV-DNA should be measured. If the result is positive, they should receive NA for the entire duration of treatment and at least six months after its completion. In the case of drugs carrying a high risk of reactivation, the period should be extended to 12 months [44, 45]. HBsAg(+) patients without detectable HBV-DNA and HBsAg(–), but with the detected presence of anti-HBc-total, scheduled for therapy with a high or moderate risk of reactivation, should also start taking NA prior to the initiation of immunosuppressive therapy. During therapy HBV-DNA and ALT levels should be evaluated every three months regardless of whether NA is used concurrently. HBV-DNA detection in patients not receiving NA (i.e. treated with drugs carrying a low reactivation risk) should result in prompt initiation of NA treatment. If the period of waiting for HBV-DNA assay results is expected to be quite long, the introduction of NA should be considered directly after the level of ALT is found to be elevated. The optimum NA for use in situations involving a risk of HBV reactivation are ETV or TDF. Anti-HBs(–) individuals scheduled for the above therapies should be considered for anti-HBV vaccination [45].

Prevention of HBV reactivation during therapy of HCV infections

The risk of reactivation of HBV infection during HCV therapy based on drugs with direct antiviral activity exists mainly in patients with HBsAg. According to currently available data reactivation in HBsAg(–), anti-HBc-total(+) patients is highly unlikely, however it cannot be ruled out [46]. Individuals with HBsAg or anti-HBc-total should be tested for HBV-DNA prior to the initiation of treatment. During therapy ALT levels should be monitored every two to four weeks in accordance with the following recommendations:

a) in cases where HBV-DNA is undetectable and ALT levels are normal prior to treatment, if the ALT rises above the upper limit of normal during DAA therapy, HBV-DNA should be measured immediately and, without waiting for the result, treatment with a nucleoside analogue (entecavir) or a nucle-

otide analogue (tenofovir) should be initiated in parallel to DAA therapy;
b) in cases where HBV-DNA is undetectable, and ALT levels exceed the upper limit of normal and fail to decrease during the first four weeks of DAA treatment, the HBV-DNA test should be repeated, and performed regularly until the end of therapy. If HBV viraemia is detected, the procedure to follow is outlined in item a);
c) in cases where HBV-DNA is detectable prior to treatment, one of the NA listed above should be introduced a month before the initiation of DAA therapy;
d) in patients treated for HBV infection prior to the initiation of DAA the treatment should be sustained and DAA therapy should be continued in parallel.

Pre-exposure prophylaxis

In addition to HCWs and medical school/university students, HBV vaccination should also be given to professionals who are exposed to infection while performing their professional duties, including the police, firefighters, prison officers, deployed soldiers, municipal workers, etc. An evaluation of vaccine response should be performed at least four weeks after the administration of the last dose. It is the responsibility of the employer to provide a safe working environment to employees in accordance with appropriate provisions of the Labour Code.

Post-exposure prophylaxis

The type of post-exposure prophylaxis depends on the immunity status of the exposed individual and the serological status of the exposure source. Eligibility for HBV prophylaxis should be assessed by testing the exposure source for HBsAg (subject to their prior approval) and by evaluating the exposed individual for HBsAg and (in previously immunized individuals) – the anti-HBs titre. Vaccination should be provided as soon as possible, not later than seven days after exposure; anti-HBs immunoglobulin should be administered, as specified in the product's SPC, usually not later than within 72 hours. Non-vaccinated individuals should receive a course of vaccination and a single dose of HBIG. Vaccinated individuals with anti-HBs < 10 mIU/ml should be administered one dose of the vaccine. If the source of exposition is HBsAg positive or unknown and exposed individual has anti-HBsAg < 10 mIU/ml or response to vaccination is unknown, one dose of HBIG in addition to one dose of vaccine can be considered. Following the exposure of an infection-prone individual to biological material from an individual with active HBV infection or with unknown serological status, the recommended procedure is to determine HBV infection markers (HBsAg, anti-HBc IgM) at 6, 12 and 24 weeks post-exposure.

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