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Review

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Prevention of Hepatitis B reactivation in the setting of immunosuppression

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Advances in the treatment of malignant and inflammatory diseases have developed over time, with increasing use of chemotherapeutic and immunosuppressive agents of a range of drug classes with varying mechanism and potency in their effects on the immune system. These advances have been met with the challenge of increased risk of hepatitis B virus (HBV) reactivation in susceptible individuals. The magnitude of risk of HBV reactivation is associated with the individual's HBV serological status and the potency and duration of immunosuppression. Individuals with chronic hepatitis B (CHB) and previously infected but serologically cleared HBV infection are both susceptible to HBV reactivation. HBV reactivation in the setting of immunosuppression is a potentially life threatening condition leading to liver failure and death in extreme cases. It is important to recognize that HBV reactivation in the setting of immunosuppression is potentially preventable. Therefore, identification of patients at risk of HBV reactivation and institution of prophylactic antiviral therapy prior to initiation of immunosuppression is essential. **(Clin Mol Hepatol 2016;22:219-237)**

Keywords: Hepatitis B reactivation; Prophylaxis; Chemotherapy; Immunosuppression; Guidelines

INTRODUCTION

Hepatitis B is a disease prevalent globally, with approximately 2 billion people exposed to hepatitis B and of these, 240 million are chronically infected (chronic hepatitis B, CHB).[1] This review will highlight the impact of concomitant hepatitis B virus (HBV) infection amongst patients with malignant, inflammatory and autoimmune conditions who undergo immunosuppression. It is apparent that immunosuppression for a range of disease states may be associated with HBV reactivation in susceptible individuals. HBV reactivation leads to a spectrum of clinical outcomes, the most concerning being symptomatic hepatitis, liver failure and death. Clinicians must be aware of such potential adverse outcomes, and screen for and manage HBV accordingly in conjunction with the immunosuppressive regime prescribed for the primary disease. Current recommendations and the existing evidence base for these recommendations will be presented in this review.

Abbreviations:

AGA, American gastroenterological association; ALT, alanine aminotransferase; Anti-HBc, hepatitis B core antibody; Anti-HBs, hepatitis B surface antibody; BMT, bone marrow transplant; CHB, chronic hepatitis B; DNA, deoxyribonucleic acid; EASL, European association for the study of the liver; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBV reactivation, hepatitis B virus reactivation; HDV, hepatitis D virus; HSCT, haematopoetic stem cell transplant; IL, interleukin; LPAM, lymphocyte Peyer's patch adhesion molecule; OR, odds ratio; R-CHOP, rituximab-cyclophosphamide, hydroxydaunorubicin (doxorubicin or adriamycin), oncovin (vincristine) and prednisolone; R-CHEOP, rituximab-cyclophosphamide, hydroxydaunorubicin (doxorubicin or adriamycin), etoposide, oncovin (vincristine) and prednisolone; RR, risk ratio; RNA, ribonucleic acid; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor

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HOW AND WHY DOES HBV REACTIVATION OCCUR WITH IMMUNOSUPPRESSION?

HBsAg positive patients

Chronic HBV infection is characterised by the interaction between the virus, the immune system and the liver. Serologically, the presence of hepatitis B surface antigen (HBsAg) defines CHB. Observing the natural history of HBV infection, there are four phases of infection depending on the interaction between the virus and the host immune system; immune tolerance, immune clearance, immune control or immune escape. Any modulation to the immune system may disrupt the interaction between virus and host and contribute to HBV reactivation. Clinically, this has been observed in pregnant women who likely owing to peri-partum changes in the immune system may experience post-partum flares of hepatitis B infection.[2] A case of HBV reactivation with liver failure due to excess endogenous adrenocortical activity due to an adrenal tumour (Cushing's syndrome) has also been reported.[3]

Of concern are the iatrogenic effects of chemotherapy and immunosuppression for malignant, inflammatory and autoimmune diseases on individuals with CHB. The interaction between the immune system and HBV may be disrupted by drug-induced modulation of the immune system resulting in HBV reactivation, which has the potential to cause significant liver injury.

Liver injury resulting from HBV reactivation in the setting of immunosuppressive therapy may occur through 2 mechanisms. Uncontrolled viral replication may occur during immunosuppression. Rapid rises in hepatitis B viral particles may cause direct cytolytic destruction of hepatocytes. After chemotherapy or immunosuppression has been ceased, immune reconstitution may cause severe immune mediated injury to infected hepatocytes. An exaggerated immune response against hepatocytes expressing viral proteins may occur, leading to necrosis of liver cells. The delayed reactivation associated with immune reconstitution may occur up to six months after cessation of immunosuppression, and in the case of certain immunosuppressive agents (eg rituximab) can occur as late as 12 months post-treatment due to a prolonged immune reconstitution phase observed for more potent immunosuppressive drugs.[4,5]

Iatrogenic HBV reactivation due to immunosuppression can result in asymptomatic biochemical hepatitis or more concerning, acute symptomatic hepatitis that in severe cases can lead to fulminant liver failure and death.[6]

HBsAg negative, anti-HBc positive patients

Patients with serological evidence of past infection with HBV by far outnumber those with CHB across the globe. Patients with previously documented CHB may experience spontaneous clearance of HBsAg at a rate of 0.5% per year.[7] Individuals may alternatively have serological evidence of past HBV exposure, both scenarios leading to an HBsAg negative/hepatitis B core antibody (anti-HBc) positive state. These patients remain at risk of HBV reactivation in the setting of immunosuppression owing the persistence of the HBV in the form of cccDNA in hepatocytes and other tissues.[8,9]

Anti-HBs positive patients

There is limited evidence to date that the presence of anti-HBs protects against HBV reactivation. Anti-HBs antibodies may develop in HBsAg negative/anti-HBc positive individuals indicating the development of natural immunity. In a cohort of HBsAg negative/anti-HBc positive patients with lymphoma, patients who were anti-HBs negative prior to rituximab-based chemotherapy were observed to have a higher 2-year cumulative incidence of HBV reactivation than those who were anti-HBs positive (68.3% vs. 34.4%; P=0.01).[10] In a study of 29 patients with lymphoma, a threshold anti-HBs titre >100 IU/mL was associated with 0% HBV reactivation, and lower anti-HBs titre was independently associated with HBV reactivation.[11] Cho et al similarly observed 0% HBV reactivation in patients with pre-chemotherapy anti-HBs titres >100 IU/mL, but incidence of HBV reactivation of 8.3% at 6-months and 17.3% at 24 months post-chemotherapy in those with anti-HBs titres below this threshold.[12] In patients receiving hematopoetic stem cell transplantation, the *donor* anti-HBs titre was associated with a decreased risk of HBV reactivation.[13] These findings are yet to be validated. Until then, the presence or titre of anti-HBs cannot be used to assess risk of HBV reactivation, nor guide decisions on the use of antiviral prophylaxis for HBV reactivation.

WHAT ARE THE NON-HEPATIC CONSEQUENCES OF HBV REACTIVATION?

The occurrence of HBV reactivation may influence the clinician to interrupt immunosuppression or chemotherapy to mitigate the severity of the reactivation and prevent liver failure or mortality. Treatment interruption occurred in 71% of breast cancer patients

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who experienced HBV reactivation in comparison with only 33% of patients in whom HBV reactivation did not occur (P=0.019).[14] The potential outcome of any treatment interruption is a higher morbidity or mortality associated with the primary diseases process. Although data is limited as to the magnitude of the impact of treatment interruption on morbidity and mortality in relation to HBV reactivation across diseases states, these outcomes also form part of the rationale for HBV screening and prophylaxis in patients receiving any form of immunosuppression.

HOW DO WE DEFINE HBV REACTIVATION?

HBV reactivation has been variably defined across the existing studies, which makes the interpretation and direct comparison of some studies challenging. Across studies, the HBV DNA assays used have varied in their lower limits of detection, potentially underestimating the prevalence of HBV reactivation and delaying the timepoint at which HBV reactivation may be first detected. "Hepatitis" has been variably reported as alanine aminotransferase (ALT) elevation above upper limit of normal, or by "fold" increases from baseline; whether the hepatitis is symptomatic or asymptomatic is inconsistently documented. Suggested definitions for HBV reactivation are listed beneath, however a consensus is yet to be reached for the purposes of future studies:

1. In HBsAg positive patients:
- Detectable HBV DNA in individual who previously had undetectable HBV DNA by highly sensitive assay (lower limit of detection, <20 IU/mL).
- ≥1 log rise in HBV DNA in individual who previously had a detectable HBV DNA.[15]
- Biochemical hepatitis (ALT flare):
  - ≥3 fold rise in ALT from baseline levels exceeding the reference range or an absolute ALT ≥100 IU/mL,[15] preceded by a rise in HBV DNA.
  - Consensus is needed as to a grading of the severity of biochemical hepatitis and associated clinical symptoms for the purposes of reporting in future studies.[16]

2. In HBsAg negative/anti-HBc positive patients:
- Seroreversion (or reverse seroconversion) has been described in which an individual undergoing immunosuppression develops detectable HBsAg, HBV DNA and/or biochemical hepatitis as a result of reactivation of occult infection.[17]

3. In conjunction with the serological and biochemical changes, the occurrence of jaundice, liver failure or

Table 1. Incidence of Hepatitis B reactivation due to immunosuppression according to disease

Disease	Incidence of HBV reactivation without HBV prophylaxis		References
	HBsAg positive (%)	HBsAg negative/anti-HBc positive (%)	
Lymphoma	18-73	34-68	6, 10, 33, 51-53
Acute leukaemias	61	2.8-12.5	31, 32
Chronic leukaemias	NA*	NA*	NA*
Multiple myeloma	NA	6.8-8	24, 47
Bone marrow/haematopoetic stem cell transplantation	66-81	6-10	13, 59, 61
Breast cancer	21-41	NA	14, 134, 157, 158
Nasopharyngeal cancer	33	NA	66
Hepatocellular cancer (systemic chemotherapy)	36	11	68, 159
Hepatocellular cancer (trans-arterial chemoembolization)	21-30	9.3	71-73
Rheumatoid arthritis	12.3	3-5	160-163
Psoriasis/psoriatic arthritis	NA*	NA*	NA*
Inflammatory bowel disease	36	0-7*	80, 81
Autoimmune diseases	NA*	17*	92
Renal Transplantation	45-70	0.9	93, 97-99

HBV, hepatitis B virus; NA, not available..
*Case reports or small case series reporting HBV reactivation.

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death may be considered clinical endpoints resulting from HBV reactivation.

HOW COMMON IS HBV REACTIVATION?

Immunosuppression has been associated with clinically significant reactivations of HBV in patients with both malignant disease and non-malignant inflammatory or autoimmune diseases. A range of immunosuppressive drugs and drug classes has been implicated in HBV reactivation. A broad range of prevalence of HBV reactivation is reported in the literature, largely due to the fact that the majority of the studies reporting the rates of HBV reactivation are case reports or small case series using variable definitions of HBV reactivation. Furthermore, reports in the literature arise from populations with varying prevalence of chronic HBV and HBV exposure, thereby influencing the absolute numbers of cases of HBV reactivation observed. In a recent systematic review, the observed the rate of HBV reactivation in patients receiving chemotherapy for solid tumours without HBV prophylaxis was 4-68% (median 25%).[18] Table 1 lists the range of rates of HBV reactivation reported for specific diseases.

Haematological malignancies

The greatest body of evidence for HBV reactivation in the setting of immunosuppression arises from patients treated for haematological malignancies. Reactivation of HBV has been reported in patients treated for lymphoma,[4,10,12,19-33] leukaemia[32,34-44] and multiple myeloma[24,45-48] (see Table 1).

The HBV itself may be a risk factor for the occurrence of non-Hodgkin's lymphoma, and thereby it makes this subgroup of patients particularly at risk of HBV reactivation when treated for their malignancy.[49,50] In one cohort of patients with lymphoma the prevalence of CHB was 26%, but the prevalence of CHB could be even higher in other populations where HBV is endemic.[15] HBV reactivation can occur in 18-73% of HBsAg positive patients being treated for lymphoma.[6,10,33,51-53] Higher HBV reactivation rates have been observed in patients receiving treatment regimens that utilize high dose corticosteroids and/or rituximab.[52,53] HBV reactivation also occurs in lymphoma patients who have achieved remission;[4] fulminant liver failure due to HBV reactivation requiring liver transplantation in 3 HBsAg-negative/anti-HBc positive patients has been reported.[25]

Amongst patients treated for acute or chronic forms of leukaemia, regimens which include (but not limited to) imantinib and erlotinib (tyrosine kinase inhibitor class drug) appear to be associated with HBV reactivation in susceptible individuals.[37-40,43,54-56] A similar association between the tyrosine kinase inhibitor bortezomib and HBV reactivation has been observed in cases of myeloma.[48,57]

Haematopoetic stem cell and bone marrow transplantation

Patients who receive a bone marrow (BMT) or haematopoetic stem cell transplant (HSCT) for haematological malignancy are a particularly at-risk population that experience prolonged immunosuppression during the conditioning chemotherapy leading up to the transplant, post-transplant immunosuppressive therapy and a protracted immune deficiency phase while engraftment occurs.[13,48,58-63] Fatal HBV reactivation has been observed in HBsAg positive patients, as well as HBsAg negative/anti-HBc positive patients.[59,62,63] In a multicenter retrospective study including 33 patients with CHB receiving both autologous and allogeneic stem cell transplantation, the rates of HBV reactivation at 2 years post-transplant were 66% and 81% respectively; the majority of the reactivations occurred within the first 12 months post-transplant.[59] The incidence of HBV reactivation is observed to be lower, albeit not insignificant in patients with past exposure to HBV infection (HBsAg negative/anti-HBc positive). Amongst 764 patients who received a haematopoetic stem cell transplant, 137 (18%) were HBsAg negative/anti-HBc positive; HBV reactivation was observed in 14 cases (10%) within a median of 19 (range 9-77) months after stem cell transplantation.[13]

Solid tumours

Amongst oncology patients, the prevalence of CHB has been reported in 12% of those with solid tumours.[15] Without antiviral prophylaxis, approximately 20% of patients with CHB being treated for malignancy will experience HBV reactivation.[15] Amongst women being treated for breast cancer who were also positive for HBsAg prior to treatment, 41% have been observed to develop HBV reactivation.[14]

HBV infection may be a carcinogenic risk factor for nasopharyngeal carcinoma thereby potentially contributing to a higher prevalence of HBV exposure and chronic infection in this subgroup of oncology patients.[64] Not unexpectedly, HBV reactivation has been reported in patients who received chemotherapy for nasopharyn-

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geal carcinoma, some being fatal.[65-67] In one cohort of 1301 patients with nasopharyngeal carcinoma, the prevalence of CHB was 10.9%.[67] Just over half the patients who were HBsAg positive received systemic chemotherapy (as opposed to locoregional radiotherapy alone) and of these, 44.2% had a hepatic adverse event, 3.5% classified as a severe hepatic event. It is unclear how many of these cases were due to HBV reactivation or other cause (eg drug toxicity) but there were no cases of liver failure in this cohort of patients.

Patients treated for HBV-related hepatocellular cancer are also at risk of HBV reactivation.[68-73] HBV reactivation has been observed in the setting of both systemic and transarterial chemoembolization (Table 1).

Rheumatological diseases

HBV reactivation has been reported in patients receiving immunosuppression for rheumatoid arthritis (see Table 1). In a cohort of HBsAg negative/anti-HBc positive patients with rheumatoid arthritis, 5% experienced HBV reactivation, and the incidence of reactivation was significantly higher amongst those who received etanercept (86% vs 36%, P=0.008). Numerous case reports of HBV reactivation (some with fatal liver failure) have been published with the use of methotrexate, B-cell depleting agents and tumor necrosis factor (TNF)-alpha inhibitors. The contribution of specific drug classes in the development of HBV reactivation will be discussed further later in this review.

Patients with psoriasis and psoriatic arthritis with positive serological markers for past exposure to- or for CHB have also been reported in multiple case reports to experience HBV reactivation, however authors of small case series have concluded that patients with psoriasis have a negligible risk of HBV reactivation even with the use of biological agents.[74,75] The latter results should be interpreted with caution, owing to the significant episodes of HBV reactivation associated with the use of biological agents in patients other diseases. These patients should still be considered at risk of HBV reactivation and be screened and managed according to current guidelines.

Inflammatory bowel disease

The prevalence of HBV amongst patients with inflammatory bowel diseases (IBD, including Crohn's disease and ulcerative colitis) ranges from 0.6-17% for HBsAg positive patients and 1.6-42% for HBsAg negative/anti-HBc positive patients[76-79] and appears to correlate with prevalence in HBV in the general population. One multicenter study of patients with IBD treated with immunosuppression observed a HBV reactivation rate of 36% in HBsAg positive patients, but 0% reactivation in HBsAg negative/anti-HBc positive patients.[80] In a subsequent study, 2/29 (7%) of patients who were HBsAg negative/anti-HBc positive developed detectable HBV DNA during treatment with anti-TNF-alpha agents without associated clinical or biochemical hepatitis.[81] Treatment for IBD may include high dose corticosteroids and/or anti-TNF-alpha agents, both of which have been associated with cases of HBV reactivation; contrary to the observations of Loras et al.[80,81] cases of clinically significant HBV reactivation have been reported in HBsAg negative/anti-HBs positive patients, and some have been associated with fatal liver failure.[82-90] Whether patients with inflammatory bowel diseases and serological markers of HBV are at lower risk of HBV reactivation under immunosuppression compared with other diseases and malignancies has been a subject of contention in the literature. This is due in part to the relatively low volume of data available on HBV reactivation in IBD patients. However, it is clear from available data that HBV is still common amongst patients with IBD, and clinically significant HBV reactivations may occur under immunosuppression. Therefore IBD patients should be screened for serological markers of HBV at the time of diagnosis of IBD, and a prophylactic treatment and/or monitoring plan for HBV reactivation instituted prior to immunosuppression according to current guidelines.

Autoimmune diseases

Patients with autoimmune conditions such as systemic lupus erythematosus (SLE), vasculitis, polymyositis/dermatomyositis, idiopathic thrombocytopaenic purpura and autoimmune haemolytic anaemia may also receive immunosuppressive regimes, which in the setting of HBV may put them at risk of HBV reactivation. Rituximab, the B-cell depleting agent which has been associated with HBV reactivation when used for haematological malignancies is also a potential therapy in SLE, Sjogren's syndrome, vasculitis, dermatomyositis, neurological diseases (multiple sclerosis, neuromyelitis optica, antibody-mediated paraneoplastic syndromes and IgM-mediated polyneuropathy), endocrinopathies (type 1 Diabetes and Graves disease), dermatological conditions (autoimmune blistering diseases) and non-malignant haematological conditions such as immune thrombocytopaenic purpura and autoimmune haemolytic anaemia.[91] Cases of HBV reactivation have been reported in patients immunosuppressed for a

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range of autoimmune conditions however due to low numbers of cases, the true incidence of HBV reactivation is not clear. In a cohort of 35 patients with a range of such autoimmune conditions and concomitantly HBsAg negative/anti-HBc positive, 6 patients (17%) were observed to have HBV reactivation (detectable HBV DNA) 4-8 weeks after initiation of immunosuppressive treatment.[92] Notwithstanding the limitations of the available data, patients with autoimmune conditions receiving immunosuppression should be considered at risk of HBV reactivation and managed accordingly.

Solid organ transplantation

Similar to patients who have undergone BMT, patients who have solid organ transplantation are prescribed long-term immunosuppression to prevent organ rejection. The need for pre-transplant HBV evaluation and prophylaxis in these patients must be emphasized as these patients are not only susceptible to the hepatic consequences of HBV reactivation, but are also at risk of morbidity and mortality due to graft loss.

Renal transplantation

HBV reactivation has been clearly documented in patients in the setting of renal transplantation (see table 1), some cases resulting in death due to liver failure.[93-99] Furthermore, patients with pre-existing chronic HBV infection who undergo renal transplantation experience higher rates of cirrhosis and hepatocellular carcinoma than those in the general population, indicating more rapid progression of HBV-related liver disease in these patients, if untreated.[100]

Liver transplantation

Patients who have undergone liver transplantation for cirrhosis due to chronic HBV or HBV-related hepatocellular carcinoma are at particular risk of a fulminant form of HBV reactivation; fibrosing cholestatic hepatitis. The latter is a rapidly progressive form of HBV reactivation that can result in graft loss, liver failure and death. Management guidelines for HBV infection in this special population have been provided by the American Association for the Study of Liver Disease.[101]

Although it is beyond the scope of this review to provide a detailed discussion on the prevention and management of HBV reactivation amongst these patients, it is important to recognize that these patients will need long-term HBV prophylaxis co-administered with their immunosuppressive regime.

WHAT ARE THE FACTORS ASSOCIATED WITH HBV REACTIVATION?

The patient's virological and serological status, the specific immunosuppressive drug or class of drug prescribed, and the duration of immunosuppression contribute to the risk of HBV reactivation in patients receiving immunosuppression.

Virological and serological status

The virological and serological risk factors associated with HBV reactivation (in descending order of risk) are detectable HBV DNA, HBsAg, hepatitis B e antigen (HBeAg) and anti-HBc.[7-9,17,102] Patients positive for HBsAg are up to 8 times more likely to experience HBV reactivation than HBsAg negative/anti-HBc positive patients.[103-105] Amongst HBsAg positive patients, HBeAg positive patients are more likely to experience HBV reactivation than HBeAg negative patients.[103]

Mutations of the HBsAg may confer risk of HBV reactivation.[106] In a recent study of 93 patients with CHB (29 of whom developed HBV reactivation) the HBsAg genetic-features were analyzed. Seventy-six percent of HBV-reactivated patients (vs. 3.1% of the 64 control-patients, $P<0.001$) carried HBsAg mutations localized in immune active HBsAg regions. Of the 13 HBsAg mutations found in these patients, 8 are known to hamper HBsAg recognition by humoral response and the remaining 5 were localized in Class-I/II-restricted T-cell epitopes, suggesting a role in HBV-escape from T-cell mediated responses.[106] These observations suggest that patients infected with HBV expressing such HBsAg mutations may have enhanced capability to evade the immune response may be more susceptible to HBV reactivation with chemotherapy. Colson et al observed HBsAg and HBV-reverse transcription mutations in patients who were initially HBsAg negative/anti-HBc positive who experienced reverse sero-conversion.[107] Sequencing of HBV DNA after HBV reactivation in patients who were initially HBsAg negative/anti-HBc positive patients demonstrated that the reactivated virus is characterized by low genetic heterogeneity, with the wild-type G1896 or G1896A variant prevalent.[108] These findings taken together speak to the possible mechanisms of HBV reactivation in susceptible individuals, however the clinical applications are yet to be determined.

Immunosuppression drug class

The therapy of malignant, inflammatory and autoimmune conditions continues to evolve with novel and targeted agents being

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Table 2. Risk estimates of HBV reactivation according to drug class[109,110]

Risk estimate of HBV reactivation	Drug class	Drug
High (>10%)	B-cell depleting agents	Rituximab (anti-CD20) Ofatumumab (anti-CD20)
	Anthracycline derivatives	Doxorubicin Epirubicin
	Corticosteroids	High dose eg prednisone ≥20 mg for ≥4 weeks
Moderate (1-10%)	TNFa inhibitors	Infliximab Etanercept Adalimumab
	Cytokine inhibitors and Integrin inhibitors	Abatacept (anti-CD80, -86) Ustekinimab (anti-IL12, -23) Natalizumab (binds α4-integrin) Vedolizumab (binds integrin $\alpha_4\beta_7$ [LPAM-1])
	Tyrosine kinase inhibitors	Imantinib Nilotinib
	Corticosteroids	Moderate dose eg prednisone <20 mg for ≥4 week
Low (<1%)	Corticosteroids	Low dose eg prednisone for <1 week
	Corticosteroids	Intra-articular corticosteroids
	Traditional immunosuppression	Azathioprine 6-mercaptopurine Methotrexate

HBV, hepatitis B virus.
TNF, tumour necrosis factor; IL, interleukin; LPAM, lymphocyte Peyer's patch adhesion molecule.

developed for a range of disease states. Many of these novel immunosuppressive agents have been associated with clinical evidence of HBV reactivation as outlined above. The risk of HBV reactivation attributed to specific drug classes has been estimated by the American Gastroenterological Association (AGA) based on a comprehensive review of the literature, bearing in mind the limitations of the available data (mainly case reports or series for some drugs; Table 2).[109,110]

The B-cell depleting agents appear to have a potent and durable immunosuppressive effect and are thereby associated with the highest risk of HBV reactivation. Rituximab and ofatumumab are two agents within this class largely used to treat haematological malignancy, however rituximab has been used a range of non-malignant diseases as discussed.[91,111] Both HBsAg positive and HBsAg negative/anti-HBc positive patients who receive these agents are susceptible to HBV reactivation. The rate of HBV reactivation with these agents in HBsAg negative/anti-HBc positive patients has been reported at 16.9%, and seroreversion rate of 20-40%.[22,109,112] HBV reactivation has occurred up to 12 months after cessation of B-cell depleting drugs (and some cases occurring beyond 12 months) indicating the durability of the immunosuppressive effect of this drug class likely due to a prolonged immune reconstitution phase. Amongst 63 HBsAg negative/anti-HBc positive patients with haematological malignancy who received rituximab without antiviral prophylaxis, the 2-year cumulative rate of HBV reactivation was 41.5%, occurring at a median of 23 weeks (range, 4 to 100 weeks) after rituximab treatment.[10] These observations would indicate that extended antiviral prophylaxis and monitoring is required in patients receiving these agents.

TNF-alpha inhibitors such as infliximab, etanercept and adalimumab are used to treat inflammatory bowel disease, rheumatological disease, psoriasis and autoiummune diseases. Drugs of this class have been associated with HBV reactivation.[113] A large study of 257 cases exposed to anti-TNF agents for a variety of indications reported HBV reactivation in 39% in HBsAg positive patients, 7 times higher than the incidence of HBV reactivation in HBsAg negative/anti-HBc positive patients in this cohort.[114]

Cytokine and integrin inhibitors have also been associated with HBV reactivation. Drugs of this class and their target molecules are listed in table 2. Evidence of role of these drugs in HBV reacti-

vation exist largely as case reports however the risk of HBV reactivation associated with these agents may be attributed to their known relative potency of immunosuppression according to the agents' mechanism of action.[115,116]

Tyrosine kinase inhibitors including imantinib and nilotinib are considered moderately immunosuppressive and have been associated with HBV reactivation in the setting of chronic myeloid leukaemia and gastrointestinal stromal tumours amongst other diseases.[37-40,54,55,117]

Corticosteroids are very commonly used immunosuppessive drugs across many disease processes. Corticosteroids directly affect T-cell function but also promote HBV DNA replication through interacting with the HBV glucocorticoid responsive element (a transcriptional regulatory element)[118] Corticosteroids are prescribed at a range of dosages and durations according to indication, however it has been observed that a 4-week course of prednisone is associated with HBV reactivation after drug withdrawal (immune-reconstitution phase) and worsened liver histology.[119] In patients with chronic airways disease, long-term steroid use is associated with HBV reactivation in 11.1% of those treated with oral steroids and 3.2% of those treated with inhaled steroids.[120] Continuous oral corticosteroid therapy (>3 months) and high-dose (defined as >20 mg prednisone/day) was associated with HBV reactivation with odds ratio (OR) of 5.7 and 4.9 respectively, when compared with HBV reactivation in those receiving inhaled corticosteroids.[120] Prednisone at a dose of <10mg/day (or equivalent), short term (<2 weeks) administration of oral (systemic) corticosteroids, intraarticular injection and topical therapies may be considered low immunosuppressive risk therapies as these have not been associated with HBV reactivation. It is therefore apparent that corticosteroids have the potential to induce HBV reactivation, but that the risk varies according to the dose, duration and route of administration.

Traditional immunomodulating drugs such as azathioprine, 6-mercaptopurine and methotrexate appear to have the lowest potential for HBV reactivation. There are no documented cases of HBV reactivation associated with the use of azathioprine or 6-mercaptopurine alone. Cases of HBV reactivation have been reported with methotrexate, however corticosteroids or other immunomodulators were co-administered in most instances, compounding the risk of HBV reactivation.[121,122]

Hepatitis B and Delta co-infection

To date, only a single case report of hepatitis delta virus (HDV) reactivation in association with HBV reactivation exists.[123] This patient was co-infected with hepatitis C virus (HCV RNA positive), HBV (HBsAg positive, HBV DNA undetectable at baseline) and had evidence of cleared HDV infection (anti-HDV positive). A rituximab-CHEOP regime was prescribed to treat lymphoma; HBV DNA became detectable during chemotherapy and HDV RNA was positive at 77.6 million copies/mL 15 months after chemotherapy. The patient was managed successfully with lamivudine, which was subsequently switched to emtricitabine/tenofovir. Given the singularity of this report, currently no evidence-based guide for the management of hepatitis B and delta co-infection in the setting of immunosuppression or cancer chemotherapy and patients should be managed according to their HBV status.

HOW DO WE MANAGE HEPATITIS B REACTIVATION?

The role of antiviral therapy once HBV reactivation is already established has been examined by several studies. Lamivudine therapy started at the time of ALT elevation did not appear to change the natural course of chemotherapy-associated HBV reactivation in a prospectively followed cohort of patients treated for non-Hodgkin's lymphoma; 2 patients in this cohort died despite lamivudine use at the onset of HBV reactivation.[5] Numerous case reports and series describe death due to liver failure despite the introduction of lamivudine at the onset of HBV reactivation.[124-128] Only a few cases of successful treatment of HBV reactivation with entecavir or tenofovir have been published.[42,129-131] Despite the paucity of data regarding the efficacy of entecavir and tenofovir to treat established HBV reactivation, the ability of these drugs to rapidly reduce HBV DNA make them attractive alternatives to lamivudine in patients who experience HBV reactivation to potentially abrogate the risk of liver failure and mortality. Ideally, these adverse outcomes should be avoided through prophylaxis of HBV reactivation.

"PREVENTION IS BETTER THAN CURE": HOW DO WE PREVENT HEPATITIS B REACTIVATION?

Given the significant rates of HBV reactivation with immunosuppression and the poor outcomes observed when antiviral treatment is introduced only once HBV reactivation is already established, the role of antiviral prophylaxis must be considered in

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Table 3. Summary of American Gastroenterology Association guidelines on the prevention and treatment of hepatitis B reactivation during immunosuppressive drug therapy[109,110]

Population at risk of HBV reactivation	Screening test	Is antiviral prophylaxis recommended?		Antiviral drug recommended for prophylaxis	Monitoring in untreated HBsAg negative/anti-HBc positive patients
		HBsAg positive	HBsAg negative/ anti-HBc positive		
High risk of HBV reactivation (>10%) • B-cell depleting agents • Anthracycline derivatives • High dose corticosteroids (≥20 mg prednisone for ≥4 weeks)	HBsAg and anti-HBc; HBV DNA if serology +ve	Yes (B1) Continue at least 6 months after completion of chemotherapy and at least 12 months for B-cell depleting agents	Yes (B1) if taking: • B-cell depleting agents • Anthracycline derivatives Continue until at least 12 months after completion of chemotherapy for B-cell depleting agents	Drug with high barrier to resistance is favoured over lamivudine (B2).	No recommendation provided
Moderate risk of HBV reactivation (1-10%) • TNFa inhibitors • Cytokine or Integrin inhibitors • Tyrosine kinase inhibitors • High dose corticosteroids (≥20 mg prednisone for ≥4 weeks)	HBsAg and anti-HBc; HBV DNA if serology +ve	Yes (B2) Continue until at least 6 months after completion of chemotherapy	Yes (B2) if taking: • TNFa inhibitors • Cytokine or Integrin inhibitors • Tyrosine kinase inhibitors Continue until at least 6 months after completion of chemotherapy	Drug with high barrier to resistance is favoured over lamivudine (B2).	No recommendation provided
Low risk of HBV reactivation (<1%) • Traditional immunosuppression • Intra-articular corticosteroids • Systemic corticosteroids for <1 week	Routine screening not recommended. Screen for HBV as per CDC guidelines[154]; manage accordingly	Not recommended (B2)	Not recommended (B2)	Not applicable	No recommendation provided

Evidence grade A: high quality; B: moderate quality; C: low quality. Recommendation grade 1: strong; 2: weak.
HBV, hepatitis B virus; CDC, center for disease control.

susceptible patients who will receive immunosuppressive therapy. A systematic review and metanalysis of 5 randomised controlled trials.[5,71,132-134] comparing antiviral prophylaxis to treatment at the onset of HBV reactivation concluded that the overall risk ratio (RR) favoured the prophylactic use of antivirals over no antivirals, with RR 0.13 (95% confidence interval [CI], 0.06-0.30).[109] In a systematic review of patients being treated with immunosuppressive chemotherapy for solid tumours, antiviral prophylaxis reduced the risk for HBV reactivation (OR, 0.12; 95% CI, 0.06-0.22), HBV-related hepatitis (OR, 0.18; 95% CI, 0.10-0.32), and chemotherapy disruption (OR, 0.10; 95% CI, 0.04-0.27).[18]

The World Health Organization (WHO) published guidelines on the management of CHB in 2015.[1] The WHO provided limited recommendations stating that CHB patients who were either eAg positive or anti-HBe positive can experience HBV reactivation precipitated by immunosuppression from chemo– or immunosuppressive therapy or renal transplantation, and that these patients should receive antiviral therapy.[1]

The current AGA recommendations (published in 2015) are based on the HBV reactivation risk stratification according to the combination of serological markers of HBV and the chemotherapy/immunosuppression regimen prescribed and are more detailed and specific with regard to the patient risk groups in whom antiviral prophylaxis should be considered (Table 3).[109,110]

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Which antiviral drug should be used for prophylaxis of hepatitis B Reactivation?

The nucleos(t)ide analogue antiviral drugs lamivudine, adefovir, telbivudine, entecavir and tenofovir may all be of potential use in the prevention of HBV reactivation in patients undergoing immunosuppression. The majority of reports concern the use of lamivudine or entecavir for the prophylaxis of HBV reactivation. Both drugs appear to reduce the incidence of HBV reactivation in immunosuppressed individuals. Entecavir (and potentially tenofovir) may be superior to lamivudine because of more potent viral suppression and lower risk of antiviral resistance (and therefore lower risk of viral breakthrough/reactivation) than lamivudine, resistance occurring in up to 20% of patients on lamivudine after just one year of use. Fatal HBV reactivation despite lamivudine prophylaxis owing to the development of the M204 drug resistance mutation has been reported in a patient who received R-CHOP for lymphoma.[135] The data regarding adefovir and telbivudine in the prevention and management of HBV reactivation is limited to the liver transplantation setting and is outside of the scope of discussion of this review. These drugs are not recommended as first line drugs for prophylaxis of HBV reactivation in the context of chemotherapy or immunosuppression.[109,110]

Lamivudine

A systematic review of lamivudine prophylaxis in chemotherapy patients determined that prophylaxis was associated with a relative risk of 0.0 to 0.21 for HBV reactivation and a relative risk of 0.0 to 0.2 for HBV-related death when compared without lamivudine prophylaxis.[136] In patients with breast cancer, prophylactic lamivudine was superior to HBV treatment once HBV reactivation was established in reducing HBV recurrence (OR, 0.12; 95% CI, 0.04-0.31), HBV-related hepatitis (OR, 0.13; 95% CI, 0.04-0.37) and the rate of chemotherapy interruption (OR, 0.37; 95% CI, 0.23-0.60).[137] Patients given lamivudine prophylaxis during chemotherapy have an 87% decrease in HBV reactivation compared to patients not given prophylaxis, the number needed to treat to prevent one reactivation being just 3 patients.[138] Lamivudine prophylaxis is associated with a 92% reduction in treatment delays and premature terminations of chemotherapy due to HBV reactivation.[138] A single study compared lamivudine to adefovir prophylaxis in chemotherapy patients. Amongst 70 HBsAg positive patients who received chemotherapy, HBV reactivation was observed in 13/35 (37.1%) on lamivudine was not significantly different to the incidence in patients 10/35 (28.6%) on adefovir (P=0.611).[139] Taken together, these studies indicate that lamivudine significantly reduces but does not necessarily abrogate the risk of HBV reactivation in the setting of immunosuppression.

The use of lamivudine prophylaxis has been demonstrated to be cost-effective, owing to the reduced number and severity of HBV reactivations. Reduced numbers of cancer deaths in patients who receive prophylaxis have been observed, presumably due to a reduced need for withholding chemotherapy.[140]

Lamivudine may have a role where total chemotherapy and post-chemotherapy follow-up duration spans less than 12 months (thereby reducing risk of drug resistance and virological breakthrough), the HBV DNA is undetectable at baseline and the patient is not receiving any of the "high risk" treatment regimes. The latter approach requires further evaluation, but may be an attractive strategy e.g. in countries with high prevalences of HBV where the cost of the more potent antivirals may be prohibitive.

Entecavir

There are seven studies to date comparing entecavir to lamivudine or no prophylaxis in patients with haematological malignancy, lymphoma alone, stem cell transplantation and solid tumours.[23,132,141-144] Lower rates of HBV reactivation are generally observed with the use of entecavir in these studies, however these studies vary in their design (ranging from retrospective audit to randomized-controlled study) and hence the strength of their findings. In the single randomized controlled study (published in abstract form), 61 patients who received entecavir prophylaxis were compared to 60 patients who received lamivudine.[132] Entecavir was associated with a relative risk reduction of 0.22 (0.08-0.61) for HBV reactivation and had significantly fewer chemotherapy interruptions (1.6% vs. 18.3%).[132] In a retrospective study of 213 patients HBsAg positive patients who received chemotherapy for solid tumours, HBV reactivation was observed in 0% of the 70 patients on entecavir compared with 7% of the 143 patients in the lamivudine group (P=0.02).[144] Amongst 216 HBsAg positive patients who underwent allogeneic stem cell transplantation, the cumulative incidence rates of HBV reactivation at 6, 12 and 24 months following transplantation were 3.0%, 7.0% and 24.0% in the 119 lamivudine patients, and 0%, 0% and 2.0% in the 97 entecavir patients, respectively.[145] Taken together, these data suggest that entecavir is superior to lamivudine in prevention of HBV reactivation in the setting of immunosuppression.

Tenofovir

There is only one case series report to date examining the role

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of tenofovir in prevention of HBV reactivation. In a heterogeneous cohort of 25 patients who received tenofovir prophylaxis prior to immunosuppression, 0% experienced HBV reactivation.[131] Despite the paucity of data on the use of tenofovir for HBV prophylaxis in immunosuppression, it is of theoretical benefit due to the potency of its antiviral effect and low drug resistance profile.

The cost-effectiveness of entecavir and tenofovir for the prophylaxis of HBV reactivation has to date not been studied.

How long should antiviral prophylaxis be prescribed?

For most immunosuppressive regimes, current guidelines suggest that antiviral prophylaxis should be prescribed continuously until at least 6 months after the cessation of chemotherapy or immunosuppression and for at least 12 months for those receiving B-cell depleting agents (Table 3).

In the absence of antiviral prophylaxis, HBV reactivation has been observed in some patients as late as 6-12 months after cessation of chemotherapy in both HBsAg positive and HBsAg negative/anti-HBc positive patients, and also when the antiviral prophylaxis has been curtailed to just 2 months post-completion of antiviral therapy.[5] Patients who have receive B-cell depleting agents appear to be susceptible to delayed HBV reactivation (up to 12 months post-treatment and beyond).[10] This is likely because agents of this class have potent and durable immunosuppressive effects with a prolonged immune reconstitution phase, during which time patients remain susceptible to HBV reactivation. Subsequent monitoring for delayed HBV reactivation after cessation of antiviral prophylaxis is essential.

Recipients of BMT or HSCT are a special population that must be considered. Both lamivudine and entecavir have been used with the aim of preventing HBV reactivation in these cases.[145-150] Whether antiviral prophylaxis can be withdrawn is unclear. HBV reactivation has been observed as early as 12 weeks post-discontinuation of lamivudine in the BMT setting.[147] HBV reactivation has been diagnosed as late as 4 years after transplantation in a patient who was anti-HBs positive at baseline.[151] In these patients, entecavir (or tenofovir) may be more suitable than long-term lamivudine due to the higher barrier to drug resistance conferred by entecavir.[145] The European Association for the Study of Liver Disease (EASL) guidelines (2009) provide a recommendation for this patient population: that nucleos(t)ide analogue prophylaxis is recommended for anti-HBc positive patients receiving bone marrow or stem cell transplantation (grade of recommendation C2); a duration of therapy is not specified.[152] As these patients are potentially at risk of HBV reactivation for years after the transplant, long-term antiviral therapy may need to be considered at the clinician's discretion.

HOW SHOULD SCREENING FOR HBV PRIOR TO IMMUNOSUPPRESSION BE PERFORMED?

It is essential for clinicians caring for patients at risk of HBV reactivation under immunosuppression to be aware of this risk and screen for HBV in order to institute appropriate prophylactic therapy and/or monitoring. Screening may also uncover previously undiagnosed chronic HBV infection and potentially the presence of associated cirrhosis and/or hepatocellular cancer. These liver-related complications of chronic HBV infection require specific management and may influence how the underlying disease process is managed.

There are several approaches to screening for HBV in this patient population:

a. Screen all patients prior to chemotherapy/immunosuppression.[152,153] This strategy would identify patients who would potentially benefit from:
   - Antiviral prophylaxis
   - HBV serology and HBV DNA monitoring (without antiviral prophylaxis)
   - Immunisation against HBV
   - Evaluation for complications of CHB
   - Contact tracing of family members for CHB and their subsequent management.
b. Screen only patients at risk of HBV according to CDC "high risk" groups.[154,155]
c. Screen only patients who, if serological testing was positive, would be prescribed antiviral prophylaxis.[109,110,156]

Consideration must also be given to which serological test(s) are to be used for screening:

a. Test HBsAg, anti-HBc and anti-HBs. Test HBV DNA if HBsAg or antiHBc are positive (the latter in case of occult HBV infection).
b. Test HBsAg, anti-HBc only. The role of anti-HBs in HBV reactivation is unclear. Furthermore, immunization against HBV may not be efficacious during immunosuppression. Therefore, one may argue that anti-HBs status may not be relevant prior to chemotherapy.
c. Test anti-HBc only. If positive, proceed to test for HBsAg and HBV DNA.

There is a paucity of data on the best and most cost-effective approach to screening for HBV in patients at risk of HBV reactivation. The AGA recommends HBV serological screening in patients with "moderate to high risk" according to their risk stratification paradigm (Table 3).[109,110] The clinical decision on who and how to screen will likely be influenced by the characteristics of the population being managed and the resources available to the individual, the institution and nation to fund the serological testing and manage positive results.

HOW SHOULD WE MONITOR HBsAg NEGATIVE/ANTI-HBc POSITIVE PATIENTS WHO DO NOT RECEIVE ANTIVIRAL PROPHYLAXIS?

The data summarized in this review and the current clinical guidelines[109,110] indicate that not all HBsAg negative/anti-HBc positive patients will benefit from antiviral prophylaxis e.g. patients with undetectable HBV DNA who are prescribed lower potency or limited duration immunosuppressive drug regimes. In those who do not receive antiviral prophylaxis, monitoring for the rare cases of HBV reactivation is advised, however there is a lack of evidence as to how this monitoring should be carried out. The EASL recommends ALT and HBV DNA testing every 1-3 months and treatment upon any evidence of HBV reactivation, but this is based on a weak level of evidence (C1).[152] The current AGA guidelines do not give a recommendation on this point. An alternative approach may be to test for the reappearance of HBsAg in HBsAg negative/anti-HBc positive patients, which may occur prior to HBV DNA elevation or biochemical hepatitis. In the absence of evidence based monitoring guidelines, clinicians will need to be guided by the prevalence of HBV and HBV reactivation in their populations, the cost-effectiveness of serial serological and biochemical testing as well as the access to testing and follow-up that may vary across different countries.

HOW DO WE MONITOR PATIENTS AFTER THE CESSATION OF ANTIVIRAL PROPHYLAXIS?

Some patients who receive antiviral therapy at the initiation of chemotherapy or immunosuppression may need to remain on antivirals long term if there is underlying chronic liver disease and ongoing treatment criteria for CHB are met.[152,153,155] In those who receive antiviral prophylaxis without otherwise meeting ongoing treatment criteria for CHB, specific guidelines as to how to perform post-prophylaxis monitoring are not available owing to a paucity of evidence. Clinical intuition and the available evidence would suggest that these patients should be monitored for at least 12 months, if not, long-term, particularly if there is a likelihood for the relapse of their underlying disease process requiring resumption of immunosuppression, and reinstitution of antiviral prophylaxis is required. Monitoring for HBsAg seroreversion, HBV DNA and/or ALT elevation could form part of the post-prophylaxis monitoring, however the time interval required between testing is unclear due to a lack of evidence base. Intuitively, more frequent monitoring may be required soon after cessation of antiviral prophylaxis (eg 3-monthly for the first year) and less frequent testing may be require beyond this.

CONCLUSIONS

Awareness of the potential for iatrogenic HBV reactivation as a complication of immunosuppression is essential. Those at risk for HBV reactivation must be screened serologically according to current evidence based-guidelines. Prophylaxis for HBV reactivation with antiviral nucleos(t)ide analogues should be commenced in susceptible individuals before the initiation of chemotherapy to abrogate the risk of HBV reactivation and the associated adverse clinical outcomes.

Conflicts of Interest

The author has no conflicts to disclose.

REFERENCES

1. WHO Guidelines Approved by the Guidelines Review Committee. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015.
2. Elefsiniotis I, Vezali E, Vrachatis D, Hatzianastasiou S, Pappas S, Farmakidis G, et al. Post-partum reactivation of chronic hepatitis B virus infection among hepatitis B e-antigen-negative women. World J Gastroenterol 2015;21:1261-1267.
3. Tsou PL, Lee HS, Jeng YM, Huang TS. Submassive liver necrosis in a hepatitis B carrier with Cushing's syndrome. J Formos Med Assoc 2002;101:156-158.
4. Dai MS, Chao TY, Kao WY, Shyu RY, Liu TM. Delayed hepatitis B

http://dx.doi.org/10.3350/cmh.2016.0024

virus reactivation after cessation of preemptive lamivudine in lymphoma patients treated with rituximab plus CHOP. Ann Hematol 2004;83:769-774.
5. Hsu C, Hsiung CA, Su IJ, Hwang WS, Wang MC, Lin SF, et al. A revisit of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in non-Hodgkin's lymphoma: a randomized trial. Hepatology 2008;47:844-853.
6. Lok AS, Liang RH, Chiu EK, Wong KL, Chan TK, Todd D. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. Gastroenterology 1991;100:182-188.
7. Liaw YF, Sheen IS, Chen TJ, Chu CM, Pao CC. Incidence, determinants and significance of delayed clearance of serum HBsAg in chronic hepatitis B virus infection: a prospective study. Hepatology 1991;13:627-631.
8. Bréchot C, Degos F, Lugassy C, Thiers V, Zafrani S, Franco D, et al. Hepatitis B virus DNA in patients with chronic liver disease and negative tests for hepatitis B surface antigen. N Engl J Med 1985;312:270-276.
9. Chemin I, Jeantet D, Kay A, Trépo C. Role of silent hepatitis B virus in chronic hepatitis B surface antigen(-) liver disease. Antiviral Res 2001;52:117-123.
10. Seto WK, Chan TS, Hwang YY, Wong DK, Fung J, Liu KS, et al. 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.
11. Pei SN, Ma MC, Wang MC, Kuo CY, Rau KM, Su CY, et al. Analysis of hepatitis B surface antibody titers in B cell lymphoma patients after rituximab therapy. Ann Hematol 2012;91:1007-1012.
12. Cho Y, Yu SJ, Cho EJ, Lee JH, Kim TM, Heo DS, et al. High titers of anti-HBs prevent rituximab-related viral reactivation in resolved hepatitis B patient with non-Hodgkin's lymphoma. J Med Virol 2016;88:1010-1017.
13. Mikulska M, Nicolini L, Signori A, Rivoli G, Del Bono V, Raiola AM, et al. Hepatitis B reactivation in HBsAg-negative/HBcAb-positive allogeneic haematopoietic stem cell transplant recipients: risk factors and outcome. Clin Microbiol Infect 2014;20:1040-1046.
14. Yeo W, Chan PK, Hui P, Ho WM, Lam KC, Kwan WH, et al. Hepatitis B virus reactivation in breast cancer patients receiving cytotoxic chemotherapy: a prospective study. J Med Virol 2003;70:553-561.
15. Yeo W, Chan PK, Zhong S, Ho WM, Steinberg JL, Tam JS, et al. 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.
16. Hoofnagle JH. Reactivation of hepatitis B: definition and terminology. Emerging Trends Conference on HBV Reactivation. Crystal City, VA, USA 2013;17-20.
17. Wands JR, Chura CM, Roll FJ, Maddrey WC. Serial studies of hepatitis-associated antigen and antibody in patients receiving antitumor chemotherapy for myeloproliferative and lymphoproliferative disorders. Gastroenterology 1975;68:105-112.
18. Paul S, Saxena A, Terrin N, Viveiros K, Balk EM, Wong JB. Hepatitis B virus reactivation and prophylaxis during solid tumor chemotherapy: a systematic review and meta-analysis. Ann Intern Med 2016;164:30-40.
19. Liu WP, Wang XP, Zheng W, Ping LY, Zhang C, Wang GQ, et al. Hepatitis B virus reactivation after withdrawal of prophylactic antiviral therapy in patients with diffuse large B cell lymphoma. Leuk Lymphoma 2016;57:1355-1362.
20. Faggioli P, De Paschale M, Tocci A, Luoni M, Fava S, De Paoli A, et al. Acute hepatic toxicity during cyclic chemotherapy in non Hodgkin's lymphoma. Haematologica 1997;82:38-42.
21. Tsutsumi Y, Kawamura T, Saitoh S, Yamada M, Obara S, Miura T, et al. Hepatitis B virus reactivation in a case of non-Hodgkin's lymphoma treated with chemotherapy and rituximab: necessity of prophylaxis for hepatitis B virus reactivation in rituximab therapy. Leuk Lymphoma 2004;45:627-629.
22. Yeo W, Chan TC, Leung NW, Lam WY, Mo FK, Chu MT, et al. Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. J Clin Oncol 2009;27:605-611.
23. Kim SJ, Hsu C, Song YQ, Tay K, Hong XN, Cao J, et al. Hepatitis B virus reactivation in B-cell lymphoma patients treated with rituximab: analysis from the Asia Lymphoma Study Group. Eur J Cancer 2013;49:3486-3496.
24. Matsui T, Kang JH, Nojima M, Tomonari A, Aoki H, Yamazaki H, et al. Reactivation of hepatitis B virus in patients with undetectable HBsAg undergoing chemotherapy for malignant lymphoma or multiple myeloma. J Med Virol 2013;85:1900-1906.
25. Sperl J, Frankova S, Kieslichova E, Oliverius M, Janousek L, Honsova E, et al. Urgent liver transplantation for chemotherapy-induced HBV reactivation: a suitable option in patients recently treated for malignant lymphoma. Transplant Proc 2013;45:2834-2837.
26. Lu S, Xu Y, Mu Q, Cao L, Chen J, Zhu Z, et al. The risk of hepatitis B virus reactivation and the role of antiviral prophylaxis in hepatitis B surface antigen negative/hepatitis B core antibody positive patients with diffuse large B-cell lymphoma receiving rituximab-based chemotherapy. Leuk Lymphoma 2015;56:1027-1032.
27. Hsu C, Tsou HH, Lin SJ, Wang MC, Yao M, Hwang WL, et al. Chemotherapy-induced hepatitis B reactivation in lymphoma patients with resolved HBV infection: a prospective study. Hepatology 2014;59:2092-2100.
28. Yang F, Zhu HL, He C, Li JJ, Xiang B, Cui X, et al. Effect of antiviral prophylaxis strategy for chemotherapy-associated hepatitis B reactivation in non-Hodgkin's lymphoma patients with hepatitis B virus infection: a retrospective cohort study. Indian J Hematol Blood Transfus 2014;30:97-104.

29. Chen KL, Chen J, Rao HL, Guo Y, Huang HQ, Zhang L, et al. Hepatitis B virus reactivation and hepatitis in diffuse large B-cell lymphoma patients with resolved hepatitis B receiving rituximab-containing chemotherapy: risk factors and survival. Chin J Cancer 2015;34:225-234.
30. Kusumoto S, Tanaka Y, Suzuki R, Watanabe T, Nakata M, Takasaki H, et al. Monitoring of hepatitis B virus (HBV) DNA and risk of HBV reactivation in B-cell lymphoma: a prospective observational study. Clin Infect Dis 2015;61:719-729.
31. Totani H, Kusumoto S, Ishida T, Masuda A, Yoshida T, Ito A, et al. Reactivation of hepatitis B virus (HBV) infection in adult T-cell leukemia-lymphoma patients with resolved HBV infection following systemic chemotherapy. Int J Hematol 2015;101:398-404.
32. Chen CY, Huang SY, Cheng A, Chou WC, Yao M, Tang JL, et al. High risk of hepatitis B reactivation among patients with acute myeloid leukemia. PloS One 2015;10:e0126037.
33. Pei SN, Chen CH. Risk and prophylaxis strategy of hepatitis B virus reactivation in patients with lymphoma undergoing chemotherapy with or without rituximab. Leuk Lymphoma 2015;56:1611-1618.
34. Galbraith RM, Eddleston AL, Williams R, Zuckerman AJ. Fulminant hepatic failure in leukaemia and choriocarcinoma related to withdrawal of cytotoxic drug therapy. Lancet 1975;2:528-530.
35. Ishiga K, Kawatani T, Suou T, Tajima F, Omura H, Idobe Y, et al. Fulminant hepatitis type B after chemotherapy in a serologically negative hepatitis B virus carrier with acute myelogenous leukemia. Int J Hematol 2001;73:115-118.
36. Marusawa H, Imoto S, Ueda Y, Chiba T. Reactivation of latently infected hepatitis B virus in a leukemia patient with antibodies to hepatitis B core antigen. J Gastroenterol 2001;36:633-636.
37. Ikeda K, Shiga Y, Takahashi A, Kai T, Kimura H, Takeyama K, et al. Fatal hepatitis B virus reactivation in a chronic myeloid leukemia patient during imatinib mesylate treatment. Leuk Lymphoma 2006;47:155-157.
38. Kang BW, Lee SJ, Moon JH, Kim SN, Chae YS, Kim JG, et al. Chronic myeloid leukemia patient manifesting fatal hepatitis B virus reactivation during treatment with imatinib rescued by liver transplantation: case report and literature review. Int J Hematol 2009;90:383-387.
39. Wang YD, Cui GH, Li M, Gowrea B, Xia J, Hu Y. Hepatitis B virus reactivation in a chronic myeloid leukemia patient treated with imatinib mesylate. Chin Med J (Engl) 2012;125:2636-2637.
40. 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.
41. Nakano N, Kusumoto S, Tanaka Y, Ishida T, Takeuchi S, Takatsuka Y, et al. Reactivation of hepatitis B virus in a patient with adult T-cell leukemia-lymphoma receiving the anti-CC chemokine receptor 4 antibody mogamulizumab. Hepatol Res 2014;44:354-357.
42. Türker K, Albayrak M, Öksüzoğlu B, Balc E, Oğan MC, Iskender G, et al. Entecavir as a first-line treatment for hepatitis B virus reactivation following polychemotherapy for chronic lymphocytic leukemia and invasive ductal carcinoma: a report of two cases and review of the literature. Eur J Gastroenterol Hepatol 2015;27:39-45.
43. Ando T, Kojima K, Isoda H, Eguchi Y, Honda T, Ishigami M, et al. Reactivation of resolved infection with the hepatitis B virus immune escape mutant G145R during dasatinib treatment for chronic myeloid leukemia. Int J Hematol 2015;102:379-382.
44. Dominguez N, Manzano ML, Muñoz R, Martin A, Fernandez I, Castellano G. Late reactivation of occult hepatitis B virus infection in a patient with chronic lymphocytic leukemia after rituximab and fludarabine-based regimen. Leuk Lymphoma 2014;56:1160-1163.
45. Yang JD, Girotra M, Restrepo A, Waheed S, Barlogie B, Duarte-Rojo A. Hepatitis B reactivation in patients with multiple myeloma and isolated positive hepatitis B core antibody: a call for greater cognizance. Ann Hepatol 2014;13:461-465.
46. Han JW, Yang H, Lee HL, Bae SH, Choi JY, Lee JW, et al. Risk factors and outcomes of hepatitis B virus reactivation in hepatitis B surface antigen negative patients with hematological malignancies. Hepatol Res 2015 Oct 7. [Epub ahead of pint]
47. Lee JY, Lim SH, Lee MY, Kim H, Sinn DH, Gwak GY, et al. Hepatitis B reactivation in multiple myeloma patients with resolved hepatitis B undergoing chemotherapy. Liver Int 2015;35:2363-2369.
48. Li J, Huang B, Li Y, Zheng D, Zhou Z, Liu J. Hepatitis B virus reactivation in patients with multiple myeloma receiving bortezomib-containing regimens followed by autologous stem cell transplant. Leuk Lymphoma 2015;56:1710-1017.
49. Lim ST, Fei G, Quek R, Lim LC, Lee LH, Yap SP, et al. The relationship of hepatitis B virus infection and non-Hodgkin's lymphoma and its impact on clinical characteristics and prognosis. Eur J Haematol 2007;79:132-137.
50. Dalia S, Suleiman Y, Croy DW, Sokol L. Association of Lymphomagenesis and the Reactivation of Hepatitis B Virus in Non-Hodgkin Lymphoma. Cancer Control 2015;22:360-365.
51. Liao CA, Lee CM, Wu HC, Wang MC, Lu SN, Eng HL. Lamivudine for the treatment of hepatitis B virus reactivation following chemotherapy for non-Hodgkin's lymphoma. Br J Haematol 2002;116:166-169.
52. Cheng AL, Hsiung CA, Su IJ, Chen PJ, Chang MC, Tsao CJ, et al. Steroid-free chemotherapy decreases risk of hepatitis B virus (HBV) reactivation in HBV-carriers with lymphoma. Hepatology 2003;37:1320-1328.
53. Wu CY, Hsiao LT, Chiou TJ, Gau JP, Liu JH, Yu YB, et al. Lymphocyte/monocyte ratio and cycles of rituximab-containing therapy are risk factors for hepatitis B virus reactivation in patients with diffuse large B-cell lymphoma and resolved hepatitis B. Leuk Lymphoma 2015;56:2357-2364.
54. Lakhani S, Davidson L, Priebat DA, Sherker AH. Reactivation of chronic hepatitis B infection related to imatinib mesylate therapy. Hepatol Int 2008;2:498-499.

http://dx.doi.org/10.3350/cmh.2016.0024

55. Thia TJ, Tan HH, Chuah TH, Chow WC, Lui HF. Imatinib mesylate-related fatal acute hepatic failure in a patient with chronic myeloid leukaemia and chronic hepatitis B infection. Singapore Med J 2008;49:e86-e89.
56. Bui N, Wong-Sefidan I. Reactivation of hepatitis B virus after withdrawal of erlotinib. Curr Oncol 2015;22:430-432.
57. Hussain S, Jhaj R, Ahsan S, Ahsan M, Bloom RE, Jafri SM. Bortezomib induced hepatitis B reactivation. Case reports in medicine. 2014;2014:964082.
58. Pompili M, Basso M, Hohaus S, Bosco G, Nosotti L, D'Andrea M, et al. Prospective study of hepatitis B virus reactivation in patients with hematological malignancies. Ann Hepatol 2015;14:168-174.
59. Locasciulli A, Bruno B, Alessandrino EP, Meloni G, Arcese W, Bandini G, et al. Hepatitis reactivation and liver failure in haemopoietic stem cell transplants for hepatitis B virus (HBV)/hepatitis C virus (HCV) positive recipients: a retrospective study by the Italian group for blood and marrow transplantation. Bone Marrow Transplant 2003;31:295-300.
60. Gupta A, Punatar S, Gawande J, Bagal B, Mathew L, Bhat V, et al. Hepatitis B-related serological events in hematopoietic stem cell transplant patients and efficacy of lamivudine prophylaxis against reactivation. Hematol Oncol 2015 Feb 18. [Epub ahead of print]
61. Nakamoto S, Kanda T, Nakaseko C, Sakaida E, Ohwada C, Takeuchi M, et al. Reactivation of hepatitis B virus in hematopoietic stem cell transplant recipients in Japan: efficacy of nucleos(t)ide analogues for prevention and treatment. Int J Mol Sci 2014;15:21455-1467.
62. Senecal D, Pichon E, Dubois F, Delain M, Linassier C, Colombat P. Acute hepatitis B after autologous stem cell transplantation in a man previously infected by hepatitis B virus. Bone Marrow Transplant 1999;24:1243-1244.
63. Dhédin N1, Douvin C, Kuentz M, Saint Marc MF, Reman O, Rieux C, et al. Reverse seroconversion of hepatitis B after allogeneic bone marrow transplantation: a retrospective study of 37 patients with pretransplant anti-HBs and anti-HBc. Transplantation 1998;66:616-619.
64. Ye YF, Xiang YQ, Fang F, Gao R, Zhang LF, Xie SH, et al. Hepatitis B virus infection and risk of nasopharyngeal carcinoma in southern China. Cancer Epidemiol Biomarkers Prev 2015;24:1766-1773.
65. Tan EH, Chua ET, Wee J, Tan T, Fong KW, Ang PT, et al. Concurrent chemoradiotherapy followed by adjuvant chemotherapy in Asian patients with nasopharyngeal carcinoma: toxicities and preliminary results. Int J Radiat Oncol Biol Phys 1999;45:597-601.
66. Yeo W, Hui EP, Chan AT, Ho WM, Lam KC, Chan PK, et al. Prevention of hepatitis B virus reactivation in patients with nasopharyngeal carcinoma with lamivudine. Am J Clin Oncol 2005;28:379-384.
67. Liu X, Li X, Jiang N, Lei Y, Tang LL, Chen L, et al. Prognostic value of chronic hepatitis B virus infection in patients with nasopharyngeal carcinoma: analysis of 1301 patients from an endemic area in China. Cancer 2014;120:68-76.
68. Yeo W, Lam KC, Zee B, Chan PS, Mo FK, Ho WM, et al. Hepatitis B reactivation in patients with hepatocellular carcinoma undergoing systemic chemotherapy. Ann Oncol 2004;15:1661-1666.
69. Lao XM, Zheng XR, Lin X. Hepatitis B virus reactivation and liver function after chemoembolization for hepatocellular carcinoma: How is it different from systemic chemotherapy? Asia Pac J Clin Oncol 2013;9:381-382.
70. Jang JW. Hepatitis B virus reactivation in patients with hepatocellular carcinoma undergoing anti-cancer therapy. World J Gastroenterol 2014;20:7675-7685.
71. Jang JW, Choi JY, Bae SH, Yoon SK, Chang UI, Kim CW, et al. A randomized controlled study of preemptive lamivudine in patients receiving transarterial chemo-lipiodolization. Hepatology 2006;43:233-240.
72. Peng JW, Lin GN, Xiao JJ, Jiang XM. Hepatitis B virus reactivation in hepatocellular carcinoma patients undergoing transcatheter arterial chemoembolization therapy. Asia Pac J Clin Oncol 2012;8:356-361.
73. Shao W, Zhang F, Cong N, Li J, Song J. The hepatitis B virus reactivation after transarterial chemoembolization in Chinese hepatocellular carcinoma patients with low serum hepatitis B virus DNA level. Ther Clin Risk Manag 2015;11:1367-1370.
74. Navarro R1, Concha-Garzón MJ, Castaño C, Casal C, Guiu A, Daudén E. Outcome of patients with serology suggestive of past hepatitis B virus infection during antitumor necrosis factor therapy for psoriasis. Int J Dermatol 2014;53:909-911.
75. Sanz-Bueno J, Vanaclocha F, García-Doval I, Torrado R, Carretero G, Daudén E, et al. Risk of reactivation of hepatitis B virus infection in psoriasis patients treated with biologics: a retrospective analysis of 20 cases from the BIOBADADERM database. Actas Dermosifiliogr 2015;106:477-482.
76. Gisbert JP, Chaparro M, Esteve M. Review article: prevention and management of hepatitis B and C infection in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2011;33:619-633.
77. Huang ML, Xu XT, Shen J, Qiao YQ, Dai ZH, Ran ZH. Prevalence and factors related to hepatitis B and C infection in inflammatory bowel disease patients in China: a retrospective study. J Crohns Colitis 2014;8:282-287.
78. Kim ES, Cho KB, Park KS, Jang BI, Kim KO, Jeon SW, et al. Prevalence of hepatitis-B viral markers in patients with inflammatory bowel disease in a hepatitis-B-endemic area: inadequate protective antibody levels in young patients. J Clin Gastroenterol 2014;48:553-558.
79. He Y, Xu P, Chen Y, Yang R, Chen B, Zeng Z, et al. Prevalence and influences of hepatitis B virus infection on inflammatory bowel disease: a retrospective study in southern China. Int J Clin Exp Med 2015;8:8078-8085.
80. Loras C, Gisbert JP, Minguez M, Merino O, Bujanda L, Saro C, et al. Liver dysfunction related to hepatitis B and C in patients with inflammatory bowel disease treated with immunosuppressive therapy.

Gut 2010;59:1340-1346.
81. Loras C, Gisbert JP, Saro MC, Piqueras M, Sanchez-Montes C, Barrio J, et al. Impact of surveillance of hepatitis b and hepatitis c in patients with inflammatory bowel disease under anti-TNF therapies: multicenter prospective observational study (REPENTINA 3). J Crohns Colitis 2014;8:1529-1538.
82. Esteve M, Saro C, González-Huix F, Suarez F, Forné M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. Gut 2004;53:1363-1365.
83. Ojiro K, Naganuma M, Ebinuma H, Kunimoto H, Tada S, Ogata H, et al. Reactivation of hepatitis B in a patient with Crohn's disease treated using infliximab. J Gastroenterol 2008;43:397-401.
84. Zeitz J, Mullhaupt B, Fruehauf H, Rogler G, Vavricka SR. Hepatic failure due to hepatitis B reactivation in a patient with ulcerative colitis treated with prednisone. Hepatology 2009;50:653-654.
85. Miyake Y, Hasebe A, Tanihira T, Shiraishi A, Imai Y, Tatsukawa H, et al. Hepatitis B virus reactivation induced by infliximab administration in a patient with Crohn's disease. Case Reports Hepatol 2013;2013:461879.
86. Ueno Y, Tanaka S, Shimamoto M, Miyanaka Y, Hiyama T, Ito M, et al. Infliximab therapy for Crohn's disease in a patient with chronic hepatitis B. Digestive diseases and sciences. 2005;50:163-166.
87. Millonig G, Kern M, Ludwiczek O, Nachbaur K, Vogel W. Subfulminant hepatitis B after infliximab in Crohn's disease: need for HBV-screening? World J Gastroenterol 2006;12:974-976.
88. Colbert C, Chavarria A, Berkelhammer C. Fulminant hepatic failure in chronic hepatitis B on withdrawal of corticosteroids, azathioprine and infliximab for Crohn's disease. Inflamm Bowel Dis 2007;13:1453-1454.
89. Esteve M, Loras C, González-Huix F. Lamivudine resistance and exacerbation of hepatitis B in infliximab-treated Crohn's disease patient. Inflamm Bowel Dis 2007;13:1450-1451.
90. Sacco R, Bertini M, Bresci G, Romano A, Altomare E, Capria A. Entecavir for hepatitis B virus flare treatment in patients with Crohn's disease. Hepatogastroenterology 2010;57:242-245.
91. Sanz I. Indications of rituximab in autoimmune diseases. Drug Discov Today Ther Strateg 2009;6:13-19.
92. Kato M, Atsumi T, Kurita T, Odani T, Fujieda Y, Otomo K, et al. Hepatitis B virus reactivation by immunosuppressive therapy in patients with autoimmune diseases: risk analysis in Hepatitis B surface antigen-negative cases. J Rheumatol 2011;38:2209-2214.
93. Dusheiko G, Song E, Bowyer S, Whitcutt M, Maier G, Meyers A, et al. Natural history of hepatitis B virus infection in renal transplant recipients--a fifteen-year follow-up. Hepatology 1983;3:330-336.
94. Bain VG. Hepatitis B in transplantation. Transpl Infect Dis 2000;2:153-165.
95. Gane E, Pilmore H. Management of chronic viral hepatitis before and after renal transplantation. Transplantation 2002;74:427-437.
96. Kletzmayr J, Watschinger B. Chronic hepatitis B virus infection in renal transplant recipients. Semin Nephrol 2002;22:375-389.
97. Berger A, Preiser W, Kachel HG, Sturmer M, Doerr HW. HBV reactivation after kidney transplantation. J Clin Virol 2005;32:162-165.
98. Murakami R, Amada N, Sato T, Orii T, Kikuchi H, Haga I, et al. Reactivation of hepatitis and lamivudine therapy in 11 HBsAg-positive renal allograft recipients: a single centre experience. Clin Transplant 2006;20:351-358.
99. Savas N, Colak T, Selcuk H, Yilmaz U, Haberal M. Clinical course of hepatitis B virus infection in renal allograft recipients. Dig Dis Sci 2007;52:3440-3443.
100. Fornairon S, Pol S, Legendre C, Carnot F, Mamzer-Bruneel MF, Brechot C, et al. The long-term virologic and pathologic impact of renal transplantation on chronic hepatitis B virus infection. Transplantation 1996;62:297-299.
101. Lucey MR, Terrault N, Ojo L, Hay JE, Neuberger J, Blumberg E, et al. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Liver Transpl 2013;19:3-26.
102. Thomas HC. Best practice in the treatment of chronic hepatitis B: a summary of the European Viral Hepatitis Educational Initiative (EVHEI). J Hepatol 2007;47:588-597.
103. Yeo W, Zee B, Zhong S, Chan PK, Wong WL, Ho WM, et al. Comprehensive analysis of risk factors associating with Hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. Br J Cancer 2004;90:1306-1311.
104. Zhong S, Yeo W, Schroder C, Chan PK, Wong WL, Ho WM, et al. High hepatitis B virus (HBV) DNA viral load is an important risk factor for HBV reactivation in breast cancer patients undergoing cytotoxic chemotherapy. J Viral Hepat 2004;11:55-59.
105. Shouval D, Shibolet O. Immunosuppression and HBV reactivation. Semin Liver Dis 2013;33:167-177.
106. Salpini R, Colagrossi L, Bellocchi MC, Surdo M, Becker C, Alteri C, et al. HBsAg genetic elements critical for immune escape correlate with HBV-reactivation upon immunosuppression. Hepatology 2015;61:823-833.
107. Colson P, Borentain P, Coso D, Motte A, Aurran-Schleinitz T, Charbonnier A, et al. Hepatitis B virus reactivation in HBsAg-negative patients is associated with emergence of viral strains with mutated HBsAg and reverse transcriptase. Virology 2015;484:354-363.
108. Inuzuka T, Ueda Y, Morimura H, Fujii Y, Umeda M, Kou T, et al. Reactivation from occult HBV carrier status is characterized by low genetic heterogeneity with the wild-type or G1896A variant prevalence. J Hepatol 2014;61:492-501.
109. 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

http://dx.doi.org/10.3350/cmh.2016.0024

therapy. Gastroenterology 2015;148:221-244 e3.
110. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT. American gastroenterological association institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 2015;148:215-219.
111. Dalakas MC. B cells as therapeutic targets in autoimmune neurological disorders. Nat Clin Pract Neurol. 2008;4:557-567.
112. Pei SN, Chen CH, Lee CM, Wang MC, Ma MC, Hu TH, et al. Reactivation of hepatitis B virus following rituximab-based regimens: a serious complication in both HBsAg-positive and HBsAg-negative patients. Ann Hematol 2010;89:255-262.
113. Nathan DM, Angus PW, Gibson PR. Hepatitis B and C virus infections and anti-tumor necrosis factor-alpha therapy: guidelines for clinical approach. J Gastroenterol Hepatol 2006;21:1366-1371.
114. Pérez-Alvarez R, Díaz-Lagares C, García-Hernández F, Lopez-Roses L, Brito-Zerón P, Pérez-de-Lis M, et al. Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: analysis of 257 cases. Medicine 2011;90:359-371.
115. Germanidis G, Hytiroglou P, Zakalka M, Settas L. Reactivation of occult hepatitis B virus infection, following treatment of refractory rheumatoid arthritis with abatacept. J Hepatol 2012;56:1420-1421.
116. Fanouriakis A, Vassilopoulos D, Repa A, Boumpas DT, Sidiropoulos P. Hepatitis B reactivation following treatment with abatacept in a patient with past hepatitis B virus infection. Rheumatology (Oxford) 2014;53:195-196.
117. Walker EJ, Simko JP, Ko AH. Hepatitis B viral reactivation secondary to imatinib treatment in a patient with gastrointestinal stromal tumor. Anticancer Res 2014;34:3629-3634.
118. Tur-Kaspa R, Shaul Y, Moore DD, Burk RD, Okret S, Poellinger L, et al. The glucocorticoid receptor recognizes a specific nucleotide sequence in hepatitis B virus DNA causing increased activity of the HBV enhancer. Virology 1988;167:630-633.
119. Hoofnagle JH, Davis GL, Pappas SC, Hanson RG, Peters M, Avigan MI, et al. A short course of prednisolone in chronic type B hepatitis. Report of a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1986;104:12-17.
120. Kim TW, Kim MN, Kwon JW, Kim KM, Kim SH, Kim W, et al. Risk of hepatitis B virus reactivation in patients with asthma or chronic obstructive pulmonary disease treated with corticosteroids. Respirology 2010;15:1092-1097.
121. Flowers MA, Heathcote J, Wanless IR, Sherman M, Reynolds WJ, Cameron RG, et al. Fulminant hepatitis as a consequence of reactivation of hepatitis B virus infection after discontinuation of low-dose methotrexate therapy. Ann Intern Med 1990;112:381-382.
122. Hagiyama H, Kubota T, Komano Y, Kurosaki M, Watanabe M, Miyasaka N. Fulminant hepatitis in an asymptomatic chronic carrier of hepatitis B virus mutant after withdrawal of low-dose methotrexate therapy for rheumatoid arthritis. Clin Exp Rheumatol 2004;22:375-376.
123. Andersen ES, Gerstoft J, Weis N. Reactivation of hepatitis D virus after chemotherapy for diffuse large B cell lymphoma despite lamivudine prophylaxis. Int J Hematol 2010;92:378-380.
124. Lim LL, Wai CT, Lee YM, Kong HL, Lim R, Koay E, et al. Prophylactic lamivudine prevents hepatitis B reactivation in chemotherapy patients. Aliment Pharmacol Ther 2002;16:1939-1944.
125. Gwak GY, Koh KC, Kim HY. Fatal hepatic failure associated with hepatitis B virus reactivation in a hepatitis B surface antigen-negative patient with rheumatoid arthritis receiving low dose methotrexate. Clin Exp Rheumatol 2007;25:888-889.
126. Simpson ND, Simpson PW, Ahmed AM, Nguyen MH, Garcia G, Keeffe EB, et al. Prophylaxis against chemotherapy-induced reactivation of hepatitis B virus infection with Lamivudine. J Clin Gastroenterol 2003;37:68-71.
127. Law JK, Ho JK, Hoskins PJ, Erb SR, Steinbrecher UP, Yoshida EM. Fatal reactivation of hepatitis B post-chemotherapy for lymphoma in a hepatitis B surface antigen-negative, hepatitis B core antibody-positive patient: potential implications for future prophylaxis recommendations. Leuk Lymphoma 2005;46:1085-1089.
128. Inoue T, Fuke H, Yamamoto N, Ito K, Yutaka KY, Yamanaka, et al. Lamivudine for treatment of spontaneous exacerbation and reactivation after immunosuppressive therapy in patients with hepatitis B virus infection. Hepatogastroenterology 2007;54:889-891.
129. Sanchez MJ, Buti M, Homs M, Palacios A, Rodriguez-Frias F, Esteban R. Successful use of entecavir for a severe case of reactivation of hepatitis B virus following polychemotherapy containing rituximab. J Hepatol 2009;51:1091-1096.
130. Okagawa Y, Takada K, Hisai H, Koshiba Y, Wada H, Miyazaki E, et al. Successful treatment with entecavir for reactivation of hepatitis B virus following systemic chemotherapy in a hepatitis B surface antigen-negative patient with colorectal cancer. Intern Med 2014;53:1759-1762.
131. Koskinas JS, Deutsch M, Adamidi S, Skondra M, Tampaki M, Alexopoulou A, et al. The role of tenofovir in preventing and treating hepatitis B virus (HBV) reactivation in immunosuppressed patients. A real life experience from a tertiary center. Eur J Intern Med 2014;25:768-771.
132. Huang YH, Hsiao LT, Hong YC, Chiou TJ, Yu YB, Gau JP, et al. Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. J Clin Oncol 2013;31:2765-2772.
133. Lau GK, Yiu HH, Fong DY, Cheng HC, Au WY, Lai LS, et al. Early is superior to deferred preemptive lamivudine therapy for hepatitis B patients undergoing chemotherapy. Gastroenterology 2003;125:1742-1749.
134. Long M, Jia W, Li S, Jin L, Wu J, Rao N, et al. A single-center, pro-

spective and randomized controlled study: Can the prophylactic use of lamivudine prevent hepatitis B virus reactivation in hepatitis B s-antigen seropositive breast cancer patients during chemotherapy? Breast Cancer Res Treat 2011;127:705-712.
135. Win LL, Powis J, Shah H, Feld JJ, Wong DK. Death from Liver Failure despite Lamivudine Prophylaxis during R-CHOP Chemotherapy due to Rapid Emergence M204 Mutations. Case Reports Hepatol 2013;2013:454897.
136. Loomba R, Rowley A, Wesley R, Liang TJ, Hoofnagle JH, Pucino F, et al. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. Ann Intern Med 2008;148:519-528.
137. Tang W, Chen L, Zheng R, Pan L, Gao J, Ye X, et al. Prophylactic effect of lamivudine for chemotherapy-induced hepatitis B reactivation in breast cancer: a meta-analysis. PloS one 2015;10:e0128673.
138. Martyak LA, Taqavi E, Saab S. Lamivudine prophylaxis is effective in reducing hepatitis B reactivation and reactivation-related mortality in chemotherapy patients: a meta-analysis. Liver Int 2008;28:28-38.
139. Ho EY, Yau T, Rousseau F, Heathcote EJ, Lau GK. Preemptive adefovir versus lamivudine for prevention of hepatitis B reactivation in chronic hepatitis B patients undergoing chemotherapy. Hepatol Int 2015;9:224-230.
140. Saab S, Dong MH, Joseph TA, Tong MJ. Hepatitis B prophylaxis in patients undergoing chemotherapy for lymphoma: a decision analysis model. Hepatology 2007;46:1049-1056.
141. Chen FW, Coyle L, Jones BE, Pattullo V. Entecavir versus lamivudine for hepatitis B prophylaxis in patients with haematological disease. Liver Int 2013;33:1203-1210.
142. Kojima H, Tsujimura H, Sugawara T, Mimura N, Ise M, Sakai C, et al. 521 Prospective Study of Hepatitis B Virus Reactivation in Hbsag-Negative Patients after Chemotherapy with Rituximab: HBV-DNA Monitoring and Entecavir Prophylaxis.[Abstract]. Hepatology 2012;56(Suppl 2):S206.
143. Li HR, Huang JJ, Guo HQ, Zhang X, Xie Y, Zhu HL, et al. Comparison of entecavir and lamivudine in preventing hepatitis B reactivation in lymphoma patients during chemotherapy. J Viral Hepat 2011;18:877-883.
144. Chen WC, Cheng JS, Chiang PH, Tsay FW, Chan HH, Chang HW, et al. A comparison of entecavir and lamivudine for the prophylaxis of hepatitis B virus reactivation in solid tumor patients undergoing systemic cytotoxic chemotherapy. PloS one 2015;10:e0131545.
145. Shang J, Wang H, Sun J, Fan Z, Huang F, Zhang Y, et al. A comparison of lamivudine vs entecavir for prophylaxis of hepatitis B virus reactivation in allogeneic hematopoietic stem cell transplantation recipients: a single-institutional experience. Bone Marrow Transplant 2016;51:581-586.
146. Endo T, Sakai T, Fujimoto K, Yamamoto S, Takashima H, Haseyama Y, et al. A possible role for lamivudine as prophylaxis against hepatitis B reactivation in carriers of hepatitis B who undergo chemotherapy and autologous peripheral blood stem cell transplantation for non-Hodgkin's lymphoma. Bone Marrow Transplant 2001;27:433-436.
147. Myers RP, Swain MG, Urbanski SJ, Lee SS. Reactivation of hepatitis B e antigen-negative chronic hepatitis B in a bone marrow transplant recipient following lamivudine withdrawal. Can J Gastroenterol 2001;15:599-603.
148. Hsiao LT, Chiou TJ, Liu JH, Chu CJ, Lin YC, Chao TC, et al. Extended lamivudine therapy against hepatitis B virus infection in hematopoietic stem cell transplant recipients. Biol Blood Marrow Transplant 2006;12:84-94.
149. Moses SE, Lim ZY, Sudhanva M, Devereux S, Ho AY, Pagliuca A, et al. Lamivudine prophylaxis and treatment of hepatitis B Virus-exposed recipients receiving reduced intensity conditioning hematopoietic stem cell transplants with alemtuzumab. J Med Virol 2006;78:1560-1563.
150. Aoki J, Kimura K, Kakihana K, Ohashi K, Sakamaki H. Efficacy and tolerability of Entecavir for hepatitis B virus infection after hematopoietic stem cell transplantation. SpringerPlus 2014;3:450.
151. Hashino S, Nozawa A, Izumiyama K, Yonezumi M, Chiba K, Kondo T, et al. Lamivudine treatment for reverse seroconversion of hepatitis B 4 years after allogeneic bone marrow transplantation. Bone Marrow Transplant 2002;29:361-363.
152. European Association For The Study Of The Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012;57:167-185.
153. Liaw YF, Kao JH, Piratvisuth T, Chan HL, Chien RN, Liu CJ, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. Hepatol Int 2012;6:531-561.
154. Weinbaum CM, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR Recomm Rep 2008;57:1-20.
155. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009;50:661-662.
156. Artz AS, Somerfield MR, Feld JJ, Giusti AF, Kramer BS, Sabichi AL, et al. American Society of Clinical Oncology provisional clinical opinion: chronic hepatitis B virus infection screening in patients receiving cytotoxic chemotherapy for treatment of malignant diseases. J Clin Oncol 2010;28:3199-3202.
157. Yeo W, Ho WM, Hui P, Chan PK, Lam KC, Lee JJ, et al. Use of lamivudine to prevent hepatitis B virus reactivation during chemotherapy in breast cancer patients. Breast Cancer Res Treat 2004;88:209-215.
158. Kim MK, Ahn JH, Kim SB, Im YS, Lee SI, Ahn SH, et al. Hepatitis B reactivation during adjuvant anthracycline-based chemotherapy in

http://dx.doi.org/10.3350/cmh.2016.0024

patients with breast cancer: a single institution's experience. Korean J Intern Med 2007;22:237-243.
159. Jang JW, Kim YW, Lee SW, Kwon JH, Nam SW, Bae SH, et al. Reactivation of hepatitis B virus in HBsAg-negative patients with hepatocellular carcinoma. PloS one 2015;10:e0122041.
160. Lee YH, Bae SC, Song GG. Hepatitis B virus reactivation in HBsAg-positive patients with rheumatic diseases undergoing anti-tumor necrosis factor therapy or DMARDs. Int J Rheum Dis 2013;16:527-531.
161. Urata Y, Uesato R, Tanaka D, Kowatari K, Nitobe T, Nakamura Y, et al. Prevalence of reactivation of hepatitis B virus replication in rheumatoid arthritis patients. Mod Rheumatol 2011;21:16-23.
162. Nakamura J, Nagashima T, Nagatani K, Yoshio T, Iwamoto M, Minota S. Reactivation of hepatitis B virus in rheumatoid arthritis patients treated with biological disease-modifying antirheumatic drugs. Int J Rheum Dis 2014 Apr 4. [Epub ahead of print]
163. Varisco V, Viganò M, Batticciotto A, Lampertico P, Marchesoni A, Gibertini P, et al. Low Risk of Hepatitis B Virus Reactivation in HBsAg-negative/Anti-HBc-positive Carriers Receiving Rituximab for Rheumatoid Arthritis: A Retrospective Multicenter Italian Study 2016 Feb 15. [Epub ahead of print]