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Hepatitis B Virus Genotypes: Clinical Relevance and Therapeutic Implications

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Abstract At least ten hepatitis B virus (HBV) genotypes (A to J) with distinct geographic distributions have been recognized. HBV genotype is not only predictive of clinical outcome but also implicated in responsiveness to antiviral therapy, especially interferon-based regimens. HBV genotype-specific immunologic and virological pathogenesis may contribute to heterogeneous clinical outcomes in chronic hepatitis B patients. For example, patients with genotypes C and D infection have a lower rate of spontaneous HBeAg seroconversion. In addition, genotype C and D have a higher frequency of basal core promoter A1762T/G1764A mutation than genotype A and B. Genotypes C and D also carry a higher risk of cirrhosis and HCC development than genotype A and B. Therapeutically, genotype A and B patients have a better response to interferon-based therapy than genotypes C and D patients, but the response to nucleos(t)ide analogues is comparable across all HBV genotypes. In conclusion, genotyping of HBV can help practicing physicians identify chronic hepatitis B patients who are at risk of disease progression and optimize anti-viral therapy in clinical practice.

Keywords Chronic hepatitis B · Hepatitis B virus (HBV) · Genotype · HBV viral mutation · Hepatocellular carcinoma · Cirrhosis · Interferon-based therapy · Nucleos(t)ide analogues

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Introduction

Hepatitis B virus (HBV) is one of the most common viral infections in humans [1] and is endemic in Asia and the Pacific islands, Africa, Southern Europe and Latin America. The prevalence of chronic HBV infection in the general population ranges from 2 % to 20 % [1]. Persistent HBV infection has a wide spectrum of clinical manifestations, including inactive carrier state, chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC) [2, 3]. Eventually, 15-40 % of HBV carriers have a lifetime risk to develop cirrhosis, liver failure, or HCC [4].

HBV is the smallest human DNA virus with a genome of 3200 base pairs [5]. In the replication cycle of HBV, the partially double-stranded circular DNA will transform into covalently closed circular DNA (cccDNA) in the nucleus of hepatocyte. Through reverse transcription, pregenomic RNA is transcribed from cccDNA to serve as the template of negative-strand DNA and then fully double-stranded DNA through

DNA polymerase within the nucleocapsid, finally with the assembly of envelope protein to form mature HBV virions [6]. Because of the spontaneous error rate of viral reverse transcriptase, the HBV genome evolves with an estimated rate of nucleotide substitution at $1.4–3.2\times10^{-5}$/sites/year [5]. This unique replication strategy leads to the occurrence of various genotypes, subtypes, mutants, recombinants, and even quasispecies in the long-time evolution of HBV [7–9].

Based on advances in molecular biology, genotypic classifications of HBV and their geographic and ethnic distributions have been possible [10]. Although increasing evidence reveals that HBV genotype is associated with HBV endemicity, transmission mode, as well as clinical outcomes, the precise role of genotype in molecular pathogenesis and anti-viral response remains to be firmly established. In this article, recent advances in the impact of HBV genotype on the disease progression and responses to antiviral treatments in chronic hepatitis B patients will be reviewed and discussed.

Molecular Epidemiology and Geographic Distribution of HBV Genotypes

Based on more than 8 % in the surface gene or 4-8 % genetic divergence in the entire HBV genomic sequence, at least 10 HBV genotypes (A to J) and several subtypes have been identified [11–14]. The geographic and ethnic distributions of HBV genotypes and subtypes are shown in Table 1. For example, genotype A is highly prevalent in sub-Saharan Africa (subtype A1), Northern Europe (subtype A2), and Western Africa (subtype A3). Genotypes B and C are common in Asian Pacific region. Genotype B is divided into B1-B6 subtypes. Among them, B1 is isolated in Japan, B2-5 and B7 are found in East Asia, and B6 is found in indigenous populations living in the Arctic, such as Alaska, Northern Canada and Greenland. Genotype C, including subtypes C1-C5, mainly exist in East and Southeast Asia. Genotype D with subtypes D1-D5 is prevalent in Africa, Europe, the Mediterranean region and India. Genotype E is restricted to West Africa. Genotype F with four subtypes (F1-F4) is found in Central and South America. Genotype G has been reported in France, Germany and the United States. Genotype H is found in Central America. Recently, genotype I was isolated in Vietnam and Laos [15, 16]. The newest HBV genotype, J, was identified in Japan [17].

Table 1 Geographic distribution of hepatitis B virus genotypes and subtypes

Genotypes	Subtypes	Geographic location
A	A1	Sub-Saharan Africa
	A2	Northern Europe
	A3	Western Africa
B	B1	Japan
	B2-5	East Asia, Taiwan, China, Indonesia, Vietnam, Philippines
	B6	Alaska, Northern Canada, Greenland
C	C1-3	Taiwan, China, Korea and Southeast Asia.
	C4	Australia
	C5	Philippines, Vietnam
D	D1-5	Africa, Europe, Mediterranean countries and India
E		Restricted to West Africa
F	F1-4	Central and South America
G		France, Germany and the United States
H		Central America
I		Vietnam and Laos
J		Japan

On the basis of the geographic distribution patterns of HBV genotypes, the worldwide distribution of HBV can be divided into two distinct regions. Genotype B and C are prevalent in East Asia, whereas genotype A and D are prominent genotypes in Africa, Europe and India. Similar to the specific global distribution of HBV genotypes, there are different transmission modes of HBV [1]. For example, genotypes B and C are prevalent in highly endemic areas, such as Asian countries, where perinatal or vertical transmission plays an important role in spreading HBV, whereas the remaining genotypes are frequently found in areas where horizontal transmission (close personal conduct between young children, blood or sexual contamination between adults) is the main mode of transmission. Thus, it is important to elucidate the relation between genotype distribution of HBV and distinct modes of transmission in the molecular epidemiology of HBV. In our study, HBV genotyping was applied to investigate the modes of intrafamilial HBV transmission. We found that the prevalence of HBsAg in children from families with clustering of HBV carriers was significantly higher than that in the general population of Taiwan (77.8 % vs. 15 %). The possible intrafamilial modes of transmission were determined by identifying the concordant HBV genotype between carrier children and their parents [18]. The modes of transmission may influence the distribution of HBV in a given country where universal hepatitis B vaccination has not yet been launched. For example, through promiscuous sexual contacts, HBV genotype A is prevalent in patients with acute hepatitis B in Japan [19]. In a nationwide survey, Matsuura et al. further found that the prevalence of HBV genotype A in chronic hepatitis B patients in Japan increased from 1.7 % in 2000 to 3.5 % in 2006 [20]. Therefore, HBV genotyping can serve as an epidemiologic tool to determine the correlation of HBV genotype distribution with modes of transmission.

Clinical Significance of HBV Genotype

Ample evidence indicates that specific HBV genotype can influence the consequences of HBV infection (Table 2). Most retrospective or case–control studies suggest that patients with genotype C infection have more severe liver disease, including cirrhosis and HCC, than those with genotype B [21–24]. These findings were in line with a seminal cohort study, the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) cohort study. This community-based prospective cohort study on 2762 Taiwanese HBV carriers, demonstrated that HBV genotype C was associated with a greater risk of HCC than genotype B; the adjusted hazard ratio (HR) was 2.35 (95 % confidence interval (CI):1.68 to 3.30; $P<.001$) [25]. Our recent hospital-based ERADICATE-B study (Elucidation of Risk Factors for Disease Control or Advancement in Taiwanese Hepatitis B Carriers) also showed similar findings. A total of 2688 non-cirrhotic Taiwanese chronic hepatitis B patients were followed for a mean of 14.7 years. HCC risk increased when patients had HBV-genotype C infection (HR:3.4; 95 % CI:2.5-4.6) [26]. These findings confirmed that genotype C correlates with a higher risk of HCC development. Of interest, several reports showed that there were age-related differences of HBV genotype distribution in HCC patients. In earlier studies from Taiwan, HBV genotype B was the major type (75 %) of HCC patients younger than 35 years and children with HCC, and most were cases of non-cirrhotic chronic hepatitis B. Genotype C was associated with HCC development at older ages [21, 27]. Consistent with our study, Yin et al. also found that HBV genotype C2 was more prevalent in HCC patients compared with genotype B2 patients. However, the proportion of HBV genotype B2 in HCC patients decreased consecutively from <30 to 50–59 years group ($P=0.024$) [28]. The clinicopathological features of patients with resectable HCC were also different between genotype B and C. In Taiwan, among 193 resectable HBV-related HCC patients, genotype B patients had a higher rate of solitary tumor (94 % vs. 86 %, $P=0.048$) but more satellite nodules (22 % vs. 12 %, $P=0.05$) than genotype C patients. These characteristics may contribute to the recurrence patterns and prognosis of HBV-related HCC patients with genotype B or C infection [29, 30].

As for other genotypes, HCC is more frequent in patients with HBV genotype D and F infection than those with genotype A infection [31, 32].

Immunologic Manifestations of HBV Genotype-Specific Pathogenesis

The pathogenic differences among various HBV genotypes have been partially clarified. As a non-cytopathic virus, the immunopathogenesis of HBV infection is mainly mediated by cellular responses to epitopes of HBV proteins expressed on the surface of hepatocytes with consequent liver injury [33, 34].

Table 2 HBV genotype-specific pathogenesis and clinical implications in patients with chronic hepatitis B

Genotypes compared[a]	B vs. C		A vs. D	
	B	C	A	D
Immunologic aspects of pathogenesis				
HBeAg Seroconversion	Earlier	Later	Earlier	Later
HBsAg seroclearance	More	Less	More	Less
Histologic activity	Lower	Higher	Lower	Higher
Virological aspects of pathogenesis				
Serum HBV DNA level	Lower	Higher	ND	ND
Frequency of precore A1896 mutation	Higher	Lower	Lower	Higher
Frequency of basal core promoter A1762T/G1764A mutation	Lower	Higher	Lower	Higher
Frequency of pre-S deletion mutation	Lower	Higher	ND	ND
Intracellular expression of HBV DNA	Lower	Higher	Lower	Higher
Secretion of HBeAg	Lower	Higher	ND	ND
Clinical implications				
Incidence of progression to cirrhosis and hepatocellular carcinoma	Lower	Higher	Lower	Higher
Response to interferon-based therapy	Higher	Lower	Higher	Lower
Response to nucleos(t)ide analogues	No significant difference between genotype A to D			

[a] Because of the unique distribution of HBV genotypes in Asian and Western countries, sufficient data for meaningful comparisons are available only for comparisons between genotypes B and C or betweens genotype A and D

ND no available data

Persistent HBV replication may trigger strong and continued immune responses against the virus and result in severe liver damage [35]. In the natural history of chronic HBV infection, seroconversion of HBeAg and seroclearance of HBsAg have been recognized as important events in HBV control. Earlier HBeAg seroconversion usually confers a favorable clinical outcome, whereas late or absent HBeAg seroconversion after multiple hepatitis flares may accelerate the progression of chronic hepatitis to cirrhosis; it therefore has a poor clinical outcome [36–38]. In our cohort study of 272 Taiwanese patients with chronic HBV infection, genotype C patients were more likely to have HBeAg-positive chronic hepatitis B despite multiple hepatitis flares [39]. In addition, genotype C infection was associated with lower rates of spontaneous HBeAg seroconversion than genotype B (27 % vs. 47 %, $P<0.025$) during follow-up. The estimated annual rates of HBeAg seroconversion in genotype B and C infections were 15.5 % and 7.9 %, respectively [40]. Furthermore, a long-term follow-up study with 460 Taiwanese HBV children indicated that the seropositive rate of HBeAg after 20 years of follow-up was 70 % in genotype C and 40 % in genotype B carriers [27]. Taking these lines of evidence together, genotype C patients may experience delayed HBeAg seroconversion and thus a longer duration of high HBV replication than genotype B patients. With long-term immunologic response, genotype C patients are correspondingly more prone to develop advanced fibrosis, cirrhosis and HCC than genotype B patients.

Regarding genotypes A and D, one prospective study of Spanish patients with chronic HBV infection showed that no differences was observed in the probability of HBeAg seroconversion between patients infected with genotype A and D. However, the rate of sustained remission after HBeAg seroconversion was higher in genotype A than genotype D (55 % vs. 32 %, $P<0.01$) [41]. In addition, compared to genotypes C and D, genotype A and B patients had a higher rate of spontaneous HBsAg seroclearance [41, 42]. Taken together, these facts suggest the immunologic response differs between genotypes B and C as well as genotypes A and D during the early phase of chronic HBV infection. Therefore, from the view point of immunologic mechanisms, genotype C and D patients, compared to genotype A and B patients, have late or absent HBeAg seroconversion after multiple hepatitis flares that may accelerate the progression of chronic hepatitis, thereby conferring a worse clinical outcome.

Virological Manifestations of HBV Genotype-Specific Pathogenesis

Recently, hepatitis B viral load and genetic variants associated with clinical outcomes have been identified [43]. The associations between HBV viral load and mutations and liver disease progression suggest that hepatitis B viral characteristics may play a role in HBV genotype-specific pathogenesis.

In a prospective study with 4841 Taiwanese male HBV-infected patients without HCC at enrollment, Yu et al. found that HBV viral load was higher in genotype C than genotype B patients, while genotype C-infected patients who also had very high viral load had a 26-fold higher risk of HCC than those with other genotypes and low or undetectable viral loads [44]. In an earlier study, we had reported that genotype C infections had a higher frequency of basal core promoter (BCP) A1762T/G1764A mutation than genotype B [45]. Furthermore, Yang et al. reported that among those infected with HBV genotype C, wild-type precore 1896 sequence, and BCP A1762T/G1764A mutation was associated with higher risk of HCC (adjusted HR:2.99, 95 % CI:1.57 to 5.70, $P<.001$) than those with genotype B infection, wild-type precore 1896 and BCP sequences [25]. Similarly, patients with genotype D infection, who had more progressive liver disease, also had a higher prevalence of BCP A1762T/G1764A mutation than those with genotype A infection [46].

Previous reports also showed that the deletion mutations within the pre-S gene were significantly associated with the development of cirrhosis and HCC [47–49]. Through endoplasmic reticulum stress inducing oxidative DNA damage, pre-S gene deletion mutations may lead to mutagenesis in the host genome, and contribute to hepatocarcinogenesis [50]. In our case–control study, the presence of pre-S deletion was an independent risk factor associated with HCC development (odds ratio (OR):3.72; 95 % CI:1.44-9.65; $P=0.007$). In addition, the frequency of pre-S deletion was significantly higher in genotype C patients than genotype B patients [47]. A meta-analysis further confirmed that the OR of HCC for pre-S deletion was 3.77 (95 % CI:2.57 to 5.52). Of particular note, the summary OR for pre-S deletion was higher in genotype C patients than genotype B patients [51•].

Recently, virological differences among HBV genotypes were demonstrated both in vitro and in vivo. In an in vitro study, intracellular expression of HBV DNA were higher for genotypes C than B and genotypes D than A [52]. Our in vitro study also showed that secretion of HBeAg in genotype B was lower than that in genotype C [53]. The intracellular accumulation of HBV DNA may play a role in inducing liver cell damage. In addition, the higher replication capacity of genotype C HBV may explain why this genotype is associated with more severe liver disease than others. Further investigation revealed that the expression of intracellular core protein increased when BCP mutation was introduced in genotype C strains [53]. Our in vivo study also revealed that HBV BCP mutation A1762T/G1764A is significantly associated with cytoplasmic localization of intracellular HBcAg, which is closely related to active necroinflammation of hepatocytes [54].

In summary, the specific virological manifestations of HBV genotype B and C include: (1) Genotype C has a higher frequency of BCP A1762T/G1764A mutation and pre-S deletion mutations than genotype B. (2) Serum HBV viral load was higher in genotype C than genotype B. (3) The expression of intracellular HBV DNA increased in genotype C. (4) The expression of intracellular core protein increased in genotype C with BCP A1762T/G1764A mutation. (5) More HBeAg was secreted by genotype C than by genotype B. These findings may partly explain why genotype C is associated with more severe liver disease than others [55]. The HBV genotype-specific immunologic and virological manifestations are compared in Table 2.

HBV Genotype and Response to Anti-Viral Therapy

The therapeutic endpoints for chronic hepatitis B treatment include sustained suppression of HBV replication to below the detection limit of real-time PCR assays, biochemical remission, histological improvement, HBeAg loss or HBeAg seroconversion for HBeAg-positive patients, and ideally HBsAg loss or even HBsAg seroconversion [56•, 57•, 58•]. Currently, two types of therapy are recommended: standard interferon (IFN) or pegylated interferon (PEG-IFN) and five nucleos(t)ide analogues, including lamivudine, telbivudine, entecavir, adefovir dipivoxil and tenofovir disoproxil [56•, 57•, 58•]. The impact of HBV genotype on therapeutic responses to both IFN-based and nucleos(t)ide analogues has been increasingly recognized [59, 60]. Due to patients infected with genotype E-J being rarer, their responses to antiviral therapy remain largely unknown. The influences of HBV genotype on response to antiviral therapy could only be reliably demonstrated in genotype A, B, C and D (Table 2).

Interferon-Based Therapy. In HBeAg-positive patients treated with standard IFN, patients with genotype A and B had significantly higher rates of sustained response, defined as normalization of serum ALT level and HBeAg seroconversion post-treatment, than those with genotype C and D [45, 61–63]. For HBeAg-positive Asian population, genotype B patients are more susceptible to IFN-based therapy, regardless of pegylated or standard type IFN products, whereas genotype C Asian patients have a higher likelihood of response to PEG-IFN compared to standard IFN [64, 65]. Furthermore, Zhao et al. assessed the efficacy of low-dose, 24-week standard IFN or PEG-IFN treatment in HBeAg-positive Chinese patients. They found that HBV genotype B infection and younger age were independent factors associated with sustained response of low-dose, 24-week IFN regimen [66]. Another multi-center study on PEG-IFN for HBeAg-positive patients revealed that the rate of HBeAg clearance also differed according to HBV genotypes: genotype A, 47 %; genotype B, 44 %; genotype C, 28 %; and genotype D, 25 % [67]. Subsequent analysis consistently demonstrated a higher rate of HBsAg clearance in genotype A compared to other genotypes in both HBeAg-positive and HBeAg-negative chronic hepatitis B [68]. In addition, compared to genotype C and D patients, durable loss of HBeAg at 3 years after PEG-IFN treatment was higher in genotype A and B patients [69]. Among HBeAg-negative patients treated with PEG-IFN, HBsAg clearance was significantly higher in genotype A (20 %) than genotype B (6 %), genotype C (9 %), and genotype D (6 %) [70•]. Based on available evidence, a meta-analysis further confirmed that HBV genotypes are informative concerning responses to IFN-based therapy. HBV genotype A has better responses to IFN treatment than genotype D patients, regardless of HBeAg status. HBV genotype B has a higher response rate to IFN treatment than genotype C in HBeAg-positive patients [71]. Recent pooled data from the two large global trials of HBeAg-positive patients with PEG-IFN treatment showed that higher levels of ALT and lower levels of HBV DNA predicted a sustained response to PEG-IFN therapy for genotype A, B, C-infected patients. On the contrary, genotype D-infected patients had the lowest chance of sustained response, irrespective of ALT or HBV DNA levels [72•].

Recently, the clinical significance of quantitative HBsAg has become increasingly recognized [73•]. The on-treatment decline of quantitative serum HBsAg level has been proven useful as a predictor of response for IFN-based therapy. For HBeAg-positive genotype B and C patients, HBeAg seroconversion was significantly associated with serum HBsAg level <1500 IU/mL at week 12 of PEG-IFN α-2a treatment, whereas patients with serum HBsAg level >20,000 IU/mL at week 12 of PEG-IFN α-2a treatment did not respond [74•]. Similar, for HBeAg-positive genotype A and D patients, without serum HBsAg level decline at week 12 of Peg-IFN predicted a poor response of HBeAg loss at 26 weeks after treatment (the negative predictive value: 97 %) [75•]. On-treatment decline of serum HBsAg level was also significantly associated with sustained viral suppression as well as long-term HBsAg clearance in HBeAg-negative patients, irrespective of genotype [76]. HBsAg kinetics during PEG-IFN treatment also varied between different HBV genotypes. For example, at the end of treatment, mean decrease of HBsAg level was high with genotype A infection, intermediate in genotypes B and D, and low in genotypes C and E. During follow-up, serum HBsAg continued to decrease in genotypes A and D, whereas rebound was observed in genotypes B, C and E [77]. According to on-treatment kinetics of serum HBsAg, response-guided treatment for CHB patients treated with PEG-IFN has been established. Recently, the week 12 stopping rule, no HBsAg decline and <2 log copies/ml decline in HBV DNA at week 12 therapy of PEG-IFN, has been proposed and validated in HBeAg-

negative patients. Of particular note is that this rule performed best among genotype D-infected patients (negative predictive value: 100 %) [78•, 79••]. However, the stopping rules for PEG-IFN therapy based on HBsAg kinetics have not been confirmed across all HBV genotype patients, therefore more cohort studies are needed to prove stopping rules for the treatment of chronic hepatitis B (Fig. 1).

Nucleoside and Nucleotide Analogues

In sharp contrast to IFN-based therapy, the therapeutic responses to nucleos(t)ide analogues as well as the development of resistance were comparable among patients with different genotypes [71, 80–86]. Although HBV genotypes seem to not have an impact on the response and resistance to nucleos(t)ide analogue treatment, our retrospective study found that HBV genotype B was independently associated with earlier detection of lamivudine-resistant strains. In addition, genotype B was significantly associated with development of lamivudine resistance within the first 12 months of lamivudine therapy compared with genotype C (OR:8.27; P=0.004) [87]. Therefore, more frequent monitoring of genotypic resistance might be needed for specific HBV genotypes during nucleos(t)ide analogues therapy.

The rates of HBsAg loss or seroconversion are continuously increasing in CHB patients after stopping a finite course of IFN treatment, whereas complete clearance of HBsAg is rare in patients treated with nucleos(t)ide analogues. Marcellin et al. has been reported that five of 158 HBeAg-positive patients treated with tenofovir disoproxil lost HBsAg at 48 weeks of treatment [88]. Among these five patients with HBsAg loss, two and three were infected with genotype A and D, respectively. Although the proportion of patients with HBsAg loss is too small to reach any conclusion, the association between HBV genotype and nucleos(t)ide analogues-induced HBsAg loss deserves further study.

Conclusions

In the past decade, advances in molecular research have clarified the clinical implications of HBV genotype. In brief, compared to genotype A and B patients, genotype C and D patients have a higher risk of disease progression as well as a poorer clinical outcome. In addition, genotype A and B patients have a better response to IFN-based therapy than genotype C and D patients. However, the association between HBV genotype and therapeutic response to nucleos(t)ide analogues seems minimal. Despite numerous lines of evidence connecting HBV genotype and the disease progression as well as responses to antiviral therapy, HBV genotyping is still not recommended as part of the management of chronic hepatitis B in the recent update guidelines for the management of HBV infection [56•, 57•, 58•]. Nevertheless, it is recommended that HBV carriers should be routinely genotyped to identify those who are at higher risk of liver disease progression, and who can benefit most from IFN-based therapy on the basis of accumulating lines of evidence. In the foreseeable future, clinical trials stratified by different genotypes and treatment regimens are mandatory for designing individualized therapies for chronic hepatitis B patients.

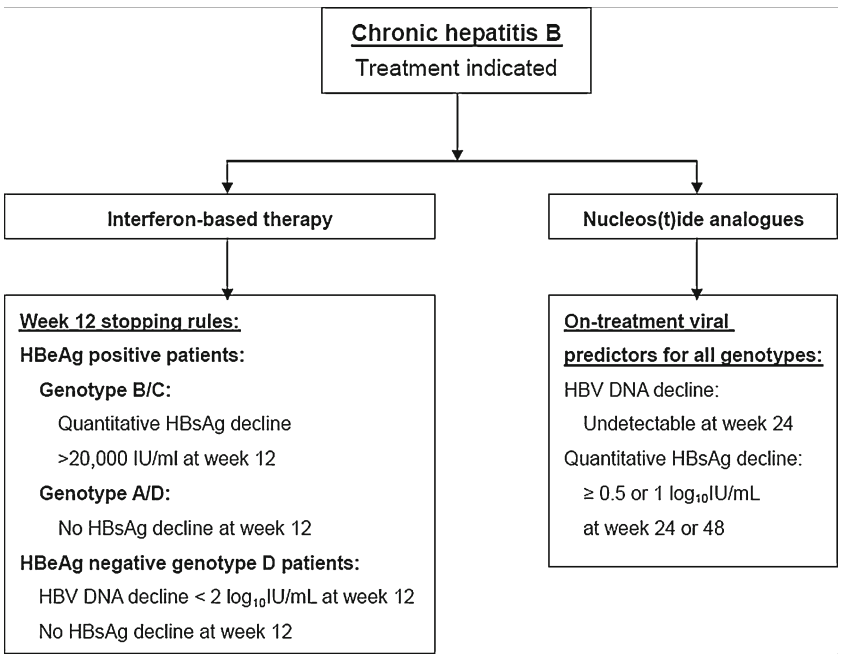

Fig. 1 Hypothetical algorithm for HBV genotype-specific antiviral treatment in chronic hepatitis B

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Conflict of Interest Chih-Lin Lin declares that he has no conflict of interest.

Jia-Horng Kao declares that he has no conflict of interest.

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Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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