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EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

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Hepatitis B flares in chronic hepatitis B: Pathogenesis, natural course, and management

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Summary

Hepatitis B flare, defined as an event with abrupt rise of alanine aminotransferase (ALT) levels to >5 times the upper limit of normal during chronic hepatitis B virus (HBV) infection, is considered to be the result of a human leukocyte antigen-I restricted, cytotoxic T lymphocyte mediated immune response against HBV and its downstream mechanisms. It may occur spontaneously, during or after antiviral therapy and in the setting of immunosuppression and/or chemotherapy. The clinical spectrum of hepatitis B flares varies from asymptomatic to symptomatic and typical overt acute hepatitis, even with hepatic decompensation or failure. Flares may also occur in viraemic patients with cirrhosis with higher incidence of decompensation/mortality, hence requiring immediate antiviral therapy. An upsurge of serum HBV DNA and hepatitis B surface antigen levels usually precedes the abrupt rise of ALT levels. Rising or stable and high HBV DNA during flares represent ineffective immune clearance and further hepatocytolysis, even hepatic decompensation, may occur. Such patients require immediate antiviral therapy. In contrast, bridging hepatic necrosis and/or alpha-fetoprotein levels >100 ng/ml or decreasing HBV DNA during flares represent a more effective immune clearance and frequently leads to seroclearance of HBV DNA and/or hepatitis B e antigen with remission. If patients are non-cirrhotic and there is no concern of developing decompensation, patients may be observed for 3–6 months before deciding on the need of antiviral therapy. Severe and repeated flares are prone to develop into decompensation or lead to the develop-

ment of cirrhosis, thus a timely treatment to prevent the hepatitis B flare is better than to cope with the flare. Screening, monitoring and prophylactic or pre-emptive antiviral therapy is mandatory for patients who are going to receive immunosuppressants or chemotherapy.
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Introduction

Chronic hepatitis B virus (HBV) infection is a dynamic state of interactions among HBV, hepatocytes and immune cells of the host. Accordingly, hepatitis activity with alanine aminotransferase (ALT) elevation and episodic abrupt rise of ALT, so called acute exacerbation or hepatitis flare, may occur spontaneously [1]. Hepatitis B flares may also occur during or after antiviral therapy or in the setting of immunosuppression and/or chemotherapy [2]. Based on earlier findings that less active hepatitis usually has an ALT level below 5 times the upper limit of normal (ULN), while active hepatitis has an ALT value far above this level [3], a chronic hepatitis B (CHB) flare was initially defined as "an abrupt elevation of ALT over 300 U/L (normal <40 U/L) in patients with a baseline ALT level <200 U/L (<5× ULN)" [4]. Later, it was defined as "an abrupt elevation of serum ALT to >5× ULN or a greater than 3-fold increase in ALT, whichever was higher" [5], and then as "intermittent elevations of aminotransferase activity to more than 10 times ULN and more than twice the baseline value" [6]. All of these definitions agree that "an abrupt ALT elevation >5× ULN" is the minimum criterion of a hepatitis flare. This ALT threshold has been widely accepted in the categorical analyses of therapeutical trials or clinical studies since 1990s. Acute superinfection with other hepatitis virus(es) in patients with chronic HBV infection also presents with an abrupt high rise of ALT and should be differentiated from the hepatitis flare caused by HBV (hepatitis B flare) using serologic or virologic assays [2,3,7].

In recent decades, ultrasensitive assays for serum HBV DNA and hepatitis B surface antigen (HBsAg) levels as well as new therapeutic agents have become available. Hence, new advances in the understanding of the natural history, the immunopathogenesis of the hepatitis B flare and its management have emerged. The following is an update and appraisal of the issues related to

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Abbreviations: ADV, adefovir; AFP, alphafetoprotein; ALT, alanine aminotransferase; anti-CD$_{20}$, CD$_{20}$ antibodies; anti-TNF, anti-tumour necrosis factors; ART, antiretroviral therapy; BHN, bridging hepatic necrosis; cccDNA, covalently closed circular DNA; CHB, chronic hepatitis B; CTL, cytotoxic T lymphocyte; ETV, entecavir; HBcAg, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; IFN-α, interferon alpha; IFN-γ, interferon gamma; LAM, lamivudine; Nuc, nucleos(t)ide analogue; Peg IFN, pegylated interferon; Treg, regulatory T cell; ULN, upper limit of normal; TDF, tenofovir.

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Key Points

- Acute hepatitis B flares (ALT >5x ULN) are results of a HLA-I restricted, CTL mediated response against HBV. Stronger endogenous immune responses result in more hepatocytolysis, higher ALT levels and more effective clearance of HBV

- Flares with rising and high HBV DNA may lead to hepatic decompensation, thus requiring immediate antiviral therapy for prevention or rescue

- While flares in cirrhotic patients always require immediate antiviral therapy, flares in non-cirrhotic patients with decreasing HBV DNA may be followed by HBV and/or HBeAg loss with remission, and therefore, may be observed for 3-6 months for real indication of antiviral therapy

- Severe flares (decompensation, bridging hepatic necrosis, AFP >100 ng/ml) are prone to progress to cirrhosis, thus timely treatment to prevent the hepatitis flare is better than to treat the flare

- Screening, monitoring and prophylactic or pre-emptive antiviral therapy is mandatory for patients who are going to receive immunosuppressants or chemotherapy

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Spontaneous hepatitis B flare

Clinical and pathological presentations

During the natural course of chronic HBV infection, hepatitis B flares start to occur during the hepatitis B e antigen (HBeAg) positive immune clearance phase [1,4,5,8]. Hepatitis B flares also occur in the HBeAg-negative reactive phase, but less frequently than during the HBeAg-positive phase [9–11]. In a hospital based study of CHB, the annual incidence of hepatitis flares was calculated to be 27% in 358 HBeAg-positive patients and 10% in 279 HBeAg-negative counterparts during a mean follow-up period of 2 years after entry [9]. It is not uncommon to have multiple episodic hepatitis B flares in one individual patient [4,8,11].

Clinical presentations

The clinical spectrum of hepatitis B flares varies from totally asymptomatic to symptomatic and to a feature similar to overt acute hepatitis (around 30%), with extreme manifestations of severe flares complicating hepatic decompensation (jaundice and coagulopathy) or even leading to hepatic failure [8–12]. Some hepatitis B flares may present as overt acute hepatitis, seropositive for HBsAg but negative for IgM class antibody to the hepatitis B core antigen (IgM anti-HBc) in patients who have had no past history of HBV infection or liver disease [13]. Hepatitis B flares may also occur in viraemic CHB patients with cirrhosis, including those after curative resection of hepatocellular carcinoma (HCC), and are associated with a higher rate of hepatic decompensation (13.9% vs. 2–3% in CHB) and mortality than in those of CHB without cirrhosis [14].
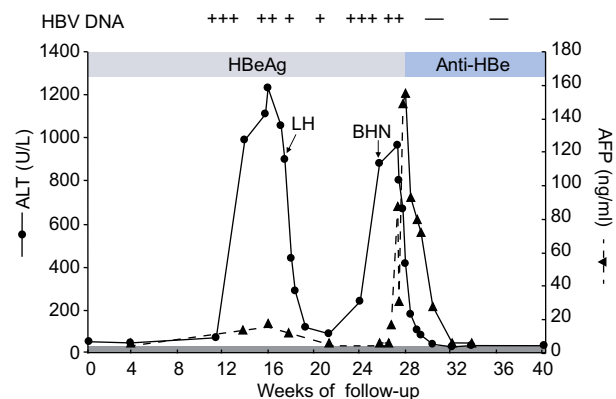

Fig. 1. Clinical course of a patient with two episodes of hepatitis flare. The abrupt elevation of serum alanine aminotransferase (ALT) is followed by a rise of serum alphafetoprotein (AFP), with a time lag of 1–2 weeks between the peak levels of ALT and AFP. AFP level was low during the flare with lobular hepatitis (LH) but >100 ng/ml during the (second) flare with bridging hepatic necrosis (BHN), which was followed by subsequent HBeAg seroconversion to its antibody (anti-HBe).

Laboratory findings and AFP level

The biochemical abnormalities, including serum ALT and bilirubin, of hepatitis B flares are similar to but in general less severe than those of acute hepatitis or acute superinfections [3]. Using enzyme immunoassay, 10–25% of hepatitis B flares were seropositive for IgM anti-HBc, but usually at a low serum/cutoff ratio compared to acute hepatitis B [8,11,15]. About 25–30% of hepatitis B flares are associated with an elevation of serum alpha-fetoprotein (AFP), of which the peak level is determined by 3 to 4 weekly or biweekly measurements after the onset of abrupt ALT elevation (Fig. 1). The peak serum AFP levels usually appear 1–2 weeks after the peak of ALT and may increase even over 2500 ng/ml, and usually return to a normal level within 3–12 months after the flare [16]. Of note, HCC should always be ruled out in patients with any elevated AFP level.

Histological findings

Liver biopsies during hepatitis B flares invariably show lobular necroinflammatory changes, which are distributed unevenly and may be so extensive that bridging hepatic necrosis (BHN) may occur [4,8,9]. BHN is evident in more than 80% of the patients with AFP >100 ng/ml during hepatitis B flares [7]. It was further demonstrated that patients with high AFP or BHN during the hepatitis flare had a high degree of AFP-producing oval cell activation (23.7–25.7% of hepatocytes), in contrast to 2.4–5.6% in patients with APF <100 ng/ml or no BHN [17]. Therefore, properly measured AFP-levels during the hepatitis flare of >100 ng/ml can be used as a surrogate marker of BHN.

Pathogenesis of the hepatitis B flare

HBV is not directly cytopathic by itself and the hepatocellular injuries are considered to be the results of a complex interplay among HBV, hepatocytes and immune cells of the host [1–4,7]. It has been documented by weekly to monthly assays that there is an upsurge of serum HBV DNA prior to the abrupt elevation of ALT [18–20]. There is also a parallel elevation of the serum HBsAg level along with the upsurge of serum HBV DNA (Fig. 2). Using a
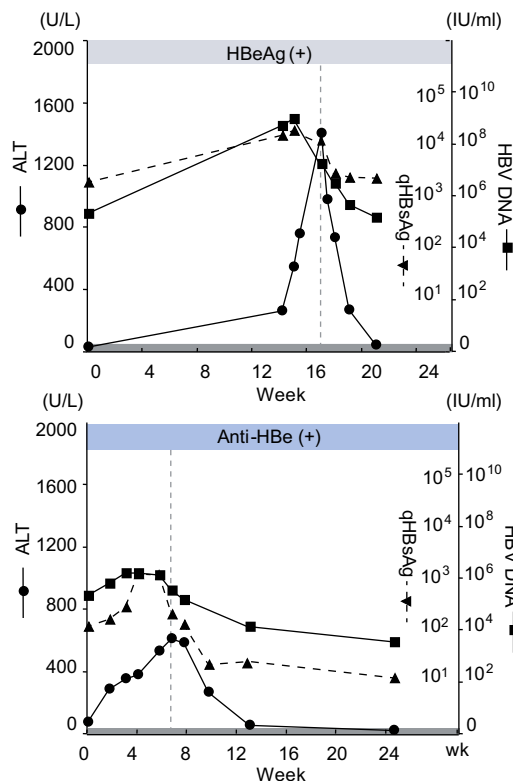
Fig. 2. Serial serum levels of HBV DNA and hepatitis B surface antigen (qHBsAg) during a hepatitis B flare. There is a surge of HBV DNA and HBsAg levels prior to the peak of the abrupt elevation of serum alanine aminotransferase (ALT) in both hepatitis B e antigen (HBeAg) positive and HBeAg-negative anti-HBe positive patients.

hybridization assay for HBV DNA and a conventional enzyme immunoassay to measure the HBeAg level, an earlier study showed significant parallel increases in serum HBeAg and HBV DNA levels and accumulation of intracellular viral proteins several weeks before the hepatitis flare. In addition, there was a subsequent increase in anti-HBe production and HBeAg/

anti-HBe immune complex formation, implicating the important role of the immune response to HBV in initiating the hepatitis flare [21]. Immunohistologic studies during the hepatitis flares have shown CD8+ T cells in the mononuclear cell infiltrates, strong membranous expression of human leukocyte antigen class I (HLA-I), and cytoplasmic or membranous/submembranous hepatitis B core antigen (HBcAg) expression [22,23]. Earlier immunologic studies showed a 2–4 fold elevation of HBcAg/HBeAg-specific precursor T cell frequencies, with an increase of HBcAg/HBeAg-specific T cell proliferation before and during the hepatitis flares [24], an increased production of interferon gamma (IFN-γ) at the time of hepatitis flares [25] and Th1 phenotypic cytokines (IL-2 and IFN-γ) were upregulated during high ALT levels [26]. It was demonstrated that an increase in circulating and intrahepatic IL-17-producing CD4+ T cells correlated well with ALT level and liver injury [27]. Longitudinal immunologic studies showed a decline of HBcAg-specific regulatory T cell (Treg) frequencies, associated with an increase in HBcAg-specific cytotoxic T lymphocyte (CTL) frequencies prior to the peak of the hepatitis flare [28–30], IL-10-producing regulatory B cell frequencies and serum IL-10 level peaked with the increase in viral load and decreased at the same time or shortly after the peak of ALT [31], large fluctuations in serum IFN-α and IL-8 concentrations with peak levels coinciding with a sharp increase in viral load preceding the onset of the hepatitis flare, and the increases in serum IFN-α and IL-8 promoted a pathway for the natural killer (NK)-cell mediated liver damage [32]. It was also shown that hepatitis flares were temporarily associated with high serum levels of INF-γ inducible chemokines CXCL-9 and CXCL-10 [33], and that increase, peak and decline in the levels of the programmed cell death protein 1 (PD-1) and its ligand PD-L1 went parallel with the ascend, peak and decline of HBV-specific T cells and serum ALT levels [34]. Integrated together (Table 1), these findings suggest that hepatitis B flares are the results of dynamic changes of the innate and adaptive immune responses with HLA-I restricted, CTL mediated immune cytolysis of HBV antigen(s) expressing hepatocytes and its downstream apoptotic mechanisms [3,7]. Accordingly, a higher ALT level represents a more vigorous endogenous immune response against HBV. It is still not clear, however, what triggers the initiation of the immune cascade.

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Table 1. Dynamic changes during hepatitis B flares.

	ALT during hepatitis B flare			[Ref.]
	Ascending	Peak	Descending	
HBV DNA	Increasing to peak	Increase/decline	Decline/stable	[18-20]
HBeAg	Increasing to peak	Increase/decline	Decline/stable	[21]
HBeAg/HBcAg-specific T cell response	Increasing	Increasing	Peak/decline/stable	[24]
HBV-specific Treg	Decline	Nadir	Increase	[28-30]
HBV-specific Tc	Increasing	Peak	Decline	[24,28-30,34]
IFN-γ, IL-2	Increasing	Peak/increasing	Peak/decline	[25,26]
IFN-α, IL-8	Increasing to peak	Peak/decline	Decline	[32]
CXCL-9/CXCL-10	Increasing	Peak	Decline	[33]
IL-10	Increasing to peak	Peak/decline	Decline	[31]
PD-1/PD-L1	Increasing	Peak	Decline	[34]

ALT, alanine aminotransferase; HBcAg, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; IFN, interferon; IL, interleukin; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Tc, cytotoxic T cell; Treg, regulatory T cell.

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Natural course following the hepatitis B flare

Short-term course

CHB patients with a rising ALT levels may develop a hepatitis flare and those with an ALT >5× ULN may deteriorate to severe hepatitis or hepatic decompensation. Asian-Pacific guidelines recommend that such patients should be monitored closely with weekly or biweekly serum ALT, bilirubin, and prothrombin time measurements to detect clinical deterioration or hepatic decompensation in time for immediate antiviral therapy for prevention or rescue [35]. Hepatitis B flares, not complicated with decompensation or mortality, are usually followed by decreasing ALT to pre-flare levels within one month. Less than 20% of the flares subside later than 3 months in HBeAg-positive patients [8], but 30% of the flares in HBeAg-negative patients are followed by persistently abnormal ALT [11]. A large study showed that patients with ALT >5× the ULN at entry had a spontaneous HBeAg seroclearance rate >50%, and a rate of >60% during the 12 and 18-month follow-up, respectively; in contrast, patients with ALT <5× ULN at entry had <5% and <10% spontaneous clearance rates, respectively, at the corresponding time points [36], as shown in Table 2. Another large study showed that patients with ALT >5× ULN at entry had a spontaneous HBeAg seroconversion rate of 51% at 2 years, in contrast to 26% in those with ALT <5× ULN at entry [37]. Collectively, these findings suggest that patients with serum ALT >5× ULN are different from those with serum ALT <5× ULN in terms of the strength of the endogenous immune response against HBV, and also provide a solid scientific basis to set an ALT level >5× ULN as a diagnostic threshold for the hepatitis flare [3,36].

HBeAg/HBV DNA seroclearance

Given that the very stable covalently closed circular DNA (cccDNA) in hepatocyte nuclei is reduced by hepatocyte killing and further diluted by subsequent regeneration [38], the immune mediated cytolysis of HBV-containing hepatocytes and the non-cytolytic actions of CTL-secreted cytokines, including IFN-γ and tumour necrosis factor (TNF)-α, in abolishing HBV gene expression and replication, may enhance the elimination or suppression of HBV. Subsequently, HBsAg, HBeAg and/or HBV DNA levels may decrease (Fig. 3A) and even may lead to HBeAg/HBV DNA seroclearance or HBeAg seroconversion [3,4,18]. In a short-term scale, around two thirds of spontaneous HBeAg seroconversions are preceded by hepatitis B flares in the preceding three months [4,18]. However, only a few hepatitis B flares are followed by spontaneous HBeAg/HBV DNA seroclearance within 3 months, unless the hepatitis B flare is severe enough to cause BHN and/or AFP elevation over 100 ng/ml [3], as shown in Table 2. The HBV genotype may also play some role in the pathogenesis of the hepatitis B flare and its outcomes. A study showed that HBeAg seroconversion in genotype B HBV-infected patients correlated with age at entry but not with maximal ALT level during the clinical course. In contrast, HBeAg seroconversion in genotype C HBV-infected patients was much enhanced in patients with a maximal ALT >5× ULN (vs. ALT <5× ULN, $p = 0.03$) [39]. Another study showed that hepatitis flares in genotype B HBV-infected patients had a significantly higher number of IFN-γ producing cells (Th1 response), a lower number of IL-10 producing cell (Th2 response), and a higher cumulative HBeAg seroconversion rate, as compared with those in genotype C HBV-infected patients [40]. These findings might implicate that genotype C HBV infection requires more vigorous immune response to achieve viral clearance and that HBeAg seroconversion occurs earlier and more
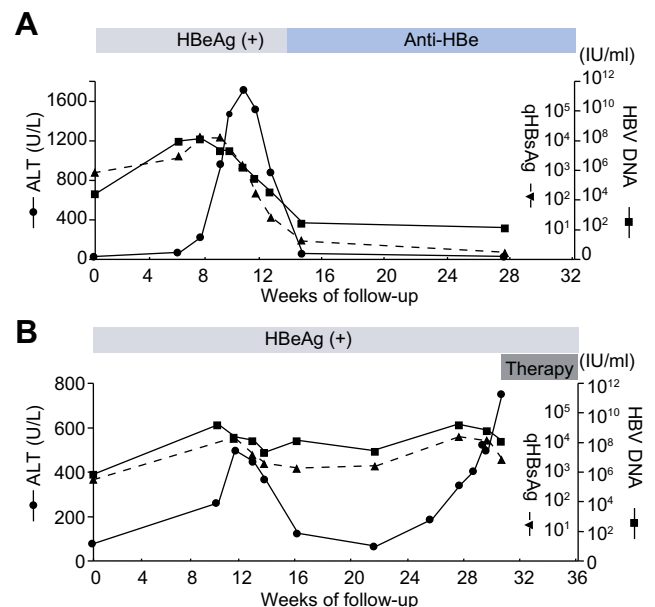
Table 2. Hepatitis B flare and spontaneous HBeAg seroclearance.

Hepatitis flare	Spontaneous HBeAg seroclearance			[Ref.]
	3 mo	12 mo	18 mo	
No				
ALT <5x ULN	<2%[a]	5%[b]	8%[c]	[36]*
Yes				
ALT				
>5x ULN	19%[a]	50%[b]	67%[c]	[36]*
5-10x ULN	5%[d]	45%[e]	58%[f]	[36]*
>10x ULN	25%[d]	52%[e]	70%[f]	[36]*
AFP				
>100 ng/ml	31%[1]	62%[2]	72%[3]	[36]*
<100 ng/ml	4%[1]	15%[2]	19%[3]	[36]*
BHN				
Yes		67%[4]		[8]
No		16%[4]		[8]

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; BHN, bridging hepatic necrosis; HBeAg, hepatitis B e antigen.
*Calculated from the database of reference [36].
Significant difference between pairs of percentages with same letters: [a,b,c,d,1,2,3,4]p <0.001; [e]p = 0.304; [f]p = 0.042.

Fig. 3. Changes of serum alanine aminotransferase (ALT) and HBV DNA in two hepatitis B e antigen (HBeAg) positive patients with a hepatitis B flare. (A) Patient A: hepatitis B flare with decreasing HBV DNA prior to the peak of rising ALT level represents 'effective immune clearance of HBV'. The patient developed subsequent spontaneous HBeAg seroconversion. (B) Patient B: hepatitis B flare with increasing HBV DNA level despite high rise of ALT represents 'ineffective immune clearance of HBV'. The patient is at the risk of prolonged activity and hepatic decompensation requiring immediate antiviral therapy. qHBsAg, quantity of hepatitis B surface antigen.

frequently in genotype B than in genotype C HBV-infected patients [39]. Whether other HBV genotypes have such genotype-related difference in the hepatitis B flare remains to be explored.

It is important to note that patients, whose serum HBV DNA is rising further or not decreasing along with increasing ALT, may have ineffective (abortive) immune clearance and HBeAg seroconversion usually will not follow after the flare (Fig. 3B). Furthermore, a study showed that HBV DNA >3×10^8 IU/ml along with increasing ALT during the hepatitis flare is predictive of subsequent hepatic decompensation, with a sensitivity and a specificity both of 86% and a negative predictive value of 99% [41]. Such patients as well as cirrhotic patients with hepatitis flares require immediate anti-HBV therapy. In contrast, patients whose serum HBV DNA starts to decrease before the ALT peak may have effective immune clearance, which may lead to HBV DNA/HBeAg seroclearance and disease remission [3]. The key difference between effective and ineffective immune clearance perhaps relies on whether the Th1 response has been enhanced or not [28,40]. Therefore, if there is no concern about hepatic decompensation, it is reasonable to observe non-cirrhotic patients with hepatitis B flares for 3–6 months to see whether antiviral therapy is indeed needed [35].

Longer-term outcomes

Spontaneous HBeAg seroconversion or HBV DNA suppression with sustained remission usually occurs after multiple episodes of hepatitis flares. Patients who fail to clear HBeAg and/or HBV DNA after a hepatitis B flare may have normal ALT for a variable duration, and the hepatitis B flare may recur afterwards due to reactivation of the original HBV pool and may re-emerge repeatedly until HBV is suppressed to an inactive level (HBeAg-negative, ALT normal and HBV DNA <2000 IU/ml). Those who underwent spontaneous HBeAg seroconversion before age 30 have a much lower 15-year cumulative incidence of HBeAg-negative hepatitis and low 15-year incidence of cirrhosis (3.7%) or HCC (2.1%) [42]. Besides age of the patient and age at HBeAg seroconversion, studies have shown that severe hepatitis B flares with hepatic decompensation or more extensive hepatocytolysis with BHN or AFP >100 ng/ml, especially if occurring repeatedly (repeated BHN or repeated AFP >100 ng/ml) or if flares are not followed by ALT normalization or go along with delayed HBeAg/HBV DNA seroclearance over 40 year of age, are prone to develop into liver cirrhosis [42,43]. Flares due to HBeAg sero-reversion are also a factor for progression to liver cirrhosis [43].

Since more severe hepatitis B flares may be complicated with hepatic decompensation and have an increased risk of cirrhosis development, it is conceivably to better prevent their occurrence than to contend with the hepatitis B flare. Therefore, all HBsAg-positive subjects should be monitored and treated timely before the hepatitis B flare has occurred [35]. Patients with hepatitis B flare who fail to clear HBV, especially those with BHN or AFP >100 ng/ml, need more aggressive antiviral therapy.

Antiviral therapy related hepatitis B flares

Hepatitis B flares are not uncommon during and after withdrawal of antiviral therapy in patients with CHB with or without cirrhosis.

Interferon based therapy

Conventional interferon-α (IFN-α)
The best known example of a hepatitis flare in relation to drug therapy is the one associated with IFN-α therapy or following withdrawal of a short course of corticosteroids prior to IFN-α therapy. IFN may increase T cell activity and NK cell function and hence, may induce a hepatitis flare. A study showed that the hepatitis flare developed typically during the second to third month of therapy in 45–49% of the patients treated with conventional IFN-α and in 71% of the patients treated with IFN-α after prednisolone withdrawal. The study further showed that the hepatitis flare was an independent predictor and an ALT increase >344 U/L was the most powerful predictor of a sustained response [44]. It was shown that the hepatitis flare followed by IL-12 elevation with a significant subsequent rise in Th1 cytokines (IFNγ and IL-2) was important for HBeAg seroconversion, associated with IFN-α therapy [45].

Pegylated IFN- (Peg IFN)
Hepatitis flares were also observed during or after Peg IFN therapy. ALT elevation over 5 times baseline level were reported in only 5–6% of the HBeAg-positive patients treated with 48-weeks Peg IFNα-2a, not significantly higher than 4% in the lamivudine (LAM) treated control group [46]. ALT flare >10× ULN was observed in 12% of HBeAg-negative patients treated with 48-week Peg IFNα-2a *vs.* 6% in LAM treated controls [47]. Hepatitis flares with ALT >5× ULN were observed in around 30% of our HBeAg-positive and 22% of the HBeAg-negative patients during 48–52 weeks of Peg IFNα-2a therapy (Liaw 2014, unpublished data). Of the 266 patients treated with Peg IFNα-2b, 25% encountered a hepatitis flare with a median ALT peak of 12.3× ULN (∼60×), half during the 52 weeks of therapy and half during the 26 weeks of follow-up. Among these hepatitis flares, those followed by a HBV DNA decline ⩾1 log within 4 months were associated with a high rate of HBeAg loss (58%) and HBsAg loss (33%), in contrast to 20% and 0%, respectively of flares preceded by a HBV DNA increase ⩾1 log within prior 4 months [48]. These contrasting features and response outcomes are compatible with the contrast between effective and ineffective immune clearance in spontaneous hepatitis B flares (Fig. 3).

Though not a head to head comparison, the results of these studies show that the incidence of a hepatitis flare related to one year of Peg IFN therapy varies among studies, possibly due to different clinical features, such as HBV genotype, baseline viral load and ALT levels of the study patients. Even the highest incidence of hepatitis flares (30%) among the Peg IFN studies is lower than that (up to 50%) related to 4–6 months of conventional IFN therapy. The reason(s) for this difference are not known. Given that Peg IFN is superior in efficacy to conventional IFN in CHB [49], perhaps Peg IFN may have more effective mechanism(s) other than its immunomodulatory effect so that immune mediated hepatitis flares are less needed for a better response. Recent studies do suggest that the efficacy of Peg IFN may be not related to its potent effects on NK cells [50] and that it may target the epigenetic regulation of the nuclear cccDNA minichromosome by antiviral cytokines [51] or induce a specific non-hepatotoxic degradation of nuclear HBV cccDNA [52]. In addition, compared to conventional IFN, Peg IFN induced a longer-lasting effect on the human interferon-stimulated gene expression without involvement of the immune cell response [53].

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	HBeAg status	During therapy		1-yr off-therapy		[Ref.]
		>5x ULN	>10x ULN	>5x ULN	>10x ULN	
LAM	Positive	17%	6%	12%	7%	[55]
	Positive and negative	n.a. n.a.	6% 9-12%	n.a. n.a.	n.a. n.a.	[62] [63,64]
	Negative	3%	2-6%	29%	11%	[47,61]
ADV	Positive	21%	10%	24%	n.a.	[57,60]
	Positive and negative	3%	2%	n.a.	n.a.	[65]
	Negative	n.a.	n.a.	n.a.	33%	[58]
LdT	Positive and negative	n.a. n.a.	4% 5-6%	n.a. n.a.	n.a. n.a.	[62] [63,64]
ETV	Positive	10%	3%	2%	1%	[59]
	Negative	2%	<1%	12%	8%	[61]
TDF	Positive and negative	6%	3%	n.a.	n.a.	[65]

ADV, adefovir; ETV, entecavir; LAM, lamivudine; LdT, telbivudine; HBeAg, hepatitis B e antigen; n.a., not available; TDF, tenofovir; ULN, upper limit of normal.

Oral antiviral therapy

Pretherapy hepatitis B flares
Under therapy with nucleos(t)ide analogues (Nucs), which have no direct immunomodulating effects, patients with pretherapy ALT levels >5× ULN have the highest response rate, suggesting that patients with a stronger endogenous immune response against HBV have enhanced their response to direct antivirals by hepatocytes killing and regeneration leading to reduce cccDNA [54,55]. Along this line, it was also documented that withdrawal of a short course of steroid enhanced the host Th1 response and induced a hepatitis B flare with enhanced response to lamivudine (LAM) [56].

Hepatitis flares during Nuc therapy
A hepatitis flare with an ALT increase >10x ULN may occur in up to 10% of patients, being higher in HBeAg-positive patients and lower under therapy with the more potent Nucs entecavir (ETV) or tenofovir (TDF) [57–65], as shown in Table 3. Such flares are not associated with bilirubin increase or hepatic decompensation and usually occur in association with a reduction in serum HBV DNA levels by >2 log copies/ml within 8 weeks of Nuc therapy [59,61,65], compatible with the notion that these flares are the results of a transient restoration of HBV-specific T cell responses [66,67].

Hepatitis flares following emergence of drug resistance
Hepatitis B flares that occur after 24 weeks of Nuc therapy are usually caused by drug resistance. Following an upsurge of drug-resistant HBV viraemia during continuing Nuc therapy, ALT increases gradually and may even lead to a hepatitis flare, decompensation or liver failure [3,68]. During 12 months of continuous LAM therapy after emergence of LAM resistance in a series of 66 patients, 44 (67%) developed a hepatitis flare with ALT >5× ULN, 26 (39%) with ALT >10× ULN, and 9 (14%) were associated with a serum bilirubin >2 mg/dl, 7 (11%) developed decompensation and 11 (19%) out of 57 HBeAg-positive patients seroconverted to anti-HBe [69]. Timely rescue therapy using Nucs with a different resistance profile can prevent or rescue patients with a drug resistance-induced hepatitis flare or decompensation [35,70]. Drug resistance is no more an issue during therapy with ETV or TDF but LAM is still widely used in low resource regions [71].

Hepatitis B flares after withdrawal of Nuc therapy
In contrary to a hepatitis B flare associated with HBV suppression during Nuc therapy, hepatitis flares after cessation of Nuc therapy are preceded by an increase in serum HBV DNA as HBV replication returns [3,72]. The temporal relationship between HBV DNA and ALT levels is similar to that during spontaneous hepatitis B flares [33]. The off-therapy flares are also similar to spontaneous hepatitis flares in the spectrum of clinical presentation that hepatic decompensation and fatality may occur if not retreated in time [72–75]. Hepatitis flares may occur after cessation of Nuc therapy in the majority of the patients who remained HBeAg-positive [55,75]. Even in patients who underwent HBeAg seroconversion during Nuc therapy, hepatitis flares with or without HBeAg reversion may occur, especially in older patients, those infected with genotype C HBV, and if the consolidation duration of therapy is not long enough [76–78].

Virologic relapse (HBV DNA >2000 IU/ml) after cessation of Nuc therapy is even more frequent in HBeAg-negative patients. Clinical relapse (HBV DNA >2000 IU/ml with ALT >1.2–2× ULN) was reported to be 76% after withdrawal of long-term adefovir (ADV) therapy [79], but was only 43% after ETV cessation [74]. The relapses mostly occurred within 6 months after cessation of LAM or ADV but more than 6 months after stopping ETV [74]. Hepatitis flares with ALT >5× ULN occurred in 21% of the 33 patients within one year after ADV withdrawal and ALT subsided spontaneously in most of the patients who were not retreated, with increasing HBsAg seroclearance over time [79]. Hepatitis with hepatic decompensation only occurs in those not monitored or who did not resume Nuc therapy in time [74]. Therefore, proper off-therapy monitoring is mandatory after cessation of Nuc therapy.

Hepatitis B flares associated with immune restoration

As an immune-mediated disease entity, immunosuppression and immune restoration may influence the clinical course and result in a hepatitis flare in patients with chronic HBV infection.

Hepatitis B flares in pregnant women

Pregnant women have mechanisms that prevent rejection of the baby by the maternal immune system, including an increase in corticosteroids [80]. A study in mothers with chronic HBV infection showed that serum HBV DNA increased while ALT decreased significantly during pregnancy and that ALT levels increased to 1.8–13.2× the ULN with a decline in serum HBV DNA within 6 months after delivery. The study further showed that women who received Nuc therapy during the third trimester for prevention of perinatal HBV transmission had a higher chance (62% vs. 36%) of a significant increase in liver disease activity [81]. Another study showed that a postpartum flare (ALT >5× ULN) usually occurred 8–10 weeks after delivery, and was observed in 50% of the mothers with postpartum Nuc therapy ⩽4 weeks vs. 40% of those with postpartum Nuc therapy >4 weeks [82]. The postpartum flares were usually mild and resolved spontaneously [81,82]. In addition, an age-HBeAg status matched control study showed that pregnant women had a higher chance of a postpartum ALT rise (50 vs. 11%; p = 0.01) and HBeAg loss (14.3% vs. 2.2%; p = 0.02) compared with controls during the same duration (10–12 months after entry) of follow-up [83]. It is therefore important to follow postpartum mothers closely for at least 6 months, especially those who are HBeAg-positive or have stopped Nuc therapy, and then to continue follow-up as for ordinary subjects with chronic HBV infection. Hepatitis and hepatitis B flares occurring in women of childbearing age or flares related to pregnancy require proper management or antiviral therapy according to the guidelines [35,70].

Hepatitis B flares in HBV/HIV coinfected patients

Hepatitis B flares during active antiretroviral therapy (ART) in HBV and human immunodeficiency virus (HIV) coinfected patients may be a consequence of immune restoration with a robust increase in CD4 cell count in the presence of high HBV load [84]. A prospective study after the initiation of HBV-active-ART in HIV/HBV coinfected patients showed that 8 (22%) of 36 patients developed hepatitis B flares with ALT >5× ULN at week 8 of therapy in association with increased plasma levels of immune mediators of elevated Th1 response, enhanced T cell activation and monocyte recruitment [85]. TDF is active against both HBV and HIV and can be used to treat such flares or as part of a highly active ART [35].

Hepatitis B flares during anti-TB therapy

In HBV endemic regions, tuberculosis (TB) is not uncommon. A study from Taiwan showed that 15 out of 42 patients who developed symptomatic hepatitis during anti-TB therapy were HBsAg-positive and 11 of them were seropositive for HBV DNA (spot hybridization assay) with late onset hepatitis (110 ± 62 days, 73% >2 months vs. 52 ± 56 days and 26% in HBsAg-negative counterparts; p <0.005), which was likely following immune restoration [86]. It is mandatory to monitor HBsAg-positive patients during anti-TB therapy for timely antiviral therapy.

Hepatitis B flares in patients with immuno/chemotherapy

Chemotherapy with or without corticosteroids

Back in 1991, it was reported that reactivation of HBV replication with icteric hepatitis occurred in 22% of HBsAg-positive patients and in 2% of anti-HBc and/or anti-HBs positive patients with malignant lymphoma receiving chemotherapy, and that HBV reactivation-related liver failure occurred in 7% and 2%, respectively [87]. However, it had not caused due attention until the early 2000s when prevention of HBV reactivation in this setting became available [88]. Now, it is well recognized that immunosuppression or chemotherapy for haematologic or other solid tumours as well as stem cell or solid organ transplantation in patients with chronic HBV infection or with occult HBV infection is associated with an increased risk of HBV reactivation, with increasing serum HBV DNA during immunosuppressive/chemotherapy, followed by ALT elevation in between therapy administrations or after the end of the therapy, and that the hepatitis B flare which may occur can even lead to hepatic decompensation or fatality [89]. Hepatitis B flares may also occur following transarterial chemoembolization for HCC in 30% of the patients [90]. A systemic review of 14 studies (2 randomized, controlled trials) showed that the pooled incidence of HBV related hepatitis, liver failure, and mortality was 33.4%, 13%, and 6.7%, respectively. In contrast, prophylactic LAM therapy reduced the corresponding incidence to 4%, 0%, and 2%, respectively [91]. Addition of corticosteroid in the regimen of chemotherapy may increase the risk and severity of HBV reactivation. A randomized control trial showed a 2-fold increase in the incidence of HBV reactivation and hepatitis B flare, and a 3-fold increase in hepatitis B flares with ALT >10× ULN in patients who received prednisolone [92].

Anti-CD₂₀

Addition of B cell depleting monoclonal antibodies against CD20 (anti-CD$_{20}$) such as rituximab in the chemotherapy regimen increased the risk and severity of HBV reactivation even more, also in HBsAg-negative anti-HBc positive patients, including those that are combined seropositive for anti-HBs [93]. A most recent prospective study in 150 HBsAg-negative anti-HBc positive patients, undergoing cyclic chemotherapy including rituximab for lymphoma, showed an incidence of HBV reactivation and hepatitis flare (3-fold increase in ALT and >100 U/L) of 10.4% and 6.4%, respectively, which occurred during or after rituximab-CHOP therapy. With ETV therapy started at the detection of HBV reactivation, no HBV-related hepatic failure or mortality occurred [94].

Anti-TNF

Since the introduction of anti-TNF agents such as infliximab for the treatment of rheumatoid arthritis or inflammatory bowel disease and psoriasis, hepatitis B reactivation, hepatitis flares and death have been reported sporadically. A systemic analysis of case reports during a mean follow-up of 14 months showed that HBV reactivation occurred during anti-TNF therapy in 35 (39%) of 89 HBsAg-positive patients and hepatitis B flares (ALT >5× ULN) occurred in 12 (34%) of the 35 patients with 5 developing liver failure. The corresponding rates in 168 HBsAg-negative anti-HBc-positive patients was 7-fold lower than in HBsAg-positive patients. The risk was significantly reduced (23% vs. 62%, p = 0.003) in those who received antiviral prophylaxis [95].

Currently, there is a universal consensus that it is mandatory to screen the HBsAg and anti-HBc status for all patients who are going to receive immunosuppression or chemotherapy and start prophylactic or pre-emptive antiviral therapy, preferably using
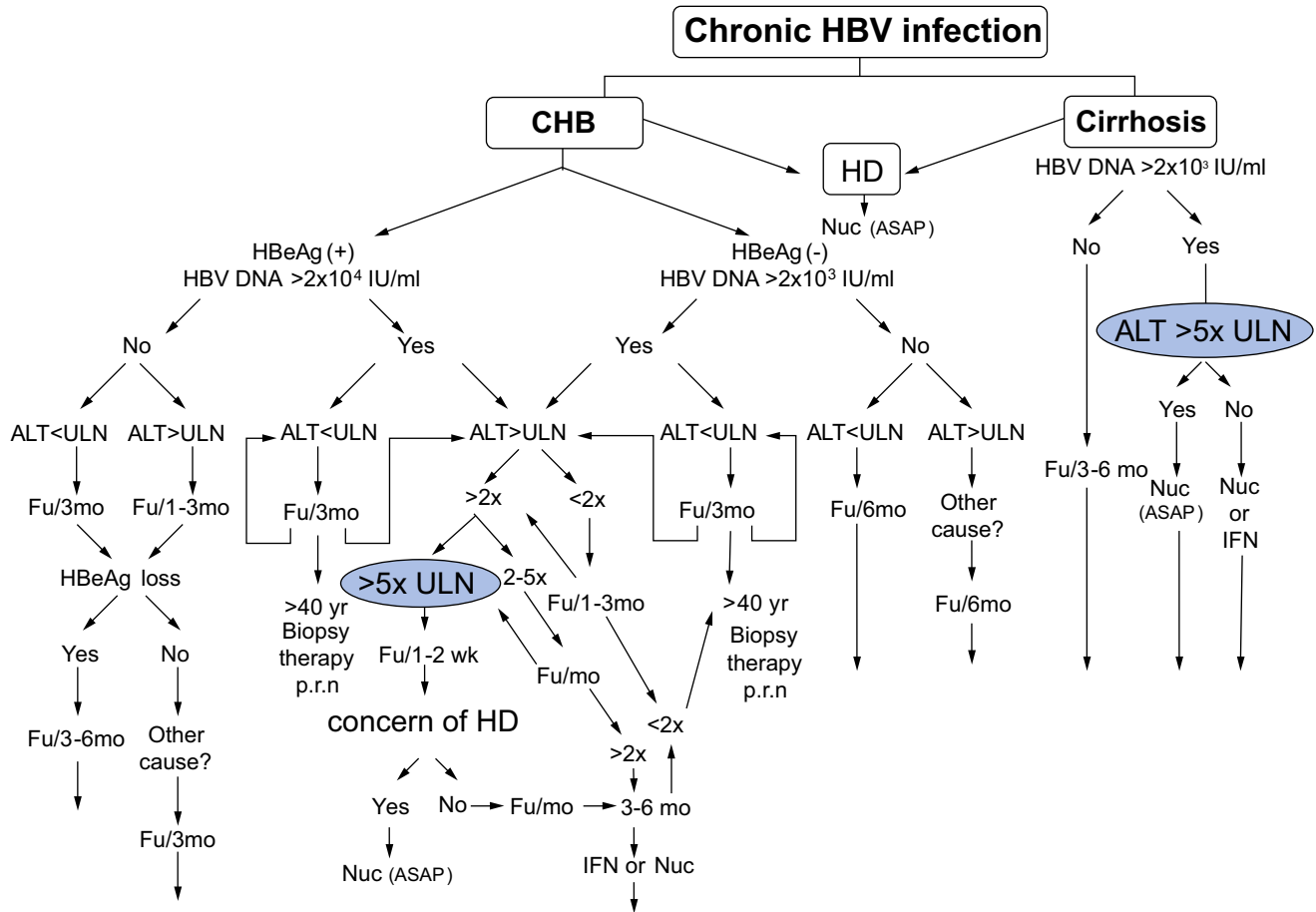
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Fig. 4. A decision tree for patients with chronic hepatitis B virus (HBV) infection, including patients with hepatitis B flares (ALT >5× ULN). Follow-up tests of patients with increasing ALT or ALT >5× ULN include serum bilirubin, alpha-fetoprotein and prothrombin time. ALT, alanine aminotransferase; ASAP, as soon as possible; CHB, chronic hepatitis B; Fu, follow-up; HBeAg, hepatitis B e antigen; HCC, hepatocellular carcinoma; HD, hepatic decompensation; IFN, interferon; mo, month; Nuc, nucleos(t)ide analogue; p.r.n, if necessary; ULN, upper limit of normal; wk, week; y, year of age.

ETV or TDF, to prevent HBV reactivation, hepatitis flares and serious complications [35,70,89,96].

Implications and perspectives

In summary, episodic hepatitis B flares with ALT >5× ULN are not uncommon in patients with chronic HBV infection. ALT/hepatitis flares are the results of HLA-I restricted, CTL-mediated immune responses against HBV. Thus, higher ALT reflects more vigorous immune-mediated hepatocytolysis and is associated with stronger clearance of HBV and a higher chance of HBeAg loss and/or HBV DNA seroclearance, both in the setting of the natural course of infection and related to drug therapy. While flares in cirrhotic patients always require immediate antiviral therapy, flares with decreasing serum HBV DNA levels represent effective immune clearance of HBV that is likely to be followed by spontaneous HBeAg/HBV DNA seroconversion or seroclearance (Fig. 3A); thus, such patients may wait for 3–6 months to see whether drug therapy is needed. In contrast, hepatitis B flares with stable or increasing serum HBV DNA levels reflect ineffective immune clearance of HBV so that the patients are at risk of further hepatocytolysis or recurrent hepatitis B flare(s) and even hepatic decompensation, which requires timely treatment (Fig. 3B). In addition to the immediate risk of hepatic decompensation, more

than one severe hepatitis flare is a factor for future development of liver cirrhosis. Therefore, patients with ALT levels of 2–5× ULN who have a low chance of spontaneous HBV clearance should be considered for anti-HBV therapy to stop further liver injuries and to prevent hepatitis B flares and their adverse sequelae. These management decisions are summarised in a decision tree (Fig. 4). Proper monitoring is required in patients who stopped antiviral therapy. In the setting of anti-HBV therapy, hepatitis B flares before, during and even after therapy are beneficial in terms of better response to therapy. Along this line, inducing a hepatitis flare by priming with a short course of corticosteroid or Nuc therapy before planned anti-HBV therapy was reported in small studies. However, the benefit should be weighed against the risk of an adverse hepatitis B flare. Screening, monitoring and prophylaxis or pre-emptive anti-HBV therapy is mandatory in hepatitis B patients who are going to receive immunosuppression or cancer chemotherapy. In addition, HCC surveillance is also mandatory in all hepatitis B patients at risk.

Financial support

Conflict of interest

Acknowledgments

References

[1] Liaw YF, Chu CM. Hepatitis B virus infection. Lancet 2009;373:582–592.

[2] Perrillo RP. Acute flares in chronic hepatitis B: the natural and unnatural history of an immunologically mediated liver disease. Gastroenterology 2001;120:1009–1022.

[3] Liaw YF. Hepatitis flares and hepatitis B e antigen seroconversion: implication in anti-hepatitis B virus therapy. J Gastroenterol Hepatol 2003;18:246–252.

[4] Liaw YF, Chu CM, Su IJ, Huang MJ, Lin DY, ChangChien CS. Clinical and histological events preceding hepatitis B e antigen seroconversion in chronic type B hepatitis. Gastroenterology 1983;84:216–219.

[5] Lok AS, Lai CL. Acute exacerbations in Chinese patients with chronic hepatitis B virus (HBV) infection. Incidence, predisposing factors and etiology. J Hepatol 1990;10:29–34.

[6] Lok AS, McMahon BJ. Practice Guidelines Committee, American Association for the Study of Liver Diseases. Chronic hepatitis B. Hepatology 2001;34:1225–1241.

[7] Liaw YF, Tsai SL. Pathogenesis and clinical significance of spontaneous exacerbation and remissions in chronic HBV infection. Viral Hepat Rev 1997;3:143–154.

[8] Liaw YF, Yang SS, Chen TJ, Chu CM. Acute exacerbation in hepatitis B e antigen-positive chronic type B hepatitis: a clinicopathological study. J Hepatol 1985;1:227–233.

[9] Liaw YF, Tai DI, Chu CM, Pao CC, Chen TJ. Acute exacerbation in chronic type B hepatitis: comparison between HBeAg and antibody positive patients. Hepatology 1987;7:20–23.

[10] Hsu YS, Chien RN, Yeh CT, Sheen IS, Chiou HY, Chu CM, et al. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. Hepatology 2002;35:1522–1527.

[11] Bonino F, Brunetto MR. Chronic hepatitis B e antigen (HBeAg) negative, anti-HBe positive hepatitis B: an overview. J Hepatol 2003;39:S160–S163.

[12] Sheen IS, Liaw YF, Tai DI, Chu CM. Hepatic decompensation associated with hepatitis B e antigen clearance in chronic type B hepatitis. Gastroenterology 1985;89:732–735.

[13] Chu CM, Liaw YF, Pao CC, Huang MJ. The etiology of acute hepatitis superimposed upon previously unrecognized asymptomatic HBsAg carriers. Hepatology 1989;9:452–456.

[14] Liaw YF, Chen JJ, Chen TJ. Acute exacerbation in patients with liver cirrhosis: a clinicopathological study. Liver 1990;10:177–184.

[15] Koike K, Iino S, Kurai K, Mitamura K, Endo Y, Oka H. IgM anti-HBc in anti-HBe positive chronic type B hepatitis with acute exacerbations. Hepatology 1987;7:573–576.

[16] Liaw YF, Tai DY, Chen TJ, Chu CM, Huang MJ. Alpha-fetoprotein changes in the course of chronic hepatitis: relation to bridging hepatic necrosis and hepatocellular carcinoma. Liver 1986;6:133–137.

[17] Peng CY, Chen SH, Chu CM, Sheen IS, Tai DI, Tsai SL, et al. Oval cell activation during acute exacerbation in patients with chronic hepatitis type B or C. Asian Pacific Association for the Study of the Liver Meeting 2002;145–148.

[18] Liaw YF, Pao CC, Chu CM, Sheen IS, Huang MJ. Changes of serum hepatitis B virus DNA in two types of clinical events preceding spontaneous hepatitis B e antigen seroconversion in chronic type B hepatitis. Hepatology 1987;7:1–3.

[19] Liaw YF, Pao CC, Chu CM. Changes of serum HBV DNA in relation to serum transaminase level during acute exacerbation in patients with chronic type B hepatitis. Liver 1988;8:231–235.

[20] Liu CJ, Chen PJ, Lai MY, Kao JH, Chang CF, Wu HL, et al. A prospective study characterizing full-length hepatitis B virus genomes during acute exacerbation. Gastroenterology 2003;124:80–90.

[21] Maruyama T, Iino S, Koike K, Yasuda K, Milich DR. Serology of acute exacerbation in chronic hepatitis B virus infection. Gastroenterology 1993;105:1141–1151.

[22] Chu CM, Liaw YF. Intrahepatic distribution of HBsAg and HBcAg in chronic hepatitis B virus infection: hepatocyte with cytoplasmic/membranous HBcAg as a possible target for immune hepatocytolysis. Gastroenterology 1987;92:220–225.

[23] Chu CM, Shyu WC, Kuo RW, Liaw YF. HLA class I antigen display on hepatocyte membrane in chronic hepatitis B virus infection: its role in the pathogenesis of chronic type B hepatitis. Hepatology 1988;8:712–717.

[24] Tsai SL, Chen PJ, Lai MY, Yang PM, Sung JL, Huang JH, et al. Acute exacerbations of chronic type B hepatitis are accompanied by increased T cell responses to hepatitis B core and e antigens. Implications for hepatitis B e antigen seroconversion. J Clin Invest 1992;89:87–96.

[25] Takehara T, Hayashi N, Katayama K, Kasahara A, Fusamoto H, Kamada T, et al. Hepatitis B core antigen-specific interferon gamma production of peripheral blood mononuclear cells during acute exacerbation of chronic hepatitis B. Scand J Gastroenterol 1992;27:727–731.

[26] Fukuda R, Ishimura N, Nguyen TX, Chowdhury A, Ishihara S, Kohge N, et al. The expression of IL-2, IL-4 and interferon-gamma (IFN-gamma) mRNA using liver biopsies at different phases of acute exacerbation of chronic hepatitis B. Clin Exp Immunol 1995;100:446–451.

[27] Zhang JY, Zhang Z, Lin F, Zou ZS, Xu RN, Jin L, et al. Interleukin-17-producing CD4(+) T cells increase with severity of liver damage in patients with chronic hepatitis B. Hepatology 2010;51:81–91.

[28] Feng IC, Koay LB, Sheu MJ, Kuo HT, Sun CS, Lee C, et al. HBcAg-specific CD4+CD25+ regulatory T cells modulate immune tolerance and acute exacerbation on the natural history of chronic hepatitis B virus infection. J Biomed Sci 2007;14:43–57.

[29] Tsai SL, Wang SL, Feng IC, Kuo HT, Koay LB, Sheu MJ, et al. Acute exacerbations of chronic hepatitis B are accompanied by decline of core antigen-specific regulatory T-cell frequencies: implications for successful anti-HBV treatments. Hepat Monthly 2007;7:183–200.

[30] Koay LB, Feng IC, Sheu MJ, Kuo HT, Lin CY, Chen JJ, et al. Hepatitis B virus (HBV) core antigen-specific regulatory T cells confer sustained remission to anti-HBV therapy in chronic hepatitis B with acute exacerbation. Hum Immunol 2011;72:687–698.

[31] Das A, Ellis G, Pallant C, Lopes AR, Khanna P, Peppa D, et al. IL-10-producing regulatory B cells in the pathogenesis of chronic hepatitis B virus infection. J Immunol 2012;189:3925–3935.

[32] Dunn C, Brunetto M, Reynolds G, Christophides T, Kennedy PT, Lampertico P, et al. Cytokines induced during chronic hepatitis B virus infection promote a pathway for NK cell-mediated liver damage. J Exp Med 2007;204:667–680.

[33] Tan AT, Koh S, Goh W, Zhe HY, Gehring AJ, Lim SG, et al. A longitudinal analysis of innate and adaptive immune profile during hepatic flares in chronic hepatitis B. J Hepatol 2010;52:330–339.

[34] Wenjin Z, Chuanhui P, Yunle W, Lateef SA, Shusen Z. Longitudinal fluctuations in PD1 and PD-L1 expression in association with changes in anti-viral immune response in chronic hepatitis B. BMC Gastroenterol 2012;12:109.

[35] Liaw YF, Kao JH, Piratvisuth T, Chan HLY, Chien RN, Liu CJ, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. Hepatol Int 2012;6:531–561.

[36] Liaw YF. Current trends in therapy for chronic viral hepatitis. J Gastroenterol Hepatol 1997;12:S346–S353.

[37] Yuen MF, Yuan HJ, Hui CK, Wong DK, Wong WM, Chan AO, et al. A large population study of spontaneous HBeAg seroconversion and acute exacerbation of chronic hepatitis B infection: implications for antiviral therapy. Gut 2003;52:416–419.

[38] Levrero M, Pollicino T, Petersen J, Belloni L, Raimondo G, Dandri M. Control of cccDNA function in hepatitis B virus infection. J Hepatol 2009;51:581–592.

[39] Chu CM, Liaw YF. Genotype C hepatitis B virus infection is associated with a higher risk of reactivation of hepatitis B and progression to cirrhosis than genotype B: a longitudinal study of hepatitis B e antigen-positive patients with normal aminotransferase levels at baseline. J Hepatol 2005;43:411–417.

[40] Yuen MF, Wong DK, Zheng BJ, Chan CC, Yuen JC, Wong BC, et al. Difference in T helper responses during hepatitis flares in hepatitis B e antigen (HBeAg)-positive patients with genotypes B and C: implication for early HBeAg seroconversion. J Viral Hepat 2007;14:269–275.

Review

Review

[41] Jeng WJ, Sheen IS, Liaw YF. Hepatitis B virus DNA level predicts hepatic decompensation in patients with acute exacerbation of chronic hepatitis B. Clin Gastroenterol Hepatol 2010;8:541–545.

[42] Chen YC, Chu CM, Liaw YF. Age-specific prognosis following spontaneous hepatitis B e antigen seroconversion in chronic hepatitis B. Hepatology 2010;51:435–444.

[43] Liaw YF, Tai DI, Chu CM, Chen TJ. The development of cirrhosis in patients with chronic type B hepatitis: a prospective study. Hepatology 1988;8: 493–496.

[44] Nair S, Perrillo RP. Serum alanine aminotransferase flares during interferon treatment of chronic hepatitis B: is sustained clearance of HBV DNA dependent on levels of pretreatment viremia? Hepatology 2001;34: 1021–1026.

[45] Rossol S, Marinos G, Carucci P, Singer MV, Williams R, Naoumov NV. Interleukin-12 induction of Th1 cytokines is important for viral clearance in chronic hepatitis B. J Clin Invest 1997;99:3025–3033.

[46] Lau GK, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, et alPeginterferon Alfa-2a HBeAg-Positive Chronic Hepatitis B Study Group. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. N Engl J Med 2005;352:2682–2695.

[47] Marcellin P, Lau GK, Bonino F, Farci P, Hadziyannis S, Jin R, et alPeginterferon Alfa-2a HBeAg-Negative Chronic Hepatitis B Study Group. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2004;351: 1206–1217.

[48] Flink HJ, Sprengers D, Hansen BE, van Zonneveld M, de Man RA, Schalm SW, et alHBV 99-01 Study Group. Flares in chronic hepatitis B patients induced by the host or the virus? Relation to treatment response during Peg-interferon {alpha}-2b therapy. Gut 2005;54:1604–1609.

[49] Cooksley WG, Piratvisuth T, Lee SD, Mahachai V, Chao YC, Tanwandee T, et al. Peginterferon alpha-2a (40 kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B. J Viral Hepat 2003;10: 298–305.

[50] Micco L, Peppa D, Loggi E, Schurich A, Jefferson L, Cursaro C, et al. Differential boosting of innate and adaptive antiviral responses during pegylated-interferon-alpha therapy of chronic hepatitis B. J Hepatol 2013;58: 225–233.

[51] Belloni L, Allweiss L, Guerrieri F, Pediconi N, Volz T, Pollicino T, et al. IFN-α inhibits HBV transcription and replication in cell culture and in humanized mice by targeting the epigenetic regulation of the nuclear cccDNA minichromosome. J Clin Invest 2012;122:529–537.

[52] Lucifora J, Xia Y, Reisinger F, Zhang K, Stadler D, Cheng X, et al. Specific and nonhepatotoxic degradation of nuclear hepatitis B virus cccDNA. Science 2014;343:1221–1228.

[53] Allweiss L, Volz T, Lütgehetmann M, Giersch K, Bornscheuer T, Lohse AW, et al. Immune cell responses are not required to induce substantial hepatitis B virus antigen decline during pegylated interferon-alpha administration. J Hepatol 2014;60:500–507.

[54] Chien RN, Liaw YF, Atkins Mfor Asian Hepatitis Lamivudine Trial Group. Pretherapy alanine transaminase level as a determinant for hepatitis B e antigen seroconversion during lamivudine therapy in patients with chronic hepatitis B. Hepatology 1999;30:770–774.

[55] Liaw YF, Leung NWY, Chang TT, Guan R, Tai DI, Ng KY, et alAsian hepatitis lamivudine study group.. Effects of extended lamivudine therapy in Asian patients with chronic hepatitis B. Gastroenterology 2000;119:172–180.

[56] Liaw YF, Tsai SL, Chien RN, Yeh CT, Chu CM. Prednisolone priming enhances Th1 response and efficacy of subsequent lamivudine therapy in patients with chronic hepatitis B. Hepatology 2000;32:604–609.

[57] Marcellin P, Chang TT, Lim SG, Tong MJ, Sievert W, Shiffman ML, et alAdefovir Dipivoxil 437 Study Group. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. N Engl J Med 2003;348:808–816.

[58] Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, et alAdefovir Dipivoxil 438 Study Group. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. N Engl J Med 2005;352:2673–2681.

[59] Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, et alBEHoLD AI463022 Study Group. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med 2006;354:1001–1010.

[60] Zeng M, Mao Y, Yao G, Wang H, Hou J, Wang Y, et al. A double-blind randomized trial of adefovir dipivoxil in Chinese subjects with HBeAg-positive chronic hepatitis B. Hepatology 2006;44:108–116.

[61] Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, et alBEHoLD AI463027 Study Group. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2006;354:1011–1020, Erratum in: N Engl J Med. 2006;354:1863.

[62] Lai CL, Gane E, Liaw YF, Hsu CW, Thongsawat S, Wang Y, et alGlobe Study Group. Telbivudine versus lamivudine in patients with chronic hepatitis B. N Engl J Med 2007;357:2576–2588.

[63] Hou J, Yin YK, Xu D, Tan D, Niu J, Zhou X, et al. Telbivudine versus lamivudine in Chinese patients with chronic hepatitis B: results at 1 year of a randomized, double-blind trial. Hepatology 2008;47:447–454.

[64] Liaw YF, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, et alThe GLOBE Study Group. 2-Year GLOBE trial results: telbivudine is superior to lamivudine in patients with chronic hepatitis B. Gastroenterology 2009;136:486–495.

[65] Marcellin P, Heathcote EJ, Buti M, Gane E, de Man RA, Krastev Z, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med 2008;359:2442–2455.

[66] Boni C, Penna A, Bertoletti A, Lamonaca V, Rapti I, Missale G, et al. Transient restoration of anti-viral T cell responses induced by lamivudine therapy in chronic hepatitis B. J Hepatol 2003;39:595–605, Erratum in: J Hepatol 2004;40:1053-1054.

[67] Evans A, Riva A, Cooksley H, Phillips S, Puranik S, Nathwani A, et al. Programmed death 1 expression during antiviral treatment of chronic hepatitis B: impact of hepatitis B e-antigen seroconversion. Hepatology 2008;48:759–769.

[68] Liaw YF, Chien RN, Yeh CT, Tsai SL, Chu CM. Acute exacerbation and hepatitis B virus clearance after emergence of YMDD motif mutation during lamivudine therapy. Hepatology 1999;30:567–572.

[69] Liaw YF, Chien RN, Yeh CT. No benefit to continue lamivudine therapy after emergence of YMDD mutations. Antivir Ther 2004;9:257–262.

[70] European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. J Hepatol 2012;57:167–185.

[71] Liaw YF. Antiviral therapy of chronic hepatitis B: opportunities and challenges in Asia. J Hepatol 2009;51:403–410.

[72] Honkoop P, de Man RA, Niesters HG, Zondervan PE, Schalm SW. Acute exacerbation of chronic hepatitis B virus infection after withdrawal of lamivudine therapy. Hepatology 2000;32:635–639.

[73] Lim SG, Wai CT, Rajnakova A, Kajiji T, Guan R. Fatal hepatitis B reactivation following discontinuation of nucleoside analogues for chronic hepatitis B. Gut 2002;51:597–599.

[74] Jeng WJ, Sheen IS, Chen YC, Hsu CW, Chien RN, Chu CM, et al. Off therapy durability of response to Entecavir therapy in hepatitis B e antigen negative chronic hepatitis B patients. Hepatology 2013;58:1888–1896.

[75] Zhang NP, Reijnders JG, Perquin M, Hansen BE, Janssen HL. Frequency and clinical outcomes of flares related to nucleos(t)ide analogue therapy in patients with chronic hepatitis B. J Viral Hepat 2011;18:e252–e257.

[76] Song BC, Suh DJ, Lee HC, Chung YH, Lee YS. Hepatitis B e antigen seroconversion after lamivudine therapy is not durable in patients with chronic hepatitis B in Korea. Hepatology 2000;32:803–806.

[77] Chien RN, Yeh CT, Tsai SL, Chu CM, Liaw YF. The determinants for sustained HBeAg response to lamivudine therapy. Hepatology 2003;38:1267–1273.

[78] Lee HW, Lee HJ, Hwang JS, Sohn JH, Jang JY, Han KJ, et al. Lamivudine maintenance beyond one year after HBeAg seroconversion is a major factor for sustained virologic response in HBeAg-positive chronic hepatitis B. Hepatology 2010;51:415–421.

[79] Hadziyannis SJ, Sevastianos V, Rapti I, Vassilopoulos D, Hadziyannis E. Sustained responses and loss of HBsAg in HBeAg-negative patients with chronic hepatitis B who stop long-term treatment with adefovir. Gastroenterology 2012;143:629–636.

[80] Trowsdale J, Betz AG. Mother's little helpers: mechanisms of maternal-fetal tolerance. Nat Immunol 2006;7:241–246.

[81] ter Borg MJ, Leemans WF, de Man RA, Janssen HL. Exacerbation of chronic hepatitis B infection after delivery. J Viral Hepat 2008;15:37–41.

[82] Nguyen V, Tan PK, Greenup AJ, Glass A, Davison S, Samarasinghe D, et al. Anti-viral therapy for prevention of perinatal HBV transmission: extending therapy beyond birth does not protect against post-partum flare. Aliment Pharmacol Ther 2014;39:1225–1234.

[83] Tan HH, Lui HF, Chow WC. Chronic hepatitis B virus (HBV) infection in pregnancy. Hepatol Int 2008;2:370–375.

[84] Drake A, Mijch A, Sasadeusz J. Immune reconstitution hepatitis in HIV and hepatitis B coinfection, despite lamivudine therapy as part of HAART. Clin Infect Dis 2004;39:129–132.

[85] Crane M, Oliver B, Matthews G, Avihingsanon A, Ubolyam S, Markovska V, et al. Immunopathogenesis of hepatic flare in HIV/hepatitis B virus (HBV)-coinfected individuals after the initiation of HBV-active antiretroviral therapy. J Infect Dis 2009;199:974–981.

[86] Wu JC, Lee SD, Yeh PF, Chan CY, Wang YJ, Huang YS, et al. Isoniazid-rifampin-induced hepatitis in hepatitis B carriers. Gastroenterology 1990;98: 502–504.

[87] Lok AS, Liang RH, Chiu EK, Wong KL, Chan TK, Todd D. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. Gastroenterology 1991;100:182–188.

[88] Lau GK, He ML, Fong DY, Bartholomeusz A, Au WY, Lie AK, et al. Preemptive use of lamivudine reduces hepatitis B exacerbation after allogeneic hematopoietic cell transplantation. Hepatology 2002;36:702–709.

[89] Hwang JP, Lok AS. Management of patients with hepatitis B who require immunosuppressive therapy. Nat Rev Gastroenterol Hepatol 2014;11: 209–219.

[90] Jang JW, Choi JY, Bae SH, Yoon SK, Chang UI, Kim CW, et al. A randomized controlled study of preemptive lamivudine in patients receiving transarterial chemo-lipiodolization. Hepatology 2006;43:233–240.

[91] Loomba R, Rowley A, Wesley R, Liang TJ, Hoofnagle JH, Pucino F, et al. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. Ann Intern Med 2008;148:519–528.

[92] Cheng AL, Hsiung CA, Su IJ, Chen PJ, Chang MC, Tsao CJ, et al. Lymphoma Committee of Taiwan Cooperative Oncology Group. Steroid-free chemotherapy decreases risk of hepatitis B virus (HBV) reactivation in HBV-carriers with lymphoma. Hepatology 2003;37:1320–1328.

[93] Huang YH, Hsiao LT, Hong YC, Chiou TJ, Yu YB, Gau JP, et al. Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. J Clin Oncol 2013;31:2765–2772.

[94] Hsu C, Tsou HH, Lin SJ, Wang MC, Yao M, Hwang WL, et al on behalf of the Taiwan Cooperative Oncology Group. Chemotherapy-induced hepatitis B reactivation in lymphoma patients with resolved HBV infection: a prospective study. Hepatology 2014;59:2092–2100.

[95] Pérez-Alvarez R, Díaz-Lagares C, García-Hernández F, Lopez-Roses L, Brito-Zerón P, Pérez-de-Lis M, et alBIOGEAS Study Group. Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: analysis of 257 cases. Medicine 2011;90:359–371.

[96] Vallet-Pichard A, Fontaine H, Mallet V, Pol S. Viral hepatitis in solid organ transplantation other than liver. J Hepatol 2011;55:474–482.

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