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Review Article

Prognosis of Severe Acute Flares of Chronic Hepatitis B

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Abstract

The diagnosis of severe acute flares of chronic hepatitis B is guided by raised alanine aminotransferase enzyme levels almost five times the upper limit of normal during the chronic phase of hepatitis B virus (HBV) infection preceded by elevated levels of hepatitis B surface antigen and hepatitis B virus deoxyribonucleic acid (HBV DNA). Elevation of HBV DNA levels during acute flares indicates an ineffective immune clearance mechanism in the host, which is associated with the lytic activity of hepatocytes with or without hepatic decompensation that might require urgent intervention with antiviral drug therapy. Bridging hepatic necrosis associated with alpha-fetoprotein levels >100 ng/mL or decreasing HBV DNA levels during acute flares are pathognomics of better immune clearance of HBV that eventually progresses to seroclearance. The clinical manifestation of acute hepatitis flares can be asymptomatic or might begin with symptomatic acute hepatitis, which subsequently might progress to hepatic decompensation. It occurs due to the immune response against HBV, which is cytotoxic T-lymphocyte mediated and human leukocyte antigen-1 specific. Certain precipitating factors for the occurrence of acute flares in the case of chronic hepatitis B infected patients include the initiation or the end of treatment with antiviral drug therapy, immunosuppressive or chemotherapy treatment, or spontaneous reactivation with or without concurrent reinfection with HBV or any other hepatotropic viruses. Severe or repeated acute flares might progress to hepatic decompensation and liver cirrhosis. Therefore, it is important to prevent acute hepatitis B flares with the appropriate administration of antiviral drug therapy.

Introduction

According to the National Health and Nutrition Examination Survey report 2020 presented by the US Department of Health and Human Services, the prevalence of any past or present hepatitis B virus (HBV) infection was 4.3%, with a higher preponderance among males (5.3%) versus females (3.4%). According to the same survey, the prevalence of past or present HBV infection was highest among non-Hispanic Asian adults (21.1%) versus non-Hispanic blacks (10.8%) and non-Hispanic whites (2.1%) or Hispanic adults (3.8%). In addition, the risk of hepatitis B infection was greater among adults not born in the US. In the last 20 years, the global prevalence of past or present HBV infection has dropped from 5.7% to 4.3%.[1] Chronic hepatitis B (CHB) infection is endemic in India, with an estimated prevalence of 2–8%[2] and the lifetime risk of a newborn baby being infected with hepatitis B is 4%.[3] When a CHB infected patient develops symptoms of acute hepatitis, it may be the clinical presentation of actual acute hepatitis B (AHB) infection or might be due to severe acute flares of chronic hepatitis B (AFOCHB). It is important to distinguish the patients with self-limiting AHB infection from CHB-AF as the latter might require treatment with antiviral agents.[4] The annual incidence of hepatitis B flares was 10% in 279 hepatitis B envelope antigen (HBeAg) negative patients and 27% in 358 HBeAg positive patients in a hospital-based study of CHB with a 2-year mean duration of follow-up.[5] There are many cases with multiple episodic hepatitis B flares in a single patient.[6–8] It is challenging to differentiate between new and reactivated old cases of HBV infection due

Keywords: Hepatitis B surface antigen; Chronic hepatitis B; Alanine aminotransferases; Hepatitis B virus; DNA; Antiviral agents.

Abbreviations: AFOCHB, acute flares of chronic hepatitis B; Anti-HBs titers, Anti-Hepatitis B surface antigen antibody; ALT, Alanine Aminotransferases; AST, Aspartate Aminotransferases; AHB, Acute Hepatitis B; CD, Cluster of Differentiation; CHB, Chronic Hepatitis B; CHB-AF, Chronic Hepatitis B Acute Flares; DAAs, Directly Acting Antivirals; G-CSF, Granulocyte Colony-Stimulating Factor; HBV, Hepatitis B Virus; HBeAg, Hepatitis B envelope antigen; HBsAg, Hepatitis B surface antigen; HBV DNA, Hepatitis B Virus-Deoxyribonucleic Acid; IgG, Immunoglobulin G; IgM, Immunoglobulin M; MELD, Model for End-Stage Liver Disease; NUC, Nucleoside; PT, Prothrombin Time; US, United States; US FDA, United States Food and Drug Administration; ULN, Upper Limit of Normal.

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Table 1. Five phases of hepatitis B infection

Different phase	HB-sAg	HBeAg	Anti-HBe	HBV DNA	Alanine aminotransferases enzymes	Inflammation in liver	Histology features
Immune tolerant	+	+	–	Increased [>1million IU/mL]	Normal	Mild/no	Normal, mild inflammation
Immune clearance HBeAg positive phase	+	+	–	Increased [>20,000 IU/mL]	Elevated	Moderate/severe	Moderate-severe hepatitis with possible fibrosis
Inactive carrier	+	–	+	Low/undetectable [<2,000 IU/mL]	Normal	Mild/No	usually normal, mild inflammation may be there
HBeAg negative CHB	+	–	+/–	Fluctuating [<2,000 IU/mL]	Fluctuating	Active	Minimal necroinflammation but variable fibrosis
HBsAg negative	–	–	–	Not detected or very low	Normal	No	–
*Reactivation/Flare	–	–	+	Variable, increased level more often [>2,000 IU/mL]	Elevated	Moderate/severe	Moderate-severe hepatitis with likely fibrosis and cirrhosis

*Reactivation/flares of AHB in CHB infection is not separate phase per se but can occur in either of the five phases as described. AHB, acute Hepatitis B; Anti-HBe, hepatitis B e antibody; CHB, Chronic Hepatitis B; HBeAg, Hepatitis B envelope Antigen; HBsAg, Hepatitis B surface Antigen; HBV DNA, Hepatitis B Virus Deoxyribonucleic acid level; IU/mL, International Unit per milliliter.

to the increased worldwide prevalence of HBV infection. The gold standard investigation to differentiate AHB infection from severe acute flares of chronic hepatitis B infection is liver biopsy.

Definition of acute flares of chronic hepatitis B infection

Several definitions of AFOCHB infection have been published in the literature.[4,6,9] All of the previously mentioned definitions consider the basic fact of "an increase in liver alanine aminotransferase (ALT) enzyme level to more than five times the upper limit of normal (ULN)" that is the most commonly used definition followed in clinical practice as a criterion to diagnose the hepatitis flare episodes in cases with pre-existing CHB infection.

Different phases of hepatitis B infection

Five phases exist in the natural history of HBV infection (Table 1.) that might not occur sequentially, and the same patient might not present all these phases.[10]

1. Immune tolerant phase: HBV infection is usually acquired during the perinatal period or in early childhood with elevated serum HBV DNA levels and the presence of HBeAg; however, ALT levels are normal with minimal or no inflammation on liver biopsy.
2. Immune clearance HBeAg positive phase or HBeAg positive chronic HBV infection: This phase of infection usually occurs after several years of immune tolerance, resulting in HBeAg seroconversion, HBeAg positivity, lower HBV DNA levels, and increased ALT enzyme levels with moderate to severe necroinflammation associated with a high risk of progression to liver fibrosis.
3. Inactive HBV carrier phase: In this phase, the HBeAg status is negative with normal levels of ALT enzymes, which might be associated with low or below detectable levels of hepatitis B deoxyribonucleic acid (some might have >2,000 IU/L).
4. HBeAg negative CHB phase: In this phase of infection, there are variable HBV DNA and ALT enzyme levels with negative HBeAg.
5. HBsAg negative phase: In this phase, after the loss of HBsAg, the presence of anti-HBc antibodies and serum HBV DNA levels remain undetected with a slow rate of HBV replication that might persist with detectable HBV DNA in the liver. Immune suppression could trigger acute hepatitis flares in HBsAg negative phase patients.[11]

Acute exacerbations, flares, or reactivation of HBV that cause an increase in ALT enzymes (>5 times ULN) might present in any of the following phases.[6,12,13] An immune flare is more commonly seen in the HBeAg positive immune clearance phase (88.2–90.5%) than in the HBeAg negative phase (23.8–50%) that occurs mostly due to spontaneous viral activation that is indicative of immune clearance activity. AHB flares are not commonly associated with anti-HBe positive patients (62.5%) with chronic HBV infection. Superinfection by a non-B hepatitis virus is one of the rare but important contributing factors that cause acute flares of hepatitis B. Acute flares of hepatitis B do occur occasionally in patients with HBeAg negative CHB and can subsequently end with viral clearance. Reactivation of HBV may be due to increased viral replication in patients with inactive HBV with normal ALT enzymes. Acute flares of hepatitis B might occur in HBsAg negative patients with resolved HBV infection.

Pathogenesis of severe acute flares of hepatitis B in Chronic Hepatitis B patients

Severe acute flares or reactivation of hepatitis B occurs due to an increase in the replication of HBV in a patient with resolved or inactive HBV infection. This process of reactivation might occur spontaneously or after a course of cancer chemotherapy and immune-suppressive treatment or due to alterations in the immune function of the patient.[14] The diagnosis of HBV reactivation is based on an increase in HBV DNA levels that might be associated with an imbalance in liver enzymes. Several cases of hepatitis B reactivation in HBsAg posi-

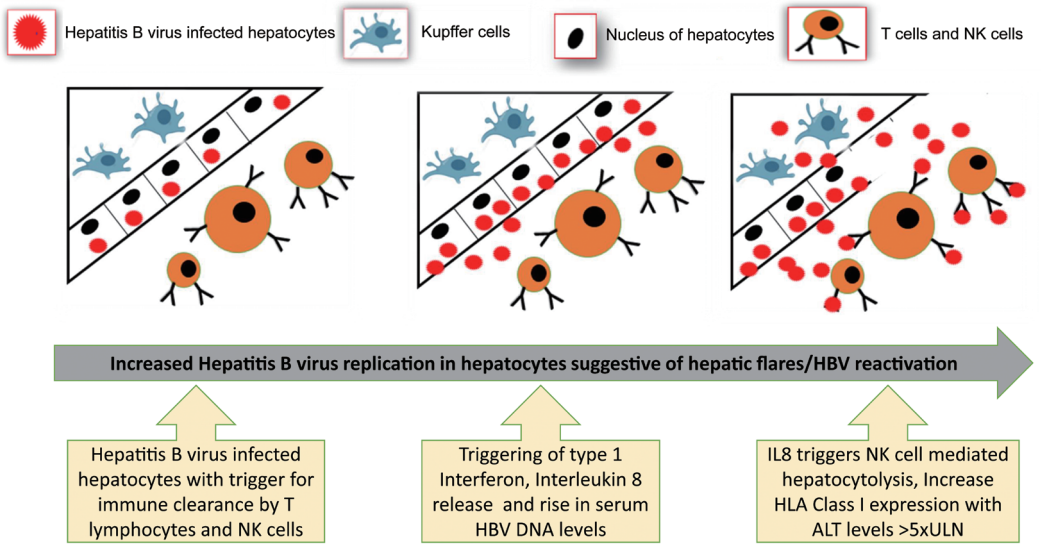

Fig. 1. Pathogenesis of severe acute flares of hepatitis B in CHB infected patients. CHB, Chronic Hepatitis B; HBV, Hepatitis B Virus.

tive patients on chemotherapy have been observed where HBV DNA was negative. One of the causes might be increased viral replication that precedes fully apparent hepatitis, and there might be a decrease in HBV DNA levels followed by peak levels of ALT enzymes.[15] Acute flares of hepatitis B due to HBV reactivation following immunosuppressive therapy usually present with an increase in viral replication followed by a destruction of HBV infected hepatocytes by an immune-mediated mechanism.[16,17] Upon the withdrawal of immunosuppression, immune reconstitution results in a phase of disease activity, which is characterized by an increase in ALT enzymes and declining HBV DNA levels that clinically manifests as jaundice and acute liver failure. The hepatic injury recovers and HBV DNA falls to baseline levels during the recovery phase.[14] HBV flares or reactivation are usually seen in HBsAg positive patients but might be observed in resolved HBV infection with HBsAg absent in the serum but Immunoglobulin G (IgG) anti-HBc present in the serum.[18] Patients on immunosuppressive therapy need an adequate evaluation of all serum markers of HBV infection. Patients with previous markers of hepatitis B infection or previous exposure to HBV (*e.g.*, anti-HBs, IgG anti-HBc, or both) need regular monitoring to detect sudden reactivation of HBV in the liver. A progressive decrease in anti-HBs titers increases the risk of reverse seroconversion.[19] The following is the diagrammatic representation of the pathogenesis of severe acute flares of hepatitis B in CHB infected patients (Fig. 1) and the predictors of HBV reactivation (Table 2[20–25]).

Determinants of prognosis of patients with severe acute flares/ reactivation of chronic hepatitis B

A study was conducted that enrolled 75 patients who underwent liver biopsy and had a clinical course of CHB infection for >2

Table 2. Predictive Factors of HBV Reactivation

Serial number	Predictive factors of HBV reactivation
1	Detectable baseline HBV DNA level before start of cytotoxic chemotherapy.
2	Use of corticosteroids and diagnosis of any neoplasia.
3	Patients with HBeAg and HBV DNA before initiation of chemotherapy.[20]
4	Severe acute hepatitis flares are common in male patients infected with genotype C hepatitis virus, core promoter mutations, and delayed HBeAg seroclearance.[21]
5	Higher frequency of seroreversion in patients with delayed HBeAg seroclearance.[22]
6	Carriers of HBV, HBeAg negative and having the nt 1896 mutation (G–A) are easily prone to severe acute HBV reactivation during cytotoxic chemotherapy than those with wild type virus.[23]
7	Nucleoside (NUC) therapy induced HBeAg seroconverters may not have durable response after stopping therapy. HBV reactivation is higher in NUC-induced seroconverters than in spontaneous seroconverters.[24]
8	For patients before 30 years of age who are HBeAg seroconverted may be exposed to the risk of HBeAg seroreversion.[24]
9	In patients with the MELD score of ≥28 may require liver transplantation, and those with MELD score between 28 to 32 with 3–4 at-risk criteria, or MELD score of ≥32 need proper evaluation.[25]

HBeAg, Hepatitis B envelope Antigen; HBV, Hepatitis B Virus; MELD, Model for End-Stage Liver Disease.

Table 3. Independent predictors of in-hospital mortality

Serial number	Clinical characteristics (risks involved)	Number of risk factors	Mortality (%)
1	Low platelet and high bilirubin	Two	69
2	Thrombocytopenia	One	11
3	Elevated bilirubin	One	13
4	Normal platelet count and bilirubin levels	No risk factor	0

months with increased liver enzymes and higher levels of HBV DNA. In total, 32 (43%) patients were diagnosed with acute flares of chronic HBV infection on liver biopsy. At the 6-month follow-up, HBsAg clearance was lower (9.4%) in the CHB-AF group. In the CHB-AF group, aspartate (AST) and ALT enzyme levels, platelet count, bilirubin levels, and anti-core antibody (IgM anti-HBc) levels were lower (p<0.01). The variables, such as peak bilirubin level, peak AST levels, and lowest platelet count within the first 8 weeks had more predictive power for the occurrence of severe acute flares of hepatitis, which were analyzed using receptor operating characteristic curves. The optimal values of bilirubin level <4.5 mg/dL, platelet count <2.4×10^5/μL, peak and AST levels <550 IU/L were given a score of one each. On performing internal validation, a score of two was confirmed with 86% specificity and 70.1% sensitivity diagnostic accuracy in predicting CHB-AF. Patients with hepatitis B infection with AHB flares with genotype C were associated with an increased risk of progression to cirrhosis.[26] Serum bilirubin and prothrombin activities are significant predictors of clinical outcomes in patients with severe acute flares or exacerbation of CHB. Viral kinetics until the start of antiviral therapy predicts the severity of acute flares or exacerbation of CHB.[27] During acute exacerbation of HBeAg positive CHB, a serum HBV DNA threshold value of 1.55×10^9 copies/mL helps to identify patients who need immediate antiviral therapy.[28] The underlying severity of pre-existing liver disease remains the common risk factor for severe AHB flares during CHB infection. Based on the study by Yuen MF *et al.*, various parameters that are independently associated with adverse outcomes in patients with severe acute flares, exacerbation, and reactivation of hepatitis B infection[29] include decreased albumin levels, elevated bilirubin levels, prolonged prothrombin time, pre-existing cirrhosis, a high Child–Pugh score, and decreased platelet count. However, certain factors are known to increase the duration of hospital stay or admission, such as elevated peak bilirubin level, prolonged peak prothrombin time, prolonged time to reach peak prothrombin time, presence of encephalopathy, and presence of ascites. A study conducted in Hong Kong (N=46) in CHB with acute flare patients with no cases of hepatic encephalopathy revealed that 24% of patients died or received liver transplantation during hospital admission. In the same study, independent predictors for in-hospital mortality reported were low platelet count and high serum bilirubin (Table 3).[30] However, those patients with liver cirrhosis had limited hepatic reserve, recovered more slowly, and were susceptible to complications, such as sepsis, gastrointestinal bleeds, and acute renal failure. Such patients should be monitored regularly once or twice a week for serum ALT enzymes and bilirubin levels, and for prothrombin time measurements to detect clinical deterioration or hepatic decompensation in time for immediate antiviral therapy for prevention or rescue.[31] A few studies from Hong Kong, Taiwan, and Japan reported the presence of pre-existing liver cirrhosis or severe hepatic dysfunction with prolonged prothrombin time, elevated serum bilirubin, and high Child–Pugh scores increased the risk of fatal outcomes.[32–34]

Treatment for patients with severe acute flares of chronic hepatitis B infection

Various treatments are available for CHB patients with severe acute flares, such as the administration of an oral nucleoside(tide) analog as soon as possible. Liver transplantation could be a choice for patients with liver failure that is secondary to severe acute flares. Other supportive therapy with the addition of granulocyte colony-stimulating factor (G-CSF) therapy could be beneficial.[35] During severe AFOCHB, the use of interferon-based therapy is contraindicated because it might lead to hepatic decompensation or acute liver failure. Oral nucleos(t)ide analogs (*e.g.*, lamivudine) are the drug of choice in such cases.[36] However, the timing of the start of treatment with lamivudine therapy will impact the viral load and mortality outcomes, and improvements are greater when the baseline bilirubin is <20 mg/dL or the Model for End-Stage Liver Disease (MELD) score is ≤30.[37] Few studies have suggested an increase in mortality outcomes with entecavir due to lactic acidosis and an increased risk of drug-resistant mutations. The 3-month survival increased to 57% when tenofovir was used in severe AFOCHB. A reduction in >2 log in HBV DNA levels at 2 weeks was an independent predictor of survival. The definitive treatment for severe AFOCHB with acute-on-chronic liver failure (ACLF) is liver transplantation with 5-year survival >90%.[38] Corticosteroids are used in CHB with ACLF due to their anti-inflammatory activity. One study revealed that dexamethasone use and a rapid decline in serum bilirubin in the first 5 days was an independent factor predictive of survival.[39] There have been 24 reported cases of hepatitis B reactivation to the US FDA in patients with hepatitis C infection treated with directly acting antiviral agents (DAAs) with a history of concurrent or past HBV infections. This could have serious consequences or fatal liver failure that might require liver transplantation. When HCV infection is treated, due to immune reconstitution, HBV DNA is detected with an immediate surge in the host immune responses, which manifests as severe acute flares of hepatitis B or HBV reactivation. Therefore, it is important to perform HBV testing before a patient starts DAA therapy and continuous monitoring is required during therapy that might need intervention with anti-HBV agents as and when required.[40]

Future directions

Diagnosis and prognostic parameters might evolve with an increased understanding of the disease pathogenesis. Effective immune clearance by T cells is a promising area for the development of immune checkpoint inhibitors and therapeutic vaccines that add to the current regimes that are used to treat acute flares of hepatitis B. The genetic markers associated with recurrent episodic hepatitis B flares need to be investigated. Experimental studies are required to determine effective immunotherapy combined with antiviral agents that could revive T cells to inhibit viral replication and anti-

gen load when a lower safety concern is required for the functional cure of acute flares of hepatitis B.

Conclusions

Increases in the levels of aminotransferase enzymes is an indicator of immune-mediated hepatocytolysis activity that is associated with increased clearance of HBV. Patients with ALT levels two–five times the ULN with less spontaneous HBV clearance need to be started on anti-HBV drug therapy to prevent the occurrence of hepatitis B flares and related complications.[41] In addition, HBV infected patients who are on antiviral therapy need to be monitored or who are going to receive immunosuppression or cancer chemotherapy to avoid the recurrence of acute flares of hepatitis B. The topic of hepatitis B reactivation during pregnancy and organ failure was not included in this review. This review was limited to the overall prognosis of hepatitis B flares without a discussion of each drug. The assessment of the benefit of starting patients on anti-HBV therapy should be weighed against the risk of developing adverse hepatitis B flares that consider the abovementioned factors for a better prognosis.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conceptualization, review of literature, manuscript drafting (MM, RM), manuscript editing and reviewing (RM). All authors have made a significant contribution to this study and have approved the submission of the final manuscript (MM, RM).

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