Hepatitis B Virus Reactivation in the Setting of Immunosuppressive Drug Therapy

Jessica Su, MD, and Joseph K. Lim, MD

Dr Su is an internal medicine resident in the Department of Internal Medicine at Yale School of Medicine in New Haven, Connecticut. Dr Lim is a professor of medicine and director of the Viral Hepatitis Program in the Section of Digestive Diseases and Yale Liver Center at Yale School of Medicine.

Address correspondence to:
Dr Joseph K. Lim
Yale Liver Center
Section of Digestive Diseases
Yale School of Medicine
333 Cedar Street
LMP 1080
New Haven, CT 06520-8019
Tel: 203-737-6063
Fax: 203-785-7273
E-mail: joseph.lim@yale.edu

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Abstract: Chronic hepatitis B virus (HBV) infection remains a global health burden, affecting an estimated 257 million people, and is associated with substantial morbidity and mortality due to cirrhosis and hepatocellular carcinoma. Reactivation of HBV infection among individuals with resolved and/or chronic HBV infection may result in clinical hepatitis with a rise in serum HBV DNA and serum alanine aminotransferase, and delayed identification may result in fulminant hepatitis and fatal liver failure. Routine screening for HBV is recommended in patients undergoing immunosuppressive drug regimens known to be associated with HBV reactivation (HBVr). A subset of patients identified to have positive hepatitis B surface antigen and/or hepatitis B core antibody may require preemptive antiviral therapy to reduce the risk of HBVr. This article summarizes the current evidence and society guidelines governing the evaluation and management of HBVr in the context of cancer chemotherapy and immunosuppressive drug therapy.

It is estimated that up to one-third of people worldwide may have been infected with hepatitis B virus (HBV).[1-3] Despite new antiviral therapies that have been developed in the last 2 decades, current therapy for chronic HBV infection remains suppressive rather than curative. Not only does HBV infection remain one of the leading causes of chronic liver disease and hepatocellular carcinoma around the world, but many patients who have been infected with HBV are unaware of their exposure and risk for having chronic HBV infection.[1,4] Individuals infected with HBV are subsequently placed at increased risk of HBV reactivation (HBVr), whether through initiation of immunosuppressive drug therapy or chemotherapy or by undergoing an organ transplantation. Because HBVr can result in poor outcomes such as acute liver failure and death if undetected and untreated, identification and risk stratification of patients who are at increased risk of HBVr are essential to determine who would benefit from antiviral prophylaxis.

Hepatitis B Virus Reactivation

When discussing HBVr, baseline virologic profiles are separated into 2 broad categories: patients who are initially positive for hepatitis B surface antigen (HBsAg) in the serum with HBV DNA less than 2000 IU/mL in the serum, and patients who are initially negative for HBsAg and HBV DNA in the serum. Patients who are HBsAg-positive with an HBV DNA of 2000 IU/mL or greater have active chronic infection and may independently meet criteria for antiviral therapy. In patients who are HBsAg-positive with low (<2000 IU/mL) or undetectable baseline HBV DNA levels, or alternatively who have chronic occult HBV infection (HBsAg-negative/hepatitis B core antibody [HBcAb]-positive with detectable HBV DNA), HBVr is defined by the reappearance of HBV DNA and/or a rapid rise in HBV DNA levels by at least 100-fold from baseline. In contrast, HBVr in patients with resolved HBV infection based on negative HBsAg, positive HBcAb, and undetectable HBV DNA is defined on the basis of HBsAg seroreversion (HBsAg-negative to -positive) or recurrence of HBV DNA viremia.[1] Effectively, HBVr reflects a loss of immune control, the clinical impact of which can range from a subclinical rise in alanine aminotransferase (ALT) levels to fatal fulminant hepatitis.[5]

Identifying and risk-stratifying patients who are at increased risk of HBVr are important goals, as failure to start prophylaxis or delayed detection of HBVr may lead to severe hepatic injury and liver failure that may not be reversible even after initiation of antiviral therapy. Development of HBVr may also lead to interrupted or suboptimal immunosuppression.[6] This article aims to discuss current evidence and society guidelines addressing the screening, risk stratification, and prophylaxis for HBVr in patients receiving immunosuppressive therapies.

Hepatitis B Virus Reactivation in the Setting of Immunosuppressive Therapies

Immunosuppression is one of the main factors leading to increased risk of HBVr. Major categories for immunosuppressive agents include chemotherapy and cancer-related immunosuppression, autoimmune disease–related immunosuppression, and posttransplantation immunosuppression. With the increasing availability of direct-acting antiviral (DAA) agents for hepatitis C virus (HCV) therapy, HBVr has also been observed in patients with HBV/HCV coinfection. For the purposes of this article, HBVr after transplantation and immunosuppression will not be discussed in detail, as this topic is broad and nuanced, particularly when it pertains to transplantation of organs from HBV-infected donors.[4]

B-Cell–Depleting Agents and Cancer Chemotherapy

B-cell–depleting agents such as rituximab (Rituxan, Genentech), an anti-CD20 monoclonal antibody, are associated with a particularly high risk of HBVr. HBVr has been observed not only in patients with positive HBsAg but also in patients with negative HBsAg and resolved HBV infection.[7] B cells play a key role in humoral immune response, contributing to control of HBV infection by producing neutralizing antibodies that eliminate circulating viruses. However, T lymphocytes are thought to be the main drivers in suppression of HBV replication.[8] Therefore, the high incidence of HBVr in patients receiving B-cell–depleting agents suggests that B cells may also play a role in HBV immune control.[1] Other chemotherapeutic classes associated with moderate to high risk for HBVr include anthracycline derivatives, cytokine or integrin inhibitors, and tyrosine kinase inhibitors.

Direct-Acting Antiviral Agents for Hepatitis C Virus Therapy

HBVr has been rarely observed in patients with HBV/HCV coinfection receiving DAA therapy for HCV infection, but has typically occurred within 4 to 8 weeks after initiation of DAA therapy. Clinical manifestations range from asymptomatic to decompensated liver failure, liver transplantation, and death in some cases, despite initiation of HBV treatment after detection of HBVr.[5,9] DAA agents are not known to cause immunosuppression, and the mechanism by which DAA agents increase the risk of HBVr remains poorly understood. It has been proposed that HBV/HCV coinfection may result in viral interference that is favorable for control of HBV infection and that the milieu of the host immune system changes after initiation of DAA agents due to reduced immune surveillance. However, the underlying mechanisms of viral interference require further clarification.[10] The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America recommend that all patients starting DAA therapy for HCV infection should be screened for HBV coinfection. Patients who meet criteria for HBV infection treatment should be started on antiviral therapy if they are not already receiving HBV suppressive therapy. Patients who do not receive HBV infection therapy should undergo regular monitoring of serum liver function tests and/or HBV DNA during DAA therapy.[11]

Other classes of immunosuppressive therapies that are associated with HBVr include tumor necrosis factor–α inhibitors, histone deacetylase inhibitors, proteasome inhibitors, moderate- to high-dose corticosteroids, and

Table 1. Screening Tests for Hepatitis B Virus in the Context of Immunosuppressive Drug Therapy

Society	Recommended Screening Tests
American Association for the Study of Liver Diseases[24]	HBsAg and HBcAb
Centers for Disease Control and Prevention[13]	HBsAg, HBcAb, and HBsAb
American Gastroenterological Association[14]	HBsAg and HBcAb
American Society of Clinical Oncology[16]	HBsAg and HBcAb
European Association for the Study of the Liver[23]	HBsAg, HBcAb, and HBsAb

HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen.

traditional immunosuppressive agents (eg, azathioprine and methotrexate), particularly in the context of solid organ or hematopoietic stem cell transplantation.

Hepatitis B Virus Screening and Risk Stratification in Patients on Immunosuppression or Chemotherapy

Populations Requiring Hepatitis B Virus Screening

When considering which patients to screen for HBV infection, further risk stratification based on the type of immunotherapy or chemotherapy is necessary in addition to following general guidelines for HBV screening. The AASLD guidelines for general HBV screening include screening patients who (1) were born in countries with a high prevalence of HBV infection (HBsAg-positive in ≥2% of the population); (2) were not previously vaccinated and have parents born in regions with an 8% or higher prevalence of HBsAg; (3) have behaviors that increase the risk of HBV exposure (eg, intravenous drug use); (4) have household or sexual contact with someone who is HBsAg-positive or at increased risk of HBV infection; (5) are undergoing HCV treatment with DAA agents; (6) have abnormal liver function tests of unknown etiology; and (7) are immunosuppressed (including patients who have HIV, are on dialysis, are status post–organ transplantation, and are receiving chemotherapy and immunosuppressive therapy).[12] It is important to note that in addition to host risk factors included in other guidelines,[13-16] the AASLD, the American Gastroenterological Association (AGA), and the American Society of Clinical Oncology (ASCO) address the risk of HBVr associated with chemotherapy and immunosuppressive agents. Despite these guidance documents, multiple studies have revealed very low rates of HBV screening (14%-20%) among patients undergoing cancer chemotherapy in the United States,[17,18] Canada,[19] China,[20] and Japan.[21] In a large retrospective cohort study of 19,304 US veterans undergoing anti-CD20 therapy, which is associated with the highest risk for HBVr, only 53% of patients underwent HBsAg testing.[22] These results underscore the need for systems-based approaches to increasing HBV testing in patients undergoing immunosuppressive drug therapy.

Serologic Tests for Hepatitis B Virus Screening

Screening recommendations for HBV include HBsAg and HBcAb, followed by a sensitive HBV DNA test if positive (Table 1).[1,14,16] Recommendations from various societies are mixed with regard to the role of hepatitis B surface antibody (HBsAb) in addition to HBsAg and HBcAb. The Centers for Disease Control and Prevention[13] and the European Association for the Study of the Liver (EASL)[23] recommend HBsAb as part of screening while the AASLD,[24] ASCO,[16,25] and AGA[14] do not. Currently, there are limited data to support the utility of HBsAb titers in risk stratification for HBVr. Importantly, although the presence of HBsAb may be associated with a lower risk for HBVr among HBsAg-negative/HBcAb-positive individuals, HBsAb does not confer protection against HBVr and, therefore, is not recommended in risk stratification or the decision to pursue antiviral prophylaxis.[14]

Risk Stratification After Hepatitis B Virus Screening

As per the AGA guidance,[14] patients who have serologies indicating prior exposure to HBV with positive HBcAb and who are receiving chemotherapy or immunosuppressive therapy can be further stratified into high risk, moderate risk, or low risk depending on HBsAg status and the type of immunosuppression (Table 2).

The high-risk group is defined as having greater than a 10% risk of HBVr and includes individuals treated with B-cell–depleting agents such as rituximab or ofatumumab (Arzerra, Novartis), regardless of HBsAg status[1,14,26,27]; anthracycline derivatives such as doxorubicin or epirubicin, with positive HBsAg[1,14,28,29]; and 4 weeks or more of corticosteroids at moderate dose (10-20 mg prednisone daily or equivalent) or high dose (>20 mg prednisone daily or equivalent), with positive HBsAg.[1,14,30]

The moderate-risk group is defined as having a 1% to 10% risk of HBVr and includes individuals treated with tumor necrosis factor–α inhibitors such as infliximab (Remicade, Janssen), etanercept (Enbrel, Amgen), or adalimumab (Humira, AbbVie), regardless of HBsAg status[1,14,31-34]; cytokine or integrin inhibitors such as

Table 2. Risk Stratification for HBVr[14]

High Risk (HBVr >10%)	Moderate Risk (HBVr 1%-10%)	Low Risk (HBVr <1%)
HBsAg-positive or HBcAb-positive alone: patients taking B-cell–depleting agents (eg, rituximab, ofatumumab)	HBsAg-positive or HBcAb-positive alone: patients taking TNF-α inhibitors (eg, etanercept, adalimumab, certolizumab pegol, infliximab) Patients taking cytokine or integrin inhibitors (eg, abatacept, ustekinumab, natalizumab, vedolizumab) Patients taking tyrosine kinase inhibitors (eg, imatinib, nilotinib)	HBsAg-positive or HBcAb-positive alone: patients taking traditional immunosuppressive agents (eg, azathioprine, 6-mercaptopurine, methotrexate) Patients taking intra-articular corticosteroids, or taking any dose of oral corticosteroid daily for ≤1 week
HBsAg-positive: patients taking anthracycline derivatives (eg, doxorubicin, epirubicin) Patients taking moderate dose (10-20 mg prednisone daily or equivalent) or high dose (>20 mg prednisone daily or equivalent) corticosteroid for ≥4 weeks	HBsAg-positive: patients taking low dose (<10 mg prednisone daily or equivalent) corticosteroid for ≥4 weeks	HBcAb-positive alone: patients taking low dose (<10 mg prednisone daily or equivalent) corticosteroid for ≥4 weeks
	HBcAb-positive alone: patients taking moderate dose (10-20 mg prednisone daily or equivalent) or high dose (>20 mg prednisone daily or equivalent) corticosteroid for ≥4 weeks, or taking anthracycline derivatives (eg, doxorubicin, epirubicin)	

HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBVr, hepatitis B virus reactivation; TNF, tumor necrosis factor.

abatacept (Orencia, Bristol-Myers Squibb), ustekinumab (Stelara, Janssen), or vedolizumab (Entyvio, Takeda), regardless of HBsAg status; and tyrosine kinase inhibitors such as imatinib, regardless of HBsAg status.[1,14,35] This group also includes individuals treated with 4 weeks or more of corticosteroids at low dose (<10 mg prednisone daily or equivalent), with positive HBsAg; 4 weeks or more of corticosteroids at moderate dose (10-20 mg prednisone daily or equivalent) or high dose (>20 mg prednisone daily or equivalent), with negative HBsAg; and anthracycline derivatives, with negative HBsAg.[1,14,36,37] Other drug classes that may be associated with moderate risk outside of the AGA guidance include histone deacetylase inhibitors such as romidepsin (Istodax, Celgene), proteasome inhibitors such as bortezomib (Velcade, Millennium Pharmaceuticals), and immunophilin inhibitors such as cyclosporine and tacrolimus.[1]

The low-risk group is defined as having less than a 1% risk of HBVr and includes individuals treated with traditional immunosuppressive antimetabolites such as azathioprine, 6-mercaptopurine, and methotrexate, regardless of HBsAg status; intra-articular corticosteroids, regardless of HBsAg status; 1 week or less of oral corticosteroids, regardless of HBsAg status; and 4 weeks or more of corticosteroids at low dose (<10 mg prednisone daily or equivalent), with negative HBsAg.[1,14,30]

For patients who are HBsAg-negative but HBcAb-positive, the strongest data supporting a significant risk for HBVr are found in association with B-cell–depleting therapies (eg, anti-CD20). With other immunosuppressive therapies, the evidence for a significant risk of HBVr in patients with negative HBsAg is more controversial, and the overall risk of individual drug classes is estimated to be low or moderate.[1] It is also important to note the effect of treatment with multiple immunosuppressive agents on HBVr, as they are commonly used in combination regimens for chemotherapy or immunosuppression. Although there are few studies that have clarified differential HBVr incidence between single vs combination immunosuppressive drug regimens, current data suggest that the addition of cyclophosphamide, doxorubicin, or fludarabine to combination regimens is associated with an increased incidence of HBVr.[38]

Table 3. Society Recommendations for Prophylactic Antiviral Therapy in Eligible Patients Undergoing IDT

Society	Eligible Patients for Prophylactic Antiviral Therapy
American Association for the Study of Liver Diseases[39]	All HBsAg-positive patients at the onset of cancer chemotherapy or IDT
American Gastroenterological Association[14]	All HBsAg-positive and HBsAg-negative/HBcAb-positive patients who are undergoing IDT associated with high risk (>10%) or moderate risk (1%-10%) for HBVr
European Association for the Study of the Liver[23]	All HBsAg-positive patients receiving chemotherapy or IDT; all HBsAg-negative/HBcAb-positive patients who are at high risk (>10%) for HBVr
American Society of Clinical Oncology[16]	All HBsAg-positive patients undergoing IDT; all HBsAg-negative/HBcAb-positive patients undergoing high-risk IDT (anti-CD20 and stem cell transplantation). Patients may alternatively be monitored with serum alanine aminotransferase and HBV DNA; on-demand antiviral therapy can be considered if HBVr occurs.

HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBVr, hepatitis B virus reactivation; IDT, immunosuppressive drug therapy.

Table 4. Antiviral Therapy and Duration for Preemptive Antiviral Prophylaxis for HBV Reactivation

Society	Antiviral Agent(s)	Treatment Duration
American Association for the Study of Liver Diseases[39]	Tenofovir or entecavir is preferred; lamivudine or telbivudine may be used if the anticipated treatment duration is short (<12 months) and baseline serum HBV DNA is undetectable.	6 months following completion of chemotherapy or IDT
American Gastroenterological Association[14]	Third-generation nucleos(t)ide analogues such as entecavir and tenofovir are recommended over first- or second-generation agents (eg, lamivudine, adefovir, telbivudine).	≥6 months after discontinuation of IDT for high- and moderate-risk patients; ≥12 months for patients on B-cell–depleting agents (eg, rituximab)
American Society of Clinical Oncology[16]	Consult a specialist who is an expert in the management of HBV infection.	6 months after stopping chemotherapy; 12 months after completion of anti-CD20 therapy
European Association for the Study of the Liver[23]	Entecavir or tenofovir is recommended.	12 months after cessation of IDT and 18 months after cessation of rituximab-based regimens

HBV, hepatitis B virus; IDT, immunosuppressive drug therapy.

Prophylaxis for Hepatitis B Virus Reactivation

Identifying the appropriate patients to initiate prophylactic antiviral therapy to protect against HBVr remains challenging, with important differences in recommendations across society guidelines (Table 3). The AASLD recommends prophylactic antiviral therapy for all HBsAg-positive patients who are starting cancer chemotherapy or immunosuppressive drug therapy, and cites insufficient data to make broad recommendations regarding treatment in HBsAg-negative/HBcAb-positive patients.[39] The AGA recommends antiviral prophylaxis for HBsAg-positive and HBsAg-negative/HBcAb-positive patients who are at high or moderate risk of HBVr while undergoing immunosuppressive drug therapy.[14] The EASL recommends antiviral prophylaxis for all HBsAg-positive patients receiving chemotherapy or immunosuppressive drug therapy and for HBsAg-negative/HBcAb-positive patients who are at high risk of HBVr.[23] The ASCO recommends antiviral prophylaxis for all HBsAg-positive patients receiving immunosuppressive drug therapy. For HBsAg-negative/HBcAb-positive patients, the ASCO recommends that those receiving B-cell–depleting therapies and stem cell

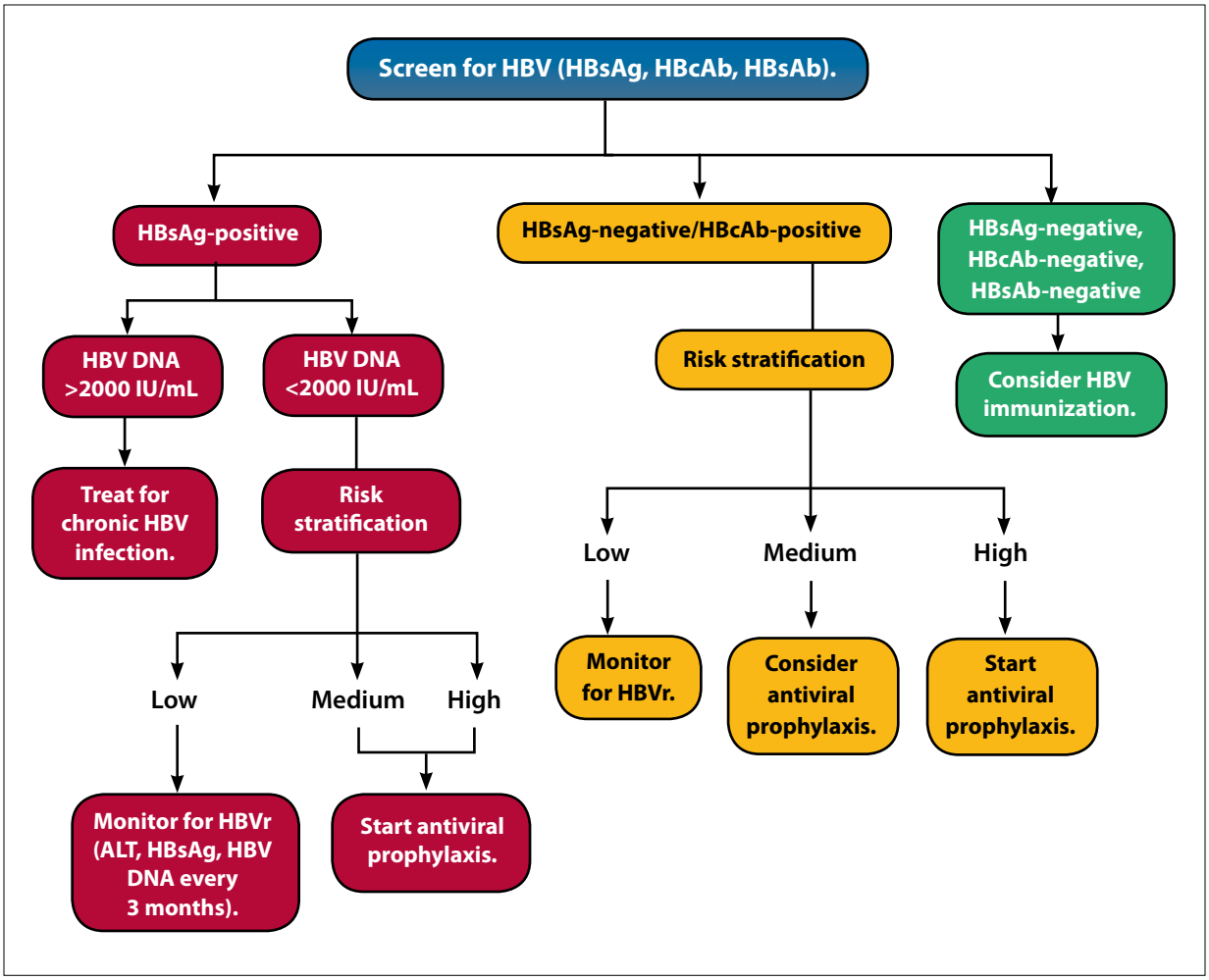

Figure. Suggested algorithm for HBV screening in the context of immunosuppressive drug therapy.

ALT, alanine aminotransferase; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBVr, hepatitis B virus reactivation.

transplantation should either receive prophylaxis or be monitored with HBV DNA and ALT levels followed by treatment if HBVr occurs.[16,40]

Current society guidance documents addressing preemptive antiviral prophylaxis (Table 4) suggest the use of antiviral drugs with high potency and a high barrier to resistance; nucleoside reverse transcriptase inhibitors tenofovir and entecavir are generally recommended over lamivudine or telbivudine,[1,4,14,40-44] although consideration may be given for lamivudine or telbivudine if the anticipated duration of treatment is short (<12 months).[24,45]

Given the high prevalence of HBV infection in developing countries as well as the variability in cost of antiviral therapies, in patients for whom the cost of antiviral therapy would be prohibitive, it may be reasonable to choose a less expensive regimen over a more expensive one with a higher barrier to resistance. The small risk of developing resistance may be acceptable, particularly in patients who are positive for HBsAg but have undetectable or very low viral load, and who are expected to require antiviral prophylaxis for no greater than 6 months.[1,14,46,47]

Duration of Antiviral Prophylaxis

For patients who pursue antiviral prophylaxis, treatment should ideally be started 2 to 4 weeks before or as soon as possible following the initiation of immunosuppressive drug therapy, and should be continued for at least 6 months after discontinuation of immunosuppressive drug

therapy. Specifically, for patients receiving B-cell–depleting agents, antiviral prophylaxis should be continued for at least 12 months after discontinuation of immunosuppression due to an ongoing risk of reactivation that may rarely persist for periods beyond 1 year as a result of delayed immune recovery.[1,14,48]

Surveillance for Hepatitis B Virus Reactivation

Data are currently insufficient to make evidence-based recommendations regarding a watchful waiting strategy with specified intervals for serum ALT and/or HBV DNA monitoring. Although limited data are available to identify differences in clinical outcomes between preemptive antiviral therapy vs watchful waiting with rescue treatment after identification of HBVr, cases of fatal reactivation flares with fulminant liver failure have been reported with the latter approach even after antiviral therapy has been initiated.[1,14] In the absence of firm guidelines addressing surveillance parameters, routine testing for HBV DNA and serum ALT every 3 months may be reasonable. Similarly, limited data are available to guide monitoring parameters following withdrawal of antiviral prophylaxis, although assessment of serum ALT and HBV DNA at 3 to 6 months may be appropriate.[1] A proposed testing and management algorithm is illustrated in the Figure.

Conclusion

Multiple unanswered issues remain in the epidemiology, risk stratification, diagnosis, and management of HBVr that require further investigation. With the advent of new classes of immunosuppressive drug treatment, additional data are needed to provide estimates of HBVr risk and inform clinical management. Future studies should further examine different strategies for the diagnostic testing, management, and surveillance of HBVr both during and following completion of immunosuppressive drug therapy. Due to conflicting data on the role of HBsAb status and the impact of risk for HBVr across drug classes, additional examinations of qualitative and quantitative titers of HBsAb would help clarify its importance both in pre–immunosuppressive drug therapy HBV screening and on the impact of preemptive management decisions. Overall, HBVr remains a significant source of morbidity in patients with HBsAg-positive chronic HBV infection and with resolved HBV infection (HBsAg-negative/HBcAb-positive). Current society recommendations provide important guidance on screening, diagnosis, and management, although additional studies are needed to address ongoing challenges in the care of patients at risk for HBVr.

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