Review Article

Reactivation and Flare of Chronic Hepatitis B: Natural History, Diagnosis, Therapy and Prevention

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ABSTRAK

Hampir 30% dari populasi dunia telah terkena virus Hepatitis B (HBV) dan 400 juta jiwa telah terinfeksi kronis. 20-30% dari pembawa virus HBsAg membentuk reaktivasi atau endemisasi HBV, terbentuk dari penggunaan sitotoksik atau terapi imunosupresif untuk pengobatan dari varietas yang lebih luas pada penyakit klinis. Reaktifasi atau flare adalah indikasi pertama dari infeksi HBV. Terkadang sulit untuk membedakan antara Hepatitis B akut atau reaktivasi (flare). Diagnosis yang akurat pada kasus tersebut sangat penting untuk dapat diputuskan apakah akan dilakukan pengobatan atau tidak, karena hepatitis B akut tidak membutuhkan persyaratan untuk pengobatan, sedangkan reaktivasi bisa dimungkinkan mendapat indikasi lanjut dari diagnosis tersebut. Usaha yang dilakukan untuk deteksi dini, pengobatan dan pencegahan reaktivasi atau flare dari hepatitis B kronis sangat penting untuk mengurangi kesakitan dan kematian.

Kata kunci: *Reaktifasi, flare (pembusukan akut) dari Hepatitis B Kronis, Hepatitis B Kronis, analog nucleos(t)ida*

ABSTRACT

Almost 30% of the world population has been exposed to hepatitis B virus (HBV) and 400 million of these are chronically infected. 20–30% of HBsAg carriers may develop reactivation or flare (acute exacerbation) of chronic hepatitis B with elevation of biochemical levels, high serum HBV DNA level with or without sero-coversion to HBeAg. In countries with intermediate or high endemicity for HBV, compounded in use cytotoxic or immunosuppressive therapy for the treatment of a wide variety of clinical disease, reactivation or flare may be the first presentation of HBV infection. Sometime it is difficult to differentiate between acute hepatitis B and reactivation (flare). Accurate diagnosis in these cases is very important for deciding whether to start treatment or not, because acute hepatitis B does not require treatment, while reactivation or flare may take benefit from it. Effort to early detect, to treat and to prevent the reactivation or flare of chronic hepatitis B is very crucial to reduce morbidity and mortality.

Keywords: Reactivation, flare (acute exacerbation) of chronic hepatitis B, acute hepatitis B, nucleos(t)ide analogues

INTRODUCTION

2 billions people or one-third of the world's population has been infected with hepatitis B virus (HBV). It is estimated that 360 million people have chronic carriers.[1] HBV is responsible for chronic hepatitis progressing to cirrhosis (10–20%), and as much as 20–30% of compensated cirrhosis will lead to hepatic decompensate, and 5–15% of compensated cirrhosis will lead to hepatocellular (HCC).[2]

The prevalence of HBV infection varies markedly throughout regions of the world. In high endemic areas, like central Asian republics, Southeast Asia, Sub-Saharan Africa and the Amazon basin, the HBV carrier is over 8%. Most of infections occur during infancy or childhood. Globally, perinatal HBV transmission accounts for an estimated 21% of HBV related deaths. Since the most infections in children were asymptomatic, there is a little evidence of acute disease related to HBV, but the rates of chronic liver disease and liver cancer in adults are high.[1, 3]

Reactivation and flare of chronic HBV are typically in natural history of HBV infection. Reactivation or flare of chronic HBV infection can occur in the immune-clearance phase affecting 40–50% of hepatitis HBeAg-positive patients and 15–30% HBeAg negative patients. Although this clinical performance is usually transient and asymptomatic, 1-2% of patients later develop severe flare, acute liver failure or death.[4]

In countries with intermediate or high endemicity for HBV, compounded by the recent increase in use cytotoxic or immunosuppressive therapy for the treatment of a wide variety of clinical disease, flare of chronic hepatitis B may be the first presentation of HBV infection. Sometime it is difficult to differentiate between acute hepatitis B and reactivation or flare of chronic hepatitis B. Accurate diagnosis in these cases is very important for deciding whether to start treatment or not. The reason of acute hepatitis B does not require treatment, while reactivation or flare may take benefit from it.[5] An Effort to early detect, to treat and to prevent the reactivation or flare of chronic hepatitis B are very crucial to reduce morbidity and mortality.

The aim of this review is to understand the natural history of chronic HBV, how to manage of reactivation and flare of chronic hepatitis B, and to distinguish between acute hepatitis and reactivation or flare of chronic hepatitis B.

PATHOGENESIS OF HBV

Hepatitis B virus is a noncytopathic, hepatotropic virus of the *Hepadnaviridae* family that causes variable degree of liver disease in human. Infection with HBV can be either acute or chronic; while adult infections have relatively low rate of chronicity (around 5%), neonatal infections usually have a high persistence rate (up to 90%). The immune responses to HBV antigens are responsible both for viral clearance during acute infection and for disease pathogenesis. In patients with fulminant HBV infection, rapid clearance is achieved after severe injury as a result of a vigorous host immune response. The stronger host immune response may influence the greater hepatocellular injury, inversely. [6, 7]

HBV replicates in hepatocytes to produce HBsAg particles and virions. Both types of particle can be taken up by antigen presenting cells, which degrade the viral proteins to peptides that are then presented on the cell surface bound to MHC class I or II molecules. These peptide antigens can be recognized

by CD8+ or CD4+ cells, respectively, which are thereby sensitized. Virus specific CD8+ cytotoxic cells (with help CD4+ T cells) can recognize viral antigen presented on MHC class I chains on infected hepatocytes. This recognition reaction can lead to either direct lysis of the infected hepatocyte or the release of interferon-γ and TNA-α, which can down-regulate viral replication in surrounding hepatocytes without direct cell killing.[8]

NATURAL HISTORY

Phases of Chronic HBV Infection

To understand the clinical performance of HBV infection, one should know the natural history of this infection that evolved through four phases of chronic HBV infection, although not all patients go through every phase. Those with chronic HBV infection may present: (1) in a state of immune tolerance, (2) immune clearance or HBeAg-positive chronic hepatitis, (3) immune control or inactive HBsAg carrier, or (4) immune escape or HBeAg-negative chronic hepatitis (see table 1). [9, 10, 11]

Immune tolerance phase

Most Asian patients acquire HBV infection through the perinatal route or at infancy where the immune system is still immature. The earlier of the acquisition infection is the higher probability of developing chronic infection. This is the characterized of these phases: viral replication is very high but hepatic damage is minimal (liver histological findings minimal or no inflammation), normal serum transaminase levels, positive HBeAg, negative anti-HBe and high levels of HBV DNA. A study from Taiwan followed 240 patients found only 5% progressed to cirrhosis and none to hepatocellular during a follow-up period of 10.5 years.[11] In perinatal or childhood infection, the immune tolerant phase may last for fewer than 10 years or more than 20 years. In infection occurring in adults this phase is much shorter because the immune system is more mature.

Immune clearance/HBeAg-positive chronic hepatitis

At the age of 20–40 years the majority of chronic hepatitis B patients undergo

Table 1. The Phases of Chronic B Virus Infection.[9]

Phase	Liver histology	HBV DNA	ALT	HBeAg Anti-HBe	Duration	Natural history
Immune tolerance	Minimal inflammation	>20.000 IU/ml	Normal	Present Negative	20 - 30 years	Low risk of progression to advanced liver disease
Immune clearance	Variable inflammation +/- fibrosis	>20.000 IU/ml (fluctuating)	Elevated (fluctuating)	Present Positive/ negative	Can be protracted	Associated with hepatic flares
Immune control or inactive HBsAg carrier state	Minimal inflammation and liver damage	< 2.000 IU/ml	Normal	Absent	Years	Low risk of advanced liver disease 10-20% have reactivation of HBV replication after many years
Immune escape (HBeAg negative)	Inflammation and often significant fibrosis	> 2.000 – 20.000 IU/ml	Elevated	Absent	-	Can enter to immune clearance or immune control High risk of progression to advanced liver disease

immune clearance of the virus. Due to an as yet uncertain trigger, as the host immune system matures and begins to recognize HBV-related epitopes of the hepatocytes; immune-mediated hepatocellular injury ensues. This phase is characterized by elevation of serum transaminase levels, high levels of serum HBV DNA (but usually lower than during the immune tolerance phase), and histological findings of active inflammation and often fibrosis in the liver. A hallmark of this phase is flare of aminotransferases, which are believed to be the manifestations of immune-mediated lysis of infected hepatocytes secondary to increased T-cell response to HBcAg and HBeAg. Most patients remain asymptomatic, making it difficult to detect the transition from immune tolerance phase based on clinical ground alone. However, some patients present with a symptomatic flare of hepatitis that mimics acute hepatitis or even with fulminant hepatitis failure. It is now recognized that duration of this phase and frequency and severity of the flared, correlate with the risk of cirrhosis and hepatocellular. [9, 11]

Immune control or inactive HBsAg carrier state

HBeAg is marker of high viral replication and associated with disease progression. HBeAg sero-conversion is considered as a key event in the evolution of chronic hepatitis B. After sero-convesion, most patients remain negative for HBeAg and positive for anti-HBe. Sero-conversion is usually accompanied by stabilization of hepatitis. It characterized by normalization of ALT levels and decreases in HBV DNA to low or undetectable levels and depending on the assays used. This condition is commonly referred as the inactive carrier state. An estimated 20–30% of HBsAg carriers may develop reactivation of hepatitis B with elevation of biochemical levels, high serum HBV DNA level with or without sero-conversion to HBeAg.[12, 13]

Immune escape or reactivation of HBV replication or HBeAg negative chronic hepatitis B phase

Chronic hepatitis may recur in up to one-third of inactive HBV carriers without reversion of HBeAg in their serum. Some of these carriers are likely infected with one of the HBV variants that cannot express HBeAg because of the precore or core-promoter regions mutations of the HBV genome. This phase is characterized by the absence of HBeAg, elevated levels of serum ALT, and histological findings of continued necro-inflammation of the liver. Compared to the HBeAg-positive chronic hepatitis, patients with HBeAg negative chronic hepatitis are generally older. The patients also have more advanced disease as evidenced by liver histology because this represents a later phase in the course of chronic HBV infection. Serum HBV DNA levels are lower than in HBeAg positive patients but may reach 10^{8-9} IU/ml. The hallmark of this phase is its fluctuating course, 64% had fluctuating ALT levels during monitoring for a median period of 21 months. [7, 9]

Phases of HBV Reactivation

According to the American Association for the Study of Liver Disease (AASLD)[14], flare (acute exacerbation) of chronic hepatitis B is defined as an intermittent elevation of aminotransferase activity to more than 10 times upper limit of normal and more than twice the baseline value. And reactivation of chronic hepatitis B is a well-characterized syndrome marked by abrupt reappearance or rise of HBV DNA in the serum of patient with previously

inactive or resolved (previous HBV infection without further virology, biochemical or histological evidence of active virus infection or disease) HBV infection.[14,15] Reactivation is also often, but not always, accompanied by reappearance of disease activity or a flare of hepatitis.[15] Based on the understanding of the pathogenesis, HBV reactivation is best defined as an increase of HBV viral replication from a low to high replicate level in patients with chronic or past HBV infection (usually serum HBV DNA increase more than 1 log higher than the pre-exacerbation baseline).[16]

Asian-Pacific consensus described that one of the cause of severe flare that manifest as acute on chronic liver failure is reactivation of hepatitis B. It characterized by jaundice and coagulopathy, complicated within 4 weeks by ascites or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease.[17]

There are two kinds of flare occurred in chronic hepatitis B. The first one is exacerbation in the immune-clearance phase. The second one occurred after inactive carrier phase or in immune escape phase. The exacerbation occurred in immune escape phase (HBeAg negative phase) is called reactivation (figure 1).[18]

Reactivation and flare of chronic hepatitis B can be spontaneously, but (especially for reactivation) most commonly triggered by immunosuppressive therapy cancer, autoimmune disease, organ transplantation and superimposed infections.[4, 14] The most commonly reported types of chemotherapy related to HBV reactivation are those used for the treatment of hematologic malignancy, such as acute leukemia, myelo-proliferative disorders, lympho-proliferative disorders, and plasma cell dyscrasias. [16]

Several studies have confirmed of HBV reactivation following chemotherapy, and the median interval between the initiation of chemotherapy and onset of reactivation is 4 months (range, 1–9 months). The rate of HBV reactivation ranges from 24–88% in patients with chronic HBV who have positive serum HBsAg, and from 3–22% in patients who are HBcAb positive. The mortality rate in HBV reactivation ranges from 23–71%.[19]

Spontaneous flare of chronic hepatitis B infection was seen with cumulative probability of 15–37% after 4 years of follow up. The short-term prognosis of patients with spontaneous severe of flare to acute on chronic liver failure-like presentation is extremely poor, with a

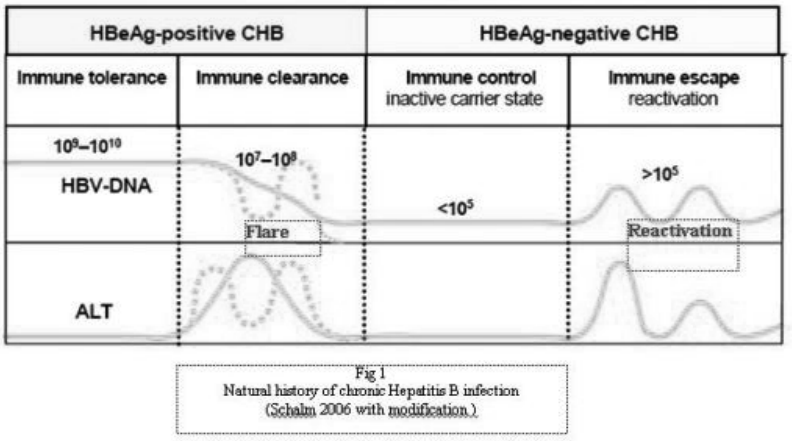

Figure 1. The Natural history of chronic hepatitis B infection.[18]

Table 2. Three Phases of HBV Reactivation[14]

Phase	Feature	Diagnostic Markers	Comments
1	Increase in viral replication	HBV DNA	Rise of > 1 log ^{10} IU/ml
		HBeAg	In HBeAg negative
		HBsAg	Reverse sero-conversion
2	Appearance of disease activity	ALT	Rise of > 3 times baseline
		Symptoms	Indicative of more severe injury
		Jaundice	
3	Recovery	HBV DNA	Fall to baseline values
		ALT	Fall to baseline values
		HBsAg	Maybe cleared late

mortality rate ranging from 30–70%.[20] There are three phases of HBV reactivation, but not all the patients have all three phases (see table 2).[14] Reactivation starts with the abrupt increase in viral replication that typically occurs soon after initiating immune suppression or chemotherapy. The increasing degree in viral replication is measured by the rise in HBV DNA in serum. In patients without HBeAg, this marker may reappear in the serum. The second phase starts when immune-suppression is withdrawn or decrease and hepatocellular injury or hepatitis arises, as shown by rises in serum aminotransferase levels and, in more severe instances, symptoms and jaundice. During this phase, HBV DNA levels may start to fall. The third phase of reactivation is recovery, as the evidence of liver injury resolves and HBV markers return to baseline values.

DIAGNOSIS

Although HBV reactivation can occur spontaneously, it usually occurs after chemotherapy or immune-suppression. The clinical presentation cases can vary, ranging from subclinical, asymptomatic course to severe acute hepatitis and even death. Although reactivation of HBV is mainly found in HBsAg positive patients, it can be observed in serologically recovered anti-HBc-positive, HBsAg-negative patients.[21] The current generally accepted definition of HBV reactivation following chemotherapy, is the development of hepatitis with a serum ALT greater than three times the upper limit of normal, or an absolute increase of 100 IU/L, associated with a demonstrable increase in HBV DNA by at least a 10-fold, or an absolute increase to > 10^8 IU/mL.[22] The typical presentation of severe flare or acute exacerbation is a short onset of jaundice and very high ALT level, sometimes preceded by prodromal constitutional symptoms, in patient with chronic HBV. Patient that suffered from acute on chronic liver failure is characterized by jaundice and coagulopathy, complicated within 4 weeks by ascites and or encephalopathy.[17]

The symptoms of severe flare of chronic hepatitis B can be similar to those of acute hepatitis B. Hence, severe flare might be misdiagnosis as acute hepatitis B in some case. In areas of intermediate to high HBV endemicity, endemic for chronic hepatitis B, reactivation or flare of chronic hepatitis B accounts for 27–70% of presumed acute hepatitis B. So it is important to understand the factors that differentiated severe flare of chronic hepatitis B from acute hepatitis B. A detailed history taking, IgM anti-HBc

Table 3. Factors to Differentiate Severe Flare of Chronic Hepatitis B from Acute Hepatitis B [24]

Factor	severe acute exacerbation of chronic hepatitis B	acute hepatitis B
Useful history	Past history of chronic hepatitis B Family history of chronic hepatitis B	Recent at risk blood, percutaneous or sexual exposure to HBV
Ig M anti-HBc titer	Negative to low (< 1: 1000)	High (> 1 : 1000)
HBV DNA level	High (> 100 000 copies/ml)	Low (< 100 000 copies/ml)
Histology	Evidence of chronicity	No evidence of chronicity
Follow up HBsAg after 6 months	Positive	Negative in over 95% of patients
Uncertain :		
· Basal core promoter mutation	Present	Absent
· Precore stop codon mutation	Present	Absent
Not useful :		
· Symptoms and signs	Prodromal symptom Jaundice and itching Abdominal discomfort	Prodromal symptom Jaundice and itching Abdominal discomfort
· Alanine transaminase	Very high	Very high

titer, HBV level and follow up HBsAg after 6 months are clue for diagnostic.

An Indian study suggest that a low titer of IgM anti-HBc (< :1000) and high HBV DNA level (> 141.500 copies/ml) are useful to identify severe acute exacerbation of chronic HBV from acute hepatitis B.[23]

THERAPY

The severity of the flare depends on the state of underlying liver disease. As patients with severe flare of chronic hepatitis B may not have underlying cirrhosis, they may recover to relatively normal liver function in contrast to those with end-stage-cirrhosis.[4,24] It is important to recognize this clinical presentation of chronic hepatitis B. In severe flare of chronic hepatitis B when immune clearance is already excessive, interferon-based treatment may be dangerous in further aggravating the hepatic decompensating and thus contraindicated. Most data in the published work involves the use of lamivudine to treat this condition.[24] An aggressive supportive treatment and discontinuation of cytotoxic chemotherapy has been the mainstay of treatment. [25]

Severe flare of chronic HBV patient need an intensive supportive care including close monitoring and treatment complication. For antiviral treatment to be effective, it should be administered early, preferably before serum bilirubin has gone up too high to 'the point of no return'. After a median treatment period of 6 weeks, all of the 25 patients with pre-therapy bilirubin level < 20 mg/dl in the treatment group (lamivudine 150 mg/day) group survived, while five (20%) of 20 patients in controlled group died (p= 0.013).[26] The definitive treatment for severe flare of chronic hepatitis B is liver transplantation.[4] In uncertain cases of acute hepatitis B vs. severe flare of chronic hepatitis B, one should manage these patients as severe flare and retested HBsAg after 6 months. Antiviral therapy is not indicated in the most patients with acute hepatitis, but may be indicated in certain groups of patients: (1) patients with fulminant hepatitis B, hepatic encephalopathy, persistent symptoms or marked jaundice

(bilirubin >10 mg/dL) for more than 4 weeks after presentation, or those who are immune-compromised, have concomitant infection with hepatitis C or D, or have pre-existing live disease. [4]

PREVENTION

The Centers for Disease Control and Prevention (CDC) recommends testing patients for HBsAg, anti-HBc and anti-HBs before they receive immunosuppressive therapy. The Practice Guideline of the American (AASLD) also recommend of HBV screening before beginning immunosuppressive therapy.[27] Although the CDC recommendations to test HBV before starting immunosuppressive therapy, surveys of oncologists have found that only 13–19% routinely test patients before initiating the immune-suppressive therapy.[28] Day Fl et al (2011) reported that the majority of Australian medical oncologist have not adapted universal screening before chemotherapy. Oncologists who did not screen most commonly cited inadequate evidence for a benefit of screening (72%).[29] Two decade ago, occult B hepatitis infection/OBI (anti HBc and or anti HBs positive, HBsAg negative with HBV DNA < 200 IU/mL) and resolved or past hepatitis B were not recognized to be at risk of HBV reactivation when receiving conventional systemic chemotherapy. But now patients with OBI represent an important group with a high risk for reactivation.[30]

One potential means of minimizing the risk of HBV reactivation is the avoidance of corticosteroid therapy as part of chemotherapeutic/antiemetic regimes in HBsAg carriers.[25] Closely monitoring and evaluating chronic hepatitis B is an important action to prevent and to minimize of flare. Because viral replication occurs before clinical evidence of hepatitis it raises the possibility of using lamivudine in prophylactic manner before the administration of chemotherapy.[25] A systematic studied evaluated that 550 HBsAg-positive patients receiving a cancer therapy. In patients who did not receive prophylactic antiviral therapy: 36.8% had HBV reactivation, 33.44% had HBV-related hepatitis, 13% had liver failure, and 5.5% died. Prophylactic use of lamivudine decreased the risk for HBV reactivation and HBV-related hepatitis by 79–100%. [27] Elevated serum ALT level, serum HBV DNA $>10^5$ copies/ml, positive serum HBeAg are risk factors for HBV reactivation. HBsAg positive patients undergoing chemotherapy should be treated with lamivudine 100 mg/day orally for at least 3 months after completion of chemotherapy, when white blood count has returned to pre-chemotherapy level. A high pre-chemotherapy HBV DNA (> 10^4 copies/ml) was the most important risk factor for HBV reactivation after withdrawal of preemptive lamivudine. Therefore, continue lamivudine for the longer period time until there is evidence of sero-conversion of HBeAg or HBsAg and closely monitors every 4 weeks. [16, 31]

SUMMARY

The presentation of reactivation or flare of chronic hepatitis B is quite common and is often difficult to clinically and biochemically differentiate from acute hepatitis B. A low titer of IgM anti-HBc (< 1:1000) and high HBV DNA level (> 141.500 copies/mL) are useful to identify flare of chronic HBV from acute hepatitis B. In uncertain cases of acute hepatitis B vs. severe flare of chronic hepatitis B, one should manage these patients as flare

and retested HBsAg after 6 months. Antiviral therapy is not indicated in the most patients with acute hepatitis, but may be indicated

Although HBV reactivation can occur spontaneously, it usually occurs after chemotherapy or immune-suppression. It is recommended to screen HBsAg and Anti-HBc before beginning immunosuppressive therapy. When there is positive of HBV infection, prophylactic use of lamivudine should be started, because it decreases the risk for HBV reactivation and HBV-related hepatitis.

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