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WHEN CHRONIC HEPATITIS B TURNS ACUTE: UNDERSTANDING AND MANAGING FLARES

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Abstract

Hepatitis B flare is a sudden exacerbation of chronic hepatitis B, defined by an abrupt ALT rise >5× upper limit of normal. Clinically, it may resemble acute hepatitis B, but low IgM anti-HBc titers and high HBV DNA levels aid differentiation. Flares arise from immune-mediated hepatocyte injury, triggered spontaneously, by immunosuppressive or antiviral therapy, pregnancy, viral superinfection, or viral genotype variations. Presentation ranges from asymptomatic biochemical changes to severe hepatitis, coagulopathy, and acute liver failure. Evaluation requires thorough history, physical examination, laboratory testing, imaging, and sometimes liver biopsy. Management focuses on supportive care and early nucleos(t)ide analogue therapy, as interferon can precipitate hepatic decompensation in severe immune-driven flares. Prognosis depends on baseline liver health; patients without cirrhosis generally recover, while acute-on-chronic liver failure carries high short-term mortality and may necessitate liver transplantation. Prompt recognition and timely antiviral therapy are essential to prevent liver failure, highlighting the importance of individualized strategies for optimal outcomes in hepatitis B flares.

Keyword: *chronic hepatitis B, flare , ALT elevation, HBV DNA, antiviral therapy*

INTRODUCTION

Hepatitis virus infection remains one of the communicable diseases that continues to pose a significant public health problem, affecting morbidity, mortality, overall population health status, and life expectancy. Almost all cases of hepatitis are caused by one of five viruses: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV). All hepatitis viruses that infect humans are RNA viruses, except for hepatitis B virus, which is a DNA virus.[1]

Approximately 296 million people worldwide have chronic hepatitis B, with 1.5 million new infections and about 820,000 deaths reported in 2019. Yet only around 10% of affected individuals are diagnosed. While most treated patients live outside Africa, the continent remains highly endemic, with a 60% lifetime infection risk and about 82 million chronic cases—nearly one-quarter of the global burden. The majority of new infections and most HBsAg-positive children under five are in the WHO African region, where diagnosis and treatment rates remain extremely low.[2]

Accurate national data on hepatitis B and C in Indonesia are still limited. Gaps in surveillance, the country's vast geography, and limited access to testing mean that many infections likely go undetected. As a result, most available data come from selected groups, such as blood donors or other higher-risk populations. Before the introduction of universal infant hepatitis B vaccination, HBsAg prevalence in the general population ranged from 4–20%, placing Indonesia in the intermediate-to-high endemicity category. Rates were considerably higher among patients with cirrhosis and hepatocellular carcinoma. Information on hepatitis C remains sparse, with reported anti-HCV prevalence of about 1–1.5% among blood donors.[3]

Acute exacerbations in chronic hepatitis B occur frequently and may be triggered by several identifiable and

treatable factors. These exacerbation episodes can result from changes in the host's immune response to HBV. Consequently, spontaneous elevations of alanine aminotransferase (ALT) levels and sudden episodic increases in ALT may occur, which are referred to as acute exacerbations or hepatitis flares.[4]

Despite the substantial global burden of hepatitis B and the high endemicity in Indonesia, important knowledge gaps remain regarding the clinical characteristics, triggers, and management of acute exacerbations in chronic hepatitis B, particularly in resource-limited and highly endemic settings. Rapid developments in antiviral therapy, monitoring strategies, and risk stratification highlight the need for an updated clinical synthesis that integrates current evidence with practical considerations for early detection and management. Therefore, this review aims to comprehensively summarize the current understanding of acute exacerbations in chronic hepatitis B, including their pathophysiology, precipitating factors, clinical implications, and evidence-based approaches to diagnosis and treatment.

DEFINITION

A hepatitis B flare is typically identified by a sharp rise in alanine aminotransferase (ALT), defined as an increase to more than five times the upper limit of normal (ULN) or at least three times the patient's baseline level. An ALT elevation above five times ULN is considered the minimum threshold. Because acute superinfection with other hepatitis viruses can present with a similar sudden ALT spike, serologic or virologic testing is needed to confirm that the flare is HBV-related. From a virologic perspective, a flare is also characterized by a rise in HBV DNA of at least 2 log10 IU/mL. A severe flare is defined by an HBV DNA increase of ≥2 log10 IU/mL accompanied by ALT levels ≥10 times the ULN.[4]

NATURAL HISTORY OF HEPATITIS B

Hepatitis B virus (HBV), a member of the *Hepadnaviridae* family, is a 42-nm double-stranded DNA virus. It consists of a 27-nm nucleocapsid core (HBcAg) surrounded by a lipid envelope containing hepatitis B surface antigen (HBsAg). Ten HBV genotypes (A–J) have been identified, with distribution varying by geographic region.

The course of chronic HBV infection is currently described in five phases, based on HBeAg status, HBV DNA levels, ALT values, and the presence of liver inflammation. The updated terminology distinguishes between "infection" and "hepatitis" to better reflect disease activity.[5,6]

Phase 1 – HBeAg-positive chronic infection (formerly immune-tolerant phase):
Characterized by positive HBeAg, very high HBV DNA levels, and persistently normal ALT. Liver inflammation and fibrosis are minimal or absent, although high viral replication may still contribute to early carcinogenesis. This phase is common in individuals infected perinatally or during early life and is associated with high infectivity.[6]

Phase 2 – HBeAg-positive chronic hepatitis (formerly immune-clearance phase):
Occurs when the immune system begins attacking infected hepatocytes. HBeAg remains positive, HBV DNA is elevated, and ALT rises. Liver histology shows moderate to severe necroinflammation with accelerating fibrosis. This phase often develops years after initial infection and is more typical in adults.[6]

Phase 3 – HBeAg-negative chronic infection (inactive carrier state):
Marked by anti-HBe positivity, low or undetectable HBV DNA (<2000 IU/mL), and normal ALT. Some patients may have slightly higher viral loads with minimal liver injury. The risk of cirrhosis or hepatocellular carcinoma is generally low in this stage.[6]

Phase 4 – HBeAg-negative chronic hepatitis (reactivation phase):
Characterized by negative or low HBeAg, usually positive anti-HBe, fluctuating HBV DNA and ALT levels, and ongoing liver inflammation with fibrosis. Spontaneous remission is uncommon. [6]

Phase 5 – HBsAg-negative phase (resolved or occult infection):
Defined by loss of HBsAg with positive anti-HBc, with or without anti-HBs. ALT is

typically normal and serum HBV DNA is usually undetectable.[6]

Hepatitis B flares most commonly arise during the HBeAg-positive immune-active phase but may also occur in the HBeAg-negative phase. Significant ALT elevations, particularly >5× the upper limit of normal, can progress to severe hepatitis or liver decompensation.[5]
Acute exacerbations are generally seen in two settings:

1. Flares during the immune-active phase, including HBeAg-negative chronic hepatitis; and
2. Reactivation due to increased viral replication in previously inactive carriers or even in individuals who are HBsAg-negative.
3.

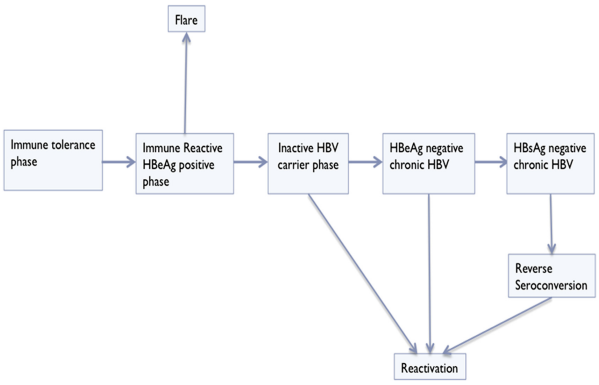

Figure 1. Acute Exacerbation In The Natural Course Of Chronic Hepatitis B. These Phases Do Not Necessarily Occur Sequentially In All Patients.[7]

PATHOGENESIS

Hepatitis B virus (HBV) is not directly cytopathic; liver injury results from a complex interaction between the virus, hepatocytes, and the host immune response. During a hepatitis B flare, serum HBV DNA typically rises first, followed by a sharp increase in ALT. This viral surge is often accompanied by higher levels of HBsAg and HBeAg.[8]
Flares reflect shifts in both innate and adaptive immunity. Immune responses targeting HBV antigens presented via HLA class I molecules activate cytotoxic CD8+ T cells (with CD4+ T-cell support), leading to destruction of infected hepatocytes. Antigen-presenting cells, dendritic cells, macrophages, and other non-parenchymal cells contribute by releasing interferon-α/β, cytokines, and chemokines. Increased Th1/Th2 activity, natural killer (NK) cell activation, elevated IFN-γ (often associated with CXCL-9 and CXCL-10), PD-1/PD-L1 signaling, and Toll-like receptor activation have all been observed during acute exacerbations.[8] Thus, elevated ALT during a flare reflects an intensified endogenous immune response against HBV rather than direct viral toxicity. However, the precise trigger initiating this immunologic cascade remains unclear.[8,9]

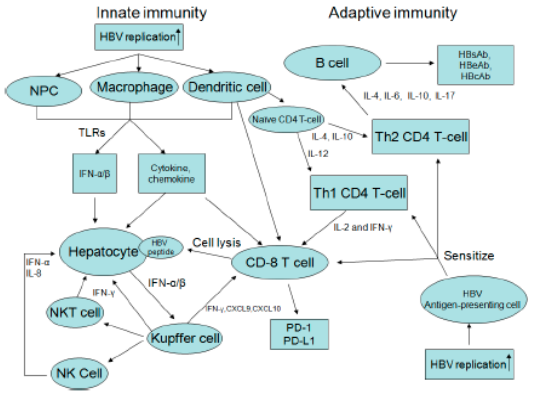

Figure 2. Immune Mechanisms Underlying Hepatitis B Flare in Chronic Infection[9]

CLASSIFICATION

Hepatitis B flares in chronic infection can occur in various clinical settings and are strongly influenced by the patient's immune status. Most flares that cannot be explained by superinfection with other hepatotropic viruses result from shifts in the balance between HBV replication and the host immune response. These episodes may arise secondary to increased replication of wild-type or mutant HBV strains, or they may be triggered by therapeutic interventions that modify immune function, such as interferon therapy, corticosteroids, or chemotherapy.[10]

Spontaneous Reactivation Hepatitis B

Acute exacerbations may be triggered by reactivation of HBV and are sometimes mistaken for acute viral hepatitis. The precise cause of reactivation is often unclear, but it is likely related to changes in immune control over viral replication, similar to mechanisms seen in other latent viral infections. Reactivation appears more

common in men who have sex with men, individuals with HIV infection, those with concurrent bacterial infections, and patients undergoing surgery. Physical or emotional stress and pregnancy may also act as precipitating factors. Flares are reported more frequently in adulthood, possibly due to alterations in immune tolerance to HBV. Hepatitis B flares may occur in several clinical situations: [10]

Non-replicative phase (anti-HBe positive, HBV DNA undetectable): ALT levels rise as viral replication suddenly reappears.

Replicative phase (HBeAg and HBV DNA positive): Increased viral replication leads to higher HBV DNA levels and worsening liver biochemistry, usually without HBeAg loss. This episode may represent an unsuccessful attempt at seroconversion.

Precore mutant infection: HBV DNA levels increase while HBeAg remains negative, reflecting viral replication despite the absence of HBeAg expression.

Table 1. Causes and Clinical Settings of Hepatitis B Flare

No	Causes and Clinical Settings
1	**Spontaneous reactivation.** Occurs without an obvious external trigger
2	**Immunosuppressive therapy–related reactivation** - Chemotherapy for malignancy - Anti-rejection (post-transplant) drugs - Corticosteroids
3	**Antiviral therapy–related** - Interferon treatment - Nucleos(t)ide analogues - Corticosteroid withdrawal
4	**HBV genetic variants** - Precore mutants - Core promoter mutants - HBV DNA polymerase mutants
5	**Superinfection with other hepatotropic viruses** - Hepatitis A virus (HAV) - Hepatitis C virus (HCV) - Hepatitis D virus (HDV)
6	**HIV co-infection** - HBV reactivation - Immune reconstitution inflammatory syndrome (IRIS)
7	**Pregnancy**

Immunosuppressive Therapy and HBV Reactivation

In patients with chronic hepatitis B, HBV reactivation is a known risk during treatment with chemotherapy or other immunosuppressive drugs. When the immune system is suppressed, it can no longer effectively control the virus, allowing HBV to replicate more actively and infect more liver cells.

Problems often arise when these medications are reduced or stopped. As the immune system recovers, it may suddenly recognize and attack HBV-infected hepatocytes, leading to a hepatitis flare. In general, the stronger the immunosuppression, the greater the viral rebound—and the more severe the flare once immune function returns.

Unfortunately, flares related to chemotherapy or immunosuppressive therapy are frequently recognized only after liver enzymes begin to rise. At that stage, starting antiviral treatment may not fully prevent liver injury, since the immune-driven damage is already in progress.[10,11]

HBV reactivation during immunosuppressive therapy is uncommon with low doses of corticosteroids, azathioprine, or methotrexate. However, it is more frequently associated with stronger immunosuppressive agents, particularly TNF-α inhibitors and monoclonal antibodies such as infliximab or adalimumab.[7] Reactivation related to immunosuppressive therapy generally occurs in two phases:

1. Viral replication phase:
HBV DNA levels rise significantly. HBeAg may reappear in previously HBeAg-negative patients, and in some cases, individuals who were HBsAg-negative may become HBsAg-positive again.
2. Immune restoration phase:
After immunosuppressive therapy is reduced or stopped, immune function recovers. ALT levels increase as the immune system attacks infected hepatocytes, while HBV DNA levels begin to decline. Clinically, patients may develop jaundice and, in severe cases, acute liver failure. With recovery, liver inflammation gradually improves and HBV DNA returns to baseline levels.

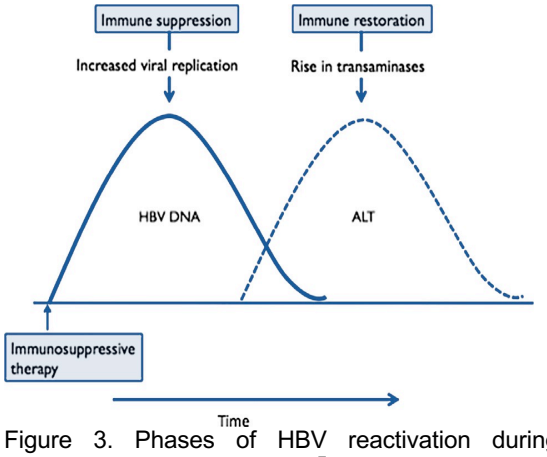

Figure 3. Phases of HBV reactivation during immunosuppressive therapy. [7]

Antiviral Therapy–Induced Hepatitis B Flare

Hepatitis B treatment can sometimes trigger a flare. This may happen during interferon therapy, with nucleos(t)ide analogues, or after stopping corticosteroids.

With interferon, the immune system becomes more active—especially T cells and NK cells—which can lead to a stronger attack on infected liver cells. Flares usually appear in the second or third month of treatment. In patients with advanced liver disease, this reaction can be severe and may worsen liver function. For this reason, interferon is generally avoided in patients with Child-Pugh B or C cirrhosis because of the risk of decompensation. [10]

Nucleos(t)ide analogues:

Drugs such as lamivudine and famciclovir are generally considered safe and effective. However, about 10% of patients treated with lamivudine may experience a rise in aminotransferase levels, typically three to ten times above baseline. Similar flares have also been reported with famciclovir.

Unlike interferon-related flares, ALT elevations during lamivudine therapy usually occur early—within the first 4–6 weeks—and are often accompanied by a marked decline in HBV DNA levels. The exact reason for these early flares is not fully understood, but they may reflect a recovering T-cell response as viral replication decreases. [10]

Hepatitis flare during nucleos(t)ide analogue therapy. Flares are more common in HBeAg-positive patients and are less frequently seen with potent agents such as entecavir or tenofovir. They are often associated with a rapid decline in HBV DNA (≥2 log copies/mL within the first 8 weeks), suggesting a temporary restoration of HBV-specific T-cell responses as viral replication decreases.[8]

Flare due to antiviral resistance. When a flare develops after 24 weeks of therapy, drug resistance should be suspected. Rising levels of resistant HBV strains can lead to gradual ALT elevation, potentially progressing to severe hepatitis, liver decompensation, or even failure. Switching to or adding a nucleos(t)ide analogue with a different resistance profile can help control these cases.[8]

Flare after stopping nucleos(t)ide analogue therapy. These flares are usually preceded by a rebound in HBV DNA, indicating renewed viral replication. They occur most often in patients who remain HBeAg-positive, but can also affect those who achieved HBeAg seroconversion—particularly older patients, those with genotype C infection, or those treated for a short duration. Severe outcomes are more likely in patients who are not closely monitored or who fail to restart therapy promptly. For this reason, careful follow-up after treatment discontinuation is essential.[8]

Prednisone withdrawal: Hepatitis flares after stopping prednisone are thought to result from renewed lymphocyte activation, particularly a shift toward a stronger Th1 immune response at a time when viral antigen expression is increasing. ALT levels typically peak about 4–6 weeks after corticosteroid withdrawal. The severity of the flare may be influenced by the initial steroid dose and the duration of therapy, with higher doses and shorter courses potentially altering the intensity of the rebound response.[10]

HBV Genotype Variations and Hepatitis Flare

Hepatitis B flares may also be linked to viral genetic variations. In particular, patients infected with precore mutant HBV—often HBeAg-negative—may develop flares due to a stronger immune response against core-related viral peptides expressed on hepatocytes. Episodic flares have been associated with shifts in viral populations, including increases in precore mutants or reversion to wild-type strains.

Flares are reported more frequently in men and in patients infected with HBV genotype C. Compared with other genotypes, genotype C infection is more often associated with persistent HBeAg positivity, more advanced liver fibrosis, and a higher likelihood of requiring nucleos(t)ide analogue therapy.[10,7,12]

Flares Triggered by Other Viral Infections

Patients with chronic hepatitis B may develop a flare—or even acute liver failure—when superinfected with other hepatotropic viruses such as hepatitis A (HAV), hepatitis C (HCV), or hepatitis D (HDV). Mortality is reported to be particularly high when acute HAV occurs in individuals with underlying chronic HBV. Fulminant liver failure is also well described in cases of HDV superinfection or acute HCV infection in HBV carriers.

In these situations, the flare is driven not only by HBV activity but also by complex viral interactions and immune responses. The clinical course depends on factors such as background HBV replication, HBeAg status, and regional viral prevalence. Superinfection may suppress HBV replication temporarily, leading to HBeAg or even HBsAg seroconversion in some cases. However, this viral interference can also destabilize immune control and precipitate significant hepatic inflammation. [10]

Interaction with HIV

The relationship between HIV and HBV infection is complex. Elevated liver enzymes are common in people living with HIV and may result from drug toxicity, HBV or HCV coinfection, or immune-related mechanisms. Studies have shown that patients with HIV–HBV coinfection often have higher HBV DNA levels, and hepatitis B flares occur in approximately 20–25% of cases after initiation of HAART (highly active antiretroviral therapy). With the introduction of more potent antiretroviral regimens, immune reconstitution inflammatory syndrome (IRIS) has become more frequent. As immune function improves, an enhanced immune response against HBV can trigger a hepatitis flare, typically within the first weeks of therapy. Flares have also been reported after discontinuation of antiviral drugs. Some reports associate flares with immune restoration related to ritonavir use, while others suggest that suppression of HIV replication may alter cytokine balance and disrupt prior immune tolerance to HBV. Lamivudine has also been implicated in flares among HIV–HBV coinfected patients, particularly during treatment or after withdrawal. [10 ,13]

In three cases reported by Perrillo, hepatitis flares developed after 13–18 months of lamivudine therapy. Flares have also been observed when lamivudine was discontinued and replaced with a different antiretroviral regimen.

In addition, increased hepatotoxicity related to antiretroviral therapy—particularly with ritonavir—should be considered in patients with chronic hepatitis B who develop rising serum aminotransferase levels.[10]

Pregnancy

Pregnancy is associated with relative immune suppression, which may increase HBV replication and raise HBV DNA levels while ALT levels often decline. After delivery, immune function rebounds, and ALT may rise significantly as HBV DNA decreases—resulting in a postpartum flare. Most postpartum flares occur within 8–10 weeks after delivery and are usually mild and self-limited, although severe cases can occur. Antiviral therapy during pregnancy and its discontinuation after childbirth may also trigger flares. Therefore, close monitoring for at least six months postpartum is recommended, especially in

HBeAg-positive women or those who stop antiviral therapy.[8,14,15]

Clinical Manifestations

The presentation of a hepatitis B flare ranges widely. Some patients remain asymptomatic, while others develop symptoms resembling acute hepatitis, such as fatigue, nausea, abdominal discomfort, or jaundice. In more severe cases, a flare can progress to hepatic decompensation, marked by jaundice, coagulopathy, and potentially acute liver failure. Certain patients present with overt acute hepatitis features, testing positive for HBsAg and negative for IgM anti-HBc, even without a prior known history of HBV infection or underlying liver disease. Flares may also occur in individuals with chronic hepatitis B who have progressed to cirrhosis—most commonly within the first few years after cirrhosis develops. This includes patients who have undergone curative liver resection for hepatocellular carcinoma. In these populations, flares are associated with a substantially higher risk of liver decompensation and mortality compared with patients who do not have cirrhosis.[8,11,16]

According to the Asian Pacific Association for the Study of the Liver guidelines, a typical presentation of HBV reactivation in patients with chronic hepatitis B is the rapid onset of jaundice accompanied by a marked rise in ALT levels. This may be preceded by nonspecific prodromal symptoms such as fatigue, malaise, or low-grade fever.

Because clinical deterioration can occur quickly, close monitoring is recommended—ALT, bilirubin, and prothrombin time should be checked once or twice weekly to promptly detect worsening liver function or impending decompensation, allowing timely treatment or preventive measures.

In most cases, ALT levels begin to decline within about one month. Symptom resolution within three months is seen in fewer than one-fifth of HBeAg-positive patients, whereas nearly one-third of HBeAg-negative patients may continue to have persistently abnormal ALT levels beyond this period. [8,17]

The differences between acute hepatitis B infection and hepatitis B flare are summarized in Table 2.

Table 2. Simplified Differences Between Acute Hepatitis B and Hepatitis B Flare [7]

Feature	Acute Hepatitis B	Hepatitis B Flare
Clinical History	Recent exposure (surgery, transfusion, occupational)	Known chronic HBV or prior risk history
Portal Hypertension	Absent	May be present
IgM anti-HBc	High titer positive	Negative or low titer
HBV DNA Level	Low or undetectable	High
HBsAg at 6 Months	Usually clears	Usually persists
Histology	No chronic liver damage	Fibrosis or cirrhosis may be present
Liver Stiffness (LSM)	Normal	Often elevated
AFP	Normal	May be elevated
HBeAg	Low level	Often high level
Symptoms	Acute hepatitis-like (prodrome, jaundice)	Similar presentation; may overlap
Transaminases (ALT/AST)	Elevated	Elevated

Evaluation of Hepatitis B Flare

Assessment of a patient with suspected hepatitis B flare should be comprehensive, combining clinical history, physical examination, and targeted investigations.

History should explore symptoms suggestive of acute hepatitis, although some patients may remain asymptomatic. It is important to ask about prior HBV infection, family history of hepatitis B or hepatocellular carcinoma, and potential

risk factors for new or superimposed viral infections. Coexisting conditions such as obesity, diabetes, metabolic syndrome, and fatty liver disease should also be considered. Anamnesis[17]

Physical examination may reveal nonspecific prodromal symptoms and jaundice. Particular attention should be given to signs of cirrhosis or hepatic decompensation. Anamnesis[17]

Laboratory tests often resemble those seen in acute hepatitis, with elevated ALT and bilirubin. Evaluation includes complete blood count, liver biochemistry (ALT, AST, ALP, GGT, albumin, prothrombin time), HBV serology (HBsAg, anti-HBc, anti-HBs), and virologic markers (HBeAg, anti-HBe, HBV DNA). IgM anti-HBc may be positive but typically at lower levels than in true acute infection. Alpha-fetoprotein (AFP) can rise in about one-quarter of cases, usually peaking shortly after ALT elevation and gradually normalizing over months; however, hepatocellular carcinoma must always be excluded when AFP is elevated. Liver ultrasound is useful to assess liver and spleen size. [8,17]

Histologically, liver biopsy may show patchy but extensive necroinflammatory activity, and in severe cases, bridging hepatic necrosis can be observed. [8,17]

Management

Patients experiencing a hepatitis B flare require supportive care with close monitoring for potential complications, particularly signs of liver failure. In severe flares marked by intense immune activity, interferon therapy is contraindicated because it may precipitate hepatic decompensation. In this setting, oral nucleos(t)ide analogues are the preferred treatment option. [18]

The decision to initiate antiviral therapy is generally based on four key factors: serum HBV DNA level, HBeAg status, ALT level, and liver histology.

Currently, treatment options for chronic hepatitis B fall into two main categories: 1) Interferons (pegylated interferon alfa-2a and alfa-2b), 2) Nucleos(t)ide analogues, such as lamivudine, adefovir, entecavir, and tenofovir

These two drug classes differ in mechanism of action, route of administration, duration of therapy, and safety profile (table 3).[19]

Table 3. The Comparison of Interferon and Nucleoside Analog [19]

Parameter	Interferon (Peg-IFN)	Nucleos(t)ide Analogues (NAs)
Treatment duration	Finite (≤48 weeks)	Long-term, often indefinite
Route	Subcutaneous injection	Oral
Use in decompensated cirrhosis	Contraindicated	Recommended
Adverse effects	Frequent, systemic	Generally mild
HBV DNA suppression (1 year)	Moderate	Potent
HBeAg seroconversion (1 year)	Lower	Higher
HBsAg seroconversion	Higher probability	Lower, may increase with prolonged therapy
Biochemical response	Comparable	Comparable
Histologic improvement	Comparable	Comparable
Resistance	None	Possible (agent-dependent)
Durability after stopping therapy	More sustained if response achieved	High relapse risk if discontinued

According to the *Perhimpunan Peneliti Hati Indonesia* (PPHI) consensus, first-line therapy for chronic hepatitis B currently includes pegylated interferon, entecavir, or tenofovir. Second-line alternatives include lamivudine and adefovir. However, no single regimen can be considered superior for all patients, as treatment choice should be individualized based on clinical condition, disease severity, comorbidities, and therapeutic goals.[19]

Pegylated Interferon (Peg-IFN) Therapy

Two formulations are currently available: pegylated interferon alfa-2a (180 µg once weekly) and pegylated interferon alfa-2b (1–1.5 µg/kg once weekly), both administered subcutaneously for 48 weeks. [19]

Peg-IFN is contraindicated in patients with decompensated cirrhosis, active psychiatric disorders, pregnancy, or active autoimmune disease. Common adverse effects include flu-like symptoms, bone marrow suppression, mood disturbances, and autoimmune reactions. Most side effects are reversible after treatment discontinuation. [19]

Nucleos(t)ide Analogue Therapy

Oral antiviral options include entecavir (0.5 mg daily for treatment-naïve patients; 1 mg daily in lamivudine resistance), tenofovir disoproxil fumarate (300 mg daily), tenofovir alafenamide (25 mg daily), lamivudine (100 mg daily), and adefovir dipivoxil (10 mg daily). [19]

According to the European Association for the Study of the Liver (EASL) guidelines, nucleos(t)ide analogues are classified based on their genetic barrier to resistance. Agents such as lamivudine, adefovir, and telbivudine have a low barrier to resistance, whereas entecavir and tenofovir (both TDF and TAF) have a high barrier.

Whenever possible, therapy should prioritize high-barrier agents, along with routine monitoring of complete blood count, liver and renal function, and HBV DNA levels. Importantly, nucleos(t)ide analogues remain the only effective strategy for preventing HBV reactivation in patients undergoing immunosuppressive therapy.[6]

According to the Asian Pacific Association for the Study of the Liver (APASL) guidelines, in cases of hepatitis B flare, nucleos(t)ide analogue therapy should be initiated as early as possible, without delaying treatment while awaiting HBV DNA results. Early antiviral therapy is crucial to prevent further hepatic deterioration. In severe flare complicated by acute-on-chronic liver failure, the only definitive treatment is liver transplantation, either from a living donor or a deceased donor. This approach offers excellent outcomes, with reported five-year survival rates exceeding 90%.[17]

According to the American Association for the Study of Liver Diseases (AASLD) guidelines, in patients with cirrhosis, high-potency nucleos(t)ide analogues such as tenofovir and entecavir are preferred due to their strong antiviral effect and low risk of resistance. Agents with a low barrier to resistance are not recommended, as resistance can lead to hepatic decompensation. While pegylated interferon is not contraindicated in compensated cirrhosis, nucleos(t)ide analogues are generally considered safer for these patients. [5]

Figure 4 illustrates a decision tree for managing patients with chronic HBV infection experiencing a hepatitis B flare

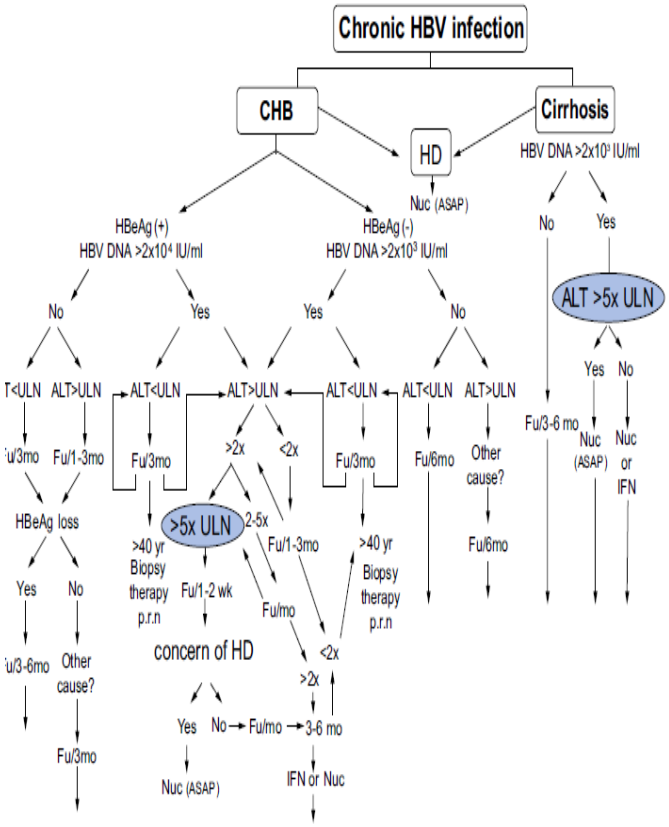

Figure 4. Decision Tree for Patients with Chronic Hepatitis B, Including Those Experiencing a Hepatitis B Flare (ALT >5× ULN)[8]

PROGNOSIS

The prognosis of a hepatitis B flare largely depends on the underlying liver condition and other individual factors. Patients experiencing a severe flare without preexisting cirrhosis generally recover with relatively normal liver function, whereas those with cirrhosis have a higher risk of complications. In one study, after HBeAg seroconversion and cessation of therapy, 90% of patients experienced viral

relapse, and 38% developed ALT flares, compared with those who continued long-term treatment. This highlights the importance of ongoing monitoring and careful management after therapy discontinuation..[17,20]

The mortality rate for chronic hepatitis B exacerbations requiring hospitalization is approximately 36.2%. Poor prognosis is independently associated with factors such as preexisting cirrhosis, higher Child-Pugh scores, low albumin, elevated bilirubin, prolonged prothrombin time (PT), thrombocytopenia, presence of ascites, and hepatic encephalopathy. Patients with PT >30 seconds face mortality rates up to 85.7%, and those with albumin ≤35 g/L combined with bilirubin >200 μM have mortality as high as 92.3%. These markers play a key role in assessing risk and guiding intensive care.

A study from Taiwan found that among HBeAg-positive patients without preexisting cirrhosis, 5.1% progressed to liver decompensation, with serum HBV DNA identified as a significant risk factor. A cut-off of 1.55 × 10^9 copies/mL predicted progression to decompensation. In patients with cirrhosis, limited hepatic reserve slows recovery and increases vulnerability to complications such as sepsis, gastrointestinal bleeding, and acute kidney injury. Preexisting cirrhosis and liver dysfunction are consistently associated with high mortality. Once acute-on-chronic liver failure (ACLF) develops, prognosis is poor, with 3-month mortality around 50–55% without liver transplantation.[17]

SUMMARY

Hepatitis B flare is defined by a sudden rise in serum ALT >5× ULN, which serves as the minimal criterion for diagnosis. Clinically and biochemically, it is often difficult to distinguish from acute hepatitis B. Low IgM anti-HBc titers (<1:1000) combined with high HBV DNA levels (>100,000 copies/mL) help differentiate flare from acute infection.

Management focuses on supportive care and monitoring for potential complications. Antiviral therapy should be initiated promptly. Interferon is generally avoided in flares with excessive immune activity due to the risk of liver decompensation; nucleos(t)ide analogues are preferred.

The severity of a flare depends largely on the underlying liver disease and can progress to liver failure or death if not properly managed.

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