American Gastroenterological Association Institute Guideline on
the Prevention and Treatment of Hepatitis B Reactivation During
Immunosuppressive Drug Therapy

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(AGA) headquarters in Bethesda, Maryland and pertinent disclosure are published with the report.
This document presents the official recommendations of the American Gastroenterological Association (AGA) on the prevention and treatment of hepatitis B reactivation during immunosuppressive therapy. The guideline was developed by the Clinical Practice and Quality Measures Committee (currently the Clinical Practice Guideline Committee) and approved by the AGA Governing Board. The guideline was developed utilizing a process outlined elsewhere.\(^1\) Briefly, the AGA process for developing clinical practice guidelines incorporates GRADE methodology\(^2\) and best practices as outlined by the Institute of Medicine.\(^3\)

GRADE methodology was utilized to prepare the background information for the guideline and the technical review which accompanies it. Optimal understanding of this guideline will be enhanced by reading applicable portions of the technical review. Four Members of the guideline panel, along with AGA support staff met in person with the authors of the technical review on May 31, 2014. The information in the technical review was discussed in a systematic manner facilitating subsequent creation of the guideline recommendations for or against each intervention. The strength of each recommendation was also rated as either strong or weak, (i.e. conditional).\(^4\)

Hepatitis B reactivation (HBVr) following immunosuppressive therapy is associated with significant morbidity and mortality. It is well recognized that this is a preventable consequence of hepatitis B infection. While the definition of HBVr has been variable in the literature, it is desirable that the end clinical manifestation of hepatic decompensation or acute liver failure be prevented. A spectrum of serological patterns indicate ongoing or recovered HBV infection and risk for HBVr among these groups varies depending upon the type of immunosuppression. Several aspects of HBVr prevention remain unclear including: the optimal population to screen,
in whom to use prophylaxis with HBV therapeutic agents, the best specific therapeutic agent to use, the duration of prophylaxis, and the type and duration of monitoring if prophylaxis is not used in those at risk. The technical review and guideline are an effort to help Investigators and practicing medical providers in addressing the key areas in HBVr. The technical review and guideline have not addressed the issue of flares of chronic HBV infection over time, HBVr in coinfection with human immunodeficiency virus infection and in solid organ transplantation or hematopoietic stem cell transplantation.

1: Should antiviral prophylaxis over no prophylaxis be used for prevention of HBVr (hepatitis B reactivation) with immunosuppression? 2: Is antiviral prophylaxis needed for HBsAg-negative, anti-HBc-positive patients who will undergo ISDT?

The pooled effect estimates of 5 randomized controlled trials (RCTs) evaluating antiviral prophylaxis in 139 HBsAg-positive or anti-HBc-positive patients versus 137 controls offered on-demand rescue treatment in the presence of HBVr demonstrate that prophylaxis was associated with an 87% relative risk reduction (RRR) of reactivation (95% CI: 70%-94%) and an 84% RRR (95% CI: 58%-94%) of HBV associated hepatitis flares. Although these effects were determined to be significant, the authors recognized that the relative magnitude of effect would be expected to occur across a risk gradient with different immunosuppressive drugs. Therefore,
The immunosuppressants were categorized into low, moderate, or high risk groups based on estimates of reactivation using available evidence.

The high risk group was defined by anticipated HBVr incidence in >10% of cases, and included:

1) HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive patients taking B cell depleting agents (e.g., rituximab, ofatumumab)

2) HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive patients taking anthracycline derivatives (e.g., doxorubicin, epirubicin)

3) HBsAg-positive/anti-HBc-positive patients taking high dose corticosteroids (≥20 mg prednisone daily or equivalent for a duration of ≥4 weeks).

Recommendation:

For patients at high risk: The AGA recommends antiviral prophylaxis over no prophylaxis in patients undergoing immunosuppressive drug therapy.

GRADE: Strong recommendation, moderate quality evidence.

Comments: Treatment should be continued for at least 6 months after discontinuation of immunosuppressive therapy (at least 12 months for B-cell depleting agents).

The moderate risk group was defined by anticipated HBVr incidence of 1-10% of cases, and included:

1) HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive patients taking TNF alpha inhibitors (e.g., etanercept, adalimumab, infliximab)

2) HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive patients taking other cytokine or integrin inhibitors (e.g., abatecept, usteknimab, natalizumab, vedolizumab)
3) HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive patients taking tyrosine kinase inhibitors (e.g., imatinib, nilotinib)

4) HBsAg-negative/anti-HBc-positive patients taking high-dose corticosteroids (≥20 mg prednisone daily or equivalent for duration of ≥4 weeks).

**Recommendation:**

*Patients at moderate risk:* The AGA suggests antiviral prophylaxis over monitoring in patients undergoing immunosuppressive drug therapy.

**GRADE:** Weak recommendation, moderate quality evidence.

**Comments:** Treatment should be continued for 6 months after discontinuation of immunosuppressive therapy. Patients who place a higher value on avoiding the long-term use of antiviral therapy and cost associated with its use and a lower value on avoiding the small risk of reactivation (particularly in those who are HBsAg-negative), may reasonably select no prophylaxis over antiviral prophylaxis.

The low risk group was defined by anticipated HBVr incidence of <1% of cases, and included:

1) HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive patients taking traditional immunosuppressive agents (e.g., azathioprine, 6-mercaptopurine, methotrexate)

2) HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive patients taking intra-articular corticosteroids

3) HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive patients taking corticosteroids for ≤1 week
Recommendation:

*Patients at low risk:* The AGA suggest against routinely using antiviral prophylaxis in patients undergoing immunosuppressive drug therapy.

GRADE: Weak recommendation, moderate quality evidence.

3: Does the presence of anti-HBs in addition to anti-HBc in HBsAg-negative patients confer additional protection against HBVr?

It has been suggested that the presence of anti-HBs antibodies may provide additional protection against reactivation. More than two thirds of anti-HBc-positive patients in the various studies had detectable anti-HBs. Among such patients, HBV reactivation was observed in 11 (4.3%), a frequency which is only slightly lower than the total group of anti-HBc-positive patients. The small number of cases did not allow comparison as to whether the patients who had anti-HBs had clinically less severe hepatitis. The effect of titer or level of anti-HBs on HBVr has not been well reported. Due to a lack of studies that have used anti-HBs titers to guide initiating antiviral prophylaxis or infer protection, it has been concluded that there is insufficient evidence to support the use of anti-HBs titers in making a recommendation regarding prophylaxis.

Recommendation:

The AGA suggests against using anti-HBs status to guide antiviral prophylaxis for any risk groups.

GRADE: Weak recommendation, very low quality evidence.
4: Is prophylactic treatment with third generation nucleos (t) ide analogues more effective than first or second generation nucleos (t) ide agents?

Lamivudine is associated with a high rate of drug resistance, particularly when used beyond one year. Rates of lamivudine resistance of 20% at one year and 30% at two years have been reported in non-immunocompromised patients and would be anticipated to be even higher in patients on immune suppressive drug treatment. A single randomized control trial of entecavir versus lamivudine prophylaxis shows decreased risk of hepatitis B reactivation, hepatitis B flare, and chemotherapy disruption with the use of entecavir over lamivudine.

Recommendation:

The AGA suggests antivirals with high barrier to resistance over lamivudine for prophylaxis in patients undergoing immunosuppressive drug therapy.

GRADE: Weak recommendation, moderate quality evidence.

Comments: Given the geographic variability in cost of antiviral therapy, those patients who put a higher value on the cost and a lower value on avoiding the potentially small risk of resistance development (particularly in those who have an undetectable viral load and who are expected to use antiviral prophylaxis for 6 months or less) may reasonably select the least expensive antiviral hepatitis B medication over more expensive antivirals but with higher barrier to resistance.

5: Is HBV DNA monitoring followed by on demand antiviral therapy associated with different outcomes than prophylactic antiviral therapy?
Monitoring HBV DNA during immunosuppressive therapy may allow for early detection and treatment of HBVr and the latter may attenuate liver injury and improve patient outcomes which differ little from those observed in patients given prophylactic antiviral therapy. The best evidence that improved outcomes are achievable with prophylactic antiviral therapy as opposed to deferred treatment comes from randomized, controlled trials that compare both means of drug administration. When taken collectively, data from the observational studies suggest that the overall rate of HBVr is considerably lower when prophylactic antiviral therapy is compared with on demand treatment. Most of these studies however are of poor quality, use differing definitions of HBV reactivation, and inconsistently report outcomes other than the frequency of reactivation, severe elevation of ALT, and reactivation-related death. Also, they differ in the regularity with which HBV DNA monitoring is carried out and in the methodology used for quantification, both of which can influence the timing at which HBVr is first appreciated. The observational studies do not allow valid cross comparisons between studies. In summary, the most appropriate HBV DNA monitoring interval needed to achieve good clinical outcomes with deferred antiviral therapy cannot be determined from existing data and concerns remain as to whether the intensity of monitoring achieved in highly resourced trials can successfully be reproduced in regular care. Cost of routine HBV DNA testing is a secondary but important practical issue. Further there are considerable added personnel resource requirements for monitoring the HBV DNA assay performed frequently. These issues would need to be addressed before implementation of a defined policy.

**Recommendation:**
The AGA makes no recommendation for a strategy of HBV DNA monitoring followed by rescue treatment as an alternative to antiviral prophylaxis.

GRADE: no recommendation – knowledge gap.

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**6: Is treatment of established hepatitis B reactivation with third generation nucleos (t) ide agents more effective than first or second generation drugs?**

There are no trials that allow direct comparison of the clinical effectiveness of third generation oral antivirals with earlier generation antivirals in patients who develop hepatitis B reactivation during immunosuppressive therapy. However, there is indirect evidence from seven randomized controlled trials that shows decreased drug failure and from one randomized control trial that shows decreased virologic resistance development at five years following the use of third generation drugs compared to lamivudine in non-immunosuppressed patients.

**Recommendation:**

The AGA recommends antivirals with high barrier to resistance over lamivudine for established hepatitis B reactivation in patients undergoing immunosuppressive drug therapy.

GRADE: Strong recommendation, moderate quality evidence
Should patients who will undergo long term immune suppressive drug therapy be screened for HBV before starting?

Studies investigating the impact of HBV screening in patients treated with immunosuppressive therapy are limited. Cost effectiveness studies of HBV screening in oncology patients have shown that screening is cost beneficial in non-Hodgkin’s lymphoma patients slated to receive rituximab and may be cost effective in breast cancer patients slated to receive adjuvant chemotherapy if HBV infection is prevalent. Furthermore a cost effectiveness study of HBV screening in the general population demonstrated that screening is cost effective even when the prevalence of HBV infection was as low as 0.3%. Deterrents to screening in this patient population remain the cost of testing, the remote possibility of false-positive screening results, and the potential emotional and financial impact of a new diagnosis of HBV infection. In contrast, the benefits of screening include early identification of chronic HBV infection or resolved HBV infection in patients who will be treated with immunosuppressive therapy such that prophylaxis can be utilized, if appropriate, to minimize the risk of reactivation and associated morbidity and mortality.

**Recommendation:**

*Patients at moderate or high risk:* The AGA recommends screening for HBV (HBsAg and anti-HBc, followed by a sensitive HBV DNA test if positive) in patients who will undergo immunosuppressive drug therapy.

GRADE: Strong recommendation, moderate quality evidence.
Patients at low risk: The AGA suggests against routinely screening for HBV in patients who will undergo immunosuppressive drug therapy and are at low risk for HBV.

GRADE: Weak recommendation, moderate quality evidence.

Comments: Patients belonging to populations with a baseline risk likely exceeding 2% for chronic HBV should be screened according to CDC and USPSTF recommendations.

Summary

Hepatitis B reactivation is increasingly recognized as a clinical problem and has associated significant morbidity and mortality. Managing the complexity of HBV involves screening of individuals at risk, stratifying patients for risk based on HBV serologic status and type of immunosuppressison, and careful consideration of the type of treatment to be used as prophylaxis. Using the GRADE framework, this guideline offers recommendations about screening, the use of immunoprophylaxis based on risk stratification, and the class of agents to be used. Despite the large number of published studies, in most cases our recommendations are weak because either the (1) quality of the available data and/or (2) the baseline risk for HBV is low or uncertain and/or (2) the balance of risks and benefits for a particular strategy does not overwhelmingly support its use. However, there are moderately robust data to support a strong recommendation for the use of prophylaxis in those at high risk of HBV. There is a large knowledge gap in making any recommendation on the strategy of monitoring HBV DNA and intervening with a therapeutic regimen after diagnosing HBV.

Recognizing these and other limitations, the recommendations included here represent a rigorous, evidenced based summary of extensive literature describing the prevention and
treatment of HBVr. Review of this guideline, plus the associated technical review, will facilitate
effective shared decision making with patients at risk for HBVr.

guideline-development-process (accessed 6/30/2014)

2. Sultan S, Falck-Ytter Y, Inadomi JM. The AGA institute process for developing clinical practice
guidelines part one: grading the evidence. Clinical Gastroenterology and Hepatology 2013;
11:329–332

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on Prevention and Treatment of Hepatitis B Reactivation During Immunosuppressive Drug
Therapy Gastroenterology 2014;xx:xxxx

5. Table 1 in Clinical Gastroenterology and Hepatology 2013; 11:329-32.

Table 1. GRADE Quality of Evidence, Strength of Recommendations, and Implications

<table>
<thead>
<tr>
<th>Implications of strong and conditional (weak) guideline recommendations</th>
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<tbody>
<tr>
<td>Strong recommendations</td>
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<tr>
<td>Patients: most people in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.</td>
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<tr>
<td>Clinicians: most patients should receive the recommended course of action. Adherence to this recommendation according to guidelines could be used as a quality criterion or a performance indicator.</td>
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<td>Policy makers: the recommendation can be adapted as a policy in most situations.</td>
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<tr>
<td>Conditional (weak) recommendations</td>
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<td>Patients: the majority of people in this situation would want the suggested course of action, but many would not. Decision aids are useful in helping individuals make decisions consistent with their values and preferences.</td>
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<tr>
<td>Clinicians: examined a summary of the evidence to help patients make a decision that is consistent with their own values and preferences (shared decision making).</td>
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<tr>
<td>Policy makers: there is a need for substantial debate and involvement of stakeholders.</td>
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