Hepatitis B virus reactivation associated with immunosuppressive therapy

AUTHORS: Anna SF Lok, MD, Peter A L Bonis, MD
SECTION EDITOR: Rafael Esteban, MD
DEPUTY EDITOR: Jennifer Mitty, MD, MPH

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INTRODUCTION

The natural course of hepatitis B virus (HBV) infection is determined through the interplay between viral replication and the host's immune response. HBV persists in the body of all patients with infection, even those with evidence of serological recovery. Thus, individuals with a history of HBV infection who receive immunosuppressive therapy are at risk for HBV reactivation and a flare of their HBV disease. This can result in increased serum aminotransferase levels, fulminant hepatic failure, and/or death [1]. In addition, reactivation of HBV can lead to an interruption of immunosuppressive therapy (eg, chemotherapy), delaying treatment of the underlying disease.

This topic review will discuss the clinical manifestations, diagnosis, management, and prevention of HBV reactivation among those receiving immunosuppressive therapy. Discussions of HBV reactivation in the setting of hepatitis C treatment, and the clinical manifestations, diagnosis, and treatment of chronic HBV infection are found elsewhere:

- (See "Patient evaluation and selection for antiviral therapy for chronic hepatitis C virus infection".)
- (See "Overview of the management of chronic hepatitis C virus infection".)
- (See "Hepatitis B virus: Screening and diagnosis in adults".)
- (See "Hepatitis B virus: Clinical manifestations and natural history".)
- (See "Hepatitis B virus: Overview of management".)

HBV REACTIVATION

Overview — Prior to initiating immunosuppressive therapy, we test patients for evidence of hepatitis B virus (HBV) infection; for adults receiving glucocorticoids alone, we only screen those who will receive doses of prednisone ≥20 mg/day for at least four weeks. This approach to HBV screening, which tests patients for HBV regardless of their risk for infection, is supported by several guideline panels [2-7].

Serologic testing should include assessment of HBV core antibody (anti-HBc) and HBV surface antigen (HBsAg). We do not routinely check HBV surface antibody (anti-HBs), because this information is not used to determine if preventive therapy is indicated (the presence of anti-HBs decreases but does not eliminate the risk of HBV reactivation). (See 'HBsAg-negative' below.)

Depending upon the results of this initial testing, the following applies:

- All patients who are HBsAg positive should have baseline HBV DNA levels measured. Baseline HBV DNA testing should also be considered in patients who are HBsAg negative, anti-HBc positive (eg, those at moderate or high risk of reactivation). (See 'Categorizing level of risk' below and 'Preventing HBV reactivation' below.)

- If the patient is HBsAg positive, further testing for hepatitis B should include hepatitis B e antigen (HBeAg) and hepatitis B e antibody (anti-HBe), in addition to HBV DNA. They should also be tested for other concurrent infections, such as hepatitis D virus, hepatitis C virus, and HIV. (See "Hepatitis B virus: Clinical manifestations and natural history", section on 'Coinfection with HCV or HDV' and "Screening and diagnostic testing for HIV infection".)

- Patients without evidence of HBV should be vaccinated. If possible, vaccination should be administered before immunosuppressive treatment is started since vaccination may not be effective in patients who are immunosuppressed. (See "Hepatitis B virus immunization in adults".)

Among individuals with serologic evidence of HBV infection, the risk of HBV reactivation should be assessed to determine if preventive therapy should be administered. (See 'How to assess risk' below and 'Preventing HBV reactivation' below.)

HBV reactivation is diagnosed when there is an abrupt, marked increase in HBV replication. The criteria used to diagnose HBV reactivation are described below. (See 'Diagnosis of reactivation' below.)

Some individuals with HBV reactivation are asymptomatic and have normal liver chemistries. Others can have a flare of their HBV infection with increased aminotransferase levels and signs and symptoms of liver disease. On rare occasions, HBV flares can be fatal. (See 'HBV flare' below.)

Patients with HBV reactivation (with or without a flare) should be treated with entecavir or tenofovir. The duration of treatment depends upon the type of immunosuppressive therapy that is used, the HBV DNA level, and the degree of underlying liver disease. (See 'Management' below.)

Who is at risk for HBV reactivation — Patients with serologic evidence of HBV infection (HBsAg-positive or anti-HBc-positive) are at risk for HBV reactivation if they receive immunosuppressive therapy. Such patients include those being treated for malignancy or an autoimmune disorder, as well as those undergoing solid or hematopoietic stem cell transplantation.

- **Patients receiving chemotherapy** — HBV reactivation has been described in patients receiving cancer chemotherapy for a variety of hematologic and solid tumors [8-30]. HBV reactivation has also been reported in patients receiving chemoembolization for hepatocellular carcinoma and chemoradiation [12,13,25,31].

  The rate of HBV reactivation has been reported to be as high as 70 percent among HBsAg-positive individuals receiving standard chemotherapy [8-10,30]. In a systematic review of patients receiving chemotherapy for solid tumors, the risk of reactivation for patients who were HBsAg positive ranged from 4 to 68 percent, with most studies reporting a reactivation risk greater than 10 percent [30]. For those with resolved infection (defined as HBsAg-negative, anti-HBc-positive, HBV DNA-negative), reactivation ranged from 0.3 to 9.0 percent.

  While any chemotherapy regimen can potentially lead to HBV reactivation, the risk depends in part upon the type of regimen. The risk is higher with the use of regimens that include anti-CD20 monoclonal antibodies and/or glucocorticoids [32]. (See 'Type of immunosuppressive therapy' below.)

- **Patients being treated for autoimmune disorders** — Several reports describe HBV reactivation among patients with autoimmune conditions being treated with a variety of immunosuppressive agents. As examples:

  - Case series have demonstrated reactivation of HBV in patients with Crohn disease undergoing treatment with the tumor necrosis factor (TNF) inhibitor infliximab. As an

example, in a study of 80 patients with Crohn disease receiving infliximab, two of the three individuals identified as being HBsAg positive developed severe hepatitis (leading to one death) after withdrawal of infliximab therapy [33]. Reactivation was not observed in three patients who were HBV surface antibody (anti-HBs) positive with normal aminotransferases.

- Flares of hepatitis have also been described in a variety of patients being treated for other autoimmune conditions. In addition to TNF inhibitors [34-40], these patients received immunosuppressive drugs such as methotrexate (particularly following its withdrawal) [41-43], abatacept [44], and ustekinumab [45].

More detailed discussion of TNF inhibitors and anti-CD 20 agents are found below. (See 'Type of immunosuppressive therapy' below.)

- **Patients undergoing transplantation** — Reactivation of HBV replication can occur in patients undergoing solid organ or hematopoietic stem cell transplantation. Reactivation has occurred in patients who were HBsAg positive as well as in those who are HBsAg negative. Some HBsAg-negative patients undergoing allogeneic transplant have undergone seroreversion (ie, became HBsAg positive) [46]. (See "Kidney disease associated with hepatitis B virus infection" and "Liver transplantation in adults: Preventing hepatitis B virus infection in liver transplant recipients" and "Prophylaxis of infections in solid organ transplantation" and "Overview of infections following hematopoietic cell transplantation" and "Evaluation for infection before hematopoietic cell transplantation".)

Men appear to be at higher risk for HBV reactivation than women [15,47]. However, the level of risk depends mostly upon the patient's HBsAg status and the type of immunosuppressive agent(s) the patient receives. (See 'HBV serologic status' below and 'Type of immunosuppressive therapy' below and 'Categorizing level of risk' below.)

How to assess risk

HBV serologic status — The risk for HBV reactivation among those receiving immunosuppressive therapy depends upon the HBsAg status of the patient.

HBsAg-positive — Individuals who are HBsAg positive are at greater risk for HBV reactivation compared with those who are HBsAg negative. HBsAg-positive individuals who are hepatitis B e antigen (HBeAg) positive and/or have high baseline levels of HBV DNA may be at highest risk [11,14]. As an example, one report evaluated 137 consecutive patients (23 HBsAg-positive, 37 anti-HBs-positive, and 77 with no serologic evidence of HBV) who underwent hematopoietic cell transplantation [14]. Hepatitis developed in 32 patients (23 percent) with a

mean onset 136 days after transplantation, and resulted from HBV reactivation in 13 of the 32 patients (40 percent). Hepatitis due to HBV reactivation was significantly more common in HBsAg-positive patients compared with HBsAg-negative patients (hazard ratio 33, 95% CI 7.35-142.86). The most important risk factor for reactivation was a HBV DNA level of $>10^5$ copies/mL (approximately 10^4 international units/mL).

HBsAg-negative — Patients who have resolved infection (ie, HBsAg-negative, anti-HBc-positive) are also at risk for reactivation with immunosuppressive therapy. Most reports of reactivation in HBsAg-negative individuals occur in those receiving anti-CD20 agents (eg, rituximab) or bone marrow/hematopoietic stem cell transplant [48-50]. (See 'Type of immunosuppressive therapy' below.)

Reactivation can occur even in persons who are anti-HBs positive. However, patients who have detectable anti-HBs have a lower risk of HBV reactivation [44,47,48]. As an example, in a prospective study evaluating the risk of HBV reactivation in 150 HBsAg-negative and anti-HBc-positive patients undergoing chemotherapy with a rituximab-containing regimen for lymphoma, HBV reactivation occurred in 9 of the 116 patients (8 percent) who were positive for anti-HBs at baseline and 8 of the 35 (23 percent) who were negative for anti-HBs [48].

Type of immunosuppressive therapy — The risk for HBV reactivation also depends upon the immunosuppressive agent(s) used. A more detailed discussion on the level of risk is found below. (See 'Categorizing level of risk' below.)

The number of drugs that are associated with HBV reactivation is constantly expanding. Such agents include traditional chemotherapeutic agents and glucocorticoids, as well as biologic agents (eg, anti-CD 20 agents, anti-TNF agents), and new classes of drugs, such as tyrosine kinase inhibitors and mechanistic target of rapamycin (mTOR)-inhibitors. (See "Overview of biologic agents in the rheumatic diseases" and "Pharmacology of mammalian (mechanistic) target of rapamycin (mTOR) inhibitors".)

As examples:

- **Anti-CD 20 agents** – The US Food and Drug Administration has issued boxed warnings for the monoclonal anti-CD20 antibodies rituximab and ofatumumab regarding an increased risk of hepatitis B reactivation among patients positive for HBsAg or anti-HBc [51]. This warning is based upon several reports, including meta-analyses that have described severe hepatitis flares with these agents [19,47,52-54]. (See 'HBV flare' below.)

  In HBsAg-positive patients, the risk of HBV reactivation with rituximab is not well defined, but in a meta-analysis of patients with lymphoproliferative diseases, it ranged from 16 to

80 percent [52]. Most experts believe that anti-CD20 agents are associated with the highest risk of HBV reactivation among immunosuppressive therapies [8]. (See 'Categorizing level of risk' below.)

For HBsAg-negative patients, reports of HBV reactivation have ranged from 3 to 41 percent among those receiving a regimen of rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (R-CHOP) [8,10,49]. In a meta-analysis of 15 studies, the estimated risk of clinical HBV reactivation (defined as an increase in alanine transaminase [ALT] to greater than three times the upper limit of normal and either a documented increase in HBV DNA from baseline or HBsAg seroreversion) was approximately 6 percent in those receiving rituximab for lymphoma [55]. The frequency of reactivation may be lower for HBsAg-negative patients receiving treatment for rheumatologic conditions [56], although there are insufficient data to adequately assess this risk. For such patients, the "lower" risk may be related to differences in other concomitant immunosuppressive agents used in rheumatology versus oncology patients.

More detailed discussions of anti-CD20 agents are found elsewhere. (See "Rituximab: Principles of use and adverse effects in rheumatoid arthritis" and "Initial treatment of advanced stage diffuse large B cell lymphoma".)

- **Glucocorticoids** – Among HBsAg-positive patients receiving glucocorticoids, HBV reactivation has occurred with both high-dose, rapidly tapered regimens and moderate-dose, prolonged regimens [8]. However, reactivation has not been well described with low-dose regimens (ie, <20 mg of prednisone per day), even over prolonged periods.

  HBV replication increases in the presence of glucocorticoids. The increased viral replication may be due, in part, to a glucocorticoid responsive element in the HBV genome that stimulates viral replication and transcriptional activity [57]. Despite the increase in viral replication, serum aminotransferases tend to decline. The opposite occurs once glucocorticoids are withdrawn; viral replication declines while aminotransferases increase [57-60]. The peak rise in aminotransferases typically occurs four to six weeks after withdrawal [61,62].

  The use of glucocorticoids can also increase the risk of HBV reactivation when they are administered as part of a chemotherapy regimen. As an example, in a study of 50 HBsAg-positive individuals with non-Hodgkin lymphoma who were randomly assigned to chemotherapy with or without glucocorticoids [63], the cumulative incidence of HBV reactivation at nine months was significantly lower for those who received the "steroid-

free" regimen (38 versus 73 percent). However, tumor response rate was also lower with the steroid-free regimen.

- **TNF inhibitors** – TNF inhibitors have also been associated with HBV reactivation. Most reports have been from small observational studies among those with Crohn disease, rheumatic diseases, and psoriasis [33-40,64,65]. (See 'Who is at risk for HBV reactivation' above.)

  Among HBsAg-positive patients, the frequency of HBV reactivation has ranged from 0 to 40 percent [8]. The use of concurrent or prior immunosuppressive therapy may impact the risk of reactivation [66].

  In contrast, HBV reactivation is uncommon in those who are HBsAg negative [8,36,56,66,67]. As an example, in a prospective study that followed 146 HBsAg-negative, anti-HBc-positive patients who were treated with a TNF inhibitor for a rheumatologic disease, none developed detectable HBV DNA levels over a median follow-up period of 56 months [56].

Categorizing level of risk — The estimated risk of reactivation is based upon a combination of the patient's serologic status (ie, HBsAg-positive or HBsAg-negative), as well as the type of immunosuppressive therapy that the patient will receive. The American Gastroenterological Association (AGA) and the American Association for the Study of Liver Diseases (AASLD) have attempted to categorize the level of risk for HBV reactivation among individuals receiving certain immunosuppressive agents [2,8,68].

The level of risk determines whether preventive therapy, rather than early detection and treatment, should be initiated. However, patients with chronic hepatitis B who meet treatment criteria should receive antiviral therapy, regardless of the type of immunosuppressive therapy they receive. For such patients, antiviral treatment should be continued after completing immunosuppressive therapy until a therapeutic endpoint is reached. (See 'Preventing HBV reactivation' below and "Hepatitis B virus: Overview of management", section on 'Indications for antiviral therapy' and "Hepatitis B virus: Overview of management", section on 'Duration and treatment endpoints'.)

The AGA and the AASLD differ regarding the level of risk for certain patients, in particular those who are HBsAg negative. We divide the estimated level of risk during immunosuppressive therapy into groups that are mostly consistent with the AASLD recommendations [68].

Very high risk — Patients are at very high risk of reactivation (>20 percent risk of reactivation) if they are HBsAg positive and are going to receive anti-CD20 therapy (ie, rituximab,

ofatumumab, obinutuzumab) or undergo hematopoietic cell transplantation.

High risk — Patients are considered at high risk for reactivation (11 to 20 percent risk of reactivation) if they are HBsAg positive and are going to receive high-dose glucocorticoids (eg, ≥20 mg/day for at least four weeks) or the anti-CD52 agent, alemtuzumab.

Moderate risk — HBsAg-positive individuals are at moderate risk of reactivation (1 to 10 percent) if they are going to receive any of the following: cytotoxic chemotherapy **without** glucocorticoids; anti-TNF therapy; or anti-rejection therapy for solid organ transplants.

Patients who are HBsAg negative and anti-HBc positive are at moderate risk for reactivation if they are going to receive anti-CD20 therapy or undergo hematopoietic cell transplantation.

Low risk — HBsAg-positive individuals are at low risk (<1 percent) for reactivation if they receive methotrexate or azathioprine. HBsAg-negative and anti-HBc-positive individuals are at low risk if they receive high-dose glucocorticoids (eg, ≥20 mg/day) or the anti-CD52 agent alemtuzumab.

Very low risk — HBV reactivation occurs rarely in HBsAg-negative and anti-HBc-positive patients receiving the following: cytotoxic chemotherapy without glucocorticoids, anti-TNF therapy, methotrexate, or azathioprine.

Uncertain risk — There are certain groups in which the risk of reactivation remains uncertain. As an example, the available data suggest that patients with resolved infection (HBsAg-negative and anti-HBc-positive) undergoing solid organ transplant may be at low risk for reactivation, but the magnitude of risk has not been well defined and may be impacted by the type of immunosuppressive therapy that is being used. As a result, the approach to preventing HBV reactivation in such patients varies. (See 'Preventing HBV reactivation' below.)

Clinical manifestations of reactivation — Most patients with HBV reactivation are asymptomatic, and the only manifestation is an increase in the HBV DNA level. (See 'Diagnosis of reactivation' below.)

Other patients can have a flare of their HBV infection with increased aminotransferase levels, with or without clinical signs and symptoms (eg, nausea, vomiting). Severe flares can be associated with jaundice, hepatic decompensation, and death; poor outcomes are more likely to occur in patients who have underlying cirrhosis. (See 'HBV flare' below and "Hepatitis B virus: Clinical manifestations and natural history".)

Diagnosis of reactivation — HBV reactivation is diagnosed by an increase in HBV DNA. HBV DNA is measured as a part of routine screening for certain individuals receiving

immunosuppressive therapy (see 'Early detection and treatment' below). HBV DNA may also be obtained as part of the evaluation of abnormal liver chemistry tests. (See 'Differential diagnosis' below.)

HBV reactivation is typically diagnosed when a patient with serologic evidence of HBV has [6,8]:

- A detectable HBV DNA level when they previously had undetectable HBV DNA
- A >1 to 2 logarithmic (10- to 100-fold) increase in HBV DNA
- Seroreversion (when a patient previously HBsAg negative/anti-HBc positive becomes HBsAg positive)

Treatment of HBV reactivation

Antiviral therapy — We recommend antiviral treatment for all patients who develop HBV reactivation. Among those who are asymptomatic, the goal is to prevent a flare of their disease. Severe hepatitis and/or hepatic failure can develop in up to 25 to 50 percent of patients with HBV reactivation [69,70], and limited data suggest that this risk may be greater in patients with hematologic malignancies and/or those receiving rituximab-based chemotherapy [70]. (See 'HBV flare' below.)

- We suggest that tenofovir or entecavir be administered to patients who are treatment naïve. There are two formulations of tenofovir, tenofovir alafenamide and tenofovir disoproxil fumarate. We prefer these agents, rather than lamivudine, since patients receiving lamivudine are at increased risk of developing drug-resistant virus. A more detailed discussion of these agents, including factors involved in regimen selection, is presented in a separate topic review. (See "Hepatitis B virus: Overview of management", section on 'Antiviral therapy'.)
- We prefer tenofovir, rather than entecavir, for patients who received prior lamivudine therapy. Entecavir monotherapy is associated with a high rate of resistance in lamivudine-refractory patients. (See "Entecavir in the treatment of chronic hepatitis B virus infection", section on 'Resistance'.)

If antiviral therapy is not started, these patients must be monitored closely.

Data on the efficacy of antiviral therapy in reducing morbidity and mortality in patients with HBV reactivation are scarce. Case reports have demonstrated clinical improvement with antiviral treatment in some patients, especially when treatment was administered early in the course [71-73]; however, progression to hepatic failure, liver transplantation, and death have also been

reported [15,48,74]. As an example, in one study of HBsAg-positive patients undergoing chemotherapy, lamivudine was initiated at the time of HBV virologic reactivation in eight patients [74]. Despite antiviral therapy, seven individuals subsequently developed hepatitis, including one who progressed to hepatic failure. (See 'Prognosis' below.)

Management of immunosuppression — For patients with HBV reactivation, antiviral therapy should be started as soon as possible. However, the need to interrupt immunosuppressive therapy should be considered on a case-by-case basis. As an example, for patients without or with only a mild hepatitis flare, immunosuppressive therapy may be continued, particularly if the underlying condition is life-threatening or severe. By contrast, for patients with a moderate or severe hepatitis flare, immunosuppressive or cancer chemotherapy may need to be temporarily reduced or held until the HBV DNA and ALT decrease to lower levels. (See 'HBV flare' below.)

Preventing HBV reactivation

Who should receive antiviral therapy — Antiviral therapy initiated concurrently or prior to immunosuppressive therapy can decrease the risk of HBV reactivation. Many studies have evaluated the efficacy of prophylactic therapy [9,31,74-85]. In a meta-analysis of 16 studies, 774 HBsAg-positive patients with solid tumors received antiviral prophylaxis during chemotherapy, and the risk of HBV reactivation (defined as a >10-fold increase in HBV DNA levels from baseline or an absolute increase >10^5 copies/mL) was reduced by approximately 90 percent (odds ratio [OR] 0.12 [95% CI 0.06 to 0.22]) [30]. Antiviral prophylaxis also reduced HBV-related hepatitis (OR 0.18 [95% CI 0.10 to 0.32]), and chemotherapy interruption (OR 0.10 [95% CI 0.04 to 0.27]); however, there was not a significant reduction in acute liver failure or death.

The decision to administer preventive therapy depends upon the level of risk (see 'Categorizing level of risk' above):

- **Moderate to very high risk** – We recommend that antiviral therapy be administered concurrently or prior to initiating immunosuppressive therapy to patients who are at moderate to very high risk of HBV reactivation. In such patients, we prefer preventive therapy, rather than waiting for evidence of reactivation, since studies in this population have demonstrated that antiviral therapy started after the onset of reactivation may not prevent a flare [9,31,48,74,77,78,80,81]. As an example, in one study, a flare occurred in 10 of 17 patients who developed HBV reactivation while being treated for lymphoma with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone. The flares developed after initiation of entecavir, and in 4 patients, the flares were severe [48]. Although preventive therapy has been best studied in the setting of chemotherapy, we

believe these findings can be extrapolated to other populations (eg, patients with Crohn disease or rheumatoid arthritis) who are also at risk for HBV reactivation. (See 'Who is at risk for HBV reactivation' above.)

There are no data to guide how long antiviral therapy should be administered before initiating immunosuppressive therapy. For most patients, we initiate antiviral treatment for HBV and immunosuppressive therapy concurrently [86]. However, for patients with a high baseline serum HBV DNA level (eg, >4 $\log_{10}$ international units/ml), we prefer to delay immunosuppressive therapy until the HBV DNA level is suppressed to <3 $\log_{10}$ international units/mL. If immunosuppressive therapy cannot be delayed until that point, the risks and benefits of immediate immunosuppressive therapy versus a delay until the HBV DNA is suppressed must be balanced.

- **Low risk or very low risk** – Among those at low risk or very low risk of reactivation, we perform frequent monitoring so that HBV reactivation can be detected early in its course and appropriate therapy can be initiated. There are no studies evaluating the use of preventive therapy in patients at low risk for HBV reactivation. (See 'Early detection and treatment' below.)

  However, in situations in which close monitoring is not possible, it may be safer to administer prophylactic antiviral even when the risk of reactivation is low. (See 'Which agents to use' below.)

- **Uncertain risk** – When the risk of HBV reactivation remains uncertain, the decision to initiate preventive antiviral therapy can vary, and there is no high-quality evidence to support one approach over another [6]. As an example, for certain solid organ transplant recipients (eg, kidney) with resolved HBV infection, some experts administer antiviral therapy to all recipients. However, others may administer prophylaxis only when the patient receives agents that are associated with a high risk of HBV reactivation (eg, B cell-depleting agents) or when the patient receives high-dose triple immunosuppressive therapy (eg, in the first 6 to 12 months post-transplant) or treatment for rejection. (See "Kidney transplantation in adults: Hepatitis B virus infection in kidney transplant recipients".)

Patients with chronic HBV who meet treatment criteria should receive antiviral therapy, regardless of the type of immunosuppressive therapy they receive. For such patients, antiviral treatment should be continued after completing immunosuppressive therapy until a therapeutic endpoint is reached. (See "Hepatitis B virus: Overview of management", section on

'Indications for antiviral therapy' and "Hepatitis B virus: Overview of management", section on 'Duration and treatment endpoints'.)

Which agents to use — We suggest tenofovir or entecavir as preventive therapy. Interferon should never be used. (See "Hepatitis B virus: Overview of management", section on 'Antiviral therapy'.)

Most experience with preventive therapy has been with the use of lamivudine [9,31,74-85,87]. However, tenofovir and entecavir are less likely to cause drug-resistant virus and are more likely to result in viral suppression compared with lamivudine. These findings are supported by the results of a randomized controlled trial of 121 HBsAg-positive patients receiving chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); baseline HBV DNA levels were $<10^3$, aminotransferase levels were normal, and no patient had previously received antiviral therapy [88]. Compared with lamivudine (100 mg/day), entecavir (0.5 mg/day) initiated one week prior to chemotherapy and then continued for six months after chemotherapy significantly reduced the rate of HBV reactivation (defined as a 10-fold increase in HBV DNA level or an absolute increase in HBV DNA levels of 10^5 or greater; 6.6 versus 30 percent) and HBV-related hepatitis (0 versus 13 percent). Although there are no trials comparing tenofovir with lamivudine, we believe that tenofovir (tenofovir alafenamide or tenofovir disoproxil fumarate) should perform as well as entecavir.

In addition, a retrospective analysis of 340 HBsAg-positive patients receiving R-CHOP found that those who received entecavir were significantly less likely to have HBV reactivation compared with those receiving lamivudine (6.3 versus 39 percent) [89].

Duration of therapy — The duration of therapy for treatment and prevention is the same and depends upon the type of immunosuppressive therapy, the patient's baseline HBV DNA level, and the degree of underlying liver disease.

In general, we suggest:

- Treatment be maintained for at least 6 months after withdrawal of immunosuppression (with the exception of anti-CD20 therapy).
- Treatment be maintained for at least 12 months after stopping anti-CD20 agents since there is a lag in the recovery of B cell function among such patients. (See "Rituximab: Principles of use and adverse effects in rheumatoid arthritis" and "Initial treatment of advanced stage diffuse large B cell lymphoma".)

Antiviral therapy may need to be continued long-term for patients who have undergone hematopoietic stem cell or solid organ transplantation since they often remain on chronic immunosuppressive medications. In addition, certain HBsAg-positive patients (eg, those with a baseline HBV DNA >2000 international units/mL or evidence of cirrhosis) may need prolonged treatment. (See "Hepatitis B virus: Overview of management" and "Hepatitis B virus: Overview of management", section on 'Indications for antiviral therapy'.)

However, the duration of preventive therapy is not well studied. The largest report included 46 patients who started lamivudine prior to initiation of chemotherapy and continued lamivudine for a median of 3.1 months after completion of chemotherapy [90]. HBV reactivation was observed in 11 patients (24 percent) after withdrawal of lamivudine, occurring in 50 percent of patients with a pre-chemotherapy HBV DNA level >10^4 copies/mL (approximately 2000 international units/mL) and 10 percent of those with lower levels.

Early detection and treatment — We suggest monitoring most patients at low risk or very low risk for HBV reactivation rather than administering preventive antiviral therapy. (See 'Who should receive antiviral therapy' above.)

We obtain HBV DNA and liver chemistries while immunosuppressive therapy is being administered and for six months after treatment is discontinued. Laboratory testing should be obtained every one to three months [6], although the optimal frequency of monitoring has not been established.

For patients with evidence HBV reactivation, antiviral therapy should be started as soon as possible. (See 'Diagnosis of reactivation' above and 'Treatment of HBV reactivation' above.)

HBV FLARE

Clinical and laboratory findings — Some patients who experience HBV reactivation will develop a hepatitis flare characterized by abnormal liver enzymes. A HBV flare is typically defined as a rise in aminotransferases with an alanine transaminase (ALT) that is at least three to five times the baseline value and more than two to three times the upper limit of normal [8,91]. Patients experiencing a flare may or may not experience clinical signs and symptoms of hepatitis. (See 'Clinical manifestations of reactivation' above.)

Flares can occur at various times during the course of immunosuppressive therapy. They can be seen while the patient is receiving immunosuppressive therapy (eg, patients receiving anti-rejection therapy after a solid organ transplant) or after withdrawal of therapy (eg, glucocorticoids, TNF-alpha inhibitors) [33,62]. Among patients receiving chemotherapy, flares

often occur during the gaps between cycles, most often after the first two to three cycles [15,16,92-94]. HBV DNA level increases while receiving immunosuppressive therapy or chemotherapy. When the immune system recovers, for example, between cycles of chemotherapy, liver cell injury and necrosis can result from immune-mediated damage to infected hepatocytes [68].

Determining if a flare is due to HBV reactivation — Patients with a flare secondary to HBV reactivation should have an increase in the ALT level that is consistent with a flare **and** evidence of HBV reactivation. (See 'Diagnosis of reactivation' above and 'Clinical and laboratory findings' above.)

Reconstitution of the immune system after withdrawal of immunosuppression may result in liver cell injury despite a decrease in HBV DNA. Thus, the serum HBV DNA may be low or undetectable when a patient with a flare is being evaluated; in this situation, it may be hard to confirm that HBV reactivation is the cause. Severe flares may also be accompanied by an increase in the IgM hepatitis B core antibody (IgM anti-HBc) titer, leading to misdiagnosis of acute HBV in patients who are not previously known to be HBsAg positive. An increase in alpha fetoprotein to levels >5000 ng/mL have also been reported [95,96].

Differential diagnosis — Patients receiving immunosuppressive therapy may have an increase in their HBV DNA and/or aminotransferase levels, as well as signs and symptoms of clinical hepatitis that can be attributed to etiologies other than HBV reactivation. These include:

- **Acute HBV** – Patients without a history of HBV infection may develop acute HBV with elevated aminotransferase levels. Similar to patients with a severe HBV flare, patients with acute HBV have an elevated IgM anti-HBc titer [97]. (See "Hepatitis B virus: Screening and diagnosis in adults", section on 'Acute hepatitis' and 'HBV flare' above.)

- **Immune clearance phase of chronic HBV** – HBeAg seroconversion (ie, patients who are HBeAg positive who become HBeAg negative) is frequently, but not always, accompanied by an abrupt increase in serum ALT. The rise in aminotransferase levels is believed to result from a sudden increase in immune-mediated lysis of infected hepatocytes. Similar to patients with HBV reactivation due to immunosuppressive therapy, such patients often have an elevation in serum HBV DNA. Thus, patients who are HBeAg positive at baseline should have their HBeAg repeated in the setting of a flare to determine if the increased ALT levels are associated with HBeAg clearance. A more detailed discussion on the natural history of HBV infection is found elsewhere. (See "Hepatitis B virus: Clinical manifestations and natural history", section on 'Phases of chronic HBV infection'.)

- **Emergence of drug resistance** – Some patients will develop an increase in their HBV DNA level while receiving antiviral medications for HBV. In this situation, it is possible that HBV resistance has developed. This is most likely to occur in treatment-naïve patients receiving lamivudine or treatment-experienced patients receiving entecavir. An HBV resistance test can be performed to determine if resistance has developed. Resistance to tenofovir has not been confirmed, and resistance to entecavir is rare in patients who have not been treated with lamivudine or telbivudine previously. (See "Entecavir in the treatment of chronic hepatitis B virus infection", section on 'Resistance' and "Tenofovir and adefovir for the treatment of chronic HBV infection", section on 'Risk of resistance' and "Hepatitis B virus: Overview of management", section on 'Persistent viremia/breakthrough infection'.)

- **Hepatotoxins** – Medications (including chemotherapy) and/or other toxins can cause hepatic injury. These include alcohol, drugs, and radiation toxicity. Such patients would have an increase in their transaminase levels and/or signs and symptoms of hepatitis without an elevated HBV DNA level. A discussion on drug-induced liver injury is found elsewhere. (See "Drug-induced liver injury" and "Chemotherapy hepatotoxicity and dose modification in patients with liver disease: Conventional cytotoxic agents" and "Chemotherapy hepatotoxicity and dose modification in patients with liver disease: Molecularly targeted agents".)

- **Infection with other viruses** – Patients with HBV infection may develop an increase in their aminotransferase levels as a result of an infection with a different virus. These include other hepatitis viruses (eg, A, C, D, or E), as well as those likely to cause disease in immunocompromised hosts (eg, cytomegalovirus and herpes viruses). The type of virus is typically determined through serology and polymerase chain reaction testing. (See "Hepatitis A virus infection in adults: Epidemiology, clinical manifestations, and diagnosis", section on 'Diagnosis' and "Screening and diagnosis of chronic hepatitis C virus infection" and "Hepatitis E virus infection" and "Overview of infections following hematopoietic cell transplantation" and "Infection in the solid organ transplant recipient".)

- **Other causes of liver disease** – Patients with malignancy are at risk for hepatic dysfunction related to their underlying disease or associated conditions. These include graft versus host disease, sinusoidal obstruction syndrome (hepatic veno-occlusive disease), acalculous cholecystitis, tumor infiltration or metastasis, sepsis, and/or infarction. (See "Clinical manifestations and diagnosis of chronic graft-versus-host disease", section on 'Liver' and "Acalculous cholecystitis: Clinical manifestations, diagnosis, and management" and "Ischemic hepatitis, hepatic infarction, and ischemic cholangiopathy", section on 'Hepatic infarction'.)

A more detailed discussion on the causes of abnormal liver function tests is found elsewhere. (See "Approach to the patient with abnormal liver biochemical and function tests".)

Management — Among patients experiencing a flare, antiviral treatment should be started as soon as HBV reactivation has been identified as the cause. The goal of antiviral therapy is to prevent progression to hepatic decompensation. (See 'Differential diagnosis' above and 'Treatment of HBV reactivation' above.)

The effects of antiviral therapy take time and may not prevent progression to hepatic decompensation if treatment is delayed until the patient shows evidence of severe liver disease (eg, jaundice or marked ALT increase). After initiation of therapy, patients should be monitored closely. Aminotransferase levels and prothrombin time should be monitored at least monthly until the ALT becomes normal; after that, laboratory monitoring can be performed every three months. Early referral to a transplant center should be considered in patients who appear to have a severe and progressive course, although transplant may not be feasible in patients with a malignancy. (See "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis".)

In addition to antiviral therapy, management may include adjusting the immunosuppressive regimen. (See 'Management of immunosuppression' above.)

Prognosis — Case reports have demonstrated clinical improvement with antiviral treatment in some patients who developed a flare of HBV, especially when treatment was administered early in the course [71-73]. However, other patients develop a severe HBV flare and die, even after initiation of treatment [48,71]. In addition, a severe flare may lead to an unnecessary interruption of therapy for the patient's underlying condition. Thus, we prefer strategies that initiate antiviral therapy before a flare occurs. (See 'Preventing HBV reactivation' above and 'Early detection and treatment' above.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Diagnosis of hepatitis B".)

SUMMARY AND RECOMMENDATIONS

- Before initiating immunosuppressive therapy (including prednisone monotherapy at doses ≥20 mg/day administered for more than four weeks), we test patients for evidence of

hepatitis B virus (HBV) infection. (See 'Overview' above and "Chemotherapy hepatotoxicity and dose modification in patients with liver disease: Conventional cytotoxic agents", section on 'Hepatitis B'.)

- Serologic testing should include assessment of HBV surface antigen (HBsAg) and HBV core antibody (anti-HBc). We do not routinely check HBV surface antibody (anti-HBs) since the presence of anti-HBs does not eliminate the risk of HBV reactivation. Additional testing (eg, HBV DNA) may be warranted depending upon the results. (See 'Overview' above.)

- Patients with serologic evidence of HBV infection (HBsAg-positive or anti-HBc-positive) are at risk for HBV reactivation if they receive immunosuppressive therapy. The level of risk is influenced by the HBsAg status and the type of immunosuppressive agent to be used. (See 'Who is at risk for HBV reactivation' above and 'How to assess risk' above and 'Categorizing level of risk' above.)

- Most patients with HBV reactivation are asymptomatic, and the only manifestation is an increase in the HBV DNA level. Other patients can have a flare of their HBV infection with increased aminotransferase levels, with or without clinical signs and symptoms (eg, nausea, vomiting). (See 'Clinical manifestations of reactivation' above and 'HBV flare' above.)

- HBV reactivation is diagnosed by an increase in HBV DNA or seroreversion, which precedes an increase in the alanine aminotransferase level (ALT). (See 'Diagnosis of reactivation' above and 'HBV flare' above.)

- For patients who have HBV reactivation (with or without an ALT increase), we recommend antiviral therapy (**Grade 1C**). If a patient is treatment-naïve, we suggest tenofovir or entecavir, rather than lamivudine (**Grade 2B**). We prefer tenofovir, rather than entecavir, for patients who received prior lamivudine therapy. If antiviral therapy is not started, these patients must be monitored closely. (See 'Treatment of HBV reactivation' above and 'Management' above.)

- For patients who are at moderate to very high risk of HBV reactivation, we recommend that antiviral therapy be administered prior to initiating immunosuppressive therapy (**Grade 1B**). For such patients, we suggest tenofovir or entecavir be administered, rather than lamivudine (**Grade 2B**). (See 'Preventing HBV reactivation' above.)

- For most patients at low risk or very low risk for HBV reactivation, we suggest monitoring closely for HBV reactivation, rather than administering preventive antiviral therapy (**Grade**

2C). We then initiate treatment if reactivation occurs. (See 'Who should receive antiviral therapy' above and 'Early detection and treatment' above.)

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Contributor Disclosures

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