Defining and Grading HBV Reactivation

Alissa Visram M.D., and Jordan J. Feld M.D., M.P.H.

HBV Reactivation: A Hidden Menace With Global Implications

Chronic hepatitis B virus (HBV) infection affects more than 240 million people worldwide.¹ Although chronic infection can lead to progressive liver injury, the majority of people are asymptomatic and therefore unrecognized until presenting with stigmata of advanced liver disease.² Individuals chronically infected with HBV are at increased risk of viral reactivation when undergoing immunosuppressive therapy.

Understanding HBV Reactivation

The natural course of HBV infection, as illustrated in Figure 1, is dependent on the interaction between the host's immune response and the virus. In the initial phase of immune tolerance, infected children have high levels of viral replication with no associated liver injury. While the immune system matures, infected persons enter a phase of immune clearance in which hepatocytes infected with HBV are targeted and damaged through immune surveillance, resulting in hepatitis flares. In most individuals, the immune system eventually is able to control viremia, leading to hepatitis B e antigen (HBeAg) clearance, suppression of HBV deoxyribonucleic acid (DNA) levels, and normalization of serum transaminase levels. The immune control phase can persist indefinitely; however, in cases of iatrogenic or natural immunosuppression, the loss of immune control results in the reactivation of HBV replication within hepatocytes. Upon reconstitution of the immune system, these hepatocytes are once again targeted and damaged by immune surveillance in an effort to clear the virus.³ The consequences of reactivation range from a subclinical rise in HBV DNA levels, with no associated liver injury, to fulminant or even fatal hepatitis.

HBV reactivation occurs most frequently in patients who are chronically infected (hepatitis B surface antigen [HBsAg] positive); however, it also has been documented in patients with

resolved or occult hepatitis B infection (HBsAg negative, anti-HBc positive) because these individuals still have traces of replication-competent virus in their livers. Reappearance of HBsAg is termed *reverse seroconversion* and typically only occurs with severe immunosuppression such as with bone marrow transplantation or B cell-depleting agents (rituximab, ofatumumab). Although the risk of HBV reactivation is highest with the treatment of hematologic malignancies, it may occur with chemotherapy for solid tumors and with immunosuppression for nonmalignant diseases such as rheumatologic, dermatologic, or gastrointestinal conditions.⁴⁻⁸ The rate of reactivation depends on both the degree and duration of immunosuppression.^{9,10}

Fortunately, HBV reactivation can be effectively prevented with the use of safe and well-tolerated oral antiviral medications administered prior to the initiation of immunosuppressive therapy. Pre-emptive therapy has been shown to be much more effective at preventing HBV reactivation than starting treatment with antivirals only after an increase in HBV DNA or alanine aminotransferase (ALT).¹¹ Effective prevention of HBV reactivation with pre-emptive antiviral therapy requires pre-emptive screening to identify patients with chronic infection, most of whom are asymptomatic and unaware of their infection. Although most guidelines agree that screening for chronic HBV infection prior to the initiation of immunosuppressive therapy is important, there still is debate about the optimal strategy: selective screening of high-risk individuals only versus universal screening of all individuals receiving immunosuppressive agents. Although targeted high-risk screening seems attractive in low-prevalence countries, it requires that physicians prescribing immunosuppressive therapy recognize the important risk factors, remember to screen, and then manage positive results appropriately. There often is confusion about what constitutes high risk. Although HBV is transmitted sexually and through blood products, most immunocompetent adults (> 95%) will

Abbreviations: ALT, alanine aminotransferase; DNA, deoxyribonucleic acid; HBc, anti-hepatitis B core; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; INR, international normalized ratio; ULN, upper limit normal.

From the Toronto Centre for Liver Disease, University of Toronto, McLaughlin-Rotman Centre for Global Health, Toronto, ON, Canada.

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spontaneously clear acute infection with the loss of HBsAg and no long-term sequelae. In contrast, neonates and young children who are exposed through vertical (mother-to-child) exposure or early horizontal (family member or friend-to-child) exposure have a high rate of progression to chronic infection (90%). As a result, if high-risk screening is adopted,

Figure 1 Natural history of chronic hepatitis B infection.³ Most chronically infected individuals transition from immune tolerance with high HBV DNA levels but normal ALT through the immune clearance phase with ALT flares and variable HBV DNA levels and ultimately enter the immune control phase with low HBV DNA levels and normal ALT. Immunosuppression leads to a reappearance of HBV replication with rising HBV DNA and potentially associated ALT flares and severe hepatitis.

individuals born in endemic countries should be targeted for screening. To date, screening rates among oncologists, rheumatologists, and other practitioners unfortunately remain low.

Low screening rates likely result from poor recognition of the issue by individual physicians, combined with inconsistent, unclear, or discordant society guidelines. Part of the inconsistency in guidelines likely stems from a somewhat limited evidence base supporting screening. Although there are numerous studies documenting HBV reactivation and its consequences, as well as small, randomized controlled trials supporting the use of pre-emptive antiviral therapy, the data are not extensive and often are difficult to compare and combine because of differing definitions and endpoints used. Some studies compare rates of rises in HBV DNA, whereas others evaluate episodes of clinical hepatitis with differing grading systems of severity, as illustrated by some examples in Table 1. Development of standard definitions used by all investigators would allow smaller studies to be combined, thus providing more robust risk estimates that would allow for greater consensus on management strategies.

Assessing the Consequences of HBV Reactivation

Grading HBV reactivation requires consideration of both virologic and hepatic outcomes as well as other consequences of HBV reactivation—in particular, interruption, change, or cessation of previously intended immunosuppressive therapy. Even a relatively minor episode of HBV reactivation that leads to chemotherapy interruption could have

Figure 2 Worldwide rates of chronic hepatitis B infection. Reprinted from the Centers of Disease Control and Prevention Web site.¹

TABLE 1 Diagnostic Criteria for HBV Reactivation Cited in the Literature

Definition	Reference
Elevated ALT and HBV DNA > 2,000 IU/mL in a person known to have the inactive HBsAg carrier state or resolved hepatitis	12,13
Seroconversion from anti-HBe to HBeAg positivity or the reappearance of anti-hepatitis B core (HBc) immunoglobulin M	14
Seroconversion from HBsAg negative to HBsAg positive with reappearance of serum HBV DNA	9,15,16
HBV DNA level of 10-fold or more from the baseline level or an absolute increase of HBV DNA level to >10 ³ IU mL ⁻¹ in the absence of other acute viral hepatitis or systemic infection	7,17-19
HBV DNA level of 10-fold or more from the baseline level or reappearance of HBV DNA in the serum	11,20

TABLE 2 Proposed Grading System for HBV Reactivation

Virological		Hepatic		Immunosuppression	
V₁	HBV DNA increase by > 1 log IU/mL (or from undetectable to detectable)	H₀	No hepatitis ALT remains < 2 ULN; no change in bilirubin or INR	I₀	No consequence
V₂	Reverse Seroconversion Reappearance of HBsAg with or without associated rise in HBV DNA (as in A)	H₁	Hepatitis ALT 2 to 10x ULN with no associated change in bilirubin or INR	I₁	No interruption, but increased frequency of HBV DNA and ALT monitoring
		H₂	Severe hepatitis ALT > 10× ULN and/or elevation of bilirubin (> 2 ULN) or INR (> 1.3)	I₂	Interruption of immunosuppressive therapy with re-initiation of same drug after hepatitis flare resolved
		H₃	Fulminant Hepatitis Criteria for 2 with development of encephalopathy or ascites	I₃	Interruption of immunosuppressive regimen with re-initiation of second line, suboptimal, therapy
		H₄	Death Due to liver failure	I₄	Discontinuation of immunosuppression

INR, international normalized ratio; ULN, upper limit normal.

significant clinical consequences.²¹ It is first important to define what has occurred in terms of the virus itself; an increase in viral replication is required for the term *HBV reactivation* to be applied. Increases in HBV DNA replication by 10-fold (1-log) are generally considered clinically significant, as is the reappearance of HBsAg in a previously HBsAg-negative individual (reverse seroconversion). The hepatic consequences of reactivation range from asymptomatic increase in serum transaminases to severe hepatitis with jaundice all the way to fulminant hepatitis with liver failure, which may be fatal.²⁰ A universal grading system for HBV reactivation would provide a basis for communicating the clinical severity of a patient's episode of reactivation and a system for stratifying the appropriate management, but more importantly would prove useful in comparing results across studies in the literature. Therefore, we have proposed a grading system for HBV reactivation that defines the type of virological event (reverse seroconversion or rise in HBV DNA), the severity of liver injury, and the consequences related to the immunosuppressive therapy (see Table 2).

For example, an HBsAg positive-patient failed treatment with methotrexate in a dose of 25 mg weekly. HBV DNA remained negative during methotrexate, and persistently normal serum aminotransferase levels were observed. The patient was switched to adalimumab; and 1 year after treatment was begun, the ALT increased to three-fold previous values accom-

panied by de novo detection of HBV DNA. Antiviral therapy was started, the patient rapidly improved, and adalimumab was continued. This patient would be scored as V₁H₁I₀. In contrast, an HBsAg-negative, anti-HBc-positive patient with lymphoma was treated with six cycles of cyclophosphamide, doxorubicin, vincristine, and prednisolone, as well as rituximab. Because the patient had an aggressive form of lymphoma, rituximab maintenance was started. During the ninth month of therapy, the patient experienced the de novo detection of a serum HBV DNA of 5.3 log IU and reverse seroconversion to HBsAg positive, for which rituximab was immediately discontinued. The patient became jaundiced and slowly improved on antiviral therapy. This patient would be scored as V₂H₂I₄.

HBV reactivation is a potentially life-threatening consequence of immunosuppressive therapy; however, it fortunately is largely preventable. Prevention of reactivation requires screening for HBV prior to starting immunosuppressive therapy. More consistent grading of HBV reactivation will allow for generation of robust evidence to determine the optimal screening strategy, one that is supported across medical disciplines leading to wide implementation. The proposed grading schema would be a useful tool, although it still requires validation.■

CORRESPONDENCE

Jordan J. Feld, 399 Bathurst Street, 6B FP RM 158, Toronto, ON, M5T 2S8, Canada. E-mail: jordan.feld@uhn.ca

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