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AGA SECTION

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

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This document presents the official recommendations of the American Gastroenterological Association (AGA) on the prevention and treatment of hepatitis B virus reactivation (HBVr) 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 using a process outlined elsewhere.[1] Briefly, the AGA process for developing clinical practice guidelines incorporates Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology[2] and best practices as outlined by the Institute of Medicine.[3] GRADE methodology was used to prepare the background information for the guideline and the technical review that accompanies it (Table 1).[4] 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 (ie, conditional).[1]

HBVr after immunosuppressive therapy is associated with significant morbidity and mortality. It is well recognized that this is a preventable consequence of hepatitis B infection. Although the definition of HBVr has varied in the literature, it is desirable to prevent the end clinical manifestation of hepatic decompensation or acute liver failure. A spectrum of serological patterns indicates ongoing or recovered hepatitis B virus (HBV) infection, and the risk of HBVr among patients presenting with these serological patterns varies depending on 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, and HBVr in solid organ transplantation or hematopoietic stem cell transplantation.

1. Is Antiviral Prophylaxis Needed For Hepatitis B Surface Antigen–Positive Patients Who Will Undergo Immunosuppressive Drug Therapy?

2. Is Antiviral Prophylaxis Needed for Hepatitis B Surface Antigen–Negative, Antibody to Hepatitis B Core Antigen–Positive Patients Who Will Undergo Immunosuppressive Drug Therapy?

The pooled effect estimates of 5 randomized controlled trials evaluating antiviral prophylaxis in 139 hepatitis B surface antigen (HBsAg)-positive or antibody to hepatitis B core antigen (anti-HBc)–positive patients versus 137 controls offered on-demand rescue treatment in the presence of HBVr showed that prophylaxis was associated with an 87% relative risk reduction of reactivation (95% confidence interval, 70%–94%) and an 84% relative risk

Abbreviations used in this paper: **AGA, American Gastroenterological Association; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBVr, hepatitis B virus reactivation.**

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

Implications of strong and conditional (weak) guideline recommendations
- Strong recommendations
  - 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 patients make decisions consistent with their values and preferences.
  - 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.
  - Policy makers: The recommendation can be adapted as a policy in most situations.
- Conditional (weak) recommendations
  - 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 patients make decisions consistent with their values and preferences.
  - Clinicians: Examine a summary of the evidence to help patients make a decision that is consistent with their own values and preferences (shared decision making).
  - Policy makers: There is a need for substantial debate and involvement of stakeholders.

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reduction (95% confidence interval, 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 incidence of HBVr in >10% of cases and included the following:

1. HBsAg-positive/anti-HBc–positive or HBsAg-negative/anti-HBc–positive patients treated with B cell–depleting agents (eg, rituximab, ofatumumab)
2. HBsAg-positive/anti-HBc–positive patients treated with anthracycline derivatives (eg, doxorubicin, epirubicin)
3. HBsAg-positive/anti-HBc–positive patients treated with moderate-dose (10–20 mg prednisone daily or equivalent) or high-dose (>20 mg prednisone daily or equivalent) corticosteroids daily for ≥4 weeks.

The AGA recommends antiviral prophylaxis over no prophylaxis for patients at high risk undergoing immunosuppressive drug therapy. *(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 incidence of HBVr of 1% to 10% of cases and included the following:

1. HBsAg-positive/anti-HBc–positive or HBsAg-negative/anti-HBc–positive patients treated with tumor necrosis factor alpha inhibitors (eg, etanercept, adalimumab, certolizumab, infliximab)
2. HBsAg-positive/anti-HBc–positive or HBsAg-negative/anti-HBc–positive patients treated with other cytokine or integrin inhibitors (eg, abatacept, ustekinumab, natalizumab, vedolizumab)
3. HBsAg-positive/anti-HBc–positive or HBsAg-negative/anti-HBc–positive patients treated with tyrosine kinase inhibitors (eg, imatinib, nilotinib)
4. HBsAg-positive/anti-HBc–positive patients treated with low-dose (<10 mg prednisone daily or equivalent) corticosteroids for duration of ≥4 weeks
5. HBsAg-negative/anti-HBc–positive patients treated with moderate-dose (10–20 mg prednisone daily or equivalent) or high-dose (>20 mg prednisone daily or equivalent) corticosteroids daily for ≥4 weeks
6. HBsAg-negative/anti-HBc–positive patients treated with anthracycline derivatives (eg, doxorubicin, epirubicin).

The AGA suggests antiviral prophylaxis over monitoring for patients at moderate risk undergoing immunosuppressive drug therapy. (*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 long-term use of antiviral therapy and the 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 incidence of HBVr of <1% of cases and included the following:

1. HBsAg-positive/anti-HBc–positive or HBsAg-negative/anti-HBc–positive patients treated with traditional immunosuppressive agents (eg, azathioprine, 6-mercaptopurine, methotrexate)

2. HBsAg-positive/anti-HBc–positive or HBsAg-negative/anti-HBc–positive patients treated with intra-articular corticosteroids
3. HBsAg-positive/anti-HBc–positive or HBsAg-negative/anti-HBc–positive patients treated with any dose of oral corticosteroids daily for $\leq$1 week
4. HBsAg-negative/anti-HBc–positive patients treated with low-dose ($<$10 mg prednisone or equivalent) corticosteroids for $\geq$4 weeks.

The AGA suggests against routinely using antiviral prophylaxis in patients undergoing immunosuppressive drug therapy who are at low risk for HBVr. (*Weak recommendation; Moderate-quality evidence*)

3. Does the Presence of Antibody to Hepatitis B Surface Antigen in Addition to Anti-HBc in HBsAg-Negative Patients Confer Additional Protection Against HBVr?

It has been suggested that the presence of antibody to hepatitis B surface antigen (anti-HBs) 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, HBVr was observed in 11 (4.3%), a frequency that is only slightly lower than among 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.

The AGA suggests against using anti-HBs status to guide antiviral prophylaxis for all risk groups. (*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 1 year. Rates of lamivudine resistance of 20% at 1 year and 30% at 2 years have been reported in nonimmunocompromised patients and would be anticipated to be even higher in patients on immunosuppressive drug treatment. A single randomized controlled trial of entecavir versus lamivudine prophylaxis showed decreased risk of HBVr, hepatitis B flare, and disruption of chemotherapy with the use of entecavir over lamivudine.

The AGA suggests use of antiviral drugs with a high barrier to resistance over lamivudine for prophylaxis in patients undergoing immunosuppressive drug therapy. (*Weak recommendation; Moderate-quality evidence*)

Comments: ***Given the geographic variability in cost of antiviral therapy, those patients who put a higher value on 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) may reasonably select the least expensive antiviral hepatitis B medication over more expensive antiviral drugs with a higher barrier to resistance.***

5. Is HBV DNA Monitoring Followed by On-Demand Antiviral Therapy as Effective as Prophylactic Antiviral Therapy?

Monitoring HBV DNA levels 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 compared 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. However, most of these studies are of poor quality, use differing definitions of HBVr, and inconsistently report outcomes other than the frequency of reactivation, severe elevation of ALT level, and reactivation-related death. Also, they differ in the regularity with which HBV DNA monitoring is performed 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. The 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.

The AGA makes no recommendation for a strategy of HBV DNA monitoring followed by rescue treatment as an alternative to antiviral prophylaxis. (No recommendation – knowledge gap)

6. Is Treatment of Established HBVr 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 antiviral drugs with earlier-generation antiviral drugs in patients who develop HBVr during immunosuppressive therapy. However, there is indirect evidence from 7 randomized controlled trials that showed decreased drug failure and from one randomized control trial that showed decreased development of virological resistance at 5 years after the use of third-generation drugs compared with lamivudine in non-immunosuppressed patients.

The AGA recommends antiviral drugs with a high barrier to resistance over lamivudine for established HBVr in patients undergoing immunosuppressive drug therapy. (*Strong recommendation; Moderate-quality evidence*)

7. Should Patients Who Will Undergo Long-term Immunosuppressive Drug Therapy Be Screened for HBV Before Starting Treatment?

Studies investigating the impact of HBV screening in patients treated with immunosuppressive therapy are limited. Cost-effectiveness studies of HBV screening in patients with cancer have shown that screening is cost-beneficial in patients with non-Hodgkin lymphoma slated to receive rituximab and may be cost-effective in patients with breast cancer slated to receive adjuvant chemotherapy if HBV infection is prevalent. Furthermore, a cost-effectiveness study of HBV screening in the general population showed that screening is cost-effective even when the prevalence of HBV infection is 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 used, if appropriate, to minimize the risk of reactivation and associated morbidity and mortality.

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

The AGA suggests against routinely screening for HBV in patients who will undergo immunosuppressive drug therapy and are at low risk. (*Weak recommendation; Moderate-quality evidence*)

Comments: *Patients in populations with a baseline prevalence likely exceeding 2% for chronic HBV should be screened according to Centers for Disease Control and Prevention and US Preventive Services Task Force recommendations.*

Summary

HBVr is increasingly recognized as a clinical problem and has associated significant morbidity and mortality. Managing the complexity of HBVr involves screening patients at risk, stratifying patients for risk based on HBV serological status and type of immunosuppression, 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 (1) the quality of the available data and/or the baseline risk of HBVr 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 for HBVr. 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 HBVr.

Recognizing these and other limitations, the recommendations included here represent a rigorous, evidence-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.

References

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Conflicts of interest
All members were required to complete disclosure statements. These statements are maintained at the American Gastroenterological Association Institute headquarters in Bethesda, Maryland, and pertinent disclosures are published with the report.