

Immunosuppressive therapy and the risk of hepatitis B reactivation: Consensus report

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ABSTRACT

This consensus report includes expert opinions and recommendations regarding the screening, and if necessary, the follow-up, prophylaxis, and treatment of hepatitis B before the treatment in patients who will undergo immunosuppressive therapy due to an emergency risk of hepatitis B reactivation. To increase awareness regarding the risk of hepatitis B reactivation in immunosuppressive patients, academicians from several university health research and training centers across Turkey came together and discussed the importance of the subject, current status, and issues in accordance with the current literature data and presented solutions.

Keywords: Hepatitis B, immunosuppressive therapy, reactivation risk, antiviral prophylaxis

INTRODUCTION

The subject was addressed and interpreted under the following titles:

1. The prevalence of hepatitis B in Turkey
2. How to interpret hepatitis B serology
3. The meaning and outcomes of hepatitis B reactivation
4. The reactivation risk rate by serological status
5. The reactivation risk rate by immunosuppressive diseases
6. The reactivation risk rate by immunosuppressive agents
7. How to screen for the risk of hepatitis B reactivation
8. How to administer prophylaxis for hepatitis B reactivation and which agents should be used
9. How to treat a reactivated patient

At the end of the consensus report, an algorithm summarizing the approach for treating patients with the risk of

hepatitis B reactivation due to immunosuppressive therapy was included (Figure 1).

1. The prevalence of Hepatitis B in Turkey

In Turkey, one of the most important studies on Hepatitis B virus (HBV) epidemiology was conducted by the Turkish Association for the Study of the Liver in 23 provinces that screened a total of 5460 individuals between 2009 and 2010. In the adult (≥ 18 years) age group, 4% hepatitis B surface antigen (HBsAg) positivity, 30.6% total hepatitis B core antigen-antibody (anti-HBc) positivity, and 31.9% antibodies against HBsAg (anti-HBs) positivity was detected (1). According to these rates, there were 2,060,000 HBsAg-positive adults in Turkey in 2010 (2). These results indicate that HBV is moderately frequent in Turkey and accounts for approximately 40%-45% of chronic hepatitis and liver cirrhosis cases; and together with hepatitis D virus, the ratio reaches up to half of the patients. A total of 15,760,000 individuals correspond-

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ing to approximately one third of the adult population showed an encounter with HBV, indicating that these individuals carry covalently closed circular DNA (cccDNA) of the virus in their liver. Furthermore, according to the results of this epidemiological study, only 26% of individuals are aware that they are HBV carriers (1). To solve this issue of low awareness, the individuals in the risk groups should be efficiently and accurately screened.

In conclusion, HBV is moderately frequent in our country. The rate of individuals who are aware that they are HBV carriers is relatively low. To solve this issue of low awareness, the individuals in the risk groups should be efficiently screened.

2. How to interpret Hepatitis B serology

HBV is associated with several antigens and antibodies. The different stages of the infection can be diagnosed by exploiting the combinations of these antigens and antibodies. HBV has three major antigens:

- HBsAg: Hepatitis B surface antigen
- HBeAg: Hepatitis B e antigen
- HBcAg: Hepatitis B core antigen. This antigen is absent in the blood and is found in hepatocytes.

There are three major antibodies formed against HBV:

- Anti-HBs: Antibody against HBsAg
- Anti-HBe: Antibody against HBeAg
- Anti-HBc: Antibody against HBcAg. It is called anti-HBc IgM if it is formed in the acute phase and anti-HBc IgG if it emerges after the acute phase of the disease.

HBsAg: It is the first antigen that appears in the blood during the acute phase of infection. It is the only indicator that can be detected in the blood approximately 3-5 weeks after virus exposure and sustains for 4-14 weeks (3). A positive result in the workup is suggestive of two conditions:

(1) It reflects the acute phase of infection in patients whose clinical presentation and laboratory findings are consistent with B-type acute viral hepatitis (AVH). The diagnosis of B-type AVH cannot be made only on the basis of the positivity of this test.

(2) If immunity does not develop after the disease and HBsAg positivity lasts for more than 6 months, it is called chronic HBV infection. These patients may present with the following conditions: HBeAg-positive chronic infection or chronic hepatitis B (CHB), HBeAg-negative chronic infection or CHB, occult hepatitis, liver cirrhosis, and liver cancer.

HBeAg: It emerges in the acute phase after HBsAg and is cleared from the bloodstream before the clearance of HBsAg. Its presence in the blood reflects actively growing virus and a high level of infectivity. It remains in the blood indicates for 10 weeks in the acute phase and its persistence suggests chronicity. When HBeAg becomes negative, anti-HBe usually becomes positive. HBeAg negativity occurs in HBeAg-negative chronic HBV infection and HBeAg-negative chronic hepatitis B phases of chronic HBV infection. In HBeAg-negative chronic HBV infection, HBV DNA titer is <2000 IU/mL and alanine aminotransferase (ALT) is normal, indicating the absence of liver disease. Conversely, in HBeAg-negative chronic hepatitis B, HBeAg is lost due to precore and/or basal core promoter mutations. This phase is characterized by the continuous or intermittent HBV DNA of >2000 IU/mL and ALT elevation, indicating that liver disease has already developed (4). CHB cases can be divided into two groups: HBeAg-positive and HBeAg-negative. Approximately 75% of CHB cases in our country are HBeAg-negative.

Anti-HBc: It is the first antibody formed during the course of the disease. It may be present in all cases: acute, chronic, and immunized. Anti-HBc IgM positivity is the most reliable indicator of the acute phase. In some cases, when HBsAg rapidly becomes undetectable, anti-HBs is detectable. In an acute phase, these two tests may be negative. This period is called the "window period," but even in this case, anti-HBc IgM test is positive. A positive anti-HBc IgG test indicates that the individual has already encountered HBV. As anti-HBc IgG is the most reliable indicator of the infection, it is an excellent screening test to reveal whether an individual has encountered HBV or not. Even if the patient has been immunized after the virus is cleared from the blood, it remains positive throughout life, although in a low titer. If anti-HBc IgG is found to be negative after the tests, it suggests that the individual has never encountered the virus; if HBsAg is negative and anti-HBs is positive, it suggests that the individual has been vaccinated.

Anti-HBe: It emerges after the development of antibodies against HBcAg. It may be positive in immunized individuals, inactive carriers, and the majority of patients with chronic hepatitis.

Anti-HBs: It emerges in the convalescent period. After acute hepatitis, it may not be positive in 5%-10% of the cases. It reflects immunization and remains positive for life. If HBsAg does not become undetectable in the blood and anti-HBs does not emerge after acute infection,

chronicity must be suspected. Anti-HBs positivity may develop by a natural encounter with the virus or vaccination.

HBV DNA: It is the most reliable indicator of viral replication. It can be detected quantitatively (IU/mL) using polymerase chain reaction. In acute infection, it can be detected in the blood 10-20 days before HBsAg detection (5). It usually becomes undetectable in acute phase upon symptom onset. In inactive carriers, it is usually <2000 IU/mL.

The European Association for the Study of Liver (EASL) guideline divides chronic HBV infection into five phases (4):

- Phase 1: HBeAg-positive chronic HBV infection
- Phase 2: HBeAg-positive chronic hepatitis B
- Phase 3: HBeAg-negative chronic HBV infection
- Phase 4: HBeAg-negative chronic hepatitis B
- Phase 5: HBsAg-negative phase

Phase 1: HBeAg-positive chronic HBV infection. Previously, it was called as the "immune tolerant" phase. It is characterized by the presence of HBeAg in serum, very high level of HBV DNA, and chronic normal ALT level (≤ 40 IU/mL).

Phase 2: HBeAg-positive chronic hepatitis B. It is characterized by the presence of HBeAg in serum, high level of HBV DNA, and elevated ALT.

Phase 3: HBeAg-negative chronic HBV infection. Previously, it was called as the "inactive carrier" phase. It is characterized by the presence of antibodies against HBeAg (anti-HBe) in serum, undetectable or low (<2.000 IU/mL) levels of HBV DNA, and normal ALT level (≤ 40 IU/mL).

Phase 4: HBeAg-negative chronic hepatitis B. It is characterized by usually detectable anti-HBe together with the absence of HBeAg in serum, persistent or fluctuating moderate-to-high serum HBV DNA levels (mostly lower than HBeAg-positive patients), and fluctuating or persistent high ALT levels.

Phase 5: HBsAg-negative phase. It is characterized by HBsAg negativity in serum with the presence of antibody against HBcAg (anti-HBc) positivity with or without detectable antibody against HBsAg (anti-HBs). If low levels of HBV DNA positivity is present, it is called an "occult HBV infection."

Serological and virological results at various phases of HBV infection are given in Table 1.

In conclusion, by interpreting different combinations of HBV antigens and antibodies, the different stages of the infection can be diagnosed and risks can be identified.

3. The meaning and the outcomes of Hepatitis B reactivation

HBV reactivation is the emergence of a necroinflammatory liver disease along with increased viral replication in patients with inactive or recovered HBV infection or HBeAg-negative CHB. HBV reactivations may occur under immunosuppression (immunosuppressive therapy, cancer chemotherapy, transplantation, after pregnancy, and during HIV infection) due to medication-induced reasons (under interferon therapy, with resistance to or discontinuation of oral antiviral agents) and in the natural course of the disease (during the conversion from HBeAg-positive chronic HBV infection to HBeAg-positive CHB, during HBeAg and HBsAg seroconversions, and with basal core promoter and precore mutations). The increased viral replication during immunosuppressive therapy or cancer chemotherapy results in liver damage during immune reconstitution (6,7). HBV reactivation has three phases:

Phase 1- increased viral replication: It is the phase right after immunosuppression. Increase in HBV DNA, HBeAg positivity in patients who were previously HBeAg negative and HBsAg positivity accompanying reverse seroconversion is observed. This phase can be summarized as follows (8):

- In HBsAg-positive and HBV DNA-positive patient → HBV DNA increases
- In HBsAg-positive and HBV DNA-negative patient → HBV DNA becomes positive
- In HBsAg-negative and anti-HBc-positive patient → HBsAg becomes positive (reverse seroconversion) or HBV DNA becomes positive with HBsAg remaining negative

Phase 2- hepatic injury period: Liver damage usually occurs upon the discontinuation, interruption, or dose reduction during immunosuppression. ALT level increases (3-fold or more of the upper limit of normal) and HBV DNA starts to decrease; in severe cases, other symptoms showing jaundice and hepatic damage emerge. Sometimes, liver damage may also develop during the course of immunosuppression.

Phase 3- recovery period: Liver damage regresses, HBV DNA and ALT return to the baseline levels, and HBsAg may become negative in the late phase (6). Sometimes, hepatitis phase may persist, and chronic hepatitis may develop.

HBV reactivation may result in the discontinuation of immunosuppressive agent or therapy. This discontinuation rate was found to be 71% in patients with reactivation due to chemotherapy and 33% in patients without reactivation (8). Early discontinuation of the therapy results in increased morbidity and mortality caused by the primary disease. Furthermore, hepatitis at various grades may develop in patients due to the immune activation triggered by the discontinuation of medications (8):

1. ALT levels may not change (silent type)
2. ALT levels may increase without the development of jaundice (mild type)
3. Jaundice may accompany the ALT increase (moderate type)
4. Liver failure may accompany jaundice (severe type)
5. Fatal type

In conclusion, HBV reactivation may present with different manifestations ranging from asymptomatic to a severe and fatal clinical presentation and may result in the discontinuation of immunosuppression or chemotherapy. Early discontinuation of the therapy results in increased morbidity and mortality caused by the primary disease.

4. The reactivation risk rate by serological status

The risk of hepatitis B reactivation due to immunosup-

pressive therapy is closely associated with the presence of serological and virological hepatitis B markers in a patient. Among the risk factors, the strongest one is high HBV DNA (>2.000 IU/mL) level (9,10). Among the HBsAg- and/or anti-HBc IgG-positive patients, the risk of reactivation is more in patients with a detectable or high level of HBV DNA than in those with a negative or low level of HBV DNA. The reactivation risk in HBsAg-positive patients is 8-fold more than in patients with isolated anti-HBc IgG positivity (11). The reactivation risk is more in HBeAg-positive patients than in negative patients (12). The rate of reactivation of genotype B and genotype C is more than that of genotype A (8,13). Although there are studies showing that high titers of anti-HBs antibody positivity is protective for Anti HBc IgG patients, current information states that neither anti HBs positivity nor titer is decisive while planning the antiviral treatment (14, 15). Furthermore, the risk of HBV infection is more in individuals with HBsAg mutation than in those without it (16). Risk of reactivation by serological status is given in Table 2 (17).

In conclusion, the hepatitis B reactivation risk due to the immunosuppressive therapy is closely associated with the hepatitis B serology in patients.

5. The reactivation risk rate by immunosuppressive diseases

Malignant, inflammatory, and autoimmune diseases play a determinative role in the incidence of HBV reactivation (18). HBV reactivation rates in immunosuppressive diseases and serological markers of HBV infection are summarized in Table 3.

Table 1. Serological and virological results at various phases of HBV infection

	HBsAg	HBeAg	Anti-HBc IgM	Anti-HBc IgG	Anti-HBe	Anti-HBs	HBV DNA (IU/mL)
Acute viral hepatitis	Positive	Positive	Positive	Negative	Negative	Negative	Negative/Positive
Acute viral hepatitis-window period	Negative	Positive	Positive	Negative	Negative	Negative	Negative/Positive
Immune to HBV (past infection)	Negative	Negative	Negative	Positive	Positive	Positive	Negative
HBeAg-negative chronic HBV infection	Positive	Negative	Negative	Positive	Positive	Negative	<2000
HBeAg-positive chronic hepatitis B	Positive	Positive	Negative	Positive	Negative	Negative	>2000
HBeAg-negative chronic hepatitis B	Positive	Negative	Negative	Positive	Negative/Positive	Negative	>2000
Isolated anti-HBc positivity	Negative	Negative	Negative	Positive	Negative	Negative	Negative Positive (occult hepatitis)
Immune to HBV (vaccinated)	Negative	Negative	Negative	Negative	Negative	Positive	Negative

In conclusion, malignant, inflammatory, and autoimmune diseases play a determinative role in the incidence of HBV reactivation.

6. The reactivation risk rate by immunosuppressive agents

The risk of HBV reactivation varies with the class of immunosuppressive medications. When medications suppressing B cells, anthracycline derivatives, and high-dose corticosteroid are used, the risk of reactivation is >10%. With the use of tumor necrosis factor- α (TNF- α), cytokine, integrin, and tyrosine kinase inhibitors, and a modest dose of corticosteroid, the risk of reactivation varies between 1% and 10% depending on hepatitis B serology. In case of using a low-dose or intra-articular corticosteroid or conventional immunosuppressive medications (azathioprine, 6-mercaptopurine, methotrexate), the risk of reactivation is <1% (18,19).

Antimetabolites

The number of reported antimetabolite-induced HBV reactivations is very low (20). Reactivation during azathioprine or methotrexate use is rare. Antimetabolites are low-risk medications (21). The data regarding subjects using high-dose methotrexate is very limited (22).

TNF- α inhibitors

TNF- α inhibition may lead to increased HBV replication (20). Anti-TNF- α medications include infliximab, adalimumab, certolizumab, golimumab, and etanercept. In a study investigating the incidence of HBV reactivation in 468 patients with isolated anti-HBc positivity and majority of them using infliximab, the reactivation rate was 1.7% (23). The incidence in HBsAg-positive patients was 12.3%. Among TNF- α inhibitors, reactivation is reported more with infliximab and adalimumab than with etanercept. When anti-TNF- α medications are used alone, the risk of reactivation varies between 1% and 10% depending on the hepatitis B serology of the patient (24).

Transarterial chemoembolization applications

Reactivation may also occur after transarterial chemoembolization procedure in patients with a mass in the liver. Although a chemotherapeutic agent is directly administered into the mass in such cases, the reactivation with systemic involvement has been rarely reported (25). Anthracyclines (e.g., doxorubicin) are also given to the individuals receiving transarterial chemoembolization applications as a part of the treatment. Anthracycline derivatives have been demonstrated to increase HBV DNA secretion in experimental studies (24).

Table 2. Risk of reactivation by serological status

Risk status	Serology
High	HBsAg-positive, HBeAg-positive/negative, HBV DNA>2000 IU/mL
Medium	HBsAg-negative, Anti-HBc IgG-positive, Anti-HBs-negative
Low	HBsAg-negative, Anti-HBc IgG-positive, Anti-HBs-positive

Steroids

Steroid use is considered to be an independent risk factor for reactivation (26). Prednisolone is frequently used for the treatment of many inflammatory diseases. However, the use of these medications both as monotherapy and in a combination is accompanied by an increased increased HBV reactivation risk (26). Steroids decrease specific T-cell responses and increase the virus replication. The risk of infection is directly proportional to the duration and dose of the steroid (27). The levels of risk due to steroid use are listed in Table 4 (24).

Systemic chemotherapy

HBV reactivation is frequent during systemic chemotherapy treatments. This is associated with the administered chemotherapeutic agent as well as the origin of cancer (hematological/non-hematological) (28). Individuals with hematological cancer are more prone to acquire HBV reactivation, and these patients are considered to be at a high risk. For example, the reactivation incidence in lymphoma patients is near up to 50% (28). During the treatment of hematological malignancy in HBsAg-positive patients, the risk of HBV reactivation has been reported to be 40%-50% (29). The mortality rate in these patients after reactivation has been reported to be 4%-41% (26). This probability further increases, especially in regimens containing high-dose steroids or rituximab (immunotherapy) (30). HBV reactivation has also been reported in patients with a solid tumor (e.g., breast, colon, lung cancer) (26). The reactivation risk in HBs-positive patients who are receiving chemotherapy for a solid tumor is moderate. The risk of HBV reactivation in solid tumor varies by the administered therapy (31).

Biological antibodies

Patients using rituximab and ofatumumab, both of which are anti-CD 20 antibodies, have been found to be at high-risk for HBV reactivation (32). With the standard non-Hodgkin lymphoma treatment, the risk of reactivation is 25% even 12 months after the end of treatment (26). Accord-

Table 3. The incidence of HBV reactivation by immunosuppressive disease (18)

Disease	Incidence of HBV reactivation in individuals not receiving prophylaxis	
	HBsAg-positive (%)	HBsAg-negative/anti-HBc-positive (%)
Lymphoma	18-73	34-68
Acute leukemias	61	2.8-12.5
Chronic leukemias	ND*	ND*
Multiple myeloma	ND*	6.8-8
Bone marrow/hematopoietic stem cell transplantation	66-81	6-10
Breast cancer	21-41	ND*
Nasopharyngeal cancer	33	ND*
Hepatocellular cancer (systemic chemotherapy)	36	11
Hepatocellular cancer (transarterial chemoembolization)	21-30	9.3
Rheumatoid arthritis	12.3	3-5
Psoriasis/psoriatic arthritis	ND*	ND*
Inflammatory bowel diseases	36	0-7**
Autoimmune diseases	ND*	17**
Renal transplantation	45-70	0.9

*No data; **Case reports or small case series

ing to FDA data, many cases of HBV reactivation have been reported due to the use of rituximab and ofatumumab; thus, these medications belong to the high-risk group. Therefore, in 2013, a warning stating that these medications may cause fulminant hepatitis, hepatic failure, and death had been published. This warning applies not only to HBsAg-positive cases but also to HBsAg-negative/total anti-HBc IgG-positive cases with a previous history of hepatitis B infection (26,32). Biological agents including tyrosine kinase inhibitors (e.g., imatinib, nilotinib, and dasatinib), cytokine, and integrin inhibitors (ustekinumab, natalizumab, alemtuzumab, vedolizumab) are associated with a moderate risk of HBV reactivation (24). Therefore, all of these agents should be cautiously considered.

Hemopoietic stem cell and organ recipients

Hemopoietic stem cell and organ recipients have the high-risk of HBV reactivation. These patients undergo an intense immunosuppression. Therefore, they lose their previously acquired HBV immunity and have an increased

(almost half) risk of HBV reactivation (both in HBsAg-positive and anti-HBc positive patients). In this patient group, chronic infection risk is high if virus reactivation occurs (33). In a retrospective study, 137 HBsAg-negative and anti-HBc-positive cases were examined, and HBV reactivation was observed in 10% of them within 77 months after transplantation (34). The risk in complete organ recipients is high (50%-90%). After transplantation, these patients should be followed-up for hepatic failure, progression to cirrhosis, and hepatocellular cancer. In transplantation patients, the serology of the donor is also important. In case the donor is anti-HBc IgG-positive, the recipient should receive antiviral prophylaxis (35).

HBV reactivation risk rates due to immunosuppressive agents are shown in Table 4.

In conclusion, the risk of HBV reactivation varies with the class of immunosuppressive medications. When medications suppressing B cells, anthracycline derivatives, and high-dose corticosteroids are used, the risk of reactivation is >10%. With the use of TNF- α , cytokine, integrin, and tyrosine kinase inhibitors, and a modest dose of corticosteroid, the risk of reactivation varies between 1% and 10%. With the use of low-dose or intra-articular corticosteroid or conventional immunosuppressive medications (azathioprine, 6-mercaptopurine, methotrexate), the risk of reactivation is even <1%.

7. How to screen for the risk of Hepatitis B reactivation

EASL, The Asian Pacific Association for the Study of the Liver, and The Centers for Disease Control and Prevention (CDC) report that in countries with HBsAg prevalence of >2%, HBsAg, anti-HBc IgG, and anti-HBs screening must definitely be performed before any immunosuppressive therapy (36-38). In patients who are going to receive immunosuppressive therapy or chemotherapy, screening before the treatment to avoid HBV reactivation is highly recommended (18). This strategy provides following benefits:

- Antiviral prophylaxis
- HBV serology and HBV monitorization (without antiviral therapy)
- Immunization against HBV
- Evaluation of HBV complications
- Contacting other family members for chronic HBV and planning their treatment as required

During the screening, HBsAg, anti-HBc, and anti-HBs tests must be performed. If HBsAg or anti-HBc is positive, HBV DNA must be studied.

Table 4. HBV reactivation risk rates by medication groups (24)

HBV reactivation risk rate	Medication group	Medication
High (>10%)	Medications causing B-cell suppression	Rituximab Ofatumumab
	Anthracycline derivatives	Doxorubicin Epirubicin (HBsAg-positive/anti-HBc-positive)
	Corticosteroids	≥4 weeks, HBsAg-positive/anti-HBc-positive, moderate/high dose (10-20 mg/>20 mg)
Medium (1%-10%)	TNF-α inhibitors	Infliximab Etanercept Adalimumab Certolizumab
	Other cytokine inhibitors and integrin inhibitors	Abatacept Ustekinumab Natalizumab Vedolizumab
	Tyrosine kinase inhibitors	Imatinib Nilotinib
	Anthracycline derivatives	Doxorubicin Epirubicin (HBsAg-negative/anti-HBc-positive)
	Corticosteroids	≥4 weeks, HBsAg-positive/anti-HBc-positive, low dose (<10 mg)
	Corticosteroids	≥4 weeks, HBsAg-negative/anti-HBc-positive, moderate/high dose (10-20 mg/>20 mg)
	Conventional immunosuppression	Azathioprine 6-mercaptopurine Methotrexate
Low (<1%)	Intra-articular corticosteroids	
	Corticosteroids	≤1 week
	Corticosteroids	≥4 weeks, HBsAg-negative/anti-HBc-positive, low dose (<10 mg)

In conclusion, in patients who are going to undergo immunosuppressive therapy, HBsAg, anti-HBc IgG, and anti-HBs screening must be performed before the treatment to avoid HBV reactivation. If HBsAg or anti-HBc is positive, HBV DNA must be studied.

8. How to administer prophylaxis for Hepatitis B reactivation and which agents should be used

Randomized trials have shown that prophylactic antiviral therapy is more effective than pre-emptive strategies (39). The timing of prophylaxis and choice of antiviral agent depends on the risk of reactivation, planned dura-

tion of chemotherapy, level of HBV DNA, and previous antiviral therapy (if available) (40). HBV prophylaxis should be initiated 1-3 weeks before the immunosuppressive therapy, if possible, or at least concomitantly with the immunosuppressive therapy (7,36,37,40).

Two weeks after the initiation of antiviral therapy, the suppression of HBV DNA by more than 2 log increases the possibility of survival in the patients. In case of active hepatitis, chemotherapy can be delayed until transaminase level becomes less than 3 fold of normal level (40,41).

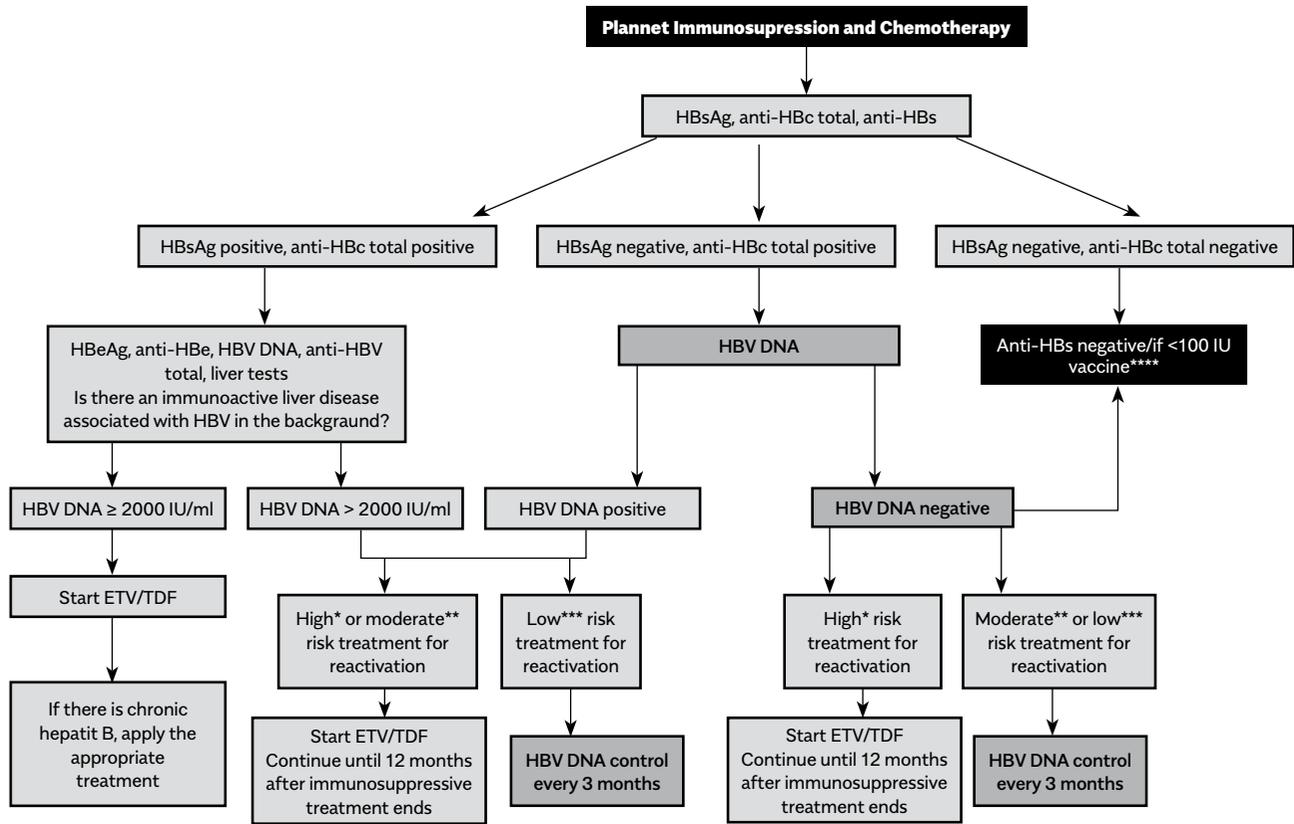


Figure 1. Approach for a patient carrying the risk of hepatitis B reactivation due to immunosuppressive therapy (adapted from the references 19, 48, 49, and 50)

*In HBsAg-positive or -negative/anti-HBc-positive patients: rituximab, ofatumumab, and hemopoietic stem cell transplantation; in only HBsAg-positive/anti-HBc-positive patients: alemtuzumab, doxorubicin, epirubicin, prednisolone >20 mg/day or 10-20 mg/day for ≥4 weeks; in HBsAg-negative/anti-HBc-positive patients: starting with pulse corticosteroid administrations and then prednisolone >20 mg/day for ≥4 weeks
 **Anti-TNF agents (etanercept, adalimumab, golimumab, certolizumab, infliximab), cytokine and integrin inhibitors (abatacept, ustekinumab, natalizumab, and vedolizumab), tyrosine kinase inhibitors (imatinib and nilotinib), cyclosporine, tacrolimus, bortezomib, histone deacetylase inhibitors, and systemic cancer chemotherapy; in HBsAg-positive/anti-HBc-positive patients: low-dose (<10 mg) corticosteroid for ≥4 weeks; in only HBsAg-negative/anti-HBc-positive patients: moderate/high dose (10-20 mg/>20 mg) corticosteroid for ≥4 weeks together with doxorubicin and epirubicin
 ***Azathioprine, 6-mercaptopurine, methotrexate, high-dose corticosteroid (>20 mg/d prednisolone) for <1 week and intra-articular corticosteroid injections; in only HBsAg-negative/anti-HBc-positive patients: low-dose (<10 mg) corticosteroid for ≥4 weeks

Prophylactic therapy should be continued for additional 12 months after the discontinuation of immunosuppressive therapies (7,19,36,37,42). If immunosuppression is going to last for a long period, prophylaxis should not be discontinued (6). Administering lifelong prophylaxis after liver transplantation is the standard approach (7,36).

The ideal oral antiviral agents that can be used for prophylaxis are entecavir and tenofovir. Compared with the other nucleos(t)ide analogs, such as lamivudine, adefovir, and telbivudine, these two agents are more potent

in terms of HBV DNA suppression and also have a high genetic barrier against the development of medication resistance and rapid exert rapid action. Therefore, these agents should be preferred in all patients for prophylaxis against HBV reactivation (36,43,44).

Patients should be monitored by liver tests, and HBV DNA analysis should be performed every 3 months during the prophylaxis and for at least 12 months more after the discontinuation (4,8). HBsAg-negative and anti-HBc IgG-positive (anti-HBs-positive or -negative) patients

with negative HBV DNA who do not receive prophylaxis are recommended to be monitored by liver tests every 1-3 months and by HBV DNA every 3 months until 6-12 months after the end of immunosuppressive therapy (36). Patients who are not receiving prophylaxis should also be monitored in a similar manner.

In conclusion, prophylactic antiviral therapy is more effective than pre-emptive strategies. The ideal approach is to start HBV prophylaxis before immunosuppressive therapy. Entecavir and tenofovir, which potently suppress HBV DNA and have a strong genetic barrier against resistance development and exert rapid actions, should be preferred for prophylaxis.

9. How to treat a reactivation patient

If HBV reactivation is detected during chemotherapy or immunosuppressive therapy, the treatment is delayed or may be discontinued. The decision of treatment interruption depends on the severity of the clinical presentation. Except for the silent type and mild type, where the patients show transaminase levels below 5-fold, the treatment should be interrupted. The treatment should also be interrupted in patients showing serum ALT/AST levels above 3-fold in presence of symptoms or jaundice (8,24,41,45). Chemotherapy discontinuation may decrease or stop the rate of HBV replication. In the absence of antiviral prophylaxis, HBV reactivation may occur in immune reconstitution phase after chemotherapy. The interruption of chemotherapy or immunosuppressive therapy due to reactivation may pose a great risk for the primary disease (46). Therefore, a proper evaluation of prophylaxis requirements for patients before chemotherapy is important.

If HBV reactivation occurs, antiviral therapy should be initiated as soon as possible. In some cases, patients may be asymptomatic, whereas 20%-25% of them may develop severe hepatitis and hepatic failure. Tenofovir or entecavir are the recommended agents, and the decision for the treatment can be based on the patient's condition and renal functions. In patients who have previously used lamivudine, tenofovir should be preferred (47).

In conclusion, reactivation is a serious and fatal condition, and the response to antiviral therapies administered after reactivation is not enough. Furthermore, the discontinuation of immunosuppressive medication causing reactivation may result in the progression of the primary disease. Therefore, initiating antiviral prophylaxis before immunosuppressive therapy or chemotherapy can be lifesaving.

RECOMMENDATION

In patients who are going to undergo immunosuppressive therapy, HBsAg, anti-HBc IgG, and anti-HBs screening must be performed before treatment. However, this screening is ignored most of the time, and patients face severe outcomes of reactivation. To avoid putting these patients at risk, establishing a central warning system in the hospital computer system and ensuring that the necessary screening is performed before the initiation of immunosuppressive therapy via a reminder showing up on the screens of the related branch specialists might be beneficial.

It should be remembered that prophylactic antiviral therapy for a suitable patient may be lifesaving.

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