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**Hepatitis B reactivation in patients with hepatitis B core antibody positive and surface antigen negative on immunosuppressants**

Wu CC *et al*. Hepatitis B reactivation in patients with previous hepatitis B exposure on immunosuppressants

Clement Chun-Ho Wu, Rajneesh Kumar

**Clement Chun-Ho Wu, Rajneesh Kumar,** Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore 169608, Singapore

**Clement Chun-Ho Wu, Rajneesh Kumar,** Duke-NUS Medical School, Singapore 169608, Singapore

**ORCID number:** Clement Chun-Ho Wu (0000-0002-9869-1334); Rajneesh Kumar (0000-0003-2269-4835).

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**Corresponding author:** **Rajneesh Kumar, MBBS, MD, MRCP, Adjunct Professor, Doctor,** Department of Gastroenterology and Hepatology, Singapore General Hospital, Outram Rd, Singapore 169608, Singapore. rajneeshkrs@gmail.com

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**Abstract**

Hepatitis B viral (HBV) reactivation in the immunosuppressed is a significant problem even in patients who have achieved serological clearance due to the persistence of HBV as cccDNA. HBV reactivation will continue to pose a significant healthcare burden given the high prevalence of HBV and increasing use of immunosuppressants. Screening of hepatitis B surface antigen, antibody to Hepatitis B core antigen antibody and HBV DNA levels should be done routinely in all patients planned for significant immunosuppressant use. We aimed to examine the factors affecting reactivation risk. This depended on HBV disease status, the underlying disease requiring immunosuppression, and the specific immunosuppressive regime. While antiviral prophylaxis can prevent reactivation, it increases cost and still has risk of delayed reactivation after stopping antivirals and close follow-up and on-demand treatment is a good alternative for patients at risk of reactivation.

**Key words**: Previous hepatitis B exposure; Immunosuppression; Cost-effectiveness; Hepatitis B reactivation

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**Core tip:** Hepatitis B reactivation remains a common clinical problem, in countries with high endemicity of Hepatitis B, prevalence of Hepatitis B exposure can be very high where hepatitis B virus (HBV) DNA and HbsAg is negative. This group of patients when undergoing chemotherapy or immunusuppresion can have reactivation and HBV DNA can be positive, this review summaries the key studies and guide in rationale approach.

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**INTRODUCTION**

Hepatitis B virus (HBV) is a common disease, with approximately 250 million people being HBsAg positive[1] and 1.6 billion people being antibody to hepatitis B core antigen (anti-HBc) positive[2]. Even in patients who have achieved serological clearance, HBV persists in the host’s hepatocytes as covalently closed circular DNA (cccDNA)[3]. The natural history of HBV infection involves an interaction between HBV viral replication and the host’s immune response[4]. In HBV reactivation, initiation of immunosuppression removes immune surveillance pressure against HBV, enhancing viral replication[5]. This phase is defined by an increase in serum HBV DNA levels without any hepatitis. Upon cessation of immunosuppression, host immunity recovers and there is a rapid T-cell-mediated damage of infected hepatocytes, resulting in hepatitis[5]. Both processes can occur even in patients with serological clearance of HBV due to its persistence as cccDNA[3,6]. Reactivation can lead to hepatitis, liver failure, disruption or delay of immunosuppressive treatment, and can be fatal[7]. From an economic point of view, resultant morbidity from HBV reactivation is associated with significant healthcare costs[8].

The management of HBV reactivation in immunosuppressed patients with chronic Hepatitis B is well established[9-11]. However, the management of patients with past or resolved HBV infection remains controversial[12]. Although patients with hepatitis B surface antigen (HBsAg)-negative, anti-HBc positive patients have a lower risk of HBV reactivation compared to HBsAg-positive patients, the prevalence of anti-HBc is higher than that of HBsAg, ranging from 5% in countries in the western hemisphere, to > 50% in east Asian countries[7,11]. Coupled with the increased development and use of immunosuppressants for various conditions[13], HBV reactivation will continue to be an important clinical challenge, with HBsAg-negative, anti-HBc positive patients forming a significant portion of patients at risk of HBV reactivation. In this article, we will review literature pertaining to screening, treatment and follow-up strategies in patients with previous Hepatitis B exposure who are planned for immunosuppression.

In this narrative review, we carried out a search of the PubMed database for studies published until January 2019 using the keywords “Hepatitis B reactivation, HBsAg negative, anti-HBc positive, antiviral prophylaxis, immunosuppression, monitoring, cost-effectiveness” and identified relevant literature. The references cited in these papers were also checked to complement the search.

**IMPORTANT DEFINITIONS**

The definition of key terms in the study of HBV reactivation has been varied. This has resulted in a wide range of HBV reactivation rates reported in literature[14,15]. Compounded with the lack of systematically collected data, this made it difficult to discern the risk of reactivation in specific populations of immunocompromised individuals and specific classes of immunosuppressants[10]. We defined these key terms in accordance with the American Association for the Study of Liver Diseases (AASLD) 2018 Hepatitis B Practice Guidance[10] for ease of reference (Table 1). Risk of HBV reactivation was classified as low when the incidence rate of HBV reactivation was < 1%, moderate when the incidence rate was between 1%-10% and high when incidence rate exceeded 10%.

**RISK FACTORS FOR HBV REACTIVATION**

The main risk factors for HBV reactivation can be subdivided into: (1) virologic factors; (2) patient factors; and (3) type of immunosuppression (Table 2). The virologic factors associated with an increased risk of reactivation in HBsAg-negative and anti-HBc-positive patients include high baseline HBV DNA levels, absence of anti-HBs antibody and presence of Hepatitis B core-related antigen (HBcrAg). High HBV DNA at baseline was found to be the most important risk factor for HBV reactivation in this population of patients[16], and major guidelines have recommended that HBsAg-negative, anti-HBc positive patients with detectable serum HBV DNA be managed similarly to HBsAg-positive patients, in view of increased HBV reactivation risk[9]. A meta-analysis which investigated the effect of anti-HBs status in patients with past Hepatitis B infection found that the presence of anti-HBs reduced HBV reactivation risk overall. The rate of HBV reactivation was 5% in patients who had both positive anti-HBc and anti-HBs serology, compared to 14% in patients who only had a positive anti-HBc[17]. This effect was true for higher risk patients who had lymphoma or underwent rituximab-containing chemotherapy[17]. Baseline HBcrAg positivity was also associated with increased HBV reactivation risk. In a prospective study involving 124 HBsAg-negative, anti-HBc positive patients undergoing high-risk immunosuppression (either rituximab-containing chemotherapy or allogenic hematopoietic stem cell transplant, cumulative HBV reactivation rates were significantly higher in HBcrAg patients compared to those who were HBcrAg negative (71.8% *vs* 31%, *P* = 0.002)[18].

Patient factors increasing HBV reactivation risk include increased age, male gender, presence of liver cirrhosis and underlying disease that required immunosuppression[19,20]. A meta-analysis performed by Cholongitas *et al*[21] showed that rates of HBV reactivation were higher in patients with hematological disease (10.9%) compared to patients with non-hematological disease (3.6%). Patients with liver cirrhosis and hepatocellular carcinoma (HCC) are at a higher risk of chemotherapy-related reactivation of HBV[22].

The type of immunosuppression plays a key role in a patient’s HBV reactivation risk. Patients on B-cell depleting-therapies including rituximab have a high risk of HBV reactivation. In a meta-analysis done by Mozessohn *et al*[23], HBsAg-negative and anti-HBc-positive patients on Rituximab had a pooled reactivation rate of 16.4%. B cell-depleting agents also been well described to have a significantly increased risk of HBV-associated liver failure[24]. Notably, the increased risk of HBV reactivation appears more pronounced in patients who are on rituximab for hematological malignancies[17], compared to rheumatological conditions such as rheumatoid arthritis[25,26].

Tumor necrosis factor-α inhibitors such as infliximab and tyrosine kinase inhibitors such as imatinib have moderate risk of reactivation in HBsAg-negative, anti-HBc-positive patients[27,28]. Anthracycline derivatives such as doxorubicin are associated with a moderate risk of HBV reactivation in patients with previous HBV exposure, and is particularly concerning for patients with HBV-related HCC undergoing doxorubicin-containing transarterial chemoembolization[5]. Patients who receive high dose corticosteroids as monotherapy or in conjunction with other immunosuppressive agents have an increased risk of HBV reactivation[29].

Immune checkpoint inhibitors such as anti-CTLA4 (ipilimumab) and anti-PD-L1 (pembrolizumab) have been increasingly used to treat numerous cancers[30]. A retrospective study by Wen *et al*[31] found that the use of these drugs in HBsAg-negative, anti-HBc-positive patients did not result in any cases of HBV reactivation, even in the absence of antiviral therapy. Thus far, there has only been one reported case of HBV reactivation in a patient with HIV co-infection who received pembrolizumab for treatment of non-small cell lung cancer[32]. Data on the risk of HBV reactivation in such patients remains limited, and more studies are needed to verify these findings.

**HBV SCREENING**

Most patients with previous or chronic HBV infection are asymptomatic and may not be diagnosed prior to commencement of immunosuppression. There is wide variability in the approach to HBV screening before immunosuppression[33]. The decision for hepatitis B screening prior in patients who will be receiving immunosuppression is based on a balance between the cost savings of early HBV detection and subsequent administration of antiviral prophylaxis *vs* the cost of screening large numbers of patients.

Major clinical practice guidelines differ in their recommendations for HBV screening in individuals undergoing immunosuppression. The American Society of Clinical Oncology presented a more selective screening strategy[33], and recommended HBV screening only in patients with HBV risk factors[34,35] or those who will be receiving cancer therapy associated with a high risk of reactivation, such as B-cell depleting agents or stem cell transplantation[22]. A cost effectiveness modelling study[8] in a population of patients with hematologic neoplasms at high risk of HBV reactivation showed screening for HBV infection to be both clinically efficacious and cost effective, with initial cost of the screening strategy being offset by monetary savings from prevention of clinical events.

Given the increased use of immunosuppressants, with an increased risk of severe HBV reactivation, universal HBV screening has been found to be cost effective in populations with high prevalence of HBV[10]. In populations with lower prevalence of HBV, screening has been found to be cost effective only in patients with higher HBV reactivation risk and those with comorbidities predisposing to higher risk of mortality following reactivation[36]. While cost effectiveness arguments are compelling, it is difficult to quantify the negative impact of inability or delay in administration of chemotherapy in patients with HBV reactivation. The AASLD, Asia Pacific Association for the Study of the Liver, European Association for the Study of the Liver are in favor of universal screening prior to commencement of immunosuppressants[9-11]. HBV screening should occur at least 1 wk prior to initiation of immunosuppression, with the view of starting antiviral prophylaxis at least 1 wk or as soon as possible upon commencement of immunosuppression.

In the setting of long-term or indefinite immunosuppressive therapy, HBV screening is cost effective even when prevalence of Hepatitis B infection is as low as 0.3%[22]. However, HBV screening should not be routine in patients undergoing a low risk immunosuppression regime given that prophylaxis or pre-emptive treatment would not be routinely offered.

Both HBsAg and anti-HBc should be used for HBV screening[10] prior to commencement of immunosuppression. Further testing for HBV DNA should be done only if HBsAg is reactive, or in HBsAg-negative patients with positive anti-HBc antibodies. This is to detect occult infection which needs to be managed in the same manner as HBsAg-positive serology. Presence of detectable HBV DNA levels in HBsAg-negative patients with positive anti-HBc antibodies is associated with higher reactivation rates compared to patients who have an undetectable serum HBV DNA[9].

For patients with resolved HBV infection receiving chemotherapy for hematological malignancies, further testing for anti-HBs may be useful to stratify HBV reactivation risk status. A meta-analysis performed by Paul *et al*[17] showed that the absence of anti-HBs increased HBV reactivation risk[37], and such patients should be considered for antiviral prophylaxis. Another study found that patients with resolved HBV infection who underwent allogenic bone marrow transplant for hematological malignancies and received post-transplant HBV vaccination for augmentation of did not have any cases of HBV reactivation compared to 12 cases of reactivation in patients who did not undergo vaccination. This was postulated to be due to an augmentation of the anti-HBs response[38]. The utility of anti-HBs screening in HBsAg-negative, anti-HBc positive patients on other immunosuppressive regimens has not been investigated.

In recent years, HBcrAg has been advocated as a novel biomarker for screening and monitoring of HBsAg-negative, anti-HBc-positive patients who have undetectable HBV DNA titres[39]. These patients could either have prior self-limiting HBV exposure or have chronic HBV infection with HBsAg seroclearance, where HBV remains in very low replicative and transcriptional levels despite HBsAg negativity[40]. Serum HBcrAg correlates well with intrahepatic cccDNA[41,42], itself being a surrogate measure of the proliferative potential of HBV[3]. Seto *et al*[18] showed that in HBsAg-negative, anti-HBc-positive patients with lymphoma undergoing rituximab-containing chemotherapy, HBcrAg positivity was associated with HBV reactivation (*P* = 0.011, HR: 3.65). This association was found in the same study to be stronger than anti-HBs negativity in predicting HBV reactivation risk[18]. The use of HBcrAg for further risk stratification holds much promise in areas of high anti-HBc seroprevalence, where cost effectiveness of antiviral prophylaxis remains a major concern[43]. The use of HBCrAg remains nascent and has not entered widespread clinical use[44]. Further studies of HBcrAg in patients with moderate and low HBV reactivation risk would enhance the generalizability of this test for screening.

**TREATMENT STRATEGIES**

Two main strategies - Antiviral prophylaxis and On-demand treatment (Table 1), are used to attenuate the risk of HBV reactivation in HbsAg-negative, anti-HBc positive immunocompromised individuals. Antiviral prophylaxis involves the initiation of HBV antiviral therapy in patients where there are no other indications for commencing treatment other than an anticipated HBV reactivation. On-demand treatment refers to commencement of antiviral treatment only upon diagnosis of HBV reactivation, but usually involves more intensive surveillance both during and after an immunosuppressive regimen.

**DIFFERENCE IN CLINICAL OUTCOMES BETWEEN TREATMENT STRATEGIES**

Choosing between the two strategies involves weighing the difference in clinical outcomes, and well as cost effectiveness. Major guidelines[9-11] acknowledge that HBsAg-negative, anti-HBc-positive patients are generally of a lower risk profile than patients who are HBsAg-positive, and permit close surveillance with early on-demand treatment in patients with a moderate (1%-10%) and low risk (< 1%) risk of HBV reactivation. In patients with high risk of reactivation (> 10%), such as those with hematological malignancies receiving B-cell depleting chemotherapy, antiviral prophylaxis was found to be superior to on-demand treatment[45]. Recent studies have shown that on-demand treatment strategy may be comparable to antiviral prophylaxis even in this high-risk group, albeit with some caveats. Liu *et al*[46] described a randomized control trial where lymphoma patients with past Hepatitis B infection were randomized to start antiviral prophylaxis with entecavir *vs* close follow-up with on-demand treatment prior to commencement of chemotherapy. The study contained both patients who were receiving B cell-depleting therapy, and those who were not. Despite the incidence of reactivation being higher in the on-demand treatment arm, there were no reported HBV-related liver decompensation events or deaths. It should be noted that a large proportion of patients in this study (73.2%) were anti-HBs-positive, which could have protected against HBV reactivation.

Retrospective analyses[25,26] found that patients with past (HBsAg-negative, anti-HBc positive) HBV infection who received rituximab for rheumatological diseases without antiviral prophylaxis had low (3.3%-5%) rates of HBV reactivation. The HBV reactivation episodes were also mild, with no HBV-related hepatitis, hepatic decompensation or death. However, these retrospective studies were done in patients with rheumatological disease, with a lower risk profile than patients undergoing a similar immunosuppressive regime for hematological malignancy.

**COST EFFECTIVENESS OF TREATMENT STRATEGIES**

While cost effectiveness of antiviral prophylaxis in HBsAg-positive patients is known[10], the cost effectiveness of strategies to attenuate the risk of HBV reactivation in patients with past HBV infection is not well established[9]. The cost effectiveness of antiviral prophylaxis is broadly dependent on disease prevalence, and the savings arising from the clinical events that are prevented as a result of prophylaxis. In turn, the savings accrued from prevented clinical events is correlated with the severity of the events prevented[43]. HBV reactivation in HBsAg-negative, anti-HBc-positive patients are usually milder than patients who are HBsAg positive, and rarely result in hepatitis, hepatic decompensation or death[25,26,46]. In a cost effectiveness modelling study[8] in a population of patients with hematologic neoplasms at high risk of HBV reactivation, antiviral prophylaxis was found to be cost effective in HBsAg-positive patients, but not in patients who were HBsAg-negative and anti-HBc-positive. A prospective study by Seto *et al*[47] found that in HBsAg-negative, anti-HBc-positive patients with lymphoid malignancies undergoing systemic therapy with B-cell depleting agents (Rituximab or obinutuzumab), close biweekly surveillance with early on-demand therapy in event of HBV reactivation was a viable option compared to antiviral prophylaxis, and may be cost effective. Liu *et al*[46] also found that patients with past HBV infection, particularly those with positive anti-HBs, had a low risk of HBV reactivation and monitoring HBV DNA and ALT closely was more cost effective than antiviral prophylaxis.

It must be emphasized, however, that a strategy of close HBV serology monitoring with early on-demand treatment is logistically demanding. Patients would be required to come for frequent follow-up appointments and existing cost-effectiveness studies do not take into account the productivity costs borne by the patient as a result of this strategy. Similarly, it is also difficult to quantify the negative impact of inability or delay in administration of chemotherapy in patients with HBV reactivation. Decisions regarding risk attenuation strategies of HBV reactivation in immunocompromised patients with previous HBV exposure must be individualized. We suggest a treatment algorithm (Figure 1) which took into account various factors determining the clinical risk and outcomes of both treatment strategies in HBsAg-negative, anti-HBc-positive patients undergoing immunosuppression.

**CHOICE OF TREATMENT AGENT**

For patients who are commenced on antiviral treatment either as prophylaxis or as on-demand treatment, antiviral agents with a high genetic barrier to resistance was recommended[23]. However, the cost of these medications is high. The major clinical societies’ guidelines have noted that in the event of resource constraints, less expensive earlier-generation antivirals with a lower genetic barrier to resistance may be used in patients with a lower risk of resistance (*i.e.*, Undetectable HBV DNA at baseline, and an anticipated prophylaxis duration of less than 6 mo). Patients who are started on antiviral prophylaxis should be continued on antiviral treatment for at least 12 mo after cessation of rituximab-containing immunosuppressants, due to risk of delayed reactivation with rituximab[48] and 6 mo for all other immunosuppressive regimes. Patients should undergo routine testing for HBV DNA and serum ALT and AST for 3-6 mo after discontinuation of antiviral therapy to monitor for HBV reactivation post withdrawal.

**CONCLUSION**

HBV reactivation remains a concern even after serological clearance due to virus persistence in the host genome as cccDNA. HBV reactivation will continue to remain a significant problem due to high global prevalence of HBV and the increasing use of immunosuppressants. HBV screening with HBsAg, anti-HBc, anti-HBs and HBV DNA should be done in all patients prior to commencement of immunosuppression. HBcrAg shows promise in further characterization of patient’s reactivation risk profile. More studies should be done to assess applicability in low and moderate risk immunosuppressants and determining if HBcrAg can be used to identify optimal timepoint of stopping antiviral therapy.

The decision for prophylaxis or close monitoring with early on-demand treatment needs to be individualized, and depends on the risk of reactivation, cost effectiveness and difference in clinical outcome between the two scenarios. More research is needed to better identify patients who are at elevated risk for HBV reactivation, but concurrently low risk for HBV reactivation associated complications, in order to ascertain the population in whom close monitoring with early on-demand treatment would be a viable option. The risk profile of emerging medications including immune checkpoint mediators needs to be further studied to expand our knowledge on the optimal method of attenuating HBV reactivation risk in immunosuppressed patients with previous HBV exposure.

**REFERENCES**

1 **Ott JJ**, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine* 2012; **30**: 2212-2219 [PMID: 22273662 DOI: 10.1016/j.vaccine.2011.12.116]

2 **Lavanchy D.** Worldwide epidemiology of HBV infection, disease burden, and vaccine prevention. *J Clin Virol* 2005; **34 Suppl 1**: S1-3 [DOI: 10.1016/S1386-6532(05)00384-7]

3 **Kumar R**, Pérez-Del-Pulgar S, Testoni B, Lebossé F, Zoulim F. Clinical relevance of the study of hepatitis B virus covalently closed circular DNA. *Liver Int* 2016; **36 Suppl 1**: 72-77 [PMID: 26725901 DOI: 10.1111/liv.13001]

4 **Gonzalez SA**, Perrillo RP. Hepatitis B Virus Reactivation in the Setting of Cancer Chemotherapy and Other Immunosuppressive Drug Therapy. *Clin Infect Dis* 2016; **62 Suppl 4**: S306-S313 [PMID: 27190320 DOI: 10.1093/cid/ciw043]

5 **Loomba R**, Liang TJ. Hepatitis B Reactivation Associated With Immune Suppressive and Biological Modifier Therapies: Current Concepts, Management Strategies, and Future Directions. *Gastroenterology* 2017; **152**: 1297-1309 [PMID: 28219691 DOI: 10.1053/j.gastro.2017.02.009]

6 **Nassal M**. HBV cccDNA: viral persistence reservoir and key obstacle for a cure of chronic hepatitis B. *Gut* 2015; **64**: 1972-1984 [PMID: 26048673 DOI: 10.1136/gutjnl-2015-309809]

7 **Shouval D**, Shibolet O. Immunosuppression and HBV reactivation. *Semin Liver Dis* 2013; **33**: 167-177 [PMID: 23749673 DOI: 10.1055/s-0033-1345722]

8 **Crespo J**, Esteban R, Torres C, Oyagüez I, Casado MÁ, Buti M. Cost-effectiveness of a hepatitis B virus screening strategy to prevent reactivation in patients with hematologic neoplasms. *Rev Esp Enferm Dig* 2017; **109**: 619-626 [PMID: 28648087 DOI: 10.17235/reed.2017.4693/2016]

9 **Sarin SK**, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, Chen DS, Chen HL, Chen PJ, Chien RN, Dokmeci AK, Gane E, Hou JL, Jafri W, Jia J, Kim JH, Lai CL, Lee HC, Lim SG, Liu CJ, Locarnini S, Al Mahtab M, Mohamed R, Omata M, Park J, Piratvisuth T, Sharma BC, Sollano J, Wang FS, Wei L, Yuen MF, Zheng SS, Kao JH. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016; **10**: 1-98 [PMID: 26563120 DOI: 10.1007/s12072-015-9675-4]

10 **Terrault NA**, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; **67**: 1560-1599 [PMID: 29405329 DOI: 10.1002/hep.29800]

11 **European Association for the Study of the Liver.** Electronic address: easloffice@easloffice.eu.; European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67**: 370-398 [PMID: 28427875 DOI: 10.1016/j.jhep.2017.03.021]

12 **Feld JJ**. Hepatitis B Reactivation: The Controversies Continue. *Dig Dis* 2017; **35**: 351-358 [PMID: 28468014 DOI: 10.1159/000456587]

13 **Viganò M**, Serra G, Casella G, Grossi G, Lampertico P. Reactivation of hepatitis B virus during targeted therapies for cancer and immune-mediated disorders. *Expert Opin Biol Ther* 2016; **16**: 917-926 [PMID: 27088278 DOI: 10.1080/14712598.2016.1177017]

14 **Seto WK**, Chan TS, Hwang YY, Wong DK, Fung J, Liu KS, Gill H, Lam YF, Lie AK, Lai CL, Kwong YL, Yuen MF. Hepatitis B reactivation in patients with previous hepatitis B virus exposure undergoing rituximab-containing chemotherapy for lymphoma: a prospective study. *J Clin Oncol* 2014; **32**: 3736-3743 [PMID: 25287829 DOI: 10.1200/JCO.2014.56.7081]

15 **Koo YX**, Tan DS, Tan IB, Tao M, Chow WC, Lim ST. Hepatitis B virus reactivation and role of antiviral prophylaxis in lymphoma patients with past hepatitis B virus infection who are receiving chemoimmunotherapy. *Cancer* 2010; **116**: 115-121 [PMID: 19899164 DOI: 10.1002/cncr.24742]

16 **Lau GK**. Hepatitis B reactivation after chemotherapy: two decades of clinical research. *Hepatol Int* 2008; **2**: 152-162 [PMID: 19669300 DOI: 10.1007/s12072-008-9056-3]

17 **Paul S**, Dickstein A, Saxena A, Terrin N, Viveiros K, Balk EM, Wong JB. Role of surface antibody in hepatitis B reactivation in patients with resolved infection and hematologic malignancy: A meta-analysis. *Hepatology* 2017; **66**: 379-388 [PMID: 28128861 DOI: 10.1002/hep.29082]

18 **Seto WK**, Wong DK, Chan TS, Hwang YY, Fung J, Liu KS, Gill H, Lam YF, Cheung KS, Lie AK, Lai CL, Kwong YL, Yuen MF. Association of Hepatitis B Core-Related Antigen With Hepatitis B Virus Reactivation in Occult Viral Carriers Undergoing High-Risk Immunosuppressive Therapy. *Am J Gastroenterol* 2016; **111**: 1788-1795 [PMID: 27644733 DOI: 10.1038/ajg.2016.436]

19 **Loomba R**, Rowley A, Wesley R, Liang TJ, Hoofnagle JH, Pucino F, Csako G. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med* 2008; **148**: 519-528 [PMID: 18378948 DOI: 10.7326/0003-4819-148-7-200804010-00008]

20 **Yeo W,** Chan PK, Zhong S, Ho WM, Steinberg JL, Tam JS, Hui P, Leung NW, Zee B, Johnson PJ. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. *J Med Virol* 2000; **62**: 299-307 [PMID: 11055239 DOI: 10.1002/1096-9071(200011)62:3<299::AID-JMV1>3.0.CO;2-0]

21 **Cholongitas E**, Haidich AB, Apostolidou-Kiouti F, Chalevas P, Papatheodoridis GV. Hepatitis B virus reactivation in HBsAg-negative, anti-HBc-positive patients receiving immunosuppressive therapy: a systematic review. *Ann Gastroenterol* 2018; **31**: 480-490 [PMID: 29991894 DOI: 10.20524/aog.2018.0266]

22 **Reddy KR**, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT; American Gastroenterological Association Institute. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015; **148**: 215-9; quiz e16-7 [PMID: 25447850 DOI: 10.1053/j.gastro.2014.10.039]

23 **Mozessohn L**, Chan KK, Feld JJ, Hicks LK. Hepatitis B reactivation in HBsAg-negative/HBcAb-positive patients receiving rituximab for lymphoma: a meta-analysis. *J Viral Hepat* 2015; **22**: 842-849 [PMID: 25765930 DOI: 10.1111/jvh.12402]

24 **Khan ZH,** Ilyas K, Ghazanfar H, Khan HH, Hussain Q, Hammad S, Munir A, Asim R. Fatal Fulminant Hepatitis from Rituximab-induced Hepatitis B Reactivation in a Patient with Follicular Lymphoma: A Case Report and a Brief Review of Literature. *Cureus* 2018; **10**: e2257 [PMID: 29725560 DOI: 10.7759/cureus.2257]

25 **Spinicci M**, Emmi G, Dies L, Barilaro A, Vitiello G, Mencarini J, Cavallo A, Bartoloni A, Bartalesi F. Short article: Safety of targeted prophylaxis strategy in patients with resolved hepatitis B virus infection receiving rituximab for immune-mediated diseases. *Eur J Gastroenterol Hepatol* 2018; **30**: 756-760 [PMID: 29649073 DOI: 10.1097/MEG.0000000000001132]

26 **Varisco V**, Viganò M, Batticciotto A, Lampertico P, Marchesoni A, Gibertini P, Pellerito R, Rovera G, Caporali R, Todoerti M, Covelli M, Notarnicola A, Atzeni F, Sarzi-Puttini P. Low Risk of Hepatitis B Virus Reactivation in HBsAg-negative/Anti-HBc-positive Carriers Receiving Rituximab for Rheumatoid Arthritis: A Retrospective Multicenter Italian Study. *J Rheumatol* 2016; **43**: 869-874 [PMID: 26879359 DOI: 10.3899/jrheum.151105]

27 **Lan JL**, Chen YM, Hsieh TY, Chen YH, Hsieh CW, Chen DY, Yang SS. Kinetics of viral loads and risk of hepatitis B virus reactivation in hepatitis B core antibody-positive rheumatoid arthritis patients undergoing anti-tumour necrosis factor alpha therapy. *Ann Rheum Dis* 2011; **70**: 1719-1725 [PMID: 21719446 DOI: 10.1136/ard.2010.148783]

28 **Lai GM**, Yan SL, Chang CS, Tsai CY. Hepatitis B reactivation in chronic myeloid leukemia patients receiving tyrosine kinase inhibitor. *World J Gastroenterol* 2013; **19**: 1318-1321 [PMID: 23483799 DOI: 10.3748/wjg.v19.i8.1318]

29 **Perrillo RP**, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015; **148**: 221-244.e3 [PMID: 25447852 DOI: 10.1053/j.gastro.2014.10.038]

30 **Kudo M**. Immune Checkpoint Blockade in Hepatocellular Carcinoma: 2017 Update. *Liver Cancer* 2016; **6**: 1-12 [PMID: 27995082 DOI: 10.1159/000449342]

31 **Wen X**, Wang Y, Ding Y, Li D, Li J, Guo Y, Peng R, Zhao J, Zhang X, Zhang XS. Safety of immune checkpoint inhibitors in Chinese patients with melanoma. *Melanoma Res* 2016; **26**: 284-289 [PMID: 27116334 DOI: 10.1097/CMR.0000000000000256]

32 **Pandey A**, Ezemenari S, Liaukovich M, Richard I, Boris A. A Rare Case of Pembrolizumab-Induced Reactivation of Hepatitis B. *Case Rep Oncol Med* 2018; **2018**: 5985131 [PMID: 30416833 DOI: 10.1155/2018/5985131]

33 **Hwang JP**, Somerfield MR, Alston-Johnson DE, Cryer DR, Feld JJ, Kramer BS, Sabichi AL, Wong SL, Artz AS. Hepatitis B Virus Screening for Patients With Cancer Before Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update. *J Clin Oncol* 2015; **33**: 2212-2220 [PMID: 25964247 DOI: 10.1200/JCO.2015.61.3745]

34 **Weinbaum CM,** Williams I, Mast EE, Wang SA, Finelli L, Wasley A, Neitzel SM, Ward JW; Centers for Disease Control and Prevention (CDC). Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep* 2008; **57**: 1-20 [PMID: 18802412]

35 **LeFevre ML**; U.S. Preventive Services Task Force. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2014; **161**: 58-66 [PMID: 24863637 DOI: 10.7326/M14-1018]

36 **Day FL**, Karnon J, Rischin D. Cost-effectiveness of universal hepatitis B virus screening in patients beginning chemotherapy for solid tumors. *J Clin Oncol* 2011; **29**: 3270-3277 [PMID: 21788556 DOI: 10.1200/JCO.2011.35.1635]

37 **Lee JY**, Lim SH, Lee MY, Kim H, Sinn DH, Gwak GY, Choi MS, Lee JH, Jung CW, Jang JH, Kim WS, Kim SJ, Kim K. Hepatitis B reactivation in multiple myeloma patients with resolved hepatitis B undergoing chemotherapy. *Liver Int* 2015; **35**: 2363-2369 [PMID: 25832927 DOI: 10.1111/liv.12838]

38 **Takahata M**, Hashino S, Onozawa M, Shigematsu A, Sugita J, Fujimoto K, Endo T, Kondo T, Tanaka J, Imamura M, Teshima T. Hepatitis B virus (HBV) reverse seroconversion (RS) can be prevented even in non-responders to hepatitis B vaccine after allogeneic stem cell transplantation: long-term analysis of intervention in RS with vaccine for patients with previous HBV infection. *Transpl Infect Dis* 2014; **16**: 797-801 [PMID: 25154638 DOI: 10.1111/tid.12283]

39 **Mak LY**, Wong DK, Cheung KS, Seto WK, Lai CL, Yuen MF. Review article: hepatitis B core-related antigen (HBcrAg): an emerging marker for chronic hepatitis B virus infection. *Aliment Pharmacol Ther* 2018; **47**: 43-54 [PMID: 29035003 DOI: 10.1111/apt.14376]

40 **Yuen MF**, Wong DK, Fung J, Ip P, But D, Hung I, Lau K, Yuen JC, Lai CL. HBsAg Seroclearance in chronic hepatitis B in Asian patients: replicative level and risk of hepatocellular carcinoma. *Gastroenterology* 2008; **135**: 1192-1199 [PMID: 18722377 DOI: 10.1053/j.gastro.2008.07.008]

41 **Wong DK**, Tanaka Y, Lai CL, Mizokami M, Fung J, Yuen MF. Hepatitis B virus core-related antigens as markers for monitoring chronic hepatitis B infection. *J Clin Microbiol* 2007; **45**: 3942-3947 [PMID: 17942661 DOI: 10.1128/JCM.00366-07]

42 **Honda M**, Shirasaki T, Terashima T, Kawaguchi K, Nakamura M, Oishi N, Wang X, Shimakami T, Okada H, Arai K, Yamashita T, Sakai Y, Yamashita T, Mizukoshi E, Kaneko S. Hepatitis B Virus (HBV) Core-Related Antigen During Nucleos(t)ide Analog Therapy Is Related to Intra-hepatic HBV Replication and Development of Hepatocellular Carcinoma. *J Infect Dis* 2016; **213**: 1096-1106 [PMID: 26621908 DOI: 10.1093/infdis/jiv572]

43 **Kim HY**, Yoo JJ, Oh S, Yu SJ, Kim YJ, Yoon JH, Kim W, Jung YJ, Kim BH, Kim CM, Park JW, Lee JH. Scoring system for risk stratification of viral reactivation during prophylactic antiviral treatment in Korean patients with hepatitis B undergoing anticancer chemotherapy: A multicenter study. *J Med Virol* 2018; **90**: 1593-1603 [PMID: 29900560 DOI: 10.1002/jmv.25241]

44 **Chen EQ**, Feng S, Wang ML, Liang LB, Zhou LY, Du LY, Yan LB, Tao CM, Tang H. Serum hepatitis B core-related antigen is a satisfactory surrogate marker of intrahepatic covalently closed circular DNA in chronic hepatitis B. *Sci Rep* 2017; **7**: 173 [PMID: 28282964 DOI: 10.1038/s41598-017-00111-0]

45 **Huang H**, Li X, Zhu J, Ye S, Zhang H, Wang W, Wu X, Peng J, Xu B, Lin Y, Cao Y, Li H, Lin S, Liu Q, Lin T. Entecavir vs lamivudine for prevention of hepatitis B virus reactivation among patients with untreated diffuse large B-cell lymphoma receiving R-CHOP chemotherapy: a randomized clinical trial. *JAMA* 2014; **312**: 2521-2530 [PMID: 25514302 DOI: 10.1001/jama.2014.15704]

46 **Liu WP**, Xiao XB, Xue M, Wang GQ, Wang XP, Song YQ, Zhu J. Prophylactic Use of Entecavir for Lymphoma Patients With Past Hepatitis B Virus Infection: A Randomized Controlled Trial. *Clin Lymphoma Myeloma Leuk* 2019; **19**: 103-108 [PMID: 30581161 DOI: 10.1016/j.clml.2018.11.008]

47 **Seto WK**, Sau-Yan Chan T, Hwang YY, Mak LY, Ka-Ho Wong D, Fung J, Sze-Hang Liu K, Cheung KS, Lai CL, Kwong YL, Yuen MF. Monitoring and Treatment of Patients Undergoing Immunotherapy With Anti-CD20 Who are Exposed to HBV. *Clin Gastroenterol Hepatol* 2018 [PMID: 30243760 DOI: 10.1016/j.cgh.2018.09.020]

48 **Ceccarelli L**, Salpini R, Sarmati L, Svicher V, Bertoli A, Sordillo P, Ricciardi A, Perno CF, Andreoni M, Sarrecchia C. Late hepatitis B virus reactivation after lamivudine prophylaxis interruption in an anti-HBs-positive and anti-HBc-negative patient treated with rituximab-containing therapy. *J Infect* 2012; **65**: 180-183 [PMID: 22138369 DOI: 10.1016/j.jinf.2011.11.021]

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**Table 1 Definition of key terms used in the study of hepatitis B virus reactivation**

|  |  |
| --- | --- |
| **Key term** | **Definition** |
| Resolved Hepatitis B infection | Negative HBsAg, positive anti-HBc, positive anti-HBs |
| Past Hepatitis B infection | Negative HBsAg, positive anti-HBc, negative or unknown anti-HBs |
| HBV reactivation | In HBsAg-negative, anti-HBc-positive patients: Newly detectable HBV DNA level OR; Occurrence of HBsAg sero-reversion (reappearance of HBsAg) |
| Hepatitis B flare  | ALT increase to ≥ 3 times the baseline level and > 100 U/L |
| HBV-associated liver failure | Impaired synthetic function (Total bilirubin > 3 mg/dL or international normalized ratio > 1.5) OR Ascites OR Encephalopathy OR Death following HBV-associated liver failure attributed to HBV reactivation |
| Antiviral prophylaxis | Antiviral treatment in a patient where there are no other indications for commencing treatment other than an anticipated HBV reactivation |
| On-demand treatment | Commencement of antiviral treatment upon diagnosis of HBV reactivation |

HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; Anti-HBc: Antibody to Hepatitis B core antigen; Anti-HBs: Antibody to Hepatitis B surface antigen.

**Table 2 Risk factors determining risk of hepatitis B reactivation in HBsAg negative, anti-HBc positive patients. Hepatitis B chemoprophylaxis can be considered in patients with 2 or more high risk factors for hepatitis B reactivation**

|  |  |
| --- | --- |
| **Category**  | **Risk factor** |
| Virological factors | (1) High baseline HBV DNA; (2) Absence of anti-HBs antibody; (3) Presence of Hepatitis B core-related antigen |
| Patient factors | (1) Male gender; (2) Liver cirrhosis; (3) Immunosuppression required because of hematological malignancy |
| Type of immunosuppressive regime | High risk: B-cell depleting therapies |
| Medium risk: Anthracycline derivatives, high dose corticosteroids, systemic cancer chemotherapy, cytokine-based therapies, immunophilin inhibitors, tyrosine-kinase inhibitors, protease inhibitors |
| Low risk: Immune checkpoint inhibitors, low-moderate dose corticosteroids, antimetabolite therapies |



**Figure 1 Treatment algorithm for HBsAg negative, anti-HBc positive patients undergoing immunosuppression.** Future research may help determine whether HBcrAg has a role in determining whether patients with HBsAg negative with anti-HBc positive with undetectable DNA undergo HBV chemoprophylaxis or “on-demand” treatment. HBV: Hepatitis B virus.