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GUIDELINES

APASL clinical practice guideline on hepatitis B reactivation related to the use of immunosuppressive therapy

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Abstract

Background & Aim Hepatitis B reactivation related to the use of immunosuppressive therapy remains a major cause of liver-related morbidity and mortality in hepatitis B endemic Asia-Pacific region. This clinical practice guidelines aim to assist clinicians in all disciplines involved in the use of immunosuppressive therapy to effectively prevent and manage hepatitis B reactivation.

Methods All publications related to hepatitis B reactivation with the use of immunosuppressive therapy since 1975 were reviewed. Advice from key opinion leaders in member countries/administrative regions of Asian-Pacific Association for the study of the liver was collected and synchronized. Immunosuppressive therapy was risk-stratified according to its reported rate of hepatitis B reactivation.

Recommendations We recommend the necessity to screen all patients for hepatitis B prior to the initiation of immunosuppressive therapy and to administer pre-emptive nucleos(t)ide analogues to those patients with a substantial risk of hepatitis and acute-on-chronic liver failure due to hepatitis B reactivation.

Keywords APASL · Hepatitis B reactivation · Immunosuppressive therapy · Guideline

Introduction

More than four decades ago, based on serial measurement of hepatitis B virus (HBV) antigen and serum alanine aminotransferase (ALT) level, hepatitis due to HBV reactivation (HBVr) had been described in both hepatitis B surface antigen (HBsAg) positive and HBsAg negative but antibody (anti-HBs) positive patients with myeloproliferative and lymphoproliferative diseases treated with anti-tumor chemotherapy [1, 2]. In the 90s, prospective study showed that nearly half of the HBsAg-positive patients with malignant lymphoma treated with cytotoxic therapy, suffered from hepatitis due to HBVr [3]. With the subsequent use of more aggressive immunosuppressive therapy (IST) such as the conditioning regimens in allogeneic hematopoietic stem cell therapy, fatality due to HBVr in HBsAg positive patients with hematological malignancy became an increasingly important clinical problem [4, 5]. Hence, close monitoring of HBsAg-positive patients with malignancies receiving cytotoxic therapy was recommended [6]. Further progress in various medical disciplines with the use of more potent immunosuppressive therapy and targeted monoclonal therapy such as rituximab, a human/murine, chimeric anti-CD20 monoclonal antibody, fatal fulminant hepatic failure due to HBVr was noted even in those who had recovered from past HBV infection-HBsAg negative but hepatitis B core antibody (anti-HBc) positive with HBV DNA detectable only by sensitive nested PCR [7–13]. At the turn of the twenty-first century, with the availability of potent nucleos(t)ide analogues (NUCs), pre-emptive use of lamivudine and

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then entecavir and tenofovir were shown in randomized controlled trials to be highly effective in preventing HBVr and its liver-related morbidity and mortality in both HBsAg positive and HBsAg negative but anti-HBs and anti-HBc positive patients treated with cytotoxic chemotherapy [13–16].

Up till 2020, numerous clinical guidelines had been formulated aiming to reduce the occurrence of hepatitis due to HBVr in patients treated with IST [17–21]. Nevertheless, hepatitis due to HBVr leading to acute on chronic liver failure remains a major health threat in Asia-Pacific region, where HBV infection is endemic [22]. The major barriers appear to be related to the non-compliance of medical practitioners in other non-hepatology disciplines. This is further compounded by the recent rapid expansion on the use of new immunosuppressive agents such as tyrosine-kinase inhibitors (TKIs), [23–26] immune checkpoint inhibitors (ICIs) [27–29] used in the treatment of various cancers and tumor necrosis factor (TNF) antagonists [30–35] for many autoimmune diseases. Recently, in those chronic hepatitis C (CHC) patients coinfected with hepatitis B, HBVr has also been reported during and after treatment with direct-acting antiviral agents (DAAs) [36–48].

The deterring factors for the successful implementation of the guidelines include lack of attention to the prevalence of HBVr, unawareness of the ease of implementation of suitable preventive measures, miscalculations of the total costs to society and potentials for improvement in quality of care taking into consideration of the wide availability of potent generic NUCs at a very low cost and simple virological testing [49, 50]. We aim to develop a user-friendly clinical practise guideline for all related medical disciplines which will help to curtail the morbidity and mortality related to HBVr in subjects treated with IST, especially in HBV endemic Asia-Pacific region.

Methods

With the initiation by the steering committee of Asian-Pacific Association for the study of the liver (APASL), a panel of experts from 21 different administrative regions/countries in Asia-Pacific region was invited to form a working party which formulated this clinical practise guidance for HBVr in patients treated with IST. The panel includes not only hepatologists, but also oncologists, rheumatologists, transplant surgeons, nephrologists and interventional radiologists. The first working party meeting was conducted on 9th Nov 2019 in Boston during the American Association for the study of liver diseases (AASLD) annual meeting when the key questions related to HBVr were laid down, methods to develop the guidance were defined and drafting of recommendations was assigned. This guidance addresses the following questions: (1) What is the definition of HBVr? (2) Who should be screened? (3) What should be done for screening? (4) How should a patient planned for IST be managed and monitored? All panel members were required to disclose their relationships with industry during the guidelines formulation until accepted for publication by Hepatology International (official journal of APASL). The Chair (G Lau) and Co-Chairs (ML Yu, G Wong, A Thompson) of the guidelines committee must be free of any conflict of interest (COI) or other biases that could undermine the integrity or credibility of the work. The Chair, Co-Chairs and all panel members with relevant COI were required to declare the situation and recused themselves from any relevant discussions, voting, and drafting of recommendations. The Chair and Co-Chairs were responsible for writing up the guidelines with the support of all panel members. All recommendations were graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [51]. The recommendations were presented at the 30th APASL hybrid annual meeting in Bangkok, Thailand (6th Feb 2021), with the comments incorporated.

Immunopathogenesis of hepatitis due to HBV reactivation

Hepatitis B virus (HBV) is a hepatotropic virus and after entry into hepatocytes, the HBV nucleocapsid containing partially double-stranded HBV DNA (dsDNA) enters the nucleus where the viral polymerase repairs dsDNA into full-length, covalently closed circular (cccDNA), the nuclear reservoir of HBV. Reverse transcription, viral replication, and encapsidation occur in the cytoplasm before either viral assembly and release or recycling of the nascent nucleocapsid into the nucleus to replenish the pool of cccDNA [52]. It is the persistence of these low levels of cccDNA in hepatocytes which are thought to explain the long-term risk of HBVr with potent IST that exists even in individuals who have cleared the HBV infection, with serological clearance of hepatitis B surface antigen (HBsAg) [53]. The clinical outcome of HBV infection is highly dependent on a complex interplay between the virus-specific host immune response involving cytotoxic HBV-specific CD8 T cell and natural killer (NK)/NK-T cell responses, cytokine-mediated non-cytolytic responses as well as B-cell-mediated humoral immunity [54]. In keeping with this, resolution of HBV infection with loss of HBsAg with or without the development of anti-HBs has been demonstrated to require CD4 helper T cells for the efficient development of virus-specific adaptive CD8 T cell responses and B-cell antibody production [55].

To date, the key biological pathways leading to the development or severity of clinically significant hepatitis due to HBVr are not well defined, other than by extrapolation from the mechanism of action of the etiological agent. There are

also little data linking HBV sequence variation to risk or severity of HBV reactivation, and it should be assumed that all HBV genotypes and variants may be associated with reactivation. Nonetheless, based on serial measurements, HBV serological markers and liver function test, hepatitis due to HBVr have been identified as a 2-stage process. The initial phase is characterized by enhanced viral replication accompanied by markedly increase hepatic expression of viral antigen. It is postulated that this initial phase of HBVr occurs as a result of drug treatment that directly or indirectly inhibits the anti-HBV immune response targeted against HBV, with the highest risk associated with B cell depleting therapies [56, 57] and hematopoietic stem cell transplant (HSCT) [4–6]. HBVr has also been reported with the use of IST in solid organ transplantation, traditional chemotherapies including trans-arterial chemo-embolisation for hepatocellular carcinoma, [58] as well as the more recent tyrosine kinase inhibitors, [59] tumor necrosis factor antagonist [30–35] and proteasome inhibitor for the treatment of various malignancy and autoimmune diseases [60]. The HBV genome also contains a steroid-responsive element, and prolonged corticosteroid therapy has been associated with a moderate to high risk of HBVr [61]. HBVr has also been reported to occur indirectly in HCV and HDV co-infected patients as a result of antiviral therapy for HCV, or HDV respectively [62, 63]. This phenomenon reflects virus-virus interactions where the host immune response to one hepatitis virus inhibits replication of the other—normally HCV or HDV are dominant over HBV—and antiviral therapy for the dominant virus results in a secondary down-regulation of immune pathways that allow HBV replication to increase. The second phase occurred during immune reconstitution on withdrawal of the IST, [6] continuous rapid inhibition of HCV by direct-acting antiviral agents (DAAs) [40] or HIV by non-HBV active HAART therapy [64]. The immune response to the markedly enhanced hepatic expression of HBV antigen leads to liver injury, manifested as hepatitis, icteric hepatitis and fulminant acute-on-chronic hepatic failure (Fig. 1).

Incidence of HBVr treated with immunosuppressive agents

HBsAg positive patients (Table 1)

Data from Japan and Hong Kong have shown a 45–100% risk of HBVr and 15% hepatic failure in HBsAg positive patients receiving HSCT without antiviral prophylaxis [65, 66]. Two

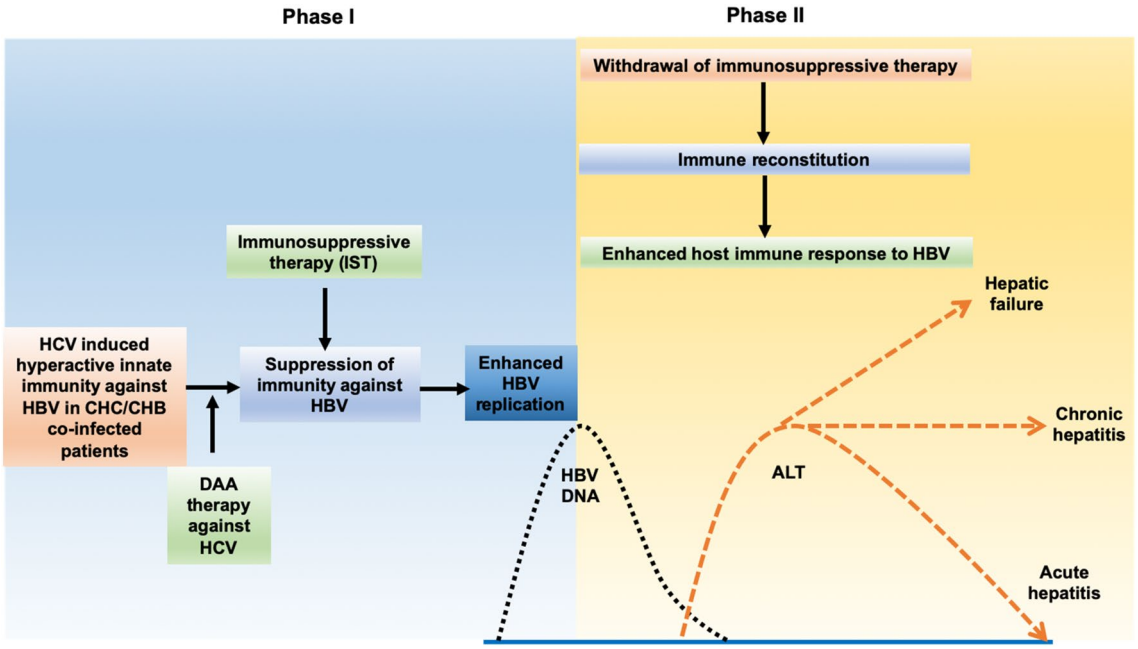

Fig. 1 Pathogenesis of hepatitis due to hepatitis B virological reactivation (HBVr). Hepatitis due to HBVr is a two-phase process with an initial phase of enhanced HBV replication and hepatocyte expression of HBV antigen due to attenuation of host immunity against HBV. The use of steroid could further augment viral replication due to its effect on steroid-responsive elements in HBV. Attenuation of host immunity against HBV replication can also be related to removal of hyperactive innate immunity with DAA therapy against co-infected HCV. The second phase is characterized by immune reconstitution on withdrawal of immunosuppressive effect on HBVr due to withdrawal of the immunosuppressive therapy or continuous rapid suppression of HCV by DAAs. This will initiate the mounting of host immune response against heavily HBV antigen-laden hepatocyte, resulting in liver injury, manifested as elevation of serum ALT with mild hepatitis, icteric hepatitis, hepatic failure or even death

Table 1 HBV reactivation and related complications among HBsAg-positive patients without NUC prophylaxis in Asia-Pacific region

Authors (year)	Country/Region	Study design	HBVr case (n)	Total case (n)	HBVr rate	HBV-related hepatitis (n)	HBV-related hepatitis rate	HBV-related mortality rate
Hematopoetic stem cell transplantation								
Nakamoto (2014) [65]	Japan	OB	2	2	100%	2	100%	0%
Lau (2002) [66]	HK	OB	9	20	45%	3	15%	NA
Cancer diseases								
Cytotoxic agents								
Lymphoma								
Lok (1991) [3]	HK	OB	13	27	48%	7	26%	3.7%
Lau (2003) [14]	HK	RCT	8	15	53%	7	47%	0.0%
Cheng (2003) [70]	Taiwan	OB steroid +	18	25	72%	15	60%	4.0%
		OB steroid-	9	25	36%	8	32%	0.0%
Hsu (2008) [16]	Taiwan	RCT CHOP	14	25	56%	12	48%	0.0%
Total			62	117	53%	49	42%	0–4%
Hematologic malignancies								
Chen (2018) [71]	Taiwan	OB	71	115	62%	NA	NA	NA
Breast Cancer								
Yeo (2004) [67]	HK	OB	17	41	41%	NA	NA	
Long (2011) [104]	China	RCT	6	21	29%	0	0.0%	0.0%
Kim (2007) [68]	Korea	OB + anthracycline	23	111	21%	23	21%	
Lee (2014) [73]	Korea	OB ± anthracycline	13	92	14%	6	6.5%	0.0%
Total			59	265	22%	29	11%	0–1%
Hepatocellular carcinoma								
TACE								
Jang (2006) [74]	Korea	RCT	15	35	43%	11	31%	3.0%
Jang (2006) [75]	Korea	OB	62	205	30%	32	16%	0.5%
Total			77	240	32%	43	18%	0.5–3%
Systemic Chemotherapy								
Yeo (2004) [72]	HK	OB	37	102	36%	23	23%	12%
Tyrosine kinase inhibitor								
Uhm (2018) [23]	Korea	OB-CML	12	46	26%	NA	NA	0.0%
Wang (2019) [24]	Taiwan	OB-CML	5	13	38.5%	3	23%	0.0%
Yao (2019) [25]	Taiwan	OB-NSCLC-EGFRI	16	171	9.4%	NA	NA	NA
Total			33	230	14%			
Immune checkpoint inhibitors								
Pu (2020) [27]	Asia-Pacific	Review	2	22	9.1%	2	9.1%	0%
Zhang (2019) [28]	China	OB	5	29	17%	4	14%	0%
Lee (2020) [29]	Taiwan	OB	1	6	17%	1	17%	0%
Total			8	57	14%	7	11.7%	0%

Table 1 (continued)

Authors (year)	Country/Region	Study design	HBVr case (n)	Total case (n)	HBVr rate	HBV-related hepatitis (n)	HBV-related hepatitis rate	HBV-related mortality rate
Rheumatic disorders								
Lan (2011) [30]	Taiwan	OB (anti-TNF)	5	8	63%	5	63%	0%
Tamori (2011) [31]	Japan	OB (anti-TNF)	2	5	40%	NA	NA	0%
Ryu (2012) [32]	Korea	OB (anti-TNF)	4	29	14%	2	6.9%	0%
Tan (2012) [33]	China	OB (c-DMARD)	2	23	9%	0	0%	0%
Lee (2013) [34]	Korea	Review	14	74	19%		NA	NA
Chen (2017) [35]	Taiwan	OB (c-DMARD)	30	123	24%		NA	NA
Total			57	262	22%	7	11.7%	0%

meta-analyses in Asia-Pacific region have shown > 30% risk of HBVr among HBsAg-positive lymphoma patients receiving rituximab-containing regimens [56, 57]. Among HBsAg-positive breast cancers patients receiving chemotherapy in Asia-Pacific region, the risks of HBVr and HBV-related hepatitis flare were around 22% (range 14–41%) and 11% (range 0–21%), respectively [67–69, 73]. The risk of HBVr among HBsAg-positive cancer patients receiving steroid-containing regimen was 26–72%, compared to 13–36% among those receiving non-steroid-containing regimens [70]. For patients with HBV-related HCC receiving transarterial chemo-embolization (TACE), data from South Korea observed a risk of 32% (30–43%) for HBVr and 18% (16–31%) for HBV-related hepatitis flare [74, 75]. Baseline HBV DNA levels > 2000 IU/ml, baseline cirrhosis and history of multiple-modality therapy for HCC were associated with a higher risk of HBVr [72, 74, 75].

Targeted therapies, monoclonal antibodies, biologics (Table 1)

TKIs are currently widely used as target therapy for lung cancers and chronic myeloid leukemia (CML). The HBVr risk was 26–38.5% among CML patients receiving imatinib from Taiwan and Korea studies [23, 24]. A recent Taiwanese study observed a moderate HBVr risk of 9.4% among patients with non-small cell lung cancers receiving epidermal growth factor receptor inhibitor [25].

ICIs are now approved for the treatment of various cancers. Case series studies from Taiwan and China showed that the risk of HBVr and its related hepatitis among HBsAg-positive cancer patients with ICIs therapy to be 14% (range 9.1–17%) and 11.7% (range 9.1–17%), respectively [27–29].

TNF- α inhibitors used for autoimmune diseases, such as rheumatic disorders and inflammatory bowel diseases, have been reported to be associated with HBVr risks between 14 and 63%, amid a relatively small case number in the published series [30–32]. The American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy also considered anti-TNF as moderate risk [17].

Disease-modifying antirheumatic drugs (bDMARDs/sDMARDs) had a HBVr risk of around 22% (range 9–63%) among HBsAg-positive patients [31–35]. HBVr, hepatitis flare-up and even fulminant hepatic failure had been observed in HBsAg-positive rheumatic patients receiving tocilizumab, an IL-6 receptor monoclonal antibody [76, 77]. Further studies are called upon in this field as anti- IL-6 was being used in the current COVID-19 pandemic in some parts of the world [78].

HBsAg (−)/anti-HBc (+) patients (Table 2)

Data from Asia-Pacific region observed 6%–29% risk of HBVr in resolved HBV patients receiving HSCT without antiviral prophylaxis [65, 79–81]. A meta-analysis showed that lymphoma patients receiving rituximab-containing regimens had significantly higher risk of HBVr than those receiving non-rituximab-containing regimens (10% vs 4%) [82]. Kusumoto et al. had shown that in the phase 3 GOYA and GALLIUM studies, there was no significant difference in the risk of HBV reactivation between obinutuzumab- and rituximab-based immunochemotherapy ($p = 0.17$) [83]. A meta-analysis of 328 solid tumor patients with resolved HBV infection from 3 studies showed a median HBVr risk of 3% (range 0.3–9%) [69]. Recently, a study in Hong Kong showed a one-year incidence of HBsAg seroreversion of 1.8% among patients with isolated anti-HBc seropositivity receiving steroid therapy [84]. All combinations of corticosteroids dosage and duration greater than 7 days increased the risk of hepatitis flare [84].

Data of HBVr risk among HBsAg (-)/anti-HBc (+) patients receiving TKI or ICI are limited. A recent Taiwanese study observed that none of 123 CML patients with resolved HBV receiving TKI experienced HBVr [24].

Table 2 HBV reactivation and related complications among HBsAg-negative patients without pre-emptive NUCs

Authors (year)	Country/Region	Study design	HBVr case (*n*)	Total case (*n*)	HBVr rate	HBV-related hepatitis (*n*)	HBV-related hepatitis rate	HBV-related mortality rate
Hematopoetic stem cell transplantation								
Nakamoto (2014) [65]	Japan	OB	6	83	7%	NA	NA	NA
Seto (2017) [79]	HK	OB	13	62	21%	NA	NA	NA
Wu (2020) [80]	China	OB	25	441	6%	NA	NA	NA
Nishikawa (2020) [81]	Japan	OB	13	67	19%	NA	NA	NA
	Total		57	653	8.7%			
Lymphoma—anti-CD20-containing C/T								
Yeo (2009) [8]	HK	RCT	5	21	24%	5	24%	4%
Matsue (2010) [9]	Japan	OB	5	56	9%	5	8.9%	0%
Koo (2011) [105]	Singapore	OB	2	62	3%	2	3.2%	1.6%
Huang (2013) [10]	Taiwan	RCT	7	39	18%	2	5.1%	0%
Seto (2014) [11]	HK	OB	19	63	30%	0	0.0%	0%
Hsu (2014) [12]	Taiwan	OB	27	143	19%	10	7.0%	0%
Kusumoto (2019) [83]	Asia Pacific, Europe, Canada	OB	25	232	10.8	NA	NA	NA
	Total		65	384	16.9%	24	6%	
Lymphoma—non-rituximab C/T								
Lok (1991) [3]	HK	OB	2	45	4%	2	4.4%	0%
Yeo (2009) [8]	HK	RCT	0	25	0%	0	0.0%	0%
	Total		2	70	3%	2	3%	
Hematologic malignancies								
Chen (2018) [71]	Taiwan	OB (585 anti-HBc [+])	41	1676	2.4%	36	2.1%	0.06%
TKI								
Wang (2019) [24]	Taiwan	OB-CML (55% anti-HBc +)	0	123	0.0%	0	0%	0.0%
Rheumatic disorders								
Lan (2011) [30]	Taiwan	OB (anti-TNF)	1	70	1.4%	1	1.4%	0%
Tamori (2011) [31]	Japan	OB (anti-TNF)	1	45	2.2%	1	2.2%	0%
Tan (2012) [33]	China	OB (c-DMARD)	2	188	1.1%	1	0.5%	0%
Mori (2011) [106]	Japan	OB (anti-TNF)	2	60	3.3%	0	0.0%	0%
Urata (2011) [107]	Japan	OB (anti-TNF)	7	135	5.2%	NA	NA	0%
Watanabe (2019) [108]	Japan	OB (c-DMARD)	7	152	4.6%			
	Total		20	650	3.1%	3	0.8%	

Relating to TNF-α inhibitors and DAMARDs, data from Asia-Pacific regions demonstrated a HBVr risk of around 3.1% (range 1.1–5.2%) [30–32]. A recent Taiwanese study reported one (1.6%) out of 64 rheumatic patients receiving tocilizumab experienced HBVr [76]. Further studies are needed in these areas.

HBVr among patients with HBV and HCV co-infections (Table 3)

The recent advance of DAAs has dramatically improved the treatment success of CHC infection, making HCV

Table 3 Hepatitis B virus reactivation (HBVr) among patients with HBV and hepatitis C virus (HCV) co-infection or HCV infection with resolved HBV infection after direct-acting antiviral (DAA) treatment in Asia-Pacific region

Authors (year)	Country/ Region	Total patients (*n*)	Observation periods (months post-EOT)	Patients with HBVr [*n* (%)]	Patients with HBVr and hepatitis [*n* (%)]	Patients with HBVr and icteric hepatitis [*n* (%)]	Mortality in patients with HBVr [*n* (%)]	Pre-DAA HBV DNA (−) in patients with HBVr [*n* (%)]	Predictors
HBsAg-positive HBV/HCV co-infected patients									
Gane (2016) [37]	New Zealand	8	3	6 (38)	0/8 (0)	0/8 (0)	0/6 (0)	3/6 (50)	NA
Doi (2017) [38]	Japan	4	3	2 (50)	0/4 (0)	0/4 (0)	0/2 (0)	2/2 (100)	NA
Kawagishi (2017) [39]	Japan	1	3	1 (100)	0/1 (0)	0/1 (0)	0/1 (0)	1/1 (100)	NA
Wang (2017) [40]	China	10	3	3 (30)	3/10 (30)	1/10 (10)	0/3 (0)	NA	NA
Tamori (2018) [41]	Japan	22*	3	3 (14)	2/22 (9)	0/0 (0)	0/3 (0)	3/3 (100)	NA
Liu (2018) [42]	Taiwan	111	3	50 (45)	5/111 (5)	1/111 (1)	0/50 (0)	11/50 (22)	NA
Liu (2017) [44]	Taiwan	12	3	2 (17)	0/12 (0)	0/12 (0)	0/2 (0)	1/2 (50)	NA
Lee (2018) [45]	Taiwan	7	3	2 (29)	1/7 (14)	0/7 (0)	0/2 (0)	1/2 (50)	NA
Yeh (2020) [46]	Taiwan	66*	3–36 (mean 11)	30 (45)	6/66 (9)	3/66 (5)	2/30 (7)**	15/30 (50)	BL ALT ≥ 80 U/L; HBsAg > 10 IU/ml
Total		241		99 (41.1)	17 (7.1)	5 (2.1)	2/99 (2.0)	37/96 (38.5)	
HBsAg-negative patients positive for anti-HBc antibody and/or anti-HBs antibody									
Doi (2017) [38]	Japan	155	3	3 (1.9)	0/155 (0)	0/155 (0)	0/3 (0)	3/3 (100)	BL High ALT; Low Anti-HBs titer‡
Kawagishi (2017) [39]	Japan	84	1	4 (2.6)	1/84 (1)	0/84 (0)	0/4 (0)	4/4 (100)	BL Anti-HBs (-) or < 30 mIU/ml; EOT Anti-HBs (-) or < 12 mIU/ml‡
Yeh (2017) [43]	Taiwan	57	3	0 (0)	0/57 (0)	0/57 (0)	0 (0)	NA	NA
Sulkowski (2016) [47]	Taiwan/ Korea	103	3	0 (0)	0/103 (0)	0/103 (0)	0 (0)	NA	NA
Wang (2017) [40]	China	124	3	0 (0)	0/124 (0)	0/124 (0)	0 (0)	NA	NA
Tamori (2018) [41]	Japan	765	3	1 (0.1)	0/765 (0)	0/765 (0)	0 (0)	1/1 (100)	NA

Table 3 (continued)

Authors (year)	Country/ Region	Total patients (*n*)	Observation periods (months post-EOT)	Patients with HBVr [*n* (%)]	Patients with HBVr and hepatitis [*n* (%)]	Patients with HBVr and icteric hepatitis [*n* (%)]	Mortality in patients with HBVr [*n* (%)]	Pre-DAA HBV DNA (−) in patients with HBVr [*n* (%)]	Predictors
Ogawa (2018) [48]	Japan	63	3	1 (2)	0/63 (0)	0/63 (0)	0/1 (0)	1/1 (100)	NA
Liu (2017) [44]	Taiwan	81	3	0 (0)	0/81 (0)	0/81 (0)	0 (0)	NA	NA
Lee (2018) [45]	Taiwan	53	3	0	(0)	0/53 (0)	0 (0)	NA	NA
Total		1485	3	9 (0.6)	1 (0.07)	0 (0)	0 (0)	9/9 (100)	

HBVr, HBV DNA increases greater than 1 log10 IU/ml or HBV DNA reappearance

HBsAg hepatitis B surface antigen, *anti-HBc* anti-hepatitis B core antibody, *anti-HBs* anti-hepatitis B surface antibody, *EOT* end of treatment, *n* number

*Excluding patients with concomitant anti-HBV NUC therapy at initiation of DAA therapy

**Both patients had cirrhosis at baseline

‡Subjects of both positive and negative HBsAg analyzed together

elimination possible in the near future [85]. The successful HCV eradication rate with DAAs is comparable between HCV mono-infected and HBV/HCV co- patients. However, coinfected patients are at risk of HBVr during and after DAA therapy and this occurs earlier and is clinically more significant than HBVr occurring with interferon-based therapy [37–47, 86–88]. Data from Asia-Pacific region demonstrated a risk of 41.1% (range 14–100%) for HBVr, 7.1% (range 0–30%) for HBV-related hepatitis flare, 2.1% (range 0–10%) for HBV-related icteric hepatitis, and 2% (range 0–7%) mortality (Table 3). The risk of HBVr was not associated with baseline HBV DNA levels. Patients with undetectable HBV DNA at baseline are still at risk of HBVr. In a recent study, baseline quantitative HBsAg (qHBsAg) titers were associated with HBVr. The 1-year cumulative incidence rate of HBVr was 42.5% in patients with baseline qHBsAg > 10 IU/ml, compared to 18.5% in those with baseline qHBsAg < 10 IU/ml [46].

Risk stratification (Table 4)

There are three key risk factors associated with HBVr, [21, 89] namely: (1) Host factors: male sex, older age, presence of cirrhosis, and type of disease treated with IST, such as bone marrow transplant or solid-organ transplantation; (2) HBV virologic factors: HBsAg seropositivity, high baseline HBV DNA levels, HBeAg seropositivity, and absence of anti-HBs among patients with resolved HBV infection, or co-infection with HCV, HDV, or HIV; (3) Type and degree of IST: B-cell–depleting therapies, such as rituximab and ofatumumab, anthracycline derivatives, such as doxorubicin and epirubicin, medium (10–20 mg/day) or high dose (≥20 mg/day) prednisone therapy for ≥4 weeks, steroid-containing chemotherapy, and TNF-α inhibitors, such as infliximab and etanercept.

A risk gradient for HBVr exists between people who are HBsAg-positive and people who are HBsAg-negative but anti-HBs positive [89–91]. The risk of HBVr is 5 to 8 times higher among those patients who are HBsAg-positive as compared to those who were HBsAg negative but anti-HBc positive. Among patients who are HBsAg-positive the best predictor of reactivation has been shown to be the level of HBV DNA at baseline [85]. The risk of HBVr in patients who are HBsAg negative and anti-HBc positive is lower, where high risk has been reported for patients being treated with B cell therapies or undergoing HSCT. In individuals who are HBsAg-negative and anti-HBc positive, the presence and titer of anti-HBs antibodies have been associated with some protection against HBVr [82, 92]. However data are limited, and at present, there is insufficient evidence to support the use of anti-HBs titres for clinical decision-making in this situation.

Based on the type and duration of IST and the status of HBV infection, the risk of HBVr was established to be low (<1%), moderate (1–10%) and high (>10%) (Table 4) [21, 90].

Table 4 Risk stratification of HBV reactivation among HBsAg-positive patients and HBsAg-negative/anti-HBc-positive patients

Risk level	HBV serology	
	HBsAg(+)	HBsAg(-)/anti-HBc(+)
High (> 10%)	Anti-CD20 monoclonal antibodies: Rituximab, Ofatumumab, Obinutuzumab Steroid (high dose) ≥ 20 mg/day for ≥ 4 weeks Anti-TNF agents with higher potency: Adalimumab, Infliximab, Golimumab, Certolizumab Anthracyclines Hematopoietic stem cell transplantation (both allogeneic and autologous) DAA for HBV/HCV coinfection (high risk in meta-analysis and prospective study), except non-cirrhotics with HBsAg < 10 IU/ml Immune Checkpoint inhibitors (moderate to high risk): Anti-PD-1: nivolumab, pembrolizumab Anti-PD-L1: atezolizumab Anti-CTLA-4: ipilimumab Tyrosine kinase inhibitors (moderate-to-high): Imatinib, Nilotinib, Dasatinib, Erlotinib, Gefitinib, Osimertinib, Afatinib	Anti-CD20 monoclonal antibodies: Rituximab, Ofatumumab, Obinutuzumab Allogeneic hematopoietic stem cell transplantation
Moderate (1–10%)	Cytotoxic chemotherapy (except anthracyclines) Anti-TNF agents with lower potency: Etanercept Steroid (median dose): 10–20 mg/day for ≥ 4 weeks Proteasome inhibitor: Bortezomib Ustekinumab	Anthracyclines Autologous hematopoietic stem cell transplantation Anti-TNF agents with higher potency: Adalimumab, Infliximab, Golimumab, Certolizumab Proteasome inhibitor: Bortezomib Ustekinumab
Low (< 1%)	Methotrexate Azathioprine Steroid (low dose < 10 mg/day) DAA for HBV/HCV coinfection for non-cirrhotic patients with HBsAg < 10 IU/ml	Cytotoxic chemotherapy (except anthracyclines) Steroid (high dose) ≥ 20 mg/day Anti-TNF agents with lower potency: Etanercept Tyrosine kinase inhibitors Imatinib, Nilotinib, Dasatinib DAA for HCV
Uncertain (More studies needed, no prophylaxis recommendation until further evidence)	Abatacept Tocilizumab Ibrutinib Alemtuzumab Natalizumab Ocrelizumab Ibritumomab	Immune Checkpoint inhibitors Anti-PD-1: nivolumab, pembrolizumab Anti-PD-L1: atezolizumab Anti-CTLA-4: ipilimumab

The rationale of pre-emptive use of nucleos(t)ide analogues

Soon after the global registration of lamivudine, the first randomized controlled trial to compare "early" pre-emptive (start lamivudine before or at the initiation of cytotoxic chemotherapy for lymphoma) to "deferred" treatment (lamivudine initiated only when HBVr was detected on monitoring) was conducted in Chinese with lymphoma. The rationale was based on the hypothesis that if one can inhibit the enhanced HBV replication during the initial phase of intense IST, then on immune-reconstitution during withdrawal of the IST, the amount of HBV antigen-laden hepatocytes as target for host immunity and hence the incidence of liver injury should be drastically reduced. This will be in contrast to the "deferred" approach as the immune response to HBV-antigen laden hepatocytes has already been initiated and indeed the markedly enhanced HBV replication has already been abating. In keeping with this, "early" pre-emptive approach is found to be superior to "deferred" use of lamivudine resulting in a marked reduction in the incidence of HBVr and hepatitis in HBsAg positive with lymphoma treated with intense cytotoxic IST [14]. Similarly, in a prospective, open-label cohort study on Chinese adults of HBV inactive carriers with concurrent IgAN (proteinuria ≥ 3.5 g/day), this pre-emptive "early" use of lamivudine was found to be

highly effective in preventing HBVr and its related hepatitis [93]. Subsequent systemic review and meta-analysis, based on 14 studies showed that the relative risk for both HBVr and HBV-related hepatitis ranged from 0.00 to 0.21, favoring preemptive use of lamivudine. A significantly higher proportion of participants not treated with pre-emptive lamivudine suffered from a disruption of chemotherapy [94]. However, due to the low-resistant barrier of lamivudine, some patients might develop YMDD mutation and deter the effectiveness of such a pre-emptive approach. Hence, lamivudine was later replaced by high resistant barrier NUCs with adefovir, entecavir and tenofovir [13, 95, 96]. With a higher safety profile with long-term use of entecavir, tenofovir and lately TAF, their pre-emptive use to prevent HBVr in patients planned for IS therapy have been validated in randomized control trials (Table 5).

Assessment by hepatologists for termination of NUC treatment

All patients who are planned for IST should have HBsAg, anti-HBs and anti-HBc tested at baseline (Fig. 2). The risk of IST for HBVr should be assessed (Table 4). For HBsAg-positive patients, serum HBV DNA, and possibly qHBsAg should be checked and monitored. Current data on other biomarkers, such as anti-HBs and anti-HBc titres, HBV core-related antigen (HBcrAg), ultra-sensitive HBsAg evaluation and HBV RNA, in the diagnosis and monitoring of HBV reactivation over the course of immunosuppressive treatments are not sufficient to be of any added practical clinical use [97]. Assessment of liver fibrosis, either invasively or non-invasively, should then be performed under the guidance of a hepatologist. All HBV treatment guidelines recommend patients with significant fibrosis (F2 or greater) should receive NUCs treatment, while close monitoring may be indicated for patients without significant fibrosis. Therefore, using liver fibrosis assessment to stratify preventive therapy in low to moderate risk patients is a logical approach. Various non-invasive assessments have been developed and adopted in some international management guidelines [98, 99]. Liver stiffness measurement (LSM) with transient elastography is most widely validated and is an accurate and reproducible method to predict advanced fibrosis or cirrhosis ($\geq F3$) in CHB patients [98, 99]. The key challenge of this tool is the confounding effect of alanine aminotransferase (ALT) level, such that decrease in LSM may only reflect ALT normalization. In HBVr patients, LSM should therefore be assessed after normalization of ALT levels to accurately diagnose the degree of fibrosis [98]. However, Jia et al. showed in a large cohort of Chinese patients with CHB, ALT levels up to five times the ULN did not significantly affect the diagnostic power of LSM [100]. Li et al. showed that patients with mildly elevated ALT levels had higher LSM cut-off values than patients with normal ALT levels on predicting F2-F4 (6.5 vs 6 kPa) and F4 (10.2 vs 7.8 kPa) [101]. Using cut-offs regardless of ALT levels, the diagnostic accuracy of LSM was 81% for F2-F4, and 89% for F4. Applying ALT-stratified cut-off values, the diagnostic accuracy of LSM was 82% for predicting F2-F4, and 86% for predicting F4 [101]. In regions where transient elastography is not readily accessible, serum test formulae based on common laboratory parameters have the advantages of high applicability. Examples include aspartate aminotransferase (AST) to platelet ratio index (APRI), Forns index and Fibrosis-4 (FIB-4) score [102].

Both HBsAg positive and HBsAg negative but anti-HBc positive patients treated with IST considered high risk should be initiated pre-emptive high-resistant barrier NUCs. For those with moderate risk, all HBsAg positive and those HBsAg negative but anti-HBc positive patients with advanced liver fibrosis or cirrhosis should be initiated pre-emptive high-resistant barrier NUCs. The preferred NUCs are entecavir, tenofovir or TAF. For those HBsAg negative and anti-HBc positive patients without advance fibrosis or cirrhosis, serum ALT should be monitored every 3 months. If elevated ALT > 2 × baseline detected at monitoring, HBsAg and HBV DNA should be performed and high-resistant barrier NUCs initiated if either test positive. For those with low-risk , pre-emptive NUCs should be initiated in both HBsAg positive and HBsAg negative but anti-HBc positive with advanced fibrosis or cirrhosis. Serum ALT should be monitored every 3 months in both HBsAg positive and HBsAg negative but anti-HBc positive patients with low-risk. The AASLD, AGA and EASL recommend antiviral treatment should be continued for at least 6 months after discontinuation of IST and at least 12 months for B cell-depleting agents. [17, 19, 20] Our panel recommended that under the guidance of a hepatologist, termination of NUCs would be considered 6 months after the completion of IST for HBsAg positive patients, without advanced liver fibrosis or cirrhosis *and* with low level of HBV DNA (< 2000 IU/ml) before initiation of NUCs. For those who remain HBsAg negative but anti-HBc positive, termination of NUCs should be considered 6 months after the completion of IST. HBV DNA monitoring-guided preemptive NUCs are effective for preventing HBV-related hepatitis in these patients [83]. Close monitoring every 3 months and prompt initiation of NUCs may be more cost-effective. In the future with more solid evidence, new biomarkers, such as HBV RNA, HBcrAg, may be helpful to decide when to terminate NUCs after completion of IST [103].

Comparison to previous guidelines

In the Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update, a section "Antiviral

Table 5 Randomized controlled trials supporting the benefit of pre-emptive antiviral therapy in preventing HBV reactivation

Authors (year)	Conditions	Treatment	HBV status	Antivirals vs controls (*n*)	Antiviral duration	Definition of HBVr	Rate of HBVr	Hepatitis due to HBVr
Lau (2003) [14]	Lymphoma	CEOP, ABVD, CHOP, COPP	HBsAg +	15 lamivudine vs 15 controls	1 week prior–6 weeks after	HBV DNA levels 10 × baseline	0% (0/15) vs 53% 0% (8/15) $p < 0.01$	0% (0/15) vs 47% (7/15) $p < 0.01$
Jang (2006) [15]	HCC	TACE	HBsAg +	36 lamivudine vs 37 controls	Beginning–12 months after	HBV DNA levels 10 × baseline	3% (1/36) vs 41% (15/37) $p < 0.001$	3% (1/36) vs 30% (11/37) $p < 0.01$
Hsu (2008) [16]	Non-Hodgkin lymphoma	CHOP	HBsAg +	26 lamivudine vs 25 controls	Beginning–2 months after	HBV DNA levels 10 × baseline	12% (3/26) vs 56% (14/25) $p < 0.01$	8% (2/26) vs 48% (12/25) $p < 0.01$
Huang (2013) [10]	CD20 + non-Hodgkin lymphoma	R-CHOP	HBsAg − anti-HBc +	41 entecavir vs 39 controls	1 week prior–3 months after	HBV DNA level at 2,000 IU/ml Reverse HBsAg seroconversion	2% (1/41) vs 18% (7/39) $p < 0.05$	2% (1/41) vs 3% (1/39) $p = 1.0$
Huang (2014) [95]	Lymphoma	R-CHOP	HBsAg +	61 entecavir vs 60 lamivudine	1 week prior–6 months after	HBV DNA levels 10 × baseline or an absolute increase of 10^5 copies/ml or greater compared with the baseline	7% (4/61) vs 60% (18/60) $p < 0.01$	0% (0/61) vs 13% (8/60) $p < 0.01$
Ho (2015) [96]	CHB patients undergoing chemotherapy	Chemotherapy	HBsAg +	35 lamivudine vs 35 adefovir dipivoxil	1 week prior–6 months after	1 log increase in HBV DNA levels higher than that of the preceding samples	37% (13/35) vs 29% (10/35) $p = 0.611$*	3% (1/35) vs 6% (2/35) $p = 1.00$
Buti (2017) [13]	Hematologic malignancy	Rituximab-based regimens	HBsAg − anti-HBc +	33 tenofovir disoproxilfumarate vs 28 controls	Beginning–18 months after	HBsAg and/or HBV DNA detection, or ≥ 1 log increase in HBV DNA levels from baseline	0% (0/33) vs 11% (3/28) $p = 0.091$	0% (0/33) vs 4% (1/28) $p = 0.274$

All controls received antiviral therapy if reactivation occurred. *In HBsAg + and in HBsAg− anti-HBc + patients receiving cancer chemotherapy. + positive, − negative, *ABVD* adriamycin, bleomycin, vinblastine, dacarbazine, *anti-HBc* anti-hepatitis B core antibody IgG, *CEOP* cyclophosphamide, epirubicin, vincristine, prednisolone, *CHOP* cyclophosphamide, doxorubicin, vincristine, prednisolone, *COPP* cyclophosphamide, vincristine, procarbazine, prednisolone, *HBsAg* hepatitis B antigen, *IU* international unit, *R-CHOP* rituximab-CHOP, *TACE* transarterial chemoembolization with epirubicin and cisplatin

*The study showed that the rate of developing drug resistance mutations was comparable among the two groups [62% (8/13) vs 0% (0/10), $p = 0.003$]

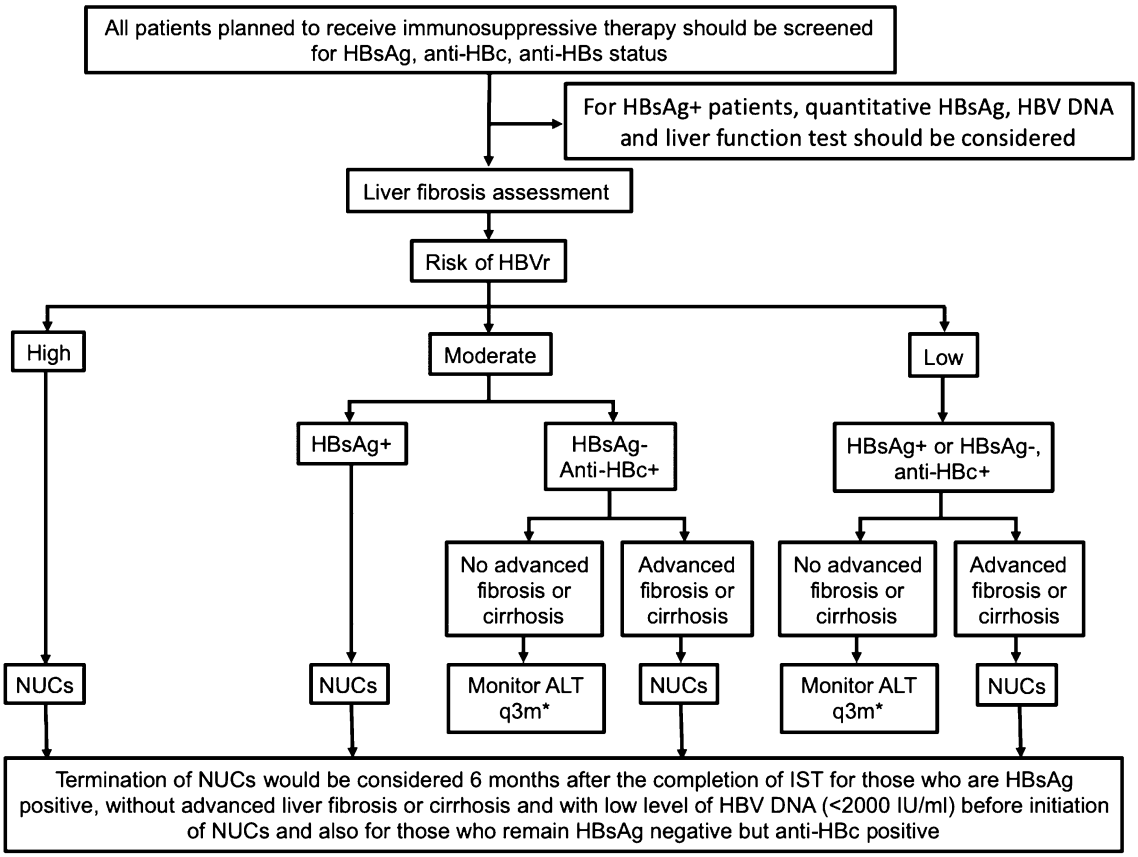

Fig. 2 Algorithm for the management of hepatitis B reactivation. All high-risk patients and moderate risk HBsAg + patients should be treated with pre-emptive NUCs irrespective of fibrosis status. All patients with advanced fibrosis or cirrhosis should be treated with NUCs irrespective risk stratifications. All HBsAg + patients should be treated with NUCs except for low-risk patients without advanced fibrosis or cirrhosis. Low-risk HBsAg + without advanced fibrosis or cirrhosis should be monitored with ALT testing every three months. Moderate and low risks HBsAg − anti-HBc + patients without advanced fibrosis or cirrhosis should be monitored with ALT testing every three months

prophylaxis before immunosuppressive therapy or chemotherapy" was included to discuss this important topic [18]. Over the last few years, more data have been made available to allow better stratification of the risk of HBVr with various immunosuppressive agents, namely new biologics, targeted therapies, immunotherapies and anti-HCV direct-acting antiviral agents. The recommendations remain the same for HBsAg-positive patients to whom pre-emptive NUC therapy should be started. The main changes lay on the HBsAg-negative but anti-HBc positive patients, as in the 2015 guidelines it was mentioned that further studies are needed to compare the efficacy and cost-effectiveness of different preventive strategies (pre-emptive NUCs *versus* monitoring). Furthermore, HBsAg-negative, anti-HBc positive patients with undetectable serum HBV DNA and who receive IST regardless of anti-HBs status should be followed carefully by means of LFT with or without HBV DNA testing, and be treated with NUCs upon confirmation of HBVr. Liver fibrosis assessment was included in the algorithm as patients with advanced fibrosis and cirrhosis run a higher risk of mortality and morbidity with HBVr. Also, new data on HBVr with HBV/HCV coinfected patients treated with DAAs are included. The evolving data over the last few years have better elucidated the risk of HBVr in HBsAg-negative, anti-HBc positive patients. Hence, pre-emptive NUCs are now recommended for HBsAg-negative, anti-HBc positive patients in the moderate-risk and high-risk groups.

Recommendations

1. Definition
   1.1. Reactivation of HBV
   1.1.1. Exacerbation of chronic HBV infection (HBsAg +)
   • ≥ 2 log increase in HBV DNA levels from baseline levels

[Grading: evidence—II-2, recommendation -1]

• Detection of HBV DNA with level > 100 IU/ml in a person with undetectable HBV DNA at baseline

[Grading: evidence—II-2, recommendation -1]

1.1.2. Reactivation of past HBV infection (HBsAg negative, anti-HBc positive) after the start of immunosuppressive therapy

• Reverse HBsAg seroconversion, HBsAg-negative becomes HBsAg-positive

[Grading: evidence—II-2, recommendation -1]

• Appearance of HBV DNA in absence of HBsAg, HBV DNA-undetectable becomes HBV DNA-detectable

[Grading: evidence—II-2, recommendation -1]

2. Who should be screened?

All patients planned to receive immunosuppressive therapy should be screened.

[Grading: evidence—II-2, recommendation -1]

3. What will be screened?

3.1 Screening should include HBsAg, anti-HBs and anti-HBc.

[Grading: evidence—II-2, recommendation -1]

3.2 For those HBsAg-positive patients, additional test for quantitative HBV DNA and HBsAg should be considered.

[Grading: evidence—II-2, recommendation -1]

3.3 All HBsAg positive and HBsAg negative but anti-HBc positive patients should have the degree of liver fibrosis assessed by a hepatologist. *[Grading: evidence—III, recommendation -2]*

4. Management

4.1 It is mandatory and life-saving to administer pre-emptive NUCs promptly to the followings:

• In high-risk group, all HBsAg positive or HBsAg negative but anti-HBc positive patients

[Grading: evidence—I, recommendation -1]

• In moderate-risk group, all HBsAg positive and those who are anti-HBc positive with advanced liver fibrosis or cirrhosis

[Grading: evidence—II-2, recommendation -1]

4.2 It is essential to administer pre-emptive NUCs to the following:

• In low-risk group, all HBsAg positive or HBsAg negative but anti-HBc positive with advanced liver fibrosis or cirrhosis *[Grading: evidence - II-2, recommendation -1]*

4.3 Preferred NUCs include entecavir, tenofovir and TAF

[Grading: evidence—I, recommendation -1]

4.4 Termination of NUCs should be considered 6 months after the completion of immunosuppressive therapy:

• For HBsAg-positive patients, without advanced liver fibrosis or cirrhosis

[Grading: evidence—II-2, recommendation -1]

• For HBsAg-positive patients with low level of HBV DNA (< 2000 IU/ml) before initiation of NUCs

[Grading: evidence—II-2, recommendation -1]

• For those who remain HBsAg negative but anti-HBc positive

[Grading: evidence—II-2, recommendation -1]

5.1 Liver function test* should be monitored every 12-weekly

5.1 In moderate-risk group, HBsAg negative but anti-HBc-positive patients with no advanced liver fibrosis or cirrhosis

[Grading: evidence—II-2, recommendation -1]

5.2 In low-risk group, HBsAg positive or HBsAg negative but anti-HBc positive with no advanced liver fibrosis or cirrhosis

[Grading: evidence—II-2, recommendation -2]

5.3 If ALT > 2 × baseline, check HBsAg, HBV DNA and treat with NUCs for HBsAg seroreversion and/or HBV DNA detectable

[Grading: evidence—II-2, recommendation -1]

*Liver function test includes ALT, AST, bilirubin, albumin, globulin

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